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Stockley's Drug Interactions

Ninth edition

Stockley's Drug Interactions

A source book of interactions, their mechanisms, clinical importance and management

Ninth edition

Edited by

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Preface

This, the 9th edition of *Stockley's Drug Interactions*, continues to build on the experience gained by the editorial team, from a history of more than 30 years of analysing the literature on drug interactions. In the words of Ivan Stockley, from his original guidance to us: 'most readers want answers quickly, and therefore we have to write concisely and crisply to produce a picture which emerges very rapidly. We are not in the business of writing a discursive essay or great literature. Our business is bread-and-butter, rapid and unambiguous communication, for which we use direct and simple English, avoiding jargon wherever we can, recognising that our readers have varied backgrounds. Some may have forgotten (or never known) some of what we, with our familiarity with the subject, come to regard as basic pharmacology or medicine. At the same time we need to avoid patronising the well-informed reader by "mickey-mousing" it.' This is the philosophy we work with, and we hope to continue to pay due respect to Ivan Stockley's intentions by adhering to this fitting guidance.

In some areas we have become slightly more discursive, in the hope of better explaining the relevance of an interaction to specific patient groups. However, we have addressed the needs of those in a hurry by including a short summary of the interaction, with the advice on the management of the interaction discussed separately from the detailed clinical evidence and mechanism information. For those with more time, or those wishing to know the full picture, the clinical evidence and mechanism sections provide more detailed background on the interaction. Whichever approach is taken, the aim of *Stockley's Drug Interactions* is, as ever, to inform busy doctors, pharmacists, nurses and other healthcare professionals of the facts about drug interactions, without their having to do the time-consuming literature searches and full assessment of the papers for themselves. If you need some insight into the general philosophy underlying the way the information is handled in this publication, you should have a look at the section, 'Before using this book. . .'.

This publication is unique in the Stockley family of products by not including a symbol to rate the severity of the interaction. We continue to review this decision, but we currently believe that, in this fully comprehensive text, it is not always possible to simply assign one rating – certainly drug groups are often not identical in the way they interact, and to assign one symbol to the discussion of a group of drugs risks incorrectly implying that all members may interact similarly. Further, it overlooks the range of differences in the individual patient that a practitioner may need to consider. An otherwise fit and healthy patient will react very differently to a patient with a multitude of medical problems, and, in some instances, the interaction may only occur in the presence of certain disease states, for example renal impairment, or perhaps only in children. We therefore prefer to discuss these various risks and differences, where applicable, and allow the reader to make the decision on the severity of the interaction with the full knowledge of their particular patient. We believe that the ratings symbols have a useful place in our other products, such as *Stockley's Drug Interactions Pocket Companion*, where the interaction information is designed to be abridged, and summarised in a few lines: in this situation the symbol presents a worst-case scenario.

For this edition of *Stockley's Drug Interactions*, the concise and easy-to-read format of the monographs has been maintained. As with previous editions, all of the existing interactions monographs have been reviewed, revalidated and updated, and many new ones have been added, making a total in excess of 3700 monographs, representing at 20% increase in content on the previous edition. This serves to highlight the ever-increasing wealth of information on this topic. Indeed we now cite well over 22,000 references, more, we think, than any other reference text on this subject. We also review relevant information provided by regulatory bodies outside of the UK, in particular the EMEA in Europe and the FDA in the US, which continues to enhance the international flavour of the publication. In addition, we have created three new chapters, covering Nutritional agents, Supplements and Vitamins, Thyroid hormones, and Urological drugs, to reflect the increasing literature available on these particular topic areas.

Previous editions have found us struggling with the best way to deal with the interactions of herbal medicines in this reference, which is primarily an evidence-based text. As before, we have included the interactions of herbal medicines for which clinical evidence is available. However, we have long felt that the overwhelming numbers of theoretical and *in vitro* papers are worthy of analysis alongside the modest amount of clinical data on herbal medicines interactions. Our sister publication *Stockley's Herbal Medicines Interactions*, first published in 2009, has therefore been written to deal with this theoretical data, which does not fit with the philosophy of *Stockley's Drug Interactions*.

This edition has also seen a growth in our editorial team, which includes experienced clinical pharmacists and medical writers, and we have been pleased to have the advice and assistance of pharmacists with a greater knowledge of community pharmacy and specialist clinical subjects than those in our existing team. In particular, the advice of Rosy Weston, a specialist HIV pharmacist, has been of great help, and our thanks go out to her. The diverse practical experience of our team and advisors helps us to maintain the quality and realistic nature of the management advice given.

The Editorial team have also had assistance from many other people in developing this publication, and the Editor gratefully acknowledges the assistance and guidance that they have provided. The *Martindale* team continue to be a great source of advice and support, and particular thanks is due to the editor, Sean Sweetman, both for his direct assistance with producing the publication, and for allowing us access to the *Martindale* databases, from which we derive much of our nomenclature. We greatly appreciate the help of Chloë Hatwal in putting together the final typeset pages. Thanks are also due to Tamsin Cousins, for patiently handling the various aspects of producing our publications in print. We are also grateful for the support of both Paul Weller and Robert Bolick.

Stockley's Drug Interactions continues to be available on the Pharmaceutical Press electronic platform, *MedicinesComplete* (available at www.medicinescomplete.com), where it is updated quarterly; as well as being available on other platforms as an e-book. With the continued development of the integratable Alerts product and the *MedicinesComplete* platform, we remain indebted to Julie McGlashan, Elizabeth King, and all those involved in the technical aspects of these products, for their advice and support. For more details about these digital products please visit: www.pharmpress.com/Stockley

Finally, thanks are due to those who take the time to provide us with feedback, either directly, or in the form of questions about the publication. We continue to value this input to evolve the publication and to ensure it meets the needs of the users. We are particularly grateful to those who have taken the time to answer our questions about specific aspects of practice. Anyone who wishes to contact the Stockley team can do so at the following address: stockley@rpsgb.org

London, February 2010

Abbreviations

ACE—angiotensin-converting enzyme
ADP—adenosine diphosphate
AIDS—acquired immunodeficiency syndrome
ALT—alanine aminotransferase
am—*ante meridiem* (before noon)
aPTT—activated partial thromboplastin time
AST—aspartate aminotransferase
AUC—area under the time–concentration curve
$AUC_{0–12}$—area under the time–concentration curve measured over 0 to 12 hours
AV—atrioventricular
BCRP—breast cancer resistance protein (ABCG2)
BNF—British National Formulary
BP—blood pressure
BP—British Pharmacopoeia
BPC—British Pharmaceutical Codex
BPH—benign prostatic hyperplasia
bpm—beats per minute
BUN—blood urea nitrogen
CAPD—continuous ambulatory peritoneal dialysis
CDC—Centers for Disease Control (USA)
CNS—central nervous system
COMT—catechol-*O*-methyl transferase
COPD—chronic obstructive pulmonary disease
COX—cyclo-oxygenase
CSF—cerebrospinal fluid
CSM—Committee on Safety of Medicines (UK) (now subsumed within the Commission on Human Medicines)
DNA—deoxyribonucleic acid
ECG—electrocardiogram
ECT—electroconvulsive therapy
ED_{50}—the dose at which 50% of subjects respond
EEG—electroencephalogram
e.g.—*exempli gratia* (for example)
EMEA—European Agency for the Evaluation of Medicinal Products
FDA—Food and Drug Administration (USA)
$FEF_{25–75}$—maximum expiratory flow over the middle 50% of the vital capacity
FEV_1—forced expiratory volume in one second
FSH—follicle simulating hormone
FVC—forced vital capacity
g—gram(s)
GABA—gamma-aminobutyric acid
h—hour(s)
HAART—highly active antiretroviral therapy
HbA_{1c}—glycosylated (glycated) haemoglobin
HIV—human immunodeficiency virus
HRT—hormone replacement therapy
ibid—*ibidem*, in the same place (journal or book)
i.e.—*id est* (that is)
INR—international normalised ratio
ITU—intensive therapy unit
IU—International Units
IUD—intra-uterine device
kg—kilogram(s)
L—litre(s)
LDL—low-density lipoprotein
LFT—liver function test
LH—luteinising hormone
LMWH—low-molecular-weight heparin
MAC—minimum alveolar concentration
MAO—monoamine oxidase
MAOI—monoamine oxidase inhibitor
MAO-A—monoamine oxidase, type A
MAO-B—monoamine oxidase, type B
MCA—Medicines Control Agency (UK) (now MHRA)
MHRA—Medicines and Healthcare products Regulatory Agency (UK)
MIC—minimum inhibitory concentration
mEq—milliequivalent(s)
mg—milligram(s)
mL—millilitre(s)
mmHg—millimetre(s) of mercury
mmol—millimole
mol—mole
MRSA—methicillin resistant *Staphylococcus aureus*
NICE—National Institute for Health and Clinical Excellence (UK) (formerly the National Institute for Clinical Excellence)
nM—nanomole
nmol—nanomole
NNRTI—non-nucleoside reverse transcriptase inhibitor
NRTI—nucleoside reverse transcriptase inhibitor
NSAID—non-steroidal anti-inflammatory drug
NYHA—New York Heart Association
PABA—para-amino benzoic acid
PCP—pneumocystis pneumonia
pH—the negative logarithm of the hydrogen ion concentration
pm—*post meridiem* (after noon)
pO_2—plasma partial pressure (concentration) of oxygen
PPI—proton pump inhibitor
ppm—parts per million
RIMA—reversible inhibitor of monoamine oxidase type A
RNA—ribonucleic acid
sic—written exactly as it appears in the original
SNRI—serotonin and noradrenaline reuptake inhibitor
SSRI—selective serotonin reuptake inhibitor
SVT—supraventricular tachycardia
T3—Triiodothyronine
TPN—total parenteral nutrition
TSH—thyroid-stimulating hormone
UGT—uridine diphospho glucuronosyltransferase
UK—United Kingdom
US and USA—United States of America
USP—United States Pharmacopeia

Before using this book . . .

. . . you should read this short explanatory section so that you know how the drug interaction data have been set out here, and why – as well as the basic philosophy that has been followed in presenting it.

The monographs

This publication has over 3700 monographs with a common format, which are subdivided into sections like these:

- An abstract or summary for quick reading.
- **Clinical evidence**, detailing one, two or more illustrative examples of the interaction, followed by most or all of other supportive clinical evidence currently available.
- **Mechanism**, in brief.
- **Importance and management**, a short discussion designed to aid rapid clinical decision making. For example:
  – Is the interaction established or not?
  – What is its incidence?
  – How important is it?
  – How can it be managed?
  – And what, if any, are the non-interacting alternatives?
- **References**, a list of all of the relevant references. The length of the references list gives a very fair indication of the extent of the documentation. A long list indicates a well documented interaction, whereas a short list indicates poor documentation.

Some of the monographs have been compressed into fewer subsections instead of the more usual five, simply where information is limited or where there is little need to be more expansive.

The monographs do not carry the drug interaction Hazard/Severity ratings as used in the electronic *Stockley Interactions Alerts*, but what is written in each monograph should speak for itself.

Quality of information on interactions

The data on interactions are of widely varying quality and reliability. The best come from clinical studies carried out on large numbers of patients under scrupulously controlled conditions. The worst are anecdotal, uncontrolled, or based solely on *animal* studies. Sometimes they are no more than speculative and theoretical scaremongering guesswork, hallowed by repeated quotation until they become virtually set in stone.

The aim has been to filter out as much useless noise as possible, so wherever possible 'secondary' references are avoided, and 'primary' references which are available in good medical and scientific libraries are used instead – although sometimes unpublished, good quality, in-house reports on drug company files have been used where the drug company has kindly allowed access to the information. Product literature (for example, the Summary of Product Characteristics in the UK and the Prescribing Information in the US) rather than the research reports that lie behind them are also cited because they are the only source of published information about new drugs.

The quality of drug company literature is very variable. Some of it is excellent, helpful and very reliable, but regrettably a proportion contains a welter of speculative and self-protective statements, probably driven more by the company's medico-legal policy than anything else, and the nervousness of drug regulatory authorities. It is almost unbelievable (but true all the same) that drug companies that are scrupulous in the way they do their research, come out with statements about possible interactions that are little more than guesswork.

When drawing your own conclusions

The human population is a total mixture, unlike selected batches of laboratory animals (same age, weight, sex, and strain etc.). For this reason human beings do not respond uniformly to one or more drugs. Our genetic make up, ethnic background, sex, renal and hepatic functions, diseases and nutritional states, ages and other factors (the route of administration, for example) all contribute towards the heterogeneity of our responses. This means that the outcome of giving one or more drugs to any individual for the first time is never totally predictable because it is a new and unique 'experiment'. Even so, some idea of the probable outcome of using a drug or a pair of drugs can be based on what has been seen in other patients: the more extensive the data, the firmer the predictions.

The most difficult decisions concern isolated cases of interaction, many of which only achieved prominence because they were serious. Do you ignore them as 'idiosyncratic' or do you, from that moment onwards, contraindicate the use of the two drugs totally?

There is no simple 'yes' or 'no' answer to these questions, but one simple rule-of-thumb is that isolated cases of interaction with old and very well-tried pairs of drugs are unlikely to be of general importance, whereas those with new drugs may possibly be the tip of an emerging iceberg and should therefore initially be taken much more seriously until more is known. The delicate balance between these two has then to be set against the actual severity of the reaction reported and weighed up against how essential it is to use the drug combination in question.

When deciding the possible first-time use of any two drugs in any particular patient, you need to put what is currently known about these drugs against the particular profile of your patient. Read the monograph. Consider the facts and conclusions, and then set the whole against the backdrop of your patients unique condition (age, disease, general condition, and so forth) so that what you eventually decide to do is well thought out and soundly based. We do not usually have the luxury of knowing absolutely all the facts, so that an initial conservative approach is often the safest.

I

General considerations and an outline survey of some basic interaction mechanisms

Drug interactions overview

(a) What is a drug interaction?

An interaction is said to occur when the effects of one drug are changed by the presence of another drug, herbal medicine, food, drink or by some environmental chemical agent. Much more colourful and informal definitions by patients are that it is ". . . when medicines fight each other. . .", or ". . . when medicines fizz together in the stomach . . .", or ". . .what happens when one medicine falls out with another. . ."

The outcome can be harmful if the interaction causes an increase in the toxicity of the drug. For example, there is a considerable increase in risk of severe muscle damage if patients taking statins start taking azole antifungals (see 'Statins + Azoles', p.1321). Patients taking monoamine oxidase inhibitor antidepressants (MAOIs) may experience an acute and potentially life-threatening hypertensive crisis if they eat tyramine-rich foods such as cheese (see 'MAOIs or RIMAs + Tyramine-rich foods', p.1395).

A reduction in efficacy due to an interaction can sometimes be just as harmful as an increase: patients taking warfarin who are given rifampicin (rifampin) need more warfarin to maintain adequate anticoagulation (see 'Coumarins + Antibacterials; Rifamycins', p.424), while patients taking 'tetracyclines', (p.390) or 'quinolones', (p.374) need to avoid antacids and milky foods (or separate their ingestion) because the effects of these antibacterials can be reduced or even abolished if admixture occurs in the gut.

These unwanted and unsought interactions are adverse and undesirable but there are other interactions that can be beneficial and valuable, such as the deliberate co-prescription of antihypertensive drugs and diuretics in order to achieve antihypertensive effects possibly not obtainable with either drug alone (see 'Antihypertensives + Other drugs that affect blood pressure', p.1051). The mechanisms of both types of interaction, whether adverse or beneficial, are often very similar, but the adverse interactions are the focus of this publication.

Definitions of a drug interaction are not rigidly adhered to in this publication because the subject inevitably overlaps into other areas of adverse reactions with drugs. So you will find in these pages some 'interactions' where one drug does not actually affect another at all, but the adverse outcome is the simple additive effects of two drugs with similar effects (for example the combined effects of two or more CNS depressants, or two drugs which affect the QT interval). Sometimes the term 'drug interaction' is used for the physico-chemical reactions that occur if drugs are mixed in intravenous fluids, causing precipitation or inactivation. The long-established and less ambiguous term is 'pharmaceutical incompatibilities'. Incompatibilities are not covered by this publication.

(b) What is the incidence of drug interactions?

The more drugs a patient takes the greater the likelihood that an adverse reaction will occur. One hospital study found that the rate was 7% in those taking 6 to 10 drugs but 40% in those taking 16 to 20 drugs, which represents a disproportionate increase.[1] A possible explanation is that the drugs were interacting.

Some of the early studies on the frequency of interactions uncritically compared the drugs that had been prescribed with lists of possible drug interactions, without appreciating that many interactions may be clinically trivial or simply theoretical. As a result, an unrealistically high incidence was suggested. Most of the later studies have avoided this error by looking at only potentially clinically important interactions, and incidences of up to 8.8% have been reported.[2-4] Even so, not all of these studies took into account the distinction that must be made between the incidence of potential interactions and the incidence of those where clinical problems actually arise. The simple fact is that some patients experience quite serious reactions while taking interacting drugs, while others appear not to be affected at all.

A screening of 2 422 patients over a total of 25 005 days revealed that 113 (4.7%) were taking combinations of drugs that could interact, but evidence of interactions was observed in only 7 patients, representing an incidence of 0.3%.[2] In another study of 44 hospital inpatients taking 10 to 17 drugs over a 5-day period, 77 potential drug interactions were identified, but only one probable and four possible adverse reactions (6.4%) were detected.[5] A further study, among patients taking antiepileptic drugs, found that 6% of the cases of toxicity were due to drug interactions.[6] These figures are low compared with those of a hospital survey that monitored 927 patients who had received 1004 potentially interacting drug combinations. Changes in drug dose were made in 44% of these cases.[7] A review of these and other studies found that the reported incidence rates ranged from 2.2 to 70.3%, and the percentage of patients actually experiencing problems was less than 11.1%. Another review of 639 elderly patients found a 37% incidence of interactions.[8] Yet another review of 236 geriatric patients found an 88% incidence of clinically significant interactions, and a 22% incidence of potentially serious and life-threatening interactions.[9] A 4.1% incidence of drug interactions on prescriptions presented to community pharmacists in the US was found in a further survey,[10] whereas the incidence was only 2.9% in another American study,[11] and just 1.9% in a Swedish study.[12] An Australian study found that about 10% of hospital admissions were drug-related, of which 4.4% were due to drug interactions.[13] A very high incidence (47 to 50%) of potential drug interactions was found in a study carried out in an Emergency Department in the US.[14] One French study found that 16% of the prescriptions for a group of patients taking antihypertensive drugs were contraindicated or unsuitable,[15] whereas another study in a group of geriatric patients found only a 1% incidence.[16] The incidence of problems would be expected to be higher in the elderly because ageing affects the functioning of the kidneys and liver.[17,18]

These discordant figures need to be put into the context of the under-reporting of adverse reactions of any kind by medical professionals, for reasons that may include pressure of work or the fear of litigation. Both doctors and patients may not recognise adverse reactions and interactions, and some patients simply stop taking their drugs without saying why. None of these studies give a clear answer to the question of how frequently drug interactions occur, but even if the incidence is as low as some of the studies suggest, it still represents a very considerable number of patients who appear to be at risk when one thinks of the large numbers of drugs prescribed and taken every day.

(c) How seriously should interactions be regarded and handled?

It would be very easy to conclude after browsing through this publication that it is extremely risky to treat patients with more than one drug at a time, but this would be an over-reaction. The figures quoted in the previous section illustrate that many drugs known to interact in some patients, simply fail to do so in others. This partially explains why some quite important drug interactions remained virtually unnoticed for many years, a good example of this being the increase in serum digoxin levels seen with quinidine (see 'Digoxin and related drugs + Quinidine', p.1111).

Examples of this kind suggest that patients apparently tolerate adverse interactions remarkably well, and that many experienced physicians accommodate the effects (such as rises or falls in serum drug levels) without consciously recognising that what they are seeing is the result of an interaction.

One of the reasons it is often difficult to detect an interaction is that, as already mentioned, patient variability is considerable. We now know many of the predisposing and protective factors that determine whether or not an interaction occurs but in practice it is still very difficult to predict what will happen when an individual patient is given two potentially interacting drugs. An easy solution to this practical problem is to choose a non-interacting alternative, but if none is available, it is frequently possible to give interacting drugs together, if appropriate precautions are taken. If the effects of the interaction are well-monitored they can often be allowed for, often simply by adjusting the doses of the interacting drugs. Many interactions are dose-related so that if the dose of the causative drug is reduced, the effects on the other drug will be reduced accordingly. Thus a non-prescription dose of cimetidine may not inhibit the metabolism of phenytoin, whereas a larger dose may clearly increase phenytoin levels (see 'Phenytoin + H_2-receptor antagonists', p.637).

The dose of the affected drug may also be critical. For example, isoniazid causes the levels of phenytoin to rise, particularly in those individuals who are slow acetylators of isoniazid, and levels may become toxic. If the serum phenytoin levels are monitored and its dose reduced appropriately, the concentrations can be kept within the therapeutic range (see 'Phenytoin + Antimycobacterials', p.628). Some interactions can be accommodated by using another member of the same group of drugs. For example, the serum levels of doxycycline can become subtherapeutic if phenytoin, barbiturates or carbamazepine are given, but other tetracyclines do not seem to be affected (see 'Tetracyclines + Antiepileptics; Enzyme-inducing', p.389). Erythromycin causes serum lovastatin levels to rise because it inhibits its metabolism, but does not affect pravastatin levels because these two statins are metabolised in different ways (see 'Statins', (p.1313)). It is therefore clearly important not to uncritically extrapolate the interactions seen with one drug to all members of the same group.

It is interesting to note in this context that a study in two hospitals in Maryland, US, found that when interacting drugs were given with warfarin (but not theophylline) the length of hospital stay increased by a little over 3 days, with a rise in general costs because of the need to do more tests to get the balance right.[19] So it may be easier, quicker and cheaper to use a non-interacting alternative drug (always provided that its price is not markedly greater).

The variability in patient response has lead to some extreme responses among prescribers. Some clinicians have become over-anxious about interactions so that their patients are denied useful drugs that they might reasonably be given if appropriate precautions are taken. This attitude is exacerbated by some of the more alarmist lists and charts of interactions, which fail to make a distinction between interactions that are very well documented and well established, and those that have only been encountered in a single patient, and which in the final analysis are probably totally idiosyncratic. 'One swallow does not make a summer', nor does a serious reaction in a single patient mean that the drugs in question should never again be given to anyone else.

At the other extreme, there are some health professionals who, possibly because they have personally encountered few interactions, fail to consider drug interactions, so that some of their patients are potentially put at risk. An example of this is the fact that cisapride continued to be prescribed with known interacting drugs, even after the rare risk of fatal torsade de pointes arrhythmias, which can cause sudden death, was well established.[20] The responsible position lies between these two extremes, because a very substantial number of interacting drugs can be given together safely, if the appropriate precautions are taken. There are relatively few pairs of drugs that should always be avoided.

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Table 1.1 Some drug absorption interactions

Drug affected	*Interacting drugs*	*Effect of interaction*
Ciclosporin (Cyclosporine)	Orlistat	Orlistat inhibits the absorption of dietary fats and therefore also lipophilic molecules such as ciclosporin
Digoxin	Metoclopramide Propantheline	Reduced digoxin absorption Increased digoxin absorption (due to changes in gut motility)
Digoxin Levothyroxine Warfarin	Colestyramine	Reduced absorption due to binding/complexation with colestyramine
Ketoconazole	Antacids H_2-receptor antagonists Proton pump inhibitors	Reduced ketoconazole absorption due to reduced dissolution
Penicillamine	Antacids (containing Al^{3+} and/or Mg^{2+}), iron compounds, food	Formation of less soluble penicillamine chelates resulting in reduced absorption of penicillamine
Methotrexate	Neomycin	Neomycin-induced malabsorption state
Quinolones	Antacids (containing Al^{3+} and/or Mg^{2+}), milk, Zn^{2+}(?), Fe^{2+}	Formation of poorly absorbed complexes
Tetracyclines	Antacids (containing Al^{3+}, Ca^{2+}, Mg^{2+}, and/or Bi^{2+}), milk, Zn^{2+}, Fe^{2+}	Formation of poorly soluble chelates resulting in reduced antibacterial absorption (see Fig. 1.1, p.3)

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Mechanisms of drug interactions

Some drugs interact together in totally unique ways, but as the many examples in this publication amply illustrate, there are certain mechanisms of interaction that are encountered time and time again. Some of these common mechanisms are discussed here in greater detail than space will allow in the individual monographs, so that only the briefest reference need be made there.

Mechanisms that are unusual or peculiar to particular pairs of drugs are detailed within the monographs. Very many drugs that interact do so, not by a single mechanism, but often by two or more mechanisms acting in concert, although for clarity most of the mechanisms are dealt with here as though they occur in isolation. For convenience, the mechanisms of inter-

actions can be subdivided into those that involve the pharmacokinetics of a drug, and those that are pharmacodynamic.

Pharmacokinetic interactions

Pharmacokinetic interactions are those that can affect the processes by which drugs are absorbed, distributed, metabolised and excreted (the so-called ADME interactions).

Drug absorption interactions

Most drugs are given orally for absorption through the mucous membranes of the gastrointestinal tract, and the majority of interactions that go on within the gut result in reduced rather than increased absorption. A clear distinction must be made between those that decrease the *rate* of absorption and those that alter the *total amount* absorbed. For drugs that are given long-term, in multiple doses (e.g. warfarin) the rate of absorption is usually unimportant, provided the total amount of drug absorbed is not markedly altered. On the other hand for drugs that are given as single doses, intended to be absorbed rapidly (e.g. analgesics such as paracetamol (acetaminophen)), where a rapidly achieved high concentration is needed, a reduction in the rate of absorption may result in failure to achieve an adequate effect. 'Table 1.1', (p.2), lists some of the drug interactions that result from changes in absorption.

(a) Effects of changes in gastrointestinal pH

The passage of drugs through mucous membranes by simple passive diffusion depends upon the extent to which they exist in the non-ionised lipid-soluble form. Absorption is therefore governed by the pKa of the drug, its lipid-solubility, the pH of the contents of the gut and various other parameters relating to the pharmaceutical formulation of the drug. Thus the absorption of salicylic acid by the stomach is much greater at low pH than at high. On theoretical grounds it might be expected that alterations in gastric pH caused by drugs such as the H_2-receptor antagonists would have a marked effect on absorption, but in practice the outcome is often uncertain because a number of other mechanisms may also come into play, such as chelation, adsorption and changes in gut motility, which can considerably affect what actually happens. However, in some cases the effect can be significant. Rises in pH due to the proton pump inhibitors (see 'Azoles + Proton pump inhibitors', p.246), and the H_2-receptor antagonists (see 'Azoles + H_2-receptor antagonists', p.245), can markedly reduce the absorption of ketoconazole.

(b) Adsorption, chelation and other complexing mechanisms

Activated charcoal is intended to act as an adsorbing agent within the gut for the treatment of drug overdose or to remove other toxic materials, but inevitably it can affect the absorption of drugs given in therapeutic doses. Antacids can also adsorb a large number of drugs, but often other mechanisms of interaction are also involved. For example, the tetracycline antibacterials can chelate with a number of divalent and trivalent metallic ions, such as calcium, aluminium, bismuth and iron, to form complexes that are both poorly absorbed and have reduced antibacterial effects (see 'Figure 1.1', (see below)). These metallic ions are found in dairy products and antacids. Separating the doses by 2 to 3 hours goes some way towards reducing the effects of this type of interaction. The marked reduction in the bioavailability of penicillamine caused by some antacids seems also to be due to chelation, although adsorption may have some part to play. Colestyramine, an anionic exchange resin intended to bind bile acids and cholesterol metabolites in the gut, binds to a considerable number of drugs (e.g. digoxin, warfarin, levothyroxine), thereby reducing their absorption. 'Table 1.1', (p.2), lists some drugs that chelate, complex or adsorb other drugs.

(c) Changes in gastrointestinal motility

As most drugs are largely absorbed in the upper part of the small intestine, drugs that alter the rate at which the stomach empties can affect absorption. Propantheline, for example, delays gastric emptying and reduces paracetamol (acetaminophen) absorption, see 'Paracetamol (Acetaminophen) + Antimuscarinics', p.211, whereas metoclopramide, see 'Paracetamol (Acetaminophen) + Domperidone or Metoclopramide', p.212, has the opposite effect. However, the total amount of drug absorbed remains unaltered. Drugs with antimuscarinic effects decrease the motility of the gut, thus the tricyclic antidepressants can increase the absorption of other drugs, probably because they increase the time available for dissolution and absorption but in the case of levodopa (see 'Levodopa + Tricyclic antidepressants', p.806), they may reduce the absorption, possibly because the exposure time to intestinal mucosal metabolism is increased. The same reduced levodopa absorption has also been seen with 'homatropine', (p.796). These examples illustrate that what actually happens is sometimes very unpredictable because the final outcome may be the result of several different mechanisms.

(d) Induction or inhibition of drug transporter proteins

The oral bioavailability of some drugs is limited by the action of drug transporter proteins, which eject drugs that have diffused across the gut lining back into the gut. At present, the most well characterised drug transporter is 'P-glycoprotein', (p.8). Digoxin is a substrate of P-glycoprotein, and drugs that induce this protein, such as rifampicin (rifampin), may reduce the bioavailability of digoxin (see 'Digoxin and related drugs + Rifampicin (Rifampin)', p.1113.

(e) Malabsorption caused by drugs

Neomycin causes a malabsorption syndrome, similar to that seen with non-tropical sprue. The effect is to impair the absorption of a number of drugs including 'digoxin', (p.1080), and 'methotrexate', (p.745).

Drug distribution interactions

(a) Protein-binding interactions

After absorption, drugs are rapidly distributed around the body by the circulation. Some drugs are totally dissolved in the plasma water, but many others are transported with some proportion of their molecules in solution and the rest bound to plasma proteins, particularly the albumins. The extent of this binding varies enormously but some drugs are extremely highly bound. For example, dicoumarol has only four out of every 1000 molecules remaining unbound at serum concentrations of 0.5 mg%. Drugs can also become bound to albumin in the interstitial fluid, and some, such as digoxin, can bind to the heart muscle tissue.

The binding of drugs to the plasma proteins is reversible, an equilibrium being established between those molecules that are bound and those that are not. Only the unbound molecules remain free and pharmacologically active, while those that are bound form a circulating but pharmacologically inactive reservoir which, in the case of drugs with a low-extraction ratio, is temporarily protected from metabolism and excretion. As the free molecules become metabolised, some of the bound molecules become unbound and pass into solution to exert their normal pharmacological

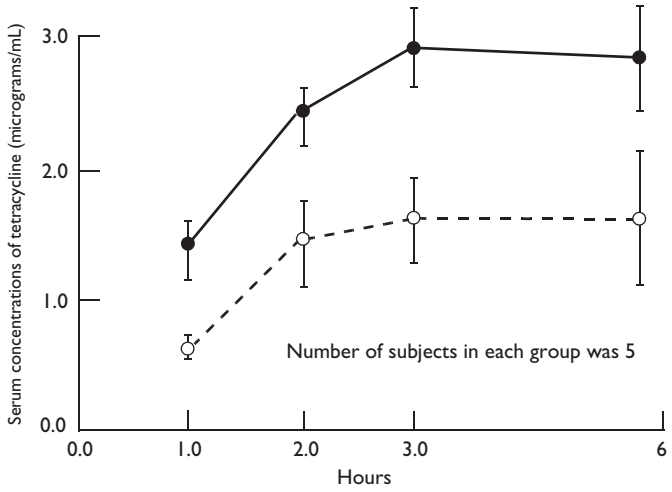

Fig. 1.1 A drug chelation interaction. Tetracycline forms a less-soluble chelate with iron if the two drugs are allowed to mix within the gut. This reduces the absorption and depresses the serum levels and the antibacterial effects (after Neuvonen PJ, *BMJ* (1970) 4, 532, with permission). The same interaction can occur with other ions such as Al^{3+}, Ca^{2+}, Mg^{2+}, Bi^{2+} and Zn^{2+}.

actions, before they, in their turn are metabolised and excreted.

Depending on the concentrations and their relative affinities for the binding sites, one drug may successfully compete with another and displace it from the sites it is already occupying. The displaced (and now active) drug molecules pass into the plasma water where their concentration rises. So for example, a drug that reduces the binding from 99% to 95% would increase the unbound concentration of free and active drug from 1% to 5% (a fivefold increase). This displacement is only likely to raise the number of free and active molecules significantly if the majority of the drug is within the plasma rather than the tissues, so that only drugs with a low apparent volume of distribution (V_d) will be affected. Examples include the sulfonylureas, such as tolbutamide (96% bound, V_d 10 litres), oral anticoagulants, such as warfarin (99% bound, V_d 9 litres), and phenytoin (90% bound, V_d 35 litres). However, another important factor is clearance. Clinically important protein-binding interactions are unlikely if only a small proportion of the drug is eliminated during a single-passage through the eliminating organ (low-extraction ratio drugs), as any increase in free fraction will be effectively cleared. Most drugs that are extensively bound to plasma proteins and subject to displacement reactions (e.g. warfarin, sulfonylureas, phenytoin, methotrexate, and valproate) have low-extraction ratios, and drug exposure is therefore independent of protein-binding.

An example of displacement of this kind happens when patients stabilised on warfarin are given cloral hydrate because its major metabolite, trichloroacetic acid, is a highly bound compound that successfully displaces warfarin. This effect is only very short-lived because the now free and active warfarin molecules become exposed to metabolism as the blood flows through the liver, and the amount of drug rapidly falls. This transient increase in free warfarin levels is unlikely to change the anticoagulant effect of warfarin because the clotting factor complexes that are produced when warfarin is taken have a very long half-life, and thus take a long time to reach a new steady state. Normally no change in the warfarin dose is needed (see 'Coumarins + Cloral hydrate and related drugs', p.449).

In vitro many commonly used drugs are capable of being displaced by others but in the body the effects seem almost always to be buffered so effectively that the outcome is not normally clinically important. It would therefore seem that the importance of this interaction mechanism has been grossly over-emphasised.[1-3] It is difficult to find an example of a clinically important interaction due to this mechanism alone. It has been suggested that this interaction mechanism is likely to be important only for drugs given intravenously that have a high-extraction ratio, a short pharmacokinetic-pharmacodynamic half-life and a narrow therapeutic index. Lidocaine has been given as an example of a drug fitting these criteria.[3] Some drug interactions that were originally assumed to be due to changes in protein binding have subsequently been shown to have other interaction mechanisms involved. For example, inhibition of metabolism has subsequently been shown to be important in the interactions between 'warfarin and phenylbutazone', (p.488), and 'tolbutamide and sulfonamides', (p.574).

However, knowledge of altered protein binding is important in therapeutic drug monitoring. Suppose for example a patient taking phenytoin was given a drug that displaced phenytoin from its binding sites. The amount of free phenytoin would rise but this would be quickly eliminated by metabolism and excretion thereby keeping the amount of free active phenytoin the same. However, the total amount of phenytoin would now be reduced. Therefore if phenytoin was monitored using an assay looking at total phenytoin levels it may appear that the phenytoin is subtherapeutic and that the dose may therefore need increasing. However, as the amount of free active phenytoin is unchanged this would not be necessary and may even be dangerous.

Basic drugs as well as acidic drugs can be highly protein bound, but clinically important displacement interactions do not seem to have been described. The reasons seem to be that the binding sites within the plasma are different from those occupied by acidic drugs (alpha-1-acid glycoprotein rather than albumin) and, in addition, basic drugs have a large V_d with only a small proportion of the total amount of drug being within the plasma.

(b) Induction or inhibition of drug transporter proteins

It is increasingly being recognised that distribution of drugs into the brain, and some other organs such as the testes, is limited by the action of drug transporter proteins such as P-glycoprotein. These proteins actively transport drugs out of cells when they have passively diffused in. Drugs that are inhibitors of these transporters could therefore increase the uptake of drug substrates into the brain, which could either increase adverse CNS effects, or be beneficial. For more information, see 'Drug transporter proteins', (p.8).

Table 1.2 Drugs affecting or metabolised by the cytochrome P450 isoenzyme CYP1A2

Inhibitors	Cimetidine	Oestrogens
	Fluoroquinolones	Rofecoxib
	Ciprofloxacin	Tacrine
	Enoxacin	Tiabendazole
	Fluvoxamine	Ticlopidine
	Methoxsalen	Zileuton
	Mexiletine	
Inducers	Barbiturates	Tobacco smoke
	Phenytoin	
Substrates	Alosetron	Theophylline*
	Caffeine	Tizanidine*
	Clozapine	*Tricyclic antidepressants*
	Duloxetine	Amitriptyline
	Flecainide	Clomipramine
	Melatonin	Imipramine
	Olanzapine	*Triptans*
	Rasagiline	Frovatriptan
	Ropinirole	Zolmitriptan
	Ropivacaine	*R*-Warfarin
	Tacrine	

*Considered the preferred *in vivo* substrates, see Bjornsson TD, Callaghan JT, Einolf HJ, *et al.* The conduct of *in vitro* and *in vivo* drug–drug interaction studies: a PhRMA perspective. *J Clin Pharmacol* (2003) 43, 443–69.

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3. Benet LZ, Hoener B-A. Changes in plasma protein binding have little clinical relevance. *Clin Pharmacol Ther* (2002) 71, 115–121.

Drug metabolism (biotransformation) interactions

Although a few drugs are cleared from the body simply by being excreted unchanged in the urine, most are chemically altered within the body to less lipid-soluble compounds, which are more easily excreted by the kidneys. If this were not so, many drugs would persist in the body and continue to exert their effects for a long time. This chemical change is called 'metabolism', 'biotransformation', 'biochemical degradation' or sometimes 'detoxification'. Some drug metabolism goes on in the serum, the kidneys, the skin and the intestines, but the greatest proportion is carried out by enzymes that are found in the membranes of the endoplasmic reticulum of the liver cells. If liver is homogenised and then centrifuged, the reticulum breaks up into small sacs called microsomes which carry the enzymes, and it is for this reason that the metabolising enzymes of the liver are frequently referred to as the 'liver microsomal enzymes'.

Drugs are metabolised by two major types of reaction. The first, so-called phase I reactions (involving oxidation, reduction or hydrolysis), turn drugs into more polar compounds, while phase II reactions involve coupling drugs with some other substance (e.g. glucuronic acid, known as glucuronidation) to make compounds that are usually inactive.

The majority of phase I oxidation reactions are carried out by the haem-containing enzyme cytochrome P450. Cytochrome P450 is not a single entity, but is in fact a very large family of related isoenzymes. However, in practice, only a few specific subfamilies seem to be responsible for most (about 90%) of the metabolism of the commonly used drugs. The most important isoenzymes are CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4. Other enzymes involved in phase I metabolism include monoamine oxidases and epoxide hydrolases.

Less is known about the enzymes responsible for phase II conjugation reactions. However, UDP-glucuronyltransferases (UGT), methyltransferases, and N-acetyltransferases (NAT) are examples. UGTs are the sub-

ject of much study and look to become increasingly important in explaining the mechanisms behind a number of interactions.

Although metabolism is very important for the body to remove drugs, it is increasingly recognised that drugs can be adsorbed, distributed, or eliminated by transporters, the most well understood at present being 'P-glycoprotein', (p.8).

(a) Changes in first-pass metabolism

1. Changes in blood flow through the liver. After absorption in the intestine, the portal circulation takes drugs directly to the liver before they are distributed by the blood flow around the rest of the body. A number of highly lipid-soluble drugs undergo substantial biotransformation during this first-pass through the gut wall and liver and there is some evidence that some drugs can have a marked effect on the extent of first pass metabolism by altering the blood flow through the liver. However, there are few clinically relevant examples of this, and many can be explained by other mechanisms, usually altered hepatic metabolism (see *Inhibition or induction of first-pass metabolism*, below). One possible example is the increase in rate of absorption of dofetilide with verapamil, which has resulted in an increased incidence of torsade de pointes (see 'Dofetilide + Verapamil', p.288).

Another is the increase in bioavailability of high-extraction beta blockers with hydralazine, possibly caused by altered hepatic blood flow, or altered metabolism (see 'Beta blockers + Hydralazine', p.1010).

2. Inhibition or induction of first-pass metabolism. The gut wall contains metabolising enzymes, principally cytochrome P450 isoenzymes. In addition to the altered metabolism caused by changes in hepatic blood flow (see *Changes in blood flow through the liver*, above) there is evidence that some drugs can have a marked effect on the extent of first-pass metabolism by inhibiting or inducing the cytochrome P450 isoenzymes in the gut wall or in the liver. An example is the effect of grapefruit juice, which seems to inhibit the cytochrome P450 isoenzyme CYP3A4, mainly in the gut, and therefore reduces the metabolism of oral calcium-channel blockers. Although altering the amount of drug absorbed, these interactions are usually considered drug metabolism interactions. The effect of grapefruit on the metabolism of other drugs is discussed further under 'Drug-food interactions', (p.11).

(b) Enzyme induction

When barbiturates were widely used as hypnotics it was found necessary to keep increasing the dose as time went by to achieve the same hypnotic effect, the reason being that the barbiturates increase the activity of the microsomal enzymes so that extent of metabolism and excretion increases. This phenomenon of enzyme stimulation or induction not only accounts for the need for an increased barbiturate dose but if another drug that is metabolised by the same range of enzymes is also present, its enzymatic metabolism is similarly increased and larger doses are needed to maintain the same therapeutic effect. However, note that not all enzyme-inducing drugs induce their own metabolism (a process known as auto-induction).

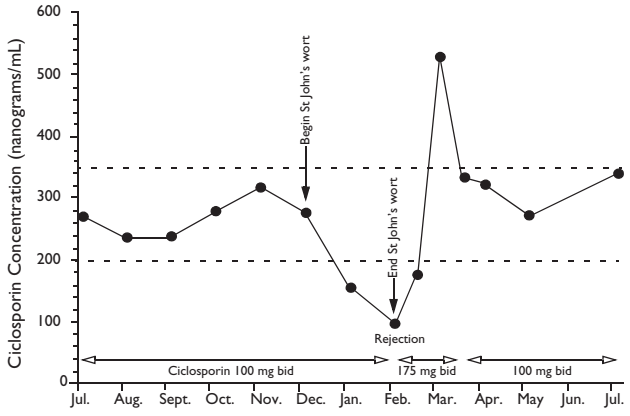

Fig. 1.2 An enzyme induction interaction. Chronology of ciclosporin trough concentrations (—●—) in a patient self-medicating with St John's wort. ---------- = desired ciclosporin therapeutic range (after Barone GW, Gurley BJ, Ketel BL, Lightfoot ML, Abul-Ezz SR. Drug interaction between St. John's Wort and Cyclosporine. *Ann Pharmacother* (2000) 34: 1013–16, with permission).

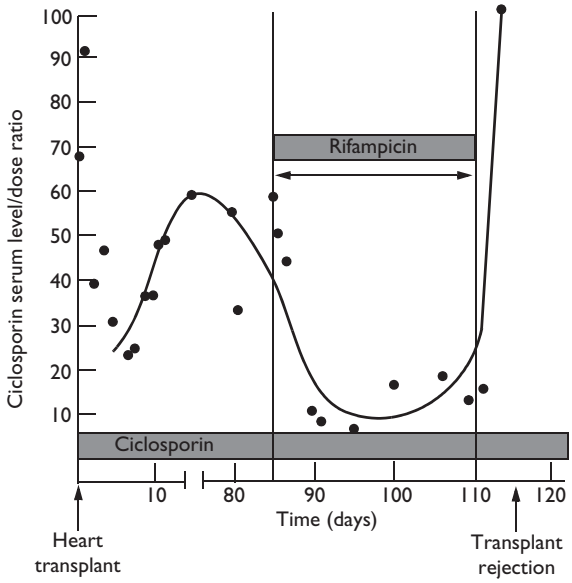

Fig. 1.3 An enzyme induction interaction. Rifampicin (600 mg daily plus isoniazid) increased the metabolism of ciclosporin in this patient, thereby reducing the trough serum levels. He subsequently died because his heart transplant was rejected (after *Transplant Proc*, 16, Van Buren D, Wideman CA, Ried M, Gibbons S, Van Buren CT, Jarowenko M, Flechner SM, Frazier OH, Cooley DA, Kahan BD. The antagonistic effect of rifampicin upon cyclosporine bioavailability. 1642–5, Copyright Elsevier (1984)).

The metabolic pathway that is most commonly induced is phase I oxidation mediated by the cytochrome P450 isoenzymes. The main drugs responsible for induction of the most clinically important cytochrome P450 isoenzymes are listed in 'Table 1.2', (p.4), 'Table 1.3', (p.6), and 'Table 1.4', (p.6). 'Figure 1.2', (see below) shows the reduction in trough ciclosporin levels when it is given with the enzyme inducer, St John's wort. This herb induces the metabolism of ciclosporin by induction of CYP3A4 and possibly also P-glycoprotein (consider also 'Ciclosporin + St John's wort (*Hypericum perforatum*)', p.1253). 'Figure 1.3', (see above), shows the effects of another enzyme inducer, rifampicin (rifampin) on the serum levels of ciclosporin presumably by its effects on CYP3A4 (consider also 'Ciclosporin + Antimycobacterials', p.1224). Phase II glucuronidation can also be induced. An example is when rifampicin induces the glucuronidation of 'zidovudine', (p.942).

The extent of the enzyme induction depends on the drug and its dose, but it may take days or even 2 to 3 weeks to develop fully, and may persist for a similar length of time when the enzyme inducer is stopped. This means that enzyme induction interactions are delayed in onset and slow to resolve. Enzyme induction is a common mechanism of interaction and is not confined to drugs; it is also caused by the chlorinated hydrocarbon insecticides such as dicophane and lindane, and smoking tobacco.

If one drug reduces the effects of another by enzyme induction, it may be possible to accommodate the interaction simply by raising the dose of the drug affected, but this requires good monitoring, and there are obvious hazards if the inducing drug is eventually stopped without remembering to reduce the dose again. The raised drug dose may be an overdose when the drug metabolism has returned to normal.

(c) Enzyme inhibition

More common than enzyme induction is the inhibition of enzymes. This results in the reduced metabolism of an affected drug, so that it may begin to accumulate within the body, the effect usually being essentially the same as when the dose is increased. Unlike enzyme induction, which may take several days or even weeks to develop fully, enzyme inhibition can occur within 2 to 3 days, resulting in the rapid development of toxicity. The metabolic pathway that is most commonly inhibited is phase I oxidation by cytochrome P450 isoenzymes. The main drugs responsible for inhibition of the most clinically important cytochrome P450 isoenzymes are listed in 'Table 1.2', (p.4), 'Table 1.3', (p.6), and 'Table 1.4', (p.6). For example a marked increase occurred in the plasma levels of a single dose of sildenafil after ritonavir had also been taken for 7 days, probably

Table 1.3 Drugs affecting or metabolised by the CYP2 family of cytochrome P450 isoenzymes

Isoenzyme	*Inhibitors*	*Inducers*	*Substrates*
CYP2B6	Clopidogrel Thiotepa Ticlopidine	Phenobarbital Phenytoin Rifampicin (Rifampin)	Bupropion Cyclophosphamide Ifosfamide Paclitaxel
CYP2C8	Gemfibrozil Trimethoprim	Rifampicin (Rifampin)	Pioglitazone Repaglinide Rosiglitazone
CYP2C9	Amiodarone *Azoles* Fluconazole Miconazole Voriconazole Fluvastatin *SSRIs* Fluoxetine Fluvoxamine Sulfinpyrazone Ticlopidine Zafirlukast	Aprepitant Rifampicin (Rifampin)	Irbesartan Losartan Nateglinide *NSAIDs* Celecoxib Diclofenac Etoricoxib Valdecoxib Phenytoin *Statins* Fluvastatin Rosuvastatin *Sulphonylureas* Glibenclamide Gliclazide Glimepiride Glipizide Tolbutamide* *S*-Warfarin*
CYP2C19	Fluvoxamine Isoniazid *Proton pump inhibitors* Esomeprazole Omeprazole Ticlopidine Valdecoxib		Cilostazol Diazepam Escitalopram Moclobemide Omeprazole Phenytoin Proguanil
CYP2D6	Amiodarone Bupropion Cimetidine Cinacalcet Dextropropoxyphene Diphenhydramine Duloxetine Propafenone Quinidine Ritonavir *SSRIs* Fluoxetine Paroxetine Terbinafine Valdecoxib	Rifampicin (Rifampin)	*Anticholinesterases, centrally-acting* Donepezil Galantamine *Antipsychotics* Clozapine Risperidone Thioridazine *Beta blockers* Carvedilol Metoprolol Propranolol Cyclobenzaprine Flecainide Mexiletine *Opioids* Codeine Dextromethorphan* Dihydrocodeine Hydrocodone Oxycodone Propafenone Tamoxifen Tolterodine *Tricyclics* Desipramine Imipramine Nortriptyline Trimipramine Venlafaxine
CYP2E1	Disulfiram	Alcohol Isoniazid	Chlorzoxazone* Paracetamol

*Considered the preferred *in vivo* substrates, see Bjornsson TD, Callaghan JT, Einolf HJ, *et al*. The conduct of *in vitro* and *in vivo* drug–drug interaction studies: a PhRMA perspective. *J Clin Pharmacol* (2003) 43, 443–69.

Table 1.4 Drugs affecting or metabolised by the cytochrome P450 isoenzyme CYP3A4

Inhibitors	Aprepitant *Azoles* Itraconazole Ketoconazole Voriconazole Cimetidine Delavirdine Diltiazem Grapefruit juice	Imatinib *Macrolides* Clarithromycin Erythromycin Troleandomycin Nefazodone Nicardipine Protease inhibitors Verapamil
Inducers	Aprepitant Bosentan Carbamazepine Efavirenz Nevirapine Phenobarbital (and probably other barbiturates)	Phenytoin Rifabutin Rifampicin (Rifampin) Rufinamide St John's wort (*Hypericum perforatum*)
Substrates	Amiodarone *Anticholinesterases, centrally-acting* Donepezil Galantamine *Antihistamines* Astemizole Terfenadine Aprepitant *Azoles* Itraconazole Voriconazole *Benzodiazepines* Alprazolam Triazolam Midazolam* Bosentan Bromocriptine Buspirone* Cabergoline *Calcium-channel blockers* Diltiazem Felodipine* Lercanidipine Carbamazepine Ciclosporin Cilostazol Cisapride *Corticosteroids* Budesonide Dexamethasone Fluticasone Hydrocortisone Methylprednisolone Cyclophosphamide Delavirdine Disopyramide Docetaxel Dutasteride Eletriptan Eplerenone Ergot derivatives Ifosfamide Irinotecan Lidocaine, oral Maraviroc *Oestrogens* Combined hormonal contraceptives *Opioids* Alfentanil	Buprenorphine Fentanyl Methadone *Phosphodiesterase type-5 inhibitors* Sildenafil Tadalafil Vardenafil Pimozide *Progestogens* Hormonal contraceptives Propafenone *Protease inhibitors* Amprenavir Atazanavir Darunavir Fosamprenavir Indinavir Nelfinavir Ritonavir Saquinavir Tipranavir Quetiapine Quinidine Reboxetine Rifabutin Sibutramine Sirolimus Solifenacin *Statins* Atorvastatin Lovastatin Simvastatin* Tacrolimus Tamoxifen Tolterodine Toremifene *Tricyclics* Amitriptyline Imipramine Tyrosine kinase inhibitors Dasatinib Erlotinib Imatinib Vinca alkaloids Vinblastine Vincristine Zolpidem Zopiclone

*Considered the preferred *in vivo* substrates, see Bjornsson TD, Callaghan JT, Einolf HJ, *et al*. The conduct of *in vitro* and *in vivo* drug–drug interaction studies: a PhRMA perspective. *J Clin Pharmacol* (2003) 43, 443–69.

because ritonavir inhibits the metabolism of sildenafil by CYP3A4 (see 'Phosphodiesterase type-5 inhibitors + Protease inhibitors', p.1539).

An example of inhibition of phase I hydrolytic metabolism, is the inhibition of epoxide hydrolase by valpromide, which increases the levels of 'carbamazepine', (p.613). Phase II conjugative metabolism can also be inhibited. Examples are the inhibition of carbamazepine glucuronidation by 'sodium valproate', (p.613), and the inhibition of methyltransferase by aminosalicylates causing raised levels of 'azathioprine', (p.774).

The clinical significance of many enzyme inhibition interactions depends on the extent to which the serum levels of the drug rise. If the serum levels remain within the therapeutic range the interaction may not be clinically important.

(d) Genetic factors in drug metabolism

An increased understanding of genetics has shown that some of the cytochrome P450 isoenzymes are subject to 'genetic polymorphism', which simply means that some of the population have a variant of the isoenzyme with different (usually poor) activity. The best known example is CYP2D6, for which a small proportion of the population have a variant with low activity and are described as being poor or slow metabolisers (about 5 to 10% in white Caucasians, 0 to 2% in Asians and black people). Which group any particular individual falls into is genetically determined. The majority who possess the isoenzyme are called fast or extensive metabolisers. It is possible to find out which group any particular individual falls into by looking at the way a single dose of a test or probe drug is metabolised. This varying ability to metabolise certain drugs may explain why some patients develop toxicity when given an interacting drug while others remain symptom free. CYP2D6, CYP2C9 and CYP2C19 also show polymorphism, whereas CYP3A4 does not, although there is still some broad variation in the population without there being distinct groups. The effects of CYP2C19 polymorphism are discussed in more detail in 'Gastrointestinal drugs', (p.1142). At present, genotyping of cytochrome P450 isoenzymes is primarily a research tool and is not widely used clinically. In the future, it may become standard clinical practice and may be used to individualise drug therapy.[1]

(e) Cytochrome P450 isoenzymes and predicting drug interactions

It is interesting to know which particular isoenzyme is responsible for the metabolism of drugs because by doing *in vitro* tests with human liver enzymes it is often possible to explain why and how some drugs interact. For example, ciclosporin is metabolised by CYP3A4, and rifampicin (rifampin) is a known, potent inducer of this isoenzyme, whereas ketoconazole inhibits its activity, so that it comes as no surprise that rifampicin reduces the levels of ciclosporin and ketoconazole increases them.

What is very much more important than retrospectively finding out why two drugs interact, is the knowledge such *in vitro* tests can provide about forecasting which other drugs may possibly also interact. This may reduce the numbers of expensive clinical studies in subjects and patients and avoids waiting until significant drug interactions are observed in clinical use. A lot of effort is being put into this area of drug development.[2-6] However, at present such prediction is, like weather forecasting, still a somewhat hit-and-miss business because all of the factors that may modify or interfere with metabolism are not known. It is far too simplistic to think that we have all the answers just because we know which liver isoenzymes are concerned with the metabolism of a particular drug, but it is a very good start.

'Table 1.2', (p.4), 'Table 1.3', (p.6), and 'Table 1.4', (p.6), are lists of drugs that are inhibitors, inducers, or substrates of the clinically important cytochrome P450 isoenzymes, and each drug has a cross reference to a monograph describing a drug interaction thought to occur by that mechanism. If a new drug is shown to be an inducer, or an inhibitor, and/or a substrate of a given isoenzyme, these tables could be used to predict likely drug interactions. However, what may happen *in vitro* may not necessarily work in clinical practice because all of the many variables which can come into play are not known (such as how much of the enzyme is available, the concentration of the drug at the site of metabolism, and the affinity of the drug for the enzyme). Remember too that some drugs can be metabolised by more than one cytochrome P450 isoenzyme (meaning that this other isoenzyme may be able to 'pick up' more metabolism to compensate for the inhibited pathway); some drugs (and their metabolites) can both induce a particular isoenzyme and be metabolised by it; and some drugs (or their metabolites) can inhibit a particular isoenzyme but not be metabolised by it. With so many factors possibly impinging on the outcome of giving two or more drugs together, it is very easy to lose sight of one of the factors (or not even know about it) so that the sum of 2 plus 2 may not turn out to be the 4 that you have predicted.

For example, ritonavir and other protease inhibitors are well known potent inhibitors of CYP3A4, and in clinical use increase the levels of many drugs that are substrates of this isoenzyme. Methadone is a substrate of CYP3A4, and some *in vitro* data show that ritonavir (predictably) increased methadone levels. However, unexpectedly, in clinical use the protease inhibitors seem to decrease methadone levels, by a yet unknown mechanism (see, 'Opioids; Methadone + Protease inhibitors', p.200).

Another factor complicating the understanding of metabolic drug interactions is the finding that there is a large overlap between the inhibitors or inducers and substrates of P-glycoprotein (a 'drug transporter protein', (p.8)) and those of CYP3A4. Therefore, both mechanisms may be involved in many of the drug interactions previously thought to be due to effects on CYP3A4.

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4. Yao C, Levy RH. Inhibition-based metabolic drug–drug interactions: predictions from *in vitro* data. *J Pharm Sci* (2002) 91, 1923–35.
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Drug excretion interactions

With the exception of the inhalational anaesthetics, most drugs are excreted either in the bile or in the urine. Blood entering the kidneys along the renal arteries is, first of all, delivered to the glomeruli of the tubules where molecules small enough to pass through the pores of the glomerular membrane (e.g. water, salts, some drugs) are filtered through into the lumen of the tubules. Larger molecules, such as plasma proteins, and blood cells are retained within the blood. The blood flow then passes to the remaining parts of the kidney tubules where active energy-using transport systems are able to remove drugs and their metabolites from the blood and secrete them into the tubular filtrate. The renal tubular cells additionally possess active and passive transport systems for the reabsorption of drugs. Interference by drugs with renal tubular fluid pH, with active transport systems and with blood flow to the kidney can alter the excretion of other drugs.

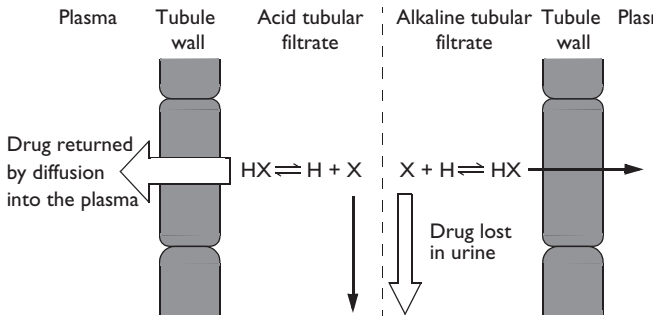

Fig. 1.4 An excretion interaction. If the tubular filtrate is acidified, most of the molecules of weakly acid drugs (HX) exist in an un-ionised lipid-soluble form and are able to return through the lipid membranes of the tubule cells by simple diffusion. Thus they are retained. In alkaline urine most of the drug molecules exist in an ionised non-lipid soluble form (X). In this form the molecules are unable to diffuse freely through these membranes and are therefore lost in the urine.

(a) Changes in urinary pH

As with drug absorption in the gut, passive reabsorption of drugs depends upon the extent to which the drug exists in the non-ionised lipid-soluble form, which in its turn depends on its pKa and the pH of the urine. Only the non-ionised form is lipid-soluble and able to diffuse back through the lipid membranes of the tubule cells. Thus at high pH values (alkaline),

weakly acid drugs (pKa 3 to 7.5) largely exist as ionised lipid-insoluble molecules, which are unable to diffuse into the tubule cells and will therefore remain in the urine and be removed from the body. The converse will be true for weak bases with pKa values of 7.5 to 10.5. Thus pH changes that increase the amount of drug in the ionised form (alkaline urine for acidic drugs, acid urine for basic drugs) will increase the loss of the drug, whereas moving the pH in the opposite direction will increase their retention. 'Figure 1.4', (p.7), illustrates the situation with a weakly acidic drug. The clinical significance of this interaction mechanism is small, because although a very large number of drugs are either weak acids or bases, almost all are largely metabolised by the liver to inactive compounds and few are excreted in the urine unchanged. In practice, therefore, only a handful of drugs seem to be affected by changes in urinary pH (possible exceptions include changes in the excretion of 'quinidine', (p.313), or 'analgesic-dose aspirin', (p.151), due to alterations in urinary pH caused by antacids, and the increase in the clearance of 'methotrexate', (p.758), with urinary alkalinisers). In cases of overdose, deliberate manipulation of urinary pH has been used to increase the removal of drugs such as methotrexate and salicylates.

Table 1.5 Examples of interactions probably due to changes in renal transport

Drug affected	*Interacting drug*	*Result of interaction*
Cephalosporins Dapsone Methotrexate Penicillins Quinolones	Probenecid	Serum levels of drug affected raised; possibility of toxicity with some drugs
Methotrexate	Salicylates and some other NSAIDs	Methotrexate serum levels raised; serious methotrexate toxicity possible
Pramipexole	Cimetidine	Serum levels of drug affected raised

(b) Changes in active renal tubular excretion

Drugs that use the same active transport systems in the renal tubules can compete with one another for excretion. For example, probenecid reduces the excretion of penicillin and other drugs. With the increasing understanding of drug transporter proteins in the kidneys, it is now known that probenecid inhibits the renal secretion of many other anionic drugs by organic anion transporters (OATs).[1] Probenecid possibly also inhibits some of the ABC transporters in the kidneys. The ABC transporter, P-glycoprotein, is also present in the kidneys, and drugs that alter this may alter renal drug elimination. See, 'Drug transporter proteins', (p.8), for further discussion. Some examples of drugs that possibly interact by alterations in renal transport are given in 'Table 1.5', (see above).

(c) Changes in renal blood flow

The flow of blood through the kidney is partially controlled by the production of renal vasodilatory prostaglandins. If the synthesis of these prostaglandins is inhibited the renal excretion of some drugs may be reduced. An interaction where this is the suggested mechanism is the rise in serum lithium seen with some NSAIDs, see 'Lithium + NSAIDs', p.1360.

(d) Biliary excretion and the entero-hepatic shunt

1. Enterohepatic recirculation. A number of drugs are excreted in the bile, either unchanged or conjugated (e.g. as the glucuronide) to make them more water soluble. Some of the conjugates are metabolised to the parent compound by the gut flora and are then reabsorbed. This recycling process prolongs the stay of the drug within the body, but if the gut flora are diminished by the presence of an antibacterial, the drug is not recycled and is lost more quickly. This may possibly explain the rare failure of the hormonal contraceptives that can be brought about by the concurrent use of penicillins or tetracyclines, but see *Mechanism* in 'Combined hormonal contraceptives + Antibacterials; Penicillins', p.1170. Antimicrobial-induced reductions in gut bacteria may reduce the activation of 'sulfasalazine', (p.1163).

2. Drug transporter proteins. Increasing research shows that numerous drug transporter proteins (both from the ABC family and SLC family, see 'Drug transporter proteins', (p.8)) are involved in the hepatic extraction and secretion of drugs into the bile.[2] The relevance of many of these to drug interactions is still unclear, but the bile salt export pump (ABCB11) is known to be inhibited by a variety of drugs including ciclosporin, glibenclamide, and bosentan. Inhibition of this pump may increase the risk of cholestasis, and the manufacturer of bosentan states that they should be avoided in patients taking bosentan (see 'Sulfonylureas + Bosentan', p.586, and 'Ciclosporin + Endothelin receptor antagonists', p.1238).

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2. Faber KN, Müller M, Jansen PLM. Drug transport proteins in the liver. *Adv Drug Deliv Rev* (2003) 55, 107–24.

Drug transporter proteins

Drugs and endogenous substances are known to cross biological membranes, not just by passive diffusion, but by carrier-mediated processes, often known as transporters. Significant advances in the identification of various transporters have been made, although the contribution of many of these to drug interactions in particular, is still unclear.[1,2] The most well known is P-glycoprotein, which is a product of the MDR1 gene (ABCB1 gene) and a member of the ATP-binding cassette (ABC) family of efflux transporters.[1] Its involvement in drug interactions is discussed below.

Another ABC transporter is sister P-glycoprotein, otherwise called the bile salt export pump (BSEP or ABCB11).[1] It has been suggested that inhibition of this pump may increase the risk of cholestasis, see *Drug transporter proteins* under 'Drug excretion interactions', (p.7).

Other transporters that are involved in some drug interactions are the organic anion transporters (OATs), organic anion-transporting polypeptides (OATPs) and organic cation transporters (OCTs), which are members of the solute carrier superfamily (SLC) of transporters.[1] The best known example of an OAT inhibitor is probenecid, which affects the renal excretion of a number of drugs, see *Changes in active kidney tubule excretion*, under 'Drug excretion interactions', (p.7).

Table 1.6 Drugs affecting or transported by P-glycoprotein

Inhibitors	*Inducers*	*Substrates*
Ciclosporin	Protease inhibitors	Digoxin*
Clarithromycin	Ritonavir	Loperamide
Itraconazole	Tipranavir	Talinolol
Quinidine	Rifampicin (Rifampin)	
Ranolazine	St John's wort (*Hypericum perforatum*)	
Valspodar		
Verapamil		

* Considered the preferred *in vivo* substrate.

P-glycoprotein interactions

Some drug interactions occur because they interfere with the activity of P-glycoprotein. This is an efflux pump found in the membranes of certain cells, which can push metabolites and drugs out of the cells and have an impact on the extent of drug absorption (in the intestine), distribution (to the brain, testis, or placenta) and elimination (in the urine and bile). So, for example, the P-glycoprotein in the cells of the gut lining can eject some already-absorbed drug molecules back into the intestine resulting in a reduction in the total amount of drug absorbed. In this way P-glycoprotein acts as a barrier to absorption. The activity of P-glycoprotein in the endothelial cells of the blood-brain barrier can also eject certain drugs from the brain, limiting CNS penetration and effects.

The pumping actions of P-glycoprotein can be induced or inhibited by some drugs. So, for example, the induction (or stimulation) of the activity of P-glycoprotein by rifampicin (rifampin), that occurs within the lining cells of the gut causes digoxin to be ejected into the gut more vigorously. This results in a fall in the plasma levels of digoxin (see 'Digoxin and related drugs + Rifampicin (Rifampin)', p.1113). In contrast, verapamil appears to inhibit the activity of P-glycoprotein, and is well known to increase digoxin levels (see 'Digoxin and related drugs + Calcium-channel blockers; Verapamil', p.1091). Ketoconazole also has P-glycoprotein inhibitory effects, and has been shown to increase the CSF levels of ritonavir, possibly by preventing the efflux of ritonavir from the CNS (see 'Protease inhibitors + Azoles; Ketoconazole', p.964). Thus the induction or inhibition of P-glycoprotein can have an impact on the pharmacokinetics

of some drugs. Note that there is evidence that P-glycoprotein inhibition may have a greater impact on drug distribution (e.g. into the brain) than on drug absorption (e.g. plasma levels).[2]

There is an overlap between CYP3A4 and P-glycoprotein inhibitors, inducers and substrates. Therefore, both mechanisms may be involved in many of the drug interactions traditionally thought to be due to changes in CYP3A4. 'Table 1.6', (p.8), lists some P-glycoprotein inhibitors and inducers. Many drugs that are substrates for CYP3A4 (see 'Table 1.4', (p.6)) are also substrates for P-glycoprotein. Digoxin and talinolol are examples of the few drugs that are substrates for P-glycoprotein but not CYP3A4, and they are therefore useful in studying some interactions that may occur by this mechanism.

P-glycoprotein is also expressed in some cancer cells (where it was first identified). This has led to the development of specific P-glycoprotein inhibitors, such as valspodar, with the aim of improving the penetration of cytotoxic drugs into cancer cells.

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2. Lin JH, Yamazaki M. Clinical relevance of P-glycoprotein in drug therapy. *Drug Metab Rev* (2003) 35, 417–54.

Pharmacodynamic interactions

Pharmacodynamic interactions are those where the effects of one drug are changed by the presence of another drug at its site of action. Sometimes the drugs directly compete for particular receptors (e.g. beta$_2$ agonists, such as salbutamol, and beta blockers, such as propranolol) but often the reaction is more indirect and involves interference with physiological mechanisms. These interactions are much less easy to classify neatly than those of a pharmacokinetic type.

Additive or synergistic interactions

If two drugs that have the same pharmacological effect are given together the effects can be additive. For example, alcohol depresses the CNS and, if taken in moderate amounts with normal therapeutic doses of any of a large number of drugs (e.g. anxiolytics, hypnotics, etc.), may cause excessive drowsiness. Strictly speaking (as pointed out earlier) these are not interactions within the definition given in 'What is a drug interaction?', (p.1). Nevertheless, it is convenient to consider them within the broad context of the clinical outcome of giving two drugs together.

Additive effects can occur with both the main effects of the drugs as well as their adverse effects, thus an additive interaction can occur with antimuscarinic antiparkinson drugs (main effect) or butyrophenones (adverse effect) that can result in serious antimuscarinic toxicity (see 'Antipsychotics + Antimuscarinics', p.833).

Sometimes the additive effects are solely toxic (e.g. additive ototoxicity, nephrotoxicity, bone marrow depression, QT interval prolongation). Examples of these reactions are listed in 'Table 1.7', (see below). It is common to use the terms 'additive', 'summation', 'synergy' or 'potentiation' to describe what happens if two or more drugs behave like this. These words have precise pharmacological definitions but they are often used rather loosely as synonyms because in practice it is often very difficult to know the extent of the increased activity, that is to say whether the effects are greater or smaller than the sum of the individual effects.

Serotonin syndrome

In the 1950s a serious and life-threatening toxic reaction was reported in patients taking iproniazid (an MAOI) when they were given pethidine (meperidine). For further information about this interactions, see under 'MAOIs or RIMAs + Opioids; Pethidine (Meperidine)', p.1381. The reasons were then not understood and even now we do not have the full picture. What happened is thought to have been due to over-stimulation of the 5-HT$_{1A}$ and 5-HT$_{2A}$ receptors and possibly other serotonin receptors in the central nervous system (in the brain stem and spinal cord in particular) due to the combined effects of these two drugs. It can occur exceptionally after taking only one drug, which causes over-stimulation of these 5-HT receptors, but much more usually it develops when two or more drugs (so-called serotonergic or serotomimetic drugs) act in concert. The characteristic symptoms (now known as serotonin syndrome) fall into three main areas, namely altered mental status (agitation, confusion, mania), autonomic dysfunction (diaphoresis, diarrhoea, fever, shivering) and neuromuscular abnormalities (hyperreflexia, incoordination, myoclonus, tremor). These are the 'Sternbach diagnostic criteria' named after Dr Harvey Sternbach who drew up this list of clinical features and who suggested that at least three of them need to be seen before classifying this toxic reaction as serotonin syndrome rather than neuroleptic malignant syndrome.[1]

The syndrome can develop shortly after one serotonergic drug is added to another, or even if one is replaced by another without allowing a long enough washout period in between, and the problem usually resolves within about 24 hours if both drugs are withdrawn and supportive measures given. Non-specific serotonin antagonists (cyproheptadine, chlorpromazine, methysergide) have also been used for treatment. Most patients recover uneventfully, but there have been a few fatalities.

Table 1.7 Additive, synergistic or summation interactions

Drugs	*Result of interaction*
Antipsychotics + Antimuscarinics	Increased antimuscarinic effects; heat stroke in hot and humid conditions, adynamic ileus, toxic psychoses
Antihypertensives + Drugs that cause hypotension (e.g. Phenothiazines, Sildenafil)	Increased antihypertensive effects; orthostasis
Beta-agonist bronchodilators + Potassium-depleting drugs	Hypokalaemia
CNS depressants + CNS depressants Alcohol + Antihistamines Benzodiazepines + Anaesthetics, general Opioids + Benzodiazepines	Impaired psychomotor skills, reduced alertness, drowsiness, stupor, respiratory depression, coma, death
Drugs that prolong the QT interval + Other drugs that prolong the QT interval Amiodarone + Disopyramide	Additive prolongation of QT interval, increased risk of torsade de pointes
Methotrexate + Co-trimoxazole	Bone marrow megaloblastosis due to folic acid antagonism
Nephrotoxic drugs + Nephrotoxic drugs (e.g. Aminoglycosides, Ciclosporin, Cisplatin, Vancomycin)	Increased nephrotoxicity
Neuromuscular blockers + Drugs with neuromuscular blocking effects (e.g. Aminoglycosides)	Increased neuromuscular blockade; delayed recovery, prolonged apnoea
Potassium supplements + Potassium-sparing drugs (e.g. ACE inhibitors, Angiotensin II receptor antagonists, Potassium-sparing diuretics)	Hyperkalaemia

Following the first report of this syndrome, many other cases have been described involving 'tryptophan and MAOIs', (p.1393), the 'tricyclic antidepressants and MAOIs', (p.1391), and, more recently, the 'SSRIs', (p.1384), but other serotonergic drugs have also been involved and the list continues to grow.

It is still not at all clear why many patients can take two, or sometimes several serotonergic drugs together without problems, while a very small number develop this serious toxic reaction, but it certainly suggests that there are other factors involved that have yet to be identified. The full story is likely to be much more complex than just the simple additive effects of two drugs.

1. Sternbach H. The serotonin syndrome. *Am J Psychiatry* (1991) 148, 705–13.

Antagonistic or opposing interactions

In contrast to additive interactions, there are some pairs of drugs with activities that are opposed to one another. For example the coumarins can prolong the blood clotting time by competitively inhibiting the effects of dietary vitamin K. If the intake of vitamin K is increased, the effects of the coumarin are opposed and the prothrombin time can return to normal,

thereby cancelling out the therapeutic benefits of anticoagulant treatment (see 'Coumarins and related drugs + Food; Vitamin K_1-rich', p.464). Other examples of this type of interaction are listed in 'Table 1.8', (see below).

Table 1.8 Opposing or antagonistic interactions

Drug affected	*Interacting drugs*	*Results of interaction*
ACE inhibitors or Loop diuretics	NSAIDs	Antihypertensive effects opposed
Anticoagulants	Vitamin K	Anticoagulant effects opposed
Antidiabetics	Glucocorticoids	Blood glucose-lowering effects opposed
Antineoplastics	Megestrol	Antineoplastic effects possibly opposed
Levodopa	Antipsychotics (those with dopamine antagonist effects)	Antiparkinsonian effects opposed

Drug or neurotransmitter uptake interactions

A number of drugs with actions that occur at adrenergic neurones can be prevented from reaching those sites of action by the presence of other drugs. The tricyclic antidepressants prevent the re-uptake of noradrenaline (norepinephrine) into peripheral adrenergic neurones. Thus patients taking tricyclics and given parenteral noradrenaline have a markedly increased response (hypertension, tachycardia); see 'Tricyclic and related antidepressants + Inotropes and Vasopressors', p.1507. Similarly, the uptake of guanethidine (and related drugs guanoclor, betanidine, debrisoquine, etc.) is blocked by 'chlorpromazine, haloperidol, tiotixene', (p.1059), a number of 'amfetamine-like drugs', (p.1058), and the 'tricyclic antidepressants', (p.1060), so that the antihypertensive effect is prevented. The antihypertensive effects of clonidine are also prevented by the tricyclic antidepressants, one possible reason being that the uptake of clonidine within the CNS is blocked (see 'Clonidine and related drugs + Tricyclic and related antidepressants', p.1054). Some of these interactions at adrenergic neurones are illustrated in 'Figure 1.5', (see below).

Drug-herb interactions

The market for herbal medicines and supplements in the Western world has markedly increased in recent years, and, not surprisingly, reports of interactions with 'conventional' drugs have arisen. The most well known and documented example is the interaction of St John's wort (*Hypericum perforatum*) with a variety of drugs, see below. There have also been isolated reports of other herb-drug interactions, attributable to various mechanisms, including additive pharmacological effects.

Based on these reports, there are a growing number of reviews of herbal medicine interactions, which seek to predict likely interactions based on the, often hypothesised, actions of various herbs. Many of these predictions seem tenuous at best.

Rather than add to the volume of predicted interactions, at present, *Stockley's Drug Interactions* includes only those interactions for which there are published reports. Our sister publication, *Stockley's Herbal Medicines Interactions*, attempts to deal with these interactions in much greater depth, assessing the theoretical as well as the clinical evidence for the interactions of herbal medicines, dietary supplements and nutraceuticals.

To aid collection of data in this area, health professionals should routinely ask patients about their use of herbal medicines and supplements, and report any unexpected responses to treatment.

An additional problem in interpreting these interactions, is that the interacting constituent of the herb is usually not known and is therefore not

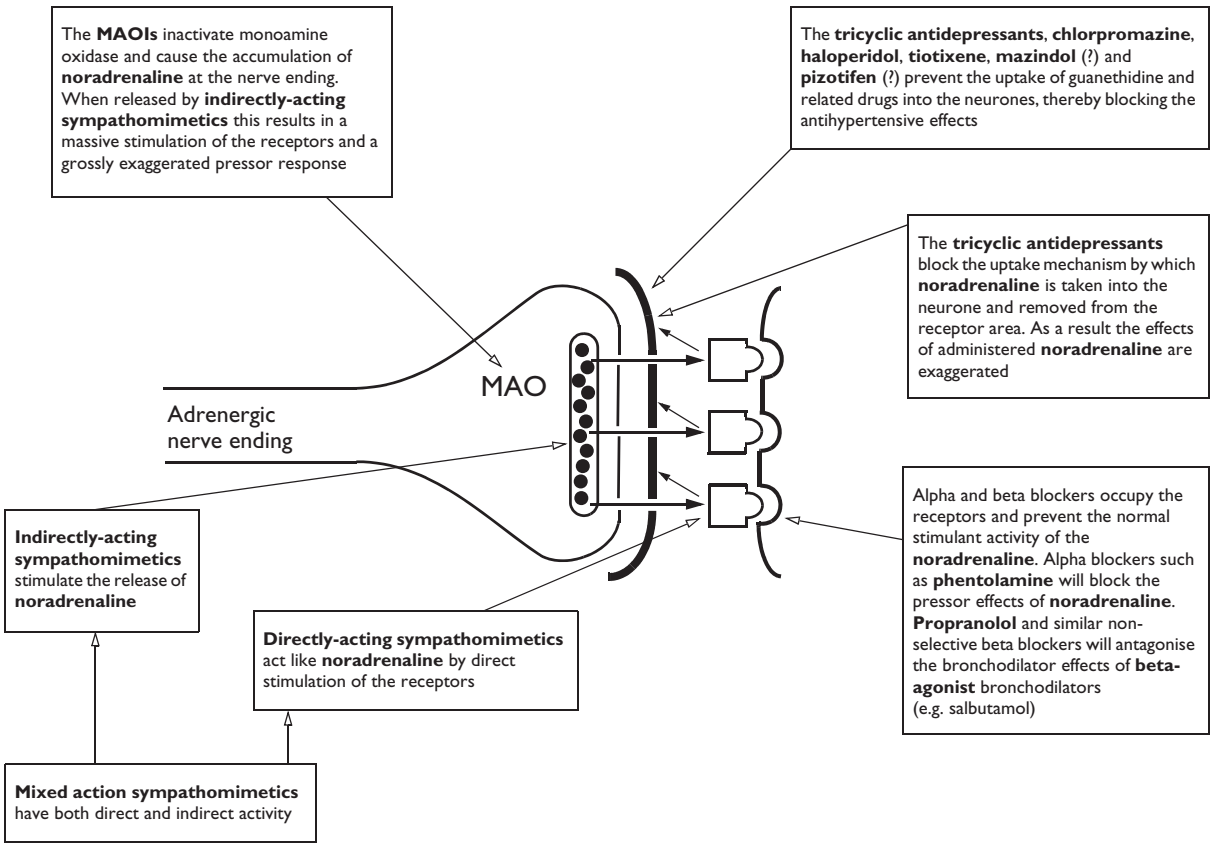

Fig. 1.5 Interactions at adrenergic neurones. A highly simplified composite diagram of an adrenergic neurone (molecules of noradrenaline (norepinephrine) indicated as (●) contained in a single vesicle at the nerve-ending) to illustrate in outline some of the different sites where drugs can interact. More details of these interactions are to be found in individual monographs.

standardised for. It could vary widely between different products, and batches of the same product.

St John's wort (Hypericum perforatum)

An increasing number of reports have implicated St John's wort (*Hypericum perforatum*) in drug interactions. Evidence has shown that the herb can induce the cytochrome P450 isoenzyme CYP3A4, and can also induce 'P-glycoprotein', (p.8). Hence St John's wort decreases the levels of 'ciclosporin', (p.1253) and 'digoxin', (p.1115), respectively. Other less certain evidence suggests that CYP2E1 and CYP1A2 may also be induced. St John's wort has serotonergic properties, and this has resulted in a pharmacodynamic interaction with the 'SSRIs', (p.1492), namely the development of serotonin syndrome. St John's wort contains many possible constituents that could be responsible for its pharmacological effects. The major active constituents are currently considered to be hyperforin (a phloroglucinol) and hypericin (a naphthodianthrone). Hypericin is the only constituent that is standardised for, and then only in some St John's wort preparations.

1. Miller LG. Herbal medicinals. Selected clinical considerations focusing on known or potential drug-herb interactions. *Arch Intern Med* (1998) 158, 2200–11.
2. Fugh-Berman A. Herb-drug interactions. *Lancet* (2000) 355, 134–8. Correction. ibid. 1020.
3. Wang Z, Gorski JC, Hamman MA, Huang S-M, Lesko LJ, Hall SD. The effects of St John's wort *(Hypericum perforatum)* on human cytochrome P450 activity. *Clin Pharmacol Ther* (2001) 70, 317–26.
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5. Henderson L, Yue QY, Bergquist C, Gerden B, Arlett P. St John's wort (*Hypericum perforatum*): drug interactions and clinical outcomes. *Br J Clin Pharmacol* (2002) 54, 349–56.
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7. Dresser GK, Schwarz UI, Wilkinson GR, Kim RB. Coordinate induction of both cytochrome P4503A and MDR1 by St John's wort in healthy subjects. *Clin Pharmacol Ther* (2003) 73, 41–50.

Drug-food interactions

It is well established that food can cause clinically important changes in drug absorption through effects on gastrointestinal motility or by drug binding, see 'Drug absorption interactions', (p.3). In addition, it is well known that tyramine (present in some foodstuffs) may reach toxic concentrations in patients taking 'MAOIs', (p.1395). With the growth in understanding of drug metabolism mechanisms, it has been increasingly recognised that some foods can alter drug metabolism. Currently, grapefruit juice causes the most clinically relevant of these interactions, see *Grapefruit juice*, below.

(a) Cruciferous vegetables and charcoal-broiled meats

Cruciferous vegetables, such as brussels sprouts, cabbage, and broccoli, contain substances that are inducers of the cytochrome P450 isoenzyme CYP1A2. Chemicals formed by 'burning' meats additionally have these properties. These foods do not appear to cause any clinically important drug interactions in their own right, but their consumption may add another variable to drug interaction studies, so complicating interpretation. In drug interaction studies where alteration of CYP1A2 is a predicted mechanism, it may be better for patients to avoid these foods during the study.

(b) Grapefruit juice

By chance, grapefruit juice was chosen to mask the taste of alcohol in a study of the effect of alcohol on felodipine, which led to the discovery that grapefruit juice itself markedly increased felodipine levels, see 'Calcium-channel blockers + Grapefruit juice', p.1034. In general, grapefruit juice inhibits intestinal CYP3A4, and only slightly affects hepatic CYP3A4. This is demonstrated by the fact that intravenous preparations of drugs that are metabolised by CYP3A4 are not much affected, whereas oral preparations of the same drugs are. These interactions result in increased drug levels.

Some drugs that are not metabolised by CYP3A4 show decreased levels with grapefruit juice, such as 'fexofenadine', (p.670). The probable reason for this is that grapefruit juice is an inhibitor of some drug transporters (see 'Drug transporter proteins', (p.8)), and possibly affects organic anion-transporting polypeptides (OATPs), although inhibition of P-glycoprotein has also been suggested.

The active constituent of grapefruit juice is uncertain. Grapefruit contains naringin, which degrades during processing to naringenin, a substance known to inhibit CYP3A4. Because of this, it has been assumed that whole grapefruit will not interact, but that processed grapefruit juice will. However, subsequently some reports have implicated the whole fruit. Other possible active constituents in the whole fruit include bergamottin and dihydroxybergamottin.

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Conclusions

It is now quite impossible to remember all the known clinically important interactions and how they occur, which is why this publication has been produced, but there are some broad general principles that need little memorising:

- Be on the alert with any drugs that have a narrow therapeutic window or where it is necessary to keep serum levels at or above a suitable level (e.g. certain anticoagulants, antidiabetic drugs, antiepileptics, antihypertensives, anti-infectives, antineoplastic cytotoxics, digitalis glycosides, immunosuppressants, etc.).
- Remember some of those drugs that are key enzyme inducers (e.g. phenytoin, barbiturates, rifampicin (rifampin), etc) or enzyme inhibitors (e.g. azole antifungals, HIV-protease inhibitors, erythromycin, SSRIs).
- Think about the basic pharmacology of the drugs under consideration so that obvious problems (additive CNS depression for example) are not overlooked, and try to think of what might happen if drugs that affect the same receptors are used together. Don't forget that many drugs affect more than one type of receptor.
- Keep in mind that the elderly are at risk because of reduced liver and renal function on which drug clearance depends.

2

ACE inhibitors and Angiotensin II receptor antagonists

ACE inhibitors (angiotensin-converting enzyme inhibitors) prevent the production of angiotensin II from angiotensin I. The angiotensin II receptor antagonists are more selective, and target the angiotensin II type I (AT_1) receptor, which is responsible for the pressor actions of angiotensin II.

Angiotensin II is involved in the renin-angiotensin-aldosterone system, which regulates blood pressure, sodium and water homoeostasis by the kidneys, and cardiovascular function. Angiotensin II stimulates the synthesis and secretion of aldosterone and raises blood pressure via a direct vasoconstrictor effect.

Angiotensin converting enzyme (ACE) is identical to bradykinase, so ACE inhibitors may additionally reduce the degradation of bradykinin and affect enzymes involved in the production of prostaglandins.

Many of the interactions of the ACE inhibitors and angiotensin II receptor antagonists involve drugs that affect blood pressure. Consequently in most cases the result is either an increase in the hypotensive effect (e.g. 'alcohol', (p.51)) or a decrease in the hypotensive effect (e.g. 'indometacin', (p.32)).

In addition, due to their effects on aldosterone, the ACE inhibitors and angiotensin II antagonists may increase potassium concentrations and can therefore have additive hyperkalaemic effects with other drugs that cause elevated potassium levels. Furthermore, drugs that affect renal function may potentiate the adverse effects of ACE inhibitors and angiotensin II antagonists on the kidneys.

Most ACE inhibitor and angiotensin II receptor antagonist interactions are pharmacodynamic, that is, interactions that result in an alteration in drug effects rather than drug disposition, so in most cases interactions of individual drugs will be applicable to the group. *In vitro* experiments suggest that the role of cytochrome P450 isoenzymes in the metabolism and interactions of the angiotensin II receptor antagonists (candesartan, eprosartan, irbesartan, losartan and valsartan) is small, although losartan, irbesartan, and to a minor extent, candesartan, are metabolised by CYP2C9. Only losartan and irbesartan were considered to have a theoretical potential for pharmacokinetic drug interactions involving CYP2C9.[1] See 'Angiotensin II receptor antagonists + Azoles', p.39. The ACE inhibitors do not appear to undergo interactions via cytochrome P450 isoenzymes.

'Table 2.1', (see below) lists the ACE inhibitors and the angiotensin II receptor antagonists. Although most of the interactions of the ACE inhibitors or angiotensin II receptor antagonists are covered in this section, if the ACE inhibitor or angiotensin II receptor antagonist is the affecting drug, the interaction is dealt with elsewhere.

1. Taavitsainen P, Kiukaanniemi K, Pelkonen O. In vitro inhibition screening of human hepatic P_{450} enzymes by five angiotensin-II receptor antagonists. *Eur J Clin Pharmacol* (2000) 56, 135–40.

Table 2.1 ACE inhibitors and Angiotensin II receptor antagonists

Group	*Drugs*
ACE inhibitors	Alacepril, Benazepril, Captopril, Cilazapril, Delapril, Enalapril, Fosinopril, Imidapril, Lisinopril, Moexipril, Perindopril, Quinapril, Ramipril, Spirapril, Temocapril, Trandolapril, Zofenopril
Angiotensin II receptor antagonists	Candesartan, Eprosartan, Irbesartan, Losartan, Olmesartan, Telmisartan, Valsartan

ACE inhibitors + Aliskiren

The concurrent use of ramipril and aliskiren does not result in a clinically significant pharmacokinetic interaction, although additive blood pressure-lowering effects occur. However, the concurrent use of aliskiren and ACE inhibitors may increase the risk of hyperkalaemia.

Clinical evidence, mechanism, importance and management

In a study, 17 healthy subjects were given **ramipril** 2.5 mg daily, titrated to 10 mg daily by day 3, and aliskiren 300 mg daily, either alone or together for periods of 6 or 7 days. **Ramipril** increased the peak levels and AUC of aliskiren by 31% and 12%, respectively. Aliskiren increased the AUC of **ramipril** by 22%, but did not affect its plasma levels. The AUC of the active metabolite of **ramipril**, ramiprilat was unchanged, but its peak plasma levels decreased by 15%. These pharmacokinetic changes are unlikely to be clinically relevant and dose adjustments are not needed on concurrent use.[1] However, the concurrent use of **ramipril** with aliskiren results in additive blood pressure reduction.[2]

In one study, where aliskiren was given with an ACE inhibitor to patients with diabetes, increases in serum potassium were more frequent (5.5%) compared with an incidence of 0.9% that had been reported in hypertensive patients.[3]

The concurrent use of aliskiren and ramipril does not appear to result in a clinically significant pharmacokinetics interaction: no such interaction would be expected with other ACE inhibitors, but this ideally needs confirmation. However, as would be expected, concurrent use appears to result in an increased blood pressure-lowering effect, which would generally be considered desirable. Nevertheless, be alert for a greater than desired hypotensive effect. Also note that, the manufacturer of aliskiren warns that patients receiving other drugs that inhibit the renin-angiotensin system, and/or those with reduced renal function and/or diabetes are at an increased risk of hyperkalaemia during the use of aliskiren.[3] An increased frequency of monitoring potassium levels may be prudent.

1. Vaidyanathan S, Valencia J, Kemp C, Zhao C, Yeh C-M, Bizot M-N, Denouel J, Dieterich HA, Dole WP. Lack of pharmacokinetic interactions of aliskiren, a novel direct renin inhibitor for the treatment of hypertension, with the antihypertensives amlodipine, valsartan, hydrochlorothiazide (HCTZ) and ramipril in healthy volunteers. *Int J Clin Pract* (2006) 60, 1343–56.
2. O'Brien E, Barton J, Nussberger J, Mulcahy D, Jensen C, Dicker P, Stanton A. Aliskiren reduces blood pressure and suppresses plasma renin activity in combination with a thiazide diuretic, an angiotensin-converting enzyme inhibitor, or an angiotensin receptor blocker. *Hypertension* (2007) 49, 276–84.
3. Rasilez (Aliskiren hemifumarate). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, April 2009.

ACE inhibitors + Allopurinol

A case of hypersensitivity has been attributed to the use of captopril with allopurinol. Anaphylaxis and myocardial infarction occurred when one man taking enalapril was given allopurinol. The concurrent use of ACE inhibitors and allopurinol may increase the risk of leucopenia and serious infection, especially in renal impairment.

Clinical evidence

No significant pharmacokinetic changes were seen in 12 healthy subjects given allopurinol and **captopril** alone and in combination.[1] A report describes fever, arthralgia and myalgia in a diabetic man with chronic renal failure who was also given **captopril** and allopurinol. He improved when the **captopril** was withdrawn.[2] A man taking **enalapril** had an acute anaphylactic reaction with severe coronary spasm, culminating in myocardial infarction, within 20 minutes of taking allopurinol 100 mg. He recovered and continued to take **enalapril** without allopurinol.[3]

The UK manufacturer of **captopril** also warns that neutropenia and agranulocytosis, resulting in serious infection, have occurred in patients taking **captopril** and other ACE inhibitors, and that the concurrent use of allopurinol may be a complicating factor, especially in those with renal impairment.[4]

Mechanism

Not understood. It is uncertain whether these are interactions because allopurinol alone can cause severe hypersensitivity reactions, particularly in the presence of renal failure. Captopril can also induce a hypersensitivity reaction.

Importance and management

These interactions are not clearly established, and the reaction appears to be rare and unpredictable. All that can be constructively said is that patients taking both drugs should be very closely monitored for any signs of hypersensitivity (e.g. skin reactions) or a low white cell count (e.g. sore throat, fever), especially if they have renal impairment. The UK manufacturer of captopril recommends that differential white blood cell counts should be performed before adding allopurinol, then every 2 weeks during the first 3 months of treatment, and periodically thereafter.[4] Similar caution and advice is given by the UK manufacturers of several other ACE inhibitors. For other possible interactions with ACE inhibitors that might result in an increased risk of leucopenia see also 'ACE inhibitors + Azathioprine', p.18 and 'ACE inhibitors + Procainamide', p.37.

1. Duchin KL, McKinstry DN, Cohen AI, Migdalof BH. Pharmacokinetics of captopril in healthy subjects and in patients with cardiovascular diseases. *Clin Pharmacokinet* (1988) 14, 241–59.
2. Samanta A, Burden AC. Fever, myalgia, and arthralgia in a patient on captopril and allopurinol. *Lancet* (1984) i, 679.
3. Ahmad S. Allopurinol and enalapril. Drug induced anaphylactic coronary spasm and acute myocardial infarction. *Chest* (1995) 108, 586.
4. Capoten (Captopril). E. R. Squibb & Sons Ltd. UK Summary of product characteristics, September 2008.

ACE inhibitors + Angiotensin II receptor antagonists

The concurrent use of ACE inhibitors and angiotensin II receptor antagonists increases the risk of hypotension, renal impairment and hyperkalaemia.

Clinical evidence, mechanism, importance and management

Both ACE inhibitors and angiotensin II receptor antagonists can have adverse renal effects and can cause hyperkalaemia. These effects might be expected to be additive when they are used together. In one randomised clinical study in patients with heart failure taking ACE inhibitors (74% taking **enalapril**, **lisinopril**, **captopril**, or **ramipril**), the addition of **candesartan** resulted in higher rates of withdrawals for renal impairment (increase in creatinine 7.8% versus 4.1% with placebo) and hyperkalaemia (3.4% versus 0.7% with placebo).[1]

In another double-blind study in patients with heart failure, the concurrent use of **valsartan** and **captopril** resulted in a higher incidence of adverse events leading to a dose reduction or a discontinuation of study treatment than either drug alone. For hypotension, treatment was discontinued in 90 patients (1.9%) taking both drugs, 70 patients (1.4%) taking **valsartan**, and 41 patients (0.8%) taking **captopril**. For renal causes treatment was discontinued in 61 patients (1.3%) taking both drugs, 53 patients (1.1%) taking **valsartan** and 40 patients (0.8%) taking **captopril**; and for hyperkalaemia treatment was discontinued in 12 patients (0.2%) taking both drugs, 7 patients (0.1%) taking **valsartan** and 4 patients (0.1%) taking **captopril**.[2]

A placebo-controlled study in 24 patients with diabetic nephropathy taking **enalapril** 40 mg daily found that the addition of **irbesartan** 300 mg daily had a greater effect on reduction of albuminuria and blood pressure than **enalapril** alone. Plasma potassium levels of greater than 5.2 mmol/L occurred in one patient taking **enalapril** alone and in one patient taking **irbesartan** with **enalapril**. Six patients taking both drugs experienced transient hypotension or tiredness.[3]

Another study in patients with hypertension not controlled with **lisinopril** 20 mg daily found that either an increase in the **lisinopril** dose to 40 mg daily, or the addition of **candesartan** 16 mg daily for 2 weeks then 32 mg daily, controlled hypertension in 37% and 43% of patients, respectively. Eleven patients taking **lisinopril** and 9 patients taking **lisinopril** with **candesartan** developed hyperkalaemia resulting in discontinuation in 4 patients taking **lisinopril** with **candesartan**.[4]

In the ONTARGET study, patients with vascular disease or high-risk diabetes without heart failure were given either **ramipril** 10 mg daily (8 576 patients), **telmisartan** 80 mg daily (8 542 patients), or both drugs

(8 502 patients). The use of **ramipril** with **telmisartan** reduced the average systolic blood pressure by up to 5 mmHg, but did not have an additive effect on the renin-angiotensin system. The combination was associated with more adverse effects including hypotensive symptoms, syncope, renal impairment and hyperkalaemia without an increase in benefit. Discontinuation of treatment because of hypotensive symptoms occurred in 406 patients taking both drugs, compared with 149 taking **ramipril** alone and 229 taking **telmisartan** alone. In patients at high vascular risk, the use of both drugs reduced proteinuria to a greater extent than **ramipril** alone, but overall worsened major renal outcomes.[5-7]

Monitor blood pressure, renal function and serum potassium carefully if the concurrent use of an ACE inhibitor and an angiotensin II receptor antagonist is considered desirable.

1. McMurray JJV, Östergren J, Swedberg K, Granger CB, Held P, Michelson EL, Olofsson B, Yusuf S, Pfeffer MA; CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *Lancet* (2003) 362, 767–71.
2. Pfeffer MA, McMurray JJV, Velazquez EJ, Rouleau J-L, Køber L, Maggioni AP, Solomon SD, Swedberg K, Van de Werf F, White H, Leimberger JD, Henis M, Edwards S, Zelenkofske S, Sellers MA, Califf RM; Valsartan in Acute Myocardial Infarction Trial Investigators. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med* (2003) 349, 1893–1906.
3. Jacobsen P, Andersen S, Rossing K, Jensen BR, Parving H-H. Dual blockade of the renin-angiotensin system versus maximal recommended dose of ACE inhibition in diabetic nephropathy. *Kidney Int* (2003) 63, 1874–80.
4. Izzo JL, Weinberg MS, Hainer JW, Kerkering J, Tou CKP. Antihypertensive efficacy of candesartan-lisinopril in combination vs. up-titration of lisinopril: the AMAZE trials. *J Clin Hypertens (Greenwich)* (2004) 6, 485–93.
5. ONTARGET Investigators, Yusuf S, Teo KK, Pogue J, Dyal L, Copland I, Schumacher H, Dagenais G, Sleight P, Anderson C. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med (2008) 358, 1547–59.
6. Mann JFE, Schmieder RE, McQueen M, Dyal L, Schumacher H, Pogue J, Wang X, Maggioni A, Budaj A, Chaithiraphan S, Dickstein K, Keltai M, Metsärinne K, Oto A, Parkhomenko A, Piegas LS, Svendsen TL, Teo KK, Yusuf S; ONTARGET investigators. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. Lancet (2008) 372, 547–53.
7. Guthrie RM. Review of ONTARGET: treating patients at high risk for vascular events with telmisartan, ramipril, or both. Postgrad Med (2009) 121, 202–4.

ACE inhibitors + Antacids

Aluminium/magnesium hydroxide-containing antacids reduce the bioavailability of captopril by 40% and fosinopril by about one-third. An antacid did not affect ramipril pharmacokinetics.

Clinical evidence

In 10 healthy subjects an antacid containing **aluminium/magnesium hydroxide** and **magnesium carbonate** reduced the AUC of a single 50-mg dose of **captopril** by about 40%, when compared with the fasting state. However, this did not alter the extent of the reduction in blood pressure.[1]

Another study found that *Mylanta* [**aluminium/magnesium hydroxide** and simeticone[2]] reduced the bioavailability of **fosinopril** 20 mg by about one-third.[3]

It is briefly noted in a review that antacid use did not affect the pharmacokinetics of ramiprilat, the active metabolite of **ramipril**.[4]

Mechanism

The mechanism of this interaction is uncertain, but is unlikely to be due to elevated gastric pH as cimetidine did not have a similar effect.[3]

Importance and management

Evidence about interactions between ACE inhibitors and antacids it limited. Greater decreases in captopril bioavailability (caused by 'food', (p.28)) were found not to be clinically relevant, therefore, it is unlikely the change seen with antacids will be clinically important. However, with fosinopril, the manufacturers[2,5] suggest separating administration of antacids by at least 2 hours.

The UK manufacturers of **quinapril**[6] and **trandolapril**[7] also warn that antacids may reduce the bioavailability of ACE inhibitors, quite possibly based on the way that captopril and fosinopril interact, but there seems to be no evidence of a clinically significant interaction in practice.

1. Mäntylä R, Männistö PT, Vuorela A, Sundberg S, Ottoila P. Impairment of captopril bioavailability by concomitant food and antacid intake. *Int J Clin Pharmacol Ther Toxicol* (1984) 22, 626–9.
2. Monopril (Fosinopril sodium). Bristol-Myers Squibb Company. US Prescribing information, July 2008.
3. Moore L, Kramer A, Swites B, Kramer P, Tu J. Effect of cimetidine and antacid on the kinetics of the active diacid of fosinopril in healthy subjects. *J Clin Pharmacol* (1988) 28, 946.
4. Todd PA, Benfield P. Ramipril. A review of its pharmacological properties and therapeutic efficacy in cardiovascular disorders. *Drugs* (1990) 39, 110–35.
5. Staril (Fosinopril sodium). E. R. Squibb & Sons Ltd. UK Summary of product characteristics, January 2009.
6. Accupro (Quinapril hydrochloride). Pfizer Ltd. UK Summary of product characteristics, June 2009.
7. Gopten (Trandolapril). Abbott Laboratories Ltd. UK Summary of product characteristics, July 2009.

ACE inhibitors + Antipsychotics

Marked postural hypotension occurred in a patient given chlorpromazine and captopril. The hypotensive adverse effects of antipsychotics such as the phenothiazines may be additive with the effects of ACE inhibitors.

Clinical evidence, mechanism, importance and management

A patient fainted and developed marked postural hypotension (standing blood pressure 66/48 mmHg) when given **captopril** 6.25 mg twice daily and **chlorpromazine** 200 mg three times daily. He had previously taken **chlorpromazine** with nadolol, prazosin and hydrochlorothiazide without any problems, although his blood pressure was poorly controlled on these drugs. As the patient's blood pressure was elevated when taking **chlorpromazine** or **captopril** alone, there appeared to be a synergistic hypotensive effect between the two drugs.[1]

The manufacturers of several ACE inhibitors warn that ACE inhibitors may enhance the hypotensive effects of certain antipsychotics, and that postural hypotension may occur. Some of these warnings are based, not unreasonably, on the adverse reactions seen with other ACE inhibitors or antihypertensives, but not necessarily on direct observations.[2] If postural hypotension occurs advise patients to lay down and elevate their legs if they feel faint or dizzy, and, when recovered, to get up slowly. Dose adjustments may be necessary to accommodate this interaction.

1. White WB. Hypotension with postural syncope secondary to the combination of chlorpromazine and captopril. *Arch Intern Med* (1986) 146, 1833–4.
2. Knoll Ltd. Personal communication,1993.

ACE inhibitors + Aprotinin

A retrospective study in patients undergoing cardiopulmonary bypass surgery found that pre-operative ACE inhibitor use with intra-operative aprotinin use increased the risk of renal failure.

Clinical evidence

The effects of preoperative ACE inhibitor use and/or intra-operative use of aprotinin were studied in a retrospective analysis of risk factors for acute renal failure in 1209 patients who underwent coronary artery bypass graft, valve, or combined procedures. Patients with preoperative renal impairment were excluded from the study, and only those with a low baseline risk of renal complications and no immediately identifiable cause of acute renal failure were included. Multivariate analysis indicated that risk factors for acute renal failure in the study patients were increasing age, valve procedures, red blood cell and platelet transfusions, lowest haematocrit during cardiopulmonary bypass, and the combination of ACE inhibitor and aprotinin use. The use of either an ACE inhibitor alone or aprotinin alone was not a significant predictor of acute renal failure.[1]

Mechanism

Aprotinin is a proteolytic enzyme inhibitor that has many actions including antagonism of the kallikrein-kinin system, which in turn affects bradykinins and renin. It would therefore be expected to have complex interactions with the ACE inhibitors,[2] which also affect these proteins.

It has been suggested that ACE inhibitors promote vasodilation of the efferent arteriole of the glomerulus, which reduces glomerular perfusion pressure. This can be compensated by vasodilation of the afferent arteriole to preserve glomerular perfusion pressure. Aprotinin may counter this compensatory response by causing vasoconstriction of the afferent arteriole, which reduces glomerular perfusion pressure and reduces renal excretory function. It was also suggested that this may not be generally clinically relevant, but in a situation such as cardiopulmonary bypass sur-

gery, where there are altered haemodynamics, there is the theoretical possibility of affecting renal haemodynamics.[1]

Importance and management

Patients taking ACE inhibitors may potentially be at increased risk of renal failure following cardiac surgery if aprotinin is used intra-operatively. The authors suggest more study is needed, but do advise the avoidance of aprotinin in such patients. They suggest that consideration should be given to stopping the ACE inhibitor for 2 to 3 days before surgery.[1] For information about the peri-operative use of ACE inhibitors, consider also 'Anaesthetics, general + ACE inhibitors or Angiotensin II receptor antagonists', p.102.

1. Kincaid EH, Ashburn DA, Hoyle JR, Reichert MG, Hammon JW, Kon ND. Does the combination of aprotinin and angiotensin-converting enzyme inhibitor cause renal failure after cardiac surgery? *Ann Thorac Surg* (2005) 80, 1388–93.
2. Waxler B, Rabito SF. Aprotinin: a serine protease inhibitor with therapeutic actions: its interaction with ACE inhibitors. *Curr Pharm Des* (2003) 9, 777–87.

ACE inhibitors + Aspirin

The antihypertensive efficacy of captopril and enalapril may be reduced by high-dose aspirin in about 50% of patients. Low-dose aspirin (less than or equal to 100 mg daily) appears to have little effect. It is unclear whether aspirin attenuates the benefits of ACE inhibitors in heart failure. The likelihood of an interaction may depend on disease state and its severity.
Renal failure has been reported in a patient taking captopril and aspirin.

Clinical evidence

A. Effects on blood pressure

(a) Captopril

In 8 patients with essential hypertension, aspirin 600 mg every 6 hours for 5 doses did not significantly alter the blood pressure response to a single 25 to 100-mg dose of captopril. However, the prostaglandin response to captopril was blocked and the blood pressure response to captopril was blunted in 4 of the 8 patients.[1] In another study, in 15 patients with hypertension, aspirin 75 mg daily did not alter the antihypertensive effects of captopril 25 mg twice daily.[2]

(b) Enalapril

Two groups of 26 patients, one with mild to moderate hypertension taking enalapril 20 mg twice daily and the other with severe primary hypertension taking enalapril 20 mg twice daily (with nifedipine 30 mg and atenolol 50 mg daily), were given test doses of aspirin 100 mg and 300 mg daily for 5 days. The 100-mg dose of aspirin did not alter the efficacy of the antihypertensive drugs, but the 300-mg dose reduced the antihypertensive efficacy in about half the patients in both groups. In these patients, the antihypertensive effects were diminished by 63% in those with mild to moderate hypertension and by 91% in those with severe hypertension.[3] In contrast, another study in 7 patients with hypertension taking enalapril (mean daily dose 12.9 mg) found that aspirin 81 mg or 325 mg daily for 2 weeks did not have any significant effect on blood pressure.[4] A further study in 18 patients also found that aspirin 100 mg daily for 2 weeks did not alter the antihypertensive effect of enalapril 20 or 40 mg daily.[5]

(c) Unspecified ACE inhibitors

In a randomised study, the use of low-dose aspirin 100 mg daily for 3 months did not alter blood pressure control in patients taking ACE inhibitors, when compared with placebo.[6] Similarly, in a re-analysis of data from the Hypertension Optimal Treatment (HOT) study, long-term low-dose aspirin 75 mg daily did not interfere with the blood pressure-lowering effects of the antihypertensive drugs studied, when compared with placebo. Of 18 790 treated hypertensive patients, 41% received an ACE inhibitor, usually in combination with felodipine.[7]

B. Effects in coronary artery disease and heart failure

Various pharmacological studies have looked at the *short-term* effects of the combination of ACE inhibitors and aspirin on haemodynamic parameters. In one study in 40 patients with decompensated heart failure, aspirin 300 mg given on the first day and 100 mg daily thereafter antagonised the short-term haemodynamic effects of **captopril** 50 mg given every 8 hours for 4 days. The **captopril**-induced increase in cardiac index and the reduction in peripheral vascular resistance and pulmonary wedge pressure were all abolished.[8] A placebo-controlled study in 9 patients with chronic heart failure found that aspirin 75 mg daily for 7 days inhibited both the arterial and venous dilator responses to a single 25-mg dose of **captopril**.[9] In another study, in 15 patients with chronic heart failure receiving treatment with ACE inhibitors (mainly **enalapril** 10 mg twice daily), aspirin in doses as low as 75 mg impaired vasodilatation induced by arachidonic acid.[10] In yet another study, aspirin 325 mg daily worsened pulmonary diffusion capacity and made the ventilatory response to exercise less effective in patients taking **enalapril** 10 mg twice daily, but did not exert this effect in the absence of ACE inhibitors.[11] However, results from studies are inconsistent. In a review,[12] five of 7 studies reported that aspirin did not alter the haemodynamic effects of ACE inhibitors whereas the remaining two did. In one of these studies showing an adverse interaction between aspirin and **enalapril**, **ticlopidine** did not interact with **enalapril**.[13]

A number of large clinical studies of ACE inhibitors, mostly post-myocardial infarction, have been re-examined to see if there was a difference in outcome between those receiving aspirin at baseline, and those not. The results are summarised in 'Table 2.2', (p.16). However, in addition to the problems of retrospective analysis of non-randomised parameters, the studies vary in the initiation and duration of aspirin and ACE inhibitor treatment and the length of follow-up, the degree of heart failure or ischaemia, the prognosis of the patients, and the final end point (whether compared with placebo or with the benefits of aspirin or ACE inhibitors). The conclusions are therefore conflicting, and, although two meta-analyses of these studies found no interaction, an editorial[14] disputes the findings of one of these analyses.[15]

In addition to these sub-group analyses, there have been a number of retrospective cohort studies. A retrospective study involving 576 patients with heart failure requiring hospitalisation, found a trend towards an increased incidence of early readmissions (within 30 days after discharge) for heart failure among subjects taking ACE inhibitors and aspirin, compared with those taking ACE inhibitors without aspirin (16% versus 10%). In patients without coronary artery disease the increase in readmissions was statistically significant (23% versus 10%).[16] However, long-term survival in heart failure was not affected by the use of aspirin with ACE inhibitors. Furthermore, among patients with coronary artery disease, there was a trend towards improvement in mortality in patients receiving the combination, compared with an ACE inhibitor without aspirin (40% versus 56%).[17] A lack of adverse interaction was also found in a retrospective study involving 14 129 elderly patients who survived an acute myocardial infarction, for which they had been hospitalised. However, the added benefit of the combination over patients who received either aspirin or ACE inhibitors alone was not statistically significant.[18] Similarly, in another cohort of patients discharged after first hospitalisation for heart failure, there was no increase in mortality rates or readmission rates in those taking aspirin and ACE inhibitors.[19] A study in elderly patients with heart failure and resident in nursing homes included 12 703 who were taking an ACE inhibitor (51% were taking **captopril**; 33% **enalapril**; 9% **lisinopril**; with the rest taking **benazepril**, **fosinopril**, **quinapril**, or **ramipril**) and of these, 2046 also took aspirin (mostly 325 mg daily). The mortality rate, hospitalisation rate, or rate of decline in physical function after one year in patients taking ACE inhibitors, were not decreased by the use of aspirin. The findings were not affected by the presence of ischaemic heart disease and did not vary with the type or dose of ACE inhibitor used.[20] In another retrospective analysis in patients with stable left ventricular systolic dysfunction, no decrease in survival was seen in patients receiving ACE inhibitors, when comparing those also receiving aspirin (mean dose 183 mg daily; 74% of patients received 200 mg or less) and those not receiving aspirin.[21] Conversely, another study found that, compared with patients not taking aspirin, the use of high-dose aspirin (325 mg daily or more) with an ACE inhibitor was associated with a small but statistically significant 3% increase in the risk of death, whereas low-dose aspirin (160 mg daily or less) was not.[22]

C. Effects on renal function

Acute renal failure developed in a woman taking **captopril** when she started to take aspirin for arthritis. Renal function improved when both were stopped.[23] However, in a re-analysis of data from the Hypertension Optimal Treatment (HOT) study, long-term low-dose aspirin 75 mg daily had no effect on changes in serum creatinine, estimated creatinine clearance or the number of patients developing renal impairment, when compared with placebo. Of 18 790 treated hypertensive patients, 41% received an ACE inhibitor.[7] A study in 10 patients with chronic congestive heart failure, due

Table 2.2 Sub-group analyses of clinical studies assessing the interaction between aspirin and ACE inhibitors

Study and patients	*Aspirin dose*	*ACE inhibitor*	*Follow-up*	*Finding*	*Refs*
Evidence of an interaction					
SOLVD 6512 patients treated for heart failure or prevention of heart failure	Not reported	Enalapril	37 to 41 months	Combined treatment associated with reduced benefits compared with enalapril alone.	1
CONSENSUS II 6090 patients with acute MI	Not reported	Enalapril	6 months	Effect of enalapril less favourable in those taking aspirin at baseline.	2
GUSTO-I 31622 post-MI patients without heart failure	Not reported	Not reported	11 months (starting 30 days post MI)	Combined use associated with higher mortality than aspirin alone (mortality rates 3.3% vs 1.6%).	3
EPILOG 2619 patients undergoing coronary angioplasty	325 mg daily	Not reported	12 months	Combined use associated with higher mortality than aspirin alone (mortality rates 3.7% vs 1.2%).	3
AIRE 1986 patients after acute MI, with heart failure	Not reported	Ramipril 2.5 to 5 mg twice daily started 3 to 10 days after MI	15 months (average)	Trend towards greater benefit of ramipril in those not receiving aspirin.	4
No evidence of an interaction					
BIP Secondary prevention of MI in 1197 patients with coronary artery disease	250 mg daily	Captopril or enalapril	5 years (average)	Lower death rate in those on combined therapy than those on ACE inhibitor alone (19% vs 27%).	5
SAVE 2231 patients with left ventricular dysfunction after MI	Not reported	Captopril 75 to 150 mg daily	42 months (average)	Trend towards greater benefits of captopril when taken with aspirin.	6
HOPE Prevention of cardiovascular events in 9297 patients without left ventricular dysfunction or heart failure	Not reported	Ramipril 10 mg daily	About 4.5 years	Benefits of ramipril not affected by aspirin.	7
CATS Early treatment of acute MI in 298 patients	80 to 100 mg daily	Captopril	1 year	Benefits of captopril not affected by aspirin. Better prognosis in those on aspirin.	8
ISIS-4 Early treatment of acute MI in 58050 patients	Not reported	Captopril 100 mg daily	At 5 weeks and 1 year	Benefits of captopril not affected by aspirin.	9
Meta-analysis of AIRE, SAVE, SOLVD and TRACE 12763 patients with left ventricular dysfunction or heart failure with or without MI	Not reported	Captopril, enalapril, ramipril, trandolapril	35 months (average)	Benefits of ACE inhibitors observed even if aspirin given.	10
Meta-analysis of CCS-1, CONSENSUS II, GISSI-3, and ISIS-4 Early treatment of MI in 96712 patients	160 to 325 mg daily	Captopril, enalapril, lisinopril	30 days	ACE inhibitor reduced 30-day mortality from 15.1% to 13.8%. ACE inhibitor plus aspirin reduced 30-day mortality from 6.7% to 6.3%.	11
TRACE 1749 patients with left ventricular dysfunction after acute MI	Not reported	Trandolapril 1 to 4 mg daily	24 to 50 months	Trend towards greater benefit of trandolapril in those receiving aspirin (mortality of 45% with ACE inhibitor, and 34% with ACE inhibitor plus aspirin).	12
SMILE 1556 patients with acute MI	Not reported	Zofenopril 7.5 mg increasing to 30 mg twice daily for 6 weeks	At 6 weeks and 1 year	Benefits of zofenopril not significantly affected by aspirin.	13

Continued

Table 2.2 Sub-group analyses of clinical studies assessing the interaction between aspirin and ACE inhibitors (continued)

Study and patients	*Aspirin dose*	*ACE inhibitor*	*Follow-up*	*Finding*	*Refs*
Meta-analysis of AIRE, HOPE, SAVE, SOLVD, and TRACE 22060 patients with either; left ventricular dysfunction or heart failure without MI, coronary artery disease without left ventricular dysfunction, or acute MI	Not reported	Captopril, enalapril, ramipril, trandolapril	More than 3 years	Benefits of ACE inhibitors observed even if aspirin given.	14

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to ischaemic heart disease, taking ACE inhibitors (**captopril**, **cilazapril**, **enalapril**, **ramipril**) and aspirin 75 to 125 mg daily found that when they were given a single 50-mg dose of diclofenac or placebo, after aspirin had been discontinued for at least one week, diclofenac caused a significant deterioration in renal function compared with placebo or aspirin. Compared with placebo, both aspirin and diclofenac caused slight but significant increases in serum creatinine. However, there was no overall change in renal function (determined by glomerular filtration rate, urine flow, osmolality clearance, and sodium and potassium excretion) between placebo and low-dose aspirin. Long-term, low-dose aspirin appeared not to worsen renal function in patients with heart failure taking ACE inhibitors.[24]

D. Pharmacokinetic studies

A single-dose study in 12 healthy subjects found that the pharmacokinetics of **benazepril** 20 mg and aspirin 325 mg were not affected by concurrent use.[25]

Mechanism

Some, but not all the evidence suggests that prostaglandins may be involved in the hypotensive action of ACE inhibitors, and that aspirin, by inhibiting prostaglandin synthesis, may partially antagonise the effect of ACE inhibitors on blood pressure. This effect appears to depend on the dose of aspirin and may also be dependent on sodium status and plasma renin, and therefore it does not occur in all patients.

The beneficial effects of ACE inhibitors in heart failure and ischaemic heart disease are thought to be due, in part, to the inhibition of the breakdown of kinins, which are important regulators of prostaglandin and nitric oxide synthesis. Such inhibition promotes vasodilatation and afterload reduction. Aspirin may block these beneficial effects by inhibiting cyclo-oxygenase and thus prostaglandin synthesis, causing vasoconstriction, decreased cardiac output and worsening heart failure.[12,26]

Importance and management

Low-dose aspirin (less than or equal to 100 mg daily) does not alter the **antihypertensive efficacy** of captopril and enalapril. No special precautions would therefore seem to be required with ACE inhibitors and these low doses of aspirin. A high dose of aspirin (2.4 g daily) has been reported to interact in 50% of patients in a single study. Aspirin 300 mg daily has been reported to interact in about 50% of patients in another study, whereas 325 mg daily did not interact in further study. Thus, at present, it appears that if an ACE inhibitor is used with aspirin in doses higher than 300 mg daily, blood pressure should be monitored more closely, and the ACE inhibitor dose raised if necessary. Intermittent use of aspirin should be considered as a possible cause of erratic control of blood pressure in patients taking ACE inhibitors.

Both ACE inhibitors and aspirin are often taken by patients with **coronary artery disease**, and ACE inhibitors are used in **chronic heart failure**, which is often associated with coronary heart disease. The information about a possible interaction between ACE inhibitors and aspirin in heart failure is conflicting. This may be due to much of the clinical data being obtained from retrospective non-randomised analyses.[26] It may

also be a factor of different disease states. For example, an interaction may be less likely to be experienced in patients with heart failure of ischaemic aetiology than those with non-ischaemic causes, because of the added benefits of aspirin in ischaemic heart disease.[27] The available data, and its implications, have been extensively reviewed and commented on.[12,14,26-35] Some commentators have advised that, if possible, aspirin should be avoided in patients requiring long-term treatment for heart failure, particularly if heart failure is severe.[14,30] Others suggest avoiding aspirin in heart failure unless there are clear indications, such as atherosclerosis.[12,26,31,32] The use of lower doses of aspirin (80 to 100 mg daily rather than greater than or equal to 325 mg daily) in those with heart failure taking ACE inhibitors has also been suggested.[27,28,31]

US guidelines from 2005 on chronic heart failure[36] state that, "Many physicians believe the data justify prescribing aspirin and ACE inhibitors together when there is an indication for use of aspirin", while recognising that not all physicians agree. The guidelines say that further study is needed. The 2005 update of the European Society of Cardiology (ESC) guidelines stated that there was little evidence to support using ACE inhibitors and aspirin together in heart failure. The guidelines said aspirin could be used as prophylaxis after myocardial infarction, but that it should be avoided in patients with recurrent hospitalisation for worsening heart failure.[37] However, the ESC guidelines published in 2008 do not comment on the use of ACE inhibitors and aspirin. They note that antiplatelet agents are not as effective as warfarin in reducing the risk of thromboembolism in patients with atrial fibrillation and that there is no evidence that antiplatelet drugs reduce atherosclerotic risk in patients with heart failure.[38] NICE guidelines in the UK say that all patients with heart failure due to left ventricular systolic dysfunction should be considered for treatment with an ACE inhibitor, and that aspirin (75 to 150 mg daily) should be prescribed for patients with the combination of heart failure and atherosclerotic arterial disease (including coronary heart disease).[39] Data from ongoing randomised studies may provide further insight. Until these are available, low-dose aspirin and ACE inhibitors may continue to be used where there is a clear indication for both.

An increased risk of deterioration in **renal function** or **acute renal failure** appears to occur rarely with the combination of aspirin and ACE inhibitors. The routine monitoring of renal function, which is advised with ACE inhibitors, should be sufficient to detect any interaction.

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ACE inhibitors + Azathioprine

Anaemia has been seen in patients given azathioprine with enalapril or captopril. Leucopenia occasionally occurs when captopril is given with azathioprine.

Clinical evidence

(a) Anaemia

Nine out of 11 kidney transplant patients taking ACE inhibitors (**enalapril** or **captopril**) had a fall in their haematocrit from 34% to 27%, and a fall in their haemoglobin from 11.6 g/dL to 9.5 g/dL when ciclosporin was replaced by azathioprine. Two patients were switched back to ciclosporin, and had a prompt rise in their haematocrit. Another 10 patients taking both

drugs similarly developed a degree of anaemia when compared with 10 patients not taking an ACE inhibitor (haematocrit of 33% compared with 41%, and a haemoglobin of 11.5 g/dL compared with 13.9 g/dL).[1] A later study by the same group of workers (again in patients taking **enalapril** or **captopril**) confirmed these findings; however, no pharmacokinetic interaction was found between **enalapril** and azathioprine.[2]

(b) Leucopenia

A patient whose white cell count fell sharply when taking both **captopril** 50 mg daily and azathioprine 150 mg daily, did not develop leucopenia when each drug was given separately.[3] Another patient who was given **captopril** (increased to 475 mg daily [sic] then reduced to 100 mg daily) immediately after discontinuing azathioprine, developed leucopenia. She was later successfully treated with **captopril** 4 to 6 mg daily [sic].[4] Other patients have similarly developed leucopenia when given both drugs:[5,6] in one case this did not recur when the patient was rechallenged with **captopril** alone (at a lower dose).[6]

Mechanism

The anaemia appears to be due to suppression of erythropoietin by the ACE inhibitors, and azathioprine may cause patients to be more susceptible to this effect.[2] The cause of the leucopenia is unknown. It may just be due to the additive effects of both drugs.

Importance and management

Anaemia caused by captopril and enalapril has been seen in kidney transplant patients and in dialysis patients (see 'ACE inhibitors or Angiotensin II receptor antagonists + Epoetins', p.26). The evidence that this effect can be potentiated by azathioprine is limited, but it would be prudent to monitor well if these drugs are used together.

The evidence that the concurrent use of ACE inhibitors and azathioprine increases the risk of leucopenia is also limited. However, the UK manufacturer of captopril recommends that it should be used with extreme caution in patients receiving **immunosuppressants**, especially if there is renal impairment. They advise that in such patients differential white blood cell counts should be performed before starting captopril, then every 2 weeks in the first 3 months of treatment, and periodically thereafter.[7] The UK manufacturers of a number of other ACE inhibitors also state that the use of ACE inhibitors with **cytostatic** or **immunosuppressive drugs** may lead to an increased risk of leucopenia. For other potential interactions with ACE inhibitors that might lead to an increased risk of leucopenia, see also 'ACE inhibitors + Allopurinol', p.13, and 'ACE inhibitors + Procainamide', p.37.

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ACE inhibitors + Beta blockers

The combination of an ACE inhibitor with a beta blocker is in established clinical use. Enhanced blood pressure-lowering effects occur, as would be expected. Although not all combinations have been studied, no clinically significant pharmacokinetic interactions appear to occur between the ACE inhibitors and beta blockers.

Clinical evidence

(a) Atenolol

In a double-blind, crossover study in hypertensive subjects, the combination of atenolol 50 mg daily and **enalapril** 20 mg daily increased the hypotensive effect of either drug alone, but the effect was 30 to 50% less than additive.[1]

(b) Bisoprolol

In a single-dose, placebo-controlled, crossover study in 16 healthy men, bisoprolol 5 mg given with **imidapril** 10 mg did not significantly influence the pharmacokinetics of its active metabolite imidaprilat, and the pharmacodynamic effects, including blood pressure and heart rate reductions, were mainly additive.[2]

(c) Propranolol

In 10 healthy subjects propranolol 80 mg three times daily did not affect the pharmacokinetics of a single 20-mg dose of **quinapril**.[3] In another study the pharmacokinetics of **ramipril** 5 mg daily were unaffected by propranolol 40 mg twice daily.[4] Similarly, the manufacturer of **fosinopril** reports that the bioavailability of fosinoprilat, its active metabolite, was not altered by propranolol.[5,6] Another study found no significant pharmacokinetic interaction between **cilazapril** 2.5 mg daily and propranolol 120 mg daily in healthy subjects, but the reductions in blood pressure were roughly doubled and long-lasting in 6 healthy subjects and in 13 patients with hypertension.[7,8] A later report by the same authors found similar results in 17 patients.[9]

Mechanism, importance and management

Both ACE inhibitors and beta blockers lower blood pressure by different mechanisms, and therefore the enhanced blood pressure-lowering effects of the combination would be expected. No pharmacokinetic interactions have been demonstrated. The combination of an ACE inhibitor and a beta blocker is clinically useful in a number of cardiovascular disorders.

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ACE inhibitors + Calcium-channel blockers

The combination of an ACE inhibitor and a dihydropyridine calcium-channel blocker is in established clinical use for hypertension, and, although only certain combinations have been studied, no clinically significant pharmacokinetic interactions appear to occur between these groups of drugs.

Clinical evidence

(a) Amlodipine

A study in 12 healthy subjects indicated that there was no pharmacokinetic interaction between single doses of amlodipine 5 mg and **benazepril** 10 mg.[1]

(b) Felodipine

In healthy subjects, no pharmacokinetic interaction occurred between single doses of felodipine 10 mg and **ramipril** 5 mg. The blood pressure-lowering effect of the combination was greater, and **ramipril** attenuated the reflex tachycardia caused by felodipine.[2]

(c) Manidipine

In a single-dose crossover study in 18 healthy subjects, the concurrent use of manidipine 10 mg and **delapril** 30 mg did not significantly alter the pharmacokinetics of either drug or their main metabolites.[3]

(d) Nicardipine

In a study in 12 patients with hypertension taking **enalapril** 20 mg daily, the addition of nicardipine 30 mg three times daily for 2 weeks did not alter the pharmacokinetics of **enalapril**.[4] The manufacturer of **spirapril** briefly noted in a review that the concurrent use of spirapril and nicardipine increased **spirapril** plasma levels by about 25% and increased the levels of its active metabolite, spiraprilat, by about 45%. The bioavailability of nicardipine was reduced by 30%. It was assumed that the interaction took place at the absorption site. However, the changes were not considered clinically relevant.[5]

(e) Nifedipine

No evidence of either a pharmacokinetic or adverse pharmacodynamic interaction was seen in 12 healthy subjects given single doses of slow-release nifedipine 20 mg and **lisinopril** 20 mg; the effects on blood pressure were additive.[6] Similarly, in healthy subjects, there was no pharmacokinetic interaction between single doses of slow-release nifedipine 20 mg and **benazepril** 10 mg; the effects on blood pressure were additive and the tachycardic effect of nifedipine was attenuated by benazepril.[7] The manufacturer of **fosinopril** notes that the bioavailability of fosinoprilat, the active metabolite of **fosinopril**, was not altered by nifedipine.[8,9] Similarly, the manufacturer of **moexipril** notes that in healthy subjects no clinically important pharmacokinetic interaction occurred between **moexipril** and nifedipine.[10]

(f) Nilvadipine

In a single-dose, placebo-controlled study in 16 healthy subjects, no pharmacokinetic interaction occurred between nilvadipine 8 mg and **imidapril** 10 mg, and the pharmacodynamic effects, including the reduction in blood pressure and the decrease in total peripheral resistance, were mostly additive.[11]

Mechanism

No pharmacokinetic interactions are expected. Enhanced blood pressure-lowering effects occur, as would be expected.

Importance and management

No important pharmacokinetic interactions have been demonstrated. The combination of an ACE inhibitor and a dihydropyridine calcium-channel blocker is clinically useful in the treatment of hypertension. A number of products combining an ACE inhibitor with a calcium-channel blocker are available. It is generally advised that these combination products are only used in patients who have already been stabilised on the individual components in the same proportions.

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8. Staril (Fosinopril sodium). E. R. Squibb & Sons Ltd. UK Summary of product characteristics, January 2009.
9. Monopril (Fosinopril sodium). Bristol-Myers Squibb Company. US Prescribing information, July 2008.
10. Perdix (Moexipril hydrochloride). UCB Pharma Ltd. UK Summary of product characteristics, April 2009.
11. Breithaupt-Grögler K, Ungethüm W, Meurer-Witt B, Belz GG. Pharmacokinetic and dynamic interactions of the angiotensin-converting enzyme inhibitor imidapril with hydrochlorothiazide, bisoprolol and nilvadipine. *Eur J Clin Pharmacol* (2001) 57, 275–84.

ACE inhibitors + Capsaicin

An isolated report describes a woman taking an ACE inhibitor who developed a cough each time she used a topical cream containing capsaicin.

Clinical evidence, mechanism, importance and management

A 53-year-old woman who had been taking an unnamed ACE inhibitor for several years, complained of cough each time she applied *Axsain*, a cream containing capsaicin 0.075%, to her lower extremities. Whether this reaction would have occurred without the ACE inhibitor was not determined,[1] but cough is a recognised adverse effect of ACE inhibitors and pre-treatment with an ACE inhibitor has been shown to enhance the cough caused by *inhaled* capsaicin.[1] Topical application of capsaicin may rarely result in coughing due to irritation of the mucous membranes of the respiratory tract.[2] This potential interaction is probably of little general clinical importance.

1. Hakas JF. Topical capsaicin induces cough in patient receiving ACE inhibitor. *Ann Allergy* (1990) 65, 322.
2. Axsain Cream (Capsaicin). Cephalon Ltd. UK Summary of product characteristics, July 2009.

ACE inhibitors + Cefradine

No clinically significant pharmacokinetic interaction appears to occur between captopril and cefradine.

Clinical evidence, mechanism, importance and management

No clinically significant pharmacokinetic interaction was noted in a single-dose study in 9 healthy subjects given captopril 25 mg and cefradine 500 mg.[1] Captopril and cefradine are both thought to be absorbed through common transport pathways, by intestinal peptide transporters, and as such it was considered that they might impair or delay the absorption of each other.[1] However, an *in vitro* study found that peptide transporters do not control intestinal absorption and renal reabsorption of ACE inhibitors and therefore other proteins or other mechanisms might be involved in the intestinal transport of ACE inhibitors.[2] No particular precautions seen necessary on concurrent use.

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ACE inhibitors + Clonidine

Potentiation of the antihypertensive effect of clonidine by ACE inhibitors can be clinically useful.[1] However, limited evidence suggests that the effects of captopril may be delayed when patients are switched from clonidine.[2] Note that sudden withdrawal of clonidine may cause rebound hypertension.

1. Catapres Tablets (Clonidine hydrochloride). Boehringer Ingelheim Ltd. UK Summary of product characteristics, July 2009.
2. Gröne H-J, Kirchertz EJ, Rieger J. Mögliche Komplikationen und Probleme der Captoprilthерapie bei Hypertonikern mit ausgeprägten Gefäßschäden. *Therapiewoche* (1981) 31, 5280–7.

ACE inhibitors + Colloids

Acute hypotension has been seen in a few patients taking enalapril when they were given a rapid infusion of albumin-containing stable plasma protein solution (SPPS). Another case occurred in an infant taking captopril when given albumin 4%. A few other cases have been described with gelatin-type colloids in patients taking ACE inhibitors (cilazapril, enalapril, lisinopril).

Clinical evidence

(a) Albumin

A woman taking **enalapril** 10 mg in the morning, underwent surgery for groin lymph node resection under spinal and general anaesthesia. When she was given a rapid infusion of 500 mL of the albumin solution, stable plasma protein solution (SPPS, *Commonwealth Serum Laboratories, Melbourne, Australia*), her pulse rose to 90 to 100 bpm and systolic blood pressure fell from 100 mmHg to 60 mmHg and a red flush was noted on all exposed skin. The blood pressure was controlled at 90 to 95 mmHg

with metaraminol 4.5 mg, given over 10 minutes. When the SPPS was finished, the blood pressure and pulse rate spontaneously restabilised.[1] SPPS is a 5% plasma protein solution prepared by the cold ethanol fractionation process and pasteurisation from human plasma (volunteer donors). It contains sodium octanoate as a stabiliser.[1] Two very similar cases have been recorded in patients taking **enalapril** when given SPPS.[2,3] The manufacturer of SPPS notes that **captopril** has also been involved in this hypotensive interaction.[4]

A 20-month-old infant taking **captopril** was haemodynamically stable for 35 minutes after induction of anaesthesia while awaiting a donor kidney, but then developed hypotension after a bolus dose of 20 mL of albumin 4% (*Albumex*) was given. This was reversed with dopamine infusion.[5]

(b) Gelatin-based colloids

A report describes 3 cases of severe hypotension in patients taking ACE inhibitors (**lisinopril**, **enalapril**) while undergoing joint replacement surgery, and after they had been given a gelatin-based plasma expander (*Gelofusin*), which contains 4% succinylated gelatin in saline. The hypotension was resistant to ephedrine and methoxamine, and responded to adrenaline (epinephrine) or dobutamine, which was required for 24 hours and 3 days, respectively, in two cases. Anaphylactoid reactions were excluded as a cause of the hypotension.[6] In another similar case, a patient taking **cilazapril** developed hypotension refractory to sodium chloride 0.9% after induction of anaesthesia, and this worsened when a gelatin-type colloid (*Gelafundina*) was given.[7]

Mechanism

Not fully established, but it is believed that SPPS contains low levels of pre-kallikrein activator, which stimulates the production of bradykinin, which can cause vasodilatation and hypotension. Normally the bradykinin is destroyed by kininase II (ACE), but this is delayed by the ACE inhibitor so that the hypotensive effects are exaggerated and prolonged.[3,8] In the case with albumin 4%, a sample of the albumin used was analysed, and it was found to contain less prekallikrein activating factor than maximum permissible levels.[5] It was suggested that the infusion of gelatin-based colloids somehow resulted in raised plasma kinin levels associated with inhibition of ACE.[6]

Importance and management

The interaction with SPPS would appear to be established and of clinical importance, and would apply to all ACE inhibitors. The author of one report suggested that if rapid expansion of intravascular volume is needed in patients taking ACE inhibitors, an artificial colloid might be a safer choice than SPPS.[1] The manufacturer of SPPS also recommended using an alternative plasma volume expander, including other albumin solutions.[4] It should be noted that following these reports SPPS was withdrawn from the Australasian market.[9] However, note that a case has also occurred with albumin 4%, and cases have also been attributed to synthetic colloid solutions containing gelatin. It may be that this is just an unpredictable effect of colloids in patients taking ACE inhibitors.

For discussion of the marked hypotension sometimes seen during induction of anaesthesia in patients taking ACE inhibitors, see also 'Anaesthetics, general + ACE inhibitors or Angiotensin II receptor antagonists', p.102.

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ACE inhibitors + Co-trimoxazole or Trimethoprim

Two reports describe serious hyperkalaemia, apparently caused by the use of trimethoprim with sulfamethoxazole, and enalapril or quinapril in association with renal impairment.

Clinical evidence

A 40-year-old woman with a lung transplant (taking ciclosporin, azathioprine, prednisolone, **enalapril**, gentamicin inhalation, salbutamol and acetylcysteine) developed life-threatening hyperkalaemia of 6.8 mmol/L when she was given high-dose co-trimoxazole 120 mg/kg daily for suspected pneumocystis pneumonia. The co-trimoxazole (sulfamethoxazole with trimethoprim) and **enalapril** were stopped and she was treated with sodium chloride 0.9%, mannitol and furosemide. After 12 hours her serum potassium had decreased to 4.6 mmol/L and she began to recover over a period of a week, but she then developed fatal septic shock with multi-organ failure.[1]

In another case, an elderly man taking **quinapril** 20 mg daily for essential hypertension was found to have hyperkalaemia (serum potassium 7 to 7.4 mmol/L) and azotaemia 20 days after starting to take co-trimoxazole for mild acute pyelonephritis. Co-trimoxazole and **quinapril** were stopped, and nifedipine was given to control blood pressure. The patient was given dextrose, insulin, sodium polystyrene sulfonate and calcium gluconate, and the azotaemia and hyperkalaemia resolved over 36 hours.[2]

Mechanism

Hyperkalaemia has been reported in patients receiving co-trimoxazole alone.[3] This is attributed to the trimethoprim component, which can have a potassium-sparing effect on the distal part of the kidney tubules. ACE inhibitors reduce aldosterone synthesis, which results in reduced renal loss of potassium. The interaction is probably due to the additive effects of these two mechanisms, compounded by impaired renal function.[1,2]

Importance and management

Clinical examples of this interaction seem to be few, but the possibility of hyperkalaemia with either trimethoprim or ACE inhibitors alone, particularly with other factors such as renal impairment, is well documented. Thus it may be prudent to monitor potassium levels if this combination is used. It has been suggested that trimethoprim should probably be avoided in elderly patients with chronic renal impairment taking ACE inhibitors, and that patients with AIDS taking an ACE inhibitor for associated nephropathy should probably discontinue the ACE inhibitor during the use of high-dose co-trimoxazole.[2]

1. Bugge JF. Severe hyperkalaemia induced by trimethoprim in combination with an angiotensin-converting enzyme inhibitor in a patient with transplanted lungs. *J Intern Med* (1996) 240, 249–52.
2. Thomas RJ. Severe hyperkalemia with trimethoprim-quinapril. *Ann Pharmacother* (1996) 30, 413–14.
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ACE inhibitors or Angiotensin II receptor antagonists + Dialysis or Transfusion membranes

An anaphylactoid reaction can occur in patients taking ACE inhibitors and possibly angiotensin II receptor antagonists within a few minutes of starting haemodialysis using high-flux polyacrylonitrile membranes ('AN69') or modified ST-AN69 membranes. Anaphylactoid reactions have also been reported in patients taking ACE inhibitors undergoing low-density lipoprotein apheresis.

Hypotensive reactions associated with blood transfusions through leucoreduction filters have occurred in patients taking ACE inhibitors.

Clinical evidence, mechanism, importance and management

(a) Apheresis

1. Low-density lipoprotein (LDL) apheresis. Anaphylactoid reactions occurred in 2 patients taking **captopril** or **enalapril** during removal of low-density lipoproteins (LDL apheresis) with dextran sulfate adsorption.[1] Further reactions were reported in 6 patients taking either **captopril** or **enalapril** and undergoing dextran sulfate apheresis. When the interval between the last dose of the ACE inhibitor and the apheresis was prolonged to 12 to 30 hours no further adverse reactions occurred.[2] However, other workers found lengthening the interval to be ineffective in one patient.[3]
A patient who experienced an anaphylactoid reaction while taking **ramipril** and undergoing dextran sulfate LDL apheresis took **losartan** 12.5 mg daily instead of ramipril without any reaction during the next four LDL apheresis procedures.[4] Another patient given **imidapril** had blurred vision and lacrimation with hypotension during dextran sulfate apheresis. Further study in this patient when given **losartan** 50 mg daily instead of **imidapril** found that during LDL apheresis, blood pressure reduction was mild and the patient did not experience noticeable adverse effects. The blood pressure reduction was attributed to the effect of **losartan** on angiotensin receptors, but as bradykinin levels were increased (by the **losartan**) this may also have contributed.[5] The authors concluded that low-dose **losartan** appears to be safe in patients undergoing LDL apheresis with dextran sulfate,[4,5] despite an increase in bradykinin levels.[5]
The manufacturer of **enalapril** suggests temporarily withholding the ACE inhibitor before each apheresis,[6] but other manufacturers of ACE inhibitors recommend using a different class of antihypertensive drug[7,8] or changing the method of lipoprotein reduction.[7,9]

2. Therapeutic plasma exchange. In a review of 299 patients undergoing therapeutic plasma exchange, all 14 patients taking ACE inhibitors experienced hypotension and/or flushing. The ACE inhibitors taken were **enalapril** (8 patients), **captopril** (6 patients); 2 of the patients also received **lisinopril** or **benazepril**. In addition, 20 of 285 patients not receiving ACE inhibitors experienced similar adverse effects. Therefore the patients taking ACE inhibitors accounted for 14 of 34 (41%) of patients experiencing these reactions. The 14 patients taking ACE inhibitors underwent 186 apheresis procedures. In 53 of these procedures an ACE inhibitor was given in the 24 hours before the procedure and hypotension and/or flushing occurred in 41 of the 53 procedures. Six of the 14 patients also underwent apheresis while not receiving an ACE inhibitor. One patient experienced transient hypotension; no reactions occurred in the other 5 patients. The authors recommended that ACE inhibitors should be withheld for at least 24 hours before apheresis.[10]

(b) High-flux dialysis

1. ACE inhibitors. In a retrospective study, 9 of 236 haemodialysis patients treated with high-flux polyacrylonitrile membranes ('AN69') were found to have had anaphylactoid reactions (severe hypotension, flushing, swelling of face and/or tongue, and dyspnoea) within 5 minutes of starting haemodialysis. Treatment with an ACE inhibitor had been recently started in all 9 patients (7 taking **enalapril**, the other 2 taking **captopril** or **lisinopril**). The anaphylactoid reactions resolved in all 6 patients who discontinued the ACE inhibitor. Two other patients were given a filter rinsing procedure (the 'Bioprime' rinse method) and a new dialysis membrane, and in the final patient further anaphylactoid reactions were prevented by cellulose-triacetate haemofiltration while the ACE inhibitor was continued.[11] Similar reactions have been reported elsewhere and are thought to be bradykinin mediated.[12-14]
The CSM in the UK has advised that the combination of ACE inhibitors and such membranes should be avoided, either by substituting an alternative membrane or an alternative antihypertensive drug.[15] Modified AN69 membranes (surface-treated AN69 membranes; ST-AN69) which reduce the generation of bradykinin have been developed and used in patients taking ACE inhibitors. However, there are reports of anaphylactoid reactions in 5 patients taking ACE inhibitors during haemodialysis with these modified membranes.[16,17]

2. Angiotensin II receptor antagonists. In a multicentre study, 324 of 406 haemodialysis patients who were given an initial dose of **losartan** 25 mg daily, increased after one week to 50 mg daily for 6 months completed the study. Ninety-six patients were dialysed with AN69 membranes. Two of these patients had possible anaphylactoid reactions. One of them became hypotensive 13 minutes after the start of a haemodialysis session and developed malaise, nausea, vomiting, dysaesthesia and generalised heat sensation, severe enough to stop the dialysis session. The second patient had mild generalised heat sensation and dysaesthesia within one minute of the start of haemodialysis but did not require discontinuation of the dialysis. The symptoms did not occur on subsequent haemodialysis even though **losartan** was continued and an AN69 membrane was used. Neither patient developed signs of hypersensitivity such as oedema, bronchospasm, pruritus, or urticaria. Also, 9 of the patients who had an anaphylactoid reaction while taking ACE inhibitors during haemodialysis with AN69 membranes did not have anaphylactoid reactions when taking **losartan** and dialysed with these membranes.[18] Another patient taking **losartan** and undergoing haemodialysis developed breathlessness and became agitated with profuse sweating about one hour after the start of his first dialysis after changing from a *Haemophan* (COBE 400) membrane to an **AN69 membrane** in an attempt to improve the efficacy of dialysis.[19] However, it has been suggested that in this latter case, the adverse effects were not the result of an anaphylactoid reaction mediated by bradykinin.[20]
There are few reports of anaphylactoid-like reactions involving angiotensin II receptor antagonists and the use of AN69 membranes. The authors of one report found **losartan** to be a safe drug in haemodialysis patients and its use with AN69 was not associated with an increase in anaphylactoid reactions.[18] However, other authors advise caution.[19,20]

(c) Transfusion reactions

A report describes 8 patients receiving ACE inhibitors and blood transfusions through bedside **leucoreduction filters** who experienced severe hypotensive reactions. The reactions were attributed to bradykinin generation during blood filtration and prevention of bradykinin breakdown due to the ACE inhibitors. Six of the patients tolerated subsequent transfusions, but 3 patients had discontinued their medication the day before the planned transfusion and one received washed (plasma-depleted) components. One patient experienced a second reaction, but then received washed red cells and had no reaction.[21]

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8. Perdix (Moexipril hydrochloride). UCB Pharma Ltd. UK Summary of product characteristics, April 2009.
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ACE inhibitors + Diuretics; Loop, Thiazide and related

The combination of captopril or other ACE inhibitors with loop or thiazide diuretics is normally safe and effective, but first-dose hypotension (dizziness, lightheadedness, fainting) can occur, particularly if the dose of diuretic is high, and often in association with various predisposing conditions. Renal impairment, and even acute renal failure, have been reported. Diuretic-induced hypokalaemia may still occur when ACE inhibitors are used with these potassium-depleting diuretics.

Clinical evidence

(a) First dose hypotensive reaction

The concurrent use of **captopril** or other ACE inhibitors and loop or thiazide diuretics is normally safe and effective, but some patients experience first-dose hypotension (i.e. dizziness, lightheadedness, fainting) after taking the first one or two doses of the ACE inhibitor. This appears to be associated with, and exaggerated by, certain conditions (such as heart failure, renovascular hypertension, haemodialysis, high levels of renin and angiotensin, low-sodium diet, dehydration, diarrhoea or vomiting) and/or hypovolaemia and sodium depletion caused by diuretics, particularly in high doses. A study describes one woman whose blood pressure of 290/150 mmHg did not respond to a 10-mg intravenous dose of **furosemide**. After 30 minutes she was given **captopril** 50 mg orally and within 45 minutes her blood pressure fell to 135/60 mmHg and she required an infusion of saline to maintain her blood pressure.[1] In another study, a man taking **captopril** developed severe postural hypotension shortly after **furosemide** given.[2]

Starting with a low dose of the ACE inhibitor reduces the risk of first-dose hypotension. In a study in 8 patients with hypertension who had been taking a diuretic (mainly **furosemide** or **hydrochlorothiazide**) for at least 4 weeks, **captopril** was started in small increasing doses from 6.25 mg. Symptomatic postural hypotension was seen in 2 of the 8 patients, but it was only mild and transient.[3]

Hypotension is more common in patients with heart failure who are taking large doses of diuretics. In a study in 124 patients with severe heart failure, all taking **furosemide** (mean dose 170 mg daily; range 80 to 500 mg daily) and 90 also receiving the potassium-sparing diuretic spironolactone, the addition of **captopril** caused transient symptomatic hypotension in 44% of subjects. The **captopril** dose had to be reduced, and in 8 patients it was later discontinued. In addition, 4 patients developed symptomatic hypotension after one to 2 months of concurrent use, and **captopril** was also discontinued in these patients.[4]

There is some evidence that in patients with heart failure the incidence of marked orthostatic hypotension requiring treatment discontinuation in the first 36 hours was lower with **perindopril** 2 mg daily than **captopril** 6.25 mg three times daily (6 of 357 cases versus 16 of 368 cases, respectively).[5] However, the effect of other drugs, such as antihypertensives, vasodilators and diuretics, taken by the patients was not assessed in this study.

(b) Hypokalaemia

In one study, the reduction in plasma potassium was greater with **hydrochlorothiazide** 25 mg daily than with **hydrochlorothiazide** given with **cilazapril** 2.5 mg daily, showing that cilazapril reduced the potassium-depleting effect of **hydrochlorothiazide**.[6] In a placebo-controlled study in hypertensive patients given **quinapril** 2.5 mg, 10 mg or 40 mg daily, **hydrochlorothiazide** 6.25 mg, 12.5 mg, or 25 mg daily, or one of nine possible combinations of **quinapril** and **hydrochlorothiazide** with these doses, minimal changes in serum potassium occurred with **quinapril** or placebo alone. The percentage of patients with decreases in serum potassium of 0.5 mmol or more increased with dose of **hydrochlorothiazide** alone. The degree of attenuation of the hypokalaemic effect of **hydrochlorothiazide** was related to the dose of **quinapril**, with the 2.5-mg dose attenuating the hypokalaemic effect of **hydrochlorothiazide** 6.25 or 12.5 mg, but not that of **hydrochlorothiazide** 25 mg. At doses of **quinapril** 40 mg daily, dose-related decreases in serum potassium were not apparent.[7]

In one analysis, 7 of 21 patients taking potassium-depleting diuretics given ACE inhibitors for heart failure developed hypokalaemia. This was corrected by potassium supplementation in 2 cases, an increase in the ACE inhibitor dose in 3 cases, and the use of a potassium-sparing diuretic in the remaining 2 cases.[8] In another report, a woman taking **furosemide** 80 to 120 mg daily remained hypokalaemic despite also taking **ramipril** 10 mg daily and spironolactone 50 to 200 mg daily.[9] However, note that the addition of spironolactone to ACE inhibitors and loop or thiazide diuretics has generally resulted in an increased incidence of hyperkalaemia. For further information on this effect, see 'ACE inhibitors + Diuretics; Potassium-sparing', p.25.

(c) Hyponatraemia

An isolated report describes a patient taking **enalapril** 20 mg daily and atenolol 100 mg daily who developed severe hyponatraemia 3 days after **bendroflumethiazide** 10 mg daily was started. However, on two other occasions she only developed mild hyponatraemia when given **bendroflumethiazide** alone.[10] An earlier study reported changes in sodium balance due to **captopril** in all 6 patients with renovascular hypertension and in 11 of 12 patients with essential hypertension: sodium loss occurred in 12 of the 18 patients.[1]

(d) Renal impairment

The risk of ACE inhibitor-induced renal impairment in patients with or without renovascular disease can be potentiated by diuretics.[11-14] In an analysis of 74 patients taking **captopril** or **lisinopril**, reversible acute renal failure was more common in those who were also taking a diuretic (**furosemide** and/or **hydrochlorothiazide**) than those who were not (11 of 33 patients compared with 1 of 41 patients).[13] Similarly, in a prescription-event monitoring study, **enalapril** was associated with raised creatinine or urea in 75 patients and it was thought to have contributed to the deterioration in renal function and subsequent deaths in 10 of these patients. However, 9 of these 10 were also receiving loop or thiazide diuretics, sometimes in high doses.[15] Retrospective analysis of a controlled study in patients with hypertensive nephrosclerosis identified 8 of 34 patients who developed reversible renal impairment when given **enalapril** and various other antihypertensives including a diuretic (**furosemide** or **hydrochlorothiazide**). In contrast, 23 patients given placebo and various other antihypertensives did not develop renal impairment. Subsequently, **enalapril** was tolerated by 7 of the 8 patients without deterioration in renal function and 6 of these patients later received diuretics.[16] One patient was subsequently given **enalapril** with recurrence of renal impairment, but discontinuation of the diuretics (**furosemide**, **hydrochlorothiazide**, and triamterene) led to an improvement in renal function despite the continuation of **enalapril**.[17]

Renal impairment in patients taking ACE inhibitors and diuretics has also been described in patients with heart failure. A patient with congestive heart failure and pre-existing moderate renal impairment developed acute non-oliguric renal failure while taking **enalapril** 20 mg daily and **furosemide** 60 to 80 mg daily, which resolved when the sodium balance was restored.[18] In a study involving 90 patients with severe congestive heart failure who were receiving **furosemide** and spironolactone, a decline in renal function occurred in 18 patients during the first month after initiation of **captopril**; mean serum creatinine levels rose from 220 to 300 micromol/L. All the patients were receiving high daily doses of **furosemide** and all had renal impairment before receiving the first dose of **captopril**.[4]

Acute, fatal, renal failure developed in 2 patients with cardiac failure within 4 weeks of starting to take **enalapril** with **furosemide**, and in 2 similar patients renal impairment developed over a longer period.[19] Reversible renal failure developed in a patient with congestive heart failure when **captopril** and **metolazone** were given.[20]

(e) Pharmacokinetic and diuresis studies

1. Furosemide. A study in healthy subjects given single doses of **enalapril** and furosemide found no evidence of any pharmacokinetic interaction between these drugs.[21] Another study in hypertensive patients found that **captopril** did not affect the urinary excretion of furosemide, nor its subsequent diuretic effects.[22] However, a further study in healthy subjects found that, although **captopril** did not alter urinary excretion of furosemide, it did reduce diuresis.[23] Yet another study in healthy subjects found that **captopril** reduced the urinary excretion of furosemide, and halved the diuretic response during the first 20 minutes and decreased the natriuretic response to almost 30%, whereas **enalapril** and **ramipril** did not significantly alter

the diuretic effects of furosemide.[24] In one single-dose study in healthy subjects the concurrent use of **benazepril** and furosemide reduced the urinary excretion of furosemide by 10 to 20%, whereas **benazepril** pharmacokinetics were unaffected.[25] In one study, **lisinopril** did not alter the plasma levels or urinary excretion of furosemide, nor did it alter urinary electrolyte excretion.[26] Similarly, furosemide did not affect the pharmacokinetics of **lisinopril** either in single-dose or multiple-dose regimens.[27]

2. Hydrochlorothiazide. In a single-dose, randomised, crossover study in 19 elderly patients the pharmacokinetics of **enalapril** 10 mg were unaffected by hydrochlorothiazide 25 mg. However, there was a significant reduction in renal clearance and a significant increase in the AUC of its metabolite, enalaprilat, resulting in higher serum levels of the active drug. This acute interaction was not thought to be clinically significant for long-term use.[28]

No pharmacokinetic interaction occurred between **cilazapril** and hydrochlorothiazide in healthy subjects or patients with hypertension.[6] Similarly, no significant pharmacokinetic interaction occurred between **imidapril** and hydrochlorothiazide in healthy subjects[29] and neither **captopril** nor **ramipril** altered the diuresis induced by hydrochlorothiazide.[24]

The manufacturer of **spirapril** briefly noted in a review that there was no clinically relevant pharmacokinetic interaction between spirapril and hydrochlorothiazide.[30] Furthermore no pharmacokinetic interaction was found when **spirapril** and hydrochlorothiazide were given together as a bi-layer tablet.[31] In a single-dose study in healthy subjects there was no clinically important pharmacokinetic interaction when **moexipril** was given with hydrochlorothiazide.[32]

Mechanism

The first dose hypotension interaction is not fully understood. One suggestion is that if considerable amounts of salt and water have already been lost as a result of using a diuretic, the resultant depletion in the fluid volume (hypovolaemia) transiently exaggerates the hypotensive effects of the ACE inhibitor.

The cases of hypokalaemia are simply a result of the potassium-depleting effects of the diuretics outweighing the potassium-conserving effects of the ACE inhibitor. The converse can also occur.

Thiazides can cause hyponatraemia, but the enhanced effect may have been due to an alteration in renal haemodynamics caused by the ACE inhibitor: sustained angiotensin-converting enzyme blockade can produce natriuresis.[1]

Marked decreases in blood pressure may affect renal function, and in addition, the renin-angiotensin system plays an important role in the maintenance of the glomerular filtration rate when renal artery pressure is diminished.[12] However, diuretic-induced sodium depletion may also be an important factor in the renal impairment sometimes observed with ACE inhibitors.

Importance and management

The **first-dose hypotension** interaction between ACE inhibitors and diuretics is well established. The BNF in the UK notes that the risk is higher when the dose of diuretic is greater than furosemide 80 mg daily or equivalent,[33] and suggests that, in patients taking these doses of diuretics, ACE inhibitors should be initiated under close supervision, and consideration should be given to temporarily stopping the diuretic or reducing its dose at least 24 hours before the ACE inhibitor is added. If this is not considered clinically appropriate, the response to the first dose of the ACE inhibitor should be monitored for at least 2 hours, or until blood pressure has stabilised. In all patients taking diuretics, an ACE inhibitors should be started at a very low dose, even in patients at low risk (e.g. those with uncomplicated essential hypertension taking low-dose thiazides). To be on the safe side, all patients should be given a simple warning about what can happen and what to do when they first start concurrent use. The immediate problem (dizziness, lightheadedness, faintness), if it occurs, can usually be solved by the patient lying down. Taking the first dose of the ACE inhibitor just before bedtime is also preferable. Any marked hypotension is normally transient, but if problems persist it may be necessary temporarily to reduce the diuretic dose. There is usually no need to avoid the combination just because an initially large hypotensive response has occurred. A number of products combining an ACE inhibitor with a thiazide diuretic are available for the treatment of hypertension. These products should be used only in those patients who have been stabilised on the individual components in the same proportions.

The use of ACE inhibitors in patients taking potassium-depleting diuretics does not always prevent **hypokalaemia** developing. Serum potassium should be monitored.

There is only one isolated report of **hyponatraemia**, but be aware that ACE inhibitors may affect the natriuresis caused by diuretics.

The cases of **renal impairment** cited emphasise the need to monitor renal function in patients taking ACE inhibitors and diuretics. If increases in blood urea and creatinine occur, a dose reduction and/or discontinuation of the diuretic and/or ACE inhibitor may be required. In a statement, the American Heart Association comments that acute renal failure complicating the use of an ACE inhibitor is almost always reversible and repletion of extracellular fluid volume and discontinuation of the diuretic is the most effective approach. In addition, withdrawing the interacting drugs, supportive management of fluid and electrolytes, and temporary dialysis, where indicated, are the mainstays of treatment.[14] The concurrent use of ACE inhibitors, diuretics and NSAIDs may be particularly associated with an increased risk of renal failure, see 'ACE inhibitors + NSAIDs', p.32. The possibility of undiagnosed renal artery stenosis should also be considered.

None of the **pharmacokinetic** changes observed appear to be clinically significant.

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ACE inhibitors + Diuretics; Potassium-sparing

The concurrent use of ACE inhibitors and potassium-sparing diuretics (e.g. amiloride), including the aldosterone antagonists (eplerenone, spironolactone) can result in clinically relevant or severe hyperkalaemia, particularly if other important risk factors are present.

Clinical evidence

(a) Amiloride

The serum potassium levels of 2 patients taking furosemide and unnamed potassium-sparing diuretics and potassium supplements rose by 18% and 24%, respectively, when they were given **captopril** 37.5 to 75 mg daily. The rises occurred within one or two days. No clinical signs or symptoms of hyperkalaemia were seen, but one of the patients had an increase in serum potassium to above the upper limits of normal.[1] In a post-marketing survey, 2 patients who had **enalapril**-associated renal impairment and died were also receiving amiloride and furosemide; one was also taking potassium supplements.[2] Four patients with diabetes, with some renal impairment, developed life-threatening hyperkalaemia with severe cardiac arrhythmias and deterioration of renal function, within 8 to 18 days of starting to take amiloride with hydrochlorothiazide and **enalapril**. Two suffered fatal cardiac arrests. Potassium levels were between 9.4 and 11 mmol/L. A fifth diabetic patient with normal renal function developed hyperkalaemia soon after receiving amiloride with hydrochlorothiazide and **captopril**.[3] A further case of hyperkalaemia and cardiac arrest was associated with **enalapril** and furosemide with amiloride.[4] In a brief report, the manufacturers of **enalapril** noted that, of 47 serious cases of hyperkalaemia, 25 patients were taking one or more (unnamed) potassium-sparing drugs.[5]

However, a retrospective comparison of 35 patients with congestive heart failure found no differences in the serum potassium levels of 16 patients taking furosemide, amiloride and **enalapril**, when compared with another group of 19 patients taking furosemide and amiloride alone. Patients were excluded from the comparison if they had significant renal impairment or were taking other drugs likely to affect serum potassium.[6]

(b) Eplerenone

In the large Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS)[7] the rate of serious hyperkalaemia (defined as serum potassium 6 mmol/L or greater) was 5.5% in patients randomised to eplerenone 25 mg to 50 mg daily (mean 43 mg daily[8]) compared with 3.9% in those receiving placebo: this represented a 1.4-fold increase. More eplerenone recipients required hospitalisation for serious hyperkalaemia than placebo recipients (12 versus 3). The risk of serious hyperkalaemia was increased in those with a baseline creatinine clearance of less than 50 mL/minute (10.1% in the eplerenone group and 5.9% in the placebo group). Eplerenone reduced the risk of serious hypokalaemia (defined as serum potassium 3.5 mmol/L or less) by 60% (8.4% versus 13.1%). About 86% of patients in this study were also receiving an ACE inhibitor or an angiotensin II receptor antagonist, and about 60% were receiving a (loop[8]) diuretic.[7] However, the US manufacturer states that the rate of maximum potassium levels greater than 5.5 mmol/L were similar in EPHESUS regardless of the use of ACE inhibitor or angiotensin II receptor antagonist.[8] Nevertheless, they mention another study in diabetics with microalbuminuria, where a higher dose of eplerenone 200 mg given with **enalapril** 10 mg increased the frequency of hyperkalaemia (defined as serum potassium greater than 5.5 mmol/L) from 17% with enalapril alone to 38% with the combination: this represented a 2.2-fold increase.[8]

In another study in 153 patients with left ventricular hypertrophy given eplerenone 200 mg daily, **enalapril** 40 mg daily, or eplerenone 200 mg with **enalapril** 10 mg daily, serious hyperkalaemia (maximum plasma potassium level 6 mmol/L or greater) occurred in 7 patients taking eplerenone (10.9%), 2 taking **enalapril** (2.8%) and 3 patients taking eplerenone with **enalapril** (4.5%). Three patients in the eplerenone group, but none in the **enalapril** or **enalapril** with eplerenone groups were withdrawn because of hyperkalaemia. Some patients were also given hydrochlorothiazide at week 8, but any contribution of the thiazide to the effects on potassium levels was not noted.[9] Consider also 'ACE inhibitors + Diuretics; Loop, Thiazide and related', p.23.

(c) Spironolactone

Twenty-five of 262 patients taking ACE inhibitors and spironolactone, and admitted to hospital for medical emergencies, were found to have serious hyperkalaemia (defined as serum potassium levels greater than 6 mmol/L: 11 patients had levels of at least 8 mmol/L). These 25 patients were elderly (mean age 74 years) and being treated for hypertension, heart failure, diabetic nephropathy, proteinuria, or nephrotic syndrome; 22 had associated renal impairment and 12 had signs of volume depletion. Concurrent use of the ACE inhibitor and spironolactone had been started an average of 25 weeks before admission. The ACE inhibitors involved were **enalapril**, **captopril**, **lisinopril** or **perindopril,** and the average dose of spironolactone used was 57 mg daily; 10 patients were also receiving a loop or thiazide diuretic. Nineteen patients had ECG changes associated with hyperkalaemia; 2 of them died, another 2 required temporary pacing for third-degree heart block, and 2 others survived after sustained ventricular tachycardia and fibrillation. Of the 19 patients with ECG changes, 17 required at least one haemodialysis session and 12 were admitted to intensive care.[10] Other authors reported a higher 36% incidence of hyperkalaemia (serum potassium levels greater than 5 mmol/L) in 42 patients hospitalised for heart failure and prescribed spironolactone. It was suggested that this may be due to the excessively large doses of spironolactone prescribed,[11] although the specific doses were not mentioned.

Similar risk factors were found in an analysis of 44 patients with congestive heart failure who were taking spironolactone and ACE inhibitors or angiotensin II receptor antagonists, and were admitted for treatment of life-threatening hyperkalaemia. Their mean age was 76 years, the mean dose of spironolactone was 88 mg daily (range 25 to 200 mg daily) and 40 patients also received loop diuretics. In addition, 35 patients had type 2 diabetes. Haemodialysis was given to 37 patients, but in 6 patients renal function did not recover and 2 patients developed fatal complications.[12] A prospective 3-month study of patients who developed hyperkalaemia (potassium levels at least 6 mmol/L) while in hospital identified 112 patients; 40 of these cases (36%) were considered to be drug-related. Eight patients were receiving spironolactone with an ACE inhibitor.[13] A study in patients with chronic heart failure taking spironolactone 25 or 50 mg daily, furosemide and either **enalapril**, candesartan, or losartan, for 12 months, found that hyperkalaemia occurred in about 9% of patients and hypokalaemia in about 5% of patients.[14] A number of other cases of serious hyperkalaemia have been described in patients taking ACE inhibitors (**captopril**, **enalapril**, **lisinopril**), spironolactone, and loop (furosemide or bumetanide) or thiazide (hydroflumethiazide) diuretics.[2,15-19] Many of the patients were elderly and were receiving spironolactone 50 to 100 mg daily,[2,15,18] but one diabetic patient with moderate renal impairment was receiving just 25 mg of spironolactone daily.[17] In one report, the 4 cases had associated **enalapril**-induced deterioration in renal function and died.[2] Another patient died from complete heart block.[15]

One of the factors that affects the incidence of hyperkalaemia appears to be the dose of spironolactone. In a preliminary investigation for the Randomised Aldactone Evaluation Study (RALES), 214 patients with congestive heart failure taking an ACE inhibitor and a loop diuretic with or without digitalis, were randomised to receive placebo or various doses of spironolactone for 12 weeks. The incidence of hyperkalaemia (defined as serum potassium level of 5.5 mmol/L or greater) was 5% for the placebo group, whereas it was 5%, 13%, 20%, and 24% when spironolactone was given in single daily doses of 12.5 mg, 25 mg, 50 mg, or 75 mg, respectively.[20] The main RALES study involving 1663 patients found a 30% reduction in the risk of mortality in patients with severe heart failure when they were given spironolactone in addition to treatment including an ACE inhibitor, a loop diuretic and in most cases digoxin. During the first year of follow-up, the median creatinine concentration in the spironolactone group increased by about 4 to 9 micromol/L and the median potassium level increased by 0.03 mmol/L, but there was a low incidence of serious hyperkalaemia (2% in the spironolactone group compared with 1% in the placebo group). However, the dose of spironol-

actone was fairly low (mean dose 26 mg daily; range 25 mg every other day to 50 mg daily depending on serum potassium levels and response). In addition, patients with a serum creatinine of more than 221 micromol/L or a serum potassium of more than 5 mmol/L were excluded.[21] In a Canadian population-based time-series analysis, the increase in use of spironolactone for heart failure in patients taking ACE inhibitors after publication of the RALES study was found be associated with 50 additional hospitalisations for hyperkalaemia for every 1000 additional prescriptions for spironolactone, and there was a 6.7-fold increase in the number of patients dying from hyperkalaemia. The authors say that spironolactone-related hyperkalaemia is a much greater problem in every day practice than in the setting of a clinical study, and give a number of reasons for this including, less frequent monitoring of potassium levels, the presence of conditions predisposing to hyperkalaemia, failure to detect subsequent development of renal impairment, inappropriately high doses of spironolactone, increase in dietary potassium intake, and the use of spironolactone in heart failure with causes not included in the RALES study.[22] In another study, the use of spironolactone with ACE inhibitors in patients with class IV chronic heart failure was associated with a 14.6 odds ratio for developing hyperkalaemia when compared with ACE inhibitors alone. Predictors for hyperkalaemia included increases in creatinine following treatment, and diabetes.[23]

(d) Triamterene

A retrospective analysis found that **captopril**, given to 6 patients taking *Dyazide* (hydrochlorothiazide with triamterene), had not increased the potassium levels.[24]

Mechanism

ACE inhibitors reduce the levels of aldosterone, which results in the retention of potassium. This would be expected to be additive with the potassium-retaining effects of amiloride and triamterene and aldosterone antagonists such as spironolactone and eplerenone, leading to hyperkalaemia, but usually only if other risk factors are present (see *Importance and management* below).

Importance and management

Hyperkalaemia with ACE inhibitors and potassium-sparing diuretics, and particularly the aldosterone antagonist spironolactone, is well documented and well established. If it occurs it can be serious and potentially life threatening. Its incidence depends on the presence of other risk factors, and clinically important hyperkalaemia usually only appears to develop if one or more of these are also present, particularly renal impairment. Other risk factors in patients with heart failure include advanced age[18] and diabetes[12,25] (hyperkalaemia has been found to be relatively common in both non-insulin-dependent and insulin-dependent diabetics).[26] In addition, spironolactone in doses greater than 25 mg daily increase the risk of hyperkalaemia. A 7-year, case-control study in elderly patients found that patients treated with ACE inhibitors, and admitted to hospital with hyperkalaemia, were about 20 times more likely to have also been taking a potassium-sparing diuretic (adjusted odds ratio, 20.3) in the previous week, compared with control patients receiving ACE inhibitors who were not admitted for hyperkalaemia.[27]

A retrospective study in hospitalised patients who developed hyperkalaemia found that risk factors associated with a rapid rate of increase in serum potassium levels in decreasing order of importance were: the use of potassium supplements, severe renal impairment, the use of ACE inhibitors or angiotensin II receptor antagonists, the use of potassium-sparing diuretics, diabetes mellitus. Further, the presence of two or more of these risk factors is associated with an even faster development of hyperkalaemia. As the speed at which hyperkalaemia develops is also correlated with its severity, the authors recommend close monitoring in patients with two or more risk factors, and that a rapid increase in serum potassium (greater than 0.5 mmol/L per day) should prompt the identification and possible removal of any risk factors for hyperkalaemia.[28]

Because ACE inhibitors have potassium-sparing effects, potassium-sparing diuretics such as amiloride and triamterene should normally not be given concurrently. If, however, the use of both drugs is thought to be appropriate the serum potassium levels should be closely monitored so that any problems can be quickly identified. Note that the concurrent use of a potassium-depleting diuretic (a loop or thiazide diuretic) with the potassium-sparing diuretic may not necessarily prevent the development of hyperkalaemia. The combination of an ACE inhibitor and spironolactone can be beneficial in some types of heart failure, but close monitoring of serum potassium and renal function is needed, especially with any changes in treatment or the patient's clinical condition. The combination should be avoided in patients with renal impairment with a glomerular filtration rate of less than 30 mL/min.[25] In addition, the dose of spironolactone should not exceed 25 mg daily.[25] Similarly, the UK manufacturer of eplerenone says that caution is required when it is given with ACE inhibitors, especially in renal impairment, and that potassium levels and renal function should be monitored.[29]

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ACE inhibitors or Angiotensin II receptor antagonists + Epoetins

Epoetins may cause hypertension and thereby reduce the effects of antihypertensive drugs. An additive hyperkalaemic effect is theoretically possible with ACE inhibitors or angiotensin II receptor antagonists and epoetins. It is not entirely clear whether ACE inhibitors or angiotensin II receptor antagonists affect the efficacy of epoetins or not, but any interaction may take many months to develop.

Clinical evidence

A. Antihypertensive effects

The most frequent adverse effect of epoetins is an increase in blood pressure, so it is important to control any existing hypertension before epoetin is started (the manufacturers contraindicate epoetin in uncontrolled hypertension). Blood pressure should be monitored before and during the use of epoetins, and if necessary antihypertensives should be started or increased if the pressure rises.[1-3]

B. Epoetin efficacy

(a) Decreased epoetin effects

In a retrospective analysis of 43 haemodialysis patients given epoetin regularly for about 10 months, the dose of epoetin was not significantly different between patients taking **captopril** (20 patients) and a control group (23 patients) who did not receive any ACE inhibitors (116.7 units/kg per week versus 98.3 units/kg per week, respectively). However, the haemoglobin and haematocrit values were significantly less at about 10 g/dL and 29.3%, respectively, in the **captopril** group than the values of 11.4 g/dL and 33.3% in the control group.[4] Another study in 108 patients who had been receiving haemodialysis for an average of 7 years found that those taking an ACE inhibitor (**enalapril**, **imidapril**, **captopril**, **cilazapril**, **benazepril**, or **temocapril**) required higher maintenance doses of epoetin than those not taking ACE inhibitors.[5] A retrospective study of 40 dialysis patients found that the 20 patients taking an ACE inhibitor (**captopril** 12.5 to 75 mg daily, **enalapril** 2.5 to 5 mg daily or **fosinopril** 10 to 20 mg daily) had some evidence of increased epoetin requirements after one year, when compared with the control group. However, this was not significant until 15 months when the cumulative epoetin dose requirements were about doubled (12 092 units/kg versus 6 449 units/kg).[6] Similarly, a prospective study with a 12-month follow-up period found that 20 patients receiving **enalapril** 5 to 20 mg daily required significantly higher doses of epoetin compared with 20 patients receiving nifedipine or 20 patients receiving no antihypertensive.[7] Another study in 49 haemodialysis patients given epoetin found that higher doses were required in those patients also taking **lisinopril** 2.5 to 20 mg daily (16 patients), **captopril** 12.5 to 37.5 mg daily (4 patients), **perindopril** 4 mg daily (one patient) or **ramipril** 2.5 mg daily (one patient) than in those patients not taking an ACE inhibitor.[8] A further study in 47 haemodialysis patients also found that 17 of 22 patients taking an ACE inhibitor (**enalapril** 20 to 40 mg daily or **captopril** 25 to 75 mg daily, for at least 3 months) did not respond to epoetin, compared with 6 of the 25 patients not taking ACE inhibitors. Furthermore, haematocrit and erythropoietin levels were lower and epoetin doses were higher in the patients taking an ACE inhibitor.[9] In another prospective study, 15 patients in whom ACE inhibitors (**enalapril**, **captopril**, or **perindopril**) were withdrawn and replaced with amlodipine, felodipine or doxazosin, had an increase in their mean haematocrit level and a decrease in their mean epoetin dose requirement.[10]

Higher epoetin requirements with ACE inhibitors were also reported in studies in peritoneal dialysis patients,[11-13] and in patients receiving haemodialysis.[14]

In a prospective study, hypertensive patients undergoing haemodialysis for more than 12 months and receiving epoetin were given either **losartan** 50 mg daily increased to 100 mg daily (20 patients) or amlodipine (20 patients) for 12 months. Twenty normotensive haemodialysis patients receiving epoetin were included as controls. It was found that patients in the **losartan** group, but not those in the amlodipine or control groups, required higher doses of epoetin to maintain the same haemoglobin levels. This was apparent at 6 months and at 12 months the epoetin dose had increased from the pre-study level of 90 units/kg per week to 129.5 units/kg per week.[15]

(b) No interaction

A prospective study carried out over a 6-month period in more than 10 000 patients found that ACE inhibitors did not interfere with the haemoglobin level and epoetin dose, in haemodialysis patients. The findings did not exclude the possibility that individual patients may need more epoetin during the use of an ACE inhibitor or that haemoglobin levels may rise after withdrawal of the ACE inhibitor.[13]

A cross-sectional study that included 515 haemodialysis patients receiving epoetin found that the mean epoetin dose and prevalence of epoetin resistance was similar in patients also taking ACE inhibitors, angiotensin II receptor antagonists, both ACE inhibitors and angiotensin II receptor antagonists, other antihypertensive drugs, or those who received no antihypertensives. However, the length of treatment with ACE inhibitors or other drugs was not known.[16] Another study also found that neither ACE inhibitors nor angiotensin II receptor antagonists could be considered as independent factors for increasing epoetin requirements and they did not significantly affect haemoglobin levels. This study did find an association between the number of antihypertensives given to a patient and epoetin dose requirement, as well as female gender, diabetes, age and systolic blood pressure.[17]

A retrospective review of 14 haemodialysis patients receiving epoetin, compared the haematocrit and dose of epoetin for 16 weeks before, and 16 weeks after, starting ACE inhibitors (8 taking **captopril**, mean dose 35 mg daily and 6 taking **enalapril**, mean dose 7.85 mg daily). This study did not find any evidence of a clinically significant interaction when ACE inhibitors were added.[18] Another study involving 17 chronic haemodialysis patients found that ACE inhibitors (5 taking **captopril** and 12 taking **enalapril**) for 3 and 12 months did not increase the epoetin dose requirements or reduce the haematocrits.[19]

In a retrospective study, the response to epoetin in haemodialysis patients who had taken ACE inhibitors (mainly **lisinopril** 5 to 40 mg daily, with some taking **enalapril** 2.5 to 40 mg daily or **fosinopril** 10 to 20 mg daily) for at least 4 months was found to be similar to that in patients who had not been taking ACE inhibitors.[20] Another study by the same authors, which was completed by 33 of 51 eligible haemodialysis patients, those taking an ACE inhibitor (mainly **lisinopril**, with some taking **enalapril** or **captopril**) at the start of the study continued with this drug for 4 months and were then switched to another antihypertensive (usually amlodipine) for a further 4 months. Patients not initially taking an ACE inhibitor were switched to an ACE inhibitor, usually **lisinopril** (mean daily dose 25 mg), at 4 months. Dose requirements of epoetin and haematocrit values were similar in each treatment period.[21] A short report of a study in 252 haemodialysis patients receiving epoetin found no reduction in the response to epoetin in 48 of the patients who were also taking ACE inhibitors.[22] A retrospective analysis of haemodialysis patients taking either moderately low doses of ACE inhibitors and epoetin (329 patients) or with epoetin alone (1884 patients), over a 12-week period, was evaluated by comparing haematocrit values. The ACE inhibitors were **enalapril** (113 patients), **captopril** (96 patients), or **alacepril**, **benazepril**, **cilazapril**, **delapril**, **imidapril**, or **lisinopril** (120 patients) and it was found that these ACE inhibitors had no effect on epoetin treatment.[23] Another retrospective analysis of 175 patients undergoing dialysis and receiving epoetin, also found that there was no change in the response to epoetin in 32 of the patients who were also taking **enalapril** for at least 3 months.[24]

A prospective study in 15 haemodialysis patients found that **losartan** 50 to 100 mg daily for 3 months did not significantly affect endogenous erythropoietin levels or affect the dose requirements of epoetin.[25] Another study in 14 haemodialysis patients found no difference in epoetin requirements between patients receiving **losartan** 25 mg daily or placebo,[26] but again the **losartan** was only given for 3 months.

However, given the results of the studies[6,15] reported under *Decreased epoetin effects*, above, it is possible that these studies were not continued for long enough to detect an effect. Further, the lack of effect in one of the studies[23] may also reflect the relatively low doses or low target haematocrit.

(c) ACE inhibitors compared with Angiotensin II receptor antagonists

In one retrospective analysis of dialysis patients, 18 of 24 receiving losartan had decreases in haemoglobin, and 14 of these were using epoetin. A three to fourfold increase in the epoetin dose was required in these patients to restore the haemoglobin levels.[27] This study suggests that angiotensin II receptor antagonists can behave similarly to ACE inhibitors. However, in a prospective study in 25 patients who had been undergoing haemodialysis for more than one year, 12 patients were given **temocapril** 2 mg daily and 13 patients were given **losartan** 25 to 50 mg daily for 12 months. **Temocapril** decreased haemoglobin levels from 9.8 g/dL to 9.1 g/dL at 3 months and reached a minimum of 9 g/dL at 6 months; haemoglobin levels recovered to 9.7 g/dL at the end of the study by increasing the dose of epoetin. In contrast, no change was found in haemoglobin levels in the patients receiving **losartan**. The dose of epoetin was gradually increased from 76 to 121 units/kg per week in the **temocapril** group, but in the **losartan** group the epoetin dose was not significantly increased (94 versus 101 units/kg per week).[28] Similar results were found in a study with **captopril** and **losartan**.[29]

A follow-up to a retrospective study found that the use of ACE inhibitors did not affect haemoglobin response rates or the epoetin dose. Similarly, the use of angiotensin II receptor antagonists did not affect haemoglobin response rates or the epoetin dose in patients from countries where more

than 70% of patients had haemoglobin levels greater than or equal to 11 g/dL (epoetin doses tended to be higher in these countries). However, patients taking angiotensin II receptor antagonists, who were from countries where only 60 to 70% of patients had a haemoglobin level of greater than or equal to 11 g/dL, had a reduced response to epoetin (higher epoetin doses and lower haemoglobin response rates).[30]

A survey of anaemia in more than 4000 kidney transplant recipients in 16 European countries found an association between post-transplant anaemia and the use of ACE inhibitors or angiotensin II receptor antagonists. However, haemoglobin levels in patients taking ACE inhibitors were not significantly different to levels in patients who had not received these drugs, whereas haemoglobin levels were lower in patients taking angiotensin II receptor antagonists.[31]

C. Hyperkalaemia

The manufacturers of epoetin alfa and beta comment that increased potassium levels have been reported in a few patients with chronic renal failure receiving epoetin, and that serum potassium levels should be monitored regularly.[1-3] An additive hyperkalaemic effect is therefore theoretically possible with patients also receiving ACE inhibitors or angiotensin II receptor antagonists.

Mechanism

Epoetin can cause hypertension, possibly associated with haemodynamic changes produced by the increase in haematocrit.[32]

It has been argued that ACE inhibitors might possibly reduce the efficacy of epoetin in haemodialysis patients for several reasons. A dose-dependent decrease in haematocrit is regularly observed when patients are given ACE inhibitors or angiotensin II receptor antagonists. In most patients this decrease is small and not clinically important. However, in conditions such as erythrocytosis associated with renovascular hypertension or renal transplantation, the haematocrit-lowering effects of these drugs may be marked.[33] Furthermore, ACE inhibitors may reduce polycythaemia that occurs following renal transplantation, and ACE inhibitors reduce the plasma levels of endogenous erythropoietin.[4,18,34] Another suggestion is that ACE inhibitors and angiotensin II receptor antagonists may reduce testosterone levels in men receiving haemodialysis, but not in women, and this may be associated with resistance to epoetin.[35] As suppression of angiotensin II levels has been found in dialysis patients receiving epoetin, it has been suggested that the effect of ACE inhibitors on erythropoietin may be associated with a feedback loop between erythropoietin and the renin-angiotensin system.[36] Many other factors have also been proposed.[36,37]

Drugs that block angiotensin II cause reduced levels of aldosterone, which results in the retention of potassium. This would be expected to be additive with other drugs that cause hyperkalaemia.

Importance and management

Blood pressure should be routinely monitored in patients receiving epoetin, and this monitoring would seem sufficient to detect any interaction that affects the blood pressure-lowering effects of the ACE inhibitors or angiotensin II receptor antagonists. The dose of ACE inhibitor may need to be increased, but if blood pressure rises cannot be controlled, a transient interruption of the use of epoetin is recommended. Similarly, serum electrolytes, including potassium, should be routinely monitored in patients using epoetin. If potassium levels rise, consider withholding epoetin until the level is corrected.[1,2]

The overall picture of the effect of ACE inhibitors on epoetin resistance is unclear, and it would seem that an interaction, if it happens, takes a long time to develop. The dose of ACE inhibitor and also of epoetin may be important factors for the development of epoetin resistance with the effect possibly being most apparent with high doses of ACE inhibitor, particularly if the patient is given low-dose epoetin. It has been suggested that any epoetin resistance due to high-dose ACE inhibitor should be able to be counteracted by increased dose of epoetin.[38] There is even less evidence regarding any interaction with angiotensin II antagonists, although one study suggests epoetin resistance may develop in patients given high-dose losartan for 6 months or more.[15] As epoetin dose is governed by response, no immediate intervention is generally necessary. More long-term study is needed.

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ACE inhibitors + Food

Food has little or no effect on the extent of absorption of cilazapril, enalapril, fosinopril, lisinopril, quinapril, ramipril, spirap-

ril, and trandolapril although the rate of absorption may be decreased. Food reduced the absorption of imidapril and moexipril, reduced the conversion of perindopril to perindoprilat, and may reduce the absorption of captopril.

Clinical evidence, mechanism, importance and management

(a) Captopril

Although food reduced the AUC of captopril 25 to 100 mg by up to 56%[1-4] this had no effect on the maximum decrease in blood pressure.[1,3,4] One study in 10 healthy subjects reported that food caused a one-hour delay in the maximum hypotensive effect of captopril.[1] Another study, in 10 hypertensive patients, found that the extent and duration of the antihypertensive efficacy of captopril 50 mg twice daily for one month was not affected by whether it was taken before or after food.[5] However, decreasing the dose of an ACE inhibitor might reduce the duration of the hypotensive effect and it has been suggested that these results should be confirmed with lower doses of captopril.[5]

(b) Moexipril

In one study, food reduced the AUC of the active metabolite of moexipril (moexiprilat) by 40 to 50%.[6] Food did not reduce moexipril-induced ACE-inhibition and therefore the reduced bioavailability was not expected to be clinically relevant.[7]

(c) Perindopril

Although food did not significantly affect the pharmacokinetics of a single 4-mg dose of perindopril, the AUC of its active metabolite perindoprilat was reduced by 44%.[8] The blood pressure-lowering effects were not assessed, but it seems possible that they would not be affected (see *Captopril*, above). Nevertheless, the UK manufacturer recommends that perindopril should be taken in the morning before a meal.[9]

(d) Other ACE inhibitors

Single-dose studies have found that food has no statistically significant effect on the pharmacokinetics of **lisinopril**,[10] or **enalapril**, and its active metabolite, enalaprilat.[11] Similarly, food had minimal effects on the pharmacokinetics of **cilazapril** (AUC decreased by only 14%).[12] Food caused small increases in the time to reach maximum plasma levels of **quinapril** and its active metabolite. However, as the increase was less than 30 minutes this is not expected to alter the therapeutic effect.[13] Likewise, the manufacturers of **spirapril** briefly mention in a review that food delayed its absorption by one hour, but it did not affect the bioavailability of **spirapril** or spiraprilat, its active metabolite.[14] The US manufacturers of **fosinopril**,[15] **ramipril**,[16] and **trandolapril**[17] state that food may slow their absorption, but both the UK[18-20] and US[15-17] manufacturers state that the extent of absorption is unaffected.

The UK manufacturer of **imidapril** states that a fat-rich meal significantly reduces the absorption of **imidapril**, and recommends that the drug be taken at the same time each day, about 15 minutes before a meal.[21]

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14. Grass P, Gerbeau C, Kutz K. Spirapril: pharmacokinetic properties and drug interactions. *Blood Pressure* (1994) 3 (Suppl 2), 7–13.
15. Monopril (Fosinopril sodium). Bristol-Myers Squibb Company. US Prescribing information, July 2008.
16. Altace (Ramipril). King Pharmaceuticals, Inc. US Prescribing information, July 2008.
17. Mavik (Trandolapril). Abbott Laboratories. US Prescribing information, April 2009.
18. Staril (Fosinopril sodium). E. R. Squibb & Sons Ltd. UK Summary of product characteristics, January 2009.
19. Tritace (Ramipril). Sanofi-Aventis. UK Summary of product characteristics, April 2007.
20. Gopten (Trandolapril). Abbott Laboratories Ltd. UK Summary of product characteristics, July 2009.
21. Tanatril (Imidapril hydrochloride). Chiesi Ltd. UK Summary of product characteristics, November 2007.

ACE inhibitors + Garlic

In a single report, a patient taking lisinopril developed marked hypotension and became faint after taking garlic capsules.

Clinical evidence, mechanism, importance and management

A man whose blood pressure was 135/90 mmHg while taking **lisinopril** 15 mg daily began to take garlic 4 mg daily (*Boots odourless garlic oil capsules*). After 3 days he became faint on standing and was found to have a blood pressure of 90/60 mmHg. Stopping the garlic restored his blood pressure to 135/90 mmHg within a week. The garlic on its own did not lower his blood pressure. The reasons for this interaction are not known, although garlic has been reported to cause vasodilatation and reduce blood pressure.[1] This seems to be the first and only report of this reaction, so its general importance is small. There seems to be nothing documented about garlic and any of the other ACE inhibitors.

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ACE inhibitors + Gold

Peripheral vasodilatation has occurred in some patients given ACE inhibitors and gold. Isolated cases of loss of consciousness, cardiovascular collapse and cerebrovascular accident have been reported. In some patients the reaction occurred soon after the ACE inhibitor was started, while in others there appeared to be a lag time of several months or more.

Clinical evidence

A retrospective analysis of patients given gold compounds at one clinic from 1996 to 2000 identified 8 patients who had experienced a nitritoid reaction (adverse effects associated with the use of gold compounds, consisting of facial flushing, nausea, dizziness, and occasionally, hypotension, as a result of peripheral vasodilatation) of which one was considered serious. They had been given weekly doses of **sodium aurothiomalate** 25 to 50 mg for between 13 months and 13 years before the reaction occurred. However, in 2 of the patients who had been receiving gold for 2 years and 13 years, respectively, the nitritoid reaction occurred one to 4 weeks after starting the ACE inhibitor (**ramipril** in one patient; not specified in the other).[1]

A report describes 4 patients receiving long-term gold for rheumatoid arthritis who developed nitritoid reactions. These reactions occurred soon after starting an ACE inhibitor (**captopril**, **enalapril**, or **lisinopril**). All the patients had been receiving a monthly injection of **sodium aurothiomalate** 50 mg for at least 2 years and none had ever had such a reaction before. The reactions were controlled by changing treatment to **aurothioglucose**, discontinuing the ACE inhibitor, or reducing the dose of **sodium aurothiomalate** to 25 mg.[2]

Another report notes 2 further cases observed by one of the authors of the earlier report[2] and also describes a patient given a weekly and then monthly intramuscular injection of **sodium aurothiomalate** 50 mg for 4 months before she started taking **lisinopril** 20 mg daily. Seven months later she experienced paraesthesiae in her hands and tongue and palpitations a few minutes after the **sodium aurothiomalate** injection; mild paraesthesiae occurred again after her next injection. The following four injections were without any adverse effects, but then within 5 to

10 minutes of the next injection she became dizzy and flushed with nausea and vomiting and collapsed, requiring cardiopulmonary resuscitation. One day later she developed bloody diarrhoea and, the following day, a peeling erythematous rash, which gradually resolved over a few weeks; these were possible adverse effects of the gold. **Sodium aurothiomalate** was replaced with hydroxychloroquine and **lisinopril** was continued.[3]

Two patients who had been receiving **sodium aurothiomalate** 50 mg/month for over 20 years without adverse effects developed nitritoid reactions. One of the patients who had been taking **ramipril** 10 mg daily for about 15 months, experienced nausea, angina, and hypotension 10 minutes after an injection of **sodium aurothiomalate**. Although it was concluded that the reaction was due to a vasovagal episode, secondary to the injection and possibly exaggerated by atenolol, on review of the case, it was considered that an interaction with **ramipril** was also a possibility. About 10 months after the second patient had started taking **perindopril** 2 mg daily gradually increased to 6 mg daily, he lost consciousness whilst driving his car 20 minutes after an injection of **sodium aurothiomalate**. On admission to hospital it was concluded that he had experienced a vasovagal attack secondary to ischaemic heart disease. A month later he developed chest pain 10 minutes after the gold injection and he remained conscious but was hypotensive with a heart rate of 40 bpm. Both patients had been receiving **sodium aurothiomalate** for many years, and the possibility of an interaction occurring several months after starting an ACE inhibitor was suggested.[4] There is a further report of a patient who had taken **enalapril** for 3 years and **sodium aurothiomalate** for 6 years who experienced mild nitritoid symptoms following two successive injections of **sodium aurothiomalate** and then a cerebrovascular accident within several hours of her next injection.[5]

Mechanism

Not understood. The nitritoid reaction is a recognised reaction that can occur in patients receiving gold compounds. Most reactions are associated with sodium aurothiomalate (incidence of about 5%), but they have also been reported with auranofin and sodium aurothioglucose.[5,6] It has been suggested that the difference in frequency with sodium aurothiomalate compared with other gold compounds may be related to differences in bioavailability, with the aqueous sodium aurothiomalate being rapidly absorbed, whereas the oil-based aurothioglucose or auranofin are absorbed more slowly.[1,5]

ACE inhibitors prevent bradykinin breakdown, so patients may have higher bradykinin levels.[1] It has been suggested that ACE inhibitors may 'unmask' a hypersensitivity reaction, possibly by potentiation of kinins, resulting in an exaggerated inflammatory response.[3] However, reactions involving bradykinin, may be delayed for several months after starting an ACE inhibitor.[4] An *in vitro* study found that captopril binds strongly with gold, ejecting thiomalate into solution.[7]

Importance and management

Although the nitritoid reaction is an established adverse effect of gold compounds, patients also taking ACE inhibitors may be at an increased risk. A possible interaction should be borne in mind if a patient experiences these reactions and is also taking an ACE inhibitor. The cases reported indicate that reactions may occur soon after starting an ACE inhibitor or there may be a lag time of several months or more. It has been recommended that patients taking ACE inhibitors who require gold compounds should, if possible, be given aurothioglucose. If this is not available, a 50% reduction in the sodium aurothiomalate dose is recommended, with the patient in the recumbent position, and under observation for 20 minutes following the next few injections.[1]

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ACE inhibitors + H_2-receptor antagonists

In general, no clinically significant interactions appear to occur between the H_2-receptor antagonists (including cimetidine) and the ACE inhibitors. However, note that cimetidine modestly reduces the bioavailability of temocapril.

Clinical evidence, mechanism, importance and management

In studies in healthy subjects, **cimetidine** did not appear to alter the pharmacokinetics or pharmacological effects of **captopril**[1] or **enalapril**,[2] or the pharmacokinetics of **fosinopril**[3] or **quinapril**.[4] The manufacturers of **cilazapril** say that no clinically significant interactions have occurred with H_2-receptor antagonists (not specifically named)[5] and the manufacturers of **benazepril**,[6] **moexipril**,[7] **ramipril**,[8] and **trandolapril**[9] say that no important pharmacokinetic interaction occurred with **cimetidine**. The manufacturers of **spirapril** briefly note in a review that **cimetidine** did not alter the plasma concentrations of **spirapril** or its active metabolite spiraprilat.[10] None of these pairs of drugs appears to interact to a clinically relevant extent, and no special precautions appear to be necessary.

Preliminary findings in 18 healthy subjects suggest that **cimetidine** 400 mg twice daily had no effect on the metabolism of **temocapril** 20 mg daily, but the AUC was reduced by 26% on the fifth day of concurrent use.[11] The clinical relevance of this is uncertain, but changes of this magnitude with other ACE inhibitors have often not been clinically relevant.

1. Richer C, Bah M, Cadilhac M, Thuillez C, Giudicelli JF. Cimetidine does not alter free unchanged captopril pharmacokinetics and biological effects in healthy volunteer. *J Pharmacol* (1986) 17, 338–42.
2. Ishizaki T, Baba T, Murabayashi S, Kubota K, Hara K, Kurimoto F. Effect of cimetidine on the pharmacokinetics and pharmacodynamics of enalapril in normal volunteers. *J Cardiovasc Pharmacol* (1988) 12, 512–9.
3. Moore L, Kramer A, Swites B, Kramer P, Tu J. Effect of cimetidine and antacid on the kinetics of the active diacid of fosinopril in healthy subjects. *J Clin Pharmacol* (1988) 28, 946.
4. Ferry JJ, Cetnarowski AB, Sedman AJ, Thomas RW, Horvath AM. Multiple-dose cimetidine administration does not influence the single-dose pharmacokinetics of quinapril and its active metabolite (CI-928). *J Clin Pharmacol* (1988) 28, 48–51.
5. Vascace (Cilazapril monohydrate). Roche Products Ltd. UK Summary of product characteristics, March 2009.
6. Lotensin (Benazepril hydrochloride). Novartis Pharmaceuticals Corporation. US Prescribing information, May 2009.
7. Perdix (Moexipril hydrochloride). UCB Pharma Ltd. UK Summary of product characteristics, April 2009.
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ACE inhibitors or Angiotensin II receptor antagonists + Heparins

Heparin may increase the risk of hyperkalaemia with ACE inhibitors or angiotensin II receptor antagonists.

Clinical evidence, mechanism, importance and management

An extensive review of the literature found that heparin (both **unfractionated** and **low-molecular-weight heparins**) and **heparinoids** inhibit the secretion of aldosterone, and this can cause hyperkalaemia.[1] The CSM in the UK suggests that plasma potassium levels should be measured in all patients with risk factors (including those taking potassium-sparing drugs) before starting heparin, and monitored regularly thereafter, particularly if heparin is to be continued for more than 7 days.[2] Note that ACE inhibitors and angiotensin II receptor antagonists are potassium sparing, via their effects on aldosterone. Some workers[1] have suggested that the monitoring interval should probably be no greater than 4 days in patients at a relatively high risk of hyperkalaemia. Other risk factors include renal impairment, diabetes mellitus, pre-existing acidosis or raised plasma potassium.[2]

If hyperkalaemia occurs, the offending drugs should be stopped (although this may not be practical in the case of heparin). When the hy-

perkalaemia has been corrected (by whatever medical intervention is deemed appropriate) the drugs can cautiously be reintroduced.

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2. Committee on Safety of Medicines/Medicines Control Agency. Suppression of aldosterone secretion by heparin. *Current Problems* (1999) 25, 6.

ACE inhibitors + Insect allergen extracts

There are a few case reports of severe anaphylactoid reactions in patients receiving ACE inhibitors during desensitisation with bee or wasp venom.

Clinical evidence

A report describes 2 cases of anaphylactoid reactions during **wasp venom immunotherapy** in patients taking **enalapril**. In one patient, generalised pruritus and severe hypotension occurred within a few minutes of the first venom injection. Desensitisation was achieved after the **enalapril** was stopped, and then the immunotherapy was maintained by discontinuing the **enalapril** 24 hours before the monthly venom injection. However, on one occasion, when the **enalapril** had not been stopped, the patient experienced a severe anaphylactoid reaction 30 minutes after the venom injection. In the other patient, an anaphylactoid reaction occurred after the second dose of venom. The ACE inhibitor was replaced with nifedipine so that venom immunotherapy could be continued. However, **enalapril** was reintroduced a few months later and subsequent venom administration induced an anaphylactoid reaction. **Enalapril** was stopped again so that desensitisation could be maintained.[1]

In another report, a 43-year-old man who had been taking ACE inhibitors for 2 years (**lisinopril** 40 mg daily for the previous 5 months) had a hypotensive reaction to an insect sting. After skin testing, he received venom immunotherapy. About 4 months later, he had a severe anaphylactic reaction 5 minutes after being given a maintenance dose of **wasp venom** and **mixed vespid venom**. The ACE inhibitor was replaced with a calcium-channel blocker, and he subsequently tolerated full-strength venom immunotherapy injections.[2]

A retrospective review of patients evaluated for **Hymenoptera venom** allergy, at a single medical centre from 2000 to 2005, identified 79 patients undergoing venom immunotherapy. ACE inhibitors (**lisinopril**, **ramipril**, or **benazepril**) were taken by 17 patients (21%): 7 patients continued to take the ACE inhibitor when immunotherapy was started and 10 began to take an ACE inhibitor after starting immunotherapy. None of the patients receiving ACE inhibitors had systemic reactions during venom immunotherapy (compared with 13 of 62 patients not taking an ACE inhibitor). However, the patients taking ACE inhibitors were older (mean age 56 years versus 36 years) and had received immunotherapy for longer (mean 72 months versus 30 months) than those who were not taking an ACE inhibitor. Twelve of the 17 patients (71%) taking an ACE inhibitor reported having field stings, but none of these patients had a systemic reaction. One patient did have a reaction to a field sting early in his venom immunotherapy treatment, before he started to take an ACE inhibitor, but he did not experience a reaction on rechallenge while taking an ACE inhibitor.[3]

Mechanism

ACE inhibitors might potentiate the hypotension associated with anaphylactic reactions by inhibiting the breakdown of bradykinin and decreasing concentrations of the vasoconstrictor angiotensin II.[4] It has also been suggested that similar reactions may occur after an insect sting.[4] This is supported by a case report that describes a woman who had generalised angioedema in response to bee stings on at least three occasions while taking captopril and then cilazapril, but experienced only localised swelling before and after treatment with an ACE inhibitor.[5]

Importance and management

One retrospective review[3] suggested that ACE inhibitors do not increase the risk of anaphylaxis to venom immunotherapy; however, isolated reactions, especially following reintroduction of an ACE inhibitor in two cases mentioned above,[1] suggest that in some patients ACE inhibitors may increase the risk of anaphylaxis. On the basis of these few reports, it cannot be said with certainty that an interaction occurs; but it is possible that ACE inhibitors could exacerbate the response to insect venoms and insect venom immunotherapy.

The use of ACE inhibitors in patients with **Hymenoptera venom** allergy (bee, wasp or stinging ant allergy) or those undergoing venom immunotherapy requires caution because of the potential severity of the reaction. If an ACE inhibitor is considered necessary, appropriate measures should be put in place. These include minimising the risk of exposure to insect stings e.g. by physical protection, and ensuring the patient carries adrenaline (epinephrine) [such as an *EpiPen*] for emergency self-treatment.[4] Some authors[1,2,4] and manufacturers advise temporarily withholding the ACE inhibitor before each desensitisation (24 hours was sufficient in one case), while others suggest temporary substitution of a different antihypertensive e.g. a calcium-channel blocker. ACE inhibitors with active metabolites with prolonged terminal half-lives (including **benazepril**, **quinapril**, and **ramipril**) may require discontinuation for longer periods.[4,6] Note that some evidence suggests that anaphylactic shock in patients taking beta blockers may be resistant to treatment with adrenaline (epinephrine), see 'Beta blockers + Inotropes and Vasopressors', p.1011. Therefore beta blockers are probably not a suitable alternative.

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2. Ober AI, MacLean JA, Hannaway PJ. Life-threatening anaphylaxis to venom immunotherapy in a patient taking an angiotensin-converting enzyme inhibitor. *J Allergy Clin Immunol* (2003) 112, 1008–9.
3. White KM, England RW. Safety of angiotensin-converting enzyme inhibitors while receiving venom immunotherapy. Ann Allergy Asthma Immunol (2008) 101, 426–30.
4. Stumpf JL, Shehab N, Patel AC. Safety of angiotensin-converting enzyme inhibitors in patients with insect venom allergies. *Ann Pharmacother* (2006) 40, 699–703.
5. Black PN, Simpson IJ. Angio-oedema and ACE inhibitors. *Aust N Z J Med* (1995) 25, 746.
6. Melamed J. Response to life-threatening anaphylaxis to venom immunotherapy in a patient taking an angiotensin-converting enzyme inhibitor. *J Allergy Clin Immunol* (2004) 113, 1224.

ACE inhibitors + Interleukin-3

Marked hypotension occurred when three patients taking ACE inhibitors were given interleukin-3.

Clinical evidence, mechanism, importance and management

Twenty-six patients with ovarian or small-cell undifferentiated cancers were given chemotherapy followed by recombinant human interleukin-3. Three of the 26 were taking ACE inhibitors (not named) and all three developed marked hypotension (WHO toxicity grade 2 or 3) within one to 4 hours of the first interleukin-3 injection. Their blood pressures returned to normal while continuing the interleukin-3 when the ACE inhibitors were stopped. When the interleukin-3 was stopped, they once again needed the ACE inhibitors to control their blood pressure. None of the other 23 patients had hypotension, except one who did so during a period of neutropenic fever.[1] The authors of the report suggest (and present some supporting evidence) that the drugs act synergistically to generate large amounts of nitric oxide in the blood vessel walls. This relaxes the smooth muscle in the blood vessel walls causing vasodilatation and consequent hypotension.[1] Information seems to be limited to this single report, but it would be prudent to monitor blood pressure even more closely if patients taking ACE inhibitors are given interleukin-3.

1. Dercksen MW, Hoekman K, Visser JJ, ten Bokkel Huinink WW, Pinedo HM, Wagstaff J. Hypotension induced by interleukin-3 in patients on angiotensin-converting enzyme inhibitors. *Lancet* (1995) 345, 448.

ACE inhibitors + Iron compounds

Serious systemic reactions occurred when three patients taking enalapril were given infusions of ferric sodium gluconate; however, there was no increase in the incidence of such adverse reactions in patients taking ACE inhibitors in a very large clinical study. Oral ferrous sulfate may decrease the absorption of captopril, but this is probably of little clinical importance.

Clinical evidence

(a) Intravenous iron

A man with iron-deficiency anaemia taking furosemide and digoxin was given 125 mg of **ferric sodium gluconate** (*Ferlixit*[1]) intravenously in 100 mL of saline daily. Four days later, **enalapril** 5 mg daily was started. After the infusion of only a few drops of his next dose of **ferric sodium**

gluconate, he developed diffuse erythema, abdominal cramps, hypotension, nausea and vomiting. He recovered after being given hydrocortisone 200 mg. Three days later, in the absence of the **enalapril**, he restarted the iron infusions for a further 10 days without problems, and was later treated uneventfully with **enalapril**.[2] Two other patients taking **enalapril** reacted similarly when given intravenous infusions of **ferric sodium gluconate**. Neither was given any more intravenous iron and later had no problems while taking **enalapril** alone. During the same 13-month period in which these three cases occurred, 15 other patients, who were not taking ACE inhibitors, also received intravenous iron with no adverse reactions.[2] In contrast, an interim report of a randomised, crossover study involving 1117 dialysis patients given a placebo or a single intravenous dose of 125 mg of **ferric sodium gluconate complex** (*Ferrlecit*) in sucrose, found no evidence of any significant difference in the incidence of immediate allergic reactions or other adverse reactions to the iron in the 308 patients also taking ACE inhibitors.[3] The findings of the full study, which included 707 patients taking ACE inhibitors, were the same.[4] Similarly, the longer-term follow-up of patients from this study who continued to receive intravenous **ferric sodium gluconate complex**, found that there was no difference in the incidence or severity of adverse events in the 372 patients taking ACE inhibitors, when compared with the 949 patients who were not taking ACE inhibitors.[5]

(b) Oral iron

A double-blind study in 7 healthy subjects, given a single 300-mg dose of **ferrous sulfate** or placebo with **captopril** 25 mg, found that the AUC of unconjugated plasma **captopril** (the active form) was reduced by 37% although the maximum plasma levels were not substantially changed. The AUC of total plasma **captopril** was increased by 43%, although this was not statistically significant. There were no significant differences in blood pressure between treatment and placebo groups.[6]

Mechanism

Uncertain. Intravenous iron may cause a variety of systemic reactions including fever, myalgia, arthralgia, hypotension, and nausea and vomiting, which are believed to be due to the release of various inflammatory mediators such as bradykinin, caused by iron-catalysed toxic free radicals. The authors of the report suggest that ACE inhibitors like enalapril decrease the breakdown of kinins so that the toxic effects of the iron become exaggerated.[2]

The reduced levels of unconjugated captopril seen in the presence of oral iron are probably due to reduced absorption resulting from a chemical interaction between ferric ions and captopril in the gastrointestinal tract producing a captopril disulfide dimer and ferrous iron.[6]

Importance and management

The interaction with intravenous iron is not firmly established because up to 25% of all patients given iron by this route develop a variety of systemic reactions, ranging from mild to serious anaphylactoid reactions. In addition, information from the large clinical study indicates that there is no increased risk in patients taking ACE inhibitors. This suggests that no extra precautions are required if intravenous iron is given to patients taking any ACE inhibitor.

There is limited evidence that oral iron may reduce the absorption of captopril. The clinical relevance of this is unknown, but probably small. Information about the effect of oral iron on other ACE inhibitors is lacking.

1. Rolla G. Personal communication, 1994.
2. Rolla G, Bucca C, Brussino L. Systemic reactions to intravenous iron therapy in patients receiving angiotensin converting enzyme inhibitor. *J Allergy Clin Immunol* (1994) 93, 1074–5.
3. Warnock DG, Adkinson F, Coyne DW, Strobos J, Ferrlecit® Safety Study Group. ACE inhibitors and intravenous sodium ferric gluconate complex in sucrose (SFGC): lack of any significant interaction. *J Am Soc Nephrol* (2000) 11, 170A.
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6. Schaefer JP, Tam Y, Hasinoff BB, Tawfik S, Peng Y, Reimche L, Campbell NRC. Ferrous sulphate interacts with captopril. *Br J Clin Pharmacol* (1998) 46, 377–81.

ACE inhibitors + Moracizine

Moracizine causes some moderate alterations in the pharmacokinetics of captopril, but these are unlikely to be clinically important.

Clinical evidence, mechanism, importance and management

In a pharmacokinetic study, 19 healthy subjects were given moracizine 250 mg or **captopril** 50 mg, both every 8 hours, either alone or together, for 22 doses. When taken together the pharmacokinetics of the moracizine and total **captopril** remained unchanged, but the maximum blood levels of the free **captopril** and its AUC decreased by 32% and 14%, respectively. The half-life of the free **captopril** was reduced by 44%.[1] These modest changes are unlikely to be clinically relevant.

1. Pieniaszek HJ, Shum L, Widner P, Garner DM, Benedek IH. Pharmacokinetic interaction of moricizine and captopril in healthy volunteers. *J Clin Pharmacol* (1993) 33, 1005.

ACE inhibitors + NSAIDs

There is evidence that most NSAIDs can increase blood pressure in patients taking antihypertensives, including ACE inhibitors, although some studies have not found the increase to be clinically relevant. Some variation between drugs possibly occurs, with indometacin appearing to have the most significant effect. The combination of an NSAID and an ACE inhibitor can increase the risk of renal impairment and hyperkalaemia.

Clinical evidence

A. Effects on blood pressure

Various large epidemiological studies and meta-analyses of clinical studies have been conducted to assess the effect of NSAIDs on blood pressure in patients taking antihypertensives, and the findings of these are summarised in 'Table 23.2', (p.1027). In these studies, NSAIDs were not always associated with an increase in blood pressure, and the maximum increase was 6.2 mmHg. The effect has been shown for both coxibs and non-selective NSAIDs. In two meta-analyses,[1,2] the effects were evaluated by NSAID. The confidence intervals for all the NSAIDs overlapped, showing that there was no statistically significant difference between them, with the exception of the comparison between **indometacin** and **sulindac** in one analysis.[2] Nevertheless, an attempt was made at ranking the NSAIDs based on the means. In one analysis,[1] the effect was said to be greatest for **piroxicam**, **indometacin**, and **ibuprofen**, intermediate for **naproxen**, and least for **sulindac** and **flurbiprofen**. In the other meta-analysis,[2] the effect was said to be greatest for **indometacin** and **naproxen**, intermediate for **piroxicam**, and least for **ibuprofen** and **sulindac**. An attempt was also made to evaluate the effect by antihypertensive.[1] The mean effect was greatest for beta blockers, intermediate for vasodilators (this group included ACE inhibitors and calcium-channel blockers), and least for diuretics. However, the differences between the groups were not significant.

The findings of individual studies that have studied the effects of specific NSAIDs on ACE inhibitors are outlined in the subsections below.

(a) Celecoxib

In a double-blind study in hypertensive patients taking **lisinopril** 10 to 40 mg daily, celecoxib did not have a clinically or statistically significant effect on blood pressure. The 24-hour blood pressure increased by 2.6/1.5 mmHg in 91 patients taking celecoxib 200 mg twice daily for 4 weeks compared with 1/0.3 mmHg in 87 patients taking placebo.[3] In another large study in 810 elderly patients with osteoarthritis and controlled hypertension given either celecoxib 200 mg or rofecoxib 25 mg daily for 6 weeks, approximately 40% of the patients randomised to the celecoxib group were receiving ACE inhibitors. Systolic blood pressure increased by a clinically significant amount (greater than 20 mmHg) in 11% of patients receiving celecoxib,[4] while in another study, only 4 of 87 (4.6%) of hypertensive patients taking ACE inhibitors had clinically significant increases in blood pressure after taking celecoxib 200 mg twice daily for 4 weeks.[5] A further study in 25 hypertensive patients with osteoarthritis taking **trandolapril** (with or without hydrochlorothiazide) found that the 24-hour blood pressure was not significantly increased by celecoxib 200 mg daily, but, at its peak activity, celecoxib increased blood pressure

by about 5/4 mmHg.[6] In another randomised study, 16% of 138 patients given celecoxib 200 mg daily developed hypertension within 6 weeks (defined as a 24-hour systolic blood pressure greater than 135 mmHg). These patients had well-controlled hypertension at baseline; 83% were receiving an ACE inhibitor and 64% an additional antihypertensive.[7] The proportion of patients who developed hypertension was similar to that with naproxen (19%) and less than that with rofecoxib (30%).

(b) Ibuprofen

In 90 patients taking ACE inhibitors, giving ibuprofen for 4 weeks resulted in clinically significant increases in blood pressure in 15 of the patients. For the group as a whole, diastolic blood pressure was increased by 3.5 mmHg.[5] In one single-dose study in 8 healthy subjects, ibuprofen 800 mg or indometacin 50 mg abolished the hypotensive effect of **captopril** 50 mg when they received a high sodium diet, but not when they received a low sodium diet.[8] A case report describes attenuation of the antihypertensive effects of **captopril** by ibuprofen in an elderly woman.[9] However, two studies in African women found that ibuprofen 800 mg three times daily for one month did not alter the antihypertensive effect of either **fosinopril** 10 to 40 mg daily or **lisinopril** 10 to 40 mg daily (given with hydrochlorothiazide 25 mg daily).[10,11] It was thought that the diuretic might have enhanced salt depletion and renin stimulation making the antihypertensive action of the combination less prostaglandin dependent.[10]

(c) Indometacin

1. Captopril. In a randomised, double-blind study, 105 patients with hypertension were given captopril 25 to 50 mg twice daily for 6 weeks, which reduced their blood pressure by a mean of 8.6/5.6 mmHg. Indometacin 75 mg daily was then added for one week, which caused a rise in blood pressure in the group as a whole of 4.6/2.7 mmHg (an attenuation of the effect of captopril of about 50%). Clear attenuation was seen in 67% of the patients, and occurred regardless of baseline blood pressure.[12] This same interaction has been described in numerous earlier studies, in both patients with hypertension and healthy subjects, given indometacin.[8,13-20] A man whose blood pressure was well controlled with captopril 75 mg daily had a rise in his blood pressure from 145/80 mmHg to 220/120 mmHg when he started using indometacin suppositories 200 mg daily.[21] In contrast, a randomised, placebo-controlled, crossover study in 11 patients found that indometacin 50 mg twice daily did not alter the antihypertensive efficacy of captopril 50 mg twice daily.[22]

2. Enalapril. In 9 patients with hypertension, indometacin 50 mg twice daily for one week significantly reduced the antihypertensive effect of enalapril 20 to 40 mg daily by about 18 to 22%.[23] In another study in 18 patients, indometacin 25 mg three times daily attenuated the antihypertensive effect of enalapril 20 to 40 mg daily. The reduction in hypotensive effect was about 42% when assessed by 24-hour ambulatory blood pressure monitoring (9.4/4.1 mmHg increase in blood pressure with indometacin), and 12 to 23% when assessed by clinic blood pressure monitoring.[24] Similar results were found in other studies.[25-28] A further study in 10 normotensive subjects receiving a fixed sodium intake and enalapril 20 mg daily, with or without indometacin 50 mg twice daily for one week, found that indometacin reduced the natriuretic response to the ACE inhibitor.[29] A single case report describes a patient taking enalapril 10 mg daily whose hypertension was not controlled when indometacin 100 mg daily in divided doses was added.[30] However, other studies found that indometacin did not significantly alter the blood pressure response to enalapril.[19,22,31]

3. Lisinopril. In a placebo-controlled, crossover study in 56 patients taking lisinopril 10 to 20 mg daily, indometacin 50 mg twice daily for 2 weeks produced mean blood pressure increases of 5.5/3.2 mmHg.[32] Similarly, results of an earlier study suggested that indometacin increased the blood pressure of 9 patients taking lisinopril.[26] In contrast in a placebo-controlled study in 16 patients, indometacin 50 mg twice daily for 4 weeks was found to have little effect on the antihypertensive efficacy of lisinopril 40 mg daily.[33]

4. Other ACE inhibitors. A placebo-controlled, randomised, crossover study in 16 hypertensive patients found that indometacin 50 mg twice daily reduced the blood pressure-lowering effects of **cilazapril** 2.5 mg daily. The reduction was greater when **cilazapril** was added to indometacin than when indometacin was added to **cilazapril** (approximately 60% versus 30% reduction in hypotensive effect measured 3 hours after the morning dose).[34] In 10 hypertensive patients the antihypertensive effects of **perindopril** 4 to 8 mg daily were also found to be reduced by about 30% by indometacin 50 mg twice daily.[35] A brief mention is made in a review that, in healthy subjects, the pharmacodynamics of **ramipril** were unaffected by indometacin (dose not stated) given for 3 days.[36] Indometacin 25 mg three times daily did not alter the hypotensive effects of **trandolapril** 2 mg daily in 17 hypertensive patients.[37]

(d) Naproxen

In a randomised study, 19% of 130 patients given naproxen 500 mg twice daily developed hypertension within 6 weeks (defined as a 24-hour systolic blood pressure greater than 135 mmHg). These patients had well-controlled hypertension at baseline; 83% were receiving an ACE inhibitor and 66% an additional antihypertensive.[7] The proportion of patients who developed hypertension was similar to that with celecoxib (16%) and less than that with rofecoxib (30%).

(e) Rofecoxib

The manufacturer of rofecoxib noted that in patients with mild-to-moderate hypertension, rofecoxib 25 mg daily, taken with **benazepril** 10 to 40 mg daily, for 4 weeks, was associated with a small attenuation of the antihypertensive effect (average increase in mean arterial pressure of 2.8 mmHg).[38] Similarly, a case report describes a patient taking **lisinopril** 10 mg daily whose blood pressure rose from 127/78 mmHg to 143/89 mmHg when he was given rofecoxib 25 mg daily. His blood pressure was controlled by increasing the dose of **lisinopril** to 20 mg daily.[39]

In another study, in 810 elderly patients with osteoarthritis and controlled hypertension given either celecoxib 200 mg or rofecoxib 25 mg daily for 6 weeks, approximately 29% of the patients randomised to the rofecoxib group were receiving ACE inhibitors. Systolic blood pressure increased by a clinically significant amount (greater than 20 mmHg) in 17% of the patients receiving rofecoxib.[4] In another similar randomised study, 30% of 138 patients given rofecoxib 25 mg daily developed hypertension within 6 weeks (defined as a 24-hour systolic blood pressure greater than 135 mmHg). These patients had well-controlled hypertension at baseline; 84% were receiving an ACE inhibitor and 62% an additional antihypertensive.[7] The proportion of patients who developed hypertension was greater than with celecoxib (16%) or naproxen (19%).

(f) Sulindac

In one study, sulindac 200 mg twice daily given to patients taking **captopril** 100 to 200 mg twice daily caused only a small rise in blood pressure (from 132/92 mmHg to 137/95 mmHg).[15] Sulindac 150 mg twice daily did not attenuate the blood pressure response to **captopril** when it was substituted for ibuprofen in an elderly woman.[9] Similarly, sulindac 200 mg twice daily did not blunt the antihypertensive effect of **enalapril** in 9 patients with hypertension.[31] Two studies in black women also found that sulindac 200 mg twice daily for one month did not alter the antihypertensive effect of **fosinopril** 10 to 40 mg daily or **lisinopril** 10 to 40 mg daily (given with hydrochlorothiazide 25 mg daily).[10,11]

(g) Other NSAIDs

In 6 hypertensive patients taking **enalapril**, a single 8-mg dose of **lornoxicam** was found to have no effect on systolic blood pressure, but a small rise in diastolic pressure (from 88.2 mmHg to 93.3 mmHg) occurred after 2 hours.[25] In 29 patients with hypertension **oxaprozin** 1.2 g daily for 3 weeks did not affect the pharmacodynamics of **enalapril** 10 to 40 mg daily.[40]

Twenty-five hypertensive patients with osteoarthritis taking **trandolapril** 2 to 4 mg daily (with or without hydrochlorothiazide) had an increase in blood pressure of about 3/4 mmHg when they were given **diclofenac** 75 mg twice daily.[6] However, **diclofenac** 75 mg twice daily for one month did not alter the antihypertensive effect of **lisinopril** 10 to 40 mg daily (given with hydrochlorothiazide).[11]

A study found that only 5 of 91 (5.5%) hypertensive patients stable taking ACE inhibitors had clinically significant increases in blood pressure when they were given **nabumetone** 1 g twice daily for 4 weeks.[5] A study in 17 black women found that **nabumetone** 1 g twice daily for one month did not alter the antihypertensive effect of **fosinopril** 10 to 40 mg daily (given with hydrochlorothiazide).[10]

B. Effects on renal function

A case report describes a patient with heart failure treated intermittently with **ibuprofen** and later with **naproxen** and **indometacin** for gout, who developed acute renal failure when also given **captopril**. Treatment with an NSAID alone was without adverse effects on renal function and treatment with **captopril** alone appeared to improve his renal function.[41] In a retrospective analysis, 3 of 162 patients who had been taking ACE inhibitors and NSAIDs developed reversible renal failure, compared with none of 166 patients taking ACE inhibitors alone and none of 2116 patients tak-

ing NSAIDs alone. One patient was taking **naproxen** or **salsalate** and had a progressive decline in renal function over 19 months after **captopril** was started. Another man taking unnamed NSAIDs developed reversible renal failure 4 days after starting to take **captopril**.[42] In another similar analysis, in patients aged over 75 years, 2 out of 12 patients given an ACE inhibitor and an NSAID developed acute renal failure (one died) and a further 4 patients had a deterioration in their renal function. All of these 6 patients were also taking diuretics (see 'ACE inhibitors + Diuretics; Loop, Thiazide and related', p.23), but of the 6 with unaffected renal function, only two were taking diuretics.[43] A randomised, crossover study in 17 black patients receiving **fosinopril** with hydrochlorothiazide and NSAIDs for a month, found that acute renal failure (a decrease in glomerular filtration rate of greater than or equal to 25%) occurred in 4 of the 17 patients when receiving **ibuprofen**, 1 of 17 when receiving **sulindac** and 0 of 17 when receiving **nabumetone**.[10]

In a multivariate analysis, the use of ACE inhibitors or angiotensin II receptor antagonists with NSAIDs or diuretics was associated with significant renal impairment when two or more drugs from these groups was taken.[44] In a nested case-control study using the UK General Practice Research Database, the relative risk of acute renal failure was 3.2 with NSAID use, 3.5 with ACE inhibitor use, and 10.6 with NSAIDs and a cardiovascular drug. The risk was not more than additive with NSAIDs and ACE inhibitors.[45] In a case-control study, recently starting an NSAID was associated with a 2.2-fold increased risk of hospitalisation for renal impairment in patients taking ACE inhibitors.[46] In 2002, 28 of 129 reports to the Australian Adverse Drug Reactions Advisory Committee of acute renal failure were associated with the concurrent use of ACE inhibitors (or angiotensin II receptor antagonists), diuretics, and NSAIDs (including coxibs), and these cases had a fatality rate of 10%. In patients taking this triple combination, renal failure appeared to be precipitated by mild stress such as diarrhoea or dehydration. In other patients, the addition of a third drug (usually an NSAID) to a stable combination of the other two, resulted in acute renal failure.[47]

A placebo-controlled study in 10 patients with chronic congestive heart failure taking an ACE inhibitor (**captopril**, **cilazapril**, **enalapril**, **ramipril**), and aspirin 75 to 125 mg daily (for ischaemic heart disease) found that when they were given a single 50-mg dose of **diclofenac** after aspirin had been discontinued for at least one week, there was a significant deterioration in renal function compared with placebo or aspirin. Compared with placebo, both aspirin and **diclofenac** caused slight but significant increases in serum creatinine.[48]

In contrast, a retrospective analysis found no evidence that the adverse effects of ACE inhibitors on renal function were greater in those taking NSAIDs.[49] A further study in 17 hypertensive patients with normal baseline renal function, found that **indometacin** 25 mg three times daily did not adversely affect renal function when it was given with **trandolapril** 2 mg daily for 3 weeks.[50]

C. Hyperkalaemia

Hyperkalaemia, resulting in marked bradycardia, was attributed to the use of **loxoprofen** in an elderly woman taking **imidapril**.[51] A 77-year-old woman with mild hypertension and normal renal function taking **enalapril** 2.5 mg daily arrested and died 5 days after starting to take **rofecoxib** for leg pain. Her potassium was found to be 8.8 mmol/L. Infection and dehydration could have contributed to the hyperkalaemia in this patient.[52]

D. Pharmacokinetic studies

The manufacturer of **spirapril** briefly noted in a review that there was no relevant pharmacokinetic interaction between spirapril and **diclofenac**.[53] In 29 patients with hypertension, **oxaprozin** 1.2 g daily for 3 weeks did not affect the pharmacokinetics of **enalapril** 10 to 40 mg daily.[40] A brief mention is made in a review that, in healthy subjects, the pharmacokinetics of **ramipril** were unaffected by **indometacin** [dose not stated] given for 3 days.[36]

Mechanism

Some, but not all the evidence suggests that prostaglandins may be involved in the hypotensive action of ACE inhibitors, and that NSAIDs, by inhibiting prostaglandin synthesis, may partially antagonise the effect of ACE inhibitors. Another suggestion is that NSAIDs promote sodium retention and so blunt the blood pressure lowering effects of several classes of antihypertensive drugs, including ACE inhibitors. This interaction may be dependent on sodium status and on plasma renin, and so drugs that affect sodium status e.g. diuretics may possibly influence the effect. Therefore, the interaction does not occur in all patients. It may also depend on the NSAID, with indometacin being frequently implicated, and sulindac less so, as well as on the dosing frequency.[6]

Both NSAIDs and ACE inhibitors alone can cause renal impairment. In patients whose kidneys are under perfused, they may cause further deterioration in renal function when used together.[54] Impaired renal function is a risk factor for hyperkalaemia with ACE inhibitors.

Importance and management

The interaction between indometacin and ACE inhibitors is well established, with several studies showing that indometacin can reduce the **blood pressure-lowering** effect of a number of ACE inhibitors. The interaction may not occur in all patients. If indometacin is required in a patient taking any ACE inhibitor, it would be prudent to monitor blood pressure. In a few small comparative studies, indometacin has been shown to have less effect on the calcium-channel blockers amlodipine, felodipine, and nifedipine, than on enalapril.[24,27,28] Therefore, a calcium-channel blocker may sometimes be an alternative to an ACE inhibitor in a patient requiring indometacin. Consider also, 'Calcium-channel blockers + Aspirin or NSAIDs', p.1027.

Limited information suggests that sulindac has little or no effect on ACE inhibitors, and may therefore be less likely to cause a problem, but further study is needed. The coxibs appear to have similar or greater effects on ACE inhibitors than conventional NSAIDs.

Although information about other NSAIDs is limited, the mechanism suggests that all of them are likely to interact similarly. Until more is known, it may be prudent to increase blood pressure monitoring when any NSAID is added or discontinued in a patient taking any ACE inhibitor, and intermittent use of NSAIDs should be considered as a possible cause of erratic control of blood pressure. In addition, sodium status and therefore diuretic use may affect any interaction. However, some consider that the clinical importance of an interaction between NSAIDs and antihypertensives is less than has previously been suggested.[55] While their findings do not rule out a 2/1 mmHg increase in blood pressure with NSAIDs in treated hypertensives, they suggest that if patients in primary care have inadequate control of blood pressure, other reasons may be more likely than any effect of concurrent NSAIDs.[55] Further study is needed. For the effects of NSAIDs on other antihypertensive drug classes see 'Beta blockers + Aspirin or NSAIDs', p.997, 'Calcium-channel blockers + Aspirin or NSAIDs', p.1027, and 'Thiazide diuretics + NSAIDs', p.1138.

There is an increased risk of **deterioration in renal function** or acute renal failure with the combination of NSAIDs and ACE inhibitors, especially if poor renal perfusion is present. Renal function should be monitored periodically in patients taking ACE inhibitors with NSAIDs, particularly in volume depleted patients. In a statement, the American Heart Association comments that acute renal failure complicating the use of an ACE inhibitor is almost always reversible and repletion of extracellular fluid volume and discontinuation of any diuretic is the best approach. In addition, withdrawal of interacting drugs, supportive management of fluid and electrolytes, and temporary dialysis, where indicated, are the mainstays of treatment.[56] The Australian Adverse Drug Reactions Advisory Committee consider that the triple combination of ACE inhibitors, diuretics and NSAIDs (including coxibs) should be avoided if possible, and that great care should be taken when giving ACE inhibitors and NSAIDs to patients with renal impairment.[47] Deterioration in renal function increases the risk of **hyperkalaemia**.

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ACE inhibitors and other antihypertensives + Orlistat

In a handful of cases, patients taking enalapril and/or losartan and other antihypertensive drugs (amlodipine, atenolol, hydrochlorothiazide) had marked increases in blood pressure, hypertensive crises and, in one case, intracranial haemorrhage, within 7 to 60 days of starting orlistat.

Clinical evidence

The Argentinian System of Pharmacovigilance identified the following 3 cases of a possible interaction of orlistat with antihypertensives. An obese man whose hypertension was controlled at 120/80 mmHg with daily doses of **losartan** 100 mg, **atenolol** 100 mg, and **hydrochlorothiazide** 12.5 mg developed a hypertensive crisis (BP 260/140 mmHg) 7 days after starting to take orlistat 120 mg three times daily. The orlistat was stopped and the crisis was controlled. When later rechallenged with orlistat, his diastolic blood pressure rose to 100 to 110 mmHg after 5 days, but the systolic blood pressure increased only slightly. His blood pressure returned to baseline values 3 days after stopping the orlistat.[1] Two other patients reacted similarly. One whose blood pressure was controlled at 130/85 mmHg with **enalapril** 20 mg daily and **losartan** 50 mg daily developed an intracranial haemorrhage and hypertension (BP 160/100 mmHg) with occasional systolic peaks of around 200 mmHg one week after starting orlistat 120 mg three times daily. The other patient who was taking **enalapril** 20 mg daily and **amlodipine** 5 mg daily began to develop hypertensive peaks (BP 180/120 mmHg) 60 days after starting orlistat 120 mg twice daily. The hypertension responded when his medication was changed to **losartan** with **hydrochlorothiazide**, but 20 days later new hypertensive peaks developed (BP 180/110 to 120 mmHg). When the orlistat was withdrawn, the hypertension was controlled within 48 hours.[1]

The Uppsala Adverse Drug Reaction database has two reports of aggravated hypertension in women taking antihypertensives and orlistat.[1] Hypertension has also been reported in previously normotensive individuals taking orlistat, which, in one case, responded to stopping orlistat.[2,3]

However, the manufacturer has found no evidence of an association between orlistat and hypertension. In clinical studies, orlistat use was associated with a small reduction in blood pressure compared with placebo, which was as a result of weight reduction. Moreover, the incidence of hypertension of new onset and hypertensive crisis did not differ between orlistat and placebo (1.2% versus 1.3%, and 0% versus 0.1%, respectively).[4] In studies in healthy subjects, orlistat had no effect on steady-state **losartan** pharmacokinetics,[5] and no clinically significant effect on the pharmacokinetics of single-dose **captopril**, **atenolol**, **furosemide** or **nifedipine**.[6]

Mechanism

Not understood. Suggestions include a decrease in the absorption of the drugs due to accelerated gastrointestinal transit, increased defaecation, diarrhoea, or an increase in the amount of fat in the chyme.[1] An explanation for the difference between the clinical cases and pharmacokinetic studies may be that the latter tended to be single-dose studies in healthy subjects. Alternatively, these cases could just be idiosyncratic and not related to orlistat treatment.

Importance and management

The interactions between the antihypertensives and orlistat seem to be confined to the reports cited here, and their general significance is unclear. Given that the manufacturers report that specific drug interaction studies have not found any evidence of an interaction, the incidence seems likely to be small.

1. Valsecia ME, Malgor LA, Farías EF, Figueras A, Laporte J-R. Interaction between orlistat and antihypertensive drugs. *Ann Pharmacother* (2001) 35, 1495–6.
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3. Persson M, Vitols S, Yue Q-Y. Orlistat associated with hypertension. Author's reply. *BMJ* (2001) 322, 111.
4. Huber MH. Orlistat associated with hypertension. Roche concludes that there is no evidence of a causal association. *BMJ* (2001) 322, 110.
5. Zhi J, Moore R, Kanitra L, Mulligan TE. Pharmacokinetic evaluation of the possible interaction between selected concomitant medications and orlistat at steady state in healthy subjects. *J Clin Pharmacol* (2002) 42, 1011–19.
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ACE inhibitors + Potassium compounds

ACE inhibitors maintain serum potassium levels. Hyperkalaemia is therefore possible if potassium supplements or potassium-containing salt substitutes are given, particularly in those patients where other risk factors are present.

Clinical evidence

(a) Potassium levels increased by concurrent use

1. Potassium supplements. The serum potassium levels of a patient taking a potassium supplement rose by 66% when **captopril** was added, with signs of a deterioration in renal function. Four other patients taking potassium supplements and furosemide (2 also taking unnamed potassium-sparing diuretics) had rises in their potassium levels of only 8 to 24% when given **captopril**. The rises occurred within one or 2 days. No clinical signs or symptoms of hyperkalaemia were seen, but 3 of the 5 patients had rises to above the upper limits of normal.[1] A post-marketing survey identified 10 patients in whom **enalapril** appeared to have been associated with renal impairment and death. Eight of them were also taking potassium supplements and/or potassium-sparing diuretics, and hyperkalaemia appeared to have been the immediate cause of death in two of them.[2] In a review of 47 patients taking **enalapril** for heart failure, and who experienced serious hyperkalaemia, 8 had also received potassium supplements.[3]
In another survey of 53 patients taking ACE inhibitors who had hyperkalaemia in the absence of significant renal impairment, less than 5% were taking a potassium supplement, but 30% were using a potassium-containing salt substitute (see *Dietary potassium*, below).[4]

2. Dietary potassium. Two patients with renal impairment, one taking **lisinopril** and the other taking **enalapril**, developed marked hyperkalaemia shortly after starting to take '*Lo salt*' (a salt substitute containing 34.6 g potassium in every 100 g). One developed a life-threatening arrhythmia.[5] A similar report describes a man taking **captopril** who developed hyperkalaemia and collapsed 2 weeks after starting to use a salt substitute containing potassium.[6] In a further report, severe hyperkalaemia occurred in a patient receiving a very-low-calorie diet with a protein supplement who was taking **lisinopril** 10 mg daily. The protein supplement contained 48 mmol of potassium, and salad topped with lemon juice and potassium chloride salt added at least another 72 mmol of potassium daily.[7] In 53 patients taking ACE inhibitors who had hyperkalaemia in the absence of significant renal impairment, 30% were using a salt substitute, and 72% were eating a moderate-to-high potassium diet, consisting of 2 or more servings of a potassium-rich food daily.[4] Hyperkalaemia and acute renal failure has also been reported in a diabetic patient taking **lisinopril** 20 mg twice daily following the use of a potassium-based water softener.[8]

(b) Potassium levels unaltered by concurrent use

A retrospective analysis of 14 patients without renal impairment taking potassium supplements and either furosemide or hydrochlorothiazide, found that the levels of serum potassium, during a 4-year period, had not significantly increased after the addition of **captopril**.[9] Another study in 6 healthy subjects found that intravenous potassium chloride caused virtually the same rise in serum potassium levels in those given **enalapril** as in those given a placebo.[10]

Mechanism

The potassium-retaining effects of the ACE inhibitors (due to reduced aldosterone levels) are additive with an increased intake of potassium, particularly when there are other contributory factors such as poor renal function or diabetes.

Importance and management

The documentation of this interaction appears to be limited, but it is well established. In practice, a clinically relevant rise in potassium levels usually occurs only if other factors are also present, the most important of which is impaired renal function. In general, because ACE inhibitors have potassium-sparing effects, potassium supplements should not routinely be given concurrently. If a supplement is needed, serum potassium should be closely monitored. This is especially important where other possible contributory risk factors are known to be present. A retrospective study in hospitalised patients who developed hyperkalaemia found that risk factors associated with a rapid rate of increase in serum potassium levels in decreasing order of importance were: the use of potassium supplements, severe renal impairment, the use of ACE inhibitors or angiotensin II receptor antagonists, the use of potassium-sparing diuretics, and then diabetes mellitus. Further, the presence of two or more of these risk factors (e.g. the use of an ACE inhibitor and a potassium supplement) was associated with an even faster rate of development of hyperkalaemia. As the rate of development of hyperkalaemia is also correlated with its severity, the authors recommend close monitoring in patients with two or more risk factors, and that a rapid increase in serum potassium (greater than 0.5 mmol/L per day) should prompt the identification and possible removal of any risk factors for hyperkalaemia.[11]

Other sources of dietary potassium should also be borne in mind. Patients with heart disease and hypertension are often told to reduce their salt (sodium) intake. One way of doing this is to use potassium-containing salt substitutes. However, it appears that there is some risk associated with excess use of these substitutes, especially in patients taking ACE inhibitors.

1. Burnakis TG, Mioduch HJ. Combined therapy with captopril and potassium supplementation. A potential for hyperkalemia. *Arch Intern Med* (1984) 144, 2371–2.
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3. Brown C, Rush J. Risk factors for the development of hyperkalemia in patients treated with enalapril for heart failure. *Clin Pharmacol Ther* (1989) 45, 167.
4. Good CB, McDermott L, McCloskey B. Diet and serum potassium in patients on ACE inhibitors. *JAMA* (1995) 274, 538.
5. Ray KK, Dorman S, Watson RDS. Severe hyperkalaemia due to the concomitant use of salt substitutes and ACE inhibitors in hypertension: a potentially life threatening interaction. *J Hum Hypertens* (1999) 13, 717–20.
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7. Stoltz ML, Andrews CE. Severe hyperkalemia during very-low-calorie diets and angiotensin converting enzyme use. *JAMA* (1990) 264, 2737–8.
8. Graves JW. Hyperkalemia due to a potassium-based water softener. *N Engl J Med* (1998) 339,1790–1.
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10. Scandling JD, Izzo JL, Pabico RC, McKenna BA, Radke KJ, Ornt DB. Potassium homeostasis during angiotensin-converting enzyme inhibition with enalapril. *J Clin Pharmacol* (1989) 29, 916–21.
11. Indermitte J, Burkolter S, Drewe J, Krähenbühl S, Hersberger KE. Risk factors associated with a high velocity of the development of hyperkalaemia in hospitalised patients. *Drug Safety* (2007) 30, 71–80.

ACE inhibitors + Probenecid

Probenecid decreases the renal clearance of captopril and enalapril.

Clinical evidence, mechanism, importance and management

In 4 healthy subjects the steady-state levels of unchanged and total **captopril**, given by intravenous infusion, were slightly increased (by 14% and 36%, respectively) by the use of probenecid. Renal clearance of unchanged **captopril** decreased by 44%, but total clearance was reduced by only 19%.[1] These moderate changes are unlikely to be clinically important.

In 12 healthy subjects probenecid 1 g twice daily for 5 days increased the AUC of a single 20-mg oral dose of **enalapril** and its active metabolite, enalaprilat by about 50%. The renal clearance of **enalapril** was decreased

by 73%.[2] A moderate increase in the hypotensive effects might be expected, but there do not appear to be any reports of adverse effects.

1. Singhvi SM, Duchin KL, Willard DA, McKinstry DN, Migdalof BH. Renal handling of captopril: effect of probenecid. *Clin Pharmacol Ther* (1982) 32, 182–9.
2. Noormohamed FH, McNabb WR, Lant AF. Pharmacokinetic and pharmacodynamic actions of enalapril in humans: effect of probenecid pretreatment. *J Pharmacol Exp Ther* (1990) 253, 362–8.

ACE inhibitors + Procainamide

The combination of captopril or other ACE inhibitors and procainamide possibly increases the risk of leucopenia. No pharmacokinetic interaction occurs between captopril and procainamide.

Clinical evidence, mechanism, importance and management

In 12 healthy subjects the concurrent use of **captopril** 50 mg twice daily and procainamide 250 mg every 3 hours did not affect the pharmacokinetics of either drug.[1] A study in 9 patients undergoing treatment for heart failure (including 8 who were taking ACE inhibitors) found that the pharmacokinetics of a single intravenous dose of procainamide 750 mg and its metabolite *N*-acetylprocainamide were not significantly different to the pharmacokinetics in 7 matched control subjects without left ventricular dysfunction (one taking an ACE inhibitor). However, there was wider interpatient variation in pharmacokinetic parameters in the patients with heart failure.[2] The US manufacturer of **captopril** noted that in patients with heart failure who developed neutropenia, about 50% had a serum creatinine of about 140 micromol/L or greater, and more than 75% were also receiving procainamide.[3] Similarly, the UK manufacturer of **captopril** notes that neutropenia or agranulocytosis and serious infection have occurred in patients taking **captopril**, and that the concurrent use of procainamide may be a complicating factor. They recommend that the combination should be used with caution, especially in patients with renal impairment. They suggest that differential white blood cell counts should be performed before concurrent use, then every 2 weeks in the first 3 months of treatment and periodically thereafter.[4] The UK manufacturers of a number of other ACE inhibitors suggest that the concurrent use of ACE inhibitors and procainamide may lead to an increased risk of leucopenia.

For reports of other possible interactions with ACE inhibitors that might result in an increased risk of leucopenia see also 'ACE inhibitors + Allopurinol', p.13 and 'ACE inhibitors + Azathioprine', p.18.

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2. Tisdale JE, Rudis MI, Padhi ID, Borzak S, Svensson CK, Webb CR, Acciaioli J, Ware JA, Krepostman A, Zarowitz BJ. Disposition of procainamide in patients with chronic congestive heart failure receiving medical therapy. *J Clin Pharmacol* (1996) 36, 35–41.
3. Capoten (Captopril). Par Pharmaceutical, Inc. US Prescribing information, June 2003.
4. Capoten (Captopril). E. R. Squibb & Sons Ltd. UK Summary of product characteristics, September 2008.

ACE inhibitors + Rifampicin (Rifampin)

An isolated report describes a rise in blood pressure in one hypertensive patient, which was attributed to an interaction between enalapril and rifampicin. Rifampicin may reduce the plasma levels of the active metabolites of imidapril and spirapril.

Clinical evidence

A man taking **enalapril** and a variety of other drugs (warfarin, acebutolol, bendroflumethiazide, dipyridamole, metoclopramide and *Gaviscon*) developed a fever. He was given streptomycin, oxytetracycline and rifampicin, because of a probable *Brucella abortus* infection, whereupon his blood pressure rose from 164/104 mmHg to 180/115 mmHg over the next 5 to 6 days. It was suspected that an interaction with the rifampicin was possibly responsible. Subsequent studies in the same patient found that rifampicin, reduced the $AUC_{0\text{-}7}$ of enalaprilat, the active metabolite of **enalapril**, by 31%, although the AUC of **enalapril** was unchanged.[1] There is also the hint of this interaction in another report, where **enalapril** did not control blood pressure in a patient taking rifampicin.[2]

The manufacturer of **spirapril** briefly noted in a review that the use of rifampicin with **spirapril** modestly decreased plasma levels of **spirapril** and its active metabolite, spiraprilat.[3] The manufacturer of **imidapril** notes that rifampicin reduces the plasma levels of imidaprilat, the active metabolite of **imidapril**.[4]

Mechanism

The mechanism of this interaction is not clear, because rifampicin is a potent liver enzyme inducer, which might have been expected to cause the production of more, rather than less, of the active metabolites of these ACE inhibitors. However, the authors of one of the reports postulated that the rifampicin might have increased the loss of the enalaprilat in the urine,[1] and others suggested that rifampicin causes a non-specific stimulation of the elimination of spiraprilat.[3]

Importance and management

The general importance of these interactions is uncertain. The isolated reports with enalapril suggest minor clinical relevance. The manufacturers of spirapril did not consider the modest pharmacokinetic changes to be clinically relevant.[3] However, the manufacturers of imidapril state that rifampicin might reduce the antihypertensive efficacy of imidapril,[4] but this awaits clinical assessment.

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2. Tada Y, Tsuda Y, Otsuka T, Nagasawa K, Kimura H, Kusaba T, Sakata T. Case report: nifedipine-rifampicin interaction attenuates the effect on blood pressure in a patient with essential hypertension. *Am J Med Sci* (1992) 303, 25–7.
3. Grass P, Gerbeau C, Kutz K. Spirapril: pharmacokinetic properties and drug interactions. *Blood Pressure* (1994) 3 (Suppl 2), 7–13.
4. Tanatril (Imidapril hydrochloride). Chiesi Ltd. UK Summary of product characteristics, November 2007.

ACE inhibitors + Sevelamer

Sevelamer did not alter the pharmacokinetics of enalapril in one study.

Clinical evidence, mechanism, importance and management

In 28 healthy subjects the concurrent use of a single 2.418-g dose of sevelamer hydrochloride (equivalent to 6 capsules) did not alter the AUC of a single 20-mg dose of **enalapril** or its active metabolite, enalaprilat.[1] Thus it appears that sevelamer does not bind to **enalapril** within the gut to reduce its absorption. Other ACE inhibitors would not be expected to interact with sevelamer, but this needs confirmation.

1. Burke SK, Amin NS, Incerti C, Plone MA, Lee JW. Sevelamer hydrochloride (Renagel®), a phosphate-binding polymer, does not alter the pharmacokinetics of two commonly used antihypertensives in healthy volunteers. *J Clin Pharmacol* (2001) 41, 199–205.

ACE inhibitors + Sibutramine

Sibutramine has only a minimal effect on blood pressure control with ACE inhibitors.

Clinical evidence, mechanism, importance and management

In a randomised, double-blind study over 52 weeks in 220 obese, hypertensive patients, whose hypertension was well controlled with an ACE inhibitor (**benazepril**, **enalapril** or **lisinopril**) with or without a thiazide diuretic, two-thirds of the patients were also given sibutramine and one-third were given placebo. Sibutramine 20 mg daily caused small increases in mean blood pressure compared with placebo (133.1/85.5 mmHg compared with 130.4/82.8 mmHg, at 52 weeks, respectively), but overall, hypertension remained well controlled.[1] Another double-blind, placebo-controlled study in 86 obese patients taking ACE inhibitors and/or other antihypertensives, found that sibutramine 10 mg daily for 6 months reduced ventricular mass, but caused no significant alterations in blood pressure, although average heart rate increased from 78 to 82 bpm.[2] No

particular precautions therefore seem necessary if patients taking ACE inhibitors are given sibutramine.

1. McMahon FG, Weinstein SP, Rowe E, Ernst KR, Johnson F, Fujioka K, and the Sibutramine in Hypertensives Clinical Study Group. Sibutramine is safe and effective for weight loss in obese patients whose hypertension is well controlled with angiotensin-converting enzyme inhibitors. *J Hum Hypertens* (2002) 16, 5–11.
2. Faria AN, Ribeiro Filho FF, Lerário DDG, Kohlmann N, Ferreira SRG, Zanella MT. Effects of sibutramine on the treatment of obesity in patients with arterial hypertension. *Arq Bras Cardiol* (2002) 78, 176–80.

Angiotensin II receptor antagonists + Aliskiren

The concurrent use of irbesartan, or valsartan with aliskiren does not result in clinically significant pharmacokinetic interactions. However, the concurrent use of aliskiren and angiotensin II receptor antagonists may increase the risk of hyperkalaemia. The concurrent use of irbesartan or valsartan with aliskiren results in a greater reduction in blood pressure.

Clinical evidence, mechanism, importance and management

In a study, 11 patients with mild to moderate renal impairment and 17 healthy subjects were given aliskiren 300 mg daily for 7 days. **Irbesartan** 300 mg daily was then started, and both drugs were given for a further 7 days. The steady-state pharmacokinetics of aliskiren were not affected by the concurrent use of **irbesartan**.[1]

In a study in 23 patients with hypertension, the addition of aliskiren 75 or 150 mg daily to **irbesartan** 150 mg for 3 weeks resulted in lower night-time blood pressures, when compared with **irbesartan** alone, and there was a non-significant reduction in daytime blood pressure with aliskiren 75 mg daily. There was a trend for both daytime and night-time blood pressures to rise rather than fall when the dose of aliskiren was increased from 75 to 150 mg daily, but these changes were not statistically significant. The plasma levels of aliskiren were not affected by **irbesartan**.[2]

In another study, 18 healthy subjects were given **valsartan** 320 mg daily with aliskiren 300 mg daily for 4 days. When compared with the use of either drug alone, **valsartan** decreased the AUC and peak plasma levels of aliskiren by 26% and 28%, respectively, and aliskiren decreased the AUC and peak plasma levels of **valsartan** by 14% and 12%, respectively.[3] These pharmacokinetic changes were not considered to be clinically relevant.[3]

The concurrent use of aliskiren and angiotensin II receptor antagonists does not appear to result in clinically significant pharmacokinetics interactions (seen with **valsartan** and **irbesartan**). However, as would be expected, concurrent use does appear to result in an increased blood pressure-lowering effect, which would generally be considered desirable. Nevertheless, be alert for a greater than desired hypotensive effect. Also note that, the manufacturer of aliskiren warns that patients receiving other drugs that inhibit the renin-angiotensin system, and/or those with reduced renal function and/or diabetes are at an increased risk of hyperkalaemia during the use of aliskiren.[4] This is presumably based on the results of a study with ramipril, see 'ACE inhibitors + Aliskiren', p.13.

1. Vaidyanathan S, Bigler H, Yeh CM, Bizot M-N, Dieterich HA, Howard D, Dole WP. Pharmacokinetics of the oral direct renin inhibitor aliskiren alone and in combination with irbesartan in renal impairment. *Clin Pharmacokinet* (2007) 46, 661–75.
2. O'Brien E, Barton J, Nussberger J, Mulcahy D, Jensen C, Dicker P, Stanton A. Aliskiren reduces blood pressure and suppresses plasma renin activity in combination with a thiazide diuretic, an angiotensin-converting enzyme inhibitor, or an angiotensin receptor blocker. *Hypertension* (2007) 49, 276–84.
3. Vaidyanathan S, Valencia J, Kemp C, Zhao C, Yeh C-M, Bizot M-N, Denouel J, Dieterich HA, Dole WP. Lack of pharmacokinetic interactions of aliskiren, a novel direct renin inhibitor for the treatment of hypertension, with the antihypertensives amlodipine, valsartan, hydrochlorothiazide (HCTZ) and ramipril in healthy volunteers. *Int J Clin Pract* (2006) 60, 1343–56.
4. Rasilez (Aliskiren hemifumarate). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, April 2009.

Angiotensin II receptor antagonists + Antacids

Aluminium/magnesium hydroxide-containing antacids slightly reduce irbesartan and olmesartan absorption.

Clinical evidence, mechanism, importance and management

(a) Irbesartan

In a single-dose, crossover study in 18 healthy subjects, 10 mL of an antacid containing **aluminium/magnesium hydroxide** (*Unimaalox*) given with, or 2 hours before, a single 300-mg dose of irbesartan had little effect on irbesartan pharmacokinetics. The only difference was that the AUC of irbesartan was reduced by 10% when the antacid was given 2 hours before the irbesartan, when compared with irbesartan alone. However, this change is not considered to be clinically relevant.[1]

(b) Olmesartan

The steady-state AUC of olmesartan 20 mg daily was 12% lower when it was given 15 minutes after a daily dose of an **aluminium/magnesium hydroxide** antacid, when compared with olmesartan alone, but this was not considered to be clinically significant.[2]

1. Marino MR, Vachharajani NN. Drug interactions with irbesartan. *Clin Pharmacokinet* (2001) 40, 605–14.
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Angiotensin II receptor antagonists + Aspirin or NSAIDs

Indometacin may attenuate the antihypertensive effect of losartan, valsartan, or other angiotensin II receptor antagonists. However, low-dose aspirin does not appear to alter the antihypertensive effect of losartan. No clinically relevant *pharmacokinetic* interactions occur between telmisartan and ibuprofen, or between valsartan and indometacin. The combination of an NSAID and angiotensin II receptor antagonist can increase the risk of renal impairment and hyperkalaemia.

Clinical evidence

A. Effects on blood pressure

Various large epidemiological studies and meta-analyses of clinical studies have been conducted to assess the effect of NSAIDs on blood pressure in patients treated with antihypertensives, and the findings of these are summarised in 'Table 23.2', (p.1027). In these studies, NSAIDs were not always associated with an increase in blood pressure, and the maximum increase was 6.2 mmHg.

(a) Aspirin

A double-blind, placebo-controlled study in 10 patients with hypertension taking **losartan** (mean daily dose 47.5 mg) found that both aspirin 81 mg daily and aspirin 325 mg daily for 2 weeks did not have a significant effect on blood pressure.[1]

(b) Indometacin

In a study in 111 patients with hypertension, **losartan** 50 mg daily for 6 weeks reduced their blood pressure by a mean of 7.9/5.3 mmHg. Indometacin 75 mg daily was then added for one week and this caused a rise in blood pressure in the group as a whole of 3.8/2.2 mmHg (reduction of about 45% in the effect of **losartan**). A rise in ambulatory diastolic blood pressure was seen in 69% of the patients taking **losartan** during indometacin use.[2] In contrast, a much smaller study in 10 patients with essential hypertension taking **losartan** found that indometacin 50 mg twice daily for one week caused sodium and fluid retention, but did not significantly attenuate the antihypertensive effects of **losartan**.[3]

In a placebo-controlled, crossover study in 56 hypertensive patients whose blood pressure was adequately controlled by **valsartan** 80 to 160 mg daily, the addition of indometacin 50 mg twice daily for 2 weeks produced an increase in mean blood pressure of 2.1/1.9 mmHg.[4] A study in normotensive subjects given a fixed sodium intake and **valsartan** 80 mg daily, with or without indometacin 50 mg twice daily for one week, found that indometacin reduced the natriuretic response to angiotensin receptor blockade.[5]

B. Effects on renal function

In 2002, 28 of 129 reports to the Australian Adverse Drug Reactions Advisory Committee of acute renal failure were associated with the concurrent use of ACE inhibitors or angiotensin II receptor antagonists, diuretics, and NSAIDs (including coxibs), and these cases had a fatality rate of 10%. In patients taking this triple combination, renal failure appeared to be precipitated by mild stress such as diarrhoea or dehydration. In other patients, the addition of a third drug (usually an NSAID) to a stable combination of the other two, resulted in acute renal failure.[6] In a multivariate analysis,

the use of an ACE inhibitor or angiotensin II receptor antagonist, and NSAIDs or diuretics was associated with significant renal impairment when two or more drugs from these groups was taken.[7]

C. Pharmacokinetic studies

(a) Ibuprofen

In a crossover study in 12 healthy subjects, **telmisartan** 120 mg daily had no effect on the pharmacokinetics of ibuprofen 400 mg three times daily for 7 days. Similarly, the pharmacokinetics of **telmisartan** were unaffected by the concurrent use of ibuprofen, when compared with previous studies of telmisartan alone.[8]

(b) Indometacin

In 12 healthy subjects, the pharmacokinetics of single oral doses of **valsartan** 160 mg or indometacin 100 mg were not significantly changed when the drugs were given together, although the pharmacokinetics of valsartan showed wide variations between subjects.[9]

Mechanism

Some evidence suggests that prostaglandins may be partially involved in the hypotensive action of angiotensin II receptor antagonists, and that NSAIDs, by inhibiting prostaglandin synthesis, may antagonise their effects. However, a non-specific mechanism such as sodium retention may also be involved, as indometacin has been shown to reduce the hypotensive effect of other classes of antihypertensive drugs.[4,5] Both NSAIDs and angiotensin II receptor antagonists alone can cause renal impairment: in patients whose kidneys are under perfused, they may cause further deterioration in renal function if they are used together. Renal impairment increases the risk of hyperkalaemia.

Importance and management

As with other antihypertensives, the **blood pressure-lowering effect** of angiotensin II receptor antagonists may be attenuated by NSAIDs such as indometacin. Patients taking losartan or valsartan or other angiotensin II receptor antagonists, who require indometacin and probably other NSAIDs, should be monitored for alterations in blood pressure control. Low-dose aspirin is unlikely to alter the blood pressure-lowering effect of angiotensin II receptor antagonists. However, for a discussion of the controversy as to whether low-dose aspirin might attenuate the benefits of *ACE inhibitors* in patients with heart failure, see 'ACE inhibitors + Aspirin', p.15.

Poor renal perfusion may increase the risk of **renal failure** if angiotensin II receptor antagonists are given with NSAIDs and so regular hydration of the patient and monitoring of renal function is recommended.[10] The Australian Adverse Drug Reactions Advisory Committee consider that the triple combination of angiotensin II receptor antagonists or ACE inhibitors with diuretics and NSAIDs (including coxibs) should be avoided if possible.[6]

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2. Conlin PR, Moore TJ, Swartz SL, Barr E, Gazdick L, Fletcher C, DeLucca P, Demopoulos L. Effect of indomethacin on blood pressure lowering by captopril and losartan in hypertensive patients. *Hypertension* (2000) 36, 461–5.
3. Olsen ME, Thomsen T, Hassager C, Ibsen H, Dige-Petersen H. Hemodynamic and renal effects of indomethacin in losartan-treated hypertensive individuals. *Am J Hypertens* (1999) 12, 209–16.
4. Fogari R, Zoppi A, Carretta R, Veglio F, Salvetti A: Italian Collaborative Study Group. Effect of indomethacin on the antihypertensive efficacy of valsartan and lisinopril: a multicentre study. *J Hypertens* (2002) 20: 1007–14.
5. Fricker AF, Nussberger J, Meilenbrock S, Brunner HR, Burnier M. Effect of indomethacin on the renal response to angiotensin II receptor blockade in healthy subjects. *Kidney Int* (1998) 54, 2089–97.
6. ADRAC. ACE inhibitor, diuretic and NSAID: a dangerous combination. *Aust Adverse Drug React Bull* (2003) 22, 14–15. Available at: http://www.tga.gov.au/adr/aadrb/aadr0308.pdf (accessed 28/01/10).
7. Loboz KK, Shenfield GM. Drug combinations and impaired renal function –the 'triple whammy'. *Br J Clin Pharmacol* (2005) 59, 239–43.
8. Stangier J, Su C-APF, Fraunhofer A, Tetzloff W. Pharmacokinetics of acetaminophen and ibuprofen when coadministered with telmisartan in healthy volunteers. *J Clin Pharmacol* (2000) 40, 1338–46.
9. Ciba. Data on file, Protocol 43.
10. Olmetec (Olmesartan medoxomil). Daiichi Sankyo UK Ltd. UK Summary of product characteristics, October 2009.

Angiotensin II receptor antagonists + Azoles

Fluconazole reduces the conversion of losartan to its active metabolite and decreases the metabolism of irbesartan. Fluconazole is unlikely to affect the pharmacokinetics of other angiotensin II receptor antagonists; one study found it does not appear to influence the pharmacokinetics of eprosartan. Itraconazole does not significantly affect the pharmacokinetics or antihypertensive effects of losartan, and ketoconazole does not affect the pharmacokinetics of eprosartan or losartan.

Clinical evidence, mechanism, importance and management

(a) Fluconazole

In a study, healthy subjects were given **losartan** 100 mg daily (16 subjects) and **eprosartan** 300 mg twice daily (16 subjects) for 20 days, with fluconazole 200 mg daily on days 11 to 20. Fluconazole increased the AUC and maximum plasma levels of **losartan** by 69% and 31%, respectively, and reduced those of E-3174, the active metabolite of **losartan**, by 41% and 54%, respectively. However, fluconazole had no significant effect on the pharmacokinetics of **eprosartan**.[1] In a randomised, crossover study, 11 healthy subjects were given a single 50-mg dose of **losartan** after taking fluconazole (400 mg on day one and 200 mg daily on days 2 to 4). The AUC of **losartan** was increased by 27% while its maximum plasma level was reduced by 23%. The AUC and the maximum plasma levels of E-3174 were reduced by 47% and 77%, respectively. However, no significant changes in the hypotensive effect of **losartan** were noted.[2]

A study in 15 healthy subjects given **irbesartan** 150 mg daily for 20 days found that fluconazole 200 mg daily on days 11 to 20 increased the steady-state AUC and maximum levels by about 55% and 18%, respectively.[3]

It is thought that fluconazole inhibits the conversion of **losartan** to its active metabolite mainly by inhibiting the cytochrome P450 isoenzyme CYP2C9,[1,2,4,5] although other isoenzymes may play a minor role. Similarly, **irbesartan** is primarily metabolised by CYP2C9,[6] and is therefore also affected by fluconazole.[3]

The lack of pharmacodynamic changes with **losartan** and fluconazole suggests that the pharmacokinetic interaction may not be clinically important, but the possibility of a decreased therapeutic effect should be kept in mind.[2]

The modest increases in **irbesartan** levels were considered unlikely to be clinically relevant and a dose reduction would not generally be required.[7]

Other angiotensin II receptor antagonists would not be expected to interact, see the 'introduction', (p.12), to this section.

(b) Itraconazole

In 11 healthy subjects the pharmacokinetics and hypotensive effects of a single 50-mg dose of **losartan** and its active metabolite, E-3174, were not significantly affected by itraconazole 200 mg daily for 4 days.[2] Inhibition of the cytochrome P450 isoenzyme CYP3A4 alone (caused by itraconazole) does not appear to prevent the conversion of **losartan** to E-3174. No special precautions would appear to be needed if these drugs are used concurrently.

(c) Ketoconazole

A placebo-controlled, crossover study in 11 healthy subjects given a single 30-mg intravenous dose of **losartan**, found that ketoconazole 400 mg daily for 4 days did not affect the conversion of **losartan** to its active metabolite, E-3174, or the plasma clearance of **losartan**.[8] Inhibition of the cytochrome P450 isoenzyme CYP3A4 alone (caused by ketoconazole) does not appear to prevent the conversion of **losartan** to E-3174.

The plasma clearance of a 20-mg intravenous dose of E-3174, the active metabolite of losartan, was also unaffected by pretreatment with ketoconazole.[8] Similarly, in a study involving 27 healthy subjects, ketoconazole 200 mg daily for 5 days was found to have no effect on the pharmacokinetics of **eprosartan** or **losartan** and its active metabolite.[9] No special precautions would appear to be needed if these drugs are used concurrently.

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Angiotensin II receptor antagonists + Beta blockers

There appears to be no clinically significant pharmacokinetic interaction between atenolol and valsartan, and, as expected, concurrent use enhances the blood pressure-lowering effects. The combination of angiotensin II receptor antagonists and beta blockers is in established clinical use.

Clinical evidence, mechanism, importance and management

In a single-dose, crossover study in 12 healthy subjects, the pharmacokinetics of **valsartan** 160 mg and **atenolol** 100 mg were not significantly altered by concurrent use. The combination had some additive effects on resting blood pressure.[1]

Although pharmacokinetic information is apparently limited to this drug pair, no significant adverse pharmacokinetic interaction would be expected between angiotensin II receptor antagonists and beta blockers, and the combination is clinically useful in a number of cardiovascular disorders.

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Angiotensin II receptor antagonists + Calcium-channel blockers

No significant pharmacokinetic interactions occur between nifedipine and candesartan or irbesartan, or between amlodipine and olmesartan, telmisartan or valsartan. Nisoldipine increases the exposure to telmisartan. Calcium-channel blockers have been given uneventfully with eprosartan, irbesartan, losartan, and telmisartan.

Clinical evidence, mechanism, importance and management

(a) Amlodipine

1. Losartan. A double-blind study in 198 patients with hypertension found that a fixed combination of amlodipine 5 mg with losartan 100 mg compared favourably in terms of blood pressure control and tolerability with either amlodipine 10 mg or losartan 100 mg given alone.[1]

2. Olmesartan. Analysis of data from four phase I studies in healthy subjects and one phase III study in patients with hypertension found that the clearance of olmesartan and amlodipine were not significantly affected on concurrent use. The effect of both drugs in combination was greater than either drug alone, but slightly less than the sum of the effects of each drug.[2]

3. Telmisartan. In a study in 12 healthy subjects, telmisartan 120 mg daily had no clinically relevant effect on the pharmacokinetics of amlodipine 10 mg daily for 9 days, and there was no evidence of any marked effect of amlodipine on the pharmacokinetics of telmisartan. Although there were no serious adverse effects, mild to moderate adverse events (most commonly headache) occurred slightly more frequently with the combination, compared with amlodipine alone (19 events versus 12 events).[3] A placebo-controlled study in patients with moderate or severe hypertension found that combinations of telmisartan 40 to 80 mg with amlodipine 5 to 10 mg were effective at lowering blood pressure and the number of patients with adverse effects was comparable between combination and monotherapy groups.[4]

4. Valsartan. In 12 healthy subjects the pharmacokinetics of single oral doses of valsartan 160 mg and amlodipine 5 mg were not significantly altered by concurrent use, although the pharmacokinetics of valsartan showed wide variations between subjects.[5]

(b) Nifedipine

In 12 healthy subjects nifedipine 30 mg daily did not significantly affect the pharmacokinetics of **candesartan** 16 mg daily.[6]

In vitro studies indicated that nifedipine inhibited the oxidation of **irbesartan**, which was mediated by the cytochrome P450 isoenzyme CYP2C9.[7] However, a randomised, crossover study in 11 healthy subjects given **irbesartan** 300 mg daily alone or with nifedipine 30 mg daily for 4 days, found that nifedipine did not alter the pharmacokinetics of **irbesartan**.[7] The manufacturer says that **irbesartan** has been safely given with antihypertensives such as long-acting calcium-channel blockers.[8] Similarly the manufacturer of **eprosartan** notes that it has been safely given with calcium-channel blockers (such as sustained-release nifedipine).[9]

(c) Nisoldipine

In a study, 37 patients with hypertension were given **telmisartan** 40 mg daily, nisoldipine 10 mg daily or both drugs together for 3 weeks. The doses were then increased to **telmisartan** 80 mg daily, nisoldipine 20 mg daily, or a combination of **telmisartan** 80 mg daily and nisoldipine 10 mg daily for a further 3 weeks. The AUC of **telmisartan** 80 mg was increased by 132% when it was given with nisoldipine 10 mg and its clearance was lower, compared with telmisartan alone. There was a non-significant trend towards higher maximum plasma levels and AUC of nisoldipine when it was given with **telmisartan**. **Telmisartan** alone or with nisoldipine significantly reduced blood pressure whereas, in this study, nisoldipine alone had only a minor effect on blood pressure. More study is required to confirm whether this pharmacokinetic interaction enhances antihypertensive efficacy with unchanged tolerability.[10]

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5. Novartis Pharmaceuticals Ltd. Data on file, Protocol 37.
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8. Aprovel (Irbesartan). Bristol-Myers Squibb Pharmaceuticals Ltd. UK Summary of product characteristics, March 2009.
9. Teveten (Eprosartan mesylate). Solvay Healthcare Ltd. UK Summary of product characteristics, October 2009.
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Angiotensin II receptor antagonists + Diuretics; Loop, Thiazide and related

Symptomatic hypotension may occur when an angiotensin II receptor antagonist is started in patients taking high-dose diuretics. Potassium levels may be either increased, decreased or not affected. No clinically relevant pharmacokinetic interactions appear to occur between candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan or valsartan and hydrochlorothiazide, although the bioavailability of hydrochlorothiazide may be modestly reduced. Similarly, there is no clinically significant pharmacokinetic interaction between valsartan and furosemide.

Clinical evidence, mechanism, importance and management

(a) Hypotension

Angiotensin II receptor antagonists and thiazide or related diuretics have useful additive effects in the control of hypertension and are generally well tolerated. For example, in one double-blind, placebo-controlled study in 604 patients with hypertension, **losartan** 50 mg given with **hydrochlorothiazide** 12.5 mg daily produced an additive reduction in trough sitting systolic and diastolic blood pressure, and the incidence of dizziness and headache was not significantly different from placebo.[1] However, symp-

tomatic hypotension, especially after the first dose, may occur when angiotensin II receptor antagonists are started in patients with heart failure or those with hypertension who also have sodium and/or volume depletion, such as those taking **high-dose diuretics**. It is recommended that any volume and/or sodium depletion should be corrected before the angiotensin II receptor antagonist is given. In some situations it may be appropriate to reduce the dose of the diuretic and/or use a lower starting dose of the angiotensin II receptor antagonist. A similar problem occurs with the ACE inhibitors, see 'ACE inhibitors + Diuretics; Loop, Thiazide and related', p.23.

(b) Pharmacokinetic studies

The changes in **furosemide** and **hydrochlorothiazide** pharmacokinetics appear to be of no practical importance, and the combination with an angiotensin II receptor antagonist can produce a significant and useful additional reduction in blood pressure. Details of these studies are given below.

1. Furosemide. In 12 healthy subjects, the relative bioavailability of furosemide 40 mg was reduced by about 26% when it was given with **valsartan** 160 mg. However, this pharmacokinetic interaction had no influence on the diuretic effect of furosemide. The simultaneous use of **valsartan** and furosemide did not modify the pharmacokinetics of **valsartan**.[2]

2. Hydrochlorothiazide. In 18 healthy subjects the concurrent use of hydrochlorothiazide 25 mg daily and **candesartan** 12 mg daily for 7 days increased the AUC and maximum serum levels of **candesartan** by 18% and 23%, respectively, and reduced the AUC of hydrochlorothiazide by 14%, but these changes were not considered to be clinically relevant.[3]
In 18 healthy subjects **eprosartan** 800 mg decreased the AUC of hydrochlorothiazide 25 mg by about 20%, but this was not considered to be clinically important. In addition, hydrochlorothiazide had no effect on **eprosartan** pharmacokinetics.[4]
In a study in 12 patients with mild or moderate hypertension given **losartan** 50 mg alone or with hydrochlorothiazide 12.5 mg daily for 7 days, the AUC of hydrochlorothiazide was decreased by 17% during concurrent use (not clinically significant) while the pharmacokinetics of **losartan** were unchanged.[5]
A single-dose study in 12 healthy subjects found that **valsartan** 160 mg reduced the systemic availability of hydrochlorothiazide 25 mg (AUC decreased by 31%), but the mean amount of hydrochlorothiazide excreted in the urine did not seem to change significantly. The pharmacokinetics of **valsartan** were not significantly affected by hydrochlorothiazide.[6]
In a randomised, crossover study in 13 healthy subjects, **telmisartan** 160 mg daily was given with hydrochlorothiazide 25 mg daily for 7 days. There was no difference in AUC and maximum plasma concentrations of either drug compared with when they were given alone.[7]
No clinically significant pharmacokinetic interactions have been found between **irbesartan**[8] or **olmesartan**[9] and hydrochlorothiazide.

(c) Serum potassium levels

Angiotensin receptor II antagonists are potassium sparing, whereas loop and thiazide diuretics are potassium depleting. Giving an angiotensin receptor II antagonist with a diuretic could result in an increase, a decrease, or no change to the potassium levels, although logically adding an angiotensin II receptor antagonist to established treatment with a diuretic would seem more likely to raise potassium, and vice versa. Serum potassium should be routinely monitored when angiotensin II antagonists are used in patients with heart failure, renal impairment, or in the elderly.

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3. Jonkman JHG, van Lier JJ, van Heiningen PNM, Lins R, Sennewald R, Högemann A. Pharmacokinetic drug interaction studies with candesartan cilexetil. *J Hum Hypertens* (1997) 11 (Suppl 2), S31–S35.
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Angiotensin II receptor antagonists + Diuretics; Potassium-sparing

There is an increased risk of hyperkalaemia if angiotensin II receptor antagonists are given with potassium-sparing diuretics (such as amiloride and the aldosterone antagonists, eplerenone and spironolactone), particularly if other risk factors are also present.

Clinical evidence

In a study in 13 hypertensive patients aged 61 to 83 years with mild chronic heart failure, the concurrent use of **valsartan** 80 mg daily and spironolactone 100 mg daily was considered to be effective and safe. However in one patient, the serum potassium increased from 4.3 mmol/L to 5.8 mmol/L.[1]

An 84-year-old woman, taking several drugs including **losartan** 50 mg daily and spironolactone 25 mg daily, developed hyperkalaemia (potassium level 8.4 mmol/L), bradycardia, drowsiness and respiratory depression. She recovered after haemodialysis and ventilatory assistance.[2] There is also a report of life-threatening hyperkalaemia (9.4 mmol/L) in a patient with mild renal impairment given **candesartan** 8 mg daily and spironolactone 25 mg daily. Hyperkalaemia did not recur when she was given **candesartan** and a loop diuretic.[3]

Life-threatening hyperkalaemia occurred in 6 patients with congestive heart failure who were taking **spironolactone** and an angiotensin II receptor antagonist (**candesartan**, **losartan** or **telmisartan**). Analysis of these patients, together with another 38 similar patients who had received ACE inhibitors, identified certain conditions that may lead to the development of severe hyperkalaemia. These were advanced age, dose of **spironolactone** greater than 25 mg, reduced renal function and type 2 diabetes.[4]

A study in patients with chronic heart failure taking spironolactone 25 or 50 mg daily, furosemide and either enalapril, **candesartan** 8 mg daily, or **losartan** 50 mg daily, for 12 months, found that hyperkalaemia occurred in about 9% of patients In patients given furosemide 40 mg and **spironolactone** 25 mg daily, hypokalaemia occurred in 14.3% and 6.5% of patients taking **losartan** or **candesartan**, respectively, but did not occur when patients were given **spironolactone** 50 mg daily.[5]

Mechanism

Angiotensin II receptor antagonists reduce the levels of aldosterone, which results in the retention of potassium. This would be expected to be additive with the potassium-retaining effects of amiloride, triamterene, spironolactone and eplerenone, leading to hyperkalaemia, but usually only if other risk factors are present.

Importance and management

The concurrent use of potassium-sparing diuretics (namely **amiloride**, **triamterene** and the aldosterone antagonists **eplerenone** and spironolactone) may increase serum potassium. There is a greater risk of hyperkalaemia if renal impairment and/or heart failure or diabetes are present. Because angiotensin II receptor antagonists have potassium-sparing effects, amiloride and triamterene should not normally be given concurrently. Aldosterone antagonists such as spironolactone may be useful in heart failure, but the combined use of angiotensin II receptor antagonists requires increased monitoring of serum potassium. Note that the combination should be avoided in patients with a glomerular filtration rate of less than 30 mL/minute.[6]

A retrospective study in hospitalised patients who developed hyperkalaemia found that risk factors associated with a rapid rate of increase in serum potassium levels in decreasing order of importance were: the use of potassium supplements, severe renal impairment, the use of ACE inhibitors or angiotensin II receptor antagonists, the use of potassium-sparing diuretics, diabetes mellitus. Further, the presence of two or more of these risk factors is associated with an even faster development of hyperkalaemia. As the rate at which hyperkalaemia develops is also correlated with its severity, the authors recommend close monitoring in patients with two

or more risk factors, and that a rapid increase in serum potassium (greater than 0.5 mmol/L per day) should prompt the identification and possible removal of any risk factors for hyperkalaemia.[7] Hyperkalaemia associated with spironolactone is dose-related, but in the presence of an angiotensin II receptor antagonist, its occurrence may increase even if the dose of spironolactone is as low as 25 mg daily and so potassium levels should be closely monitored.[5] It has been recommended that the dose of spironolactone should not exceed 25 mg daily if an angiotensin II receptor antagonist is also given.[6]

The UK manufacturer of eplerenone says that caution is required when it is given with angiotensin II receptor antagonists, especially in renal impairment, and that potassium levels and renal function should be monitored.[8] This seems prudent.

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8. Inspra (Eplerenone). Pfizer Ltd. UK Summary of product characteristics, October 2009.

Angiotensin II receptor antagonists + Food

Food slightly increases the AUC of eprosartan and losartan, slightly reduces the AUC of telmisartan, and modestly reduces the AUC of valsartan. Food has no effect on the AUC of candesartan, irbesartan or olmesartan.

Clinical evidence, mechanism, importance and management

(a) Candesartan

Food does not affect the bioavailability of candesartan,[1,2] and the manufacturer states that it may be given with or without food.

(b) Eprosartan

Food delays eprosartan absorption, and slightly increases its AUC and maximum plasma concentrations by up to 25%. The UK manufacturer recommends that eprosartan is given with food,[3] but the US manufacturer suggests that the change in absorption is not clinically significant, and that eprosartan may be taken with or without food.[4]

(c) Irbesartan

In a study in 16 healthy men, a high-fat breakfast had no clinically relevant effects on the bioavailability of a single 300-mg dose of irbesartan,[5] therefore it may be taken with or without food.

(d) Losartan

In a crossover study in healthy subjects, the AUC and maximum levels of a single 100-mg dose of losartan, given 30 minutes before a high-fat breakfast was increased by 17% and 35%, respectively, when compared with the fasted state. Food caused a less than 10% decrease in AUC and maximum level of the losartan metabolite, E-3174.[6] These minor changes are unlikely to be clinically significant, and the manufacturer says that losartan may be given with or without food.[7,8]

(e) Olmesartan

Food does not affect the bioavailability of olmesartan,[9,10] and the manufacturer states that it may be given with or without food.

(f) Telmisartan

Food slightly reduces the AUC of telmisartan by about 6 to 20% depending on dose,[11,12] but this would not be expected to cause a reduction in therapeutic efficacy, and telmisartan may be taken with or without food.[12]

(g) Valsartan

Food modestly decreased the AUC of valsartan by 40%,[13] but the manufacturer states that it may be taken with or without food.[13,14]

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2. Atacand (Candesartan cilexetil). AstraZeneca. US Prescribing information, October 2009.
3. Teveten (Eprosartan mesylate). Solvay Healthcare Ltd. UK Summary of product characteristics, October 2009.
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7. Cozaar (Losartan potassium). Merck Sharp & Dohme Ltd. UK Summary of product characteristics, August 2009.
8. Cozaar (Losartan potassium). Merck & Co., Inc. US Prescribing information, June 2009.
9. Benicar (Olmesartan medoxomil). Daiichi Sankyo, Inc. US Prescribing information, July 2007.
10. Olmetec (Olmesartan medoxomil). Daiichi Sankyo UK Ltd. UK Summary of product characteristics, October 2009.
11. Micardis (Telmisartan). Boehringer Ingelheim Pharmaceuticals Inc. US Prescribing information, November 2009.
12. Micardis (Telmisartan). Boehringer Ingelheim Ltd. UK Summary of product characteristics, May 2009.
13. Diovan (Valsartan). Novartis. US Prescribing information, December 2008.
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Angiotensin II receptor antagonists + H_2-receptor antagonists

Cimetidine may cause a small rise in valsartan levels, but did not significantly affect the pharmacokinetics and blood pressure-lowering effect of losartan in one study. Ranitidine does not appear to significantly alter the pharmacokinetics of eprosartan.

Clinical evidence, mechanism, importance and management

(a) Cimetidine

1. Losartan. In a randomised, crossover study in 8 healthy subjects, when losartan 100 mg was given after cimetidine 400 mg four times daily for 6 days, the pharmacokinetics and pharmacodynamics of losartan and its active metabolite, E-3174, were not changed to a clinically relevant extent, although there was a minor increase of 18% in the AUC of losartan.[1] No special precautions are needed if these drugs are used concurrently.

2. Valsartan. In a single-dose, crossover study, cimetidine 800 mg, given one hour before valsartan 160 mg, increased the initial rate of absorption of valsartan (attributed to a raised gastric pH) resulting in a roughly 50% increase in its maximum plasma concentration. However, the AUC was only slightly increased and there were large inter-subject variations in the pharmacokinetics of valsartan.[2] The changes in valsartan pharmacokinetics seen with cimetidine are unlikely to be clinically relevant.

(b) Ranitidine

A single 400-mg dose of **eprosartan** was given to 17 healthy subjects, both alone and after ranitidine 150 mg twice daily for 3 days. The ranitidine caused some slight changes in the pharmacokinetics of the **eprosartan** (maximum plasma concentration and AUC reduced by about 7% and 11%, respectively), but these were not statistically significant.[3]

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2. Schmidt EK, Antonin K-H, Flesch G, Racine-Poon A. An interaction study with cimetidine and the new angiotensin II antagonist valsartan. *Eur J Clin Pharmacol* (1998) 53, 451–8.
3. Tenero DM, Martin DE, Ilson BE, Boyle DA, Boike SC, Carr AM, Lundberg DE, Jorkasky DK. Effect of ranitidine on the pharmacokinetics of orally administered eprosartan, an angiotensin II antagonist, in healthy male volunteers. *Ann Pharmacother* (1998) 32, 304–8.

Angiotensin II receptor antagonists + Mannitol

A report describes mannitol-induced acute renal failure in a diabetic patient taking losartan.

Clinical evidence, mechanism, importance and management

A man with diabetic nephropathy taking **losartan** 25 mg twice daily for hypertension developed acute renal failure after being given a total of 420 g of intravenous mannitol over 4 days for haemorrhagic glaucoma. The patient recovered after the mannitol and **losartan** were discontinued, and after receiving haemodialysis.[1] It is not fully understood why this combination caused acute renal failure, but it may result in a marked decrease in glomerular filtration rate. The general relevance of this isolated case in unclear, but the authors of the report recommend caution on concurrent use.[1]

1. Matsumura M. Mannitol-induced toxicity in a diabetic patient receiving losartan. *Am J Med* (2001) 110, 331.

Angiotensin II receptor antagonists + Potassium compounds

There may be a risk of hyperkalaemia if angiotensin II receptor antagonists are given with potassium supplements or potassium-containing salt substitutes, particularly in those patients where other risk factors are present.

Clinical evidence, mechanism, importance and management

Angiotensin II receptor antagonists are potassium-sparing, as a result of their effects on aldosterone, and their potential to cause clinically important hyperkalaemia is well established. The incidence of hyperkalaemia varies depending on the clinical indication and other disease conditions, being lowest in essential hypertension, and highest in heart failure, diabetes, and renal impairment. For example, the incidence of hyperkalaemia in clinical studies in patients with hypertension was 0.9% with **eprosartan**[1,2] and 1.5% with **losartan**;[3] in patients with type 2 diabetes with nephropathy, the incidence was 9.9% with **losartan**[3] and 18.6% with **irbesartan**;[4] and in those with heart failure the incidence was 6.3% with **candesartan**.[5]

A retrospective study in hospitalised patients who developed hyperkalaemia found that risk factors associated with a rapid rate of increase in serum potassium levels in decreasing order of importance were: the use of potassium supplements, severe renal impairment, the use of ACE inhibitors or angiotensin II receptor antagonists, the use of potassium-sparing diuretics, and then diabetes mellitus. Further, the presence of two or more of these risk factors is associated with an even faster rate of development of hyperkalaemia. As the rate of development of hyperkalaemia is also correlated with its severity, the authors recommend close monitoring in patients with two or more risk factors (which would include those taking potassium supplements with angiotensin II receptor antagonists), and that a rapid increase in serum potassium (greater than 0.5 mmol/L per day) should prompt the identification and possible removal of any risk factors for hyperkalaemia.[6]

Potassium supplements are generally unlikely to be needed in patients taking angiotensin II receptor antagonists, particularly if they have other risk factors for hyperkalaemia, and it may be prudent for such patients to be told to avoid using potassium-containing **salt substitutes**. If concurrent use is considered necessary, potassium levels should be closely monitored.

1. Teveten (Eprosartan mesylate). Solvay Healthcare Ltd. UK Summary of product characteristics, October 2009.
2. Teveten (Eprosartan mesylate). Abbott Laboratories. US Prescribing information, August 2007.
3. Cozaar (Losartan potassium). Merck Sharp & Dohme Ltd. UK Summary of product characteristics, August 2009.
4. Avapro (Irbesartan). Bristol-Myers Squibb Company. US Prescribing information, April 2007.
5. Atacand (Candesartan cilexetil). AstraZeneca. US Prescribing information, October 2009.
6. Indermitte J, Burkolter S, Drewe J, Krähenbühl S, Hersberger KE. Risk factors associated with a high velocity of the development of hyperkalaemia in hospitalised patients. *Drug Safety* (2007) 30, 71–80.

Angiotensin II receptor antagonists + Rifampicin (Rifampin)

Rifampicin increases the metabolism of losartan and its active metabolite, E-3174, which may result in reduced antihypertensive effects.

Clinical evidence, mechanism, importance and management

Ten healthy subjects were given **losartan** 50 mg daily for a week and then, after a 6-day washout period, **losartan** 50 mg daily with rifampicin 300 mg twice daily for a week. It was found that rifampicin reduced the AUC of **losartan** by 36%, reduced its half-life from 2 to 0.9 hours, and increased its clearance by 60%. The AUC of the active metabolite, E3174, was reduced by 41% and its half-life was reduced from 5.1 hours to 2.5 hours. Diastolic blood pressure was significantly reduced by **losartan** alone, but not by the combination.[1] The presumed reason for this interaction is that rifampicin (a recognised enzyme inducer) increases the metabolism of **losartan** to its active metabolite by the cytochrome P450 isoenzyme CYP2C9.

The clinical importance of this interaction still awaits assessment, but it would seem likely that the antihypertensive effects of **losartan** would be reduced by rifampicin. If both drugs are used, be alert for the need to increase the **losartan** dose. There seems to be no information regarding other angiotensin II receptor antagonists, but note that **irbesartan**, and to a limited extent **candesartan**, are also metabolised by CYP2C9 (see under 'ACE inhibitors and Angiotensin II receptor antagonists', (p.12)).

1. Williamson KM, Patterson JH, McQueen RH, Adams KF, Pieper JA. Effects of erythromycin or rifampin on losartan pharmacokinetics in healthy volunteers. *Clin Pharmacol Ther* (1998) 63, 316–23.

Angiotensin II receptor antagonists; Losartan + Amodiaquine

Amodiaquine inhibited the metabolism of losartan to its active metabolite, E-3174.

Clinical evidence, mechanism, importance and management

A study in 12 healthy subjects found that amodiaquine 600 mg taken 2 to 3 hours before a single 25-mg dose of losartan, significantly increased the metabolic ratio of losartan to its metabolite by 72% compared with baseline values for losartan. This was due to decreases in the metabolism of losartan to its active metabolite, E-3174, by amodiaquine and/or its metabolite, *N*-desethylamodiaquine, which inhibit the cytochrome P450 isoenzyme CYP2C9.[1]

The clinical relevance of the findings of this study is unclear. The reduction in metabolism of losartan to its active metabolite might suggest that the therapeutic effects of losartan could be reduced. However, note that the effect of fluconazole (see 'Angiotensin II receptor antagonists + Azoles', p.39), which is a known potent inhibitor of CYP2C9, was probably not clinically relevant, which suggests the effect of amodiaquine is also unlikely to be clinically relevant.

1. Wennerholm A, Nordmark A, Pihlsgård M, Mahindi M, Bertilsson L, Gustafsson LL. Amodiaquine, its desethylated metabolite, or both, inhibit the metabolism of debrisoquine (CYP2D6) and losartan (CYP2C9) in vivo. *Eur J Clin Pharmacol* (2006) 62, 539–46.

Angiotensin II receptor antagonists; Losartan + AST-120

AST-120 does not appear to have an important effect on the pharmacokinetics of losartan.

Clinical evidence, mechanism, importance and management

When a single 100-mg dose of losartan was given 30 minutes before a high-fat breakfast, with AST-120 3 g three times daily for 48 hours started 30 minutes after the breakfast, the AUC of losartan was not significantly altered, although there was a minor 12% decrease in the maximum losartan level. Similarly, various other schedules (losartan with breakfast, then AST-120 started 30 minutes later, or AST-120 started 30 minutes after breakfast, then losartan given 30 minutes after that), did not significantly alter the AUC of losartan, when compared with losartan given 30 minutes before breakfast. However, there were minor to modest increases in the AUC of losartan (of up to 37%) when these schedules were compared with losartan given in the fasting state, which was attributed to the effect of food.[1]

AST-120 is a predominantly carbon-based oral absorbent, and might therefore interfere with absorption of other drugs. Data from this pharma-

cokinetic study indicate that AST-120 has minimal effects on the pharmacokinetics of losartan. The authors suggest that giving AST-120 one hour after losartan may be preferred.[1]

1. Marier JF, Guilbaud R, Kambhampati SR, Mathew P, Moberly J, Lee J, Salazar DE. The effect of AST-120 on the single-dose pharmacokinetics of losartan and losartan acid (E-3174) in healthy subjects. *J Clin Pharmacol* (2006) 46, 310–20.

Angiotensin II receptor antagonists; Losartan + Erythromycin

The pharmacokinetics and blood pressure-lowering effect of losartan do not seem to be affected by erythromycin.

Clinical evidence, mechanism, importance and management

When 10 healthy subjects were given losartan 50 mg daily for a week and then, after a 6-day washout period, losartan 50 mg daily with erythromycin 500 mg four times daily for a week, it was found that erythromycin had no significant effect on the pharmacokinetics of losartan or its active metabolite, E-3174. In addition, erythromycin did not alter the blood pressure-lowering effect of losartan.[1] Inhibition of the cytochrome P450 isoenzyme CYP3A4 alone does not appear to prevent the conversion of losartan to E-3174. There would therefore appear to be no reason to take any special precautions if both drugs are used concurrently.

1. Williamson KM, Patterson JH, McQueen RH, Adams KF, Pieper JA. Effects of erythromycin or rifampin on losartan pharmacokinetics in healthy volunteers. *Clin Pharmacol Ther* (1998) 63, 316–23.

Angiotensin II receptor antagonists; Losartan + Fluorouracil

Fluorouracil inhibits the metabolism of losartan to its active metabolite, E-3174, and the extent of inhibition appears to increase as the total cumulative dose of fluorouracil increases.

Clinical evidence, mechanism, importance and management

In a study, 17 patients with colorectal cancer, receiving fluorouracil 425 mg/m^2 and folinic acid as a one-hour infusion for at least 3 consecutive days for each cycle of treatment, were given a single 25-mg dose of losartan at least 2 days before the start of the first cycle of fluorouracil, and a further 25-mg dose on the last day of the cycle. Five of the patients also received losartan 25 mg at the end of the third cycle. The ratio of losartan to its active metabolite, E-3174, increased from an average of 0.5 to 0.64 (28%) after the first cycle of fluorouracil, but there was large interpatient variation (ranging between a 71% decrease and a 223% increase) with increases in 10 of the patients and no change in one patient. The metabolic ratio increased significantly after the third cycle of fluorouracil from 0.44 to 2.32 (a 5.3-fold increase) even though in 2 of the 5 patients the ratio had decreased after the first cycle of fluorouracil. Fluorouracil appears to inhibit the metabolism of losartan to E-3174 by cytochrome P450 isoenzyme CYP2C9 and the inhibition becomes more pronounced as the cumulative dose of fluorouracil is increased.[1]

The clinical relevance of the findings of this study is unclear. The reduction in metabolism of losartan to its active metabolite might suggest that the therapeutic effects of losartan could be reduced, but this remains to be established.

1. Gunes A, Coskun U, Boruban C, Gunel N, Babaoglu MO, Sencan O, Bozkurt A, Rane A, Hassan M, Zengil H, Yasar U. Inhibitory effect of 5-fluorouracil on cytochrome P450 2C9 activity in cancer patients. *Basic Clin Pharmacol Toxicol* (2006) 98, 197–200.

Angiotensin II receptor antagonists; Losartan + Grapefruit juice

Grapefruit juice has a minor effect on the pharmacokinetics of losartan and its active metabolite, E-3174.

Clinical evidence, mechanism, importance and management

In a study in 9 healthy subjects, grapefruit juice approximately doubled the time for a single 50-mg dose of losartan to be detected in the serum (from 40 minutes to 1.3 hours) and reduced the AUC of its active metabolite, E-3174, by 21%. Losartan is partly metabolised by the cytochrome P450 isoenzyme CYP3A4 and transported by P-glycoprotein, both of which can be affected by grapefruit juice. This may explain the minor changes seen.[1] However, this interaction is unlikely to be clinically relevant.

1. Zaidenstein R, Soback S, Gips M, Avni B, Dishi V, Weissgarten Y, Golik A, Scapa E. Effect of grapefruit juice on the pharmacokinetics of losartan and its active metabolite E3174 in healthy volunteers. *Ther Drug Monit* (2001) 23, 369–73.

Angiotensin II receptor antagonists; Losartan + Phenobarbital

Phenobarbital minimally alters the levels of losartan and its active metabolite.

Clinical evidence, mechanism, importance and management

In a placebo-controlled study 15 healthy subjects were given phenobarbital 100 mg daily for 16 days with a single 100-mg dose of losartan. Phenobarbital slightly reduced the AUC of losartan and its active metabolite, E-3174, by about 20%, but this was not considered to be clinically significant.[1]

1. Goldberg MR, Lo MW, Deutsch PJ, Wilson SE, McWilliams EJ, McCrea JB. Phenobarbital minimally alters plasma concentrations of losartan and its active metabolite E-3174. *Clin Pharmacol Ther* (1996) 59, 268–74.

Angiotensin II receptor antagonists; Losartan + Phenytoin

Phenytoin inhibited the metabolism of losartan to its active metabolite, E-3174.

Clinical evidence, mechanism, importance and management

In this crossover study in 16 healthy subjects the concurrent use of phenytoin and losartan 50 mg daily for 10 days reduced the AUC of the active metabolite of losartan, E-3174, by 63%, but did not significantly alter the AUC of losartan. The pharmacokinetics of phenytoin were not affected by losartan. In this study phenytoin was given at a dose of 4 mg/kg rounded to the nearest 100 mg, not to exceed 400 mg daily, and the dose was adjusted on the fourth day, if necessary, based on serum phenytoin levels. Phenytoin did not alter the effect of losartan on blood pressure. The effect of phenytoin appeared to be CYP2C9 genotype-specific, with increases in losartan AUC seen in the 14 subjects who were CYP2C9 extensive metabolisers (that is, those with normal levels of this isoenzyme) and decreases in the 2 subjects who were poor metabolisers (that is those lacking this isoenzyme).[1]

Both phenytoin and losartan are substrates for the cytochrome P450 isoenzyme CYP2C9. It appears that phenytoin had an inhibitory effect on losartan metabolism. The conversion of losartan to E-3174 represents about 5 to 15% of the clearance of an oral losartan dose,[1] but E-3174 is much more active than losartan.

The clinical importance of this interaction still awaits assessment. Until more is known, if phenytoin is added to established treatment with losartan, it may be prudent to initially monitor blood pressure more closely. More study is needed.

1. Fischer TL, Pieper JA, Graff DW, Rodgers JE, Fischer JD, Parnell KJ, Goldstein JA, Greenwood R, Patterson JH. Evaluation of potential losartan-phenytoin drug interactions in healthy volunteers. *Clin Pharmacol Ther* (2002) 72, 238–46.

Angiotensin II receptor antagonists; Losartan + Tamoxifen

Tamoxifen may inhibit the metabolism of losartan to its active metabolite.

Clinical evidence

In a study, 13 patients were given a single 25-mg dose of losartan 2 days before and 2 weeks after starting to take tamoxifen 20 mg daily. The metabolism of losartan was reduced in 10 patients (as assessed by an increase in the losartan to E3174 metabolic ratio), but there was a wide inter-individual variation. The change in metabolic ratio in the 13 patients ranged from a decrease of 11% to an increase of 532%, with a median increase of 127%.[1]

Mechanism

Losartan is metabolised to its active metabolite E3174 by the cytochrome P450 isoenzyme CYP2C9, and this study indicates that tamoxifen inhibits this isoenzyme.

Importance and management

The clinical relevance of the findings of this study is unclear. The reduction in metabolism of losartan to its active metabolite might suggest that the therapeutic effects of losartan could be reduced. However, note that the effect of fluconazole (see 'Angiotensin II receptor antagonists + Azoles', p.39), which is a known potent inhibitor of CYP2C9, was probably not clinically relevant, which suggests the effect of tamoxifen is also unlikely to be clinically relevant.

1. Boruban MC, Yasar U, Babaoglu MO, Sencan O, Bozkurt A. Tamoxifen inhibits cytochrome P450 2C9 activity in breast cancer patients. *J Chemother* (2006) 18, 421–4.

Angiotensin II receptor antagonists; Telmisartan + Paracetamol (Acetaminophen)

No pharmacokinetic interaction occurs between telmisartan and paracetamol.

Clinical evidence, mechanism, importance and management

In a single-dose study in 12 healthy subjects telmisartan 120 mg had no effect on the pharmacokinetics of paracetamol 1 g. The pharmacokinetics of telmisartan were also unaffected by paracetamol, when compared with previous studies of telmisartan alone.[1]

1. Stangier J, Su C-APF, Fraunhofer A, Tetzloff W. Pharmacokinetics of acetaminophen and ibuprofen when coadministered with telmisartan in healthy volunteers. *J Clin Pharmacol* (2000) 40, 1338–46.

3

Alcohol

For social and historical reasons alcohol is usually bought from a store or in a bar or restaurant, rather than from a pharmacy, because it is considered to be a drink and not a drug. However, pharmacologically it has much in common with medicinal drugs that depress the central nervous system. Objective tests show that as blood-alcohol levels rise, the ability to perform a number of skills gradually deteriorates as the brain becomes progressively disorganised. The myth that alcohol is a stimulant has arisen because at parties and social occasions it helps people to lose some of their inhibitions and it allows them to relax and unwind. Professor JH Gaddum put it amusingly and succinctly when, describing the early effects of moderate amounts of alcohol, he wrote that "logical thought is difficult but after dinner speeches easy." The expansiveness and loquaciousness that are socially acceptable can lead on, with increasing amounts of alcohol, to unrestrained behaviour in normally well-controlled individuals, through to drunkenness, unconsciousness, and finally death from respiratory failure. These effects are all a reflection of the progressive and deepening depression of the CNS.

'Table 3.1', (p.47) gives an indication in very broad terms of the reactions of men and women to different amounts and concentrations of alcohol.

On the whole women have a higher proportion of fat in which alcohol is not very soluble, their body fluids represent a smaller proportion of their total body mass, and their first-pass metabolism of alcohol is less than men because they have less alcohol dehydrogenase in their stomach walls. Consequently if a man and woman of the same weight matched each other, drink for drink, the woman would finish up with a blood alcohol level about 50% higher than the man. The values shown assume that the drinkers regularly drink, have had a meal and weigh between 9 and 11 stones (55 to 70 kg). Higher blood-alcohol levels would occur if alcohol was drunk on an empty stomach and lower values in much heavier individuals. The liver metabolises about one unit of alcohol per hour so the values will fall with time.

Since alcohol impairs the skills needed to drive safely, almost all national and state authorities have imposed maximum legal blood alcohol limits. In a number of countries this has been set at 80 mg/100 mL (35 micrograms per 100 mL in the breath) but impairment is clearly detectable at lower concentrations, for which reason some countries have imposed much lower legal limits, even down to 0 mg/100 mL in some cases. Even within countries the legal limit can vary, depending on the type of vehicle being driven and the age of the driver.

Alcohol can interact with many drugs both by pharmacokinetic and/or pharmacodynamic mechanisms. The quantity and frequency of alcohol consumption can affect the bioavailability of alcohol and other drugs. Several hepatic enzymes are important in the metabolism of alcohol; primarily alcohol dehydrogenases convert alcohol into acetaldehyde, but other enzymes, in particular the cytochrome P450 isoenzyme CYP2E1, are also involved, especially in moderate to heavy alcohol consumption. The cytochrome P450 isoenzymes CYP3A4 and CYP1A2 may also have a role in the metabolism of alcohol.

Alcohol can induce CYP2E1 (and possibly other isoenzymes) after prolonged heavy intake, and this can result in an increased metabolic rate and lower blood levels of drugs metabolised via this system. Conversely, short term binge drinking is likely to cause inhibition of this enzyme group by direct competition for binding sites and therefore decrease the metabolism of other drugs.

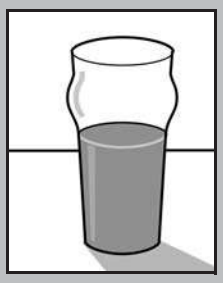
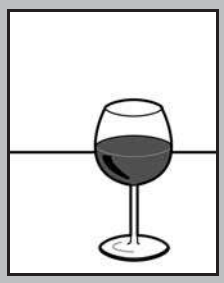
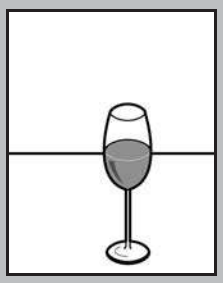
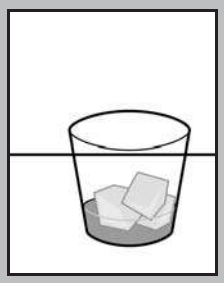
Probably the most common drug interaction of all occurs if alcohol is drunk by those taking other drugs that have CNS depressant activity, the result being even further CNS depression. Blood-alcohol levels well within the legal driving limit may, in the presence of other CNS depressants, be equivalent to blood-alcohol levels at or above the legal limit in terms of worsened driving and other skills. This can occur with some antihistamines, antidepressants, anxiolytics, hypnotics, opioid analgesics, and others. This section contains a number of monographs that describe the results of formal studies of alcohol combined with a number of recognised CNS depressants, but there are still many other drugs that await study of this kind, and which undoubtedly represent a real hazard.

A less common interaction that can occur between alcohol and some drugs, chemical agents, and fungi, is the flushing (*Antabuse*) reaction. This is exploited in the case of disulfiram (*Antabuse*) as a drink deterrent (see 'Alcohol + Disulfiram', p.66), but it can occur unexpectedly with some other drugs, such as some antifungals and cephalosporins, chlorpropamide and metronidazole, and can be both unpleasant and possibly frightening, but it is not usually dangerous.

Table 3.1 Reactions to different concentrations of alcohol in the blood

Amounts of alcohol drunk

Man 11 stones (70 kg)	**Woman 9 stones (55 kg)**	**Blood-alcohol levels mg% (mg per 100 mL)**	**Reactions to different % of alcohol in the blood**
2 units	1 unit	25 to 30	Sense of well-being enhanced. Reaction times reduced
4 units	2 units	50 to 60	Mild loss of inhibition, judgement impaired, increased risk of accidents at home, at work and on the road; no overt signs of drunkenness
5 units	3 units	75 to 80	Physical co-ordination reduced, more marked loss of inhibition; noticeably under the influence; at the maximum legal limit for driving in some countries
7 units	4 units	100 or more	Clumsiness, loss of physical control, tendency to extreme responses; definite intoxication
10 units	6 units	150	Slurred speech, possible loss of memory the following day, probably drunk and disorderly
24 units	14 units	360	Dead drunk, sleepiness, possible loss of consciousness
33 units	20 units	500	Coma and possibly death

1 unit	= half a pint (300 mL medium strength beer)	= glass of wine (100 mL)	= single sherry or martini (50 mL)	= single spirit (25 mL)
				
	alcohol 3 to 4%	alcohol 11%	alcohol 17 to 20%	alcohol 37 to 40%

After *Which?* October 1984, page 447 and others.

Alcohol + Alpha blockers

The plasma levels of both indoramin and alcohol may be raised by concurrent use, and the combination has been reported to increase drowsiness, which may possibly increase the risks when driving or using machinery. Prazosin appears to enhance the hypotensive effects of alcohol.

Clinical evidence

(a) Indoramin

When 10 healthy subjects were given a single 50-mg oral dose of indoramin together with alcohol 0.5 g/kg in 600 mL of alcohol-free lager, the AUC of indoramin was increased by 25% and its peak plasma levels were raised by 58%.[1,2] When the subjects were given a single 175 microgram/kg intravenous dose of indoramin together with the same oral dose of alcohol, a 26% rise in blood-alcohol levels occurred during the first 1.25 hours after dosing, but no change in indoramin pharmacokinetics were seen. The combination of alcohol and indoramin caused more sedation than either drug alone.[2]

(b) Prazosin

A study in 10 Japanese hypertensive patients found that alcohol 1 mL/kg decreased blood pressure for several hours. Treatment with prazosin 1 mg three times daily caused a significant reduction in blood pressure and enhanced alcohol-induced hypotension.[3]

Mechanism

Uncertain. Increased absorption of indoramin from the gut or reduced liver metabolism may be responsible for the raised indoramin serum levels. The increase in sedation would appear to be due to the additive sedative effects of the two drugs. The effects may be restricted to Oriental/Asian patients because the alcohol flush syndrome, caused by accumulation of vasodilative acetaldehyde due to a genetic alteration in aldehyde dehydrogenase, is rare in whites and blacks.[3]

Importance and management

Information is limited but the interaction between indoramin and alcohol appears to be established. The clinical importance of the raised levels of both drugs is uncertain. However since indoramin sometimes causes drowsiness when it is first given, there is the possibility that alertness will be reduced, which could increase the risks of driving or handling machinery. Patients should be warned. The clinical significance of the drop in blood pressure with prazosin is uncertain, as the dose of prazosin was relatively small and the dose of alcohol was relatively large; therefore these findings may not apply to more moderate drinking or higher doses of prazosin. Note that chronic moderate to heavy drinking may decrease the effects of antihypertensives, see 'Alcohol + Antihypertensives', p.51.

1. Abrams SML, Pierce DM, Franklin RA, Johnston A, Marrott PK, Cory EP, Turner P. Effect of ethanol on indoramin pharmacokinetics. *Br J Clin Pharmacol* (1984) 18, 294P–295P.
2. Abrams SML, Pierce DM, Johnston A, Hedges A, Franklin RA, Turner P. Pharmacokinetic interaction between indoramin and ethanol. *Hum Toxicol* (1989) 8, 237–41.
3. Kawano Y, Abe H, Kojima S, Takishita S, Omae T. Interaction of alcohol and an α_1-blocker on ambulatory blood pressure in patients with essential hypertension. *Am J Hypertens* (2000) 13, 307–12.

Alcohol + Amfetamines and related drugs

Dexamfetamine can reduce the deleterious effects of alcohol to some extent, but some impairment still occurs making it unsafe to drive. Ecstasy may reduce subjective sedation associated with alcohol, without reversing the effects of alcohol on impulsivity or psychomotor skills. Another report suggests the combination of metamfetamine and alcohol produces an increase in perceived total intoxication, and may also increase cardiac adverse effects. Alcohol may enhance the transient immune dysfunction associated with ecstasy. Alcohol may slightly increase the plasma levels of ecstasy, while alcohol levels may be slightly reduced by ecstasy.

Clinical evidence

(a) Dexamfetamine

In 12 healthy subjects alcohol 0.85 g/kg (2 mL/kg of 100 proof vodka in orange juice) worsened the performance of a SEDI task (Simulator Evaluation of Drug Impairment).[1] This task is believed to parallel the skills needed to drive safely, and involves tests of attention, memory, recognition, decision making and reaction times. When the subjects were also given dexamfetamine 90 or 180 micrograms/kg, there was a dose-related improvement in the performance of the SEDI task, but the subjective assessment of intoxication was unchanged. Blood-alcohol levels reached a maximum of about 100 mg% at approximately one hour, and the bioavailability of alcohol was slightly increased.[1]

Earlier reports using different testing methods found that in some tests dexamfetamine modified the effects of alcohol,[2,3] but the total picture was complex. Other reports found no antagonism.[4,5] Another study found that in stress situations, where relief of fatigue or boredom alone will not produce improved performance, dexamfetamine failed to improve attentive motor performance impaired by alcohol.[6]

(b) Ecstasy (MDMA, Methylenedioxymethamphetamine)

1. Effect on behaviour or psychomotor skills. A study in 9 healthy subjects found that the combination of alcohol 0.8 g/kg and ecstasy 100 mg induced a longer lasting euphoria and sense of well-being than either ecstasy or alcohol alone. Ecstasy reversed the subjective feelings of sedation associated with alcohol, but did not reverse feelings of drunkenness, or the effects of alcohol on psychomotor performance.[7] Similarly, in a placebo-controlled, crossover study in 18 recreational users of ecstasy, alcohol-induced impairment in response inhibition tasks was not affected by single 75- or 100-mg doses of ecstasy. This indicated that the CNS-stimulating effects of ecstasy do not overcome alcohol-induced impairment of impulse-control or risk-taking behaviour.[8] In a placebo-controlled study, 18 healthy subjects were given a single 75- or 100-mg dose of ecstasy with sufficient alcohol to give a blood-alcohol level of 5 mg%. Alcohol alone impaired the performance of some psychomotor tests and driving performance. The addition of ecstasy improved the performance in some, but not all, of these tests. Subjects reported that the combined use of ecstasy and alcohol counteracted the feelings of sedation and lethargy caused by alcohol alone.[9] Another report also indicates that although ecstasy may reduce sedation in response to alcohol, it does not reduce the impairment psychomotor skills caused by alcohol.[10]

2. Effect on immune system. A study in 6 healthy subjects found that a single dose of ecstasy produced a time-dependent immune dysfunction. Ecstasy impaired CD4 T-cell function, which is responsible for cellular immunity. Alcohol alone may produce a decrease in T-helper cells and in B lymphocytes, which are responsible for humoral immunity. Concurrent ecstasy and alcohol increased the suppressive effect of ecstasy on CD4 T-cells and increased natural killer cells.[11]

3. Pharmacokinetic studies. A study in 9 healthy subjects found that alcohol 0.8 g/kg increased the maximum plasma levels of a single 100-mg dose of ecstasy by 13%, with no change in its AUC. The AUC and maximum plasma levels of alcohol were reduced by 9% and 15%, respectively, after ecstasy use.[7] Another single-dose study in 18 recreational users of ecstasy found a similar decrease in mean blood-alcohol levels and a small increase in ecstasy levels when the two drugs were given together, but the results were not statistically significant.[8]

(c) Metamfetamine

One study found that, while the combination of alcohol and metamfetamine diminished the subjective feelings of alcohol intoxication, there was actually an increase in feelings of total intoxication.[12] The combination of alcohol and metamfetamine may increase cardiac toxicity.[12]

Mechanism

Not understood. Although alcohol is a CNS depressant and the amfetamines are CNS stimulants, there is no simple antagonism between the two.[3]

Importance and management

Clear-cut conclusions cannot be drawn from the evidence presented in the reported studies. There is some evidence that the effects of alcohol are modified or reduced by amfetamines, but driving skills appear to remain impaired to some extent. The study using ecstasy suggests that this inter-

action may have implications for road safety, as subjects may consider they are driving better when actual performance is impaired by alcohol.[7] The increase in perceived total intoxication noted in one report has been suggested as a possible reason for the popularity of the illicit use of the combination.[12]

Information about an increase in cardiac toxicity with the combination of metamfetamine and alcohol is limited, and no general conclusions can be drawn.

The effects of ecstasy and alcohol on immune function require more study; however, it has been suggested that the transient defect in immunological homoeostasis could have clinical consequences such as increased susceptibility to infectious diseases.[11]

1. Perez-Reyes M, White WR, McDonald SA, Hicks RE. Interaction between ethanol and dextroamphetamine: effects on psychomotor performance. *Alcohol Clin Exp Res* (1992) 16, 75–81.
2. Kaplan HL, Forney RB, Richards AB, Hughes FW. Dextro-amphetamine, alcohol, and dextro-amphetamine-alcohol combination and mental performance. In Harger RN, ed. Alcohol and traffic safety. Bloomington, Indiana: Indiana Univ Press; 1966 p. 211–14.
3. Wilson L, Taylor JD, Nash CW, Cameron DF. The combined effects of ethanol and amphetamine sulfate on performance of human subjects. *Can Med Assoc J* (1966) 94, 478–84.
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Alcohol + Aminosalicylic acid

Alcohol can abolish the lipid-lowering effects of aminosalicylic acid.

Clinical evidence, mechanism, importance and management

The effectiveness of PAS-C (purified aminosalicylic acid recrystallised in vitamin C) and diet on the treatment of hyperlipidaemia types IIa and IIb was studied in a group of 63 subjects. It was noted that when 3 of the subjects drank unstated amounts of alcohol (beer or cocktails), the effects of the PAS-C on lowering serum cholesterol, triglyceride and LDL-cholesterol levels were completely abolished.[1] The reasons are not understood.

There seems to be no evidence that alcohol affects the treatment of tuberculosis with aminosalicylic acid.

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Alcohol + Amisulpride

No pharmacokinetic interaction appears to occur between amisulpride and alcohol.

Clinical evidence, mechanism, importance and management

No significant pharmacokinetic interactions were seen in 18 healthy subjects given single 50- and 200-mg doses of amisulpride with alcohol 0.8 g/kg, nor were the detrimental effects of alcohol on performance increased by amisulpride.[1] Nevertheless, the manufacturer advises that the central effects of alcohol may be enhanced by amisulpride, and so they do not recommend the combination.[2]

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Alcohol + Antiepileptics

Moderate social drinking does not appear to cause a clinically significant alteration in the serum levels of carbamazepine, ethosuximide, gabapentin, phenobarbital, phenytoin, sodium valproate or tiagabine. However, the adverse effects of both alcohol and some antiepileptics, such as enhanced sedation, may be additive.

Clinical evidence, mechanism, importance and management

A study in 29 non-drinking epileptics found that when they drank 1 to 3 glasses of an alcoholic beverage (1 to 3 units) over a 2-hour period, twice a week for 16 weeks, the serum levels of **carbamazepine**, **ethosuximide** and **phenytoin** were unchanged, when compared with a control group of 23 epileptics given drinks without alcohol. There was a marginal change in **phenobarbital** levels, and some increase in serum **valproate** levels. However, this effect is hard to interpret as **valproate** levels are known to fluctuate and are hard to reproduce. Other antiepileptics used were **clonazepam**, **primidone** and **sultiame**, but too few patients used these drugs to allow valid statistical analysis. Maximum blood-alcohol levels ranged from 5 to 33 mg%. More important than any changes that occurred in serum antiepileptic levels, was the finding that social drinking had no effect on the frequency of tonic-clonic convulsions, partial complex seizures, or on the epileptic activity as measured by EEGs.[1]

In study of patients with head injuries the clearance of unbound **valproate** was found to be modestly increased (by up to 14%) in subjects who had measurable alcohol levels at the time of admission, when compared with those without detectable alcohol levels.[2] Another study in healthy subjects excluded any pharmacodynamic or pharmacokinetic interaction between **tiagabine** and alcohol. In this study, **tiagabine** 4 mg three times daily did not alter the effect of a single dose of alcohol, as assessed in a range of cognitive tests.[3] A study in 17 subjects who were considered to be heavy drinkers (average 34 drinks per week), found that **gabapentin** in doses of 1 g and 2 g did not affect the pharmacokinetics of alcohol, nor did it affect a number of subjective, physiological or performance measures, when compared with alcohol alone. However, the increase in heart rate seen with alcohol was increased to a *statistically* significant extent by gabapentin (exact figures not given).[4]

For the effect of chronic heavy drinking on the pharmacokinetics of carbamazepine or phenytoin, see 'Alcohol + Carbamazepine', p.61 and 'Alcohol + Phenytoin', p.82.

There are very few studies, but there seem to be no reasons for epileptic patients to avoid alcohol in moderate social amounts (1 or 2 drinks per occasion; no more than 3 to 6 drinks per week).[5] However, patients who drink moderate to heavy amounts of alcohol (3 to 4 drinks or more) should be warned that they are at increased risk of seizures, with the greatest risk occurring 7 to 48 hours after the last drink.[5] The British Epilepsy Association comments that most people with epilepsy find they can have one or two units of alcohol, perhaps more, without increasing the chances of having a seizure, whereas other people find that even a small amount of alcohol triggers their seizures.[6] Patients who drink heavily may also get alcohol withdrawal seizures, and binge drinking has been associated with seizures even in non-epileptic people. The British Epilepsy Association also say that anyone taking antiepileptics is likely to be more sensitive to the effects of alcohol and alcohol can exaggerate the adverse effects of the antiepileptics.[6] Some antiepileptics such as **carbamazepine**, **clonazepam**, '**phenobarbital**', (p.55), **primidone**, and **topiramate** have sedative effects, which may be additive with those of alcohol.

Individuals need to decide what level of alcohol intake is appropriate for them, and be aware that a change in medication, or an increase in dose of antiepileptic, may make them more susceptible to the effects of alcohol. Patients should also be made aware that drinking alcohol when taking antiepileptics may reduce their ability to perform certain skilled tasks, such as driving.

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Alcohol + Antihistamines

Some antihistamines cause drowsiness, which can be increased by alcohol. The detrimental effects of alcohol on driving skills are considerably increased by the use of the older more sedative antihistamines and appear to be minimal or absent with the newer non-sedating antihistamines.

Clinical evidence

(a) Non-sedating antihistamines

A double-blind study found that **terfenadine** 60 to 240 mg alone did not affect psychomotor skills, nor did it alter the adverse effects of alcohol.[1] Another study had similar findings.[2] However, a later study found that **terfenadine** 240 mg slowed brake reaction times in the laboratory when given either alone or with alcohol.[3] **Acrivastine** 4 and 8 mg, given with and without alcohol, was found in a study to behave like **terfenadine** (which interacts minimally or not at all).[4] Other studies have shown that **astemizole** 10 to 30 mg daily,[5-7] **desloratadine**,[8] **ebastine** 20 mg,[9] **fexofenadine** 120 to 240 mg,[10,11] **levocabastine** 2 nasal puffs of 0.5 mg/mL,[12] **loratadine** 10 to 20 mg[2,13] and **mizolastine** 10 mg[14] do not interact with alcohol. **Cetirizine** 10 mg did not appear to interact with alcohol in two studies[14,15] but some slight additive effects were detected in other studies.[13,16] Similarly, a single oral dose of **rupatadine** 10 mg did not interact with alcohol, but a 20-mg dose given with alcohol produced more cognitive and psychomotor impairment than alcohol alone.[16]

(b) Sedating antihistamines

The effects of alcohol (blood levels about 50 mg%) and antihistamines, alone or together, on the performance of tests designed to assess mental and motor performance were examined in 16 subjects. **Clemizole** 40 mg alone or **tripelennamine** 50 mg alone did not significantly affect the performance under the stress of delayed auditory feedback, neither did they potentiate the effect of alcohol.[17] **Clemastine** in 3-mg doses had some additive detrimental effects with alcohol on co-ordination, whereas **clemastine** 1.5 mg and 1 mg did not.[18,19] A study in 5 subjects showed that the detrimental effects of 100 mL of whiskey on the performance of driving tests on a racing car simulator (blood-alcohol level estimated as less than 80 mg%) were not increased by **cyclizine** 50 mg.[20] However 3 of the subjects experienced drowsiness after **cyclizine**, and other studies have shown that **cyclizine** alone causes drowsiness in the majority of subjects.[21] Significant impairment of psychomotor performance was seen in healthy subjects given **chlorphenamine** 12 mg with alcohol 0.5 g/kg.[5] A further study similarly found significant impairment in driving skills when **chlorphenamine** was given with alcohol, see (*c*) below. In 13 healthy subjects alcohol 0.75 g/kg given with **dexchlorpheniramine** 4 mg/70 kg significantly impaired the performance of a number of tests (standing steadiness, reaction time, manual dexterity, perception, etc.).[22] A study in 17 subjects found that **mebhydrolin** 0.71 mg/kg enhanced the alcohol-induced deficits in the performance of a number of tests of perceptual, cognitive and motor functions.[23] No interaction was detected in one study of the combined effects of **pheniramine aminosalicylate** 50 mg or **cyproheptadine hydrochloride** 4 mg and alcohol 0.95 mL/kg.[24] **Triprolidine** 10 mg alone can significantly affect driving performance,[2] and marked deterioration in driving skills has been demonstrated with 10 mL of *Actifed Syrup* (**triprolidine** with pseudoephedrine) alone and with a double whiskey.[25]

(c) Significantly-sedating antihistamines

Diphenhydramine in doses of 25 or 50 mg was shown to increase the detrimental effects of alcohol on the performance of choice reaction and co-ordination tests in subjects who had taken 0.5 g/kg of alcohol.[18] The interaction between **diphenhydramine** in doses of 50, 75 or 100 mg and alcohol 0.5 to 0.75 g/kg has been confirmed in other reports.[1,17,26-28] **Emedastine**, in oral doses of 2 or 4 mg twice daily, was found to be sedating and impair driving ability in 19 healthy subjects. The addition of alcohol increased this impairment.[29] A marked interaction can also occur with **hydroxyzine**[11,16] or **promethazine**.[30] A very marked deterioration in driving skills was clearly demonstrated in a test of car drivers given 20 mL of *Beechams Night Nurse* (**promethazine** with dextromethorphan), 10 mL of *Benylin* (**diphenhydramine** with dextromethorphan), or 30 mL of *Lemsip Night time flu medicine* (**chlorphenamine** with dextromethorphan). Very poor scores were seen when they were also given a double Scotch whiskey about 1.5 hours later.[25]

Mechanism

When an interaction occurs it appears to be due to the combined or additive central nervous depressant effects of both the alcohol and the antihistamine. The highly-sedating antihistamines are highly lipophilic and readily cross the blood-brain barrier; consequently they have considerable sedative effects that may persist into the next day. The sedating antihistamines do not cross the blood-brain barrier so readily, and are therefore less sedating. Most of the non-sedating antihistamines, such as fexofenadine, do not appear to cross the blood-brain barrier,[11] and would therefore not be expected to cause much, if any, sedation. The authors of one study found that the sedating effects of cetirizine and emedastine were more marked in women than in men, and they noted that they had also previously seen this with acrivastine, clemastine and mizolastine.[29] The reason for this is not established although it has been suggested that a smaller volume of distribution in women may result in higher plasma antihistamine levels.

Importance and management

An adverse interaction between alcohol and the **highly-sedating antihistamines** (see 'Table 15.1', (p.663)) is well established and clinically important. Marked drowsiness can occur with these antihistamines taken alone, which makes driving or handling other potentially dangerous machinery much more hazardous. This can be further worsened by alcohol. Patients should be strongly warned. Remember that some of these antihistamines are present in non-prescription products licensed as antiemetics and sedatives, and as components of cough, cold, and influenza remedies (e.g. some preparations of *Benylin*, *Lemsip*, and *Night Nurse*). Emedastine may also cause marked sedation when used orally, but it is usually given as eye drops, and its use would therefore not be expected to result in a clinically relevant interaction with alcohol.

The situation with some of the **sedating antihistamines** is less clear cut, and tests with some of them failed to detect an interaction with normal doses and moderate amounts of alcohol; however, it has been clearly seen with *Actifed Syrup* (containing triprolidine). It would therefore be prudent to issue some cautionary warning, particularly if the patient is likely to drive.

The **non-sedating antihistamines** seem to cause little or no drowsiness in most patients and the risks if taken alone or with alcohol appear to be minimal or absent. However, the incidence of sedation varies with the non-sedating antihistamine (e.g. sedation appears to be lower with fexofenadine and loratadine than with acrivastine or cetirizine)[31] and with the individual (e.g. women may be more affected than men).[29] Therefore, patients should be advised to be alert to the possibility of drowsiness if they have not taken the drug before. Any drowsiness would be apparent after the first few doses. The manufacturer of cetirizine suggests avoiding excessive amounts of alcohol,[32] and, although they note that cetirizine has not been shown to potentiate the effects of alcohol, the manufacturers of **levocetirizine** advise caution with the concurrent use of alcohol.[33]

The possible interactions of alcohol with other antihistamines not cited here do not seem to have been formally studied, but increased drowsiness and increased driving risks would be expected with any that cause some sedation. Patients should be warned about drinking alcohol when taking sedative antihistamines. The risks with antihistamines given as eye drops or nasal spray (e.g. **azelastine**, **epinastine**) are probably minimal, but this needs confirmation.

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Alcohol + Antihypertensives

Chronic moderate to heavy drinking raises blood pressure and reduces, to some extent, the effectiveness of antihypertensive drugs. A few patients may experience postural hypotension, dizziness and fainting shortly after having drunk alcohol. Alpha blockers may enhance the hypotensive effect of alcohol in subjects susceptible to the alcohol flush syndrome.

Clinical evidence, mechanism, importance and management

(a) Hypertensive reaction

A study in 40 men with essential hypertension (taking **beta blockers**, **captopril**, **diuretics**, **methyldopa**, **prazosin** or **verapamil**) who were moderate to heavy drinkers, found that when they reduced their drinking over a 6-week period from an average of 450 mL of alcohol weekly (about 6 drinks daily) to 64 mL of alcohol weekly, their average blood pressure fell by 5/3 mmHg.[1] The reasons for this effect are uncertain.

The Atherosclerosis Risk in Communities (ARIC) study involving 8334 subjects who were free from hypertension at baseline and were assessed after 6 years, found that higher levels of consumption of alcoholic beverages (210 g or more of alcohol per week; approximately 3 drinks or more per day) were associated with a higher risk of hypertension. Low to moderate consumption of alcohol (up to 3 drinks daily) was associated with an increase in blood pressure in black, but not in white men.[2] A study in Japanese men found that the effect of alcohol intake on the risk of developing hypertension was dose-dependent, starting at low-to-moderate levels of alcohol (less than 23 g daily).[3]

These findings are consistent with those of other studies in hypertensive[4] and normotensive[5] subjects. It seems likely that this effect will occur with any antihypertensive. Patients with hypertension who are moderate to heavy drinkers should be encouraged to reduce their intake of alcohol. It may then become possible to reduce the dosage of the antihypertensive. It should be noted that epidemiological studies show that regular light to moderate alcohol consumption is associated with a *lower* risk of cardiovascular disease.[6]

(b) Hypotensive reaction

A few patients taking some antihypertensives feel dizzy or begin to 'black out' or faint if they stand up quickly or after exercise. This orthostatic and exertional hypotension may be exaggerated in some patients shortly after drinking alcohol, possibly because it can lower the cardiac output (noted in patients with various types of heart disease[7,8]). For other reports of postural hypotension with alcohol, see 'alpha blockers', (p.48), and 'calcium-channel blockers', (p.60). Some manufacturers of antihypertensives e.g. **ACE inhibitors** (enalapril and captopril)[9,10] and **thiazide diuretics** (hydrochlorothiazide)[11] warn that acute alcohol intake may enhance the hypotensive effects, particularly at the start of treatment,[10] and this could apply to any antihypertensive. Patients just beginning antihypertensive treatment should be warned.

(c) CNS and other effects

For mention of the possibility of increased sedation with alcohol and clonidine or indoramin, see 'Clonidine and related drugs + CNS depressants', p.1054 and 'Alcohol + Alpha blockers', p.48.

For the possible CNS effects of beta blockers and alcohol, see 'Alcohol + Beta blockers', p.58.

For mention of the disulfiram-like reaction when tolazoline is given with alcohol, see 'Alcohol + Tolazoline', p.88.

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Alcohol + Antimuscarinics

Propantheline appears not to affect blood-alcohol levels, whereas atropine may cause a modest reduction. Marked impairment of attention can occur if alcohol is taken in the presence of atropine or glycopyrronium (glycopyrrolate), probably making driving more hazardous. No adverse interaction usually appears to occur with hyoscine (scopolamine) and alcohol, although hyoscine hydrobromide presents more of a theoretical risk than hyoscine butylbromide.

Clinical evidence, mechanism, importance and management

(a) Atropine

In a study in 3 subjects, a single 3-mg oral dose of atropine, given 2 hours before alcohol reduced the AUC of alcohol by a modest 20%.[1] Another study in healthy subjects found that oral atropine 500 micrograms given with alcohol 0.5 g/kg either did not affect or improve reaction times and co-ordination; however, there was a marked impairment of attention, which was large enough to make driving more hazardous.[2] Patients should be warned.

(b) Glycopyrronium

A study in healthy subjects found that glycopyrronium 1 mg given with alcohol 0.5 g/kg either did not affect or improve reaction times and co-ordination; however, there was a marked impairment of attention, which was large enough to make driving more hazardous.[2] Patients should be warned.

(c) Hyoscine (Scopolamine)

A double-blind crossover study in 12 healthy subjects found that a transdermal hyoscine preparation (*Scopoderm-TTS*) did not alter the effects of alcohol on the performance of several psychometric tests (Critical Flicker Fusion Frequency, Choice Reaction Tasks), nor was the clearance of alcohol or hyoscine changed. Blood-alcohol levels of up to 80 mg%, and 130 mg%, were studied.[3] In a study investigating the metabolism of alcohol, 10 patients were given hyoscine butylbromide 20 mg with oral alcohol 0.225 g/kg. Peak serum alcohol levels were not significantly altered, but were delayed from about 23 minutes to 50 minutes by the hyoscine, when compared with alcohol alone. Gastric emptying time was also significantly increased, from about 44 minutes to 71 minutes.[4] Although the evidence would seem to suggest that a clinically significant pharmacokinetic interaction is unlikely, the manufacturer of *Scopoderm-TTS* suggests caution in patients receiving drugs that act on the CNS, and advises that patients should not drink alcohol.[5] This is presumably because drowsiness and other CNS adverse effects have occasionally been reported with transdermal hyoscine.[5,6] The manufacturers of travel tablets and injections containing hyoscine hydrobromide recommend avoiding alcohol.[7,8] However, unlike hyoscine and hyoscine hydrobromide, the quaternary derivatives, such as hyoscine butylbromide or hyoscine methobromide, do not readily pass the blood-brain barrier,[9] and would therefore be expected to be less likely to cause additive adverse effects with alcohol.

(d) Propantheline

In a study in 3 subjects oral propantheline (15 mg four times daily or 30 mg three times daily for 5 days, with 30 mg or 60 mg two hours before alcohol) did not affect blood-alcohol levels.[1]

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Alcohol + Antimycobacterials

The hepatotoxicity of some antimycobacterials may possibly be increased by high alcohol consumption. Alcohol may increase the risk of epileptic episodes in patients taking cycloserine. A psychotoxic reaction in a patient taking ethionamide was attributed to concurrent heavy alcohol consumption. Isoniazid slightly increases the hazards of driving after drinking alcohol. Isoniazid-induced hepatitis may also possibly be increased by alcohol, and the effects of isoniazid are possibly reduced in some heavy drinkers. Acute alcohol intake does not appear to affect the pharmacokinetics of a single-dose of isoniazid.

Clinical evidence, mechanism, importance and management

(a) Combined antitubercular regimens

Hepatotoxicity can occur with several antimycobacterial drugs including **ethionamide, isoniazid, pyrazinamide** and **rifampicin** and high alcohol consumption/chronic alcoholism has been reported to increase the risk.[1,2] However, one study in patients with active tuberculosis taking **rifampicin** and **pyrazinamide**, found that of the 14 patients who developed hepatotoxicity, only 5 of these reported alcohol use (not quantified), and alcohol was not found to be associated with an increased risk of hepatotoxicity.[3] Similarly, another study found that alcohol consumption was not a risk factor for antimycobacterial-induced hepatotoxicity.[4]

(b) Cycloserine

A brief report describes an enhancement of the effects of alcohol in 2 patients taking cycloserine.[5] The clinical significance of this report is unclear. However, the manufacturer of cycloserine states that it is 'incompatible' with alcohol because of an increased risk of epileptic episodes, and contraindicate its use in alcohol abuse.[6]

(c) Ethionamide

A psychotoxic reaction seen in a patient taking ethionamide was attributed to the concurrent heavy consumption of alcohol.[7] It is unclear whether this represents a clinically meaningful interaction but it appears to be the only case on record. However, because of this reaction, the manufacturer advises that patients should avoid drinking excessive amounts of alcohol.[8]

(d) Isoniazid

The effects of isoniazid 750 mg with alcohol 0.5 g/kg were examined in 100 subjects given various psychomotor tests, and in a further 50 drivers using a driving simulator. No major interaction was seen in the psychomotor tests, but the number of drivers who drove off the road on the simulator was increased.[9,10] There would therefore appear to be some extra risks for patients taking isoniazid who drink and drive, but the effect does not appear to be large. Patients should nevertheless be warned.

The incidence of severe progressive liver damage due to isoniazid is said to be higher in those who drink alcohol regularly,[11-13] and the clinical effects of isoniazid are also said to be reduced by heavy drinking in some patients.[11] The manufacturer advises care in giving isoniazid to patients with chronic alcoholism.[14]

Acute alcohol intake in 16 healthy subjects did not have any effect on the pharmacokinetics of a single 200-mg dose of isoniazid.[15] Alcohol is metabolised to acetaldehyde in the liver and isoniazid has been found to interact with acetaldehyde *in vitro*. The clinical significance of this is unknown, but if this binding occurs *in vivo,* it could lead to decreased bioavailability of isoniazid and possibly the acetaldehyde-modified drug formed could mediate some adverse effects.[16]

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Alcohol + Antipsychotics

The detrimental effects of alcohol on the skills related to driving are made worse by chlorpromazine, and, to a lesser extent, by flupentixol, sulpiride and thioridazine. Small or single-dose studies with haloperidol or tiapride suggest that any interaction would seem to be mild; nevertheless, all antipsychotic drugs that cause drowsiness have the potential to enhance the effects of alcohol. There is also some evidence to suggest that drinking can precipitate the emergence of extrapyramidal adverse effects in patients taking antipsychotics.

Clinical evidence

(a) Effect on driving and other skills

Twenty-one subjects showed a marked deterioration in the performance of a number of skills related to driving when they were given **chlorpromazine** 200 mg daily and alcohol (blood levels 42 mg%). Many complained of feeling sleepy, lethargic, dull, groggy, and poorly coordinated; and most considered themselves more unsafe to drive than with alcohol alone.[1] A later study confirmed these findings with **chlorpromazine** 1 mg/kg and blood-alcohol levels of 80 mg%.[2] Increased sedation was clearly seen in another study with alcohol and **chlorpromazine**,[3] and clear impairment of psychomotor skills related to driving have also been found.[4]

Single 500-microgram doses of **haloperidol** or **flupentixol** strongly impaired attention, but did not significantly interact with alcohol in one study.[5] However, a double-blind study in subjects given **flupentixol** 500 micrograms three times a day for 2 weeks found that, when combined with alcohol 0.5 g/kg, their performance of a number of tests (choice reaction, coordination, attention) was impaired to such an extent that driving or handling other potentially dangerous machinery could be hazardous.[6]

Sulpiride 50 mg three times daily for 2 weeks caused a mild decrease in psychomotor skills with alcohol in healthy subjects, but not as much as that seen with **chlorpromazine** and alcohol.[4,7] **Thioridazine** 25 mg caused some additive effects with alcohol, with a moderately deleterious effect on attention.[5] Another study found that **thioridazine** and alcohol affected skills related to driving, but not as much as the effects seen with **chlorpromazine**.[2] A further study found no difference between the effects of **thioridazine** and a placebo with alcohol.[4,8]

A study in 9 alcoholics given **tiapride** 400 to 600 mg daily found that wakefulness was not impaired when alcohol 0.5 g/kg was given, and in fact appeared to be improved, but the effect on driving skills was not studied.[9]

(b) Precipitation of extrapyramidal adverse effects

A report describes 7 patients who developed acute extrapyramidal adverse effects (akathisia, dystonia) while taking **trifluoperazine**, **fluphenazine**, **perphenazine**, or **chlorpromazine** and drinking alcohol.[10] The author stated that these were examples of numerous such alcohol-induced toxicity reactions observed by him over an 18-year period involving phenothiazines and butyrophenones. Elsewhere he describes the emergence of drug-induced parkinsonism in a woman taking **perphenazine** and amitriptyline when she began to drink alcohol.[11] Eighteen cases of **haloperidol**-induced extrapyramidal reactions among young drug abusers, in most instances associated with the ingestion of alcohol, have also been described.[12] Similarly, a study involving 41 patients with schizophrenia found that those with a substance use disorder (alcohol or cannabis with or without cocaine) displayed more extrapyramidal symptoms compared with non-abusing patients.[13]

(c) Toxicity

A study involving 332 fatal poisonings in Finland found that alcohol was present in 65% of cases involving **promazine**, and when alcohol was present, relatively small overdoses of **promazine** could result in fatal poisoning.[14] It appears that **promazine** and possibly **levomepromazine** may be more toxic when combined with alcohol.[15]

(d) Pharmacokinetic studies

A study in 12 patients taking **chlorpromazine** 600 mg to 1.2 g daily long-term, found that **chlorpromazine** had no apparent effect on alcohol metabolism. However, about half of the patients had a statistically significant decrease (up to 33%) in urinary excretion of **chlorpromazine** and its metabolites during the 24-hour period following the consumption of 50 to 75 mL of alcohol.[16]

A study in 7 schizophrenics found that when they were given 40 g of alcohol to drink at about the same time as their regular injection of **fluphenazine decanoate** (25 to 125 mg every 2 weeks), their serum **fluphenazine** levels were reduced by 30% at 2 hours and by 16% at 12 hours.[17]

Mechanism

Uncertain. Additive CNS depressant effects are one explanation of this interaction. One suggestion to account for the emergence of the drug adverse effects is that alcohol lowers the threshold of resistance to the neurotoxicity of these drugs. Also alcohol may possibly impair the activity of tyrosine hydroxylase so that the dopamine/acetylcholine balance within the corpus striatum is upset.[11] In addition, chlorpromazine has been found to inhibit alcohol dehydrogenase, which may facilitate the formation of biogenic amines that have been implicated in extrapyramidal adverse effects.[18]

Pharmacokinetic interactions between acute and chronic alcohol ingestion, and single or multiple doses of antipsychotic drug are complex; acute alcohol intake can decrease metabolic clearance, whereas chronic intake can increase clearance.[19] Alcohol may also affect the peripheral circulation and membrane permeability, which might affect absorption from an injection site.[17]

Importance and management

The documentation is limited. The manufacturers of flupentixol[20] and haloperidol[21] warn that, in common with other antipsychotic drugs, the effects of alcohol maybe enhanced. Warn patients that if they drink alcohol while taking chlorpromazine, and to a lesser extent flupenthixol, sulpiride or thioridazine (probably other related drugs as well), they may become very drowsy, and should not drive or handle other potentially dangerous machinery. Some risk is possible with any antipsychotic that causes drowsiness, including those used as antiemetics, such as **prochlorperazine**.

The authors of the reports describing the emergence of serious adverse effects to antipsychotics in those who drink alcohol, consider that patients should routinely be advised to abstain from alcohol during antipsychotic treatment.

It has been suggested that a less dangerous alternative to promazine, and possibly levomepromazine, should be chosen when indications of alcohol abuse or suicide risk are present.[15]

The clinical importance of the pharmacokinetic studies is uncertain, but the changes observed were mostly slight.

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Alcohol + Antiretrovirals

Heavy alcohol intake may affect the virological response to HAART. Theoretically, alcohol consumption may induce liver enzymes, which interfere with the metabolism of some antivirals such as the protease inhibitors. Alcohol reduces the metabolism of abacavir but this does not appear to be clinically significant.

Clinical evidence, mechanism, importance and management

(a) Alcohol and HAART regimens

A study of 94 HIV-positive patients receiving HAART, which included 2 **nucleoside analogues** plus either **indinavir**, **ritonavir**, **saquinavir**, **nelfinavir**, or **ritonavir**/**saquinavir**, found that the amount of alcohol consumed did not affect the antiviral response. However, the proportion of complete responders was slightly lower (57%) in heavy drinkers (more than 60 g of alcohol per day) compared with 68% in both non-drinkers and moderate drinkers (less than 60 g of alcohol per day), although this was not a significant finding. There was also a high prevalence of infection with hepatitis C virus, and liver decompensation occurred in 2 patients (both heavy drinkers).[1] Alcohol may affect thymus-induced immune repletion in HIV-positive patients and it has been reported that heavy alcohol users taking antiretrovirals are twice as likely not to achieve a positive virological response, compared with those who do not use alcohol.[2]

Alcohol consumption can induce the cytochrome P450 isoenzyme CYP3A4 and there is concern that HAART may not be as effective in some individuals who consume alcohol.[3] CYP3A4 is involved in the metabolism of the protease inhibitors **amprenavir**, **fosamprenavir**, **indinavir**, **lopinavir**, **nelfinavir**, **ritonavir**, and **saquinavir** and the NNRTIs **delavirdine**, **efavirenz**, and **nevirapine**, and therefore CYP3A4 induction may result in enhanced drug metabolism and reduced therapeutic levels.[4] Avoidance of alcohol has been suggested for HIV-positive patients receiving protease inhibitor therapy,[3,4] but at present there does not seem to be any clinical data to support this. Nevertheless, a reduction in alcohol consumption would seem sensible. More studies are needed. Note that some preparations of **ritonavir** contain alcohol, see 'Alcohol + Disulfiram', p.66.

(b) Effect of alcohol on abacavir

A study in 24 HIV-positive patients found that alcohol 0.7 g/kg increased the AUC of a single 600-mg dose of abacavir by 41%. The half-life of abacavir was increased by 26%, from 1.42 to 1.79 hours. The pharmacokinetics of alcohol were not affected by abacavir.[5] Alcohol may inhibit the formation of abacavir carboxylate resulting in a trend towards increased abacavir glucuronide formation and reduced abacavir metabolism. The increase in exposure to abacavir was not considered to be clinically significant, since it is within levels seen in other studies using higher doses, which demonstrated no additional safety concerns at doses of up to three times the recommended daily dose of abacavir.[5] No special precautions therefore appear to be necessary.

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Alcohol + Apomorphine

Apomorphine may increase the effects of alcohol and the hypotensive adverse effects of apomorphine may possibly be increased by alcohol.

Clinical evidence, mechanism, importance and management

In a study, 12 healthy subjects were given alcohol-containing drinks to give a blood-alcohol level of about 100 mg%, followed by a single 5-mg dose of apomorphine. Subjective and objective measures of drunkenness were significantly increased by apomorphine, but the peak blood-alcohol levels were not altered.[1]

The manufacturer of a preparation of apomorphine used for erectile dysfunction advised that interaction studies in subjects given apomorphine found that alcohol increased the incidence and extent of hypotension (one of the adverse effects of apomorphine). They also pointed out that alcohol can diminish sexual performance.[2] The US manufacturer advises the avoidance of alcohol.[3]

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Alcohol + Aspirin or other Salicylates

A small increase in the gastrointestinal blood loss caused by aspirin occurs in patients if they also drink alcohol, but any increased damage to the lining of the stomach is small and appears usually to be of minimal importance in most healthy individuals. However, heavy drinkers who regularly take aspirin should be warned of the increased risk of gastric bleeding. Some limited information suggests that aspirin can raise or lower blood-alcohol levels, and alcohol may cause slight changes in salicylate levels.

Clinical evidence

(a) Gastrointestinal effects

The mean daily blood loss from the gut of 13 healthy men was 0.4 mL while taking no medication, 3.2 mL while taking 2.1 g of soluble unbuffered aspirin (*Disprin*) and 5.3 mL while taking aspirin with 180 mL of Australian whiskey (alcohol 31.8%). In this study, alcohol alone did not cause gastrointestinal bleeding.[1] Similar results were reported in another study in healthy subjects.[2]

An epidemiological study of patients admitted to hospital with gastrointestinal haemorrhage showed a statistical association between bleeding and the ingestion of aspirin alone, and the combination with alcohol produced a significant synergistic effect.[3] A large case-controlled study found similar results: the overall relative risk of bleeding with regular use of aspirin, at doses greater than 325 mg, was 7 among drinkers and 5.1 among people who never drank alcohol. For those who drank less than 1 to 20 drinks a week there was no evidence of a trend of increasing or decreasing relative risk as levels of alcohol consumption increased, but among those who consumed 21 or more drinks a week there was a large association with upper gastrointestinal bleeding (crude estimated risk 27). For regular aspirin use at doses of 325 mg or less, the overall relative risk among all current drinkers and among people who never drank alcohol was 2.8 and 2.2, respectively.[4] Another case-control study suggested that the odds ratio for gastrointestinal complications in those regularly consuming more than 5 drinks during a drinking session was increased from 2.8 to 8.1 when aspirin was also taken. This was also increased when compared with the use of aspirin alone (odds ratio 3).[5]

Endoscopic examination revealed that aspirin and alcohol have additive damaging effects on the gastric mucosa (not on the duodenum), but the extent is small.[6] However, a further case-control study found that large amounts of red wine (roughly over 500 mL of wine daily) increased the risk of upper gastrointestinal bleeding associated with low-dose aspirin, and small amounts of red wine (roughly less than 200 mL of wine daily) reduced this risk.[7] Another study, using gastric mucosal potential difference as a measure of mucosal damage, found that aspirin with alcohol caused additive damage to the mucosa.[8] In a review of the evidence, it was considered that while more study was needed, data available are highly suggestive that the gastrointestinal toxicity of alcohol and aspirin are combined in individuals who are heavy daily drinkers and heavy aspirin users.[9]

No increased gastrointestinal bleeding occurred in 22 healthy subjects given three double gins or whiskies (equivalent to 142 mL of alcohol 40%) and 728 mg of buffered sodium acetylsalicylate (*Alka-Seltzer*).[10]

(b) Effect on blood-alcohol levels

Five healthy subjects were given a standard breakfast with and without aspirin 1 g followed one hour later by alcohol 0.3 g/kg. The aspirin increased the peak blood-alcohol levels by 39% and the AUC by 26%.[11] Similarly, in another study, 28 healthy subjects were given a midday meal (two sandwiches and a cup of tea or coffee), followed 90 minutes later by 600 mg of aspirin or a placebo, and then 30 minutes later by two standard drinks (35.5 mL of vodka 37.5% (21.6 g of alcohol) plus 60 mL of orange juice), which were drunk within a 15-minute period. The blood-alcohol levels of the men were raised by 31% after one hour (from about 24 to 32 mg%) and by 18% (from about 21 to 25 mg%) after 2 hours. The blood-alcohol levels of the women were raised by 32% (from about 37 to 49 mg%) after one hour and by 21% (from about 38 to 46 mg%) after 2 hours.[12]

However, a later study (effectively a repeat of a study[11] above) in

12 healthy subjects found that aspirin did not appear to affect blood-alcohol levels.[5] A crossover study in 10 healthy male subjects found that after taking aspirin 75 mg daily for one week, their mean blood alcohol AUC following a 0.3 g/kg-dose was not significantly altered. However, individual *maximum* blood levels varied; one subject showed a rise, two were unchanged, and five were lowered: overall the reduction was 23%.[13]

(c) Effect on salicylate levels

One study (effectively a repeat of a study[11] above) in 12 healthy subjects found that alcohol reduced peak aspirin levels by 25%.[5] In a study in 5 healthy subjects the AUC and maximum levels of a single 500-mg dose of aspirin were found to be increased by a modest 11% by 50 mL of 40% alcohol, but decreased by 13% and 17%, respectively, when taken with 200 mL of beer.[14]

Mechanism

(a) Gastrointestinal effects

Aspirin and alcohol can damage the mucosal lining of the stomach, one measure of the injury being a fall in the gastric potential difference. Once the protective mucosal barrier is breached, desquamation of the cells occurs and damage to the capillaries follows. Aspirin causes a marked prolongation in bleeding times, and this can be increased by alcohol.[15] The total picture is complex.

(b) Effect on blood-alcohol levels

The increased blood-alcohol levels in the presence of food and aspirin may possibly occur because the aspirin reduces the enzymic oxidation of the alcohol by alcohol dehydrogenase in the gastric mucosa, so that more remains available for absorption.[11] Any decreases with low-dose aspirin may possibly be due to delayed gastric emptying.[13]

(c) Effect on salicylate levels

It is possible that several mechanisms are involved in the alteration of aspirin bioavailability by alcohol, including increased dissolution and altered gastric emptying.[14]

Importance and management

The combined effect of aspirin and alcohol on the stomach wall is established. Aspirin 3 g daily for a period of 3 to 5 days induces an average blood loss of about 5 mL or so. Some increased loss undoubtedly occurs with alcohol, but it seems to be quite small and unlikely to be of much importance in most healthy individuals using moderate salicylate doses drinking moderate amounts of alcohol. In one study it was found that alcohol was a mild damaging agent or a mild potentiating agent for other drugs that damaged the gastrointestinal mucosa.[6] However, it should be remembered that chronic and/or gross overuse of salicylates and alcohol may result in gastric ulceration. People who consume at least 3 or more alcoholic drinks daily and who regularly take more than 325 mg of aspirin have been shown to have a high risk of bleeding.[16] The FDA in the US has ruled that non-prescription pain relievers and fever reducers, containing aspirin or salicylates, must carry a warning label advising people who consume moderate amounts of alcohol to consult their doctor before using these drugs, and that stomach bleeding may occur with these drugs.[17] However, the Australian Medicines Evaluation Committee has decided against such action as, for most people with mild to moderate alcohol intake, there is little risk especially if the aspirin is taken only as needed.[16]

Information about the increase in blood-alcohol levels caused by aspirin after food is very limited and contradictory, and of uncertain practical importance. However, no practically relevant interaction has been seen with other drugs (such as the 'H_2-receptor antagonists', (p.70)), which have been extensively studied, and which appear to interact by the same mechanism. The pattern for these drugs is that the increases in blood-alcohol levels are appreciable with small doses of alcohol, but usually they become proportionately too small to matter with larger doses of alcohol (i.e. those that give blood and breath levels at or around the legal driving limit in the UK).

The change in salicylate levels with alcohol is almost certainly too small to be of clinical relevance.

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Alcohol + Barbiturates

Alcohol and the barbiturates are CNS depressants, which together can have additive and possibly even synergistic effects. Activities requiring alertness and good co-ordination, such as driving a car or handling other potentially dangerous machinery, can be made more difficult and more hazardous. Alcohol may also continue to interact the next day if the barbiturate has hangover effects.

Clinical evidence

A study in healthy subjects of the effects of a single 0.5-g/kg dose of alcohol, taken in the morning after a dose of **amobarbital** 100 mg every night for 2 weeks, found that the performance of co-ordination skills was much more impaired than with either drug alone.[1]

This increased CNS depression due to the combined use of alcohol and barbiturates has been described in other clinical studies with **phenobarbital**.[2,3] However, a study in healthy subjects found that although **phenobarbital** 45 mg daily for one week and alcohol (35 to 45 mg%) affected some perceptual-motor tests when given separately, these effects were not always found when they were given together.[4] Nevertheless, high doses of **phenobarbital** can affect driving skills[5] and increased CNS depression has featured very many times in coroners' reports of fatal accidents and suicides involving barbiturates and alcohol.[6] A study of the fatalities due to this interaction indicated that with some barbiturates the CNS depressant effects are more than additive.[7] There is also some evidence that blood-alcohol levels may be reduced in the presence of a barbiturate.[8,9]

For the interaction between thiopental and alcohol, see 'Anaesthetics, general + Alcohol', p.102.

Mechanism

Both alcohol and the barbiturates are CNS depressants, and simple additive CNS depression provides part of the explanation. Acute alcohol ingestion may inhibit the liver enzymes concerned with the metabolism of barbiturates such as phenobarbital and **pentobarbital**, but chronic exposure to alcohol increases hepatic microsomal enzyme activity and may reduce sedation from barbiturates in patients without liver impairment.[10,11] Similarly, chronic exposure to a barbiturate such as phenobarbital may increase alcohol metabolism due to enzyme induction and consequently reduce blood-alcohol levels.[7]

Importance and management

Few formal studies in normal clinical situations have been made of the interactions between alcohol and the barbiturates, and most of these studies are old and involved barbiturates used as hypnotics. However, the effects

(particularly those that result in fatalities) are very well established, serious, and of clinical importance. The most obvious hazards are increased drowsiness, lack of alertness, and impaired co-ordination, which make the handling of potentially dangerous machinery (e.g. car driving), and even the performance of everyday tasks (e.g. walking downstairs) more difficult and dangerous. Only amobarbital and phenobarbital appear to have been specifically studied, but this interaction would be expected with all of the barbiturates. Some barbiturate hangover effects may be present the next morning and may therefore continue to interact significantly with alcohol. Patients should be warned.

For comments on the use of alcohol in epileptic patients taking drugs including phenobarbital, see 'Alcohol + Antiepileptics', p.49.

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Alcohol + Benzodiazepines and related drugs

Benzodiazepine and related hypno-sedatives increase the CNS depressant effects of alcohol to some extent. The risks of car driving and handling other potentially dangerous machinery are increased. The risk is heightened because the patient may be unaware of being affected. Some benzodiazepines used at night for sedation are still present in appreciable amounts the next day and therefore may continue to interact. Alcohol may also increase the plasma levels of brotizolam, clobazam, diazepam, and possibly triazolam, whereas alprazolam may increase blood-alcohol levels. Alcohol has been reported to increase aggression or amnesia and/or reduce the anxiolytic effects of some benzodiazepines.

Clinical evidence

(a) Additive CNS depressant effects

It is very difficult to assess and compare the results of the very many studies of this interaction because of the differences between the tests, their duration, the dosages of the benzodiazepines and alcohol used, whether the drugs were given chronically or acutely, and a number of other variables. However, the overall picture seems to be that benzodiazepines and related drugs including **diazepam**,[1-12] **alprazolam**,[13-15] **bromazepam**,[16] **brotizolam**,[17] **chlordiazepoxide**,[12,18-22] **clobazam**,[23] **dipotassium clorazepate**,[24] **flunitrazepam**,[25,26] **flurazepam**,[27-31] **loprazolam**,[28,32] **lorazepam**,[10,33-36] **lormetazepam**,[37] **medazepam**,[38] **midazolam**,[39] **nitrazepam**,[3,40,41] **oxazepam**,[6] **temazepam**,[41-43] **triazolam**,[29,42,44-46] and **zopiclone**[46] enhance the effects of alcohol i.e. cause increased drowsiness, impaired performance and driving skills.

Patients taking benzodiazepines including **lorazepam**[34] or **triazolam**[44] may be unaware of the extent of the impairment that occurs. Furthermore, changes in CNS functioning may possibly occur in heavy social drinkers; a placebo-controlled study in 20-year-olds suggested that **lorazepam** 2 mg had more impairment on delayed auditory verbal memory performance in those who were heavy social drinkers (more than 20 drinks; 200 g of alcohol per week) than light social drinkers (20 g or less of alcohol per week).[47]

Some of the benzodiazepines and related drugs that are used primarily to aid sleep, such as **flunitrazepam**,[25,26] **flurazepam**,[27,28,30,31,48] **nitrazepam**,[3,40] and **temazepam**,[48,49] when taken the night before alcohol or in the evening with alcohol, can still interact with alcohol the next morning. However, **midazolam**,[39] **loprazolam**,[28] **lormetazepam**,[37] **triazolam**,[31,46] **zolpidem**,[50] and **zopiclone**[25,30,46] have been reported not to do so. The sedative effects of **midazolam** alone, and **midazolam** with fentanyl have been shown to have dissipated within 4 hours, and to not be affected by alcohol after this time.[51,52] However, some patients may metabolise **midazolam** more slowly and so an interaction could still be possible,[53] especially in older patients or those receiving additional drugs.[54]

Some contrasting effects have also been reported. One study suggested that alcohol might mitigate the effects of **loprazolam** on psychological performance.[32] Similarly, some antagonism has been reported between **chlordiazepoxide** and alcohol, but this is unlikely to be of practical importance.[18,19] The development of tolerance between benzodiazepines and alcohol with chronic use has also been suggested.[55,56]

(b) Increased aggression, anxiety, or amnesia

The anxiolytic effects of **lorazepam**[35] and possibly **chlordiazepoxide**[20] may be opposed by alcohol. **Alprazolam** and alcohol together may possibly increase behavioural aggression.[57] Similarly, **flunitrazepam** abuse can cause violent behaviour, impulsive decision-making and anterograde amnesia: a report looking at violent crimes committed by abusers of **flunitrazepam** found that alcohol was almost always also present.[58] Alcoholic drinks also enhance the effects of **flunitrazepam** when it is used as a 'date rape' drug.[59]

(c) Pharmacokinetic effects

Several studies have reported that alcohol increases the plasma levels of **diazepam**[13,60] and that alcohol accelerates the absorption of **diazepam**,[5] but others have suggested that alcohol has no significant effect on diazepam pharmacokinetics.[9,11,61] Plasma levels of **brotizolam**[17] and **clobazam**[23] may be increased by alcohol. One study reported that the plasma levels of **triazolam** were increased by alcohol,[44] but other studies have found only a minimal pharmacokinetic interaction.[45,46] However, two *in vitro* studies have demonstrated that alcohol weakly inhibits the metabolism of **triazolam**;[62,63] one study showed that this was due to inhibition of the cytochrome P450 subfamily CYP3A.[62] Another *in vitro* study reported that the formation of **flunitrazepam** metabolites was weakly inhibited by alcohol,[64] but a pharmacokinetic study suggested that there was no interaction.[26] Alcohol appears to have minimal effects on the pharmacokinetics of **alprazolam**,[13] and **zopiclone**.[46,65]

The pharmacokinetics of alcohol do not appear to be affected to a clinically significant extent by **diazepam**,[11] **flunitrazepam**,[26] **zolpidem**,[50] or **zopiclone**,[46] but **alprazolam**[13] may increase blood-alcohol levels.

Mechanism

The CNS depressant actions of the benzodiazepines and alcohol are mainly additive and it appears that different aspects of CNS processing may be involved.[41,66]

A pharmacokinetic interaction can sometimes occur, but the mechanisms seem to be quite complex. Acute alcohol intake increases the absorption and raises the serum levels of some benzodiazepines[23,60] and there may be direct competitive *inhibition* of metabolism.[67] It has been suggested that clearance of benzodiazepines via phase I metabolism, by *N*-demethylation and/or hydroxylation, tends to be more affected by alcohol intake than that of drugs such as lorazepam, oxazepam or lormetazepam that only undergo phase II conjugation. In addition, phase I metabolism is inhibited or decreases with increasing age and liver disease.[67] However, phase I metabolism is *increased* by chronic administration of substances that induce the cytochrome P450 isoenzyme system, such as alcohol,[67] and moderate alcohol consumption may cause intestinal CYP3A induction resulting in reduced bioavailability of some benzodiazepines, such as midazolam.[68]

Importance and management

Extensively studied, well established and clinically important interactions. The overall picture is that these drugs worsen the detrimental effects of alcohol.[69] Up to a 20 to 30% increase in the impairment of psychomotor function has been suggested.[44] The deterioration in skills will depend on the particular drug in question, its dosage and the amounts of alcohol taken. With modest amounts of alcohol the effects may be quite small in most patients (although a few may be more markedly affected[11]), but anyone taking any of these drugs should be warned that their usual response to alcohol may be greater than expected, and their ability to drive a car, or carry out any other tasks requiring alertness, may be impaired. They may be

quite unaware of the deterioration or that the effects may still be present the following day. Benzodiazepines and alcohol are frequently found in the blood of car drivers involved in traffic accidents, which suggests that the risks are real.[56,69-72] Furthermore, alcohol may contribute to fatal poisonings and other deaths involving benzodiazepines, particularly diazepam[73-76] and temazepam.[77] Alcohol may contribute to drug-related accidents and deaths due to a disregard for safety;[72,78] and there is also an association between alcohol and benzodiazepines and violence-related accidents.[72]

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Alcohol + Beta blockers

The haemodynamic and pharmacokinetic effects of atenolol and metoprolol in healthy subjects do not appear to be changed by alcohol. There is some evidence that alcohol modestly reduces the haemodynamic effects of propranolol, and some of the effects of sotalol may also be changed by alcohol. Some evidence suggests that the effects of alcohol and atenolol with chlortalidone or propranolol are additive on the performance of some psychomotor tests, but the importance of this is uncertain.

Clinical evidence, mechanism, importance and management

(a) CNS effects

In 12 healthy subjects the performance of a number of psychomotor tests was found to be impaired by alcohol 0.6 g/kg and by one tablet of *Tenoretic* (**atenolol** 100 mg with chlortalidone 25 mg). When alcohol and *Tenoretic* were taken together there was some evidence of additive effects but the practical importance of this is not clear.[1]

In 12 healthy subjects **propranolol** 40 mg every 6 hours had no effect on the impairment of performance of a number of psychomotor tests caused by 50 mL/70 kg of alcohol, except that **propranolol** antagonised the effect of alcohol in one test (pursuit meter).[2] However, in another study, **propranolol** enhanced the effects of alcohol on some tests (inebriation and divided attention).[3]

The manufacturer of **oxprenolol** warns that the effects of alcohol and beta blockers on the CNS have been observed to be additive.[4] Similarly, one manufacturer of **bisoprolol** notes that, although bisoprolol did not impair driving performance in one study, some patients may be affected, and this should be considered, particularly when alcohol is also given.[5]

(b) Haemodynamic and pharmacokinetic effects

In 8 healthy subjects the pharmacokinetics of single 100-mg doses of **atenolol** or **metoprolol** were unaffected 6 hours after they had drunk the equivalent of 200 mL of absolute alcohol. No clinically significant changes in blood pressure or pulse rate were seen.[6] A similar study in 23 healthy subjects found that **atenolol** 100 mg did not affect the pharmacokinetics of alcohol 1 g/kg. However, alcohol increased the reduction in heart rate and blood pressure in response to **atenolol** (from 60 bpm to 56 bpm and from 124/82 mmHg to about 109/76 mmHg at 2 and 3 hours after ingestion).[7]

A study in 6 healthy subjects found that alcohol (sufficient to maintain blood-alcohol levels of 80 mg%) raised the mean AUC of a single 80-mg oral dose of **propranolol** by about 17% in 5 subjects and decreased it by 37% in the other subject, but this was considered unlikely to be clinically important. No changes in heart rate or blood pressure were seen.[8] In contrast, a double-blind study in 14 healthy subjects found that alcohol (equivalent to 32 to 72 mL of absolute alcohol) increased the clearance of a single 80-mg dose of **propranolol** and diminished its ability to lower blood pressure. **Propranolol** was not able to abolish the alcohol-induced rise in heart rate.[9] Similarly, another study found that alcohol decreased the rate of absorption and increased the rate of elimination of **propranolol**, but the clinical significance of this small alteration was not assessed.[10] Other studies have found that **propranolol** enhances the decrease in blood pressure seen with alcohol,[11,12] but attenuates[11] or does not alter[12] its effects on heart rate. Furthermore, alcohol may increase peak propranolol levels by 2- to 3.5-fold.[12]

A study in 6 healthy subjects found that although the blood pressure lowering effects of **sotalol** 160 mg were increased by alcohol, **sotalol** did not cancel out the alcohol-induced rise in heart rate.[9]

It would seem prudent to be alert for changes in response to beta blockers that may be due to alcohol. See also, 'Alcohol + Antihypertensives', p.51.

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5. Cardicor (Bisoprolol hemifumarate). Merck Serono. UK Summary of product characteristics, June 2006.
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Alcohol + Bicalutamide, Flutamide or Nilutamide

Alcohol intolerance (facial flushing, malaise, hypotension) has been reported in patients taking nilutamide, but not in those taking bicalutamide or flutamide.

Clinical evidence, mechanism, importance and management

Several studies have described alcohol intolerance (facial flushes, malaise, hypotension) in patients taking nilutamide.[1-4] The incidence has been reported to be between 3% and 19%.[1-3,5] It is recommended that patients who experience this reaction should avoid drinking alcohol.[5]

Flutamide and bicalutamide have not been reported to produce these effects when patients drink alcohol,[3] and so in some cases they may be considered as an alternative option to nilutamide.

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Alcohol + Bromocriptine

There is some very limited evidence to suggest that the adverse effects of bromocriptine may possibly be increased by alcohol.

Clinical evidence, mechanism, importance and management

Intolerance to alcohol, which improved on continued treatment, has been briefly mentioned in a report about patients taking bromocriptine for acromegaly.[1] In another report two patients with high prolactin levels were said to have developed bromocriptine adverse effects, even in low doses, while continuing to drink. When they abstained, the frequency and the severity of the adverse effects fell, even with higher doses of bromocriptine.[2] This, it is suggested, may be due to some alcohol-induced increase in the sensitivity of dopamine receptors.[2] There would seem to be little reason, on the basis of this extremely sparse evidence, to tell all patients taking bromocriptine not to drink alcohol, but if adverse effects develop, it would be reasonable to warn them to try avoiding alcohol.

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Alcohol + Bupropion

The concurrent use of bupropion and alcohol does not appear to affect the pharmacokinetics of either drug; however, some adverse CNS effects may occur on concurrent use.

Clinical evidence, mechanism, importance and management

Single-dose studies in healthy subjects found that the pharmacokinetics of bupropion 100 mg were not affected by the concurrent use of alcohol, and bupropion did not affect blood-alcohol levels.[1,2] However, rare cases of adverse neuropsychiatric events and reduced alcohol tolerance have been reported in patients who drink alcohol while taking bupropion.[3,4] Because of this, the manufacturers recommend that the consumption of alcohol should be minimised or avoided.[3,4] Moreover, because abrupt withdrawal from alcohol is a risk factors for seizures, and there is a small dose-related risk of seizures with bupropion, the manufacturers contraindicate the use of bupropion in patients undergoing abrupt withdrawal from alcohol, and caution its use in alcohol abuse.[3,4]

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2. Hamilton MJ, Bush MS, Peck AW. The effect of bupropion, a new antidepressant drug, and alcohol and their interaction in man. *Eur J Clin Pharmacol* (1984) 27, 75–80.
3. Zyban (Bupropion hydrochloride). GlaxoSmithKline UK. UK Summary of product characteristics, January 2009.
4. Zyban (Bupropion hydrochloride). GlaxoSmithKline. US Prescribing information, July 2009.

Alcohol + Buspirone

The use of buspirone with alcohol may cause drowsiness and weakness, although it does not appear to impair the performance of a number of psychomotor tests.

Clinical evidence, mechanism, importance and management

A study in 12 healthy subjects found that, in contrast to lorazepam, buspirone 10 or 20 mg did not appear to interact with alcohol (i.e. worsen the performance of certain psychomotor tests), but it did make the subjects feel drowsy and weak.[1,2] Similarly, another study in 13 healthy subjects found that giving buspirone (15 and 30 mg/70 kg) with alcohol caused sedation, but very little impairment of performance. In this study, the sedative effects were broadly similar to those seen with alprazolam plus alcohol, but alprazolam plus alcohol clearly impaired performance.[3] Similar findings were reported in another earlier comparison with diazepam.[4] A further study reported that single 5 to 15-mg doses of buspirone had a minimal effect on performance in both light and moderate female social drinkers.[5]

The UK manufacturer notes that there is no information on higher therapeutic doses of buspirone given with alcohol, and they suggest that it would be prudent to avoid alcohol while taking buspirone.[6] They also caution patients of the potential hazards of driving or handling other potentially dangerous machinery until they are certain that buspirone does not adversely affect them.[6] The evidence would appear to support this suggestion.

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Alcohol + Butyraldoxime

A disulfiram-like reaction can occur in those exposed to *N*-butyraldoxime if they drink alcohol.

Clinical evidence, mechanism, importance and management

Workers in a printing company complained of flushing of the face, neck and upper trunk, shortness of breath, tachycardia and drowsiness very shortly after drinking alcohol (about 45 mL of whiskey), and were found to have increased levels of acetaldehyde in their blood. The reason appeared to be that the printing ink they were using contained *N*-butyraldoxime, an antioxidant which, like 'disulfiram', (p.66), can inhibit the metabolism of alcohol causing acetaldehyde to accumulate.[1] It is possible that it is a metabolite of *N*-butyraldoxime that causes this effect, rather than *N*-butyraldoxime itself.[2] This reaction would seem to be more unpleasant and socially disagreeable than serious. No treatment normally seems necessary.

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Alcohol + Caffeine

Objective tests show that caffeine may counteract some of the effects of alcohol. However, it does not completely sober up those who have drunk too much, and may even make them more accident-prone.

Clinical evidence

(a) Effect on skills related to driving

A study in a large number of healthy subjects given a cup of **coffee** containing caffeine 300 mg/70 kg, either alone or immediately after drinking alcohol 0.75 g/kg, found that caffeine did not antagonise the deleterious effect of alcohol on the performance of psychomotor skill tests. Only reaction times were reversed.[1] Two other studies also found that caffeine did not antagonise the effects of alcohol in a variety of tests.[2,3] A further study in 8 subjects found that, contrary to expectations, caffeine increased the frequency of errors in the performance of a serial reaction time task,[4] although a later study did not find this effect.[5] Caffeine has also been reported to *increase* the detrimental effects of alcohol.[6]

In contrast, more recent studies (usually using caffeine in capsule form) have found that some of the performance-impairing effects of alcohol such as increased reaction time,[7-9] increased errors with four choice reaction time,[10] impaired performance of divided attention tasks,[5] sedation,[11] and slowing of psychomotor speed[10] can be antagonised by caffeine given with the alcohol. However, caffeine does not appear to restore most subjective effects e.g. feelings of drunkenness.[7,11,12] One study found that the alcohol-caffeine combination typically altered the effects of caffeine alone rather than altering the effects of alcohol alone. For example the addition of alcohol reduced the jitteriness and alertness produced by caffeine, and although caffeine modestly antagonised alcohol impairment of driving, there was still a 9% increase in brake-response time, when compared with placebo.[12]

(b) Pharmacokinetic effects

In a placebo-controlled, crossover study in 8 healthy subjects, the AUC of a 400-mg caffeine capsule was 30% greater when it was taken with alcohol 0.8 g/kg than when taken alone. Blood-alcohol levels were not affected by caffeine use.[7] Similarly, other studies reported that alcohol increases serum-caffeine levels[2] and that blood-alcohol levels were not modified by caffeine.[1,2,8] However, one study in 8 healthy subjects reported that caffeine 3.3 mg/kg reduced blood-alcohol levels, measured 30 minutes after a single 0.7-g/kg dose of ethanol, from 38 mg% to 26 mg%.[9]

Mechanism

Not fully understood. Caffeine is a CNS stimulant, which seems to oppose some of the CNS depressant effects of alcohol. It appears that only those objective tests able to detect an enhancement due to a CNS stimulant show the clearest antagonistic effects.[7]

Alcohol appears to modestly inhibit the hepatic metabolism of caffeine.[2]

Importance and management

It is not known why some studies report that caffeine antagonises some of the detrimental effects of alcohol and others report no interaction. However, the type of psychomotor tests, the amount of alcohol and caffeine consumed, and the timing and administration of the caffeine may affect the results.

Caffeine does appear to improve some of the detrimental effects of alcohol in some psychomotor tests, which is probably why there is a long-standing and time-hallowed belief in the value of strong black coffee to sober up those who have drunk too much. In addition, it is just possible that the time taken to drink the coffee gives the liver just a little more time to metabolise some of the alcohol. However, it seems that it is not effective

in all aspects of alcohol impairment, particularly subjective effects. In addition, caffeine does not reduce blood-alcohol levels. **Coffee** and other sources of caffeine do not make it safe to drive or handle dangerous machinery, and it may even make drivers more accident-prone.

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Alcohol + Calcium carbimide

Alcohol causes a disulfiram-like reaction in patients taking calcium carbimide. Calcium carbimide has been used as an alcohol deterrent.

Clinical evidence, mechanism, importance and management

Calcium carbimide interacts with alcohol in a similar way to disulfiram and by a similar mechanism[1] (see 'Alcohol + Disulfiram', p.66). Both of these drugs bind to aldehyde dehydrogenase, but calcium carbimide is said to have fewer adverse effects because it does not bind to dopamine beta hydroxylase.[2] However, marked cardiovascular effects and fatalities have occurred in those who drank alcohol while taking calcium carbimide.[3,4] Like disulfiram it is used to deter alcoholics from continuing to drink.[1,2]

1. Peachey JE, Brien JF, Roach CA, Loomis CW. A comparative review of the pharmacological and toxicological properties of disulfiram and calcium carbimide. *J Clin Psychopharmacol* (1981) 1, 21–6.
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Alcohol + Calcium-channel blockers

Blood-alcohol levels can be raised and may remain elevated for a much longer period of time in patients taking verapamil. Alcohol may also increase the bioavailability of felodipine, nifedipine and possibly prolonged-release diltiazem, but amlodipine appears not to interact. An increased incidence of postural hypotension has been reported in patients who took felodipine with alcohol.

Clinical evidence

(a) Amlodipine

A study in 30 healthy subjects found that single and multiple doses of amlodipine 10 mg for 15 days (with or without lisinopril and simvastatin) had no effect on the pharmacokinetics of alcohol 0.8 g/kg, and subjective psychological performance was unaffected. Alcohol did not alter the pharmacokinetics of amlodipine.[1]

(b) Felodipine

A study in 8 healthy subjects given enough alcohol to maintain their blood levels at 80 to 120 mg% found that their felodipine levels (following a single 10-mg oral dose) were approximately doubled (AUC increased by 77%, maximum blood levels increased by 98%). Diuresis was approximately doubled and heart rates were increased.[2]

In a study, 8 non-smoking, healthy subjects were given a single 10-mg dose of an extended-release preparation of felodipine, with 250 mL red wine, on an empty stomach and 4 hours before a meal. Red wine reduced felodipine levels for the first 4 hours of the study, when compared with 250 mL water, but felodipine levels rose rapidly 5 hours after dosing, resulting in a peak level that was higher with red wine than with water.[3]

Another study suggested that alcohol increased the haemodynamic effects of felodipine (lower total peripheral resistance, lower blood pressure, higher heart rate) and increased the rate of adverse effects (e.g. postural lightheadedness).[4] However, the alcohol was given in grapefruit juice, which is known to increase felodipine levels; indeed, felodipine levels were reported as being higher than expected in this study, so it is possible these effects were, at least in part, due to an interaction with 'grapefruit juice', (p.1034).

(c) Isradipine

In a placebo-controlled study, 9 healthy subjects were given isradipine 5 or 10 mg followed by alcohol 0.5 or 1 g/kg. The performance impairment in response to alcohol was not affected by isradipine. However, increases in heart rate, and decreases in blood pressure appeared to be enhanced when both drugs were taken together. Furthermore, isradipine 10 mg caused a small decrease in breath-alcohol levels.[5]

(d) Nifedipine

Alcohol (75 mL of alcohol 94% with 75 mL of orange juice) given to 10 healthy subjects increased the AUC of a single 20-mg dose of nifedipine by 54%, but no significant changes in heart rate or blood pressure were seen.[6] Another study, involving 226 patients taking sustained-release nifedipine, found that reported alcohol use was associated with reduced nifedipine clearance (8.6 mL/minute per kg compared with 10.8 mL/minute per kg for alcohol use and no alcohol, respectively).[7] In another study no evidence was found that nifedipine 10 or 20 mg antagonised the effects of alcohol.[8]

(e) Nimodipine

In a randomised study in 6 healthy subjects, a single 30 or 60-mg dose of nimodipine had no significant effect on the subjective or psychomotor response to a single oral 0.7-g/kg dose of alcohol, and there were no clinically significant changes in blood pressure or heart rate. Nimodipine 60 mg reduced the peak breath-alcohol level by 20 mg%, but this was considered slight.[9]

(f) Verapamil

In one study, 10 healthy subjects were given verapamil 80 mg three times daily for 6 days with alcohol 0.8 g/kg on day 6. Peak blood-alcohol levels were found to be raised by almost 17% (from about 106 to 124 mg%) and the $AUC_{0\text{-}12}$ was raised by almost 30%. The time that blood-alcohol levels exceeded 100 mg% was prolonged from 0.2 to 1.3 hours and the subjects said they felt more intoxicated.[10] In another study no evidence was found that verapamil 80 or 160 mg antagonised the effects of alcohol.[8] A further randomised study in 6 healthy subjects found that a single 80-mg dose of verapamil had no significant effect on the subjective or psychomotor response to a single oral 0.7-g/kg dose of alcohol, and no clinically significant changes were noted in blood pressure or heart rate. The pharmacokinetics of alcohol were not affected by verapamil.[9]

Mechanism

Not understood. It seems possible that verapamil inhibits the metabolism of alcohol by the liver, thereby reducing its loss from the body. Alcohol also appears to inhibit the metabolism of nifedipine, and to increase the bioavailability of felodipine. Red wine may have caused "dose dumping" of felodipine from the extended-release preparation, which altered its pharmacokinetic profile, but the reason why the felodipine levels remained low until after a meal is unclear.[3] An *in vitro* study demonstrated that alcohol inhibited the oxidative metabolism of nifedipine by the cytochrome P450 subfamily CYP3A.[11]

Importance and management

Information seems to be limited to these reports and they need confirmation. Information regarding **verapamil** is conflicting, with one study finding no pharmacokinetic interaction and another finding an almost 17% increase in blood-alcohol levels. This increase could be enough to raise legal blood levels to illegal levels if driving. Moreover the intoxicant effects of alcohol persisted for a much longer period of time (five times longer) in

this study. Therefore, despite the conflicting findings, it may be prudent to bear the possibility of an interaction in mind. The decreases in breath-alcohol levels with **felodipine** and **nimodipine** were modest, and unlikely to be of clinical significance because performance indicators were not altered. However, the bioavailability of **felodipine** and **nifedipine** appear to be increased by alcohol. The manufacturers of some calcium-channel blockers warn that inter-individual variations in the response to these drugs can occur and some patients ability to drive or operate machinery may be impaired, particularly at the start of treatment and in conjunction with alcohol.[12,13] Patients should therefore be advised about these effects. The manufacturers of a prolonged-release **diltiazem** preparation (*Adizem*) similarly warn that alcohol may increase the rate of diltiazem release, and therefore suggest that alcohol should not be taken at the same time as this preparation.[14]

Note that long-term moderate to heavy drinking can impair the efficacy of antihypertensives, see 'Alcohol + Antihypertensives', p.51.

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12. Adalat Retard (Nifedipine). Bayer plc. UK Summary of product characteristics, May 2008.
13. Univer (Verapamil hydrochloride). Cephalon Ltd. UK Summary of product characteristics, September 2008.
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Alcohol + Cannabis

The detrimental effects of drinking alcohol and smoking cannabis may be additive on some aspects of driving performance. However, there is some evidence that regular cannabis use *per se* does not potentiate the effects of alcohol. Smoking cannabis may alter the bioavailability of alcohol.

Clinical evidence and mechanism

(a) CNS effects

Simultaneous use of alcohol and oral Δ^9-tetrahydrocannabinol (THC, the major active ingredient of cannabis) reduced the performance of psychomotor tests, suggesting that those who use both drugs together should expect the deleterious effects to be additive.[1] In a further placebo-controlled study, subjects smoked cannabis containing 100 or 200 micrograms/kg of Δ^9-tetrahydrocannabinol and drank alcohol (to achieve an initial blood level of 70 mg%, with further drinks taken to maintain levels at 40 mg%) 30 minutes before driving. They found that cannabis, even in low to moderate doses, negatively affected driving performance in real traffic situations. Further, the effect of combining moderate doses of both alcohol and cannabis resulted in dramatic performance impairment as great as that observed with blood-alcohol levels of 140 mg% alone.[2,3] Similar results (including a suggestion of a synergistic impairment of performance[4]) have been found in a number of other studies,[4,5] including different doses of cannabis and regular cannabis users.[5]

A study in 22 healthy subjects, who occasionally used cannabis cigarettes and drank moderate amounts of alcohol, found that the number of euphoric events in response to a cannabis cigarette was greater after alcohol ingestion, and the duration of euphoric events was longer. The speed of onset of the effects of cannabis was also faster when it was smoked after the ingestion of alcohol.[6]

One study in 14 regular cannabis users (long-term daily use) and 14 infrequent cannabis users found that regular use reduced the disruptive effects of alcohol on some psychomotor skills relevant to driving, whereas infrequent use did not have this effect. In this study, neither group had smoked any cannabis in the 12 hours before the alcohol test.[7] Another study found that moderate doses of alcohol and cannabis, consumed either alone or in combination, did not produce significant behavioural or subjective impairment the following day.[8]

A study in 12 healthy subjects who regularly used both cannabis and alcohol found that alcohol 0.5 g/kg significantly increased break latency without affecting body sway, whereas cannabis given as a cigarette containing tetrahydrocannabinol 3.33%, increased body sway but did not affect brake latency. There were no significant additive effects on brake latency, body sway, or mood when the two drugs were used together.[9] A population-based study of 2,777 drivers involved in fatal road crashes, who drank alcohol and/or used cannabis, found that although both cannabis and alcohol increased the risk of being responsible for a fatal crash, no statistically significant interaction was observed between the two drugs.[10]

(b) Pharmacokinetic studies

Fifteen healthy subjects given alcohol 0.7 g/kg developed peak plasma alcohol levels of about 78 mg% at 50 minutes, but if they smoked a cannabis cigarette 30 minutes after the drink, their peak plasma alcohol levels were only 55 mg% and they occurred 55 minutes later. In addition, their subjective experience of the drugs decreased when used together.[11] However, another study found that smoking cannabis 10 minutes before alcohol consumption did not affect blood-alcohol levels.[8] A further study found that blood-alcohol levels were not affected by Δ^9-tetrahydrocannabinol given orally one hour before alcohol.[1] A study in 22 healthy subjects, who occasionally used cannabis cigarettes and drank moderate amounts of alcohol, found that plasma Δ^9-tetrahydrocannabinol levels were higher when alcohol was consumed before smoking a cannabis cigarette.[6]

Importance and management

Several studies have found that cannabis and alcohol produce additive detrimental effects on driving performance, but other studies have not found any potentiation. This is probably due to the variety of simulated driving tests used and possibly the time lag between the administration of alcohol and cannabis; behavioural impairment after cannabis has been reported to peak within 30 minutes of smoking.[8] Nevertheless, both drugs have been shown to affect some aspects of driving performance and increase the risk of fatal car accidents. Concurrent use of cannabis and alcohol before driving should therefore be avoided.

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Alcohol + Carbamazepine

Moderate social drinking does not affect the serum levels of carbamazepine. Heavy drinking may possibly increase the metabolism of carbamazepine, and this may be further increased in alcoholics who abstain from drinking alcohol.

Clinical evidence, mechanism, importance and management

(a) Heavy drinking and alcohol withdrawal

A study in 7 alcoholics who consumed a mean dose of 750 mL of spirits (240 g of alcohol) daily found that the early (0 to 4 hours) bioavailability of a single 400-mg dose of carbamazepine was not affected by 9 days of controlled alcohol withdrawal. However, over the 4 to 12-hour period, carbamazepine levels were higher, and those of its epoxy metabolite lower, in alcoholics following alcohol exposure, when compared with abstinence. This effect was thought to be due to the acute inhibition of carbamazepine metabolism by alcohol and/or accelerated carbamazepine metabolism in the abstinence phase. The absorption rate of carbamazepine in alcoholics appeared to be slower, when compared with 8 healthy subjects, probably due to alcoholism-induced chronic gastrointestinal changes; however, this did not significantly affect the maximum serum levels of alcohol. However, adverse effects occurred in all of the healthy subjects but in none of the alcoholics, possibly indicating that long-term alcohol exposure may make the patient less sensitive to acute carbamazepine exposure.[1]

The long-term use of alcohol can cause induction of hepatic enzyme systems possibly resulting in increased metabolism and reduced plasma levels of carbamazepine. The risk of seizures may also increase on tapering or stopping alcohol because of an increase in metabolism and elimination caused by the relative lack of a competing substrate.[2]

(b) Moderate social drinking

Alcohol 25 g did not affect the bioavailability of carbamazepine in 8 healthy subjects.[1] A study in non-drinking epileptics (21 in the experimental alcohol group, 18 in the control group) found that the serum levels of carbamazepine were unchanged by moderate drinking (1 to 3 glasses of an alcoholic beverage, containing 9.85 g of alcohol, twice weekly), and there was no influence on tonic-clonic convulsions or partial complex seizures.[3]

For comment on moderate social drinking in epileptics and also the possible increased sedative effect of carbamazepine with alcohol, see 'Alcohol + Antiepileptics', p.49.

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Alcohol + Carmofur

A disulfiram-like reaction occurred in a patient taking carmofur when he was given a coeliac plexus blockade with alcohol.

Clinical evidence, mechanism, importance and management

A man with pancreatic carcinoma taking carmofur 500 mg daily for 25 days experienced a disulfiram-like reaction (facial flushing, diaphoresis, hypotension with BP 60/30 mmHg, and tachycardia of 128 bpm) within 30 minutes of being given a coeliac plexus alcohol blockade for pain relief. Blood acetaldehyde levels were found to have risen sharply, supporting the belief that the underlying mechanism is similar to the disulfiram-alcohol interaction (see 'Alcohol + Disulfiram', p.66, for further explanation). It is suggested that alcohol blockade should be avoided for 7 days after treatment with carmofur.[1]

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Alcohol + Cephalosporins

Disulfiram-like reactions can occur in those who take cefamandole, cefmenoxime, cefoperazone, cefotetan, latamoxef (moxalactam) and possibly cefonicid, and drink alcohol. This is not a general reaction of the cephalosporins, but is confined to those with particular chemical structures.

Clinical evidence

A young man with cystic fibrosis was given **latamoxef** 2 g intravenously every 8 hours for pneumonia. After 3 days of treatment he drank, as was his custom, a can of beer with lunch. He rapidly became flushed with a florid macular eruption over his face and chest. This faded over the next 30 minutes but he complained of severe nausea and headache. Similarly, a patient taking **latamoxef** became flushed, diaphoretic and nauseated after drinking a cocktail of vodka and tomato juice.[1] This reaction has also been described in two subjects who drank alcohol while receiving **latamoxef**,[2] two of 10 subjects given **latamoxef** and alcohol,[3] and a patient taking **latamoxef** given theophylline elixir containing alcohol 20%.[4] It has also been seen in a patient taking **latamoxef** following the injection of alcohol into the para-aortic space for coeliac plexus block.[5] The symptoms experienced by these patients have included flushing of the face, arms and neck, shortness of breath, headache, tachycardia, dizziness, hyper- and hypotension, and nausea and vomiting.

Similar reactions have been described in patients or subjects receiving **cefamandole**,[6,7] **cefoperazone**,[8-15] **cefmenoxime**,[16] **cefonicid**[17] and **cefotetan**,[18] after drinking wine, beer, or other alcoholic drinks, or after the ingestion of an 8.5% alcoholic elixir.[16]

This disulfiram-like reaction is not a general reaction of all the cephalosporins. One study found no interaction in those taking **cefpirome** and alcohol,[19] and in another, **ceftizoxime** was reported not to interact with alcohol.[20] No interaction was seen with **cefonicid** and alcohol in one placebo-controlled study;[21] however, a case report describes a disulfiram-reaction in one patient taking the combination.[17]

Mechanism

These reactions appear to have the same pharmacological basis as the disulfiram/alcohol reaction (see 'Alcohol + Disulfiram', p.66). Three of these cephalosporins (latamoxef, cefamandole and cefoperazone) can raise blood acetaldehyde levels in *rats* when alcohol is given, but to a lesser extent than disulfiram.[2,11,22] It appears that any reaction normally only occurs with cephalosporins that possess a methyltetrazolethiol group in the 3-position on the cephalosporin molecule,[11,23] but it has also been seen with cefonicid, which possesses a methyl sulphonthiotetrazolic group instead.[17] Some amine-containing cephalosporins (**cefalexin**, **cefadroxil** and **cefradine**) have also been reported to interact with acetaldehyde *in vitro*, but the clinical significance of this is unknown.[24]

Importance and management

Established but unpredictable interactions of varying incidence. In studies, two out of 10 subjects taking latamoxef and alcohol reacted,[3] five out of 8 taking cefotetan reacted,[18] and 8 out of 9 taking cefoperazone reacted.[14,15] The reaction appears normally to be more embarrassing or unpleasant and frightening than serious, with the symptoms subsiding spontaneously after a few hours. There is evidence that the severity varies; in one study cefoperazone was said to be worse than latamoxef, which in turn was said to be worse than **cefmetazole**.[25] Treatment is not usually needed but there are two reports[4,6] of two elderly patients who needed treatment for hypotension, which was life-threatening in one case;[4] plasma expanders and dopamine have been used as treatment.[4,6]

Because the reaction is unpredictable, warn all patients taking these potentially interacting cephalosporins (cefamandole, cefmenoxime, cefmetazole, cefonicid, cefoperazone, cefotetan, latamoxef) that it can occur during and up to 3 days after the course of treatment is over. Advise them to avoid alcohol. Those with renal or hepatic impairment in whom the drug clearance is prolonged should wait a week. It should not be forgotten that some foods and pharmaceuticals contain substantial amounts of alcohol, and a reaction with some topically applied alcohol-containing products cannot be excluded (see 'Alcohol + Disulfiram', p.66).

A number of other cephalosporins are possible candidates for this reaction because they possess the methyltetrazolethiol group in the 3-position. These include, **ceforanide**, **cefotiam**, and **cefpiramide**,[11,23] but there do not appear to be any reports of an interaction between alcohol and these drugs.

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Alcohol + Ciprofloxacin

Ciprofloxacin does not significantly affect the pharmacokinetics of alcohol or its effects on psychomotor performance. There is an isolated report of a cutaneous reaction to ciprofloxacin, which may have been precipitated by alcohol consumption.

Clinical evidence, mechanism, importance and management

In a study in 12 healthy subjects, ciprofloxacin 500 mg twice daily for 3 days had no significant effect on the pharmacokinetics of a single 30-g oral dose of alcohol (75 mL of vodka), and the performance of a number of psychomotor tests was unaffected.[1] A study in 8 healthy male subjects found that ciprofloxacin 750 mg twice daily for 7 days decreased the elimination rate of alcohol 0.63 g/kg by about 10% and increased its AUC by 11%, which would not be expected to be clinically significant. It was suggested that ciprofloxacin reduced the number of aerobic bacteria in the gut, which reduced alcohol dehydrogenase activity and therefore reduced ethanol metabolism.[2]

There is an isolated report of red blotches developing on the face and body of a tetraplegic patient taking ciprofloxacin 250 mg twice daily, which developed within 10 minutes of drinking 2 cans of beer containing alcohol 4.7%. He did not feel unwell or drowsy, and the blotches faded over a period of 30 minutes. Previous courses of ciprofloxacin had not produced any adverse effects and the same brand of alcohol caused no problems in the absence of ciprofloxacin.[3] The general clinical importance of this report is unknown, but it seems likely to be small.

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Alcohol + Clomethiazole

Clomethiazole has been successfully used to treat alcohol withdrawal, but the long-term use of alcohol with clomethiazole can cause serious CNS depression, due to additive CNS depressant effects. This is potentially fatal, even with short-term use in alcoholics with cirrhosis. The concurrent use of clomethiazole and alcohol may affect driving skills, and the bioavailability of clomethiazole may be increased by alcohol.

Clinical evidence, mechanism, importance and management

(a) Enhanced adverse effects and bioavailability

The following is taken from an editorial in the British Medical Journal, which was entitled 'Chlormethiazole and alcohol: a lethal cocktail'.[1]

Clomethiazole is commonly used to treat withdrawal from alcohol because of its hypnotic, anxiolytic and anticonvulsant effects. It is very effective if a rapidly reducing dosage regimen is followed over six days, but if it is used long-term and drinking continues it carries several serious risks.

Alcoholics readily transfer dependency to clomethiazole and may visit several practitioners and hospitals to get their supplies. Tolerance develops so that very large amounts may need to be taken (up to 25 g daily). Often alcohol abuse continues and the combination of large amounts of alcohol and clomethiazole can result in coma and even fatal respiratory depression, due mainly to simple additive CNS depression.[1]

Other factors contributing to the increase in CNS depression seen include increases in the bioavailability of clomethiazole, probably caused by alcohol impairing first pass metabolism,[2] and, in the case of those with alcoholic cirrhosis, the systemic bioavailability of clomethiazole may be increased tenfold because of venous shunting.[3] A randomised study in 8 healthy subjects found that alcohol 0.8 g/kg increased the AUC of a single 192-mg dose of clomethiazole by 82%.[2] However, one study in 6 healthy subjects reported that intravenous alcohol 0.8 mL/kg given acutely had no effect on the disposition or elimination of clomethiazole. It was proposed that alcohol given orally might affect the absorption or rate of uptake of clomethiazole.[4]

Clomethiazole should not be given long-term for alcohol withdrawal states[1] or to those who continue to drink alcohol.[5] Use for more than 9 days is not recommended.[5,6] It has been said that if prescribers choose to manage detoxification at home, it should be done under very close supervision, issuing prescriptions for only one day's supply to ensure daily contact and to minimise the risk of abuse. Further, if the patient shows evidence of tolerance or clomethiazole dependency or of continuing to drink alcohol, the only safe policy is rapid admission for inpatient care.[1] The manufacturer warns that alcohol combined with clomethiazole particularly in alcoholics with cirrhosis can lead to fatal respiratory depression, even with short-term use.[5]

(b) Effects on driving and related skills

There do not appear to be any studies on the combined effects of clomethiazole and alcohol on driving and related skills, but concurrent use would be expected to increase the risks.

There is a report of a man who had a blood-alcohol level of 23 mg% who was driving dangerously and caused a traffic accident. The clinical signs of impairment were far greater than expected and further analysis of the blood sample identified a high level of clomethiazole (5 mg/L). In 13 other impaired driving cases where clomethiazole was detected in blood samples, the concentrations ranged from 0.3 to 3.3 mg/L.[7] The manufacturer warns that clomethiazole may potentiate or be potentiated by CNS depressant drugs, including alcohol.[5]

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Alcohol + Cloral hydrate

Both alcohol and cloral hydrate are CNS depressants, and their effects may be additive, or possibly even synergistic. Some patients may experience a disulfiram-like flushing reaction if they drink alcohol after taking cloral hydrate for several days.

Clinical evidence

Studies in 5 healthy subjects given cloral hydrate 15 mg/kg and alcohol 0.5 g/kg found that both drugs given alone impaired their ability to carry out complex motor tasks. When taken together, the effects were additive, and possibly even more than additive. After taking cloral hydrate for 7 days, one of the subjects experienced a disulfiram-like reaction (bright red-purple flushing of the face, tachycardia, hypotension, anxiety and persistent headache) after drinking alcohol.[1,2]

The disulfiram-like reaction has been described in other reports.[3] Note that the earliest report was published more than a century ago in 1872 and described two patients taking cloral hydrate who experienced this reaction after drinking half a bottle of beer.[2]

Mechanism

Alcohol, cloral and trichloroethanol (to which cloral hydrate is metabolised) are all CNS depressants. During concurrent use, the metabolic pathways used for their elimination are mutually inhibited: blood-alcohol levels rise because the trichloroethanol competitively depresses the oxidation of alcohol to acetaldehyde, while trichloroethanol levels also rise because its production from cloral hydrate is increased and its further conversion and clearance as the glucuronide is inhibited. As a result the rises in the blood levels of alcohol and trichloroethanol are exaggerated, and their effects are accordingly greater.[1,2,4,5] In one subject, blood levels of acetaldehyde during the use of cloral hydrate with alcohol were only 50% of those after alcohol alone, so that the flushing reaction, despite its resemblance to the disulfiram reaction, may possibly have a partially different basis.[2]

Importance and management

A well-documented and established interaction, which has been comprehensively reviewed.[1,2] Only a few references are given here. Patients given cloral hydrate should be warned about the extensive CNS depression that can occur if they drink, and of the disulfiram-like reaction that may occur if they drink after taking cloral hydrate for a period of time. Its incidence is uncertain. The legendary Mickey Finn, which is concocted of cloral hydrate and alcohol, is reputed to be so potent that deep sleep can be induced in an unsuspecting victim within minutes of ingestion, but the evidence seems to be largely anecdotal. Very large doses of both drugs would be likely to cause serious and potentially life-threatening CNS depression.

It seems likely that **cloral betaine**, **triclofos** and other compounds closely related to cloral hydrate will interact with alcohol in a similar manner, but this requires confirmation.

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Alcohol + Cocaine

Alcohol increases the levels of cocaine and its active metabolite cocaethylene. Subjective effects such as euphoria are enhanced and some of the CNS-depressant effects of alcohol, such as sedation, are attenuated by cocaine. The combination may be potentially more toxic, with increased cardiovascular effects particularly heart rate.

Clinical evidence

A study in 8 cocaine users found that intranasal cocaine 100 mg and alcohol 0.8 g/kg produced a greater euphoria and feeling of well-being than cocaine alone, and reduced alcohol sedation without altering the feeling of drunkenness. Compared with placebo, the peak heart-rate was increased by 17 bpm, 23 bpm, and 41 bpm, with alcohol, cocaine, or the combination, respectively. In addition, the combination resulted in higher plasma levels of cocaine and the appearance of cocaethylene, an active and potentially toxic metabolite produced by the interaction of the two drugs.[1] Other similar studies have reported comparable findings.[2,3] A further study found that intranasal cocaine 96 mg/70 kg improved behavioural performance, measured by the digit symbol substitution test (DSST), whereas alcohol 1 g/kg decreased DSST performance. The combination of alcohol 1 g/kg with intranasal cocaine 48 or 96 mg/70 kg reduced the DSST below that found with cocaine alone. The combination also additively increased heart rate and diastolic blood pressure. Blood-alcohol levels were not significantly affected by the concurrent use of intranasal cocaine.[4] A study in 6 male subjects found that alcohol 0.85 g/kg, taken 30 minutes after snorting cocaine, did not alter the effect of cocaine on heart rate, did not alter cocaine or blood-alcohol levels, and did not affect subjective ratings of drunkenness.[5]

In contrast, a study in 11 healthy male subjects found that when alcohol 0.85 g/kg was given 15 minutes before snorting cocaine (either 1.25 mg/kg or 1.9 mg/kg), the bioavailability of cocaine was increased, and there were significant increases in heart rate, cardiac output, and blood pressure.[6]

Mechanism

In the presence of alcohol, cocaine is metabolised in the liver to cocaethylene, which appears to have the same stimulant effects as cocaine, but a longer half-life (2 hours compared with about 38 minutes for cocaine). *Animal* studies suggest that this metabolite is more toxic than cocaine.[7] In addition, chronic alcohol exposure may facilitate the metabolism of cocaine, promoting the formation of intermediate metabolites that may cause liver damage, potentiating the hepatotoxic properties of alcohol.[8] It has been suggested that the ingestion of alcohol before snorting cocaine results in greater absorption of cocaine through the nasal vasculature due to increased dilatation by ethanol.[5]

Importance and management

It has been suggested that the enhanced psychological effects associated with alcohol and cocaine may lead to the use of larger amounts of the combination with an increased risk for toxic effects,[2] such as cardiotoxicity.[1] It has been reported that users of alcohol and cocaine who also have coronary artery disease have 21.5 times the risk for sudden death than users of cocaine alone.[7] The longer half-life of the metabolite cocaethylene explains why many people who experience cocaine-related heart attacks and strokes do so when the cocaine levels in their blood are low, as cocaethylene can remain active in the body for 7 hours after cocaine has disappeared.[7] Patients with coronary artery disease or alcoholics may be particularly vulnerable to the combined toxic effects of alcohol and cocaine.

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4. Higgins ST, Rush CR, Bickel WK, Hughes JR, Lynn M, Capeless MA. Acute behavioral and cardiac effects of cocaine and alcohol combinations in humans. *Psychopharmacology (Berl)* (1993) 111, 285–94.
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Alcohol + Codergocrine mesilate (Ergoloid mesylates)

Codergocrine mesilate causes a very small reduction in blood-alcohol levels.

Clinical evidence, mechanism, importance and management

Thirteen subjects were given 0.5 g/kg of alcohol 25% in orange juice after breakfast, before and after taking 4.5 mg of codergocrine mesilate (ergoloid mesylates, *Hydergine*) every 8 hours for nine doses. The codergocrine caused a small reduction in blood-alcohol levels (maximum serum levels reduced from 59 mg% to 55.7 mg%), and the clearance was reduced by a

modest 11%.[1] The reason is not understood. This interaction is almost certainly not of clinical importance.

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Alcohol + Co-trimoxazole

A disulfiram-like reaction has been reported when two patients taking co-trimoxazole drank beer.

Clinical evidence, mechanism, importance and management

A 31-year-old man who had been taking prophylactic double-strength co-trimoxazole twice daily for 3 days experienced flushing, palpitations, dyspnoea, headache and nausea 10 to 20 minutes after drinking about 780 mL of beer. Symptoms resolved gradually over 2 to 3 hours, but occurred again the next day when he drank about 170 mL of beer. A similar experience occurred in another man taking double-strength co-trimoxazole after drinking of one litre of beer. However, on the previous day, he drank 4 to 5 beers (approximately 1.4 L) without a problem, even though he had taken co-trimoxazole.[1] The clinical and practical significance of these case reports is unknown as there do not appear to be any other reports of this interaction. Note that some formulations of co-trimoxazole contain ethanol.

1. Heelon MW, White M. Disulfiram-cotrimoxazole reaction. *Pharmacotherapy* (1998) 18, 869–70.

Alcohol + Cyproterone acetate

Excessive alcohol consumption may reduce the antiandrogenic effect of cyproterone acetate in the treatment of hypersexuality, but the relevance of this effect in prostatic carcinoma is not known; there seems to be no evidence that normal social amounts of alcohol interact.

Clinical evidence, mechanism, importance and management

The UK manufacturer of cyproterone acetate (*Androcur*) says that alcohol appears to reduce its effects, and so it is of no value in chronic alcoholics.[1] This appears to be based solely on a simple and unelaborated statement in an abstract of studies[2] in 84 men whose hyper- or abnormal sexuality was treated with cyproterone acetate, which stated that "antiandrogens do not inhibit male sexual behaviour during alcohol excess."

The suggested reasons for this reaction are unknown, but it may possibly be due to several factors. These include enzyme induction by the alcohol, which could possibly increase the metabolism and clearance of cyproterone; increased sexual drive caused by alcohol, which might oppose the effects of cyproterone; and reduced compliance by alcoholic patients, who forget to take their tablets while drinking to excess.[3]

It seems therefore that cyproterone may not be effective in alcoholic patients, but there is nothing to suggest that the effects of cyproterone are opposed by normal moderate social amounts of alcohol. The relevance of this in prostatic carcinoma is not known; nevertheless, it has been suggested that the use of alcohol during treatment with cyproterone acetate is not advisable.[4] It would seem prudent to limit alcohol intake in patients taking cyproterone.

1. Androcur (Cyproterone acetate). Schering Health Care Ltd. UK Summary of product characteristics, May 2008.
2. Laschet U, Laschet L. Three years clinical results with cyproterone-acetate in the inhibiting regulation of male sexuality. *Acta Endocrinol (Copenh)* (1969) 138 (Suppl), 103.
3. Schering Health Care Limited. Personal communication, January 1997.
4. Androcur (Cyproterone acetate). Bayer Inc. Canadian Prescribing information, March 2007.

Alcohol + Dimethylformamide

A disulfiram-like reaction can occur in workers exposed to dimethylformamide vapour if they drink alcohol; incidences of 20% and 70% have been reported. Alcohol may possibly enhance the toxic effects of dimethylformamide on liver function.

Clinical evidence

A 3-year study in a chemical plant where dimethylformamide (DMF) was used found that about 20% (19 out of 102 men) exposed to DMF vapour experienced flushing of the face, and often of the neck, arms, hands, and chest, after drinking alcohol. Sometimes dizziness, nausea, and tightness of the chest also occurred. A single glass of beer was enough to induce a flush lasting 2 hours. The majority of the men experienced the reaction within 24 hours of exposure to DMF, but it could occur even after 4 days.[1] Three further cases of this interaction are described in other reports.[2,3]

Another study, in 126 factory workers exposed to DMF and 54 workers who had no contact with DMF, indicated that DMF adversely affected liver function, and that concurrent alcohol had a synergistic effect (both drugs are hepatotoxic), although individual differences in tolerance to the interaction were observed. Flush symptoms after alcohol consumption were reported by 86 out of 126 (approximately 70%) of workers exposed to DMF, compared with 2 out of 54 (4%) of controls.[4]

Mechanism

Subjects exposed to DMF vapour develop substantial amounts of DMF and its metabolite (*N*-methylformamide) in their blood and urine.[1] This latter compound in particular has been shown in *rats* given alcohol to raise their blood acetaldehyde levels by a factor of five, so it would seem probable that the *N*-methylformamide is similarly responsible for this disulfiram-like reaction in man.[5] For more details of this mechanism, see under 'Alcohol + Disulfiram', p.66.

Importance and management

An established interaction, with the incidence reported to be between about 20% and 70%.[1] Those who come into contact with DMF, even in very low concentrations, should be warned of this possible interaction with alcohol. It would appear to be more unpleasant than serious in most instances, and normally requires no treatment, however the hepatotoxic effects are clearly more of a concern.

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Alcohol + Dimethyl sulfoxide (DMSO)

Dimethyl sulfoxide appears to increase the psychomotor impairment that occurs in response to alcohol.

Clinical evidence, mechanism, importance and management

A case report describes a man who had applied 'relatively large' amounts of dimethyl sulfoxide to his hands in the course of his work, for 2 days before, and while drinking 6 or 7 bottles of beer over 6 hours. Seven hours after he had drunk the last bottle of beer he was noted to be driving erratically, and a positive alcohol breath test was recorded (details not given). The amount of alcohol ingested and the timescale was not expected to result in a positive breath test, and interaction with DMSO was suspected.[1] Anecdotal reports imply that this is not the only case of increased psychomotor impairment that has been attributed to this interaction.[1,2]

A study in 30 healthy subjects found that the absorption of oral alcohol 0.75 g/kg was not affected by DMSO applied topically, either 1 hour before or with the alcohol. However, even though DMSO appeared to increase the clearance of alcohol, the subjects developed twice the psychomotor impairment, when compared with alcohol alone.[2]

Although the effect of DMSO on blood-alcohol levels is unclear (the study only measured clearance, which was increased, and the case only reported breath alcohol levels, which were increased), it seems clear that the concurrent use of both drugs increases psychomotor impairment. Those applying DMSO should be reminded that gloves should be worn; those be-

ing treated with DMSO should be warned of the potential consequences of consuming alcohol.

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Alcohol + Disopyramide

In healthy subjects, the renal clearance of disopyramide may be slightly increased by alcohol-induced diuresis.

Clinical evidence, mechanism, importance and management

A crossover study in 6 healthy subjects found that the half-life and total body clearance of disopyramide were not affected by alcohol, but the amount of the metabolite mono-*N*-dealkylated disopyramide excreted in the urine was reduced. Alcohol increased diuresis in 5 of the 6 subjects, and the renal clearance of disopyramide was increased by 19% in these subjects.[1] The overall clinical effect is likely to be minimal.

1. Olsen H, Bredesen JE, Lunde PKM. Effect of ethanol intake on disopyramide elimination by healthy volunteers. *Eur J Clin Pharmacol* (1983) 25, 103–5.

Alcohol + Disulfiram

Drinking alcohol while taking disulfiram will result in flushing and fullness of the face and neck, tachycardia, breathlessness, giddiness, hypotension, and nausea and vomiting. This is called the disulfiram or *Antabuse* reaction. It is used to deter alcoholic patients from drinking. A mild flushing reaction of the skin may possibly occur in particularly sensitive individuals if alcohol is applied to the skin or if alcohol vapour is inhaled.

Clinical evidence

(a) Alcoholic drinks

One of the earliest descriptions of a disulfiram-like interaction with alcohol was made in 1937 by Dr EE Williams[1] who noted it amongst workers in the rubber industry who were handling **tetramethylthiuram disulphide**:

"Even beer will cause a flushing of the face and hands, with rapid pulse, and some of the men describe palpitations and a terrible fullness of the face, eyes and head. After a glass of beer the blood pressure falls about 10 points, the pulse is slightly accelerated and the skin becomes flushed in the face and wrists. In 15 minutes the blood pressure falls another 10 points, the heart is more rapid, and the patient complains of fullness in the head."

The later observation of the same reaction with the ethyl congener of **tetramethylthiuram disulphide**, disulfiram, led to its introduction as an alcoholic drink deterrent.[2] Patients experience throbbing in head and neck, giddiness, sweating, nausea, vomiting, thirst, chest pain, difficulty in breathing, and headache. The severity of the reaction can depend upon the amount of alcohol ingested, but some individuals are extremely sensitive. Respiratory depression, cardiovascular collapse, cardiac arrhythmias, unconsciousness, and convulsions may occur. There have been fatalities.[3]

An unusually severe reaction has been described in the case report of a patient who developed hypotension (blood pressure 63/15 mmHg), tachycardia of 140 bpm, and ST depression after drinking a can of beer 2 weeks after starting to take disulfiram; he needed noradrenaline (norepinephrine) to maintain an adequate blood pressure.[4] Another unusual and isolated report describes painful, intermittent and transient myoclonic jerking of the arms and legs as the predominant manifestation of the disulfiram reaction in one patient.[5] A further unusual case has been reported in which a woman with a history of bipolar disorder and alcoholism, who was taking disulfiram, was admitted to hospital with a 3- to 4-day history of changes in her mental state, including difficulties with orientation, concentration and visual hallucinations. The confusional state was attributed to alcohol consumption while taking disulfiram, and the probability of this was supported by an earlier similar, though shorter, episode experienced by the patient.[6] Some alcoholics find that disulfiram potentiates the euphoric effects of low doses of alcohol, which alone would be relatively ineffective.[7]

(b) Products containing alcohol

A mild disulfiram reaction is said to occur in some patients who apply alcohol to the skin, but it is probably largely due to inhalation of the vapour.[8] It has been reported after using **after-shave lotion** (50% alcohol),[8] **tar gel** (33% alcohol)[9] and a **beer-containing shampoo** (3% alcohol).[10] A **contact lens wetting solution** (containing **polyvinyl alcohol**) used to irrigate the eye has also been implicated in a reaction,[11,12] although the probability of an interaction with this secondary alcohol has been disputed.[13] It has also been described in a patient who inhaled vapour from paint in a poorly ventilated area and from the inhalation of '**mineral spirits**'.[14] A 36-year-old man with no known cardiac disorders, taking disulfiram 500 mg daily, had a myocardial infarction, which was attributed to **fermented vinegar** in a salad dressing and the use of an **after-shave lotion**.[15]

Furthermore, an unusual case describes a woman taking disulfiram who reported vaginal stinging and soreness during sexual intercourse, and similar discomfort to her husband's penis, which seemed to be related to the disulfiram dosage and how intoxicated her husband was.[16]

The UK manufacturer of the oral solution of **ritonavir** (*Norvir*) says that since it contains alcohol 43% v/v (which they say is about equivalent to 27 mL of wine per dose) the preparation should not be taken with disulfiram or other drugs such as **metronidazole** because a disulfiram-like reaction is possible.[17] However, in practice the risk is probably fairly small because the recommended dose of **ritonavir** in this form is only 7.5 mL. **Ritonavir** (*Norvir*) soft capsules also contain alcohol 12% w/w.[18] The oral concentrate of sertraline (*Zoloft oral concentrate*) is contraindicated with disulfiram due to the alcohol content (12%).[19]

Mechanism

Partially understood. Alcohol is normally rapidly metabolised within the liver, firstly by alcohol dehydrogenase to acetaldehyde, then by acetaldehyde dehydrogenase, and then by a series of biochemical steps to water and carbon dioxide. Disulfiram inhibits the enzyme acetaldehyde dehydrogenase so that the acetaldehyde accumulates.[3] The authors of the report of a case of myocardial infarction suggest that an increased acetaldehyde level in the blood may have caused cause coronary vasospasm and myocardial infarction.[15]

Although the symptoms of the disulfiram-alcohol reaction are due partly to the high levels of acetaldehyde, not all of the symptoms can be reproduced by injecting acetaldehyde, so that some other biochemical mechanism(s) must also be involved. The conversion of dopamine to noradrenaline is also inhibited and the depletion of noradrenaline in the heart and blood vessels allows acetaldehyde to act directly on these tissues to cause flushing, tachycardia and hypotension.[20] Prostaglandin release may also be involved.[21] It has been suggested that the mild skin flush that can occur if alcohol is applied to the skin is not a true disulfiram reaction.[22]

However, some individuals appear to be more sensitive than others, which might be partially due to liver function and variations in the metabolism of disulfiram to its active metabolite by the cytochrome P450 isoenzymes.[23,24]

Importance and management

An extremely well-documented and important interaction exploited therapeutically to deter alcoholics from drinking alcohol. Initial treatment should be closely supervised because an extremely intense and potentially serious reaction occurs in a few individuals, even with quite small doses of alcohol. Apart from the usual warnings about drinking alcohol, patients should also be warned about the unwitting ingestion of alcohol in some pharmaceutical preparations.[25] The risk of a reaction is real. It has been seen following a single-dose of an alcohol-containing **cough mixture**,[26] whereas the ingestion of small amounts of **communion wine** and the absorption of alcohol from a **bronchial nebuliser spray** or **ear drops** did not result in any reaction in 3 individuals.[27] The severity of the reaction is reported to be proportional to the dosage of both disulfiram and alcohol.[28] Patients should also be warned about the exposure to alcohol from some foods, cosmetics, solvents etc. The manufacturers advise that certain foods (sauces and vinegars), liquid medicines, remedies (cough mixtures, tonics, back rubs), and toiletries (aftershave, perfumes and aerosol sprays) may contain sufficient alcohol to elicit a reaction.[20,28] Caution should also be exercised with low-alcohol and "non-alcohol" or "alcohol-free" beers and wines, which may provoke a reaction when consumed in sufficient quantities.[20] Disulfiram is eliminated slowly from the body and therefore drinking alcohol may produce unpleasant symptoms up to 14 days after taking the last dose of disulfiram.[28]

Treatment

The disulfiram reaction can be treated, if necessary, with ascorbic acid. A dose of 1 g given orally is reported to be effective in mild cases (heart rate less than 100 bpm and general condition good). It works within 30 to 45 minutes. Moderately severe cases (heart rate 100 to 150 bpm, blood pressure 150/100 mmHg) can be treated with 1 g of intravenous ascorbic acid and this is effective within 2 to 5 minutes. Critically ill patients may need other standard supportive emergency measures.[29]

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Alcohol + Edible fungi

A disulfiram-like reaction can occur if alcohol is taken after eating the smooth ink(y) cap fungus (*Coprinus atramentarius*) or certain other edible fungi.

Clinical evidence

A man who drank 3 pints of beer 2 hours after eating a meal of freshly picked and fried **ink(y) caps** (***Coprinus atramentarius***) developed facial flushing and a blotchy red rash over the upper half of his body. His face and hands swelled, and he became breathless, sweated profusely, and vomited during the 3 hours when the reaction was most severe. On admission to hospital he was tachycardic and 12 hours later he was in atrial fibrillation, which lasted for 60 hours. The man's wife, who ate the same meal but without an alcoholic drink, did not show the reaction.[1]

This reaction has been described on many occasions in medical and pharmacological reports[2-7] and in books devoted to descriptions of edible and poisonous fungi. Only a few are listed here. Mild hypotension and "….alarming orthostatic features…." are said to be common symptoms[8] but the arrhythmia seen in the case cited here[1] appears to be rare. Recovery is usually spontaneous and uncomplicated. A similar reaction has been described after eating ***Boletus luridus***,[6,9] and other fungi including ***Coprinus micaceus***, ***Clitocybe claviceps*** and certain **morels**.[9,10] An African relative of ***Coprinus atramentarius***, ***Coprinus africanus***, which also causes this reaction, is called the **Ajeimutin** fungus by the Nigerian Yoruba people. The literal translation of this name is the 'eat-without-drinking-alcohol' mushroom.[11]

Mechanism

An early and attractive idea was that the reaction with *Coprinus atramentarius* was due to the presence of disulfiram (one group of workers actually claimed to have isolated it from the fungus[12]), but this was not confirmed by later work,[13,14] and it now appears that the active ingredient is coprine (*N*-5-(1-hydroxycyclopropyl)-glutamine).[15,16] This is metabolised in the body to 1-aminocyclopropanol, which appears, like disulfiram, to inhibit aldehyde dehydrogenase (see 'Alcohol + Disulfiram', p.66). The active ingredients in the other fungi are unknown.

Importance and management

An established and well-documented interaction. It is said to occur up to 24 hours after eating the fungus. The intensity depends upon the quantity of fungus and alcohol consumed, and the time interval between them.[1,4,17] Despite the widespread consumption of edible fungi and alcohol, reports of this reaction in the medical literature are few and far between, suggesting that even though it can be very unpleasant and frightening, the outcome is usually uncomplicated. Treatment appears normally not to be necessary.

The related fungus ***Coprinus comatus*** (the '**shaggy ink cap**' or '**Lawyers wig**') is said not to interact with alcohol,[8,18] nor is there anything to suggest that it ever occurs with the **common field mushroom** (***Agaricus campestris***) or the cultivated variety (***Agaricus bisporis***).[18]

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Alcohol + Erythromycin

Alcohol can cause a moderate reduction in the absorption of erythromycin ethylsuccinate. There is some evidence that intravenous erythromycin can raise blood-alcohol levels but the extent and the practical importance of this is unknown.

Clinical evidence, mechanism, importance and management

(a) Effects on alcohol

A study in 10 healthy subjects found that erythromycin base 500 mg three times daily did not alter the pharmacokinetics of oral alcohol 0.8 g/kg, and the subjects' perception of intoxication was unaltered.[1] In contrast, another study in 8 healthy subjects, primarily investigating the effects of intravenous erythromycin lactobionate 3 mg/kg on gastric emptying, found that when they were given a liquid meal of orange juice, alcohol 0.5 g/kg and lactulose 10 g immediately after a solid meal, the mean peak blood-alcohol levels were raised by about 40% and the AUC over the first hour was increased by 33%. After that the curve was virtually the same as that

seen with a saline placebo. The authors suggest that the increased blood-alcohol levels are a result of erythromycin causing more rapid gastric emptying, so that the alcohol is exposed to metabolism by the gastric mucosa for a shorter time.[2]

What this means in terms of an increase in the effects of alcohol (e.g. on driving) is not known.

(b) Effects on erythromycin

When a single 500-mg dose of erythromycin ethylsuccinate was taken by 9 healthy subjects with two 150-mL alcoholic drinks (one immediately and the other 2.5 hours later) the erythromycin AUC was decreased by about 27% and its absorption was delayed. One subject had a 185% *increase* in absorption. The alcoholic drink was pisco sour, which contains lemon juice, sugar and pisco (a brandy-like liqueur). Blood-alcohol levels achieved were about 50 mg%.[3]

The reason for the reduced absorption of erythromycin is not understood but it is suggested that the slight delay occurs because alcohol delays gastric emptying, so erythromycin reaches its absorption site in the duodenum a little later.[3] The extent to which this reduced absorption might alter the antibacterial effects of erythromycin is uncertain but it seems likely to be small.

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Alcohol + Fluvastatin

Alcohol does not significantly interact with fluvastatin.

Clinical evidence, mechanism, importance and management

Ten healthy subjects took a single 40-mg dose of fluvastatin and 70 g of alcohol diluted in lemonade. This acute ingestion of alcohol had no effect on the peak serum levels of fluvastatin or its AUC, but the half-life was reduced by almost one-third.[1] In a second related study, 20 patients with hypercholesterolaemia were given 40 mg of fluvastatin and 20 g of alcohol daily for 6 weeks. The AUC of fluvastatin was slightly increased and the half-life was increased by almost one-third, but the lipid profile with fluvastatin plus alcohol was little different from fluvastatin alone.[1,2] The conclusion was reached that although long-term moderate drinking has some small effect on the pharmacokinetics of fluvastatin, its safety and efficacy are unaltered.[1] There would seem to be no reason for patients taking fluvastatin to avoid alcohol.

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Alcohol + Food

Food and milk decrease the absorption of alcohol and meals increase the metabolism of alcohol. Foods rich in serotonin (e.g. bananas) taken with alcohol may produce adverse effects such as diarrhoea and headache. Previous alcohol consumption and the glycaemic load of a meal appear to interact to influence both mood and memory.

Clinical evidence, mechanism, importance and management

(a) Alcohol absorption and metabolism

In one study 10 subjects were given 25 mL of alcohol (equivalent to a double whiskey) after drinking about 850 mL of water or **milk** during the previous 90 minutes. Blood-alcohol levels at 90 minutes were reduced by about 40%, and at 120 minutes by about 25% by the presence of the **milk**. The intoxicant effects of the alcohol were also clearly reduced.[1] In a randomised, crossover study, 24 healthy subjects were given alcohol 0.3 g/kg either one hour before or after an **evening meal**. It was found that the maximum alcohol levels were increased by 87% from 21.3 to 39.9 mg%, and the AUC was increased by 63% when alcohol was given in the fasting rather than the fed state. However there was large inter and intra-individual variability in alcohol bioavailability.[2] Other studies have shown similar effects,[3-5] and have found that this is not limited to specific components of food,[4,5] as well as demonstrating that food reduces the feeling of intoxication and reduces the time required to eliminate alcohol from the body.[3]

After food, the rate of gastric emptying is slower, and hepatic blood flow and the activities of alcohol-metabolising enzymes are increased, which allows greater first-pass metabolism of alcohol. Thus, the effects of alcohol are greatest when taken on an empty stomach.

(b) Dietary serotonin

Serotonin (5-hydroxytryptamine, 5-HT) is excreted in the urine as 5-hydroxyindole-3-acetic acid (5-HIAA) and 5-hydroxytryptophol (5-HTOL). The ratio of 5-HTOL to 5-HIAA is normally very low (less than 0.01). A study in 10 healthy subjects found that 4 hours after the ingestion of alcohol 0.5 g/kg the ratio was increased by about 70-fold. When the same amount of alcohol was given with 3 **bananas**, a food rich in serotonin, the ratio was increased about 100-fold at 4 hours and was still significantly raised at 24 hours. Within 4 hours, 7 of the 10 subjects experienced adverse effects including diarrhoea, headache and fatigue. The symptoms were attributed to high levels of 5-HTOL, which is usually a minor metabolite of serotonin. Other foods rich in serotonin such as **pineapple**, **kiwi fruit** or **walnuts** may produce similar effects if taken with even moderate amounts of alcohol.[6]

(c) Glycaemic load

Breakfasts that release glucose at different speeds were found to interact with alcohol drunk the previous evening to influence cognition and mood. When less than 4.5 g of alcohol had been drunk, a breakfast high in rapidly available glucose was associated with better memory later in the morning. In contrast, when more than 4.5 g of alcohol had been drunk, a breakfast high in slowly available glucose resulted in better memory. After a high glycaemic-load lunch, the rapidly available glucose breakfast resulted in a more confused feeling than the slowly available glucose breakfast or fasting, in those who had drunk more than 4.5 g of alcohol the previous evening.[7]

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Alcohol + Furazolidone

A disulfiram-like reaction may occur in patients taking furazolidone if they drink alcohol.

Clinical evidence

A patient taking furazolidone 200 mg four times daily complained of facial flushing, lachrymation, conjunctivitis, weakness, and light-headedness within 10 minutes of drinking beer. These effects occurred on several occasions and lasted 30 to 45 minutes.[1] A man prescribed furazolidone 100 mg four times daily and who had taken only three doses, developed intense facial flushing, wheezing and dyspnoea (lasting one hour), within one hour of drinking about 60 mL of brandy. The same thing happened again the next day after drinking a *Martini* cocktail. No treatment was given.[2] A report originating from the manufacturers of furazolidone stated that by 1976, 43 cases of a disulfiram-like reaction had been reported, of which 14 were produced experimentally using above-normal doses of furazolidone.[3] A later study in 1986 described 9 out of 47 patients (19%) who complained of a disulfiram-like reaction after drinking alcohol while taking furazolidone 100 mg four times daily for 5 days.[4]

Mechanism

Uncertain. It seems possible that furazolidone acts like disulfiram by inhibiting the activity of acetaldehyde dehydrogenase (see *Mechanism*, under 'Alcohol + Disulfiram', p.66).

Importance and management

An established and clinically important interaction of uncertain incidence. One report suggests that possibly about 1 in 5 may be affected.[4] Reactions of this kind appear to be more unpleasant and possibly frightening than serious, and normally need no treatment; however, patients should be warned about what may happen if they drink alcohol.

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Alcohol + Ginseng

***Panax ginseng* (Asian ginseng) increases the clearance of alcohol and lowers blood-alcohol levels.**

Clinical evidence

Fourteen healthy subjects, each acting as their own control, were given alcohol (72 g/65 kg as a 25% solution) with and without a *Panax ginseng* (Asian ginseng) extract (3 g/65 kg) mixed in with it. They drank the alcohol or the alcohol/ginseng mixture over a 45-minute period in 7 portions, the first four at 5-minute intervals and the next three at 10-minute intervals. Measurements taken 40 minutes later showed that the presence of the ginseng lowered blood-alcohol levels by an average of about 39%. The alcohol levels of 10 subjects were lowered by 32 to 51% by the ginseng, 3 showed reductions of 14 to 18%, and one showed no changes at all.[1]

Mechanism

The reasons for this interaction are uncertain, but it is suggested that *Panax ginseng* possibly increases the activity of the enzymes (alcohol and aldehyde dehydrogenase)[2] that are concerned with the metabolism of the alcohol, thereby increasing the clearance of the alcohol.

Importance and management

What this reduction in blood-alcohol levels means in practical terms is not clear but the authors of the report suggest the possibility of using ginseng to treat alcoholic patients and those with acute alcohol intoxication;[1] however, this needs confirmation in further clinical studies. The available data suggests that the concurrent use of alcohol and *Panax ginseng* is unlikely to be detrimental.

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Alcohol + Glutethimide

The combination of glutethimide and alcohol results in greater impairment in some psychomotor tests, but improvement in others. Alcohol does not interact with glutethimide taken the previous night.

Clinical evidence, mechanism, importance and management

In a series of studies, blood-alcohol levels were raised by a mean of 11% by glutethimide, while plasma and urinary glutethimide levels were reduced.[1] Neither glutethimide nor alcohol alone significantly impaired reaction times, but the combination did. However, in two other tests (tracking efficacy and finger tapping) impairment was greatest after glutethimide alone and reduced by the presence of alcohol.[1] In contrast, a later study found that glutethimide did not subjectively or objectively impair the performance of a number of psychomotor skill tests related to driving, and did not interact with alcohol given the morning after the glutethimide dose.[2] Both drugs are CNS depressants and their effects would be expected to be additive.

The information is limited and somewhat contradictory, nevertheless patients should be warned about the probable results of taking glutethimide and alcohol together. Driving, handling dangerous machinery, or undertaking any task needing alertness and full co-ordination, is likely to be made more difficult and hazardous. There is no evidence of a hangover effect, which could result in an interaction with alcohol the next day.[2]

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Alcohol + Glyceryl trinitrate (Nitroglycerin)

Patients who take glyceryl trinitrate while drinking may feel faint and dizzy.

Clinical evidence, mechanism, importance and management

The results of studies[1,2] on the combined haemodynamic effects of alcohol and glyceryl trinitrate give support to earlier claims that their concurrent use increases the risk of exaggerated hypotension and fainting.[3,4] Their vasodilatory effects would appear to be additive.[5] The greatest effect was seen when the glyceryl trinitrate was taken one hour or more after starting to drink alcohol.[1] It is suggested that this increased susceptibility to postural hypotension should not be allowed to stop patients from using glyceryl trinitrate if they have been drinking alcohol, but they should be warned about the possible effects and told what to do if they feel faint and dizzy (i.e. sit or lie down).[1]

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Alcohol + Griseofulvin

An isolated case report describes a very severe disulfiram-like reaction when a man taking griseofulvin drank a can of beer. Other isolated reports describe flushing and tachycardia, or increased alcohol effects, when patients taking griseofulvin consumed alcohol.

Clinical evidence

A man took griseofulvin 500 mg daily for about 2 weeks without problems. Subsequently he drank a can of beer, took his usual dose of griseofulvin about one hour later, and within 30 to 60 minutes developed a severe disulfiram-like reaction (flushing, severe nausea, vomiting, diarrhoea, hypotension, and paraesthesias of all extremities). He was successfully treated with intravenous sodium chloride 0.9%, potassium, dopamine, and intramuscular promethazine.[1]

Another isolated case of flushing and tachycardia has been attributed to the concurrent use of alcohol and griseofulvin; rechallenge produced the same effects.[2]

It has been suggested that griseofulvin can increase the effects of alcohol, but the descriptions of this response are very brief. One of them describes a man who had a decreased tolerance to alcohol and emotional instability manifested by crying and nervousness, which was said to be so severe that the drug was stopped.[3] Another states that this effect has been noted in a very small number of patients, but gives no further information.[4]

Mechanism

Not understood. The reaction described above might possibly have the same pharmacological basis as the disulfiram/alcohol reaction, see 'Alcohol + Disulfiram', p.66.

Importance and management

The documentation is extremely sparse, which would seem to suggest that adverse interactions between alcohol and griseofulvin are uncommon; however, the disulfiram-like reaction described was unusually severe in one patient.

Concurrent use need not be avoided but it may be prudent to warn patients about the possible effects (e.g. flushing and tachycardia).

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2. Robinson MM. Griseofulvin therapy of superficial mycoses. *Antibiot Annu* (1959–60) 7, 680–6.
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Alcohol + H_2-receptor antagonists

Although some studies have found that blood-alcohol levels can be raised to some extent in those taking an H_2-receptor antagonist and possibly remain elevated for longer than usual, others report that no significant interaction occurs. Drinking may worsen the gastrointestinal disease for which these H_2-receptor antagonists are being given. Hypoglycaemia associated with alcohol may be enhanced by H_2-receptor antagonists.

Clinical evidence

(a) Cimetidine

A double-blind study in 6 healthy subjects found that cimetidine 300 mg four times daily for 7 days, increased the peak plasma levels of alcohol 0.8 g/kg by about 12% (from 146 to 163 mg%) and increased the AUC by about 7%. The subjects assessed themselves as being more intoxicated while taking cimetidine and alcohol than with alcohol alone.[1]

An essentially similar study[2,3] found that blood-alcohol levels were raised by 17% (from 73 to 86 mg%) by cimetidine. However, another study found that cimetidine almost doubled peak blood-alcohol levels.[4] A study in 6 healthy subjects also found that cimetidine 400 mg twice daily for one week approximately doubled the AUC of a single 0.15-g/kg oral dose of alcohol and raised peak alcohol levels by about 33%. No changes were seen when the alcohol was given intravenously.[5] A further study in healthy subjects given cimetidine for only 2 days found that peak plasma alcohol levels were raised by 17%, and the time that blood levels remained above the 80 mg% mark (the legal driving limit in some countries) was prolonged by about one-third.[6]

A study in 6 subjects given 0.75 g/kg of alcohol found that a single 800 mg dose of cimetidine, raised blood alcohol levels at 45 minutes by 32% (from about 76 mg% to 100 mg%), and the AUC at 120 minutes was increased by 25%. Each of the subjects said they felt more inebriated after taking cimetidine.[7]

In subjects with substantial first-pass metabolism of alcohol, cimetidine increased the blood levels of repeated small drinks of alcohol to a greater degree than that which occurred after an equivalent single dose. The levels reached were associated with psychomotor impairment.[8]

In contrast, another study found that a combination of chlorphenamine (which blocks H_1-receptors) and cimetidine reduced the rate of absorption and peak blood-alcohol levels, and suppressed alcohol-induced flushing.[9]

A study in 10 healthy subjects given alcohol 0.5 g/kg before and after cimetidine 400 mg twice daily for 7 days, found that hypoglycaemia following alcohol ingestion was enhanced.[10]

In contrast to these findings a number of studies, using a variety of doses of cimetidine, and a variety of types of alcohol, have found that no interaction occurs.[11-21]

(b) Famotidine

Two studies that found an interaction between other H_2-receptor antagonists and alcohol found that famotidine had no significant effect on blood-alcohol levels.[4,7] Similarly a number of other studies, using a variety of doses of famotidine, and a variety of types of alcohol, have found no interaction occurs.[14-16,18,19,21] However, a study in 10 healthy subjects given alcohol 0.5 g/kg before and after famotidine 40 mg once daily for 7 days, found that marked hypoglycaemia occurred following alcohol ingestion.[10]

(c) Nizatidine

A study in subjects given 0.75 g/kg of alcohol found that a single 300-mg dose of nizatidine raised blood-alcohol levels at 45 minutes by 20% (from about 76 mg% to 90 mg%), and the AUC at 120 minutes was increased by 20%.[7]

Another report briefly mentions that nizatidine has similar effects on alcohol absorption to cimetidine,[22] whereas two other studies found no interaction between nizatidine and alcohol.[21,23]

(d) Ranitidine

A placebo-controlled study in 8 healthy subjects found that ranitidine 300 mg daily for 7 days did not affect the peak plasma levels of alcohol 0.8 g/kg.[2,3] However, another study found that ranitidine 150 mg twice daily for 8 days increased the peak levels of a 0.3 g/kg oral dose of alcohol by 34%.[4] A further study in healthy subjects given ranitidine for only 2 days found that peak plasma alcohol levels were raised by 28%, and the time that blood levels remained above the 80 mg% mark (the legal driving limit in some countries) was prolonged by about one-third.[6]

A study in subjects given 0.75 g/kg of alcohol found that a single 300-mg dose of ranitidine raised blood-alcohol levels at 45 minutes by 6% (from about 75 mg% to 81 mg%), and the AUC at 120 minutes was increased by 10%.[7]

Ranitidine 150 mg twice daily for 7 days considerably increased blood-alcohol levels and the high levels persisted for longer in social drinkers (with substantial first-pass metabolism) receiving 4 drinks of 0.15 g/kg of alcohol at 45-minute intervals.[24] Another report briefly mentions that ranitidine has similar effects on alcohol absorption to cimetidine.[22]

A study in 10 healthy subjects given alcohol 0.5 g/kg before and after ranitidine 150 mg twice daily for 7 days, found that hypoglycaemia following alcohol ingestion was enhanced.[10]

In contrast to these findings a number of studies, using a variety of doses of ranitidine, and a variety of types of alcohol, have found no interaction occurs.[12,14,16-21,25-27]

Mechanism

It would appear that the interacting H_2-receptor antagonists inhibit the activity of alcohol dehydrogenase (ADH) in the gastric mucosa so that more alcohol passes unmetabolised into the circulation, thereby raising the levels.[28-32] Most of the studies assessing the interaction of H_2-receptor antagonists with larger quantities of alcohol have not found an interaction. The decrease in first pass metabolism with increasing amounts of alcohol could explain this, as it implies that a significant interaction with H_2-receptor antagonists would be more likely with smaller quantities of alcohol.[8,33] Other factors that affect the first pass metabolism of alcohol, such as fasting, chronic alcoholism and female gender may also affect the outcome. The increase in blood-alcohol levels with cimetidine or ranitidine and a low alcohol dose may also be explained by the effect of H_2-receptor antagonists or alcohol on gastric emptying times.[27,33] In one study the decrease in first-pass metabolism correlated with a ranitidine-induced increase in the rate of gastric emptying and an increase in blood-alcohol levels.[34] However, with small quantities of alcohol the magnitude of the effect on peak levels may be too small to increase effects on psychomotor performance,[33,35] although two studies suggested that an effect might occur.[8]

The hypoglycaemic effect is not considered to be due to effects on alcohol absorption but may be an effect of H_2-receptor antagonists on glucose metabolism.[10]

Importance and management

The contrasting and apparently contradictory results cited here clearly show that this interaction is by no means established. Extensive reviews of the data concluded that the interaction is not, in general, clinically significant.[32,33,36-38] Under conditions mimicking social drinking there is some evidence that H_2-receptor antagonists may[10,24] or may not[20] increase blood-alcohol levels to those associated with impairment of psychomotor skills. However, as yet, there are insufficient grounds to justify any general warning regarding alcohol and H_2-receptor antagonists. However, note that many of the conditions for which H_2-receptor antagonists are used may be made worse by alcohol, so restriction of alcohol intake may be prudent. Other factors that may affect this interaction are discussed under *Mechanism*, above.

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Alcohol + Hormonal contraceptives or HRT

Estradiol does not affect blood-alcohol levels, but alcohol clearance may be reduced in women taking combined hormonal contraceptives; nevertheless the detrimental effects of alcohol may be reduced to some extent. Small amounts of alcohol may possibly improve some aspects of cognitive function in patients using HRT. Alcohol does not affect the pharmacokinetics of ethinylestradiol; however, acute ingestion of alcohol markedly increases the levels of circulating estradiol in women using oral HRT; a smaller increase is seen with transdermal HRT. In addition, alcohol intake appears to increase the risk of breast cancer in women receiving HRT.

Clinical evidence

(a) Effect of oestrogens on alcohol

A controlled study in 54 women found that those taking an oral combined hormonal contraceptive (30, 35, or 50 micrograms of oestrogen) unexpectedly tolerated the effects of alcohol better than those not taking oral contraceptives (as measured by a reaction-time test and a bead-threading test), but their blood-alcohol levels and its rate of alcohol clearance were unchanged.[1] Similarly, a study in 12 healthy postmenopausal women found that HRT (**estradiol** 1 mg daily and **medroxyprogesterone acetate** 10 mg daily for 10 out of each 25 days) did not affect blood-alcohol levels.[2] A study of 214 postmenopausal women suggested that small amounts of alcohol may enhance visuospatial processes (improved cognitive function measured by block design performance). HRT also appeared to be linked with better visuospatial performance, but only when the task was difficult. There was a trend (not statistically significant) towards improved performance with alcohol consumption (up to approximately half a standard drink per day) and oestrogen replacement therapy.[3]

(b) Effect of alcohol on oestrogens

Alcohol ingestion did not have any significant effect on **ethinylestradiol** pharmacokinetics in 9 healthy women taking a combined oral contraceptive (ethinylestradiol/gestodene 30/75 micrograms). In this study, alcohol was given as a single dose of 0.4 g/kg (2 to 3 standard drinks) on day 14 then 0.4 g/kg twice daily for 7 days. In contrast, 12 healthy postmenopausal women receiving HRT (**estradiol** 1 mg daily and **medroxyprogesterone acetate** 10 mg daily for 10 out of each 25 days) were given an alcoholic drink (0.7 g/kg, a dose shown to achieve mean peak alcohol serum levels of about 97 mg% after about 1 hour) during the oestrogen-only phase of the HRT cycle. It was found that their peak **estradiol** levels rose threefold and were significantly above the baseline for 5 hours. No significant increases in the levels of circulating estrone (an oestrogen secreted by the ovaries) were seen.[2] A similar, smaller 1.2-fold increase in peak **estradiol** levels was seen in another study when women using **transdermal estradiol** were given alcohol.[4]

(c) Risk of breast cancer

Since both alcohol and HRT are linked with a small increase in breast cancer risk, it has been postulated that the combination of HRT and alcohol could have additive risks.[5] A prospective study of 51 847 postmenopausal women confirmed an association with alcohol intake and breast cancer risk (for oestrogen receptor-positive (ER+) tumours, but not oestrogen receptor-negative (ER–) tumours). Furthermore, among women who consumed alcohol, postmenopausal hormone use was associated with an increased risk for the development of ER+ tumours. For women with the highest alcohol intake (10 g (approximately 1 drink) or more daily) the relative risk of developing oestrogen receptor-positive/progesterone receptor-positive (ER+PR+) breast cancer was 1.2 and 1.8 for non-users and users of HRT, respectively, compared with non-drinkers who had never used postmenopausal hormones; the relative risk of developing ER+PR– tumours was even greater, being approximately 2.5 and 3.5, respectively.[6] Another study also reported a similar increased risk of developing ER+PR+ tumours with alcohol and oestrogen replacement therapy, but only a slight risk for ER+PR– tumours; the risk for ER–PR– breast cancer was, however, greatest.[7] The Women's Health Study found that an alcohol intake of greater than 10 g of alcohol per day and postmenopausal hormone use was associated with a relative risk of developing breast cancer of 1.84, compared with those who did not consume alcohol or take postmenopausal hormones.[8]

Mechanism

The reasons for the changes in estradiol levels are not understood. Alcohol can increase *endogenous* estradiol levels in postmenopausal women, although the findings are variable. Another possible explanation is altered clearance of estradiol in women who drink alcohol.[9] The effects on ethinylestradiol are in contrast. This may be because the ethinyl group in ethinylestradiol confers protection from the effects of alcohol.[10]

Importance and management

The authors say that they do not recommend women taking oral contraceptives should attempt to drink more than usual, since even if alcohol is tolerated better, blood-alcohol levels are not reduced.[1] However, two other studies suggest that peak blood-alcohol levels may be reduced in those taking oral contraceptives, but alcohol clearance is also reduced and so alcohol may be present for longer in women who are taking oral contraceptives.[11,12]

Regular consumption of alcohol as low as 1 to 2 drinks per day may possibly contribute to a modest increased risk of some types of breast cancer,[9] and it has been suggested that women taking HRT should limit their alcohol intake;[5] about one drink or less per day has been proposed.[9] More study is needed to confirm the amount and frequency of alcohol consumption needed to have a deleterious effect in women who use HRT.

1. Hobbes J, Boutagy J, Shenfield GM. Interactions between ethanol and oral contraceptive steroids. *Clin Pharmacol Ther* (1985) 38, 371–80.
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9. Singletary KW, Gapstur SM. Alcohol and breast cancer. Review of epidemiologic and experimental evidence and potential mechanisms. *JAMA* (2001) 286, 2143–51.
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11. Jones MK, Jones BM. Ethanol metabolism in women taking oral contraceptives. *Alcohol Clin Exp Res* (1984) 8, 24–8.
12. Zeiner AR, Kegg PS. Menstrual cycle and oral contraceptive effects on alcohol pharmacokinetics in caucasian females. *Curr Alcohol* (1981) 8, 47–56.

Alcohol + Inotropes and Vasopressors

Alcohol does not affect the cardiovascular response to isoprenaline. Alcohol increases the plasma levels of noradrenaline, but reduces its effects on diastolic blood pressure. Similarly alcohol reduces the increase in blood pressure in response to methoxamine.

Clinical evidence, mechanism, importance and management

(a) Isoprenaline (Isoproterenol)

A study in 21 healthy subjects found that a 1-mL/kg oral dose of 20% alcohol did not alter the effects of isoprenaline, given in doses of up to 1.78 micrograms, on blood pressure and heart rate.[1]

(b) Methoxamine

In a placebo-controlled study, 8 subjects were given 1 mL/kg of 20% alcohol, followed after 90 to 150 minutes by an infusion of methoxamine 200, 400, 800, 1600, and 2000 micrograms/minute, each for one minute. The increase in blood pressure was reduced after a cumulative 5 mg dose of methoxamine (from about 33/31 mmHg to 19/11 mmHg), but heart rate was not significantly affected.[2] This study suggests that patients who have drunk alcohol may require higher doses of methoxamine.

(c) Noradrenaline (Norepinephrine)

In a placebo-controlled study, 8 subjects were given 1 mL/kg of 20% alcohol, followed after 45 minutes by an infusion of noradrenaline 24, 48 and 90 nanograms/kg per minute, each for 20 minutes. There was a significant increase in plasma noradrenaline levels after the ingestion of alcohol at the lower two doses of noradrenaline. Systolic blood pressure was not significantly affected, but there was a significant (approximately twofold) decrease in diastolic blood pressure at each dosing level. Heart rate was not significantly affected.[2] This study suggests that patients who have drunk alcohol may require higher doses of noradrenaline; however, as noradrenaline is titrated to effect, this interaction seems unlikely to be clinically relevant.

1. Eisenhofer G, Lambie DG, Johnson RH. No effect of ethanol ingestion on β-adrenoceptor-mediated circulatory responses to isoprenaline in man. *Br J Clin Pharmacol* (1985) 20, 684–7.
2. Eisenhofer G, Lambie DG, Johnson RH. Effects of ethanol ingestion on α-adrenoceptor-mediated circulatory responses in man. *Br J Clin Pharmacol* (1984) 18, 581–6.

Alcohol + Interferons

Studies have found a reduced response to interferon in patients who drink alcohol. Those who drink the most seem to exhibit the lowest response to interferon.

Clinical evidence, mechanism, importance and management

In a study involving 245 patients, alcohol intake, and its effect on treatment, were retrospectively evaluated, between 1 and 3 years after diagnosis of hepatitis C virus-related chronic liver disease. Less than 50% of the patients who drank alcohol stopped after being diagnosed with liver disease, despite being advised to abstain from alcohol. Alcohol intake affected fibrosis, especially in women, and response to interferon therapy. Seventeen out of 65 patients (26.1%) who were treated with **interferon alfa** had a sustained response to therapy. However, the number of responders decreased as alcohol intake increased; there were more drinkers (63.1%) than abstainers (10.7%) among the 73.8% of patients who did not respond.[1] A study in non-drinkers, light drinkers (less than 70 g ethanol per day) and heavy drinkers (more than 70 g ethanol per day), with hepatitis C, assessed the response to interferon (alpha and beta). It was found that drinking reduced the response to interferon; with 47%, 57%, and 100% of subjects not responding in the non-drinking group, moderate drinking group, and heavy drinking group, respectively.[2] Other studies have found similar results,[3,4] with one study finding that heavy drinkers, who abstained from drinking for at least 6 months before receiving interferon, had similar outcomes to infrequent drinkers.[3]

One manufacturer notes that hepatotoxicity has been reported with **interferon beta-1a**. They say the potential additive toxicity with hepatotoxic drugs such as alcohol has not been determined, and caution is warranted.[5]

There appears to be insufficient information to suggest that patients receiving interferons should avoid alcohol completely; however, alcohol intake, particularly heavy drinking, may increase the risk of hepatotoxicity and reduce the response to treatment with interferon.

1. Loguercio C, Di Pierro M, Di Marino MP, Federico A, Disalvo D, Crafa E, Tuccillo C, Baldi F, del Vecchio Blanco C. Drinking habits of subjects with hepatitis C virus-related chronic liver disease: prevalence and effect on clinical, virological and pathological aspects. *Alcohol Alcohol* (2000) 35, 296–301.
2. Okazaki T, Yoshihara H, Suzuki K, Yamada Y, Tsujimura T, Kawano K, Yamada Y, Abe H. Efficacy of interferon therapy in patients with chronic hepatitis C. Comparison between non-drinkers and drinkers. *Scand J Gastroenterol* (1994) 29, 1039–43.
3. Ohnishi K, Matsuo S, Matsutani K, Itahashi M, Kakihara K, Suzuki K, Ito S, Fujiwara K. Interferon therapy for chronic hepatitis C in habitual drinkers: comparison with chronic hepatitis C in infrequent drinkers. *Am J Gastroenterol* (1996) 91, 1374–9.
4. Mochida S, Ohnishi K, Matsuo S, Kakihara K, Fujiwara K. Effect of alcohol intake on the efficacy of interferon therapy in patients with chronic hepatitis C as evaluated by multivariate logistic regression analysis. *Alcohol Clin Exp Res* (1996) 20 (Suppl), 371A–377A.
5. Avonex (Interferon beta-1a). Biogen Idec Ltd. UK Summary of product characteristics, June 2008.

Alcohol + Ivermectin

Alcohol may increase the bioavailability of ivermectin.

Clinical evidence, mechanism, importance and management

Anecdotal reports from Nigeria suggest that ivermectin is more potent when taken with palm wine, a local alcoholic drink, and a few cases of ataxia and postural hypotension occurring with ivermectin were considered to be due to an interaction with alcohol.[1] Ivermectin formulated as an alcoholic solution has been found to have about twice the systemic availability of tablets and capsules.[2] In one study, 20 healthy subjects were given ivermectin 150 micrograms/kg with either 750 mL of beer (alcohol 4.5%) or 750 mL of water. Beer increased the plasma levels of ivermectin at 1 to 4 hours by about 51% to 66%, respectively, when compared with water. No adverse effects were reported in either group.[1] The evidence suggests that concurrent use may be of benefit, if adverse effects such as

postural hypotension are not troublesome; this may be more of a problem in those with pre-existing heart disease.

1. Shu EN, Onwujekwe EO, Okonkwo PO. Do alcoholic beverages enhance availability of ivermectin? *Eur J Clin Pharmacol* (2000) 56, 437–8.
2. Edwards G, Dingsdale A, Helsby N, Orme MLE, Breckenridge AM. The relative systemic bioavailability of ivermectin after administration as capsule, tablet, and oral solution. *Eur J Clin Pharmacol* (1988) 35, 681–4.

Alcohol + Kava

There is some evidence that kava may worsen the CNS depressant effects of alcohol.

Clinical evidence, mechanism, importance and management

Forty healthy subjects underwent a number of cognitive tests and visuomotor tests after taking alcohol alone, kava alone, or both together. The subjects took 0.75 g/kg of alcohol (enough to give blood-alcohol levels above 50 mg%) and the kava dose was 1 g/kg. The kava drink was made by mixing middle grade Fijian kava (Kava-Kava; the pepper plant *Piper methysticum*) with water and straining it to produce about 350 mL of kava liquid. It was found that kava alone had no effect on the tests, but when the kava was given with alcohol it potentiated both the perceived and measured impairment that occurred with alcohol alone.[1] However, another study found that a kava extract (WS 1490) did not enhance the negative effects of alcohol on performance tests.[2]

No very strong conclusions can be drawn from the results of the studies, but it is possible that car driving and handling other machinery may be more hazardous if kava and alcohol are taken together. However, note that the use of kava-kava is restricted in the UK because of reports of idiosyncratic hepatotoxicity.[3]

1. Foo H, Lemon J. Acute effects of kava, alone or in combination with alcohol, on subjective measures of impairment and intoxication and on cognitive performance. *Drug Alcohol Rev* (1997) 16, 147–55.
2. Herberg K-W. Zum Einfluß von Kava-Spezialextrakt WS 1490 in Kombination mit Ethylalkohol auf sicherheitsrelevante Leistungsparameter. The influence of kava-special extract WS 1490 on safety-relevant performance alone and in combination with ethyl alcohol. *Blutalkohol* (1993) 30, 96–105.
3. Committee on Safety of Medicines/Medicines and Healthcare Regulatory Authority. Kava-kava and hepatotoxicity. *Current Problems* (2003) 29, 8.

Alcohol + Ketoconazole

A few cases of disulfiram-like reactions have been reported in patients who drank alcohol while taking ketoconazole.

Clinical evidence, mechanism, importance and management

One patient (an alcoholic), out of group of 12 patients with Candida infections taking ketoconazole 200 mg daily, experienced a disulfiram-like reaction (nausea, vomiting, facial flushing) after drinking alcohol.[1] No further details are given, and the report does not say whether any of the others drank alcohol. A woman taking ketoconazole 200 mg daily developed a disulfiram-like reaction when she drank alcohol.[2] Another report describes a transient 'sunburn-like' rash or flush on the face, upper chest and back of a patient taking ketoconazole 200 mg daily when she drank modest quantities of wine or beer.[3] The reasons for the reactions are not known but it seems possible that ketoconazole may act like disulfiram and inhibit the activity of acetaldehyde dehydrogenase (see *Mechanism*, under 'Alcohol + Disulfiram', p.66). The incidence of this reaction appears to be very low (these appear to be the only reports) and its importance is probably small. Reactions of this kind are usually more unpleasant than serious; the manufacturers note that symptoms resolve within a few hours.[4] Nevertheless, to avoid these effects, the manufacturer advises avoidance of alcohol while taking ketoconazole.[5]

1. Fazio RA, Wickremesinghe PC, Arsura EL. Ketoconazole treatment of *Candida esophagitis*—a prospective study of 12 cases. *Am J Gastroenterol* (1983) 78, 261–4.
2. Meyboom RHB, Pater BW. Overgevoeligheid voor alcoholische dranken tijdens behandeling met ketoconazol. *Ned Tijdschr Geneeskd* (1989) 133, 1463–4.
3. Magnasco AJ, Magnasco LD. Interaction of ketoconazole and ethanol. *Clin Pharm* (1986) 5, 522–3.
4. Nizoral Tablets (Ketoconazole). Janssen-Cilag Ltd. UK Summary of product characteristics, October 2008.
5. Nizoral Tablets (Ketoconazole). Janssen-Cilag Ltd. UK Patient information leaflet, April 2008.

Alcohol + Levamisole

The manufacturer of levamisole notes that a disulfiram-like reaction has been reported when levamisole was given with alcohol.[1] Reactions of this kind are usually more unpleasant than serious; and symptoms often resolve within a few hours. It would seem prudent to warn patients of the possibility.

1. Ascaridil (Cloridrato de levamisole). Janssen-Cilag (Brazil). Brazilian Prescribing information, March 2008.

Alcohol + Levosimendan

Levosimendan appears not to interact adversely with alcohol.

Clinical evidence, mechanism, importance and management

A double-blind, randomised, crossover study in 12 healthy subjects given oral alcohol 0.8 g/kg with intravenous levosimendan 1 mg found no clinically significant pharmacokinetic or pharmacodynamic interactions.[1] There therefore seems no reason to avoid the use of levosimendan in patients that have recently consumed alcohol.

1. Antila S, Järvinen A, Akkila J, Honkanen T, Karlsson M, Lehtonen L. Studies on psychomotoric effects and pharmacokinetic interactions of the new calcium sensitizing drug levosimendan and ethanol. *Arzneimittelforschung* (1997) 47, 816–20.

Alcohol + Lithium

Some limited evidence suggests that the use of lithium carbonate with alcohol may make driving more hazardous.

Clinical evidence, mechanism, importance and management

In 9 out of 10 healthy subjects alcohol 0.5 g/kg raised the serum levels of a single 600-mg dose of lithium carbonate by 16%. Four subjects had at least a 25% increase in lithium levels. However these rises were not considered to be clinically important.[1] Two studies suggest that lithium does not affect blood-alcohol levels.[2,3]

In a study, 20 healthy subjects were given lithium carbonate (to achieve lithium serum levels of 0.75 mmol/L) and alcohol 0.5 g/kg, and undertook various psychomotor tests to assess any impairment of skills related to driving. Lithium carbonate alone prolonged reaction times and increased the inaccuracy of responses, whereas alcohol alone increased the number of mistakes in tests of co-ordination and attention; both drugs together were therefore considered to present extra risks than either drug alone.[2] In a placebo-controlled study, 35 alcoholic patients were given about 1.25 g/kg of alcohol after taking lithium for 14 days (mean serum lithium level of 0.89 mmol/L). Patients considered themselves to be less intoxicated when taking lithium with alcohol (compared with placebo) and there was an improvement in performance in 3 of the 6 cognitive tests used, but not in the tests of skills related to driving.[3]

Information is very limited but patients should be warned about the possible increased risk of driving or other potentially hazardous activities when taking both drugs.

1. Anton RF, Paladino JA, Morton A, Thomas RW. Effect of acute alcohol consumption on lithium kinetics. *Clin Pharmacol Ther* (1985) 38, 52–5.
2. Linnoila M, Saario I, Maki M. Effect of treatment with diazepam or lithium and alcohol on psychomotor skills related to driving. *Eur J Clin Pharmacol* (1974) 7, 337–42.
3. Judd LL, Huey LY. Lithium antagonizes ethanol intoxication in alcoholics. *Am J Psychiatry* (1984) 141, 1517–21.

Alcohol + Liv 52

***Liv 52,* an Ayurvedic herbal remedy, appears to reduce hangover symptoms after drinking, reducing blood-alcohol and acetaldehyde levels at 12 hours. However *Liv 52* also raises the**

blood-alcohol levels of moderate drinkers for the first few hours after drinking.

Clinical evidence

Nine healthy subjects who normally drank socially (alcohol 40 to 100 g weekly) took *Liv 52* two hours before drinking alcohol (four 60 mL doses of whiskey, equivalent to 90 g of alcohol). After taking 6 tablets of *Liv 52* their 1-hour blood-alcohol levels were increased by 15% (from 75 mg% to 86.2 mg%), and after taking 3 tablets of *Liv 52* daily for 2 weeks, their 1-hour blood-alcohol levels were raised by 27% (from 75 to 95.3 mg%).[1] Acetaldehyde levels in the blood and urine were markedly lowered at 12 hours, and hangover symptoms seemed to be reduced.[1] In a similar study, the blood-alcohol levels of 9 moderate drinkers were raised over the first 2 hours by about 28 to 44% after taking three tablets of *Liv 52* twice daily for two weeks, and by 17 to 19% over the following 2 hours.[2] Only a minor increase in blood-alcohol levels occurred in 8 occasional drinkers.[2]

Mechanism

Not understood. The *Liv 52* preparation in this study was said to contain the active principles from *Capparis spinosa*, *Cichorium intybus*, *Solanum nigrum*, *Cassia occidentalis*, *Terminalia arjuna*, *Achillea millefolium*, *Tamarix gallica* and *Phyllanthus amarus*.[1] These appear to increase the absorption of alcohol, or reduce its metabolism by the liver, thereby raising the blood-alcohol levels. It is suggested that the reduced hangover effects may possibly occur because it prevents the binding of acetaldehyde to cell proteins allowing a more rapid elimination.[1]

Importance and management

Direct pharmacokinetic evidence seems to be limited to these two studies.[1,2] *Liv 52* appears to reduce the hangover effects after drinking, but at the same time it can significantly increase the blood-alcohol levels of moderate drinkers for the first few hours after drinking. Increases of up to 30% may be enough to raise blood-alcohol levels from legal to illegal, when driving. Moderate drinkers should be warned. Occasional drinkers appear to develop higher blood-alcohol levels than moderate drinkers but *Liv 52* does not seem to increase them significantly.[2]

1. Chauhan BL, Kulkarni RD. Alcohol hangover and Liv.52. *Eur J Clin Pharmacol* (1991) 40, 187–8.
2. Chauhan BL, Kulkarni RD. Effect of Liv.52, a herbal preparation, on absorption and metabolism of ethanol in humans. *Eur J Clin Pharmacol* (1991) 40, 189–91.

Alcohol + Mecamylamine

Mecamylamine appears to reduce some of the effects of alcohol, without affecting alcohol levels.

Clinical evidence, mechanism, importance and management

In a crossover study in 22 healthy subjects, a single 7.5- to 12.5-mg dose of mecamylamine reduced the levels of alcohol (0.7 or 0.8 g/kg) by about 14% (estimated from graph), and reduced the pleasurable and stimulant effects of alcohol.[1] A placebo-controlled study in 27 healthy subjects given a single 7.5- or 15-mg dose of mecamylamine with alcohol 0.8 g/kg found that none of the physiological effects of mecamylamine or alcohol, or blood-alcohol levels, were affected by concurrent use. Mecamylamine reduced the stimulant effects of alcohol and reduced the desire for more alcohol; this effect appeared greater in men.[2]

These studies suggest that mecamylamine may safely be given with alcohol; however, the manufacturer of mecamylamine warns that alcohol may enhance its hypotensive effect,[3] an effect common to many antihypertensive drugs, see 'Alcohol + Antihypertensives', p.51.

1. Blomqvist O, Hernandez-Avila CA, Van Kirk J, Rose JE, Kranzler HR. Mecamylamine modifies the pharmacokinetics and reinforcing effects of alcohol. *Alcohol Clin Exp Res* (2002) 26, 326–31.
2. Chi H, de Wit H. Mecamylamine attenuates the subjective stimulant-like effects of alcohol in social drinkers. *Alcohol Clin Exp Res* (2003) 27, 780–86.
3. Inversine (Mecamylamine). Targacept, Inc. US Prescribing information, July 2002.

Alcohol + Mefloquine

Mefloquine does not normally appear to interact with alcohol, although excessive alcohol intake may possibly contribute to its adverse effects on the liver. An isolated report describes two incidents of severe psychosis and depression when a man taking mefloquine drank large quantities of alcohol.

Clinical evidence, mechanism, importance and management

Mefloquine 250 mg or placebo was given to two groups of 20 healthy subjects on three occasions, each time the day before they drank enough alcohol to achieve blood levels of about 35 mg%. Mefloquine did not affect blood-alcohol levels, nor did it increase the effects of alcohol on two real-highway driving tests, or on psychomotor tests done in the laboratory. In fact, the mefloquine group actually drove better than the placebo group.[1]

A 40-year-old man with no previous psychiatric history, taking mefloquine 250 mg weekly for malaria prophylaxis, had no problems with the first 2 doses. However, on two separate occasions when taking the third and fourth doses he also drank about half a litre of whisky, whereupon he developed severe paranoid delusions, hallucinations and became suicidal. When he stopped drinking he had no further problems while taking subsequent doses of mefloquine. He was used to drinking large amounts of alcohol and had experienced no problems while previously taking proguanil and chloroquine.[2]

The broad picture is that mefloquine appears not to worsen the psychomotor effects of moderate amounts of alcohol. Just why an unusual toxic reaction developed in one individual is not known, although mefloquine alone can increase the risk of psychiatric events.[3,4] It has been suggested that many of the adverse effects of mefloquine are associated with liver damage, and concurrent insults to the liver, such as from alcohol and dehydration, may be related to the development of severe or prolonged adverse reactions to mefloquine. In a review of 516 published case reports of mefloquine adverse effects, 11 cited alcohol as a possible contributing factor.[4] It was suggested that travellers taking mefloquine should avoid alcohol, particularly within 24 hours of their weekly mefloquine dose.[4] However, the manufacturers have not issued such a warning.[5,6] More study is needed.

1. Vuurman EFPM, Muntjewerff ND, Uiterwijk MMC, van Veggel LMA, Crevoisier C, Haglund L, Kinzig M, O'Hanlon JF. Effects of mefloquine alone and with alcohol on psychomotor and driving performance. *Eur J Clin Pharmacol* (1996) 50, 475–82.
2. Wittes RC, Saginur R. Adverse reaction to mefloquine associated with ethanol ingestion. *Can Med Assoc J* (1995) 152, 515–17.
3. van Riemsdijk MM, Sturkenboom MCJM, Pepplinkhuizen L, Stricker BHC. Mefloquine increases the risk of serious psychiatric events during travel abroad: a nationwide case-control study in the Netherlands. *J Clin Psychiatry* (2005) 66, 199–204.
4. Croft AM, Herxheimer A. Hypothesis: Adverse effects of the antimalaria drug, mefloquine: due to primary liver damage with secondary thyroid involvement? *BMC Public Health* (2002) 2:6.
5. Lariam (Mefloquine hydrochloride). Roche Products Ltd. UK Summary of product characteristics, August 2009.
6. Lariam (Mefloquine hydrochloride). Roche Pharmaceuticals. US Prescribing information, September 2008.

Alcohol + Meprobamate

The intoxicant effects of alcohol can be considerably increased by the presence of meprobamate. Driving or handling other potentially dangerous machinery is made much more hazardous.

Clinical evidence

A study in 22 subjects, given meprobamate 400 mg four times daily for one week, found that with blood-alcohol levels of 50 mg% the performance of a number of coordination and judgement tests was much more impaired than with either drug alone.[1] Four of the subjects were quite obviously drunk while taking both meprobamate and alcohol, and showed marked incoordination and social disinhibition. Two could not walk without assistance. The authors say this effect was much greater than anything seen with alcohol alone.

Other studies confirm this interaction, although the effects appeared to be less pronounced.[2-6]

Mechanism

Both meprobamate and alcohol are CNS depressants, which appear to have additive effects. There is also some evidence that alcohol may inhibit or increase meprobamate metabolism, depending on whether it is taken acutely or chronically, but the contribution of this to the enhanced CNS depression is uncertain.[7,8] Meprobamate does not appear to increase blood-alcohol levels.[5]

Importance and management

A well-documented and potentially serious interaction. Normal daily dosages of meprobamate in association with relatively moderate blood-alcohol levels, well within the UK legal limit for driving, can result in obviously hazardous intoxication. Patients should be warned; the patient information leaflet for meprobamate says that alcohol should be avoided.[9]

1. Zirkle GA, McAtee OB, King PD, Van Dyke R. Meprobamate and small amounts of alcohol: effects on human ability, coordination, and judgement. *JAMA* (1960) 173, 1823–5.
2. Reisby N, Theilgaard A. The interaction of alcohol and meprobamate in man. *Acta Psychiatr Scand* (1969) 208 (Suppl), 5–204.
3. Forney RB, Hughes FW. Meprobamate, ethanol or meprobamate-ethanol combinations on performance of human subjects under delayed audiofeedback (DAF). *J Psychol* (1964) 57, 431–6.
4. Ashford JR, Cobby JM. Drug interactions. The effects of alcohol and meprobamate applied singly and jointly in human subjects. III. The concentrations of alcohol and meprobamate in the blood and their effects on performance; application of mathematical models. *J Stud Alcohol* (1975) (Suppl 7), 140–61.
5. Cobby JM, Ashford JR. Drug interactions. The effects of alcohol and meprobamate applied singly and jointly in human subjects. IV. The concentrations of alcohol and meprobamate in the blood. *J Stud Alcohol* (1975) (Suppl 7), 162–76.
6. Ashford JR, Carpenter JA. Drug interactions. The effect of alcohol and meprobamate applied singly and jointly in human subjects. V. Summary and conclusions. *J Stud Alcohol* (1975) (Suppl 7), 177–87.
7. Misra PS, Lefèvre A, Ishii H, Rubin E, Lieber CS. Increase of ethanol, meprobamate and pentobarbital metabolism after chronic ethanol administration in man and in rats. *Am J Med* (1971) 51, 346–51.
8. Rubin E, Gang H, Misra PS, Lieber CS. Inhibition of drug metabolism by acute ethanol intoxication: a hepatic microsomal mechanism. *Am J Med* (1970) 49, 801–6.
9. Meprobamate. Genus Pharmaceuticals. UK Patient information leaflet, September 2004.

Alcohol + Methaqualone

The CNS depressant effects of alcohol and its detrimental effects on the skills relating to driving or handling other potentially dangerous machinery are increased by the concurrent use of methaqualone with or without diphenhydramine.

Clinical evidence

(a) Methaqualone

A retrospective study of drivers arrested for driving under the influence of drugs and/or alcohol found that, generally speaking, those with blood methaqualone levels of 1 mg/L or less had no symptoms of sedation, whereas those with levels above 2 mg/L demonstrated staggering gait, drowsiness, incoherence and slurred speech. These effects were increased if the drivers had also been drinking alcohol. The authors state that the levels of methaqualone needed for driving skills to become impaired are considerably lowered by alcohol, but no precise measure of this is presented in the paper.[1]

(b) Methaqualone with diphenhydramine

A double-blind study in 12 healthy subjects given two *Mandrax* tablets (methaqualone 250 mg with diphenhydramine 25 mg) showed that the resulting sedation and reduction in cognitive skills were enhanced by alcohol 0.5 g/kg. Residual amounts of a single dose of *Mandrax* continued to interact for as long as 72 hours. Methaqualone blood levels are also raised by regular moderate amounts of alcohol.[2] Similar effects on sedation were seen in another study.[3]

Mechanism

Alcohol, methaqualone and 'diphenhydramine', (p.50), are all CNS depressants, the effects of which are additive. A hangover can occur because the elimination half-life of methaqualone is long (10 to 40 hours).

Importance and management

An established interaction of importance. Those taking either methaqualone or methaqualone with diphenhydramine should be warned that handling machinery, driving a car, or any other task requiring alertness and full coordination, will be made more difficult and hazardous if they drink alcohol. Levels of alcohol below the legal driving limit with normal amounts of methaqualone may cause considerable sedation. Patients should also be told that a significant interaction may possibly occur the following day, because methaqualone has a long half-life.

Note that methaqualone has been withdrawn from the market in many countries because of problems of abuse.

1. McCurdy HH, Solomons ET, Holbrook JM. Incidence of methaqualone in driving-under-the-influence (DUI) cases in the State of Georgia. *J Anal Toxicol* (1981) 5, 270–4.
2. Roden S, Harvey P, Mitchard M. The effect of ethanol on residual plasma methaqualone concentrations and behaviour in volunteers who have taken Mandrax. *Br J Clin Pharmacol* (1977) 4, 245–7.
3. Saario I, Linnoila M. Effect of subacute treatment with hypnotics, alone or in combination with alcohol, on psychomotor skills related to driving. *Acta Pharmacol Toxicol (Copenh)* (1976) 38, 382–92.

Alcohol + Methotrexate

There is some inconclusive evidence that the consumption of alcohol may increase the risk of methotrexate-induced hepatic cirrhosis and fibrosis.

Clinical evidence, mechanism, importance and management

It has been claimed that alcohol can increase the hepatotoxic effects of methotrexate.[1] Two reports of patients treated for psoriasis indicate that this may be so. In one, 3 out of 5 patients with methotrexate-induced cirrhosis were reported to have taken alcohol concurrently (2 patients greater than 85 g of alcohol per week, one patient 25 to 85 g of alcohol per week):[2] in the other, the subject was known to drink excessively.[3] The evidence is by no means conclusive and no direct causal relationship has been established. However, one manufacturer of methotrexate advises the avoidance of drugs, including alcohol, which have hepatotoxic potential,[4] and another contraindicates the use of methotrexate in patients with alcoholism or alcoholic liver disease.[5]

1. Almeyda J, Barnardo D, Baker H. Drug reactions XV. Methotrexate, psoriasis and the liver. *Br J Dermatol* (1971) 85, 302–5.
2. Tobias H, Auerbach R. Hepatotoxicity of long-term methotrexate therapy for psoriasis. *Arch Intern Med* (1973) 132, 391–400.
3. Pai SH, Werthamer S, Zak FG. Severe liver damage caused by treatment of psoriasis with methotrexate. *N Y State J Med* (1973) 73, 2585–7.
4. Methotrexate Tablets. Hospira UK Ltd. UK Summary of product characteristics, January 2005.
5. Rheumatrex (Methotrexate sodium). Stada Pharmaceuticals Inc. US Prescribing information, October 2003.

Alcohol + Methylphenidate

Alcohol may increase methylphenidate levels and exacerbate some of its CNS effects.

Clinical evidence, mechanism, importance and management

In 17 subjects who had taken methylphenidate orally or intranasally with alcohol on at least 10 separate occasions, the primary reason for concurrent use was given as an alteration in psychotropic effects with increased euphoria and energy and a diminished sense of drunkenness. In addition, a minority of subjects also reported occasionally experiencing unpleasant adverse effects such as increased nausea (3 subjects), insomnia (2), and jaw clenching (1).[1] In a study in 20 subjects, alcohol 0.6 g/kg was given either 30 minutes before or 30 minutes after a single 0.3-mg/kg dose of methylphenidate. Alcohol significantly increased the AUC and maximum serum levels of methylphenidate, regardless of the timing of administration, by about 25% and 40%, respectively.[2]

Methylphenidate has a short half-life mainly due to conversion to the inactive metabolite ritalinic acid, but the concurrent use of alcohol and methylphenidate has been reported to result in production of a minor metabolite, ethylphenidate, which has CNS activity.[3,4] However, a more recent study found that the ethylphenidate formed is predominantly of the inactive enantiomer, so is unlikely to contribute to the additive CNS effects of alcohol and methylphenidate.[2]

The UK manufacturer of methylphenidate advises that alcohol may exacerbate the CNS effects of methylphenidate and therefore recommends that alcohol should be avoided during treatment.[5] In addition, methylphenidate should be given cautiously to patients with a history of drug dependence or alcoholism because of its potential for abuse.[1,5,6]

1. Barrett SP, Pihl RO. Oral methylphenidate-alcohol co-abuse. *J Clin Psychopharmacol* (2002) 22, 633–4.

2. Patrick KS, Straughn AB, Minhinnett RR, Yeatts SD, Herrin AE, DeVane CL, Malcolm R, Janis GC, Markowitz JS. Influence of ethanol and gender on methylphenidate pharmacokinetics and pharmacodynamics. *Clin Pharmacol Ther* (2007) 81, 346–53.
3. Markowitz JS, DeVane CL, Boulton DW, Nahas Z, Risch SC, Diamond F, Patrick KS. Ethylphenidate formation in human subjects after the administration of a single dose of methylphenidate and ethanol. *Drug Metab Dispos* (2000) 28, 620–4.
4. Markowitz JS, Logan BK, Diamond F, Patrick KS. Detection of the novel metabolite ethylphenidate after methylphenidate overdose with alcohol coingestion. *J Clin Psychopharmacol* (1999) 19, 362–6.
5. Ritalin (Methylphenidate hydrochloride). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, June 2007.
6. Ritalin (Methylphenidate hydrochloride). Novartis. US Prescribing information, April 2009.

Alcohol + Metoclopramide

There is some evidence that metoclopramide can increase the rate of alcohol absorption, raise maximum blood-alcohol levels, and possibly increase alcohol-related sedation.

Clinical evidence, mechanism, importance and management

A study in 7 subjects found that 20 mg of intravenous metoclopramide increased the rate of alcohol absorption, and the peak blood-alcohol levels were raised from 55 mg% to 86 mg%.[1] Increases in blood-alcohol levels were also seen in 2 healthy subjects[1] and in a small study[2] in which metoclopramide was given orally.[1] Another study in 7 healthy subjects found that 10 mg of intravenous metoclopramide accelerated the rate of absorption of alcohol 70 mg/kg given orally, and increased its peak levels, but not to a statistically significant extent. Blood-alcohol levels remained below 12 mg%. More importantly the sedative effects of the alcohol were increased.[3] The reasons for this effect are not fully understood, but it appears to be related to an increase in gastric emptying. These studies were done to find out more about intestinal absorption mechanisms rather than to identify daily practicalities, so the importance of their findings is uncertain. However, it seems possible that the effects of alcohol will be increased by metoclopramide. Note that metoclopramide alone can sometimes cause drowsiness, and if affected, patients should not drive or operate machinery.

1. Gibbons DO, Lant AF. Effects of intravenous and oral propantheline and metoclopramide on ethanol absorption. *Clin Pharmacol Ther* (1975) 17, 578–84.
2. Oneta CM, Simanowski UA, Martinez M, Allali-Hassani A, Parés X, Homann N, Conradt C, Waldherr R, Fiehn W, Coutelle C, Seitz HK. First pass metabolism of ethanol Is strikingly influenced by the speed of gastric emptying. *Gut* (1998) 43, 612–19.
3. Bateman DN, Kahn C, Mashiter K, Davies DS. Pharmacokinetic and concentration-effect studies with intravenous metoclopramide. *Br J Clin Pharmacol* (1978) 6, 401–7.

Alcohol + Metronidazole and related drugs

A number of patients taking oral metronidazole have developed a disulfiram-like reaction after drinking alcohol. There is one report of its occurrence when metronidazole was applied as a vaginal insert, and another when metronidazole was given intravenously. Some clinical studies have not confirmed the interaction, and its existence is disputed in some reports. The interaction is alleged to occur with all other 5-nitroimidazoles (e.g. tinidazole).

Clinical evidence

A man who had been in a drunken stupor for 3 days was given two metronidazole tablets (a total of 500 mg) one hour apart by his wife in the belief that they might sober him up. Twenty minutes after the first tablet he was awake and complaining that he had been given disulfiram (which he had taken some months before). Immediately after the second tablet, he took another drink and developed a classic disulfiram-like reaction with flushing of the face and neck, nausea and epigastric discomfort.[1] Other individual cases have been reported,[2] including a reaction with a metronidazole vaginal insert.[3]

In a test of the value of metronidazole 250 mg twice daily as a possible drink-deterrent, all 10 alcoholic patients studied experienced some disulfiram-like reactions of varying intensity (facial flushing, headaches, sensation of heat, fall in blood pressure, vomiting) when given alcohol.[4] In another study in 60 alcoholic patients, given metronidazole 250 to 750 mg daily, most developed mild to moderate disulfiram-like reactions during an alcohol tolerance test.[5] A lower incidence of this reaction, between 2 and 24%, has also been reported.[6-8]

Pharmaceutical preparations containing alcohol have also been implicated. A 2-year-old child became flushed and dyspnoeic when metronidazole was given with both *Stopayne* syrup (an analgesic/sedative combination) and a phenobarbital syrup, both of which contained alcohol.[9] Another reaction has been seen in a patient receiving intravenous metronidazole and a co-trimoxazole preparation containing alcohol 10%.[10] A further patient who had just finished a 7-day course of metronidazole developed severe, prolonged nausea and vomiting postpartum: she had received a single 800-mg dose of prophylactic clindamycin intravenously before the birth and it was thought that the benzyl alcohol present in the clindamycin preparation could have caused the reaction. However, other factors such as intrathecal anaesthesia may have also contributed to the adverse effects.[11] For mention of other preparations containing alcohol, see 'Alcohol + Disulfiram', p.66.

An interaction has also been reported in association with metabolic acidosis in an intoxicated man 4 hours after he was given intravenous metronidazole as prophylaxis following injury.[12] A fatality occurred in a frail 31-year old woman, which was attributed to cardiac arrhythmias caused by acetaldehyde toxicity resulting from the interaction between alcohol and metronidazole, linked to autonomic distress caused by a physical assault.[13] Alcohol is also said to taste unpleasant[1,4] or to be less pleasurable[8] while taking metronidazole. Some drug abusers apparently exploit the reaction for 'kicks'.[14]

In contrast, a study in 207 patients with inflammatory bowel disease, assessed using a phone survey, the presence of adverse reactions to alcohol in patients taking chronic metronidazole and/or mercaptopurine or neither drug; all of the patients consumed less than 4 alcoholic beverages per day. There was a trend towards more adverse effects in both the metronidazole and mercaptopurine study groups, but no statistically significant interaction between alcohol and metronidazole was found.[15] There are other reports, including two well-controlled studies, showing that metronidazole has no disulfiram-like effects.[16-18]

Mechanism

Not understood. In the disulfiram reaction, the accumulation of acetaldehyde appears to be responsible for most of the symptoms, see *Mechanism*, under 'Alcohol + Disulfiram', p.66. Some workers have reported an increase in acetaldehyde levels due to the interaction between metronidazole and alcohol,[13] but others have reported no effect[18] or a reduction in plasma acetaldehyde levels.[19] Furthermore, some studies with metronidazole indicate a lack of a disulfiram-like reaction,[16,17] and it has been suggested that if such a reaction does occur it may be by a mechanism other than the inhibition of hepatic acetaldehyde dehydrogenase.[18] It appears that metronidazole, like disulfiram, can inhibit other enzymes related to alcohol metabolism including xanthine oxidase and alcohol dehydrogenase.[20,21] Inhibition of xanthine oxidase may cause noradrenaline excess, and inhibition of alcohol dehydrogenase can lead to activation of microsomal enzyme oxidative pathways that generate ketones and lactate, which could produce acidosis.[12]

Importance and management

A reasonably well studied interaction, but it remains a controversial issue. The incidence is variously reported as between 0 and 100%, with more recent reports disputing its existence.[18,19] Nevertheless because of the uncertainty, all patients given metronidazole should be warned about what may happen if they drink alcohol. The manufacturers recommend avoiding alcohol when metronidazole is taken, and for at least 48 hours after it has been stopped (UK) or 24 hours after it has been stopped (US).[22,23] In the US, for the capsules, and extended-release preparation, 72 hours is recommended.[24,25] However, the authors of one report suggest a cautious trial of alcohol in patients that are starting and will be taking metronidazole on a chronic basis.[15]

The reaction, when it occurs, normally seems to be more unpleasant and possibly frightening than serious, and usually requires no treatment, although one report describes a serious reaction when intravenous metronidazole was given to an intoxicated man,[12] and one possible fatality has been reported.[13] The risk of a reaction with metronidazole used intravaginally seems to be small because the absorption is low (about 20% compared with about 100% orally), but evidently it can happen, even if only rarely.[3] Patients should be warned. It has been alleged that the disulfiram-like reaction with alcohol occurs with all of the related 5-nitroimidazoles,[26,27] but there do not appear to be any published reports of it occurring with **nimorazole**, **ornidazole**, **secnidazole** or **tinidazole**. The

manufacturer of **tinidazole** notes that, as with related compounds, there is a possibility of a disulfiram-like reaction with alcoholic beverages, and recommends that alcohol should be avoided until 72 hours after discontinuing tinidazole.[28]

1. Taylor JAT. Metronidazole—a new agent for combined somatic and psychic therapy for alcoholism: a case study and preliminary report. *Bull Los Angel Neuro Soc* (1964) 29, 158–62.
2. Alexander I. 'Alcohol—Antabuse' syndrome in patients receiving metronidazole during gynaecological treatment. *Br J Clin Pract* (1985) 39, 292–3.
3. Plosker GL. Possible interaction between ethanol and vaginally administered metronidazole. *Clin Pharm* (1987) 6, 189 and 192–3.
4. Ban TA, Lehmann HE, Roy P. Rapport préliminaire sur l'effect thérapeutique du Flagyl dans l'alcoolisme. *Union Med Can* (1966) 95, 147–9.
5. Sansoy OM. Evaluation of metronidazole in the treatment of alcoholism. A comprehensive three-year study comprising 60 cases. *Rocky Mtn Med J* (1970) 67, 43–7.
6. de Mattos H. Relações entre o alcoolismo e aparelho digestivo. Experiência com metronidazol. *Hospital (Rio J)* (1968) 74, 1669–76.
7. Channabasavanna SM, Kaliaperumal VG, Mathew G, Itty A. Metronidazole in the treatment of alcoholism: a controlled trial. *Indian J Psychiatry* (1979) 21, 90–3.
8. Penick SB, Carrier RN, Sheldon JB. Metronidazole in the treatment of alcoholism. *Am J Psychiatry* (1969) 125, 1063–6.
9. Tunguy-Desmarais GP. Interaction between alcohol and metronidazole. *S Afr Med J* (1983) 63, 836.
10. Edwards DL, Fink PC, Van Dyke PO. Disulfiram-like reaction associated with intravenous trimethoprim–sulfamethoxazole and metronidazole. *Clin Pharm* (1986) 5, 999–1000.
11. Krulewitch CJ. An unexpected adverse drug effect. *J Midwifery Womens Health* (2003) 48, 67–8.
12. Harries DP, Teale KFH, Sunderland G. Metronidazole and alcohol: potential problems. *Scott Med J* (1990) 35, 179–180.
13. Cina SJ, Russell RA, Conradi SE. Sudden death due to metronidazole/ethanol interaction. *Am J Forensic Med Pathol* (1996) 17, 343–6.
14. Giannini AJ, DeFrance DT. Metronidazole and alcohol—potential for combinative abuse. *J Toxicol Clin Toxicol* (1983) 20, 509–15.
15. Ginzburg L, Present DH. Alcohol is well tolerated in IBD patients taking either metronidazole or 6-mercaptopurine. *Am J Gastroenterol* (2003) 98 (Suppl), S241.
16. Goodwin DW. Metronidazole in the treatment of alcoholism: a negative report. *Am J Psychiatry* (1967) 123, 1276–8.
17. Gelder MG, Edwards G. Metronidazole in the treatment of alcohol addiction: a controlled trial. *Br J Psychiatry* (1968) 114, 473–5.
18. Visapää J-P, Tillonen JS, Kaihovaara PS, Salaspuro MP. Lack of disulfiram-like reaction with metronidazole and ethanol. *Ann Pharmacother* (2002) 36, 971–4.
19. Williams CS, Woodcock KR. Do ethanol and metronidazole interact to produce a disulfiram-like reaction? *Ann Pharmacother* (2000) 34, 255–7.
20. Fried R, Fried LW. The effect of Flagyl on xanthine oxidase and alcohol dehydrogenase. *Biochem Pharmacol* (1966) 15, 1890–4.
21. Gupta NK, Woodley CL, Fried R. Effect of metronidazole on liver alcohol dehydrogenase. *Biochem Pharmacol* (1970) 19, 2805–8.
22. Flagyl Tablets (Metronidazole). Winthrop Pharmaceuticals UK Ltd. UK Summary of product characteristics, August 2008.
23. Flagyl (Metronidazole). Pfizer Inc. US Prescribing information, August 2006.
24. Flagyl 375 (Metronidazole). Pfizer Inc. US Prescribing information, August 2006.
25. Flagyl ER (Metronidazole). Pfizer Inc. US Prescribing information, August 2006.
26. Ralph ED. Nitroimidazoles. In: Koren G, Prober CG, Gold R, eds. Antimicrobial therapy in infants and children. New York: Marcel Dekker; 1988 p. 729–45.
27. Andersson KE. Pharmacokinetics of nitroimidazoles. Spectrum of adverse reactions. *Scand J Infect Dis* (1981) 26 (Suppl), 60–7.
28. Fasigyn (Tinidazole). Pfizer Ltd. UK Summary of product characteristics, July 2005.

Alcohol + Mirtazapine

The sedative effects of mirtazapine may be increased by alcohol.

Clinical evidence, mechanism, importance and management

In 6 healthy subjects alcohol (equivalent to 60 g) had a minimal effect on plasma levels of mirtazapine 15 mg.[1] However the sedation and CNS impairment seen with mirtazapine is additive with that produced by alcohol, and the manufacturers recommend avoiding concurrent use.[1,2] Mirtazapine does not affect the absorption of alcohol.[3]

1. Remeron (Mirtazapine). Schering-Plough. US Prescribing information, March 2009.
2. Zispin (Mirtazapine). Organon Laboratories Ltd. UK Summary of product characteristics, February 2009.
3. Sitsen JMA, Zivkov M. Mirtazapine: clinical profile. *CNS Drugs* (1995) 4 (Suppl 1), 39–48.

Alcohol + Muscle relaxants

Three reported cases of modest overdosage with methocarbamol and alcohol resulted in death due to combined CNS depression. Concurrent use of small or moderate amounts of alcohol with muscle relaxants may increase drowsiness and reduce alertness.

Clinical evidence, mechanism, importance and management

(a) Baclofen

The manufacturer of baclofen warns that it may enhance the sedative effect of alcohol.[1] However, tolerance to the sedative effect of baclofen has been reported in alcohol-addicted patients after a period of abstinence, as well as after a relapse.[2]

(b) Dantrolene

The manufacturer of dantrolene advises caution if it is given with alcohol[3] and the patient information leaflet suggests that alcohol should be avoided because it may increase drowsiness.[4]

(c) Methocarbamol

Fatal cerebral anoxia produced by CNS respiratory depression occurred in a 31-year-old man after he took significant amounts of methocarbamol and alcohol. Two other lethal overdoses have been reported with these 2 drugs. In all 3 cases the methocarbamol doses exceeded the recommended daily dosages, but were estimated to be less than the reported maximum tolerated single dose of 12 g. Acute alcohol intoxication combined with methocarbamol usage can lead to combined CNS depression, which may be sufficient to cause death.[5] The manufacturers of methocarbamol warn that it may potentiate the effects of alcohol[6,7] and the patient information leaflet suggests that patients taking methocarbamol should avoid alcohol.[8]

(d) Other muscle relaxants

For enhanced CNS effects with alcohol with other muscle relaxants, see 'benzodiazepines', (p.56), 'meprobamate', (p.74), and 'tizanidine', (p.1573).

1. Lioresal Tablets (Baclofen). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, July 2009.
2. Addolorato G, Leggio L, Abenavoli L, Caputo F, Gasbarrini G. Tolerance to baclofen's sedative effect in alcohol-addicted patients: no dissipation after a period of abstinence. *Psychopharmacology (Berl)* (2005) 178, 351–2.
3. Dantrium Capsules (Dantrolene sodium). SpePharm UK Ltd. UK Summary of product characteristics, September 2008.
4. Dantrium (Dantrolene sodium). SpePharm UK Ltd. UK Patient information leaflet, September 2008.
5. Ferslew KE, Hagardorn AN, McCormick WF. A fatal interaction of methocarbamol and ethanol in an accidental poisoning. *J Forensic Sci* (1990) 35, 477–82.
6. Robaxin (Methocarbamol). Shire Pharmaceuticals Ltd. UK Summary of product characteristics, October 2003.
7. Robaxin (Methocarbamol). Schwarz Pharma. US Prescribing information, March 2008.
8. Robaxin (Methocarbamol). Shire Pharmaceuticals Ltd. UK Patient information leaflet, December 2007.

Alcohol + Nefazodone

In one study nefazodone 400 mg was found not to increase the sedative-hypnotic effects of alcohol.[1]

1. Frewer LJ, Lader M. The effects of nefazodone, imipramine and placebo, alone and combined with alcohol, in normal subjects. *Int Clin Psychopharmacol* (1993) 8, 13–20.

Alcohol + Niclosamide

Alcohol may possibly increase the adverse effects of niclosamide.

Clinical evidence, mechanism, importance and management

The manufacturer of niclosamide advises avoiding alcohol while taking niclosamide. The reasoning behind this is that while niclosamide is virtually insoluble in water, it is slightly soluble in alcohol. Therefore taking niclosamide with alcohol might possibly increase its absorption by the gut, resulting in an increase in its adverse effects. There are no formal reports of this but the manufacturer says that they have some anecdotal information that is consistent with this suggestion.[1]

1. Bayer. Personal communication, July 1992.

Alcohol + Nicotine

Nicotine (as a patch) may possibly enhance the effect of alcohol on heart rate and reduce the time to peak alcohol levels. The concurrent use of alcohol and a nicotine nasal spray did not affect the pharmacokinetics of either drug.

Clinical evidence, mechanism, importance and management

A placebo-controlled study in 12 otherwise healthy tobacco smokers found that alcohol-induced increases in heart rate were enhanced by pre-

treatment with a 21-mg nicotine transdermal patch. The time to peak alcohol levels with a 0.4 g/kg dose of ethanol was faster with nicotine pretreatment (43 minutes) compared with 52 minutes in the absence of nicotine; however, this effect was not seen with a 0.7 g/kg dose of alcohol.[1] Another study in 12 otherwise healthy tobacco smokers found that although alcohol 0.4 or 0.8 g/kg (equivalent to approximately 2 or 4 drinks, respectively) influenced selected subjective responses and heart rate, pretreatment with alcohol did not affect the subjects responses to low-dose nicotine 3 to 20 micrograms/kg given as a nasal spray (20 microgram/kg dose is equivalent to about one-half of a cigarette). The concurrent use of nicotine and alcohol did not influence the blood levels of either drug.[2]

1. Kouri EM, McCarthy EM, Faust AH, Lukas SE. Pretreatment with transdermal nicotine enhances some of ethanol's acute effects in men. *Drug Alcohol Depend* (2004) 75, 55–65.
2. Perkins KA, Fonte C, Blakesley-Ball R, Stolinski A, Wilson AS. The influence of alcohol pretreatment on the discriminative stimulus, subjective, and relative reinforcing effects of nicotine. *Behav Pharmacol* (2005) 16, 521–9.

Alcohol + Nicotinic acid (Niacin)

An isolated report describes delirium and metabolic acidosis when a patient taking nicotinic acid for hypercholesterolaemia drank about one litre of wine. The manufacturers warn that the concurrent use of nicotinic acid and alcohol may result in an increase in adverse effects such as flushing and pruritus, and possibly liver toxicity.

Clinical evidence, mechanism, importance and management

An isolated report describes delirium and metabolic acidosis after a patient taking nicotinic acid 3 g daily for hypercholesterolaemia drank about one litre of wine. Delirium had occurred on a previous similar occasion after he drank a large quantity of beer while taking nicotinic acid. It is suggested that the nicotinic acid may have caused liver impairment, which was exacerbated by the large amount of alcohol. The patient did have some elevations in liver enzymes.[1] Acidosis has been associated with alcohol intoxication[2] (although the frequency of this association has been disputed[3]) and there has been a report of lactic acidosis associated with the use of high-dose (3 g daily) nicotinic acid,[4] and therefore a combined effect would seem possible. However, no general conclusions can be drawn from this single case.

Hepatic toxicity can occur with nicotinic acid and the manufacturers advise caution in patients who consume substantial quantities of alcohol. They also suggest the avoidance of alcohol around the same time as nicotinic acid is taken, as the adverse effects of flushing and pruritus may be increased.[5,6]

1. Schwab RA, Bachhuber BH. Delirium and lactic acidosis caused by ethanol and niacin coingestion. *Am J Emerg Med* (1991) 9, 363–5.
2. Zehtabchi S, Sinert R, Baron BJ, Paladino L, Yadav K. Does ethanol explain the acidosis commonly seen in ethanol-intoxicated patients? *Clin Toxicol* (2005) 43, 161–6.
3. Ginsburg BY, Porter R, Nelson LS. Is acidosis commonly seen in patients with elevated ethanol levels? *Clin Toxicol* (2006) 44, 193.
4. Earthman TP, Odom L, Mullins CA. Lactic acidosis associated with high-dose niacin therapy. *South Med J* (1991) 84, 496–7.
5. Niaspan (Nicotinic acid). Merck Serono. UK Summary of product characteristics, January 2006.
6. Niaspan (Niacin). Abbott Laboratories. US Prescribing information, September 2009.

Alcohol + Nitrofurantoin

There appears to be no good clinical evidence for an alleged interaction between alcohol and nitrofurantoin.

Clinical evidence, mechanism, importance and management

Despite claims in some books and reviews, an extensive literature search failed to find any experimental or clinical evidence for an alleged disulfiram-like reaction between alcohol and nitrofurantoin.[1] A study in healthy subjects failed to demonstrate any such interaction[2] and a survey of the reports in the manufacturer's database also failed to find good evidence for alcohol intolerance.[3] It is concluded that this 'interaction' is erroneous.[1]

1. Rowles B, Worthen DB. Clinical drug information: a case of misinformation. *N Engl J Med* (1982) 306, 113–4.
2. Miura K, Reckendorf HK. The nitrofurans. *Prog Med Chem* (1967) 5, 320–81.
3. D'Arcy PF. Nitrofurantoin. *Drug Intell Clin Pharm* (1985) 19, 540–7.

Alcohol + Nitrous oxide

In a double-blind study in 11 healthy subjects there were several instances when alcohol 0.25 to 5 g/kg (equivalent to 1 to 3 drinks) enhanced the effects of nitrous oxide 30% in oxygen, inhaled for 35 minutes. Some effects were seen with the drug combination, which were not seen with either drug alone; these included subjective effects and delayed free recall.[1] For mention of the effect of alcohol following anaesthesia, see 'Anaesthetics, general + Alcohol', p.102.

1. Zacny JP, Camarillo VM, Sadeghi P, Black M. Effects of ethanol and nitrous oxide, alone and in combination, on mood, psychomotor performance and pain reports in healthy volunteers. *Drug Alcohol Depend* (1998) 52, 115–23.

Alcohol + NSAIDs

Alcohol may increase the risk of gastrointestinal haemorrhage associated with NSAIDs. The skills related to driving are impaired by indometacin and phenylbutazone and this is made worse if patients drink alcohol while taking phenylbutazone, but this does not appear to occur with indometacin. A few isolated reports attribute acute renal failure to the concurrent use of NSAIDs and acute excessive alcohol consumption.

Clinical evidence, mechanism, importance and management

(a) Gastrointestinal complications

In healthy subjects the concurrent use of alcohol with **ibuprofen** 2.4 g over 24 hours increased the damaging effect of **ibuprofen** on the stomach wall, although this did not reach statistical significance.[1] A case-control study, involving 1224 patients admitted to hospital with upper gastrointestinal bleeding and 2945 controls, found that alcohol consumption was associated with a threefold increase in the incidence of acute upper gastrointestinal haemorrhage from light drinking (less than one alcoholic drink per week) to heavy drinking (21 alcoholic drinks or more per week). There was some evidence to suggest that the risk of upper gastrointestinal bleeding was increased by the concurrent use of **ibuprofen**.[2] Another case-control study suggested that the odds ratio for gastrointestinal complications in those regularly consuming more than 5 drinks during a drinking session was increased from 2.8 to 6 when an NSAID was also taken. This was also increased when compared with the use of an NSAID alone (odds ratio 3.8).[3] A third case-control study found that the use of prescription NSAIDs or non-prescription **naproxen** or **ibuprofen** in those with a history of alcohol abuse produced a risk ratio of adverse gastrointestinal effects that was greater than the expected additive risk. Both NSAID use and excessive alcohol consumption carry the risk of gastrointestinal adverse effects. This information suggests that NSAIDs should be used with caution in heavy drinkers.[4] The FDA in the US has ruled that non-prescription pain relievers and fever reducers containing **ibuprofen**, **ketoprofen**, or **naproxen** must carry a warning label advising people who consume moderate amounts of alcohol to consult their doctor before using these drugs, and that stomach bleeding may occur with these drugs.[5]

(b) Psychomotor skills and alcohol levels

A study in a large number of healthy subjects found that the performance of various psychomotor skills related to driving (choice reaction, coordination, divided attention tests) were impaired by single doses of **indometacin** 50 mg or **phenylbutazone** 200 mg. Alcohol 0.5 g/kg made things worse in those taking **phenylbutazone**, but the performance of those taking **indometacin** was improved to some extent.[6] The reasons are not understood. The study showed that the subjects were subjectively unaware of the adverse effects of **phenylbutazone**. Information is very limited, but patients should be warned if they intend to drive. In two studies, **ibuprofen** 800 mg had no significant effect on blood-alcohol levels of healthy subjects.[7,8]

The pharmacokinetics of alcohol 1 g/kg and the results of performance tests were found to be similar in subjects given **dipyrone** 1 g or a placebo.[9] No special precautions seem to be necessary.

(c) Renal complications

A normal healthy young woman with no history of renal disease developed acute renal failure after taking **ibuprofen** 400 mg the evening before, 400 mg the following morning, and then 375 mL of **rum** later in the day, followed by two further 400-mg tablets of **ibuprofen**.[10] Another similar case was reported in a 22-year-old woman who had taken **ibuprofen** 1.2 g the morning after binge drinking.[11] Both recovered.[10,11] A further case describes renal impairment in a young woman, which was associated with the use of **ketoprofen** 600 mg and binge drinking.[12] It is suggested that volume depletion caused by the alcohol (and compounded by vomiting) predisposed these patients to NSAID-induced renal toxicity.[11,12] The general importance of these isolated cases remains to be determined.

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Alcohol + Olanzapine

Postural hypotension and possibly drowsiness may be increased when alcohol is given with olanzapine.

Clinical evidence, mechanism, importance and management

The manufacturer says that patients taking olanzapine have shown an increased heart rate and accentuated postural hypotension when given a single-dose of alcohol.[1] In a study, 9 of 11 subjects experienced orthostatic hypotension when they drank alcohol one hour after taking olanzapine 10 mg.[2] No pharmacokinetic interaction has been seen.[1-3] In practical terms this means that patients should be warned of the risk of faintness and dizziness if they stand up quickly, and advised to sit or lie down if this occurs. The manufacturers also say that drowsiness is a common adverse effect of olanzapine, and they advise caution in patients taking other products that can cause CNS depression, including alcohol.[3,4]

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4. Zyprexa (Olanzapine). Eli Lilly and Company Ltd. UK Summary of product characteristics, July 2009.

Alcohol + Ondansetron

Ondansetron does not appear to affect the pharmacokinetics of alcohol, but may increase its subjective effects.

Clinical evidence, mechanism, importance and management

In a placebo-controlled study, 12 healthy subjects were given ondansetron 8 mg with an oral dose of alcohol (0.65 and 0.75 [g/kg] for women and men, respectively). It was found that ondansetron did not significantly alter the pharmacokinetics of alcohol or increase the objective measures of sedation that occurred in response to alcohol. However, *subjective* measures of impairment and intoxication caused by alcohol were increased by ondansetron.

It therefore seems unlikely that a particularly detrimental effect occurs if patients receiving ondansetron drink alcohol, but they may well feel more intoxicated.[1]

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Alcohol + Opioids

In general the opioid analgesics can enhance the CNS depressant effects of alcohol, which has been fatal in some cases: this appears to be a particular problem with dextropropoxyphene. This may be related to that fact that the bioavailability of dextropropoxyphene is increased by alcohol. Alcohol has been associated with rapid release of hydromorphone and morphine from extended-release preparations, which could result in potentially fatal doses. The acute use of alcohol and methadone appears to result in lower blood-alcohol levels.

Clinical evidence

(a) Buprenorphine

A study in 12 patients taking buprenorphine found that alcohol 14.7 g/70 kg produced a lower blood-alcohol level, when compared with a group of patients not taking buprenorphine (56 mg% compared with 40 mg%), but this was not statistically significant.[1] See also, *Methadone*, below.

(b) Codeine

Double-blind studies in a large number of professional army drivers found that 50 mg of codeine and alcohol 0.5 g/kg, both alone and together, impaired their ability to drive safely on a static driving simulator. The number of collisions, neglected instructions and the times they drove off the road were increased.[2,3] Alcohol does not appear to affect the pharmacokinetics of codeine.[4] See also, *Controlled-release opioids*, below.

(c) Dextropropoxyphene

In a study in 8 healthy subjects, alcohol alone (blood levels of 50 mg%) impaired the performance of various psychomotor tests (motor co-ordination, mental performance and stability of stance) more than dextropropoxyphene 65 mg alone. When given together there was some evidence that the effects were greater than with either drug alone, but in some instances the impairment was no greater than with alcohol alone. The effect of alcohol clearly predominated.[5] In contrast, other studies have found that dextropropoxyphene does not enhance the psychomotor impairment seen with alcohol,[6,7] but the bioavailability of the dextropropoxyphene has been reported to be raised by 25 to 31% by alcohol.[7,8] A retrospective study involving 332 fatal poisonings in Finland found that alcohol was present in 73% of cases involving dextropropoxyphene and, when alcohol was present, relatively small overdoses of dextropropoxyphene could result in fatal poisoning.[9] Further reports describe alcohol reducing the lethal dose of dextropropoxyphene.[10-12]

(d) Hydromorphone

A young man died from the combined cardiovascular and respiratory depressant effects of hydromorphone and alcohol.[13] He fell asleep, the serious nature of which was not recognised by those around him. Post-mortem analysis revealed alcohol and hydromorphone concentrations of 90 mg% and 100 nanograms/mL, respectively, neither of which is particularly excessive. A study in 9 healthy subjects found that pre-treatment with hydromorphone 1 or 2 mg did not significantly affect the subject-rated effects of alcohol 0.5 or 1 g/kg. However, hydromorphone enhanced the sedative scores of alcohol on the adjective rating scale.[14] See also, *Controlled-release opioids*, below.

(e) Methadone

A study in 21 opioid-dependent subjects who had been receiving methadone or **buprenorphine** for 3 months, and 21 matched non-drug-using controls, found that although alcohol (target blood-alcohol level around 50 mg%) resulted in decreased driving performance, there appeared to be no difference in simulated driving tests in the opioid-treated patients, when compared with controls. It was suggested that restrictions on opioids and driving are not necessary in stabilised patients receiving maintenance

buprenorphine or methadone treatment, but little is known about the effects in the initial treatment period. This study also found that blood-alcohol levels were lower in the opioid-treated patients, when compared with the controls, despite both groups receiving the same amount of alcohol.[15] A study in 14 patients taking methadone also found that alcohol 14.7 g/70 kg produced a lower blood-alcohol level, when compared with a group of patients not taking methadone (56 mg% compared with 40 mg%).[1]

However, clinical anecdotal reports have indicated that taking methadone with alcohol produces an additive and/or synergistic response,[16] which may result in serious respiratory depression and hypotension.[17]

(f) Controlled-release opioids

Pharmacokinetic data in healthy subjects has shown that consuming alcohol with a particular 24-hour extended-release formulation of **hydromorphone** *(Palladone XL Capsules; Purdue Pharma, USA)* could lead to rapid release (dose dumping) and absorption of a potentially fatal dose of hydromorphone.[18,19] Although no reports of serious problems had been received, the FDA in the US asked for the product to be withdrawn from the market.[20] Health Canada warned that this interaction might occur with other slow-release opioid analgesics.[21] However, the Canadian distributor of hydromorphone has commented that the controlled-release technology employed in *Palladone XL* is not the same as that of many other controlled-release opioid formulations. Dose-dumping with alcohol is said not to occur with:

- **morphine** sustained-release tablets: *MS Contin*,[22,23] *MST continus* suspension and tablets, *MXL* capsules,[23]
- **codeine** controlled-release tablets: *Codeine Contin*,[22,23]
- **dihydrocodeine** controlled-release tablets: *DHC Continus* tablets,[23]
- **hydromorphone** controlled-release capsules: *Hydromorph Contin*,[22] *Palladone SR*,[23]
- **oxycodone** controlled-release tablets: *OxyContin*,[22,23]
- **tramadol** (once daily and twice daily formulations).[23]

In contrast, in laboratory studies, an extended-release capsule preparation of **morphine** (*Avinza; King Pharmaceuticals, USA*) was found to release morphine earlier than expected when exposed to alcohol, and this effect increased dramatically with increasing alcohol concentration.[24,25] The product literature for *Avinza* now carries a warning to avoid alcohol, including medications containing alcohol, while taking this preparation.[25] Although most opioid preparations do not appear to interact with alcohol in this way, the concurrent use of alcohol and opioid analgesics is never advisable because of the potential for an interaction between CNS depressant drugs, see above.

Mechanism

Both opioids and alcohol are CNS depressants, and there may be enhanced suppression of the medullary respiratory control centre.[10-12] Acute administration of alcohol appears to increase methadone effects due to inhibition of hepatic microsomal enzymes, but chronic alcoholism reduces the AUC and half-life of methadone because cytochrome P450 isoenzymes are induced.[16]

Importance and management

The reports describing increased sedation and even fatalities emphasise the importance of warning patients about the potentially hazardous consequences of drinking while taking potent CNS depressants like the opioids. This seems to be a particular risk with dextropropoxyphene overdosage, and it has been suggested that a less dangerous alternative could be chosen when indications of alcohol abuse or suicide risk are present.[26] The US manufacturers recommend caution when prescribing dextropropoxyphene in patients who use alcohol in excess.[27] There is less information about therapeutic doses of dextropropoxyphene with moderate social drinking. In general it is suggested that alcohol intake should be avoided where possible, or limited in those taking opioids, but some manufacturers actually contraindicate alcohol. The objective evidence is that the interaction with moderate doses of alcohol and opioids is quite small (with the exception of the dose dumping effect). It would seem prudent to warn patients that opioids can cause drowsiness and this may be exaggerated to some extent by alcohol. They should be warned that driving or handling potentially hazardous machinery may be more risky, but total abstinence from alcohol does not seem to be necessary. Smaller doses, such as those available without a prescription, would be expected to have a smaller effect, but this does not appear to have been studied. One of the manufacturers of methadone contraindicates its use with all CNS depressants, including alcohol,[17] but this seems to pose almost unworkable restrictions on its use.

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Alcohol + Orlistat

A study in healthy subjects found that orlistat 120 mg three times daily for 6 days had no significant effect on the pharmacokinetics of alcohol.[1] There is nothing to suggest that alcohol should be avoided while taking orlistat.

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Alcohol + Paracetamol (Acetaminophen)

Many case reports describe severe liver damage, sometimes fatal, in some alcoholics and persistent heavy drinkers who take only moderate doses of paracetamol. However, other controlled studies have found no association between alcohol intake and paracetamol-induced hepatotoxicity. There is controversy about the use of paracetamol in alcoholics. Some consider standard therapeutic doses can be used, whereas others recommend the dose of paracetamol should be reduced, or paracetamol avoided. Occasional and light to moderate drinkers do not seem to be at any extra risk.

Clinical evidence

(a) Increased hepatotoxicity

Three chronic alcoholic patients developed severe liver damage after taking paracetamol. They had AST levels of about 7 000 to 10 000 units. Two of them had taken 10 g of paracetamol over 24 or 48 hours before admission (normal dosage is up to 4 g daily), and the third patient had taken about 50 g of paracetamol over 72 hours. One of them developed hepatic encephalopathy and died, and subsequent post-mortem revealed typical paracetamol toxicity. Two of them also developed renal failure.[1] A case of severe liver impairment has also been reported in a moderate social drinker who regularly drank 3 glasses of wine with dinner, but had stopped drinking alcohol whilst taking paracetamol for a viral infection.[2]

There are numerous other case reports of liver toxicity in alcoholics or chronic heavy alcohol users attributed to the concurrent use of alcohol and paracetamol. In the reports cited here, which include a total of about 30 patients, about one-third had been taking daily paracetamol doses of up to 4 g daily, and one-third had taken doses within the range 4 to 8 g daily.[3-19] Fasting possibly makes things worse.[20] A later survey reviewed a total of 94 cases from the literature, and described a further 67 patients who were regular users of alcohol, 64% of whom were alcoholics, who developed liver toxicity after taking paracetamol. In 60% of cases the paracetamol dose did not exceed 6 g daily and in 40% of cases the dose did not exceed 4 g daily. More than 90% of the patients developed AST levels ranging from 3 000 to 48 000 units.[21]

(b) No effect on hepatotoxicity

In a retrospective review of 553 cases of paracetamol-induced severe hepatotoxicity treated at a liver failure unit over a 7-year period, there was no association between the level of alcohol consumption and the severity of the hepatotoxicity (mean INR and serum creatinine levels in the first 7 days after overdose). Alcohol consumption was categorised into 4 groups ranging from non-drinkers to heavy drinkers (greater than 60 g of alcohol daily in men and 40 g daily in women).[22]

In a randomised, placebo-controlled study, there was no difference in measures of hepatotoxicity (mean AST levels, mean INR) between 102 alcoholic patients who received paracetamol 1 g four times daily for 2 days, and 99 alcoholic patients who received placebo. In this study, patients had entered an alcohol detoxification centre, and were given paracetamol immediately after stopping alcohol use[23] (the assumed time of greatest susceptibility, see *Mechanism*, below). A systematic review by the same research group concluded that the use of therapeutic doses of paracetamol in alcoholic patients is not associated with hepatic injury.[24]

(c) Effect on alcohol levels

Paracetamol 1 g was found to have no effect on the single-dose pharmacokinetics of alcohol in 12 healthy subjects.[25] Another study found that blood-alcohol levels were raised by 1 g of paracetamol but this was not statistically significant.[26]

Mechanism

Uncertain. The interaction between paracetamol and alcohol is complex, because acute and chronic alcohol consumption can have opposite effects.[27,28] Paracetamol is usually predominantly metabolised by the liver to non-toxic sulfate and glucuronide conjugates. Persistent heavy drinking appears to stimulate a normally minor biochemical pathway involving the cytochrome P450 isoenzyme CYP2E1, and possibly the CYP3A subfamily, which allows the production of unusually large amounts of highly hepatotoxic metabolites via oxidation.[20,28,29] Unless sufficient glutathione is present to detoxify these metabolites (alcoholics often have an inadequate intake of protein), they become covalently bound to liver macromolecules and damage results. Fasting may also make things worse by reducing the availability of glucose, and thus shifting paracetamol metabolism from glucuronidation towards microsomal oxidation.[20] However, most studies have failed to demonstrate an increase in hepatotoxic metabolites in alcoholics.[27,30] In fact alcoholics may possibly be most susceptible to toxicity during alcohol withdrawal because, while drinking, alcohol may possibly compete with the paracetamol for metabolism, and even inhibit it. Acute ingestion of alcohol by non-alcoholics may possibly protect them against damage because the damaging biochemical pathway is inhibited rather than stimulated. The relative timing of alcohol and paracetamol intake is therefore critical;[27] for example, a study in 10 healthy subjects found that ingestion of 500 mg of paracetamol 8 hours after an intravenous infusion of alcohol (roughly equivalent to a bottle of wine) resulted in an increased production of the toxic metabolite of paracetamol, *N*-acetyl-*p*-benzoquinoneimine (NABQI), when compared with dextrose 5%.[31]

Importance and management

The incidence of unexpected paracetamol toxicity in chronic alcoholics is uncertain, but possibly fairly small, bearing in mind the very wide-spread use of paracetamol and alcohol. Note that most of the evidence for an interaction comes from anecdotal case reports and case series, albeit in large numbers. However, the damage, when it occurs, can be serious and therefore some have advised that alcoholics and those who persistently drink heavily should avoid paracetamol or limit their intake considerably.[21] The normal daily recommended 'safe' maximum of 4 g is said to be too high in some alcoholics.[21] Because of this, the FDA in the US have required that all paracetamol-containing non-prescription products bear the warning that those consuming 3 or more alcoholic drinks every day should ask their doctor whether they should take paracetamol.[32] However, others consider that the evidence does not prove that there is an increase in paracetamol hepatotoxicity in alcoholics,[24,27] and is insufficient to support any change in paracetamol use or dose in alcoholics.[24,33] They note that the alternatives, aspirin and NSAIDs, are associated with a greater risk of gastrointestinal adverse effects in alcoholics,[24] see 'Alcohol + Aspirin or other Salicylates', p.54 and 'Alcohol + NSAIDs', p.78'. Further study is needed. The risk for non-alcoholics, moderate drinkers and those who very occasionally drink a lot appears to be low, although some chronic moderate social drinkers may be at risk, especially if alcohol intake is abruptly stopped.[34]

Note that chronic alcohol intake increases the risk of hepatotoxicity after paracetamol *overdose*.

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Alcohol + Paraldehyde

Both alcohol and paraldehyde have CNS depressant effects, which can be additive. The use of paraldehyde in the treatment of acute alcohol intoxication has caused fatalities.

Clinical evidence, mechanism, importance and management

A report describes 9 patients who died suddenly and unexpectedly after treatment for acute alcohol intoxication with 30 to 90 mL of paraldehyde (the authors quote a normal dose range of 8 to 30 mL; fatal dose 120 mL or more, usually preceded by coma). None of the patients had hepatic impairment, although one did have some fatty changes.[1] Both drugs are CNS depressants and may therefore be expected to have additive effects at any dosage, although an *animal* study suggested that the effect might be less than additive,[2] and cross-tolerance may occur as paraldehyde is pharmacologically similar to alcohol.[3] Nevertheless, it would seem prudent to avoid giving paraldehyde to intoxicated patients wherever possible.

1. Kaye S, Haag HB. Study of death due to combined action of alcohol and paraldehyde in man. *Toxicol Appl Pharmacol* (1964) 6, 316–20.
2. Gessner PK, Shakarjian MP. Interactions of paraldehyde with ethanol and chloral hydrate. *J Pharmacol Exp Ther* (1985) 235, 32–6.
3. Weller RA, Preskorn SH. Psychotropic drugs and alcohol: pharmacokinetic and pharmacodynamic interactions. *Psychosomatics* (1984) 25, 301–3, 305–6, 309.

Alcohol + Penicillins

No adverse interaction normally occurs between alcohol and phenoxymethylpenicillin or amoxicillin.

Clinical evidence, mechanism, importance and management

A long-standing and very common belief among members of the general public (presumably derived from advice given by doctors and pharmacists) is that alcohol should be strictly avoided while taking any antibacterial. It has been claimed that alcohol increases the degradation of penicillin in the gut and reduces the amount available for absorption.[1] However, one study showed that the pharmacokinetics of **phenoxymethylpenicillin** (**penicillin V**) were unaffected by alcoholic drinks,[2] and another study found that alcohol delayed the absorption of **amoxicillin** but did not affect the total amount absorbed.[3] An *in vitro* study did report that acetaldehyde, at concentrations occurring *in vivo* during alcohol metabolism, reacted with amine containing penicillins (**amoxicillin**, **ampicillin**, and **ciclacillin**), which theoretically could lead to decreased drug bioavailability and possibly adverse effects.[4] However, there seems to be no clinical evidence to support claims of an adverse interaction.

1. Kitto W. Antibiotics and ingestion of alcohol. *JAMA* (1965) 193, 411.
2. Lindberg RLP, Huupponen RK, Viljanen S and Pihlajamäki KK. Ethanol and the absorption of oral penicillin in man. *Int J Clin Pharmacol Ther Toxicol* (1987) 25, 536–8.
3. Morasso MI, Hip A, Márquez M, González C, Arancibia A. Amoxicillin kinetics and ethanol ingestion. *Int J Clin Pharmacol Ther Toxicol* (1988) 26, 428–31.
4. Nuñez-Vergara LJ, Yudelevich J, Squella JA, Speisky H. Drug-acetaldehyde interactions during ethanol metabolism *in vitro*. *Alcohol Alcohol* (1991) 26, 139–46.

Alcohol + Phenytoin

Acute alcohol intake may possibly increase serum phenytoin levels, but moderate social drinking appears to have little clinical effect. However, chronic heavy drinking reduces serum phenytoin levels so that above-average doses of phenytoin may be needed to maintain adequate levels.

Clinical evidence

(a) Acute alcohol ingestion

In a study designed to test the effects of acute alcohol intoxication in epileptics, 25 patients were given about 340 mL of alcohol 25%. Blood-alcohol levels ranged from 39 to 284 mg%. All patients had signs of alcohol intoxication without any effect on seizure frequency.[1] The metabolism of a single dose of phenytoin was not affected in one study in healthy subjects by the acute ingestion of alcohol.[2]

(b) Heavy drinking

In a group of 15 drinkers (consuming a minimum of 200 g of ethanol daily for at least 3 months) phenytoin levels measured 24 hours after the last dose of phenytoin were approximately half of those in 76 non-drinkers. The phenytoin half-life was reduced by 30%.[3]

Another study confirmed that alcoholics without liver disease have lower than expected plasma levels of phenytoin while drinking.[4] Two reports describe a chronic alcoholic who was resistant to large doses of phenytoin;[5] and seizures, which developed in a man when an increase in his alcohol consumption appeared to cause a reduction in his serum phenytoin levels.[6]

(c) Moderate social drinking

A study in non-drinking epileptics (17 in the experimental group, 14 in the control group) found that the serum levels of phenytoin were unchanged by moderate drinking, and there was no influence on tonic-clonic convulsions or partial complex seizures. The experimental group drank 1 to 3 glasses of an alcoholic beverage (equivalent to a glass of beer containing 9.85 g of ethanol) over a 2-hour period, twice a week, for 16 weeks, and their maximum blood-alcohol levels ranged from 5 to 33 mg%.[7]

Mechanism

Supported by *animal* data,[8] the evidence suggests that repeated exposure to large amounts of alcohol induces liver microsomal enzymes so that the rate of metabolism and clearance of phenytoin is increased. Conversely, acute alcohol intake may decrease hepatic metabolism.[9]

Importance and management

An established and clinically important interaction, although the documentation is limited. Heavy drinkers may need above-average doses of phenytoin to maintain adequate serum levels. However, be aware that patients with liver impairment usually need lower doses of phenytoin, so the picture may be more complicated. Note that, the manufacturers of phenytoin suggest that acute alcohol intake may increase phenytoin levels,[10,11] but a single-dose study suggests that no significant interaction occurs. Moderate drinking appears to be safe in those taking phenytoin.[1,7] Consider also 'Alcohol + Antiepileptics', p.49.

1. Rodin EA, Frohman CE, Gottlieb JS. Effect of acute alcohol intoxication on epileptic patients. *Arch Neurol* (1961) 4, 115–18.
2. Schmidt D. Effect of ethanol intake on phenytoin metabolism in volunteers. *Experientia* (1975) 31, 1313–14.
3. Kater RMH, Roggin G, Tobon F, Zieve P, Iber FL. Increased rate of clearance of drugs from the circulation of alcoholics. *Am J Med Sci* (1969) 258, 35–9.
4. Sandor P, Sellers EM, Dumbrell M, Khouw V. Effect of short- and long-term alcohol use on phenytoin kinetics in chronic alcoholics. *Clin Pharmacol Ther* (1981) 30, 390–7.
5. Birkett DJ, Graham GG, Chinwah PM, Wade DN, Hickie JB. Multiple drug interactions with phenytoin. *Med J Aust* (1977) 2, 467–8.
6. Bellibas SE, Tuglular I. A case of phenytoin-alcohol interaction. *Therapie* (1995) 50, 487–8.
7. Höppener RJ, Kuyer A, van der Lugt PJM. Epilepsy and alcohol: the influence of social alcohol intake on seizures and treatment in epilepsy. *Epilepsia* (1983) 24, 459–71.
8. Rubin E, Lieber CS. Hepatic microsomal enzymes in man and rat: induction and inhibition by ethanol. *Science* (1968) 162, 690–1.
9. Tanaka E. Toxicological interactions involving psychiatric drugs and alcohol: an update. *J Clin Pharm Ther* (2003) 28, 81–95.
10. Epanutin Capsules (Phenytoin sodium). Pfizer Ltd. UK Summary of product characteristics, January 2008.
11. Dilantin Kapseals (Phenytoin sodium). Pfizer Inc. US Prescribing information, September 2007.

Alcohol + Phosphodiesterase type-5 inhibitors

Sildenafil, tadalafil and vardenafil do not usually alter the effects of alcohol on blood pressure, although postural hypotension has been seen in some subjects given tadalafil and alcohol, and headache and flushing has been reported in one patient taking sildenafil and alcohol. Alcohol does not affect the pharmacokinetics of tadalafil or vardenafil.

Clinical evidence, mechanism, importance and management

(a) Sildenafil

Sildenafil 50 mg did not potentiate the hypotensive effect of alcohol (mean maximum blood-alcohol levels of 80 mg%) in healthy subjects.[1,2] A study in 8 healthy subjects also found that sildenafil 100 mg did not affect the haemodynamic effects of red wine (e.g. heart rate, mean arterial pressure).[3] However, a case report describes potentiation of the adverse effects of sildenafil when alcohol was consumed within one hour of taking the drug: a 36-year-old hypertensive patient receiving regular treatment with amlodipine was given sildenafil 25 mg, which he took 3 times a week without any adverse effects. However, after having 2 drinks of whiskey (55.2 g of alcohol) he experienced severe headache and flushing about 15 minutes after taking sildenafil. The next day he took sildenafil 25 mg without any alcohol and no symptoms developed, but one week later, a challenge dose of sildenafil was given after a single 30-mL drink of whiskey and similar symptoms of severe headache and flushing occurred.[4] The UK patient information leaflet says that drinking alcohol can temporarily impair the ability to get an erection and advises patients not to drink large amounts of alcohol before taking sildenafil.[5]

(b) Tadalafil

A study in 48 healthy subjects given a single 20-mg dose of tadalafil followed by alcohol 0.6 mg/kg found that standing and supine blood pressure, and heart rate were not significantly altered, when compared with placebo and alcohol.[6] Similar or the same work is quoted by the manufacturers. In addition they note that some subjects given both alcohol and tadalafil experienced dizziness and postural hypotension, and the effects of alcohol on cognitive function were unchanged by tadalafil 10 mg.[7] The pharmacokinetics of tadalafil 10 or 20 mg and alcohol were also unaffected by concurrent use.[7,8] However, the manufacturers say that because both alcohol and tadalafil can cause peripheral vasodilation, additive blood pressure lowering effects are possible,[8,9] especially with substantial amounts of alcohol (5 units) and the US manufacturer states that this may result in postural hypotension, increased heart rate, dizziness and headache.[8] Alcohol may also affect the ability to have an erection.[9]

(c) Vardenafil

A placebo-controlled study in 12 healthy subjects found that when alcohol 0.5 g/kg was given with vardenafil 20 mg the pharmacokinetics of both drugs were not significantly altered, and there were no clinically relevant changes in systolic or diastolic blood pressure. Both alcohol and vardenafil alone increased heart rate, the use of both drugs further increased heart rate, but this was only significant when compared with vardenafil alone.[10] The manufacturers note that alcohol (mean blood level of 73 mg%) did not affect the pharmacokinetics of vardenafil 20 mg.[11] There would therefore seem to be no need to avoid the combination. However, alcoholic drink can worsen erection difficulties.[12]

1. Viagra (Sildenafil citrate). Pfizer Ltd. UK Summary of product characteristics, January 2009.
2. Viagra (Sildenafil citrate). Pfizer Inc. US Prescribing information, August 2008.
3. Leslie SJ, Atkins G, Oliver JJ, Webb DJ. No adverse hemodynamic interaction between sildenafil and red wine. *Clin Pharmacol Ther* (2004) 76, 365–70.
4. Bhalla A. Is sildenafil safe with alcohol? *J Assoc Physicians India* (2003) 51, 1125–6.
5. Viagra (Sildenafil). Pfizer Ltd. UK Patient information leaflet, January 2009.
6. Mitchell M, Sanderson B, Payne C, Bedding A. Pharmacodynamic interaction between alcohol and tadalafil in healthy volunteers. *Int J Impot Res* (2002) 14, S64.
7. Cialis (Tadalafil). Eli Lilly and Company Ltd. UK Summary of product characteristics, September 2008.
8. Cialis (Tadalafil). Eli Lilly and Company Ltd. US Prescribing information, July 2009.
9. Cialis (Tadalafil). Eli Lilly and Company Ltd. UK Patient information leaflet, March 2008.
10. Wensing G, Bauer R, Unger S, Rohde G, Heinig R. Simultaneous administration of vardenafil and alcohol does not result in a pharmacodynamic or pharmacokinetic interaction in healthy male subjects. *Int J Clin Pharmacol Ther* (2006) 44, 216–24.
11. Levitra (Vardenafil hydrochloride trihydrate). Bayer plc. UK Summary of product characteristics, June 2009.
12. Levitra (Vardenafil). Bayer plc. UK Patient information leaflet, June 2009.

Alcohol + Procainamide

Alcohol may modestly increase the clearance of procainamide.

Clinical evidence, mechanism, importance and management

In a study in 11 healthy subjects, alcohol 0.73 g/kg followed by alcohol 0.11 g/kg every hour, increased the clearance and decreased the elimination half-life of a single 10-mg/kg oral dose of procainamide by 34% and 25%, respectively. This was due to increased acetylation of procainamide to its active metabolite *N*-acetylprocainamide.[1] The clinical relevance of these modest changes is probably small.

1. Olsen H, Mørland J. Ethanol-induced increase in procainamide acetylation in man. *Br J Clin Pharmacol* (1982) 13, 203–8.

Alcohol + Procarbazine

A flushing reaction has been seen when patients taking procarbazine drank alcohol.

Clinical evidence

One report describes 5 patients taking procarbazine whose faces became very red and hot for a short time after drinking wine.[1] Another says that flushing occurred in 3 patients taking procarbazine after they drank beer.[2] Two out of 40 patients taking procarbazine in a third study complained of facial flushing after taking a small alcoholic drink, and one patient thought that the effects of alcohol were markedly increased.[3] Yet another study describes a 'flush syndrome' in 3 out of 50 patients who drank alcohol while taking procarbazine.[4]

Mechanism

Unknown, but it seems possible that in man, as in *rats*,[5] the procarbazine inhibits acetaldehyde dehydrogenase in the liver causing a disulfiram-like reaction (see 'Alcohol + Disulfiram', p.66).

Importance and management

An established interaction but of uncertain incidence. It seems to be more embarrassing, possibly frightening, than serious, and if it occurs it is unlikely to require treatment; however, patients should be warned. The manufacturers say it is best to avoid alcohol.[6] Note also that some alcoholic beverages contain significant amounts of tyramine (see 'Table 32.2', (p.1394)), so there is a slight possibility that the tyramine reaction might occur if a patient taking procarbazine consumes significant quantities of these, as procarbazine is a weak inhibitor of MAO, see 'Procarbazine + Sympathomimetics', p.763.

1. Mathé G, Berumen L, Schweisguth O, Brule G, Schneider M, Cattan A, Amiel JL, Schwarzenberg L. Methyl-hydrazine in the treatment of Hodgkin's disease and various forms of haematosarcoma and leukaemia. *Lancet* (1963) ii, 1077–80.
2. Dawson WB. Ibenzmethyzin in the management of late Hodgkin's disease. In 'Natulan, Ibenzmethyzin'. Report of the proceedings of a symposium, Downing College, Cambridge, June 1965. Jelliffe AM and Marks J (Eds). Bristol: John Wright; 1965. P. 31–4.
3. Todd IDH. Natulan in management of late Hodgkin's disease, other lymphoreticular neoplasms, and malignant melanoma. *BMJ* (1965) 1, 628–31.
4. Brulé G, Schlumberger JR, Griscelli C. *N*-isopropyl-α-(2-methylhydrazino)-*p*-toluamide, hydrochloride (NSC-77213) in treatment of solid tumors. *Cancer Chemother Rep* (1965) 44, 31–8.
5. Vasiliou V, Malamas M, Marselos M. The mechanism of alcohol intolerance produced by various therapeutic agents. *Acta Pharmacol Toxicol (Copenh)* (1986) 58, 305–10.
6. Matulane (Procarbazine hydrochloride). Sigma-tau Pharmaceuticals, Inc. US Prescribing information, February 2004.

Alcohol + Proton pump inhibitors

Lansoprazole, omeprazole and pantoprazole do not interact with alcohol: other proton pump inhibitors therefore seem unlikely to interact.

Clinical evidence

(a) Lansoprazole

A study in 30 healthy subjects given 0.6 g/kg of alcohol before and after taking lansoprazole 30 mg daily for 3 days found that the pharmacokinetics of alcohol were not significantly changed, and blood-alcohol levels were not raised, by lansoprazole.[1]

(b) Omeprazole

A number of studies have shown that omeprazole does not affect blood-alcohol levels.[2-6]

(c) Pantoprazole

In a placebo-controlled study 16 healthy subjects were given pantoprazole 40 mg daily for 7 days, with alcohol 0.5 g/kg in 200 mL of orange juice 2 hours after a standard breakfast on day 7. The maximum serum levels and the AUC of alcohol were not significantly changed by pantoprazole.[7]

Mechanism

The proton pump inhibitors do not affect alcohol dehydrogenase activity[3,8] (compare with the 'H_2-receptor antagonists', (p.70)), and would not be expected to alter the first-pass metabolism of alcohol.

Importance and management

The proton pump inhibitors do not appear to interact with alcohol, and no special precautions are necessary with concurrent use; although note that some of the conditions for which these drugs are used may be made worse by alcohol, so restricting alcohol intake may be prudent.

1. Girre C, Coutelle C, David P, Fleury B, Thomas G, Palmobo S, Dally S, Couzigou P. Lack of effect of lansoprazole on the pharmacokinetics of ethanol in male volunteers. *Gastroenterology* (1994) 106, A504.
2. Guram M, Howden CW, Holt S. Further evidence for an interaction between alcohol and certain H_2-receptor antagonists. *Alcohol Clin Exp Res* (1991) 15, 1084–5.
3. Roine R, Hernández-Muñoz R, Baraona E, Greenstein R, Lieber CS. Effect of omeprazole on gastric first-pass metabolism of ethanol. *Dig Dis Sci* (1992) 37, 891–6.
4. Jönsson K-Å, Jones AW, Boström H, Andersson T. Lack of effect of omeprazole, cimetidine, and ranitidine on the pharmacokinetics of ethanol in fasting male volunteers. *Eur J Clin Pharmacol* (1992) 42, 209–212.
5. Minocha A, Rahal PS, Brier ME, Levinson SS. Omeprazole therapy does not affect pharmacokinetics of orally administered ethanol in healthy male subjects. *J Clin Gastroenterol* (1995) 21, 107–9.
6. Brown AS, James OF. Omeprazole, ranitidine, and cimetidine have no effect on peak blood ethanol concentrations, first pass metabolism or area under the time-ethanol curve under 'real-life' drinking conditions. *Aliment Pharmacol Ther* (1998) 12, 141–5.
7. Heinze H, Fischer R, Pfützer R, Teyssen S, Singer MV. Lack of interaction between pantoprazole and ethanol: a randomised, double-blind, placebo-controlled study in healthy volunteers. *Clin Drug Invest* (2001) 21, 345–51.
8. Battiston L, Tulissi P, Moretti M, Pozzato G. Lansoprazole and ethanol metabolism: comparison with omeprazole and cimetidine. *Pharmacol Toxicol* (1997) 81, 247–52.

Alcohol + Quetiapine

Postural hypotension and possibly drowsiness may be increased when alcohol is given with quetiapine. Quetiapine does not appear to affect the pharmacokinetics of alcohol.

Clinical evidence, mechanism, importance and management

A randomised, crossover study in 8 men with psychotic disorders found that quetiapine 250 mg three times daily did not affect the mean breath-alcohol concentration after they took 0.8 g/kg of alcohol in orange juice. Some statistically significant changes in the performance of psychomotor tests were seen, but these were considered to have little clinical relevance.[1] However, the US manufacturers of quetiapine say that, in clinical studies, the motor and cognitive effects of alcohol were potentiated by quetiapine. Therefore the US manufacturer of quetiapine[2] advises avoiding alcohol, and the UK manufacturer[3] advises caution with the concurrent use of alcohol. Note that drowsiness is the most common adverse effect of quetiapine, occurring in over 10% of patients (over 30% in some studies).[2,3] Quetiapine may occasionally induce postural hypotension,[2,3] which could be exacerbated by alcohol. In practical terms this means that patients should be warned of the risk of faintness and dizziness if they stand up quickly, and advised to sit or lie down if this occurs.

1. Zeneca Pharma. Personal communication, October 1997.
2. Seroquel (Quetiapine fumarate). AstraZeneca. US Prescribing information, December 2009.
3. Seroquel (Quetiapine fumarate). AstraZeneca UK Ltd. UK Summary of product characteristics, September 2009.

Alcohol + Reboxetine

A study in 10 healthy subjects found that reboxetine does not affect cognitive or psychomotor function, and there is no interaction with alcohol.[1]

1. Kerr JS, Powell J, Hindmarch I. The effects of reboxetine and amitriptyline, with and without alcohol on cognitive function and psychomotor performance. *Br J Clin Pharmacol* (1996) 42, 239–41.

Alcohol + Retinoids

The consumption of alcohol may increase the serum levels of etretinate in patients taking acitretin. A single case report describes a marked reduction in the effects of isotretinoin following the acute intake of alcohol.

Clinical evidence, mechanism, importance and management

(a) Acitretin

A study, in 10 patients with psoriasis taking acitretin, found that the concurrent use of alcohol seemed to be associated with an increase in the formation of etretinate, a metabolite that has a much longer half-life than acitretin.[1] A later study by some of the same authors, in 86 patients taking acitretin, similarly found that alcohol increases the levels of etretinate, and the magnitude of the increase appeared to be related to the amount of alcohol that they drank.[2] The implications of these studies are not known, but it is suggested that it may have some bearing on the length of the period after acitretin therapy during which women are advised not to conceive.[1,2]

(b) Isotretinoin

A former alcoholic, who no longer drank alcohol, was treated for acne conglobata, with some success, with isotretinoin 60 mg daily for 3 months. When for 2 weeks he briefly started to drink alcohol again as part of his job (he was a sherry taster) his skin lesions reappeared and the isotretinoin adverse effects (mucocutaneous dryness) vanished. When he stopped drinking alcohol his skin lesions became controlled again and the drug adverse effects re-emerged. The following year, while receiving another course of isotretinoin, the same thing happened when he started and stopped drinking alcohol. The reasons are not known, but one suggestion is that the alcohol briefly induced the liver microsomal enzymes responsible for the metabolism of isotretinoin, thereby reducing both its therapeutic and adverse effects.[3] The general importance of this apparent interaction is not known.

1. Larsen FG, Jakobsen P, Knudsen J, Weismann K, Kragballe K, Nielsen-Kudsk F. Conversion of acitretin to etretinate in psoriatic patients is influenced by ethanol. *J Invest Dermatol* (1993) 100, 623–7.
2. Grønhøj Larsen F, Steinkjer B, Jakobsen P, Hjorter A, Brockhoff PB, Nielsen-Kudsk F. Acitretin is converted to etretinate only during concomitant alcohol intake. *Br J Dermatol* (2000) 1164–9.
3. Soria C, Allegue F, Galiana J, Ledo A. Decreased isotretinoin efficacy during acute alcohol intake. *Dermatologica* (1991) 182, 203.

Alcohol + Salbutamol (Albuterol)

A patient with high blood-alcohol levels developed lactic acidosis after being exposed to fire smoke and receiving salbutamol.

Clinical evidence, mechanism, importance and management

An isolated report describes a 49-year-old male alcoholic who developed severe lactic acidosis after exposure to fire smoke and treatment of bronchospasm with salbutamol. The correction of lactic acidosis followed salbutamol withdrawal and a transitory increase in lactate after salbutamol re-introduction suggested hypersensitivity to salbutamol. However, the patient also had a very high plasma-alcohol level (240 mg%), and the metabolism of the alcohol was thought to have competed with the conversion of lactate to pyruvate resulting in reduced lactate clearance, thus potentiating the acidosis caused by the salbutamol.[1] The clinical significance of this report is unclear as beta agonist-induced exacerbation of lactic acidosis has been reported in asthmatics, both adults and children. The authors of the above report suggest close monitoring of lactate levels in alcoholic patients receiving beta-agonists.[1]

1. Taboulet P, Clemessy J-L, Fréminet A, Baud FJ. A case of life-threatening lactic acidosis after smoke inhalation – interference between ß-adrenergic agents and ethanol? *Intensive Care Med* (1995) 21, 1039–42.

Alcohol + Sibutramine

There does not seem to be a clinically relevant interaction between sibutramine and alcohol.

Clinical evidence, mechanism, importance and management

In a randomised study, 20 healthy subjects were given sibutramine 20 mg, with 0.5 g/kg of alcohol diluted in ginger beer or placebo. Sibutramine did not potentiate the cognitive or psychomotor effects of alcohol, and in one

test sibutramine slightly reduced the impairment caused by alcohol.[1] However, the manufacturer notes that the consumption of alcohol is generally not compatible with the dietary modifications that are recommended in those given sibutramine.[2]

1. Wesnes KA, Garratt C, Wickens M, Gudgeon A, Oliver S. Effects of sibutramine alone and with alcohol on cognitive function in healthy volunteers. *Br J Clin Pharmacol* (2000) 49, 110–17.
2. Reductil (Sibutramine hydrochloride monohydrate). Abbott Laboratories Ltd. UK Summary of product characteristics, October 2007.

Alcohol + SNRIs

No important psychomotor interaction normally appears to occur between duloxetine or venlafaxine and alcohol. However, the manufacturer warns that use of duloxetine with heavy alcohol intake may be associated with severe liver injury.

Clinical evidence, mechanism, importance and management

(a) Duloxetine

In a single-dose study in healthy subjects, duloxetine 60 mg and alcohol, given in a dose sufficient to produce blood levels of about 100 mg%, did not worsen the psychomotor impairment observed with alcohol alone.[1] Nevertheless, the UK manufacturer advises caution,[2] and the US manufacturer warns that duloxetine should ordinarily not be prescribed for patients with substantial alcohol use as severe liver injury may result.[3]

(b) Venlafaxine

In a study in 15 healthy subjects, venlafaxine 50 mg every 8 hours was found to have some effect on psychomotor tests (digit symbol substitution, divided attention reaction times, profile of mood scales), but these changes were small and not considered to be clinically significant. No pharmacodynamic or pharmacokinetic interactions occurred when alcohol 0.5 g/kg was also given.[4]

In therapeutic doses venlafaxine does not appear to interact significantly with alcohol; however, the manufacturers state that, as with all centrally-active drugs, patients should be advised to avoid alcohol whilst taking venlafaxine.[5,6] This is presumably because both drugs act on the CNS and also because alcohol is more likely to be abused by depressed patients.

1. Skinner MH, Weerakkody G. Duloxetine does not exacerbate the effects of alcohol on psychometric tests. *Clin Pharmacol Ther* (2002) 71, 53.
2. Cymbalta (Duloxetine hydrochloride). Eli Lilly and Company Ltd. UK Summary of product characteristics, July 2009.
3. Cymbalta (Duloxetine hydrochloride). Eli Lilly and Company. US Prescribing information, February 2009.
4. Troy SM, Turner MB, Unruh M, Parker VD, Chiang ST. Pharmacokinetic and pharmacodynamic evaluation of the potential drug interaction between venlafaxine and ethanol. *J Clin Pharmacol* (1997) 37, 1073–81.
5. Efexor (Venlafaxine hydrochloride). Wyeth Pharmaceuticals. UK Summary of product characteristics, March 2008.
6. Effexor (Venlafaxine hydrochloride). Wyeth Pharmaceuticals Inc. US Prescribing information, July 2009.

Alcohol + Sodium cromoglicate (Cromolyn sodium)

No adverse interaction occurs between sodium cromoglicate and alcohol.

Clinical evidence, mechanism, importance and management

A double-blind, crossover study in 17 healthy subjects found that the inhalation of 40 mg of sodium cromoglicate had little or no effect on the performance of a number of tests on human perceptual, cognitive, and motor skills, whether taken alone or with alcohol 0.75 g/kg. Nor did it affect blood-alcohol levels.[1] This is in line with the common experience of patients, and no special precautions seem to be necessary if patients taking sodium cromoglicate want to drink alcohol.

1. Crawford WA, Franks HM, Hensley VR, Hensley WJ, Starmer GA, Teo RKC. The effect of disodium cromoglycate on human performance, alone and in combination with ethanol. *Med J Aust* (1976) 1, 997–9.

Alcohol + Sodium oxybate

The concurrent use of sodium oxybate and alcohol appears to increase respiratory depression, lead to an increase in adverse effects, and is expected to increase sedation.

Clinical evidence, mechanism, importance and management

In a randomised placebo-controlled study, 16 healthy subjects were given alcohol 0.3 g/kg with sodium oxybate 50 mg/kg. The study found that the pharmacokinetics of both drugs were not significantly changed when taken together and sodium oxybate did not alter the effects of alcohol on blood pressure and heart rate, although there were two episodes of postural hypotension (systolic BP 71 to 73 mmHg). Vomiting occurred more frequently compared with alcohol or gamma-hydroxybutyric acid alone, and oxygen saturations were decreased by just over 2% by the combination (modest effect), which was greater than the effect of alcohol alone, which suggests that the combination increases respiratory depression.[1]

Sodium oxybate is the sodium salt of **gamma hydroxybutyrate** (GHB) a CNS depressant substance with well known abuse potential. When used clinically it is predicted to have additive effects with alcohol and other CNS depressants and the manufacturers specifically say it should not be used with these.[2,3] Patients should be warned not to drink alcoholic beverages while taking sodium oxybate.[2,3] In light of the findings in the study the manufacturers recommendations appear cautious, but prudent.

1. Thai D, Dyer JE, Benowitz NL, Haller CA. Gamma-hydroxybutyrate and ethanol effects and interactions in humans. *J Clin Psychopharmacol* (2006) 26, 524–9.
2. Xyrem (Sodium oxybate). UCB Pharma Ltd. UK Summary of product characteristics, July 2008.
3. Xyrem (Sodium oxybate). Jazz Pharmaceuticals, Inc. US Prescribing information, November 2005.

Alcohol + SSRIs

Citalopram, escitalopram, fluoxetine, paroxetine and sertraline have no significant pharmacokinetic interaction with alcohol, but some modest increase in sedation may possibly occur with fluvoxamine and paroxetine.

Clinical evidence and mechanism

(a) Citalopram

The manufacturers of citalopram say that no pharmacodynamic interactions have been noted in clinical studies in which citalopram was given with alcohol.[1,2]

(b) Escitalopram

The manufacturers of escitalopram say that no pharmacokinetic interactions are expected to occur if alcohol is given with escitalopram, and no pharmacodynamic interaction has been seen.[3]

(c) Fluoxetine

In a study in healthy subjects the concurrent use of fluoxetine 30 to 60 mg and alcohol (about 120 mL of whiskey) did not affect the pharmacokinetics of either drugs, and fluoxetine did not alter the effect of alcohol on psychomotor activity (stability of stance, motor performance, manual coordination).[4] Similarly, in 12 healthy subjects, blood-alcohol levels of 80 mg% impaired the performance of a number of psychomotor tests but the addition of fluoxetine 40 mg daily taken for 6 days before the alcohol had little further effect.[5] Another study also found no change in the performance of a number of psychophysiological tests when fluoxetine was given with alcohol.[6] No problems were found in a study of 20 alcohol-dependent patients taking fluoxetine 60 mg daily when they drank alcohol, or in approximately 31 patients taking fluoxetine 20 mg daily who drank unspecified small quantities of alcohol.[7]

(d) Fluvoxamine

One study found that fluvoxamine 150 mg daily with alcohol impaired alertness and attention more than alcohol alone.[8] However, another study in subjects given 40 g of alcohol (blood-alcohol levels up to 70 mg%) found no evidence to suggest that the addition of fluvoxamine 50 mg twice daily worsened the performance of the psychomotor tests, and it even appeared to reverse some of the effects.[9] The pharmacokinetics of alcohol were hardly affected by fluvoxamine, but the steady state maximum plas-

ma levels of the fluvoxamine were increased by 20%, although the fluvoxamine AUC was unchanged.[9] It was suggested that alcohol may have promoted the dissolution of fluvoxamine and increased the absorption rate without affecting bioavailability.[9] Another study also found that fluvoxamine does not appear to enhance the detrimental effects of alcohol on the performance of psychomotor tests.[10]

(e) Paroxetine

Studies have found that paroxetine alone caused little impairment of a series of psychomotor tests related to car driving, and with alcohol the effects were unchanged, except for a significant decrease in attentiveness and an increase in reaction time.[11,12] Another study suggested that the alcohol-induced sedation was antagonised by paroxetine.[13]

(f) Sertraline

Sertraline (in doses of up to 200 mg for 9 days) was found not to impair cognitive or psychomotor performance, and it also appeared not to increase the effects of alcohol.[14]

Importance and management

The results of the few studies reported above suggest that no pharmacokinetic or pharmacodynamic interactions occur between most SSRIs and alcohol, although modest effects were seen with fluvoxamine and possibly paroxetine. However, most manufacturers of SSRIs suggest that concurrent use with alcohol is not advisable. This is presumably because both drugs act on the CNS and also because of the risk of alcohol abuse in depressed patients.[15]

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Alcohol + Sulfiram

Disulfiram-like reactions have been seen in at least three patients who drank alcohol after using a solution of sulfiram on the skin for the treatment of scabies.

Clinical evidence

A man who used undiluted *Tetmosol* (a solution of sulfiram) for 3 days on the skin all over his body developed a disulfiram-like reaction (flushing, sweating, skin swelling, severe tachycardia and nausea) on the third day, after drinking 3 double whiskies. The same thing happened on two subsequent evenings again after he drank 3 double whiskies.[1] Similar reactions have been described in 2 other patients who drank alcohol while using *Tetmosol* or *Ascabiol* (also containing sulfiram).[2,3]

Mechanism

Sulfiram (tetraethylthiuram *monosulphide*) is closely related to disulfiram (tetraethylthiuram *disulphide*) and can apparently undergo photochemical conversion to disulfiram when exposed to light. The longer it is stored, the higher the concentration.[4,5] The reaction with alcohol appears therefore to be largely due to the presence of disulfiram,[6] see 'Alcohol + Disulfiram', p.66.

Importance and management

An established interaction. It has been suggested that alcohol should be avoided before, and for at least 48 hours after the application of sulfiram, but this may not always be necessary. The writer of a letter,[7] commenting on one of the cases cited,[1] wrote that he had never encountered this reaction when using a diluted solution of *Tetmosol* on patients at the Dreadnought Seamen's Hospital in London who he described as "not necessarily abstemious". This would suggest that the reaction is normally uncommon and unlikely to occur if the solution is correctly diluted (usually with 2 to 3 parts of water), thereby reducing the amount absorbed through the skin. However, one unusually sensitive patient is said to have had a reaction (flushing, sweating, tachycardia) after using diluted *Tetmosol*, but without drinking alcohol. It was suggested that she reacted to the alcohol base of the formulation passing through her skin.[8]

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Alcohol + Tacrolimus or Pimecrolimus

Alcohol may cause facial flushing or skin erythema in patients receiving tacrolimus ointment; this reaction appears to be fairly common. Alcohol intolerance has been reported rarely with pimecrolimus cream.

Clinical evidence

Six patients reported facial flushing with small quantities of beer or wine during facial treatment with tacrolimus ointment. Re-exposure to tacrolimus 0.1% ointment, applied to the face twice daily for 4 days, followed by 100 mL of white wine on the fifth day, resulted in a facial flush reaction in all the patients, which occurred within 5 to 15 minutes of alcohol ingestion. The intensity of the erythema varied among the patients and was not confined to the treated areas, but started to fade after 30 minutes; a slight headache occurred in one patient. Forearm skin was also exposed to an epicutaneous patch containing 70 mg of tacrolimus 0.1% ointment, but these sites remained unchanged following alcohol exposure. After a tacrolimus washout period of at least 4 weeks, controlled exposure to alcohol in 2 patients was tolerated normally.[1] Another report describes one patient using tacrolimus ointment for mild eyelid eczema who experienced eyelid erythema, limited to the area the tacrolimus ointment was applied, after drinking wine. Two other patients experienced an erythematous rash after drinking alcohol when using topical tacrolimus; areas affected included the elbows, ears, eyes and face. The response to alcohol disappeared within 2 weeks of discontinuing tacrolimus ointment.[2]

Three patients experienced application site erythema following the consumption of alcohol after using topical tacrolimus or pimecrolimus for the treatment of facial dermatoses. Two of the patients then participated in a double-blind, controlled evaluation of the reaction. Both patients consumed alcohol (240 mL of red or white wine) without experiencing flushing, but following tacrolimus or pimecrolimus application, they experienced moderate or severe facial flushing (limited to the area of application) 5 to 10 minutes after alcohol consumption. The intensity of the erythema was sharply reduced after taking aspirin 325 mg twice daily for 3 days before alcohol consumption, but cetirizine 10 mg daily with cimetidine 400 mg twice daily for 3 days appeared to have little effect.[3]

There are other reports of this interaction between tacrolimus and alcohol,[3-8] including 3 cases in children aged 6 months to 3.5 years who were

given oral medicines containing alcohol while receiving tacrolimus ointment.[8] The reaction is usually confined to the face[4,8] and the intensity may be related to the amount of alcohol ingested.[4] In an open study of 316 patients, alcohol intolerance (facial flushing) was observed in 19% of the patients using tacrolimus 0.1% ointment[6] and in a controlled study, 6.9% of patients experienced the reaction with tacrolimus 0.1% ointment, and 3.4% of patients experienced the reaction with tacrolimus 0.03% ointment.[5]

Mechanism

The mechanism of this interaction is not understood. It has been proposed that tacrolimus may act on the same biochemical pathway as alcohol, potentiating a capsaicin-mediated release of neuropeptides, which increase vasodilatory effects. Alternatively, cutaneous aldehyde dehydrogenase inhibition in areas where tacrolimus has been applied may increase cutaneous aldehyde levels that, through prostaglandins as mediators, could lead to vasodilation following alcohol consumption.[1,4]

Importance and management

The interaction between topical tacrolimus and alcohol is established and appears to occur in about 6 to 7% of patients treated with tacrolimus 0.1% ointment. Patients should be warned of the possibility of a flushing reaction with alcohol and that consumption of alcohol may need to be avoided if this occurs. Clinicians should be aware of the interaction and obtain a careful history, including alcohol use (including alcohol intake from medicinal products), in patients who present with new acute symptoms while using tacrolimus. It has been suggested that aspirin may possibly reduce the symptoms of this reaction,[3] but this needs further study. Alcohol intolerance with pimecrolimus has been reported,[3,9] but appears to be rare.[10]

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9. Elidel (Pimecrolimus). Novartis Pharmaceuticals Corp. US Prescribing information, August 2007.
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Alcohol + Tetracyclic antidepressants

Mianserin and maprotiline can cause drowsiness and impair the ability to drive or handle other dangerous machinery, particularly during the first few days of treatment. This impairment may be increased by alcohol. Pirlindole does not appear to interact with alcohol.

Clinical evidence

(a) Maprotiline

A double-blind, crossover study in 12 healthy subjects found that a single 75-mg oral dose of maprotiline subjectively caused drowsiness, which was increased by 1 g/kg of alcohol. The performance of a number of psychomotor tests was also worsened after the addition of alcohol.[1] However, in a later study, the same group found that maprotiline 50 mg twice daily for 15 days did not increase the detrimental effects of alcohol.[2] A case report attributes two epileptic seizures in a 21-year old woman taking maprotiline 125 mg daily to an increase in her alcohol intake during the preceding week (3 to 4 beers or 3 to 4 glasses of champagne each night). She was also taking alprazolam 500 micrograms four times daily.[3]

(b) Mianserin

A double-blind, crossover study in 13 healthy subjects given 10 to 30 mg of mianserin twice daily for 8 days, with and without alcohol 1 g/kg, found that their performance in a number of psychomotor tests (choice reaction, coordination, critical flicker frequency) were impaired both by mianserin alone and by the concurrent use of alcohol. The subjects were aware of feeling drowsy, muzzy, and less able to carry out the tests.[4] These results confirm the findings of other studies.[5,6]

(c) Pirlindole

A study in healthy subjects given pirlindole 75 to 150 mg daily for 4 days indicated that it did not affect the performance of a number of psychomotor tests, both with and without 0.4 g/kg of alcohol.[7]

Mechanism

The CNS depressant effects of mianserin, and possibly maprotiline, appear to be additive with those of alcohol. In the case report it was suggested that the seizures occurred due to high levels of maprotiline caused by the alcohol intake.[3]

Importance and management

Drowsiness is a frequently reported adverse effect of mianserin, particularly during the first few days of treatment. Patients should be warned that driving or handling dangerous machinery will be made more hazardous if they drink. It would also be prudent to warn patients taking maprotiline of the possible increased risk if they drink.[2] Pirlindole appears not to interact.

The general relevance of the case of seizures with maprotiline and alcohol is unclear.

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Alcohol + Tetracyclines

Doxycycline serum levels may fall below minimum therapeutic levels in alcoholic patients, but tetracycline is not affected. There is nothing to suggest that moderate amounts of alcohol have a clinically relevant effect on the serum levels of any tetracycline in non-alcoholic subjects.

Clinical evidence

(a) Alcoholic patients

A study into the effects of alcohol on **doxycycline** and **tetracycline** pharmacokinetics found that the half-life of **doxycycline** was 10.5 hours in 6 alcoholics (with normal liver function) compared with 14.7 hours in 6 healthy subjects. The serum **doxycycline** levels of 3 of the alcoholic patients fell below the generally accepted minimum inhibitory concentration at 24 hours. The half-life of **tetracycline** was the same in both groups. All of the subjects were given **doxycycline** 100 mg daily after a 200-mg loading dose, and **tetracycline** 500 mg twice daily after an initial 750-mg loading dose.[1]

(b) Non-alcoholic patients

Single 500-mg doses of **tetracycline** were given to 9 healthy subjects with water or alcohol 2.7 g/kg. The alcohol caused a 33% rise in the maximum serum levels of **tetracycline** from 9.3 to 12.4 micrograms/mL, and a 50% rise in the AUC of **tetracycline**.[2] The clinical relevance of this rise is unknown.

Another study in healthy subjects found that cheap red wine, but not whisky (both 1 g/kg) delayed the absorption of **doxycycline**, probably because of the presence of acetic acid, which slows gastric emptying. However, the total absorption was not affected. The authors concluded that acute intake of alcoholic beverages has no clinically relevant effects on the pharmacokinetics of **doxycycline**.[3]

Mechanism

Heavy drinkers can metabolise some drugs much more quickly than non-drinkers due to the enzyme-inducing effects of alcohol.[4] The interaction with doxycycline would seem to be due to this effect, possibly allied with some reduction in absorption from the gut.

Importance and management

Information is limited, but the interaction between doxycycline and alcohol appears to be established and of clinical significance in alcoholics but not in non-alcoholic individuals. One possible solution to the problem of enzyme induction is to give alcoholic subjects double the dose of doxycycline,[5] or in some cases tetracycline may be a suitable non-interacting alternative. There is nothing to suggest that moderate or even occasional heavy drinking has a clinically relevant effect on any of the tetracyclines in non-alcoholic subjects.

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Alcohol + Thiopurines

Alcohol has been tolerated in patients receiving mercaptopurine. A single case report describes liver toxicity in a patient taking azathioprine, which was attributed to his alcohol intake.

Clinical evidence, mechanism, importance and management

A study in 207 patients with inflammatory bowel disease assessed (using a phone survey) the presence of adverse reactions to alcohol in patients taking **mercaptopurine** and/or metronidazole long-term, or neither drug. All of the patients consumed less than 4 alcoholic beverages per day. The proportion of patients experiencing any clinically significant adverse effects was: metronidazole group 16.3%, **mercaptopurine** group 14.5%, control group (not taking either drug) 8.97%. Although there was a trend towards more adverse effects in the drug study groups, this was not statistically significant. The authors suggest a cautious trial of alcohol is advisable in patients that are starting and will be taking either of the medications on a chronic basis.[1]

A case report describes a man taking **azathioprine** for Crohn's disease, who developed peliosis hepatis (liver toxicity) several months after three episodes of excessive alcohol consumption. The patient's liver function returned to normal after stopping **azathioprine**. **Azathioprine** alone is rarely associated with peliosis hepatis, which has been suggested to occur as a result of glutathione depletion. The authors considered that the excessive alcohol intake in this patient led to glutathione depletion, which increased **azathioprine** toxicity, resulting in the liver damage seen.[2] This appears to be an isolated case, but it reinforces the need for cautious alcohol use in patients taking thiopurines.

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Alcohol + Tianeptine

In one study alcohol reduced the absorption of tianeptine and lowered its plasma levels by about 30%.

Clinical evidence, mechanism, importance and management

In 12 healthy subjects the absorption and peak plasma levels of a single 12.5-mg dose of tianeptine were reduced by about 30% by alcohol. The subjects were given vodka diluted in orange juice to give blood-alcohol levels between 64 and 77 mg%. The plasma levels of the major metabolite of tianeptine were unchanged.[1] No behavioural studies were done so that the clinical significance of these studies is uncertain.

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Alcohol + Tolazoline

A disulfiram-like reaction may occur in patients taking tolazoline if they drink alcohol.

Clinical evidence, mechanism, importance and management

Seven healthy subjects were given tolazoline 25 mg daily for 4 days. Within 15 to 90 minutes of drinking 90 mL of port wine (alcohol 18.2%), 2 hours after the last dose of tolazoline, 6 experienced tingling over the head, and 4 developed warmth and fullness of the head.[1] The reasons are not understood, but this reaction is not unlike a mild disulfiram reaction, and may possibly have a similar mechanism (see *Mechanism*, under 'Alcohol + Disulfiram', p.66). Patients given tolazoline should be warned about this reaction if they drink alcohol, and advised to limit their consumption. Reactions of this kind with drugs other than disulfiram are usually more unpleasant or frightening than serious, and treatment is rarely needed. In infants given tolazoline, it would seem sensible to avoid preparations containing alcohol, where possible.

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Alcohol + Trazodone

Trazodone can make driving or handling other dangerous machinery more hazardous, particularly during the first few days of treatment, and further impairment may occur with alcohol.

Clinical evidence, mechanism, importance and management

A study in 6 healthy subjects comparing the effects of single-doses of amitriptyline 50 mg and trazodone 100 mg found that both drugs impaired the performance of a number of psychomotor tests, causing drowsiness and reducing 'clearheadedness' to approximately the same extent. Only manual dexterity was further impaired when the subjects taking trazodone were given sufficient alcohol to give blood levels of about 40 mg%.[1]

Another study similarly found that the impairment of psychomotor performance by trazodone was increased by alcohol.[2] This appears to be due to simple additive depression of the CNS. This is an established interaction, and of practical importance. Patients should be warned that their ability to drive, handle dangerous machinery or to do other tasks needing complex psychomotor skills might be impaired by trazodone, and further worsened by alcohol.

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Alcohol + Trichloroethylene

A flushing skin reaction similar to a mild disulfiram reaction can occur in those who drink alcohol following exposure to trichloroethylene. Alcohol may also increase the risk of liver toxicity due to trichloroethylene exposure.

Clinical evidence

An engineer from a factory where trichloroethylene was being used as a degreasing agent, developed facial flushing, a sensation of increased pressure in the head, lachrymation, tachypnoea and blurred vision within 12 minutes of drinking 85 mL of bourbon whiskey. The reaction did not develop when he was no longer exposed to the trichloroethylene. Other workers in the same plant reported the same experience.[1] Vivid red blotches, in a symmetrical pattern on the face, neck, shoulders and back, were seen in other workers when they drank about 2 pints of beer[2] after having been exposed for a few hours each day for 3 weeks to increasing concen-

trations of trichloroethylene vapour (up to 200 ppm). Note that this was twice the maximum permissible level for trichloroethylene in air at that time.[3] This reaction has been described as the "degreasers' flush".[2]

A later study involving 188 workers occupationally exposed to trichloroethylene found a statistically significant synergistic toxic interaction between trichloroethylene and alcohol. There were 30 cases (15.9%) of degreasers' flush and 10 cases (5.3%) of clinical liver impairment.[4]

There is also some evidence that short-term exposure to the combination may possibly reduce mental capacity, although in this study the concentration of trichloroethylene was quite high (200 ppm).[5]

Another study investigated the metabolism of trichloroethylene in 5 healthy subjects who inhaled trichloroethylene 50 ppm for 6 hours per day for 5 days and then again 2 weeks later in the presence of alcohol. Inhalation of trichloroethylene with blood-alcohol levels of 60 mg% resulted in increased blood and expired air concentrations of trichloroethylene 2 to 3 times greater than without alcohol.[6] A simulation study suggested that drinking moderate amounts of alcohol (0.23 to 0.92 g/kg) before the start of work or at lunchtime, but not at the end of work, could cause pronounced increases in blood-trichloroethylene levels and decreases in the urinary excretion rates of trichloroethylene metabolites. However, when alcohol was consumed the previous evening there was a negligible effect on the metabolism of trichloroethylene (exposure below 100 ppm).[7]

Mechanism

Uncertain. One suggested mechanism is a disulfiram-like inhibition of acetaldehyde metabolism by trichloroethylene (see *Mechanism*, under 'Alcohol + Disulfiram', p.66). Another suggested mechanism is inhibition of trichloroethylene metabolism in the presence of alcohol, resulting in increased plasma levels and possibly an accumulation of trichloroethylene in the CNS.[6]

Importance and management

The flushing reaction is an established interaction that has been reported to occur in about 16% of workers who are exposed to trichloroethylene and then drink alcohol. It would seem to be more unpleasant and socially disagreeable than serious, and normally requires no treatment. However, the hepatotoxicity of trichloroethylene and other organic solvents may be increased by alcohol; increased body fat has been reported to increase the risk of solvent toxicity and heavy alcohol consumption may further increase the risk of liver toxicity.[8]

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Alcohol + Tricyclic antidepressants

The ability to drive, to handle dangerous machinery or to do other tasks requiring complex psychomotor skills may be impaired by amitriptyline, and to a lesser extent by doxepin or imipramine, particularly during the first few days of treatment. This impairment can be increased by alcohol. Amoxapine, clomipramine, desipramine, and nortriptyline appear to interact with alcohol only minimally. Information about other tricyclics appears to be lacking, although most manufacturers of tricyclics warn that the effects of alcohol may be enhanced. There is also evidence that alcoholics (without liver disease) may need larger doses of desipramine and imipramine to control depression. However, the toxicity of some tricyclics may be increased by alcohol, and in alcoholics with liver disease.

Clinical evidence

(a) Amitriptyline

A single-dose, crossover study in 5 healthy subjects found that the plasma levels of amitriptyline 25 mg over an 8-hour period were markedly increased by alcohol (blood-alcohol level maintained at approximately 80 mg%). Compared with amitriptyline alone, the $AUC_{0\text{-}8}$ increased by a mean of 44% following alcohol consumption, and was associated with decreased standing steadiness, recent memory and alertness.[1] Amitriptyline 800 micrograms/kg impaired the performance of three motor skills tests related to driving in 21 healthy subjects. When alcohol to produce blood levels of about 80 mg% was also given the performance was even further impaired.[2] Similar results have been very clearly demonstrated in considerable numbers of subjects using a variety of psychomotor skill tests,[1-6] the interaction being most marked during the first few days of treatment, but tending to wane as treatment continues.[5] Unexplained blackouts lasting a few hours have been described in 3 women after they drank only modest amounts of alcohol;[7] they had been taking amitriptyline or imipramine for a month. There is some limited evidence from *animal* studies that amitriptyline may possibly enhance the fatty changes induced in the liver by alcohol,[8] but this still needs confirmation from human studies.

A study involving 332 fatal poisonings in Finland found that alcohol was present in 67% of cases involving amitriptyline, and when alcohol was present, relatively small overdoses of amitriptyline could result in fatal poisoning.[9] It appears that amitriptyline may be more toxic when given with alcohol, and it has been suggested that a less dangerous alternative could be chosen when indications of alcohol abuse or suicide risk are present.[10]

(b) Amoxapine

The interaction between amoxapine and alcohol is said to be slight,[11] but two patients who experienced reversible extrapyramidal symptoms (parkinsonism, akathisia) while taking amoxapine, which was apparently caused by drinking alcohol.[12]

(c) Clomipramine

Studies in subjects with blood-alcohol levels of 40 to 60 mg% found that clomipramine had only slight or no effect on various choice reaction, coordination, memory and learning tests.[4,13,14] A case describes a fatal poisoning in a chronic alcoholic patient taking clomipramine for depression. The ultimate toxic effect was thought to be due to alcohol-induced decreased biotransformation of clomipramine, as post-mortem examination revealed toxic liver damage, and low levels of the metabolite were found in blood and hair samples.[15]

(d) Desipramine

Plasma desipramine levels were transiently, but non-significantly increased after healthy subjects drank alcohol, and breath-alcohol concentrations were not affected by the antidepressant. Further, skilled performance tests in subjects given desipramine 100 mg indicated that no significant interaction occurred with alcohol.[16] The half-life of oral desipramine was about 30% lower in recently detoxified alcoholics (without liver disease), when compared with healthy subjects, and the intrinsic clearance was 60% greater.[17]

(e) Doxepin

A placebo-controlled, crossover study in 20 healthy subjects given various combinations of alcohol and doxepin found that with blood-alcohol levels of 40 to 50 mg% their choice reaction test times were prolonged and the number of mistakes increased. Coordination was obviously impaired after 7 days of treatment with doxepin, but not after 14 days.[4] In an earlier study doxepin appeared to cancel out the deleterious effects of alcohol on the performance of a simulated driving test.[18] It appears that doxepin may be more toxic when given with alcohol, and it has been suggested that a less dangerous alternative could be chosen when indications of alcohol abuse or suicide risk are present.[10]

(f) Imipramine

Imipramine 150 mg daily has been reported to enhance some of the hypno-sedative effects of alcohol,[19] and unexplained blackouts lasting a few hours have been described in 3 women after they drank only modest amounts of alcohol;[7] they had been taking amitriptyline or imipramine for only a month. The half-life of oral imipramine was about 45% lower in recently detoxified alcoholics (without liver disease) compared with healthy subjects, and the intrinsic clearance was 200% greater.[17]

(g) Nortriptyline

Studies in subjects with blood-alcohol levels of 40 to 60 mg% found that nortriptyline had only slight or no effects on various choice reaction, coordination, memory and learning tests,[4,13,20] although the acute use of alcohol with nortriptyline impaired learning in one study.[13]

Mechanism

Part of the explanation for the increased CNS depression is that both alcohol and some of the tricyclics, particularly amitriptyline, cause drowsiness and other CNS depressant effects, which can be additive with the effects of alcohol.[6] The sedative effects have been reported to be greatest with amitriptyline, then doxepin and imipramine, followed by nortriptyline, and least with amoxapine, clomipramine, desipramine, and **protriptyline**.[21-24] In addition acute alcohol intake causes marked increases (100 to 200%) in the plasma levels of amitriptyline, probably by inhibiting its first pass metabolism.[1,25] Alcohol-induced liver damage could also result in impaired amitriptyline metabolism.[23] The lower serum levels of imipramine and desipramine seen in abstinent alcoholics are attributable to induction of the cytochrome P450 isoenzymes by alcohol.[17]

Importance and management

The increased CNS depression resulting from the interaction between amitriptyline and alcohol is well documented and clinically important. The interaction between alcohol and doxepin or imipramine is less well documented and the information is conflicting. Amoxapine, clomipramine, desipramine, and nortriptyline appear to interact only minimally with alcohol. Direct information about other tricyclics seems to be lacking, but there appear to be no particular reasons for avoiding concurrent use, although tricyclics with greater sedation such as **trimipramine** are more likely to interact. During the first 1 to 2 weeks of treatment many tricyclics (without alcohol) may temporarily impair the skills related to driving.[11] Therefore it would seem prudent to warn any patient given a tricyclic that driving or handling dangerous machinery may be made more hazardous if they drink alcohol, particularly during the first few days of treatment, but the effects of the interaction diminish during continued treatment. Most manufacturers of tricyclic antidepressants warn that the effects of alcohol may be enhanced by tricyclics and several suggest avoiding the concurrent use of alcohol.

Also be aware that alcoholic patients (without liver disease) may need higher doses of imipramine (possibly doubled) and desipramine to control depression, and if long-term abstinence is achieved the dosages may then eventually need to be reduced.

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Alcohol + Trinitrotoluene

Men exposed to trinitrotoluene (TNT) in a munitions factory were found to have a greater risk of TNT-induced liver damage if they had a long history of heavy alcohol drinking than if they were non-drinkers.[1]

1. Li J, Jiang Q-G, Zhong W-D. Persistent ethanol drinking increases liver injury induced by trinitrotoluene exposure: an in-plant case-control study. *Hum Exp Toxicol* (1991) 10, 405–9.

Alcohol + Triptans

Alcohol does not appear to alter the pharmacokinetics of frovatriptan, naratriptan or sumatriptan.

Clinical evidence, mechanism, importance and management

In a retrospective analysis of data from 178 healthy subjects involved in phase I studies, alcohol consumption did not affect the pharmacokinetics **frovatriptan**.[1]

In a study in 16 healthy subjects the pharmacokinetics of a single 5-mg dose of **naratriptan** were not altered when it was given 30 minutes after alcohol (amount not specified).[2]

A single 0.8-g/kg dose of alcohol was given to 16 healthy subjects, followed 30 minutes later by 200 mg of sumatriptan. No statistically significant changes were seen in the pharmacokinetics of **sumatriptan**.[3]

There is nothing to suggest that alcohol should be avoided while taking **frovatriptan**, **naratriptan** or **sumatriptan**.

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Alcohol + Vitamin A (Retinol)

Heavy consumption of alcohol may increase betacarotene levels and affect vitamin A metabolism; there have been reports of possible increased toxicity.

Clinical evidence, mechanism, importance and management

A study involving 30 abstinent male alcoholics found that 5 of 15 given high-dose vitamin A (10 000 units daily by mouth) for 4 months developed liver abnormalities during treatment, compared with 1 of 15 patients given placebo. Two of the 6 patients admitted intermittent alcohol consumption. Five of these patients continued with vitamin A and the abnormal liver function tests resolved in 4 of these patients.[1]

The interaction between alcohol and vitamin A is complex. They have overlapping metabolic pathways; a similar 2-step process is involved in the metabolism of both alcohol and vitamin A, with alcohol dehydrogenases and acetaldehyde dehydrogenases being implicated in the conversion of vitamin A to retinoic acid.[2,3] Alcohol appears to act as a competitive inhibitor of vitamin A oxidation.[2,4] In addition, chronic alcohol intake can induce cytochrome P450 isoenzymes that appear to increase the breakdown of vitamin A (retinol and retinoic acid) into more polar metabolites in the liver, which can cause hepatocyte death. So chronic alcohol

consumption may enhance the intrinsic hepatotoxicity of high-dose vitamin A. Alcohol has also been shown to alter retinoid homoeostasis by increasing vitamin A mobilisation from the liver to extrahepatic tissues, which could result in depletion of hepatic stores of vitamin A.[2,3]

It appears that consumption of substantial amounts of alcohol is associated with vitamin A deficiency partially due to poor nutrition and also the direct effects of alcohol on the metabolism of vitamin A. Vitamin A supplementation may therefore be indicated in heavy drinkers, but is complicated by the hepatotoxicity of large amounts of vitamin A, which may be potentiated by alcohol.[3] It would therefore seem reasonable to try to control alcohol consumption when vitamin A supplementation is required. Patients who consume alcohol, particularly heavy drinkers or alcoholics, should be questioned about their use of vitamin supplements as some non-prescription vitamin A and D supplements contain substantial amounts of vitamin A.

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2. Wang X-D. Alcohol, vitamin A, and cancer. *Alcohol* (2005) 35, 251–8.
3. Leo MA, Lieber CS. Alcohol, vitamin A, and ß-carotene: adverse interactions, including hepatotoxicity and carcinogenicity. *Am J Clin Nutr* (1999) 69, 1071–85.
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Alcohol + Xylene

Some individuals exposed to xylene vapour, who subsequently drink alcohol, may experience dizziness and nausea. A flushing skin reaction has also been seen.

Clinical evidence, mechanism, importance and management

Studies in subjects exposed to *m*-xylene vapour at concentrations of approximately 145 or 280 ppm for 4 hours who were then given 0.4 or 0.8 g/kg of alcohol found that about 10 to 20% experienced dizziness and nausea.[1,2] One subject exposed to 300 ppm of *m*-xylene vapour developed a conspicuous dermal flush on his face, neck, chest and back. He also developed some erythema with alcohol alone.[3] A study using a population-based pharmacokinetic and pharmacodynamic model predicted that the probability of experiencing CNS effects following exposure to xylene at the current UK occupational exposure standard (100 ppm time-weighted average over 8 hours) increased markedly with alcohol dose; the effects were non-linear.[4]

The reasons for these reactions are not fully understood, but it is possible that xylene plasma levels are increased because alcohol impairs its metabolic clearance by the cytochrome P450 isoenzyme CYP2E1.[4] After alcohol intake, blood-xylene levels have been reported to rise about 1.5- to 2-fold;[2] acetaldehyde levels may also be transiently increased.[2]

Alcoholic beverages are quite often consumed during lunchtime or after work, and since the excretion of xylene is delayed by its high solubility and storage in lipid-rich tissues, the simultaneous presence of xylene and alcohol in the body is probably not uncommon and could result in enhancement of the toxicity of xylene.[5]

1. Savolainen K, Riihimäki V, Vaheri E, Linnoila M. Effects of xylene and alcohol on vestibular and visual functions in man. *Scand J Work Environ Health* (1980) 6, 94–103.
2. Riihimäki V, Savolainen K, Pfäffli P, Pekari K, Sippel HW, Laine A. Metabolic interaction between m-xylene and ethanol. *Arch Toxicol* (1982) 49, 253–63.
3. Riihimäki V, Laine A, Savolainen K, Sippel H. Acute solvent-ethanol interactions with special reference to xylene. *Scand J Work Environ Health* (1982) 8, 77–9.
4. MacDonald AJ, Rostami-Hodjegan A, Tucker GT, Linkens DA. Analysis of solvent central nervous system toxicity and ethanol interactions using a human population physiologically based kinetic and dynamic model. *Regul Toxicol Pharmacol* (2002) 35, 165–76.
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4

Alpha blockers

The selective and non-selective alpha blockers are categorised and listed in 'Table 4.1', (see below). The principal interactions of the alpha blockers are those relating to enhanced hypotensive effects. Early after the introduction of the selective alpha blockers it was discovered that, in some individuals, they can cause a rapid reduction in blood pressure on starting treatment (also called the 'first-dose effect' or 'first-dose hypotension'). The risk of this may be higher in patients already taking other antihypertensive drugs. A similar hypotensive effect can occur when the dose of the alpha blocker is increased, or if treatment is interrupted for a few days and then re-introduced.

The first-dose effect has been minimised by starting with a very low dose of the alpha blocker, and then escalating the dose slowly over a couple of weeks. Some manufacturers recommend giving the first dose on retiring to bed, or if not, avoiding tasks that are potentially hazardous if syncope occurs (such as driving) for the first 12 hours. If symptoms such as dizziness, fatigue or sweating develop, patients should be warned to lie down, and to remain lying flat until they abate completely.

It is unclear whether there are any real differences between the alpha blockers in their propensity to cause this first-dose effect. However, tamsulosin is reported to have some selectivity for the alpha receptor 1A subtype, which are found mostly in the prostate and so have less effect on blood pressure: an initial titration of the dose is therefore not considered to be necessary. Nevertheless, it would be prudent to exercise caution with all the drugs in this class.

Other alpha blockers are also used to increase urinary flow-rate and improve obstructive symptoms in benign prostatic hyperplasia. In this setting, their effects on blood pressure are more of an adverse effect, and their additive hypotensive effect with other antihypertensives may not be beneficial.

Some alpha blockers (e.g. alfuzosin, doxazosin, tamsulosin) are metabolised via the cytochrome isoenzyme system, particularly by CYP3A4, and so potent CYP3A4 inhibitors may possibly increase their plasma levels, see 'Alpha blockers + CYP3A4 or CYP2D6 inhibitors', p.96.

Table 4.1 Alpha blockers

Drug	*Principal indications*
Selective alpha$_1$ blockers (Alpha blockers)	
Alfuzosin	BPH
Bunazosin	Hypertension
Doxazosin	BPH; Hypertension
Indoramin	BPH; Hypertension; Migraine
Prazosin	BPH; Heart failure; Hypertension; Raynaud's syndrome
Tamsulosin	BPH
Terazosin	BPH; Hypertension
Other drugs with alpha-blocking actions	
Moxisylate	Peripheral vascular disease; Erectile dysfunction
Phenoxybenzamine	Hypertensive episodes in phaeochromocytoma
Tolazoline	Peripheral vascular disease; Pulmonary hypertension
Phentolamine	Erectile dysfunction; Hypertensive episodes in phaeochromocytoma
Urapidil	Hypertension

Alpha blockers + ACE inhibitors or Angiotensin II receptor antagonists

Severe first-dose hypotension and synergistic hypotensive effects, that occurred when a patient taking enalapril was given bunazosin, have been replicated in healthy subjects. The first-dose effect seen with alpha blockers (particularly alfuzosin, prazosin and terazosin) is likely to be potentiated by ACE inhibitors and probably angiotensin II receptor antagonists. In one small study tamsulosin did not have any clinically relevant effects on blood pressure that was already well controlled by enalapril.

Clinical evidence

(a) Alfuzosin

The manufacturer of alfuzosin[1] warns that patients receiving antihypertensive drugs are at particular risk of developing postural hypotension after the first dose of the alpha blocker.

(b) Bunazosin

A patient taking **enalapril** developed severe first-dose hypotension after being given bunazosin, resulting in this interaction being further studied in 6 healthy subjects. When **enalapril** 10 mg or bunazosin 2 mg was given, their mean blood pressure over 6 hours was reduced by 9.5/6.7 mmHg. When bunazosin was given one hour after **enalapril** the blood pressure fell by 27/28 mmHg. Blood pressure still fell by 19/22 mmHg, even when the dose of **enalapril** was reduced to 2.5 mg.[2]

(c) Doxazosin

For comment that doxazosin appeared to have less effect on blood pressure in patients with BPH receiving ACE inhibitors than in those taking beta blockers or diuretics, see 'Alpha blockers + Beta blockers', p.94.

(d) Prazosin

The manufacturer of prazosin[3] warns that patients receiving antihypertensive drugs (they specifically name ACE inhibitors) are at particular risk of developing postural hypotension after the first dose of alpha blocker.

(e) Tamsulosin

In a placebo-controlled study in 6 hypertensive men with blood pressure well controlled by **enalapril**, the addition of tamsulosin 400 micrograms daily for 7 days then 800 micrograms daily for a further 7 days had no clinically relevant effects on blood pressure (assessed after 6 and 14 days of tamsulosin). In addition, no first-dose hypotensive effect was seen on the day tamsulosin was started, or on the day the tamsulosin dose was increased.[4]

(f) Terazosin

Retrospective analysis of a large multinational study in patients with BPH given terazosin 5 or 10 mg daily found that terazosin only affected the blood pressure of patients taking ACE inhibitors (**enalapril**, **lisinopril** or **perindopril**) if the blood pressure was uncontrolled. No change in blood pressure was seen in those with normal blood pressure (i.e. those without hypertension and those with hypertension controlled by ACE inhibitors). The most common adverse effect in the 10-week terazosin phase was dizziness, and the incidence of this appeared to be lower in those taking antihypertensives (13 to 16%) than in those not taking antihypertensives (21 to 25%).[5] However, the manufacturer of terazosin notes that the incidence of dizziness in patients taking terazosin was higher when they were also receiving an ACE inhibitor.[6]

Mechanism

The first-dose effect of alpha blockers (see 'Alpha blockers', (p.92)) may be potentiated by ACE inhibitors. Tamsulosin possibly has less effect on blood pressure since it has some selectivity for alpha receptors in the prostate.

Importance and management

Direct information is limited. Acute hypotension (dizziness, fainting) sometimes occurs unpredictably with the first dose of some alpha blockers (particularly, alfuzosin, prazosin and terazosin; but there is insufficient evidence to suggest that the alpha blockers differ significantly in their propensity to cause this effect). Note that the acute hypotensive reaction appears to be short-lived.

When starting an alpha blocker it is often recommended that those already taking an antihypertensive should have their dose reduced to a maintenance level, while initiating the alpha blocker at a low dose, with the first dose taken just before going to bed. Patients should also be warned about the possibility of postural hypotension and how to manage it (i.e. lay down, raise the legs and, when recovered, get up slowly). Similarly, when adding an antihypertensive to an alpha blocker, it may be prudent to decrease the dose of the alpha blocker and re-titrate as necessary.

There is limited evidence that tamsulosin and possibly terazosin may not cause an additional hypotensive effect when given in the longer term in patients with BPH who have hypertension already well controlled with ACE inhibitors. Nevertheless, caution should be exercised in this situation, and a dose reduction of the ACE inhibitor may be required.

Angiotensin II receptor antagonists would be expected to interact in the same way as ACE inhibitors. Some manufacturers of angiotensin II receptor antagonists warn that enhanced hypotensive effects can occur with other antihypertensive drugs, but they do not specifically mention alpha blockers.

1. Xatral (Alfuzosin hydrochloride). Sanofi-Aventis. UK Summary of product characteristics, February 2009.
2. Baba T, Tomiyama T, Takebe K. Enhancement by an ACE inhibitor of first-dose hypotension caused by an alpha$_1$-blocker. *N Engl J Med* (1990) 322, 1237.
3. Hypovase (Prazosin hydrochloride). Pfizer Ltd. UK Summary of product characteristics, August 2007.
4. Lowe FC. Coadministration of tamsulosin and three antihypertensive agents in patients with benign prostatic hyperplasia: pharmacodynamic effect. *Clin Ther* (1997) 19, 730–42.
5. Kirby RS. Terazosin in benign prostatic hyperplasia: effects on blood pressure in normotensive and hypertensive men. *Br J Urol* (1998) 82, 373–9.
6. Hytrin (Terazosin monohydrochloride dihydrate). Amdipharm. UK Summary of product characteristics, June 2009.

Alpha blockers + Aspirin or NSAIDs

Indometacin reduces the blood pressure lowering effects of prazosin in some individuals. However, indometacin and other alpha blockers do not appear to interact adversely. Diclofenac may possibly increase the elimination rate of tamsulosin.

Clinical evidence

(a) Doxazosin

The manufacturers comment that doxazosin has been given without any evidence of adverse interaction to patients receiving NSAIDs,[1] including ibuprofen and indometacin.[2] *In vitro* data in human plasma indicated that although doxazosin is highly bound to plasma proteins, it does not affect the protein binding of **indometacin**.[1,2]

(b) Prazosin

A study in 9 healthy subjects found that **indometacin** 50 mg twice daily for 3 days had no statistically significant effect on the hypotensive effect of a single 5-mg dose of prazosin. However, in 4 of the subjects it was noted that the maximum fall in the mean standing blood pressure due to the prazosin was 20 mmHg less when they were taking **indometacin**. Three of these 4 felt faint when given prazosin alone, but not while they were also taking the **indometacin**.[3] The manufacturer says that prazosin has been given with **indometacin** (and also **aspirin** and **phenylbutazone**) without any adverse interaction in clinical experience to date.[4]

(c) Tamsulosin

Other *in vitro* studies showed that **diclofenac** did not change the free fraction of tamsulosin in human plasma,[5,6] nor was the protein binding of **diclofenac** affected by tamsulosin.[6] The US manufacturer reported that incubation of tamsulosin and **diclofenac** with human liver microsomes showed ambiguous *in vitro* evidence of a metabolic interaction.[6] However, based on *in vitro* data some UK manufacturers suggest that **diclofenac** may increase the elimination rate of tamsulosin.[5,7,8]

(d) Terazosin

The manufacturers of terazosin also note that no adverse interactions have been seen between terazosin and analgesics/anti-inflammatories.[9]

Mechanism

Not established. It seems probable that indometacin inhibits the production of hypotensive prostaglandins by the kidney.

Importance and management

Information about the interactions between alpha blockers and NSAIDs or aspirin appears to be limited, but the general picture suggests that no interaction of significance occurs. A possible exception is the use of indometacin with prazosin, which is consistent with the way indometacin reduces the effects of many other different antihypertensives (e.g. see 'ACE inhibitors + NSAIDs', p.32, and 'Beta blockers + Aspirin or NSAIDs', p.997). It apparently does not affect every patient. If indometacin is added to established treatment with prazosin, be alert for a reduced antihypertensive response. It is not known exactly what happens in patients taking both drugs long-term, but note that with other interactions between antihypertensives and NSAIDs the effects seem to be modest.

1. Cardura (Doxazosin mesilate). Pfizer Ltd. UK Summary of product characteristics, August 2009.
2. Cardura (Doxazosin mesylate). Pfizer Inc. US Prescribing information, July 2009.
3. Rubin P, Jackson G, Blaschke T. Studies on the clinical pharmacology of prazosin. II: The influence of indomethacin and of propranolol on the action and disposition of prazosin. *Br J Clin Pharmacol* (1980) 10, 33–9.
4. Hypovase (Prazosin hydrochloride). Pfizer Ltd. UK Summary of product characteristics, August 2007.
5. Omnic MR (Tamsulosin hydrochloride modified-release capsules). Astellas Pharma Ltd. UK Summary of product characteristics, October 2006.
6. Flomax (Tamsulosin hydrochloride). Astellas Pharma Inc. US Prescribing information, December 2009.
7. Stronazon MR (Tamsulosin hydrochloride modified-release capsules). Actavis UK Ltd. UK Summary of product characteristics, June 2007.
8. Contiflo XL (Tamsulosin hydrochloride). Ranbaxy (UK) Ltd. UK Summary of product characteristics, January 2007.
9. Hytrin (Terazosin monohydrochloride dihydrate). Amdipharm. UK Summary of product characteristics, June 2009.

Alpha blockers + Beta blockers

The risk of first-dose hypotension with prazosin is higher if the patient is already taking a beta blocker. This is also likely to be true of other alpha blockers, particularly alfuzosin and terazosin. In a small study tamsulosin did not have any clinically relevant effects on blood pressure that was already well controlled by atenolol. Alpha blockers and beta blockers may be combined for additional lowering of blood pressure in patients with hypertension.

Clinical evidence

(a) Alfuzosin

In a single-dose study in 8 healthy subjects no pharmacokinetic interaction occurred when alfuzosin 2.5 mg was given with **atenolol** 100 mg.[1] However, the manufacturer reports that, in a similar study, **atenolol** increased the maximum plasma level and AUC of alfuzosin by 28% and 21%, respectively, and alfuzosin increased atenolol levels by 26% and 14%, respectively. There were also significant reductions in mean blood pressure and heart rate.[2] One manufacturer notes that postural hypotension may occur in patients receiving antihypertensives when they start alfuzosin.[3]

(b) Doxazosin

A study involving 2363 patients, with hypertension controlled with a single antihypertensive drug, investigated the effects of adding doxazosin for BPH. The dose of doxazosin was increased gradually to 4 mg daily and then the patients were monitored for 14 weeks. The addition of doxazosin was found to be well tolerated, and adverse effects mainly occurred early after onset of treatment or in patients with lower systolic and diastolic blood pressure. However, the antihypertensive effect was more marked in patients taking beta blockers or diuretics than in patients taking ACE inhibitors or calcium-channel blockers.[4] The manufacturers of doxazosin state that no adverse drug interaction has been observed between doxazosin and beta blockers,[5,6] although they do note that the most common adverse reactions associated with doxazosin are of a postural hypotension type.[5] They specifically note that doxazosin has been given with **atenolol** and **propranolol** without evidence of an adverse interaction.[6]

(c) Indoramin

One manufacturer of indoramin states that concurrent use with beta blockers may enhance hypotensive effects, and that titration of the dose of the beta blocker may be needed when initiating the indoramin.[7]

(d) Prazosin

A marked hypotensive reaction (dizziness, pallor, sweating) occurred in 3 out of 6 hypertensive patients taking **alprenolol** 400 mg twice daily when they were given the first 500-microgram dose of prazosin. In all 6 patients the reduction in blood pressure was greater after the first prazosin dose than after 2 weeks of treatment with prazosin 500 micrograms three times daily with no beta blocker (mean reduction 22/11 mmHg compared with 4/4 mmHg). A further 3 patients already taking prazosin 500 micrograms three times daily had no unusual fall in blood pressure when they were given a 200-mg dose of **alprenolol**.[8] The severity and the duration of the first-dose effect of prazosin were also found to be increased in healthy subjects given a single dose of **propranolol**.[9]

Two studies have shown that the pharmacokinetics of prazosin are not affected by either **alprenolol**[8] or **propranolol**.[10]

(e) Tamsulosin

In a placebo-controlled study in 8 hypertensive men with blood pressure well controlled by **atenolol**, the addition of tamsulosin 400 micrograms daily for 7 days, then 800 micrograms daily for a further 7 days, had no clinically relevant effect on blood pressure (assessed after 6 and 14 days of tamsulosin). No hypotension was seen with the first dose of tamsulosin or when the dose of tamsulosin was increased.[11] *In vitro* evidence suggested that **propranolol** and tamsulosin did not change the free fraction of either drug in human plasma.[12]

(f) Terazosin

Retrospective analysis of a large multinational study, in patients with BPH given terazosin 5 or 10 mg daily, found that terazosin only affected the blood pressure of patients taking beta blockers (**atenolol**, **labetalol**, **metoprolol**, **sotalol**, and **timolol**) if the blood pressure was uncontrolled. No change in blood pressure was seen in those with normal blood pressure (i.e. those without hypertension and those with hypertension controlled by beta blockers). The most common adverse effect in the 10-week terazosin phase was dizziness, and the incidence of this appeared to be lower in those taking antihypertensives (13 to 16%) than in those not taking antihypertensives (21 to 25%).[13]

Mechanism

The normal cardiovascular response (a compensatory increased cardiac output and heart rate) that should follow the first-dose hypotensive reaction to alpha blockers is apparently compromised by the presence of a beta blocker. The problem is usually only short lasting because some physiological compensation occurs within hours or days, and this allows the blood pressure to be lowered without falling precipitously. Tamsulosin possibly has less effect on blood pressure since it has some selectivity for alpha receptors in the prostate.

Importance and management

An established interaction. Some patients experience acute postural hypotension, tachycardia and palpitations when they begin to take prazosin or other alpha blockers. A few patients even collapse in a sudden faint within 30 to 90 minutes, and this can be exacerbated if they are already taking a beta blocker. The evidence seems to suggest that this is greater with alfuzosin and terazosin, but it is unclear whether there are any real differences between the alpha blockers in their propensity to cause these effects.

When starting an alpha blocker it is recommended that those already taking a beta blocker should have their dose of beta blocker reduced to a maintenance dose and begin with a low dose of the alpha blocker, with the first dose taken just before going to bed. They should also be warned about the possibility of postural hypotension and how to manage it (i.e. lay down, raise the legs and, when recovered, get up slowly). Similarly, when adding a beta blocker to an alpha blocker, it may be prudent to decrease the dose of the alpha blocker and re-titrate as necessary. There is limited evidence that tamsulosin and possibly terazosin may not cause an additional hypotensive effect when taken long term by patients with BPH who have hypertension already well controlled with beta blockers. Nevertheless, caution should be exercised in this situation, and a dose reduction of the beta blocker may still be required.

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3. Xatral (Alfuzosin hydrochloride). Sanofi-Aventis. UK Summary of product characteristics, February 2009.
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5. Cardura (Doxazosin mesilate). Pfizer Ltd. UK Summary of product characteristics, August 2009.
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Alpha blockers + Calcium-channel blockers

Alpha blockers and calcium-channel blockers may be combined for additional blood pressure lowering in patients with hypertension. Blood pressure may fall sharply when calcium-channel blockers are first given to patients already taking alpha blockers (particularly prazosin and terazosin), and *vice versa*. In a small study, tamsulosin did not have any clinically relevant effects on blood pressure well controlled by nifedipine. Verapamil may increase the AUC of prazosin and terazosin, and may also increase the adverse effects related to tamsulosin. The concurrent use of diltiazem and alfuzosin can raise the levels of both drugs.

Clinical evidence

(a) Alfuzosin

The US manufacturer notes that when **diltiazem** 240 mg daily was given with alfuzosin 2.5 mg three times daily the maximum serum levels and AUC of alfuzosin were raised by 50% and 30%, respectively, and the maximum serum levels and AUC of **diltiazem** were raised by 40%. However, no changes in blood pressure were seen.[1]

(b) Doxazosin

In a study, 6 normotensive subjects were given **nifedipine** 20 mg twice daily for 20 days with doxazosin 2 mg once daily for the last 10 days. Although there was a tendency for first-dose hypotension, no serious adverse events or postural symptoms were seen. The same results were noted in 6 other normotensive subjects given the drugs in the opposite order, and no pharmacokinetic interactions were found.[2] The US manufacturer notes a study in which slight (less than 20%) alterations were found in the pharmacokinetics of **nifedipine** and doxazosin when they were given concurrently; however, these pharmacokinetic effects would not be expected to be clinically significant. As would be expected, blood pressures were lower when both drugs were given.[3]

For comment that doxazosin appeared to have less effect on blood pressure in patients with BPH receiving calcium-channel blockers than in those taking beta blockers or diuretics, see 'Alpha blockers + Beta blockers', p.94.

(c) Prazosin

1. Nifedipine. In a placebo-controlled, crossover study 12 hypertensive subjects were given nifedipine 20 mg and prazosin 2 mg, separated by one hour. The combination of the two drugs reduced blood pressure more than either drug alone, although the effects of prazosin were delayed when it was given after nifedipine.[4] Another study similarly showed that prazosin, given 2 hours before nifedipine, caused an enhanced hypotensive effect.[5]

Two patients with severe hypertension given prazosin 4 or 5 mg experienced a sharp fall in blood pressure shortly after being given nifedipine *sublingually*. One of them complained of dizziness and had a reduction in standing blood pressure from 232/124 to 88/48 mmHg about 20 minutes after taking nifedipine 10 mg. However, in a further 8 patients with hypertension taking prazosin, the reduction in blood pressure 20 minutes after the addition of *sublingual* nifedipine was smaller (mean reduction of 25/12 mmHg when lying and 24/17 mmHg when standing).[6] It is not clear what contribution prazosin had to the effect seen with *sublingual* nifedipine, since the experiment was not repeated using a prazosin placebo, but blood pressure in these patients had earlier remained unchanged 1 hour after taking prazosin alone. It should also be noted that *sublingual* nifedipine alone may cause a dangerous drop in blood pressure.

2. Verapamil. A study in 8 normotensive subjects given a single 1-mg dose of prazosin found that the peak serum prazosin levels were raised by 85% (from 5.2 to 9.6 nanograms/mL) and the prazosin AUC was increased by 62% when it was given with a single 160-mg dose of verapamil. The standing blood pressure 4 hours after dosing was unchanged after verapamil alone, but fell from 114/82 to 99/73 mmHg with prazosin alone, and was further reduced to 89/68 mmHg when both drugs were given together.[7] A similar pharmacokinetic interaction was noted in another study in hypertensive patients.[8] In this study, the first 1-mg dose of prazosin alone caused a 23 mmHg fall in standing systolic blood pressure, and half the patients (3 of 6) experienced symptomatic postural hypotension. A similar fall in blood pressure occurred when the first 1-mg dose of prazosin was given to 6 patients who had been taking verapamil for 5 days: 2 patients experienced symptomatic postural hypotension.[8]

(d) Tamsulosin

1. Nifedipine. In a placebo-controlled study in 8 hypertensive men with blood pressure well controlled by nifedipine, the addition of tamsulosin 400 micrograms daily for 7 days then 800 micrograms daily for a further 7 days had no clinically relevant effect on blood pressure (assessed after 6 and 14 days of tamsulosin). In addition, no first-dose hypotension was seen on the first day of tamsulosin, or when the tamsulosin dose was increased.[9]

2. Verapamil. A study into the safety of tamsulosin, with particular regard to the use of other medications, found that the concurrent use of verapamil increased the risk of adverse events related to tamsulosin by threefold. The use of other calcium-channel blockers (not specified) did not appear to increase adverse effects, although there was a trend towards an increase.[10]

(e) Terazosin

1. Dihydropyridine calcium-channel blockers. Retrospective analysis of a large multinational study, in patients with BPH given terazosin 5 or 10 mg daily, found that terazosin only affected the blood pressure of patients taking calcium-channel blockers (**amlodipine**, **felodipine**, **flunarizine**, **isradipine** and **nifedipine**) if the blood pressure was uncontrolled. No change in blood pressure was seen in those with normal blood pressure (i.e. those without hypertension and those with hypertension controlled by calcium-channel blockers). The most common adverse effect in the 10-week terazosin phase was dizziness, and the incidence of this appeared to be lower in those taking antihypertensives (13 to 16%) than in those not taking antihypertensives (21 to 25%).[11]

2. Verapamil. When verapamil 120 mg twice daily was given to 12 hypertensive patients taking terazosin 5 mg daily, the peak plasma levels and the AUC of terazosin were increased by about 25%. In contrast, in another 12 patients taking verapamil 120 mg twice daily, the addition of terazosin (1 mg increased to 5 mg daily) did not affect verapamil pharmacokinetics.[12] Both groups of patients had significant falls in standing blood pressure when they first started taking both drugs. Symptomatic orthostatic hypotension (which lessened within about 3 weeks) occurred in 4 patients when verapamil was first added to terazosin, and in 2 patients when terazosin was first added to verapamil.[12]

Mechanism

Not fully understood. It would seem that the vasodilatory effects of the alpha blockers and the calcium-channel blockers can be additive or synergistic, particularly after the first dose.[2,5,13] Tamsulosin possibly has less effect on blood pressure since it has some selectivity for alpha receptors in the prostate. It has been suggested that the interaction between tamsulosin and verapamil occurs because verapamil has alpha antagonist effects,[10] but as tamsulosin is, in part, metabolised by the cytochrome P450 isoenzyme CYP3A4,[14] which verapamil modestly inhibits, there may be a pharmacokinetic component to the interaction.

The fall in blood pressure seen with prazosin or terazosin and verapamil may, in part, result from a pharmacokinetic interaction, involving reduced hepatic metabolism, although the exact mechanism is not certain.[7,12,13] The pharmacokinetic interaction between alfuzosin and diltiazem appears to occur because diltiazem is a moderate inhibitor of CYP3A4, which is the principal enzyme involved in the hepatic metabolism of alfuzosin.[1]

Importance and management

The interaction between calcium-channel blockers and alpha blockers would appear to be established and of clinical importance, although the documentation is limited. Marked additive hypotensive effects can occur when concurrent use is first started, and the effects may be increased if a pharmacokinetic interaction also occurs (for example with alfuzosin and diltiazem, and prazosin or terazosin with verapamil). When starting an alpha blocker it is recommended that patients already taking a calcium-channel blocker should have their dose of calcium-channel blocker reduced and begin with a low-dose of alpha blocker, with the first dose taken just before going to bed. Caution should also be taken when calcium-channel blockers are added to established treatment with an alpha blocker. Patients should be warned about the possibilities of exaggerated hypotension, and told what to do if they feel faint and dizzy (i.e. lay down, raise the legs, and, when recovered, get up slowly). There is limited evidence that tamsulosin and possibly terazosin may not cause an additional hypotensive effect when taken longer term in patients with BPH who have hypertension already well controlled with calcium-channel blockers. Nevertheless, caution should be exercised in this situation, and a dose reduction of the calcium-channel blocker may be required. It seems likely that any pharmacokinetic interaction will be accounted for by this dose titration.

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14. Flomax (Tamsulosin hydrochloride). Astellas Pharma Inc. US Prescribing information, December 2009.

Alpha blockers + Cimetidine

No important interaction occurs between cimetidine and either alfuzosin or doxazosin in healthy subjects. Tamsulosin does not appear to have a clinically significant interaction with cimetidine, but caution is recommended with high tamsulosin doses.
For mention of an interaction between tolazoline and cimetidine or ranitidine, see 'Tolazoline + H_2-receptor antagonists', p.1076.

Clinical evidence, mechanism, importance and management

(a) Alfuzosin

In 10 healthy subjects cimetidine 1 g daily in divided doses for 20 days was found to have minimal effects on the pharmacokinetics of a single 5-mg dose of alfuzosin. The maximum serum levels and AUC of alfuzosin were increased by up to 24%, (not statistically significant) and the half-life was shortened by 14%. Cimetidine did not appear to increase the incidence of postural hypotension seen with alfuzosin.[1] These changes were not thought to be clinically relevant, and there would seem to be no reason for avoiding concurrent use. However, caution has been recommended for elderly patients, where the bioavailability of alfuzosin is generally increased and, consequently, even a small increase in plasma levels might be clinically relevant.[1] Other H_2-receptor antagonists would not be expected to interact, but there does not seem to be any evidence to support this suggestion.

(b) Doxazosin

The manufacturers of doxazosin note that, in a placebo-controlled study in healthy subjects, cimetidine 400 mg twice daily increased the AUC of a single 1-mg dose of doxazosin given on day 4 by 10%.[2,3] This seems unlikely to be of clinical significance, especially as this is within the expected intersubject variation of the doxazosin AUC.[3]

(c) Tamsulosin

A study in 10 healthy subjects found that giving cimetidine 400 mg four times daily with a single 400-microgram dose of tamsulosin resulted in a 44% increase in the AUC of tamsulosin and a 26% reduction in tamsulosin clearance. Adverse events were not increased by concurrent use.[4] The UK manufacturer of tamsulosin considers that no dosage adjustment is necessary.[5] However, the US manufacturer advises caution, particularly with doses greater than 400 micrograms.[6] In practice this probably means being aware that an increase in the adverse effects of tamsulosin might occur as a result of this interaction. Other H_2-receptor antagonists would not be expected to interact, but there does not seem to be any evidence to support this suggestion.

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3. Cardura (Doxazosin mesilate). Pfizer Ltd. UK Summary of product characteristics, August 2009.
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5. Flomaxtra XL (Tamsulosin hydrochloride). Astellas Pharma Ltd. UK Summary of product characteristics, October 2006.
6. Flomax (Tamsulosin hydrochloride). Astellas Pharma Inc. US Prescribing information, December 2009.

Alpha blockers + CYP3A4 or CYP2D6 inhibitors

Potent CYP3A4 inhibitors may increase the levels of alfuzosin, and inhibitors of CYP3A4 and CYP2D6 may increase the levels of tamsulosin. *In vitro* studies suggest that doxazosin may also be affected by potent CYP3A4 inhibitors.

Clinical evidence, mechanism, importance and management

(a) Alfuzosin

The US manufacturer of alfuzosin XL briefly cites a study in which **ketoconazole** 400 mg increased the AUC and maximum levels of a 10-mg dose of alfuzosin by 3.2-fold and 2.3-fold, respectively. They therefore contraindicate the concurrent use of potent CYP3A4 inhibitors (they name **itraconazole**, **ketoconazole** and **ritonavir**).[1] Based on the information available the contraindication with alfuzosin seems somewhat cautious, although **ritonavir** may be expected to have a greater effect than **ketoconazole**. If any of the potent CYP3A4 inhibitors named is given with alfuzosin it would seem prudent to use the minimum dose of the alpha blocker and titrate the dose as necessary, monitoring for adverse effects, particularly first-dose hypotension when the dose is increased. Be aware that risks are likely to be greater in patients also taking other antihypertensives.

(b) Doxazosin

Doxazosin is extensively metabolised in the liver, and *in vitro* studies suggest that CYP3A4 is the primary enzyme involved, although CYP2D6 and CYP2C19 metabolic pathways also contribute.[2] The US manufacturer advises caution when a potent CYP3A4 inhibitor, such as **atazanavir**, **clarithromycin**, **indinavir**, **itraconazole**, **ketoconazole**, **nefazodone**, **nelfinavir**, **ritonavir**, **saquinavir**, **telithromycin** or **voriconazole** is given with doxazosin.[2] The clinical relevance of these predictions is unclear, but until more is known some caution seems prudent. If concurrent use is undertaken be aware that the effects of doxazosin may be increased.

(c) Tamsulosin

The US manufacturer states that tamsulosin is extensively metabolised (mainly by CYP2D6 and CYP3A4). They therefore state that tamsulosin 400 micrograms should not be given with strong inhibitors of CYP3A4 (e.g. **ketoconazole**). In addition, they suggest that tamsulosin should be used with caution in combination with moderate or strong inhibitors of CYP2D6 (e.g. **fluoxetine**) and moderate inhibitors of CYP3A4 (e.g. **erythromycin**), in patients that are CYP2D6 poor metabolisers (that is, those with low levels or those deficient in this isoenzyme), particularly at doses higher than 400 micrograms.[3] The clinical relevance of these pre-

dictions is unclear, and the metaboliser status of a patient is rarely known. Until more is known some caution seems prudent. If concurrent use is undertaken be aware that the effects of tamsulosin may be increased.

1. Uroxatral (Alfuzosin hydrochloride extended-release tablets). Sanofi-Aventis US LLC. US Prescribing information, June 2009.
2. Cardura XL (Doxazosin mesylate extended release tablets). Pfizer Inc. US Prescribing information, February 2006.
3. Flomax (Tamsulosin hydrochloride). Astellas Pharma Inc. US Prescribing information, December 2009.

Alpha blockers + Diuretics

As would be expected, the use of an alpha blocker with a diuretic may result in an additive hypotensive effect, but aside from first-dose hypotension, this usually seems to be a beneficial interaction in patients with hypertension. The effects in patients with congestive heart failure may be more severe.

Clinical evidence

(a) Alfuzosin

In a single-dose study in 8 healthy subjects no pharmacokinetic interaction occurred when alfuzosin 5 mg was given with **hydrochlorothiazide** 25 mg.[1] The manufacturer notes that postural hypotension may occur when patients receiving antihypertensives start alfuzosin.[2]

(b) Doxazosin

A study, involving 2363 patients with hypertension controlled with a single antihypertensive drug, investigated the effects of adding doxazosin for BPH. The dose of doxazosin was increased gradually to 4 mg daily and then the patients were monitored for a further 14 weeks of treatment. The addition of doxazosin was found to be well tolerated, and adverse effects mainly occurred early after onset of treatment or in patients with lower systolic and diastolic blood pressure. However, the antihypertensive effect was more marked in patients taking diuretics or beta blockers than in patients taking ACE inhibitors or calcium-channel blockers.[3] The manufacturer of doxazosin notes that no adverse drug interaction has been seen between doxazosin and **thiazides** (including **hydrochlorothiazide**)[4,5] or **furosemide**.[4] However, they point out that doxazosin doses of greater then 4 mg daily increase the likelihood of adverse effects such as postural hypotension and syncope.[5]

(c) Indoramin

The manufacturers of indoramin state that concurrent use with diuretics (especially **thiazides**) may enhance the hypotensive action.[6,7]

(d) Tamsulosin

The US manufacturer of tamsulosin[8] notes that when 10 healthy subjects taking tamsulosin 800 micrograms daily were given a single 20-mg intravenous dose of **furosemide** the AUC of tamsulosin was reduced by about 12%. Both the UK and US manufacturers note that as levels remained within the normal range no change in dosage is necessary.[8,9] *In vitro* evidence suggested that tamsulosin and **trichlormethiazide** did not change the free fraction of either drug in human plasma.[10]

(e) Terazosin

A study in 296 hypertensive patients found that terazosin 5 mg daily lowered the supine and standing blood pressure by 4.8/8.1 mmHg and 2.6/6.1 mmHg, respectively, when compared with placebo. When **methyclothiazide** 5 mg daily was also given, the blood pressure was reduced by 20.6/14.4 mmHg and 23.3/14.6 mmHg, respectively, when compared with placebo. A similar reduction in blood pressure (17.3/12.4 mmHg and 16/11.2 mmHg, respectively) occurred when the dose of **methyclothiazide** was halved. The combination, starting with terazosin and then adding a thiazide diuretic, was considered to be effective and well tolerated.[11]

Retrospective analysis of a large multinational study in patients with BPH given terazosin 5 or 10 mg daily found that terazosin only affected the blood pressure of patients taking diuretics (**amiloride**, **bendroflumethiazide**, **chlortalidone**, **hydrochlorothiazide** and **spironolactone**) if the blood pressure was uncontrolled. No change in blood pressure was seen in those with normal blood pressure (i.e. those without hypertension and those with hypertension controlled by diuretics). The most common adverse effect in the 10-week terazosin phase was dizziness, and the incidence of this appeared to be lower in those taking antihypertensives (13 to 16%) than in those not taking antihypertensives (21 to 25%).[12] However, the UK manufacturer of terazosin notes that the incidence of dizziness in patients taking terazosin was higher when they were also taking a diuretic.[13] Similarly, in clinical studies in patients with hypertension, a higher proportion experienced dizziness when they took terazosin with a diuretic, than when they took a placebo with a diuretic (20% versus 13%).[14]

Mechanism, importance and management

The acute first-dose hypotension that can occur with alpha blockers can be exacerbated by 'beta blockers', (p.94) and 'calcium-channel blockers', (p.95), but there seems to be no direct evidence that diuretics normally do the same. However, the manufacturer of **prazosin** suggests that it is particularly important that patients with congestive heart failure who have undergone vigorous diuretic treatment should be started on the lowest dose of prazosin (500 micrograms two to four times daily), with the initial dose given at bedtime. The reason is that left ventricular filling pressure may decrease in these patients with a resultant fall in cardiac output and systemic blood pressure.[15] There seems to be no reason for avoiding concurrent use if these precautions are taken. The only other direct evidence of a possible problem is with terazosin, and the manufacturer of terazosin states that when it is added to a diuretic, dose reduction and re-titration may be necessary.[13]

No guidance is given with the other alpha blockers, but as most manufacturers note that postural hypotension is a possibility, it may be prudent to warn patients about the possibilities of exaggerated hypotension, and tell them what to do if they feel faint and dizzy (i.e. lay down, raise the legs, and, when recovered, get up slowly).

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4. Cardura (Doxazosin mesilate). Pfizer Ltd. UK Summary of product characteristics, August 2009.
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6. Doralese Tiltab (Indoramin hydrochloride). GlaxoSmithKline UK. UK Summary of product characteristics, June 2007.
7. Baratol (Indoramin hydrochloride). Shire Pharmaceuticals Ltd. UK Summary of product characteristics, March 2004.
8. Flomax (Tamsulosin hydrochloride). Astellas Pharma Inc. US Prescribing information, December 2009.
9. Flomaxtra XL (Tamsulosin hydrochloride). Astellas Pharma Ltd. UK Summary of product characteristics, October 2006.
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14. Rudd P. Cumulative experience with terazosin administered in combination with diuretics. *Am J Med* (1986) 80 (Suppl 5B), 49–54.
15. Hypovase (Prazosin hydrochloride). Pfizer Ltd. UK Summary of product characteristics, August 2007.

Alpha blockers + Dutasteride or Finasteride

No clinically important interaction has been found to occur between finasteride and doxazosin. In one study terazosin did not interact with finasteride, but in another there was a suggestion of modestly increased finasteride levels. No clinically significant interaction appears to occur between dutasteride and tamsulosin or terazosin.

Clinical evidence, mechanism, importance and management

(a) Dutasteride

A study in 24 subjects given dutasteride 500 micrograms daily for 14 days found that when they were also given **tamsulosin** 400 micrograms daily or **terazosin** (titrated to 10 mg daily) for 14 days, the pharmacokinetics of the alpha blockers remained unchanged.[1] Furthermore, a clinical study in 327 men demonstrated that the combination of **tamsulosin** and dutasteride was well tolerated over a period of 6 months.[2]

(b) Finasteride

In a parallel study, 48 healthy subjects were divided into three groups. One group took **terazosin** 10 mg daily for 18 days, another took finasteride 5 mg daily for 18 days, and the third group took both drugs. The pharmacokinetics and pharmacodynamics of both drugs remained unchanged, and the serum levels of testosterone and dihydrotestosterone were also unaltered by concurrent use.[3] However, another study, comparing groups of healthy subjects taking finasteride and alpha blockers, found that after 10 days of combined use, the maximum finasteride level was 16% higher and the AUC 31% higher. The levels of the group taking finasteride and **doxazosin** were not significantly different. The clinical significance of the possible modest increased finasteride levels with **terazosin** is not clear,[4] but is likely to be small.

Incubation of **tamsulosin** and finasteride with human liver microsomes showed no *in vitro* evidence of clinically significant metabolic interactions.[5]

1. GlaxoSmithKline. Personal Communication, August 2003.
2. Barkin J, Guimarães M, Jacobi G, Pushkar D, Taylor S, van Vierssen Trip OB on behalf of the SMART-1 investigator group. Alpha-blocker therapy can be withdrawn in the majority of men following initial combination therapy with the dual 5α-reductase inhibitor dutasteride. *Eur Urol* (2003) 44, 461–6.
3. Samara E, Hosmane B, Locke C, Eason C, Cavanaugh J, Granneman GR. Assessment of the pharmacokinetic-pharmacodynamic interaction between terazosin and finasteride. *J Clin Pharmacol* (1996) 36, 1169–78.
4. Vashi V, Chung M, Hilbert J, Lawrence V, Phillips K. Pharmacokinetic interaction between finasteride and terazosin, but not finasteride and doxazosin. *J Clin Pharmacol* (1998) 38, 1072–6.
5. Flomax (Tamsulosin hydrochloride). Astellas Pharma Inc. US Prescribing information, December 2009.

Alpha blockers + Food

Food appears to have no clinical effect on the pharmacokinetics of alfuzosin, doxazosin, or terazosin; however, food may affect the absorption from some extended-release preparations of these alpha blockers. The bioavailability of tamsulosin is reduced by food.

Clinical evidence, mechanism, importance and management

The manufacturer of **alfuzosin** says that its pharmacokinetics are not affected by food,[1] but the extent of absorption of the extended-release preparation is 50% lower under fasting conditions[2] and therefore extended-release preparations should be taken immediately after a meal.[2,3]

In a crossover study in 12 hypertensive subjects, the mean maximum plasma concentration and AUC of **doxazosin** were not significantly affected by food. However, when compared with the fasting state, food increased the maximum levels and AUC of extended-release doxazosin (*Cardura XL*) by 32% and 18%, respectively.[4] The US manufacturer says that, in order to provide the most consistent exposure, *Cardura XL* should be given with breakfast,[4] but the UK manufacturer says that the modified-release tablet may be taken with or without food.[5]

The manufacturer of **tamsulosin** states that under fasted conditions, there is a 30% increase in bioavailability and a 40% to 70% increase in the maximum levels, when compared with fed conditions.[6] However, some manufacturers recommend that, for uniformity of absorption, **tamsulosin** should be taken after the same meal each day.[6-8] With other formulations (e.g. the prolonged-release tablet *Flomaxtra XL*) the rate and extent of absorption of **tamsulosin** is not affected by food and the manufacturer says *Flomaxtra XL* may be taken with or without food.[9]

The manufacturer of **terazosin** states that food has little or no effect on its bioavailability.[10]

1. Xatral (Alfuzosin hydrochloride). Sanofi-Aventis. UK Summary of product characteristics, February 2009.
2. Uroxatral (Alfuzosin hydrochloride extended-release tablets). Sanofi-Aventis US LLC. US Prescribing information, June 2009.
3. Xatral XL (Alfuzosin hydrochloride prolonged-release tablets). Sanofi-Aventis. UK Summary of product characteristics, May 2007.
4. Cardura XL (Doxazosin mesylate extended release tablets). Pfizer Inc. US Prescribing information, February 2006.
5. Cardura XL (Doxazosin mesilate modified-release tablets). Pfizer Ltd. UK Summary of product characteristics, September 2007.
6. Flomax (Tamsulosin hydrochloride). Astellas Pharma Inc. US Prescribing information, December 2009.
7. Omnic MR (Tamsulosin hydrochloride modified-release capsules). Astellas Pharma Ltd. UK Summary of product characteristics, October 2006.
8. Stronazon MR (Tamsulosin hydrochloride modified-release capsules). Actavis UK Ltd. UK Summary of product characteristics, June 2007.
9. Flomaxtra XL (Tamsulosin hydrochloride). Astellas Pharma Ltd. UK Summary of product characteristics, October 2006.
10. Hytrin (Terazosin monohydrochloride dihydrate). Amdipharm. UK Summary of product characteristics, June 2009.

Alpha blockers + Miscellaneous

The manufacturers of several of the alpha blockers provide lists of drugs that are not expected to interact. These are shown in 'Table 4.2', (p.99). In some cases these predictions are based on *in vitro* studies or from observation of clinical usage. Although this type of data can provide a guide, remember that it gives only the broadest indication of whether or not a drug interacts.

Alpha blockers + Nitrates

There may be an enhanced hypotensive effect if alpha blockers are given with nitrates.

The UK manufacturer of **alfuzosin** warns that it might interact with nitrates.[1] Although this interaction is not specifically mentioned for other alpha blockers, most manufacturers warn of enhanced hypotensive effects with other drugs that can lower blood pressure. Consider also 'Antihypertensives + Other drugs that affect blood pressure', p.1051.

In addition, the manufacturer of **prazosin** warns that when prazosin is initially given to patients with congestive heart failure who have undergone vigorous diuretic or other vasodilator treatment, the resultant decrease in left ventricular filling pressure may be associated with a significant fall in cardiac output and systemic blood pressure. Observance of the recommended starting dose of **prazosin** followed by gradual dosage increase is particularly important in such patients.[2]

1. Xatral (Alfuzosin hydrochloride). Sanofi-Aventis. UK Summary of product characteristics, February 2009.
2. Hypovase (Prazosin hydrochloride). Pfizer Ltd. UK Summary of product characteristics, August 2007.

Alpha blockers; Bunazosin + Rifampicin (Rifampin)

Rifampicin markedly reduces bunazosin serum levels.

Clinical evidence, mechanism, importance and management

In 15 healthy subjects a 7-day course of rifampicin 600 mg daily reduced the mean maximum serum levels of bunazosin 6 mg daily by 82% (from 11.6 to 2.1 nanograms/mL). The bunazosin AUC was reduced by more than sevenfold. The duration of the blood pressure lowering effect of bunazosin was shortened, the heart rate increase was less pronounced, and some adverse effects of bunazosin (fatigue, headache) disappeared.[1,2] The probable reason is that the rifampicin (a recognised, potent enzyme inducer) increases the metabolism of bunazosin by the liver so that its levels are reduced, and its effects therefore diminished.

The evidence seems to be limited to this study, but anticipate the need to raise the bunazosin dosage if rifampicin is added. Information about other alpha blockers does not seem to be available.

1. Al-Hamdan Y, Otto U, Kirch W. Interaction of rifampicin with bunazosin, an $alpha_1$-adrenoceptor antagonist. *J Clin Pharmacol* (1993) 33, 998.
2. Nokhodian A, Halabi A, Ebert U, Al-Hamdan Y, Kirch W. Interaction of rifampicin with bunazosin, an α_1-adrenoceptor antagonist, in healthy volunteers. *Drug Invest* (1993) 6, 362–4.

Alpha blockers; Indoramin + MAOIs

Based on early theoretical considerations, the manufacturers of indoramin contraindicate its use with MAOIs.

Clinical evidence, mechanism, importance and management

The concurrent use of MAOIs is contraindicated by the manufacturers of indoramin.[1,2] This was included in the datasheet at the time indoramin was first licensed, and was based on a theoretical suggestion that the effects of

Table 4.2 Drugs that are not expected to interact with alpha blockers as listed by the manufacturers

	Doxazosin[1, 2]	*Prazosin*[3]	*Tamsulosin*[4, 5, 6]	*Terazosin*[7]
Amitriptyline			No expected interaction (*in vitro* study)	
Analgesics	No expected interaction with codeine or paracetamol (acetaminophen)	No expected interaction with dextropropoxyphene (propoxyphene) or phenylbutazone		No expected interaction
Antacids	No expected interaction			
Antiarrhythmics		No expected interaction with procainamide or quinidine		No expected interaction
Antibacterials	No expected interaction with amoxicillin, co-trimoxazole, or erythromycin			No expected interaction
Antidiabetic drugs	No expected interaction with oral hypoglycaemic drugs	No expected interaction with chlorpropamide, insulin, phenformin, tolazamide, or tolbutamide	No expected interaction with glibenclamide (glyburide) (*in vitro* study)	No expected interaction
Antigout drugs	No expected interaction with uricosuric drugs	No expected interaction with allopurinol, colchicine, or probenecid		No expected interaction
Anxiolytics and Hypnotics	No expected interaction with diazepam	No expected interaction with chlordiazepoxide or diazepam	No expected interaction with diazepam (*in vitro* study)	No expected interaction
Chlorphenamine	No expected interaction			
Cold and flu remedies	No expected interaction			
Corticosteroids	No expected interaction			
Phenobarbital		No expected interaction		
Phenytoin	No expected interaction (*in vitro* study)			
Salbutamol (Albuterol)			No expected interaction (*in vitro* study)	
Simvastatin			No expected interaction (*in vitro* study)	

1. Cardura (Doxazosin mesylate). Pfizer Inc. US Prescribing information, July 2009.
2. Cardura (Doxazosin mesylate). Pfizer Ltd. UK Summary of product characteristics, August 2009.
3. Hypovase (Prazosin hydrochloride). Pfizer Ltd. UK Summary of product characteristics, June 2009.
4. Stronazon MR Capsules (Tamsulosin hydrochloride). Actavis UK Ltd. UK Summary of product characteristics, June 2007.
5. Flomaxtra XL (Tamsulosin hydrochloride). Astellas Pharma Ltd. UK Summary of product characteristics, September 2009.
6. Flomax (Tamsulosin hydrochloride). Astellas Pharma Inc. US Prescibing information, December 2009.
7. Hytrin Tablets 1 mg (Terazosin monohydrochloride dihydrate). Amdipharm. UK Summary of product characteristics, June 2009.

noradrenaline (norepinephrine) may be potentiated by indoramin,[3] leading to vasoconstriction, with a possible increase in blood pressure. However, the pharmacology of these drugs suggests just the opposite, namely that hypotension is the more likely outcome. (Note that the hypertensive effects of noradrenaline (norepinephrine) may be treated with a non-selective alpha blocker such as phentolamine.) The manufacturers are not aware of any reported interactions between indoramin and MAOIs.[3] Note that the MAOIs are not contraindicated with any of the other alpha blockers.

1. Doralese Tiltab (Indoramin hydrochloride). GlaxoSmithKline UK. UK Summary of product characteristics, June 2007.
2. Baratol (Indoramin hydrochloride). Shire Pharmaceuticals Ltd. UK Summary of product characteristics, March 2004.
3. GlaxoSmithKline. Personal communication, August 2003.

5

Anaesthetics and Neuromuscular blockers

Many patients undergoing anaesthesia may be taking long-term medication, which may affect their haemodynamic status during anaesthesia. This section is limited to drug interactions and therefore does not cover the many precautions relating to patients taking long-term medication and undergoing anaesthesia.

(a) General anaesthetics

In general anaesthesia a balanced approach is often used to meet the main goals of the anaesthetic procedure. These goals are unconsciousness/amnesia, analgesia, muscle relaxation, and maintenance of homoeostasis. Therefore general anaesthesia often involves the use of several drugs, including benzodiazepines, opioids, and anticholinesterases, as well as general anaesthetics (sometimes more than one) and neuromuscular blockers. The use of several different types of drugs in anaesthesia means that there is considerable potential for drug interactions to occur in the peri-operative period, but this section concentrates on the effects of drugs on general anaesthetics and neuromuscular blockers. The interactions of other drugs used peri-operatively are mainly covered under 'anticholinesterases', (p.396), 'benzodiazepines', (p.831), and 'opioids', (p.149).

There may be difficulty in establishing which of the drugs being used in a complex regimen are involved in a suspected interaction. It should also be borne in mind that disease processes and the procedure for which anaesthesia is used may also be factors to be taken into account when evaluating a possible interaction.

Some established interactions are advantageous and are employed clinically. For example, the hypnotic and anaesthetic effects of 'propofol and midazolam', (p.106), are found to be greater than the expected additive effects and this synergy allows for lower dosage regimens in practice. Similarly nitrous oxide reduces the required dose of inhalational general anaesthetics (see 'Anaesthetics, general + Anaesthetics, general', p.103).

The general anaesthetics mentioned in this section are listed in 'Table 5.1', (p.101). Barbiturates used as anaesthetics (e.g. thiopental) are largely covered here, whereas barbiturates used predominantly for their antiepileptic or sedative properties (e.g. phenobarbital or secobarbital) are dealt with in the appropriate sections.

Many anaesthetics have been associated with arrhythmias, due to their sensitising effects on the myocardium. A suggested listing of inhalational anaesthetics in order of decreasing sensitising effect on the myocardium is as follows: cyclopropane, halothane, enflurane/methoxyflurane, desflurane/isoflurane/sevoflurane.

(b) Local anaesthetics

The interactions discussed in this section mainly involve the interaction of drugs with local anaesthetics used for epidural or spinal anaesthesia. The interactions of lidocaine used as an antiarrhythmic is dealt with in 'Antiarrhythmics', (p.273). The local anaesthetics mentioned in this section are listed in 'Table 5.1', (p.101).

(c) Neuromuscular blockers

The competitive (non-depolarising) neuromuscular blockers and depolarising neuromuscular blockers mentioned in this section are listed in 'Table 5.2', (p.101). The modes of action of the two types of neuromuscular blocker are discussed in the monograph 'Neuromuscular blockers + Neuromuscular blockers', p.142. It should be noted that mivacurium (a competitive blocker) and suxamethonium (a depolarising blocker) are hydrolysed by cholinesterase, so share some interactions in common that are not relevant to other competitive neuromuscular blockers.

Table 5.1 Anaesthetics

General anaesthetics			
Halogenated inhalational anaesthetics	**Miscellaneous inhalational anaesthetics**	**Barbiturate parenteral anaesthetics**	**Miscellaneous parenteral anaesthetics**
Chloroform	Anaesthetic ether	Methohexital	Etomidate
Desflurane	Cyclopropane	Thiamylal	Ketamine
Enflurane	Nitrous oxide	Thiopental	Propofol
Halothane	Xenon		
Isoflurane			
Methoxyflurane			
Sevoflurane			
Trichloroethylene			
Local anaesthetics			
Amide-type	**Ester-type (ester of benzoic acid)**	**Ester-type (ester of para-aminobenzoic acid)**	
Articaine	Cocaine	Chloroprocaine	
Bupivacaine		Procaine	
Etidocaine		Propoxycaine	
Levobupivacaine		Tetracaine	
Lidocaine			
Mepivacaine			
Prilocaine			
Ropivacaine			

Table 5.2 Neuromuscular blockers

Competitive (Non-depolarising) blockers - Aminosteroid type	*Competitive (Non-depolarising) blockers - Benzylisoquinolinium type*	*Depolarising blockers*
Pancuronium	Alcuronium	Suxamethonium (Succinylcholine)
Pipecuronium	Atracurium	
Rapacuronium	Cisatracurium	
Rocuronium	Doxacurium	
Vecuronium	Gallamine	
	Metocurine	
	Mivacurium	
	Tubocurarine (d-Tubocurarine)	

Anaesthetics, general + ACE inhibitors or Angiotensin II receptor antagonists

The concurrent use of general anaesthetics and antihypertensives generally need not be avoided but it should be recognised that the normal homoeostatic responses of the cardiovascular system will be impaired. For example, marked hypotension has been seen in patients taking ACE inhibitors or angiotensin-II receptor antagonists during anaesthetic induction.

Clinical evidence, mechanism, importance and management

(a) ACE inhibitors

Marked hypotension (systolic BP 75 mmHg), which did not respond to surgical stimulation, occurred in a 42-year-old man taking **enalapril** when he was anaesthetised with **propofol**. He responded slowly to the infusion of one litre of Hartmann's solution.[1] Severe and unexpected hypotension has been seen during anaesthetic induction in patients taking **captopril**.[2] In a randomised clinical study, the incidence of hypotension during anaesthetic induction was higher in patients who had taken **captopril** or **enalapril** on the day of surgery than in those who had stopped these drugs 12 or 24 hours before surgery.[3] In 18 patients induction of anaesthesia for coronary artery bypass surgery resulted in a significant reduction in blood pressure and heart rate, irrespective of whether or not they were taking ACE inhibitors. The patients taking ACE inhibitors showed a marked decrease in cardiac index but no changes in systemic vascular resistance compared with the patients not taking ACE inhibitors.[4] In another study in patients undergoing coronary artery bypass surgery, short-lasting hypotensive episodes (less than 60 seconds) occurred in 9 of 16 patients receiving **captopril**, **enalapril**, **perindopril** or **lisinopril**, compared with 2 of 16 patients who were not taking ACE inhibitors. The patients experiencing hypotension required additional intravenous fluids and vasoconstrictors to maintain haemodynamic stability.[5] Similar findings are reported in another study, which included patients taking **captopril**, **enalapril**, **ramipril**, or **lisinopril**.[6] Another experimental study found that a single dose of **captopril** at induction of anaesthesia caused a small reduction in cerebral blood flow, when compared with control patients or patients given metoprolol.[7]

Particular care would seem to be needed with patients taking ACE inhibitors, but there is insufficient evidence to generally recommend discontinuing ACE inhibitors before surgery. Whether ACE inhibitors are discontinued or continued, haemodynamic instability may occur after induction of anaesthesia.[8] One report in patients undergoing cardiac surgery found that intravenous **enalaprilat** effectively reduced blood pressure and also exerted a beneficial effect on the endocrine regulators of macro- and microcirculation by blunting the increase in vasoconstrictors.[9]

One recommendation is that intravenous fluids should be given to all patients taking ACE inhibitors who are anaesthetised.[1] If hypotension occurs, blood pressure can be restored in most patients by giving sympathomimetics such as phenylephrine.[8] However, sympathomimetics may not be fully effective in treating hypotension due to ACE inhibitors and anaesthesia because ACE inhibitor administration may result in a decrease in the adrenergic vasoconstrictive response.[5,10] Terlipressin (a vasopressin analogue that has some effects as a vasopressin agonist) is reported to be an effective treatment for refractory hypotension during anaesthesia in patients taking ACE inhibitors.[8,11,12] One study found that severe hypotension during anaesthetic induction in patients chronically taking ACE inhibitors could be controlled with an intravenous injection of angiotensin II (*Hypertensine*).[13]

(b) Angiotensin II receptor antagonists

A study in 12 hypertensive patients taking angiotensin II receptor antagonists found that hypotension occurred in all patients after induction of anaesthesia. This was more frequent than that found in matched groups of hypertensive patients receiving either beta blockers and/or calcium-channel blockers (27 out of 45) or ACE inhibitors (18 of 27). The magnitude of hypotension was also significantly greater in those treated with angiotensin II receptor antagonists and it was less responsive to ephedrine and phenylephrine.[11] Terlipressin has been found to be effective in patients with refractory hypotension taking angiotensin II receptor antagonists.[11,12]

1. Littler C, McConachie I, Healy TEJ. Interaction between enalapril and propofol. *Anaesth Intensive Care* (1989) 17, 514–15.
2. McConachie I, Healy TEJ. ACE inhibitors and anaesthesia. *Postgrad Med J* (1989) 65, 273–4.
3. Coriat P, Richer C, Douraki T, Gomez C, Hendricks K, Giudicelli J-F, Viars P. Influence of chronic angiotensin-converting enzyme inhibition on anesthetic induction. *Anesthesiology* (1994) 81, 299–307.
4. Ryckwaert F, Colson P. Hemodynamic effects of anesthesia in patients with ischemic heart failure chronically treated with angiotensin-converting enzyme inhibitors. *Anesth Analg* (1997) 84, 945–9.
5. Licker M, Schweizer A, Höhn L, Farinelli C, Morel DR. Cardiovascular responses to anesthetic induction in patients chronically treated with angiotensin-converting enzyme inhibitors. *Can J Anaesth* (2000) 47, 433–40.
6. Colson P, Saussine M, Séguin JR, Cuchet D, Chaptal P-A, Roquefeuil B. Hemodynamic effects of anesthesia in patients chronically treated with angiotensin-converting enzyme inhibitors. *Anesth Analg* (1992) 74, 805–8.
7. Jensen K, Bunemann L, Riisager S, Thomsen LJ. Cerebral blood flow during anaesthesia: influence of pretreatment with metoprolol or captopril. *Br J Anaesth* (1989) 62, 321–3.
8. Colson P, Ryckwaert F, Coriat P. Renin angiotensin system antagonists and anesthesia. *Anesth Analg* (1999) 89, 1143–55.
9. Boldt J, Schindler E, Härter K, Görlach G, Hempelmann G. Influence of intravenous administration of angiotensin-converting enzyme inhibitor enalaprilat on cardiovascular mediators in cardiac surgery patients. *Anesth Analg* (1995) 80, 480–5.
10. Licker M, Neidhart P, Lustenberger S, Valloton MB, Kalonji T, Fathi M, Morel DR. Long-term angiotensin-converting enzyme inhibitor treatment attenuates adrenergic responsiveness without altering hemodynamic control in patients undergoing cardiac surgery. *Anesthesiology* (1996) 84, 789–800.
11. Brabant SM, Bertrand M, Eyraud D, Darmon P-L, Coriat P. The hemodynamic effects of anesthetic induction in vascular surgical patients chronically treated with angiotensin II receptor antagonists. *Anesth Analg* (1999) 88, 1388–92.
12. Eyruad D, Brabant S, Nathalie D, Fléron M-H, Gilles G, Bertrand M, Coriat P. Treatment of intraoperative refractory hypotension with terlipressin in patients chronically treated with an antagonist of the renin-angiotensin system. *Anesth Analg* (1999) 88, 980–4.
13. Eyraud D, Mouren S, Teugels K, Bertrand M, Coriat P. Treating anesthesia-induced hypotension by angiotensin II in patients chronically treated with angiotensin-converting enzyme inhibitors. *Anesth Analg* (1998) 86, 259–63.

Anaesthetics, general + Alcohol

Those who regularly drink alcohol may need more thiopental or propofol than those who do not. In theory, alcohol may increase the risk of renal damage with sevoflurane. It is also probably unwise to drink for several hours following anaesthesia because of the combined central nervous depressant effects.

Clinical evidence, mechanism, importance and management

A study in 532 healthy patients, aged from 20 to over 80 years, found that those who normally drank alcohol (more than 40 g weekly, roughly 400 mL of wine) needed more **thiopental** to achieve anaesthesia than non-drinkers. After adjusting for differences in age and weight distribution, men and women who were heavy drinkers (more than 40 g alcohol daily) needed 33% and 44% more **thiopental**, respectively, for induction than non-drinkers.[1] Chronic alcohol intake is known to increase barbiturate metabolism by cytochrome P450 enzymes,[2] see 'Alcohol + Barbiturates', p.55.

Another study found that 26 chronic alcoholics (drinkers of about 40 g of alcohol daily, with no evidence of liver impairment) needed about one-third more **propofol** to induce anaesthesia than another 20 patients who only drank socially. However, there was great interindividual variation in the amount of **propofol** needed in the alcoholic group.[3]

When 12 healthy subjects were given 0.7 g/kg of alcohol 4 hours after receiving 5 mg/kg of **thiopental** 2.5%, body sway and lightheadedness were accentuated.[4] This suggests that an interaction may occur if an ambulatory patient drinks alcohol within 4 hours of receiving an induction dose of **thiopental**. Patients should be cautioned not to drink alcohol following anaesthesia and surgery.

The manufacturer of **sevoflurane** notes that its metabolism may be increased by known inducers of the cytochrome P450 isoenzyme CYP2E1 including alcohol.[5,6] This may increase the risk of renal damage because

Table 5.3 Effects of the concurrent use of anaesthetics

Anaesthetic	*Effect*	*Refs*
Ketamine		
Barbiturate anaesthetics	Effects of ketamine prolonged. Recovery may be delayed.	1,2
Nitrous oxide		
Inhalational anaesthetics	Nitrous oxide usually reduces the MAC of inhalational anaesthetics in a simple additive manner; an inspired concentration of 60 to 70% nitrous oxide is commonly used with volatile anaesthetics.	3
Barbiturate anaesthetics	Reduces the required dose of intravenous barbiturate anaesthetics.	4
Propofol	Concurrent use produces a deeper sedation than that produced by propofol alone. Reduced propofol dose may be required.	5,6
Sevoflurane	Reduces the required dose of sevoflurane.	7
Propofol		
Inhalational anaesthetics	Generally expected to increase the effects of propofol. Reduced propofol dose may be required.	5
Halothane	Propofol levels raised by about 20% during maintenance of general anaesthesia. Propofol effects expected to be increased.	5,8
Isoflurane	Serum propofol concentrations by about 20% during the maintenance of general anaesthesia. Propofol effects expected to be increased.	5,8
Intravenous anaesthetics	Generally expected to increase the effects of propofol. Reduced propofol dose may be required.	5
Etomidate	Synergistic effect: patients given induction doses of either etomidate or propofol alone required about a 15% higher dose than those given half etomidate and half propofol in sequence.	9
Sevoflurane		
Intravenous anaesthetics	Lower concentrations may be required following the use of an intravenous anaesthetic.	10
Propofol	In a study in surgical patients concurrent use was additive (loss of consciousness and movement to skin incision assessed). Lower sevoflurane concentrations may be required following the use of propofol. Concurrent use in ECT results in a longer recovery time, probably due to deeper anaesthesia, but results in smaller increases in heart rate and blood pressure than with sevoflurane alone and a shorter seizure duration than with propofol alone. (Note that the UK manufacturers of propofol do not recommend its use in ECT.)	10-13

1. Ketalar (Ketamine hydrochloride). Pfizer Ltd. UK Summary of product characteristics, May 2009.
2. Ketalar (Ketamine hydrochloride). JHP Pharmaceuticals, LLC. US Prescribing information, December 2007.
3. Dale O. Drug interactions in anaesthesia: focus on desflurane and sevoflurane. *Baillieres Clin Anaesthesiol* (1995) 9, 105–17.
4. Aitkenhead AR, ed. Textbook of anaesthesia. 4th ed. Edinburgh: Churchill Livingstone; 2001 P. 172–4.
5. Diprivan (Propofol). AstraZeneca. US Prescribing information, August 2005.
6. Kakinohana M, Miyata Y, Tomiyama H, Sugahara K. Nitrous oxide can enhance the hypnotic effect, but not the suppression of spinal motor neuron excitability by propofol in humans. *J Anesth* (2006) 20, 173–8.
7. Ultane (Sevoflurane). Abbott Laboratories. US Prescribing information, July 2009.
8. Grundmann U, Ziehmer M, Kreienmeyer J, Larsen R, Altmayer P. Propofol and volatile anaesthetics. *Br J Anaesth* (1994) 72 (Suppl 1), 88.
9. Drummond GB, Cairns DT. Do propofol and etomidate interact kinetically during induction of anaesthesia? *Br J Anaesth* (1994) 73, 272P.
10. Sevoflurane. Abbott Laboratories Ltd. UK Summary of product characteristics, June 2007.
11. Wajima Z, Shiga T, Yoshikawa T, Ogura A. Inoue T, Ogawa R. Propofol alone, sevoflurane alone, and combined propofol-sevoflurane anaesthesia in electroconvulsive therapy. *Anaesth Intensive Care* (2003) 31, 396–400.
12. Diprivan (Propofol). AstraZeneca UK Ltd. UK Summary of product characteristics, July 2009.
13. Harris RS, Lazar O, Johansen JW, Sebel PS. Interaction of propofol and sevoflurane on loss of consciousness and movement to skin incision during general anesthesia. *Anesthesiology* (2006) 104, 1170–5.

of an increase in plasma fluoride; however, no cases appear to have been reported.

1. Dundee JW, Milligan KR. Induction dose of thiopentone: the effect of alcohol intake. *Br J Clin Pharmacol* (1989) 27, 693P–694P.
2. Weathermon R, Crabb DW. Alcohol and medication interactions. *Alcohol Res Health* (1999) 23, 40–54.
3. Fassoulaki A, Farinotti R, Servin F, Desmonts JM. Chronic alcoholism increases the induction dose of propofol in humans. *Anesth Analg* (1993) 77, 553–6.
4. Lichtor JL, Zacny JP, Coalson DW, Flemming DC, Uitvlugt A, Apfelbaum JL, Lane BS, Thisted RA. The interaction between alcohol and the residual effects of thiopental anesthesia. *Anesthesiology* (1993) 79, 28–35.
5. Sevoflurane. Abbott Laboratories Ltd. UK Summary of product characteristics, June 2007.
6. Ultane (Sevoflurane). Abbott Laboratories. US Prescribing information, September 2006.

Anaesthetics, general + Alpha blockers

The UK manufacturers of alfuzosin note that the use of general anaesthetics in patients taking alfuzosin could cause profound hypotension, and they recommend that alfuzosin should be withdrawn 24 hours before surgery.[1]

1. Xatral (Alfuzosin hydrochloride). Sanofi-Aventis. UK Summary of product characteristics, February 2009.

Anaesthetics, general + Anaesthetics, general

In general, the effects of the combined use of general anaesthetics are at least additive. See 'Table 5.3', (above), for specific comments about pairs of anaesthetics.

Anaesthetics, general + Anaesthetics, local

An isolated report describes convulsions associated with the use of propofol with topical cocaine Arrhythmias have been reported in patients given propofol and topical cocaine. Cocaine abuse may increase the risk of cardiovascular complications during inhalational anaesthesia. Abstinence from cocaine or the avoidance of anaesthetics with sympathomimetic properties has been suggested. The dosage of propofol may need to be reduced after the use of bupivacaine, ropivacaine, or lidocaine (e.g. during regional anaes-

thetic techniques). Similarly, epidural lidocaine reduces sevoflurane requirements, and is likely to have the same effect on other inhalational anaesthetics.

Clinical evidence, mechanism, importance and management

Note that drugs such as adrenaline (epinephrine), which are used with local anaesthetics, may interact with inhalational anaesthetics such as halothane to increase the risk of arrhythmias, see 'Anaesthetics, general + Inotropes and Vasopressors', p.111.

(a) Bupivacaine

In a placebo-controlled study of patients undergoing minor gynaecological surgery, giving intramuscular bupivacaine 0.5% 30 minutes before induction of anaesthesia significantly enhanced the hypnotic effect of intravenous **propofol** in a dose-dependent manner. Only the lowest dose of bupivacaine tested (250 micrograms/kg) lacked a significant effect on the hypnotic dose of **propofol**. The highest dose of bupivacaine (1 mg/kg) reduced the hypnotic requirements for **propofol** by about 40%. The dose of **propofol** should therefore be modified after the intramuscular use of bupivacaine.[1] The UK manufacturer of **propofol** also notes that required doses may be lower when general anaesthesia is used in association with regional anaesthetic techniques.[2]

(b) Cocaine

A patient with no history of epilepsy, undergoing septorhinoplasty for cosmetic reasons, was premedicated with papaveretum and hyoscine, and intubated after **propofol** and suxamethonium (succinylcholine) were given. Anaesthesia was maintained with **nitrous oxide**/oxygen and **isoflurane** 2%. During anaesthesia a paste containing cocaine 10% was applied to the nasal mucosa. During recovery the patient experienced a dystonic reaction, which developed into a generalised convulsion. The authors of the report suggest that a possible interaction between the **propofol** and cocaine might have been responsible, although they also suggest that the convulsions may have been an adverse effect of the propofol.[3]

In one study, **thiopental** with either 5 mL of lidocaine 4% or 3 mL of cocaine 5%, was found to be an effective anaesthetic when performing a laryngoscopy and biopsy. However, the procedure for applying cocaine topically in these circumstances prolongs the procedure and hence increases **thiopental** requirements. Also serious cardiac arrhythmias (bigeminal rhythms and ectopic ventricular contractions) occurred in 7 of 20 patients given cocaine (which resolved, either without treatment or with intravenous propranolol). Arrhythmias did not occur in those given lidocaine.[4] In another study, **thiopental** and suxamethonium were used to induce anaesthesia in 45 patients and anaesthesia was maintained with **nitrous oxide**/oxygen and **halothane**. When a stable level of anaesthesia had been obtained, topical cocaine 20, 35, or 50 mg in 2 mL of water was sprayed into both nostrils to shrink the nasal mucosa before nasal surgery. Two patients who received cocaine 35 mg developed atrial and ventricular extrasystoles. Two other cases of AV nodal rhythm and two cases of bradycardia, which responded to atropine, were also observed.[5] However, in another study in 20 patients, topical application of cocaine (1 mL of 25% paste or 4 mL of 4% solution) with or without adrenaline (epinephrine) 0.1%, after induction of anaesthesia with **thiopental**, did not cause any cardiac toxicity.[6]

Reviews of the anaesthetic implications of illicit drug use have stated that anaesthetists should be aware of the medical complications of cocaine abuse, such as myocardial ischaemia, hypertension and tachycardia due to sympathetic nervous system stimulation.[7,8] It was suggested that the concurrent use of cocaine and inhalational anaesthetics, such as **halothane**, that are known to significantly sensitise the myocardium to circulating catecholamines, should be avoided, and that other halogenated anaesthetics should be used with caution.[7,8] Theoretically, **isoflurane** would be a better choice of inhalational anaesthetic since it has less cardiovascular effects.[7] **Ketamine** should also be avoided because of its sympathomimetic effects. **Nitrous oxide**, **thiopental** and fentanyl were considered to be useful for general anaesthesia in patients who regularly abuse cocaine.[7,8] Although it has been suggested that anaesthesia is safe for patients with chronic cocaine abuse after abstinence for 24 hours, the occurrence of ventricular fibrillation in one such patient during anaesthesia with **thiopental** and **isoflurane**, led the authors of the case report to conclude that there should be a cocaine-free interval of at least one week before elective surgical procedures. They also suggest that if an emergency operation is required during acute cocaine intoxication, all sympathomimetic anaesthetic drugs should be avoided.[9]

(c) Lidocaine

A double-blind, randomised study of 17 patients requiring ventilatory support demonstrated that hourly laryngotracheal instillation of 5 mL of 1% lidocaine significantly reduced the dose of **propofol** required to maintain adequate sedation (overall reduction of 50%) when compared with pre-study values.[10]

In a placebo-controlled study of patients undergoing minor gynaecological surgery, giving intramuscular lidocaine 4% 10 minutes before induction of anaesthesia significantly enhanced the hypnotic effect of intravenous **propofol** in a dose-dependent manner. Only the lowest dose of lidocaine tested (500 micrograms/kg) lacked a significant effect on the hypnotic dose of **propofol**. The highest dose of lidocaine (3 mg/kg) reduced the hypnotic requirements for **propofol** by about 34%. The dose of **propofol** should therefore be modified after the intramuscular use of lidocaine or bupivacaine.[1] The UK manufacturer of **propofol** also notes that required doses may be lower when general anaesthesia is used in association with regional anaesthetic techniques.[2]

An *in vitro* study using liver microsomes found that **propofol** inhibited the metabolism of lidocaine by cytochrome P450 isoenzymes.[11] However, a further study by the same authors in 31 patients undergoing anaesthesia with either **propofol** or **sevoflurane**, and receiving epidural lidocaine, found that, compared with **sevoflurane** (which does not inhibit lidocaine metabolism), **propofol** did not affect the metabolism of epidural lidocaine. The lack of interaction in the latter study could be due to the lower doses of **propofol** involved and because other isoenzymes or extrahepatic metabolism of lidocaine might possibly be involved.[12] A study in patients undergoing surgery found that a single 2-mg/kg dose of **propofol** did not affect serum lidocaine levels in subjects who smoked and consumed alcohol chronically. Enzyme inhibition by **propofol** may be countered by enzyme induction associated with cigarette smoking and alcohol, but it is probable in this study, that the single dose of **propofol** was insufficient to produce enzyme inhibition.[13]

A randomised, double-blind, placebo-controlled study involving 44 patients found that lidocaine epidural anaesthesia (15 mL of 2% plain lidocaine) reduced the MAC of **sevoflurane** required for general anaesthesia by approximately 50% (from 1.18 to 0.52%). This implies that a lower dose of **inhalational anaesthetic** provides adequate anaesthesia during combined epidural-general anaesthesia than for general anaesthesia alone.[14]

(d) Ropivacaine

In an *in vitro* study using liver microsomes, **propofol** inhibited the cytochrome P450 isoenzyme CYP3A4-mediated metabolism of ropivacaine.[15]

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Anaesthetics, general + Anthracyclines

Pretreatment with anthracyclines may result in prolongation of the QT interval during isoflurane anaesthesia.

Clinical evidence, mechanism, importance and management

A study in women with breast cancer found that the QTc interval was prolonged (to more than 440 milliseconds) during anaesthesia with **isoflurane** (end-tidal concentration 0.5 vol%) in more than half of the 20 patients who had received chemotherapy, compared with only 1 of 20 patients who had not previously received chemotherapy. However, QTc intervals of 600 milliseconds and above, which may be associated with serious arrhythmias, were not observed. The chemotherapy, which was given about 1 month before surgery, consisted of fluorouracil and cyclophosphamide and either **doxorubicin** or **epirubicin**. Anthracyclines (such as **doxorubicin** and **epirubicin**) and **isoflurane** can prolong the QT interval. The patients had also received midazolam, which is reported to reduce QTc prolongation induced by other anaesthetics. It was noted that the use of higher **isoflurane** concentrations in patients given anthracyclines could result in greater QTc interval prolongation.[1] Several drugs used in anaesthesia may affect the QT interval. For example **thiopental** and **sufentanil** are also reported to prolong the QT interval, while **propofol** and **halothane** are said to shorten it.[1] This should be borne in mind if patients treated with anthracyclines or other drugs that prolong the QT interval undergo anaesthesia.

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Anaesthetics, general + Anticholinesterases

Inhalation anaesthetics may impair the efficacy of anticholinesterases in reversing neuromuscular blockade, although propofol does not affect the reversal of rocuronium block by neostigmine. Physostigmine pre-treatment increased propofol requirements by 20% in one study.

Clinical evidence, mechanism, importance and management

(a) Neostigmine

Inhalational anaesthetics can impair neostigmine reversal of neuromuscular blockade. In one study, neostigmine took longer to reverse pancuronium blockade after anaesthesia with **enflurane**, when compared with fentanyl or **halothane**.[1] Another study found that the reversal of vecuronium block with neostigmine 40 micrograms/kg was more dependent on the concentration of **sevoflurane** than the degree of block present. At the lowest concentration of **sevoflurane** (0.2 MAC), adequate reversal was obtained in all patients within 15 minutes, but with increasing concentrations (up to 1.2 MAC) satisfactory restoration of neuromuscular function was not achieved within 15 minutes, probably because of a greater contribution of **sevoflurane** to the degree of block.[2] In another randomised study, 120 patients were given **sevoflurane**, **isoflurane** (adjusted to 1.5 MAC), or intravenous **propofol** 6 to 12 mg/kg per hour for maintenance of anaesthesia. Neuromuscular block was induced with rocuronium and monitored using train-of-four stimulation (TOF) of the ulnar nerve. Neostigmine was given when the first response in TOF had recovered to 20 to 25%. At this point **isoflurane** or **sevoflurane** was stopped, or the **propofol** dose reduced, in half of the patients in each of the three groups. The times to recovery of the TOF ratio to 0.8 were 12 minutes and 6.8 minutes in the **sevoflurane** continued and stopped groups, respectively, 9 minutes and 5.5 minutes in the **isoflurane** continued and stopped groups, respectively, and 5.2 minutes and 4.7 minutes in the **propofol** continued and reduced groups, respectively. Only 9/20 and 15/20 patients in the **sevoflurane** and **isoflurane** continued groups, respectively, achieved a TOF ratio of 0.8 within 15 minutes. This showed that the reversal of rocuronium block by neostigmine is slowed by **sevoflurane** and to a lesser extent by **isoflurane**, but not significantly affected by **propofol**.[3] The manufacturers of neostigmine injection[4] and tablets[5] state that neostigmine should not be given during **cyclopropane** or **halothane** anaesthesia, but may be given after the withdrawal of these anaesthetics.

Note that inhalation anaesthetics potentiate neuromuscular blockers, see 'Anaesthetics, general + Neuromuscular blockers', p.113.

(b) Physostigmine

A study of 40 patients found that physostigmine pre-treatment (2 mg intravenously 5 minutes before induction of anaesthesia) increased **propofol** requirements by 20%.[6]

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Anaesthetics, general + Antiemetics

Metoclopramide pre-treatment reduces the dosage requirements of propofol and thiopental. Droperidol, but not ondansetron, reduces the dose requirements of thiopental.

Clinical evidence

(a) Metoclopramide or Droperidol

A randomised, placebo-controlled study of 60 surgical patients, half of whom were given metoclopramide 150 micrograms/kg 5 minutes before induction, found that the induction dose of **propofol** was reduced by 24% in the group given metoclopramide.[1] Similar results were seen in another study of 21 patients, in which metoclopramide 10 or 15 mg reduced the dose requirements of **propofol** by about 25% and 41%, respectively.[2] In a randomised, placebo-controlled study in 96 female patients, both metoclopramide and droperidol reduced the amount of **thiopental** needed to induce anaesthesia by about 45%.[3]

(b) Ondansetron

In a randomised, placebo-controlled study of 168 female patients ondansetron 100 or 200 micrograms/kg given intravenously 5 minutes before **thiopental** induction did not influence the hypnotic requirements of **thiopental**.[4]

Mechanism

The exact mechanism by which metoclopramide reduces propofol or thiopental dose requirements is unclear, but it appears to involve the blockade of dopamine (D_2) receptors. Droperidol probably interacts with thiopental by a similar mechanism.

Importance and management

Although the evidence is limited these interactions between metoclopramide and thiopental or propofol, and between droperidol and thiopental would appear to be established. Droperidol has not been studied with propofol, but, on the basis of other interactions it would be expected to behave like metoclopramide. When patients are pretreated with either metoclopramide or droperidol, be alert for the need to use less propofol and thiopental to induce anaesthesia. If the mechanism is correct, it seems likely that other dopamine antagonists used as antiemetics, such as **haloperidol**, will interact similarly, although this does not appear to have been studied. Ondansetron appears not to interact.

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3. Mehta D, Bradley EL, Kissin I. Metoclopramide decreases thiopental hypnotic requirements. *Anesth Analg* (1993) 77, 784–7.
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Anaesthetics, general + Antipsychotics

An isolated report describes a grand mal seizure in a man taking chlorpromazine and flupentixol when he was anaesthetised with enflurane. Another report describes delayed recovery from anaesthesia in a patient taking clozapine, but the use of alprazolam may have been a contributory factor. The sedative properties of antipsychotics may be enhanced by thiopental. Lower etomidate doses are recommended in patients taking antipsychotics.

Clinical evidence, mechanism, importance and management

An isolated report[1] describes an unexpected grand mal seizure in a schizophrenic patient without a history of epilepsy when he was given **enflurane** anaesthesia. He was taking **chlorpromazine** 50 mg three times daily (irregularly) and **flupentixol** 40 mg intramuscularly every 2 weeks. The suggested reason is that the **enflurane** had a synergistic effect with the two antipsychotics, all of which are known to lower the seizure threshold. The general importance of this interaction is not known. Another isolated report[2] describes delayed recovery in a patient taking **clozapine** after short duration (1 hour) anaesthesia induced by **thiopental**, sufentanil and atracurium and maintained with **desflurane** and nitrous oxide/oxygen. However, the patient was also taking alprazolam which may also have contributed to the delayed recovery, see 'Anaesthetics, general + Benzodiazepines', below.

The manufacturer of thiopental notes that, as would be expected, the sedative properties of antipsychotics may be potentiated by **thiopental**.[3] The manufacturer of **etomidate** recommends that the dose of **etomidate** should be reduced in patients taking antipsychotics.[4] **Droperidol** and other drugs with dopamine antagonist properties, such as many of the antipsychotics, may reduce the dose requirements of **thiopental**, see 'Anaesthetics, general + Antiemetics', p.105.

In general, drugs with sedative properties, including many antipsychotics, have the potential to enhance the sedative effects of general anaesthetics, which may result in delayed recovery. However, there appear to be no reports of a problem in practice, and so it would seem reasonable to conclude that, in most patients, any effect is modest.

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3. Thiopental Injection. Link Pharmaceuticals Ltd. UK Summary of product characteristics, January 2003.
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Anaesthetics, general + Aspirin

The anaesthetic dosage of thiopental is reduced by pretreatment with aspirin.

Clinical evidence

In a study in patients undergoing surgery, intravenous lysine aspirin increased mean free **thiopental** levels in the plasma by 39%, and 3 of 7 patients fell asleep again during recovery from **thiopental** anaesthesia.[1] Another study[2] in patients about to undergo surgery found that pretreatment with aspirin 1 g (given as intravenous lysine aspirin) one minute before induction reduced the dosage of **thiopental** by 34%, from 5.3 to 3.5 mg/kg.

Mechanism

Not understood. It has been suggested that aspirin increases the amount of free (and active) thiopental in the plasma since it competes for the binding sites on the plasma albumins.[1,2]

Importance and management

Information is limited but what is known shows that the effects of thiopental are increased by aspirin. Be alert for the need to reduce the dosage. However, note also that regular aspirin use may increase the risk of bleeding during surgery, and it is often recommended that aspirin should not be taken in the week before surgery.[3]

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3. Anon. Drugs in the peri-operative period: 4 – Cardiovascular drugs. *Drug Ther Bull* (1999) 37, 89–92.

Anaesthetics, general + Baclofen

A patient taking baclofen had severe seizures during induction of anaesthesia with propofol.

Clinical evidence, mechanism, importance and management

A 48-year-old man with a cyst in his spinal cord taking baclofen for flexor spasms underwent surgery for the relief of obstructive hydrocephalus. His last dose of baclofen was 6 hours before induction of anaesthesia with pethidine (meperidine) 40 mg followed by **propofol**. After he had received about 60 mg of **propofol** he developed severe myoclonic seizures, which lasted about 3 minutes. The patient was given additional **propofol** 40 mg because he appeared to be awakening, and severe generalised seizures lasting 2 minutes occurred. He was then given vecuronium, and anaesthesia was maintained with isoflurane and nitrous oxide/oxygen without further problem.[1]

Seizures have been reported in patients with and without epilepsy receiving **propofol**. They mainly occur at induction or emergence or are delayed after anaesthesia, suggesting changes in cerebral levels of **propofol** may be causal.[2] Baclofen can cause acute desensitisation of $GABA_B$ receptors producing persistent epileptiform discharges.[1] It was suggested that in this patient the seizures were mediated by both baclofen and **propofol**.[1] Opioid analgesics may induce seizures and opisthotonos has been reported in patients given opioids and **propofol** (see 'Anaesthetics, general + Opioids', p.115). However, generalised seizures attributed to pethidine are probably due to a metabolite. The time course therefore makes pethidine an unlikely cause of the seizure in this patient.[1]

1. Manikandan S, Sinha PK, Neema PK, Rathod RC. Severe seizures during propofol induction in a patient with syringomyelia receiving baclofen. *Anesth Analg* (2005) 100, 1468–9.
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Anaesthetics, general + Benzodiazepines

Midazolam markedly potentiates the anaesthetic action of halothane. Similarly, the effects of propofol or thiopental are greater than would be expected by simple addition when midazolam is given concurrently, although the extent varies between the endpoints measured (analgesic, motor, hypnotic). Quazepam reduces induction time for propofol anaesthesia and premedication with diazepam reduces the dose of ketamine required.

Clinical evidence

(a) Halothane

In a study in 50 women undergoing surgery, **midazolam** markedly potentiated the anaesthetic action of halothane: a mean **midazolam** dose of 278 micrograms/kg reduced the halothane MAC by about 51%.[1]

(b) Ketamine

A study in patients undergoing major abdominal surgery found that in 10 patients premedicated with rectal **diazepam** one hour before induction, the haemodynamic effects of ketamine (increases in heart rate and blood pressure) were significantly reduced, when compared with 31 controls. Also, a lower rate of ketamine infusion was required during the initial 30 minutes of anaesthesia, the half-life of ketamine was significantly increased, and the plasma levels of the hydroxylated metabolites of keta-

mine were reduced. These findings suggest that both pharmacodynamic and pharmacokinetic interactions exist between **diazepam** and ketamine. In the same study, 3 patients were given 20 mg of intravenous **clorazepate** about one hour before induction of anaesthesia, but this did not affect either the dose of ketamine required or its pharmacokinetics.[2]

(c) Propofol

Two studies found that if propofol and **midazolam** were given together, the hypnotic and anaesthetic effects were greater than would be expected by the simple additive effects of both drugs.[3,4] In one of these studies, the ED_{50} (the dose required for 50% of the patients to respond) for hypnosis was 44% less than that expected with the individual drugs and the addition of **midazolam** 130 micrograms/kg caused a 52% reduction in the ED_{50} of propofol required for anaesthesia.[3] A pharmacokinetic study found a very modest 20% increase in the levels of free **midazolam** in the plasma when it was given with propofol, but this was considered too small to explain the considerable synergism.[5] In a further placebo-controlled study in 24 patients, premedication with intravenous **midazolam**, 50 micrograms/kg given 20 minutes before induction of anaesthesia, reduced the propofol dose requirements for multiple anaesthetic end-points, including hypnotic, motor, EEG and analgesia. However, the potentiating effect and the mechanism of the interaction appeared to vary with the anaesthetic end-point and the dose of propofol. Notably, the interaction was most marked for analgesia.[6] Another placebo-controlled study in 60 children aged 1 to 3 years found that oral **midazolam** 500 micrograms/kg approximately 30 minutes before the induction of anaesthesia delayed early recovery from anaesthesia, which was induced with propofol and maintained with **sevoflurane** and **nitrous oxide**/**oxygen**. However, the time to hospital discharge was not prolonged.[7]

A further placebo-controlled study in 24 patients found that propofol decreased the clearance of **midazolam** by 37% and increased its elimination half-life by 61%.[8]

A study in 33 patients found that **quazepam** 15 or 30 mg given the night before induction of anaesthesia with propofol and fentanyl reduced the induction time when compared with a third group of patients not given a hypnotic. **Quazepam** did not affect blood pressure or heart rate, but the 30 mg dose of **quazepam** did increase anterograde amnesia.[9]

(d) Thiopental

Thiopental has been shown to act synergistically with **midazolam** at induction of anaesthesia in two studies.[10,11] In one of these studies, **midazolam** reduced the dose of thiopental required to produce anaesthesia by 50%.[11] In a further placebo-controlled study in 23 patients, premedication with intravenous **midazolam** 50 micrograms/kg, given 20 minutes before the induction of anaesthesia, reduced the thiopental dose requirements for multiple anaesthetic end-points, including hypnotic, motor, EEG and analgesia. Potentiation was greatest for the motor end-point (about 40%) and smallest for analgesia (18%).[12]

Mechanism

Propofol, barbiturates and halothane appear to interact with benzodiazepines through their effects on the GABA receptor.

Diazepam appears to undergo similar oxidative processes as ketamine and therefore competitively inhibits ketamine metabolism.[2] Clorazepate is only slowly decarboxylated and is therefore not affected.[2]

An *in vitro* study suggests that propofol may reduce the clearance of midazolam by inhibition of the cytochrome P450 isoenzyme CYP3A4.[8]

Importance and management

The interactions between propofol or thiopental and midazolam are well established. This synergy has been utilised for the induction of anaesthesia.[13] Midazolam also reduces the dose requirements of halothane. Other benzodiazepines may also potentiate the effects of general anaesthetics. In general this may reduce the dose of anaesthetic required and/or slow recovery from the anaesthetic. In many cases this interaction is exploited clinically.

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Anaesthetics, general + Beta-agonist bronchodilators

Arrhythmias developed in two patients anaesthetised with halothane when terbutaline was given.

Clinical evidence, mechanism, importance and management

Two patients developed ventricular arrhythmias while anaesthetised with **halothane** and nitrous oxide/oxygen when given **terbutaline** 250 to 350 micrograms subcutaneously for wheezing. Both developed unifocal premature ventricular contractions followed by bigeminy, which responded to lidocaine.[1] **Halothane** was replaced by **enflurane** in one case, which allowed the surgery to be completed without further incident.[1]

Halothane is known to cause arrhythmias and it has been suggested that it may increase susceptibility to the adverse cardiac effects of beta-agonist bronchodilators,[2] which can cause arrhythmias. A number of inhalational anaesthetics have been associated with arrhythmias. For a list, in order of arrhythmogenic potential, see 'Anaesthetics and Neuromuscular blockers', (p.100). This interaction is therefore, in theory, possible with any of these anaesthetics and a $beta_2$-agonist bronchodilator, although the case above appears to be the only one reported.

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Anaesthetics, general + Beta blockers

Anaesthesia in the presence of beta blockers normally appears to be safer than withdrawal of the beta blocker before anaesthesia, provided certain inhalational anaesthetics are avoided (methoxyflurane, cyclopropane, trichloroethylene) and atropine is used to prevent bradycardia. Bradycardia and marked hypotension occurred in a man using timolol eye drops when he was anaesthetised.

Acute peri-operative administration of beta blockers may reduce the dose of anaesthetic required for induction and may result in deeper anaesthesia.

Clinical evidence and mechanism

A. Cardiac depressant effects

It used to be thought that beta blockers should be withdrawn from patients before surgery because of the risk that their cardiac depressant effects would be additive with those of inhalational anaesthetics, resulting in a reduction in cardiac output and blood pressure, but it seems that any effect depends on the anaesthetic used.[1] It has been suggested that the ranking order of compatibility (from the least to the most compatible with beta blockers) is as follows: **methoxyflurane**, **cyclopropane**, **trichloroethylene**, **enflurane**, **halothane**, **isoflurane**.[1] This review pre-dated the advent of newer anaesthetics, such as sevoflurane.

(a) Cyclopropane, Methoxyflurane, and Trichloroethylene

A risk of cardiac depression certainly seems to exist with cyclopropane because its depressant effects on the heart are normally counteracted by the release of catecholamines, which would be blocked by the presence of a beta blocker. There is also some evidence (clinical and/or *animal*) that unacceptable cardiac depression may occur with methoxyflurane and trichloroethylene when a beta blocker is present. This has been the subject of two reviews.[2,3] For these three inhalational anaesthetics it has been stated that an absolute indication for their use should exist before giving them in combination with a beta blocker.[1]

(b) Enflurane, Halothane, and Isoflurane

Although a marked reduction in cardiac performance has been described in a study in *dogs* given **propranolol** and enflurane (discussed in two reviews[2,3]) these drugs have been widely used without apparent difficulties.[1] Normally beta blockers and halothane or isoflurane appear to be safe.

(c) Methohexital and Propofol

A study on the effects of adding a beta blocker to anaesthesia was undertaken in 80 patients who were given oxycodone and atropine as pre-medication and then anaesthetised with either methohexital or propofol, either alone or with **esmolol**. The QTc intervals were recorded before any drugs were given and after the administration of propofol or methohexital alone or with esmolol. The addition of **esmolol** to either methohexital or propofol significantly shortened the QTc interval. The heart rate tended to decrease in the propofol plus **esmolol** group. Blood pressure decreased significantly in all four groups but diastolic pressure was significantly lower in the propofol plus **esmolol** group, when compared with the other groups. It was concluded that haemodynamic responses were controlled with methohexital plus **esmolol** or propofol alone, but that propofol plus **esmolol** tended to cause haemodynamic depression.[4]

(d) Unnamed general anaesthetic

A 75-year-old man being treated with **timolol** eye drops for glaucoma developed bradycardia and severe hypotension when anaesthetised and responded poorly to intravenous atropine, dextrose-saline infusion and elevation of his feet.[5] It would seem that there was sufficient systemic absorption of the **timolol** for its effects to be additive with the anaesthetic and cause marked cardiodepression.

B. Reduction of anaesthetic requirements

(a) Atenolol

Intra-operative intravenous atenolol given in 5 mg stepwise doses (median dose 20 mg; range 10 to 80 mg) was found to reduce the **isoflurane** requirement by about 40% without affecting the bispectral index (a predictor of the depth of anaesthesia). Patients also received on average 21% less fentanyl compared with control patients who were not given atenolol.[6]

(b) Esmolol

Several studies have found that the use of esmolol reduces the required dose of **isoflurane** or **propofol**, or results in a deeper anaesthesia (as measured by BIS), but only in the presence of an opioid.[7-11] As there appears to be no pharmacokinetic interaction between esmolol and **propofol**[7,9] it has been suggested that esmolol could be interacting with the opioid.[7,11]

However, in one study 60 patients were given one of three treatments before induction of anaesthesia with **propofol**: esmolol 1 mg/kg followed by an infusion of 250 micrograms/kg per minute; midazolam; or placebo (sodium chloride 0.9%). No opioids were given. Esmolol and midazolam reduced the required induction doses of **propofol** by 25% and 45%, respectively. Esmolol reduced the mean heart rate by 7.6 bpm in the pre-induction period, when compared with placebo, and the only adverse effect noted was a transient episode of bradycardia (44 bpm) in one patient receiving esmolol.

Esmolol reduces cardiac output by reduction of heart rate and stroke volume and this possibly reduces the required induction dose of **propofol** by changing its distribution.[12]

Another study found that a single 80-mg dose of esmolol after induction of anaesthesia with **propofol** and either fentanyl or placebo did not affect the depth of anaesthesia (measured by bispectral index; a predictor of the depth of anaesthesia) in either group of patients, even though cardiovascular effects were seen (reduction in systolic arterial pressure and heart rate).[13]

Importance and management

The consensus of opinion is that beta blockers should not be withdrawn before anaesthesia and surgery[14,15] because of the advantages of maintaining beta-blockade, and because the risks accompanying withdrawal are considerable. But, if inhalational anaesthetics are used, it is important to select the safest anaesthetics (isoflurane, halothane), and avoid those that appear to be most risky (methoxyflurane, cyclopropane, trichloroethylene: most of which are no longer regularly used), as well as ensuring that the patient is protected against bradycardia by atropine. The manufacturers of bisoprolol, labetalol, nadolol and sotalol recommend avoiding anaesthetics such as cyclopropane and trichloroethylene,[16-19] as they cause myocardial depression,[16,17] and note that labetalol may increase the hypotensive effects of halothane.[16]

Although most manufacturers do not contraindicate the continuation of beta blockers during anaesthesia, many do recommend a specific withdrawal period if a clinical decision is made to discontinue beta blockade:

- **Acebutolol**,[20] **atenolol**,[21] **labetalol**,[16] **nebivolol**,[22] **propranolol**,[23] and **timolol**[24] should be discontinued for at least 24 hours before the procedure.
- The dose of **bisoprolol**[17,25] and **metoprolol**[26,27] should be gradual reduced and stopped at least 24 to 48 hours before anaesthesia.
- The dose of **celiprolol**[28] and **oxprenolol**[29] should be gradually reduced and stopped at least 48 hours before anaesthesia.
- One manufacturer of **sotalol**[18] advises that it may be stopped 4 days before surgery.
- **Nadolol**[19] and **pindolol**[30] should be gradually withdrawn several days before surgery.

The manufacturers of nadolol state that in no circumstances should beta blockers be discontinued before surgery in patients with phaeochromocytoma or thyrotoxicosis.[19]

The authors of the report[5] concerning topically applied beta blockers suggest that if such patients are to be anaesthetised, low concentrations of timolol should be used (possibly withhold the drops pre-operatively), and that "induction agents should be used judiciously and beta-blocking antagonists kept readily available." It is easy to overlook the fact that systemic absorption from eye drops can be high enough to cause adverse interactions.

There appear to be considerable benefits to be gained from the continued use of beta blockers during anaesthesia. Their sudden withdrawal from patients treated for angina or hypertension can result in the development of acute and life-threatening cardiovascular complications whether the patient is undergoing surgery or not. In the peri-operative period patients benefit from beta blockade because it can minimise the effects of sympathetic overactivity of the cardiovascular system during anaesthesia and surgery (for example during endotracheal intubation, laryngoscopy, bronchoscopy and various surgical manoeuvres), which can cause cardiac arrhythmias and hypertension.

Although several studies suggest that beta blockers, such as atenolol and esmolol, given before induction reduce the anaesthetic dose requirement and may potentiate hypnosis there are concerns that reducing the dose of anaesthetic may increase the risk of intra-operative awareness, and it has been suggested that the use of BIS to predict the depth of anaesthesia in the presence of beta blockers may not be valid.[31] There is a possibility that acute as well as chronic administration of beta blockers may prevent peri-operative cardiac complications,[13,15] but more study is needed on this.[15,31]

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Anaesthetics, general + Calcium-channel blockers

Impaired myocardial conduction has been seen in two patients taking diltiazem after they were anaesthetised with enflurane, and prolonged anaesthesia has been seen when patients taking verapamil were anaesthetised with etomidate, but it has been suggested that chronic administration of oral calcium-channel blockers up to the day of surgery is usually beneficial. Intravenous dihydropyridines have been used to control peri-operative hypertension, but the use of intravenous verapamil is not recommended in patients anaesthetised with either halothane or enflurane.

Clinical evidence, mechanism, importance and management

(a) Dihydropyridines

Enhanced hypotension was seen in a study in which patients were given intravenous **nimodipine** during general anaesthesia involving **halothane** or **isoflurane**.[1]

The presence of low concentrations of **isoflurane** (0.6%) or **sevoflurane** (0.9%) are reported not to have a marked effect on the pharmacological action of **nicardipine**.[2] In one study intravenous **nicardipine** 17 micrograms/kg was given to 30 neurosurgical patients anaesthetised with either **enflurane**, **isoflurane** or **sevoflurane**. Peak reductions in blood pressure occurred 3 minutes after **nicardipine** was given, and were greatest in the group receiving **sevoflurane**. However, with **isoflurane** peak reductions in blood pressure persisted for longer (30 minutes), as did increases in heart rate, even though the clearance of **nicardipine** was most rapid in patients given **isoflurane**.[3]

Some caution is clearly appropriate, especially with intravenous calcium-channel blockers given during surgery, but general experience suggests that long-term treatment with *oral* dihydropyridine calcium-channel blockers need not be avoided in most patients undergoing anaesthesia, and may be continued until the day of surgery. Further, *intravenous* dihydropyridines have been reported to be safe and effective for the control of peri-operative hypertension.[4]

(b) Diltiazem or Verapamil

The author of a review about calcium-channel blockers and anaesthetics concludes that their concurrent use in patients with reasonable ventricular function is normally beneficial, except where there are other complicating factors. Thus he warns about possible decreases in ventricular function in patients undergoing open chest surgery given *intravenous* verapamil or diltiazem.[5] A report describes a patient taking diltiazem and atenolol who had impaired AV and sinus node function before anaesthesia, which worsened following the use of **enflurane**.[6] Another patient taking diltiazem (and atenolol) had to be paced due to bradycardia of 35 bpm at induction, but despite this he developed severe sinus bradycardia, which progressed to asystole when **enflurane** was given.[6] The authors of this latter report suggest that **enflurane** and diltiazem can have additive depressant effects on myocardial conduction. The presence of low concentrations of **isoflurane** (0.6%) or **sevoflurane** (0.9%) are reported not to have a marked effect on the pharmacological action of diltiazem.[2] Two cases of prolonged anaesthesia and Cheyne-Stokes respiration have been reported in patients who were undergoing cardioversion. Both received verapamil and were induced with **etomidate**.[7] One manufacturer states that concurrent use of verapamil and inhalational anaesthetics is not recommended.[8]

The authors of a review concluded that *intravenous* verapamil or diltiazem are not recommended in patients anaesthetised with either **halothane** or **enflurane**, especially if the patients have cardiac failure or conduction disturbances.[9]

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Anaesthetics, general + Clonidine

Clonidine significantly attenuates the responses to hypercapnia in patients anaesthetised with propofol, but not with isoflurane. Clonidine reduces the dose of thiamylal required for induction of anaesthesia.

Clinical evidence, mechanism, importance and management

Note that additive hypotensive effects are theoretically possible in patients taking clonidine who are given general anaesthetics.

(a) Propofol or Isoflurane

In a study, 60 patients were premedicated with famotidine or famotidine with clonidine 5 micrograms/kg, and anaesthesia was induced with propofol and vecuronium, and maintained with either isoflurane or propofol. The cardiovascular responses (mean arterial pressure, heart rate and cardiac index) to hypercapnia were significantly attenuated in the patients given clonidine and propofol, when compared with those given propofol without clonidine or isoflurane with or without clonidine.[1]

(b) Thiamylal

In a double-blind study 60 children were given either oral clonidine 2 micrograms/kg, 4 micrograms/kg or placebo, 105 minutes before induction of anaesthesia with thiamylal 1% at a rate of 1 mg/kg every 15 seconds until completion of induction (assessed by loss of eyelash reflex). The thiamylal dose required for induction was 5.4 mg/kg, 4.5 mg/kg, and 3.4 mg/kg in the placebo, clonidine 2 micrograms/kg and clonidine 4 micrograms/kg groups respectively, indicating a dose-dependent clonidine reduction in thiamylal requirements. Systolic blood pressure decreased by 6.8%, 5.6%, and 6.6% and heart rate increased by 5.7%, 4.8%, and 4.1% with placebo, clonidine 2 micrograms/kg and 4 micrograms/kg, respectively. The authors note that smaller doses of

thiamylal may be needed if given as a bolus dose rather than by incremental administration.[2] In an earlier report, there was a greater decrease in blood pressure in children given a bolus dose of thiamylal 5 mg/kg with clonidine 4 micrograms/kg than those given thiamylal with diazepam.[3]

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Anaesthetics, general + Dexmedetomidine

Dexmedetomidine may reduce the dose requirements of thiopental, isoflurane, propofol and probably other anaesthetics. In an *animal* study, the analgesic effects of nitrous oxide were increased by dexmedetomidine.

Clinical evidence, mechanism, importance and management

Dexmedetomidine reduced the **thiopental** dose requirement for EEG burst suppression by 30% in 7 patients, when compared with 7 control patients given placebo. In this study, dexmedetomidine was given for 35 minutes before anaesthesia and during anaesthesia at a dose of 100 nanograms/kg per minute for the first 10 minutes, 30 nanograms/kg per minute for the following 15 minutes, and 6 nanograms/kg per minute thereafter. There was no pharmacodynamic synergism, and pharmacokinetic analysis showed that dexmedetomidine significantly reduced the **thiopental** distribution, probably due to reduced cardiac output and decreased regional blood flow.[1]

A placebo-controlled study in women undergoing abdominal hysterectomy found that a dexmedetomidine infusion started 15 minutes before induction of anaesthesia caused a dose-dependent reduction in the **isoflurane** MAC (by 35% and 47%, with dexmedetomidine plasma levels maintained at 0.37 nanograms/mL and 0.69 nanograms/mL, respectively).[2] In another study, in 9 healthy subjects, dexmedetomidine reduced the ED_{50} dose requirement of **isoflurane** for anaesthesia (motor response). Dexmedetomidine plasma levels of 0.35 nanograms/mL and 0.75 nanograms/mL reduced the requirements for **isoflurane** by about 30% and 50%, respectively. Subjects who had received dexmedetomidine took longer to wake up.[3]

In a study, 9 healthy subjects were given stepwise increases in **propofol** concentrations (1 to 13.8 micrograms/mL) 45 minutes after the start of either dexmedetomidine or placebo infusions.[4] Dexmedetomidine did not significantly affect the pharmacokinetics of **propofol**; however, the concurrent use of dexmedetomidine reduced the **propofol** concentration required for sedation by 65 to 80% and reduced the **propofol** concentration required for suppression of motor responses by 40%. It was suggested that the **propofol** dose for sedation and induction may have to be reduced in the presence of dexmedotomidine.[4] Another study in 40 patients given a mean dose of intravenous dexmedetomidine of 63 nanograms/kg found that concurrent use reduced the concentration and dose of **propofol** required to produce loss of consciousness.[5]

An *animal* study found that the analgesic effects of **nitrous oxide** were enhanced by dexmedetomidine.[6]

Dexmedetomidine has sedative, analgesic and anxiolytic effects[7] and therefore, like other sedatives, may reduce the dose requirements of anaesthetics. However, it may also affect the distribution of **thiopental** and possibly other **intravenous anaesthetics**.

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Anaesthetics, general + Enzyme inducers

A child developed phenytoin toxicity following halothane anaesthesia, a near fatal hepatic reaction occurred in a woman given rifampicin (rifampin) after halothane anaesthesia, and hepatitis occurred in a patient taking phenobarbital who was given halothane anaesthesia.

Clinical evidence

A 10-year-old girl receiving long-term treatment with phenytoin 300 mg daily was found to have **phenytoin** plasma levels of 25 micrograms/mL before surgery. Three days after anaesthesia with **halothane** her plasma **phenytoin** levels had risen to 41 micrograms/mL and she had marked signs of **phenytoin** toxicity.[1]

A woman taking promethazine and **phenobarbital** 60 mg three times daily died from **halothane**-associated hepatitis within 6 days of being given **halothane** for the first time.[2]

A nearly fatal, shock-producing hepatic reaction occurred in a woman 4 days after she was given **halothane** anaesthesia immediately followed by a course of **rifampicin** 600 mg daily and isoniazid 300 mg daily.[3]

Mechanism

It seems possible that the general adverse hepatotoxic effects of halothane can slow the normal rate of phenytoin metabolism. One suggested explanation for the increased adverse effects on the liver is that, just as in *animals*, pre-treatment with phenobarbital and phenytoin increases the rate of drug metabolism and therefore increases the levels of the hepatotoxic metabolites of halothane and other halogenated hydrocarbons.[4,5] As well as increased metabolism, the halothane-rifampicin interaction might also involve additive hepatotoxicity.

Importance and management

No firm conclusions can be drawn from these isolated cases, but they serve to emphasise the potential hepatotoxicity when halogenated anaesthetics are given to patients taking these drugs. It has been suggested that patients taking enzyme-inducing drugs (such as phenobarbital and phenytoin) may constitute a high-risk group for liver damage after halogenated anaesthetics.[6] Consider also 'Anaesthetics, general + Isoniazid', p.112, and 'Anaesthetics, general; Methoxyflurane + Miscellaneous', p.120.

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Anaesthetics, general + Herbal medicines

There are two isolated reports, of profound hypotension during anaesthesia, and of prolonged anaesthesia, following the long-term use of St John's wort. A report describes increased bleeding, which was tentatively attributed to the concurrent use of sevoflurane and aloe vera. The American Society of Anesthesiologists recommends that all herbal medicines should be stopped two weeks before elective surgery.

Clinical evidence and mechanism

(a) Aloe vera

A case report describes a 35-year-old woman undergoing surgery for a haemangioma of the left thigh, who had twice the expected intra-operative blood loss. The patient had been taking 4 tablets of aloe vera for 2 weeks before surgery, and so the blood loss was attributed to an interaction between the herbal medicine and **sevoflurane**, which was used to maintain anaesthesia.[1] **Sevoflurane** can inhibit platelet aggregation by inhibiting

thromboxane A_2, and aloe vera affects prostaglandin synthesis, which may also impair platelet aggregation. However, it should be noted that the patient's aPTT and INR were not assessed pre-operatively and the authors do state that the vascularity and size of the haemangioma were the most important factors in the blood loss,[1] so an interaction is by no means proven.

(b) Kava

There is one case report of kava potentiating the effect of benzodiazepines (see 'Benzodiazepines + Kava', p.852), and it has been suggested that it could potentiate other CNS depressants including **barbiturates**[2,3] (e.g. **thiopental**), and may prolong or potentiate the effects of anaesthetics.[4-6] Kava may act via GABA receptors, and kavalactones (one group of active constituents) also have skeletal muscle relaxant and local anaesthetic properties.[2,3] Toxic doses can produce muscle weakness and paralysis.[2,3]

(c) St John's wort (Hypericum perforatum)

It has been suggested that St John's wort may prolong anaesthesia.[4-7] The prediction appears to have been based on the possibility that St John's wort acts as an MAOI,[5,7,8] (although this has been disputed[9]) and the limited evidence that MAOIs may cause hepatic enzyme inhibition and potentiate the effects of barbiturates (see 'MAOIs + Barbiturates', p.1372). However, there is now increasing evidence that St John's wort induces hepatic enzymes, and might therefore increase the metabolism of barbiturates (see 'Antiepileptics + St John's wort (*Hypericum perforatum*)', p.598). This suggests that it could in fact increase requirements for **thiopental** anaesthesia. However, prolonged anaesthesia has been reported in a 21-year-old woman who had been taking St John's wort 1 g three times daily for 3 months before general anaesthetics were given for the surgical removal of an abscess. Anaesthesia was induced by intravenous **fentanyl citrate** 1 microgram/kg and **propofol** 3 mg/kg, and maintained throughout the procedure by **sevoflurane** and **nitrous oxide** using a face mask.[10]

The possible MAOI activity of St John's wort has led to the recommendation that the same considerations apply as for other MAOIs and general anaesthetics,[7,8] see 'Anaesthetics, general + MAOIs and related drugs', p.112.

Another case report describes a healthy 23-year-old woman who had been taking St John's wort on a daily basis for 6 months, who developed severe hypotension (BP 60/20 mmHg) during general anaesthesia, which responded poorly to ephedrine and phenylephrine (BP increased to 70/40 mmHg). It was suggested that the St John's wort might have caused adrenergic desensitisation with decreased responsiveness to the vasopressors.[11]

Importance and management

Not established. The evidence presented suggests that some caution may be warranted in patients using kava, or St John's wort if they are given general anaesthetics. The situation with aloe vera is less clear. Many other herbs have the potential to cause problems in the care of patients undergoing surgery (other than via drug interactions with anaesthetics) and these have been reviewed.[5-7] Because of the limited information, the American Society of Anesthesiologists have recommended discontinuation of all herbal medicines 2 weeks before an elective anaesthetic[4,6] and if there is any doubt about the safety of a product, this may be a prudent precaution.[5]

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Anaesthetics, general + Inotropes and Vasopressors

Patients anaesthetised with inhalational anaesthetics (particularly cyclopropane and halothane, and to a lesser extent desflurane, enflurane, isoflurane, methoxyflurane, and sevoflurane) can develop cardiac arrhythmias if they are given adrenaline (epinephrine) or noradrenaline (norepinephrine), unless the dosages are very low. Children appear to be less susceptible to this interaction. The addition of adrenaline to intrathecal tetracaine enhances the sedative effects of propofol.

Clinical evidence, mechanism, importance and management

As early as 1895, it was noted that an adrenal extract could cause ventricular fibrillation in a *dog* anaesthetised with **chloroform**,[1] and it is now very well recognised that similar cardiac arrhythmias can be caused by **adrenaline** (**epinephrine**) and **noradrenaline** (**norepinephrine**) in humans anaesthetised with **inhalational anaesthetics**. The mechanism appears to be a sensitisation of the myocardium to β-adrenergic stimulation, caused by the **inhalational anaesthetic**. The likelihood of arrhythmias is increased by hypoxia and marked hypercapnia. It has been reported that the highest incidence of complications has been in patients anaesthetised with **cyclopropane**, but that the incidence is also high with **trichloroethylene** and **halothane**.[2] A suggested listing of inhalational anaesthetics in order of decreasing sensitising effect on the myocardium is as follows:[3] **cyclopropane**, **halothane**, **enflurane**/**methoxyflurane**, **isoflurane**. **Sevoflurane**[4] and **desflurane**[5] appear to behave like **isoflurane**. Similarly, others consider that if **adrenaline** is used for haemostasis during surgery, **isoflurane** or **sevoflurane** carry less risk of cardiac arrhythmias than **halothane**.[6]

It has been recommended that if **adrenaline** is used to reduce surgical bleeding in patients anaesthetised with **halothane**/**nitrous oxide**/**oxygen**, the dosage of **adrenaline** should not exceed 10 mL of 1:100 000 in any given 10 minute period, or 30 mL per hour (i.e. about a 100 microgram bolus or 1.5 micrograms/kg per 10 minutes for a 70 kg person), and adequate alveolar ventilation must be assured.[7] This dosage guide should also be safe for use with other inhalational anaesthetics since **halothane** is more arrhythmogenic than the others,[3] with the exception of **cyclopropane**, which is no longer widely used. However, some have suggested that the concurrent use of **halothane** and **adrenaline** may have been a contributing factor in 3 deaths in patients undergoing tooth implant surgery.[8] Solutions containing **lidocaine** 0.5% with **adrenaline** 1:200 000 also appear to be safe because lidocaine may help to control the potential dysrhythmic effects. For example, a study in 19 adult patients anaesthetised with **halothane** found that the dose of **adrenaline** needed to cause three premature ventricular contractions in half the group was 2.11 micrograms/kg when it was given in sodium chloride 0.9% but 3.69 micrograms/kg when it was given in **lidocaine** 0.5%. Note that both these values were less than that in 16 patients anaesthetised with **isoflurane** (6.72 micrograms/kg), demonstrating that **isoflurane** was still safer.[9] It should be borne in mind that the arrhythmogenic effects of **adrenaline** are increased if sympathetic activity is increased, and in hyperthyroidism and hypercapnia.[3]

Children appear to be much less susceptible to these effects than adults. A retrospective study of 28 children found no evidence of arrhythmia during **halothane** anaesthesia, with **adrenaline** doses of up to 8.8 micrograms/kg, and a subsequent study in 83 children (aged 3 months to 17 years) found that 10 micrograms/kg doses of **adrenaline** were safe.[10]

A study in 20 patients undergoing spinal anaesthesia with tetracaine found that **propofol** sedation (as measured by bispectral index monitoring (BIS)) was enhanced when **adrenaline** was added to the intrathecal tetracaine.[11] A study in *sheep* found that **adrenaline**, **noradrenaline** and **dopamine** decreased **propofol** concentrations during a continuous propofol infusion, with the result that **propofol** anaesthesia was reversed. This was thought to be due to increased first pass clearance of **propofol** secondary to increased cardiac output. It was concluded that this could be of clinical importance if **propofol** is used in hyperdynamic circulatory conditions induced by catecholamine infusions or disease states such as sepsis.[12]

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11. Yotsui T, Kitamura A, Ogawa R. Addition of epinephrine to intrathecal tetracaine augments depression of the bispectral index during intraoperative propofol sedation. *J Anesth* (2004) 18, 147–50.
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Anaesthetics, general + Isoniazid

Isoniazid may increase the metabolism of enflurane, isoflurane or sevoflurane and thereby increase plasma-fluoride concentrations.

Clinical evidence, mechanism, importance and management

A 46-year-old woman underwent anaesthesia for renal transplantation 6 days after starting to take isoniazid 300 mg daily. Anaesthesia was induced with intravenous thiopental and maintained for 4 hours with 60% nitrous oxide, fentanyl and **isoflurane**. Serum fluoride ions increased, from 4.3 micromol preoperatively, to approximately 30 micromol between 2 and 8 hours after starting **isoflurane**. However, no impairment of renal function occurred. A second patient who was given 5 times the first patient's exposure to **isoflurane** and who had received isoniazid for 13 years had no increase in serum fluoride concentrations over preoperative values, but did show an increase in tri*fluoro*acetic acid levels.[1]

When **enflurane** was given to 20 patients who had been taking isoniazid 300 mg daily for between one week and one year, 9 had an increase in peak fluoride ion levels. These 9 patients had a fourfold higher fluoride level than both 36 control subjects not taking isoniazid and 11 other subjects taking isoniazid only. By 48 hours after anaesthesia, there was no difference in fluoride levels. Despite the increase in fluoride levels, there was no change in renal function.[2]

Isoniazid may increase the metabolism of **enflurane**, **isoflurane** or **sevoflurane**[3,4] in some patients (probably related to isoniazid acetylator phenotype[2]) and so increase the release of fluoride ions that may cause nephrotoxicity. However, there do not appear to be any reports of this resulting in a significant clinical effect on renal function.

1. Gauntlett IS, Koblin DD, Fahey MR, Konopka K, Gruenke LD, Waskell L, Eger EI. Metabolism of isoflurane in patients receiving isoniazid. *Anesth Analg* (1989) 69, 245–9.
2. Mazze RI, Woodruff RE, Heerdt ME. Isoniazid-induced enflurane defluorination in humans. *Anesthesiology* (1982) 57, 5–8.
3. Sevoflurane. Abbott Laboratories Ltd. UK Summary of product characteristics, June 2007.
4. Ultane (Sevoflurane). Abbott Laboratories. US Prescribing information, September 2006.

Anaesthetics, general + Levothyroxine

Two patients taking levothyroxine developed marked hypertension and tachycardia when they were given ketamine.

Clinical evidence, mechanism, importance and management

Two patients taking levothyroxine developed severe hypertension (240/140 mmHg and 210/130 mmHg, respectively) and tachycardia (190 bpm and 150 bpm) when they were given **ketamine**. Both were effectively treated with 1 mg of intravenous propranolol.[1] It was not clear whether this was an interaction or simply a particularly exaggerated response to **ketamine**, but care is clearly needed if **ketamine** is given to patients receiving thyroid replacement therapy.

1. Kaplan JA, Cooperman LH. Alarming reactions to ketamine in patients taking thyroid medication — treatment with propranolol. *Anesthesiology* (1971) 35, 229–30.

Anaesthetics, general + MAOIs and related drugs

It is generally recommended that MAOIs should be withdrawn at least 2 weeks before anaesthesia. Individual cases of both hypo- and hypertension have been seen and MAOIs can interact dangerously with other drugs sometimes used during surgery (particularly pethidine (meperidine) and ephedrine).

Clinical evidence

The absence of problems during emergency general anaesthesia in 2 patients taking MAOIs prompted further study in 6 others receiving long-term treatment with unnamed MAOIs. All 6 were premedicated with 10 to 15 mg of diazepam 2 hours before surgery, induced with **thiopental**, given suxamethonium (succinylcholine) before intubation, and maintained with **nitrous oxide**/**oxygen** with either **halothane** or **isoflurane**. Pancuronium was used for muscle relaxation, and morphine was given postoperatively. One patient experienced hypotension that responded to repeated 100-microgram intravenous doses of phenylephrine without hypertensive reactions. No other untoward events occurred either during or after the anaesthesia.[1]

A retrospective review of 32 patients taking **isocarboxazid** 10 mg daily who underwent elective surgery (involving **thiopental** or **ketamine** for induction of anaesthesia and maintenance with an inhalation anaesthetic with or without a muscle relaxant or analgesic) found that 5 patients experienced intra-operative hypotension, another patient developed hypertension, and bradycardia occurred in 4 patients. No postoperative complications were attributed to the interaction between the MAOI and the drugs given peri-operatively.[2]

Unexplained hypertension has been described in a patient taking **tranylcypromine** when **etomidate** and atracurium were given.[3] Severe and prolonged cardiovascular collapse occurred in one patient in whom long-term **tranylcypromine** 10 mg four times daily was discontinued 20 days before surgery. During surgery **etomidate** and suxamethonium were given for induction, and **isoflurane** and **nitrous oxide**/**oxygen** for maintenance, as well as epidural anaesthesia with bupivacaine, but without an opioid.[4]

Further reports describe a lack of adverse reactions in:

- 27 patients taking MAOIs (**tranylcypromine**, **phenelzine**, **isocarboxazid**, **pargyline**) when they were anaesthetised,[5]
- 2 patients taking **phenelzine** and anaesthetised with **propofol**,[6,7]
- 3 patients taking **tranylcypromine** or **phenelzine** and anaesthetised with **propofol** (and alfentanil),[8,9]
- one patient taking **tranylcypromine** when **ketamine** was given,[10]
- one patient taking **phenelzine** when anaesthetised with **sevoflurane**, then **isoflurane**, and an infusion of remifentanil.[11]

Further case reports describe the uneventful use of selective MAOIs in patients undergoing general anaesthesia: one patient taking **selegiline** was uneventfully anaesthetised with fentanyl, **isoflurane** and midazolam,[12] and **moclobemide** was stopped on the morning of surgery in a patient who was anaesthetised with **propofol** and later **isoflurane** in **nitrous oxide** and oxygen. Atracurium, morphine and droperidol were also used.[13]

Mechanism, importance and management

There seems to be little documentary evidence that the withdrawal of MAOIs before giving an anaesthetic is normally necessary. Scrutiny of reports[14] alleging an adverse reaction usually shows that what happened could be attributed to an interaction between the MAOI and other drugs used during the surgery (e.g. either 'directly-acting sympathomimetics', (p.1388), 'indirectly-acting sympathomimetics', (p.1388), 'pethidine (meperidine)', (p.1381), or 'fentanyl', (p.1380)) rather than with the anaesthetics.

The authors of two of the reports cited here offer the opinion that 'general and regional anaesthesia may be provided safely without discontinuation of MAOI therapy, provided proper monitoring, adequate preparation, and prompt treatment of anticipated reactions are utilised'.[1,5] This implies that the possible interactions between the MAOI and other drugs are fully recognised, but be alert for the rare unpredictable response. The conclusion of another report was that patients on low-dose MAOIs could be safely anaesthetised.[2]

The BNF[15] states that 'in view of their hazardous interactions MAOIs should normally be stopped 2 weeks before surgery.' It has also been sug-

gested that a longer period of time (more than 20 days) between discontinuing MAOIs and surgery may be required, not so much to recover MAO enzyme activity but to recover depressed adrenergic receptor function.[4] These warnings are probably more to avoid interactions with the anaesthetic adjuncts mentioned above, rather than the MAOIs themselves. Therefore in an emergency situation it would seem possible to anaesthetise a patient, but it must be remembered that the choice of anaesthetic adjuncts is likely to be restricted.

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15. British National Formulary. 58th ed. London: BMJ Publishing Group Ltd and RPS Publishing; 2009. p. 698.

Anaesthetics, general + Melatonin

Melatonin slightly reduces the dose of propofol needed for the induction of anaesthesia.

Clinical evidence

A study in 45 adult patients found that the induction dose of intravenous **propofol**, as measured by bispectral index and loss of eyelash reflex, was 15% lower in patients who had received a single 3- or 5-mg oral dose of melatonin 100 minutes preoperatively, compared with patients who had received placebo. The time to recover from the anaesthetic was not affected by premedication with melatonin. **Propofol** was given in an incremental dose fashion in this study so that any difference could be assessed, but is usually given as a bolus dose.[1]

Mechanism

Melatonin appears to have anxiolytic and sedative effects, which might reduce the required induction dose of propofol.

Importance and management

This study was conducted to assess the clinical value of using melatonin premedication, which is not an established use. The reduction in required dose of propofol was small, and on the basis of these data, it is unlikely that any untoward effects would be seen in the situation where a patient who had recently taken a melatonin supplement was anaesthetised with propofol.

1. Turkistani A, Abdullah KM, Al-Shaer AA, Mazen KF, Alkatheri K. Melatonin premedication and the induction dose of propofol. *Eur J Anaesthesiol* (2007) 24, 399–402.

Anaesthetics, general + Methylphenidate

A single report described difficulty in sedating a child taking methylphenidate, and a possible delayed interaction between ketamine and methylphenidate, which resulted in nausea, vomiting and dehydration. The use of methylphenidate after ketamine anaesthesia increased the incidence of vomiting, excessive talking, and limb movements in one study. Methylphenidate should probably be withheld before anaesthesia with inhalational anaesthetics, because of the potential risk of hypertension and/or arrhythmias.

Clinical evidence, mechanism, importance and management

A 6-year-old boy weighing 22 kg, who was taking methylphenidate 5 mg twice daily for attention deficit disorder, was found to be difficult to sedate for an echocardiogram. Sedation was attempted with oral cloral hydrate 75 mg/kg without success. One week later he received midazolam 20 mg orally, but was only mildly sedated 20 minutes later and would not lie still. Despite an additional oral dose of midazolam 10 mg mixed with oral **ketamine** 60 mg the child was still alert and uncooperative 20 minutes later. He was finally given intravenous glycopyrronium (glycopyrrolate) 100 micrograms followed by intravenous midazolam 5 mg given over 5 minutes and was successfully sedated. He recovered from sedation uneventfully, but developed nausea, vomiting and lethargy after discharge from hospital, which responded to rehydration treatment.[1] In a double-blind study, methylphenidate was given as a single 20-mg intravenous dose to try to speed recovery at the end of **ketamine** anaesthesia for short urological procedures. However, methylphenidate did not improve recovery, and increased the incidence of vomiting, excessive talking, and limb movements.[2]

In the first case, the stimulant effect of methylphenidate was thought to have antagonised the sedative effect of the midazolam and **ketamine**. It has been suggested that methylphenidate may also have delayed the absorption of the oral drugs, and inhibited liver microsomal enzymes delaying the elimination of both **ketamine** and midazolam. These effects may have resulted in hazardous plasma concentrations;[1] however, the study did not find evidence of these effects.

These appear to be the only reports, so any effect is not established. Be aware that methylphenidate may possibly antagonise the effect of sedative drugs, and may also be associated with an increased incidence of vomiting. Note that methylphenidate is an indirectly-acting sympathomimetic, and as such might be expected to increase the risk of hypertension and arrhythmias if used with **inhalational anaesthetics** (consider 'Anaesthetics, general + Inotropes and Vasopressors', p.111). Because of this, the manufacturer of one brand of methylphenidate recommends that, if surgery with halogenated anaesthetics is planned, methylphenidate treatment should not be given on the day of surgery.[3] Taken together, these reports suggest this advice may be a prudent precaution for any form of sedation and/or general anaesthesia.

1. Ririe DG, Ririe KL, Sethna NF, Fox L. Unexpected interaction of methylphenidate (Ritalin®) with anaesthetic agents. *Paediatr Anaesth* (1997) 7, 69–72.
2. Attalah MM, Saied MMA, Yahya R, Ibrahiem EI. Ketamine anesthesia for short transurethral urologic procedures. *Middle East J Anesthesiol* (1993) 12, 123–33.
3. Concerta XL (Methylphenidate hydrochloride). Janssen-Cilag Ltd. UK Summary of product characteristics, November 2009.

Anaesthetics, general + Neuromuscular blockers

Many inhalational anaesthetics increase the effects of the neuromuscular blockers, and in some cases this allows for a dosage reduction of the neuromuscular blocker. Nitrous oxide appears not to interact significantly and halothane seems less likely to interact. Propofol and xenon are reported not to interact with mivacurium or rocuronium.
Bradycardia has been reported with combinations of anaesthetics (propofol, etomidate or thiopental) and neuromuscular blockers (atracurium, suxamethonium or vecuronium), particularly in the presence of an opioid.

Clinical evidence, mechanism, importance and management

The effects of neuromuscular blockers are increased by inhalational anaesthetics, the greater the dosage of the anaesthetic the greater the increase in blockade. In broad terms **desflurane**, **ether**, **enflurane**, **isoflurane**, **methoxyflurane** and **sevoflurane** have a greater effect than **halothane**, which is more potent than **cyclopropane**, whereas **nitrous oxide** appears not to interact significantly with competitive blockers.[1-7]

The mechanism is not fully understood but seems to be multifactorial. It has been suggested that the anaesthetic may:

- have an effect via the CNS (including depression of spinal motor neurones);
- have an effect on the neuromuscular junction (including a decrease in the release of acetylcholine and in the sensitivity of the motor end-plate to acetylcholine);
- affect the muscle tissue itself.[6,8]

The duration of exposure to the anaesthetic and the duration of effect of the various neuromuscular blockers also appear to affect the degree of potentiation that occurs.[8,9]

Reports pertaining to interactions between specific neuromuscular blockers and anaesthetics are discussed in the subsections below.

(a) Atracurium

In a study in which the muscle relaxant was given about 5 minutes after the start of inhalational anaesthesia, **enflurane** prolonged the action of atracurium. It was suggested that more prolonged exposure to the anaesthetic, allowing equilibration of the anaesthetic to the tissues, might result in more significant potentiation of the neuromuscular blockers.[9] Similarly, in another study, **ketamine** prolonged the duration of neuromuscular blockade induced by atracurium.[10] In contrast, **halothane** did not significantly prolong the clinical duration of atracurium.[9]

The dosage of atracurium can be reduced by 25 to 30% if, instead of balanced anaesthesia (with **thiopental**, fentanyl and **nitrous oxide**/oxygen),[11] **enflurane** is used, and by up to 50% if **isoflurane** or **desflurane** are used.[4,12,13] Another study recommended reduced doses of neuromuscular blockers such as atracurium and **tubocurarine** in children undergoing anaesthesia with **enflurane** or **isoflurane**.[14]

Bradycardia and asystole have been reported in a patient given **propofol**, fentanyl and atracurium.[15]

(b) Cisatracurium

A myasthenic patient developed marked potentiation of neuromuscular block following the combination of **sevoflurane** and a small dose of cisatracurium 25 micrograms/kg.[16]

(c) Mivacurium

It has been suggested that higher plasma levels of mivacurium, especially of the potent *trans-trans* isomer, occur in the presence of **isoflurane**, and these could contribute to the enhanced neuromuscular blockade observed in patients given this combination. Lower infusion rates of mivacurium were required in those given **isoflurane** rather than **propofol** (which does not appear to interact).[17]

Xenon is reported not to affect the onset time, duration and recovery from mivacurium.[18]

(d) Pancuronium

In a study in which the muscle relaxant was given about 5 minutes after the start of inhalational anaesthesia, **enflurane** prolonged the action of pancuronium. It was suggested that more prolonged exposure to the anaesthetic, allowing equilibration of the anaesthetic to the tissues, might result in more significant potentiation of the neuromuscular blocker.[9] In this study, **halothane** did not significantly prolong the clinical duration of pancuronium;[9] however, in an early study, **halothane** was found to *shorten* the recovery from pancuronium.[19,20]

(e) Pipecuronium

In a study in which the muscle relaxant was given about 5 minutes after the start of inhalational anaesthesia, **enflurane** prolonged the action of pipecuronium. It was suggested that more prolonged exposure to the anaesthetic, allowing equilibration of the anaesthetic to the tissues, might result in more significant potentiation of the neuromuscular blockers.[9] In this study, **halothane** did not significantly prolong the clinical duration of pipecuronium.[9]

(f) Rapacuronium

One study demonstrated considerable prolongation of neuromuscular blockade with rapacuronium in the presence of **sevoflurane**; the recovery times were approximately doubled compared with those given in the published literature using **thiopental**/opioid-**nitrous oxide** anaesthesia. This led to the study being prematurely terminated as spontaneous recovery of neuromuscular function was required after short surgical procedures.[21]

(g) Rocuronium

The rate of infusion of rocuronium (0.39 mg/kg per hour) was significantly less in 10 patients anaesthetised with **isoflurane** and **nitrous oxide** when compared with the rate (0.61 to 0.67 mg/kg per hour) in 50 other patients anaesthetised with **etomidate**, fentanyl, midazolam, **propofol**, or **thiopental** and **nitrous oxide**.[22]

In one study when the volatile anaesthetics were given about 10 minutes before the neuromuscular blocker, **sevoflurane** was reported to increase and prolong the blockade of rocuronium more than **isoflurane** or **propofol**.[23] However, another study found that after a 40-minute equilibration period of the inhalation anaesthetic (steady-state conditions), there was no significant difference between **desflurane**, **isoflurane** and **sevoflurane** in relation to potency, infusion requirements or recovery characteristics of rocuronium; the potency of rocuronium was increased by 25 to 40% under inhalational anaesthesia, when compared with **propofol**.[24]

It is reported that the neuromuscular blocking effects of rocuronium are not prolonged by **xenon**.[25]

In *animals*, **ketamine** and **thiopental** potentiated the neuromuscular blocking effects of rocuronium, whereas **propofol** had no effect.[26]

(h) Suxamethonium (Succinylcholine)

Although it is generally assumed that **nitrous oxide** does not affect the potency of neuromuscular blockers, one study found that **nitrous oxide** did increase suxamethonium neuromuscular blockade.[27]

In children receiving suxamethonium, those anaesthetised with **halothane** had much higher levels of serum myoglobulin than those undergoing intravenous induction with **thiopental** followed by **halothane**. This suggests that prior use of **halothane** may have potentiated suxamethonium-induced muscle damage.[28]

In one study, **ketamine** did not influence suxamethonium-induced neuromuscular blockade.[29] However, the UK manufacturers of suxamethonium still warn of a possible interaction because they say that **ketamine** may reduce normal plasma cholinesterase activity.[30]

Serious sinus bradycardia (heart rates of 30 to 40 bpm) developed rapidly in two young women when they were anaesthetised with a slow intravenous injection of **propofol** 2.5 mg/kg, followed by suxamethonium 1.5 mg/kg. This was controlled with 600 micrograms of intravenous atropine. Four other patients premedicated with 600 micrograms of intramuscular atropine given 45 minutes before induction of anaesthesia did not develop bradycardia.[31] It would appear that **propofol** lacks central vagolytic activity and can exaggerate the muscarinic effects of suxamethonium.[31] Another report describes a woman who became asystolic when given an anaesthetic induction sequence of fentanyl, **propofol** and suxamethonium.[32] The authors of this report suggest that atropine or glycopyrronium (glycopyrrolate) pretreatment should attenuate or prevent such reactions.[32] Bradycardia and asystole has also been seen following the sequential use of **propofol** and fentanyl in 2 patients.[33,34] All of these three drugs (fentanyl, **propofol**, suxamethonium) alone have been associated with bradycardia and their effects can apparently be additive.

(i) Vecuronium

In a study in which the muscle relaxant was given about 5 minutes after the start of inhalational anaesthesia, **enflurane** did not significantly affect vecuronium. It was suggested that the duration of effect of the vecuronium may have been too short for interaction with a volatile anaesthetic that had not had time to equilibrate with the tissues.[9] In this study, **halothane** did not significantly prolong the clinical duration of vecuronium.[9] One study in children found that the potentiation of vecuronium was greater with **isoflurane** than with **enflurane**, and **halothane** had a lesser effect.[35] In another study, **enflurane** and **isoflurane** reduced the vecuronium infusion rate requirements by as much as 70%, when compared with fentanyl anaesthesia.[36] Another study found that although **halothane** and **isoflurane** could both increase the neuromuscular potency of vecuronium, only **isoflurane** prolonged the recovery from neuromuscular blockade.[37]

The duration of exposure to **sevoflurane** also influences the dose-response of vecuronium, but it has been suggested that **sevoflurane**-induced potentiation of neuromuscular blockers might be more rapid than with other inhalational anaesthetics.[8]

Xenon is reported to have less effect on recovery from vecuronium-induced neuromuscular block than **sevoflurane**.[38]

The original formulation of **propofol** in *Cremophor* was found to increase the blockade due to vecuronium,[39] but the more recent formulation in soybean oil and egg phosphatide has been found in an extensive study not to interact with vecuronium.[40]

Bradycardia occurring during anaesthetic induction with vecuronium

and **etomidate**, or to a lesser extent **thiopental**, has also been reported, particularly in patients also receiving fentanyl.[41] Consider also 'Neuromuscular blockers + Opioids', p.144.

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Anaesthetics, general + Opioids

The effects of inhalational anaesthetics may be enhanced by opioid analgesics, and the dose requirements of desflurane, etomidate, propofol and thiopental may be lower after opioid use. The respiratory depressant effects of ketamine and morphine may be additive. Opisthotonos or grand mal seizures have rarely been associated with the use of propofol with alfentanil and/or fentanyl.

Clinical evidence, mechanism, importance and management

(a) Inhalational anaesthetics

Opioid analgesics have been reported to reduce the MAC values of inhalational anaesthetics. For example, **fentanyl** has been shown to lower the MAC value of **desflurane**, probably in a dose-dependent manner, and this has been the subject of a review.[1] The manufacturer notes that lower doses of **desflurane** are required in patients receiving opioids.[2] **Remifentanil** at a target-controlled plasma level of 1 nanogram/mL was found to decrease the MAC of **sevoflurane** with **nitrous oxide** by 60%, and **remifentanil** 3 nanograms/mL produced a further 30% decrease in the MAC of **sevoflurane**.[3] Another study found that **remifentanil** dose-dependently decreased the level of **sevoflurane** required to maintain anaesthesia.[4] However, 100 microgram/kg doses of **morphine** given during anaesthesia did not alter the awakening concentration of **sevoflurane**.[5]

(b) Etomidate

The manufacturer of etomidate recommends that the dose of etomidate should be reduced in patients who have already received opioids.[6]

(c) Ketamine

A study in 11 healthy subjects found that the combination of ketamine and **morphine** almost abolished windup-like pain (progressive increase in pain intensity on repeated stimulation) in a skin burn injury. This effect was not found with either drug alone. Further, although ketamine alone reduced the area of secondary hyperalgesia of the local burn and increased the pain threshold, the combination did not appear to enhance this effect. The reduction of wind-up pain may be due to ketamine-induced prevention of acute tolerance to **morphine**.[7] Ketamine is a respiratory depressant like **morphine**, but less potent. Nevertheless its effects can be additive with morphine.[8]

Another study in healthy subjects using various experimental pain models found that ketamine *antagonised* the respiratory depressant effect of **remifentanil**. **Remifentanil** alone produced analgesic effects with all pain tests, but ketamine only enhanced the effect of **remifentanil** on intramuscular electrical stimulation. Acute **remifentanil**-induced hyperalgesia and tolerance were detected only by the pressure pain test and were not suppressed by ketamine. The combined effects of **remifentanil** and ketamine probably depend on the type of pain.[9]

The manufacturer notes that a prolonged recovery time may occur if opioids are used with ketamine.[10]

(d) Propofol

A 71-year-old man undergoing a minor orthopaedic operation was given a 500-microgram intravenous injection of **alfentanil** followed by a slow injection of propofol 2.5 mg/kg. Approximately 15 seconds after the propofol, the patient developed strong bilateral fits and grimaces, which lasted for 10 seconds. Anaesthesia was maintained with nitrous oxide/oxygen and halothane and there were no other intra- or postoperative complications. The patient had no history of convulsions.[11] There is a further report of opisthotonos during recovery from anaesthesia with **alfentanil**, propofol and nitrous oxide.[12] Propofol has been associated with opisthotonos (a spasm where the head and heels bend backwards and the body arches forwards) in two patients given **fentanyl** with or without **alfentanil**,[13] and seizures have been reported in patients with and without epilepsy receiving propofol. They mainly occur during induction and emergence or are delayed after anaesthesia, suggesting that they may be caused by changes in cerebral levels of propofol,[14] and post-anaesthetic opisthotonos may be due to a propofol-induced tolerance to inhibitory transmitters (glycine and

GABA).[12] Any association with the opioid remains unknown, although it has been suggested that opioids may aggravate propofol-induced opisthotonos by antagonising the actions of glycine.[12]

Alfentanil has been found to reduce the amount of propofol needed for loss of eyelash reflex and loss of consciousness, as well as enhancing the reduction in blood pressure produced by propofol.[15] Propofol inhibits both **alfentanil** and **sufentanil** metabolism causing an increase in plasma concentrations of these opioids, while **alfentanil** also increases propofol concentrations (which has been the subject of a review[16] and also described in more recent reports[17-20]). Pretreatment with **fentanyl** may also decrease the propofol requirements for induction of anaesthesia,[16] and increase blood concentrations of propofol.[21] However, another study was unable to confirm that **fentanyl** had an effect on blood propofol concentrations.[22]

A study in 2 groups of 20 patients undergoing similar types of surgery with similar propofol consumption, the duration of clinical anaesthesia with **remifentanil** and propofol was longer than with **fentanyl** and propofol.[23] **Remifentanil** has been reported to reduce the dose of propofol needed for anaesthesia and also to reduce the recovery time.[24,25] Further, propofol and **remifentanil** caused dose-dependent respiratory-depression, which, during combined use, was synergistic.[26] One study using EEG-controlled dosing of propofol and **remifentanil** for anaesthesia found their pharmacodynamic effects were no more than additive.[27] Although **remifentanil** alone appears to be ineffective at countering the response to stimuli, a study in healthy subjects has found that **remifentanil** can significantly reduce the levels of propofol required to remove a response to shouting, shaking or laryngoscopy (synergistic effect), but the effects on EEG measures were additive.[28] In another study in healthy subjects given **remifentanil** and propofol, the synergy that occurred for both analgesic and hypnotic endpoints was found to be greatest at lower levels of the drugs, which for each drug alone would not be producing maximal effects.[29] Another study found changes in BIS (bispectral index) that suggested that **remifentanil** may have some hypnotic properties or that it can potentiate the hypnotic effect of propofol.[30] It has been suggested that the increased hypnotic effects may be due to a dose-dependent decrease in cardiac output by **remifentanil**, resulting in an increase in arterial and brain propofol with increased anaesthetic effect.[31] One pharmacokinetic study found that the levels of **remifentanil** may be increased during concurrent propofol infusion,[32] while another study found that concurrent propofol reduced volume of distribution and distribution clearance of **remifentanil** by 41%. It was concluded that although propofol affects **remifentanil** bolus dose pharmacokinetics, maintenance infusion rates and recovery times would not be significantly affected.[33]

The manufacturer notes that the required induction dose of propofol may be reduced in patients who have received opioids, and that these drugs may increase the anaesthetic and sedative effects of propofol, and also cause greater reductions in blood pressure and cardiac output. They also state that propofol requirements for maintenance of anaesthesia may be reduced in the presence of opioids.[34]

Two reviews have discussed the use of opioids and propofol in anaesthesia, their pharmacokinetic and pharmacodynamic interactions, and administration and monitoring techniques.[35,36]

(e) Thiopental

Opioid analgesics would be expected to potentiate the respiratory depressant effects of barbiturate anaesthetics. A study has found that the dose of thiopental required to induce anaesthesia was reduced by pretreatment with **fentanyl**.[37] The manufacturer recommends reduced doses of thiopental in patients premedicated with opioids.[38]

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Anaesthetics, general + Parecoxib

Limited evidence suggests parecoxib does not affect the pharmacokinetics or clinical effects of propofol. Parecoxib does not appear to interact with nitrous oxide and isoflurane.

Clinical evidence, mechanism, importance and management

A randomised, placebo-controlled, crossover study in 12 healthy subjects found that pretreatment with 40 mg of intravenous parecoxib, given one hour before a 2 mg/kg intravenous bolus of **propofol**, did not significantly affect the pharmacokinetics of **propofol**. Moreover, parecoxib did not alter the clinical effects of **propofol** (e.g. the time to loss of consciousness or the speed of awakening).[1] These limited data suggest that no special precautions should be required during concurrent use.

The UK manufacturer of parecoxib says that no formal interaction studies have been done with inhalational anaesthetics, but in surgical studies, where parecoxib was given preoperatively, there was no evidence of phar-

macodynamic interactions in patients who had been given **nitrous oxide** and **isoflurane**.[2]

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Anaesthetics, general + Phenylephrine, topical

Phenylephrine eye drops given to patients undergoing general anaesthesia caused marked cyanosis and bradycardia in a baby, and hypertension in a woman.

Clinical evidence, mechanism, importance and management

A 3-week-old baby anaesthetised with **halothane** and **nitrous oxide**/**oxygen** became cyanosed shortly after 2 drops of phenylephrine 10% solution were put into one eye. The heart rate decreased from 160 to 60 bpm, ST-segment and T-wave changes were seen, and blood pressure measurements were unobtainable. The baby recovered uneventfully when anaesthesia was stopped and oxygen given. It was suggested that the phenylephrine caused severe peripheral vasoconstriction, cardiac failure and reflex bradycardia.[1] A 54-year-old woman anaesthetised with **isoflurane** developed hypertension (a rise from 125/70 to 200/90 mmHg) shortly after having two drops of phenylephrine 10% solution put into one eye. The hypertension responded to nasal glyceryl trinitrate (nitroglycerin) and increasing concentrations of isoflurane.[1] The authors of this report consider that general anaesthesia may have contributed to the systemic absorption of the phenylephrine. They suggest that phenylephrine should be given 30 to 60 minutes before anaesthesia, and not during anaesthesia; however, if it is necessary to give phenylephrine, use the lowest concentration (2.5%). They also point out that the following are effective mydriatics: single drop combinations of cyclopentolate 0.5% and phenylephrine 2.5%, or tropicamide 0.5% and phenylephrine 2.5%.

Phenylephrine is a sympathomimetic, and as such may carry some risk of potentiating arrhythmias if it is used with inhalational anaesthetics such as halothane – see 'Anaesthetics, general + Inotropes and Vasopressors', p.111. However, it is considered that it is much less likely than adrenaline (epinephrine) to have this effect, since it has primarily alpha-agonist activity.[2]

1. Van der Spek AFL, Hantler CB. Phenylephrine eyedrops and anesthesia. *Anesthesiology* (1986) 64, 812–14.
2. Smith NT, Miller RD, Corbascio AN, eds. Sympathomimetic drugs, in Drug Interactions in Anesthesia. Philadelphia: Lea and Febiger; 1981 P. 55–82.

Anaesthetics, general + Probenecid

The anaesthetic dosage of thiopental is reduced, and its effects prolonged by pretreatment with probenecid.

Clinical evidence

A study[1] in patients about to undergo surgery found that probenecid 1 g given one hour before anaesthesia reduced the thiopental dosage by 23%, from 5.3 to 4.1 mg/kg.

A further double-blind study[2] in 86 women found that probenecid given 3 hours before surgery prolonged the duration of anaesthesia with thiopental:

- In patients premedicated with atropine 7.5 micrograms/kg, pethidine (meperidine) 1 mg/kg, and 500 mg of probenecid, the duration of anaesthesia with thiopental 7 mg/kg was prolonged by 65%,
- In patients premedicated with atropine 7.5 micrograms/kg, pethidine 1 mg/kg, and *1 g of probenecid*, the duration of anaesthesia with thiopental 7 mg/kg was prolonged by 46%,
- In patients premedicated with atropine 7.5 micrograms/kg (*no pethidine*) and 500 mg of probenecid, the duration of anaesthesia with thiopental 7 mg/kg was prolonged by 26%,
- In patients premedicated with atropine 7.5 micrograms/kg (*no pethidine*) and 500 mg of probenecid, and *no surgical stimulus* the duration of anaesthesia with *thiopental 4 mg/kg* was prolonged by 109%.

Mechanism

Not understood. It has been suggested that probenecid increases the amount of free (and active) thiopental in the plasma since it competes for the binding sites on the plasma albumins.[1]

Importance and management

Information is limited but what is known shows that the effects of thiopental are increased by probenecid. As the change in propofol requirements is modest, and because the dose would be expected to be titrated to effect, this interaction seems likely to be of minimal clinical relevance.

1. Dundee JW, Halliday NJ, McMurray TJ. Aspirin and probenecid pretreatment influences the potency of thiopentone and the onset of action of midazolam. *Eur J Anaesthesiol* (1986) 3, 247–51.
2. Kaukinen S, Eerola M, Ylitalo P. Prolongation of thiopentone anaesthesia by probenecid. *Br J Anaesth* (1980) 52, 603–7.

Anaesthetics, general + Sparteine sulfate

Patients given thiamylal sodium had a marked increase in cardiac arrhythmias when they were given intravenous sparteine sulfate, but those given thiopental or etomidate did not.

Clinical evidence, mechanism, importance and management

A group of 109 women undergoing dilatation and curettage were premedicated with atropine and fentanyl, and given either **thiamylal sodium** 2% (5 mg/kg), **etomidate** 0.2% (0.3 mg/kg) or **thiopental** 2.5% (4 mg/kg) to induce anaesthesia, which was maintained with **nitrous oxide**/**oxygen**. During the surgical procedure they were given a slow intravenous injection of sparteine sulfate 100 mg. Fourteen out of 45 patients given **thiamylal sodium** developed cardiac arrhythmias; 10 had bigeminy and 4 had frequent ventricular premature contractions. Only two patients given **etomidate** or **thiopental** developed any cardiac arrhythmias. It is not understood why sparteine should interact with **thiamylal sodium** in this way. Although the arrhythmias were effectively treated with lidocaine, the authors of this report suggest that the concurrent use of sparteine and **thiamylal sodium** should be avoided.[1]

1. Cheng C-R, Chen S-Y, Wu K-H, Wei T-T. Thiamylal sodium with sparteine sulfate inducing dysrhythmia in anesthetized patients. *Ma Zui Xue Za Zhi* (1989) 27, 297–8.

Anaesthetics, general + SSRIs

One patient had a seizure when she was given methohexital while taking paroxetine. Spontaneous movements have been seen in two patients taking fluoxetine when they were anaesthetised with propofol.

Clinical evidence, mechanism, importance and management

(a) Methohexital

A generalised tonic-clonic seizure occurred in a 42-year-old woman immediately after she was anaesthetised with 120 mg of intravenous methohexital for the last in a series of six electroconvulsive therapies. She had been receiving **paroxetine** 40 mg daily throughout the series.[1] The authors suggest that paroxetine should be given with caution to patients receiving ECT or methohexital anaesthesia.[1] Note that this appears to be an isolated report.

(b) Propofol

Two women in their mid-twenties, who had been taking **fluoxetine** 20 mg daily for 4 to 6 months, had pronounced involuntary upper limb movements lasting 20 to 30 seconds immediately after anaesthetic induction with 180 mg of propofol (2 to 2.5 mg/kg). The movements ceased spontaneously and the rest of the anaesthesia and surgery were uneventful. Neither had any history of epilepsy or movement disorders. It is not clear whether this was an interaction between propofol and **fluoxetine** or just a rare (but previously reported) reaction to propofol.[2]

1. Folkerts H. Spontaneous seizure after concurrent use of methohexital anesthesia for electroconvulsive therapy and paroxetine: a case report. *J Nerv Ment Dis* (1995) 183, 115–16.
2. Armstrong TSH, Martin PD. Propofol, fluoxetine and spontaneous movement. *Anaesthesia* (1997) 52, 809–10.

Anaesthetics, general + Sulfonamides

The anaesthetic effects of thiopental are increased, but shortened, by sulfafurazole. Phenobarbital appears not to affect the pharmacokinetics of sulfafurazole or sulfisomidine.

Clinical evidence

A study in 48 patients found that intravenous **sulfafurazole** 40 mg/kg reduced the required anaesthetic dosage of **thiopental** by 36%, but the duration of action was shortened.[1] This interaction has also been observed in *animal* experiments.[2] A study in children found that **phenobarbital** did not affect the pharmacokinetics of **sulfafurazole** or **sulfisomidine**.[3]

Mechanism

It has been suggested that sulfafurazole successfully competes with thiopental for plasma protein binding sites,[4] the result being that more free and active barbiturate molecules remain in circulation to exert their anaesthetic effects and therefore smaller doses are required.

Importance and management

The evidence for an interaction between sulfafurazole and thiopental is limited, but it appears to be strong. Less thiopental than usual may be required to achieve adequate anaesthesia, but since the awakening time is shortened repeated doses may be needed.

Phenobarbital does not appear to affect the pharmacokinetics of the sulfonamides.

1. Csögör SI, Kerek SF. Enhancement of thiopentone anaesthesia by sulphafurazole. *Br J Anaesth* (1970) 42, 988–90.
2. Csögör SI, Pálffy B, Feszt G, Papp J. Influence du sulfathiazol sur l'effet narcotique du thiopental et de l'hexobarbital. *Rev Roum Physiol* (1971) 8, 81–5.
3. Krauer B. Vergleichende Untersuchung der Eliminationskinetik zweier Sulfonamide bei Kindern mit und ohne Phenobarbitalmedikation. *Schweiz Med Wochenschr* (1971) 101, 668–71.
4. Csögör SI, Papp J. Competition between sulphonamides and thiopental for the binding sites of plasma proteins. *Arzneimittelforschung* (1970) 20, 1925–7.

Anaesthetics, general + Theophylline

Cardiac arrhythmias can develop during the concurrent use of halothane and aminophylline. One report attributes seizures to an interaction between ketamine and aminophylline. Theophylline would be expected to interact similarly.

Clinical evidence, mechanism, importance and management

(a) Development of arrhythmias

A number of reports describe arrhythmias apparently due to an interaction between **halothane** and theophylline or aminophylline. One describes intraoperative arrhythmias in three out of 45 adult asthmatics who had received preoperative theophylline or aminophylline followed by **halothane** anaesthesia.[1] Nine other patients developed heart rates exceeding 140 bpm when given aminophylline and **halothane**, whereas tachycardia did not occur in 22 other patients given only **halothane**.[1] There are other reports of individual adult and child patients who developed ventricular tachycardias attributed to this interaction.[2-5] One child had a cardiac arrest.[5] The same interaction has been reported in *animals*.[6,7] One suggested reason for the interaction with **halothane** is that theophylline causes the release of endogenous catecholamines (adrenaline (epinephrine), noradrenaline (norepinephrine)), which are known to sensitise the myocardium, see 'Anaesthetics, general + Inotropes and Vasopressors', p.111. For a report describing supraventricular tachycardia, in a patient taking aminophylline who was anaesthetised with thiopental and fentanyl and then given pancuronium, see 'Neuromuscular blockers + Theophylline', p.146.

The authors of one of the reports advise avoiding concurrent use, and suggest waiting approximately 13 hours after the last dose of aminophylline before using **halothane**[2] but another[8] says that: "my own experience with the liberal use of these drugs has convinced me of the efficacy and wide margin of safety associated with their use in combination." For a list of inhalational anaesthetics, in order of arrhythmogenic potential, see 'Anaesthetics and Neuromuscular blockers', (p.100).

(b) Development of seizures

Over a period of 9 years, tachycardia and extensor-type seizures were observed in 4 patients taking theophylline or aminophylline, who were initially anaesthetised with **ketamine**, and then given **halothane** or **enflurane**.[9] Based on a subsequent study in *mice*, the authors attributed the seizures to an interaction between **ketamine** and theophylline or aminophylline, and they suggest that the combination should perhaps be avoided in some, or antiepileptic premedication be given to patients at risk. However, these cases come from one isolated report. Note that, in *mice*, **ketamine** had no effect on aminophylline-induced seizures.[10]

1. Barton MD. Anesthetic problems with aspirin-intolerant patients. *Anesth Analg* (1975) 54, 376–80.
2. Roizen MF, Stevens WC. Multiform ventricular tachycardia due to the interaction of aminophylline and halothane. *Anesth Analg* (1978) 57, 738–41.
3. Naito Y, Arai T, Miyake C. Severe arrhythmias due to the combined use of halothane and aminophylline in an asthmatic patient. *Jpn J Anesthesiol* (1986) 35, 1126–9.
4. Bedger RC, Chang J-L, Larson CE, Bleyaert AL. Increased myocardial irritability with halothane and aminophylline. *Anesth Prog* (1980) 27, 34–6.
5. Richards W, Thompson J, Lewis G, Levy DS, Church JA. Cardiac arrest associated with halothane anesthesia in a patient receiving theophylline. *Ann Allergy* (1988) 61, 83–4
6. Takaori M, Loehning RW. Ventricular arrhythmias induced by aminophylline during halothane anaesthesia in dogs. *Can Anaesth Soc J* (1967) 14, 79–86.
7. Stirt JA, Berger JM, Roe SD, Ricker SM, Sullivan SF. Halothane-induced cardiac arrhythmias following administration of aminophylline in experimental animals. *Anesth Analg* (1981) 60, 517–20.
8. Zimmerman BL. Arrhythmogenicity of theophylline and halothane used in combination. *Anesth Analg* (1979) 58, 259–60.
9. Hirshman CA, Krieger W, Littlejohn G, Lee R, Julien R. Ketamine-aminophylline-induced decrease in seizure threshold. *Anesthesiology* (1982) 56, 464–7.
10. Czuczwar SJ, Janusz W, Wamil A, Kleinrok Z. Inhibition of aminophylline-induced convulsions in mice by antiepileptic drugs and other agents. *Eur J Pharmacol* (1987) 144, 309–15.

Anaesthetics, general + Tizanidine

Premedication with oral tizanidine appears to reduce the MAC of sevoflurane.

Clinical evidence, mechanism, importance and management

In a study, 52 patients were given either oral tizanidine 4 mg or placebo 70 minutes before induction of anaesthesia with **sevoflurane** 5%. The MAC of **sevoflurane** was 2.2% and 1.8% in the control and tizanidine-treated groups, respectively. The sedation score in the tizanidine group was higher than in the placebo group, and the time to loss of consciousness in the tizanidine and control groups was about 60 seconds and 74 seconds, respectively. Tizanidine therefore exerted a hypnotic effect and reduced the MAC of **sevoflurane** by 18%. No tizanidine-related adverse effects, such as hypotension, were reported.[1] The general relevance is not yet established, but the changes seen were minimal and therefore would not be expected to clinically significant.

1. Wajima Z, Yoshikawa T, Ogura A, Imanaga K, Shiga T, Inoue T, Ogawa R. Oral tizanidine, an α_2-adrenoceptor agonist, reduces the minimum alveolar concentration of sevoflurane in human adults. *Anesth Analg* (2002) 95, 393–6.

Anaesthetics, general + Topiramate

Topiramate and may reduce the anaesthetic properties of amobarbital. One study suggests that topiramate may attenuate the effects of ketamine, whereas another did not find an interaction.

Clinical evidence, mechanism, importance and management

(a) Amobarbital

In a retrospective study, it was found that 11 of 56 epileptic patients who had undergone the intracarotid amobarbital procedure (IAP) recovered very rapidly from the anaesthetic (within 60 seconds) or had anaesthetic failure. Seven of the 11 were taking topiramate and one had recently discontinued topiramate at the time of the procedure. The other 3 patients had been taking **zonisamide** (2), or furosemide (1). A further 2 patients taking topiramate or hydrochlorothiazide had a rapid recovery (within 90 seconds).

It was suggested that the anaesthetic effect of amobarbital may be affected by the carbonic anhydrase-inhibiting activity of these drugs. No anaesthetic failures were reported in patients taking combinations of antiepileptics such as carbamazepine, phenytoin and valproate but without drugs with carbonic anhydrase-inhibiting effects.[1] The mechanism is not understood but may be due to interference with the activity of amobarbital

on $GABA_A$ receptors by effects on electrochemical gradients across cell membranes or via metabolic acidosis.

The authors recommend that topiramate, **zonisamide** or other carbonic anhydrase inhibitors should be discontinued at least 8 weeks before the IAP.[1] Similar findings are reported in a review of 40 other patients.[2]

(b) Ketamine

A study in 36 healthy subjects found that a single 50-mg dose of topiramate slightly decreased the effect of sub-anaesthetic doses of ketamine (slow intravenous injection of 120 micrograms/kg followed by 500 micrograms/kg over one hour) on a cognitive performance test (anti-saccade test). Pharmacokinetic analysis also found that ketamine levels were increased by about 25% in the subjects given topiramate.[3] A follow-up, placebo-controlled study by the same authors in 36 healthy subjects found that pretreatment with a single 50-mg dose of topiramate did not significantly affect the reaction time to ketamine (same dose as the previous study).[4] The general significance of these results in patients taking topiramate and undergoing sedation or anaesthesia with ketamine is unclear. Further study is needed.

1. Bookheimer S, Schrader LM, Rausch R, Sankar R, Engel J. Reduced anesthetization during intracarotid amobarbital (Wada) test in patients taking carbonic anhydrase-inhibiting medications. *Epilepsia* (2005) 46, 236–43.
2. Ringman JM, Grant AC. Carbonic anhydrase inhibitors and amobarbital resistance. *Epilepsia* (2005) 46, 1333.
3. Gavaudan G, Micallef-Roll J, Hasbroucq T, Masson G, Lançon, Blin O. Does topiramate blunt N-methyl-D-aspartate receptor antagonists effects in healthy humans? *Eur Arch Psychiatry Clin Neurosci* (2003) 253 (Suppl 1) I/16.
4. Micallef J, Gavaudan G, Burle B, Blin O, Hasbroucq T. A study of a topiramate pre-treatment on the effects induced by a subanaesthetic dose of ketamine on human reaction time. *Neurosci Lett* (2004) 369, 99–103.

Anaesthetics, general + Trichloroethane

Two patients had evidence of chronic cardiac toxicity after repeated exposure to trichloroethane. There was circumstantial evidence in both cases of a deterioration in cardiac function following halothane anaesthesia.

Clinical evidence, mechanism, importance and management

Two patients, who had been repeatedly exposed to trichloroethane; one during solvent abuse including *Tipp-Ex* typewriter correcting fluid thinner and the other due to industrial exposure including *Genklene* for degreasing steel, showed evidence of chronic cardiac toxicity. In both cases there was circumstantial evidence of cardiac deterioration after routine anaesthesia with **halothane**. Some **solvents** have a close chemical similarity to **inhalational anaesthetic** drugs, particularly the halogenated hydrocarbons, and these related compounds might have a toxic interaction.[1]

1. McLeod AA, Marjot R, Monaghan MJ, Hugh-Jones P, Jackson G. Chronic cardiac toxicity after inhalation of 1,1,1-trichloroethane. *BMJ* (1987) 294, 727–9.

Anaesthetics, general and/or Neuromuscular blockers + Tricyclic and related antidepressants

Tricyclic antidepressants may increase the risk of arrhythmias and hypotension during anaesthesia. Tachyarrhythmias have been seen in patients taking imipramine who were given halothane and pancuronium. Some very limited evidence suggests that amitriptyline may increase the likelihood of enflurane-induced seizure activity. A man taking maprotiline and lithium developed a tonic-clonic seizure when given propofol. Tricyclics may cause an increase in the duration of barbiturate anaesthesia.

Clinical evidence, mechanism, importance and management

(a) Development of arrhythmias

Two patients who were taking **nortriptyline** (one also taking fluphenazine) developed prolonged cardiac arrhythmias during general anaesthesia with **halothane**.[1] Two further patients taking **imipramine** developed marked tachyarrhythmias when anaesthetised with **halothane** and given **pancuronium**.[2] This adverse interaction was subsequently clearly demonstrated in *dogs*.[2] The authors concluded on the basis of their studies that:

- **pancuronium** should be given with caution to patients taking any **tricyclic antidepressant** if **halothane** is used;
- **gallamine** probably should be avoided but **tubocurarine** may be an acceptable alternative to **pancuronium**;
- **pancuronium** is probably safe in the presence of a tricyclic if **enflurane** is used.

However, this last conclusion does not agree with that reached by the authors of another report[3], who found that the combination of **pancuronium** and **enflurane** increased the risk of seizures.

One manufacturer[4] has recommended stopping tricyclics several days before elective surgery where possible. However, the BNF advises that tricyclic antidepressants need not be stopped, but there may be an increased risk of arrhythmias and hypotension (and dangerous interactions with vasopressor drugs, see 'Tricyclic and related antidepressants + Inotropes and Vasopressors', p.1507). Therefore, the anaesthetist should be informed if they are not stopped.[5]

(b) Development of seizures

1. Enflurane + Tricyclics. Two patients taking **amitriptyline** developed clonic movements of the leg, arm and hand during surgery while anaesthetised with enflurane and **nitrous oxide**. The movements stopped when the enflurane was replaced by **halothane**.[3] A possible reason is that **amitriptyline** can lower the threshold at which enflurane-induced seizure activity occurs. It is suggested that it may be advisable to avoid enflurane in patients needing tricyclic antidepressants, particularly in those who have a history of seizures, or when hyperventilation or high concentrations of enflurane are likely to be used.[3]

2. Propofol + Maprotiline. A man with a bipolar disorder taking maprotiline 200 mg four times daily and lithium carbonate 300 mg daily, underwent anaesthesia during which he received fentanyl, **tubocurarine** and propofol 200 mg. Shortly after the injection of the propofol the patient complained of a burning sensation in his face. He then became rigid, his back and neck extended and his eyes turned upwards. After 15 seconds, rhythmic twitching developed in his eyes, arms and hands. This apparent seizure lasted for about one minute until suxamethonium (succinylcholine) was given. The patient regained consciousness after several minutes and the surgery was cancelled.[6] It is not known whether the reaction was due to an interaction between propofol and the antidepressants, or due to just one of the drugs, because both propofol[7,8] and maprotiline[9] have been associated with seizures. However, the authors of this report suggest that it would now be prudent to avoid using propofol in patients taking drugs that significantly lower the convulsive threshold, and this would be expected to include tricyclic antidepressants. More study of this possible interaction is needed.

(c) Increased duration of anaesthesia

A study in *dogs* found that **imipramine** caused about a 50% increase in the duration of **thiopental**-induced sleep.[10] In an early review of electroconvulsive therapy and anaesthesia, it was noted that tricyclics interact with **barbiturates** resulting in an increased sleep time and duration of anaesthesia, and therefore it was suggested that lower doses of barbiturate anaesthetics such as **thiopental** should be given to patients taking tricyclics.[11] However, in a later review, it was noted that no complications have been attributed to the use of ECT (which has often been undertaken using **methohexital** or possibly **propofol**) in patients taking tricyclic antidepressants.[12] Apart from the study in *animals,*[10] there seems little published information to suggest that tricyclics interact significantly with barbiturate anaesthetics, but even if there is an interaction, as the dose of barbiturate should be carefully adjusted according to the patient's response any interaction will probably be accounted for by standard anaesthetic procedures. Consider also 'Tricyclic and related antidepressants + Barbiturates or Phenytoin', p.1499.

1. Plowman PE, Thomas WJW. Tricyclic antidepressants and cardiac dysrhythmias during dental anaesthesia. *Anaesthesia* (1974) 29, 576–8.
2. Edwards RP, Miller RD, Roizen MF, Ham J, Way WL, Lake CR, Roderick L. Cardiac responses to imipramine and pancuronium during anesthesia with halothane or enflurane. *Anesthesiology* (1979) 50, 421–5.
3. Sprague DH, Wolf S. Enflurane seizures in patients taking amitriptyline. *Anesth Analg* (1982) 61, 67–8.
4. Amitriptyline Oral Solution. Rosemont Pharmaceuticals Ltd. UK Summary of product characteristics, March 2008.

5. British National Formulary. 58th ed. London: BMJ Publishing Group Ltd and RPS Publishing; 2009. p. 698.
6. Orser B, Oxorn D. Propofol, seizure and antidepressants. *Can J Anaesth* (1994) 41, 262.
7. Bevan JC. Propofol-related convulsions. *Can J Anaesth* (1993) 40, 805–9.
8. Committee on Safety of Medicines. Propofol – convulsions, anaphylaxis and delayed recovery from anaesthesia. *Current Problems* (1989) 26.
9. Jabbari B, Bryan GE, Marsh EE, Gunderson CH. Incidence of seizures with tricyclic and tetracyclic antidepressants. *Arch Neurol* (1985) 42, 480–1.
10. Dobkin AB. Potentiation of thiopental anesthesia by derivatives and analogues of phenothiazine. *Anesthesiology* (1960) 21, 292–6.
11. Gaines GY, Rees DI. Electroconvulsive therapy and anesthetic considerations. *Anesth Analg* (1986) 65, 1345–56.
12. Wagner KJ, Möllenberg O, Rentrop M, Werner C, Kochs EF. Guide to anaesthetic selection for electroconvulsive therapy. *CNS Drugs* (2005) 19, 745–58.

Anaesthetics, general; Methoxyflurane + Miscellaneous

The nephrotoxic effects of methoxyflurane appear to be increased by the use of tetracyclines, and possibly some aminoglycoside antibacterials and barbiturates.

Clinical evidence, mechanism, importance and management

Methoxyflurane has been withdrawn in many countries because it is nephrotoxic. This damage can be exacerbated by the concurrent use of other nephrotoxic drugs or possibly by the chronic use of hepatic enzyme-inducing drugs. Five out of 7 patients anaesthetised with methoxyflurane who had been given **tetracycline** before or after surgery had rises in blood urea nitrogen, and three died. Post-mortem examination found pathological changes (oxalosis) in the kidneys.[1] Another study identified renal tubular necrosis associated with calcium oxalate crystals in 6 patients who had been anaesthetised with methoxyflurane and given **tetracycline** (4 patients) and **penicillin** with **streptomycin** (2 patients).[2] Other reports support the finding of increased nephrotoxicity with **tetracycline** and methoxyflurane.[3-5] Another study suggested that **penicillin**, **streptomycin** and **chloramphenicol** appear not to increase the renal toxicity of methoxyflurane,[1] but **gentamicin** and **kanamycin** possibly do so.[6] There is also some evidence that **barbiturates** can exacerbate the renal toxicity because they enhance the metabolism of the methoxyflurane and increase the production of nephrotoxic metabolites.[7,8]

The risk of nephrotoxicity with methoxyflurane would therefore appear to be increased by some of these drugs and the concurrent use of **tetracycline** or **nephrotoxic antibiotics** should be avoided. Similarly, methoxyflurane should only be used with great caution, if at all, following the chronic use of hepatic enzyme-inducing drugs.

1. Kuzucu EY. Methoxyflurane, tetracycline, and renal failure. *JAMA* (1970) 211, 1162–4.
2. Dryden GE. Incidence of tubular degeneration with microlithiasis following methoxyflurane compared with other anesthetic agents. *Anesth Analg* (1974) 53, 383–5.
3. Albers DD, Leverett CL, Sandin JH. Renal failure following prostatovesiculectomy related to methoxyflurane anesthesia and tetracycline—complicated by Candida infection. *J Urol (Baltimore)* (1971) 106, 348–50.
4. Proctor EA, Barton FL. Polyuric acute renal failure after methoxyflurane and tetracycline. *BMJ* (1971) 4, 661–2.
5. Stoelting RK, Gibbs PS. Effect of tetracycline therapy on renal function after methoxyflurane anesthesia. *Anesth Analg* (1973) 52, 431–5.
6. Cousins MJ, Mazze RI. Tetracycline, methoxyflurane anaesthesia, and renal dysfunction. *Lancet* (1972) i, 751–2.
7. Churchill D, Yacoub JM, Siu KP, Symes A, Gault MH. Toxic nephropathy after low-dose methoxyflurane anesthesia: drug interaction with secobarbital? *Can Med Assoc J* (1976) 114, 326–33.
8. Cousins MJ, Mazze RI. Methoxyflurane nephrotoxicity: a study of dose response in man. *JAMA* (1973) 225, 1611–16.

Anaesthetics, local + Acetazolamide

In a study in 6 healthy subjects, the mean procaine half-life was increased by 66% (from 1.46 to 2.43 minutes) 2 hours after they were given acetazolamide 250 mg orally. This appears to be because the hydrolysis of the procaine is inhibited by the acetazolamide.[1] As the evidence for this interaction is limited to one report, its general significance is unclear.

1. Calvo R, Carlos R, Erill S. Effects of disease and acetazolamide on procaine hydrolysis by red blood cell enzymes. *Clin Pharmacol Ther* (1980) 27, 179–83.

Anaesthetics, local + Alcohol and/or Antirheumatics

Limited evidence suggests that the failure rate of spinal anaesthesia with bupivacaine may be markedly increased in patients who are receiving antirheumatic drugs and/or who drink alcohol.

Clinical evidence, mechanism, importance and management

The observation that regional anaesthetic failures seemed to be particularly high among patients undergoing orthopaedic surgery who were suffering from rheumatic joint diseases, prompted further study of a possible interaction. It was found that the failure rate of low-dose spinal anaesthesia with **bupivacaine** 0.5% (average volume of 2 mL) increased from 5% in the control group (no alcohol or long-term treatment) to 32% to 42% in those who had been taking antirheumatic drugs (**indometacin** or unspecified) for at least 6 months or who drank at least 80 g of ethanol daily, or both. The percentage of those patients who had a reduced response (i.e. an extended latency period and/or a reduced duration of action) also increased from 3% up to 39 to 42%.[1] The reasons are not understood. This appears to be the only report of such an effect.

1. Sprotte G, Weis KH. Drug interaction with local anaesthetics. *Br J Anaesth* (1982) 54, 242P–243P.

Anaesthetics, local + Anaesthetics, local

Mixtures of local anaesthetics are sometimes used to exploit the most useful characteristics of each drug. This normally seems to be safe although it is sometimes claimed that it increases the risk of toxicity. There is a case report of a man who developed toxicity when bupivacaine and mepivacaine were mixed together. Spinal bupivacaine followed by epidural ropivacaine may also interact to produce profound motor blockade. However, the effectiveness of bupivacaine in epidural anaesthesia may be reduced if it is preceded by chloroprocaine.

Clinical evidence and mechanism

(a) Evidence of no interaction

A study designed to assess the possibility of adverse interactions retrospectively studied the records of 10 538 patients over the period 1952 to 1970 who had been given **tetracaine** combined with **chloroprocaine**, **lidocaine**, **mepivacaine**, **prilocaine** or **propoxycaine** for caudal, epidural, or peripheral nerve block. The incidence of systemic toxic reactions was found to be no greater than when used singly and the conclusion was reached that combined use was advantageous and safe.[1] An *animal* study using combinations of **bupivacaine**, **lidocaine** and **chloroprocaine** also found no evidence that the toxicity was greater than if the anaesthetics were used singly.[2]

A study investigating the use of **chloroprocaine** 3%, **bupivacaine** 0.5% or a mixture of **chloroprocaine** 1.5% with **bupivacaine** 0.375% in obstetric epidural anaesthesia found that the time to onset of analgesia, the time to maximum analgesia, and the effectiveness of analgesia were similar irrespective of the treatment regimen. **Bupivacaine** 0.5% alone had a longer duration of action than **chloroprocaine** or the mixture of anaesthetics.[3] Another study found that **lidocaine** did not affect the pharmacokinetics of **bupivacaine**.[4]

(b) Evidence of reduced analgesia

A study designed to examine the clinical impression that **bupivacaine** given epidurally did not relieve labour pain effectively if preceded by **chloroprocaine** confirmed that this was so. Using an initial 10-mL dose of **chloroprocaine** 2% followed by an 8-mL dose of **bupivacaine** 0.5%, given when pain recurred, the pain relief was less and the block took longer to occur, had a shorter duration of action and had to be augmented more frequently than if only **bupivacaine** was used.[5] This interaction could not be corrected by adjusting the pH of the local anaesthetics.[6]

(c) Evidence of enhanced effect/toxic interaction

An isolated case report describes a patient given **bupivacaine** 0.75% and **mepivacaine** 2% who demonstrated lethargy, dysarthria and mild muscle tremor. The authors of the report suggested that this correlated with a

marked increase in the percentage of unbound (active) **mepivacaine**, which was attributed to its displacement from protein binding sites by **bupivacaine**.[7] **Bupivacaine** has also been shown *in vitro* to displace **lidocaine** from α_1-acid glycoprotein.[8] Two cases of prolonged, profound motor blockade, have occurred in patients receiving patient-controlled epidural analgesia with **ropivacaine** 0.1% following spinal **bupivacaine** for caesarean section. Including these 2 patients, a total of 11 out of 23 patients given regional anaesthesia with **bupivacaine** had clinical evidence of motor weakness 8 hours after subsequently starting **ropivacaine**.[9]

Importance and management

Well studied interactions. The overall picture is that combined use does not normally result in increased toxicity, although there may be some exceptions. For example, until more is known, caution should be exercised when giving epidural ropivacaine postoperatively to patients who have had bupivacaine spinal anaesthesia, as unexpected motor block may occur.[9] Reduced effectiveness might be seen if bupivacaine is preceded by chloroprocaine.

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Anaesthetics, local + Antihypertensives

Severe hypotension and bradycardia have been seen in patients taking captopril or verapamil when they were given epidural anaesthesia with bupivacaine. Verapamil does not appear to interact with epidural lidocaine. Acute hypotension occurred in a man taking prazosin when he was given epidural anaesthesia with bupivacaine.

Clinical evidence

(a) ACE inhibitors

An 86-year-old man who had been receiving **captopril** 25 mg twice daily and bendroflumethiazide 25 mg daily [sic] for hypertension, underwent a transurethral resection of his prostate under spinal anaesthesia using 3 to 3.5 mL of heavy **bupivacaine** 0.5%. At the end of surgery, he was returned to the supine position and he suddenly developed severe sinus bradycardia (35 bpm), his arterial blood pressure fell to 65/35 mmHg and he became unrousable. Treatment with head-down tilt, oxygen and atropine 1.2 mg produced rapid improvement in cardiovascular and cerebral function. A further hypotensive episode (without bradycardia) occurred approximately one hour later, which responded rapidly to methoxamine 4 mg.[1]

(b) Alpha blockers

A man taking **prazosin** 5 mg three times daily for hypertension developed marked hypotension (BP 60/40 mmHg) within 3 to 5 minutes of receiving **bupivacaine** 100 mg through an L3–4 lumbar epidural catheter.[2] He was unresponsive to intravenous phenylephrine (five 100-microgram boluses) but his blood pressure rose within 3 to 5 minutes of starting a 0.05-micrograms/kg per minute infusion of adrenaline (epinephrine).

(c) Beta blockers

See 'Anaesthetics, local + Beta blockers', p.122, for reports of cardiotoxicity in patients given beta blockers with local anaesthetics.

(d) Calcium-channel blockers

Four patients taking long-term **verapamil** developed severe hypotension (systolic pressure as low as 60 mmHg) and bradycardia (48 bpm) 30 to 60 minutes after an epidural block with **bupivacaine** 0.5% and adrenaline (epinephrine). This was totally resistant to atropine and ephedrine, and responded only to calcium gluconate or calcium chloride. No such interaction was seen in a similar group of patients when epidural **lidocaine** was used.[3]

(e) Clonidine

See 'Anaesthetics, local + Clonidine', p.123.

Mechanism

Spinal anaesthesia can produce bradycardia and a fall in cardiac output resulting in arterial hypotension, which may be magnified by the action of the antihypertensive drug, and by hypovolaemia. Other factors probably contributed to the development of this interaction in these particular patients.

Importance and management

Direct information seems to be limited to the reports cited. Their general relevance is uncertain, but they serve to emphasise the importance of recognising that all antihypertensive drugs interfere in some way with the normal homoeostatic mechanisms that control blood pressure, so that the normal physiological response to hypotension during epidural anaesthesia may be impaired. Intravenous calcium effectively controls the hypotension and bradycardia produced by verapamil toxicity by reversing its calcium-channel blocking effects.[3,4]

Accidental intravenous administration of local anaesthetics during spinal anaesthesia may cause cardiovascular collapse and, on theoretical grounds, the serious cardiac depressant effects could be enhanced in patients taking antihypertensives, and it has been suggested that this may be a particular risk in elderly patients with impaired cardiovascular function.[5] Particular care would seem to be important with any patient given epidural anaesthesia while taking antihypertensives.

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Anaesthetics, local + Benzodiazepines

Diazepam may increase the maximum plasma concentrations of bupivacaine, but the rate of bupivacaine elimination may also be increased. Midazolam has been reported to cause a modest decrease in lidocaine, but not mepivacaine, levels. Spinal anaesthesia with bupivacaine, lidocaine, or tetracaine may increase the sedative effects of midazolam. A case of possible lidocaine toxicity has been described when a woman taking sertraline was given flurazepam and then intraoperative lidocaine.

Clinical evidence

(a) Diazepam

Twenty-one children aged 2 to 10 years were given a single 1-mL/kg caudal injection of a mixture of **lidocaine** 0.5% and **bupivacaine** 0.125% for regional anaesthesia. Pretreatment with diazepam 10 mg rectally half-an-hour before the surgery had no significant effect on the plasma levels of **lidocaine**, but the AUC and maximum plasma **bupivacaine** levels were increased by 70 to 75%.[1] In another study in adult patients giving intravenous diazepam slightly, but not significantly, increased the mean maximum plasma levels of subsequent epidural **bupivacaine** or **etidocaine**. However, the elimination half-lives of both anaesthetics were significantly decreased, by about a half.[2]

(b) Flurazepam

A single report describes possible **lidocaine** toxicity following tumescent liposuction in a patient given perioperative sedation with flurazepam

30 mg orally. Ten hours after the completion of the procedure, in which a total of 58 mg/kg of lidocaine was used, the patient developed nausea and vomiting, an unsteady gait, mild confusion, and speech impairment. Her lidocaine level was 6.3 mg/L (levels greater than 6 mg/L were considered to be associated with an increased risk of toxicity). The patient was also taking sertraline.[3]

(c) Midazolam

In a study, 20 children aged 2 to 7 years were given a caudal block with 1 mL/kg of a solution containing **lidocaine** 0.5% and **bupivacaine** 0.125%, with midazolam 400 micrograms/kg given rectally half-an-hour before surgery. Midazolam caused a slight but non-significant reduction in the AUC and plasma levels of **bupivacaine**, whereas the AUC of **lidocaine** was reduced by 24%,[4] which would not be expected to be clinically significant. In another study, midazolam 400 micrograms/kg given rectally as a premedication was found to have no significant effect on plasma **mepivacaine** levels.[5] In a further study in which patients were given intravenous midazolam following an intramuscular injection of either **bupivacaine**, **lidocaine** or sodium chloride 0.9%, it was found that both anaesthetics enhanced the effect of midazolam. This effect was dose-dependent and it was concluded that the use of **lidocaine** or **bupivacaine** for regional blocks or local infiltration could alter the effect of midazolam from sedative to hypnotic.[6]

Twenty patients undergoing surgery were given repeated 1-mg intravenous doses of midazolam as induction anaesthesia every 30 seconds until they failed to respond to three repeated commands to squeeze the anaesthetist's hand. This was considered as the induction end-point 'titrated' dose. It was found that the 10 patients who had previously been given spinal anaesthesia with **tetracaine** 12 mg needed only half the dose of midazolam (7.6 mg) than the 10 other patients who had not received **tetracaine** (14.7 mg). The reasons are not known.[7]

Mechanism

The reasons for the pharmacokinetic interaction between diazepam and bupivacaine are not understood. The authors of the case report[3] describing lidocaine toxicity with flurazepam suggested that the flurazepam and sertraline inhibited lidocaine metabolism by the cytochrome P450 isoenzyme CYP3A4. However, note that flurazepam and sertraline are not usually considered to have inhibitory effects on this isoenzyme.

Both benzodiazepines and local anaesthetics are CNS depressants and therefore their concurrent use may result in additive CNS depression.

Importance and management

The clinical importance of these interactions is uncertain, but be aware that increased bupivacaine plasma levels have been seen with diazepam. One Canadian manufacturer of bupivacaine[8] suggests that reduced doses should be given if bupivacaine is given with sedatives. Note that, as with the use of any two CNS depressant drugs, consideration should be given to the potential for increased sedation.

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Anaesthetics, local + Beta blockers

Propranolol reduces the clearance of bupivacaine and so theoretically the toxicity of bupivacaine may be increased. There has been a single report of enhanced bupivacaine cardiotoxicity in a patient also receiving metoprolol and digoxin. The coronary vasoconstriction caused by cocaine is increased by propranolol. Nadolol appears to increase the duration of anaesthesia seen with lidocaine combined with adrenaline but not with lidocaine alone. Transient hypertension has been reported in a patient taking propranolol and given mepivacaine with corbadrine.

Clinical evidence, mechanism, importance and management

(a) Bupivacaine

1. Metoprolol. A case report describes enhanced bupivacaine cardiotoxicity in a patient taking enalapril 5 mg daily, metoprolol 25 mg twice daily and **digoxin** 250 micrograms four times daily (serum digoxin level 1.1 nanograms/mL). Cardiac arrest occurred 15 minutes after the injection of bupivacaine 0.5% with adrenaline (epinephrine) for intercostal nerve block (total bupivacaine dose 100 mg). The cardiodepressant effects of metoprolol, **digoxin** and bupivacaine were thought to have combined to produce toxicity at a dose of bupivacaine not usually considered toxic. The authors suggest that patients taking **digoxin** with a beta blocker and/or calcium-channel blocker should be considered at higher risk for bupivacaine cardiotoxicity.[1] See also 'Anaesthetics, local + Antihypertensives', p.121, for further discussion of the use of local anaesthetics in patients receiving antihypertensives.

2. Propranolol. In a study in 6 healthy subjects, the clearance of bupivacaine was modestly reduced by about 35% when they were given bupivacaine 30 to 50 mg intravenously over 10 to 15 minutes after taking propranolol 40 mg every 6 hours for one day. It was suggested that propranolol inhibited the activity of the liver microsomal enzymes by changing hepatic blood flow, thereby reducing the metabolism of the bupivacaine. Changes in blood flow to the liver are unlikely to affect bupivacaine metabolism substantially because it is relatively poorly extracted from the blood. The clinical importance of this interaction is uncertain, but it is suggested that an increase in local anaesthetic toxicity might occur and caution should be exercised if multiple doses of bupivacaine are given.[2] See also 'Anaesthetics, local + Antihypertensives', p.121, for further discussion of the use of local anaesthetics in patients receiving antihypertensives.

(b) Cocaine

A study in 30 patients being evaluated for chest pain found that 2 mg/kg of an intranasal solution of cocaine 10% reduced coronary sinus flow by about 14% and coronary artery diameter by 6 to 9%. The coronary vascular resistance increased by 22%. The addition of **propranolol** 400 micrograms/minute by intracoronary infusion (to a total of 2 mg) reduced coronary sinus flow by a further 15% and increased the coronary vascular resistance by 17%. These effects were thought to occur because cocaine stimulates the alpha receptors of the coronary blood vessels causing vasoconstriction. When the beta receptors are blocked by **propranolol**, the resultant unopposed alpha-adrenergic stimulation may lead to enhanced coronary vasoconstriction (see also 'Beta blockers + Inotropes and Vasopressors', p.1011). The clinical importance of these findings is uncertain but the authors of the report suggest that beta blockers should be avoided in patients with myocardial ischaemia or infarction associated with the use of cocaine.[3]

(c) Local anaesthetics with vasoconstrictors

In a randomised, placebo-controlled, crossover study in 10 healthy subjects, the upper lateral incisor teeth were anaesthetised using **lidocaine** with or without **adrenaline** (epinephrine). The mean duration of anaesthesia using 1 mL of lidocaine 2% containing 1:100 000 adrenaline was increased by 58% (17 minutes) for pulpal anaesthesia and 19% (16.5 minutes) for soft-tissue anaesthesia in subjects pretreated with **nadolol** 80 mg orally. Pretreatment with the beta blocker did not affect the duration of anaesthesia when lidocaine without adrenaline was used.[4] It seems likely that the combined effects of **adrenaline** (epinephrine) and **nadolol** caused increased local vasoconstriction, which resulted in the lidocaine persisting for longer. Therefore when a small amount of local anaesthetic with adrenaline is injected for dental procedures an increased duration of analgesia may result. Also note that a case report describes a transient hypertensive reaction in a patient taking **propranolol** when injections of **mepivacaine** 2% with **corbadrine** 1:20 000 were given for dental anaesthesia.[5] Larger doses of adrenaline have resulted in serious hypertension and bradycardia because of the interaction between non-selective beta blockers and adrenaline (see 'Beta blockers + Inotropes and Vasopressors', p.1011). It has been suggested that, for dental procedures, the minimum amount of local anaesthetic containing the lowest concentration of adrenaline should be used. Alternatively, if excessive bleeding is unlikely, a local anaesthetic without adrenaline is preferred.[4]

Propranolol and some other beta blockers are known to reduce the metabolism of intravenous and possibly oral lidocaine, see 'Lidocaine + Beta blockers', p.297. Note that this interaction is not expected to be important when lidocaine is given as a throat spray.[6]

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Anaesthetics, local + Clonidine

Studies suggest that the plasma levels of lidocaine (after epidural use) may be reduced in patients given clonidine. The addition of clonidine to bupivacaine spinal block shortens the onset time and increases the duration of sensory and motor block.

Clinical evidence

A study in 35 children undergoing ureteroneocystostomy found that the addition of clonidine 1 microgram/kg increased the duration of caudal block with **bupivacaine** 0.125% (with adrenaline (epinephrine) 1:400 000) and reduced the postoperative morphine requirements.[1] In a study in patients undergoing transurethral resection of prostate or bladder tumours patients were given spinal anaesthesia with hyperbaric **bupivacaine** 12 mg (**bupivacaine** 0.75% and glucose 82.5 mg) alone or with clonidine 30 micrograms. Onset time of motor block was shorter in the patients given **bupivacaine** with clonidine, when compared with those given **bupivacaine** alone (time to reach Bromage 3 motor block 11.7 minutes and 20.7 minutes, respectively). The duration of the sensory and motor block was longer in those given clonidine. No differences in the heart rate or mean arterial pressures were found between the groups.[2]

Another study, in children, found that oral premedication with clonidine 4 micrograms/kg reduced the plasma levels of epidural **lidocaine** by 25 to 50%.[3] Similar findings are reported in another study in which clonidine was given with epidural **lidocaine**.[4]

Mechanism

Not fully understood. An *in vitro* study using liver microsomes found that clonidine, at clinical levels, is unlikely to affect the metabolism of lidocaine.[5] However, the haemodynamic effects of clonidine may lead to decreased hepatic blood flow and reduced metabolism.[5]

Importance and management

Evidence of an interaction between bupivacaine and clonidine appears to be limited to two studies, which suggest that clonidine may increase the response to bupivacaine without causing adverse cardiac effects. This interaction may be beneficial.

Evidence for an interaction between lidocaine and clonidine is also limited, but what is known suggests that clonidine may reduce the levels of lidocaine appearing in the plasma, following epidural administration. This interaction may also be beneficial.

Note that clonidine used as an antihypertensive could, theoretically, cause severe hypotension if given with local anaesthetics. See also 'Anaesthetics, local + Antihypertensives', p.121.

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Anaesthetics, local + CYP3A4 inhibitors

Itraconazole may reduce the clearance of bupivacaine. Itraconazole, ketoconazole or clarithromycin may slightly decrease ropivacaine clearance.

Clinical evidence, mechanism, importance and management

(a) Bupivacaine

In a placebo-controlled, crossover study in 7 healthy subjects pretreatment with **itraconazole** 200 mg daily for 4 days reduced the clearance of bupivacaine (300 micrograms/kg given intravenously over 60 minutes) by 20 to 25%.[1] It seems unlikely that a decrease of this magnitude in the clearance of bupivacaine will be clinically relevant.

(b) Ropivacaine

In a study in 8 healthy subjects, pretreatment with **itraconazole** 200 mg daily or **clarithromycin** 250 mg twice daily for 4 days did not significantly affect the pharmacokinetics of intravenous ropivacaine 600 microgram/kg. However, there was considerable interindividual variation in the findings. A small but statistically insignificant 20% increase in the AUC of ropivacaine occurred, and the peak plasma concentrations of the metabolite 2′,6′-pipecoloxylidide were decreased by **clarithromycin** and **itraconazole**, by 44% and 74%, respectively. Both **itraconazole** and **clarithromycin** inhibit the formation of this metabolite by the cytochrome P450 isoenzyme CYP3A4.[2] Similar results were found with **ketoconazole** and ropivacaine.[3] Potent inhibitors of CYP3A4 appear to cause only a minor decrease in clearance of ropivacaine, which is unlikely to be of clinical relevance.[3] For a report of erythromycin, an inhibitor of CYP3A4, enhancing the effect of fluvoxamine, an inhibitor of CYP1A2, on the clearance of ropivacaine, see 'Anaesthetics, local; Ropivacaine + Fluvoxamine', p.126.

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Anaesthetics, local + H_2-receptor antagonists

Some studies suggest that both cimetidine and ranitidine can modestly raise the plasma levels of bupivacaine, whereas other evidence suggests that no significant interaction occurs. Some studies found that cimetidine does not affect lidocaine when used as an anaesthetic, whereas others found that cimetidine increased plasma lidocaine levels. Ranitidine and probably famotidine do not appear to significantly affect the pharmacokinetics of lidocaine.

Clinical evidence

(a) Bupivacaine

1. Cimetidine. In a study in 16 women undergoing caesarean section, pretreatment with cimetidine 300 mg intramuscularly 1 to 4 hours before epidural anaesthesia with bupivacaine 0.5% had no effect on the pharmacokinetics of bupivacaine in either the women or the neonates, when compared with 20 control women, although the maternal unbound bupivacaine plasma levels rose by 22%.[1] These findings were confirmed in two similar studies in which women receiving bupivacaine were pretreated with cimetidine before caesarean section,[2,3] and a further study in 7 healthy subjects (6 women and one man) given two oral doses of cimetidine 400 mg before intramuscular bupivacaine.[4] However, in a further study in 4 healthy male subjects, the AUC of bupivacaine was increased by 40% (when compared to placebo) by cimetidine. In this study cimetidine 400 mg was given at 10 pm and 8 am the following day, with a 50-mg infusion of bupivacaine given at 11 am.[5]

2. Ranitidine. In a study in 10 subjects given extradural anaesthesia for caesarean section, pretreatment with oral ranitidine 150 mg 1.5 to 2 hours before bupivacaine increased the maximum plasma levels of bupivacaine by about 36%, when compared with 10 patients given no pretreatment.[3] A further study in 9 patients also found that pretreatment with ranitidine

150 mg increased plasma bupivacaine levels.[6] Another study found that two oral doses of ranitidine 150 mg caused a 25% increase in the mean AUC of bupivacaine, but this was not statistically significant.[5] No increased bupivacaine toxicity was described in any of these reports. However, two other studies in 36 and 28 women undergoing caesarean section found no measurable effect on the bupivacaine disposition when ranitidine 150 mg was given the night before and on the morning of anaesthesia,[2] or when ranitidine 50 mg was given intramuscularly 2 hours before anaesthesia, respectively.[7]

(b) Lidocaine

1. Cimetidine. In 5 women given epidural anaesthesia for caesarean section, the pharmacokinetics of 400 mg of lidocaine 2% (with adrenaline (epinephrine) 1:200 000) were unchanged by a single 400-mg oral dose of cimetidine given about 2 hours preoperatively.[8] Another very similar study in 9 women found no statistically significant rises in whole blood lidocaine levels (although they tended to be higher), in the presence of cimetidine 300 mg, given intramuscularly, at least one hour preoperatively.[9] However, in patients pretreated with cimetidine (200 mg orally on the night before surgery and 400 mg one hour before induction) peak plasma levels of epidural lidocaine 2% (with adrenaline 1:200 000) were 3.2 micrograms/mL. Lidocaine levels in patients who did not receive pretreatment with H_2-receptor antagonists were 2.3 micrograms/mL.[10]

2. Famotidine. In patients pretreated with famotidine (20 mg orally on the night before surgery plus 20 mg intramuscularly one hour before induction), peak plasma levels of epidural lidocaine 2% (with adrenaline 1:200 000) were 2.4 micrograms/mL. Lidocaine levels in patients who did not receive pretreatment with H_2-receptor antagonists were 2.3 micrograms/mL.[10] In another study, the effects of famotidine on lidocaine were found to be less than those of cimetidine, but greater than in patients not given an H_2-receptor antagonist.[11]

3. Ranitidine. In 7 women given epidural anaesthesia for caesarean section the pharmacokinetics of 400 mg of lidocaine 2%, (with adrenaline (epinephrine) 1:200 000) were unchanged after a single 150-mg oral dose of ranitidine given about 2 hours preoperatively.[8] A similar study in 8 women also found no statistically significant rises in whole blood lidocaine levels in the presence of ranitidine 150 mg given orally at least 2 hours preoperatively.[9]

Mechanism

Not understood. It has been suggested that cimetidine reduces the hepatic metabolism of bupivacaine and lidocaine. Protein binding displacement has also been suggested.

Importance and management

A confusing situation. No clinically important interaction has been established, but be alert for any evidence of increased bupivacaine toxicity resulting from raised total plasma levels and rises in unbound bupivacaine levels during the concurrent use of cimetidine. Ranitidine may modestly increase the levels of bupivacaine but this does not appear to be clinically significant.

Cimetidine (but not ranitidine) has been shown to raise plasma lidocaine levels when lidocaine is used as an antiarrhythmic (see 'Lidocaine + H_2-receptor antagonists', p.299), but some of the studies cited above found cimetidine did not affect lidocaine levels when lidocaine is used as a local anaesthetic. However, in the studies comparing the effects of cimetidine and famotidine, cimetidine was found to increase lidocaine levels and it was suggested that famotidine may be preferable to cimetidine as pretreatment before epidural lidocaine.[10,11]

1. Kuhnert BR, Zuspan KJ, Kuhnert PM, Syracuse CD, Brashear WT, Brown DE. Lack of influence of cimetidine on bupivacaine levels during parturition. *Anesth Analg* (1987) 66, 986–90.
2. O'Sullivan GM, Smith M, Morgan B, Brighouse D, Reynolds F. H_2 antagonists and bupivacaine clearance. *Anaesthesia* (1988) 43, 93–5.
3. Flynn RJ, Moore J, Collier PS, McClean E. Does pretreatment with cimetidine and ranitidine affect the disposition of bupivacaine? *Br J Anaesth* (1989) 62, 87–91.
4. Pihlajamäki KK, Lindberg RLP, Jantunen ME. Lack of effect of cimetidine on the pharmacokinetics of bupivacaine in healthy subjects. *Br J Clin Pharmacol* (1988) 26, 403–6.
5. Noble DW, Smith KJ, Dundas CR. Effects of H-2 antagonists on the elimination of bupivacaine. *Br J Anaesth* (1987) 59, 735–7.
6. Wilson CM, Moore J, Ghaly RG, McClean E, Dundee JW. Plasma bupivacaine concentrations associated with extradural anaesthesia for caesarean section: influence of pretreatment with ranitidine. *Br J Anaesth* (1986) 58, 1330P–1331P.
7. Brashear WT, Zuspan KJ, Lazebnik N, Kuhnert BR, Mann LI. Effect of ranitidine on bupivacaine disposition. *Anesth Analg* (1991) 72, 369–76.
8. Flynn RJ, Moore J, Collier PS, Howard PJ. Single dose oral H_2-antagonists do not affect plasma lidocaine levels in the parturient. *Acta Anaesthesiol Scand* (1989) 33, 593–6.
9. Dailey PA, Hughes SC, Rosen MA, Healey K, Cheek DBC, Shnider SM. Effect of cimetidine and ranitidine on lidocaine concentrations during epidural anesthesia for cesarean section. *Anesthesiology* (1988) 69, 1013–17.
10. Kishikawa K, Namiki A, Miyashita K, Saitoh K. Effects of famotidine and cimetidine on plasma levels of epidurally administered lignocaine. *Anaesthesia* (1990) 45, 719–21.
11. Sabatakaki A, Daifotis Z, Karayannacos P, Danou K, Kaniaris P. La famotidine ne modifie pas les taux plasmatiques de la lidocaïne pour rachianesthésie. Étude comparative de la famotidine et de la cimétidine. *Cah Anesthesiol* (1992) 40, 317–20.

Anaesthetics, local + Rifampicin (Rifampin)

Rifampicin increases the metabolism of ropivacaine.

Clinical evidence, mechanism, importance and management

A study in 10 healthy non-smokers and 8 otherwise healthy smokers given ropivacaine 600 micrograms/kg by intravenous infusion over 30 minutes found that pretreatment with rifampicin 600 mg daily for 5 days increased the clearance of the metabolite 3-hydroxyropivacaine and decreased the urinary excretion of 2′,6′-pipecoloxylidide by 93% and 46%, respectively, decreased the AUC by 52% and 38%, respectively, and decreased the half-life of ropivacaine in both non-smokers and smokers.[1] Ropivacaine undergoes oxidative hepatic metabolism mainly by the cytochrome P450 isoenzymes CYP1A2 and CYP3A4. The elimination of ropivacaine may be considerably accelerated by rifampicin, which is a potent cytochrome P450 enzyme inducer. However, in clinical use the local anaesthetic is given near the nerves to be desensitised and induction of these isoenzymes is not likely to affect the local anaesthetic before it enters the systemic blood circulation.[1] This interaction is therefore of little clinical relevance.

Rifampicin may also increase the metabolism of lidocaine to a minor extent, see 'Lidocaine + Rifampicin (Rifampin)', p.302.

1. Jokinen MJ, Olkkola KT, Ahonen J, Neuvonen PJ. Effect of rifampin and tobacco smoking on the pharmacokinetics of ropivacaine. *Clin Pharmacol Ther* (2001) 70, 344–50.

Anaesthetics, local + Tobacco

Smoking appears to have only a minor effect on ropivacaine pharmacokinetics. Tobacco smoking may enhance cocaine-associated myocardial ischaemia.

Clinical evidence, mechanism, importance and management

(a) Cocaine

In a study in 42 smokers (36 with proven coronary artery disease), the mean product of the heart rate and systolic arterial pressure increased by 11% after intranasal cocaine 2 mg/kg, by 12% after one cigarette and by 45% after both cocaine use and one cigarette. Compared with baseline measurements, the diameters of non-diseased coronary arterial segments decreased on average by 7% after cocaine use, 7% after smoking and 6% after cocaine and smoking. However, the diameters of diseased segments decreased by 9%, 5% and 19%, respectively.[1] Cigarette smoking increases myocardial oxygen demand and induces coronary-artery vasoconstriction through an alpha-adrenergic mechanism similar to cocaine and therefore tobacco smoking may enhance cocaine-associated myocardial ischaemia.[1,2]

(b) Ropivacaine

A study in 10 healthy non-smokers and 8 otherwise healthy smokers given ropivacaine 600 micrograms/kg by intravenous infusion over 30 minutes found that smoking increased the urinary excretion of the metabolite 3-hydroxyropivacaine and decreased the urinary excretion of the metabolite 2′,6′-pipecoloxylidide by 62%, but did not significantly affect the ropivacaine AUC.[3]

Ropivacaine undergoes oxidative hepatic metabolism mainly by the cytochrome P450 isoenzymes CYP1A2 and CYP3A4. Cigarette smoking is known to induce CYP1A2 and may therefore increase the metabolism of ropivacaine. However, in clinical use the local anaesthetic is given near the nerves to be desensitised and induction of isoenzymes is not likely to affect the local anaesthetic before it enters the systemic blood circulation.[3] This interaction is therefore of little clinical relevance.

Note that smoking may reduce the bioavailability of *oral* lidocaine, see 'Lidocaine + Tobacco', p.302.

1. Moliterno DJ, Willard JE, Lange RA, Negus BH, Boehrer JD, Glamann DB, Landau C, Rossen JD, Winniford MD, Hillis LD. Coronary-artery vasoconstriction induced by cocaine, cigarette smoking, or both. *N Engl J Med* (1994) 330, 454–9.
2. Hollander JE. The management of cocaine-associated myocardial ischemia. *N Engl J Med* (1995) 333, 1267–72.
3. Jokinen MJ, Olkkola KT, Ahonen J, Neuvonen PJ. Effect of rifampin and tobacco smoking on the pharmacokinetics of ropivacaine. *Clin Pharmacol Ther* (2001) 70, 344–50.

Anaesthetics, local; Bupivacaine + Antipsychotics

Exaggerated hypotension occurred in a patient taking risperidone when she was given spinal anaesthesia with bupivacaine.

Clinical evidence, mechanism, importance and management

A patient with bipolar disorder, taking lithium 600 mg twice daily and **risperidone** 2 mg at bedtime, was given spinal anaesthesia with hyperbaric bupivacaine 0.75% (12 mg), fentanyl 10 micrograms and morphine 200 micrograms for an elective caesarean section. Within a few minutes, her blood pressure decreased from 120/50 mmHg to 70/30 mmHg, for which she was given ephedrine 50 mg and Ringer's lactate solution. Her heart rate increased from about 80 bpm to 130 bpm, with little improvement in the hypotension until phenylephrine 600 micrograms was given, after which her vital signs gradually improved over 10 minutes. A previous caesarean section in the same patient, while taking lithium but not **risperidone** and using the same epidural anaesthesia, had been accompanied by hypotension to about 80/50 mmHg which had rapidly normalised with ephedrine 20 mg and phenylephrine 40 micrograms.

Hypotension is a common adverse effect of bupivacaine and lithium may cause hypotension in toxicity. However, the patient's lithium level was subtherapeutic on the morning of the caesarean section. **Risperidone** is an antagonist of alpha-adrenergic receptors, which the authors believe contributed to the difficulty in treating the peri-operative hypotension seen in the case report above. Further, it was suggested that the tachycardia without improvement in the hypotension after ephedrine was given may have been due to the beta-adrenergic effects of ephedrine combined with the alpha-adrenergic antagonism of risperidone.[1]

The general importance of this isolated case is unclear; however, it serves as a reminder that the adverse hypotensive effects that are common to many antipsychotics, could be additive with the hypotensive effects of bupivacaine.

1. Williams JH, Hepner DL. Risperidone and exaggerated hypotension during a spinal anesthetic. *Anesth Analg* (2004) 98, 240–1.

Anaesthetics, local; Bupivacaine + Dexmedetomidine

The addition of dexmedetomidine to bupivacaine spinal block shortens the onset time and increases the duration of sensory and motor block.

Clinical evidence, mechanism, importance and management

In a study in patients undergoing transurethral resection of prostate or bladder tumours patients were given spinal anaesthesia with hyperbaric bupivacaine 12 mg (bupivacaine 0.75% and glucose 82.5 mg) alone or with dexmedetomidine 3 micrograms. Onset time of motor block was shorter in the patients given bupivacaine with dexmedetomidine, when compared with those given bupivacaine alone (time to reach Bromage 3 motor block, 13.2 minutes and 20.7 minutes, respectively). The duration of the sensory and motor block was significantly longer in those given the combination. No differences in the heart rate or mean arterial pressures were found between the groups.[1]

Evidence appears to be limited to this study, but it demonstrates that concurrent use may be beneficial.

1. Kanazi GE, Aouad MT, Jabbour-Khoury SI, Al Jazzar MD, Alameddine MM, Al-Yaman R, Bulbul M, Baraka AS. Effect of low dose dexmedetomidine or clonidine on the characteristics of bupivacaine spinal block. *Acta Anaesthesiol Scand* (2006) 50, 222–7.

Anaesthetics, local; Cocaine + Adrenaline (Epinephrine)

Arrhythmias occurred in three patients given a concentrated nasal paste containing cocaine and adrenaline (epinephrine).

Clinical evidence, mechanism, importance and management

Two children and one adult patient undergoing general anaesthesia[1] developed arrhythmias shortly after nasal application of a paste containing cocaine 25% and adrenaline (epinephrine) 0.18%. All 3 patients received doses of cocaine that exceeded the maximum dose (1.5 mg/kg) recommended in the BNF[2] for healthy adults.

Cocaine has sympathomimetic actions (tachycardia, peripheral vasoconstriction, and hypertension). Combined use with sympathomimetics such as adrenaline increases these effects, and the risk of life-threatening arrhythmias. This risk may be further increased if halothane anaesthesia is used (two of the above patients received halothane[1]). See also 'Anaesthetics, general + Anaesthetics, local', p.103, and 'Anaesthetics, general + Inotropes and Vasopressors', p.111.

The use of adrenaline with topical cocaine is controversial. Some consider that the addition of adrenaline is of doubtful value and that the combination should not be used, especially in the form of a concentrated paste.[1] However, others consider the combination to be safe and useful.[3] Note also that the use of local anaesthetics containing adrenaline should be avoided in patients who abuse cocaine, unless it is certain that they have not used cocaine for at least 24 hours.[4]

1. Nicholson KEA, Rogers JEG. Cocaine and adrenaline paste: a fatal combination? *BMJ* (1995) 311, 250–1.
2. British National Formulary. 58th ed. London: BMJ Publishing Group Ltd and RPS Publishing; 2009. p. 718.
3. De R, Uppal HS, Shehab ZP, Hilger AW, Wilson PS, Courteney-Harris R. Current practices of cocaine administration by UK otorhinolaryngologists. *J Laryngol Otol* (2003) 117, 109–12.
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Anaesthetics, local; Cocaine + Disulfiram

Disulfiram increases plasma levels of inhaled and intravenous cocaine. Disulfiram increases the cardiovascular effects associated with inhaled, but not intravenous cocaine, whereas it does not significantly affect the behavioural responses to inhaled cocaine but decreases the behavioural responses to intravenous cocaine.

Clinical evidence

A preliminary study in 6 subjects taking cocaine by inhalation found that disulfiram 250 mg daily significantly increased plasma levels of cocaine 1 mg/kg by threefold and increased the plasma levels of cocaine 2 mg/kg by greater than fourfold, respectively. Concurrent treatment also increased the heart rate and blood pressure but did not affect 'high' and 'nervous' ratings.[1]

In a further study by the same authors, 7 subjects from the initial study were given disulfiram 250 mg, disulfiram 500 mg or placebo daily for 5 days. Intranasal cocaine 1 or 2 mg/kg or placebo was started after the third disulfiram dose. Following treatment with disulfiram 250 or 500 mg, the AUC of cocaine was increased three- to sixfold and plasma cocaine levels were increased two- to threefold. Increases in heart rate with disulfiram alone just reached significance, but disulfiram treatment significantly increased the heart rate responses to inhaled cocaine. Disulfiram alone had no significant effect on blood pressure. However, systolic and diastolic blood pressure increased after disulfiram 500 mg daily with cocaine 2 mg/kg, and tended to increase after the disulfiram 250 mg dose. Disulfiram had no significant effects on the behavioural responses to cocaine.[2]

In a further study, cocaine-dependent subjects were given disulfiram 62.5 mg, disulfiram 250 mg or placebo daily for 6 days, with intravenous cocaine 250 micrograms/kg (9 subjects), 500 micrograms/kg (3 subjects) or placebo, taken 2 hours after the disulfiram dose, on days 4 to 6. Disulfiram 62.5 mg and 250 mg increased the AUC of cocaine 250 micrograms/kg by 67 to 84%. Larger increases were seen with the cocaine 500 microgram/kg dose, although these did not reach statistical significance. The clearance of cocaine was also reduced. Disulfiram did not

affect the cardiovascular responses to either dose of intravenous cocaine. The behavioural responses to cocaine 250 micrograms/kg ('highs', 'rush') were significantly decreased by disulfiram; similar effects were seen with the larger dose but this did not reach statistical significance due to the small sample size.[3]

The studies above differed in the routes of administration of cocaine (intranasal versus intravenous) and the latter study noted that the dose of intravenous cocaine used produced lower overall levels of cocaine than the intranasal dose studied.[3]

Of interest, a report of a cost-effectiveness study looking at the benefits of using disulfiram to treat cocaine use in methadone-maintained opioid addicts, found that disulfiram use was associated with a reduction in the amount of cocaine used.[4]

Mechanism

Disulfiram has been reported to inhibit carboxylesterases and plasma cholinesterase, which are enzymes involved in the metabolism of cocaine.[3]

Importance and management

It would appear that disulfiram may significantly increase the plasma levels and reduce the clearance of both intranasal and intravenous cocaine. There is conflicting data as to whether this enhances the cardiovascular and behavioural effects of cocaine use. Overall, it would be prudent to exercise caution when giving disulfiram to patients using cocaine as the increase in cocaine levels may result in cocaine toxicity.

1. McCance-Katz EF, Kosten TR, Jatlow P. Chronic disulfiram treatment effects on intranasal cocaine administration: initial results. *Biol Psychiatry* (1998) 43, 540–3.
2. McCance-Katz EF, Kosten TR, Jatlow P. Disulfiram effects on acute cocaine administration. *Drug Alcohol Depend* (1998) 52, 27–39.
3. Baker JR, Jatlow P, McCance-Katz EF. Disulfiram effects on responses to intravenous cocaine administration. *Drug Alcohol Depend* (2007) 87, 202–9.
4. Jofre-Bonet M, Sindelar JL, Petrakis IL, Nich C, Frankforter T, Rounsaville BJ, Carroll KM. Cost effectiveness of disulfiram: treating cocaine use in methadone-maintained patients. *J Subst Abuse Treat* (2004) 26, 225–232.

Anaesthetics, local; Cocaine + Progesterone

There is some evidence to suggest that progesterone may attenuate some of the cardiovascular and subjective effects of smoked or intravenous cocaine, but not the effects of intranasal cocaine.

Clinical evidence, mechanism, importance and management

A preliminary, placebo-controlled study in 5 female cocaine-dependent subjects found that a single 200-mg dose of progesterone, given during days 3 to 9 of the menstrual cycle, attenuated the subjective effects of smoked cocaine.[1] In a further placebo-controlled study by the same authors, 6 male and 4 female cocaine-dependent subjects were given two doses of progesterone 200 mg at 10 pm the day before, and at 8 am on the morning of, intravenous cocaine administration. The initial dose of cocaine 300 micrograms/kg was given 2 hours after the second progesterone dose. Subjects then started a self-administration period in which 5 optional doses of cocaine were available in a 2.5-hour period. Progesterone attenuated cocaine-induced increases in diastolic blood pressure but did not affect systolic blood pressure or heart rate increases. Progesterone also attenuated subjective ratings of 'high' and 'feel the effect of the last dose' in response to cocaine, but did not affect self-administration behaviour.[2]

In a pilot study, male methadone-stabilised cocaine users were given either placebo (15 subjects) or progesterone (dose gradually increased from 100 mg to 300 mg twice daily over 4 weeks; 30 subjects) for 10 weeks. Cocaine positive urine tests showed a slight decrease in cocaine use in the progesterone group and a slight increase in use in the placebo group. However, at weeks 9 and 10, the placebo group showed a significantly lower use of cocaine (as measured by the cocaine positive urine test), when compared with the group given progesterone, suggesting a lack of efficacy of progesterone as a treatment for cocaine dependence in male users.[3]

These findings are probably more relevant to the potential use of progesterone in cocaine dependence, but they do demonstrate that the concurrent use of progesterone in patients taking cocaine is unlikely to result in an adverse outcome.

1. Sofuoglu M, Babb D, Hatsukami DK. Effects of progesterone treatment on smoked cocaine response in women. *Pharmacol Biochem Behav* (2002) 72, 431–5.
2. Sofuoglu M, Mitchell E, Kosten TR. Effects of progesterone treatment on cocaine responses in male and female cocaine users. *Pharmacol Biochem Behav* (2004) 78, 699–705.
3. Sofuoglu M, Poling J, Gonzalez G, Gonsai K, Oliveto A, Kosten TR. Progesterone effects on cocaine use in male cocaine users maintained on methadone: a randomized, double-blind, pilot study. *Exp Clin Psychopharmacol* (2007) 15, 453–60.

Anaesthetics, local; Lidocaine + Ondansetron

Ondansetron may reduce the efficacy of the sensory block induced by lidocaine.

Clinical evidence, mechanism, importance and management

In a placebo-controlled study oral ondansetron 4 mg was given to patients the evening before surgery, followed by intravenous ondansetron 4 mg given over 15 minutes before subarachnoid anaesthesia with lidocaine 5% in dextrose 8%. Ondansetron significantly reduced the sensory block measured at 30 minutes. Motor block was unaffected. In this study 54 patients were enrolled, but not all patients were assessed for both motor and sensory block.[1]

Evidence appears to be limited to this one study, but, until more is known, it may be prudent to monitor closely for a reduction in the efficacy of the sensory block with lidocaine if ondansetron is also given.

1. Fassoulaki A, Melemeni A, Zotou M, Sarantopoulos C. Systemic ondansetron antagonizes the sensory block produced by intrathecal lidocaine. *Anesth Analg* (2005) 100, 1817–21.

Anaesthetics, local; Ropivacaine + Fluvoxamine

Fluvoxamine inhibits the clearance of ropivacaine.

Clinical evidence, mechanism, importance and management

In a randomised, crossover study in 12 healthy subjects fluvoxamine decreased the mean total plasma clearance of ropivacaine by 68%, and almost doubled the half-life of ropivacaine. Fluvoxamine was given at a dose of 25 mg twice daily for 2 days, and a single 40-mg intravenous dose of ropivacaine was given over 20 minutes one hour after the morning dose of fluvoxamine on the second day.[1]

Fluvoxamine is a potent inhibitor of the cytochrome P450 isoenzyme CYP1A2 and so reduces the metabolism of ropivacaine to its major metabolite 3-hydroxyropivacaine. In one study in healthy subjects the combination of fluvoxamine with **erythromycin**, an inhibitor of CYP3A4, which on its own has little effect on the pharmacokinetics of ropivacaine, was found to decrease the clearance of ropivacaine more than fluvoxamine alone.[2]

The UK manufacturer recommends that the prolonged use of ropivacaine should be avoided in patients given potent CYP1A2 inhibitors, such as fluvoxamine.[3] Be aware that CYP3A4 inhibitors, such as erythromycin, in combination with CYP1A2 inhibitors may further reduce ropivacaine clearance.[2]

1. Arlander E, Ekström G, Alm C, Carrillo JA, Bielenstein M, Böttiger Y, Bertilsson L, Gustafsson LL. Metabolism of ropivacaine in humans is mediated by CYP1A2 and to a minor extent by CYP3A4: An interaction study with fluvoxamine and ketoconazole as in vivo inhibitors. *Clin Pharmacol Ther* (1998) 64, 484–91.
2. Jokinen MJ, Ahonen J, Neuvonen PJ, Olkkola KT. The effect of erythromycin, fluvoxamine, and their combination on the pharmacokinetics of ropivacaine. *Anesth Analg* (2000) 91, 1207–12.
3. Naropin (Ropivacaine hydrochloride monohydrate). AstraZeneca UK Ltd. UK Summary of product characteristics, August 2008.

Anaesthetics, local; Ropivacaine + Quinolones

Ciprofloxacin may decrease the clearance of ropivacaine. It is also likely that enoxacin will inhibit the metabolism of ropivacaine.

Clinical evidence, mechanism, importance and management

A study in 9 healthy subjects found that **ciprofloxacin** 500 mg twice daily decreased the mean clearance of a single 600-microgram/kg intravenous dose of ropivacaine by 31%, but there was considerable inter-individual variation in the effects of **ciprofloxacin**. The reduction in clearance probably occurs because **ciprofloxacin** inhibits the cytochrome P450 isoenzyme CYP1A2, which metabolises ropivacaine to its major metabolite 3-hydroxyropivacaine. For some patients concurrent use may cause toxi-

city.[1] Bear the potential for an interaction in mind if ropivacaine is given to a patient taking **ciprofloxacin**.

On the basis of data with 'fluvoxamine', (p.126), the UK manufacturer of ropivacaine has recommended that the prolonged use of ropivacaine should be avoided in patients taking potent CYP1A2 inhibitors such as **enoxacin**.[2]

1. Jokinen MJ, Olkkola KT, Ahonen J, Neuvonen PJ. Effect of ciprofloxacin on the pharmacokinetics of ropivacaine. *Eur J Clin Pharmacol* (2003) 58, 653–7.
2. Naropin (Ropivacaine hydrochloride monohydrate). AstraZeneca UK Ltd. UK Summary of product characteristics, August 2008.

Neuromuscular blockers + Aminoglycosides

The aminoglycoside antibacterials possess neuromuscular blocking activity. Appropriate measures should be taken to accommodate the increased neuromuscular blockade and the prolonged and potentially fatal respiratory depression that can occur if these antibacterials are used with conventional neuromuscular blocking drugs.

Clinical evidence

Two examples from many:

A 38-year-old patient anaesthetised with cyclopropane experienced severe respiratory depression after being given intraperitoneal **neomycin** 500 mg. She had also received **suxamethonium** (**succinylcholine**) and **tubocurarine**. This antibacterial-induced neuromuscular blockade was resistant to treatment with edrophonium.[1]

A 71-year-old woman received a standard bowel preparation consisting of oral erythromycin and **neomycin** (a total of 3 g). Surgery was postponed for one day and she received a second similar bowel preparation pre-operatively. Anaesthesia was induced with sufentanil and etomidate and maintained with isoflurane and sufentanil. **Rocuronium** (total dose of 60 mg over 2 hours) was used to facilitate tracheal intubation and maintain muscle relaxation. Despite clinical appearance of a reversal of the neuromuscular blockade by neostigmine 3.5 mg and glycopyrronium (glycopyrrolate) 400 micrograms, the patient complained of dyspnoea and required reintubation twice. The effects of additional doses of neostigmine were inconsistent and the use edrophonium 50 mg or calcium chloride 500 mg intravenously did not result in an improvement.[2]

Many other reports confirm that some degree of respiratory depression or paralysis can occur if aminoglycosides are given to anaesthetised patients. When a conventional neuromuscular blocker is also used, the blockade is deepened and recovery prolonged. If the antibacterial is given towards the end of surgery the result can be that a patient who is recovering normally from neuromuscular blockade suddenly develops serious apnoea, which can lead to prolonged and in some cases fatal respiratory depression.

A review of the literature[3] lists more than 100 cases over the period 1956 to 1970 involving:

- **tubocurarine** with **neomycin** or **streptomycin,**
- **gallamine** with **neomycin**, **kanamycin** or **streptomycin**,
- **suxamethonium** with **neomycin**, **kanamycin** or **streptomycin**.

The routes of antibacterial administration were oral, intraperitoneal, oesophageal, intraluminal, retroperitoneal, intramuscular, intrapleural, cystic, beneath skin flaps, extradural and intravenous.

Later reports involve:

- **pancuronium**; with **amikacin**,[4] **gentamicin**,[5] **neomycin**,[6] or **streptomycin**,[7,8]
- **pipecuronium** with **netilmicin**,[9]
- **suxamethonium** with **dibekacin**,[10]
- **tubocurarine**; with **amikacin**,[11] **dibekacin**,[10,12] **framycetin** (eye irrigation),[13] **ribostamycin**,[10,12] or **tobramycin**,[14]
- **vecuronium**; with **amikacin/polymyxin**,[15] **gentamicin**,[16-18] **gentamicin/clindamycin**,[19] **neomycin/clindamycin**,[20] or **tobramycin**.[17,21]

Aminoglycosides and neuromuscular blockers that have been reported not to interact are:

- **alcuronium** with **tobramycin**,[22]
- **atracurium** with **gentamicin** or **tobramycin**,[17]
- **suxamethonium** with **tobramycin** or **ribostamycin**.[10]

Mechanism

The aminoglycosides appear to reduce or prevent the release of acetylcholine at neuromuscular junctions (related to an impairment of calcium influx) and they may also lower the sensitivity of the post-synaptic membrane, thereby reducing transmission. These effects would be additive with those of conventional neuromuscular blockers, which act at the post-synaptic membrane.

Importance and management

Extremely well documented, very long established, clinically important and potentially serious interactions. Ten out of the 111 cases in one review[3] were fatal, related directly or indirectly to aminoglycoside-induced respiratory depression. Concurrent use need not be avoided, but be alert for increased and prolonged neuromuscular blockade with every aminoglycoside and neuromuscular blocker, although the potencies of the aminoglycosides differ to some extent. In *animal* studies, at concentrations representing the maximum therapeutic levels, the neuromuscular blocking potency of various aminoglycosides was rated (from highest to lowest): neomycin, streptomycin, gentamicin, kanamycin.[23] The postoperative recovery period should also be closely monitored because of the risk of recurarisation if the aminoglycoside is given during surgery. High-risk patients appear to be those with renal disease and hypocalcaemia, who may have elevated serum antibacterial levels, and those with pre-existing muscular weakness. Treatment of the increased blockade with anticholinesterases and calcium has met with variable success because the response seems to be inconsistent.

1. LaPorte J, Mignault G, L'Allier R, Perron P. Un cas d'apnée à la néomycine. *Union Med Can* (1959) 88, 149–52.
2. Hasfurther DL, Bailey PL. Failure of neuromuscular blockade reversal after rocuronium in a patient who received oral neomycin. *Can J Anaesth* (1996) 43, 617–20.
3. Pittinger CB, Eryasa Y, Adamson R. Antibiotic-induced paralysis. *Anesth Analg* (1970) 49, 487–501.
4. Monsegur JC, Vidal MM, Beltrán J, Felipe MAN. Parálisis neuromuscular prolongada tras administración simultánea de amikacina y pancuronio. *Rev Esp Anestesiol Reanim* (1984) 31, 30–3.
5. Regan AG, Perumbetti PPV. Pancuronium and gentamicin interaction in patients with renal failure. *Anesth Analg* (1980) 59, 393.
6. Giala M, Sareyiannis C, Cortsaris N, Paradelis A, Lappas DG. Possible interaction of pancuronium and tubocurarine with oral neomycin. *Anaesthesia* (1982) 37, 776.
7. Giala MM, Paradelis AG. Two cases of prolonged respiratory depression due to interaction of pancuronium with colistin and streptomycin. *J Antimicrob Chemother* (1979) 5, 234–5.
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Neuromuscular blockers + Anaesthetics, local

The neuromuscular blockade due to suxamethonium (succinylcholine) can be increased and prolonged by procaine. Increased toxicity occurred when mivacurium and prilocaine were given together for regional anaesthesia. Local anaesthetics have some

neuromuscular blocking activity and may theoretically also enhance the block produced by competitive neuromuscular blockers.

Clinical evidence

A study found that **procaine** prolonged the apnoea following the use of **suxamethonium** 700 micrograms/kg. A dose-relationship was established. The duration of apnoea was approximately doubled by 2.2 mg/kg of procaine intravenously, and tripled by 11.2 mg/kg, although the effects of procaine at higher doses were more marked.[1]

In a study in 10 healthy subjects, prolonged muscle weakness and symptoms of local anaesthetic toxicity were experienced after deflation of the tourniquet when 40 mL of **prilocaine** 0.5% and **mivacurium** 600 micrograms were used together for intravenous regional anaesthesia of the forearm. Giving **prilocaine** or **mivacurium** alone did not produce these effects. The slow recovery suggested that **mivacurium** was not broken down in the ischaemic limb,[2] but inhibition of plasma cholinesterase by **prilocaine** would not fully explain the prolonged weakness once the cuff was deflated.[3]

Mechanism

Uncertain. Some local anaesthetics (ester-type[4]) such as procaine appear to inhibit plasma cholinesterase,[5] which might prolong the activity of suxamethonium. There may additionally be competition between suxamethonium and procaine for hydrolysis by plasma cholinesterase, which metabolises them both.[1,6] These effects are particularly important in patients with abnormal plasma cholinesterase.[7] This may also partially explain the interaction with mivacurium.

All local anaesthetics have some neuromuscular blocking activity and may enhance the block produced by competitive neuromuscular blockers if given in sufficient doses.[7,8]

Importance and management

Information is limited but the interaction between suxamethonium and procaine appears to be established and of clinical importance. Be alert for signs of increased blockade and/or recurarisation with apnoea during the recovery period from suxamethonium, although note that in the study cited, procaine was given intravenously, and local administration would be expected to produce less dramatic effects.

In general, local anaesthetics (e.g. **lidocaine**, procaine) have some neuromuscular blocking activity and may also enhance the block produced by competitive neuromuscular blockers if given in sufficient doses. However, again, there seems to be an absence of reports of this, probably because the amount of local anaesthetic absorbed into the circulation following a local block is usually modest.[8]

Some local anaesthetics (e.g. lidocaine) are also used as antiarrhythmics. For the use of lidocaine and other antiarrhythmics with neuromuscular blockers, see 'Neuromuscular blockers + Antiarrhythmics', below.

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Neuromuscular blockers + Antiarrhythmics

The neuromuscular blockade due to suxamethonium (succinylcholine) can be increased and prolonged by lidocaine and possibly procainamide. These drugs have some neuromuscular blocking activity and may theoretically also enhance the block produced by competitive neuromuscular blockers.

Clinical evidence

A patient anaesthetised with fluroxene and nitrous oxide demonstrated 100% blockade with **suxamethonium** (**succinylcholine**) and **tubocurarine**. About 50 minutes later, when twitch height had fully returned and tidal volume was 400 mL, she was given **lidocaine** 50 mg intravenously for premature ventricular contractions. She immediately stopped breathing and the twitch disappeared. About 45 minutes later the tidal volume was 450 mL. Later it was found that the patient had a dibucaine number (a measure of cholinesterase activity) of 23%.[1]

A study has confirmed that **lidocaine** prolongs the apnoea following the use of **suxamethonium** 700 micrograms/kg. A dose-relationship was established, with the duration of apnoea approximately doubled by intravenous lidocaine 5 mg/kg, and tripled by lidocaine 16.6 mg/kg.[2]

Procainamide has been reported to increase the effects of **suxamethonium** in *animals*,[3] increase muscle weakness in a myasthenic patient,[4] and reduce plasma cholinesterase activity in *in vitro* plasma samples from healthy subjects.[5]

Mechanism

Uncertain. Therapeutic procainamide plasma concentrations of 5 to 10 micrograms/mL have been found to inhibit cholinesterase activity by 19 to 32%. Procainamide also has acetylcholine receptor channel blocking activity.[6]

Importance and management

Information is limited but the interaction between suxamethonium (succinylcholine) and lidocaine appears to be established and of clinical importance. Be alert for signs of increased blockade and/or recurarisation with apnoea during the recovery period from suxamethonium in patients given intravenous lidocaine.

Despite the potential for an interaction between suxamethonium and procainamide, no marked interaction has yet been reported. Nevertheless be aware that some increase in the neuromuscular blocking effects is possible.

Lidocaine and procainamide both have some neuromuscular blocking activity and may also enhance the block produced by competitive neuromuscular blockers. However, again, there seems to be an absence of reports of this effect in practice.

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Neuromuscular blockers + Anticholinesterases

Anticholinesterases oppose the actions of competitive neuromuscular blockers (e.g. tubocurarine) and can therefore be used as an antidote to restore muscular activity following their use. Conversely, anticholinesterases increase and prolong the actions of the depolarising neuromuscular blockers (e.g. suxamethonium (succinylcholine)). Anticholinesterases used to treat Alzheimer's disease may also interact with neuromuscular blockers.

Clinical evidence, mechanism, importance and management

There are two main types of neuromuscular blockers: competitive (non-depolarising) and depolarising (i.e. suxamethonium (succinylcholine)), see 'Table 5.2', (p.101).

(a) Competitive (non-depolarising) neuromuscular blockers

Competitive (non-depolarising) neuromuscular blockers (e.g. **tubocurarine**) compete with acetylcholine for receptors on the motor endplate. Anticholinesterases (e.g. **ambenonium**, **edrophonium**, **neostigmine**, **physostigmine**, **pyridostigmine**, etc.) can be used as an antidote to this kind of neuromuscular blockade, because they inhibit the enzymes that de-

stroy acetylcholine so that the concentration of acetylcholine at the neuromuscular junction builds up. In this way the competition between the molecules of the blocker and the acetylcholine for occupancy of the receptors swings in favour of the acetylcholine so that transmission is restored. These drugs are used routinely following surgery to reactivate paralysed muscles. However, note that the **aminoglycosides** can act as neuromuscular blockers (see 'Neuromuscular blockers + Aminoglycosides', p.127) and therefore the use of an aminoglycoside may unintentionally antagonise the effects of the anticholinesterases.

Some inhalational anaesthetics can impair the effect of anticholinesterases on neuromuscular blockers (see 'Anaesthetics, general + Anticholinesterases', p.105).

(b) Suxamethonium (Succinylcholine)

The depolarising neuromuscular blockers (such as suxamethonium) act like acetylcholine to depolarise the motor endplate, but unlike acetylcholine, they are not immediately removed by cholinesterase. The anticholinesterase drugs increase the concentration of acetylcholine at the neuromuscular junction, which enhances and prolongs this type of blockade, and therefore anticholinesterases cannot be used as an antidote for this kind of blocker. Care should be taken if an anticholinesterase has been given to antagonise a competitive neuromuscular block before the use of suxamethonium, as the duration of the suxamethonium block may be prolonged.[1]

(c) Tacrine and other centrally-acting anticholinesterases

1. Competitive (non-depolarising) neuromuscular blockers. Tacrine, like other anticholinesterases, has been used *intravenously* in anaesthetic practice to reverse the effects of competitive (non-depolarising) blockers such as **tubocurarine**.[2] However, tacrine is now more commonly used *orally* for its central effects in the treatment of Alzheimer's disease. Therefore be alert for a reduction in the effects of any competitive neuromuscular blocker in patients taking tacrine. Other centrally acting anticholinesterases (including **galantamine**, **rivastigmine** and possibly **donepezil**) would be expected to behave like tacrine.

The clinical relevance of this warning is supported by a case report, which describes prolonged **suxamethonium**-induced relaxation in a 75-year-old man who had been taking **donepezil** for 14 months. In this patient the effect of **atracurium** was found to be inadequate even at higher than usual doses, based on the patient's weight.[3]

2. Suxamethonium (Succinylcholine). Tacrine, like other anticholinesterases, has been used *intravenously* in anaesthetic practice to prolong the effects of depolarising blockers such as suxamethonium.[2,4-7] For example, one study found that only one-third of the normal dosage of suxamethonium was needed in the presence of 15 mg of intravenous tacrine.[8] However, tacrine is now more commonly used *orally* for its central effects in the treatment of Alzheimer's disease. Therefore be alert for an increase in the effects of suxamethonium in patients taking tacrine. Other centrally acting anticholinesterases (including **galantamine**, **rivastigmine** and possibly **donepezil**) would be expected to behave like tacrine.

There is a report of such an interaction in a 72-year-old woman taking **donepezil** who had prolonged paralysis after induction of anaesthesia with propofol and suxamethonium. It is possible that levels of **donepezil** in this patient were high due to the concurrent use of 'fluoxetine', (p.402), and this may have contributed to the prolonged action of suxamethonium.[9] Another report describes an 85-year-old woman taking **donepezil**, who developed prolonged neuromuscular blockade after she was given neostigmine to reverse the effects of pancuronium (she had also received suxamethonium). This patient probably had atypical pseudocholinesterase activity, and the authors suggest the interaction may not be clinically relevant in patients with normal enzyme activity.[10]

(d) Organophosphorus compounds

Organophosphorus compounds are potent anticholinesterases, see 'Neuromuscular blockers + Organophosphorus compounds', p.144.

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Neuromuscular blockers + Antineoplastics

The effects of suxamethonium (succinylcholine) can be increased and prolonged in patients receiving cyclophosphamide because their plasma cholinesterase levels are depressed. Respiratory insufficiency and prolonged apnoea have been reported. Irinotecan may prolong the neuromuscular blocking effects of suxamethonium and antagonise that of non-depolarising drugs. *Animal* data suggests that thiotepa may also enhance the effects of suxamethonium. An isolated report describes a marked increase in the neuromuscular blocking effects of pancuronium in a myasthenic patient who was given thiotepa, but normally it appears not to interact with competitive neuromuscular blockers.

Clinical evidence

(a) Cyclophosphamide

Respiratory insufficiency and prolonged apnoea occurred in a patient taking cyclophosphamide on two occasions, both during anaesthesia during which **suxamethonium** (**succinylcholine**) and **tubocurarine** were given. Plasma cholinesterase levels were found to be low. Anaesthesia without the **suxamethonium** was uneventful. Seven out of 8 patients subsequently examined also showed depressed plasma cholinesterase levels while taking cyclophosphamide.[1]

Respiratory depression and low plasma cholinesterase levels have been described in other reports in patients taking cyclophosphamide.[2-5] Similarly, in the discussion of an *in vitro* study, the authors report preliminary results from a study in patients, showing a 35 to 70% reduction in cholinesterase activity, which lasted for several days after cyclophosphamide use.[2] See also *Mechanism*, below.

(b) Irinotecan

The manufacturer of irinotecan warns that it could possibly prolong the neuromuscular blocking effects of suxamethonium (succinylcholine) and antagonise the neuromuscular blockade of competitive (non-depolarising) drugs.[6] This is based on the fact that irinotecan has anticholinesterase activity.[6,7] See 'Neuromuscular blockers + Anticholinesterases', p.128, for an explanation of this mechanism.

(c) Thiotepa

A myasthenic patient developed very prolonged respiratory depression very shortly after being given thiotepa intraperitoneally, following the use of **pancuronium**.[8] Thiotepa has also been shown to increase the duration of **suxamethonium** (**succinylcholine**) neuromuscular blockade in *dogs*.[9] However, an *in vitro* study showed that thiotepa was a poor inhibitor of plasma cholinesterase.[2] See also *Mechanism*, below.

Mechanism

Cyclophosphamide inhibits the activity of plasma cholinesterase,[4] and as a result the metabolism of the suxamethonium is reduced and its actions are enhanced and prolonged. Other alkylating agents are also reported to reduce plasma cholinesterase activity.[10] An *in vitro* study found that human motor endplate or red blood cell acetylcholinesterase was inhibited by alkylating antineoplastics, with chlormethine exerting the greatest effect, followed by dacarbazine, nimustine, cyclophosphamide and ifosfamide. Chlormethine and cyclophosphamide inhibited plasma pseudocholinesterase most strongly, followed by thiotepa, nimustine, dacarbazine, ifosfamide, and carmustine.[10]

Importance and management

The interaction between suxamethonium (succinylcholine) and cyclophosphamide is well documented and established. It is of clinical importance, but whether all patients are affected to the same extent is uncertain. The depression of the plasma cholinesterase levels may last several days,

possibly weeks, so that ideally plasma cholinesterase levels should be checked before using suxamethonium. In patients taking cyclophosphamide, suxamethonium should certainly be used with caution, and the dosage should be reduced.[2] Some have suggested that concurrent use should be avoided.[1] Irinotecan may possibly enhance the effects of suxamethonium and antagonise the effects of non-depolarising drugs. *Animal* data suggest thiotepa may enhance the effects of suxamethonium, while *in vitro* data and a case report in a patient with myasthenia,[11] suggest some other antineoplastics may also have an effect. The general silence in the literature would seem to indicate that no special precautions are generally necessary. However, patients with malignant tumours often have a reduced plasma cholinesterase activity, so care is warranted in these patients.[12]

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Neuromuscular blockers + Antipsychotics

An isolated report describes prolonged apnoea in a patient given promazine while recovering from neuromuscular blockade with suxamethonium (succinylcholine). The use of intravenous chlorpromazine before suxamethonium was found not to affect the activity of suxamethonium. Recovery from the neuromuscular blocking effects of suxamethonium is prolonged by fentanyl with droperidol.

Clinical evidence

(a) Chlorpromazine

In a study in 50 patients undergoing elective ophthalmic surgery, intravenous chlorpromazine 100 micrograms/kg given 3 minutes before **suxamethonium** (**succinylcholine**) 500 micrograms/kg did not significantly affect time to maximum neuromuscular block or reappearance and complete recovery of the twitch response, when compared with patients who had not been given chlorpromazine.[1]

(b) Fentanyl with Droperidol

The observation that patients who had received *Innovar* (fentanyl with droperidol) before anaesthesia appeared to have prolonged **suxamethonium** (**succinylcholine**) effects, seen as apnoea, prompted further study of this possible interaction.[2] An average delay in recovery from neuromuscular blockade of 36% to 80% was seen in two studies.[2,3] Another study[4] showed that the droperidol component of *Innovar* was probably responsible for this interaction.

(c) Promazine

A woman recovering from surgery during which she had received **suxamethonium** (**succinylcholine**), was given promazine 25 mg intravenously for sedation. Within 3 minutes she had become cyanotic and apnoeic, and required assisted respiration for 4 hours.[5]

Mechanism

Not understood. It has been suggested that promazine[5] and droperidol[4] depress plasma cholinesterase levels, which would reduce the metabolism of the suxamethonium and thereby prolong recovery. It has also been suggested that droperidol might act as a membrane stabiliser at neuromuscular junctions.[4]

Importance and management

Some caution would seem appropriate if promazine is given to any patient who has been given suxamethonium (succinylcholine). The use of intravenous chlorpromazine just before suxamethonium appears not to affect suxamethonium activity. There seems to be no information about other phenothiazines and other neuromuscular blockers.

Delayed recovery should be anticipated in patients given suxamethonium if droperidol is used. This is an established interaction.

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Neuromuscular blockers + Aprotinin

Apnoea developed in a number of patients after they were given aprotinin while recovering from neuromuscular blockade with suxamethonium (succinylcholine), either alone or with tubocurarine.

Clinical evidence

Three patients undergoing surgery who had received **suxamethonium** (**succinylcholine**), either alone or with **tubocurarine**, were given aprotinin intravenously in doses of 2500 to 12 000 KIU (kallikrein inactivator units) at the end of, or shortly after, the operation when spontaneous breathing had resumed. In each case respiration rapidly became inadequate and apnoea lasting periods of 7, 30 and 90 minutes occurred.[1] Seven other cases have been reported elsewhere.[2]

Mechanism

Not fully understood. Aprotinin is only a very weak inhibitor of serum cholinesterase (100 000 KIU caused a maximal 16% inhibition)[3] and on its own would have little effect on the metabolism of suxamethonium. However, it might tip the balance in those whose cholinesterase was already very depressed.

Importance and management

The incidence of this interaction is uncertain but probably low. Only a few cases have been reported. It seems probable that it only affects those whose plasma cholinesterase levels are already very low for other reasons. No difficulties should arise in those whose plasma cholinesterase levels are normal.

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Neuromuscular blockers + Benzodiazepines

A few studies report that diazepam and other benzodiazepines increase the effects of neuromuscular blockers, but many others have not found an interaction. If an interaction does occur, the response is likely to be little different from the individual variations in response of patients to neuromuscular blockers.

Clinical evidence

(a) Increased blockade

A comparative study of 10 patients given **gallamine** and 4 others given **gallamine** with intravenous **diazepam** 150 to 200 micrograms/kg found that **diazepam** prolonged the duration of activity of **gallamine** by a factor of three, and doubled the depression of the twitch response.[1] Persistent muscle weakness and respiratory depression was seen in two other patients given **tubocurarine** after premedication with **diazepam**.[2] A small

reduction (approximately 10%) in neuromuscular blocker requirement has been described when **diazepam** was given with **tubocurarine**[3] or **suxamethonium** (**succinylcholine**), but see also (b) below.[4] In a study in 10 patients, giving **diazepam** 200 micrograms/kg 3 minutes before **vecuronium** 100 micrograms/kg during anaesthetic induction shortened the time to onset of **vecuronium** and prolonged its duration of action, when compared with the activity of **vecuronium** in a similar group of patients not given **diazepam**.[5]

Another study found that recovery to 25% and 75% of the twitch height after **vecuronium** was prolonged by about 25% by 15 mg of intravenous **midazolam**, when compared with control patients.[6] The same study found that **midazolam** prolonged the recovery from the effects of **atracurium** by about 20%. However, the increased recovery time due to **midazolam** was not statistically significant when compared with control patients, but was significantly longer when compared with patients receiving 20 mg of intravenous **diazepam**.[6] See also (b) below.

(b) Reduced blockade or no interaction

The duration of paralysis due to **suxamethonium** was reduced in one study by 20% when **diazepam** (150 micrograms/kg) was also given, and the recovery time was shortened.[1] **Diazepam** also slightly reduced the time to 25% and 75% recovery of twitch height in patients given **vecuronium** by about 15% (not statistically significant).[6] In *animals*, **diazepam** increased the mean dose of **rocuronium** required by 13%, but this was not statistically significant.[7]

In other studies **diazepam** was found to have no significant effect on the neuromuscular blockade due to **alcuronium**,[8] **atracurium**,[6] **gallamine**,[9] **pancuronium**,[8,10] **suxamethonium**[8,11] or **tubocurarine**.[8,9,11,12] **Lorazepam** and **lormetazepam** have been reported to have little or no effects on **atracurium** or **vecuronium**,[6] and **midazolam** has been reported to have no effect on **suxamethonium**, **pancuronium**,[13] **rocuronium**[14] or **vecuronium**.[15,16]

Mechanism

Not understood. One suggestion is that where some alteration in response is seen it may be a reflection of a central depressant action rather than a direct effect on the myoneural junction.[9] Another study suggests that a direct action on the muscle may be responsible.[17]

Importance and management

What is known shows that the benzodiazepines may sometimes unpredictably alter the depth and prolong the recovery period from neuromuscular blockade, but the extent may not be very great and may possibly be little different from the individual variations in the response of patients to neuromuscular blockers.

Given that benzodiazepines are commonly given as premedication it seems likely that any significant interaction would have come to light by now.

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Neuromuscular blockers + Beta-agonist bronchodilators

Bambuterol can prolong the recovery time from neuromuscular blockade with suxamethonium (succinylcholine) or mivacurium. A case report describes modestly enhanced neuromuscular blockade when pancuronium or vecuronium were given after intravenous salbutamol.

Clinical evidence

(a) Bambuterol

A double-blind study in 25 patients found that the recovery time from neuromuscular blockade with **suxamethonium** (**succinylcholine**) was prolonged by about 30% in those who had been given 10 mg of bambuterol 10 to 16 hours before surgery, and by about 50% in those who had been given 20 mg of bambuterol.[1]

This confirms two previous studies,[2,3] one of which found that 30 mg of bambuterol given about 10 hours before surgery approximately doubled the duration of **suxamethonium** blockade.[2] Furthermore, in 7 patients who had abnormal plasma cholinesterase levels, 20 mg of bambuterol taken 2 hours before surgery prolonged **suxamethonium** blockade two- to threefold, and in 4 patients a phase II block occurred.[4]

Similar results have been found in a study involving 27 patients given **mivacurium**. A marked decrease in plasma cholinesterase activity, leading to reduced clearance and prolonged elimination half-life of **mivacurium,** occurred when oral bambuterol 20 mg was given 2 hours before induction of anaesthesia. The duration of action of **mivacurium** was prolonged three- to fourfold, when compared with placebo.[5]

(b) Salbutamol

A case report describes a 28-year-old man undergoing elective surgery who was given three intravenous doses of salbutamol 125 micrograms over 3.5 hours for the treatment and prophylaxis of bronchospasm. Muscle relaxation was maintained with **pancuronium** and then **vecuronium**. The neuromuscular blockade (measured by the force of contraction of the adductor pollicis in response to ulnar nerve stimulation) increased after the salbutamol injection, from 45% to 66% during **pancuronium** blockade and from 66% to 86% following **vecuronium**. In addition, recovery of neuromuscular function with neostigmine appeared to be slower than expected.[6]

Mechanism

Bambuterol is an inactive prodrug, which is slowly converted enzymatically in the body to its active form, terbutaline. The carbamate groups that are split off can selectively inhibit the plasma cholinesterase that is necessary for the metabolism of suxamethonium and mivacurium. As a result, the metabolism of these neuromuscular blockers is reduced and their effects are thereby prolonged. The effect appears to be related to the dose of the bambuterol and the time lag after administration; maximal depression of plasma cholinesterase activity appears to occur about 2 to 6 hours following oral administration, but is still markedly depressed after 10 hours.[2]

The effect of intravenous salbutamol was probably a direct effect at the neuromuscular junction.[6]

Importance and management

The interaction with bambuterol is an established interaction. It may be more important where other factors reduce plasma cholinesterase activity or affect the extent of blockade in other ways (e.g. subjects with abnormal plasma cholinesterase levels). This interaction only applies to beta agonists that are metabolised to carbamic acid (bambuterol appears to be the only one available).

The interaction between intravenous salbutamol and pancuronium or vecuronium appears to be limited to the one report cited, and is probably of only minor clinical importance.

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Neuromuscular blockers + Beta blockers

Increases or decreases (often only modest) in the extent of neuromuscular blockade have been seen in patients taking beta blockers. The bradycardia and hypotension sometimes caused by anaesthetics and beta blockers is not counteracted by atracurium.

Clinical evidence

(a) Alcuronium

Bradycardia and hypotension were seen in a patient given alcuronium while using **timolol** eye drops for glaucoma.[1]

(b) Atracurium

Eight out of 42 patients taking unnamed beta blockers given atracurium developed bradycardia (less than 50 bpm) and hypotension (systolic pressure less than 80 mmHg). Most of them had been premedicated with diazepam, induced with methohexital, and maintained with droperidol, fentanyl and nitrous oxide/oxygen. A further 24 developed bradycardia, associated with hypotension on 9 occasions. All responded promptly to 300 to 600 micrograms of intravenous atropine.[2]

A patient using **timolol** 0.5% eye drops for glaucoma developed bradycardia and hypotension when atracurium was given.[3] Bradycardia and hypotension have also been seen in a patient, who was given atracurium while taking **atenolol** for hypertension.[1]

(c) Rocuronium

A study of 16 patients who had been taking various beta blockers (**propranolol** 5, **atenolol** 5, **metoprolol** 2, **bisoprolol** 2, **oxprenolol** 1, **celiprolol** 1) for longer than one month found no difference in the onset and duration of action of rocuronium, when compared with a control group not taking beta blockers.[4]

(d) Suxamethonium (Succinylcholine)

In a study in 8 patients, the effects of suxamethonium were slightly, but not significantly, reduced by a 1-mg/15 kg intravenous dose of **propranolol**, given 15 minutes pre-operatively.

In 8 patients, intravenous **esmolol** 300 to 500 micrograms/kg per minute reduced the increase in heart rate during intubation, and slightly but significantly prolonged the recovery from blockade with suxamethonium by approximately 3 minutes, when compared with 8 patients given placebo.[5] In another study, intra-operative **esmolol** did not affect the onset and recovery time from suxamethonium blockade in patients with normal plasma cholinesterase (pseudocholinesterase) activity.[6]

(e) Tubocurarine

In a study in 8 patients, **propranolol**, given intravenously 20 to 40 minutes after the onset of action of tubocurarine, shortened the recovery from tubocurarine.[7] Another study described a shortened recovery period from tubocurarine due to **oxprenolol** or **propranolol**, but **pindolol** only slightly affected recovery in a few subjects.[8] Two patients with thyrotoxicosis showed prolonged neuromuscular blockade with tubocurarine after they had taken **propranolol** 120 mg daily for 14 days before surgery.[9]

(f) Vecuronium

For reports of bradycardia associated with vecuronium and opioids in patients also receiving beta blockers, see 'Neuromuscular blockers + Opioids', p.144.

Mechanism

The changes in the degree of blockade are not understood but the interaction appears to occur at the neuromuscular junction. It has been seen in *animal* studies.[10,11] The bradycardia and hypotension were probably due to the combined depressant effects on the heart of the anaesthetics and the beta blocker not being offset by atracurium, which has little or no effect on the vagus nerve at doses within the recommended range. Note that neuromuscular blockers with vagolytic activity can cause tachycardia and hypotension.

Importance and management

Information is fairly sparse, but these interactions appear normally to be of relatively minor importance. Be aware that changes in neuromuscular blockade (increases or decreases) can occur if beta blockers are used, but they seem to be unpredictable, and then often only modest in extent. The possible combined cardiac depressant effects of beta blockade and anaesthesia are well known (see 'Anaesthetics, general + Beta blockers', p.107). These effects may not be prevented when a neuromuscular blocker is used that has little or no effect on the vagus (such as atracurium or vecuronium).

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Neuromuscular blockers + Calcium-channel blockers

Limited evidence indicates that intra-operative intravenous diltiazem, nicardipine, nifedipine and verapamil can decrease the requirements for vecuronium and other competitive neuromuscular blockers. Intravenous nimodipine did not alter vecuronium effects in one study.
An isolated case report describes potentiation of tubocurarine and pancuronium by oral verapamil. However, long-term oral nifedipine did not alter vecuronium or atracurium effects, and long-term therapy with various calcium-channel blockers did not interact with rocuronium. Calcium-channel blockers do not ncrease the plasma potassium rise due to suxamethonium (succinylcholine).

Clinical evidence

(a) Intravenous calcium-channel blockers

A study in 24 surgical patients[1] anaesthetised with nitrous oxide and isoflurane found that **diltiazem** 5 or 10 microgram/kg per minute decreased the **vecuronium** requirements by up to 50%. Another study in 24 surgical patients found that **diltiazem** (5 mg bolus followed by a 4-microgram/kg per minute infusion) decreased **vecuronium** requirements by 45%, when compared with a control group (no **diltiazem**), or those receiving **diltiazem** at half the infusion dose.[2] Reductions in the requirements for **vecuronium** were also noted in other surgical patients receiving intravenous **diltiazem** or **nicardipine**.[3] A study in patients given **vecuronium** 100 micrograms/kg for tracheal intubation found that **nicardipine** 10 micrograms/kg shortened the onset of blockade, making it the same as in other patients given **vecuronium** 150 micrograms/kg alone. Recovery times were unaffected by the **nicardipine**.[4] Yet another study showed that **nicardipine** reduced the requirements for **vecuronium** in a dose-dependent manner: nicardipine 1, 2 and 3 micrograms/kg per minute reduced the vecuronium dose requirement to 79%, 60% and 53% of the control, respectively.[5] A study in 44 patients anaesthetised with isoflurane in nitrous oxide/oxygen found that 1 mg of intravenous **nifedipine** prolonged the neuromuscular blockade due to **atracurium** from 29 minutes to 40 minutes, and increased the neuromuscular blockade of **atracurium** or **vecuronium** from 75% to 90%.[6] In contrast, a study in 20 patients found

that an intravenous infusion of **nimodipine** had no significant effect on the time course of action of **vecuronium**.[7]

A 66-year-old woman with renal impairment, receiving 5 mg of intravenous **verapamil** three times daily for supraventricular tachycardia, underwent abdominal surgery during which she was initially anaesthetised with thiopental and then maintained on nitrous oxide/oxygen with fentanyl. **Vecuronium** was used as the muscle relaxant. The effects of the **vecuronium** were increased and prolonged, and at the end of surgery reversal of the blockade using neostigmine was difficult and extended.[8] Intravenous **verapamil** alone has caused respiratory failure in a patient with poor neuromuscular transmission (Duchenne's dystrophy).[9] Note that *in vitro* and *animal* studies have confirmed that the neuromuscular blocking effects of **tubocurarine**, **pancuronium**, **vecuronium**, **atracurium** and **suxamethonium** (**succinylcholine**) are increased by **diltiazem**, **verapamil** and **nifedipine**.[9-11]

(b) Oral calcium-channel blockers

A report describes increased neuromuscular blockade in a patient taking long-term **verapamil** 40 mg three times daily who was given **pancuronium** 2 mg and **tubocurarine** 5 mg. The neuromuscular blockade was difficult to reverse with neostigmine, but responded well to edrophonium.[12] However, the authors of this report say that many patients taking long-term **verapamil** do not show a clinically significant increase in sensitivity to muscle relaxants.[12] This case also contrasts with another study in which 30 predominantly elderly patients taking long-term **nifedipine** (mean daily dose 33 mg) showed no changes in the time to onset of maximum block nor the duration of clinical relaxation in response to **atracurium** or **vecuronium**, when compared with 30 control patients not taking nifedipine.[13] Similarly, a study in 17 patients taking calcium-channel blockers (**nifedipine** 12, **diltiazem** 2, **nicardipine** 2, **amlodipine** 1) found no changes in the neuromuscular blocking effects of **rocuronium**.[14]

A comparative study in 21 patients taking calcium-channel blockers long term (**diltiazem**, **nifedipine**, **verapamil**) and 15 other patients not taking calcium-channel blockers found that, although **suxamethonium** (**succinylcholine**) caused a modest average peak rise of 0.5 mmol/L in plasma potassium levels, there were no differences between the two groups.[15]

Mechanism

Not fully understood. One suggested explanation is that nerve impulses arriving at nerve endings release calcium ions, which in turn causes the release of acetylcholine. Calcium-channel blockers can reduce the concentration of calcium ions within the nerve so that less acetylcholine is released. This would be additive with the effects of a neuromuscular blocker.[11,12]

Importance and management

Direct information so far seems to be limited. Increased neuromuscular blockade seems possible in any patient given an intravenous calcium-channel blocker (except possibly nimodipine) during surgery, but it seems likely that any effect will be managed by routine dose titration of the neuromuscular blocker and standard pre- and post-operative monitoring. From the limited evidence available it appears that increased blockade is not likely in patients taking long-term oral calcium-channel blockers, although one case has been reported with verapamil.

It would also seem that patients taking chronic calcium-channel blocker treatment are at no greater risk of hyperkalaemia with suxamethonium than other patients.

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Neuromuscular blockers + Carbamazepine

The effects of many competitive neuromuscular blockers are reduced and shortened if carbamazepine is given for longer than one week, but they may be increased if carbamazepine is given acutely (e.g. during surgery). Carbamazepine does not appear not to interact with mivacurium.

Clinical evidence

(a) Carbamazepine given long-term

1. Atracurium or Cisatracurium. One study found that the recovery time from intravenous atracurium 500 micrograms/kg was shorter in 14 patients taking long-term carbamazepine (5.93 minutes) than in 21 non-epileptic patients (8.02 minutes). This was assessed using the recovery index (time between 25% and 75% recovery of baseline electromyogram values).[1] However, carbamazepine has also been reported to have no effect on atracurium.[2,3]

A study found that the recovery time from intravenous cisatracurium was shorter in patients taking carbamazepine or phenytoin than in patients not receiving carbamazepine or 'phenytoin', (p.145); the recovery index (times between 25% and 75% recovery) was 16.2 minutes and 21.2 minutes, respectively. Clearance of cisatracurium was increased by about 25% in patients taking carbamazepine or phenytoin, and the steady-state plasma level of cisatracurium required to maintain 95% block was increased by 20%, indicating increased resistance to the action of cisatracurium.[4]

2. Doxacurium. In a study, 9 patients taking carbamazepine for at least one week and undergoing surgery were given doxacurium. These patients took 66 minutes to reach 50% recovery compared with 161 minutes in a control group not taking carbamazepine.[5] Similar findings were obtained in another study.[6]

3. Mivacurium. In contrast to other neuromuscular blockers, the long-term (greater than 4 weeks) use of carbamazepine does not appear to affect mivacurium-induced neuromuscular blockade.[7] Similarly, a study in 32 patients who had been taking carbamazepine alone or with phenytoin or **valproic acid** for greater than 2 weeks found no resistance to mivacurium,[8] although an earlier preliminary study by the same research group found a trend towards a shorter recovery from mivacurium in 13 patients taking unspecified antiepileptics (not statistically significant).[9]

4. Pancuronium. In 18 patients undergoing craniotomy for tumours, seizure foci or cerebrovascular surgery, the recovery from neuromuscular blockade with pancuronium was on average 65% shorter in those patients taking carbamazepine.[10]

5. Pipecuronium. The effects of pipecuronium are reduced by carbamazepine.[11,12] In one study it was found that the *onset* time for pipecuronium blockade was lengthened (although this was not statistically significant) in patients with therapeutic plasma concentrations of carbamazepine, but not in those with subtherapeutic levels. However, a shorter duration of action was seen regardless of antiepileptic levels.[12]

6. Rapacuronium. A reduced duration of action has been reported with rapacuronium in a patient taking carbamazepine.[13]

7. Rocuronium. Several reports and studies have found that rocuronium has a shorter duration of action following long-term carbamazepine use,[14-17] although preliminary investigations found no effect.[18,19]

8. Suxamethonium (Succinylcholine). Eight patients who had been taking phenytoin and/or carbamazepine for at least one month took longer to recover from suxamethonium blockade, than 9 control patients; the time for return to baseline twitch height was 14.3 minutes and 10 minutes, respectively.[20]

9. Vecuronium. Several studies have found that carbamazepine shortens the recovery time from vecuronium blockade in adults[2] and in children.[21]

(b) Carbamazepine given short-term

An *in vitro* study found that the acute neuromuscular effects of **carbamazepine** reduced the concentrations required for 50% paralysis with both a depolarising neuromuscular blocker (**suxamethonium** (**succinylcholine**)) and a competitive neuromuscular blocker (**atracurium**) by about 30%.[22]

Mechanism

Not fully understood, but it appears to be multifactorial. The acute use of carbamazepine may result in neuromuscular block and potentiation of the action of competitive (non-depolarising) blockers.[22]

The long-term use of carbamazepine may produce subclinical neuromuscular blockade thought to be due to modest blockade of acetylcholine effects and a decrease in acetylcholine release; this antagonism may induce changes at the neuromuscular junction including an increased number of acetylcholine receptors on the muscle membrane (up-regulation), with decreased sensitivity.[20,21] Other suggestions to account for the reduced response with the long-term use of carbamazepine include induction of liver enzyme activity (carbamazepine is a potent inducer of cytochrome P450 isoenzymes), which would increase the metabolism and clearance of the neuromuscular blocker; and changes in plasma protein binding.[20,21] It has been shown that carbamazepine doubles the clearance of vecuronium.[21,23]

Importance and management

Established and clinically important interactions. Anticipate the need to use a larger dose of the neuromuscular blocker in patients who have taken carbamazepine for more than one week, and expect an accelerated recovery. The neuromuscular blockers appear to interact to differing extents, with mivacurium apparently unaffected.

Although evidence is limited, if carbamazepine is given acutely, it may be prudent to anticipate the need to use a smaller neuromuscular blocker dosage, or prepare for a longer recovery time.

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Neuromuscular blockers + Chloroquine, Hydroxychloroquine or Quinine

A report describes respiratory insufficiency during the recovery period following surgery, which was attributed to the use of chloroquine diorotate. Hydroxychloroquine would be expected to interact similarly. An isolated report describes recurarisation and dyspnoea in a patient given intravenous quinine after recovering from neuromuscular blockade with suxamethonium (succinylcholine) and pancuronium.

Clinical evidence, mechanism, importance and management

(a) Chloroquine

Studies were carried out on the possible neuromuscular blocking actions of chloroquine diorotate in *animals,* because it was noticed that when it was used in the peritoneal cavity to prevent adhesions following abdominal surgery in man, it caused respiratory insufficiency during the recovery period. These studies found that it had a non-depolarising blocking action at the neuromuscular junction, which was opposed by neostigmine.[1] It would seem therefore that during the recovery period the effects of the chloroquine can be additive with the residual effects of the conventional neuromuscular blocker used during the surgery.

Although this appears to be the only report of this interaction, it is consistent with the way chloroquine can unmask or aggravate myasthenia gravis, or oppose the effects of drugs used in its treatment. Be alert for this reaction if chloroquine is used. Note that **hydroxychloroquine** would be expected to interact similarly.

(b) Quinine

A 47-year-old man with acute pancreatitis, taking quinine 600 mg three times daily, was given penicillin and gentamicin intravenously before undergoing surgery, during which **pancuronium** and **suxamethonium** (**succinylcholine**) were used uneventfully. After surgery the neuromuscular blockade was reversed with neostigmine and atropine, and the patient awoke and was breathing well. A 6-hour intravenous infusion of quinine 500 mg was started 90 minutes postoperatively. Within 10 minutes (after receiving about 15 mg of quinine) he became dyspnoeic, his breathing became totally ineffective and he needed re-intubation. Muscle flaccidity persisted for 3 hours.[2] The reason for this reaction is not fully understood. A possible explanation is that it may have been the additive neuromuscular blocking effects of the gentamicin (well recognised as having neuromuscular blocking activity; see 'Neuromuscular blockers + Aminoglycosides', p.127) and the quinine (an optical isomer of quinidine; see 'Neuromuscular blockers + Quinidine', p.146) and the residual effects of the **pancuronium** and **suxamethonium**.

There seem to be no other reports of problems in patients receiving neuromuscular blockers with quinine, but this isolated case serves to emphasise the importance of being alert for any signs of recurarisation in patients given drugs possessing some neuromuscular blocking activity, particularly during the postoperative recovery period.

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2. Sher MH, Mathews PA. Recurarization with quinine administration after reversal from anaesthesia. *Anaesth Intensive Care* (1983) 11, 241–3.

Neuromuscular blockers + Corticosteroids

Two reports describe antagonism of the neuromuscular blocking effects of pancuronium by high-dose prednisone, or prednisolone and hydrocortisone. A third report in a patient with adrenocortical insufficiency describes reversal of the pancuronium block by hydrocortisone. Some evidence suggests the dosage of vecuronium may need to be almost doubled in those receiving intramuscular betamethasone. However, prolonged coadministration of high-dose corticosteroids and neuromuscular blockers may

increase the risk of myopathy, resulting in prolonged paralysis following the discontinuation of the neuromuscular blocker.

Clinical evidence

(a) Neuromuscular blocking effects

A man undergoing surgery who was taking oral **prednisone** 250 mg daily, had good muscular relaxation in response to intravenous **pancuronium** 8 mg (100 micrograms/kg) early in the operation, but one hour later he began to show signs of inadequate relaxation, and continued to do so for the next 75 minutes despite being given four additional 2-mg doses of **pancuronium**.[1] Another patient taking large doses of **hydrocortisone**, **prednisolone** and aminophylline proved to be resistant to the effects of **pancuronium**.[2] A hypophysectomised man taking **cortisone** developed profound paralysis when given **pancuronium**, which was rapidly reversed with 100 mg of **hydrocortisone sodium succinate**.[3]

Inadequate neuromuscular blockade with **vecuronium** (presenting as unexpected movements) occurred in 2 patients during neurosurgery. They had both been given a preoperative course of **betamethasone** 4 mg four times daily to reduce raised intracranial pressure.[4] This prompted a retrospective search of the records of 50 other patients, which revealed that those given intramuscular **betamethasone** preoperatively had needed almost double the dose of **vecuronium** (134 micrograms/kg per hour compared with 76 micrograms/kg per hour).[4]

These reports contrast with another, in which 25 patients who had no adrenocortical dysfunction or histories of corticosteroid use were given **pancuronium**, **metocurine**, **tubocurarine** or **vecuronium**. Neuromuscular blockade was not altered when a single intravenous dose of **dexamethasone** 400 micrograms/kg or **hydrocortisone** 10 mg/kg was given.[5]

(b) Increased risk of myopathy

A report describes 3 patients in status asthmaticus who developed acute reversible myopathy after treatment with high-dose intravenous **methylprednisolone** 320 to 750 mg daily and steroidal neuromuscular blockers (**vecuronium** or **pancuronium**), used concurrently for at least 8 days.[6] A review of the literature from 1977 to 1995 found over 75 cases of prolonged weakness associated with combined use of neuromuscular blockers and **corticosteroids**.[7] This condition has been referred to as 'blocking agent–corticosteroid myopathy' (BACM). Before 1994, virtually all cases involved either **pancuronium** or **vecuronium**, leading some authors to suggest that **atracurium** might be safer as it does not have the steroidal structure of these neuromuscular blockers.[6] However, there have since been reports of prolonged paralysis associated with extended treatment with high-dose **corticosteroids** and **atracurium**[8,9] or **cisatracurium**.[10]

Mechanism

Not understood. For the partial reversal of neuromuscular blockade, one idea, based on *animal* studies, is that adrenocortical insufficiency causes a defect in neuromuscular transmission, which is reversed by the corticosteroids.[3] Another idea is that the effects seen are connected in some way with the steroid nucleus of the pancuronium and vecuronium, and are mediated presynaptically.[4,11]

The increased myopathy may be due to an additive effect, as both neuromuscular blockers and corticosteroids can cause myopathy. Results of an *in vitro* study suggested that the combination of vecuronium and methylprednisolone might augment pharmacologic denervation, which may lead to myopathy and contribute to the prolonged weakness observed in some critically ill patients.[12]

Importance and management

The evidence for antagonism of neuromuscular-blocking effects seems to be limited to the reports cited, and involve only pancuronium and vecuronium. Careful monitoring is clearly needed if either is used in patients who have been treated with corticosteroids, being alert for the need to increase the dosage of the neuromuscular blocker. Note that *animal* studies suggest that atracurium may also possibly be affected by betamethasone to the same extent as vecuronium.[11] However, also be aware that prolonged coadministration of competitive neuromuscular blockers and corticosteroids, particularly in patients in intensive care, may result in a marked prolongation of muscle weakness (several months of rehabilitation have been needed in some cases[6]). The complex state of the critically ill patient means that the effects of neuromuscular blockers may be unpredictable.

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Neuromuscular blockers + Dantrolene

In one patient dantrolene increased the effects of vecuronium, whereas two other patients were unaffected.

Clinical evidence, mechanism, importance and management

A 60-year-old woman, given a total of 350 mg of dantrolene orally during the 28 hours before surgery to prevent malignant hyperthermia, developed increased neuromuscular blockade and a slow recovery rate when **vecuronium** was subsequently given.[1] This report contrasts with another describing two patients taking long-term dantrolene 20 to 50 mg daily who had no changes in **vecuronium**-induced neuromuscular blockade during or after surgery.[2] Dantrolene is a muscle relaxant that acts directly on the muscle by lowering intracellular calcium concentrations in skeletal muscle; it reduces the release of calcium from the sarcoplasmic reticulum. It may also possibly inhibit calcium-dependent presynaptic neurotransmitter release.[3]

Evidence of an interaction appears to be limited to this one case but, given the potential mechanism, it may be prudent to be alert for any increased effects if dantrolene is given with vecuronium, and possibly other neuromuscular blockers. These case reports indicate that the effects could be dose-related, and so patients receiving higher doses of dantrolene may be at greater risk, although more study is needed to confirm this.

1. Driessen JJ, Wuis EW, Gielen MJM. Prolonged vecuronium neuromuscular blockade in a patient receiving orally administered dantrolene. *Anesthesiology* (1985) 62, 523–4.
2. Nakayama M, Iwasaki H, Fujita S, Narimatsu E, Namiki A. Neuromuscular effects of vecuronium in patients receiving long-term administration of dantrolene. *Jpn J Anesthesiol* (1993) 42, 1508–10.
3. Dantrium Capsules (Dantrolene sodium). SpePharm UK Ltd. UK Summary of product characteristics, September 2008.

Neuromuscular blockers + Dexmedetomidine

Dexmedetomidine caused a minor increase in plasma rocuronium levels in one study.

Clinical evidence, mechanism, importance and management

A study in 10 healthy subjects under general anaesthesia with alfentanil, propofol and nitrous oxide/oxygen, found that an intravenous infusion of dexmedetomidine (950 to 990 nanograms/kg) increased plasma **rocuronium** levels by 7.6%, which was not clinically significant, and decreased the twitch tension from 51% to 44% after 45 minutes. Dexmedetomidine also decreased finger blood flow and increased systemic blood pressure. It was suggested these pharmacokinetic changes occurred due to peripheral

vasoconstriction,[1] and therefore seem possible with other neuromuscular blockers. However, the effects are unlikely to be of clinical significance.

1. Talke PO, Caldwell JE, Richardson CA, Kirkegaard-Nielsen H, Stafford M. The effects of dexmedetomidine on neuromuscular blockade in human volunteers. *Anesth Analg* (1999) 88, 633–9.

Neuromuscular blockers + Disopyramide

An isolated case report suggests that disopyramide may oppose the effects of neostigmine used to reverse neuromuscular blockade with vecuronium.

Clinical evidence, mechanism, importance and management

A case report[1] suggests that the normal antagonism of **vecuronium** neuromuscular blockade by neostigmine may be opposed by therapeutic serum levels of disopyramide (5 micrograms/mL). Disopyramide has also been shown to decrease neostigmine-induced antagonism of the neuromuscular blockade of **tubocurarine** on the *rat* phrenic nerve-diaphragm preparation.[2] The general clinical importance of these observations is not known.

1. Baurain M, Barvais L, d'Hollander A, Hennart D. Impairment of the antagonism of vecuronium-induced paralysis and intra-operative disopyramide administration. *Anaesthesia* (1989) 44, 34–6.
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Neuromuscular blockers + Diuretics

The effects of some neuromuscular blockers (e.g. pancuronium, tubocurarine) have been both increased and decreased by furosemide.

Clinical evidence

(a) Increased neuromuscular blockade

Three patients receiving kidney transplants[1] developed increased neuromuscular blockade with **tubocurarine** (seen as a pronounced decrease in twitch tension) when given furosemide 40 or 80 mg and mannitol 12.5 g intravenously. One of them had the same reaction when later given only 40 mg of furosemide but no mannitol. The residual blockade was easily antagonised with pyridostigmine 14 mg or neostigmine 3 mg with atropine 1.2 mg.

(b) Decreased neuromuscular blockade

Ten neurosurgical patients given furosemide 1 mg/kg 10 minutes before induction of anaesthesia, took 14.7 minutes to recover from 95 to 50% blockade with **pancuronium** (as measured by a twitch response) compared with 21.8 minutes in 10 similar patients who had not received furosemide.[2]

Mechanism

Uncertain. *Animal* studies indicate that what happens probably depends on the dosage of furosemide: 0.1 to 10 micrograms/kg increased the blocking effects of tubocurarine and **suxamethonium** (succinylcholine) whereas 1 to 4 mg/kg opposed the blockade.[3] One suggestion is that low doses of furosemide may inhibit protein kinase causing a reduction in neuromuscular transmission, whereas higher doses cause inhibition of phosphodiesterase resulting in increased cyclic AMP activity and causing antagonism of neuromuscular blockade. It has also been suggested that large doses of loop diuretics may affect the renal excretion of neuromuscular blockers that are cleared by this route, resulting in more rapid recovery from the blockade.[3]

Importance and management

The documentation is very limited. Be aware of changes in the response to any neuromuscular blocker if furosemide is used, although it seems likely that any effect will be detected as part of routine monitoring. Note that the manufacturers of *Moduretic* (amiloride/**hydrochlorothiazide**) suggest that these diuretics may interact similarly, and enhance the effects of the non-depolarising (competitive) neuromuscular blockers.[4] This prediction appears to be based on some old experimental data using thiazides in *animals*.

1. Miller RD, Sohn YJ, Matteo RS. Enhancement of *d*-tubocurarine neuromuscular blockade by diuretics in man. *Anesthesiology* (1976) 45, 442–5.
2. Azar I, Cottrell J, Gupta B, Turndorf H. Furosemide facilitates recovery of evoked twitch response after pancuronium. *Anesth Analg* (1980) 59, 55–7.
3. Scappaticci KA, Ham JA, Sohn YJ, Miller RD, Dretchen KL. Effects of furosemide on the neuromuscular junction. *Anesthesiology* (1982) 57, 381–8.
4. Moduretic (Amiloride/Hydrochlorothiazide). Bristol-Myers Squibb Pharmaceuticals Ltd. UK Summary of product characteristics, September 2006.

Neuromuscular blockers + Ecothiopate iodide

The neuromuscular blocking effects of suxamethonium (succinylcholine) are markedly increased and prolonged in patients receiving ecothiopate iodide.

Clinical evidence

In 1965 a study showed that ecothiopate iodide eye drops could markedly lower pseudocholinesterase levels.[1] It was noted that "within a few days of commencing therapy, levels are reached at which protracted apnoea could occur, should these patients require general anaesthesia in which muscle relaxation is obtained with **succinylcholine**". Cases of apnoea due to this interaction were reported the following year,[2,3] and other cases have been subsequently reported.[4,5] In one case, a woman given **suxamethonium** (**succinylcholine**) 200 mg had apnoea for 5.5 hours.[2] Other studies have confirmed that ecothiopate given orally[6] or as eye drops[7] markedly reduced the levels of plasma cholinesterase, and can prolong recovery after **suxamethonium**.[6]

One report describes the successful and uneventful use of **atracurium** in a patient receiving ecothiopate.[5]

Mechanism

Suxamethonium is metabolised in the body by plasma cholinesterase. Ecothiopate iodide depresses the levels of this enzyme so that the metabolism of the suxamethonium is reduced and its effects are thereby enhanced and prolonged.[3,6] One study in 71 patients found that two drops of ecothiopate iodide 0.06% three times a week in each eye caused a twofold reduction in plasma cholinesterase (pseudocholinesterase) activity in about one-third of the patients, and a fourfold reduction in 1 in 7 patients.[8] It has been reported that, on discontinuing ecothiopate, it takes between several weeks and 2 months for enzyme activity to return to normal.[7]

Importance and management

An established, adequately documented and clinically important interaction. The dosage of suxamethonium should be reduced appropriately because of the reduced plasma cholinesterase levels caused by ecothiopate. The study cited above[8] suggests that prolonged apnoea is likely in about 1 in 7 patients. One report describes the successful use of approximately one-fifth of the normal dosage of suxamethonium in a patient receiving ecothiopate 0.125% iodide solution, one drop twice a day in both eyes, and with a plasma cholinesterase activity 62% below normal. Recovery from the neuromuscular blockade was rapid and uneventful.[9] **Mivacurium** is also metabolised by plasma cholinesterase, and would be expected to interact with ecothiopate in the same way as suxamethonium.[10]

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2. Gesztes T. Prolonged apnoea after suxamethonium injection associated with eye drops containing an anticholinesterase agent. *Br J Anaesth* (1966) 38, 408–409.
3. Pantuck EJ. Ecothiopate iodide eye drops and prolonged response to suxamethonium. *Br J Anaesth* (1966) 38, 406–407.
4. Mone JG, Mathie WE. Qualitative and quantitative defects of pseudocholinesterase activity. *Anaesthesia* (1967) 22, 55–68.
5. Messer GJ, Stoudemire A, Knos G, Johnson GC. Electroconvulsive therapy and the chronic use of pseudocholinesterase-inhibitor (echothiophate iodide) eye drops for glaucoma. A case report. *Gen Hosp Psychiatry* (1992) 14, 56–60.
6. Cavallaro RJ, Krumperman LW, Kugler F. Effect of echothiophate therapy on the metabolism of succinylcholine in man. *Anesth Analg* (1968) 47, 570–4.
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9. Donati F, Bevan DR. Controlled succinylcholine infusion in a patient receiving echothiophate eye drops. *Can Anaesth Soc J* (1981) 28, 488–90.
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Neuromuscular blockers + Ephedrine

Ephedrine may reduce the onset time of rocuronium and suxamethonium (succinylcholine), Some, but not all studies suggest ephedrine has a similar effect on cisatracurium and vecuronium, but possibly not on atracurium.

Clinical evidence

(a) Atracurium

A study in 40 patients found that premedication with ephedrine 10 mg did not significantly alter the onset time of atracurium.[1]

(b) Cisatracurium

In a study in 30 patients, ephedrine 70 micrograms/kg or sodium chloride 0.9%, was given 5 seconds before the patients were anaesthetised with sufentanil and propofol, and followed by cisatracurium 150 micrograms/kg after loss of consciousness. The onset time of cisatracurium was found to be shorter after ephedrine was given with cisatracurium, than when sodium chloride 0.9% was given with cisatracurium (167 seconds compared with 235 seconds, respectively). Neuromuscular block at intubation was also greater in the patients given ephedrine, and the frequency of excellent intubating conditions was higher after ephedrine (87%) than after sodium chloride 0.9% (40%). No significant differences in haemodynamic parameters were noted between the two groups, although a trend towards a slightly higher heart rate and blood pressure was seen in the ephedrine group.[2] In contrast, another study in 60 patients found that the addition of ephedrine 0.5 mg/mL or 1 mg/mL to anaesthesia with remifentanil, propofol and cisatracurium 150 micrograms/kg had no significant effects on the onset time of cisatracurium.[3] Slight increases in the heart rate, blood pressure and overall mean arterial pressure were seen; however, no adverse cardiac events occurred.[3]

(c) Rocuronium

The effects of pretreatment with ephedrine 75, 100, or 150 micrograms/kg or sodium chloride 0.9% on intubation conditions and haemodynamics were studied in 100 patients given propofol and rocuronium 600 micrograms/kg. A significant increase in heart rate and mean arterial pressure occurred in patients pretreated with ephedrine 75 or 150 micrograms/kg. However, the overall hypotensive effect of the anaesthesia was not completely abolished. Intubation conditions were also significantly better in those pretreated with ephedrine 75 or 100 micrograms/kg but less so in the group who received ephedrine 150 micrograms/kg.[4] Similarly, ephedrine pretreatment was found to improve intubating conditions in another study in patients given propofol and rocuronium. A significant increase in the mean arterial pressure and heart rate was seen in those patients given both ephedrine and propofol in this study although no clinically significant adverse cardiac events, such as arrhythmias, occurred in this group.[5] A study in 60 patients found that ephedrine 70 micrograms/kg given with thiopental anaesthesia reduced the onset time of rocuronium 600 micrograms/kg, with no adverse cardiac effects,[6] and another study, in 40 patients, found that premedication with ephedrine 10 mg reduced the onset time of rocuronium by roughly 30%.[1]

One study in 60 patients found that the onset of rocuronium was 22% shorter after ephedrine 500 micrograms/kg was given (but 26% longer after esmolol, which decreases cardiac output).[7]

(d) Suxamethonium (Succinylcholine)

A study in patients given either ephedrine 70 micrograms/kg or sodium chloride 0.9% three minutes before the induction of anaesthesia with propofol and remifentanil, found that the onset time of suxamethonium was shorter in the ephedrine group than the sodium chloride group (26 seconds compared with 43 seconds, respectively). The heart rate and mean arterial pressure were increased in the ephedrine group at one minute; however, there were no other significant differences at all other measurement times and no adverse cardiac effects were reported.[8]

(e) Vecuronium

In a study, 119 patients were pretreated with ephedrine 30, 70 or 110 micrograms/kg or sodium chloride 0.9%, anaesthetised with fentanyl and propofol and tracheal intubation was performed 2 minutes after vecuronium 100 micrograms/kg was given. The onset time of vecuronium was shorter, intubating conditions were improved and neuromuscular blockade was greater in the patients who received ephedrine but the higher dose was associated with adverse haemodynamic effects (tachycardia and an increase in the mean arterial pressure of more than 30%). No arrhythmias occurred in the ephedrine-treated patients. It was suggested that ephedrine 70 micrograms/kg was a suitable dose to improve tracheal intubation conditions at 2 minutes after vecuronium, by increasing cardiac output but without adverse haemodynamic effects.[9] In contrast, in another study in 53 patients maintained under anaesthesia with propofol, the onset time of neuromuscular block with vecuronium 100 micrograms/kg was not affected by pretreatment with ephedrine 210 micrograms/kg when compared with sodium chloride, despite an increase in systolic blood pressure and the cardiac index (around 17%). However, the authors suggest that because vecuronium was given 10 minutes after the start of the propofol infusion this may have affected the result,[10] whereas ephedrine was given immediately before or just after propofol induction in the studies that found a beneficial effect on the onset of neuromuscular block.[2,4,5,9]

Mechanism

The onset time of neuromuscular blockers is partly dependent on circulatory factors such as muscle blood flow and cardiac output. Ephedrine is thought to decrease the onset times of neuromuscular blockers by increasing cardiac output and improving circulation time of the neuromuscular blocker to the muscle.[9,11] However, other studies that found a reduced onset time of neuromuscular blockade with ephedrine found no difference in haemodynamic parameters.[2,6] It has also been suggested that neuromuscular blockers with a fast onset of action are more likely to be affected by changes in cardiac output and blood flow than those with an intermediate onset of action such as atracurium.[11]

Importance and management

Some studies[1,2,7,9] suggest that small doses of ephedrine reduce the onset time of some neuromuscular blockers and improve intubating conditions. However, other studies[1,3,10] found that ephedrine did not significantly decrease the onset time of neuromuscular blockers. Its use may also be associated with increases in blood pressure and heart rate[3-5,10] and may lead to adverse haemodynamic affects, such as tachycardia, particularly at higher doses.[9] It should be noted that, in the studies above, no patients developed significant arrhythmias, although in most cases patients with pre-existing cardiac disease were excluded. These haemodynamic changes may be of more clinical significance in at-risk patients such as those with ischaemic heart disease.

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8. Ganidagli S, Cengiz M, Baysal Z. Effect of ephedrine on the onset time of succinylcholine. *Acta Anaesthesiol Scand* (2004) 48, 1306–9.
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Neuromuscular blockers + H_2-receptor antagonists

Isolated reports suggest that the effects of suxamethonium (succinylcholine) and vecuronium are prolonged by cimetidine. *Animal* studies suggest that the effects of tubocurarine and pancuronium may also be increased by cimetidine. Other reports suggest that no interaction generally occurs between neuromuscular blockers and other H_2-receptor antagonists, but not all combinations have been studied.

Clinical evidence

(a) Cimetidine

A study in 10 patients given cimetidine 300 mg orally at bedtime and another 300 mg 2 hours before anaesthesia, found that while the onset of action of **suxamethonium** (**succinylcholine**) 1.5 mg/kg intravenously was unchanged, when compared with 10 control patients, the time to recover 50% of the twitch height was prolonged 2- to 2.5-fold (from 8.6 to 20.3 minutes). One patient took 57 minutes to recover. His plasma cholinesterase levels were found to be normal.[1] It was later reported that some patients were also taking metoclopramide, which is known to interact in this way.[2] See also 'Neuromuscular blockers + Metoclopramide', p.141.

A study in 10 patients given 400 mg of cimetidine orally at bedtime and again 90 minutes before anaesthesia found no evidence of an effect on the neuromuscular blockade caused by **suxamethonium**, nor on its duration or recovery period, when compared with 10 control patients.[3] Another controlled study in patients given cimetidine 300 mg the night before and 1 to 2 hours before surgery, found no evidence that the duration of action of **suxamethonium** or the activity of plasma cholinesterase were altered.[2] Other studies similarly suggest that cimetidine does not alter the neuromuscular blocking effects of **suxamethonium**.[4,5]

Another study[6] in 16 patients found that cimetidine 400 mg significantly prolonged the recovery (T1–25 period) from **vecuronium**, but few patients had any response to cimetidine 200 mg. This slight prolongation of action of **vecuronium** due to cimetidine 400 mg was confirmed in another placebo-controlled study (mean time to return of T1 was 30 versus 22.5 minutes).[7] A study using a *rat* phrenic nerve hemi-diaphragm preparation found that, at clinically relevant concentrations, cimetidine produces neuromuscular paralysis and may potentiate the response to **vecuronium**.[8] A similar study using a *rat* phrenic nerve diaphragm preparation found that cimetidine increased the neuromuscular blocking effects of **tubocurarine** and **pancuronium**, but there seem to be no reports confirming this in man.[9]

Cimetidine appears not to alter the effects of **atracurium** or **rocuronium**.[10]

(b) Other H_2-receptor antagonists

A study in 8 patients found that the response to vecuronium was generally unchanged by **ranitidine** 100 mg, although some patients did show a slight prolongation in recovery.[6] A study using a *rat* phrenic nerve hemidiaphragm preparation found that, at clinically relevant concentrations, **ranitidine** produced neuromuscular paralysis and may potentiate the response to **vecuronium**, but low concentrations of **ranitidine** may antagonise the effects of **vecuronium**.[8] Another controlled study in patients given **ranitidine** 150 mg the night before and 1 to 2 hours before surgery, found no evidence that the duration of action of **suxamethonium** (**succinylcholine**) or the activity of plasma cholinesterase were altered.[2] Other studies suggest that **ranitidine** and **famotidine** do not alter the neuromuscular blocking effects of suxamethonium.[4,5]

Ranitidine does not appear to alter the effects of **atracurium**[10] or **vecuronium**.[7] Another study found that premedication with **ranitidine** did not affect **vecuronium** blockade in postpartum patients, but that the neuromuscular blockade was prolonged in these patients, when compared with non-pregnant controls.[11] A study using a *rat* phrenic nerve hemidiaphragm preparation found that **famotidine** lacked significant neuromuscular effects and did not alter the response to **vecuronium**.[8]

Mechanism

Not understood. Studies with human plasma failed to find any evidence that cimetidine in therapeutic concentrations inhibits the metabolism of suxamethonium.[2,12] However, metoclopramide may do and therefore is possibly the drug responsible for any interaction seen. *In vitro* studies with very high cimetidine concentrations found inhibition of plasma cholinesterase (pseudocholinesterase) activity.[13] The interaction between cimetidine and vecuronium is not understood, but it has been suggested that cimetidine may reduce the hepatic metabolism of vecuronium.[7]

Importance and management

Information seems to be limited to the reports cited. The most likely explanation for the discord between the results from studies with suxamethonium (succinylcholine) is that in the one study reporting increased suxamethonium effects[1] some of the patients were also given metoclopramide, which can inhibit plasma cholinesterase and prolong the effects of suxamethonium[2,5] (see also 'Neuromuscular blockers + Metoclopramide', p.141). In four other studies, cimetidine and other H_2-receptor antagonists did not alter suxamethonium effects. Therefore, it seems unlikely that an interaction exists. There is some evidence that cimetidine may slightly prolong the effects of vecuronium, but ranitidine appears not to interact. Atracurium and rocuronium appear not to be affected. Overall these possible interactions seem to be of little clinical significance.

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Neuromuscular blockers + Immunosuppressants

There is limited evidence to suggest that the neuromuscular blocking effects of atracurium, pancuronium and vecuronium may be increased in some patients taking ciclosporin. There is also some evidence of reduced neuromuscular blockade with azathioprine and antilymphocyte immunoglobulins, but other evidence suggests that there is no clinically relevant interaction with azathioprine.

Clinical evidence

(a) Azathioprine or Antilymphocyte immunoglobulins

A retrospective study found that patients taking azathioprine or antilymphocyte immunoglobulins following organ transplantation needed an increased dosage of unspecified **muscle relaxants** to achieve satisfactory muscle relaxation.[1] A control group of 74 patients not receiving immunosuppression needed 0 to 10 mg of a **competitive** (**non-depolarising**) **muscle relaxant**; 13 patients taking azathioprine needed 12.5 to 25 mg; 11 patients receiving antilymphocyte immunoglobulins (antilymphocyte globulin) needed 10 to 20 mg and two patients taking azathioprine and guanethidine needed 55 and 90 mg.[1] However, a controlled study of 28 patients undergoing renal transplantation, who were receiving **atracurium**, **pancuronium** or **vecuronium** at a constant infusion rate, found that an injection of azathioprine 3 mg/kg given over 3 minutes caused a rapid, but only small and transient decrease of neuromuscular blockade. Ten minutes after the end of the azathioprine injection, a residual interaction was only detectable in those patients who had been given **pancuronium**.[2]

(b) Ciclosporin

A retrospective study found that 4 of 36 patients receiving **atracurium** and 4 of 29 patients receiving **vecuronium** experienced prolonged neuromuscular blockade after anaesthesia for renal transplantation. Respiratory failure occurred more often in patients who were given intravenous ciclosporin during surgery.[3] Extended recovery times after **atracurium** and **vecuronium** are described in another report in renal transplant patients who had been taking oral ciclosporin.[4] Similarly, a prolonged duration of action of **vecuronium** was noted in 7 renal transplant recipients, when compared with patients with normal renal function, and ciclosporin was considered to be a factor in this.[5] Two case reports describe prolonged

neuromuscular blockade, which was attributed to intravenous ciclosporin. In the first report,[6] a woman with a 2-year renal transplant underwent surgery during which **pancuronium** 5.5 mg was used as the neuromuscular blocker. She was also given intravenous ciclosporin before and after surgery. The surgery lasted for 4 hours and no additional doses of **pancuronium** were given. Residual paralysis was inadequately reversed with neostigmine and atropine, and so edrophonium was given before extubation. However, she had to be re-intubated 20 minutes later because of increased respiratory distress. In the second report,[7] a 15-year-old girl receiving intravenous ciclosporin with serum levels of 138 micrograms/L was anaesthetised using fentanyl, thiopental and **vecuronium** 100 micrograms/kg. Anaesthesia was maintained with nitrous oxide, oxygen and isoflurane. Attempts were later made to reverse the blockade with edrophonium, atropine and neostigmine but full neuromuscular function was not restored until 3 hours and 20 minutes after the **vecuronium** was given. Another report describes a prolongation of the effects of **vecuronium** in a renal-transplant recipient taking oral ciclosporin, azathioprine, and prednisolone.[8]

Mechanism

The reasons for the reduction in neuromuscular blockade with azathioprine and antilymphocyte immunoglobulins are not understood. It has been suggested that azathioprine may inhibit phosphodiesterase at the motor nerve terminal resulting in increased release of acetylcholine.[9]

The ciclosporin interaction may be partly due to the vehicle used in intravenous preparations. One idea is that *Cremophor*, a surfactant which has been used as a solvent for ciclosporin, may increase the effective concentration of pancuronium at the neuromuscular junction.[6] In *animal* studies both compounds have been observed to increase vecuronium blockade,[10] and *Cremophor* has also been seen to decrease the onset time of pancuronium blockade in patients given *Cremophor*-containing anaesthetics.[11] However, this is not the entire answer because the interaction has also been seen with oral ciclosporin, which does not contain *Cremophor*.[8]

Importance and management

Direct information seems to be limited to the reports cited, and the interactions are not established. Although retrospective data suggest that azathioprine and antilymphocyte immunoglobulins can cause a reduction in the effects of neuromuscular blockers, and in some cases the dosage may need to be increased two- to fourfold,[1] the only prospective study found that the interaction with azathioprine was not clinically significant.[2] The general importance of the ciclosporin interaction is also uncertain, but be aware that the effects of atracurium, pancuronium or vecuronium may be increased in any patient receiving ciclosporin. Not all patients appear to develop this interaction.[3] Any effects seem likely to be managed by routine dose titration of the neuromuscular blocker and standard post-operative monitoring.

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Neuromuscular blockers + Lithium

The concurrent use of neuromuscular blockers and lithium is normally safe and uneventful, but four patients taking lithium experienced prolonged blockade and respiratory difficulties after receiving standard doses of pancuronium and/or suxamethonium (succinylcholine).

Clinical evidence

A manic depressive woman taking lithium carbonate, with a lithium level of 1.2 mmol/L, underwent surgery and was given thiopental, **suxamethonium** (**succinylcholine**) 310 mg over a period of 2 hours, and **pancuronium** 500 micrograms. Prolonged neuromuscular blockade with apnoea occurred.[1]

Three other patients taking lithium experienced enhanced neuromuscular blockade when given **pancuronium**,[2] or **pancuronium** with **suxamethonium**.[3,4] The authors of one of these reports[4] also suggest that they have seen several other cases where of the neuromuscular blockade produced by **suxamethonium** was potentiated in patients taking lithium carbonate, but give no further details. In contrast, a retrospective analysis of data from 17 patients taking lithium carbonate who received **suxamethonium** during a total of 78 ECT treatments, did not reveal any instances of unusually prolonged recovery.[5] Interactions between lithium and pancuronium[1] or suxamethonium[6,7] have been demonstrated in *dogs,* and an interaction between lithium and **tubocurarine** has been demonstrated in *cats*,[8] but no clear interaction has been demonstrated with any other neuromuscular blocker.[7,9] A case of lithium toxicity has been described in a woman taking lithium who was given **suxamethonium**, but it is doubtful if it arose because of an interaction.[10]

Mechanism

Uncertain. One suggestion is that, when an interaction occurs, it may be due to changes in the electrolyte balance caused by the lithium, which results in changes in the release of acetylcholine at the neuromuscular junction.[8,11]

Importance and management

Information is limited. There are only four definite reports of this interaction in man, and good evidence that no adverse interaction normally occurs. The concurrent use of lithium and neuromuscular blockers need not be avoided, and, on the rare occurrence an interaction occurs, it seems likely that it will be managed by routine intra-operative and post-operative monitoring.

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Neuromuscular blockers + Magnesium compounds

The effects of cisatracurium, mivacurium, pancuronium, rocuronium, tubocurarine, vecuronium, and probably other competitive neuromuscular blockers can be increased and prolonged by magnesium sulfate given parenterally. There is some evidence that magnesium may interact similarly with suxamethonium (succinylcholine), but also evidence from well-controlled studies to suggest that it does not.

Clinical evidence

(a) Competitive (non-depolarising) neuromuscular blockers

A pregnant 40-year-old with severe pre-eclampsia and receiving magnesium sulfate by infusion, underwent emergency caesarean section during which she was initially anaesthetised with thiopental, maintained with nitrous oxide/oxygen and enflurane, and given firstly suxamethonium (succinylcholine) and later **vecuronium** as muscle relaxants. At the end of

surgery she rapidly recovered from the anaesthesia but the neuromuscular blockade was very prolonged (an eightfold increase in duration).[1] In a series of randomised studies involving 125 patients, pretreatment with intravenous magnesium sulfate 40 mg/kg reduced the dose requirement of **vecuronium** by 25%, approximately halved the time to the onset of action, and prolonged the duration of action from about 25 minutes to 43 minutes.[2] Another study found that pretreatment with magnesium sulfate 40 mg/kg decreased the onset and prolonged the recovery time from **vecuronium** blockade, but magnesium sulfate 20 mg/kg had no effect.[3] Evidence of enhanced **vecuronium** neuromuscular blockade by magnesium sulfate is described in one other study,[4] and case report.[5] A further study in 20 patients found that recurarisation (sufficient to compromise respiration) occurred when magnesium sulfate 60 mg/kg was given in the postoperative period, shortly after recovery from neuromuscular block with **vecuronium**.[6] In a randomised study, neostigmine-induced recovery from **vecuronium** block was attenuated by about 30% in patients pretreated with magnesium sulfate. The authors demonstrated this was due to slower spontaneous recovery and not decreased response to neostigmine.[7]

In two patients who underwent cardiac surgery, neuromuscular block with either **pancuronium**, or **pancuronium** and **rocuronium** was prolonged by more than 10 hours. This was attributed to the effects of high doses of neuromuscular blockers potentiated by magnesium sulfate 2.5 g. Moderate renal impairment may also have been a factor.[8] A fourfold increase in the duration of neuromuscular blockade of **rocuronium** 0.9 mg/kg was reported in a pregnant woman given magnesium sulfate.[9] A further randomised, placebo-controlled study confirmed that pretreatment with magnesium sulfate 60 mg/kg increased the duration of neuromuscular block produced by **rocuronium** (time to initial recovery increased from about 25 minutes to 42 minutes), but the onset time was not affected.[10]

A patient given **cisatracurium** 14 mg during induction of anaesthesia was then given intravenous magnesium sulfate 2 g over 5 minutes for atrial fibrillation, which had developed about 15 minutes after the end of surgery. Within a few minutes of receiving magnesium, recurarisation occurred (despite, the patient having been given 2 doses of neostigmine and glycopyrrolate postoperatively), and the patient required re-intubation and artificial ventilation for about 20 minutes.[11] A study in 20 patients undergoing elective cardiac surgery found that magnesium sulfate 70 mg/kg given before induction, followed by 30 mg/kg per hour prolonged the neuromuscular blockade induced with the first maintenance dose of **cisatracurium** by just over 30 minutes.[12]

The infusion rate of **mivacurium** required to obtain relaxation in women undergoing a caesarean section was about threefold lower in 12 women who had received magnesium sulfate for pre-eclampsia than in 12 women who had not.[13] In another study in 10 hypertensive patients undergoing caesarean section and given magnesium sulfate 30 or 60 mg/kg at induction, the action of **mivacurium** was prolonged when compared with normotensive controls or hypertensive controls not given magnesium.[14]

Prolonged neuromuscular block with **rapacuronium** has also been reported in a patient undergoing emergency caesarean section who received magnesium sulfate and clindamycin,[15] although the clindamycin was thought to be mainly responsible (see also 'Neuromuscular blockers + Miscellaneous anti-infectives', p.141).

Prolonged neuromuscular blockade has been described in three women with pre-eclampsia who were given magnesium sulfate and either **tubocurarine** alone or with suxamethonium (succinylcholine).[16,17] Increased blockade by magnesium has been demonstrated with **tubocurarine** in *animals*.[16,18]

(b) Suxamethonium (Succinylcholine)

An early study in 59 women undergoing caesarean section found that those given magnesium sulfate for eclampsia and pre-eclampsia needed less suxamethonium than control patients (4.73 compared with 7.39 mg/kg per hour).[19] Prolonged neuromuscular blockade has been described in three women with pre-eclampsia who were given magnesium sulfate and either tubocurarine alone or with suxamethonium.[16,17] A 71-year-old woman given magnesium sulfate and lidocaine for ventricular tachycardia underwent emergency cardioversion and had a delayed onset and prolonged neuromuscular blockade when she was given suxamethonium.[20] Increased blockade by magnesium has been seen with suxamethonium in *animals*.[16,18]

However, a randomised study involving 20 patients found that pretreatment with a single 60-mg/kg bolus dose of magnesium sulfate did not significantly affect the onset of neuromuscular blockade, or prolong the block produced by suxamethonium.[21] Similar results were found in a non-randomised study[4] and in a double-blind, randomised study.[22] In randomised studies, the use of magnesium sulfate has also been reported to reduce suxamethonium-associated fasciculations[22] and reduce the increase in serum potassium levels produced by suxamethonium.[21]

Mechanism

Magnesium sulfate has direct neuromuscular blocking activity by inhibiting the normal release of acetylcholine from nerve endings, reducing the sensitivity of the postsynaptic membrane and depressing the excitability of the muscle membranes. These effects are seen when serum magnesium levels rise above the normal range (hypermagnesaemia) and are possibly simply additive (or perhaps more than additive) with the effects of competitive neuromuscular blockers.

Importance and management

The interaction between competitive (non-depolarising) neuromuscular blockers and parenteral magnesium is established. Magnesium may decrease the time to onset of neuromuscular blockade, prolong the duration of action, and reduce the dose requirement of competitive neuromuscular blockers. Be alert for an increase in the effects of any competitive neuromuscular blocker if intravenous magnesium sulfate has been used, and anticipate the need to reduce the dose. Some have suggested that the decreased time to onset with vecuronium may be of use clinically to improve the intubating conditions for rapid sequence induction if suxamethonium is not suitable.[2] Intravenous calcium gluconate was used to assist recovery in one case of prolonged block.[16] Also be aware that recurarisation may occur when intravenous magnesium compounds are used in the postoperative period.[6,11] The authors of one report suggest that magnesium sulfate should be avoided for at least 30 minutes after reversal of residual neuromuscular block, to minimise the risk of recurarisation.[11] Hypermagnesaemia can occur in patients receiving magnesium in antacids, enemas or parenteral nutrition, especially if there is impaired renal function, but an interaction would not normally be expected, as oral magnesium compounds generally result in lower systemic levels than intravenous magnesium due to poor absorption.[23]

The interaction between magnesium and suxamethonium is not established. Although some *animal* and clinical evidence suggests potentiation of suxamethonium can occur, well-controlled studies have not confirmed this. Therefore some authors consider that magnesium sulfate does not significantly affect the clinical response to suxamethonium.[4,24]

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Neuromuscular blockers + MAOIs

The effects of suxamethonium (succinylcholine) were enhanced in three patients taking phenelzine.

Clinical evidence, mechanism, importance and management

Two patients, one taking **phenelzine** and the other who had ceased to do so 6 days previously, developed apnoea following ECT during which **suxamethonium** (**succinylcholine**) was used. Both responded to injections of nikethamide and positive pressure ventilation with oxygen.[1] A later study observed the same response in another patient taking **phenelzine**.[2] This would appear to be explained by the finding that **phenelzine** caused a reduction in the levels of plasma cholinesterase (pseudocholinesterase) in 4 out of 10 patients studied. Since the metabolism of **suxamethonium** depends on this enzyme, reduced levels of the enzyme would result in a reduced rate of **suxamethonium** metabolism and in a prolongation of its effects. None of 12 other patients taking **tranylcypromine**, **isocarboxazid** or **mebanazine** had reduced plasma cholinesterase levels.[2]

It would clearly be prudent to be on the alert for this interaction in patients taking **phenelzine**. **Phenelzine** may be anticipated to react similarly with **mivacurium** as it is also metabolised by plasma cholinesterase.[3]

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Neuromuscular blockers + Metoclopramide

The neuromuscular blocking effects of suxamethonium (succinylcholine) and mivacurium can be increased and prolonged in patients taking metoclopramide.

Clinical evidence

Metoclopramide 10 mg given intravenously 1 to 2 hours before induction of anaesthesia prolonged the time to 25% recovery after **suxamethonium** (**succinylcholine**) by 1.83 minutes (23%) in 19 patients, when compared with 21 control patients.[1,2] A larger 20-mg dose of metoclopramide prolonged the time to recovery by 56% in a further 10 patients.[1] In another study by the same research group, the recovery from neuromuscular blockade (time from 95% to 25% suppression of the activity of the adductor pollicis muscle) due to **suxamethonium** was prolonged by 67% in 11 patients who were given metoclopramide 10 mg intravenously during surgery, one minute before the **suxamethonium**.[3]

A randomised, placebo-controlled study in 30 patients found that intravenous metoclopramide 150 micrograms/kg given about 10 minutes before anaesthetic induction with **mivacurium** 150 micrograms/kg prolonged the duration of action of **mivacurium** by about 30%.[4] Another report found that infusion rates of **mivacurium** were reduced by up to about 80% in patients given metoclopramide 10 or 20 mg intravenously, 5 minutes before induction, and metoclopramide delayed complete recovery from neuromuscular block after **mivacurium** by 36% (10 mg dose) and 50% (20 mg dose).[5] Metoclopramide 20 mg delayed the recovery from **mivacurium** block by 78% in another study.[6]

Mechanism

It has been suggested that metoclopramide may reduce the activity of plasma cholinesterase, which is responsible for the metabolism of suxamethonium and mivacurium. One *in vitro* study found that a metoclopramide level of 800 nanograms/mL inhibited plasma cholinesterase activity by 50%. However, a 10-mg dose of metoclopramide in adult patients weighing 50 to 70 kg produces peak plasma levels five times less than this (140 nanograms/mL).[7] Further, in an *in vivo* study, metoclopramide had only minimal inhibitory effects on plasma cholinesterase, and there was no difference in plasma cholinesterase levels in patients who had received metoclopramide and those who had not.[4]

Importance and management

The interaction between metoclopramide and suxamethonium is an established but not extensively documented interaction of only moderate or minor clinical importance. However, some enhancement of blockade can occur. The authors of the suxamethonium reports also point out that plasma cholinesterase activity is reduced in pregnancy and so suxamethonium sensitivity is more likely in obstetric patients.

The interaction between metoclopramide and mivacurium has only more recently been demonstrated. Metoclopramide appears to allow a reduction in the infusion rate of mivacurium and it causes a significant delay in recovery from neuromuscular block. Care is recommended during combined use.[5]

Ester-type local anaesthetics also depend on plasma cholinesterase activity for metabolism[1,7] and their effects would therefore be expected to be additive with the effects of metoclopramide, see 'Neuromuscular blockers + Anaesthetics, local', p.127.

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Neuromuscular blockers + Miscellaneous anti-infectives

Colistin, colistimethate sodium, polymyxin B, clindamycin, lincomycin, some penicillins (apalcillin, azlocillin, mezlocillin, piperacillin) and vancomycin possess some neuromuscular blocking activity. Increased and prolonged neuromuscular blockade is possible if these antibacterials are used with neuromuscular blocking drugs. In theory amphotericin B might also interact. No clinically significant interaction has been seen with cefoxitin, cefuroxime, or metronidazole.

Clinical evidence

(a) Amphotericin B

Amphotericin B can induce hypokalaemia resulting in muscle weakness,[1] which might be expected to enhance the effects of neuromuscular blockers, but there appear to be no reports in the literature confirming that a clinically significant interaction actually occurs.

(b) Cephalosporins

In a controlled study, intravenous **cefuroxime**, given shortly before **pipecuronium**[2] or **rocuronium**[3] did not alter the neuromuscular-blocking effects of these drugs. Similarly, intravenous **cefoxitin** given before, during and after surgery was not associated with a clinically important prolongation of **vecuronium** blockade.[4]

(c) Clindamycin and Lincomycin

Enhanced blockade has been seen in patients given **pancuronium** and lincomycin, which was reversed by neostigmine.[5] Respiratory paralysis was seen 10 minutes after lincomycin 600 mg was given intramuscularly to a man recovering from neuromuscular blockade with **tubocurarine**[6] and this interaction was confirmed in another report.[7] Other case reports[8-10] and clinical studies[11] describe minor to marked increases in neuromuscular blockade in patients receiving **pancuronium**,[9] **pipecuronium**,[11] **rapacuronium**[10] or **suxamethonium** (**succinylcholine**)[8] when they were given clindamycin. One patient developed very prolonged blockade after being unintentionally given clindamycin 2.4 g instead of 600 mg shortly after recovery from **suxamethonium** and **tubocurarine**.[12] Prolongation

of the neuromuscular blocking effects of **vecuronium** has also been reported in a patient who received both clindamycin and gentamicin.[13]

(d) Metronidazole

An increase in the neuromuscular blocking effects of **vecuronium** with metronidazole has been reported in *cats*;[14] however, a later study in patients found no evidence of an interaction,[15] and another study with **rocuronium** also found no evidence of an interaction with metronidazole.[3] Similarly, no interaction was seen with **rocuronium** and metronidazole/cefuroxime,[3] and another study found no significant interaction between **pipecuronium** and metronidazole.[2]

(e) Penicillins

A study in patients found that the neuromuscular blocking effects of **vecuronium** were prolonged by a number of penicillins: **apalcillin** 26%, **azlocillin** 55%, **mezlocillin** 38%, and **piperacillin** 46%.[16] Reinstitution of neuromuscular blockade and respiratory failure occurred in a postoperative patient given **piperacillin** 3 g by intravenous infusion following the reversal of **vecuronium** blockade.[17] However, a randomised, study in 30 patients found that **piperacillin** or cefoxitin, given by intravenous infusion, pre- and intraoperatively, were not associated with clinically important prolongation of the neuromuscular block induced by **vecuronium**. Of 27 patients who could be evaluated, 22 showed a modest overall decrease in recovery time and 2 patients given **piperacillin** exhibited a slight prolongation in recovery time, but these patients all responded readily to neostigmine or other anticholinesterases and subsequent recurarisation did not occur.[4]

(f) Polymyxins

A literature review of interactions between antibacterials and neuromuscular blockers identified 17 cases over the period 1956 to 1970 in which **colistin** (**polymyxin E**) or **colistimethate sodium**, with or without conventional neuromuscular blockers, were responsible for the development of increased blockade and respiratory muscle paralysis. Some of the patients had renal disease.[18] A later report describes prolonged respiratory depression in a patient receiving **pancuronium** and **colistin**. Calcium gluconate was found to reverse the blockade.[19] A placebo-controlled study found that one million units of **colistin** considerably prolonged the recovery time from **pipecuronium** blockade.[11] Six cases of enhanced neuromuscular blockade involving **polymyxin B** have also been reported.[18] An increase in the blockade due to **pancuronium** by **polymyxin B** and bacitracin wound irrigation is described in another report; pyridostigmine, neostigmine and edrophonium were ineffective antagonists of this block and only partial improvement occurred after calcium chloride was given.[20] Prolonged and fatal apnoea occurred in another patient given **suxamethonium** when his peritoneal cavity was instilled with a solution containing 100 mg of **polymyxin B** and 100 000 units of bacitracin.[21]

(g) Vancomycin

A man recovering from neuromuscular blockade with **suxamethonium** (with some evidence of residual Phase II block) developed almost total muscle paralysis and apnoea when given an intravenous infusion of vancomycin. He recovered spontaneously when the vancomycin was stopped, but it took several hours.[22] The neuromuscular blockade due to **vecuronium** was increased in a patient who was given an infusion of vancomycin (1 g in 250 mL of sodium chloride 0.9% over 35 minutes).[23] Transient apnoea and apparent cardiac arrest have also been described in a patient following a 1-g intravenous injection of vancomycin given over 2 minutes.[24] However, in both of these cases[23,24] the vancomycin was given more rapidly than the current recommendations. It is now known that rapid infusion of vancomycin can provoke histamine release, which can result in apnoea, hypotension, anaphylaxis and muscular spasm, effects similar to those seen in these two patients.

Mechanism

Not fully understood but several sites of action at the neuromuscular junction (pre and/or post, effects on ion-channels or receptors) have been suggested.

The neuromuscular blocking properties of the polymyxins (polymyxin B, colistin, colistimethate sodium) involve a number of mechanisms, which may explain the difficulty in reversing the blockade.[25]

Importance and management

The interactions involving polymyxin B, colistin, colistimethate sodium, lincomycin, and clindamycin are established and clinically important. The incidence is uncertain. Concurrent use need not be avoided, but be alert for increased and prolonged neuromuscular blockade. The recovery period should be well monitored because of the risk of recurarisation. There seem to be no reports of an interaction with amphotericin B, but it may be prudent to be aware of a potential for interaction during the recovery period.

No interaction would be expected with cefuroxime, cefoxitin, or metronidazole, but some caution would seem appropriate with azlocillin, mezlocillin and piperacillin.

The situation with vancomycin is less clear. The evidence does suggest a link between vancomycin and increased neuromuscular blockade following the use of suxamethonium, and possibly vecuronium. However, vancomycin is given routinely as antibacterial prophylaxis before surgical procedures. The sparsity of reports therefore suggests that, in practice, vancomycin rarely causes a clinically significant interaction with neuromuscular blockers.

Consider also 'Neuromuscular blockers + Aminoglycosides', p.127.

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Neuromuscular blockers + Neuromuscular blockers

Combinations of competitive neuromuscular blockers may have additive or synergistic effects. However, the sequence of administration may also affect the interaction. The previous use of a small dose of a competitive neuromuscular blocker (e.g. vecuronium) generally reduces the effects of suxamethonium (succinylcholine), but if suxamethonium is given during recovery from a competitive neuromuscular blocker, antagonism, enhancement or a combination of the two may occur. The effects of a competitive blocker may be increased if it is given after suxamethonium.

Clinical evidence, mechanism, importance and management

Neuromuscular blockers are of two types: competitive (non-depolarising) and depolarising. The competitive or non-depolarising blockers (**atracurium** and others listed in 'Table 5.2', (p.101)) compete with acetylcholine for the receptors on the endplate of the neuromuscular junction. Thus the receptors fail to be stimulated and muscular paralysis results. **Suxamethonium** (**succinylcholine**), a depolarising neuromuscular blocker, also occupies the receptors on the endplate but it acts like acetylcholine to cause depolarisation. However, unlike acetylcholine, it is not immediately removed by cholinesterase so that the depolarisation persists and the muscle remains paralysed.

(a) Combinations of competitive (non-depolarising) neuromuscular blockers

Combinations of competitive (non-depolarising) neuromuscular blockers may have additive or synergistic effects. Structural differences between the interacting neuromuscular blockers may have an effect; it has been suggested that structurally similar neuromuscular blockers tend to produce an additive response, whereas structurally different blockers may be synergistic.[1,2] For a list of competitive neuromuscular blockers by structural type, see 'Table 5.2', (p.101).

Additive effects have been found with the following structurally similar combinations:

- **atracurium** and **cisatracurium**[3] or **mivacurium**,[4]
- **pancuronium** and **vecuronium**,[5]
- **pipecuronium** and **vecuronium**,[6]
- **tubocurarine** and **metocurine**.[1]

Synergism has been reported with the following structurally similar combinations:

- **cisatracurium** and **mivacurium**,[3]
- **tubocurarine** and **atracurium**.[7]

Potentiation of neuromuscular blockade or synergy has been reported with the following structurally different combinations:

- **atracurium** and **vecuronium**,[8]
- **cisatracurium** and **rocuronium**,[3,9,10] or **vecuronium**,[3]
- **metocurine** and **pancuronium**,[1]
- **mivacurium** and **pancuronium**[2,11] or **rocuronium**,[12]
- **tubocurarine** and **pancuronium**[1] or **vecuronium**.[7]

In addition to affecting response, the initial blocker may modify the duration of action of the supplemental blocker.[13,14] The blocking action of **pancuronium** was shortened when it was given during **vecuronium**-induced partial neuromuscular blockade.[14] Conversely, the duration of action of **mivacurium**[2,15] or **vecuronium**[14] was lengthened when they were given after **pancuronium**-induced neuromuscular block. Therefore, care should be taken if a small dose of a short-acting blocker is given near the end of an operation in which a longer-acting blocker has already been given.

(b) Competitive neuromuscular blocker given first

The combination of a competitive neuromuscular blocker and **suxamethonium** (**succinylcholine**) has an intrinsic antagonistic effect. This interaction has been used clinically to reduce muscle fasciculations caused by **suxamethonium**. A small dose of competitive neuromuscular blocker given shortly before **suxamethonium** generally reduces its effects and duration of action.[16] **Suxamethonium** would be expected to antagonise competitive neuromuscular blockers due to their opposite mechanisms of action (**suxamethonium** exerts a receptor agonist-type activity whereas competitive blockers exhibit receptor antagonism). However, **suxamethonium** may also reverse a competitive block by enhancing the effect of acetylcholine postsynaptically.[17,18]

The neuromuscular blockade will also be affected by the competitive neuromuscular blocker used and whether or not an anticholinesterase has been given.[19,20] See also, 'Neuromuscular blockers + Anticholinesterases', p.128.

1. Atracurium. If suxamethonium is given during the recovery from a paralysing dose of atracurium, the resultant neuromuscular block is influenced by the depth of residual block and the dose of suxamethonium used.[19,20] In a study in 38 patients recovering from atracurium 400 micrograms/kg, lower intravenous doses of suxamethonium 0.25 to 1 mg/kg mainly antagonised the partial block, whereas higher doses (1.5 to 3 mg/kg) usually enhanced the blockade.[19] However, the degree of recovery from the underlying block also influences the effects of suxamethonium: early on when the residual block is still considerable, suxamethonium may appear to have no effect or produce a partial antagonism of the block, but later, a biphasic response may be seen (antagonism of the competitive block initially before superimposing a depolarising block); a combination of antagonism and enhancement may also occur in different muscle groups.[20]

2. Pancuronium. Following pancuronium pretreatment, the duration of suxamethonium blockade appears to be prolonged,[16] and this is probably due to the inhibition of cholinesterase by pancuronium.[21]

(c) Suxamethonium (Succinylcholine) given first

In general, when a competitive blocker is given following suxamethonium, the onset time may be reduced and the potency or duration of the block may be increased, although not always significantly. In a study in 350 patients, the previous use of suxamethonium 1 mg/kg significantly accelerated the onset of neuromuscular blockade with **atracurium**, **pancuronium**, **pipecuronium** and **vecuronium**, when these were given after full recovery from the suxamethonium block. However, the duration of blockade was only significantly prolonged with **vecuronium**.[22]

It has been suggested that suxamethonium may have a presynaptic action resulting in reduced acetylcholine output.[17] Although not always clinically significant, be aware that a reduction in the dose of competitive blocker may be necessary following the use of a depolarising neuromuscular blocker.

1. Atracurium. A study showed that the effect of the previous use of suxamethonium on atracurium neuromuscular block appears to depend on the level of recovery from suxamethonium. As with previous studies, the onset of atracurium blockade was shortened when given after full recovery from the suxamethonium. However, this effect was less apparent when the atracurium was given before full suxamethonium recovery.[23]

2. Cisatracurium. Pretreatment with suxamethonium reduced the time to onset of cisatracurium block, but did not potentiate it or prolong recovery.[24]

3. Pancuronium or Vecuronium. One study found potentiation of vecuronium when it was given up to 30 minutes after full recovery from a single 1-mg/kg intravenous dose of suxamethonium.[25] Another study found that the effects of vecuronium or pancuronium were potentiated for at least 2 hours after full recovery from an intubating dose of suxamethonium.[26]

4. Rocuronium. Pretreatment with suxamethonium decreased the onset time and increased the duration of action or rocuronium.[27]

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Neuromuscular blockers + Ondansetron

Ondansetron does not affect atracurium-induced neuromuscular blockade.

Clinical evidence, mechanism, importance and management

A double-blind, placebo-controlled study in 30 patients undergoing elective surgery found that intravenous ondansetron 8 or 16 mg given over 5 minutes had no effect on subsequent neuromuscular blockade with **atracurium**.[1] No special precautions would therefore seem necessary. The authors suggest that no interaction is likely with other non-depolarising neuromuscular blockers, but this needs confirmation.

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Neuromuscular blockers + Opioids

A woman experienced hypertension and tachycardia when she was given pancuronium after induction of anaesthesia with morphine and nitrous oxide/oxygen. Bradycardia has been reported when vecuronium was given with alfentanil, fentanyl, or sufentanil, sometimes in patients taking beta blockers and/or calcium-channel blockers.

Clinical evidence, mechanism, importance and management

(a) Pancuronium

A woman about to receive a coronary by-pass graft was premedicated with **morphine** 10 mg and hyoscine 400 micrograms, intramuscularly, one hour before the induction of anaesthesia. **Morphine** 1 mg/kg was then slowly infused while the patient was ventilated with 50% nitrous oxide/oxygen. With the onset of neuromuscular relaxation with pancuronium 150 micrograms/kg, her blood pressure rose sharply from 120/60 mmHg to 200/110 mmHg and her pulse rate increased from 54 bpm to 96 bpm, persisting for several minutes but restabilising when halothane 1% was added.[1] The suggested reason for this reaction is that pancuronium can antagonise the vagal tone (heart slowing) induced by the **morphine**, thus allowing the blood pressure and heart rate to rise. The authors of the report point out the undesirability of this in those with coronary heart disease.

(b) Vecuronium

Two patients, one aged 72 years and the other aged 84 years, undergoing elective carotid endarterectomy developed extreme bradycardia following induction with **alfentanil** and vecuronium; both were premedicated with **morphine**. The first was taking **propranolol** 20 mg every 8 hours and, as the drugs were injected, his heart rate fell from 50 bpm to 35 bpm and his blood pressure fell from 160/70 mmHg to 75/35 mmHg. He responded to atropine, ephedrine and phenylephrine. The other patient was taking nifedipine and quinidine. His heart rate fell from 89 bpm to 43 bpm, and his blood pressure dropped from 210/80 mmHg to 120/45 mmHg. Both heart rate and blood pressures recovered following skin incision.[2]

Bradycardia in the presence of vecuronium has been seen during anaesthetic induction with other drugs including **fentanyl**,[3,4] and **sufentanil** (in 3 patients taking beta blockers with or without diltiazem).[5] The lack of vagolytic effects associated with vecuronium may mean that opioid-induced bradycardia is unopposed.[4,5] The beta blockers and diltiazem may also have played a part in the bradycardia seen in some of these patients[5] (see also 'Neuromuscular blockers + Beta blockers', p.132, and 'Neuromuscular blockers + Calcium-channel blockers', p.132). Be alert for this effect if vecuronium is given with any of these drugs. Atropine 500 micrograms given intravenously at the time of induction may prevent the bradycardia.[4]

For reports of bradycardia occurring with atracurium or suxamethonium used with propofol and fentanyl, see 'Anaesthetics, general + Neuromuscular blockers', p.113.

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Neuromuscular blockers + Organophosphorus compounds

Exposure to organophosphorus insecticides such as malathion and dimpylate (diazinon) can markedly prolong the neuromuscular blocking effects of suxamethonium (succinylcholine).

Clinical evidence

A man admitted to hospital for an appendectomy became apnoeic during the early part of the operation when given **suxamethonium** (**succinylcholine**) 100 mg to facilitate tracheal intubation. He remained apnoeic throughout the 40 minutes of surgery. Restoration of neuromuscular activity occurred about 180 minutes after he had received the **suxamethonium**. Later studies showed that he had an extremely low plasma cholinesterase activity (3 to 10%), even though he had a normal phenotype for this enzyme. It subsequently turned out that he had been working with **malathion** for 11 weeks without any protection.[1]

Another report describes a man whose recovery from neuromuscular blockade with **suxamethonium** was very prolonged. He had attempted suicide approximately 2 weeks earlier with **dimpylate** (**diazinon**), a household insecticide. His pseudocholinesterase was found to be 2.5 units/L (normal values 7 to 19 units/L) and his dibucaine number (a measurement of cholinesterase activity) was too low to be measured.[2]

Other cases of prolonged **suxamethonium**-induced paralysis associated with organophosphate poisoning have been reported.[3-7] These cases have involved accidental ingestion of **chlorpyrifos**[3] or **dichlorvos**[7] in children, and one case resulted from subclinical exposure to **chlorpyrifos** and **propetamphos** following the treatment of carpets for pests.[4] Also, prolonged **suxamethonium**-induced paralysis has occurred following suicide attempts in adults with **chlorpyrifos**[6] or *Diazinon* [**dimpylate**].[5] In one report a patient was given ECT 2 weeks after attempted suicide with **chlorpyrifos** and, despite low plasma cholinesterase levels, paralysis with **suxamethonium** was carried out successfully using one-fifth of the normal dose.[6]

Mechanism

Malathion, dimpylate, and other organophosphorus insecticides inhibit the activity of plasma cholinesterase, thereby reducing the metabolism of the suxamethonium and prolonging its effects.

Importance and management

An established and well understood interaction. The organophosphorus pesticides are potent anticholinesterases used in agriculture and horticulture to control insects on crops, and in veterinary practice to control various ectoparasites. They are applied as sprays and dips. Anyone who is exposed to these toxic pesticides may therefore show changes in their responses to neuromuscular blockers. Widely used organophosphorus pesticides are said to include **azamethiphos**, **bromophos**, **chlorpyrifos**, **clofenvinfos**, **coumafos**, **cythioate**, **dichlorvos**, **dimethoate**, **dimpylate**, **dioxation**, **ethion**, **famphur**, **fenitrothion**, **fenthion**, **heptenophos**, **iodofenphos**, **malathion**, **naled**, **parathion**, **phosmet**, **phoxim**, **pirimiphos-methyl**, **propetamphos**, **pyraclofos**, **temefos**.[8] A number of the

nerve gases (such as **sarin**, **soman**, **tabun** and **VX**) are also potent anticholinesterases.

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Neuromuscular blockers + Phenytoin

The effects of many competitive neuromuscular blockers are reduced and shortened if phenytoin is given for longer than one week, but they appear to be increased if phenytoin is given acutely (e.g. during surgery). Phenytoin appears not to interact with mivacurium.

Clinical evidence

(a) Phenytoin given long-term

1. Atracurium. A reduced recovery time from atracurium-induced neuromuscular blockade was found in one study in patients taking long-term antiepileptics including phenytoin.[1] In contrast, other studies suggest that atracurium is normally minimally affected by phenytoin.[2-4]

2. Cisatracurium. A study found that the recovery time from intravenous cisatracurium was shorter in patients taking 'carbamazepine', (p.133), or phenytoin than in patients not receiving carbamazepine or phenytoin; the recovery index (times between 25% and 75% recovery) was 16.2 minutes and 21.2 minutes, respectively. Clearance of cisatracurium was increased by about 25% in patients taking carbamazepine or phenytoin. Furthermore, the steady-state plasma level of cisatracurium required to maintain 95% block was increased by 20%, indicating increased resistance to the action of cisatracurium.[5]

3. Mivacurium. A study in 32 patients who had been taking carbamazepine alone or with phenytoin or valproic acid for greater than 2 weeks found no resistance to mivacurium,[6] although an earlier preliminary study by the same research group found a trend towards a shorter recovery from mivacurium in 13 patients taking unspecified antiepileptics (not statistically significant).[7]

4. Pancuronium. In the preliminary report of a study, the reduction in the time to recover from 25 to 75% of the response to ulnar nerve stimulation, in patients who had received phenytoin for longer than one week was 40% for pancuronium.[4] In another study about 80% more pancuronium was needed in 9 patients taking long-term phenytoin (58 micrograms/kg per hour) than in 18 others not receiving phenytoin (32 micrograms/kg per hour).[8] Resistance to pancuronium and a shortening of the recovery period due to long-term phenytoin[9,10] or unspecified antiepileptics[11] has also been described in other reports.

5. Pipecuronium. Some reports suggest that the recovery period from pipecuronium is reduced by phenytoin.[12,13] In one study it was found that the *onset* time for pipecuronium blockade was lengthened (although this was not statistically significant) for patients with therapeutic plasma concentrations of phenytoin or carbamazepine, but not in those with subtherapeutic levels. However, a shorter duration of action occurred regardless of the level of the antiepileptic drug.[13]

6. Suxamethonium (Succinylcholine). Eight patients who had been taking phenytoin and/or carbamazepine for at least one month took longer to recover from suxamethonium blockade, compared with 9 control patients; the time for return to baseline twitch height was 14.3 minutes and 10 minutes, respectively.[14]

7. Miscellaneous neuromuscular blockers. In the preliminary report of a study, the reduction in the time to recover from 25 to 75% of the response to ulnar nerve stimulation, in patients who had received phenytoin for longer than one week was 58% for **metocurine**. Some reduction in response was seen with **tubocurarine** but this was not statistically significant.[4] The **metocurine** results are published in full elsewhere.[15] The recovery period from **doxacurium**,[9,16] **rapacuronium** (case report),[17] **rocuronium**[18,19] and **vecuronium**[2,20-23] is also reduced by phenytoin.

(b) Phenytoin given short-term

A retrospective review of 8 patients taking long-term phenytoin (greater than 2 weeks) and 3 others given phenytoin within 8 hours of surgery found that the average doses of **vecuronium** used from induction to extubation were 155 micrograms/kg per hour (long-term use) and 61.5 micrograms/kg per hour (acute use).[24] Others have reported similar results.[21] Short-term phenytoin use may have been a contributing factor in the prolonged clearance of **vecuronium** in another patient.[25,26] Another study found that the sensitivity of patients to **vecuronium** was increased by phenytoin given intravenously during surgery,[27] and this has also been seen in *animal* studies using **tubocurarine** and phenytoin.[28] Similarly, a study of 20 patients undergoing craniotomy found that phenytoin (10 mg/kg over about 30 minutes) given during the operation augmented the neuromuscular block produced by **rocuronium**.[29]

Mechanism

Not fully understood, but it appears to be multifactorial. The acute use of phenytoin may result in neuromuscular block and potentiation of the action of competitive (non-depolarising) blockers.

The long-term use of phenytoin may produce subclinical neuromuscular blockade thought to be due to modest blockade of acetylcholine effects and a decrease in acetylcholine release; this antagonism may induce changes at the neuromuscular junction including increased number of acetylcholine receptors on the muscle membrane (up-regulation), with decreased sensitivity.[14,20,30] Other suggestions to account for the reduced response with chronic antiepileptics include: induction of liver enzyme activity (phenytoin is a potent inducer of cytochrome P450 isoenzymes), which would increase the metabolism and clearance of the neuromuscular blocker; and changes in plasma protein binding.[14,20,30] It has been shown that phenytoin possibly increases the plasma clearance of pancuronium[10] and rocuronium.[18]

Importance and management

Established and clinically important interactions. Anticipate the need to use more (possibly up to twice as much) doxacurium, metocurine, pancuronium, pipecuronium, rocuronium and vecuronium in patients who have taken phenytoin for more than a week,[21] and expect an accelerated recovery. The effects on tubocurarine and atracurium appear only to be small or moderate, whereas mivacurium appears not to interact.

In patients are given phenytoin acutely, anticipate the need to use a smaller neuromuscular blocker dosage, or prepare for a longer recovery time.

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Neuromuscular blockers + Quinidine

The effects of both depolarising neuromuscular blockers (e.g. suxamethonium (succinylcholine)) and competitive neuromuscular blockers (e.g. tubocurarine) can be increased by quinidine. Recurarisation and apnoea have been seen in patients when quinidine was given during the recovery period from neuromuscular blockade.

Clinical evidence

A patient given **metocurine** during surgery regained her motor functions and was able to talk coherently during the recovery period. However, within 15 minutes of being given quinidine sulfate 200 mg by injection she developed muscular weakness and respiratory depression. She needed intubation and assisted respiration for a period of two and a half hours. Edrophonium and neostigmine were used to aid recovery.[1]

This interaction has also been described in case reports involving **tubocurarine**[2] and **suxamethonium** (**succinylcholine**),[3,4] and has been confirmed in *animal* studies.[5-7]

Mechanism

Not fully understood, but it has been shown that quinidine can inhibit the enzyme (choline acetyltransferase), which is concerned with the synthesis of acetylcholine at nerve endings.[8] Neuromuscular transmission would be expected to be reduced if the synthesis of acetylcholine is reduced. Quinidine also inhibits the activity of plasma cholinesterase, which is concerned with the metabolism of suxamethonium.[4]

Importance and management

The interaction between quinidine and neuromuscular blockers is an established interaction of clinical importance, but the documentation is limited. The incidence is uncertain, but it was seen in one report cited to a greater or lesser extent in 5 of the 6 patients studied.[3] It has only been reported clinically with metocurine, tubocurarine and suxamethonium, but it occurs in *animals* with **gallamine**, and it seems possible that it could occur clinically with any depolarising or non-depolarising neuromuscular blocker. Be alert for increased neuromuscular blocking effects, particularly after surgery.

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Neuromuscular blockers + Testosterone

An isolated report describes marked resistance to the effects of suxamethonium (succinylcholine) and vecuronium, apparently due to the long-term use of testosterone. Another case reports resistance to vecuronium in a patient with elevated plasma testosterone levels.

Clinical evidence, mechanism, importance and management

A transsexual who had been receiving testosterone enantate 200 mg intramuscularly twice monthly for 10 years was resistant to intravenous **suxamethonium** (**succinylcholine**) 100 mg and needed intravenous **vecuronium** 100 micrograms/kg for effective tracheal intubation before surgery. During the surgery it was found necessary to use a total of 22 mg of **vecuronium** over a 50-minute period to achieve acceptable relaxation of the abdominal muscles for a hysterectomy and salpingo-oophorectomy to be carried out.[1] Considerably higher than usual doses of **vecuronium** were required in a patient with testicular feminisation and elevated plasma testosterone levels.[2]

The reasons are not understood. However, it has been suggested that the close structural similarity between testosterone and **vecuronium**, with respect to their common steroidal core, might mean that they share similar metabolic pathways (see also 'Neuromuscular blockers + Corticosteroids', p.134). Chronic elevation of circulating testosterone may up-regulate the hepatic metabolism of steroidal molecules in general, and so enhance the hepatic elimination of **vecuronium**.[2]

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Neuromuscular blockers + Theophylline

Supraventricular tachycardia occurred in a patient taking aminophylline when pancuronium was given. Isolated cases suggest that the effects of pancuronium, but not vecuronium, can be opposed by aminophylline. Theophylline would be expected to interact similarly.

Clinical evidence, mechanism, importance and management

A report describes supraventricular tachycardia in a patient taking aminophylline who was anaesthetised with thiopental and fentanyl, and then given **pancuronium**. Three minutes later his heart rate rose to 180 bpm and an ECG revealed supraventricular tachycardia.[1] The authors of this report attributed this reaction to an interaction between the **pancuronium** and the aminophylline, because previous surgery with these drugs in the absence of aminophylline had been without incident.[1] Marked resistance to the effects of **pancuronium** (but not **vecuronium**) was seen in one patient receiving an aminophylline infusion.[2] Two other patients are reported to have shown a similar resistance to **pancuronium** but they had also been given hydrocortisone, which could have had a similar effect[3,4] (see also 'Neuromuscular blockers + Corticosteroids', p.134). These appear to be the only clinical reports of such an interaction and their general relevance

is unclear. Note that, any interaction would also be expected to apply to theophylline, although this needs confirmation.

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Neuromuscular blockers + Tobacco

There is some evidence that smokers may need more vecuronium and possibly more rocuronium, but less atracurium to achieve the same effects as non-smokers. However, results are variable and another study found that rocuronium appeared to be unaffected by smoking. Passive-smoking children appear to require less rocuronium than those not exposed to environmental tobacco smoke.

Clinical evidence, mechanism, importance and management

Variable results have been reported on the effect of smoking on neuromuscular blockers. The amount of **atracurium** required was about 25% lower in smokers, when compared with non-smokers.[1] However, in another study, smokers required more **vecuronium** than non-smokers (96.8 micrograms/kg per hour compared with 72.11 micrograms/kg per hour, respectively; a 34% increase).[2] Similarly another study in patients undergoing minor surgery found that the 20 smokers required about 20% more **rocuronium** than the 20 non-smokers.[3] However, this study has been criticised for having too few patients, which meant that it was unable to properly detect a statistically significant difference between the smokers and non-smokers.[4] In yet another study, the onset and recovery times from the neuromuscular blocking effects of **rocuronium** 600 micrograms/kg were reported to be not significantly affected by smoking more than 10 cigarettes daily.[5] In another study in children aged 4 to 10 years, those with a history of passive smoking required less **rocuronium** during similar anaesthesia than those without a familial smoking history.[6]

Tobacco smoke contains many different compounds and has enzyme-inducing properties, which may affect the dose requirements of neuromuscular blockers. In addition, the time interval in refraining from smoking will affect plasma **nicotine** concentrations; small doses of nicotine may stimulate the neuromuscular junction, but larger doses may block transmission.[2]

Although an interaction is established it seems unlikely to be generally important, as the dose of neuromuscular blocker is individualised and titrated to effect.

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Neuromuscular blockers + Trimetaphan

Trimetaphan can increase the effects of suxamethonium (succinylcholine), which may result in prolonged apnoea. This may possibly occur with other neuromuscular blocking drugs, such as alcuronium.

Clinical evidence

A man undergoing neurosurgery was given **tubocurarine** and **suxamethonium** (**succinylcholine**). Neuromuscular blockade was prolonged postoperatively, lasting about 2.5 hours, and this was attributed to the concurrent use of trimetaphan 4.5 g, given over a 90-minute period. Later, when he underwent further surgery using essentially the same anaesthetic techniques and drugs, but with a very much smaller dose of trimetaphan (35 mg over a 10-minute period), the recovery was normal.[1]

Nine out of 10 patients receiving ECT and given **suxamethonium** had an almost 90% prolongation in apnoea (from 142 seconds to 265 seconds) when trimetaphan 10 to 20 mg was used instead of 1.2 mg of atropine.[2] Prolonged apnoea has been seen in another patient given **suxamethonium** and trimetaphan.[3] On the basis of an *in vitro* study it was calculated that a typical dose of trimetaphan would double the duration of paralysis due to **suxamethonium**.[4] Prolonged neuromuscular blockade was also seen in a man given **alcuronium** and trimetaphan.[5]

Mechanism

Not fully understood. Trimetaphan can inhibit plasma cholinesterase to some extent,[2,5] which would reduce the metabolism of suxamethonium and thereby prolong its activity. Studies in *rats*[6,7] and case reports[8] also indicate that trimetaphan has direct neuromuscular blocking activity. Its effects are at least additive with the neuromuscular blocking effects of the **aminoglycosides**.[7]

Importance and management

Information is limited but the interaction appears to be established. If trimetaphan and suxamethonium (succinylcholine) are used concurrently, be alert for enhanced and prolonged neuromuscular blockade. This has also been seen with alcuronium, and trimetaphan may interact with other competitive neuromuscular blockers.[5] Respiratory arrest has been seen when large doses of trimetaphan were given in the absence of a neuromuscular blocker, so that caution is certainly needed.[8] *Animal* studies suggested that the blockade might not be reversed by neostigmine or calcium chloride,[7] but neostigmine and calcium gluconate were successfully used to reverse the effects of alcuronium and trimetaphan in one case.[5]

1. Wilson SL, Miller RN, Wright C, Hasse D. Prolonged neuromuscular blockade associated with trimethaphan: a case report. *Anesth Analg* (1976) 55, 353–6.
2. Tewfik GI. Trimetaphan. Its effect on the pseudo-cholinesterase level of man. *Anaesthesia* (1957) 12, 326–9.
3. Poulton TJ, James FM, Lockridge O. Prolonged apnea following trimethaphan and succinylcholine. *Anesthesiology* (1979) 50, 54–6.
4. Sklar GS, Lanks KW. Effects of trimethaphan and sodium nitroprusside on hydrolysis of succinylcholine *in vitro*. *Anesthesiology* (1977) 47, 31–3.
5. Nakamura K, Koide M, Imanaga T, Ogasawara H, Takahashi M, Yoshikawa M. Prolonged neuromuscular blockade following trimetaphan infusion. *Anaesthesia* (1980) 35, 1202–7.
6. Pearcy WC, Wittenstein ES. The interactions of trimetaphan (Arfonad), suxamethonium and cholinesterase inhibitor in the rat. *Br J Anaesth* (1960) 32, 156–9.
7. Paradelis AG, Crassaris LG, Karachalios DN, Triantaphyllidis CJ. Aminoglycoside antibiotics: interaction with trimethaphan at the neuromuscular junctions. *Drugs Exp Clin Res* (1987) 13, 233–6.
8. Dale RC, Schroeder ET. Respiratory paralysis during treatment of hypertension with trimethaphan camsylate. *Arch Intern Med* (1976) 136, 816–18.

Neuromuscular blockers + Ulinastatin

Ulinastatin delays the onset and hastens the recovery from vecuronium neuromuscular block.

Clinical evidence, mechanism, importance and management

A randomised, placebo-controlled study in 60 patients found that a 5000 unit/kg intravenous bolus dose of ulinastatin given before induction of anaesthesia, and again 2 minutes before intravenous **vecuronium** 100 micrograms/kg, delayed the onset of neuromuscular blockade, when compared with placebo (250 seconds compared with 214 seconds). The recovery from neuromuscular block (measured as return of post-tetanic count) was significantly shorter after ulinastatin than placebo (11 minutes compared with 17.7 minutes). The effects of ulinastatin were thought to be due to an increase in the release of acetylcholine at the neuromuscular junction and enhanced **vecuronium** elimination due to increases in liver blood flow and urine volume.[1]

If the mechanism of interaction is correct, it seems possible that other neuromuscular blockers could interact similarly. However, the clinical rel-

evance of this interaction seems likely to be small, as any effect is likely to be detected by routine monitoring.

1. Saitoh Y, Fujii Y, Oshima T. The ulinastatin-induced effect on neuromuscular block caused by vecuronium. *Anesth Analg* (1999) 89, 1565–9.

Neuromuscular blockers; Atracurium + Danazol or Tamoxifen

Two isolated case reports describe prolonged atracurium effects, which were attributed to the use of tamoxifen or danazol.

Clinical evidence, mechanism, importance and management

A case report describes a 67-year-old mastectomy patient taking methyldopa, hydrochlorothiazide, triamterene and long-term tamoxifen 10 mg twice daily who developed prolonged neuromuscular blockade after a single 500-microgram/kg dose of atracurium, which the authors suggest might be due to an interaction between atracurium and tamoxifen.[1] There is an earlier report[2] of prolonged atracurium blockade where the patient was taking danazol, another antioestrogenic drug. These interactions are probably not of general importance.

1. Naguib M, Gyasi HK. Antiestrogenic drugs and atracurium – a possible interaction? *Can Anaesth Soc J* (1986) 33, 682–3.
2. Bizzarri-Schmid MD, Desai SP. Prolonged neuromuscular blockade with atracurium. *Can Anaesth Soc J* (1986) 33, 209–12.

Neuromuscular blockers; Botulinum toxin + Miscellaneous

Theoretically, the neuromuscular blocking effects of botulinum toxin can be increased by other drugs with neuromuscular blocking effects, such as the aminoglycosides and muscle relaxants, but no such interactions appear to have been reported.

Clinical evidence, mechanism, importance and management

A case report describes a 5-month-old baby boy who was admitted to hospital because of lethargy, poor feeding, constipation and muscle weakness (later identified as being due to a *Clostridium botulinum* infection). One hour after starting intravenous treatment with ampicillin and **gentamicin** 7.5 mg/kg daily (in divided doses every 8 hours) for presumed sepsis, he stopped breathing and died. The reason appeared to be the additive neuromuscular blocking effects of the systemic botulinum toxin produced by the *Clostridium botulinum* infection and the **gentamicin**.[1] *Animal* studies confirm that **gentamicin** and **tobramycin** potentiate the neuromuscular blocking effects of systemic botulinum toxin (used to mimic botulism),[1] and there is every reason to believe that any of the other drugs known to cause neuromuscular blockade (**aminoglycosides**, conventional **neuromuscular blockers**, etc.) will behave similarly. However, note that clinically, botulinum A toxin is injected for its local effect in specific muscles, and is not used systemically; and so the situation is not analogous to that described in the case of the child with systemic botulism. Nevertheless, several manufacturers prudently advise caution if drugs that affect neuromuscular transmission are given concurrently.[2-4] **Aminoglycosides**, **spectinomycin**, and **neuromuscular blockers** are specifically named.

1. Santos JI, Swensen P, Glasgow LA. Potentiation of *Clostridium botulinum* toxin by aminoglycoside antibiotics: clinical and laboratory observations. *Pediatrics* (1981) 68, 50–4.
2. Botox (Botulinum A toxin). Allergan Ltd. UK Summary of product characteristics, June 2007.
3. NeuroBloc (Botulinum B toxin). Eisai Ltd. UK Summary of product characteristics, March 2009.
4. Myobloc (Botulinum B toxin). Solstice Neurosciences Inc. US Prescribing information, November 2004.

Neuromuscular blockers; Suxamethonium (Succinylcholine) + Dexpanthenol

An isolated report describes an increase in the neuromuscular blocking effects of suxamethonium, which was attributed to the concurrent use of dexpanthenol, but a further study using pantothenic acid (the main metabolite of dexpanthenol) failed to confirm this interaction.

Clinical evidence, mechanism, importance and management

A study in 6 patients under general anaesthesia found that their response to suxamethonium was unaffected by the infusion of 500 mg of **pantothenic acid**.[1] This study was conducted in response to an earlier case report, which reported respiratory depression requiring re-intubation following the use of intramuscular dexpanthenol (which is converted to pantothenic acid in the body) shortly after stopping a suxamethonium infusion.[1]

Apart from the single unconfirmed report there seems to be little other reason for avoiding concurrent use or for taking particular precautions. However, the US manufacturer of dexpanthenol recommends that it should not be given within one hour of suxamethonium.[2]

1. Smith RM, Gottshall SC, Young JA. Succinylcholine-pantothenyl alcohol: a reappraisal. *Anesth Analg* (1969) 48, 205–208.
2. Dexpanthenol Injection. American Regent, Inc. US Prescribing information, January 2003.

Neuromuscular blockers; Vecuronium + Clonidine

There is limited evidence to suggest that clonidine modestly increases the duration of action of vecuronium.

Clinical evidence, mechanism, importance and management

In a study in 16 surgical patients, 8 patients took oral clonidine 4 micrograms/kg to 5.5 micrograms/kg 90 minutes before their operation. Anaesthesia was induced by thiamylal, and maintained with nitrous oxide/oxygen and isoflurane supplemented by fentanyl. Clonidine increased the duration of neuromuscular blockade following the use of vecuronium by 26%, when compared with the patients not taking clonidine.[1]

The reasons for this modest increase in neuromuscular blockade are not understood. The clinical importance of this interaction would appear to be small.

1. Nakahara T, Akazawa T, Kinoshita Y, Nozaki J. The effect of clonidine on the duration of vecuronium-induced neuromuscular blockade in humans. *Jpn J Anesthesiol* (1995) 44, 1458–63.

Neuromuscular blockers; Vecuronium + Lansoprazole

There is some evidence to suggest that lansoprazole increases the duration of action of vecuronium.

Clinical evidence, mechanism, importance and management

In a study of 50 adult surgical patients, half of whom received lansoprazole 30 mg the night before their operation, it was found that there was no significant difference between the time to onset of neuromuscular blockade by **vecuronium** in the two groups, but lansoprazole increased the duration of neuromuscular blockade by about 34%.[1] This interaction needs confirmation and the clinical relevance requires assessment.

1. Ahmed SM, Panja C, Khan RM, Bano S. Lansoprazole potentiates vecuronium paralysis. *J Indian Med Assoc* (1997) 95, 422–3.

6

Analgesics and NSAIDs

The drugs dealt with in this section include aspirin and other salicylates, NSAIDs, opioid analgesics, and the miscellaneous analgesics, such as nefopam and paracetamol. 'Table 6.1', (p.150) contains a listing, with a further classification of the NSAIDs.

Interactions

(a) Aspirin and NSAIDs

Aspirin and the NSAIDs generally undergo few clinically significant pharmacokinetic interactions. The majority are highly protein bound, and have the potential to interact with other drugs via this mechanism. However, with a few exceptions, most of these interactions are not clinically important (see 'Protein-binding interactions', (p.3)).

Of the newer NSAIDs, celecoxib is metabolised by the cytochrome P450 isoenzyme CYP2C9, and inhibits CYP2D6. Rofecoxib, now withdrawn, inhibits CYP1A2, see 'Tizanidine + CYP1A2 inhibitors', p.1572. Nevertheless, most of the important interactions with NSAIDs and aspirin are pharmacodynamic. Aspirin and all non-selective NSAIDs inhibit platelet aggregation, and so can increase the risk of bleeding and interact with other drugs that have this effect. NSAIDs that are highly selective for cyclooxygenase-2 (COX-2) do not inhibit platelet aggregation.

Aspirin and all NSAIDs (including COX-2 selective NSAIDs) affect the synthesis of renal prostaglandins, and so can cause salt and water retention. This can increase blood pressure and affect antihypertensive therapy.

Aspirin and non-selective NSAIDs inhibit the mechanisms that protect the gastrointestinal mucosa and so cause gastrointestinal toxicity. COX-2 selective NSAIDs (coxibs) are less likely to have this effect, but they can still cause gastrointestinal toxicity.

(b) Opioids

Morphine is metabolised by glucuronidation by UDP-glucuronyltransferases, mainly to one active and one inactive metabolite. The glucuronidation of morphine can be induced or inhibited by various drugs. Morphine is not significantly affected by cytochrome P450 isoenzymes. The semi-synthetic morphine analogues, hydromorphone and oxymorphone, are metabolised similarly.

Codeine, dihydrocodeine, and hydrocodone are thought to be prodrugs, and require metabolic activation, possibly by CYP2D6 or glucuronyltransferases. Inhibitors of these enzymes may therefore reduce their efficacy. Oxycodone is also metabolised by CYP2D6 and CYP3A4.

Pethidine (meperidine) is metabolised by several cytochrome P450 isoenzymes. If the metabolism of pethidine is increased it can lead to increased production of the toxic metabolite, norpethidine, and increased CNS adverse effects.

Methadone is metabolised by several cytochrome P450 isoenzymes including CYP3A4, CYP2B6, and CYP2D6, although CYP2C8, CYP2C9 and CYP2C19 may also play a role.

Buprenorphine is metabolised by CYP3A4, and alfentanil is extensively metabolised by CYP3A4, and has been used as a probe drug for assessing CYP3A4 activity. Fentanyl and sufentanil are also metabolised by CYP3A4, but because they are high hepatic-extraction drugs (see 'Changes in first-pass metabolism', (p.4)) they are less affected by inhibitors or inducers of CYP3A4, although in some instances this may still lead to clinically significant effects.

(c) Paracetamol

Paracetamol is not absorbed from the stomach, and the rate of absorption is well correlated with the gastric emptying rate. Paracetamol has therefore been used as a marker drug in studies of gastric emptying. Paracetamol is primarily metabolised by the liver to a variety of metabolites, principally the glucuronide and sulfate conjugates. Hepatotoxicity of paracetamol is thought to be due to a minor metabolite, *N*-acetyl-p-benzoquinone imine (NAPQI), which is inactivated with glutathione and excreted as mercapturate and cysteine conjugates. When the liver stores of glutathione are depleted, and the rate of production of NAPQI exceeds the rate of production of glutathione, excess NAPQI attaches to liver proteins and causes liver damage. CYP2E1 may be involved in the formation of this hepatotoxic metabolite.

1. Brouwers JRBJ, de Smet PAGM. Pharmacokinetic-pharmacodynamic drug interactions with nonsteroidal anti-inflammatory drugs. *Clin Pharmacokinet* (1994) 27, 462–5.
2. Rumack BH. Acetaminophen hepatotoxicity: the first 35 years. *J Toxicol Clin Toxicol* (2002) 40, 3–20.
3. Armstrong AC, Cozza KL. Pharmacokinetic drug interactions of morphine, codeine, and their derivatives: theory and clinical reality, Part I. *Psychosomatics* (2003) 44, 167–71.
4. Armstrong AC, Cozza KL. Pharmacokinetic drug interactions of morphine, codeine, and their derivatives: theory and clinical reality, Part II. *Psychosomatics* (2003) 44, 515–20.

Table 6.1 Analgesics and NSAIDs

Group	*Drugs*
Aspirin and oral salicylates	Aloxiprin, Aspirin, Benorilate, Choline salicylate, Diflunisal, Ethenzamide, Lysine aspirin, Magnesium salicylate, Salsalate, Sodium salicylate
NSAIDs	
Fenamates	Floctafenine, Flufenamic acid, Meclofenamic acid, Mefenamic acid, Tolfenamic acid
Indole- and indene-acetic acids	Acemetacin, Etodolac, Indometacin, Sulindac
Oxicams	Lornoxicam, Meloxicam, Piroxicam, Tenoxicam
Phenylacetic acid derivatives	Aceclofenac, Alclofenac, Diclofenac
Propionic acid derivatives	Dexibuprofen, Dexketoprofen, Fenbufen, Fenoprofen, Flurbiprofen, Ibuprofen, Ketoprofen, Naproxen, Oxaprozin, Tiaprofenic acid
Pyrazolone derivatives	Azapropazone, Feprazone, Kebuzone, Metamizole sodium (Dipyrone), Oxyphenbutazone, Phenylbutazone
Selective inhibitors of cyclo-oxygenase-2 (Coxibs)	Celecoxib, Etoricoxib, Lumiracoxib, Meloxicam (see under *Oxicams*), Parecoxib, Rofecoxib, Valdecoxib
Other	Benzydamine hydrochloride, Felbinac, Ketorolac, Nabumetone, Nimesulide, Phenazone (Antipyrine), Tolmetin
Opioid and related analgesics	
Anaesthetic adjuncts	Alfentanil, Fentanyl, Remifentanil, Sufentanil
Mild to moderate pain	Codeine, Dextropropoxyphene (Propoxyphene), Dihydrocodeine
Moderate to severe pain:	
Partial agonists and agonists/antagonists	Buprenorphine (also used for opioid dependence), Butorphanol, Meptazinol, Nalbuphine, Pentazocine
Pure agonists	Dextromoramide, Diamorphine (Heroin), Dipipanone, Hydrocodone, Hydromorphone, Methadone (also used for opioid dependence), Morphine, Oxycodone, Oxymorphone, Papaveretum, Pethidine (Meperidine), Tramadol
Miscellaneous	Nefopam, Paracetamol (Acetaminophen)

Aspirin or other Salicylates + Antacids

The serum salicylate levels of patients taking large, anti-inflammatory doses of aspirin or other salicylates can be reduced to subtherapeutic levels by some antacids. The maximum plasma levels of single doses of aspirin may be increased by giving an antacid, although the extent of absorption is unaltered.

Clinical evidence

A study in 10 healthy subjects found that the mean maximum plasma level of a single 650-mg dose of aspirin was about 70% higher when it was given 10 minutes after an antacid (**aluminium/magnesium hydroxide**), when compared with aspirin alone. However, there was no change in the time to reach the peak level or the AUC. There were also no significant changes in the pharmacokinetics of the metabolites, salicylic acid and salicyluric acid.[1]

A child with rheumatic fever taking aspirin 600 mg five times daily had a serum salicylate level of between 82 and 118 mg/L while taking 30 mL of *Maalox* (**aluminium/magnesium hydroxide** suspension). When the *Maalox* was withdrawn, the urinary pH fell from a range of 7 to 8 down to a range of 5 to 6.4, whereupon the serum salicylate level rose three- to fourfold to about 380 mg/L, which required a dose reduction.[2] An associated study in 13 healthy subjects taking aspirin 4 g daily for a week found that **sodium bicarbonate** 4 g daily reduced serum salicylate levels by 44%, from 270 mg/L to 150 mg/L. This reflected a rise in the urinary pH from a range of 5.6 to 6.1 up to around 6.2 to 6.9.[2,3]

Similar changes have been reported in other studies with:

- aspirin or **choline salicylate** and **aluminium/magnesium hydroxide**;
- aspirin and **magnesium trisilicate/aluminium hydroxide**;
- aspirin or **sodium salicylate** and **sodium bicarbonate**.[4-8]

There is some evidence to suggest that this effect does not occur at low serum salicylate levels,[5,6] or if the pH of the urine is unchanged by the antacid.[6]

Mechanism

Aspirin and other salicylates are acidic compounds that are excreted by the kidney tubules and are ionised in solution. In alkaline solution, much of the drug exists in the ionised form, which is not readily reabsorbed, and therefore is lost in the urine. If the urine is made more acidic (e.g. with ammonium chloride), much more of the drug exists in the un-ionised form, which is readily reabsorbed, so that less is lost in the urine and the drug is retained in the body.[7,8]

In vitro data show that magnesium oxide and aluminium hydroxide strongly adsorb aspirin and sodium salicylate.[9] However, in three of the studies above aluminium hydroxide-containing antacids had no effect on the extent of absorption of salicylate,[1,4,6] although the rate of absorption may be increased as a result of an increase in the solubility of salicylate in a less acidic gastric environment.[1]

Importance and management

A well established and clinically important interaction for those receiving long-term treatment with large doses of salicylates, because the serum salicylate level may become subtherapeutic. This interaction can occur with both 'systemic' antacids (e.g. sodium bicarbonate) as well as some 'non-systemic' antacids (e.g. aluminium/magnesium hydroxide), but only appears to occur if there is an increase in the urinary pH. Care should be taken to monitor serum salicylate levels if any antacid is started or stopped in patients where the control of salicylate levels is critical.

No important adverse interaction would be expected in those taking occasional doses of aspirin for analgesia. Some aspirin formulations actually include antacids as buffering agents to increase absorption rates and raise peak serum levels,[10] which gives more rapid analgesia, and/or in an attempt to decrease gastric irritation. Note that antacids may also increase the rate of absorption of aspirin given as enteric-coated tablets.[11]

1. Itthipanichpong C, Sirivongs P, Wittayalertpunya S, Chaiyos N. The effect of antacid on aspirin pharmacokinetics in healthy Thai volunteers. *Drug Metabol Drug Interact* (1992) 10, 213–28.
2. Levy G. Interaction of salicylates with antacids. In: Blondheim SH, Alkan WJ, Brunner D, eds. Frontiers of Internal Medicine. 12th Int Congr Intern Med, Tel Aviv, 1974. Basel: Karger; 1975 p. 404–8.
3. Levy G, Leonards JR. Urine pH and salicylate therapy. *JAMA* (1971) 217, 81.
4. Levy G, Lampman T, Kamath BL, Garrettson LK. Decreased serum salicylate concentration in children with rheumatic fever treated with antacid. *N Engl J Med* (1975) 293, 323–5.
5. Hansten PD, Hayton WL. Effect of antacid and ascorbic acid on serum salicylate concentration. *J Clin Pharmacol* (1980) 20, 326–31.
6. Shastri RA. Effect of antacids on salicylate kinetics. *Int J Clin Pharmacol Ther Toxicol* (1985) 23, 480–4.
7. Macpherson CR, Milne MD, Evans BM. The excretion of salicylate. *Br J Pharmacol* (1955) 10, 484–9.
8. Hoffman WS, Nobe C. The influence of urinary pH on the renal excretion of salicyl derivatives during aspirin therapy. *J Lab Clin Med* (1950) 35, 237–48.
9. Naggar VF, Khalil SA, Daabis NA. The in-vitro adsorption of some antirheumatics on antacids. *Pharmazie* (1976) 31, 461–5.
10. Nayak RK, Smyth RD, Polk A, Herczeg T, Carter V, Visalli AJ, Reavey-Cantwell NH. Effect of antacids on aspirin dissolution and bioavailability. *J Pharmacokinet Biopharm* (1977) 5, 597–613.
11. Feldman S, Carlstedt BC. Effect of antacid on absorption of enteric-coated aspirin. *JAMA* (1974) 227, 660–1.

Aspirin + Bile-acid binding resins

Colestyramine and colestipol do not appear to have any clinically important effects on the absorption of aspirin.

Clinical evidence, mechanism, importance and management

(a) Colestipol

In 12 healthy subjects the extent of absorption of a single 650-mg dose of aspirin was unaffected by colestipol 10 g. However, the rate of aspirin absorption was increased by colestipol: at 60 minutes after the dose the plasma level was increased by about 40%.[1] No particular precautions seem to be necessary during concurrent use.

(b) Colestyramine

A study in 3 healthy subjects and 3 patients, and a later study in 7 healthy subjects, found that colestyramine 4 g delayed the absorption of a single 500-mg dose of aspirin (time to peak levels extended from 30 to 60 minutes) but the total amount absorbed was only reduced by 5 to 6%. Some of the subjects had slightly higher serum aspirin levels while taking colestyramine.[2] Similar results were reported in another study (a 31% lower plasma aspirin level at 60 minutes, but no difference in total absorption).[1] There would seem to be little reason for avoiding concurrent use unless rapid analgesia is needed.

1. Hunninghake DB, Pollack E. Effect of bile acid sequestering agents on the absorption of aspirin, tolbutamide, and warfarin. *Fedn Proc* (1977) 35, 996.
2. Hahn K-J, Eiden W, Schettle M, Hahn M, Walter E, Weber E. Effect of cholestyramine on the gastrointestinal absorption of phenprocoumon and acetylosalicylic acid in man. *Eur J Clin Pharmacol* (1972) 4, 142–5.

Aspirin or other Salicylates + Carbonic anhydrase inhibitors

A severe and even life-threatening toxic reaction can occur in patients taking high-dose salicylates if they are given carbonic anhydrase inhibitors, such as acetazolamide or diclofenamide.

Clinical evidence

An 8-year-old boy with chronic juvenile arthritis, taking prednisolone, indometacin and **aloxiprin**, was admitted to hospital with drowsiness, vomiting and hyperventilation (diagnosed as metabolic acidosis) within a month of the **aloxiprin** dose being increased from 3 to 3.6 g daily and starting to take **diclofenamide** 25 mg three times daily for glaucoma.[1]

Other cases of toxicity (metabolic acidosis) have included a 22-year-old woman taking **salsalate** with **acetazolamide** 250 mg four times daily,[1] and two elderly women taking large doses of aspirin with **acetazolamide** or **diclofenamide**.[2] A 50-year-old woman taking **acetazolamide** for glaucoma was admitted to hospital with confusion and cerebellar ataxia, associated with hyperchloraemic acidosis, 14 days after starting to take aspirin for acute pericarditis.[3] A man taking **diclofenamide** developed salicylate poisoning within 10 days of starting to take aspirin 3.9 g daily.[4] Coma developed in an 85-year-old woman taking aspirin 3.9 g daily when her dosage of **acetazolamide** was increased from 500 mg to 1 g daily,[5,6] and toxicity was seen in a very elderly man given both drugs: levels of unbound **acetazolamide** were found to be unusually high.[6] An elderly man became confused, lethargic, incontinent and anorexic while taking **acetazolamide** and **salsalate**. He needed intravenous hydration.[7]

Mechanism

Not fully established. One idea is that these carbonic anhydrase inhibitors (acetazolamide, diclofenamide) affect the plasma pH, so that more of the salicylate exists in the un-ionised (lipid-soluble) form, which can enter the CNS and other tissues more easily, leading to salicylate toxicity.[2] However, carbonic anhydrase inhibitors also make the urine more alkaline, which increases the loss of salicylate[8] (see also 'Aspirin or other Salicylates + Antacids', p.151). *Animal* studies confirm that carbonic anhydrase inhibitors increase the lethal toxicity of aspirin.[4] An alternative suggestion is that because salicylate inhibits the plasma protein binding of acetazolamide and its excretion by the kidney, acetazolamide toxicity, which mimics salicylate toxicity, may occur.[6]

Importance and management

Although there are few clinical reports on record, the interaction between carbonic anhydrase inhibitors and salicylates is established, well confirmed by *animal* studies, and potentially serious. One study recommended that carbonic anhydrase inhibitors should probably be avoided in those receiving high-dose salicylate treatment.[6] If they are used, the patient should be well monitored for any evidence of toxicity (confusion, lethargy, hyperventilation, tinnitus) because the interaction may develop slowly and insidiously.[2] In this context NSAIDs may be a safer alternative. Naproxen proved to be a satisfactory substitute in one case.[1] The authors of one study suggest that **methazolamide** may possibly be a safer alternative to acetazolamide because it is minimally bound to plasma proteins. They also suggest paracetamol (acetaminophen) as an alternative to salicylate in patients taking acetazolamide.[6] The reports cited here concern carbonic anhydrase inhibitors given orally, not as eye drops. It is not known whether the latter interact similarly, but there appear to be no reports.

1. Cowan RA, Hartnell GG, Lowdell CP, McLean Baird I, Leak AM. Metabolic acidosis induced by carbonic anhydrase inhibitors and salicylates in patients with normal renal function. *BMJ* (1984) 289, 347–8.
2. Anderson CJ, Kaufman PL, Sturm RJ. Toxicity of combined therapy with carbonic anhydrase inhibitors and aspirin. *Am J Ophthalmol* (1978) 86, 516–19.
3. Hazouard E, Grimbert M, Jonville-Berra A-P, De Toffol M-C, Legras A. Salicylisme et glaucome: augmentation réciproque de la toxicité de l'acétazolamide et de l'acide acétyl salicylique. *J Fr Ophtalmol* (1999) 22, 73–5.
4. Hurwitz GA, Wingfield W, Cowart TD, Jollow DJ. Toxic interaction between salicylates and a carbonic anhydrase inhibitor: the role of cerebral edema. *Vet Hum Toxicol* (1980) 22 (Suppl), 42–4.
5. Chapron DJ, Brandt JL, Sweeny KR, Olesen-Zammett L. Interaction between acetazolamide and aspirin — a possible unrecognized cause of drug-induced coma. *J Am Geriatr Soc* (1984) 32, S18.
6. Sweeney KR, Chapron DJ, Brandt JL, Gomolin IH, Feig PU, Kramer PA. Toxic interaction between acetazolamide and salicylate: case reports and a pharmacokinetic explanation. *Clin Pharmacol Ther* (1986) 40, 518–24.
7. Rousseau P, Fuentevilla-Clifton A. Acetazolamide and salicylate interaction in the elderly: a case report. *J Am Geriatr Soc* (1993) 41, 868–9.
8. Macpherson CR, Milne MD, Evans BM. The excretion of salicylate. *Br J Pharmacol* (1955) 10, 484–9.

Aspirin or other Salicylates + Corticosteroids or Corticotropin

Serum salicylate levels are reduced by the corticosteroids. This appears to be of most consequence if the corticosteroid is withdrawn. Concurrent use increases the risk of gastrointestinal bleeding and ulceration.

Clinical evidence

A 5-year-old boy taking long-term **prednisone** in doses of at least 20 mg daily, was given **choline salicylate** 3.6 g daily, and the **prednisone** was gradually tapered off to 3 mg daily over a 3-month period. Severe salicylate toxicity developed, and in a retrospective investigation of the cause, using frozen serum samples drawn for other purposes, it was found that the serum salicylate levels had risen from less than 100 mg/L up to 880 mg/L during the withdrawal of the **prednisone**.[1] Later studies in 3 other patients taking **choline salicylate** or aspirin and either **prednisone** or another unnamed corticosteroid, found about a threefold rise in salicylate levels during corticosteroid withdrawal.[1] **Hydrocortisone** was also found to increase the clearance of **sodium salicylate** in 4 other patients.[1] A serum salicylate rise has been described in a patient taking **aloxiprin** when **prednisolone** was withdrawn.[2] Other studies in both adults and children show that **prednisone**, **methylprednisolone**, **betamethasone** and **corticotropin** reduce serum salicylate levels.[3-5] Two studies also found that intra-articular **dexamethasone**, **methylprednisolone**, and **triamcinolone** transiently reduced serum salicylate levels in patients given enteric-coated aspirin.[6,7] However one study in patients found that **prednisone** 12 to 60 mg daily had no effect on the clearance of single doses of **sodium salicylate**.[8]

Mechanism

Uncertain. One idea is that the presence of the corticosteroid increases the glomerular filtration rate, which increases salicylate clearance. When the corticosteroid is withdrawn, the clearance returns to normal and the salicylate accumulates. Another suggestion is that the corticosteroids increase the metabolism of the salicylate.[3]

Importance and management

Well established interactions. Patients should be monitored to ensure that salicylate levels remain adequate when corticosteroids are added[4] and do not become excessive if they are withdrawn. It should also be remembered that concurrent use may increase the incidence of gastrointestinal bleeding and ulceration. See also 'Corticosteroids + NSAIDs', p.1266.

1. Klinenberg JR, Miller F. Effect of corticosteroids on blood salicylate concentration. *JAMA* (1965) 194, 601–4.
2. Muirden KD, Barraclough DRE. Drug interactions in the management of rheumatoid arthritis. *Aust N Z J Med* (1976) 6 (Suppl 1), 14–17.
3. Graham GG, Champion GD, Day RO, Paull PD. Patterns of plasma concentrations and urinary excretion of salicylate in rheumatoid arthritis. *Clin Pharmacol Ther* (1977) 22, 410–20.
4. Bardare M, Cislaghi GU, Mandelli M, Sereni F. Value of monitoring plasma salicylate levels in treating juvenile rheumatoid arthritis. *Arch Dis Child* (1978) 53, 381–5.
5. Koren G, Roifman C, Gelfand E, Lavi S, Suria D, Stein L. Corticosteroids-salicylate interaction in a case of juvenile rheumatoid arthritis. *Ther Drug Monit* (1987) 9, 177–9.
6. Edelman J, Potter JM, Hackett LP. The effect of intra-articular steroids on plasma salicylate concentrations. *Br J Clin Pharmacol* (1986) 21, 301–7.
7. Baer PA, Shore A, Ikeman RL. Transient fall in serum salicylate levels following intraarticular injection of steroid in patients with rheumatoid arthritis. *Arthritis Rheum* (1987) 30, 345–7.
8. Day RO, Harris G, Brown M, Graham GG, Champion GD. Interaction of salicylate and corticosteroids in man. *Br J Clin Pharmacol* (1988) 26, 334–7.

Aspirin + Dapsone

Dapsone does not significantly affect the pharmacokinetics of aspirin.

Clinical evidence, mechanism, importance and management

A comparison of the pharmacokinetics of aspirin in 8 healthy subjects and 8 patients with uncomplicated lepromatous leprosy found that the pharmacokinetics of a single 600-mg dose of aspirin was not affected by either leprosy, or by treatment with dapsone 100 mg daily for 8 days.[1] No aspirin dose adjustments would seem likely to be needed on concurrent use.

1. Garg SK, Kumar B, Shukla VK, Bakaya V, Lal R, Kaur S. Pharmacokinetics of aspirin and chloramphenicol in normal and leprotic patients before and after dapsone therapy. *Int J Clin Pharmacol Ther Toxicol* (1988) 26, 204–5.

Aspirin + Food

Food delays the absorption of aspirin.

Clinical evidence, mechanism, importance and management

A study in 25 subjects given aspirin 650 mg in five different preparations found that food roughly halved their serum salicylate levels (measured 10 and 20 minutes later), compared with those seen when the same dose of aspirin was given while fasting.[1] Similar results were found in subjects given calcium aspirin 1.5 g.[2] In another study in 8 healthy subjects who were given effervescent aspirin 900 mg, serum salicylate levels at 15 minutes were roughly halved by food, but were more or less unchanged at one hour.[3]

A further study in 16 healthy subjects found that the extent of absorption of a single 900-mg dose of soluble aspirin was not significantly affected by a high-fat meal. The rate of absorption was reduced by food and the maximum plasma level was reduced by 18%, which was not considered to

be clinically significant. Furthermore, there was no statistically significant change in the time to maximum plasma levels (20 minutes fasted; 30 minutes fed).[4]

A possible reason for the reduced rate of absorption is that food delays gastric emptying. Thus, if rapid analgesia is needed, aspirin should be taken without food, but if aspirin is needed long-term, giving it with food is thought to help to protect the gastric mucosa.

1. Wood JH. Effect of food on aspirin absorption. *Lancet* (1967) ii, 212.
2. Spiers ASD, Malone HF. Effect of food on aspirin absorption. *Lancet* (1967) i, 440.
3. Volans GN. Effects of food and exercise on the absorption of effervescent aspirin. *Br J Clin Pharmacol* (1974) 1, 137–41.
4. Stillings M, Havlik I, Chetty M, Clinton C, Schall R, Moodley I, Muir N, Little S. Comparison of the pharmacokinetic profiles of soluble aspirin and solid paracetamol tablets in fed and fasted volunteers. *Curr Med Res Opin* (2000) 16, 115–24.

Aspirin + Griseofulvin

An isolated report describes a marked fall in the serum salicylate levels of a child given aspirin and griseofulvin.

Clinical evidence, mechanism, importance and management

An 8-year-old boy with rheumatic fever taking aspirin 110 mg/kg daily and furosemide, digoxin, captopril, potassium, aluminium/magnesium hydroxide and iron, had a very marked fall in his serum salicylate levels (from a range of 18.3 to 30.6 mg/dL to less than 0.2 mg/dL) within 2 days of starting griseofulvin 10 mg/kg daily. Two days after the griseofulvin was stopped, the salicylate levels were back to their former levels. The reasons for this effect are not known, but it was suggested that the salicylate absorption was impaired in some way.[1] This appears to be the first and only report of this interaction so that its general importance is uncertain.

1. Phillips KR, Wideman SD, Cochran EB, Becker JA. Griseofulvin significantly decreases serum salicylate concentrations. *Pediatr Infect Dis J* (1993) 12, 350–2.

Aspirin + Kaolin-pectin

Kaolin-pectin causes a small reduction in the absorption of aspirin.

Clinical evidence, mechanism, importance and management

In 10 healthy subjects the absorption of aspirin 975 mg was reduced by 5 to 10% by 30 or 60 mL of kaolin-pectin.[1] A likely explanation is that the aspirin becomes adsorbed by the kaolin so that the amount available for absorption through the gut wall is reduced. However, this small reduction in absorption is unlikely to be of clinical importance.

1. Juhl RP. Comparison of kaolin-pectin and activated charcoal for inhibition of aspirin absorption. *Am J Hosp Pharm* (1979) 36, 1097–8.

Aspirin + Laxatives

Sodium sulfate and castor oil used as laxatives can cause a modest reduction in aspirin absorption.

Clinical evidence, mechanism, importance and management

In an experimental study of the possible effects of laxatives on drug absorption, healthy subjects were given 10 to 20 g of oral **sodium sulfate** and 20 g of **castor oil** (doses sufficient to provoke diarrhoea). Absorption, measured by the amount of drug excreted in the urine, was decreased at 4 hours. The reduction was 21% for **castor oil** and aspirin, and 27% for **sodium sulfate** and aspirin. However, serum levels of aspirin were relatively unchanged. The overall picture was that while these laxatives can alter the pattern of absorption, they do not seriously impair the total amount of drug absorbed.[1]

1. Mattila MJ, Takki S, Jussila J. Effect of sodium sulphate and castor oil on drug absorption from the human intestine. *Ann Clin Res* (1974) 6, 19–24.

Aspirin + Levamisole

The salicylate levels of a patient taking aspirin rose when levamisole was given, but this effect was not confirmed in a subsequent controlled study.

Clinical evidence, mechanism, importance and management

A preliminary report of a patient who had an increase in salicylate levels (magnitude not stated) when levamisole was given with aspirin 5.4 g daily[1] prompted a study in 9 healthy subjects of this possible interaction. Sustained-release aspirin 3.9 g daily in two divided doses was given over a period of 3 weeks, with levamisole 50 mg three times daily for a week, each subject acting as his own control. No significant changes in plasma salicylate levels were found.[2] The reasons for the increase in salicylate levels in the case report are unclear. No interaction would generally be expected.

1. Laidlaw D'A. Rheumatoid arthritis improved by treatment with levamisole and L-histidine. *Med J Aust* (1976) 2, 382–5.
2. Rumble RH, Brooks PM, Roberts MS. Interaction between levamisole and aspirin in man. *Br J Clin Pharmacol* (1979) 7, 631–3.

Aspirin + Pentazocine

A man regularly taking large doses of aspirin developed renal papillary necrosis when he was given pentazocine.

Clinical evidence, mechanism, importance and management

An isolated report describes a man, regularly taking aspirin 1.8 to 2.4 g daily, who developed renal papillary necrosis within 6 months of also starting to take pentazocine 800 to 850 mg daily. He developed abdominal pain, nausea and vomiting, and passed tissue via his urethra. Before starting the pentazocine and after it was stopped, no necrosis was apparent. The postulated reason for this reaction is that a pentazocine-induced reduction in blood flow through the kidney potentiated the adverse effects of chronic aspirin use.[1] The general importance of this isolated case is uncertain and no general recommendations can be made.

1. Muhalwas KK, Shah GM, Winer RL. Renal papillary necrosis caused by long-term ingestion of pentazocine and aspirin. *JAMA* (1981) 246, 867–8.

Aspirin + Phenylbutazone

Phenylbutazone reduces the uricosuric effects of high-dose aspirin. Concurrent use is likely to be associated with an increased risk of gastrointestinal damage.

Clinical evidence

The observation that several patients given aspirin and phenylbutazone developed elevated serum urate levels, prompted a study in 4 patients without gout. The study found that aspirin 2 g daily had little effect on the excretion of uric acid in the urine, but marked uricosuria occurred with aspirin 5 g daily. When phenylbutazone 200, 400 and then 600 mg daily (over 3 days) was also given the uricosuria was abolished. Serum uric acid levels rose from an average of about 40 mg/L to 60 mg/L. The interaction was confirmed in a patient with tophaceous gout. The retention of uric acid also occurs if the phenylbutazone is given first.[1]

Mechanism

Not understood. Phenylbutazone is structurally related to sulfinpyrazone, which interacts similarly, see 'Uricosuric drugs + Aspirin or other Salicylates', p.1575.

Importance and management

An established but sparsely documented interaction. The potential problems arising from this interaction should be recognised in any patient given aspirin and phenylbutazone. The concurrent use of aspirin and NSAIDs increases the risk of gastrointestinal damage and is not recommended. Although there does not appear to be any specific evidence for phenylbuta-

zone, it would be expected to interact in the same way as other NSAIDs, see 'NSAIDs + Aspirin', p.158.

1. Oyer JH, Wagner SL, Schmid FR. Suppression of salicylate-induced uricosuria by phenylbutazone. *Am J Med Sci* (1966) 225, 39–45.

Nefopam + Miscellaneous

The manufacturer states that nefopam is contraindicated in patients taking MAOIs. Caution should be used in those taking tricyclic antidepressants, antimuscarinics and sympathomimetics. The intensity and incidence of adverse effects are somewhat increased when nefopam is given with codeine, pentazocine or dextropropoxyphene (propoxyphene), and the CNS depressant effect of dihydrocodeine may have contributed to a fatal overdose with nefopam.

Clinical evidence, mechanism, importance and management

(a) Antidepressants

The manufacturer advises caution if nefopam is given with a **tricyclic antidepressant**,[1] presumably as nefopam alone may cause convulsions and the tricyclics can also lower the convulsive threshold. In addition, the antimuscarinic adverse effects of nefopam may be additive with those of tricyclics and other drugs with antimuscarinic effects[1] (see 'Antimuscarinics + Antimuscarinics', p.786). For example, the CSM in the UK has a number of reports of urinary retention caused by nefopam,[2] which would be expected to be worsened by the concurrent use of drugs with antimuscarinic activity, such as the tricyclics.

Nefopam appears to have sympathomimetic activity, therefore caution should be used when prescribing other drugs with sympathomimetic effects. The manufacturer contraindicates its use with the **MAOIs**[1] (see 'MAOIs or RIMAs + Sympathomimetics; Indirectly-acting', p.1388).

(b) Analgesics

The incidence of sedation with nefopam has been reported as 20 to 30% which, depending on the circumstances, may increase the risk of sedation if it is given with other **sedative drugs**.[3] A report describes a fatal overdose with nefopam, which was complicated by the CNS depressant effect of **dihydrocodeine**.[4]

In a study in *animals*, nefopam enhanced the analgesic potency of **morphine**,[5] and in a study in patients undergoing orthopaedic surgery intravenous nefopam had a **morphine**-sparing effect (up to 35% dose reduction).[6] However, a further study found that the effects were less than additive.[7] A study in 72 surgical patients found that the use of nefopam with **ketoprofen** had a synergistic analgesic effect.[8] See also *Other drugs*, below, for brief comment on the use of other analgesics with nefopam.

(c) Other drugs

A study was conducted in 45 healthy subjects divided into nine groups of five, each given oral nefopam 60 mg three times daily for 3 days with **aspirin** 650 mg, **codeine** 60 mg, **diazepam** 5 mg, **dextropropoxyphene (propoxyphene)** 65 mg, **hydroxyzine** 50 mg, **indometacin** 25 mg, **pentazocine** 50 mg, **phenobarbital** 60 mg, or placebo (all three times daily). The only changes were a possible additive increase in the intensity and incidence of adverse effects with nefopam and **codeine**, **pentazocine** or **dextropropoxyphene**. There was no evidence that the bioavailability of nefopam was changed by the other drugs.[9]

1. Acupan (Nefopam hydrochloride). Meda Pharmaceuticals. UK Summary of product characteristics, October 2007.
2. Committee on Safety of Medicines (CSM). Nefopam hydrochloride (Acupan). Current Problems No 24, January 1989.
3. Heel RC, Brogden RN, Pakes GE, Speight TM, Avery GS. Nefopam: a review of its pharmacological properties and therapeutic efficacy. *Drugs* (1980) 19, 249–67.
4. Urwin SC, Smith HS. Fatal nefopam overdose. *Br J Anaesth* (1999) 83, 501–2.
5. Girard P, Pansart Y, Gillardin JM. Nefopam potentiates morphine antinociception in allodynia and hyperalgesia in the rat. *Pharmacol Biochem Behav* (2004) 77, 695–703.
6. Du Manoir B, Aubrun F, Langlois M, Le Guern ME, Alquier C, Chauvin M, Fletcher D. Randomized prospective study of the analgesic effect of nefopam after orthopaedic surgery. *Br J Anaesth* (2003) 91, 836–41.
7. Beloeil H, Delage N, Nègre I, Mazoit J-X, Benhamou D. The median effective dose of nefopam and morphine administered intravenously for postoperative pain after minor surgery: a prospective randomized double-blinded isobolographic study of their analgesic action. *Anesth Analg* (2004) 98, 395–400.
8. Delage N, Maaliki H, Beloeil H, Benhamou D, Mazoit J-X. Median effective dose (ED_{50}) of nefopam and ketoprofen in postoperative patients: a study of interaction using sequential analysis and isobolographic analysis. *Anesthesiology* (2005) 102, 1211–16.
9. Lasseter KC, Cohen A, Back EL. Nefopam HCl interaction study with eight other drugs. *J Int Med Res* (1976) 4, 195–201.

NSAIDs + Allopurinol

Allopurinol does not affect indometacin clearance or phenylbutazone levels.

Clinical evidence, mechanism, importance and management

In a study in 8 patients, allopurinol 300 mg each morning was given with **indometacin** 50 mg every 8 hours for 5 days. The allopurinol had no significant effect on the AUC of **indometacin** and the amounts of **indometacin** excreted in the urine were not significantly altered.[1]

Allopurinol 100 mg three times daily for a month had no effect on the elimination of **phenylbutazone** 200 mg daily in 6 healthy subjects, and no effect on the steady-state plasma levels of **phenylbutazone** 200 or 300 mg daily in 3 patients.[2] In another study in 8 patients with acute gouty arthritis it was found that allopurinol 100 mg every 8 hours produced a small but clinically unimportant effect on the half-life of **phenylbutazone** 6 mg/kg.[3]

There seems to be no pharmacokinetic reason for avoiding the concurrent use of these NSAIDs and allopurinol.

1. Pullar T, Myall O, Haigh JRM, Lowe JR, Dixon JS, Bird HA. The effect of allopurinol on the steady-state pharmacokinetics of indomethacin. *Br J Clin Pharmacol* (1988) 25, 755–7.
2. Rawlins MD, Smith SE. Influence of allopurinol on drug metabolism in man. *Br J Pharmacol* (1973) 48, 693–8.
3. Horwitz D, Thorgeirsson SS, Mitchell JR. The influence of allopurinol and size of dose on the metabolism of phenylbutazone in patients with gout. *Eur J Clin Pharmacol* (1977) 12, 133–6.

NSAIDs + Amoxicillin

A study in healthy subjects found that diclofenac increased the clearance of amoxicillin. An isolated report describes acute interstitial nephritis with nephrotic syndrome associated with the use of naproxen and amoxicillin.

Clinical evidence, mechanism, importance and management

(a) Diclofenac

In a study in 20 healthy subjects, diclofenac 100 mg caused a slight reduction in the AUC and a slight increase in the mean renal clearance of a single 2-g dose of amoxicillin.[1] It should be noted that there was considerable individual variation and overlapping between the two groups, and the clinical significance of this finding is unclear.

(b) Naproxen

A man without any previous renal problems developed acute interstitial nephritis with nephrotic syndrome after taking naproxen for 4 days (total 4 g) and amoxicillin for 10 days (total 24 g). He appeared to recover when the drugs were stopped, but 3 months later he developed renal failure and needed haemodialysis.[2] Acute interstitial nephritis is not only a rare syndrome (reported to be only 55 cases in the world literature in 1988)[2] but this is the first case involving both of these drugs. No special precautions would normally seem to be necessary.

1. de Cássia Bergamaschi C, Motta RHL, Franco GCN, Cogo K, Montan MF, Ambrosano GMB, Rosalen PL, de Sá Del Fiol F, Groppo FC. Effect of sodium diclofenac on the bioavailability of amoxicillin. *Int J Antimicrob Agents* (2006) 27, 417–22.
2. Nortier J, Depierreux M, Bourgeois V, Dupont P. Acute interstitial nephritis with nephrotic syndrome after intake of naproxen and amoxycillin. *Nephrol Dial Transplant* (1990) 5, 1055.

NSAIDs + Anabolic steroids

Serum oxyphenbutazone levels are raised by methandienone (methandrostenolone). Phenylbutazone appears to be unaffected.

Clinical evidence

The serum levels of **oxyphenbutazone** 300 to 400 mg daily for 2 to 5 weeks were raised by 43% (range 5 to 100%) in 6 subjects given **methandienone (methandrostenolone)**.[1] Two other studies confirm this interaction with **oxyphenbutazone**.[2,3] One of them found no interaction with **phenylbutazone**.[2]

Mechanism

Uncertain. One idea is that the anabolic steroids alter the distribution of oxyphenbutazone between the tissues and plasma so that more remains in circulation. There may also possibly be some changes in metabolism.

Importance and management

The interaction is established but its importance is uncertain. There seem to be no reports of toxicity arising from concurrent use but the possibility should be borne in mind.

1. Weiner M, Siddiqui AA, Shahani RT, Dayton PG. Effect of steroids on disposition of oxyphenbutazone in man. *Proc Soc Exp Biol Med* (1967) 124, 1170–3.
2. Hvidberg E, Dayton PG, Read JM, Wilson CH. Studies of the interaction of phenylbutazone, oxyphenbutazone and methandrostenolone in man. *Proc Soc Exp Biol Med* (1968) 129, 438–43.
3. Weiner M, Siddiqui AA, Bostanci N, Dayton PG. Drug interactions.The effect of combined administration on the half-life of coumarin and pyrazolone drugs in man. *Fedn Proc* (1965) 24, 153.

NSAIDs; Azapropazone + Antacids or Laxatives

A study in 15 patients taking azapropazone 300 mg three times daily found that antacids (dihydroxyaluminium sodium carbonate, aluminium magnesium silicate), bisacodyl or anthraquinone laxatives only caused a minor (5 to 7%) reduction in azapropazone plasma levels.[1] No special precautions would seem to be needed if any of these drugs are given together with azapropazone.

1. Faust-Tinnefeldt G, Geissler HE, Mutschler E. Azapropazon-Plasmaspiegel unter Begleitmedikation mit einem Antacidum oder Laxans. *Arzneimittelforschung* (1977) 27, 2411–14.

NSAIDs; Coxibs + Antacids

Aluminium/magnesium-containing antacids had no clinically significant effect on the bioavailability of celecoxib,[1,2] or lumiracoxib.[3] Aluminium/magnesium hydroxides or calcium carbonate had no clinically significant effect on the pharmacokinetics of etoricoxib.[4]

Antacids do not appear to affect meloxicam pharmacokinetics, see 'NSAIDs; Oxicam derivatives + Antacids', p.157.

1. Celebrex (Celecoxib). Pharmacia Ltd. UK Summary of product characteristics, June 2009.
2. Celebrex (Celecoxib). Pfizer Inc. US Prescribing information, June 2009.
3. Scott G, Vinluan Reynolds C, Milosavljev S, Langholff W, Shenouda M, Rordorf C. Lack of effect of omeprazole or of an aluminium hydroxide/magnesium hydroxide antacid on the pharmacokinetics of lumiracoxib. *Clin Pharmacokinet* (2004) 43, 341–8.
4. Schwartz JI, Agrawal NGB, Kher UA, DeSmet M, Cavanaugh PF, Guillaume M, Ebel DL, Merschman SA, Wagner JA. Lack of effect of antacids on single-dose pharmacokinetics of etoricoxib. *J Clin Pharmacol* (2007) 47, 1342–6.

NSAIDs; Diclofenac + Antacids

The absorption of diclofenac is not affected by aluminium hydroxide and/or magnesium hydroxide.

Clinical evidence, mechanism, importance and management

In a study in 7 healthy subjects, about 10 mL of a 5.8% suspension of **aluminium hydroxide** had no effect on the bioavailability of a single 50-mg dose of diclofenac.[1] In another study, in 6 healthy, fasted subjects, 10 mL of **magnesium hydroxide** suspension (850 mg) was found to have no significant effect on the rate or extent of absorption of a single 50-mg dose of diclofenac.[2] However, there was a tendency to an increased rate of absorption. *Aluco Gel* (**aluminium**/**magnesium hydroxide**) had no effect on the extent of absorption of enteric-coated diclofenac, but it may have reduced the rate of absorption.[3] No particular precautions would seem to be needed if these antacids are given with diclofenac.

1. Schumacher A, Faust-Tinnefeldt G, Geissler HE, Gilfrich HJ, Mutschler E. Untersuchungen potentieller Interaktionen von Diclofenac-Natrium (Voltaren) mit einem Antazidum und mit Digitoxin. *Therapiewoche* (1983) 33, 2619–25.
2. Neuvonen PJ. The effect of magnesium hydroxide on the oral absorption of ibuprofen, ketoprofen and diclofenac. *Br J Clin Pharmacol* (1991) 31, 263–6.
3. Sioufi A, Stierlin H, Schweizer A, Botta L, Degen PH, Theobald W, Brechbühler S. Recent findings concerning clinically relevant pharmacokinetics of diclofenac sodium. In: Voltarol — New Findings, ed Kass E. Proc Int Symp Voltarol, Paris June 22nd, 1981. 15th Int Congress of Rheumatology. p 19–30.

NSAIDs; Diflunisal + Antacids

Antacids containing aluminium with or without magnesium can reduce the absorption of diflunisal by up to 40%, but no important interaction occurs if food is taken at the same time. Magnesium hydroxide can increase the rate of diflunisal absorption.

Clinical evidence

A study in 4 healthy, fasted subjects found that when a single 500-mg oral dose of diflunisal was given 2 hours before, together with, and 2 hours after three 15-mL doses of *Aludrox* (**aluminium hydroxide**), the diflunisal AUC was reduced by about 40%.[1] Another study found that the AUC of a single 500-mg dose of diflunisal was reduced by 13% when it was given with a single 30-mL dose of *Maalox* (**aluminium**/**magnesium hydroxide**), by 21% when it was given 1 hour after the antacid, and by 32% when the antacid was given four times daily.[2] However, in another study, **aluminium**/**magnesium hydroxide** had no effect on the AUC diflunisal when the diflunisal was given 30 minutes after food.[3] This study also found that the AUC of diflunisal was reduced by 26% by 15 mL of **aluminium hydroxide** gel in fasted subjects, but was not affected in fed subjects.[3] **Magnesium hydroxide** suspension markedly increased the rate of diflunisal absorption in fasted subjects. The plasma diflunisal level was increased by 130% at 30 minutes, and by 64% at one hour but the AUC was only increased by a modest 10%.[3]

Mechanism

It is unclear how aluminium antacids reduce the absorption of diflunisal, but adsorption or the formation of insoluble salts has been suggested. Food appears to diminish the effect of antacids on diflunisal absorption.[3] By raising the pH, magnesium hydroxide may promote the dissolution of diflunisal, so increasing its absorption.[3]

Importance and management

Aluminium-containing antacids appear to reduce the absorption of diflunisal in the fasted state, but not if the diflunisal is taken with food. NSAIDs should be taken with or after food to minimise gastrointestinal adverse effects, and so it would appear that this interaction has little clinical relevance.

Magnesium hydroxide increases the absorption of diflunisal in the fasted state, which may improve the onset of analgesia. However, note that magnesium hydroxide increased the endoscopically-detected gastric toxicity of ibuprofen in one study, see 'NSAIDs; Ibuprofen and related drugs + Antacids', p.156.

1. Verbeeck R, Tjandramaga TB, Mullie A, Verbesselt R, De Schepper PJ. Effect of aluminium hydroxide on diflunisal absorption. *Br J Clin Pharmacol* (1979) 7, 519–22.
2. Holmes GI, Irvin JD, Schrogie JJ, Davies RO, Breault GO, Rogers JL, Huber PB, Zinny MA. Effects of Maalox on the bioavailability of diflunisal. *Clin Pharmacol Ther* (1979) 25, 229.
3. Tobert JA, DeSchepper P, Tjandramaga TB, Mullie A, Buntinx AP, Meisinger MAP, Huber PB, Hall TLP, Yeh KC. Effect of antacids on the bioavailability of diflunisal in the fasting and postprandial states. *Clin Pharmacol Ther* (1981) 30, 385–9.

NSAIDs; Fenamates + Antacids

Magnesium hydroxide increases the rate of absorption of mefenamic acid and tolfenamic acid in fasted subjects. The rate of tolfenamic acid absorption is reduced by aluminium hydroxide alone or combined with magnesium hydroxide/magnesium carbonate, but is not affected by sodium bicarbonate.

Clinical evidence

Studies in 6 healthy, fasted subjects given a single dose of **mefenamic acid** 500 mg or **tolfenamic acid** 400 mg found that **magnesium hydroxide** increased the rate of the absorption of both drugs (the **mefenamic acid** AUC after 1 hour was increased threefold and the **tolfenamic acid** AUC

was increased sevenfold) but the total bioavailability was only slightly increased. In contrast, **aluminium hydroxide**, alone and in combination with **magnesium hydroxide**/**magnesium carbonate** (*Medisan Forte*), markedly *reduced* the rate of absorption of **tolfenamic acid**, but similarly, the total amount absorbed was not markedly changed. In this study **sodium bicarbonate** 1 g did not significantly alter the absorption of **tolfenamic acid**.[1]

Mechanism

Uncertain. It is suggested that magnesium hydroxide increases the solubility of acidic drugs such as the fenamates, possibly by forming a soluble salt and therefore enhancing their dissolution. In contrast, aluminium antacids may form insoluble salts of the drug. Note that food may reduce these effects, see 'NSAIDs; Diflunisal + Antacids', p.155.

Importance and management

Information is limited but it would appear that if rapid analgesia is needed with either mefenamic acid or tolfenamic acid, magnesium hydroxide can be given concurrently but aluminium hydroxide should be avoided. However, note that this applies to the fasted state, whereas NSAIDs are usually taken with or after food. Also note that magnesium hydroxide increased the endoscopically-detected gastric toxicity of ibuprofen in one study, see 'NSAIDs; Ibuprofen and related drugs + Antacids', below. Sodium bicarbonate does not interact.

1. Neuvonen PJ, Kivistö KT. Effect of magnesium hydroxide on the absorption of tolfenamic and mefenamic acids. *Eur J Clin Pharmacol* (1988) 35, 495–501.

NSAIDs; Ibuprofen and related drugs + Antacids

Magnesium hydroxide increased the initial absorption of ibuprofen and flurbiprofen, but had no effect on ketoprofen absorption. Unexpectedly, a pharmacodynamic study found increased gastric erosions when ibuprofen was formulated with magnesium hydroxide.
The absorption of dexketoprofen, fenoprofen, flurbiprofen and ibuprofen were not significantly affected by aluminium/magnesium hydroxide. Aluminium phosphate had no effect on ketoprofen absorption. Aluminium hydroxide caused a small reduction in ketoprofen absorption but had no effect on the bioavailability of tiaprofenic acid.
The rate of naproxen absorption is increased by sodium bicarbonate and aluminium/magnesium hydroxide, but decreased by aluminium hydroxide and magnesium oxide.
Simeticone did not affect ketoprofen bioavailability.

Clinical evidence

(a) Dexketoprofen

In 24 healthy subjects an **aluminium**/**magnesium hydroxide** antacid (*Maalox*) had no effect on the rate or extent of absorption of a single 25-mg dose of dexketoprofen, although the maximum level was slightly (13%) lower.[1]

(b) Fenoprofen

In a study in 6 subjects plasma levels of a single 600-mg dose of fenoprofen were not affected by a single 30-mL dose of *Maalox* (**aluminium**/**magnesium hydroxide**).[2]

(c) Flurbiprofen

In a group of young and old fasting healthy subjects, *Maalox* (**aluminium**/**magnesium hydroxide**) 30 mL, taken 30 minutes before a single 100-mg dose of flurbiprofen, was found to affect neither the rate nor extent of flurbiprofen absorption. Similarly, *Maalox* had no effect on steady-state pharmacokinetics of flurbiprofen when both drugs were given 90 minutes before food.[3] Another study, in fasted subjects, found that **magnesium hydroxide** increased the AUC_{0-2} of flurbiprofen by 61%, but the AUC_{0-8} was not changed, which indicated an increased rate of flurbiprofen absorption.[4]

(d) Ibuprofen

In 8 healthy, fasted subjects an antacid containing **aluminium**/**magnesium hydroxide**, given before, with, and after a single 400-mg dose of ibuprofen, did not alter the pharmacokinetics of ibuprofen.[5] In another study, the absorption of ibuprofen formulated with **aluminium** was delayed and reduced, when compared to that of ibuprofen without **aluminium**.[6]

A study in 6 healthy fasted subjects found that **magnesium hydroxide** 850 mg increased the AUC_{0-1} and the peak levels of a single 400-mg dose of ibuprofen by 65% and 31%, respectively. The time to the peak was shortened by about 30 minutes but the total bioavailability was unchanged.[7] In a pharmacodynamic study in healthy subjects, a 400-mg ibuprofen tablet buffered with 200 mg of **magnesium hydroxide**, given at a dose of two tablets three times daily for 5 days resulted in about a threefold increase in number of endoscopically-detected gastric erosions, when compared with the same dose of conventional ibuprofen tablets.[8]

A **sodium**/**potassium salt** (kanwa), often taken as an antacid in some West African countries, appeared to reduce the absorption of ibuprofen. The bioavailability of ibuprofen 400 mg given to 6 healthy subjects with a millet meal containing the salt extract (pH of 8.9) was reduced by about 80%, when compared with either the millet meal alone (pH 5.3) or following overnight fasting.[9]

(e) Ketoprofen

Five healthy, fasted subjects had a 22% reduction in the absorption of a 50-mg dose of ketoprofen (as measured by the amount excreted in the urine) when they were given a 1-g dose of **aluminium hydroxide**.[10] In 10 patients, **aluminium phosphate** 11 g (as a single then a daily dose) had no effect on the pharmacokinetics of ketoprofen 100 mg.[11]

A study in 12 healthy, fasted subjects showed that [activated] dimeticone (**simeticone**) did not significantly affect the bioavailability of a single 100-mg dose of ketoprofen.[12]

In one study, 10 mL of **magnesium hydroxide** suspension (equivalent to 850 mg) was found to have no significant effect on the rate or extent of absorption of ketoprofen 50 mg in fasted subjects, although the rate of ketoprofen absorption was already noted to be fast.[7]

(f) Naproxen

In a study in 14 healthy, fasted subjects, **sodium bicarbonate** 700 mg or 1.4 g increased the rate of absorption of a single 300-mg dose of naproxen, whereas **magnesium oxide** or **aluminium hydroxide** 700 mg reduced the rate of absorption. **Magnesium carbonate** had little effect.[13] On the other hand when 15 or 60 mL of **aluminium**/**magnesium hydroxide** (*Maalox*) was given, the rate and extent of absorption of naproxen were slightly increased.[13]

(g) Tiaprofenic acid

In a study in 7 healthy subjects, **aluminium hydroxide** did not affect the pharmacokinetics of **tiaprofenic acid**.[14]

Mechanism

Magnesium hydroxide appears to improve the rate of absorption of some acidic NSAIDs (which become more soluble as the pH rises) such as ibuprofen and flurbiprofen. An *in vitro* study found that magnesium hydroxide increased ibuprofen solubility, and increased the dissolution rate of 3 ibuprofen tablet formulations, with the greatest increase occurring with the slowest dissolving product.[15] Why this increased the gastric toxicity of ibuprofen in the one pharmacodynamic study is unclear.[8] Sodium bicarbonate appears to have a similar effect on rate of absorption. An *in vitro* study found that an insoluble ibuprofen salt was formed in the presence of aluminium ions[15] and this may explain why the rate/extent of absorption of some NSAIDs is reduced.

Importance and management

It would appear that the initial absorption of both ibuprofen and flurbiprofen is increased by magnesium hydroxide, but not if aluminium hydroxide is present as well. Thus if rapid analgesia is needed, consider using an antacid containing magnesium hydroxide but without aluminium hydroxide. However, the unexpected finding that magnesium hydroxide increased the endoscopically-detected gastric toxicity of ibuprofen[8] suggests that caution may be warranted, particularly on long-term use. Further study is needed.

The rate of naproxen absorption appears to be increased by sodium bicarbonate and decreased by aluminium hydroxide. However, note that these effects were seen in the fasted state, and may not apply when the NSAID is taken with or after food (as is recommended), as is the case with 'diflunisal', (p.155).

No particular precautions would seem to be needed if simeticone, alu-

minium phosphate or magnesium hydroxide are given with ketoprofen, and it seems doubtful if the effects of ketoprofen will be reduced to any great extent by aluminium hydroxide.

1. McEwen J, De Luca M, Casini A, Gich I, Barbanoj MJ, Tost D, Artigas R, Mauleón D. The effect of food and an antacid on the bioavailability of dexketoprofen trometamol. *J Clin Pharmacol* (1998) 38 (Suppl), 41S–45S.
2. Chernish SM, Rubin A, Rodda BE, Ridolfo AS, Gruber CM. The physiological disposition of fenoprofen in man. IV. The effects of position of subject, food ingestion and antacid ingestion on the plasma levels of orally administered fenoprofen. *J Med* (1972) 3, 249–57.
3. Caillé G, du Souich P, Vézina M, Pollock SR, Stalker DJ. Pharmacokinetic interaction between flurbiprofen and antacids in healthy volunteers. *Biopharm Drug Dispos* (1989) 10, 607–15.
4. Rao TRK, Ravisekhar K, Shobha JC, Sekhar EC, Naidu MUR, Krishna DR. Influence of magnesium hydroxide on the oral absorption of flurbiprofen. *Drug Invest* (1992) 4, 473–6.
5. Gontarz N, Small RE, Comstock TJ, Stalker DJ, Johnson SM, Willis HE. Effect of antacid suspension on the pharmacokinetics of ibuprofen. *Clin Pharm* (1987) 6, 413–16.
6. Laska EM, Sunshine A, Marrero I, Olson N, Siegel C, McCormick N. The correlation between blood levels of ibuprofen and clinical analgesic response. *Clin Pharmacol Ther* (1986) 40, 1–7.
7. Neuvonen PJ. The effect of magnesium hydroxide on the oral absorption of ibuprofen, ketoprofen and diclofenac. *Br J Clin Pharmacol* (1991) 31, 263–6.
8. Mäenpää J, Tarpila A, Jouhikainen T, Ikävalko H, Löyttyniemi E, Perttunen K, Neuvonen PJ, Tarpila S. Magnesium hydroxide in ibuprofen tablet reduces the gastric mucosal tolerability of ibuprofen. *J Clin Gastroenterol* (2004) 38, 41–5.
9. Yakasai IA. Effect of sodium/potassium salt (potash) on the bioavailability of ibuprofen in healthy human volunteers. *Eur J Drug Metab Pharmacokinet* (2003) 28, 93–9.
10. Ismail FA, Khalafallah N, Khalil SA. Adsorption of ketoprofen and bumadizone calcium on aluminium-containing antacids and its effect on ketoprofen bioavailability in man. *Int J Pharmaceutics* (1987) 34, 189–96.
11. Brazier JL, Tamisier JN, Ambert D, Bannier A. Bioavailability of ketoprofen in man with and without concomitant administration of aluminium phosphate. *Eur J Clin Pharmacol* (1981) 19, 305–7.
12. Presle N, Lapicque F, Gillet P, Herrmann M-A, Bannwarth B, Netter P. Effect of dimethicone (polysilane gel) on the stereoselective pharmacokinetics of ketoprofen. *Eur J Clin Pharmacol* (1998) 54, 351–4.
13. Segre EJ, Sevelius H, Varady J. Effects of antacids on naproxen absorption. *N Engl J Med* (1974) 291, 582–3.
14. Marečék N, Lücker PW, Penth B, Altmayer P, Wetzelsberger K. Zur Pharmakokinetik von Tiaprofensäure und zur Frage der Interaktion mit ASS und Aluminiumhydroxid. *Arzneimittelforschung* (1981) 31, 116–20.
15. Parojčić J, Corrigan OI. Rationale for ibuprofen co-administration with antacids: potential interaction mechanisms affecting drug absorption. Eur J Pharm Biopharm (2008) 69, 640–7.

NSAIDs; Indometacin or Sulindac + Antacids

A variety of different antacids have been found to slightly alter the absorption of indometacin. Aluminium/magnesium hydroxide does not affect sulindac absorption.

Clinical evidence

In 12 healthy, fasted subjects the AUC of a single 50-mg dose of indometacin was reduced by 35% when formulated with 80% *Mergel* and by 18% when taken with 90% *Mergel*. *Mergel* contains **aluminium**/**magnesium hydroxide** and **magnesium carbonate**.[1]

In another single-dose study, in 6 healthy, fasted subjects, **aluminium hydroxide** suspension 700 mg reduced the rate of indometacin absorption, and reduced the peak indometacin plasma levels. Conversely, **sodium bicarbonate** 1.4 g appeared to increase the rate of absorption, but this did not reach significance because of wide inter-individual variation.[2] In a further study 30 mL of **aluminium**/**magnesium hydroxide** caused only slight changes in the absorption of a 50-mg dose of indometacin in fasted subjects.[3]

The manufacturer of sulindac notes that an antacid (**aluminium**/**magnesium hydroxide** suspension) had no effect on the extent of the absorption of sulindac.[4]

Mechanism

Not known. Aluminium compounds might form insoluble salts with indometacin.[2] Food might reduce this effect, see 'NSAIDs; Diflunisal + Antacids', p.155.

Importance and management

Adequately but not extensively documented interactions. Some reduction in indometacin levels is possible with some aluminium-containing antacids, but given the magnitude of this effect this interaction is unlikely to be clinically relevant. Sulindac absorption is not affected.

1. Galeazzi RL. The effect of an antacid on the bioavailability of indomethacin. *Eur J Clin Pharmacol* (1977) 12, 65–8.
2. Garnham JC, Kaspi T, Kaye CM and Oh VMS. The different effects of sodium bicarbonate and aluminium hydroxide on the absorption of indomethacin in man. *Postgrad Med J* (1977) 53, 126–9.
3. Emori HW, Paulus H, Bluestone R, Champion GD, Pearson C. Indomethacin serum concentrations in man. Effects of dosage, food and antacid. *Ann Rheum Dis* (1976) 35, 333–8.
4. Clinoril (Sulindac). Merck & Co., Inc. US Prescribing information, August 2009.

NSAIDs; Miscellaneous + Antacids

The rate and extent of absorption of ketorolac, dipyrone and tolmetin were not significantly affected by aluminium/magnesium hydroxide. Nabumetone absorption was not affected by aluminium hydroxide, and an unspecified antacid did not affect etodolac absorption.

Clinical evidence

(a) Dipyrone (Metamizole sodium)

The concurrent use of 20 mL of *Maaloxan* (**aluminium**/**magnesium hydroxide** gel) was reported to have had no effect on the pharmacokinetics of the metabolites of dipyrone.[1]

(b) Etodolac

A study in 18 healthy, fasted subjects found that when they were given a single 400-mg dose of etodolac with 30 mL of an unnamed antacid both the rate and the extent of etodolac absorption were unchanged.[2]

(c) Ketorolac

In 12 healthy, fasted subjects the AUC of oral ketorolac 10 mg was found to be reduced by 11% (not statistically significant) when it was taken with an unstated amount of **aluminium**/**magnesium hydroxide** suspension (*Maalox*). The rate of absorption was not affected.[3]

(d) Nabumetone

In 15 healthy, fasted subjects, the absorption of a single 1-g dose of nabumetone (as assessed by AUC and maximum plasma level) was not significantly altered by 160 mL of **aluminium hydroxide** suspension (*Aludrox*).[4]

(e) Tolmetin

A pharmacokinetic study in 24 healthy, fasted subjects found that **aluminium**/**magnesium hydroxide** suspension (*Maalox*), given as a single 20-mL dose four times daily for 3 days, had no significant effect on the absorption of a single 400-mg dose of **tolmetin**.[5]

Mechanism

None.

Importance and management

Although information is limited, no particular precautions would seem to be needed if aluminium or aluminium/magnesium antacids are given with any of these antacids. Note that antacids have been frequently given with NSAIDs to reduce their gastric irritant effects.

1. Levy M, Zylber-Katz E, Rosenkranz B. Clinical pharmacokinetics of dipyrone and its metabolites. *Clin Pharmacokinet* (1995) 28, 216–34.
2. Troy S, Sanda M, Dressler D, Chiang S, Latts J. The effect of food and antacid on etodolac bioavailability. *Clin Pharmacol Ther* (1990) 47, 192.
3. Mroszczak EJ, Jung D, Yee J, Bynum L, Sevelius H, Massey I. Ketorolac tromethamine pharmacokinetics and metabolism after intravenous, intramuscular, and oral administration in humans and animals. *Pharmacotherapy* (1990) 10 (Suppl 6), 33S–39S.
4. von Schrader HW, Buscher G, Dierdorf D, Mügge H, Wolf D. Nabumetone — a novel anti-inflammatory drug: the influence of food, milk, antacids, and analgesics on bioavailability of single oral doses. *Int J Clin Pharmacol Ther Toxicol* (1983) 21, 311–21.
5. Ayres JW, Weidler DJ, MacKichan J, Sakmar E, Hallmark MR, Lemanowicz EF, Wagner JG. Pharmacokinetics of tolmetin with and without concomitant administration of antacid in man. *Eur J Clin Pharmacol* (1977) 12, 421–8.

NSAIDs; Oxicam derivatives + Antacids

The pharmacokinetics of lornoxicam, meloxicam, piroxicam and tenoxicam are not affected by aluminium/magnesium hydroxide antacids. Lornoxicam pharmacokinetics were also not altered by tripotassium dicitratobismuthate or aluminium hydroxide with calcium carbonate.

Clinical evidence, mechanism, importance and management

(a) Lornoxicam

In a study in 18 healthy, fasted subjects, either 10 mL of *Maalox* (**aluminium/magnesium hydroxide**) or 10 g of *Solugastril* (**aluminium hydroxide** with **calcium carbonate**) had no effect on the pharmacokinetics of a 4-mg lornoxicam film-coated tablet.[1] A later study similarly found no changes in the absorption or pharmacokinetics of a lornoxicam film-coated tablet given with **tripotassium dicitratobismuthate** 120 mg twice daily.[2] There would seem to be no reason for avoiding concurrent use.

(b) Meloxicam

In a randomised, crossover study 9 healthy, fasted subjects were given meloxicam 30 mg alone or with *Maalox* suspension (**aluminium/magnesium hydroxide** 900/600 mg) four times daily for 4 days. *Maalox* had no significant effect on the pharmacokinetics of meloxicam.[3] Therefore no adjustments of the dose of meloxicam are needed if given with this type of antacid.

(c) Piroxicam

A multiple-dose study in 20 healthy subjects found that *Mylanta* (**aluminium/magnesium hydroxide**) and *Amphojel* (**aluminium hydroxide**) did not significantly affect the bioavailability of piroxicam 20 mg daily taken after food.[4] Concurrent use need not be avoided.

(d) Tenoxicam

The bioavailability of tenoxicam 20 mg was found to be unaffected in 12 healthy subjects by **aluminium hydroxide** (*Amphojel*) or **aluminium/magnesium hydroxide** (*Mylanta*) whether taken before, with, or after the tenoxicam, and in the fasted state or with food.[5] No special precautions seem necessary.

1. Dittrich P, Radhofer-Welte S, Magometschnigg D, Kukovetz WR, Mayerhofer S, Ferber HP. The effect of concomitantly administered antacids on the bioavailability of lornoxicam, a novel highly potent NSAID. *Drugs Exp Clin Res* (1990) 16, 57–62.
2. Ravic M, Johnston A, Turner P, Foley K, Rosenow D. Does bismuth chelate influence lornoxicam absorption? *Hum Exp Toxicol* (1992) 11, 59–60.
3. Busch U, Heinzel G, Narjes H, Nehmiz G. Interaction of meloxicam with cimetidine, Maalox or aspirin. *J Clin Pharmacol* (1996) 36, 79–84.
4. Hobbs DC, Twomey TM. Piroxicam pharmacokinetics in man: aspirin and antacid interaction studies. *J Clin Pharmacol* (1979) 19, 270–81.
5. Day RO, Lam S, Paull P, Wade D. Effect of food and various antacids on the absorption of tenoxicam. *Br J Clin Pharmacol* (1987) 24, 323–8.

NSAIDs + Aspirin

There is some evidence that non-selective NSAIDs such as ibuprofen antagonise the antiplatelet effects of low-dose aspirin, but that COX-2-selective NSAIDs (coxibs) do not. Some, but not other, epidemiological studies have shown that non-selective NSAIDs reduce the cardioprotective effects of low-dose aspirin. Furthermore, some NSAIDs (particularly coxibs) are associated with increased thrombotic risk and possibly increased risk of death if used in patients with a history of myocardial infarction. The combined use of NSAIDs and low-dose aspirin increases the risk of gastrointestinal bleeds. This seems to apply equally to coxibs.
The combined use of analgesic-dose aspirin and NSAIDs increases the risk of gastrointestinal damage. There are numerous early pharmacokinetic studies of aspirin and NSAIDs, many of which found that aspirin reduced the levels of NSAIDs.

Clinical evidence

A. Cardioprotective effects

A number of pharmacodynamic studies have investigated whether or not NSAIDs affect the antiplatelet effects of low-dose aspirin. **Celecoxib** 200 mg twice daily,[1-3] **diclofenac** 75 mg twice daily,[4] **etoricoxib** 120 mg daily,[5] **lumiracoxib** 400 mg daily,[6] **meloxicam** 15 mg daily,[7] **parecoxib** 40 mg twice daily,[8] **rofecoxib** 25 mg daily,[4] and **sulindac** 200 mg twice daily[3] have all been shown not to alter the antiplatelet effects of aspirin in doses of 75 to 325 mg daily. **Naproxen**,[3,9] **indometacin**,[3] and **tiaprofenic acid**[3] may antagonise the antiplatelet effects of aspirin. The effects of **ibuprofen** are less clear, and may be related to the order of drug administration.[4]

As a consequence of the evidence from a number of pharmacodynamic studies, various cohort/case-control studies or sub-group analyses have been conducted to see if **ibuprofen** and/or other NSAIDs reduce the cardioprotective effect of low-dose aspirin in patients, see 'Table 6.2', (p.159). Because these studies are neither prospective nor randomised, their findings are only suggestive, nevertheless they provide some useful insight. In addition to these studies, there are a number of controlled studies that specifically investigated the effects of using aspirin and ibuprofen.

(a) Ibuprofen

A placebo-controlled, randomised study in patients taking aspirin 100 mg daily long-term for its cardioprotective effects found that ibuprofen 600 mg three times daily for 7 days reduced the antiplatelet effects of aspirin.[2] Further, another placebo-controlled study in healthy subjects found that ibuprofen 400 mg every 12 hours for 3 doses antagonised the antiplatelet effects of a 300-mg dose of soluble aspirin.[3] In a prospective, randomised study, 47 healthy subjects were given aspirin 81 mg daily for 8 days, and then either ibuprofen 400 mg or placebo three times daily (1, 7 and 13 hours after the aspirin dose) for 10 days. No clinically meaningful loss of the cardioprotective effects of low-dose aspirin (as measured by thromboxane B_2 inhibition) occurred with this ibuprofen regimen. However, the authors noted that the continued use of ibuprofen for longer than 10 days might possibly have resulted in a clinically relevant interaction.[10]

B. Gastrointestinal effects

(a) Low-dose aspirin

Low-dose aspirin alone (300 mg or less daily) was associated with an increased risk of hospitalisation for bleeding peptic ulcer in a case-control study. The odds ratios were 2.3 for aspirin 75 mg daily, 3.2 for aspirin 150 mg daily, and 3.9 for aspirin 300 mg daily. Use of NSAIDs combined with low-dose aspirin was associated with a greater risk of bleeding (odds ratio 7.7) than use of either NSAIDs alone (5.4) or low-dose aspirin alone (3.3).[11] Similar findings were reported in a cohort study (rate ratio for gastrointestinal bleed for low-dose aspirin 2.6, and for combined use with NSAIDs 5.6).[12]

A case-control study found that coxib use alone was associated with a lower risk of upper gastrointestinal bleeding than that found with non-selective NSAIDs. However, when coxibs were given with low-dose aspirin, the gastrointestinal advantage tended to disappear.[13] Patients taking low-dose aspirin (325 mg or less daily) with **celecoxib** had a higher frequency of gastrointestinal complications than those taking **celecoxib** alone. Moreover, there was no difference in the frequency of gastrointestinal complications between those taking low-dose aspirin with **celecoxib** and those taking low-dose aspirin with **ibuprofen** or **diclofenac**. This was despite **celecoxib** alone being associated with a lower frequency of gastrointestinal adverse effects than **ibuprofen** or **diclofenac** alone.[14] Similar results were found with **rofecoxib** 25 mg daily, which increased the incidence of ulcers in patients taking enteric-coated aspirin 81 mg daily.[15]

(b) Analgesic-dose aspirin

In a case-control study of data from 1993 to 1998 in the UK General Practice Research Database the risk of upper gastrointestinal bleeding or perforation was increased by slightly more than an additive effect in patients taking both aspirin and NSAIDs (8.2-fold), when compared with aspirin alone (2.4-fold), or NSAIDs alone (3.6-fold). The specific NSAIDs were not mentioned.[16] Another study provided similar findings,[17] as have studies specifically looking at low-dose aspirin (325 mg or less daily), see above. Analysis of Yellow Card reports to the CSM in the UK of gastrointestinal perforation/obstruction, ulceration or bleeding with **diclofenac**, **naproxen**, and **ibuprofen** revealed that 28% of the patients were receiving concurrent aspirin (dose not stated).[18]

The one pharmacodynamic study (see below), that also measured gastrointestinal blood loss, found increased bleeding when anti-inflammatory doses of aspirin were given with **sodium meclofenamate**.[6]

A case report described acute ulcerative colitis in a woman taking **rofecoxib** 25 mg daily who also took aspirin.[19]

C. Pharmacokinetic and Pharmacodynamic studies

Early studies evaluating non-aspirin NSAIDs in rheumatoid arthritis commonly permitted the concurrent use of aspirin, which was then in wide use for this condition. The unexpected finding that **indometacin** was no more effective than placebo in patients taking aspirin in one study led to a number of pharmacokinetic studies with this combination (see *Indometacin*, below), and subsequently other NSAID/aspirin combinations. These studies generally have little clinical relevance to current clinical practice where anti-inflammatory doses of aspirin should not be used in combination with NSAIDs because of the increased risk of gastrointestinal bleed-

Table 6.2 Summary of studies on the effect of NSAIDs on the cardioprotective effect of antiplatelet-dose aspirin

Study type	*Criteria*	*Outcome*	*Drugs (Number of patients)*	*Comments*	*Refs*
Studies showing a decrease in the cardioprotection of aspirin with NSAIDs					
Retrospective cohort	Discharge after CVD	Mortality	Aspirin alone (6285) Aspirin with Ibuprofen (187) Aspirin with Diclofenac (206) Aspirin with other NSAID (429)	Increased all-cause mortality and cardiovascular mortality in those taking aspirin with ibuprofen compared with the other groups.	1
Subgroup analysis of an RCT	Male physicians randomised to aspirin 325 mg on alternate days or placebo	First MI	Aspirin alone (5273) Aspirin with intermittent NSAID (5147) Aspirin with regular NSAID (598)	Use of NSAIDs for 60 days or more per year was associated with an increased risk of MI in those taking aspirin.	2
Case-control		First non-fatal MI	Aspirin alone (694) Aspirin with NSAIDs (170) NSAIDs alone (128)	Both aspirin alone, and NSAIDs alone were associated with a reduced risk of MI, but combined use was not.	3
Studies showing no effect of NSAIDs on the cardioprotection of aspirin					
Retrospective cohort	Discharge after MI	Death in first year	Aspirin alone (36211) NSAID alone (736) Aspirin with NSAID (2096) Neither (9541)	Risk of death reduced to a similar extent by aspirin, NSAIDs, and the combination.	4
Retrospective cohort	Discharge after MI and on aspirin	Death in first year	Aspirin alone (66739) Aspirin with Ibuprofen (844) Aspirin with other NSAID (2733)	Risk of death comparable between the 3 groups.	5
Retrospective cohort	General Practice Research Database	Acute MI or death from coronary heart disease	NSAID alone (417) NSAID with Aspirin (163) Aspirin alone (1119) Non-NSAID users (1878)	Incidence of acute MI unaffected by NSAID alone. NSAID with aspirin similar to aspirin alone.	6
Studies showing an increase in the cardioprotection of aspirin with NSAIDs					
Retrospective cohort	Two consecutive prescriptions for aspirin or ibuprofen	Biochemical evidence of MI	Aspirin alone (10239) Aspirin with Ibuprofen (3859)	The aspirin alone group experienced 0.0044 MIs per patient month, compared with 0.0026 in the aspirin with ibuprofen group.	7

1. MacDonald TM, Wei L. Effect of ibuprofen on cardioprotective effect of aspirin. *Lancet* (2003) 361, 573-4.
2. Kurth T, Glynn RJ, Walker AM, Chan KA, Buring JE, Hennekens CH, Gaziano JM. Inhibition of clinical benefits of aspirin on first myocardial infarction by nonsteroidal antiinflammatory drugs. *Circulation* (2003) 108, 1191-5.
3. Kimmel SE, Berlin JA, Reilly M, Jaskowiak J, Kishel L, Chittams J, Strom BL. The effects of nonselective non-aspirin non-steroidal anti-inflammatory medications on the risk of nonfatal myocardial infarction and their interaction with aspirin. *J Am Coll Cardiol* (2004) 43, 985-90.
4. Ko D, Wang Y, Berger AK, Radford MJ, Krumholz HM. Nonsteroidal antiinflammatory drugs after acute myocardial infarction. *Am Heart J* (2002) 143, 475-81.
5. Curtis JP, Wang Y, Portnay EL, Masoudi FA, Havranek EP, Krumholz HM. Aspirin, ibuprofen, and mortality after myocardial infarction: retrospective cohort study. *BMJ* (2003) 327, 1322-3.
6. García Rodríguez LA, Varas-Lorenzo C, Maguire A, González-Pérez A. Nonsteroidal antiinflammatory drugs and the risk of myocardial infarction in the general population. *Circulation* (2004) 109, 3000-6.
7. Patel TN,Goldberg KC. Use of aspirin and ibuprofen compared with aspirin alone and the risk of myocardial infarction. *Arch Intern Med* (2004) 164, 852-6.

ing (see above) and lack of proven additional benefit. However, the pharmacokinetic studies are briefly summarised below.

(a) Diclofenac

Aspirin 900 mg reduced the AUC of diclofenac 50 mg by about one-third in a single-dose study.[20] In a clinical study, there was no significant difference in efficacy between diclofenac 50 mg three times daily alone or with aspirin 900 mg three times daily.[21]

(b) Fenamates

A study in 20 healthy subjects given aspirin 600 mg and **sodium meclofenamate** 100 mg both three times daily for 14 days found no significant reductions in plasma salicylate levels, but plasma **meclofenamate** levels were reduced to some extent. However, gastrointestinal blood loss was approximately doubled compared with either drug alone.[22]

(c) Ibuprofen and related drugs

Aspirin 1.3 to 3.6 g daily more than halved the serum levels of ibuprofen 800 mg to 2.4 g daily,[23,24] without affecting salicylate levels.[24] There was little additional clinical benefit from the combination.[24] Similarly, aspirin reduced the AUC of **flurbiprofen** by about two-thirds,[25] but without any clear changes in clinical effectiveness.[26] The pharmacokinetics of the aspirin were unchanged by **flurbiprofen**.[25] Aspirin 3.9 g daily also virtually halved the AUC of **fenoprofen** 2.4 g daily,[27] and reduced the AUC of **ketoprofen** 200 mg daily[28] by about one-third. The AUC of **naproxen** was only minimally reduced (by 10 to 15%).[29,30] **Choline magnesium trisalicylate** increased the clearance of **naproxen** by 56% and decreased its serum levels by 26% in one study.[31]

(d) Indometacin

The overall picture with aspirin and indometacin is confusing and contradictory. One early study found that indometacin had no additional benefit in patients already taking aspirin.[32] Consequently, a number of studies were conducted to see if there was a drug interaction. Some studies reported that aspirin reduced serum indometacin levels[27,33-35] or its efficacy,[36] or that the combination was no more effective than either drug alone.[37] Others report that no change in indometacin levels occurred.[38-40] Further studies using buffered aspirin claimed that it increased the rate of absorption of indometacin and was associated with an increase in adverse effects (tiredness, lack of coordination).[41,42] One study found that indometacin 50 mg given as suppositories at night was found to have a significant additive effect when given with slow-release aspirin 2 or 4.5 g daily, estimated by articular index and subjective ratings of pain and morning stiffness. However, the dose of aspirin (most often the 4.5 g dose) had to be reduced in 7 of the 24 treatment periods due to adverse effects.[43]

(e) Oxicams

Aspirin 3 g daily increased the maximum plasma levels of **meloxicam** 30 mg daily by 25% and its AUC by 10%.[44] Plasma levels of **piroxicam** 40 mg then 20 mg daily were not significantly affected by aspirin 3.9 g daily, and salicylate levels were unaffected by **piroxicam**.[45] Aspirin 2.6 to 3.9 g daily more than halved the serum levels of **tenoxicam** 20 mg daily.[46]

(f) Miscellaneous NSAIDs

Aspirin 600 mg four times daily caused a 15% reduction in the plasma levels of **diflunisal** 250 mg twice daily for 3 days.[47] Single-dose studies have shown that the absorption of **nabumetone** 1 g is not significantly altered by aspirin 1.5 g.[48] The plasma levels of **tolmetin** 1.2 g daily were slightly reduced by aspirin 3.9 g daily.[49]

Mechanism

Aspirin irreversibly blocks the production of thromboxane A2 by binding to cyclo-oxygenase (COX-1) in platelets, and so inhibits platelet aggregation. The beneficial cardiovascular effects are attributed to this effect. Other NSAIDs that are COX-1 inhibitors also have this effect, but it is more short-lived since they bind reversibly. These NSAIDs can therefore competitively inhibit the binding of aspirin to platelets (a fact that was shown *in vitro* as early as the 1980s[50]). When these NSAIDs are present in sufficient quantities when a daily low-dose of aspirin is given, they therefore reduce its antiplatelet effect. *In vitro* study confirms that COX-2 selective NSAIDs have less effect.[51]

The damaging effects of aspirin and NSAIDs on the gut appear to be additive. This occurs even at the low doses of aspirin used for antiplatelet effects (doses as low as 75 mg daily).[11] The mechanisms behind the pharmacokinetic changes have not been resolved. Changes in the rates of absorption and renal clearance and competition for plasma protein binding have been proposed.

Importance and management

A. Cardioprotective effects

The evidence currently available on the antagonism of the antiplatelet effects of aspirin by ibuprofen is conflicting. However, the FDA in the US warn that ibuprofen may interfere with the antiplatelet effects of low-dose aspirin and reduce its cardioprotective benefits. Until definitive clinical information is available, they recommend that patients taking immediate-release, low-dose aspirin (81 mg daily) should take the aspirin 30 minutes before or 8 hours after taking ibuprofen to prevent any possible interaction. The recommendation applies to patients taking ibuprofen chronically but does not apply to those taking enteric-coated aspirin formulations.[52] Others have concluded that ibuprofen is more likely to interact with aspirin than not, and that the interaction is more likely to occur in those who take ibuprofen long-term and more importantly in those at high cardiovascular risk.[53] It has also been suggested that non-selective NSAIDs should be avoided in patients taking low-dose aspirin, or that it may be advisable to replace aspirin with an alternative antiplatelet drug.[54] Some have concluded that when patients taking low-dose aspirin for cardioprotection require long-term NSAIDs for inflammatory conditions, the use of diclofenac would seem preferable to ibuprofen.[55] A coxib was also suggested as an alternative,[55] but the subsequent findings of an increased risk of serious cardiovascular effects with the coxibs (as a class[56]) probably precludes this. In 2006 the CHM in the UK advised that there may be a small increased risk of thrombotic events with the non-selective NSAIDs, particularly when used at high doses and for long-term treatment.[57] In addition, the European Society of Cardiology guidelines recommend that patients resistant to antiplatelet treatment should not be given either coxibs or non-selective NSAIDs with either aspirin or clopidogrel.[58]

Further, a retrospective analysis of 58 432 patients discharged from hospital after a first myocardial infarction found that the subsequent use of coxibs in all doses and non-selective NSAIDs in high doses resulted in increased mortality.[59] On the basis of this and other studies, the European Society of Cardiology guidelines recommend that coxibs and NSAIDs should not be used in the post myocardial infarction period.[58]

B. Gastrointestinal effects

The additive risk of gastrointestinal damage from combining aspirin and NSAIDs is established. Because of this, and because of the lack of clear benefit from the combination, the use of anti-inflammatory/analgesic doses of aspirin with NSAIDs should be avoided. With antiplatelet-dose aspirin, from a gastrointestinal perspective, the lowest dose of aspirin should be used (75 mg).[11] However, when combined with low-dose aspirin, the available evidence indicates that there is no gastrointestinal benefit to be obtained from using a coxib instead of diclofenac or ibuprofen.[14] Note that the CSM in the UK advised that the combination of a non-aspirin NSAID and low-dose aspirin should be used only if absolutely necessary.[18,60] They stated that patients taking long-term aspirin should be reminded to avoid NSAIDs, including those bought without prescription.[60] If concurrent use is necessary, where appropriate, the use of a proton pump inhibitor may be considered for prophylaxis of NSAID-induced gastrointestinal damage. Note also that the European Society of Cardiology advises against the use of anti-inflammatory drugs post-myocardial infarction (see A above).

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NSAIDs + Azoles

Fluconazole markedly raises celecoxib levels, whereas ketoconazole has no effect on celecoxib levels. Fluconazole and ketoconazole moderately increase the levels of valdecoxib (the main metabolite of parecoxib). Ketoconazole moderately raises etoricoxib plasma levels. Fluconazole has no clinically relevant effect on lumiracoxib pharmacokinetics. Voriconazole markedly raises diclofenac and ibuprofen levels and fluconazole raises flurbiprofen and ibuprofen levels.

Clinical evidence

(a) Coxibs

1. Celecoxib. The manufacturer notes that **fluconazole** 200 mg daily increased the AUC of a single 200-mg dose of celecoxib by 130% and increased the maximum level by 60%. Conversely, **ketoconazole** had no effect on the pharmacokinetics of celecoxib.[1]

2. Etoricoxib. A single 60-mg dose of etoricoxib was given to healthy subjects on day 7 of an 11-day course of **ketoconazole** 400 mg daily. The AUC of etoricoxib was increased by 43% and its maximum plasma level was increased by 29%.[2]

3. Lumiracoxib. A placebo-controlled, crossover study in 13 healthy subjects[3] found that **fluconazole** 400 mg on day 1 and 200 mg on days 2 to 4 had no clinically relevant effect on the pharmacokinetics of a single 400-mg dose of lumiracoxib given on day 4.

4. Parecoxib. The manufacturer of parecoxib reports a study in which **fluconazole** increased the plasma levels of valdecoxib (the main metabolite of parecoxib) by 19% and raised its AUC by 62%.[4] **Ketoconazole** had a similar, but more moderate effect on the levels of valdecoxib (maximum plasma levels increased by 24%, AUC increased by 38%).[4]

(b) Diclofenac

In a randomised, crossover study, 10 healthy subjects were given either diclofenac 50 mg alone or one hour after the last dose of **voriconazole** (400 mg twice daily on the first day, 200 mg twice daily on the second day). The AUC of diclofenac was increased by 78% in the presence of **voriconazole**, its peak plasma level was approximately doubled and its renal clearance was decreased by 47%.[5]

(c) Ibuprofen and related drugs

1. Flurbiprofen. In a study, 14 healthy subjects were given a single 100-mg dose of flurbiprofen either alone or 30 minutes after two doses of **fluconazole** 200 mg. **Fluconazole** increased the peak plasma level and AUC of flurbiprofen by 23% and 81%, respectively, reduced its clearance by about 45% and prolonged its half-life from 3.3 hours to 5.3 hours. The AUC of the metabolite 4-hydroxyflurbiprofen was significantly reduced.[6]

2. Ibuprofen. In a study, 12 healthy subjects were given ibuprofen 400 mg, alone or one hour after the last dose of **voriconazole** (400 mg twice daily on the first day, 200 mg twice daily on the second day) or **fluconazole** (400 mg on the first day and 200 mg on the second day). **Voriconazole** increased the peak plasma level of *S*-ibuprofen by 22%, doubled its AUC, and increased its elimination half-life by 43%. **Fluconazole** increased the peak plasma level and AUC of *S*-ibuprofen by 16% and 83%, respectively, and increased its elimination half-life by 34%. **Voriconazole** and **fluconazole** had only weak effects on the pharmacokinetics of *R*-ibuprofen.[7]

Mechanism

Fluconazole is an inhibitor of the cytochrome P450 isoenzyme CYP2C9 and ketoconazole inhibits CYP3A4. Celecoxib is extensively metabolised by CYP2C9, and therefore shows marked rises in plasma levels when given with fluconazole but not ketoconazole. Etoricoxib is partially metabolised by CYP3A4, and therefore shows moderate rises in plasma levels with ketoconazole. Valdecoxib is metabolised by both CYP2C9 and CYP3A4, and therefore it is modestly affected by both fluconazole and ketoconazole. Parecoxib is a valdecoxib prodrug, and interacts similarly. From the study with lumiracoxib it appears that its pharmacokinetics are unlikely to be affected by inhibitors of CYP2C9, because, even though lumiracoxib is largely metabolised by CYP2C9, other pathways are also important (e.g. glucuronidation).[3] Voriconazole probably increased the levels of diclofenac by inhibiting its metabolism by CYP2C9 and possibly by CYP3A4,[5] and the metabolism of flurbiprofen and the *S*-enantiomer of ibuprofen by CYP2C9 is inhibited by fluconazole and voriconazole.[6,7]

Importance and management

The pharmacokinetic interactions between the coxibs and azoles are established, although their effect in clinical practice has not been assessed. The marked rise in celecoxib levels with fluconazole could be important, and the UK manufacturer recommends that the dose of celecoxib should be halved in patients receiving fluconazole,[1] whereas the US manufacturer suggests starting with the lowest recommended dose.[8] The rise in valdecoxib levels with fluconazole is less marked; nevertheless, the manufacturer recommends that for parecoxib the dose should be reduced (but they do not suggest by how much).[4] No dose adjustments are thought to be necessary if etoricoxib or parecoxib are given with ketoconazole, and if lumiracoxib is given with fluconazole.

The clinical importance of the interaction between voriconazole and diclofenac is not known, but lower doses of diclofenac may be adequate for patients also taking voriconazole.[5] Similarly, lower doses of ibuprofen,[7] or

possibly flurbiprofen, may be adequate if they are given with either fluconazole or voriconazole, especially if the initial NSAID dose is high.[7]

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NSAIDs + Bile-acid binding resins

The simultaneous use of colestyramine markedly reduced the absorption of diclofenac and sulindac, modestly reduced the absorption of ibuprofen, but only delayed and did not reduce the extent of naproxen absorption. Giving colestyramine three or more hours after oral sulindac, piroxicam, or tenoxicam still markedly reduced their plasma levels. Markedly reduced NSAID levels have also been found when colestyramine is given after intravenous meloxicam or tenoxicam.
The simultaneous use of colestipol modestly reduced the oral absorption of diclofenac, but had no effect on ibuprofen absorption.

Clinical evidence

(a) Diclofenac

A single-dose, crossover study in 6 healthy, fasting subjects found that the simultaneous use of **colestyramine** 8 g markedly reduced the AUC of a single 100-mg oral dose of enteric-coated diclofenac by 62% and reduced its maximum plasma levels by 75%. **Colestipol** 10 g reduced the AUC of diclofenac by 33% and reduced its maximum plasma levels by 58%.[1]

(b) Ibuprofen

A single-dose, crossover study in 6 healthy fasting subjects found that the simultaneous use of **colestyramine** 8 g modestly reduced the AUC of a single 400-mg oral dose of ibuprofen by 26% and reduced its maximum plasma levels by 34%. The rate of absorption was also reduced. Conversely, **colestipol** 10 g had no significant effect on the pharmacokinetics of ibuprofen.[2]

(c) Meloxicam

A study in 12 healthy subjects found that **colestyramine** 4 g taken 2 hours before a 30-mg *intravenous* dose of meloxicam increased its clearance by 49% and reduced its mean residence time in the body by 39%.[3]

(d) Naproxen

In a study in 8 healthy fasting subjects the absorption of a single 250-mg dose of naproxen was delayed but not reduced by the simultaneous use of **colestyramine** 4 g in 100 mL of orange juice. The amount of naproxen absorbed after 2 hours was reduced from 96% to 51%, but was complete after 5 hours.[4]

(e) Piroxicam or Tenoxicam

A study in 8 healthy subjects found that **colestyramine** increased the clearance of a single 20-mg oral dose of piroxicam and a single 20-mg *intravenous* dose of tenoxicam by 52% and 105%, respectively, and reduced their half-lives by 40% and 52%, respectively. In this study, **colestyramine** 4 g three times daily was started 2 hours before the intravenous tenoxicam and 3.5 hours after the oral piroxicam.[5] In another multiple-dose study **colestyramine**, given 4 hours after oral piroxicam or oral tenoxicam, gave similar results,[6] as did a study starting **colestyramine** 24 hours after the last dose of a 14-day course of **piroxicam** 20 mg daily [which has a long half-life].[7] The elimination half-life of both analgesics was roughly doubled by **colestyramine** 24 g daily.[6]

(f) Sulindac

In 6 healthy subjects **colestyramine** 4 g twice daily with meals was found to reduce the AUC of a single 400-mg dose of sulindac (given simultaneously) by 78%, and reduced the AUC of the sulfide metabolite of sulindac by 84%. Even when sulindac was given 3 hours before **colestyramine**, the AUCs of the sulindac and its sulphide metabolite were reduced by 44% and 55%, respectively.[8]

Mechanism

The studies of simultaneous oral use suggest that the anion-exchange resin colestyramine, and to a lesser extent colestipol, bind anionic NSAIDs (e.g. diclofenac) in the gut, so reducing their absorption. The studies that found reduced plasma levels when colestyramine was given after intravenous oxicams or separated by at least 3 hours from some oral NSAIDs, suggest that colestyramine can reduce the enterohepatic recirculation of these drugs.

Importance and management

Established interactions. Colestyramine markedly reduces the initial absorption of some NSAIDs (seen with diclofenac), and if these NSAIDs also undergo enterohepatic recirculation, their clearance will also be increased (seen with meloxicam, piroxicam, sulindac, and tenoxicam). This latter interaction cannot be avoided by separating the doses, and it may be best not to use colestyramine with these NSAIDs. Colestyramine can be used to speed the removal of piroxicam and tenoxicam following overdosage.[4] Diclofenac has been formulated with colestyramine in an attempt to reduce gastric mucosal damage by reducing direct mucosal contact: 140 mg of diclofenac-colestyramine is considered equivalent to 70 mg of diclofenac.[9]

Any interaction between colestyramine and naproxen or ibuprofen is probably not clinically important, although colestyramine delayed the absorption of both drugs, which may be relevant if they are being taken for the management of acute pain. Information on many other NSAIDs appears to be lacking. *Animal* studies suggest that **mefenamic acid**, **flufenamic acid** and **phenylbutazone** will also be affected by colestyramine.[10,11] Note that it is usually recommended that other drugs are given 1 hour before or 4 to 6 hours after colestyramine.

The reduction in diclofenac absorption with colestipol may be clinically relevant; if the combination is required, monitor well. Note that it is usually recommended that other drugs are given 1 hour before or 4 hours after colestipol.

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NSAIDs or Aspirin + Caffeine

Caffeine modestly increases the bioavailability, rate of absorption and plasma levels of aspirin. Adding caffeine to diclofenac may improve its efficacy in the treatment of migraine.

Clinical evidence, mechanism, importance and management

In a study in healthy subjects, caffeine citrate 120 mg given with a single 650-mg dose of aspirin increased the AUC of aspirin 36%, increased its maximum plasma levels by 15%, and increased its rate of absorption by 30%.[1] This confirms the results of previous studies.[2,3] These studies suggest that caffeine may modestly potentiate the efficacy of aspirin by a pharmacokinetic mechanism. However, a meta-analysis of randomised, controlled studies concluded that there was no therapeutic advantage to adding caffeine to analgesic doses of aspirin in patients experiencing postoperative pain.[4]

In a placebo-controlled study in patients with migraine, there was a non-significant trend towards improved analgesic effect in patients receiving **diclofenac** softgel capsules 100 mg and caffeine 100 mg, when compared with diclofenac alone, although the sample size was too small to provide meaningful results.[5]

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NSAIDs + Febuxostat

Febuxostat does not affect the pharmacokinetics of indometacin and naproxen. Naproxen, but not indometacin, increases the plasma levels of febuxostat.

Clinical evidence, mechanism, importance and management

A crossover study in 26 healthy subjects found that the concurrent use of febuxostat 80 mg daily and **indometacin** 50 mg twice daily did not affect the pharmacokinetics of either drug.[1] In a further study, 25 healthy subjects were given febuxostat 80 mg daily, **naproxen** 500 mg twice daily, or both drugs together. **Naproxen** increased the peak plasma level and AUC of febuxostat by about 28% and 40%, respectively, but this was not expected to be clinically significant. Febuxostat did not affect the pharmacokinetics of **naproxen** (24 subjects evaluated). It was concluded that febuxostat may be given with either **indometacin** or **naproxen** without dose adjustments.[1]

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NSAIDs + Fluvastatin

Fluvastatin may modestly reduce the clearance of diclofenac, but no clinically significant interactions between fluvastatin and NSAIDs appear to have been reported.

Clinical evidence, mechanism, importance and management

A study in 14 healthy subjects given fluvastatin 40 mg daily for 8 days and a single 25-mg dose of **diclofenac** found that fluvastatin increased the peak plasma level and AUC of diclofenac by 60% and 25%, respectively, although there was considerable inter-individual variation in these results. Clearance of **diclofenac** was decreased by about 15%. This was possibly due to inhibition of the cytochrome P450 CYP2C9-mediated metabolism of **diclofenac** by fluvastatin and the authors suggest that an interaction may occur in some patients.[1] However, the manufacturer of fluvastatin states that fluvastatin does not influence the metabolism of **phenazone** (**antipyrine**) so that interactions with drugs metabolised by hepatic enzyme systems are not expected.[2] They also state that in clinical studies in which fluvastatin was used with NSAIDs, no clinically significant adverse interactions occurred.[2]

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NSAIDs + Food

In general, food has no clinically significant effect on the absorption of the NSAIDs; however, the delay in absorption that occurs may be important if NSAIDs are given in acute pain management.

Clinical evidence

(a) Celecoxib

A study in 50 children found that high-fat food, increased the maximum plasma concentration of a single 250-mg/m^2 dose of celecoxib by 82% and increased its AUC by 60%. When steady-state levels were achieved with celecoxib 250 mg/m^2 twice daily, food increased its maximum plasma concentration by 99% and increased its AUC by 75%.[1] The manufacturers of celecoxib note that a high-fat meal delayed celecoxib absorption by about one to 2 hours[2,3] and the total absorption was increased by 10% to 20%.[3]

(b) Dexketoprofen

The absorption of a single 25-mg dose of dexketoprofen was delayed by food (maximum level reduced by 45% and time to maximum level delayed by about 1 hour), but the AUC was not affected.[4]

(c) Diclofenac

In a study, 13 healthy subjects were given a single 105-mg dose of diclofenac potassium suspension (*Flogan*) while fasting and after food. The pharmacokinetics of diclofenac were not changed to a clinically relevant extent by food, except that absorption was delayed (time to maximum level increased by about 30 minutes).[5] Similar findings (an increase in time to maximum level of 1.5 to 3 hours) were reported for single doses of enteric-coated diclofenac tablets.[6] However, there was no difference in the steady-state levels of diclofenac 50 mg twice daily when given before or after food.[6]

(d) Etodolac

When 18 healthy subjects were given etodolac 400 mg after a high-fat meal, peak serum levels were roughly halved, and delayed, from 1.4 hours to 3.8 hours, but the total amount absorbed was not markedly changed, when compared to the fasting state.[7]

(e) Etoricoxib

A high-fat meal reduced the maximum level of etoricoxib by 36% and delayed it by 2 hours, without affecting the extent of absorption.[8]

(f) Flurbiprofen

Food slightly increased the maximum plasma level and AUC of sustained-release flurbiprofen (*Froben SR*) by 15% and 25%, respectively, but delayed the time to achieve the maximum level by about 5 hours.[9]

(g) Ibuprofen

Food had no effect on the pharmacokinetics of the *S*- and *R*-enantiomers of ibuprofen in one study.[10] However, in another study, food delayed the absorption of both enantiomers of ibuprofen, and slightly increased the ratio of the *S*- to *R*-enantiomer.[11] A study considering the effect of food on ibuprofen pharmacokinetics found that the maximum level of a single 400-mg dose of a standard release ibuprofen tablet and two readily soluble preparations (ibuprofen lysinate and ibuprofen extrudate), was consistently lower and appeared later when the dose was given after a standardised breakfast; the extent of ibuprofen absorption was also reduced by food for all three formulations.[12] However, in a further study, food increased the maximum plasma level of sustained-release ibuprofen (*Brufen Retard)* by 42% without affecting the time to achieve the maximum level or the bioavailability.[9]

(h) Indometacin

Studies in patients and healthy subjects, given single or multiple oral doses of indometacin have found that food delays and reduces peak serum indometacin levels, but the fluctuations in levels are somewhat reduced.[13]

(i) Ketoprofen

Food significantly decreased the rate and extent of absorption of ketoprofen in both single and multiple dose studies in healthy subjects. The AUC was decreased by about 40% and the time to maximum levels decreased by about 5 hours.[14] A further study found that the rate of absorption and the peak plasma levels of ketoprofen were reduced by food, although the AUC was unaltered.[15] In another study, the absorption of ketoprofen

(200 mg daily, as a gastric-juice resistant, sustained-release formulation, given 4 hours before the first meal of the day) was about 15 to 24% greater when 16 healthy subjects were given a low-calorie/low-fat diet rather than a high-calorie/high-fat diet.[16] In a further study in 4 healthy subjects, which measured the urinary excretion of ketoprofen after a single 50-mg dose given with water, whole skimmed milk, or a traditional Egyptian breakfast, it was concluded that the rate and extent of absorption of ketoprofen had been reduced by the presence of food, and the extent of absorption was also reduced by milk.[17]

(j) Meloxicam

In one study, the rate (time to peak serum levels) and extent of absorption (AUC) of meloxicam 30 mg was not altered by food intake.[18]

(k) Nabumetone

The absorption of a single 1-g dose of nabumetone was increased by food and milk, as shown by an increase of about 50% in the maximum levels and a 40% increase in the AUC_{0-24}. However, the AUC_{0-72} was not significantly increased.[19]

(l) Naproxen

Food did not have any clinically relevant effect on the pharmacokinetics of sustained-release naproxen in two studies.[20,21] Taking a single 550-mg dose of naproxen sodium with a meal had no effect on its analgesic efficacy in postoperative pain, when compared with the fasted state.[22] However, the rate of absorption of a single 550-mg dose of *S*-naproxen betainate sodium salt monohydrate was found to be reduced by a high-fat meal, when compared with the fasting state.[23]

(m) Piroxicam

Food caused some delay in the time to reach maximum levels of piroxicam in a single-dose study, but had no effect on total absorption.[24] In another study, the steady-state plasma levels of piroxicam 20 mg daily were unaffected by food.[25]

(n) Tenoxicam

In a study in 12 healthy subjects, the bioavailability of tenoxicam 20 mg was unaffected by food, although the time taken to reach peak serum levels was delayed by about 4 hours.[26]

Mechanism

Food delays gastric emptying, therefore frequently affects the rate, but not the extent, of absorption of the NSAIDs.

Importance and management

Food reduces the rate of absorption but has little or no effect on the extent of absorption of most of the NSAIDs studied. The effect of food was seen to vary with different formulations of NSAIDs; however, these changes in absorption will have little clinical relevance when these drugs are being used regularly to treat chronic pain and inflammation. If these drugs are being used for the treatment of acute pain, giving them on an empty stomach would be preferable in terms of onset of effect, and is suggested by the manufacturers of dexketoprofen[27] and etoricoxib.[8] However, it is usually recommended that NSAIDs are given with or after food in an attempt to minimise their gastrointestinal adverse effects.

Although food delayed the absorption of celecoxib, the UK manufacturer says that it can be taken with or without food.[2] However, high-fat food may increase the total absorption of celecoxib and the US manufacturer suggests that higher doses (400 mg twice daily) should be given with food to improve absorption.[3]

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NSAIDs + Ginkgo (*Ginkgo biloba*)

An isolated case describes fatal intracerebral bleeding in a patient taking ginkgo with ibuprofen, and another case describes prolonged bleeding and subdural haematomas in another patient taking ginkgo and rofecoxib. Studies with diclofenac and flurbiprofen showed that ginkgo had no effect on the pharmacokinetics of these drugs.

Clinical evidence

A case of fatal intracerebral bleeding has been reported in a 71-year-old patient taking a ginkgo supplement (*Gingium*) 4 weeks after he started to take **ibuprofen** 600 mg daily.[1] A 69-year-old man taking a ginkgo supplement and **rofecoxib** had a subdural haematoma after a head injury, then recurrent small spontaneous haematomas. He was subsequently found to have a prolonged bleeding time, which returned to normal one week after stopping the ginkgo supplement and **rofecoxib**, and remained normal after restarting low-dose **rofecoxib**.[2]

A placebo-controlled study in 11 healthy subjects who were given ginkgo leaf (*Ginkgold*) 120 mg twice daily for three doses, followed by a single 100-mg dose of **flurbiprofen**, found that the pharmacokinetics of flurbiprofen were unchanged.[3]

A study in 12 healthy subjects who were given **diclofenac** 50 mg twice daily for 14 days, with ginkgo extract (*Ginkgold*) 120 mg twice daily on days 8 to 15, found no alteration in the AUC or oral clearance of diclofenac.[4]

Mechanism

The reason for the bleeding is not known, but ginkgo extract contains ginkgolide B, a potent inhibitor of platelet-activating factor *in vitro*, which is needed for arachidonate-independent platelet aggregation. However, in one controlled study in healthy subjects, taking a ginkgo preparation alone for two weeks had no effect on platelet function.[5] Nevertheless, there are case reports of ginkgo supplements, on their own, being associated with prolonged bleeding times,[6,7] left and bilateral subdural haematomas,[6,8] a right parietal haematoma,[9] post-laparoscopic cholecystectomy bleeding,[10]

and subarachnoid haemorrhage.[7] Ibuprofen is an inhibitor of platelet aggregation, but selective inhibitors of COX-2 such as rofecoxib have no effect on platelets and would not be expected to potentiate any bleeding effect of ginkgo.

The pharmacokinetic studies involving diclofenac and flurbiprofen were designed to identify whether ginkgo exerted an inhibitory effect on the cytochrome P450 isoenzyme CYP2C9, which is involved in the metabolism of these NSAIDs.

Importance and management

The evidence from these reports is too slim to forbid patients to take NSAIDs and ginkgo concurrently, but some do recommend caution.[11] Medical professionals should be aware of the possibility of increased bleeding tendency with ginkgo, and report any suspected cases.[9] Consider also 'Antiplatelet drugs + Ginkgo (*Ginkgo biloba*)', p.816.

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NSAIDs or Aspirin + Gold

Gold appears to increase the risk of aspirin-induced liver damage. The use of gold with fenoprofen seems to be safer with regard to liver toxicity. An isolated report suggested that naproxen may have contributed to gold-induced pneumonitis.

Clinical evidence, mechanism, importance and management

A study in patients with rheumatoid arthritis given aspirin 3.9 g or **fenoprofen** 2.4 g daily suggested that gold induction therapy (**sodium aurothiomalate**, by intramuscular injection, to a total dose of 985 mg over 6 months) increased aspirin-induced hepatotoxicity. Levels of AST, lactate dehydrogenase, and alkaline phosphatase were higher in those taking aspirin than in those taking **fenoprofen**. These indicators of liver impairment suggest that **fenoprofen** is safer than aspirin in this context. The concurrent use of gold and NSAIDs was more effective than the NSAIDs alone.[1]

A patient with rheumatoid arthritis taking gold (**sodium aurothiomalate**) developed pneumonitis soon after **naproxen** 500 mg twice daily was added. An *in vitro* study suggested the pneumonitis was due to hypersensitivity to gold. However, the patient's condition continued to deteriorate despite stopping the gold, then showed marked improvement when the **naproxen** was also stopped. The authors suggest that the **naproxen** may have altered the patient's immune system in some way to make them more sensitive to the gold.[2] This appears to be the only report of such an effect, and it is therefore unlikely to be of general relevance.

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NSAIDs or Aspirin + H_2-receptor antagonists

The H_2-receptor antagonists have no effect or cause only modest and normally clinically unimportant changes in the serum levels of aspirin and NSAIDs. More importantly H_2-receptor antagonists may protect the gastric mucosa from the irritant effects of the NSAIDs.

Clinical evidence

(a) Aspirin

Cimetidine 300 mg, given one hour before a single 1.2-g dose of aspirin caused only a modest increase in the serum salicylate levels of 3 out of 6 healthy subjects.[1] When 13 patients with rheumatoid arthritis taking enteric-coated aspirin were given **cimetidine** 300 mg four times daily for 7 days the total amount of aspirin absorbed was unaltered, but aspirin levels were slightly raised, from 161 micrograms/mL to 180 micrograms/mL.[2] The pharmacokinetics of a single 1-g dose of aspirin were largely unchanged in 6 healthy subjects given **ranitidine** 150 mg twice daily for a week.[3] However, a study in 10 healthy subjects found that the antiplatelet effects of aspirin were reduced when it was given with **ranitidine**. This was unexpected as **ranitidine** alone may cause a modest decrease in platelet aggregation so it would be expected to enhance the marked antiplatelet effects of aspirin. The reduced effect was attributed to reduced blood levels of salicylate possibly due to changes in the absorption conditions of aspirin in the presence of **ranitidine**.[4] **Famotidine** has been found to cause some small changes in the pharmacokinetics of aspirin, but this is of doubtful clinical importance.[5]

(b) Azapropazone

A randomised, pharmacokinetic study in 12 healthy subjects found that **cimetidine** 300 mg every 6 hours for 6 days increased the AUC of a single 600-mg dose of azapropazone by 25%. The AUC of **cimetidine** was altered by less than 20%. No significant changes in laboratory values (blood counts, enzyme levels) were seen, and adverse effects were minor (headaches in 3 subjects).[6]

(c) Diclofenac

In 14 healthy subjects, **famotidine** 40 mg raised the peak plasma levels of enteric-coated diclofenac 100 mg from 5.84 mg/L to 7.04 mg/L. Peak plasma diclofenac levels also occurred more rapidly (2 hours versus 2.75 hours). The extent of diclofenac absorption was unchanged.[7] Diclofenac did not affect the pharmacokinetics of **ranitidine** nor its ability to suppress gastric pH.[8] Another study also found that the pharmacokinetics of diclofenac were unaffected by **ranitidine**.[9]

(d) Dipyrone (Metamizole)

In a study in 12 patients with confirmed duodenal ulcer, but no gastrointestinal bleeding, **cimetidine** 200 mg was given three times daily with another 400 mg at night for 20 days. A single 1.5-g or 750-mg dose of dipyrone was given on days 8 and 13. In the presence of **cimetidine**, the AUC of the active metabolite of dipyrone, 4-methyl-amino-antipyrine (4-MAA), was increased by 74%, with dipyrone doses of 1.5 g, but the renal clearance of 4-MAA remained unchanged.[10]

(e) Flurbiprofen

In 30 patients with rheumatoid arthritis, **cimetidine** 300 mg three times daily for 2 weeks increased the maximum serum level of flurbiprofen 150 to 300 mg daily, but **ranitidine** 150 mg twice daily had no effect. The efficacy of the flurbiprofen (assessed by Ritchie score, 50 foot walking time, grip strength) was not altered.[11] Another study in healthy subjects found that **cimetidine** 300 mg four times daily slightly increased the serum levels of a single 200-mg dose of flurbiprofen, and raised the flurbiprofen AUC by 13%.[12] No statistically significant interaction occurred with **ranitidine** 150 mg twice daily.[12] Although the activity of flurbiprofen is thought to be related to the *S*-enantiomer, neither **cimetidine** nor **ranitidine** were shown to interact preferentially with one enantiomer over the other.[13]

(f) Ibuprofen

Cimetidine 400 mg three times daily raised the peak serum levels and AUC of a 600-mg dose of ibuprofen by 14% and 6%, respectively. No changes were seen with **ranitidine** 300 mg daily.[14] Another study found that the AUC of *R*-ibuprofen and *S*-ibuprofen increased by 37% and 19%, respectively, but these changes were not statistically significant.[15] However, five other studies with ibuprofen found no interaction with **cimetidine** or **ranitidine**,[16-20] or **nizatidine**.[17] However, analysis of the results of one study showed that peak serum ibuprofen levels in black American subjects were 54% higher and occurred sooner, whereas in white American subjects they were 27% lower and delayed.[18,21]

(g) Indometacin

Cimetidine 1.2 g daily for 2 weeks was given to 10 patients with rheumatoid arthritis taking steady-state indometacin 100 to 200 mg daily. The plasma indometacin levels fell by 18%, but there was no significant

change in the clinical effectiveness of the anti-inflammatory treatment (as measured by articular index, pain, grip strength and erythrocyte sedimentation rate).[22] Another study found no changes in the pharmacokinetics of indometacin in healthy subjects given **ranitidine**.[23] In a single-dose study in healthy subjects, indometacin did not markedly affect the bioavailability of either **cimetidine** or **ranitidine**.[24]

(h) Ketoprofen

In a study in 12 healthy subjects, **cimetidine** 600 mg twice daily did not affect the pharmacokinetics of enteric-coated ketoprofen 100 mg twice daily.[25]

(i) Lornoxicam

In 12 healthy subjects, **cimetidine** 400 mg twice daily increased the maximum serum levels and AUC of lornoxicam 8 mg twice daily by 28% and 9%, respectively. **Ranitidine** 150 mg twice daily had no significant effect on lornoxicam pharmacokinetics in these same subjects, except that one subject had a very marked increase in serum lornoxicam levels while taking both drugs. He dropped out of the study after 6 days because of severe gastric irritation. It is not clear what part, if any, the **ranitidine** had to play in this effect.[26]

(j) Meloxicam

In a randomised, crossover study, a group of 9 healthy subjects was given meloxicam 30 mg either alone, or with **cimetidine** 200 mg four times daily for 5 days. **Cimetidine** had no significant effect on the pharmacokinetics of the meloxicam.[27]

(k) Naproxen

One study found no adverse interaction between naproxen and **cimetidine** and no alteration in the beneficial effects of **cimetidine** on gastric acid secretion,[28] but another study found that cimetidine caused a moderate 39 to 60% decrease in the half-life of naproxen,[29,30] and a 20% reduction in the AUC of naproxen.[30] In one of these studies the half-life of naproxen was reduced by about 40% by **ranitidine** and by 50% by **famotidine**.[30] A further study found that **nizatidine** does not affect the pharmacokinetics of naproxen.[31]

(l) Oxaprozin

In a study in 12 healthy subjects, peak plasma levels, time to peak level and elimination half-lives of a single 1.2-g dose of oxaprozin were not significantly affected by either **cimetidine** 300 mg four times daily or **ranitidine** 150 mg twice daily. Oxaprozin clearance was reduced by 20% by both **cimetidine** and **ranitidine**.[32]

(m) Piroxicam

In 10 healthy subjects, **cimetidine** 300 mg four times daily for 7 days slightly increased the half-life and the AUC of a single 20-mg dose of piroxicam, by 8% and 16%, respectively.[33] Another study found that **cimetidine** caused a 15% rise in the AUC of piroxicam.[34] In 12 healthy subjects the half-life and AUC of a single-dose of piroxicam were increased by 41% and 31%, respectively, by **cimetidine** 200 mg three times daily, and the plasma levels were raised accordingly.[35] For example, at 4 hours they were raised by almost 25%.[35] **Ranitidine** was not found to affect the pharmacokinetics of piroxicam.[36] No clinically significant changes occurred in the steady-state serum levels of piroxicam in a further study when either **cimetidine** or **nizatidine** were given.[37]

(n) Tenoxicam

The pharmacokinetics of a single 20-mg oral dose of tenoxicam was unaltered in 6 healthy subjects after they took **cimetidine** 200 mg three times daily and 400 mg at night for 7 days.[38]

Mechanism

Uncertain. Azapropazone, 4-MAA (the active metabolite of dipyrone), lornoxicam, and piroxicam serum levels are possibly increased because their metabolism via the cytochrome P450 system is reduced by cimetidine.[6,10,26,35] There may also be some effects on renal excretion.[6]

Importance and management

Most of the interactions between the NSAIDs and cimetidine, famotidine, nizatidine or ranitidine appear to be of no particular clinical importance. The general relevance of the isolated case of increased lornoxicam levels and severe gastric irritation with ranitidine is uncertain, but probably small. The H_2-receptor antagonists as a group may protect the gastric mucosa from the irritant effects of the NSAIDs and concurrent use may therefore be generally advantageous.

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NSAIDs or Aspirin + Hormonal contraceptives or HRT

Oral hormonal contraceptives increase diflunisal clearance in women, but only to the level normally seen in men. One study found modestly reduced levels of ibuprofen with oral hormonal contraceptives, but another study did not. Oral hormonal contraceptives reduce the levels of aspirin, decrease the clearance of phenazone (antipyrine), but do not appear to affect the pharmacokinetics of phenylbutazone. Conjugated oestrogens have no clinically relevant effects on the pharmacokinetics of oxaprozin or phenazone (antipyrine).

Clinical evidence, mechanism, importance and management

(a) Aspirin

The AUCs of single 300- and 600-mg doses of aspirin were lower in 10 women after they started to take an oral combined hormonal contraceptive (**ethinylestradiol**/**norethisterone** 30 micrograms/1 mg). After the contraceptive had been discontinued, the pharmacokinetics of aspirin returned to baseline values.[1]

(b) Coxibs

For a report of pulmonary embolism in a patient taking valdecoxib with an oral combined hormonal contraceptive, and for the effects of coxibs on contraceptive metabolism, see 'Combined hormonal contraceptives + Coxibs', p.1181.

(c) Diflunisal

The clearance of a single 250-mg dose of diflunisal was 53% higher in 6 women taking oral hormonal contraceptives than in 6 control women, but was similar to the clearance in 6 men.[2] This difference is unlikely to be of clinical importance.

(d) Ibuprofen

In one study, the pharmacokinetics of *R*-ibuprofen did not differ between women taking oral combined hormonal contraceptives and two control groups (one women and one men).[3] However, in another study, the median $AUC_{0\text{-}12}$ of *S*-ibuprofen lysinate was 29% lower in users of oral contraceptives, and pain-intensity was higher (although this was possibly due to reduced pain tolerance).[4]

(e) Oxaprozin

There was no difference in the pharmacokinetics of a single 1.2-g dose of oxaprozin in 11 women taking **conjugated oestrogens** (*Premarin*) and in 11 women not taking oestrogens, except that the time to peak concentration was shorter (4 hours versus 8.9 hours).[5] This difference is unlikely to be of clinical importance.

(f) Phenazone (Antipyrine)

In a study, 12 healthy women taking an oral hormonal contraceptives were given a single 1-g intravenous dose of phenazone. When compared with 26 similar women not taking oral hormonal contraceptives, the clearance of phenazone was found to be 28% lower and its half-life was 3.4 hours greater, suggesting that oral hormonal contraceptives have modest effects on hepatic enzymes.[6] In another study in healthy women, the use of **conjugated oestrogens** for at least 3 months did not affect the clearance of single 1- to 1.2-g intravenous doses of phenazone.[7]

(g) Phenylbutazone

The pharmacokinetics of a single 400-mg dose of phenylbutazone did not change in 10 women after they started to take an oral combined hormonal contraceptive containing **ethinylestradiol**/**norethisterone** 30 micrograms/1 mg.[1]

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NSAIDs or Salicylates + Mazindol

Mazindol does not appear to interact adversely with indometacin or salicylates.

Clinical evidence, mechanism, importance and management

In an 8-week, placebo-controlled study, mazindol was given to 26 patients with obesity and arthritis, 15 of whom were taking salicylates, 11 were taking **indometacin** and one was taking dextropropoxyphene (propoxyphene) with paracetamol (acetaminophen). Additional analgesic and anti-inflammatory drugs used were ibuprofen (4 patients), phenylbutazone (1), dextropropoxyphene (7) and paracetamol (3). No symptoms attributable to salicylism or **indometacin** toxicity (gastric intolerance, headache) were observed.[1]

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NSAIDs or Aspirin + Metoclopramide

Metoclopramide increases the rate of absorption of aspirin and tolfenamic acid. Conversely, metoclopramide reduces the bioavailability of ketoprofen.

Clinical evidence

(a) Aspirin

In one study, intramuscular metoclopramide given before oral effervescent aspirin increased the rate of aspirin absorption during a migraine attack to that seen when aspirin was given alone to subjects who were headache free.[1] Similarly, in another study, intramuscular or oral metoclopramide 10 mg increased the rate of absorption of aspirin in patients with migraine.[2] However, in healthy subjects metoclopramide did not alter the pharmacokinetics of aspirin.[3] In addition, in one clinical study there was no difference in analgesic efficacy between aspirin with metoclopramide (*Migravess*) and aspirin alone (*Alka-Seltzer*) for migraine attacks.[4]

(b) Ketoprofen

In a single-dose study in 4 healthy subjects, metoclopramide 10 mg reduced the AUC of a 50-mg capsule of ketoprofen by 28%. The maximum plasma levels of ketoprofen were almost halved and the time to reach this maximum was prolonged by 30%.[5]

(c) Tolfenamic acid

Rectal metoclopramide 20 mg, given to 8 healthy subjects 30 minutes before oral tolfenamic acid 300 mg, caused a threefold increase in the serum tolfenamic acid levels at 45 minutes. However, there was no change in the maximum level or the AUC.[6] In another study, rectal metoclopramide similarly enhanced the rate of oral absorption of tolfenamic acid when it was given during a migraine attack.[7]

Mechanism

Metoclopramide speeds up gastric emptying. The relatively poorly soluble ketoprofen spends less time in the stomach where it dissolves, and as a result less is available for absorption in the small intestine. Conversely, the absorption rate of tolfenamic acid is increased, without a change in the extent of absorption.

Importance and management

The clinical importance of the reduction in ketoprofen levels is unknown, but the authors of the study recommend that ketoprofen (and possibly other NSAIDs that are poorly soluble) should be taken 1 to 2 hours before metoclopramide. Conversely, for aspirin, tolfenamic acid, and other NSAIDs, metoclopramide can be used to increase the rate of absorption,

and therefore possibly speed up the onset of analgesic effect in conditions such as migraine.

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NSAIDs + NSAIDs

The concurrent use of two or more NSAIDs increases the risk of gastrointestinal damage. Diflunisal raises serum indometacin levels about twofold but does not affect naproxen levels. The concurrent use of indometacin and flurbiprofen does not appear to affect the pharmacokinetics of either drug. Floctafenine does not alter diclofenac levels. Indometacin caused renal impairment in a patient recovering from phenylbutazone-induced acute renal failure.

Clinical evidence

(a) Gastrointestinal effects

The risk of serious upper gastrointestinal bleeding was increased by the use of more than one NSAID in a meta-analysis of data from three case-controlled studies (odds ratio 4.9 with one NSAID and 10.7 with two NSAIDs).[1] Another study provided similar findings: the odds ratio was 7.1 with one NSAID and 12.3 with two or more NSAIDs.[2] Similar findings have been reported with aspirin and NSAIDs, see 'NSAIDs + Aspirin', p.158. Analysis of yellow card reports to the CSM in the UK, of gastrointestinal perforation, obstruction, ulceration or bleeding with **diclofenac**, **naproxen**, and **ibuprofen**, revealed that 6% of the patients were receiving another non-aspirin NSAID.[3]

One pharmacodynamic study in healthy subjects found that gastric instillation of a solution of **diflunisal** before an **indometacin** solution prevented the fall in transmucosal potential difference seen with **indometacin** alone. This was interpreted as evidence that **diflunisal** protects the human gastric mucosa against the damaging effects of **indometacin**.[4] However, the relevance of this test to the adverse effects of NSAIDs used clinically is unknown. Note that fatal gastrointestinal haemorrhage has been reported in a patient taking **diflunisal** and **indometacin**.[5]

(b) Pharmacokinetic studies

No clinically significant changes in the pharmacokinetics of either **indometacin** 75 mg daily or **flurbiprofen** 150 mg daily occurred when both drugs were given together.[6]

Diflunisal 250 mg twice daily had no effect on plasma levels or urinary excretion of **naproxen** 250 mg twice daily.[7]

A study in 16 healthy subjects found that **diflunisal** 500 mg twice daily raised the steady-state plasma levels and the AUC of **indometacin** 50 mg twice daily about twofold. Combined use was associated with more gastrointestinal and CNS adverse effects, but there was no clear effect on blood loss in the faeces.[8] Another study produced similar findings.[9]

No change in free **diclofenac** levels was seen when 6 healthy subjects were given **floctafenine** 400 mg with **diclofenac** 75 mg daily for a week.[10]

(c) Renal effects

An isolated report describes deterioration in renal function in a patient during recovery from **phenylbutazone**-induced renal failure when **indometacin** 25 mg three times a day was given. The **indometacin** was discontinued with improvement of renal function.[11]

Mechanism

The damaging effects of the NSAIDs on the gut appear to be additive. Diflunisal may inhibit the glucuronidation of indometacin, or could compete for renal clearance with unmetabolised indometacin.[9] All NSAIDs have the propensity to cause renal impairment.

Importance and management

The gastrointestinal toxicity of the NSAIDs is well documented, and it appears that combined use increases this risk. The CSM in the UK have suggested that the concurrent use of more than one NSAID should be avoided.[3,12] The marked rise in the plasma levels of indometacin with diflunisal gives an additional reason why this combination in particular should not be used. Some NSAIDs cause more gastrointestinal toxicity than others; a suggested broad 'rank order' of seven NSAIDs is as follows: highest risk (azapropazone); intermediate risk (diclofenac, indometacin, ketoprofen and naproxen, with piroxicam more risky); lowest risk (ibuprofen),[12] which has been borne out in another analysis.[3] The ranking was based on epidemiological studies and the yellow card database. **Ketorolac** may also be particularly associated with gastrointestinal bleeding, and concurrent use with other NSAIDs has been identified as a risk factor,[13] therefore the manufacturer of ketorolac specifically contraindicates its use with other NSAIDs.[14]

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NSAIDs or Aspirin + Paracetamol (Acetaminophen)

Paracetamol levels are increased by diflunisal. Aspirin, diclofenac, nabumetone and sulindac pharmacokinetics do not appear to be affected by paracetamol. There is no pharmacokinetic interaction between ibuprofen and paracetamol. Propacetamol, and possibly paracetamol, increase the antiplatelet effects of diclofenac, although the evidence is limited and the clinical relevance of this is uncertain.

One epidemiological study found that paracetamol alone, and particularly when combined with NSAIDs, was associated with an increased risk of gastrointestinal bleeding, but other studies have not found such an effect. Case reports describe renal toxicity in patients taking ibuprofen or flurbiprofen in which paracetamol use was a theoretical contributing factor.

Clinical evidence, mechanism, importance and management

(a) Antiplatelet effects

In healthy subjects giving single doses of intravenous **propacetamol** 30 mg/kg and **diclofenac** 1.1 mg/kg augmented the platelet inhibitory effect of **diclofenac** by about one-third at 90 minutes post dose. At 5 minutes, the platelet inhibitory effect of both **diclofenac** alone and the combination was 100%, and by 22 to 24 hours, neither **diclofenac** alone nor the combination had any platelet inhibitory effect.[1] In a previous study, the authors had found that **propacetamol** (which is hydrolysed to

paracetamol) also inhibited platelet function, and they suggested that the effects of **diclofenac** and **propacetamol** were additive.[1] The clinical relevance of these findings is unclear, but the authors say it should be considered when assessing the risk of surgical bleeding.[1] Further study is needed.

An *in vitro* study suggested that high doses of paracetamol, and a combination of paracetamol and **diclofenac**, may cause platelet inhibition and may increase the risk of bleeding, particularly post-surgery.[2]

In 18 healthy subjects, intravenous **parecoxib** 40 mg given with intravenous paracetamol 1 g, was found not to alter platelet function when compared with paracetamol alone.[3]

(b) Gastrointestinal damage

In a case-control study of the UK General Practice Research Database from 1993 to 1998 the risk of upper gastrointestinal bleeding or perforation was slightly increased in those taking both aspirin and paracetamol (relative risk 3.3), when compared with aspirin alone (2.4), or paracetamol alone (2.4). Moreover, the risk was markedly increased in those taking NSAIDs and paracetamol (16.6), when compared with NSAIDs alone (3.6). The paracetamol doses used were at least 2 g daily. Paracetamol in doses of less than 2 g daily was not associated with an increased risk. Other drug doses and specific NSAIDs were not mentioned.[4] However, other epidemiological studies have not found any increased risk of upper gastrointestinal bleeding with paracetamol at any dose.[5] Paracetamol is usually considered not to increase the risk of upper gastrointestinal adverse effects, and the results of this case-control study are probably insufficient to change prescribing practice. Further studies are needed, controlled for the dose of the NSAID and indication for treatment.

(c) Pharmacokinetic studies

1. Aspirin. In a study in 6 healthy subjects, two doses of dextropropoxyphene with paracetamol 65 mg/650 mg, given one hour before and 3 hours after a single 1.2-g dose of soluble aspirin did not affect the plasma salicylate levels. A reduction in plasma salicylate levels was seen in one subject after a single 1.2-g dose of enteric-coated aspirin was taken with dextropropoxyphene and paracetamol, although the authors suggested that this was related to erratic absorption rather than a pharmacokinetic interaction.[6]

2. Diclofenac. In 6 healthy subjects, diclofenac 25 mg given with paracetamol 500 mg, both three times daily for 14 days, had no effect on the pharmacokinetics of diclofenac.[7]

3. Diflunisal. In a study in healthy subjects, diflunisal significantly raised serum paracetamol levels by 50% but the total bioavailability was unchanged; diflunisal levels were not affected.[8,9] This interaction has not been shown to be clinically important. Nevertheless, the manufacturer of diflunisal recommended that the combination should be used with caution, because of the association of high levels of paracetamol with hepatotoxicity.[9]

4. Ibuprofen. In a crossover study in 20 healthy subjects, ibuprofen 400 mg given with paracetamol 650 mg, both every 6 hours for 2 days, had no effect on the pharmacokinetics of either drug.[10]

5. Nabumetone. In a single-dose study, the absorption of nabumetone 1 g was not significantly altered by paracetamol 1.5 g.[11]

(d) Renal effects

Two children (aged 12 and 14 years) developed acute flank pain and reversible renal impairment during the short-term use of **flurbiprofen** or **ibuprofen**. They had also taken paracetamol.[12] Similarly, a 14-month-old infant with febrile status epilepticus was given an alternating regimen of paracetamol and **ibuprofen**, and subsequently developed acute renal failure.[13] NSAIDs can cause renal toxicity, whereas paracetamol is less likely to cause renal toxicity, except perhaps in overdose.[14] The authors of the first case report proposed that tubular toxicity of NSAIDs and paracetamol are theoretically synergistic.[12] This is because NSAIDs inhibit the production of glutathione (needed to prevent the accumulation of toxic metabolites of paracetamol) and renal ischaemia (possibly induced by NSAIDs, or by dehydration) might lead to the accumulation of paracetamol in the renal medulla.[12]

A review concluded that the available evidence does not support an increased risk of renal toxicity with the use of combination products of aspirin and paracetamol when compared with either drug alone.[15] Paracetamol is often combined with NSAIDs in the management of chronic pain. In addition, paracetamol and **ibuprofen** are often used concurrently (as alternating doses) in the management of fever, particularly in children. This latter practice has become controversial. Opponents cite the lack of efficacy data to support combined use (rather than appropriate doses of individual drugs), and the theoretical increased risk of overdose and renal toxicity.[16,17] Others consider that, in the absence of true safety issues, professional judgement should be used for recommending combined use.[18] Further study is clearly needed.

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NSAIDs + Pentoxifylline

A review of bleeding events associated with the use of postoperative ketorolac revealed that a small number of patients were also taking pentoxifylline.[1] The UK manufacturer therefore, rather cautiously, contraindicates concurrent use,[2] whereas the US manufacturer[3] made no mention of this tentative interaction. The manufacturer of dexketoprofen similarly predicts that the concurrent use of pentoxifylline increases the risk of bleeding.[4] There seems to be no evidence regarding this interaction with other NSAIDs, but as non-selective NSAIDs have antiplatelet effects and pentoxifylline can cause bleeding events, it would be prudent to be alert for this possible interaction with any of the non-selective NSAIDs.

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NSAIDs + Pesticides

Chronic exposure to lindane and other chlorinated pesticides can slightly increase the rate of metabolism of phenazone (antipyrine) and phenylbutazone.

Clinical evidence, mechanism, importance and management

(a) Phenazone (Antipyrine)

A study in 26 men occupationally exposed to a mixture of insecticides, predominantly **DDT** [**clofenotane**], **chlordane** and **lindane**, found that the half-life of phenazone 10 or 15 mg/kg was reduced from 13.1 hours, in a group of 33 unexposed subjects, to 7.7 hours in the exposed group.[1] The significance of this is unclear as changes in working practices have reduced occupational exposure to such chemicals.

(b) Phenylbutazone

The plasma half-life of phenylbutazone in a group of men who regularly used **chlorinated insecticide** sprays (mainly **lindane**) as part of their work, was found to be 20% shorter (51 hours) than in a control group (64 hours), due, it is believed, to the enzyme-inducing effects of the pesticides.[2] This modest increase in rate of metabolism is of doubtful direct clinical importance, but it illustrates the changed metabolism that can occur in those exposed to environmental chemical agents.

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NSAIDs + Phenobarbital

Phenobarbital modestly decreases the AUC of fenoprofen and increases the clearance of phenylbutazone.

Clinical evidence, mechanism, importance and management

In 6 healthy subjects pretreatment with phenobarbital 15 or 60 mg every 6 hours for 10 days reduced the AUC of a single 200-mg dose of **fenoprofen** by 23% and 37%, respectively.[1]

In 5 healthy subjects the half-life of a single 6-mg/kg dose of **phenylbutazone** was reduced by 38% after pretreatment with phenobarbital 2 to 3 mg/kg daily for 3 weeks.[2] Other studies confirm that phenobarbital increases the clearance of **phenylbutazone**.[3,4]

The probable reason for the increased clearance or decreased exposure to these NSAIDs is that phenobarbital increases their metabolism by the liver. **Phenazone** is metabolised by mixed function oxidase enzymes in the liver, for which reason it is extensively used as a model drug for studying whether other drugs induce or inhibit liver enzymes. In one study phenobarbital caused about a 40% reduction in the half-life of **phenazone** thereby demonstrating that liver enzymes were being stimulated to metabolise **phenazone** more rapidly.[5]

The clinical importance of these interactions is uncertain, but given the magnitude of the effects it seems likely to be small. Nevertheless if the effects of these NSAIDs are reduced if phenobarbital is added it would seem prudent to consider an interaction as a possible cause.

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NSAIDs + Probenecid

Probenecid reduces the clearance of dexketoprofen, diflunisal, indometacin (toxicity seen), ketoprofen, ketorolac, naproxen, meclofenamate, tenoxicam and tiaprofenic acid and raises their levels. The uricosuric effects of probenecid are not affected by indometacin but may be slightly reduced by sulindac.

Clinical evidence

(a) Diflunisal

In 8 healthy subjects probenecid 500 mg twice daily increased the steady-state plasma levels of diflunisal 250 mg twice daily by 65%, and reduced the clearances of its glucuronide metabolites.[1]

(b) Indometacin

A study in 28 patients with osteoarthritis, taking indometacin 50 to 150 mg daily orally or rectally, found that probenecid 500 mg to 1 g daily roughly doubled indometacin plasma levels and this paralleled increased effectiveness (relief of morning stiffness, joint tenderness and raised grip strength indices). However, 4 patients developed indometacin toxicity.[2]

Other studies have also found that probenecid causes a marked rise in plasma indometacin levels.[3-5] Clear signs of indometacin toxicity (nausea, headache, tinnitus, confusion and a rise in blood urea) occurred when a woman with stable mild renal impairment was given probenecid.[6] The uricosuric effects of probenecid were not altered.[3]

(c) Ketoprofen

In 6 healthy subjects probenecid 500 mg every 6 hours reduced the clearance of ketoprofen 50 mg every 6 hours by 67%.[7]

(d) Ketorolac

In a study in 8 subjects, probenecid 500 mg four times daily for 4 days increased the total AUC of a single 10-mg dose of ketorolac by more than threefold, increased its half-life from 6.6 hours to 15.1 hours, raised its maximum plasma levels by 24% and reduced its clearance by 67%.[8]

(e) Meclofenamate

Single-dose studies in 6 healthy subjects on the pharmacokinetics of sodium meclofenamate 100 mg found that pretreatment with probenecid (dosage unstated) increased its AUC and reduced its apparent plasma clearance by 60%, primarily due to a decrease in non-renal clearance.[9]

(f) Naproxen

In 12 healthy subjects, probenecid 500 mg twice daily increased the plasma levels of naproxen 250 mg twice daily by 50%.[10]

(g) Sulindac

The manufacturer of sulindac notes that probenecid increased plasma levels of sulindac and its sulfone metabolite, but had little effect on the active sulfide metabolite. Sulindac produced a modest reduction in the uricosuric action of probenecid,[11] which is said not to be clinically significant in most circumstances.[11]

(h) Tenoxicam

Probenecid 1 g twice daily for 4 days increased the maximum serum levels of a single 20-mg oral dose of tenoxicam by 25%. None of the other pharmacokinetic parameters was significantly altered.[12]

(i) Tiaprofenic acid

Probenecid appeared to reduce the urinary excretion of tiaprofenic acid in one healthy subject. The maximum urinary excretion rate was reduced by 66% and delayed by 2 hours.[13]

Mechanism

Probenecid is a known substrate for renal glucuronidation, and possibly competitively inhibits the renal glucuronidation of these NSAIDs.[14]

Importance and management

The interaction between indometacin and probenecid is established and adequately documented. Concurrent use should be well monitored because, while clinical improvement can undoubtedly occur, some patients may develop indometacin toxicity (headache, dizziness, light-headedness, nausea, etc.). This is particularly likely in those with some renal impairment. Reduce the indometacin dose as necessary. Information about other NSAIDs is not as well documented, but these interactions also appear to be established. The clinical importance of most of them is uncertain, but probably small. Reports of adverse effects seem to be lacking, but it would still be prudent to be alert for any evidence of increased adverse effects. Reduce the NSAID dose if necessary. The exception is ketorolac, which its manufacturer[15] contraindicates with probenecid.

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NSAIDs or Aspirin + Prostaglandins

Misoprostol increases the incidence of abdominal pain and diarrhoea when used with diclofenac or indometacin. Isolated cases of neurological adverse effects have been seen when naproxen or phenylbutazone were given with misoprostol. However, no important pharmacokinetic interactions seem to occur between misoprostol and aspirin, diclofenac, ibuprofen or indometacin. NSAIDs are reported not to affect the abortive effects of intravaginal misoprostol.

Clinical evidence, mechanism, importance and management

A. Oral misoprostol

(a) Gastrointestinal adverse effects

A higher incidence of abdominal pain, diarrhoea, nausea and dyspepsia occurred when **diclofenac** was given with misoprostol.[1,2] Concurrent use of **indometacin** and misoprostol also resulted in an increase in the frequency and severity of abdominal symptoms, frequency of bowel movements, and a decrease in faecal consistency.[3] The most frequent adverse effect of misoprostol alone is diarrhoea, and this may limit the dose tolerated. When using misoprostol with NSAIDs, warn patients about the possibility of increased stomach pain and diarrhoea. However, note that preparations containing **diclofenac** or **naproxen** with misoprostol are available.

(b) Neurological adverse effects

A man with rheumatoid arthritis taking long-term **naproxen** developed ataxic symptoms a few hours after starting to take misoprostol. He said he felt drunk, staggering about and vomiting. He rapidly improved when he stopped the misoprostol but the adverse symptoms recurred on two further occasions when he restarted misoprostol.[4]

Adverse effects developed in 3 patients taking **phenylbutazone** 200 to 400 mg daily when they took misoprostol 400 to 800 micrograms daily.[5] One had headaches, dizziness and ambulatory instability that disappeared and then reappeared when the misoprostol was stopped and then restarted. No problems occurred when the **phenylbutazone** was replaced by **etodolac** 400 mg daily. The other 2 patients developed symptoms including headache, dizziness, hot flushes and transient diplopia.[5,6] No problems developed when one of them was given **naproxen** and misoprostol.[6] The reasons for this reaction are not understood but theoretically it could be due to a potentiation of the adverse effects of **phenylbutazone**. The general relevance of these few reports is unclear, but bear them in mind should unexpected neurological effects occur.

(c) Other studies

No clinically important pharmacokinetic interactions have been found to occur between **aspirin** 975 mg and misoprostol 200 micrograms,[7] or between **ibuprofen** and misoprostol.[8] One study found that misoprostol 800 micrograms daily decreased the AUC of a single 100-mg dose of **diclofenac** by a modest 20%.[2] However, other studies have found that misoprostol had no effect on steady-state **diclofenac** pharmacokinetics.[9] One study found that misoprostol 200 micrograms raised the steady-state levels of **indometacin** 50 mg three times daily by about 30%,[10] whereas another found that misoprostol 400 micrograms twice daily reduced the AUC of **indometacin** 50 mg twice daily by 13% after one dose and reduced the maximum steady-state plasma concentration by 24%.[3] These modest changes in **diclofenac** and **indometacin** levels are not expected to be clinically important.

Women undergoing second trimester medical terminations of pregnancy were given oral mifepristone 600 mg on day one, then 36 to 48 hours later, intravaginal misoprostol 800 micrograms. Starting 3 hours later, misoprostol 400 micrograms was given orally every 3 hours until expulsion, up to a maximum of nine oral doses of misoprostol. The women were randomised to receive a single dose of either paracetamol 1 g with dihydrocodeine 20 mg (n=38) or **diclofenac** 100 mg (n=36), given at the time of the intravaginal dose of misoprostol. The use of **diclofenac** did not increase either the time required for termination, or the amount of misoprostol needed.[11]

B. Vaginal prostaglandins

NSAIDs and aspirin are frequently avoided before the use of **prostaglandins** for induction of uterine contractions, because of the theoretical concern that they may inhibit efficacy.[12] For example, the UK manufacturer of **dinoprostone** says that NSAIDs including aspirin should be stopped before giving intravaginal **dinoprostone** for induction of labour.[13] However, a study involving 416 women given intravaginal **misoprostol** to induce early abortion found that the concurrent use of oral NSAIDs did not interfere with the efficacy of misoprostol,[12] and the US manufacturer of **dinoprostone** does not list NSAIDs or aspirin as possible interacting drugs.[14]

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NSAIDs or Aspirin + Proton pump inhibitors

The antiplatelet activity and the pharmacokinetics of aspirin do not appear to be affected by omeprazole. There was no clinically relevant pharmacokinetic interaction between omeprazole and diclofenac, enteric-coated ketoprofen, naproxen, or piroxicam; or between pantoprazole and diclofenac or naproxen; or between esomeprazole and naproxen or rofecoxib.

Clinical evidence

(a) Aspirin

In a preliminary study in 11 healthy subjects, **omeprazole** 20 mg daily for 2 days reduced the serum levels of the salicylic acid metabolite of aspirin at 30 and 90 minutes after a single 650-mg dose of aspirin by 40% and 52%, respectively.[1] However, another study in 14 healthy subjects given **omeprazole** 20 mg daily for 4 days, with a final dose one hour before a single 125-mg dose of aspirin, found that **omeprazole** did not significant-

ly affect the plasma levels of either aspirin or salicylic acid. **Omeprazole** also did not affect the antiplatelet effects of aspirin.[2] Similarly, **omeprazole** had no effect on the bioavailability of aspirin (uncoated or enteric-coated tablets) in another study, although it increased the rate of absorption of aspirin from enteric-coated tablets.[3]

(b) Diclofenac

In a study in 13 healthy subjects, a single 105-mg dose of diclofenac potassium suspension (*Flogan*) was given during fasting and after gastric acid secretion blockade with **omeprazole**. The pharmacokinetics of the diclofenac were not changed to a clinically relevant extent by **omeprazole**.[4] Similarly, in 14 healthy subjects, the concurrent use of **omeprazole** 20 mg daily and diclofenac 50 mg twice daily for one week had no effect on the pharmacokinetics of either drug.[5]

In another study in 24 healthy subjects, the concurrent use of a single 40-mg oral dose of **pantoprazole** and diclofenac 100 mg (as enteric-coated *Voltarol*) did not affect the pharmacokinetics of either drug.[6]

(c) Ketoprofen

One study found that there were no significant changes in the pharmacokinetics of enteric-coated ketoprofen, given with or without **omeprazole**, although a trend towards higher plasma concentrations with omeprazole was noted, indicating the possibility of increased drug release in the stomach in the presence of an elevated pH.[7]

(d) Naproxen

Naproxen 250 mg twice daily, given to healthy subjects with **omeprazole** 20 mg daily,[5] **pantoprazole** 40 mg daily,[8] or **esomeprazole** 40 mg daily[9] for one week, had no effect on the pharmacokinetics of either naproxen or the proton pump inhibitor.

(e) Phenazone (Antipyrine)

In one study, the pharmacokinetics of **pantoprazole** 40 mg orally daily for 8 days was not altered to a clinically relevant extent by a single 5-mg/kg oral dose of phenazone given on day 8. **Pantoprazole** did not affect the pharmacokinetics of phenazone.[10]

(f) Piroxicam

In a study in 24 healthy subjects, the concurrent use of **omeprazole** 20 mg daily and piroxicam 10 mg daily for one week had no effect on the pharmacokinetics of either drug.[5]

(g) Rofecoxib

In a study in 30 healthy subjects, the concurrent use of **esomeprazole** 40 mg daily and rofecoxib 12.5 mg daily for one week had no effect on the pharmacokinetics of either drug, apart from a slight increase in the maximum level and AUC of rofecoxib, which was not thought to be clinically relevant.[9]

Mechanism

Data from *animal* studies suggest that the absorption and thus the effects of aspirin and NSAIDs can be reduced by omeprazole and H_2-receptor antagonists by a pH dependent mechanism.[11,12] However, note that clinical studies have not found H_2-receptor antagonists to have any important effect on the pharmacokinetics of aspirin or NSAIDs, see 'NSAIDs or Aspirin + H_2-receptor antagonists', p.165. It has been suggested that reducing gastric acidity with omeprazole results in the earlier disruption of enteric-coated tablets, and an increased absorption rate.[3]

Importance and management

The interaction between aspirin and omeprazole is not established. The balance of evidence suggests that omeprazole is unlikely to have an important effect on the pharmacokinetics and efficacy of aspirin. However, it would be of benefit to confirm this in further studies.[2,13]

No clinically significant pharmacokinetic interactions have been identified between any of the other NSAIDs and the proton pump inhibitors cited here, and no special precautions are needed during concurrent use. However, for mention that valdecoxib raises the plasma levels of omeprazole see 'NSAIDs; Parecoxib + Miscellaneous', p.177.

Note that omeprazole and other proton pump inhibitors are widely used in the management of the gastrointestinal complications of aspirin and NSAIDs.

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NSAIDs + Rifampicin (Rifampin)

The plasma levels of celecoxib, diclofenac, and etoricoxib are reduced by rifampicin, but piroxicam does not appear to be affected. Dipyrone increased the maximum level of rifampicin in one study.

Clinical evidence

(a) Celecoxib

In 12 healthy subjects pretreatment with rifampicin 600 mg daily for 5 days reduced the AUC of a single 200-mg dose of celecoxib by 64% and increased its clearance by 185%.[1] A preliminary report of another study found broadly similar results.[2]

(b) Diclofenac

A study in 6 healthy subjects found that, after taking rifampicin 450 mg daily for 6 days, the maximum serum level of diclofenac, measured 8 hours after a single 100-mg dose of an enteric-coated tablet, was reduced by 43% and the AUC was reduced by 67%.[3]

(c) Dipyrone (Metamizole sodium)

A study in untreated patients with leprosy found that the pharmacokinetics of a single 600-mg dose of rifampicin were not markedly changed by 1 g of dipyrone, but peak serum rifampicin levels occurred sooner (at 3 instead of 4 hours) and were about 50% higher.[4]

(d) Etoricoxib

Rifampicin 600 mg daily for 12 days reduced the AUC of a single 60-mg dose of etoricoxib given on day 8 by 65%. The maximum plasma concentration of etoricoxib was reduced by 40%.[5]

(e) Phenazone (Antipyrine)

Rifampicin 600 mg daily for 13 days reduced the plasma concentrations of a single 1.2-g oral dose of phenazone. The mean AUC of phenazone was reduced by 59% and had not returned to the pre-rifampicin level 13 days after the final rifampicin dose.[6]

(f) Piroxicam

A study in 6 healthy subjects given a single 40-mg dose of piroxicam before and after a 7-day course of rifampicin 600 mg daily found that rifampicin did not significantly alter the pharmacokinetics of piroxicam.[7]

Mechanism

Rifampicin is a potent inducer of hepatic enzymes, and it is likely that it increased the metabolism of the affected NSAIDs.

Importance and management

Although information is limited, these pharmacokinetic interactions appear to be established. Their clinical relevance remains to be determined, but it seems likely that the efficacy of these NSAIDs will be reduced by rifampicin. Combined use should be well monitored, and the NSAID dosage increased if necessary, or an alternative analgesic considered. The clinical relevance of the increase in rifampicin maximum levels with metamizole is uncertain, but as it was only this pharmacokinetic parameter that was altered, it seems likely to be small.

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NSAIDs + SSRIs

SSRIs may increase the risk of bleeding, including upper gastrointestinal bleeding, and the risk appears to be further increased by concurrent use of NSAIDs.

Clinical evidence

Studies and case reports have found that SSRIs alone increase the risk of upper (and lower[1]) gastrointestinal bleeding,[1-7] although some case control studies found this risk to be relatively small.[8-10] One review of studies concluded that the few epidemiological studies available provided weak evidence to support a link between SSRI use and upper gastrointestinal bleeding.[11] However, a retrospective study of the UK General Practice Research Database identified 1651 cases of upper gastrointestinal bleeding diagnosed between 1993 and 1997. The use of an SSRI increased the risk of bleeding threefold, when compared with 10 000 controls. In addition, the concurrent use of an SSRI with an NSAID greatly increased the risk of upper gastrointestinal bleeding (relative risk of bleeding compared with non-use of either drug: 15.6 for SSRIs with NSAIDs, 3.7 for NSAIDs alone, and 2.6 for SSRIs alone). Another study found a significant association between the degree of serotonin reuptake inhibition by antidepressants and risk of hospital admission for abnormal bleeding.[12] A retrospective cohort study in elderly patients taking antidepressants found a trend towards an increased risk of upper gastrointestinal bleeding for patients taking antidepressants with greater inhibition of serotonin reuptake. This association was statistically significant when controlled for previous upper gastrointestinal bleeding or age; and octogenarians, in particular, were at high risk.[13] and most of these studies found that gastrointestinal haemorrhage is potentiated by the concurrent use of NSAIDs.[1,2,7,11]

In contrast, some workers have disagreed with these results and found no evidence to suggest that SSRIs are more likely to cause gastrointestinal bleeding than other drugs.[14] One study reported that both SSRIs and NSAIDs were associated with a twofold increase in risk of gastrointestinal bleeding, but that the risk of bleeding was not substantially increased when both drugs were taken together (odds ratio for NSAIDs was 2.19, SSRIs was 2.63 and combined use was 2.93).[15] A further study found that the incidence of upper gastrointestinal bleeding in patients taking an SSRI and an NSAID was similar to that in those taking NSAIDs alone (odds ratio for NSAIDs was 7.82 and combined use was 8.32), with the SSRI alone having little risk.[9]

Mechanism

Serotonin is not synthesised by platelets but is taken up into platelets from the bloodstream. Serotonin released from platelets has an important role in regulating the haemostatic response to injury as it potentiates platelet aggregation. At therapeutic doses SSRIs can block this reuptake of serotonin by platelets leading to serotonin depletion, impairment of haemostatic function and so increase the risk of bleeding.[13,16-18]

Importance and management

Serotonin released by platelets plays an important role in haemostasis and there appears to be an association between the use of antidepressant drugs that interfere with serotonin reuptake and the occurrence of bleeding, including gastrointestinal bleeding. In addition, the concurrent use of an NSAID may potentiate the risk of bleeding. Therefore, the manufacturers of SSRIs advise caution in patients taking SSRIs with NSAIDs or other drugs that may affect coagulation or platelet function, such as 'aspirin', (p.817). Alternatives such as paracetamol (acetaminophen) or less gastrotoxic NSAIDs such as ibuprofen may be considered, but if the combination of an SSRI and NSAID cannot be avoided, prescribing of gastroprotective drugs such as proton pump inhibitors, H_2-receptor antagonists, or prostaglandin analogues should be considered, especially in elderly patients or those with a history of gastrointestinal bleeding. Patients, particularly those taking multiple drugs that may cause bleeding, should be advised to seek informed medical opinion before using non-prescription drugs such as ibuprofen on a regular basis.

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NSAIDs or Aspirin + Sucralfate

Sucralfate appears not to have a clinically important effect on the pharmacokinetics of aspirin, choline-magnesium trisalicylate, diclofenac, ibuprofen, indometacin, ketoprofen, naproxen or piroxicam.

Clinical evidence, mechanism, importance and management

Sucralfate 2 g was given to 18 healthy subjects 30 minutes before single-doses of **ketoprofen** 50 mg, **indometacin** 50 mg, or **naproxen** 500 mg. Some statistically significant changes were seen (modestly reduced

maximum plasma levels of **ketoprofen**, **indometacin**, and **naproxen**, reduced the rate of absorption of **naproxen** and **indometacin**, and increased the time to achieve maximum plasma levels with **indometacin**) but no alterations in bioavailability occurred.[1] A delay, but no reduction in the total absorption of **naproxen** is described in two studies.[2,3] Sucralfate 1 g four times daily for 2 days was found not to decrease the rate of absorption of a single 400-mg dose of **ibuprofen**[4] or of a single 650-mg dose of **aspirin**.[5] Sucralfate 5 g in divided doses did not significantly alter the absorption of a single 600-mg dose of **ibuprofen**.[6] Similarly, another study also found that sucralfate had no important effect on the pharmacokinetics of **ibuprofen** enantiomers.[7] In one study, sucralfate 2 g was found not to affect significantly the pharmacokinetics of either **piroxicam** 20 mg or **diclofenac** 50 mg.[8] In another study, sucralfate 2 g twice daily modestly reduced the AUC_{0-8} and maximum serum levels of a single 105-mg dose of **diclofenac potassium** by 20% and 38%, respectively.[9] Sucralfate 1 g every 6 hours was found not to affect the pharmacokinetics of **choline-magnesium trisalicylate** 1.5 g every 12 hours.[10]

Single-dose studies do not necessarily reliably predict what will happen when patients take drugs regularly, but most of the evidence available suggests that the effects of sucralfate are modest at most, and it is therefore unlikely to have an adverse effect on treatment with these NSAIDs.

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NSAIDs or Aspirin + *Tamarindus indica*

***Tamarindus indica* (tamarind) fruit extract markedly increases the absorption and plasma levels of aspirin and ibuprofen.**

Clinical evidence, mechanism, importance and management

(a) Aspirin

A study in 6 healthy subjects found that the bioavailability of a single 600-mg dose of aspirin was increased when it was taken with a millet meal containing *Tamarindus indica* (tamarind) fruit extract, compared with the millet meal alone or following overnight fasting. The aspirin AUC rose sixfold, the maximum plasma levels rose almost threefold (from about 10 micrograms/mL with the meal or fasting to about 29 micrograms/mL with the *Tamarindus indica* extract) and the half-life increased moderately (from about 1.04 to 1.5 hours).[1] The reasons are not known, nor has the clinical importance of these large increases been evaluated, but this interaction should be borne in mind if high (analgesic or anti-inflammatory) doses of aspirin are taken with this fruit extract. There would seem to be the possible risk of aspirin toxicity.

(b) Ibuprofen

A study in 6 healthy subjects found that the bioavailability of a single 400-mg dose of ibuprofen was increased when it was taken with a millet meal containing *Tamarindus indica* (tamarind) fruit extract compared with the millet meal alone, or following overnight fasting. The ibuprofen AUC rose approximately twofold and the maximum plasma levels rose from about 38 micrograms/mL to 45 micrograms/mL. There was also an increase in the plasma levels of the metabolites of ibuprofen. Ingestion of the meal containing *Tamarindus indica* was thought to favour the absorption of ibuprofen. This might result in an increased risk of toxicity.[2]

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NSAIDs + Tobacco

The clearance of diflunisal, phenazone (antipyrine) and phenylbutazone is greater in smokers than in non-smokers.

Clinical evidence, mechanism, importance and management

(a) Diflunisal

The clearance of a single 250-mg dose of diflunisal was 35% higher in 6 women who smoked 10 to 20 cigarettes a day than in 6 non-smoking women.[1] This change does not appear to be large enough to be of clinical importance.

(b) Phenazone (Antipyrine)

When a single 1-g dose of phenazone was given intravenously, its clearance was increased by 63% and its half-life reduced from 13.2 hours to 8 hours in 10 healthy women who smoked cigarettes, when compared with a control group of 26 non-smoking women.[2] Similar results were reported in another study.[3] This is likely to be as a result of cigarette smoking causing induction of CYP1A2, the enzyme involved in the metabolism of phenazone.[2]

This suggests that smokers may need larger doses of phenazone to achieve the same effects as non-smokers.

(c) Phenylbutazone

The half-life of a single 6-mg/kg dose of phenylbutazone was 37 hours in a group of smokers (10 or more cigarettes daily for 2 years) compared with 64 hours in a group of non-smokers. The metabolic clearance was roughly doubled.[4] The conclusion to be drawn is that those who smoke may possibly need larger or more frequent doses of phenylbutazone to achieve the same therapeutic response, but this needs confirmation.

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NSAIDs + Tricyclic antidepressants

An isolated report describes desipramine toxicity when ibuprofen was also given. The tricyclic antidepressants can delay the absorption of phenylbutazone and oxyphenbutazone from the gut.

Clinical evidence, mechanism, importance and management

(a) Ibuprofen

A 15-year-old patient with attention deficit disorder and depression treated with **desipramine**, which because of compliance problems was taken as a single 300-mg dose at bedtime, had **desipramine** levels of 164 nanograms/mL. The dose was increased to 375 mg at bedtime because of missed doses once or twice a week. He developed chest wall pain one week later, but an ECG at this time was normal. He was given ibuprofen 600 mg three times daily for the chest pain, but one week later developed blurred vision, clouding of consciousness and a grand mal seizure. He had a second seizure and ventricular tachycardia and was unresponsive until treated with physostigmine. Tricyclic toxicity was confirmed by a desipramine level of 657 nanograms/mL. This toxic level could have been due to the increase in **desipramine** dose, but as the ECG was normal one week after the increase and the fact that toxicity did not occur until 2 weeks after the dose increase and one week after starting ibuprofen, it was suggested that the toxicity might be due to inhibition of **desipramine** metabolism by ibuprofen.[1] This case is isolated and unconfirmed, and as such, no general recommendations can be made as a result of it.

(b) Oxyphenbutazone and Phenylbutazone

The absorption of a single 400-mg dose of phenylbutazone in 4 depressed women was considerably delayed (time to maximum level, 4 to 10 hours compared with 2 hours), but the total amount absorbed (measured by the urinary excretion of oxyphenbutazone) remained unchanged when they were pretreated with **desipramine** 75 mg daily for 7 days.[2] In another

5 depressed women the half-life of oxyphenbutazone was found to be unaltered by 75 mg of **desipramine** or **nortriptyline** daily.[3] *Animal* studies have confirmed that the absorption of phenylbutazone and oxyphenbutazone are delayed by the tricyclic antidepressants, probably because their antimuscarinic effects reduce gut motility,[4,5] but there seems to be no direct clinical evidence that the antirheumatic effects of either drug are reduced by this interaction. No particular precautions appear to be needed.

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NSAIDs; Acemetacin + Miscellaneous

Acemetacin is a glycolic acid ester of indometacin, and its major metabolite is indometacin. Therefore acemetacin would be expected to interact in a similar way to indometacin.

NSAIDs; Azapropazone + Chloroquine

The plasma levels of azapropazone are not significantly altered by chloroquine.

Clinical evidence, mechanism, importance and management

A study in 12 subjects given azapropazone 300 mg three times daily found that the plasma levels of azapropazone, measured at 4 hours, were not affected by chloroquine 250 mg daily for 7 days.[1] No azapropazone dose adjustment would seem to be needed if these drugs are given together.

1. Faust-Tinnefeldt G, Geissler HE. Azapropazon und rheumatologische Basistherapie mit Chloroquin unter dem Aspekt der Arzneimittelinteraktion. *Arzneimittelforschung* (1977) 27, 2170–4.

NSAIDs; Celecoxib + Selenium

Selenium enriched baker's yeast does not appear to affect the pharmacokinetics of celecoxib.

Clinical evidence, mechanism, importance and management

In a study in 73 healthy subjects, celecoxib 400 mg was given daily for 2 weeks, then selenium enriched baker's yeast (*Saccharomyces cerevisiae*) 200 micrograms daily or matched placebo were added for 30 days. Following blood chemistry analysis (urea and electrolytes, full blood count etc), there were no clinically significant changes from baseline, nor were there any changes in celecoxib steady-state plasma levels.[1]

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NSAIDs; Diclofenac topical + Miscellaneous

Topical diclofenac intended for use on the skin is very unlikely to interact adversely with any of the drugs known to interact with diclofenac given orally.

Clinical evidence, mechanism, importance and management

The manufacturer of *Pennsaid* (a topical solution containing diclofenac 16 mg/mL in dimethyl sulfoxide) says that when the maximum dosage of 1 mL is used on the skin, the maximum plasma levels of diclofenac achieved are less than 10 nanograms/mL.[1] This is 50 times lower than the maximum plasma levels achieved with oral diclofenac 25 mg. Despite these very low concentrations, the manufacturer lists all the interactions that have been observed after systemic administration of diclofenac sodium (including **aspirin**, **digoxin**, **lithium**, **oral hypoglycaemic agents**, **diuretics**, **NSAIDs** including other **diclofenac** preparations, **methotrexate**, **ciclosporin**, **quinolones** and **antihypertensives**).[1] They note that the risk of these interactions in association with topical use is not known, but is probably low.[1] None of the drugs listed have yet been reported to interact with topical diclofenac.

The manufacturers of other topical preparations (*Solaraze* 3% w/w gel and *Voltarol* 1% w/w gel patch) state that interactions are not anticipated due to the low level of systemic absorption,[2,3] although one manufacturer still warns not to give, by either the topical or systemic route, any other medicinal product containing diclofenac or other NSAIDs.[3]

1. Pennsaid (Diclofenac sodium). Dimethaid International. UK Summary of product characteristics, February 2004.
2. Solaraze 3% Gel (Diclofenac sodium). Almirall Ltd. UK Summary of product characteristics, February 2009.
3. Voltarol Gel Patch (Diclofenac epolamine). Novartis Consumer Health. UK Summary of product characteristics, November 2005.

NSAIDs; Etoricoxib + Miscellaneous

The manufacturer of etoricoxib recommends care when using etoricoxib with drugs that are metabolised by human sulfotransferases (they name oral salbutamol and minoxidil). This is because etoricoxib is an inhibitor of human sulfotransferase activity, and may increase the levels of these drugs. The increase in ethinylestradiol levels with etoricoxib is thought to occur as a result of this mechanism,[1] see 'Combined hormonal contraceptives + Coxibs', p.1181.

1. Arcoxia (Etoricoxib). Merck Sharp & Dohme Ltd. UK Summary of product characteristics, September 2009.

NSAIDs; Flurbiprofen + Cranberry juice

Limited evidence suggests that cranberry juice does not appear to affect the pharmacokinetics of flurbiprofen.

Clinical evidence

In a study in 14 healthy subjects, 230 mL of cranberry juice taken the night before, and 30 minutes before a single 100-mg dose of flurbiprofen, had no significant effect on the pharmacokinetics of flurbiprofen. Fluconazole, used as a positive control, increased the flurbiprofen AUC by about 80%.[1] In this study, the cranberry juice used was *Ocean Spray* cranberry juice cocktail from concentrate containing 27% cranberry juice.

Mechanism

Flurbiprofen is metabolised by the cytochrome P450 isoenzyme CYP2C9, and the clinical study appears to suggest that cranberry has no clinically relevant effect on this particular isoenzyme, despite the fact that it had some weak inhibitory effects *in vitro*.[1]

Importance and management

Evidence is limited, but what is known suggests that no pharmacokinetic interaction occurs between flurbiprofen and cranberry juice. Therefore no dose adjustment appears to be necessary if patients taking flurbiprofen wish to drink cranberry juice.

1. Greenblatt DJ, von Moltke LL, Perloff ES, Luo Y, Harmatz JS, Zinny MA. Interaction of flurbiprofen with cranberry juice, grape juice, tea, and fluconazole: in vitro and clinical studies. *Clin Pharmacol Ther* (2006) 79, 125–33.

NSAIDs; Ibuprofen + Moclobemide

Moclobemide did not alter the pharmacokinetics of ibuprofen, or ibuprofen-induced faecal blood loss in one study. Ibuprofen does not affect the pharmacokinetics of moclobemide.

Clinical evidence, mechanism, importance and management

A study in 24 healthy subjects found that moclobemide 150 mg three times daily for 7 days had no effect on the steady-state pharmacokinetics of ibuprofen 600 mg three times daily, and the amount of ibuprofen-induced faecal blood loss was unaffected.[1] Ibuprofen did not affect the pharmacokinetics of moclobemide. No special precautions appear to be required during concurrent use.

1. Güntert TW, Schmitt M, Dingemanse J, Jonkman JHG. Influence of moclobemide on ibuprofen-induced faecal blood loss. *Psychopharmacology (Berl)* (1992) 106, S40–S42.

NSAIDs; Ibuprofen + Nitric oxide

The manufacturer of ibuprofen injection, which is used to treat patent ductus arteriosus in preterm newborn infants, warns that its use with nitric oxide, which is used to treat hypoxic respiratory failure in neonates, may in theory increase the risk of bleeding as both drugs inhibit platelet function.[1] The clinical significance of this proposed interaction is unclear, but it may be prudent to be alert for any evidence of bruising or bleeding if both drugs are given.

1. Pedea Injection (Ibuprofen). Orphan Europe (UK) Ltd. UK Summary of product characteristics, July 2004.

NSAIDs; Ibuprofen + St John's wort (*Hypericum perforatum*)

St John's wort does not affect the pharmacokinetics of ibuprofen.

Clinical evidence

Eight healthy male subjects were given an oral dose of ibuprofen 400 mg before, and at the end of, a 21 day course of St John's wort 300 mg three times daily. The pharmacokinetics of ibuprofen were unaffected by St John's wort. The St John's wort extract was standardised to contain hypericin (probably 0.3%) and a minimum of 4% hyperforin.[1]

Mechanism

As ibuprofen is a substrate for the cytochrome P450 isoenzymes CYP2C9 and CYP2C8, the authors of the study suggest that the lack of interaction is evidence that St John's wort has no significant effects on these isoenzymes.[1]

Importance and management

St John's wort does not appear to interact with ibuprofen and therefore no special precautions seem necessary on concurrent use.

1. Bell EC, Ravis WR, Lloyd KB, Stokes TJ. Effects of St. John's wort supplementation on ibuprofen pharmacokinetics. *Ann Pharmacother* (2007) 41, 229–34.

NSAIDs; Indometacin + Cocaine

An isolated report describes marked oedema, anuria and haematemesis in a premature child attributed to an interaction between cocaine and indometacin, which were taken by the mother before the birth.

Clinical evidence, mechanism, importance and management

A woman who was a cocaine user and who was in premature labour was unsuccessfully treated with terbutaline and magnesium sulfate. Indometacin proved to be more effective, but after being given 400 mg over 2 days she gave birth to a boy estimated at 34 to 35 weeks. Before birth the child was noted to be anuric and at birth showed marked oedema, and later haematemesis.

It was suggested that the anuria and oedema were due to renal vascular constriction of the foetus caused by the cocaine combined with an adverse effect of indometacin on ADH-mediated water reabsorption. Both drugs can cause gastrointestinal bleeding, which would account for the haematemesis. The authors of this report point out that one of the adverse effects of cocaine is premature labour, and that the likelihood is high that indometacin may be used to control it. They advise screening likely addicts in premature labour for evidence of cocaine usage before indometacin is given.[1]

1. Carlan SJ, Stromquist C, Angel JL, Harris M, O'Brien WF. Cocaine and indomethacin: fetal anuria, neonatal edema and gastrointestinal bleeding. *Obstet Gynecol* (1991) 78, 501–3.

NSAIDs; Indometacin + Vaccines

Some very limited evidence suggests that the response to immunisation with live vaccines may be more severe than usual in the presence of indometacin.

Clinical evidence, mechanism, importance and management

A man with ankylosing spondylitis taking indometacin 25 mg three times daily had a strong primary-type reaction 12 days after **smallpox vaccination**. He experienced 3 days of severe malaise, headache and nausea, as well as enlarged lymph nodes. The scab that formed was unusually large (3 cm in diameter) but he suffered no long term ill-effects.[1] The suggestion was that indometacin alters the response of the body to viral infections, whether originating from vaccines or not.[1] This suggestion is supported by the case of a child taking indometacin who developed haemorrhagic chickenpox during a ward outbreak of the disease.[2] However, these appear to be isolated and relatively old reports, and are therefore probably of little general importance. Note that NSAIDs such as indometacin may mask some of the signs and symptoms of infection.

1. Maddocks AC. Indomethacin and vaccination. *Lancet* (1973) ii, 210–11.
2. Rodriguez RS, Barbabosa E. Hemorrhagic chickenpox after indomethacin. *N Engl J Med* (1971) 285, 690.

NSAIDs; Ketorolac + Vancomycin

An isolated report describes temporary acute renal failure and gastrointestinal bleeding following the use of ketorolac and vancomycin.

Clinical evidence, mechanism, importance and management

A previously healthy middle-aged man developed acute renal failure and subsequent gastrointestinal bleeding following uncomplicated surgery and treatment with ketorolac trometamol and vancomycin. The reason for the temporary renal failure is not known, but the authors of the report suggest that ketorolac inhibited the normal production of the vasodilatory renal prostaglandins so that renal blood flow was reduced. This would seem to have been additive with the nephrotoxic effects of vancomycin. Note that a vancomycin level taken on postoperative day 3 was found to be above the normal therapeutic range (although the timing of the sample was not stated).[1] Ketorolac alone can cause dose-related and transient renal impairment. The gastrointestinal bleeding appeared to be due to the direct irritant effects of the ketorolac, possibly made worse by the previous use of piroxicam[1] (see also 'NSAIDs + NSAIDs', p.168). The general importance of this interaction is uncertain. As renal function should be routinely monitored in patients given vancomycin no additional precautions seem necessary, but if renal impairment develops in a patient taking both drugs, consider an interaction as a possible cause.

1. Murray RP, Watson RC. Acute renal failure and gastrointestinal bleed associated with postoperative Toradol and vancomycin. *Orthopedics* (1993) 16, 1361–3.

NSAIDs; Naproxen + Diphenhydramine

No significant pharmacokinetic interaction appears to occur between diphenhydramine and naproxen.

Clinical evidence, mechanism, importance and management

In a study in 27 healthy subjects, diphenhydramine hydrochloride 50 mg had no clinically significant effect on the pharmacokinetics of a single 220-mg dose of naproxen sodium. The pharmacokinetics of diphenhy-

dramine were similarly unaffected by naproxen.[1] No dose adjustment of either drug appears to be necessary on concurrent use.

1. Toothaker RD, Barker SH, Gillen MV, Helsinger SA, Kindberg CG, Hunt TL, Powell JH. Absence of pharmacokinetic interaction between orally co-administered naproxen sodium and diphenhydramine hydrochloride. *Biopharm Drug Dispos* (2000) 21, 229–33.

NSAIDs; Naproxen + Sulglicotide

Sulglicotide does not affect the absorption of naproxen.

Clinical evidence, mechanism, importance and management

In a study in 12 healthy subjects, sulglicotide 200 mg had no significant effects on the pharmacokinetics of a single 500-mg dose of naproxen.[1] Sulglicotide may therefore be used to protect the gastric mucosa from possible injury by naproxen without altering its absorption.

1. Berté F, Feletti F, De Bernardi di Valserra M, Nazzari M, Cenedese A, Cornelli U. Lack of influence of sulglycotide on naproxen bioavailability in healthy volunteers. *Int J Clin Pharmacol Ther Toxicol* (1988) 26, 125–8.

NSAIDs; Naproxen + Zileuton

No clinically significant pharmacokinetic or pharmacodynamic interaction appears to occur between naproxen and zileuton.

Clinical evidence, mechanism, importance and management

In a randomised, placebo-controlled study, 24 healthy subjects were given zileuton 800 mg every 12 hours with naproxen 500 mg every 12 hours for 6 days. No clinically significant change was found in the pharmacokinetics of either drug. Naproxen did not affect the inhibitory effect of zileuton on leukotriene B_4 levels and similarly zileuton did not affect the inhibitory effect of naproxen on thromboxane B_2. The inhibition of the 5-lipoxygenase pathway by zileuton did not appear to worsen the gastrointestinal effects associated with naproxen. No special precautions would seem necessary if both drugs are given.[1]

1. Awni WM, Braeckman RA, Cavanaugh JH, Locke CS, Linnen PJ, Granneman GR, Dube LM. The pharmacokinetic and pharmacodynamic interactions between the 5-lipoxygenase inhibitor zileuton and the cyclo-oxygenase inhibitor naproxen in human volunteers. *Clin Pharmacokinet* (1995) 29 (Suppl 2) 112–24.

NSAIDs; Parecoxib + Miscellaneous

As parecoxib is rapidly metabolised to valdecoxib, the interactions are usually considered to be due to the effects of valdecoxib. The manufacturer of parecoxib cautions the concurrent use of carbamazepine, dexamethasone, phenytoin and rifampicin (rifampin). Valdecoxib increases the levels of dextromethorphan and omeprazole. Because of these interactions, caution is advised with drugs that are metabolised by the same isoenzymes.

Clinical evidence, mechanism, importance and management

Parecoxib is a parenteral drug that is rapidly metabolised in the liver to the active COX-2 inhibitor valdecoxib. Valdecoxib is predominantly metabolised by the cytochrome P450 isoenzymes CYP3A4 and CYP2C9. The interactions therefore are usually considered to be due to the effects of valdecoxib.

(a) CYP2C19 substrates

The manufacturers say that the AUC of **omeprazole** 40 mg was increased by 46% by valdecoxib 40 mg twice daily for a week. This indicates that valdecoxib is an inhibitor of CYP2C19, and although the manufacturers consider it to be a weak inhibitor,[1] they advise caution if valdecoxib is given with other drugs that are known to be metabolised by CYP2C19. They name **diazepam**, **imipramine** and **phenytoin**.[2] The implication is that the serum levels of these drugs and their effects may possibly be increased by the use of parecoxib.

(b) CYP2D6 substrates

The manufacturers say that valdecoxib 40 mg twice daily for a week caused a threefold increase in the serum levels of **dextromethorphan**. This indicates that valdecoxib is an inhibitor of CYP2D6, and therefore the manufacturers[1] suggest that caution should be observed with drugs that have a narrow therapeutic margin and are known to be predominantly metabolised by CYP2D6. They list **flecainide**, **metoprolol** and **propafenone**.[2] The implication is that the serum levels of these drugs and their effects may possibly be increased by the use of parecoxib; however, a study with metoprolol and valdecoxib did not find any clinically relevant interaction, see 'Beta blockers + Aspirin or NSAIDs', p.997.

(c) Enzyme inducers

The manufacturer of parecoxib[2] warns that, although they have not been studied, enzyme inducers (they name **carbamazepine**, **dexamethasone**, **phenytoin** and **rifampicin** (**rifampin**)) may increase the metabolism of valdecoxib. It may therefore be prudent to monitor the outcome of concurrent use for valdecoxib efficacy. However, note that dexamethasone does not usually appear to interact to a clinically relevant extent by this mechanism.

1. Pharmacia Ltd. Personal communication, May 2002.
2. Dynastat (Parecoxib sodium). Pfizer Ltd. UK Summary of product characteristics, July 2009.

NSAIDs; Phenylbutazone + Methylphenidate

Methylphenidate significantly increased the serum levels of phenylbutazone 200 to 400 mg daily in 5 out of 6 patients, due, it is suggested, to inhibition of liver metabolising enzymes.[1] The clinical importance of effect this is uncertain, especially as the report does not indicate the magnitude of the interaction.

1. Dayton PG, Perel JM, Israili ZH, Faraj BA, Rodewig K, Black N, Goldberg LI. Studies with methylphenidate: drug interactions and metabolism. In: Sellers EM ed. Clinical Pharmacology of Psychoactive Drugs. Ontario: Addiction Research Foundation, 1973. p183–202.

NSAIDs; Sulindac + Dimethyl sulfoxide (DMSO)

Isolated case reports describe serious peripheral neuropathy, which occurred when DMSO was applied to the skin of two patients taking sulindac.

Clinical evidence, mechanism, importance and management

A man with a long history of degenerative arthritis took sulindac 400 mg daily uneventfully for 6 months until, without his doctor's knowledge, he began regularly to apply a topical preparation containing DMSO 90% to his upper and lower extremities. Soon afterwards he began to experience pain, weakness in all his extremities, and difficulty in standing or walking. He was found to have both segmental demyelination and axonal neuropathy. He made a partial recovery but was unable to walk without an artificial aid.[1]

A second case describes a 68-year-old man with a history of mild osteoarthritis of the knees who was taking sulindac 150 mg twice daily. He later started to apply aqueous solutions of DMSO to his lower extremities, whilst continuing to take sulindac. Within 3 months he reported difficulty in climbing stairs, and myalgia of the thighs and legs. Over the next 5 months he experienced a progressive loss of gait, wasting of thigh and leg muscles, and more intense myalgia, cramps and fasciculations. Nerve conduction studies revealed damage to the nerves. During the year after discontinuing the DMSO, and supplementing his diet with vitamins B_6 and B_{12}, the patient had an improvement in the myalgia and physical disabilities, and a return to normal muscle strength. He continued to take the sulindac at a dose of 200 mg twice daily.[2]

The reason for this reaction is not known, but studies in *rats* have shown that DMSO can inhibit a reductase enzyme by which sulindac is metabolised,[3] and it may be that the high concentrations of unmetabolised sulindac increased the neurotoxic activity of the DMSO. Although there are only these two cases on record, its seriousness suggests that patients should not use sulindac and DMSO-containing preparations concurrently.

1. Reinstein L, Mahon R, Russo GL. Peripheral neuropathy after concomitant dimethyl sulfoxide use and sulindac therapy. *Arch Phys Med Rehabil* (1982) 63, 581–4.
2. Swanson BN, Ferguson RK, Raskin NH, Wolf BA. Peripheral neuropathy after concomitant administration of dimethyl sulfoxide and sulindac. *Arthritis Rheum* (1983) 26, 791–3.
3. Swanson BN, Mojaverian P, Boppana VK, Dudash M. Dimethylsulfoxide (DMSO) interaction with sulindac (SO). *Pharmacologist* (1981) 23, 196.

Opioids + Amfetamines and related drugs

Dexamfetamine and methylphenidate increase the analgesic effects of morphine and other opioids but reduce their sedative and respiratory depressant effects.

Clinical evidence, mechanism, importance and management

In studies during postoperative analgesia[1] and in healthy subjects,[2] **dexamfetamine** increased the analgesic effect of **morphine** and reduced its respiratory depressant effects to some extent. **Methylphenidate** 15 mg daily similarly increased the analgesic effects of various opioids (**morphine**, **hydromorphone**, **levorphanol**, **oxycodone**) and reduced the sedative effects in patients with chronic pain due to advanced cancer.[3] Similarly, two manufacturers of amfetamines advise that amfetamines potentiate the analgesic effects of **pethidine** (**meperidine**).[4,5] Therefore, the analgesic dose of an opioid may be lower than expected in patients taking amfetamines. The manufacturers also note that, in cases of **dextropropoxyphene** (**propoxyphene**) *overdose*, amfetamine CNS stimulation is potentiated and fatal convulsions can occur.[4,5]

1. Forrest WH, Brown BW, Brown CR, Defalque R, Gold M, Gordon HE, James KE, Katz J, Mahler DL, Schroff P, Teutsch G. Dextroamphetamine with morphine for the treatment of postoperative pain. *N Engl J Med* (1977) 296, 712–15.
2. Bourke DL, Allen PD, Rosenberg M, Mendes RW, Karabelas AN. Dextroamphetamine with morphine: respiratory effects. *J Clin Pharmacol* (1983) 23, 65–70.
3. Bruera E, Chadwick S, Brenneis C, Hanson J, MacDonald RN. Methylphenidate associated with narcotics for the treatment of cancer pain. *Cancer Treat Rep* (1987) 71, 67–70.
4. Adderall XR (Mixed salts of amphetamine and dextroamphetamine). Shire US Inc. US Prescribing information, March 2009.
5. Dexedrine (Dextroamphetamine sulfate). GlaxoSmithKline. US Prescribing information, July 2008.

Opioids + Antiemetics

Metoclopramide increases the rate of absorption of oral morphine and increases its rate of onset and sedative effects. Opioids may antagonise the effects of metoclopramide on gastric emptying. The use of droperidol with opioids can be beneficial, but an increase in sedation appears to occur.

Clinical evidence

(a) Alizapride

Intravenous alizapride 100 mg given to 60 women undergoing caesarean section under spinal anaesthesia, reduced **morphine**-induced pruritus, and the amount of sedation (8.3% both peri- and postoperatively) was less than with droperidol,[1] see below.

(b) Droperidol

1. Fentanyl. Epidural droperidol given with epidural fentanyl improved postsurgical analgesia following anorectal surgery and there was less nausea compared with fentanyl alone.[2]

2. Hydromorphone. Early respiratory depression has been reported when droperidol was given 10 minutes before epidural hydromorphone 1.25 mg; the patient became apnoeic 15 minutes after the epidural was given. Naloxone did not reverse the respiratory depression, but spontaneous ventilation resumed within 3 minutes of a 1-mg intravenous dose of physostigmine.[3]

3. Morphine. In a double-blind study in 179 patients following abdominal hysterectomy, droperidol 50 micrograms given with morphine 1 mg on demand via patient-controlled analgesia (PCA) provided a morphine-sparing effect and reduced the frequency of postoperative nausea and vomiting, when compared with morphine PCA alone.[4] However, in a study of 107 patients undergoing caesarean section, intravenous droperidol 2.5 mg given just after delivery reduced the incidence and severity of epidural morphine-induced pruritus, but the incidence of nausea and vomiting was not affected. Furthermore, somnolence was greater in the droperidol-treated patients (17% versus 2% in the control group) but it was never incapacitating.[5] Similar sedative effects were seen with spinal morphine and intravenous droperidol in another study.[1]

(c) Metoclopramide

1. Butorphanol. In a study in 24 healthy women, the pharmacokinetics of a single 1-mg intranasal dose of butorphanol were unaffected by a single 10-mg oral dose of metoclopramide. The pharmacokinetics of metoclopramide were also not affected, except for a delay in the time to reach maximum plasma levels (increased from one hour to 2 hours), which was probably due to reduction of gastrointestinal motility by butorphanol.[6] Metoclopramide reduced the nausea associated with butorphanol, probably by antagonism of central and peripheral dopamine receptors.[7]

2. Morphine. A single 10-mg dose of oral metoclopramide, given to 10 patients before surgery, markedly increased the extent and speed of sedation due to a 20-mg oral dose of modified-release morphine (*MST Continus Tablets*) in the first 1.5 hours after the dose. The time to peak plasma levels of morphine was almost halved, but peak plasma morphine levels and the total absorption remained unaltered.[7] A study involving 40 patients found that intravenous metoclopramide 10 mg antagonised the reduction in gastric emptying caused by premedication with intramuscular morphine 10 mg, given 20 minutes earlier. However, intramuscular metoclopramide given at the same time as the morphine had no effect on the reduced gastric emptying.[8]

Mechanism

Metoclopramide increases the rate of gastric emptying so that the rate of morphine absorption from the small intestine is increased. An alternative mechanism is that both drugs act additively on opiate receptors to increase sedation.[7] Droperidol may also enhance adverse effects such as sedation, and in some cases respiratory depression, possibly through opioid and other receptor sites in the CNS.[2] In one case, the respiratory depression was not reversed by naloxone, suggesting that droperidol was at least partially if not completely responsible.[3]

Importance and management

The effect of metoclopramide on oral morphine absorption is an established interaction that can be usefully exploited in anaesthetic practice, but the increased sedation may also present a problem if the morphine is being given long-term. The morphine-sparing effect of droperidol is also a useful interaction, but the increased sedation and possible respiratory depression and hypotension should be borne in mind. One manufacturer of fentanyl specifically warns that the concurrent use of droperidol can result in a higher incidence of hypotension.[9]

Morphine appears to antagonise the effects of metoclopramide on gastric emptying. As a reduction in gastric motility occurs with all opioids they would all be expected to interact with metoclopramide, and other motility stimulants such as **domperidone**. However, these drugs are commonly used together and the clinical significance of such effects is not clear.

Note that some sedating antihistamines, such as **cyclizine**, are also used as antiemetics, and additive sedation is likely to occur on concurrent use.

Consider also 'Opioids + Antiemetics; Ondansetron', below.

1. Horta ML, Morejon LCL, da Cruz AW, dos Santos GR, Welling LC, Terhorst L, Costa RC, Alam RUZ. Study of the prophylactic effect of droperidol, alizapride, propofol and promethazine on spinal morphine-induced pruritus. *Br J Anaesth* (2006) 96, 796–800.
2. Kotake Y, Matsumoto M, Ai K, Morisaki H, Takeda J. Additional droperidol, not butorphanol, augments epidural fentanyl analgesia following anorectal surgery. *J Clin Anesth* (2000) 12, 9–13.
3. Cohen SE, Rothblatt AJ, Albright GA. Early respiratory depression with epidural narcotic and intravenous droperidol. *Anesthesiology* (1983) 59, 559–60.
4. Lo Y, Chia Y-Y, Liu K, Ko N-H. Morphine sparing with droperidol in patient-controlled analgesia. *J Clin Anesth* (2005) 17, 271–5.
5. Horta ML, Horta BL. Inhibition of epidural morphine-induced pruritus by intravenous droperidol. *Reg Anesth* (1993) 18, 118–20.
6. Vachharajani NN, Shyu WC, Barbhaiya RH. Pharmacokinetic interaction between butorphanol nasal spray and oral metoclopramide in healthy women. *J Clin Pharmacol* (1997) 37, 979–85.
7. Manara AR, Shelly MP, Quinn K, Park GR. The effect of metoclopramide on the absorption of oral controlled release morphine. *Br J Clin Pharmacol* (1988) 25, 518–21.
8. McNeill MJ, Ho ET, Kenny GNC. Effect of i.v. metoclopramide on gastric emptying after opioid premedication. *Br J Anaesth* (1990) 64, 450–2.
9. Sublimaze (Fentanyl citrate). Janssen-Cilag Ltd. UK Summary of product characteristics, September 2009.

Opioids + Antiemetics; Ondansetron

Ondansetron reduces the analgesic efficacy of tramadol and at least doubled the tramadol dose required in one clinical study. This resulted in more vomiting despite the use of ondansetron. In

contrast, in studies in healthy subjects, ondansetron had no effect on the analgesic effects of morphine and alfentanil.

Clinical evidence

(a) Alfentanil

In a study in healthy subjects, single 8- or 16-mg doses of intravenous ondansetron were found to have no effect on the sedation or ventilatory depression due to alfentanil (a continuous infusion of 0.25 to 0.75 micrograms/kg following a 5-micrograms/kg bolus dose) and had no effect on the rate of recovery.[1] Similarly, in another study, intravenous ondansetron 8 mg did not oppose the analgesic effect of intramuscular alfentanil 30 micrograms/kg on experimentally-induced pain stimuli.[2]

(b) Morphine

A double-blind, placebo-controlled study in 12 healthy subjects found that a single 16-mg intravenous dose of ondansetron given 30 minutes after a single 10-mg intravenous dose of morphine did not alter the pharmacokinetics of morphine or its metabolites, morphine-3-glucuronide and morphine-6-glucuronide. The analgesic effect of morphine (as measured by a contact thermode system) was also unaffected by ondansetron.[3]

(c) Tramadol

Patients who were given a single 4-mg dose of ondansetron one minute before induction of anaesthesia required 26 to 35% more intravenous tramadol by patient controlled analgesia (PCA) from one to 4 hours postoperatively than those who received placebo.[4] Similarly, a 1-mg/hour ondansetron infusion increased the dose of postoperative intravenous tramadol given using a PCA pump by two- to threefold in 30 patients, when compared with 29 patients who received placebo. Moreover, in this study the group receiving ondansetron actually experienced more vomiting, probably because they used more tramadol, which caused an emetic effect not well controlled by the ondansetron.[5]

Mechanism

On theoretical grounds ondansetron (a 5-HT_3-receptor antagonist) might be expected to decrease the effects of drugs that reduce pain transmission because serotonin (5-HT) is thought to affect pain responses via presynaptic 5-HT_3 receptors in the spinal dorsal horn. This has been demonstrated for tramadol, which is not a pure opioid and also acts by enhancing the effects of serotonin and noradrenaline (norepinephrine). However, ondansetron had no effect on alfentanil or morphine analgesia in healthy subjects.

Importance and management

Although there is only data from two clinical studies, the interaction between ondansetron and tramadol appears to be established and of clinical importance. Ondansetron may double the dose requirement of tramadol, and so result in reduced pain control. The increase in dose requirements appears to increase nausea and vomiting which may not be sufficiently controlled by the ondansetron. Consequently ondansetron does not appear to be the best antiemetic to use with tramadol.[3] Although not tested, other 5-HT_3-receptor antagonists would be expected to interact similarly.

Ondansetron appears to have no effect on alfentanil or morphine.

1. Dershwitz M, Di Biase PM, Rosow CE, Wilson RS, Sanderson PE, Joslyn AF. Ondansetron does not affect alfentanil-induced ventilatory depression or sedation. *Anesthesiology* (1992) 77, 447–52.
2. Petersen-Felix S, Arendt-Nielsen L, Bak P, Bjerring P, Breivik H, Svensson P, Zbinden AM. Ondansetron does not inhibit the analgesic effect of alfentanil. *Br J Anaesth* (1994) 73, 326–30.
3. Crews KR, Murthy BP, Hussey EK, Passannante AN, Palmer JL, Maixner W, Brouwer KLR. Lack of effect of ondansetron on the pharmacokinetics and analgesic effects of morphine and metabolites after single-dose morphine administration in healthy volunteers. *Br J Clin Pharmacol* (2001) 51, 309–16.
4. De Witte JL, Schoenmaekers B, Sessler DI, Deloof T. The analgesic efficacy of tramadol is impaired by concurrent administration of ondansetron. *Anesth Analg* (2001) 92, 1319–21.
5. Arcioni R, della Rocca M, Romanò S, Romano R, Pietropaoli P, Gasparetto A. Ondansetron inhibits the analgesic effects of tramadol: a possible 5-HT_3 spinal receptor involvement in acute pain in humans. *Anesth Analg* (2002) 94, 1553–7.

Opioids + Antiepileptics; Enzyme-inducing

Patients taking enzyme-inducing antiepileptics appear to need more fentanyl than those not taking these antiepileptics. Similarly, the efficacy of buprenorphine may be reduced by carbamazepine, phenobarbital and phenytoin. Carbamazepine appears to increase the production of a more potent metabolite of codeine, normorphine. The plasma levels of tramadol are reduced by carbamazepine, and the analgesic efficacy would be expected to be reduced. There is also an increased risk of seizures with tramadol. A pharmacokinetic study confirms that phenytoin increases the production of the toxic metabolite of pethidine (meperidine). An isolated report describes pethidine toxicity in a man taking phenytoin.

Clinical evidence, mechanism, importance and management

(a) Buprenorphine

Although interaction studies have not been performed, the metabolism of buprenorphine is mediated by the cytochrome P450 isoenzyme CYP3A4 and therefore drugs that induce this isoenzyme such as **carbamazepine**, **phenobarbital** and **phenytoin** may induce the metabolism and increase the clearance of buprenorphine.[1,2] The manufacturers of buprenorphine state that inducers of CYP3A4 may reduce the efficacy of buprenorphine[1-3] and, if necessary, dose adjustments should be considered,[2] or the combination avoided.[1]

(b) Codeine

An experimental study in 7 patients with epilepsy, to find out if **carbamazepine** induces the enzymes concerned with the metabolism of codeine, found that it increased *N*-demethylation (to norcodeine and normorphine) by two- to threefold, but did not affect *O*-demethylation (to morphine). The patients were given a single 25-mg dose of codeine before and 3 weeks after starting to take **carbamazepine** 400 to 600 mg daily.[4] Similarly, an *in vitro* study found that **carbamazepine** and **phenytoin** did not alter the *O*-demethylation of codeine (methylmorphine) into morphine.[5]

Normorphine is an active metabolite, so that the authors of the first study suggest those taking both codeine and **carbamazepine** may possibly experience a stronger analgesic effect.[4] However, this needs further study. There would seem to be no reason for avoiding concurrent use.

(c) Dextropropoxyphene (Propoxyphene)

Dextropropoxyphene may increase the plasma levels of antiepileptics, particularly carbamazepine, see 'Carbamazepine or Oxcarbazepine + Dextropropoxyphene (Propoxyphene)', p.603.

(d) Fentanyl

Twenty-eight patients, undergoing craniotomy for seizure focus excision and receiving long-term treatment with antiepileptics in various combinations, needed 48 to 144% more fentanyl during anaesthesia than a control group of 22 patients who were not taking antiepileptics.[6] The fentanyl maintenance requirements were:

- 2.7 micrograms/kg per hour in the control group,
- 4 micrograms/kg per hour in patients taking **carbamazepine**,
- 4.7 micrograms/kg per hour in patients taking **carbamazepine** and **phenytoin** or **valproate**,
- 6.3 micrograms/kg per hour in patients taking **carbamazepine**, **valproate** and either **phenytoin** or **primidone**.

Similar results were reported by the same authors in a study involving 61 patients.[7] The increased opioid requirement probably occurs because these antiepileptics are potent enzyme inducers (with the exception of **valproate**), which increase the metabolism of fentanyl by the liver, so that its levels are reduced.[6] Changes in the state of opiate receptors induced by long-term antiepileptic exposure may also be involved.[7] A marked increase in the fentanyl requirements should therefore be anticipated in any patient receiving long-term treatment with **carbamazepine**, **primidone** or **phenytoin**. No fentanyl dose adjustment is expected to be needed with **valproate**.

(e) Methadone

Methadone levels can be reduced by carbamazepine, phenobarbital or phenytoin. See 'Opioids; Methadone + Antiepileptics', p.180.

(f) Pethidine (Meperidine)

A 61-year-old man who was addicted to pethidine, taking 5 to 10 g weekly, developed repeated seizures and myoclonus when he also took **phenytoin**. The problem resolved when both drugs were stopped.[8] It is known that **phenytoin** increases the metabolism of pethidine with increased production of norpethidine,[9] the metabolite of pethidine that is believed to be responsible for its neurotoxicity (seizures, myoclonus, tremors etc). A

study[10] in healthy subjects found that **phenytoin** 300 mg daily for 9 days decreased the elimination half-life of pethidine (100 mg orally and 50 mg intravenously) from 6.4 hours to 4.3 hours, and the systemic clearance increased by 27%. This seems to be the only report of an adverse interaction between **phenytoin** and pethidine so its general importance is uncertain.[8] As the study cited[10] found that pethidine given orally produced more of the toxic metabolite (norpethidine) than when given intravenously, it may be preferable to give pethidine intravenously in patients taking **phenytoin**, or use an alternative opioid. Consider also 'Opioids + Barbiturates', p.183, for the possible interaction between phenobarbital and pethidine.

(g) Tramadol

An unpublished study by the manufacturers found that the maximum plasma levels and the elimination half-life of a single 50-mg dose of tramadol were reduced by 50% by **carbamazepine** 400 mg twice daily for 9 days.[11] It is likely that **carbamazepine** increases the metabolism of tramadol. On the basis of this study the manufacturers say that the analgesic effectiveness of tramadol[12,13] and its duration of action would be expected to be reduced.[11,13] The US manufacturer recommends avoidance of concurrent use because of the increased metabolism and also the seizure risk associated with tramadol.[12] The UK manufacturer says that patients with a history of epilepsy or those susceptible to seizures should only be given tramadol if there are compelling reasons.[13] Monitor carefully if tramadol and antiepileptics, particularly **carbamazepine**, are required.

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2. Buprenorphine Hydrochloride Injection. Bedford Laboratories. US Prescribing information, August 2004.
3. Transtec Transdermal Patch (Buprenorphine). Napp Pharmaceuticals Ltd. UK Summary of product characteristics, January 2009.
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11. GD Searle. Personal Communication, November 1994.
12. Ultram ER (Tramadol hydrochloride). Ortho-McNeil, Inc. US Prescribing information, December 2007.
13. Zydol SR Tabs (Tramadol hydrochloride). Grünenthal Ltd. UK Summary of product characteristics, February 2009.

Opioids + Antiepileptics; Gabapentin

Morphine can increase the bioavailability of gabapentin. Gabapentin has been reported to enhance the analgesic effects of morphine and other opioids.

Clinical evidence, mechanism, importance and management

A single-dose, placebo-controlled study in 12 healthy subjects given controlled-release **morphine** 60 mg found that gabapentin 600 mg, given after an interval of 2 hours, had no effect on the pharmacokinetics of morphine, morphine-3- and morphine-6-glucuronides. In the presence of **morphine** the gabapentin AUC increased by 44% and its oral clearance and apparent renal clearance decreased by 23% and 16%, respectively. These changes may possibly be due to an increase in the absorption of gabapentin caused by reduced intestinal motility by morphine. The analgesic effect of **morphine** and gabapentin was evaluated by changes in the area under the curve of pain tolerance. Gabapentin with placebo had no significant analgesic effect, but a significant increase in the pain threshold and pain tolerance was found when gabapentin was given with morphine, when compared with placebo. The adverse effect profiles were similar for both the gabapentin with morphine and the morphine with placebo groups.[1] Other clinical studies have reported that gabapentin used in conjunction with opioids has an analgesic and opioid-sparing effect in acute postoperative pain management[2,3] and neuropathic pain.[4]

The modest changes in gabapentin pharmacokinetics seen in the study with morphine are unlikely to require a gabapentin dose adjustment. However, the manufacturer of gabapentin warns that patients should be carefully observed for signs of CNS depression (a pharmacodynamic effect), such as somnolence, and the dose of gabapentin or **morphine** should be reduced appropriately.[5]

1. Eckhardt K, Ammon S, Hofmann U, Riebe A, Gugeler N, Mikus G. Gabapentin enhances the analgesic effect of morphine in healthy volunteers. *Anesth Analg* (2000) 91, 185–91.
2. Ho K-Y, Gan TJ, Habib AS. Gabapentin and postoperative pain–a systematic review of randomised controlled trials. *Pain* (2006) 126, 91–101.
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Opioids; Methadone + Antiepileptics

Methadone levels can be reduced by carbamazepine, phenobarbital or phenytoin and opioid withdrawal symptoms may occur. Valproate does not appear to interact with methadone. An isolated report describes lamotrigine-associated rash and blood dyscrasias, which may have been associated with methadone use.

Clinical evidence

(a) Enzyme-inducing antiepileptics

A study in 37 patients taking methadone maintenance found that the 10 patients taking enzyme-inducing drugs (**carbamazepine**, **phenobarbital** or **phenytoin**) had low trough methadone levels of less than 100 nanograms/mL. One patient taking **carbamazepine** complained of daily withdrawal symptoms and had signs of opioid withdrawal.[1] Withdrawal symptoms have been seen in other patients taking **carbamazepine**,[2] **phenobarbital**,[3] and **phenytoin**.[1,2,4,5] Similarly, methadone withdrawal symptoms developed in 5 patients within 3 to 4 days of starting to take **phenytoin** 300 to 500 mg daily. Methadone plasma levels were reduced by about 60%. The withdrawal symptoms disappeared within 2 to 3 days of stopping **phenytoin** and the plasma methadone levels returned to their former values.[6] A further patient experienced methadone-induced respiratory depression after discontinuing **carbamazepine**.[7]

(b) Lamotrigine

Lamotrigine-associated rash and blood dyscrasias occurred in a 40-year-old opioid-dependent woman with hepatitis C. Lamotrigine was considered to be the causal factor as haematological values returned to normal 53 days after discontinuation. However, the woman was also receiving methadone maintenance and it was thought that the methadone, together with liver impairment, might possibly have caused elevated levels of lamotrigine (but note that these were not measured).[8]

(c) Valproate

Two patients who had methadone withdrawal symptoms while taking phenytoin 300 to 400 mg daily, and one of them later when taking carbamazepine 600 mg daily, became free from withdrawal symptoms when they were given valproate instead. It was also found possible to virtually halve their daily methadone dose.[2]

Mechanism

Not fully established, but carbamazepine, phenobarbital and phenytoin are recognised inducers of the cytochrome P450 isoenzyme CYP3A4, by which methadone is, in part, metabolised, and therefore increase methadone metabolism and its loss from the body. In one study it was found that phenytoin increased the urinary excretion of the main metabolite of methadone.[6]

Importance and management

Information is limited but the interaction between methadone and the enzyme-inducing antiepileptics, carbamazepine, phenobarbital and phenytoin, appears to be established and of clinical importance. Anticipate the need to increase the methadone dose in patients taking these antiepileptics. It may be necessary to give the methadone twice daily to prevent withdrawal symptoms appearing towards the end of the day. It seems probable that **primidone** and **fosphenytoin** will interact similarly because they are metabolised to phenobarbital and phenytoin, respectively. Also be aware of the need to reduce the methadone dose if any enzyme-inducing antiepileptic is stopped. Valproate appears not to interact.

It is unclear whether the methadone or the liver impairment contributed to the lamotrigine-associated rash and blood dyscrasias and therefore this isolated case is of unknown general significance.

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Opioids + Antihistamines

Increased respiratory depression has been seen with hydroxyzine and opioids in one study,[1] but not in two others.[2,3] The US manufacturer of hydroxyzine warns that it may enhance the effects of pethidine (meperidine).[4] A reduction in dose may be necessary. All sedating antihistamines (see 'Table 15.1', (p.663)) would be expected to have additive CNS depressant effects with opioids. This may lead to increased sedation and respiratory depression, and therefore some caution is warranted when both drugs are given.

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2. Zsigmond EK, Flynn K, Shively JG. Effect of hydroxyzine and meperidine on arterial blood gases in healthy human volunteers. *J Clin Pharmacol* (1989) 29, 85–90.
3. Zsigmond EK, Flynn K, Shively JG. Effect of hydroxyzine and meperidine on arterial blood gases in patients with chronic obstructive pulmonary disease. *Int J Clin Pharmacol Ther Toxicol* (1993) 31, 124–9.
4. Hydroxyzine. Watson Laboratories, Inc. US Prescribing information, May 2009.

Opioids + Azoles

Several of the opioids (buprenorphine, hydromorphone, methadone) are metabolised by CYP3A, at least in part, and their metabolism is expected to be reduced by the azoles, which, to varying extents, inhibit CYP3A4. This has been seen when fluconazole and voriconazole are given with methadone, and when ketoconazole is given with buprenorphine. No interaction appears to occur between transdermal buprenorphine and ketoconazole. It has also been suggested that ketoconazole inhibits the metabolism of morphine and oxycodone, but evidence for this is sparse.

Clinical evidence

(a) Buprenorphine

Ketoconazole increased the AUC of buprenorphine by approximately 50% and increased its maximum level by approximately 70% in one study. The levels of the metabolite, norbuprenorphine, were also affected but to a lesser extent.[1] In contrast, a study in 20 healthy subjects reported no clinically significant change in the levels of transdermal buprenorphine 10 mg or its metabolites when it was given with oral ketoconazole 200 mg twice daily for 7 days.[2]

(b) Methadone

1. Fluconazole. A randomised, double-blind, placebo-controlled study in 25 patients taking maintenance methadone found that fluconazole 200 mg daily for 2 weeks increased the steady-state serum methadone levels and AUC by about 30%, but no signs of methadone overdose were seen and no changes in the methadone dose were needed.[3] However, a case report describes a man with advanced cancer who had received regular methadone 20 mg every 8 hours and one to three 5-mg rescue doses daily for 10 days, who rapidly developed respiratory depression of 4 breaths per minute and became unresponsive 4 days after starting fluconazole 100 mg daily, initially orally, then intravenously. Within a few minutes of receiving naloxone he regained consciousness and his respiratory rate increased.[4]

2. Ketoconazole. An *in vitro* study suggested that ketoconazole decreased the hepatic metabolism of methadone by about 50 to 70%.[5]

3. Voriconazole. In a double-blind, placebo-controlled study in 23 patients taking methadone, voriconazole 400 mg twice daily for one day then 200 mg twice daily for 4 days increased the AUC of *R*-methadone (active) by 47% and *S*-methadone (inactive) by 103%. Methadone appeared to have no effect on voriconazole pharmacokinetics when compared with a reference study in healthy subjects. There were no signs or symptoms of significant opioid withdrawal or overdose and the combination was generally well tolerated.[6]

Mechanism

As the metabolism of methadone is, in part, mediated by the cytochrome P450 isoenzyme CYP3A4,[7] methadone clearance can be decreased by drugs that inhibit CYP3A4 activity such as azole antifungals. Buprenorphine is also metabolised by CYP3A4[8] and may therefore be similarly affected. Most azoles inhibit CYP3A4 to a greater or lesser extent. Although ketoconazole may significantly inhibit the *N*-demethylation of **oxycodone** to noroxycodone by CYP3A4 *in vitro*,[9] as oxycodone metabolism also by CYP2D6, the overall effect would be expected to be less than that seen with opioids predominantly metabolised by CYP3A4. *In vitro* studies suggest that ketoconazole may inhibit **hydromorphone** metabolism by CYP3A4[10] and **morphine** glucuronidation.[11]

Importance and management

It has been suggested that although a statistically significant pharmacokinetic interaction occurs between **methadone** and fluconazole, it is unlikely to be clinically important.[3] However, the serious case report of respiratory depression with fluconazole and methadone introduces a note of caution. Caution is also advised if voriconazole is given with methadone, and a dose reduction of methadone may be required, although the combination was reported as being generally well tolerated.[6] Caution may also be warranted on the concurrent use of methadone and other azoles, as they all inhibit CYP3A4 to a greater or lesser extent.

Patients given ketoconazole with sublingual or intravenous buprenorphine should be closely monitored for an increase in buprenorphine adverse effects (such as drowsiness, nausea and vomiting) and a buprenorphine dose reduction considered as necessary; one manufacturer recommends that the dose of sublingual **buprenorphine** for treating opioid addiction should be halved when starting treatment with ketoconazole.[1] However, another manufacturer of both sublingual and intravenous preparations of buprenorphine suggests that, as the magnitude of the inhibitory effect is unknown, such drug combinations should be avoided.[12,13] Itraconazole, posaconazole and voriconazole would also be expected to interact similarly, as they are also potent inhibitors of CYP3A4. In contrast, based on the study reported above, one manufacturer of a transdermal buprenorphine product states that ketoconazole did not interact to a clinically relevant extent with buprenorphine,[14] therefore, no precaution appears to be necessary in patients using *transdermal* buprenorphine.

The clinical significance of the potential effects of azoles on other opioids, such as **hydromorphone**, and **morphine** is unclear. The UK manufacturer of oxycodone advises that inhibitors of CYP3A enzymes such as **ketoconazole** may inhibit the metabolism of oxycodone.[15]

Consider also 'Opioids; Fentanyl and related drugs + Azoles', p.182.

1. Subutex (Buprenorphine hydrochloride). Schering-Plough Ltd. UK Summary of product characteristics, March 2008.
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12. Temgesic Injection (Buprenorphine hydrochloride). Schering-Plough Ltd. UK Summary of product characteristics, April 2004.
13. Temgesic Sublingual Tablets (Buprenorphine hydrochloride). Schering-Plough Ltd. UK Summary of product characteristics, April 2004.
14. BuTrans (Buprenorphine transdermal patch). Napp Pharmaceuticals Ltd. UK Summary of product characteristics, November 2008.
15. OxyNorm (Oxycodone hydrochloride). Napp Pharmaceuticals Ltd. UK Summary of product characteristics, July 2008.

Opioids; Fentanyl and related drugs + Azoles

Some patients may experience prolonged and increased alfentanil effects if they are given fluconazole or voriconazole; itraconazole and ketoconazole may interact similarly. Fluconazole and voriconazole inhibit the metabolism of fentanyl, and a fatality possibly due to the interaction with fluconazole and transdermal fentanyl has been reported. Itraconazole may interact similarly, but the evidence is conflicting.

Clinical evidence

(a) Alfentanil

A double-blind, randomised, crossover study in 9 healthy subjects given intravenous alfentanil 20 micrograms/kg after receiving **fluconazole** 400 mg, orally or by infusion, found that fluconazole reduced alfentanil clearance by about 60%. Both the alfentanil-induced ventilatory depression and its subjective effects were increased.[1]

A randomised, crossover study in 12 healthy subjects found that oral **voriconazole** (400 mg twice daily on the first day and 200 mg twice daily on the second day) caused an approximately fivefold increase in the mean AUC of intravenous alfentanil 20 micrograms/kg, given one hour after the last dose of the antifungal. The mean plasma clearance of alfentanil was decreased by 85% and its elimination half-life was prolonged from 1.5 hours to 6.6 hours. Visual adverse effects, nausea and vomiting occurred in 6, 5 and 4 subjects, respectively.[2]

In vitro data indicate that **ketoconazole** and **itraconazole** may interact in a similar way.[3-5]

(b) Fentanyl

In a crossover study in 10 healthy subjects the pharmacokinetics and pharmacodynamics of a single 3-micrograms/kg intravenous dose of fentanyl were not altered by **itraconazole** 200 mg daily for 4 days.[6] However, the manufacturer says that increased fentanyl plasma concentrations have been observed in individual subjects taking **itraconazole**,[7] and a case report describes a man with cancer and severe oropharyngeal candidiasis receiving *transdermal* fentanyl 50 micrograms/hour who developed signs of opioid toxicity (agitated delirium, bilateral myoclonus of muscles in the hand) the day after starting oral **itraconazole** 200 mg twice daily.[8]

A study in 12 healthy subjects reported that oral **voriconazole** (400 mg twice daily on day one followed by 200 mg twice daily on day 2) reduced the mean plasma clearance of a single intravenous dose of fentanyl 5 micrograms/kg by 23% and increased the AUC of fentanyl and its metabolite, norfentanyl, by 39% and 56%, respectively. The same study also found that oral **fluconazole** (400 mg on day one followed by 200 mg on day 2) reduced the clearance of the same dose of intravenous fentanyl by 16% and reduced the AUC of norfentanyl by 56%.[9] A patient receiving *transdermal* fentanyl 150 micrograms/hour for at least 3 weeks started taking oral **fluconazole** 50 mg daily but died 3 days later. Post-mortem analysis found a toxic level of fentanyl in the patient's blood and a high concentration of **fluconazole**, which the authors of this report attribute to an interaction between the fluconazole and fentanyl.[10]

Mechanism

Itraconazole, ketoconazole and voriconazole are potent inhibitors, and fluconazole is a moderate inhibitor, of the cytochrome P450 isoenzyme CYP3A4 in the liver, which is concerned with the metabolism of alfentanil and fentanyl. Other azoles also affect this isoenzyme. However, fentanyl has a high hepatic extraction, and so is more affected by changes in hepatic blood flow than changes in the isoenzymes responsible for its metabolism; it is therefore less affected by CYP3A inhibitors than alfentanil. **Sufentanil**, is similarly metabolised, but also has a high hepatic extraction and is therefore less likely to be affected by changes in liver metabolism.

Importance and management

The interaction of **alfentanil** with the azole antifungals appears to be established and clinically important. It is unlikely that a small, single dose of alfentanil will need adjustment.[2] Multiple doses or continuous infusions of alfentanil should be given with care to patients taking azole antifungals, as the clearance of alfentanil may be significantly reduced and its effects increased; it may be necessary to use a lower initial alfentanil dose.[2,4] Be alert for evidence of prolonged alfentanil effects, particularly respiratory depression, even after a single dose.

Although, itraconazole had no effect on the pharmacokinetics of intravenous **fentanyl** in one single-dose study, fluconazole and voriconazole have been reported to interact and the case reports involving *transdermal* fentanyl support the evidence for a possible clinically significant interaction. Caution should be used if azole antifungals are given concurrently with fentanyl, and a fentanyl dose adjustment should be considered, particularly in those patients with unstable advanced disease, or taking multiple medications that inhibit CYP3A4. Close monitoring is recommended. Although there is no specific information, this advice should probably also apply to all azoles (see *Mechanism*, above).

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Opioids + Baclofen

The analgesic effects of fentanyl and morphine, but probably not pentazocine, may be increased by baclofen. Increased sedation may occur and the risk of respiratory depression may increase if opioids are given with baclofen.

Clinical evidence, mechanism, importance and management

A study in three groups of 10 patients found that pretreatment with baclofen 600 micrograms/kg, either in four intramuscular doses for 5 days, or intravenously in 100 mL of glucose 5%, 45 minutes before surgery, prolonged the duration of **fentanyl** analgesia from 18 minutes to 30 minutes. Baclofen also reduced the amount of **fentanyl** needed by 30 to 40%.[1]

In a placebo-controlled study in 69 patients undergoing surgery for the removal of third molar teeth, oral baclofen (5 mg three times daily for 3 days and then a 10-mg dose, 6 hours before surgery and again immediately before surgery) enhanced the postoperative analgesic effect of intravenous **morphine** 6 mg. However, analgesia due to intravenous **pentazocine** 30 mg was not enhanced.[2]

These limited reports suggest that baclofen may potentiate the effects of **fentanyl** and **morphine**. The reasons for this effect are not understood, but it may be connected in some way with the action of baclofen on GABA receptors, as the spinal cord circuits that are important in opioid analgesia contain GABAergic receptors.[1,2] It appears that baclofen enhances the analgesic effect of **fentanyl** and **morphine**, which are pure opioid agonists that act primarily through μ-opioid receptors, whereas it does not affect pentazocine, a predominantly κ-opioid analgesic.[2]

The manufacturer of baclofen warns that increased sedation may occur

if baclofen is taken with synthetic opioids and that the risk of respiratory depression is also increased. Careful monitoring of respiratory and cardiovascular functions is essential.[3]

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Opioids + Barbiturates

A case of increased sedation with severe CNS toxicity has been reported with concurrent use of pethidine (meperidine) and phenobarbital. The analgesic effects of pethidine can be reduced by barbiturates. Secobarbital increases the respiratory depressant effects of morphine. Other barbiturates would also be expected to increase the CNS depressant effects of opioids.

Clinical evidence

(a) Codeine

A study in pain-free patients found that codeine 60 mg increased the hypnotic actions of **secobarbital** 100 mg resulting in synergism in the sedative effects.[1]

(b) Morphine

In a study in 30 healthy subjects, both intravenous **secobarbital** and intravenous morphine depressed respiration when given alone, and a much greater and more prolonged respiratory depression occurred when they were given together.[2]

(c) Pethidine (Meperidine)

1. Increased pethidine toxicity. A woman whose pain had been satisfactorily controlled with pethidine without particular CNS depression, had prolonged sedation with severe CNS toxicity when she was given pethidine after taking **phenobarbital** 30 mg four times daily for 2 weeks.[3]

2. Pethidine effects reduced. Studies in women undergoing dilatation and curettage found that **thiopental** and **pentobarbital** increased their sensitivity to pain, and opposed the analgesic effects of pethidine.[4] This confirmed the findings of previous studies.[5] A marked reduction in the analgesic effect of pethidine has been seen for up to 5 hours after high doses (6 to 10 mg/kg) of **thiopental**.[4] This reduction in efficacy also occurred with **phenobarbital**.[4]

Mechanism

Studies suggest that phenobarbital stimulates the liver enzymes concerned with the metabolism (*N*-demethylation) of pethidine (meperidine) so that the production of its more toxic metabolite (norpethidine) is increased. The toxicity seen appears to be the combined effects of this compound and the directly sedative effects of the barbiturate.[3,6]

Importance and management

Although phenobarbital has been seen to alter the metabolism of pethidine (meperidine) there is only one report of toxicity. The general clinical importance of this interaction is therefore uncertain. It has also been suggested that if pethidine is continued but phenobarbital is suddenly withdrawn, the toxic levels of norpethidine might lead to convulsions in the absence of an antiepileptic.[3] Note that the metabolite, norpethidine, is a less effective analgesic than pethidine and its increased production may increase the risk of CNS toxicity. Concurrent use should therefore be undertaken with care.

Both the barbiturates and the opioids have CNS depressant effects, which would be expected to be additive. The manufacturers of several opiates specifically mention that barbiturates can potentiate the adverse effects of opioids, such as sedation and respiratory depression. Care is therefore warranted on concurrent use. Note that most of the manufacturers of **methadone** also advise caution with other CNS depressants; however, one manufacturer suggests concurrent use is not advised.[7] For comment on the effect of phenobarbital on methadone metabolism, see 'Opioids; Methadone + Antiepileptics', p.180.

Be aware that the barbiturates may reduce the analgesic effects of the opioids, but the clinical relevance of this is unclear. Any effect is probably of most relevance in patients that have been titrated to stable doses of opioids.

For comment on the effect of phenobarbital on opioid metabolism, see 'Opioids + Antiepileptics; Enzyme-inducing', p.179.

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Opioids + Benzodiazepines

In general the concurrent use of opioids and benzodiazepines results in both beneficial analgesic effects, and enhanced sedation and respiratory depression; however, in some cases benzodiazepines have antagonised the respiratory depressant effects of opioids, and, rarely, have antagonised their analgesic effects.

Clinical evidence, mechanism, importance and management

(a) Analgesia

In one study, low-dose **midazolam** (given to achieve levels of 50 nanograms/mL) reduced the dose of **morphine** required for postoperative analgesia in the first 12 hours.[1] However, in another study postoperative pain scores were higher in patients premedicated with oral **diazepam** 10 mg than with placebo, although **morphine** consumption did not differ.[2] Similarly, in another study, the benzodiazepine antagonist flumazenil enhanced **morphine** analgesia in patients who had been premedicated with **diazepam**.[3] It is suggested that benzodiazepines antagonise the analgesic effect of opioids via their effect on supraspinal GABA receptors. Why this has been shown in some studies, but not others, is unclear. Benzodiazepines and opioids are commonly used in surgical anaesthesia, and the relevance of these findings to clinical practice is uncertain.

(b) Overdose

Sudden deaths in patients who abuse opioids are frequently associated with ingestion of other CNS depressants, particularly benzodiazepines. One retrospective study found that 96 of 172 deaths related to **oxycodone** use were reported to have additionally used benzodiazepines (**alprazolam** or **diazepam** in 83 cases).[4] Cases have been reported with **buprenorphine**,[5,6] **oxycodone**,[7] and **tramadol**[8] taken with various benzodiazepines. It has not been established exactly why this occurs, but both pharmacodynamic and pharmacokinetic mechanisms are possible. The deleterious interaction of benzodiazepines and opioids on respiration is possibly due to central effects and/or additive actions on the different neuromuscular components of respiration.[9] For **buprenorphine**, it is considered most likely that excessive CNS depression is solely due to combined pharmacological effects, and not to any pharmacokinetic interaction with benzodiazepines.[10-12]

(c) Pharmacokinetics

A study involving 22 female patients given either intramuscular **pethidine** (**meperidine**) 100 mg or intramuscular **morphine** 10 mg found that the opioids delayed the absorption of oral **diazepam** 10 mg, taken 60 minutes after the opioids. Diazepam levels were found to be lower and peak levels were not reached in the 90-minute study period, when compared with the peak level at 60 minutes in the control group.[13] The underlying mechanism is that the opioid analgesics delay gastric emptying so that the rate of absorption of **diazepam** is reduced. The maximal effect of diazepam would be expected to be delayed in patients receiving these opioids.

Another study in healthy subjects found that **dextropropoxyphene** 65 mg every 6 hours prolonged the **alprazolam** half-life from 11.6 hours to 18.3 hours, and decreased its clearance by 38% (from 1.3 to 0.8 mL/minute per kg). The pharmacokinetics of single doses of **diazepam** and **lorazepam** were not significantly affected by **dextropropoxyphene**.[14] It would seem that **dextropropoxyphene** inhibits the hydroxylation of **alprazolam** by the liver, thereby reducing its clearance from the body, but has little or no effect on the *N*-demethylation or

glucuronidation of **diazepam** or **lorazepam**, respectively. The clinical importance of this is uncertain, but the inference to be drawn is that the CNS depressant effects of **alprazolam** will be increased, over and above the simple additive CNS depressant effects likely when other benzodiazepines and **dextropropoxyphene** are taken together. More study is needed.

Extended-release **oxymorphone** did not affect the metabolism of **midazolam** in healthy subjects.[15]

(d) Respiratory depression

A 14-year-old boy with staphylococcal pneumonia secondary to influenza developed adult respiratory distress syndrome. It was decided to suppress his voluntary breathing with opioids and use assisted ventilation and he was therefore given **phenoperidine** and **diazepam** for 11 days, and later **diamorphine** with **lorazepam**. Despite receiving **diamorphine** 19.2 mg in 24 hours his respiratory drive was not suppressed. On day 17, despite serum morphine and **lorazepam** levels of 320 micrograms/mL and 5.3 micrograms/mL, respectively, he remained conscious and his pupils were not constricted.[16] Later *animal* studies suggested that **lorazepam** opposed the respiratory depressant effects of morphine.[16]

In contrast, intravenous **diazepam** 150 micrograms/kg did not alter the respiratory depressant effect of intravenous **pethidine** (**meperidine**) 1.5 mg/kg in a study in healthy subjects[17] or in patients with chronic obstructive pulmonary disease.[18] Moreover, in the setting of overdose (see *Overdose*, above), benzodiazepines might increase the respiratory depressant effects of opioids.

(e) Sedation

The sedative effects of **midazolam** and **morphine** were additive in a study in patients given these drugs intravenously before surgery.[19] A prospective study in 80 patients undergoing elective endoscopy found that deep sedation occurred frequently (68% of patients) with **pethidine** (**meperidine**) and **midazolam** used with the intent of moderate sedation.[20] Another study found that single oral doses of **diazepam** 10 or 20 mg given to 8 patients taking **buprenorphine** increased subjective effects such as sedation and strength of drug effects, and also caused a deterioration in performance measures such as cancellation time, compared with placebo.[21] A further study by the same authors found similar effects when subjects stabilised taking **buprenorphine** were given a single 40-mg dose of oral diazepam.[22]

These additive adverse effects would be expected with concurrent use of benzodiazepines and opioids and the degree of impairment will depend on the individual patient. Warn all patients of the potential adverse effects on driving and other skilled tasks.

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Opioids; Fentanyl and related drugs + Benzodiazepines

In general the concurrent use of benzodiazepines with alfentanil or fentanyl in anaesthesia is synergistic but may also result in additive adverse effects, such as respiratory depression and/or hypotension. A pharmacokinetic study found that fentanyl reduced the metabolism of midazolam. Retrospective evidence suggests that midazolam can increase the dose requirement of sufentanil, but midazolam did not alter the analgesic efficacy of fentanyl in healthy subjects.

Clinical evidence

(a) Anaesthetic induction

Giving **midazolam** with **alfentanil** or **fentanyl** for the induction of anaesthesia reduces the dose required of both the benzodiazepine and the opioid, when compared with either drug alone.[1-3] The interaction is synergistic.[2]

(b) Analgesic effects

An analysis of 43 patients who were mechanically ventilated following major trauma, and who were given infusions of **sufentanil** alone or **sufentanil** with **midazolam**, found that midazolam appeared to reduce the efficacy of sufentanil. The rate of sufentanil infusion in the group given both drugs (21 patients) was increased by more than 50%, when compared with the group given sufentanil alone (22 patients). It was found possible to reduce the sufentanil infusion in 8 of the patients given sufentanil alone, whereas this was possible in only one patient given both drugs.[4]

Conversely, in a study in healthy subjects, intravenous **midazolam** 500 micrograms to 2 mg per 70 kg did not affect the analgesia produced by intravenous **fentanyl** 100 micrograms per 70 kg in a cold pressor test.[5]

(c) Hypotension and respiratory depression

1. Neonates. Hypotension occurred in 6 neonates with respiratory distress who were given **midazolam** (a bolus of 200 micrograms/kg and/or an infusion of 60 micrograms/kg per hour) for sedation during the first 12 to 36 hours of life. Five of them were also given **fentanyl** either as an infusion (1 to 2 micrograms/kg per hour) or a bolus (1.5 to 2.5 micrograms/kg), or both. Blood pressures fell from an average of 55/40 mmHg to 36/24 mmHg in 5 of the neonates, and from 42/28 mmHg to less than 20 mmHg in the other neonate.[6] Another report describes respiratory arrest in a child of 14 months who was given both drugs.[7]

2. Adults. In a study in 12 healthy subjects, **midazolam** 50 micrograms/kg alone caused no episodes of apnoea or hypoxaemia, whereas **fentanyl** 2 micrograms/kg alone caused hypoxaemia in 6 subjects but no apnoea. When both drugs were given together 6 subjects had apnoea and 11 subjects had hypoxaemia.[8] Similarly, in a study in 12 healthy subjects, **fentanyl** with **diazepam** caused more respiratory depression than either drug alone.[9] Hypotension has also been seen in adults given fentanyl with **midazolam**[10] or **diazepam**.[11]

Acute hypotension occurred in a man receiving clonidine, captopril and furosemide who was premedicated with intramuscular **midazolam** 5 mg and anaesthetised with **sufentanil** 150 micrograms.[12] This is consistent with another report of sudden hypotension during anaesthetic induction in 4 patients given high-dose **sufentanil** who had been given **lorazepam** before induction.[13]

(d) Pharmacokinetics

A double-blind, placebo-controlled study in 30 patients undergoing orthopaedic surgery found that a single 200-microgram dose of **fentanyl** given one minute before intravenous **midazolam** 200 micrograms/kg decreased the systemic clearance of midazolam by 30%. The elimination half-life of midazolam was prolonged by about 50%.[14]

(e) Sedation

A study in patients undergoing an abdominal hysterectomy under **alfentanil** and **midazolam** anaesthesia found that although the pharmacokinet-

ics of midazolam were unchanged, postoperative sedation was more pronounced, when compared with a group of patients that did not receive alfentanil.[15]

Mechanism

Uncertain. The concurrent use of two or more CNS depressants may produce additive respiratory depressant and sedative effects. Reduced metabolism of midazolam might also enhance its effects. Why midazolam appeared to increase the analgesic dose requirement for sufentanil is unknown. An *in vitro* study found that fentanyl competitively inhibited the metabolism of **midazolam** by the cytochrome P450 isoenzyme CYP3A4.[16]

Importance and management

An interaction between alfentanil, fentanyl or sufentanil and the benzodiazepines would appear to be established. Not all pairs appear to have been studied, but they would all be expected to interact similarly, to a greater or lesser extent. Increased sedative and respiratory depressant effects are to be expected on concurrent use, and hypotension may also occur. The US manufacturer of transdermal fentanyl suggests that if benzodiazepines are also given the dose of one or both drugs should be significantly reduced.[17] It would therefore seem prudent to be alert for CNS depression and hypotension in all patients given alfentanil, fentanyl or sufentanil and a benzodiazepine, and adjust the dose according to effect.

What effect the use of midazolam has on the dose requirement of sufentanil and other opioids in the intensive care setting is unclear.

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Opioids; Methadone + Benzodiazepines

Patients taking methadone who are given diazepam may experience increased drowsiness and possibly enhanced opioid effects, although not all studies have found this. Temazepam may have contributed to the sudden death of a patient taking methadone. An isolated case of ventricular arrhythmias has been reported with concurrent use of midazolam and high-dose methadone.

Clinical evidence and mechanism

(a) Diazepam

Four addicts, taking methadone for at least 6 months, were given diazepam 300 micrograms/kg for 9 days. The pharmacokinetics of methadone were unaltered and the opioid effects of methadone remained unchanged.[1] Analysis of blood samples from a study[2] confirmed that there is no pharmacokinetic interaction between methadone and diazepam.[3]

A study in patients taking methadone noted that diazepam abuse was prevalent, and that many patients reported that diazepam boosted the effects of methadone.[4] Another study suggested that the opioid effects of methadone (subjective effects and pupil constriction) may be enhanced by acute administration of diazepam and this was significant with high-dose methadone (150% of the maintenance dose) and diazepam 40 mg.[2] A further study in patients taking methadone found that single oral doses of diazepam 10 or 20 mg, which are within the usual therapeutic range, increased the subjective effects such as sedation, strength of drug effects and euphoria, and also caused a significant deterioration in performance measures such as reaction time, when compared with placebo.[5] A study in 4 patients stabilised on methadone found that diazepam 40 mg increased the intensity of subjective effects, such as sedation, and decreased psychological performance, such as reaction times and digit symbol substitution test (DSST), generally independent of the methadone dose administered. However, high-dose methadone was associated with a reduction in oxygen saturation levels.[6]

The absence of increased opioid effects reported in an earlier pharmacokinetic study[1] may possibly be explained by the relatively low regular daily doses of diazepam used, in contrast to the higher more intermittent doses used in the study above,[2] which is the pattern of dose reportedly used by patients.

(b) Midazolam

A case of ventricular arrhythmias has been associated with high-dose methadone given with CYP3A4 substrates including midazolam.[7] Note that high-dose methadone (more than 100 mg) alone may cause QT prolongation, see 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290.

(c) Temazepam

A 39-year-old man taking methadone 60 mg daily and temazepam 20 mg twice daily was found dead. Blood levels of methadone and temazepam were not particularly high, and revealed that amitriptyline had also been taken.[8] The cause of death was therefore considered to be accidental owing to methadone toxicity enhanced by the additive CNS depressant effects of both temazepam and amitriptyline.

Importance and management

The concurrent use of methadone with low-to-moderate doses of diazepam need not be avoided, but patients given both drugs are likely to experience increased drowsiness and reduced psychomotor performance, and should be warned against driving or operating machinery under these circumstances. With a high diazepam dose the possibility of opioid enhancement should be borne in mind. Bear in mind that the concurrent use of benzodiazepines appears to be a risk factor in sudden death in patients taking methadone.

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Opioids + Calcium-channel blockers

Bradycardia and hypotension may be enhanced in patients taking opioids with calcium-channel blockers. The analgesic effects of morphine appear to be enhanced by some calcium-channel blockers, whereas nimodipine may increase morphine requirements. Diltiazem prolonged the effects of alfentanil in one study.

Clinical evidence and mechanism

(a) Delayed recovery from anaesthesia

In a study in 15 patients anaesthetised with midazolam, isoflurane, propofol and alfentanil (induced with 50 micrograms/kg, then maintained with 1 microgram/kg per minute) the AUC and half-life of **alfentanil** were increased by 24% and 50%, respectively, when they were given **diltiazem** 60 mg orally 2 hours before induction, then an infusion for 23 hours starting at induction. Tracheal extubation was performed on average 2.5 hours later in the patients receiving diltiazem than in a placebo group.[1] Diltiazem is a moderate inhibitor of the cytochrome P450 isoenzyme CYP3A4, which is responsible for the metabolism of alfentanil.[1]

(b) Effects on analgesia

A double-blind, placebo-controlled study in 26 patients undergoing surgery found that two doses of slow-release **nifedipine** 20 mg given on the day preceding surgery and a further dose given 60 to 90 minutes before surgery increased the analgesic effect of **morphine**.[2] In contrast, in a placebo-controlled study in 40 patients undergoing knee arthroplasty, 20 patients given oral **nimodipine** 90 mg one hour before surgery followed by 30 mg every 6 hours for 48 hours postoperatively, had increased intravenous **morphine** consumption via patient-controlled analgesia (PCA). No difference in pain scores was reported between the groups.[3]

Importance and management

Although information is limited, an interaction between alfentanil and diltiazem would appear to be established. Caution is required on concurrent use as there could be an increased risk of prolonged or delayed respiratory depression. The manufacturer says that the concurrent use of diltiazem and alfentanil requires special patient care and observation; it may be necessary to lower the dose of alfentanil.[4] Note that **verapamil** is also a moderate inhibitor of CYP3A4 and so might theoretically be expected to have a similar effect to diltiazem, although this needs confirmation.

The interaction between morphine and the other calcium-channel blockers is unclear, and the information conflicting, particularly that for nimodipine. It would seem prudent to bear the potential for an interaction in mind and adjust the opioid dose if necessary.

The manufacturer of **remifentanil** cautions that cardiovascular effects (bradycardia and hypotension) may be greater in patients also taking calcium-channel blockers,[5] and it would seem prudent to be alert for this effect with other related drugs (e.g. **sufentanil**).

1. Ahonen J, Olkkola KT, Salmenperä M, Hynynen M, Neuvonen PJ. Effect of diltiazem on midazolam and alfentanil disposition in patients undergoing coronary artery bypass grafting. *Anesthesiology* (1996) 85, 1246–52.
2. Carta F, Bianchi M, Argenton S, Cervi D, Marolla G, Tamburini M, Breda M, Fantoni A, Panerai AE. Effect of nifedipine on morphine-induced analgesia. *Anesth Analg* (1990) 70, 493–8.
3. Casey G, Nortcliffe S-A, Sharpe P, Buggy DJ. Perioperative nimodipine and postoperative analgesia. *Anesth Analg* (2006) 102, 504–8.
4. Rapifen (Alfentanil hydrochloride). Janssen-Cilag Ltd. UK Summary of product characteristics, July 2009.
5. Ultiva (Remifentanil hydrochloride). GlaxoSmithKline UK. UK Summary of product characteristics, September 2009.

Opioids + Cannabis

Low doses of cannabis enhanced the effect of morphine in three patients. *Animal* studies have shown that cannabinoids may enhance the potency of opioids. Additive sedation and CNS depression may occur with concurrent use of cannabis derivatives such as dronabinol with opioids.

Clinical evidence, mechanism, importance and management

A report of 3 patients with chronic pain (due to multiple sclerosis, HIV-related peripheral neuropathy, and lumbar spinal damage) found that small doses of smoked cannabis potentiated the antinociceptive effects of **morphine**. The patients were able to decrease the dose of opioid by 60 to 100%.[1] Studies in *animals* have shown that dronabinol (Δ^9-tetrahydrocannabinol), the major psychoactive constituent of cannabis, enhances the potency of opioids such as **morphine**, **codeine**, **hydromorphone**, **methadone**, **oxymorphone** and **pethidine** (**meperidine**).[2-4] It has been suggested that low doses of dronabinol given with low doses of **morphine** may increase opioid potency without increasing adverse effects.[5]

Cannabis use in **methadone**-maintained patients did not appear to affect treatment progress, although some psychological difficulties were slightly more prevalent.[6] However, other workers have suggested that heavy cannabis use is associated with a poorer progress when methadone is given in the treatment of opioid addiction.[7]

The manufacturer of a licensed buccal spray containing dronabinol and cannabidiol states that, as both of these drugs can inhibit the cytochrome P450 isoenzyme CYP3A4, they should be used with caution in patients taking other drugs metabolised by this isoenzyme (they name **alfentanil**, **fentanyl** and **sufentanil**).[8] In contrast, the manufacturer of oral dronabinol reports that no clinically relevant interactions were found in studies in patients taking various medications including opioids (not specified). However, both manufacturers advise that additive sedation and CNS depression may occur with concurrent use of these cannabinoids and opioids.[8,9]

1. Lynch ME, Clark AJ. Cannabis reduces opioid dose in the treatment of chronic non-cancer pain. *J Pain Symptom Manage* (2003) 25, 496–8.
2. Smith FL, Cichewicz D, Martin ZL, Welch SP. The enhancement of morphine antinociception in mice by Δ^9-tetrahydrocannabinol. *Pharmacol Biochem Behav* (1998) 60, 559–66.
3. Cichewicz DL, Martin ZL, Smith FL, Welch SP. Enhancement of μ opioid antinociception by oral Δ^9-tetrahydrocannabinol: dose-response analysis and receptor identification. *J Pharmacol Exp Ther* (1999) 289, 859–67.
4. Cichewicz DL, McCarthy EA. Antinociceptive synergy between Δ^9-tetrahydrocannabinol and opioids after oral administration. *J Pharmacol Exp Ther* (2003) 304, 1010–15.
5. Cichewicz DL. Synergistic interactions between cannabinoid and opioid analgesics. *Life Sci* (2004) 74, 1317–24.
6. Epstein DH, Preston KL. Does cannabis use predict poor outcome for heroin-dependent patients on maintenance treatment? Past findings and more evidence against. *Addiction* (2003) 98, 269 –79. Erratum. ibid., 538.
7. Nixon LN. Cannabis use and treatment outcome in methadone maintenance. *Addiction* (2003) 98, 1321–2.
8. Sativex (Delta-9-tetrahydrocannabinol and Cannabidiol). Bayer Inc. Canadian Prescribing information, December 2008.
9. Marinol (Dronabinol). Solvay Pharmaceuticals, Inc. US Prescribing information, March 2008.

Opioids + Carisoprodol

Carisoprodol may enhance the CNS depressant effects of the opioids.

Clinical evidence, mechanism, importance and management

A 49-year-old woman who had been taking **oxycodone** (*OxyContin*) 40 mg twice daily for more than one year was given carisoprodol 350 mg (one tablet) four times daily to treat muscle spasm and uncontrolled pain. After taking this regimen for one week without relief, she increased the dose to 8 to 10 tablets daily. She was found unconscious, was responsive only to painful stimuli, and her respiration was also depressed. She rapidly returned to full alertness when she was given naloxone 2 mg intravenously, although she had not taken any extra **oxycodone** tablets. The adverse effects were thought to be due to additive CNS depressant effects of both oxycodone and carisoprodol.[1]

In a retrospective review of deaths recorded in Jefferson County over a 12-year period, carisoprodol was present in the blood of 24 cases, but was never the sole drug detected; **dextropropoxyphene** (**propoxyphene**) was also present in 8 of the 24 cases. Respiratory depression was a major cause of death and as carisoprodol causes respiratory depression, it was considered to be probably responsible, in part, for these deaths.[2]

The manufacturer of carisoprodol reports that sedative effects can be additive with other CNS depressants such as the opioids and advises caution on concurrent use.[3]

1. Reeves RR, Mack JE. Possible dangerous interaction of OxyContin and carisoprodol. *Am Fam Physician* (2003) 67, 941–2.
2. Davis GG, Alexander CB. A review of carisoprodol deaths in Jefferson County, Alabama. *South Med J* (1998) 91, 726–30.
3. Soma (Carisoprodol). MedPointe Healthcare Inc. US Prescribing information, September 2007.

Opioids + Chlorobutanol

Chlorobutanol, used as a preservative in methadone injection, may possibly have contributed to the QT prolongation seen with methadone in one study.
Somnolence in a patient given high-dose intravenous morphine was attributed to the associated high intake of chlorobutanol preservative in the morphine injection.

Clinical evidence, mechanism, importance and management

(a) Methadone

A study in patients receiving intravenous methadone found an approximately linear relationship between the log-dose of methadone and QTc measurements. In addition, methadone and chlorobutanol (a preservative used in intravenous methadone preparations) were both found to block cardiac potassium ion channels *in vitro*, and chlorobutanol potentiated this effect with methadone.[1] High doses of methadone have been reported to cause torsade de pointes, but chlorobutanol used as a preservative in methadone injection may possibly contribute to the QT prolongation.[1]

(b) Morphine

A report describes a 19-year-old woman who required increasing doses of intravenous morphine to control pain, reaching a peak of 275 mg/hour, which was maintained for 4 days. After palliative radiotherapy the rate was reduced to 100 to 150 mg/hour, but only partial pain relief was achieved; however the patient was somnolent, which was attributed to the chlorobutanol preservative content of the morphine injection (1 mg of chlorobutanol for every 3 mg of morphine). At doses of morphine 275 mg/hour, chlorobutanol intake was 90 mg/hour, which is in excess of the dose that has been used to aid sleep (150 mg); chlorobutanol accumulation may also have occurred as it has a long half-life.[2] This appears to be an isolated report, the general importance of which is unknown.

1. Kornick CA, Kilborn MJ, Santiago-Palma J, Schulman G, Thaler HT, Keefe DL, Katchman AN, Pezzullo JC, Ebert SN, Woosley RL, Payne R, Manfredi PL. QTc interval prolongation associated with intravenous methadone. *Pain* (2003) 105, 499–506.
2. DeChristoforo R, Corden BJ, Hood JC, Narang PK, Magrath IT. High-dose morphine infusion complicated by chlorobutanol-induced somnolence. *Ann Intern Med* (1983) 98, 335–6.

Opioids + Cocaine

A case of cocaine-related torsade de pointes occurred in a patient taking methadone. Ventricular arrhythmias and increased cardiovascular effects have been reported when other patients taking methadone were given cocaine. The cardiovascular effects of cocaine and morphine appear to be similar to those seen with cocaine alone.

Clinical evidence, mechanism, importance and management

A 46-year-old woman who had been taking **methadone** 80 mg daily for over one year, started abusing cocaine by inhalation and injection and subsequently developed frequent self-limiting episodes of syncope. These syncopal events consistently occurred within an hour of cocaine use. She was admitted to hospital after collapsing and becoming comatose, and was found to have torsade de pointes. She developed irreversible anoxic brain injury secondary to cardiac arrest. Although **methadone** can cause QT prolongation, the serum methadone level was well within the therapeutic range and it was felt that several factors might have contributed to the arrhythmias including cocaine abuse.[1] Another patient taking **methadone** was withdrawn from a study due to the occurrence of premature ventricular contractions for several minutes after a single 32-mg/70 kg intravenous dose of cocaine.[2] Furthermore, increased cardiovascular effects (e.g. increased diastolic pressure and heart rate) have been reported when cocaine is given to patients taking **methadone**.[2] Both cocaine and **methadone** are considered to have effects on the QTc interval and both are potassium-channel blockers. The authors of one study suggested that the combination of these two drugs creates a potentially dangerous risk for torsade de pointes.[3]

A study in 9 healthy subjects found that although the combination of **morphine** and cocaine produced significant cardiovascular and subjective effects, for the most part, the cardiovascular effects were similar to those produced by cocaine alone. Neither cocaine nor **morphine** altered the plasma levels of the other drug.[4]

1. Krantz MJ, Rowan SB, Mehler PS. Cocaine-related torsade de pointes in a methadone maintenance patient. *J Addict Dis* (2005) 24, 53–60.
2. Foltin RW, Christiansen I, Levin FR, Fischman MW. Effects of single and multiple intravenous cocaine injections in humans maintained on methadone. *J Pharmacol Exp Ther* (1995) 275, 38–47.
3. Krantz MJ, Baker WA, Schmittner J. Cocaine and methadone: parallel effects on the QTc interval. *Am J Cardiol* (2006) 98, 1121.
4. Foltin RW, Fischman MW. The cardiovascular and subjective effects of intravenous cocaine and morphine combinations in humans. *J Pharmacol Exp Ther* (1992) 261, 623–32.

Opioids + Food

Food can delay the absorption of dextropropoxyphene (propoxyphene), but the total amount absorbed may be slightly increased. Food increases the bioavailability of oral morphine solution but delays the absorption of some controlled-release preparations of morphine. Food may increase the bioavailability of immediate-release hydromorphone and oxycodone solution, but sustained-release preparations of hydromorphone, oxycodone and tramadol appear not to be affected by food.

Clinical evidence, mechanism, importance and management

(a) Dextropropoxyphene (Propoxyphene)

A study in healthy subjects given a single 130-mg dose of dextropropoxyphene (as capsules) found that while fasting, peak plasma dextropropoxyphene levels were reached after about 2 hours. High-fat and high-carbohydrate meals delayed peak serum levels by about one hour, and high protein meals delayed the peak serum levels by about 2 hours. Both the protein and carbohydrate meals caused a small 25 to 30% increase in the total amount of dextropropoxyphene absorbed.[1] The delay in absorption probably occurs because food delays gastric emptying. Avoid food if rapid analgesic effects are needed.

(b) Hydromorphone

A crossover study in 24 healthy subjects found that food slightly reduced the peak plasma concentrations of a single 8-mg dose of immediate-release hydromorphone and increased its AUC by a modest 30%. However, these changes were not considered to be of clinical significance.[2]

A study in 24 healthy subjects found that food had no clinically significant effects on the pharmacokinetics of an extended-release once-daily hydromorphone capsule.[3] Similarly, another study in 27 healthy subjects found that food had no significant effect on the bioavailability of hydromorphone from a 24-hour controlled-release preparation (*OROS* osmotic pump delivery system).[4]

(c) Morphine

Twelve patients with chronic pain were given oral morphine hydrochloride 50 mg in 200 mL of water either while fasting or after a high-fat breakfast (fried eggs and bacon, toast with butter, and milk). The maximum blood morphine levels and the time to achieve these levels were not significantly altered by the presence of the food, but the AUC was increased by 34% and blood morphine levels were maintained at higher levels over the period from 4 to 10 hours after the morphine had been given.[5] The reasons for this effect are not understood. The inference to be drawn is that pain relief is likely to be increased if the morphine solution is given with food. This appears to be an advantageous interaction. More confirmatory study is needed.

Some differences in pharmacokinetic parameters have also been reported between the fed and fasted states for controlled-release formulations of morphine, but these are not necessarily translated into measurable differences in the pharmacodynamic effects of pain relief and adverse effects.[6] The effects also appear to vary by preparation. Studies have found that, compared with the fasting state, food increases the AUC and maximum plasma level of morphine from *MST Continus*[7] and *Oramorph SR*,[7] reduces the rate of absorption of morphine from *Kapanol*,[8] without affecting its bioavailability,[9] reduces the rate and extent of morphine absorption from *MXL* capsules[9] but does not affect the pharmacokinetics of morphine from *MS Contin* (Purdue Frederick Company, USA) between the fed and fasted states.[10] Most of these studies used single doses in healthy subjects and food was given in the form of a high-fat breakfast and although it appears that there might be some delay in the absorption of some sustained-release preparations of morphine with food, the overall effect is unlikely to be clinically significant.

Studies in *animals* suggest that ingestion of **sucrose** for a short duration may activate the endogenous opioid system and may modify morphine withdrawal.[11,12] Sucrose ingestion has also been shown to alleviate pain and distress in infants and adults.[11]

(d) Oxycodone

A study in 22 healthy subjects found that the bioavailability of oxycodone as an immediate-release solution was significantly altered by consumption of a high-fat meal: the AUC was increased by 20% and the maximum plasma level was decreased by 18%, when compared with the fasted state. A

study in healthy subjects using a preparation containing oxycodone 5 mg and ibuprofen 400 mg found no significant change in the rate of absorption of oxycodone between the fasted state and after a high-fat breakfast, and only a slight increase (of about 25%) in the AUC in the fed state.[13] However, there was no significant effect of food on the bioavailability of oxycodone given as a controlled-release tablet.[14]

(e) Tramadol

In an open, crossover study in 24 healthy subjects, tramadol sustained-release capsules were found to be bioequivalent with and without concurrent food intake (a high-fat breakfast).[15]

1. Musa MN, Lyons LL. Effect of food and liquid on the pharmacokinetics of propoxyphene. *Curr Ther Res* (1976) 19, 669–74.
2. Durnin C, Hind ID, Channon E, Yates DB, Cross M. Effect of food on the pharmacokinetics of oral immediate-release hydromorphone (Dilaudid® IR). *Proc West Pharmacol Soc* (2001) 44, 75–6.
3. Vashi V, Harris S, El-Tahtawy A, Wu D, Cipriano A. Clinical pharmacology and pharmacokinetics of once-daily hydromorphone hydrochloride extended-release capsules. *J Clin Pharmacol* (2005) 45, 547–54.
4. Sathyan G, Xu E, Thipphawong J, Gupta SK. Pharmacokinetic profile of a 24-hour controlled-release OROS® formulation of hydromorphone in the presence and absence of food. *BMC Clin Pharmacol* (2007) 7, 2.
5. Gourlay GK, Plummer JL, Cherry DA, Foate JA, Cousins MJ. Influence of a high-fat meal on the absorption of morphine from oral solutions. *Clin Pharmacol Ther* (1989) 46, 463–8.
6. Gourlay GK. Sustained relief of chronic pain. Pharmacokinetics of sustained release morphine. *Clin Pharmacokinet* (1998) 35, 173–90.
7. Drake J, Kirkpatrick CT, Aliyar CA, Crawford FE, Gibson P, Horth CE. Effect of food on the comparative pharmacokinetics of modified-release morphine tablet formulations: Oramorph SR and MST Continus. *Br J Clin Pharmacol* (1996) 41, 417–20.
8. Kaiko RF. The effect of food intake on the pharmacokinetics of sustained-release morphine sulfate capsules. *Clin Ther* (1997) 19, 296–303.
9. Broomhead A, West R, Eglinton L, Jones M, Bubner R, Sienko D, Knox K. Comparative single-dose pharmacokinetics of sustained-release and modified-release morphine sulfate capsules under fed and fasting conditions. *Clin Drug Invest* (1997) 13, 162–70.
10. Kaiko RF, Lazarus H, Cronin C, Grandy R, Thomas G, Goldenheim P. Controlled-release morphine bioavailability (MS Contin® tablets) in the presence and absence of food. *Hosp J* (1990) 6, 17–30.
11. Bhattacharjee M, Mathur R. Antinociceptive effect of sucrose ingestion in the human. *Indian J Physiol Pharmacol* (2005) 49, 383–94.
12. Jain R, Mukherjee K, Singh R. Influence of sweet tasting solutions on opioid withdrawal. *Brain Res Bull* (2004) 64, 319–22.
13. Kapil R, Nolting A, Roy P, Fiske W, Benedek I, Abramowitz W. Pharmacokinetic properties of combination oxycodone plus racemic ibuprofen: two randomized, open-label, crossover studies in healthy adult volunteers. *Clin Ther* (2004) 26, 2015–25.
14. Benziger DP, Kaiko RF, Miotto JB, Fitzmartin RD, Reder RF, Chasin M. Differential effects of food on the bioavailability of controlled-release oxycodone tablets and immediate-release oxycodone solution. *J Pharm Sci* (1996) 85, 407–10.
15. Raber M, Schulz H-U, Schürer M, Bias-Imhoff U, Momberger H. Pharmacokinetic properties of tramadol sustained release capsules. 2nd communication: investigation of relative bioavailability and food interaction. *Arzneimittelforschung* (1999) 49, 588–93.

Opioids + Glutethimide

A study in *animals* suggested that glutethimide might potentiate and prolong the analgesic effect of codeine by increasing the plasma levels of its morphine metabolite.[1] Glutethimide combined with codeine can produce a euphoric state and may be addictive; seizures and psychosis have been reported.[2] Two studies have reported 21 deaths associated with concurrent use.[3,4] Given the wide availability of alternative hypno-sedatives, it may be prudent to choose a safer alternative.

1. Popa D, Loghin F, Imre S, Curea E. The study of codeine-gluthetimide [sic] pharmacokinetic interaction in rats. *J Pharm Biomed Anal* (2003) 32, 867–77.
2. Shamoian CA. Codeine and glutethimide: euphoretic, addicting combination. *N Y State J Med* (1975) 75, 97–9.
3. Bender FH, Cooper JV, Dreyfus R. Fatalities associated with an acute overdose of glutethimide (Doriden) and codeine. *Vet Hum Toxicol* (1988) 30, 332–3.
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Opioids + Grapefruit juice

Grapefruit juice may produce a modest increase in oral methadone bioavailability. The clearance of oral alfentanil may be reduced by grapefruit juice. Grapefruit juice does not appear to affect the bioavailability of intravenous alfentanil or transmucosal fentanyl to a clinically significant extent.

Clinical evidence, mechanism, importance and management

(a) Alfentanil

A study in 10 healthy subjects found that grapefruit juice had no effect on the bioavailability of *intravenous* alfentanil. However, the clearance of *oral* alfentanil was reduced by about 40% and the maximum plasma level and oral bioavailability were increased by about 40% and 60%, respectively. This was thought to be due to selective inhibition of intestinal CYP3A by grapefruit juice.[1] Therefore should alfentanil be given orally its effects would be expected to be increased and prolonged.

(b) Fentanyl

In a study in 12 healthy subjects, grapefruit juice had a minimal effect on the peak plasma levels or clinical effects of oral transmucosal fentanyl, despite a considerable proportion of the dose being swallowed and absorbed enterally.[2] There appears to be no further data on the effects of grapefruit on oral or oral transmucosal fentanyl. However, the manufacturer of fentanyl lozenges suggests that grapefruit juice may increase the bioavailability of swallowed fentanyl and therefore advises caution with concurrent use.[3] Note that *intravenous* and *transdermal* fentanyl are not expected to be affected to the same extent as oral fentanyl, as grapefruit juice mainly inhibits intestinal and not liver CYP3A4.

(c) Methadone

A study in 8 patients taking methadone found that 200 mL of grapefruit juice given 30 minutes before, and also with, their daily dose of methadone was associated with a modest increase in methadone bioavailability. The mean AUC and the maximum plasma levels increased by about 17%.[4] A study in healthy subjects found that grapefruit juice caused a similar modest increase in methadone bioavailability following oral methadone, but had no effect on intravenous methadone bioavailability.[5] The increase in methadone levels were not considered to be clinically significant in the patients studied.[4] On the basis of this evidence dose adjustments of methadone seem unlikely to be necessary in the presence of grapefruit juice.

1. Kharasch ED, Walker A, Hoffer C, Sheffels P. Intravenous and oral alfentanil as in vivo probes for hepatic and first-pass cytochrome P450 3A activity: noninvasive assessment by use of papillary miosis. *Clin Pharmacol Ther* (2004) 76, 452–66..
2. Kharasch ED, Whittington D, Hoffer C. Influence of hepatic and intestinal cytochrome P4503A activity on the acute disposition and effects of oral transmucosal fentanyl citrate. *Anesthesiology* (2004) 101, 729–37.
3. Actiq (Fentanyl citrate lozenge). Cephalon (UK) Ltd. UK Summary of product characteristics, July 2009.
4. Benmebarek M, Devaud C, Gex-Fabry M, Powell Golay K, Brogli C, Baumann P, Gravier B, Eap CB. Effects of grapefruit juice on the pharmacokinetics of the enantiomers of methadone. *Clin Pharmacol Ther* (2004) 76, 55–63.
5. Kharasch ED, Hoffer C, Whittington D, Sheffels P. Role of hepatic and intestinal cytochrome P450 3A and 2B6 in the metabolism, disposition, and miotic effects of methadone. *Clin Pharmacol Ther* (2004) 76, 250–69.

Opioids + H_2-receptor antagonists

No clinically significant interaction appears to occur between cimetidine and butorphanol (intranasal), hydromorphone, morphine, pethidine (meperidine) or tramadol; between famotidine and hydromorphone; or between ranitidine and hydromorphone, morphine, or pethidine (meperidine). However, isolated reports describe adverse reactions in patients taking methadone, morphine or mixed opium alkaloids with cimetidine, or morphine with ranitidine.

Clinical evidence

(a) Butorphanol

In a study in 16 healthy subjects, the pharmacokinetics of intranasal butorphanol 1 mg every 6 hours and oral **cimetidine** 300 mg every 6 hours for 4 days were not significantly altered by concurrent use, except for a moderate increase in the elimination half-life of **cimetidine**.[1]

(b) Hydromorphone

The US manufacturer of hydromorphone says that the concurrent use of H_2-receptor antagonists (**cimetidine**, **famotidine**, **ranitidine**) had no significant effect on hydromorphone steady-state pharmacokinetics.[2]

(c) Methadone

An *in vitro* study briefly mentions an elderly patient receiving methadone 25 mg daily who developed apnoea 2 days after starting **cimetidine** 1.2 g daily.[3] Another elderly patient taking oral methadone 5 mg every 8 hours

and subcutaneous **morphine** 8 mg every 3 hours also developed apnoea (respiratory rate 2 breaths per minute) after receiving intravenous **cimetidine** 300 mg every 6 hours for 6 days. This was controlled with naloxone. It is unclear why the patient developed adverse effects on this occasion as no adverse effects occurred on the previous use of these drugs.[4]

(d) Morphine

1. Cimetidine. In another placebo-controlled study in 118 patients undergoing major abdominal surgery and given analgesia with morphine, preoperative or postoperative intravenous cimetidine 4 mg/kg did not affect postoperative pain intensity, sedation score, cumulative morphine consumption, or the incidence of adverse effects.[5] In a study in 7 healthy subjects, cimetidine 300 mg four times daily for 4 days had no effect on the pharmacokinetics of a single 10-mg dose of intravenous morphine. The extent and duration of the morphine-induced pupillary miosis were also unchanged.[6] In other healthy subjects, cimetidine 600 mg, given one hour before a 10-mg dose of intramuscular morphine prolonged the respiratory depression due to morphine, but the extent was small and not considered to be clinically significant.[7]

In contrast, an acutely ill patient with grand mal epilepsy, gastrointestinal bleeding and an intertrochanteric fracture, who was undergoing haemodialysis three times a week, was taking cimetidine 300 mg three times daily. After being given the sixth dose of intramuscular morphine (15 mg every 4 hours) he became apnoeic (three breaths per minute), which was managed with naloxone. He remained confused and agitated for the next 80 hours with muscular twitching and further periods of apnoea controlled with naloxone. He had received nine 10-mg intramuscular doses of morphine on a previous occasion in the absence of cimetidine without problems. About a month later he experienced the same adverse reactions when given opium alkaloids while still taking cimetidine (see below).[8] Apnoea has also been reported in a patient receiving morphine, methadone and cimetidine, see under *Methadone*, above.

2. Ranitidine. A study in 8 healthy subjects taking ranitidine 150 mg twice daily for 7 doses followed by a single 10-mg dose of oral morphine mixture suggested that ranitidine might slightly increase the bioavailability of morphine, although the increase was not statistically significant.[9] A man with terminal cancer receiving intravenous ranitidine 150 mg every 8 hours became confused, disorientated and agitated when given ranitidine after an intravenous infusion of morphine 50 mg daily was started. When the ranitidine was stopped his mental state improved but worsened when he was given ranitidine again 8 hours and 16 hours later. He again improved when the ranitidine was stopped.[10]

Similarly, another report describes hallucinations in a patient receiving ranitidine and sustained-release morphine followed by rectal **methadone**, but the author discounted the possibility of an interaction.[11]

(e) Opium alkaloids, mixed

A patient taking **cimetidine** 150 mg twice daily developed apnoea, confusion, and muscle twitching after receiving 7 doses of intramuscular *Pantopon* (hydrochlorides of mixed opium alkaloids) postoperatively. He required 4 doses of naloxone over the next 24 hours.[8]

(f) Pethidine (Meperidine)

In a study in 8 healthy subjects, **cimetidine** 600 mg twice daily for one week reduced the total body clearance of a single 70-mg intravenous dose of pethidine by a modest 22%.[12] In a similar study by the same research group, **ranitidine** 150 mg twice daily had no effect on pethidine pharmacokinetics.[13]

(g) Tramadol

In an unpublished study in healthy subjects on file with the manufacturers, **cimetidine** increased the AUC of tramadol by 15 to 27% and decreased the total body clearance by 14 to 22%.[14]

Mechanism

Cimetidine inhibits the activity of liver enzymes concerned with the *N*-demethylation of methadone[3] and the oxidation of pethidine (meperidine),[12,13] reducing their metabolism, so they could accumulate in the body, thereby exaggerating their respiratory depressant effects. A reduction in liver function might possibly have contributed towards, or even been largely responsible for the cases with methadone, because both patients were elderly. The manufacturers of methadone also suggest that H_2-receptor antagonists such as cimetidine can reduce the protein binding of methadone resulting in increased opiate action.[15,16]

The isolated case reports of possible interactions between morphine and H_2-receptor antagonists remain unexplained,[8,10] but both patients were seriously ill. *In vitro* studies have reported that the conjugation of morphine does not appear to be affected by cimetidine or ranitidine.[17]

Importance and management

The evidence generally suggests that morphine does not interact with cimetidine: those cases describing an interaction involved seriously ill patients. Concurrent use normally causes only a slight and normally unimportant prolongation of the respiratory depression due to morphine, but it might possibly have some importance in patients with pre-existing respiratory disorders. Several manufacturers note that cimetidine may inhibit the metabolism of morphine, although they do not give any specific advice regarding the management of this interaction. One US manufacturer warns that, because of the isolated report (see under *Morphine*, above), patients should be monitored for increased respiratory and CNS depression.[18] However, it should be noted that this patient was undergoing haemodialysis, and probably does not reflect the effects of this interaction in the general population. In contrast, one of the UK manufacturers gives no mention of a possible interaction with cimetidine.[19]

In vitro evidence suggests that ranitidine is unlikely to interact with morphine,[8] although one pharmacokinetic study indicated that ranitidine might cause a slight increase in morphine levels.[9] Again, the general significance of the case reports of an interaction is unclear.

Information about the interaction between **pethidine** (**meperidine**) and cimetidine is very limited. Its clinical importance is uncertain, but probably small given the minor changes seen in the pharmacokinetics of pethidine. However, some manufacturers warn that cimetidine may inhibit the metabolism of pethidine and the formation of the metabolite, norpethidine, and thus caution should be used with concurrent use.[20] Ranitidine has been shown not to affect the pharmacokinetics of pethidine.

It also seems doubtful if the interaction between **methadone** and cimetidine is of any general importance when the two isolated reports cited here are viewed against the background of the widespread use of both of these two drugs for a good number of years and the lack of other published adverse reports. However, some manufacturers warn that methadone clearance may be decreased, and the effects of methadone increased, when it is given with drugs that inhibit CYP3A4 activity including cimetidine.[15,16]

The UK manufacturer of **oxycodone** suggests that cimetidine, a non-specific inhibitor of CYP3A4, may affect its metabolism.[21] However, as CYP3A4 is only partly responsible for the metabolism of oxycodone, and cimetidine is not a potent inhibitor of this isoenzyme, any effects would be expected to be minimal. Nevertheless, until more is known, it may be prudent to be alert for increased oxycodone effects if cimetidine is given.

No clinically significant pharmacokinetic interaction appears to occur between intranasal **butorphanol** and oral cimetidine, or between **hydromorphone** and the H_2-receptor antagonists. Similarly, the minor changes in **tramadol** pharmacokinetics caused by cimetidine are unlikely to be of clinical significance.[22,23]

Consider also 'Opioids; Fentanyl and related drugs + H_2-receptor antagonists', p.190.

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16. Methadone Solution for Injection (Methadone hydrochloride). Wockhardt UK Ltd. UK Summary of product characteristics, August 2007.
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18. Avinza (Morphine sulfate extended-release capsules). King Pharmaceuticals, Inc. US Prescribing information, April 2008.
19. Zomorph (Morphine sulphate). Archimedes Pharma UK Ltd. UK Summary of product characteristics, September 2005.
20. Demerol (Meperidine hydrochloride). Sanofi-Aventis US LLC. US Prescribing information, October 2008.
21. OxyContin (Oxycodone hydrochloride). Napp Pharmaceuticals Ltd. UK Summary of product characteristics, November 2008.
22. Zydol Capsules (Tramadol hydrochloride). Grünenthal Ltd. UK Summary of product characteristics, March 2009.
23. Ultram ER (Tramadol hydrochloride). Ortho-McNeil, Inc. US Prescribing information, December 2007.

Opioids; Fentanyl and related drugs + H_2-receptor antagonists

Cimetidine, but not ranitidine, increases the plasma levels of alfentanil. Some preliminary observations suggest that the effects of fentanyl may be increased by cimetidine.

Clinical evidence, mechanism, importance and management

(a) Alfentanil

In a pharmacokinetic study in 19 intensive care patients, intravenous **cimetidine** 1.2 g daily for 2 days was given with a single 125-microgram/kg intravenous dose of alfentanil. When compared with either an aluminium/magnesium hydroxide antacid or intravenous **ranitidine** 300 mg daily, **cimetidine** increased the alfentanil half-life by 75% and 61%, respectively, and reduced the clearance by 64% and 54%, respectively. The alfentanil plasma levels were significantly raised by the **cimetidine**, probably because **cimetidine** inhibits the metabolism of the alfentanil.[1] Whether the effects of alfentanil are increased to a clinically important extent awaits assessment. However, be alert for increased alfentanil effects because pharmacokinetic changes of this size are known to be clinically important in some patients (see 'Opioids; Fentanyl and related drugs + Macrolides', p.192, and 'Opioids; Fentanyl and related drugs + Azoles', p.182). The UK manufacturer of alfentanil warns that alfentanil is metabolised mainly by CYP3A4, and therefore inhibitors of this isoenzyme, including **cimetidine**, could increase the risk of prolonged or delayed respiratory depression. The concurrent use of such drugs requires special patient care and observation; it may be necessary to lower the dose of alfentanil.[2] **Ranitidine** does not appear to interact.[1]

(b) Fentanyl

The terminal half-life of fentanyl 100 micrograms/kg was reported to be more than doubled, from 155 minutes to 340 minutes, by pretreatment with **cimetidine** (10 mg/kg the night before and 5 mg/kg 90 minutes before the fentanyl dose). This increase in half-life probably occurs because **cimetidine** inhibits the metabolism of fentanyl by the liver, thereby delaying its clearance from the body.[3] The clinical importance of this interaction has not been assessed, but if both drugs are used concurrently, be alert for increased and prolonged fentanyl effects.

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Opioids + Haloperidol

A patient taking long-term haloperidol and morphine experienced extrapyramidal symptoms when naloxone was given. Haloperidol decreased the dose requirements of sufentanil for sedation in one study.

Clinical evidence, mechanism, importance and management

(a) Morphine

An 18-year-old woman with nasopharyngeal carcinoma who had been receiving long-term haloperidol and morphine developed profound extrapyramidal adverse effects during an attempt to reverse an intrathecal morphine overdose with naloxone. It was suggested that the long-term use of morphine might suppress haloperidol-induced extrapyramidal symptoms through its antimuscarinic and dopaminergic effects. Abrupt opioid withdrawal could be potentially hazardous in patients who are also taking haloperidol.[1]

See also 'Opioids; Morphine + Miscellaneous', p.210, for limited evidence that haloperidol may increase the risk of myoclonus with morphine.

(b) Sufentanil

A study involving 30 patients in an intensive care unit investigated the effects of adding haloperidol 3 mg/hour to a sufentanil infusion. The study found that haloperidol decreased the dose requirements of sufentanil when compared with sufentanil infusion alone. No differences in adverse effects were reported between the two groups.[2]

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Opioids + Herbal medicines; Miscellaneous

Some herbal teas may contain opioids and may therefore cause additive CNS depression if taken with other opioids.

Clinical evidence, mechanism, importance and management

Some herbal preparations may actually contain opioids; the **morphine** content of two herbal teas containing *Papaveris fructus* was found to be 10.4 micrograms/mL and 31.5 micrograms/mL, respectively. Furthermore, **morphine** was detected in the urine of 5 healthy subjects one hour after drinking 2 cups of either of the herbal teas, and was maximal at 4 to 6 hours: positive urine samples were detected up to 6 to 9 hours after drinking the teas.[1] Therefore it may be expected that additive CNS depressant effects will occur if such teas are taken with other opioid preparations.

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Opioids + Hormonal contraceptives

The clearance of morphine is roughly doubled by oral combined hormonal contraceptives. Oral combined hormonal contraceptives do not appear to alter the pharmacokinetics of pethidine (meperidine). Gestodene is predicted to increase the plasma levels of buprenorphine.

Clinical evidence, mechanism, importance and management

(a) Buprenorphine

An *in vitro* study reported that **gestodene** inhibited the metabolism of buprenorphine to norbuprenorphine by the cytochrome P450 isoenzyme CYP3A4 by about 60 to 70%.[1] Based on data from a study with the CYP3A4 inhibitor ketoconazole (see 'Opioids + Azoles', p.181) where the AUC of buprenorphine was increased by about 50%, the manufacturer predicts that other CYP3A4 inhibitors, such as **gestodene**, may also increase the exposure to buprenorphine. They advise that a buprenorphine dose reduction should be considered when initiating treatment.[2] Halving the starting dose of buprenorphine has been suggested for patients taking CYP3A4 inhibitors and receiving buprenorphine as a substitute for opioid dependence.[2] However, the same manufacturer suggests that, as the magnitude of an inhibitory effect is unknown, such drug combinations should be avoided when buprenorphine is used parenterally or sublingually as a strong analgesic.[3,4] However, note that there appear to be no clinical cases or studies reporting interactions where **gestodene** is acting as a clinically

relevant CYP3A4 inhibitor or has specifically affected the metabolism of buprenorphine or other opioids.

(b) Morphine

The clearance of intravenous morphine 1 mg and oral morphine 10 mg was increased by 75% and 120%, respectively, in 6 young women taking an oral combined hormonal contraceptive.[5] It was suggested that the oestrogen component of the contraceptive increases the activity of the liver enzyme (glucuronyltransferase) concerned with the metabolism of morphine, which results in an increased clearance. This implies that the dose of morphine would need to be increased to achieve the same degree of analgesia. Whether this is required in practice needs confirmation; however as the dose of morphine is usually titrated to effect, the clinical relevance of any effect seems likely to be small.

(c) Pethidine (Meperidine)

One early study suggested that 4 of 5 women taking an oral combined hormonal contraceptive (**mestranol** with **noretynodrel** or **norethisterone**) excreted more unchanged pethidine in the urine than a control group of 4 women not taking contraceptives, who were found to excrete more of the demethylated metabolite.[6] However a later, well-controlled, comparative study in 24 healthy subjects (8 women taking **ethinylestradiol/norgestrel** 50/500 micrograms, and 8 women and 8 men not taking contraceptives) found no differences between the plasma levels or excretion patterns of pethidine between the three groups.[7] No special precautions appear to be needed if pethidine is given to women taking combined hormonal contraceptives.

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2. Subutex (Buprenorphine hydrochloride). Schering-Plough Ltd. UK Summary of product characteristics, March 2008.
3. Temgesic Injection (Buprenorphine hydrochloride). Schering-Plough Ltd. UK Summary of product characteristics, April 2004.
4. Temgesic Sublingual Tablets (Buprenorphine hydrochloride). Schering-Plough Ltd. UK Summary of product characteristics, April 2004.
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6. Crawford JS, Rudofsky S. Some alterations in the pattern of drug metabolism associated with pregnancy, oral contraceptives, and the newly-born. *Br J Anaesth* (1966) 38, 446–54.
7. Stambaugh JE, Wainer IW. Drug interactions I: meperidine and combination oral contraceptives. *J Clin Pharmacol* (1975) 15, 46–51.

Opioids + Interferons

Peginterferon alfa-2a does not appear to affect the pharmacokinetics of methadone to a clinically relevant extent, but an isolated report describes a patient who relapsed to heroin use following treatment with peginterferon. Peginterferon alfa-2b may slightly increase the levels of methadone although this is not usually clinically significant. Methadone maintenance does not appear to affect the pharmacokinetics of peginterferon alfa-2a or the virological response to interferons. Similarly, buprenorphine does not appear to influence the effect of interferon.

Clinical evidence and mechanism

A study involving 22 patients with chronic hepatitis C who had been receiving **methadone** maintenance for at least 3 months found that subcutaneous peginterferon alfa-2a 180 micrograms once weekly for 4 weeks did not influence the pharmacokinetics of methadone to a clinically significant extent, although methadone exposure was slightly increased by 10 to 15%. The pharmacokinetics of peginterferon alfa-2a did not appear to be altered by **methadone** when compared with values from other patients.[1] However, a case report describes a patient who stopped taking **methadone** and then relapsed to heroin use approximately 5 months after completing treatment for chronic hepatitis C with peginterferon 180 micrograms per week and ribavirin.[2]

A non-randomised study in 9 patients with hepatitis C and HIV infections taking **methadone** 40 to 200 mg daily for at least 8 weeks, found that two doses of peginterferon alfa-2b 1.5 micrograms/kg given one week apart had no significant effects on the pharmacokinetics of methadone. Similarly, no evidence of opiate toxicity or withdrawal occurred during concurrent use. Subjects were not taking HIV medication known to interact with methadone such as ritonavir.[3] A study involving 20 patients with chronic hepatitis C and taking **methadone** for at least 3 months reported a small approximately 15% increase in the AUC and maximum concentration of methadone when peginterferon alfa-2b 1.5 micrograms/kg per week for 4 weeks was also given, when compared with methadone alone.[4]

Several studies suggest that the use of opioids (**buprenorphine**,[5] **methadone**[5-8]) has no effect on the outcome of treatment with interferon or peginterferon in patients with chronic hepatitis C, although opioids may possibly facilitate the outbreak of infections through immunomodulating effects on the immune response against a virus.[6]

Importance and management

Interferon does not appear to significantly affect the pharmacokinetics of methadone. Despite the minor changes reported, the manufacturers of peginterferon alfa-2a and alfa-2b advise monitoring for methadone toxicity, such as increased sedation and respiratory depression with concurrent use.[9,10] Note that patients taking methadone may experience increased cravings while receiving antiviral therapy as the adverse effects of interferons may mimic opioid withdrawal symptoms, and cravings may be secondary to mood changes caused by antiviral therapy, or be related to the use of needles used to deliver interferon.[2] It may, therefore, be necessary to increase the dose of methadone during interferon treatment.[2,5] Note that, as alfa interferons are associated with a risk of psychiatric disturbance and suicide, the US manufacturer of interferon alfa-2b advises that opioids should be used with caution.[11]

There appears to be no specific pharmacokinetic data relating to the use of other interferons with methadone or other opioids. It has been suggested that interferons (interferon beta and interferon gamma) may theoretically reduce the activity of the hepatic cytochrome P450. However, the general significance of this potential interaction is unknown. Further study is needed.

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3. Berk SI, Litwin AH, Arnsten JH, Du E, Soloway I, Gourevitch MN. Effects of pegylated interferon alfa-2b on the pharmacokinetic and pharmacodynamic properties of methadone: a prospective, nonrandomized, crossover study in patients coinfected with hepatitis C and HIV receiving methadone maintenance treatment. *Clin Ther* (2007) 29, 131–8.
4. Gupta SK, Sellers E, Somoza E, Angles L, Kolz K, Cutler DL. The effect of multiple doses of peginterferon alfa-2b on the steady-state pharmacokinetics of methadone in patients with chronic hepatitis C undergoing methadone maintenance therapy. *J Clin Pharmacol* (2007) 47, 604–12. Correction. ibid., (2007) 47, 1061.
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9. Pegasys (Peginterferon alfa-2a). Roche Products Ltd. UK Summary of product characteristics, October 2009.
10. ViraferonPeg (Peginterferon alfa-2b). Schering-Plough Ltd. UK Summary of product characteristics, November 2009.
11. Intron A (Interferon alfa-2b). Schering Corporation. US Prescribing information, June 2008.

Opioids + Local anaesthetics

Chloroprocaine may reduce the efficacy of epidural morphine and fentanyl analgesia. Fentanyl and sufentanil may enhance the local anaesthetic effect of bupivacaine, but do not appear to affect respiratory depression. Similarly, extradural lidocaine does not appear to increase respiratory depression with extradural morphine. However, one case of respiratory depression has been reported with submucosal lidocaine and alphaprodine.

Clinical evidence, mechanism, importance and management

(a) Bupivacaine

A study in 50 elderly patients undergoing spinal anaesthesia, found that those given bupivacaine 7.5 mg and **sufentanil** 5 micrograms had a reduced incidence of hypotension requiring treatment with ephedrine, when compared with the patients who received bupivacaine 15 mg alone. None of the patients developed respiratory depression.[1] A study involving 40 elderly patients undergoing spinal anaesthesia found that bupivacaine

9 mg, with **fentanyl** 20 micrograms reduced the incidence of hypotension, when compared with bupivacaine 11 mg alone. Respiratory rates were not depressed in either group. The rate of failed spinal block and discomfort was similar in both groups. The addition of fentanyl allowed a reduction in the minimum dose of bupivacaine required to produce an adequate block, and consequently the incidence of hypotension was reduced.[2]

(b) Chloroprocaine

Two studies[3,4] have found that chloroprocaine decreases the duration of epidural **morphine** analgesia (16 hours when chloroprocaine was also given compared with 24 hours when lidocaine was also given).[3] Another study found that **morphine** requirements after caesarean section were much higher in women who had received chloroprocaine for epidural anaesthesia than in those receiving lidocaine.[5] The authors of one of the studies suggest that chloroprocaine should be avoided if epidural morphine is used.[3] However, another study found that following spinal anaesthesia with bupivacaine and fentanyl, chloroprocaine did not reduce the effectiveness or duration of postoperative analgesia when it was given 15 minutes before epidural **morphine**.[6] Epidural **fentanyl** also appears to be antagonised by chloroprocaine.[7]

(c) Lidocaine

In a study in 24 patients, giving extradural lidocaine with extradural **morphine** did not increase the risk of respiratory depression associated with morphine.[8] However, respiratory depression occurred in a 3-year-old boy given lidocaine with adrenaline (epinephrine) about 5 minutes after a submucosal injection of the narcotic **alphaprodine**. Naloxone reversed the respiratory depression.[9]

For further information on the interaction of opioids with *intravenous* lidocaine used to treat arrhythmias, see 'Lidocaine + Opioids', p.300.

1. Olofsson C, Nygårds E-B, Bjersten A-B, Hessling A. Low-dose bupivacaine with sufentanil prevents hypotension after spinal anesthesia for hip repair in elderly patients. *Acta Anaesthesiol Scand* (2004) 48, 1240–4.
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8. Saito Y, Sakura S, Kaneko M, Kosaka Y. Interaction of extradural morphine and lignocaine on ventilatory response. *Br J Anaesth* (1995) 75, 394–8.
9. Moore PA. Local anesthesia and narcotic drug interaction in pediatric dentistry. *Anesth Prog* (1988) 35, 17.

Opioids + Macrolides

An isolated report describes a marked increase in the effects of dextromoramide, resulting in coma, in a man taking troleandomycin. Macrolides, including troleandomycin and erythromycin, are predicted to increase buprenorphine bioavailability, and similarly, troleandomycin may reduce the metabolism of hydromorphone. It has been suggested that the metabolism of methadone and oxycodone may be decreased by some macrolides, but there do not appear to be any clinical reports confirming this.

Clinical evidence, mechanism, importance and management

(a) Buprenorphine

Although no data from clinical studies are available, the manufacturers of buprenorphine predict that inhibitors of the cytochrome P450 isoenzyme CYP3A4 such as the macrolide antibacterials (including **erythromycin**[1] and **troleandomycin**[2-4]) may increase the levels of buprenorphine. Some manufacturers recommend close monitoring and possibly a dose reduction;[1] however, it has also been said that, because the magnitude of an inhibitory effect is unknown, such drug combinations should be avoided when buprenorphine is used parenterally or sublingually as an analgesic.[3,4] The manufacturer of buprenorphine licensed for the treatment of opioid addiction suggests using half the dose of buprenorphine if potent CYP3A4 inhibitors, such as some macrolides, are given.[2]

(b) Dextromoramide

A man taking dextromoramide developed signs of overdose (a morphine-like coma, mydriasis and depressed respiration) 3 days after he started to take **troleandomycin** for a dental infection. He recovered when given naloxone. A possible explanation for this effect is that the **troleandomycin** reduced the metabolism of the dextromoramide, thereby increasing its serum levels and effects.[5] The general importance of this interaction is uncertain but concurrent use should be well monitored.

(c) Hydromorphone

An *in vitro* study found that the cytochrome P450 subfamily CYP3A, and to a lesser extent the isoenzyme CYP2C9, catalyse hydromorphone *N*-demethylation to norhydromorphone. **Troleandomycin** (an inhibitor of CYP3A) reduced norhydromorphone formation by about 45%.[6] The clinical relevance of this is unknown.

(d) Methadone

A randomised, crossover study in 12 healthy subjects found that **troleandomycin** did not significantly affect oral or intravenous methadone bioavailability. **Troleandomycin** caused only a small reduction in methadone *N*-demethylation after oral methadone, suggesting only a small role for CYP3A4 in human methadone metabolism.[7] However, one manufacturer of methadone warns that its clearance may be decreased if it is given with drugs that inhibit CYP3A4 activity, such as some macrolide antibacterials.[8] Note that decreased methadone metabolism has been seen with some of the azoles (see 'Opioids + Azoles', p.181), which are known, potent CYP3A4 inhibitors.

(e) Oxycodone

The UK manufacturer of oxycodone suggests that inhibitors of CYP3A enzymes such as **erythromycin** may inhibit the metabolism of oxycodone,[9] although oxycodone is also metabolised by CYP2D6,[9] which would make a clinically significant interaction seem unlikely.

1. Buprenorphine Hydrochloride Injection. Bedford Laboratories. US Prescribing information, August 2004.
2. Subutex (Buprenorphine hydrochloride). Schering-Plough Ltd. UK Summary of product characteristics, March 2008.
3. Temgesic Injection (Buprenorphine hydrochloride). Schering-Plough Ltd. UK Summary of product characteristics, April 2004.
4. Temgesic Sublingual Tablets (Buprenorphine hydrochloride). Schering-Plough Ltd. UK Summary of product characteristics, April 2004.
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8. Methadone Solution for Injection (Methadone hydrochloride). Wockhardt UK Ltd. UK Summary of product characteristics, August 2007.
9. OxyNorm (Oxycodone hydrochloride). Napp Pharmaceuticals Ltd. UK Summary of product characteristics, July 2008.

Opioids; Fentanyl and related drugs + Macrolides

Some patients may experience prolonged and increased alfentanil effects if they are given erythromycin or particularly troleandomycin. Troleandomycin also interacts with fentanyl but to a lesser extent. Erythromycin appears not to interact with sufentanil.

Clinical evidence

(a) Erythromycin

Erythromycin 500 mg twice daily for 7 days increased the mean half-life of **alfentanil** in 6 subjects from 84 minutes to 131 minutes and decreased its clearance by 26%. The two most sensitive subjects had considerable changes with only one day of erythromycin, and overall had a marked change. The other 4 subjects had only small or moderate changes.[1] A 32-year old man undergoing an exploratory laparotomy was given erythromycin 1 g and neomycin 1 g, both three times daily, on the day before surgery. During the induction and maintenance of anaesthesia he received a total of 20.9 mg of **alfentanil**. One hour after recovery he was found to be unrousable and with a respiratory rate of only 5 breaths per minute. He was successfully treated with naloxone.[2] Another patient given **alfentanil** and erythromycin is said to have developed respiratory arrest during recovery.[3]

In 6 healthy subjects erythromycin 500 mg twice daily for 7 days did not affect the pharmacokinetics of intravenous **sufentanil** 3 micrograms/kg in the 9 hours following administration.[4] Two of the subjects were the same as those who had an interaction with alfentanil and erythromycin, as cited above.

(b) Troleandomycin

A study in 9 healthy subjects given troleandomycin 500 mg orally found that the clearance of intravenous **alfentanil** 20 micrograms/kg was reduced by almost 70%, when compared with subjects given placebo.[5] Similar results were found in another study.[6] A further study found that oral troleandomycin (500 mg starting 105 minutes before an alfentanil infusion then 250 mg every 6 hours for 3 doses) reduced the clearance of **alfentanil** by 88%.[7] This study found that troleandomycin only reduced intravenous **fentanyl** clearance by 39%. In another study in 12 healthy subjects, peak **fentanyl** concentrations and maximum miosis following oral transmucosal fentanyl 10 micrograms/kg were minimally affected by oral troleandomycin (500 mg given about 3 hours before and 9 hours after the opioid), but fentanyl metabolism, elimination and duration of effects were significantly affected (fentanyl AUC increased by 77%; norfentanyl AUC decreased by 36%; AUC_{0-10} of miosis increased by 53%).[8]

Mechanism

Troleandomycin, and to a lesser extent erythromycin, inhibit the cytochrome P450 isoenzyme CYP3A4 in the liver, which is involved in the metabolism of alfentanil, fentanyl and sufentanil. Troleandomycin has also been reported to inhibit CYP3A5 and alfentanil appears to be metabolised by multiple CYP3A enzymes including CYP3A5.[9] Alfentanil is a low-extraction drug cleared mainly by hepatic metabolism,[6] whereas fentanyl and sufentanil are high extraction drugs (see 'Changes in first-pass metabolism', (p.4)) and are therefore less likely to be affected by changes in liver metabolism.[7,10] Alterations in intestinal or hepatic CYP3A activity also appear to have little influence on oral transmucosal fentanyl absorption and onset of effect, however, a significant proportion (approximately 75%) is swallowed and its systemic clearance may be decreased by CYP3A inhibitors.[8,11]

Importance and management

The interactions of **alfentanil** with erythromycin and troleandomycin appear to be established and clinically important. Clarithromycin and telithromycin (also CYP3A4 inhibitors, see *Mechanism*) would be expected to interact similarly. Alfentanil should be given in reduced amounts or avoided in those who are taking, or who have recently taken these drugs.[1] Be alert for evidence of prolonged alfentanil effects and respiratory depression. The interaction appears not to affect all patients given erythromycin. Alternatively, **sufentanil** in doses of 3 micrograms/kg or less may be used with erythromycin, but much larger doses of sufentanil should be given with caution.[4] Similar advice should probably apply to clarithromycin, telithromycin and particularly troleandomycin. Intravenous **fentanyl** may also be used with erythromycin, but should probably be used with caution with clarithromycin, telithromycin and troleandomycin. Caution is also advised if oral transmucosal fentanyl is given with these macrolides, as there may be increased bioavailability of swallowed fentanyl resulting in increased or prolonged opioid effects.[11] Similar advice is given for transdermal fentanyl: patients should be carefully monitored and fentanyl dose adjustments made if necessary.[12-14]

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Opioids + Magnesium compounds

Magnesium compounds can potentiate opioid analgesia, although some studies have failed to find an effect. Magnesium sulfate may also reduce opioid requirements during anaesthesia. Magnesium can delay the onset of spinal anaesthesia in patients given fentanyl with bupivacaine.

Clinical evidence, mechanism, importance and management

Several clinical studies have found that magnesium enhances the analgesic effect of opioids, including intrathecal magnesium with intrathecal **fentanyl**,[1] and intravenous magnesium with intravenous **fentanyl**,[2] **remifentanil**,[3] or **tramadol**.[4] Magnesium sulfate infusion has also been reported to decrease **sufentanil** requirements for sedation.[5] In contrast, other studies have reported no beneficial effect with peri- or postoperative use of magnesium on postoperative **morphine** or **pethidine** (**meperidine**) requirements.[6,7]

Respiratory depression occurred in a patient with congenital myopathy following intramuscular administration of morphine for pain relief during labour and the subsequent administration of magnesium for hypertension and proteinuria. This was possibly due to an interaction between the magnesium and morphine; however, other factors may also have contributed.[8]

In general, no additional serious adverse effects were reported in these studies, although one study found that the perioperative use of intravenous magnesium sulfate appeared to increase intraoperative blood loss at caesarean delivery. However, as magnesium is a tocolytic and may cause uterine atony, an increase in bleeding would be expected.[6]

Intrathecal magnesium sulfate prolonged the period of spinal anaesthesia induced by bupivacaine and **fentanyl** without additional adverse effects, but the onset of anaesthesia was also significantly delayed.[9]

Divalent cations appear to be involved in the pain pathway and magnesium sulfate can potentiate the opioid analgesic effect,[5] possibly by antagonism of *N*-methyl-D-aspartate receptor ion channels.[4,5] It has been suggested that as magnesium ions do not easily cross the blood brain barrier, the intrathecal use of magnesium may modulate pain relief via central effects, whereas the intravenous route mainly only affects peripheral mechanisms.[3] If anything, these interactions appears to be generally beneficial, and no particular precautions seem necessary.

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Opioids + NRTIs

Zidovudine had no effect on methadone levels in one study, but there is one report of a patient requiring a modest increase in

methadone dose after starting zidovudine. Similarly, case reports describe patients requiring a modest increase in their methadone dose after starting abacavir. Tenofovir, and a single dose of zidovudine with lamivudine had no effect on methadone pharmacokinetics.
Methadone can increase zidovudine levels, and reduce the levels of abacavir, stavudine, and didanosine from the tablet formulation, but not the enteric-coated capsule preparation.

Clinical evidence

(a) Abacavir

Eleven patients given **methadone** with abacavir had a 23% increase in the rate of methadone clearance but no change in the half-life or renal clearance. In addition, there was a delay, and a 34% decrease in the peak concentration of abacavir, but no change in abacavir clearance or half-life.[1] Of 3 patients taking **methadone** who started taking abacavir, lamivudine and zidovudine, 2 patients required methadone dose increases (31% and 46%, respectively). The abacavir was thought to be responsible for this effect.[2] A patient taking **methadone** experienced torsade de pointes when abacavir, lamivudine and zidovudine were also taken[3]

See also 'Opioids; Methadone + Protease inhibitors', p.200, for a report of a decrease in methadone levels in patients taking abacavir with amprenavir.

(b) Didanosine

A study in 17 subjects taking **methadone** found that the AUC and maximum levels of didanosine tablets were 57% and 66% lower, respectively, when compared with 10 control subjects. Trough levels of **methadone** did not differ from historical controls, suggesting that didanosine had no effect on methadone pharmacokinetics.[4] A later study found that there was no reduction in the AUC of didanosine given as enteric-coated capsules when **methadone** was also given.[5]

(c) Stavudine

A study in 17 subjects taking **methadone** found that the AUC and maximum levels of stavudine were 23% and 44% lower, respectively, when compared with 10 control subjects. Trough levels of **methadone** did not differ from historical controls suggesting that stavudine had no effect on methadone pharmacokinetics.[4]

(d) Tenofovir

In a study in 13 healthy subjects receiving **methadone**, tenofovir 300 mg daily for 2 weeks did not alter the pharmacokinetics of methadone, and no symptoms of opioid toxicity or opioid withdrawal were detected.[6]

(e) Zidovudine

1. Buprenorphine. In one study, there was no difference in the pharmacokinetics of oral zidovudine between patients receiving buprenorphine and control subjects.[7] Buprenorphine is not expected to cause zidovudine toxicity.

2. Methadone. A patient with AIDS needed an increase in his levomethadone (*R*-methadone) dose from 40 to 60 mg daily, within one month of starting to take zidovudine 1 g daily.[8] In contrast, a study found no evidence of any change in the pharmacokinetics of methadone in HIV-positive patients taking methadone 14 days after they started zidovudine 200 mg every 4 hours. No methadone withdrawal symptoms occurred.[9] Another study in 16 patients taking methadone found that a single-dose of a fixed combination of zidovudine 300 mg with lamivudine 150 mg *(Combivir)* had no effect on the pharmacokinetics of methadone, and there was no evidence of withdrawal or toxicity.[10]
The effect of methadone on the pharmacokinetics of zidovudine has also been studied. In one study the mean AUC of zidovudine was increased by 43% by methadone, and in 4 of 9 patients it was doubled.[9] Another study, in 8 HIV-positive patients starting methadone, found a 29% increase in the AUC of oral zidovudine and a 41% increase in the AUC of intravenous zidovudine. Three of the 8 patients stopped zidovudine because of adverse effects or haematological toxicity.[11] Decreased zidovudine clearance in patients taking methadone is described in another report.[12]

Mechanism

Uncertain. It appears that methadone reduces the bioavailability of didanosine, and to a lesser extent, stavudine, possibly because it delays gastric emptying. Thus, the enteric-coated didanosine preparation appears not to be affected.[4,5] Conversely, methadone apparently reduces the glucuronidation of zidovudine by the liver, resulting in an increase in its serum levels.[13] Methadone may also reduce the renal clearance of zidovudine.[11]

Importance and management

The increase in **zidovudine** levels with methadone is established, although the clinical relevance is uncertain. Be alert for any increase in zidovudine adverse effects. The balance of evidence suggests that zidovudine is unlikely to reduce methadone levels, and the one case reported remains unexplained, although note that some of the adverse effects of zidovudine may be mistaken for opioid withdrawal effects.

The reduction in **didanosine** levels with methadone may be clinically relevant, and the authors suggest increasing the dose of the tablet formulation. Monitor virological response. The enteric-coated didanosine preparation is not affected and it may therefore be worth considering using this preparation instead.

The reduction in **stavudine** levels with methadone is probably not clinically relevant, but again, further data are required. The changes in **abacavir** peak levels with methadone are not considered to be clinically relevant.[14] The reports suggest that it would be prudent to monitor for signs of opioid withdrawal and adjust the methadone dose if needed, when abacavir is also given.

Tenofovir does not appear to affect methadone levels.

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Opioids; Buprenorphine + NNRTIs

Preliminary evidence suggests that buprenorphine does not affect the antiretroviral efficacy or pharmacokinetics of delavirdine and efavirenz. Delavirdine may increase buprenorphine plasma levels and efavirenz may decrease buprenorphine levels. Delavirdine given with buprenorphine and naloxone has been shown to slightly prolong the QT interval.

Clinical evidence

(a) Pharmacokinetic interactions

A study in 20 opioid-dependent subjects taking **buprenorphine** with naloxone found that **efavirenz** 600 mg daily for 15 days decreased the AUC of buprenorphine and its metabolite, norbuprenorphine, by about 50% and 71%, respectively. **Delavirdine** 600 mg twice daily for 7 days caused a greater than fourfold increase in the buprenorphine AUC, but the

norbuprenorphine AUC was decreased by about 60%.[1] In this study buprenorphine did not alter the pharmacokinetics of **delavirdine** or **efavirenz**.[1]

(b) QT interval prolongation

A study in 50 opioid-dependent patients given sublingual buprenorphine with naloxone alone for at least 2 weeks and then also given an antiretroviral (**delavirdine**, **efavirenz**, nelfinavir, ritonavir-boosted lopinavir, or ritonavir) for 5 to 15 days, investigated the effect of these drugs on the QT interval. Buprenorphine with naloxone alone did not significantly alter the QT interval; however, when delavirdine and efavirenz were given there was a statistically, but probably not clinically, significant increase in the QT interval. The greatest increase in the QTc interval was seen in patients taking **delavirdine** 600 mg twice daily.[2]

Mechanism

Buprenorphine is a substrate for the cytochrome P450 isoenzyme CYP3A4. Inducers of CYP3A subfamily, such as **efavirenz** and **nevirapine**, would be expected to increase buprenorphine clearance, whereas **delavirdine**, which is an inhibitor of CYP3A, would be expected to reduce the CYP3A-mediated metabolism of buprenorphine to norbuprenorphine.

Importance and management

Despite the magnitude of the changes in buprenorphine levels seen with efavirenz and delavirdine, clinically significant consequences of these interactions (opioid withdrawal symptoms, cognitive effects and adverse effects) were not seen in this particular study and it was suggested that dose adjustments were not likely to be necessary.[1] However, the study was in HIV-negative subjects, and it has been suggested that the interaction may be of significance in HIV-positive individuals.[3] More clinical studies in HIV-positive patients are needed. Until further data are available, it would seem sensible to monitor for a reduction in buprenorphine efficacy with efavirenz or nevirapine, and adjust the dose as necessary. With delavirdine, it would seem prudent to monitor for increased buprenorphine adverse effects (such as drowsiness, respiratory depression). For details on the manufacturers' warnings and dose recommendations for buprenorphine with CYP3A4 inhibitors, see under 'Opioids + Azoles', p.181.

The increase in the QT interval reported with the concurrent use of buprenorphine and delavirdine or efavirenz is not considered to be clinically significant.[2]

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Opioids; Methadone + NNRTIs

Methadone plasma levels can be markedly reduced by efavirenz or nevirapine and withdrawal symptoms have been seen. No clinically significant interaction appears to occur between etravirine and methadone. In contrast, delavirdine slightly increased methadone levels in one study.

Clinical evidence

(a) Delavirdine

The pharmacokinetics of delavirdine 600 mg twice daily did not differ between 16 HIV-negative subjects taking methadone and 15 healthy control subjects.[1] In another study methadone did not affect delavirdine pharmacokinetics. However, delavirdine decreased methadone clearance and increased its AUC by 19%.[2]

(b) Efavirenz

An HIV-positive woman who had been taking methadone for over one year began to complain of discomfort within 4 weeks of having nelfinavir replaced by efavirenz 600 mg daily, and by 8 weeks typical methadone withdrawal symptoms were occurring late in the afternoon. It was found that the levels of *R*-methadone (the active enantiomer) had fallen from 168 nanograms/mL to 90 nanograms/mL, and those of the *S*-methadone from 100 nanograms/mL to 28 nanograms/mL. The methadone dose had to be increased from 100 mg to 180 mg daily before the symptoms disappeared.[3] A further case is reported in which a man taking methadone stopped taking efavirenz 600 mg daily because of the occurrence of withdrawal symptoms despite having has his methadone dose increased.[4] Another report describes a man who required a 133% increase in his methadone dose over 4 weeks after starting efavirenz, and mentions two other patients who complained of opioid withdrawal shortly after starting efavirenz. They also required methadone dose increases.[5]

In a pharmacokinetic study, 11 patients taking methadone 35 to 100 mg daily were given efavirenz with two nucleoside analogues. Nine of the patients developed methadone withdrawal symptoms and needed dose increases of 15 to 30 mg (mean 22%). A pharmacokinetic study of these patients found that 3 weeks after starting efavirenz their mean methadone AUCs were reduced by 57% and their maximum plasma levels by 48%.[6] Similar results were found in another study in 5 HIV-positive patients taking methadone: 4 patients experienced opioid withdrawal symptoms and a mean methadone dose increase of 52% was required.[7] In another retrospective study, 6 out of 7 patients needed methadone dose increases of 8% to 200% within 2 weeks to 8 months of starting an efavirenz-based regimen.[8] Another study in HIV patients also reported that 11 out of 18 patients taking efavirenz required a methadone dose increase (median 7.5 mg daily).[9]

(c) Etravirine

In a study, 16 subjects taking methadone for at least 14 days were also given etravirine 100 mg twice daily for 14 days. The pharmacokinetics of *R*-methadone were slightly increased (by about 10% by day 14) and those of *S*-methadone were slightly reduced (by about 11%) by etravirine. Similarly, methadone had no clinically significant effect on the pharmacokinetics of etravirine, when compared with historical controls. No relevant signs or symptoms of opioid withdrawal were reported.[10]

(d) Nevirapine

A retrospective review revealed 7 cases of patients taking methadone who developed withdrawal symptoms after starting regimens including nevirapine. The symptoms developed within 4 to 8 days, and methadone dose increases of 21 to 186% were required. Despite this, 3 patients did not respond. They elected to discontinue nevirapine, and in 2 patients somnolence developed within 2 weeks, so the methadone dose was reduced. Methadone plasma levels were available in 2 patients, and these suggested that nevirapine decreased methadone levels by about 90%.[11] In a pilot study of a once-daily nevirapine-containing regimen, 30% of patients required an increase in methadone dose.[12] A study in HIV-positive patients also reported that 32 out of 37 patients taking nevirapine required a methadone dose increase (median 20 mg daily).[9] In another study 4 of 5 patients taking methadone developed withdrawal symptoms on starting nevirapine-containing regimens and 2 patients refused further nevirapine, despite increasing their methadone dose. Another 2 patients were successfully treated with increases in their methadone doses of 33% and 100%.[13] Three other similar cases have been reported.[4,14,15]

In a pharmacokinetic study, 8 patients taking methadone 30 to 120 mg daily had methadone levels measured before and 14 days after starting an antiretroviral regimen including nevirapine 200 mg daily. The methadone AUC decreased by 52%, and the maximum level by 36%. Six patients complained of symptoms of methadone withdrawal, and required a mean increase in methadone dose of 16%.[16] Similarly, in 20 HIV-positive subjects stabilised on once-daily doses of racemic or *R*-methadone, the addition of nevirapine decreased the mean dose-adjusted AUC of methadone by 41%. This decrease resulted in symptoms of opioid withdrawal in 14 patients, which required additional doses of methadone.[17] Another pharmacokinetic study in 10 patients stabilised on methadone for at least 15 days found that nevirapine 200 mg daily reduced the AUC and maximum concentration of methadone by about 63% and 55%, respectively, but when the dose of nevirapine was increased to 400 mg daily there was no additional decrease in these pharmacokinetic parameters.[18]

Mechanism

Efavirenz and nevirapine induce the metabolism of methadone (possibly by the cytochrome P450 isoenzyme CYP3A4, or CYP2B6[19]), which results in reduced levels and effects. Etravirine also induces CYP3A4, but has only weak effects. In contrast, delavirdine is an *inhibitor* of various cytochrome P450 isoenzymes, and might therefore be expected to inhibit the metabolism of methadone, although the effects appear small.

Importance and management

The interaction between methadone and **efavirenz** or **nevirapine** is established and of clinical importance. Some authors have found that the dose increase required is much less than that predicted based on the reduction in methadone levels,[6,16] whereas others have questioned this.[5,20] It may be important not to confuse the adverse effects of the NNRTIs with opioid withdrawal symptoms.[6] It has been suggested that patients taking methadone who are given these drugs should be screened for opioid withdrawal beginning on the fourth day of the new medication. If symptoms develop, the methadone dose should be increased by 10 mg every 2 to 3 days until symptoms abate.[21] However, others have suggested dose increments should be made at one-week intervals to avoid overdose, as methadone has a long half-life (reported to range 13 to 47 hours).[22] Note that some patients may require an increase in methadone dose frequency to twice daily.[13] If efavirenz or nevirapine is stopped, the methadone dose should be gradually reduced to pretreatment levels over the course of one to 2 weeks.[21]

No dose adjustments of either **etravirine** or methadone are usually needed with concurrent use. However, despite this, the US manufacturer advises that patients are still monitored for signs of opioid withdrawal as the dose of maintenance methadone treatment may need to be altered in some patients.[23]

The US manufacturer of **delavirdine**[24] suggests that the methadone dose may need to be reduced; however, the effects in the study reported are small, and would not be expected to be of clinical significance.

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Opioids + NSAIDs

In general, the concurrent use of NSAIDs and opioids is beneficial (improved pain relief, decreased adverse effects, reduced opioid requirements), and clinically relevant pharmacokinetic interactions are lacking. However, there is some conflicting evidence as to whether respiratory depression is increased or decreased in those given diclofenac and morphine. A single case report describes marked respiratory depression in a man given buprenorphine when ketorolac was added. An isolated report describes grand mal seizures in a patient given diclofenac and pentazocine.

Clinical evidence, mechanism, importance and management

NSAIDs are often given with opioids because they usually reduce the opioid requirements and some of the opioid-induced adverse effects.[1]

Enhanced pain relief has been reported with various combinations including **dextromethorphan** with **ketorolac**[2] or **tenoxicam**,[3] **oxycodone** with **ibuprofen**,[4] and **tramadol** with **ketorolac**[5] without increased adverse effects. Consider also 'Opioids + NSAIDs; Coxibs', p.197.

However, cases of respiratory depression have been reported, see *Morphine* below, and myoclonus has been reported with high doses of morphine given with NSAIDs, see 'Opioids; Morphine + Miscellaneous', p.210.

(a) Buprenorphine

A man underwent thoracotomy for carcinoma of the middle third of his oesophagus. One hour after transfer to the recovery ward he complained of severe pain at the operative site and was given epidural buprenorphine 150 micrograms (3 micrograms/kg), and 2 hours later intramuscular **ketorolac** 30 mg because of continued pain. During the next hour he became more drowsy, stopped obeying commands and his respiratory rate dropped to 6 breaths per minute. He recovered after 6 hours of mechanical ventilation. The authors of this report suggest that it may be necessary to use less buprenorphine in the presence of ketorolac to avoid the development of these respiratory depressant effects.[6] This appears to be the only report of this possible interaction, and, as with other opioids, NSAIDs such as **etodolac** have been used with buprenorphine to reduce the postoperative pain score without increasing adverse effects.[7]

(b) Codeine

A study in 12 healthy subjects found that a single 50-mg dose of **diclofenac** did not have a clinically important effect on the pharmacokinetics of a single 100-mg dose of codeine phosphate when compared with placebo. There was no effect on the metabolic clearance of morphine, and only a slight (about 5 to 10%) increase in the levels of glucuronide metabolites. In addition, **diclofenac** did not alter the analgesic effects of codeine as assessed in a cold pressor test (a test in which opioids, but not NSAIDs, are effective).[8] Although this interaction perhaps requires confirmation in a multiple-dose study in a clinical setting, the findings in healthy subjects suggest that no special precautions are required during the concurrent use of **diclofenac** and codeine.

Single oral-dose studies in 24 healthy subjects found that the bioavailability of both codeine phosphate 25 mg and **ibuprofen** 200 mg were unaffected by concurrent use.[9]

(c) Dextropropoxyphene (Propoxyphene)

In healthy subjects the concurrent use of dextropropoxyphene 260 mg daily and **sodium meclofenamate** 400 mg daily for one week was found to have no effect on the plasma levels of either drug.[10]

The manufacturer of **sulindac** notes that dextropropoxyphene had no effect on the plasma levels of sulindac or its sulfide metabolite.[11]

(d) Methadone

In a study in 16 patients with cancer-related pain, intramuscular **diclofenac** 75 mg twice daily given for 5 days with oral methadone solution every 8 hours had no effect on the AUC or maximum plasma levels of methadone.[12] Therefore, no methadone dose adjustments appear to be necessary during concurrent use.

(e) Morphine

In a study in 11 healthy subjects, an infusion of **ketoprofen** 1.5 mg/kg with morphine 100 micrograms/kg reduced the respiratory depression associated with morphine alone. There was no change in plasma morphine levels.[13] Another study in 6 patients found that intramuscular **diclofenac**

75 mg twice daily for 5 days did not affect the half-life and AUC of oral morphine solution.[14] Other studies have reported superior pain relief with morphine and NSAIDs, including **lornoxicam**,[2] **ketoprofen**,[15] and **ketorolac**,[16]with fewer adverse effects. Consider also 'Opioids + NSAIDs; Coxibs', below.

However, in contrast to these reports, a study in 7 patients on the first postoperative day after spinal surgery found that, although rectal **diclofenac** 100 mg reduced patient-controlled morphine consumption by 20%, respiratory rates were significantly lower after the **diclofenac**, and minimal at about 200 minutes. Levels of an active metabolite, morphine-6-glucuronide did not significantly decrease until 420 minutes post-dose.[17]

NSAIDs are frequently used with opioids because of their lack of respiratory depression and opioid-sparing effects. However, this study demonstrates that there may be a risk of respiratory depression and other adverse effects due to persistently high levels of morphine-6-glucuronide for a number of hours after receiving an NSAID. During this time period, patients should be more closely monitored.[17]

For mention of an increased incidence of myoclonus when high-dose morphine was given with NSAIDs, see 'Opioids; Morphine + Miscellaneous', p.210.

(f) Oxycodone

A study involving 23 healthy subjects found that the single-dose pharmacokinetics of **ibuprofen** 400 mg and oxycodone 5 mg were similar when given alone or in combination.[18]

(g) Pentazocine

A man with Buerger's disease had a grand mal seizure while watching television 2 hours after being given a single 50-mg suppository of **diclofenac**. He was also taking pentazocine 50 mg three times daily. He may possibly have had a previous seizure some months before after taking a single 100-mg slow-release **diclofenac** tablet.[8] The reasons for this reaction are not known, but on rare occasions **diclofenac** alone has been associated with seizures (incidence said to be 1 in 100 000) and seizures have also been seen with pentazocine alone. It is not clear what part the disease itself, or watching television, had in the development of this adverse reaction.[19] Therefore no interaction between **diclofenac** and pentazocine is established, but be aware of this case if concurrent use is being considered, particularly in patients who are known to be seizure-prone.

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Opioids + NSAIDs; Coxibs

Parecoxib has no effect on the pharmacokinetics of alfentanil or fentanyl, and celecoxib and rofecoxib do not appear to affect the pharmacokinetics of tramadol. Coxibs can reduce the perioperative opioid requirement, but adverse effects are not necessarily reduced.

Clinical evidence, mechanism, importance and management

(a) Pharmacokinetic studies

In a crossover study in 12 healthy subjects, intravenous **parecoxib** 40 mg, given one hour before and 12 hours after an infusion of **alfentanil** 15 micrograms/kg or **fentanyl** 5 micrograms/kg, had no effect on the pharmacokinetics of these opioids.[1] Pupil diameter versus time curves were not affected by **parecoxib**. This interaction was investigated because both valdecoxib (the main metabolite of **parecoxib**) and **alfentanil** are substrates of the cytochrome P450 isoenzyme CYP3A4. The study suggests there should be no pharmacokinetic interaction during concurrent use.

In a study in patients receiving stable doses of **celecoxib** or **rofecoxib**, the pharmacokinetics of **tramadol** (given with paracetamol) did not appear to be affected by the coxibs. **Tramadol** is metabolised by CYP2D6 and CYP3A4, but there appeared to be no difference in the clearance of tramadol given with **celecoxib** (which is said to be a CYP2D6 inhibitor and is itself metabolised in part by CYP3A4) or **rofecoxib**.[2]

(b) Pharmacodynamic studies

Many studies have reported reduced opioid requirements and reduced opioid-related adverse effects when coxibs including **celecoxib**,[3] **parecoxib**,[4] and **rofecoxib**[5] are given perioperatively or postoperatively with various opioids including **hydrocodone**[3] and **morphine**.[5] The timing of the administration of the coxib appears to affect opioid-induced analgesia and post-infusion increases in sensitivity to pain. One study in healthy subjects found that pretreatment with **parecoxib** increased the analgesic effects of a **remifentanil** infusion and significantly diminished the increased sensitivity to pain after remifentanil was withdrawn. Giving parecoxib at the start of the remifentanil infusion did not alter its analgesic effects.[6] In another study, patients given preoperative and postoperative **rofecoxib**, or placebo, found that rofecoxib reduced **morphine** requirements and pain scores. In another group of patients given placebo preoperatively and **rofecoxib** postoperatively, rofecoxib did not significantly affect **morphine** requirements or pain scores at 24 hours after the operation compared to those given placebo pre-and postoperatively, but did show improvement at 48 hours and 72 hours after the operation. However, preoperative rofecoxib was considered to provide only moderate benefit and possibly offered little benefit over early postoperative administration.[5]

In a double-blind, placebo-controlled study in 72 patients undergoing laparoscopic cholecystectomy, oral **etoricoxib** 120 mg given 1.5 hours before surgery reduced the need for postoperative patient controlled analgesia (PCA) with **fentanyl**, but opioid-related adverse effects were not reduced.[7]

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Opioids + Opioids

The concurrent use of two opioid agonists may have enhanced effects, although acute opioid tolerance may also occur. Opioids

with mixed agonist/antagonist properties (e.g. buprenorphine, butorphanol, nalbuphine, pentazocine) may precipitate opioid withdrawal symptoms in patients taking pure opioid agonists (e.g. fentanyl, methadone, morphine).

Clinical evidence, mechanism, importance and management

Many of the opioids used clinically act primarily at μ-opioid receptors including **codeine**, **diamorphine**, **fentanyl**, **methadone**, and **morphine**, but they often have pharmacological differences, and patients tolerant to one opioid can frequently be switched to another opioid (opioid rotation) at doses lower than predicted by relative potencies.[1] Studies in *animals* have found synergistic or additive effects between μ-opioids.[1] The majority of studies in patients have reported enhanced analgesic effects with opioid combinations,[2,3] although combined opioids are not always beneficial;[4] in some cases adverse effects were increased and acute opioid tolerance has also occurred.[3] For example, a study in 69 patients who had undergone abdominal surgery and were receiving **morphine** found that the addition of a **tramadol** infusion was associated with improved patient-controlled analgesia (PCA) and smaller **morphine** requirements with no increase in adverse effects.[2] However, another study found that the effects of this combination were less than additive.[5] Furthermore, the incidence of dry mouth occurred more frequently and it was concluded that the use of two μ-opioid agonists in combination might only increase the number of adverse effects.[5] Other studies have found that transdermal **fentanyl** reduced **morphine** requirements after hysterectomy[6,7] without affecting sedation scores.[6] However, the combination of **fentanyl** and **morphine** resulted in more pronounced respiratory depression than morphine alone.[6,7] In contrast, in a study of 49 patients undergoing major abdominal surgery, relatively large doses of intraoperative **remifentanil** (mean remifentanil infusion rate 300 nanograms/kg per minute) were reported to almost double **morphine** requirements in the first 24 hours postoperatively. The results suggested that **remifentanil** caused the development of acute opioid tolerance and excessive sensitivity to pain.[8] Therefore, although some opioid combinations are useful, clinical studies are needed to ascertain the benefits and safety of specific combinations.[4]

Opioids with mixed agonist/antagonist properties (e.g. **buprenorphine**, **butorphanol**, **nalbuphine**, **pentazocine**) may precipitate opioid withdrawal symptoms in patients taking pure opioid agonists such as **fentanyl**, **methadone** and **morphine** (see 'Table 6.1', (p.150), for a classification). An example of this occurred in a 60-year-old woman who was taking slow-release **morphine** 90 mg twice daily for cancer pain and was additionally given **nalbuphine** 30 mg intravenously in an ambulance following a fractured femur. She became agitated and experienced involuntary movements, tachycardia, hypertension and sweating (typical of opioid withdrawal). Her management was further complicated by resistance to intravenous **morphine**, necessitating a femoral nerve block. The agitation, which lasted for about 4 hours after she was given the **nalbuphine**, was controlled with lorazepam.[9]

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Opioids + Phenothiazines

Chlorpromazine has been reported to increase the analgesic effect of pethidine (meperidine), but increased respiratory depression, sedation, CNS toxicity and hypotension can also occur. Other phenothiazines such as levomepromazine, promethazine, prochlorperazine, propiomazine and thioridazine may also interact with pethidine to cause some of these effects. Additive CNS depressant effects would be expected when opioids are given with phenothiazines.

Clinical evidence

(a) Pethidine (Meperidine)

In a single-dose study in healthy subjects, **chlorpromazine** had no effect on the pharmacokinetics of pethidine. However, the excretion of the metabolites of pethidine was increased, and symptoms of light-headedness, dry mouth and lethargy were significantly increased: 4 subjects experienced such marked debilitation that they required assistance to continue the study. Systolic and diastolic blood pressures were also reduced.[1]

Chlorpromazine 25 mg/70 kg given alone had no consistent effect on respiratory function in 6 healthy subjects but the respiratory depression produced by pethidine 100 mg/70 kg was exacerbated when the two drugs were given together. One subject had marked respiratory depression, beginning about 30 minutes after both drugs were given and lasting 2 hours.[2]

The respiratory depressant effects of pethidine can be increased by **promethazine** with pentobarbital,[3] **propiomazine**[4,5] and **levomepromazine**[6], but the effects of **prochlorperazine**[7] with pethidine on respiration were not statistically significant.

A 12-year-old patient taking long-term **thioridazine** 50 mg twice daily and given premedication with pethidine, diphenhydramine and glycopyrrolate, was very lethargic after surgery and stopped breathing. He responded to naloxone.[8] Promethazine may also decrease the dose requirements of pethidine during surgery, see under *Other opioids*, below.

(b) Other opioids

There have been conflicting data as to whether or not phenothiazines potentiate narcotic analgesia,[9] and it has been suggested that some patients treated with an opioid and a phenothiazine are merely too sedated to report pain.[10] However, some studies have found that **promethazine** reduces opioid requirements. The maintenance doses of a variety of opioid analgesics (**morphine**, **pethidine** (**meperidine**), **oxymorphone**, **hydromorphone**, **fentanyl**, **pentazocine**) required during surgical anaesthesia were reduced by 28 to 46% when 132 patients were premedicated with intramuscular **promethazine** 50 mg/70 kg, when compared with control patients. Similarly, on-demand **pentazocine** requirements post-caesarean section were reduced by 32% in women given **promethazine** as soon as the cord was clamped.[11] In a randomised, placebo-controlled study in 90 patients undergoing abdominal hysterectomy, the preoperative use of intravenous **promethazine** 100 micrograms/kg (given over 30 minutes, starting 30 minutes before induction), reduced the 24-hour postoperative **morphine** consumption by about 30%, when compared with placebo or postoperative **promethazine** use. Postoperative nausea and vomiting were reduced by both pre- and postoperative **promethazine**, when compared with placebo.[12]

Mechanism

There is evidence that chlorpromazine can increase the activity of liver microsomal enzymes so that the metabolism of pethidine (meperidine) to norpethidine and norpethidinic acid are increased. These metabolites probably account for the lethargy and hypotension seen in one study.[1] The effects of the phenothiazines on pethidine-induced respiratory depression may be related. Both the opioids and the phenothiazines are CNS depressants, and their effects may be additive.

Importance and management

Phenothiazines may enhance the hypotensive, sedative, and respiratory depressant effects of opioids. Patients should be monitored carefully on concurrent use, and opioid dose reductions made if necessary.

The manufacturers of **methadone** generally advise caution with other CNS depressants, however one manufacturer suggests that the concurrent use of other CNS depressants is not advised.[13]

Although lower analgesic doses of pethidine (meperidine) have been used with chlorpromazine,[14] a marked increase in respiratory depression can occur in some susceptible individuals[2] and the authors of one study[1] suggested that the risks of giving pethidine with chlorpromazine outweighed the advantages. Information about other adverse interactions between pethidine and the phenothiazines seems to be very limited: the interaction with thioridazine seems to be the only one reported. Increased

analgesia may occur but it may be accompanied by increased respiratory depression, which is undesirable in patients with existing respiratory insufficiency. The US manufacturer advises that concurrent use of pethidine with phenothiazines may also result in severe hypotension, profound sedation, or coma if usual doses of pethidine are used. They suggest that the dose of pethidine should be proportionally reduced (usually by 25 to 50%) when it is given with phenothiazines.[15]

For mention of myoclonus associated with high doses of morphine and chlorpromazine, see 'Opioids; Morphine + Miscellaneous', p.210.

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Opioids + Protease inhibitors

Ritonavir decreases pethidine (meperidine) and increases norpethidine levels, which may possibly increase toxicity on long-term use. Similarly, ritonavir and other protease inhibitors increase buprenorphine levels. Ritonavir may increase the metabolism of morphine, and decrease the metabolism of dextropropoxyphene and tramadol.

Clinical evidence

(a) Buprenorphine

A study in 20 HIV-negative, opioid-dependent patients stable on a combination of sublingual buprenorphine with naloxone (ratio 4:1) found that **atazanavir** 400 mg daily for 5 days increased the AUC and maximum plasma concentration of buprenorphine by 93% and 64%, respectively. Similarly, **ritonavir**-boosted **atazanavir** 100 mg/300 mg daily for 5 days increased the AUC and maximum plasma concentration of buprenorphine (by 67% and 37%, respectively), although to a slightly lesser degree than atazanavir alone. The study also noted that the levels of buprenorphine metabolites were increased. Buprenorphine had no significant effects on the pharmacokinetics of atazanavir or ritonavir, when compared with healthy non-opioid-dependent controls. No additional increases in the cardiac PR interval or bilirubin levels associated with atazanavir were found with the buprenorphine-maintained group compared with the control group.[1] The manufacturer of ritonavir reports that, in a study, ritonavir 100 mg twice daily increased the AUC and maximum level of buprenorphine 16 mg daily (route not specified) by 57% and 77%, respectively.[2] In a study in opioid-dependent patients taking sublingual buprenorphine and naloxone, patients were given an antiretroviral (**nelfinavir**, **ritonavir**-boosted **lopinavir**, or **ritonavir**) for 5 to 15 days to investigate the effect of these drugs on the QT interval. Buprenorphine with naloxone alone did not significantly alter the QT interval, but when an antiretroviral was also given there was a statistically, but probably not clinically, significant increase in the QT interval. The greatest increase in QTc interval was seen in patients receiving buprenorphine with naloxone and **ritonavir** 100 mg twice daily (low booster dose).[3]

One report describes 3 HIV-positive patients who experienced increased buprenorphine adverse effects (e.g. daytime sleepiness, dizziness, and reduced mental function) within about 2 days of starting to take **ritonavir**-boosted **atazanavir**. When the dose of buprenorphine was reduced there was a reduction in sedative symptoms, although in one case this led to an increase in opioid cravings.[4]

(b) Fentanyl and related drugs

For the interactions of the protease inhibitors with alfentanil or fentanyl, see 'Opioids; Fentanyl and related drugs + Protease inhibitors', p.200.

(c) Methadone

For the interactions of the protease inhibitors with methadone, see 'Opioids; Methadone + Protease inhibitors', p.200.

(d) Pethidine (Meperidine)

In 8 healthy subjects, **ritonavir** 500 mg twice daily for 10 days decreased the AUC of a single 50-mg dose of oral pethidine by 62% and increased the AUC of the metabolite, norpethidine, by 47%.[2,5] Norpethidine is pharmacologically active, and is possibly less effective an analgesic than the parent compound, and more likely to cause CNS effects such as seizures.

Mechanism

In vitro and *in vivo* studies have demonstrated that ritonavir is a potent inhibitor of the cytochrome P450 isoenzyme CYP3A4 and to a lesser extent CYP2D6, and may also induce glucuronidation.[2] An *in vitro* study suggested that buprenorphine metabolism may be inhibited by ritonavir and to a lesser extent by **indinavir** and **saquinavir**,[6] which would be expected to lead to increased buprenorphine levels. **Dextropropoxyphene** (propoxyphene) is also metabolised by CYP3A4. Substrates of CYP2D6 include **codeine**, **dihydrocodeine**, **oxycodone**, and **tramadol**. **Morphine** undergoes glucuronidation, and the morphine metabolite [morphine-6 beta-glucuronide] is believed to contribute to the analgesic effects of morphine. Buprenorphine, and to some extent, **codeine** also undergo glucuronidation.[7] The exact mechanism for the unexpected increase in buprenorphine metabolite levels reported in one study is unclear, although the authors suggest that atazanavir alone or with ritonavir may increase the gastrointestinal bioavailability of swallowed buprenorphine, thereby leading to an apparent increase in metabolite levels.[1]

Importance and management

Most of these interactions remain theoretical, but they are consistent with the way the protease inhibitors and the opioids interact with other drugs. The consequences of inhibition of CYP2D6 are most pronounced for **codeine**, and CYP2D6 inhibition will lead to decreased levels of the morphine metabolite of codeine and therefore, perhaps contrary to expectation, a reduced effect. The levels of other CYP2D6 substrates **dihydrocodeine**, **oxycodone**, and **tramadol** would be expected to be raised, and dose reductions may be necessary. This has been suggested for tramadol.[8] It would seem prudent to monitor for adverse effects such as sedation. However, note that *low-dose* ritonavir (i.e. the dose used as a pharmacokinetic enhancer with other protease inhibitors) has a less potent effect on CYP2D6 and dose reductions of drugs metabolised by CYP2D6 would not generally be required if this dose of ritonavir is given concurrently.[9]

Ritonavir is a potent inhibitor of CYP3A4 and therefore the UK manufacturer of ritonavir contraindicates its use with **dextropropoxyphene** as raised dextropropoxyphene levels may occur, which would increase the risk of serious respiratory depression or other serious adverse events.[2] However, the US manufacturer only suggests that a dose decrease may be needed.[8]

The outcome of taking ritonavir with **morphine** is less clear, but it is expected that its levels will be decreased.[2,10] It would seem prudent to monitor closely to ensure morphine is effective in patients taking ritonavir. More study is needed.

It has been suggested[11] that the starting dose of **buprenorphine** should be halved in patients taking CYP3A4 inhibitors, such as the protease inhibitors, when it is used for opioid dependence, although this may not be of clinical significance in those patients given low-dose ritonavir alone with buprenorphine who are opioid-tolerant.[2] One manufacturer of sublingual and injectable buprenorphine states that as the magnitude of an inhibitory effect is unknown, such drug combinations should be avoided when buprenorphine is used by these routes.[12,13] There appears to be less likelihood of an interaction with CYP3A4 inhibitors if buprenorphine is used transdermally, see 'Opioids + Azoles', p.181.

The manufacturers contraindicate or advise against the concurrent use of **pethidine** (**meperidine**) with ritonavir because of the risk of norpethidine

toxicity (such as seizures).[2,8,14] The long-term use of pethidine with other protease inhibitors that are given with low-dose ritonavir is also not recommended.

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Opioids; Fentanyl and related drugs + Protease inhibitors

Ritonavir increases the levels of alfentanil and fentanyl, and markedly increases alfentanil-induced miosis. Other protease inhibitors may have a similar effect.

Clinical evidence

(a) Alfentanil

A study in 11 healthy subjects found that steady-state **ritonavir** significantly reduced the clearance of both intravenous and oral alfentanil by about 3.7-fold and 10.5-fold, respectively. The oral bioavailability of alfentanil was increased from 37% to 95% by **ritonavir**. As a result of this, alfentanil-induced miosis was also significantly increased.[1] The same or a similar study has been reported elsewhere.[2]

(b) Fentanyl

In a study in healthy subjects, **ritonavir** 200 mg increased to 300 mg three times daily for a total of 7 doses increased the AUC of a single 5-mg/kg intravenous dose of fentanyl by 83%, decreased its clearance by 67%, and increased the elimination half-life twofold.[3]

Mechanism

Both fentanyl and alfentanil are metabolised by the cytochrome P450 isoenzyme CYP3A4. Ritonavir, and other protease inhibitors, are potent inhibitors of CYP3A4 and they therefore reduce the metabolism of these opioids, which results in increased levels and effects.

Importance and management

The evidence is limited, but is consistent with the way protease inhibitors and fentanyl or alfentanil are known to interact with other drugs. The UK manufacturer of alfentanil warns that potent CYP3A4 inhibitors such as ritonavir could increase the risk of prolonged or delayed respiratory depression, and says the combination should be used with special care, and that a reduced dose of alfentanil may be necessary.[4] Similarly, caution is required in patients taking ritonavir given fentanyl by any route (oral, parenteral, or transdermal). In particular, one UK manufacturer suggests avoiding the combination of ritonavir and transdermal fentanyl unless the patient can be closely monitored.[5] Fentanyl dose reductions may be needed with long-term treatment to avoid fentanyl accumulation.[5,6] Care should also be taken if low-dose ritonavir is used with other protease inhibitors as a pharmacokinetic enhancer.

The manufacturers also warn that other potent CYP3A4 inhibitors (they name **amprenavir**, **fosamprenavir**, and **nelfinavir**) may have a similar effect,[5,6] and it would seem prudent to be alert for an interaction with any protease inhibitor.

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Opioids; Methadone + Protease inhibitors

Methadone levels can be reduced by amprenavir, nelfinavir, and high-dose ritonavir, as well as ritonavir-boosted lopinavir, saquinavir, and tipranavir, Ritonavir-boosted darunavir and fosamprenavir, and indinavir, and possibly unboosted atazanavir or saquinavir, do not appear to have clinically significant effects on methadone pharmacokinetics. In addition, amprenavir levels may be reduced by methadone. Cases of QT prolongation and torsade de pointes have been reported in patients taking protease inhibitors and methadone.

Clinical evidence

(a) Amprenavir

A study involving 16 opioid-dependent subjects found that amprenavir 1.2 g twice daily for 10 days decreased the AUCs for both *R*-methadone (active enantiomer) and *S*-methadone (inactive enantiomer) by 13% and 40%, respectively. No clinically significant changes were noted in opioid effects and there was no evidence of opioid withdrawal.[1] However, in another study, in 5 patients methadone levels were reduced by 35% (range 28 to 87%) within 17 days of starting to take amprenavir 1.2 g twice daily and abacavir 600 mg twice daily. Two patients reported nausea before their daily methadone dose, which can be a sign of opiate withdrawal.[2] Note that **abacavir** may modestly reduce methadone levels, and could therefore have contributed to this effect (see 'Opioids + NRTIs', p.193).

The first study also found that amprenavir and methadone resulted in a 30% decrease in the AUC of amprenavir compared with non-matched historical controls.[1]

(b) Atazanavir

In 16 patients treated for opiate addiction, atazanavir, given for 14 days, had little effect on the steady-state pharmacokinetics of methadone, and symptoms of opiate withdrawal or excess were not detected.[3] A case of torsade de pointes has been reported in a patient taking methadone and also taking ritonavir-boosted atazanavir 100/300 mg daily (although the patient admitted poor compliance). The protease inhibitors were withdrawn and the QT interval prolongation was reversed over the next 48 hours.[4]

(c) Darunavir

A study where subjects were given methadone 55 to 150 mg daily with ritonavir-boosted darunavir 100/600 mg twice daily found that the AUC and minimum levels of *R*-methadone were reduced by 16% and 15%, respectively.[5,6]

(d) Fosamprenavir

A study in 19 patients stable taking methadone found that the concurrent use of ritonavir-boosted fosamprenavir 100/700 mg twice daily for 14 days reduced the AUC and maximum concentration of *R*-methadone by 18% and 21%, respectively, and reduced the AUC and maximum concentration of *S*-methadone by 43%. These minor changes did not result in any serious adverse effects or any significant changes in cognitive performance. None of the patients experienced opioid withdrawal and no methadone dose adjustments were required. The levels of **amprenavir**, derived from fosamprenavir, were unaffected when compared with historical control data.[7]

(e) Indinavir

A randomised, crossover study in 12 patients taking methadone found that the pharmacokinetics of methadone were unchanged by indinavir 800 mg every 8 hours for 8 days. A small decrease in indinavir peak levels and a small increase in trough levels were noted, when compared with historical controls.[8] Another study in 6 HIV-positive patients taking methadone and two nucleoside analogues similarly found that methadone levels remained unchanged when indinavir was added.[9] Similar results have been reported elsewhere.[10]

There are also clinical reports about 2 patients whose methadone levels appeared to be unaltered while taking indinavir, but who later had reduced levels when taking nelfinavir, or saquinavir with ritonavir (see *Nelfinavir*, and *Saquinavir*, below).[11,12] This would seem to confirm that indinavir does not have a clinically relevant effect on methadone levels.

(f) Lopinavir

A study in healthy subjects found that ritonavir-boosted lopinavir 100/400 mg twice daily for 10 days reduced the AUC of a single 5-mg dose of methadone by about 50%.[13] Similarly, in 15 healthy subjects taking methadone, ritonavir-boosted lopinavir 100/400 mg twice daily for 7 days decreased the AUC of methadone by 26% and increased its clearance by 42%. Four of the subjects had clinically important increases in opioid-withdrawal scores, and were all found to have sub-therapeutic trough methadone levels.[14] [Note that the same dose of ritonavir alone had no effect on methadone levels, see *Ritonavir*, below]. In another study in 8 HIV-positive patients taking methadone, a lopinavir with ritonavir-based antiretroviral regimen reduced the AUC of methadone by 36%, after 14 days of treatment. However, none of these patients experienced methadone withdrawal during the study or during 6 weeks of follow-up.[15] In yet another study (that did not measure methadone levels), none of 18 patients experienced methadone withdrawal during the 28 days after starting ritonavir-boosted lopinavir.[16] In a further study, methadone appeared to have no effect on the pharmacokinetics of lopinavir or ritonavir (given as a combined preparation).[17] A case of prolonged QT interval associated with torsade de pointes has been reported in an HIV-positive patient taking long-term methadone when ritonavir-boosted lopinavir was *stopped*.[18]

(g) Nelfinavir

A pharmacokinetic study in 13 subjects stabilised on methadone maintenance for at least one month found that nelfinavir 1.25 g twice daily for 8 days decreased the $AUC_{0\text{-}24}$ of *R*-methadone and *S*-methadone by 43% and 51%, respectively, and decreased the maximum concentration of *R*-methadone and *S*-methadone by 43% and 50%, respectively. None of the subjects developed opioid withdrawal symptoms or required methadone dose alterations. The methadone concentrations increased during the 14-day period after nelfinavir was stopped, but to a slightly lower level than before nelfinavir was added. Nelfinavir pharmacokinetics were not affected by methadone, when compared with historical data.[19] In a study looking at the levels of nelfinavir and its active metabolite M8, methadone had no significant effect on the AUC of nelfinavir, but the $AUC_{0\text{–}12}$ of M8 was reduced by 48%.[20]

An HIV-positive man who had been taking methadone 100 mg daily for several years with indinavir 800 mg and zalcitabine 750 micrograms three times daily, developed opioid withdrawal symptoms within 6 weeks of starting to take stavudine and nelfinavir 750 mg three times daily. His methadone dose was increased to 285 mg daily before therapeutic serum levels were achieved. When his antiretroviral treatment was withdrawn, his methadone dose was successfully reduced to 125 mg daily.[12] Two other patients taking nucleoside analogues had a 40 to 50% fall in their serum methadone levels when nelfinavir was added.[9,10] Similarly, in another study, 4 of 6 patients developed symptoms of methadone withdrawal within 5 to 7 days of starting nelfinavir-based therapy. The mean AUC of methadone was reduced by 56% and the subjects required a mean increase in methadone dose of 15%.[21]

A retrospective study of HIV-positive patients taking methadone reported that 5 out of 30 patients (17%) required methadone adjustments (mean 26 mg). The use of nelfinavir with methadone was effective and well tolerated.[22] A further study by the same authors reported that the mean methadone dose was increased by 10.6 mg with concurrent nelfinavir, when compared with methadone doses before nelfinavir was started.[23] A patient receiving methadone experienced torsade de pointes after starting to take nelfinavir.[24]

(h) Ritonavir

A patient taking lamivudine and zidovudine had a marked decrease in methadone levels when ritonavir was added.[9,10] Another patient receiving methadone experienced an opioid withdrawal syndrome when ritonavir was added to a similar antiretroviral regimen.[25]

A study in healthy subjects given single doses of intravenous and oral methadone and taking ritonavir up to 400 mg twice daily found that short-term (3-day) and steady-state ritonavir, respectively, increased the systemic and apparent oral clearance of methadone by about 50% and 100%. This produced a significant reduction in both the *R*-methadone and *S*-methadone AUCs. Ritonavir also increased the renal clearance of methadone by 40 to 50% and stereoselectively increased hepatic *N*-demethylation of methadone to inactive metabolites (with a greater effect on *S*- than on *R*-metabolite formation clearance). This occurred despite more than 70% inhibition of CYP3A by ritonavir.[26] Ritonavir (dose not stated) was given to 11 healthy subjects for 14 days, with a single 5-mg dose of methadone on day 11. Ritonavir reduced the maximum serum levels of methadone by 38% and the AUC by 36%.[27] However, in another study in 15 healthy subjects receiving methadone, ritonavir 100 mg twice daily for 7 days had no significant effect on methadone pharmacokinetics.[14]

In a further study, methadone apparently increased ritonavir exposure by 60%, when given alone, but had no effect on ritonavir pharmacokinetics when it was given with lopinavir.[17]

In healthy subjects the miosis caused by oral and intravenous methadone was increased by the acute use of ritonavir for 3 days but returned to below baseline after longer-term use for 14 days. It appeared that acute ritonavir inhibited, but chronic ritonavir mildly increased methadone elimination.[28] A case of torsade de pointes has been reported in a patient taking methadone, atazanavir and ritonavir, see *Atazanavir* above.

(i) Saquinavir

A study in an HIV-positive patient taking methadone and two nucleoside analogues found that methadone serum levels remained unchanged when saquinavir was added.[9] Similar results have been reported elsewhere.[10] Other studies have been undertaken with ritonavir-boosted saquinavir. An HIV-positive patient taking methadone 90 mg daily with indinavir, lamivudine and zidovudine, developed withdrawal symptoms and was hospitalised within a week of stopping these HIV drugs and starting ritonavir 400 mg, saquinavir 400 mg and stavudine 40 mg twice daily. The patient was eventually re-stabilised taking methadone 130 mg daily.[11]

A later study in 12 HIV-positive subjects taking methadone maintenance found that giving ritonavir 400 mg twice daily with saquinavir 400 mg twice daily decreased the *S*-methadone AUC by 40% and the *R*-methadone AUC by 32%. However, when these decreases were corrected for changes in protein binding, the free *R*-methadone AUC was decreased by only 20%, and the free *S*-methadone AUC by 25%. None of the subjects experienced methadone withdrawal or required a change in their methadone dose.[29] Similarly, in another study ritonavir-boosted saquinavir 100/1600 mg daily for 14 days caused no clinically relevant changes in total or free levels of either enantiomer of methadone in 12 HIV-negative subjects taking methadone. None of the subjects experienced methadone withdrawal.[30]

(j) Tipranavir

The manufacturers of tipranavir state that use of methadone and ritonavir-boosted tipranavir can result in a decrease in methadone levels of about 50%.[31,32]

Mechanism

Not known. The findings are the opposite of those originally predicted based on *in vitro* data showing *inhibition* of methadone metabolism (principally mediated by the cytochrome P450 isoenzyme CYP3A).[33] A slight increase in methadone elimination has been reported with ritonavir,[26,28] but this does not appear to be mediated by CYP3A. It is possible that protease inhibitors induce the activity of other isoenzymes or act via other mechanisms (e.g. glucuronyltransferases). The reduction in methadone levels has not always correlated with clinical effects, and it has been suggested that this may be because the pharmacokinetics of the enantiomers (one of which is inactive) are affected differently, and/or altered protein binding occurs.[7,20,26]

Importance and management

Information is limited but the interactions of methadone with **amprenavir**, **nelfinavir**, **ritonavir** and ritonavir-boosted **lopinavir**, **saquinavir**, and **tipranavir** would appear to be established. However, the picture seems to be that not all patients experience withdrawal symptoms if given these drugs. Therefore, in methadone-maintained patients, care should be taken if any of these protease inhibitors is started or stopped. It has been suggested that patients taking methadone who are given a protease inhibitor should be screened for opioid withdrawal beginning on the fourth day of the new medication. If symptoms develop, the methadone dose should be increased by 10 mg every 2 to 3 days until symptoms abate.[34] However, others have suggested dose increments should be made at one-week intervals to avoid overdose, as methadone has a long half-life (reported to range from 13 to 47 hours).[24] If the protease inhibitor is stopped the methadone dose should be gradually reduced to pretreatment levels over the course of one to 2 weeks.[34]

Although the changes in methadone levels with ritonavir-boosted **darunavir** are minimal and no dose adjustment is initially needed, the manufacturers advise monitoring with longer-term use as ritonavir may induce the metabolism of methadone, requiring a dose adjustment in some patients.[5,6]

Similarly, the levels of methadone are minimally affected by ritonavir-boosted **fosamprenavir** and no withdrawal signs were reported in one study. However, despite noting that the interaction does not appear to be clinically relevant, the manufacturers still advise monitoring patients given both drugs for signs of opioid withdrawal, as a precaution,[35,36]

Note that **amprenavir** plasma levels may also be reduced by methadone. The US manufacturer noted that amprenavir may be less effective if taken concurrently with methadone and suggested that alternative antiretroviral therapy should be considered.[37] In contrast, amprenavir levels from ritonavir-boosted fosamprenavir were not affected by the concurrent use of methadone.[7]

Indinavir appears not to interact with methadone, and very limited evidence suggests that **atazanavir** and **saquinavir** alone do not interact either.

The protease inhibitors appear to have contributed to the cases of QT prolongation and torsade de pointes reported above, and a retrospective study in HIV-positive patients reported that nelfinavir and methadone were independently associated with an increased risk of QTc prolongation.[38] Patients taking methadone in doses greater than 100 mg and with additional risk factors for QT prolongation should be carefully monitored, see 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290.

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Opioids + Quinidine

Quinidine appears to increase the *oral* absorption and effects of fentanyl, methadone, and morphine, but does not significantly alter the opioid-induced miosis when these opioids are given *intravenously*. Care should be taken if high-dose methadone is used with quinidine as cardiac conduction might possibly be affected. Quinidine may modestly increase the bioavailability of tramadol. No significant pharmacokinetic interaction appears to occur between quinidine and hydromorphone.

Clinical evidence

(a) Fentanyl

In a study in healthy subjects, quinidine sulfate 600 mg given one hour before an *intravenous* infusion of fentanyl 2.5 micrograms/kg did not alter fentanyl-induced miosis. However, the same dose of quinidine given before *oral* fentanyl 2.5 micrograms/kg (with ondansetron as an antiemetic) increased fentanyl-induced miosis. This increase was considered proportionate to the increase in the AUC of fentanyl (160%). There was no change in the elimination half-life of fentanyl.[1]

(b) Hydromorphone

An *in vitro* study suggested that quinidine did not significantly affect the metabolism of hydromorphone to norhydromorphone.[2]

(c) Methadone

In a study in healthy subjects, quinidine sulfate 600 mg, given one hour before *intravenous* methadone hydrochloride 10 mg, did not alter methadone-induced miosis. However, the same dose of quinidine given before *oral* methadone hydrochloride 10 mg (with ondansetron as an antiemetic) increased the peak methadone-induced miosis by 34%. The plasma levels of oral methadone in the absorption phase were increased, but the maximum plasma level or AUC of methadone were not affected.[3]

(d) Morphine

In a study in healthy subjects, quinidine sulfate 600 mg, given one hour before *intravenous* morphine sulfate 150 micrograms/kg, did not alter morphine-induced miosis. However, the same dose of quinidine given before *oral* morphine sulfate 30 mg (with ondansetron as an antiemetic) increased morphine-induced miosis by 56%. This increase was considered proportionate to the increase in morphine AUC (60%) and maximum level (88%). There was no change in the elimination half-life of morphine.[4] Similarly, in another study in healthy subjects, quinidine 800 mg given one hour before *intravenous* morphine 7.5 mg did not alter the respiratory depressant nor miotic effects of morphine, and there was no change in plasma morphine or morphine glucuronide levels.[5]

(e) Tramadol

A placebo-controlled study in 12 healthy subjects found that quinidine 50 mg had virtually no effect on the analgesic effect of tramadol 100 mg but it inhibited its effect on pupil size.[6] The US manufacturer reports that, in a single-dose study, quinidine 200 mg taken 2 hours before extended-release tramadol 100 mg increased the exposure to tramadol by 50 to 60%, and decreased the exposure to its M1 metabolite by a similar amount.[7]

Mechanism

Fentanyl and methadone are metabolised by the cytochrome P450 isoenzyme CYP3A4 and hydromorphone is demethylated by CYP3A4. Quinidine is also a substrate for CYP3A4 and inhibits CYP2D6, but does not appear to affect the metabolism of these opioids.[1-3] However, quinidine inhibits P-glycoprotein and this may affect fentanyl, methadone and morphine intestinal absorption.[1,3,4] The lack of effect on miosis indicate that quinidine does not appear to alter the brain distribution of fentanyl[1] or morphine.[4,5]

Tramadol is partially metabolised to the active metabolite *O*-desmethyltramadol (which affects opioid receptors), by the cytochrome P450 isoenzyme CYP2D6, which is inhibited by quinidine. However, this appears to have little effect on the analgesic efficacy of tramadol.[6]

Importance and management

The clinical significance of the increase in absorption of oral **fentanyl**, **morphine** and **methadone** caused by quinidine is unknown. However, note that both high doses of methadone and quinidine can affect the QT interval, see 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290. The clinical importance of a possible interaction with oral transmucosal fentanyl citrate (of which a significant proportion is swallowed) remains to be determined, but be aware that its effects may be increased.

Hydromorphone does not appear to be affected by quinidine although ideally this needs confirming in clinical studies.

The general significance of the interaction between quinidine and tramadol is unclear, although it would be prudent to bear the possibility of an interaction in mind should a patient taking both drugs develop an increase in tramadol adverse effects.

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Opioids; Codeine and related drugs + Quinidine

The analgesic effects of codeine, and probably also hydrocodone, are reduced or abolished by quinidine. Quinidine alters the pharmacokinetics of dihydrocodeine and oxycodone, but this does not appear to alter their effects.

Clinical evidence

(a) Codeine

Codeine 100 mg was given to 16 CYP2D6 extensive metabolisers (that is, those with normal levels of this isoenzyme) with and without a single 200-mg dose of quinidine. The quinidine reduced the peak morphine levels by about 80% (from a mean of 18 nanomol/L to less than 4 nanomol/L). Codeine given alone increased the pain threshold (pinprick pain test using an argon laser) but no significant analgesic effects were detectable when quinidine was also present.[1] Another study found that the effects of codeine in CYP2D6 extensive metabolisers who were given quinidine, were virtually the same as codeine alone in CYP2D6 poor metabolisers (that is, those lacking or deficient in CYP2D6).[2] These studies confirm the preliminary findings of an earlier study using codeine 100 mg and quinidine 50 mg.[3] The quinidine reduced the peak morphine plasma levels by more than 90% (by 92% in 7 extensive metabolisers, and by 97% in one poor metaboliser) and similarly abolished its analgesic effects.[3]

(b) Dihydrocodeine

A study in which four CYP2D6 extensive metabolisers (that is, those with normal levels of this isoenzyme) were given dihydrocodeine 40 or 60 mg found that, when they were pretreated with quinidine 200 mg, almost none of the morphinoid metabolites of dihydrocodeine normally present in the serum could be detected.[4] The same authors found essentially similar results in a later study in ten CYP2D6 extensive metabolisers given dihydrocodeine 60 mg and quinidine 50 mg.[5] However, a single-dose study involving 10 healthy subjects who were CYP2D6 extensive metabolisers investigated the effect of quinidine on the visceral and somatic analgesic effects of dihydrocodeine and its metabolite, dihydromorphine. It was found that although quinidine reduced dihydromorphine plasma levels (by inhibition of CYP2D6 reducing the metabolism of dihydrocodeine to dihydromorphine), this did not result in diminished pain tolerance thresholds. This suggested that the metabolism of dihydrocodeine to dihydromorphine may not be clinically important for analgesia.[6]

(c) Hydrocodone

In a comparative study, 5 extensive metabolisers and 6 poor metabolisers of CYP2D6 (that is, those with normal levels of this enzyme, or those lacking or deficient in this isoenzyme, respectively) were given hydrocodone, and another four CYP2D6 extensive metabolisers were given hydrocodone after pretreatment with quinidine. The metabolism of the hydrocodone to its active metabolite, hydromorphone, was found to be high in the extensive metabolisers who described 'good opiate effects', but poor in the poor metabolisers and the extensive metabolisers pretreated with quinidine who described 'poor opiate effects'.[7] For the effect of quinidine on hydromorphone metabolism, see 'Opioids + Quinidine', p.202.

(d) Oxycodone

Quinidine given as 200 mg 3 hours before and 100 mg 6 hours after a single 20-mg dose of oxycodone almost completely inhibited the formation of the metabolite, oxymorphone in 10 healthy CYP2D6 extensive metabolisers (that is, those with normal levels of this isoenzyme). Despite this, the psychomotor and subjective effects of oxycodone were not altered (note that analgesia was not assessed). The AUC of the metabolite noroxycodone was increased about 85%, and the oxycodone AUC was slightly increased by 13%.[8] Similar results were found in the preliminary report of another study.[9]

Mechanism

The evidence available shows that the conversion of codeine, dihydrocodeine and hydrocodone to their active analgesic metabolites in the body (morphine, morphinoid metabolites and hydromorphone, respectively) probably depends upon the activity of the cytochrome P450 isoenzyme CYP2D6 in the liver. Inhibition of this conversion by quinidine means that analgesic effects may be reduced or lost. This interaction is only likely to

occur in extensive metabolisers, and not in poor metabolisers, who have minimal CYP2D6 activity and who therefore may only derive minimal benefit from analgesics such as codeine, whose principal pharmacological effect appears to depend on this metabolism.[2] However, one study in healthy subjects has suggested that the analgesic effect of dihydrocodeine does not necessarily depend on its systemic metabolism to dihydromorphine.[6] Similarly, although quinidine also blocks the conversion of oxycodone to oxymorphone, it appears that this is not important for the pharmacodynamic effects of this drug.

Importance and management

The interaction between **codeine** and quinidine is well established and clinically important. Codeine will be virtually ineffective as an analgesic in extensive metabolisers of CYP2D6 (the majority of patients) taking quinidine. An alternative analgesic should be used (possibly dihydrocodeine, see below, or tramadol, see 'Opioids + Quinidine', p.202). No interaction would be expected in poor metabolisers (about 7% of Caucasians), but codeine is probably unlikely to be effective in these patients in any case. Whether the antitussive effects of codeine are similarly affected is not established, but it seems likely. Note that this interaction has been used clinically in an attempt to treat codeine dependence.[10]

The interaction of **hydrocodone** is less well established, but the evidence suggests that the analgesic effect will similarly be reduced or lost if quinidine is given. Further study is needed.

The available evidence suggests that the efficacy of **dihydrocodeine** or **oxycodone** may not be significantly affected by quinidine, but this needs confirmation.

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Opioids + Rifampicin (Rifampin)

Rifampicin markedly increases the metabolism of codeine and morphine, and reduces their effects. Rifampicin dramatically reduced the effects of oxycodone in one patient.

Clinical evidence, mechanism, importance and management

(a) Codeine

A study in 15 healthy subjects found that after taking rifampicin 600 mg daily for 3 weeks, the metabolism of a single 120-mg oral dose of codeine phosphate was markedly increased. The AUC of codeine was decreased by about 80% and both the *N*-demethylation and glucuronidation metabolic pathways were induced. Of the 15 subjects, 9 were extensive CYP2D6 metabolisers (that is, those with normal levels of this isoenzyme) and 6 were poor CYP2D6 metabolisers (those lacking or deficient in CYP2D6). The *O*-demethylation of codeine (mediated by CYP2D6) was induced only in the extensive metabolisers. In these subjects there was a 56% reduction in the AUC of morphine (the main active metabolite of codeine), and a 173% increase in the AUC of normorphine (another active metabolite). Note that morphine and its metabolites were not detected in poor metabolisers, either before or after rifampicin was given, because the pathway that leads to these metabolites is deficient or absent in these subjects. Rifampicin reduced the respiratory and psychomotor effects of codeine in extensive metabolisers, but not in poor metabolisers. In contrast, rifampicin decreased the pupillary effect of codeine in poor metabolisers, but it was not altered in extensive metabolisers, possibly due to the increase in the AUC of normorphine. The clinically more relevant question of whether, and to what extent, the analgesic effects of the codeine were reduced by this interaction was not addressed by this study.[1] However, some reduction in the effects of codeine might be expected. Therefore, if these drugs are used concurrently, be alert for the need to raise the codeine dose, or use an alternative analgesic. More study is needed.

(b) Fentanyl and related drugs

For the interactions of alfentanil and fentanyl with rifampicin, see 'Opioids; Fentanyl and related drugs + Rifampicin (Rifampin)', below.

(c) Methadone

For the interactions of methadone with rifabutin and rifampicin, see 'Opioids; Methadone + Rifamycins', p.205.

(d) Morphine

In a randomised study, 10 healthy subjects were given a single 10-mg oral dose of morphine sulfate with rifampicin 600 mg daily. It was found that rifampicin increased the clearance of the morphine by 49%, and its analgesic effects (using a modified cold pressor test) were abolished.[2] The mechanism of this interaction is uncertain as morphine is principally metabolised by glucuronidation but the findings of this study could not be attributed to rifampicin induction of glucuronosyltransferases.[2] Be alert for the need to use an increased dose of morphine in patients taking rifampicin. More study is needed.

(e) Oxycodone

A 60-year-old man who was taking rifampicin as well as oxycodone had three consecutive negative urine oxycodone screens in a 2-month period, which would normally suggest that he was not taking the oxycodone. However, oxycodone metabolites were found in his urine confirming compliance with his medication. An interaction between rifampicin and oxycodone was suspected and his oxycodone dose was increased to optimise his pain control.[3]

As oxycodone is metabolised by CYP2D6 and, to a lesser extent, CYP3A4, rifampicin, a known enzyme inducer, would be expected to increase its metabolism. The general significance of this isolated case is unclear, however be aware that the dose of oxycodone may need adjusting in patients taking rifampicin.

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Opioids; Fentanyl and related drugs + Rifampicin (Rifampin)

The serum levels and effects of transdermal fentanyl were decreased in two patients when they took rifampicin. Studies in healthy subjects have found that the bioavailability of oral transmucosal fentanyl is reduced by rifampicin. The clearance of intravenous alfentanil is markedly increased by rifampicin.

Clinical evidence, mechanism, importance and management

(a) Alfentanil

A study in 9 healthy subjects found that when they were given intravenous alfentanil 20 micrograms/kg after taking rifampicin 600 mg orally for 5 days, alfentanil clearance was increased almost threefold.[1] Rifampicin is a known inducer of the cytochrome P450 isoenzyme CYP3A4 in the liver, which is concerned with the metabolism of alfentanil; concurrent use therefore leads to an increased clearance of alfentanil. This study was primarily designed to investigate the role of CYP3A4 in the metabolism of alfentanil, but it also provides good evidence that alfentanil is likely to be much less effective in patients taking rifampicin. A much larger dose of alfentanil will almost certainly be needed.

(b) Fentanyl

In a study in 12 healthy subjects, the peak levels and maximum miosis after oral transmucosal fentanyl 10 micrograms/kg were minimally affected by oral rifampicin 600 mg daily for 5 days, but the AUC of fentanyl was decreased by 63%; the AUC of its metabolite, norfentanyl, was increased by 73%, and the $AUC_{0–10}$ of miosis was decreased by 54%.[2]

A patient with lung metastases was given transdermal fentanyl (1.67 mg patch every 3 days). Serum fentanyl levels measured 48 and 72 hours after the first day of treatment were 0.9 nanograms/mL and 0.77 nanograms/mL, respectively (within the reported minimum effective therapeutic range of 0.2 to 1.2 nanograms/mL). On day 5, due to insufficient pain control, the fentanyl patch was increased to 2.5 mg every 3 days. However, on day 7, oral rifampicin 300 mg daily, isoniazid and ethambutol were started for pulmonary tuberculosis. The following day severe pain developed and the fentanyl serum levels 48 and 72 hours after treatment on day 8 were 0.53 nanograms/mL and 0.21 nanograms/mL, respectively, despite the significant increase in the fentanyl dose. Even after the dose was increased again up to 7.5 mg every 3 days, the patient still complained of moderate pain and the fentanyl serum level 72 hours after treatment was only 0.69 nanograms/mL, less than the level achieved with the 1.67 mg dose in the absence of rifampicin.[3] A patient with colon cancer taking rifampicin 450 mg daily, isoniazid 300 mg daily and ethambutol 750 mg daily was started on a transdermal fentanyl patch at a dose of 600 micrograms daily. However, this did not control his pain and neither did titration of the fentanyl dose up to 2.5 mg daily. The patient was changed to an equivalent dose of morphine, which provided effective pain relief, but he developed a disturbance in consciousness and so his treatment was changed to an NSAID.[4]

Fentanyl is metabolised by the cytochrome P450 isoenzyme CYP3A4 and rifampicin, a potent inducer of CYP3A4, appears to reduce its serum levels and analgesic effects. Thus an increase in fentanyl dose may be needed in patients taking rifampicin.[3]

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Opioids; Methadone + Rifamycins

Serum methadone levels can be markedly reduced by rifampicin (rifampin), and withdrawal symptoms have occurred in some patients. Rifabutin appears to interact similarly, but to a lesser extent.

Clinical evidence

(a) Rifabutin

A study in 24 HIV-positive patients taking methadone found that rifabutin 300 mg daily for 13 days had only minimal effects on the pharmacokinetics of methadone. However, 75% of the patients reported at least one mild symptom of methadone withdrawal, but this was not enough for any of them to withdraw from the study. Only 3 of them asked for and received an increase in their methadone dose. The authors offered the opinion that over-reporting of withdrawal symptoms was likely to be due to the warnings that the patients had received.[1]

(b) Rifampicin (Rifampin)

The observation that former diamorphine (heroin) addicts taking methadone complained of withdrawal symptoms when given rifampicin, prompted a study[2] in 30 patients taking methadone. Withdrawal symptoms developed in 21 of the 30 patients within one to 33 days of starting rifampicin 600 to 900 mg daily and isoniazid daily. In 6 of the 7 patients most severely affected, the symptoms developed within one week, and their plasma methadone levels fell by 33 to 68%. Of 56 other patients taking methadone with other antitubercular treatment (which included isoniazid but not rifampicin), none developed withdrawal symptoms.[2-4] Other cases of this interaction have been reported.[5-9] Some patients needed two- to threefold increases in their methadone dose while taking rifampicin, in order to control the withdrawal symptoms.[6,7,9]

Mechanism

Rifampicin is a potent enzyme inducer, which increases the activity of the intestinal and liver cytochrome P450 isoenzymes concerned with the metabolism of methadone, resulting in a marked decrease in its levels.[10] In 4 patients in the study cited, the urinary excretion of the major metabolite of methadone rose by 150%.[2] Rifabutin has only a mild enzyme-inducing effect and therefore the effects are not as great.

Importance and management

The interaction between methadone and rifampicin is established, adequately documented and of clinical importance. The incidence is high: two-thirds (21) of the narcotic-dependent patients in one study[2] developed this interaction, 14 of whom were able to continue treatment. Withdrawal symptoms may develop within 24 hours. The analgesic effects of methadone would also be expected to be reduced. Concurrent use need not be avoided, but the effects should be monitored and appropriate methadone dose increases (as much as two to threefold) made where necessary.

Rifabutin appears to interact to a much lesser extent than rifampicin, so that fewer, if any, patients are likely to need a methadone dose increase.

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Opioids + St John's wort (*Hypericum perforatum*)

St John's wort reduces the plasma concentrations of methadone and withdrawal symptoms may occur.

Clinical evidence

In a study in 4 patients taking **methadone**, St John's wort (Jarsin) 900 mg daily for 14 to 47 days decreased **methadone** plasma concentration-to-dose ratios (indicating decreased **methadone** levels) by 19 to 60%. Two patients reported symptoms that suggested a withdrawal syndrome.[1]

Mechanism

St John's wort is metabolised in the liver and induces the cytochrome P450 enzyme CYP3A4, and so could affect plasma levels of drugs metabolised in this way, such as methadone.[1]

Importance and management

St John's wort appears to reduce the plasma levels of methadone causing withdrawal symptoms in some patients. Therefore, concurrent use should be avoided. It may be prudent to follow the same advice for other opioids[2] that are mainly metabolised by CYP3A4, such as **buprenorphine**, **fentanyl** or **alfentanil**.

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Opioids + Tobacco

Smokers who discontinue smoking appear to require more opioid analgesics for postoperative pain control than non-smokers; this

has been seen with both fentanyl and morphine patient-controlled analgesia. Atmospheric pollution and smoking has a similar effect on pentazocine. Codeine metabolism was not affected to a clinically relevant extent by smoking in one study.

Clinical evidence

A retrospective study of coronary artery bypass graft patients found that 20 patients who had abruptly discontinued smoking before surgery required more postoperative opioid analgesics than 69 non-smokers. The opioid analgesics included **dextropropoxyphene** (**propoxyphene**), **fentanyl**, **hydrocodone**, **oxycodone**, **morphine**, **nalbuphine** and **pethidine** (**meperidine**), but the most commonly used opioid was **fentanyl** (used in approximately two-thirds of the patients) given by patient-controlled analgesia (PCA). Smokers deprived of nicotine had an increase in opioid requirements (converted to morphine equivalents), during the first 48 hours after surgery, ranging from 29 to 33% (when normalised for body-weight or body mass index).[1] Similarly, another retrospective study in 171 women found that the average postoperative narcotic use over 12 hours (expressed as equivalent doses of morphine) was 10.9 mg for patients who had never smoked, 13 mg for former smokers, and 13.1 mg for current smokers.[2]

(a) Codeine

The metabolism of a single 25-mg dose of codeine did not differ between 9 heavy smokers (greater than 20 cigarettes daily) and 9 non-smoking control subjects, except that smokers had a slightly higher rate of codeine glucuronidation.[3] This is unlikely to be clinically important. Another study found no clinically important differences in the systemic availability of single 60-mg oral or intramuscular doses of codeine between 10 smokers and 12 non-smokers. There was no significant difference in the plasma half-life of codeine or in the conversion of codeine to morphine; however, there was a slightly higher plasma clearance of codeine in smokers than in non-smokers.[4] No differences in the efficacy of codeine are expected between smokers and non-smokers.

(b) Dextropropoxyphene (Propoxyphene)

A study in 835 patients who were given dextropropoxyphene for mild or moderate pain or headache found that its efficacy as an analgesic was decreased by smoking. The drug was rated as ineffective in about 10% of 335 non-smokers, 15% of 347 patients who smoked up to 20 cigarettes daily, and 20% of 153 patients who smoked more than 20 cigarettes daily.[5]

(c) Morphine

A study in 7 women during the acute post-caesarean recovery period found that intravenous morphine use over 24 hours (as patient-controlled analgesia; PCA) was significantly higher in smokers compared with non-smokers: weight-adjusted morphine use was 1.8 mg/kg compared with 0.64 mg/kg, respectively). It was suggested that a history of nicotine use and/or short-term nicotine abstinence could modulate morphine use and analgesia during postoperative recovery.[6] Similarly, another retrospective study found increased morphine PCA requirements in smokers compared with non-smokers.[7]

(d) Pentazocine

A study in which pentazocine was used to supplement nitrous oxide relaxant anaesthesia found that patients who came from an urban environment needed about 50% more pentazocine than those who lived in the country (3.6 micrograms/kg per minute compared with 2.4 micrograms/kg per minute). Roughly the same difference was seen between those who smoked and those who did not (3.8 micrograms/kg per minute compared with 2.5 micrograms/kg per minute).[8] In another study it was found that pentazocine metabolism was 40% higher in smokers than in non-smokers.[9]

Mechanism

It is thought that tobacco smoke contains compounds that increase the activity of the liver enzymes concerned with the metabolism of dextropropoxyphene, pentazocine and many other opioids, which increases their metabolism, decreases their levels and diminishes their effectiveness as analgesics.[2,5] However, former smokers have also been found to have increased opioid requirements and it has been suggested that smoking might have an effect on pain perception and/or opioid response, or that nicotine addiction and opioid requirements may be genetically linked.[2]

Importance and management

The interaction between tobacco smoking and opioids appears to be well established. Prescribers should be aware that smokers may require a greater amount of opioids postoperatively than non-smokers, although as pain control is tailored to requirement, this is unlikely to be clinically important. In contrast, codeine metabolism does not appear to be affected to a clinically relevant extent by smoking.

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Opioids + Tricyclic and related antidepressants

In general, the concurrent use of most opioids and tricyclics is uneventful, although lethargy, sedation, and respiratory depression have been reported. Tramadol should be used with caution with tricyclic antidepressants because of the possible risk of seizures and serotonin syndrome. Dextropropoxyphene may cause moderate rises in the serum levels of amitriptyline, nortriptyline, and possibly doxepin, and methadone may moderately raise desipramine levels. The bioavailability and the degree of analgesia of oral morphine are increased by clomipramine, desipramine, and possibly amitriptyline.

Clinical evidence

(a) Buprenorphine

A study in 12 healthy subjects found that both sublingual buprenorphine 400 micrograms and oral **amitriptyline** 50 mg impaired the performance of a number of psychomotor tests (digit symbol substitution, flicker fusion, Maddox wing, hand-to-eye coordination, reactive skills), and the subjects felt drowsy, feeble, mentally slow and muzzy. When **amitriptyline** 30 mg, increased to 75 mg daily, was given for 4 days before a single dose of buprenorphine, the psychomotor effects were not significantly increased, but the respiratory depressant effects of buprenorphine were enhanced.[1]

(b) Dextropropoxyphene (Propoxyphene)

An elderly man taking **doxepin** 150 mg daily developed lethargy and daytime sedation when he started to take dextropropoxyphene 65 mg every 6 hours. His plasma **doxepin** levels rose by almost 150% (from 20 to 48.5 nanograms/mL) and desmethyldoxepin levels were similarly increased (from 8.8 to 20.7 nanograms/mL).[2]

The **amitriptyline** concentration to dose ratio in 12 patients given **amitriptyline** and dextropropoxyphene was raised by about 20% (suggesting raised amitriptyline levels), when compared with other patients taking **amitriptyline** alone. Similarly, the plasma level of the **amitriptyline** metabolite, nortriptyline, was raised by about 30% in 14 patients given dextropropoxyphene;[3] and in another study, **nortriptyline** plasma levels were raised by 16% by dextropropoxyphene.[3]

Fifteen patients with rheumatoid arthritis given a single 25-mg dose of **amitriptyline** and dextropropoxyphene (up to 65 mg three times daily) experienced some drowsiness and mental slowness. They complained of being clumsier and had more pain, but these effects were said to be mild.[4]

(c) Methadone

The mean serum levels of **desipramine** 2.5 mg/kg daily were approximately doubled in 5 men who took methadone 500 micrograms/kg daily for 2 weeks. Previous observations in patients given both drugs had shown that **desipramine** levels were higher than expected and adverse effects de-

veloped at relatively low doses.[5] Further evidence of an increase in plasma **desipramine** levels due to methadone is described in another study.[6]

(d) Morphine

In a study in 24 patients with cancer-related pain, **clomipramine** or **amitriptyline**, in doses of 20 or 50 mg daily, increased the AUC of oral morphine by 28 to 111%. The half-life of morphine was also prolonged.[7] A previous study[8] found that **desipramine**, but not **amitriptyline**, increased and prolonged morphine analgesia, and a later study by the same group confirmed this potentially beneficial effect of **desipramine**.[9] See also, 'Opioids; Morphine + Miscellaneous', p.210, for limited evidence that amitriptyline and **doxepin** may increase the risk of myoclonus with morphine.

(e) Oxycodone

In a study in 9 healthy subjects, pretreatment with **amitriptyline** 10 mg increased to 50 mg daily for 4 days caused no major changes in the psychomotor effects of a single 280-microgram/kg oral dose of oxycodone.[10] Respiratory effects were not assessed.

(f) Pentazocine

Both pentazocine and **amitriptyline** given alone caused 11 healthy subjects to feel drowsy, muzzy and clumsy, and reduced the performance of a number of psychomotor tests. However, when the same subjects were given intramuscular pentazocine 30 mg after taking **amitriptyline** 50 mg daily for one week, the combination of drugs appeared not to impair driving or occupational skills more than either drug given alone.[11] Respiratory depression was increased more by concurrent use than by either drug alone. **Amitriptyline** modestly decreased pentazocine plasma levels by about 20% at 1.5 hours and 3.5 hours post-dose.[11]

(g) Tramadol

The CSM in the UK has publicised 27 reports of convulsions and one of worsening epilepsy with tramadol, a reporting rate of 1 in 7000 patients. Some of the patients were given doses well in excess of those recommended, and 8 patients were also taking tricyclic antidepressants, which are known to reduce the convulsive threshold.[12] Similarly, the FDA in the US has received 124 reports of seizures associated with tramadol, 28 of which included the concurrent use of tricyclic antidepressants,[13] and the Australian Adverse Drug Reaction Advisory Committee (ADRAC) has received 26 cases of convulsions associated with tramadol, some of which included the concurrent use of tricyclic antidepressants.[14] ADRAC have also received reports of serotonin syndrome, which were associated with the use of tramadol and tricyclic antidepressants.[14] Furthermore, two case reports suggest that tramadol may have contributed to the development of serotonin syndrome, one report was of a patient abusing tramadol, moclobemide and **clomipramine**,[15] and the other was of a 79-year-old patient taking morphine *(MST),* co-proxamol (dextropropoxyphene with paracetamol (acetaminophen)) and **amitriptyline**, after she started to take tramadol.[16,17] In both of these cases the patient died.

Similarly, seizures and serotonin syndrome have been reported in a woman who took **mirtazapine** with tramadol, but this may have been due to over-use of the tramadol rather than an interaction.[18] Lethargy, confusion, hypotension, bronchospasm and hypoxia has also been seen following the use of tramadol and **mirtazapine**, which resolved within hours of both drugs being stopped.[19]

Mechanism

The CNS depressant effects of the opioids and the tricyclic antidepressants are expected to be additive. The reasons for the increased morphine levels and analgesic effects that occur with some tricyclics are not understood. However, it has been suggested that the increased analgesia may be due not only to the increased serum levels of morphine, but possibly also to some alteration in the way the morphine affects its receptors. Dextropropoxyphene probably inhibits the liver metabolism of some tricyclic antidepressants[3] by inhibiting the cytochrome P450 isoenzyme CYP2D6, and as a result the serum levels of the tricyclic antidepressants rise. It is suggested that methadone may possibly inhibit the hydroxylation of desipramine, thereby raising its levels.[6]

Importance and management

The majority of the evidence, and general clinical experience, suggests that in most cases, the use of opioids with tricyclic antidepressants is uneventful. Furthermore, limited evidence suggests that concurrent use may be beneficial in pain management. However, the CNS depressant effects of both these classes of drugs should be considered when prescribing the combination, especially as there is some evidence to suggest that the respiratory depressant effects are increased: this may be clinically important in patients with a restricted respiratory capacity.[11]

Certain opioids appear to have a greater propensity to interact. Both **tramadol** and the tricyclics can lower the seizure threshold and cause serotonin syndrome when used alone. Concurrent use may result in additive effects, and therefore particular caution is warranted with this combination, especially in patients with epilepsy or those taking other drugs that affect serotonin. Mirtazapine appears to interact with tramadol in the same way as the tricyclics. Be aware that **dextropropoxyphene** and **methadone** may raise tricyclic levels: however, the general clinical significance of these interactions is uncertain but be alert for any evidence of increased CNS depression and increased tricyclic antidepressant adverse effects (such as dry mouth, constipation, and urinary retention). In this context it is worth noting that one study reported that the incidence of hip fractures in the elderly was found to be increased by a factor of 1.6 in those taking dextropropoxyphene, and further increased to 2.6 when antidepressants, benzodiazepines or antipsychotics were added.[20]

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Opioids + Urinary acidifiers or alkalinisers

Urinary methadone clearance is increased if the urine is made acid (e.g. by giving ammonium chloride) and reduced if it is made alkaline (e.g. by giving sodium bicarbonate). The urinary clearance of dextropropoxyphene (propoxyphene) and pethidine (meperidine) may also be increased by acidification of the urine.

Clinical evidence

(a) Dextropropoxyphene (Propoxyphene)

A study in 6 healthy subjects found that the cumulative 72-hour urinary excretion of unchanged dextropropoxyphene was increased sixfold by acidification of the urine with oral **ammonium chloride** and reduced by 95% by alkalinisation with **sodium bicarbonate**; the half-life of dextropropoxyphene was also shortened by ammonium chloride. The excretion of the active metabolite, norpropoxyphene, was much less dependent on urinary pH. However, the cumulative excretion of dextropropoxyphene

and norpropoxyphene, even into acidic urine, accounted for less than 25% of the dose during 72 hours.[1]

(b) Methadone

A study in patients taking methadone found that the urinary clearance in those with urinary pHs of less than 6 was greater than those with higher urinary pHs.[2] When the urinary pH of one subject was lowered from 6.2 to 5.5, the loss of unchanged methadone in the urine was nearly doubled.[3] A pharmacokinetic study in 5 healthy subjects given a 10-mg intramuscular dose of methadone found that the plasma half-life was 19.5 hours when the urine was made acidic (pH 5.2) with **ammonium chloride**, compared with 42.1 hours when the urine was made alkaline (pH 7.8) with **sodium bicarbonate**. The clearance of methadone fell from 134 mL/minute to 91.9 mL/minute when the urine was changed from acidic to alkaline.[4]

(c) Pethidine (Meperidine)

A study in 6 healthy subjects given intravenous pethidine 21.75 mg found that the 48-hour urinary recovery of pethidine and norpethidine was increased by urinary acidification with **ammonium chloride**, when compared with no urinary pH control. Recovery of pethidine increased from about 7% to 20%, and recovery of norpethidine increased from about 12% to 24%. Urinary alkalinisation reduced the urinary recovery of pethidine and norpethidine to less than 1% and 7%, respectively. These pronounced effects had negligible effects on the blood concentration/time profiles.[5] A study in 10 healthy Chinese subjects given intravenous pethidine 150 micrograms/kg found large variations in the 48-hour urinary recovery of pethidine and norpethidine depending on urinary pH; mean urinary recovery values under acidic conditions were 24% and 33%, respectively, and under alkaline conditions were 0.4% and 4%, respectively. The bioavailability was slightly lower under acidic urinary conditions due to the greater renal clearance of the drug.[6]

Mechanism

Methadone is eliminated from the body both by liver metabolism and excretion of unchanged methadone in the urine. Above pH 6 the urinary excretion is less important, but with urinary pH below 6 the half-life becomes dependent on both excretion (30%) and metabolism (70%).[3,4,7] Methadone is a weak base (pKa 8.4) so that in acidic urine little of the drug is in the un-ionised form and little is reabsorbed by simple passive diffusion. On the other hand, in alkaline solution most of the drug is in the un-ionised form, which is readily reabsorbed by the kidney tubules, and little is lost in the urine.

Acidification of the urine may also increase the renal clearance of unchanged pethidine (meperidine) and norpethidine, probably also due to reduced reabsorption in the renal tubule.[6] Dextropropoxyphene (propoxyphene) appears to be similarly affected, although this appears to be a minor route for dextropropoxyphene elimination.

Importance and management

The effect of urinary pH on the clearance of methadone is an established interaction, but of uncertain clinical importance. Be alert for any evidence of reduced methadone effects in patients whose urine becomes acidic because they are taking large doses of ammonium chloride. Lowering the urinary pH to 5 with ammonium chloride to increase the clearance can also be used to treat toxicity. Theoretically, urinary alkalinisers, such as sodium bicarbonate and **acetazolamide**, may increase the effect of methadone.

Similarly, the urinary clearance of dextropropoxyphene (propoxyphene) and pethidine (norpethidine) appear to be increased to some extent by acidification of the urine, although their bioavailabilities do not appear to be significantly affected and the clinical effect is probably small.

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Opioids; Alfentanil + Reserpine

An isolated report describes ventricular arrhythmias when a patient taking reserpine was given alfentanil during anaesthesia.

Clinical evidence, mechanism, importance and management

A hypertensive woman taking reserpine 250 micrograms daily was given intravenous alfentanil 800 micrograms over 5 minutes, before anaesthesia with thiopental and suxamethonium (succinylcholine). During surgery she was given nine 100-microgram doses of alfentanil and 70% nitrous oxide/oxygen. Bradycardia developed and frequent unifocal premature ventricular contractions occurred throughout the surgery, but they disappeared 3 to 4 hours afterwards. The arrhythmia was attributed to an interaction between reserpine and alfentanil, but just why this should occur is not understood.[1] This is an isolated report and its general relevance is unclear.

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Opioids; Alfentanil + Terbinafine

In a study, terbinafine 250 mg daily for 3 days had no statistically significant effect on alfentanil pharmacokinetics and no adverse effects were reported.[1] Therefore, no alfentanil dose adjustment appears to be necessary on concurrent use.

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Opioids; Codeine + Kaolin

An isolated report describes patients suffering from chronic diarrhoea, who were stabilised taking codeine phosphate, but who experienced a relapse when the codeine was added to *Kaolin Mixture*. An *in vitro* study suggested the bioavailability of codeine may be reduced by adsorption onto kaolin.[1] The general significance of this finding is unknown but bear this report in mind should a patient taking a kaolin-containing product report a reduced effect from codeine.

1. Yu SKS, Oppenheim RC, Stewart NF. Codeine phosphate adsorbed by kaolin. *Aust J Pharm* (1976) 57, 468.

Opioids; Codeine + Somatostatin analogues

Lanreotide and octreotide partially inhibit the metabolism of codeine, which may possibly reduce its analgesic effects.

Clinical evidence, mechanism, importance and management

A study in 6 patients with gastrointestinal carcinoid tumours found that **lanreotide** or **octreotide** 750 micrograms subcutaneously three times daily for 3 days decreased the partial metabolic clearance of codeine by *N*-demethylation (by the cytochrome P450 subfamily CYP3A) by an average of 44% and the *O*-demethylation (by CYP2D6) by 35%. However, the partial clearance by 6-glucuronidation and the total systemic clearance of codeine were not consistently changed. The effects of the somatostatins were thought to be mediated by a suppression of growth hormone secretion. The reduction in *O*-demethylation can reduce the active metabolite of codeine, morphine, which could reduce the analgesic effect of the

drug;[1] however, the clinical relevance of this does not appear to have been studied.

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Opioids; Dextropropoxyphene (Propoxyphene) + Orphenadrine

An alleged adverse interaction between dextropropoxyphene and orphenadrine, which is said to cause mental confusion, anxiety, and tremors, seems to be very rare, if indeed it ever occurs.

Clinical evidence, mechanism, importance and management

The manufacturers of orphenadrine used to state in their package insert that mental confusion, anxiety and tremors have been reported in patients receiving both orphenadrine and dextropropoxyphene. The manufacturers of dextropropoxyphene issued a similar warning. However, in correspondence with both manufacturers, two investigators[1] of this interaction were told that the basis of these statements consisted of 6 anecdotal reports from clinicians to one manufacturer and 7 to the other (some could represent the same cases). Of the 7 cases to one manufacturer, 4 occurred where patients had received twice the recommended dose of orphenadrine. In every case the adverse reactions seen were similar to those reported with either drug alone. A brief study in 5 patients given both drugs to investigate this alleged interaction failed to reveal an adverse interaction.[2] One case has been reported separately.[3]

The documentation is therefore sparse, and no case of interaction has been firmly established. The investigators calculated that the two drugs were probably being used together on 300 000 prescriptions a year, and that these few cases would be less than significant.[1] There seems therefore little reason for avoiding concurrent use.

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3. Renforth W. Orphenadrine and propoxyphene. *N Engl J Med* (1970) 283, 998.

Opioids; Methadone + Disulfiram

No adverse interaction was seen when patients taking methadone were given disulfiram.

Clinical evidence, mechanism, importance and management

Seven opioid addicts, without chronic alcoholism or liver disease, and who were receiving methadone maintenance treatment (45 to 65 mg daily) had an increase in the urinary excretion of the major pyrrolidine metabolite of methadone (an indicator of increased *N*-demethylation) when given disulfiram 500 mg daily for 7 days. However, there was no effect on the degree of opioid intoxication, nor were opioid withdrawal symptoms experienced.[1] No special precautions would therefore seem to be necessary if both drugs are given.

1. Tong TG, Benowitz NL, Kreek MJ. Methadone-disulfiram interaction during methadone maintenance. *J Clin Pharmacol* (1980) 20, 506–13.

Opioids; Methadone + Fusidic acid

Fusidic acid may possibly affect the clearance of levomethadone (*R*-methadone), and a case of opioid withdrawal has been reported. However, another study found no evidence of an interaction.

Clinical evidence, mechanism, importance and management

A patient with AIDS needed an increase in his levomethadone (*R*-methadone) dose from 60 to 80 mg daily within 6 months of starting to take fusidic acid 1.5 g daily.[1] The patient had evidence of liver enzyme induction (using antipyrine as a marker), from which it was concluded that fusidic acid had increased the metabolism and loss of methadone from the body.[1] A subsequent study in 10 patients taking levomethadone confirmed that fusidic acid 500 mg daily for 28 days increased antipyrine clearance; some patients developed clinical signs of underdosage. In contrast, fusidic acid 500 mg daily for 14 days had no effect in another 10 patients taking levomethadone.[2]

Information appears to be limited to these reports. Bear them in mind in the event of any unexpected reduction in efficacy of levomethadone (and probably methadone) in a patient taking long-term fusidic acid.

1. Brockmeyer NH, Mertins L, Goos M. Pharmacokinetic interaction of antimicrobial agents with levomethadon in drug-addicted AIDS patients. *Klin Wochenschr* (1991) 69, 16–18.
2. Reimann G, Barthel B, Rockstroh JK, Spatz D, Brockmeyer NH. Effect of fusidic acid on the hepatic cytochrome P450 enzyme system. *Int J Clin Pharmacol* (1999) 37, 562–6.

Opioids; Methadone + Lofexidine

The concurrent use of methadone and low-dose lofexidine may cause significant hypotension and additional CNS depression.

Clinical evidence, mechanism, importance and management

A small study in 14 subjects taking stable doses of methadone 80 mg daily for 3 weeks found that the addition of lofexidine 400 micrograms daily had significant effects on blood pressure and cognitive function. Systolic and diastolic blood pressures were reduced by an average of 27 mmHg and 15 mmHg, respectively. Two female subjects reported drowsiness, with low blood pressure readings of 88/55 mmHg and 80/48 mmHg, respectively, which required discontinuation of lofexidine. Cognitive tests such as simple reaction times, memory tests and mathematical processing were also affected, although only the effect on mathematical processing reached statistical significance for overall dose effect. Two patients also developed asymptomatic, transient QTc prolongation after a single dose of lofexidine, which resolved when lofexidine was stopped.[1] Further study of the concurrent use of lofexidine and methadone in the management of opioid withdrawal is needed. Patients prescribed this combination should be closely monitored for adverse effects, in particular significant reductions in blood pressure and cognitive changes.

Note that the manufacturers advise avoiding other drugs that may cause QT prolongation as the clinical significance of the small QT changes reported with lofexidine are unclear.[2] Methadone usually only causes QT prolongation in doses of 100 mg or more daily.

1. Schroeder JR, Schmittner J, Bleiberg J, Epstein DH, Krantz MJ, Preston KL. Hemodynamic and cognitive effects of lofexidine and methadone coadministration: a pilot study. *Pharmacotherapy* (2007) 27, 1111–19.
2. BritLofex (Lofexidine hydrochloride). Britannia Pharmaceuticals Ltd. UK Summary of product characteristics, July 2006.

Opioids; Methadone + Quetiapine

Quetiapine modestly increased the levels of methadone but did not appear to result in a clinically significant increase in adverse effects in one study.

Clinical evidence

In a study, 14 patients taking methadone maintenance for at least one month were given an average dose of quetiapine of 138 mg daily for an average of 30 days. The addition of quetiapine increased the mean *R*-methadone plasma concentration to dose ratio by 21%, although there was significant interpatient variability (range 23% decrease to 85% increase). No significant effects on the *S*-methadone enantiomer were seen, and there were no reports of methadone overdose or toxicity in any of the patients. Some slight differences in the metabolism of *R*-methadone were seen when patients were assessed for difference in the expression of the cytochrome P450 isoenzyme CYP2D6 and P-glycoprotein, but these were not statistically significant. However, because some changes were seen, the authors suggest that one or both of these mechanisms may possibly be responsible for the interaction seen.[1]

Evidence appears to be limited to this study, in which only small, clinically unimportant increases in methadone levels were seen. However, as

the dose of quetiapine was relatively low, and the patient numbers were small, further study is needed to establish these findings.

1. Uehlinger C, Crettol S, Chassot P, Brocard M, Koeb L, Brawand-Amey M, Eap CB. Increased (*R*)-methadone plasma concentrations by quetiapine in cytochrome P450s and *ABCB1* genotyped patients. *J Clin Psychopharmacol* (2007) 27, 273–8.

Opioids; Morphine + Miscellaneous

Some limited evidence suggests that antidepressants, antipsychotics, NSAIDs and thiethylperazine may increase the myoclonus caused by high doses of morphine.

Clinical evidence, mechanism, importance and management

In 19 patients with malignant disease taking high doses of morphine (daily doses of 500 mg or more orally or 250 mg or more parenterally), an analysis was made of the relationship between myoclonus and the use of supplemental drugs. In the 12 patients with myoclonus, 8 patients were taking antidepressants (**amitriptyline**, **doxepin**) or antipsychotics (**chlorpromazine**, **haloperidol**) compared with none of 6 patients without myoclonus. In addition, there was a higher use of NSAIDs (**indometacin**, **naproxen**, **piroxicam**, **aspirin**) and an antiemetic (**thiethylperazine**).[1] The reasons are not understood, and the findings of this paper have been questioned.[2]

1. Potter JM, Reid DB, Shaw RJ, Hackett P, Hickman PE. Myoclonus associated with treatment with high doses of morphine: the role of supplemental drugs. *BMJ* (1989) 299, 150–3.
2. Quinn N. Myoclonus associated with high doses of morphine. *BMJ* (1989) 299, 683–4.

Opioids; Pethidine (Meperidine) + Aciclovir

An isolated report describes pethidine toxicity associated with the use of high-dose aciclovir.

Clinical evidence, mechanism, importance and management

A man with Hodgkin's disease was treated with high-dose intravenous aciclovir for localised herpes zoster, and with intramuscular pethidine, oral methadone and levodopa with carbidopa. On the second day he experienced nausea, vomiting and confusion, and later dysarthria, lethargy and ataxia. Despite vigorous treatment he later died. It was concluded that some of the adverse effects were due to pethidine toxicity arising from norpethidine accumulation, associated with renal impairment caused by the aciclovir.[1] The US manufacturer of pethidine says that plasma concentrations of pethidine, and its metabolite norpethidine, may be increased by aciclovir, thus caution should be used if both drugs are given.[2]

1. Johnson R, Douglas J, Corey L, Krasney H. Adverse effects with acyclovir and meperidine. *Ann Intern Med* (1985) 103, 962–3.
2. Demerol (Meperidine hydrochloride). Sanofi-Aventis US LLC. US Prescribing information, October 2008.

Opioids; Tramadol + Pseudoephedrine

An isolated report describes ischaemic colitis when a patient taking tramadol took a decongestant containing pseudoephedrine.

Clinical evidence, mechanism, importance and management

Acute, self-limiting ischaemic colitis occurred in a 46-year-old patient taking regular tramadol, celecoxib and diazepam for back pain, who had self-medicated with an oral decongestant containing pseudoephedrine. He had taken the maximum recommended dose of pseudoephedrine (240 mg daily) for 7 days. A similar, but milder abdominal discomfort had occurred 3 months earlier when he had used the same medication for one week. The colitis was thought to be due to pseudoephedrine, but the concurrent use of tramadol might possibly have contributed by increasing adrenergic vasoconstriction.[1] Note also that celecoxib alone has, rarely, been reported to cause colitis,[2] although the bearing of this effect on this case is unknown. The general significance of this isolated case is unclear.

1. Traino AA, Buckley NA, Bassett ML. Probable ischemic colitis caused by pseudoephedrine with tramadol as a possible contributing factor. *Ann Pharmacother* (2004) 38, 2068–70.
2. Celebrex (Celecoxib). Pharmacia Ltd. UK Summary of product characteristics, June 2009.

Paracetamol (Acetaminophen) + Amantadine

Amantadine had no clinically significant effect on the pharmacokinetics of a single dose of paracetamol in one study.

Clinical evidence, mechanism, importance and management

A single 650-mg dose of paracetamol was given to 5 healthy subjects who had taken amantadine 200 mg daily for 42 days, and also after a single dose of amantadine. Although the apparent volume of distribution of paracetamol was very slightly larger following long-term amantadine use, no other pharmacokinetic parameters were altered. Therefore, from this limited information, it appears that no change in the dose of paracetamol is necessary if these two drugs are given together.[1]

1. Aoki FY, Sitar DS. Effects of chronic amantadine hydrochloride ingestion on its and acetaminophen pharmacokinetics in young adults. *J Clin Pharmacol* (1992) 32, 24–7.

Paracetamol (Acetaminophen) + Antiepileptics

The metabolism of paracetamol is increased in patients taking enzyme-inducing antiepileptics (carbamazepine, phenytoin, phenobarbital, primidone). Isolated reports describe unexpected hepatotoxicity in patients taking phenobarbital, phenytoin, or carbamazepine after taking paracetamol. Valproate does not appear to affect paracetamol metabolism.
Paracetamol modestly reduces the AUC of lamotrigine but does not appear to affect the levels of phenytoin or carbamazepine.

Clinical evidence

(a) Enzyme-inducing antiepileptics

The AUC of oral paracetamol 1 g was found to be 40% lower (and when given intravenously, 31% lower) in 6 patients with epilepsy than in 6 healthy subjects. Five of the patients were taking at least two antiepileptics (combinations of **carbamazepine**, **phenobarbital**, **primidone**, and **phenytoin**), and one was taking **phenytoin** alone.[1] Similar findings (a 38% decrease in AUC) were reported in another study in 13 patients taking enzyme-inducing antiepileptics and 2 patients taking rifampicin (rifampin). In these patients, the amount of glucuronide, but not sulfate, metabolites of paracetamol were higher than the controls, but the amount of the potentially hepatotoxic metabolite (assessed by mercapturic acid and cysteine conjugates) was not raised.[2] Similar changes in paracetamol metabolites were reported in Chinese patients taking **phenytoin** alone. However, in those taking **carbamazepine** alone there was no change in the paracetamol metabolites, when compared with control subjects.[3] Other studies have also reported a greater rate of paracetamol glucuronidation and unchanged paracetamol sulfation in patients taking **phenytoin** alone[4] and patients taking **phenytoin** and/or **carbamazepine**.[5] The latter study found an increase in the clearance of the glutathione-derived conjugates (mercapturic and cysteine conjugates), which may indicate an increased risk of paracetamol hepatotoxicity.[5]

An woman with epilepsy taking **phenobarbital** 100 mg daily developed hepatitis after taking paracetamol 1 g daily for 3 months for headaches. Within 2 weeks of stopping paracetamol her serum transaminase levels had fallen to within the reference range, which implied drug-induced liver damage.[6] Another patient taking **phenobarbital** developed liver and kidney toxicity after taking only 9 g of paracetamol over 48 hours.[7] **Phenobarbital** also appeared to have increased the toxic effects of paracetamol in an adolescent who took an overdose of both drugs, which resulted in fatal hepatic encephalopathy.[8]

Other case reports describe unexpected paracetamol hepatotoxicity in three patients taking **phenytoin**,[9-11] three patients taking **carbamazepine**,[12-14] and a patient taking **phenytoin** and **primidone**.[15] Another analysis of patients with paracetamol-induced fulminant hepatic failure suggested that mortality was higher in the group of patients receiving antiepileptics (including **phenytoin**, **phenobarbital**, **carbamazepine**, **primidone** and **valproate** alone or in combination).[16]

In a study in 10 epileptics, paracetamol 1.5 g daily, taken for 3 days, had no significant effect on the serum levels of **phenytoin** and **carbamazepine**.[17]

(b) Lamotrigine

A study in 8 healthy subjects found that paracetamol 2.7 g daily modestly reduced the AUC of a 300-mg dose of lamotrigine by 20% and reduced its half-life by 15%.[18]

(c) Valproate

Valproate is extensively metabolised in man and a significant proportion of the metabolism occurs via glucuronide conjugation. A study designed to determine whether valproate affected the disposition of drugs that are largely dependent on conjugation found that it did not affect the pharmacokinetics of paracetamol in 3 patients with epilepsy.[19]

Mechanism

The increased paracetamol clearance with carbamazepine, phenobarbital, primidone, and phenytoin is due to the well-recognised enzyme-inducing effects of these antiepileptics, which increase its metabolism (glucuronidation and oxidation) and clearance from the body. It has been suggested that this could result in an increase in the production of the hepatotoxic oxidative metabolite of paracetamol, *N*-acetyl-*p*-benzoquinone imine. If this toxic metabolite then exceeds the normal glutathione binding capacity, liver damage may occur (see 'paracetamol', (p.149)). The production of the toxic metabolite *in vitro* in *animals* and humans seems to depend on several isoenzymes, but the available evidence indicates that the cytochrome P450 isoenzyme CYP2E1 is the primary isoenzyme involved in humans.[20] Therefore, because these enzyme-inducing antiepileptics do not induce this isoenzyme, some consider the few possible cases described merely represent idiosyncratic effects.[20] However, others have suggested that, when several drugs, including phenobarbital or phenytoin are taken, inhibition of glucuronosyltransferases by one of these drugs can lead to decreased glucuronidation, increased systemic exposure, and paracetamol toxicity.[21]

Importance and management

Information is limited. The clinical importance of these interactions is not established and further study is needed. Paracetamol is possibly a less effective analgesic in patients taking enzyme-inducing antiepileptics (carbamazepine, phenobarbital, primidone, and phenytoin) as plasma-paracetamol levels may be reduced. However, levels of the potentially hepatotoxic metabolites may be increased. Some believe that the evidence indicates that the risk of liver damage after paracetamol overdose is increased, and they suggest that patients taking enzyme-inducing antiepileptics should be treated with antidotes at lower plasma levels of paracetamol.[9,11,12,15] In addition, some suggest that therapeutic doses of paracetamol should be used with caution in patients receiving these drugs.[10,11,16] Conversely, others consider that therapeutic doses of paracetamol are not associated with an increased risk of toxicity when used with enzyme-inducers. Moreover, phenytoin, by increasing glucuronidation, may actually have some hepato-protective effects.[20,22] The differences stem from different understandings of which mechanism and isoenzyme(s) are important in the production of the hepatotoxic metabolite of paracetamol[10,20] (see *Mechanism*, above). Note that, there appears to be no evidence regarding **fosphenytoin**, but as it is a prodrug of phenytoin, it would be expected to interact in much the same way.

It is unlikely that the interaction between lamotrigine and paracetamol is of practical importance, but this needs confirmation.

1. Perucca E, Richens A. Paracetamol disposition in normal subjects and in patients treated with antiepileptic drugs. *Br J Clin Pharmacol* (1979) 7, 201–6.
2. Prescott LF, Critchley JAJH, Balali-Mood M, Pentland B. Effects of microsomal enzyme induction on paracetamol metabolism in man. *Br J Clin Pharmacol* (1981) 12, 149–53.
3. Tomlinson B, Young RP, Ng MCY, Anderson PJ, Kay R, Critchley JAJH. Selective liver enzyme induction by carbamazepine and phenytoin in Chinese epileptics. *Eur J Clin Pharmacol* (1996) 50, 411–15.
4. Bock KW, Wiltfang J, Blume R, Ullrich D, Bircher J. Paracetamol as a test drug to determine glucuronide formation in man. Effects of inducers and of smoking. *Eur J Clin Pharmacol* (1987) 31, 677–83.
5. Miners JO, Attwood J, Birkett DJ. Determinants of acetaminophen metabolism: effect of inducers and inhibitors of drug metabolism on acetaminophen's metabolic pathways. *Clin Pharmacol Ther* (1984) 35, 480–6.
6. Pirotte JH. Apparent potentiation by phenobarbital of hepatotoxicity from small doses of acetaminophen. *Ann Intern Med* (1984) 101, 403.
7. Marsepoil T, Mahassani B, Roudiak N, Sebbah JL, Caillard G. Potentialisation de la toxicité hépatique et rénale du paracétamol par le phénobarbital. *JEUR* (1989) 2, 118–20.
8. Wilson JT, Kasantikul V, Harbison R, Martin D. Death in an adolescent following an overdose of acetaminophen and phenobarbital. *Am J Dis Child* (1978) 132, 466–73.
9. McClements BM, Hyland M, Callender ME, Blair TL. Management of paracetamol poisoning complicated by enzyme induction due to alcohol or drugs. *Lancet* (1990) 335, 1526.
10. Brackett CC, Bloch JD. Phenytoin as a possible cause of acetaminophen hepatotoxicity: case report and review of the literature. *Pharmacotherapy* (2000) 20, 229–33.
11. Suchin SM, Wolf DC, Lee Y, Ramaswamy G, Sheiner PA, Facciuto M, Marvin MR, Kim-Schluger L, Lebovics E. Potentiation of acetaminophen hepatotoxicity by phenytoin, leading to liver transplantation. *Dig Dis Sci* (2005) 50, 1836–8.
12. Smith JAE, Hine ID, Beck P, Routledge PA. Paracetamol toxicity: is enzyme-induction important? *Hum Toxicol* (1986) 5, 383–5.
13. Young CR, Mazure CM. Fulminant hepatic failure from acetaminophen in an anorexic patient treated with carbamazepine. *J Clin Psychiatry* (1998) 59, 622.
14. Parikh S, Dillon LC, Scharf SL. Hepatotoxicity possibly due to paracetamol with carbamazepine. Intern Med J. (2004) 34, 441–2.
15. Minton NA, Henry JA, Frankel RJ. Fatal paracetamol poisoning in an epileptic. *Hum Toxicol* (1988) 7, 33–4.
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18. Depot M, Powell JR, Messenheimer JA, Cloutier G, Dalton MJ. Kinetic effects of multiple oral doses of acetaminophen on a single oral dose of lamotrigine. *Clin Pharmacol Ther* (1990) 48, 346–55.
19. Kapetanović IM, Kupferberg HJ, Theodore W, Porter RJ. Lack of effect of valproate on paracetamol (acetaminophen) disposition in epileptic patients. *Br J Clin Pharmacol* (1981) 11, 391–3.
20. Rumack BH. Acetaminophen hepatotoxicity: the first 35 years. *J Toxicol Clin Toxicol* (2002) 40, 3–20.
21. Kostrubsky SE, Sinclair JF, Strom SC, Wood S, Urda E, Stolz DB, Wen YH, Kulkarni S, Mutlib A. Phenobarbital and phenytoin increased acetaminophen hepatotoxicity due to inhibition of UDP-glucuronosyltransferases in cultured human hepatocytes. *Toxicol Sci* (2005) 87, 146–55.
22. Cook MD, Williams SR, Clark RF. Phenytoin-potentiated hepatotoxicity following acetaminophen overdose? A closer look. *Dig Dis Sci* (2007) 52, 208–9.

Paracetamol (Acetaminophen) + Antimuscarinics

Propantheline reduced the rate, but not the extent, of paracetamol absorption. Other antimuscarinic drugs that delay gastric emptying would be expected to interact similarly. However, one study found that diphenhydramine did not appear to affect the absorption of paracetamol, although one case reports that an effect may occur in overdose.

Clinical evidence, mechanism, importance and management

One study in 10 healthy subjects reported that **diphenhydramine** 250 mg, taken with paracetamol 5 g (simulated paracetamol overdose) had little effect on the absorption of paracetamol.[1] However, a case has been described where the **diphenhydramine** component of a paracetamol product (*Tylenol PM*) taken in overdose (paracetamol 7.5 g and **diphenhydramine** 375 mg) delayed the absorption of paracetamol, so that the peak serum-paracetamol level did not occur until 8 hours after ingestion (usual maximum is 2 hours).[2] In this situation there is a danger that early paracetamol levels could be incorrectly assessed. Therefore, when assessing paracetamol overdoses, it is important to consider whether any concurrent drugs could delay the absorption of paracetamol.

In a study in 6 convalescent patients, **propantheline** 30 mg given intravenously delayed the peak serum levels of paracetamol 1.5 g from about one hour to 3 hours. The peak levels of paracetamol were lowered by about one-third, but the total amount absorbed was unchanged.[3] This effect occurs because **propantheline** is an antimuscarinic drug that slows the rate at which the stomach empties, so that the rate of absorption of paracetamol in the gut is reduced. The practical consequence of this is likely to be that rapid pain relief with single doses of paracetamol may be delayed and reduced by antimuscarinics but this needs clinical confirmation. If the paracetamol is being taken in repeated doses over extended periods this seems unlikely to be an important interaction because the total amount absorbed is unchanged. See 'Table 18.2', (p.786), for a list of drugs with known antimuscarinic effects.

1. Halcomb SE, Sivilotti ML, Goklaney A, Mullins ME. Pharmacokinetic effects of diphenhydramine or oxycodone in simulated acetaminophen overdose. *Acad Emerg Med* (2005) 12, 169–72.
2. Tsang WO, Nadroo AM. An unusual case of acetaminophen overdose. *Pediatr Emerg Care* (1999) 15, 344–6.
3. Nimmo J, Heading RC, Tothill P, Prescott LF. Pharmacological modification of gastric emptying: effects of propantheline and metoclopramide on paracetamol absorption. *BMJ* (1973) 1, 587–9.

Paracetamol (Acetaminophen) + Caffeine

Caffeine appears to increase the rate of absorption of paracetamol. Caffeine has been reported to increase or decrease the bioavailability of paracetamol.

Clinical evidence, mechanism, importance and management

In a study in 10 healthy subjects, caffeine citrate 120 mg increased the AUC of a single 500-mg dose of paracetamol by 29%, increased the maximum plasma levels by 15% and decreased the total body clearance by 32%. The decrease in time to maximum level and increase in absorption rate did not reach statistical significance.[1] A randomised, crossover study in 24 healthy subjects compared the effects of a single 1-g dose of paracetamol alone and with caffeine 130 mg. The overall bioavailability was the same between the combination and paracetamol alone, but the combination had a faster rate of absorption shown by the increase in the AUC over the first 20 minutes and early plasma concentrations.[2] There was also an increase in analgesic effects (using a pain model) throughout the observation period from about one to 3.5 hours.[2] In another study, although caffeine slightly increased the rate of absorption of paracetamol, it had no effect on the extent of absorption.[3] However, a further study states that caffeine decreased plasma paracetamol levels and its AUC, and increased paracetamol elimination in healthy men.[4]

Caffeine is commonly included in paracetamol preparations as an analgesic adjuvant, although its potential benefits and the exact mechanism for its action is still unclear. However, note that if paracetamol formulated with caffeine is given there is the potential for additive caffeine adverse effects (such as headache, jitteriness, restlessness, and insomnia). Caffeine intake should be reduced if this occurs.

1. Iqbal N, Ahmad B, Janbaz KH, Gilani A-UH, Niazi SK. The effect of caffeine on the pharmacokinetics of acetaminophen in man. *Biopharm Drug Dispos* (1995) 16, 481–7.
2. Renner B, Clarke G, Grattan T, Beisel A, Mueller C, Werner U, Kobal G, Brune K. Caffeine accelerates absorption and enhances the analgesic effect of acetaminophen. *J Clin Pharmacol* (2007) 47, 715–26.
3. Tukker JJ, Sitsen JMA, Gusdorf CF. Bioavailability of paracetamol after oral administration to healthy volunteers. Influence of caffeine on rate and extent of absorption. *Pharm Weekbl (Sci)* (1986) 8, 239–43.
4. Raińska-Giezek T. Influence of caffeine on toxicity and pharmacokinetics of paracetamol [Article in Polish]. *Ann Acad Med Stetin* (1995) 41, 69–85.

Paracetamol (Acetaminophen) + Chloroquine

Chloroquine modestly increases the levels of paracetamol, whereas chloroquine levels are minimally affected by paracetamol.

Clinical evidence, mechanism, importance and management

In a single-dose study, intravenous chloroquine increased the peak plasma levels and AUC of paracetamol by 47% and 22%, respectively.[1] Another single-dose study, in 8 healthy subjects, found that paracetamol 500 mg increased the maximum plasma level and AUC of chloroquine 600 mg by 17% and 24%, respectively.[2] These changes were thought unlikely to be clinically significant.[1] A further study, in 5 healthy subjects, found that the pharmacokinetics of a single 300-mg dose of chloroquine were not affected by a single 1-g dose of paracetamol.[3] This evidence therefore suggests that no dose adjustments would be expected to be necessary when paracetamol is given with chloroquine.

1. Adjepon-Yamoah KK, Woolhouse NM, Prescott LF. The effect of chloroquine on paracetamol disposition and kinetics. *Br J Clin Pharmacol* (1986) 21, 322–4.
2. Raina RK, Bano G, Amla V, Kapoor V, Gupta KL. The effect of aspirin, paracetamol and analgin on pharmacokinetics of chloroquine. *Indian J Physiol Pharmacol* (1993) 37, 229–31.
3. Essien EE, Ette EI, Brown-Awala EA. Evaluation of the effect of co-administered paracetamol on the gastro-intestinal absorption and disposition of chloroquine. *J Pharm Biomed Anal* (1988) 6, 521–6.

Paracetamol (Acetaminophen) + Colestyramine

The absorption of paracetamol may be reduced if colestyramine is given at the same time, but the reduction in absorption is small if colestyramine is given an hour later.

Clinical evidence

When 4 healthy subjects took colestyramine 12 g and paracetamol 2 g together, the absorption of the paracetamol was reduced by 60% (range 30 to 98%) at 2 hours, but the results were said not to be statistically significant. When the colestyramine was given one hour after the paracetamol, the absorption was reduced by only 16%.[1]

Mechanism

Colestyramine reduces absorption, presumably because it binds with the paracetamol in the gut. Separating the doses minimises mixing in the gut.

Importance and management

Although information is limited, it suggests that colestyramine should not be given within one hour of paracetamol if maximal analgesia is to be achieved. It is normally recommended that other drugs are given one hour before or 4 to 6 hours after colestyramine.

1. Dordoni B, Willson RA, Thompson RPH, Williams R. Reduction of absorption of paracetamol by activated charcoal and cholestyramine: a possible therapeutic measure. *BMJ* (1973) 3, 86–7.

Paracetamol (Acetaminophen) + Disulfiram

Disulfiram had no important effect on the metabolism of paracetamol in one study, but decreased the production of the glutathione (hepatotoxic) metabolites of paracetamol in another.

Clinical evidence, mechanism, importance and management

In a study in 5 healthy subjects without liver disease and 5 others with alcoholic liver cirrhosis, the clearance of a single 500-mg intravenous dose of paracetamol was slightly reduced (by about 10%) and the fractional clearance of paracetamol to its glucuronide, sulfate and glutathione metabolites was not altered by disulfiram 200 mg daily for 5 days.[1] In contrast, another study found that pretreatment of healthy subjects with a single 500-mg dose of disulfiram 10 hours before a single 500-mg oral dose of paracetamol reduced the recovery of glutathione metabolites (a measure of the production of the hepatotoxic metabolite, see 'paracetamol', (p.149)) by 69%.[2]

Disulfiram is an inhibitor of the cytochrome P450 isoenzyme CYP2E1, which is involved in the metabolism of paracetamol. Previously, the authors of the first study[1] had shown that in *rats,* high doses of disulfiram protected against the hepatotoxicity of paracetamol. Therefore, it was suggested that disulfiram might be useful in reducing the risks of paracetamol overdose. However, the authors of the first study concluded that disulfiram, at doses used clinically, is unlikely to have any beneficial (or adverse) effect on paracetamol metabolism.[1] In contrast, the authors of the second study consider that disulfiram may be useful in reducing the formation of the hepatotoxic metabolite of paracetamol in some situations.[2] Further study is needed.

1. Poulson HE, Ranek L, Jørgensen L. The influence of disulfiram on acetaminophen metabolism in man. *Xenobiotica* (1991) 21, 243–9.
2. Manyike PT, Kharasch ED, Kalhorn TF, Slattery JT. Contribution of CYP2E1 and CYP3A to acetaminophen reactive metabolite formation. *Clin Pharmacol Ther* (2000) 67, 275–82.

Paracetamol (Acetaminophen) + Domperidone or Metoclopramide

Metoclopramide increases the rate of absorption of paracetamol and raises its maximum plasma levels. Similarly, domperidone may increase the rate of absorption of paracetamol.

Clinical evidence, mechanism, importance and management

In a study in 5 healthy subjects (slow absorbers of paracetamol), intravenous metoclopramide 10 mg increased the peak plasma levels of a single 1.5-g dose of paracetamol by 64% and increased its rate of absorption (peak levels reached in 48 minutes instead of 120 minutes), but the total amount absorbed remained virtually unaltered.[1] Oral metoclopramide also increases the rate of paracetamol absorption,[2] probably because the rate of gastric emptying is increased. Similarly, the speed of absorption of paracetamol may also be increased by domperidone.[3] This interaction is exploited in *Paramax* (a proprietary oral preparation containing both paracetamol and metoclopramide) to increase the effectiveness and onset of analgesia for the treatment of migraine. This is obviously an advantageous interaction in this situation.

1. Nimmo J, Heading RC, Tothill P, Prescott LF. Pharmacological modification of gastric emptying: effects of propantheline and metoclopramide on paracetamol absorption. *BMJ* (1973) 1, 587–9.

2. Crome P, Kimber GR, Wainscott G, Widdop B. The effect of the simultaneous administration of oral metoclopramide on the absorption of paracetamol in healthy volunteers. *Br J Clin Pharmacol* (1981) 11, 430P–431P.
3. Calpol Infant Suspension (Paracetamol). Pfizer Consumer Healthcare. UK Summary of product characteristics, December 2005.

Paracetamol (Acetaminophen) + Erythromycin

Erythromycin increases the rate of gastric emptying and may increase paracetamol absorption.

Clinical evidence, mechanism, importance and management

In a study in healthy subjects, intravenous erythromycin 0.75 to 3 mg/kg accelerated gastric emptying in a dose-dependent manner and increased paracetamol absorption.[1] However, a study in 7 healthy subjects found that a single 250-mg dose of intravenous erythromycin promoted gastric emptying of solids during acute pain, but had no significant effect on the pharmacokinetics of paracetamol 1 g in 150 mL of water.[2] Another study found that erythromycin 200 mg intravenously, given to promote gastrointestinal motility, did not alter the pharmacokinetics of an oral dose of extended-release paracetamol.[3] A further study in 7 healthy subjects reported that the pharmacokinetics of a single 1-g oral dose of paracetamol were not significantly affected by pretreatment with oral erythromycin 250 mg four times daily for 7 days.[4] It was suggested that the concurrent use of erythromycin and paracetamol is unlikely to result in a clinically significant interaction.[4]

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Paracetamol (Acetaminophen) + Food

Food slows the rate of absorption of paracetamol, but the overall bioavailability is not usually affected. However, in some individuals food may delay and reduce peak paracetamol-plasma levels, and a high-fat meal may slightly reduce the extent of paracetamol absorption. Certain foods, such as cabbage and brussels sprouts, may affect the metabolism of paracetamol.

Clinical evidence, mechanism, importance and management

(a) Absorption of paracetamol

Several studies have demonstrated that food slows the rate of absorption of paracetamol, but the overall bioavailability is not affected[1-5] and some studies have also reported that food has no effect on the analgesic efficacy of paracetamol[6] or its onset.[7] The absorption of paracetamol is affected by the rate of gastric emptying and most foods delay this. Carbohydrate,[2] fat,[2] **guar gum** and **pectin**,[5] protein,[1] and particularly **fibre**,[2,4] may delay the absorption of paracetamol. Furthermore, the rate and extent of absorption, and the peak plasma levels of a single dose of paracetamol have been found to be impaired in vegetarians compared with non-vegetarians.[8] A high-fat diet has also been reported to slightly reduce the extent of absorption.[2]

Although overall bioavailability is not usually affected by food, there may be a delay in reaching therapeutic plasma paracetamol levels, particularly following a single dose of paracetamol. A reduction in the maximum plasma paracetamol level has been reported when it is given after food, when compared with the fasted state;[3,9] in one study the maximum plasma paracetamol level in some individuals did not reach the level reported to be required for effective analgesia.[9] The dosage form will also affect the absorption; many of the studies have used conventional paracetamol tablets, but some formulations (for example paracetamol with sodium bicarbonate)[3,7] are more rapidly absorbed and, although food may reduce the rate of absorption,[3,4] one study found that there was no difference in the onset of analgesia between the fed and fasted states.[7] Another study found that diet composition did not affect the systemic availability of paracetamol in a liquid dosage form, whereas absorption of the tablet form was delayed by a **fibre**-enriched diet.[4]

The clinical importance of these findings is uncertain. It appears that rapid pain relief with single doses of paracetamol tablets may possibly be delayed and reduced by food in some individuals, but liquid or rapidly absorbed preparations are less likely to be affected. If paracetamol is taken in repeated doses, the interaction with food is unlikely to be clinically important as the total amount absorbed is usually unchanged.

(b) Metabolism of paracetamol

In a crossover study in 10 healthy subjects, a 10-day balanced diet including cabbage 100 g and brussels sprouts 150 g at lunch and dinner was found to stimulate the metabolism of paracetamol, at least in part by enhanced glucuronidation. Compared with a control diet (which included instead, lettuce, cucumber, green beans and peas), cabbage and brussels sprouts induced a 16% decrease in the mean AUC of paracetamol, a 17% increase in the mean metabolic clearance rate, and an 8% increase in the mean 24-hour urinary recovery of the glucuronide metabolite.[10] Consumption of watercress caused a decrease in the levels of plasma and urinary oxidative metabolites of paracetamol, but the urinary excretion of paracetamol, or its glucuronide and sulfate were not significantly altered.[11] However, charcoal-broiled beef (which accelerates the oxidative metabolism of some drugs) did not affect paracetamol metabolism.[12] It seems unlikely that these foods would have a significant clinical effect, except perhaps cabbage and brussels sprouts if eaten to excess.

(c) Toxicity of paracetamol

A prospective study found that, of 49 patients with paracetamol hepatotoxicity, all had taken more than the recommended limit of 4 g of paracetamol daily. Paracetamol hepatotoxicity after a dose of 4 to 10 g daily was associated with fasting, and less commonly with alcohol use, and it was suggested that paracetamol hepatotoxicity after an overdose appears to be enhanced by fasting in addition to alcohol ingestion.[13] The metabolism of a lower 2-g dose of paracetamol was not, however, affected by food restriction in obese patients.[14] Fasting may possibly contribute to paracetamol toxicity by shunting paracetamol detoxification from the conjugative to the potentially toxic oxidative pathways.[14] Consider also, the food preservative sodium nitrate, see 'Paracetamol (Acetaminophen) + Sodium nitrate', p.217, and 'Alcohol + Paracetamol (Acetaminophen)', p.80.

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Paracetamol (Acetaminophen) + Garlic

A study in healthy subjects found that garlic did not affect the pharmacokinetics of single-dose paracetamol to a clinically relevant extent.

Clinical evidence

A study in 16 healthy subjects found that the use of an aged garlic extract (approximately equivalent to 6 to 7 cloves of garlic daily) for 3 months had little effect on the metabolism of a single 1-g oral dose of paracetamol.[1]

Mechanism

There was a very slight increase in glucuronidation of a therapeutic dose of paracetamol after the long-term use of garlic in the clinical study, and some evidence that sulfate conjugation was enhanced, but no effect on oxidative metabolism.

Importance and management

The evidence regarding an interaction between paracetamol and garlic is limited, but what is known suggests that no clinically significant interaction would be expected if paracetamol is taken with garlic. *Animal* data suggest that it is possible that some garlic constituents, or substances derived from them, might prove to protect against the hepatotoxicity from higher than therapeutic doses of paracetamol,[2] but this requires further study.

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Paracetamol (Acetaminophen) + H_2-receptor antagonists

Cimetidine, nizatidine, and ranitidine do not appear to alter the pharmacokinetics of paracetamol to a clinically relevant extent.

Clinical evidence

(a) Cimetidine

In a study in 4 healthy subjects, cimetidine (given as a single 200-mg dose or as 1 g daily in divided doses for 7 days) had no statistically significant effect on the pharmacokinetics of a single 750-mg dose of paracetamol.[1] Similarly, in another study in 10 healthy subjects, a single 800-mg dose of cimetidine given one hour before paracetamol 1 g had no effect on the paracetamol half-life or plasma clearance, and no effect on the urinary excretion of its principal metabolites (glucuronide, sulfate, mercapturate).[2] Furthermore, a study in 10 patients found that the pharmacokinetics of a single 1-g dose of paracetamol were not altered by 2 months of treatment with cimetidine 400 mg twice daily. The only difference in urinary metabolites was a modest 37% decrease in paracetamol mercapturate (indicating a reduction in the hepatotoxic metabolite).[2] Other studies have found that cimetidine does not alter the clearance[3-5] or metabolic pathways of paracetamol.[3,5]

In contrast, one study reported that cimetidine 300 mg every 6 hours decreased the fractional clearance of the oxidised metabolites (mercapturate and cysteine conjugates) of paracetamol in healthy subjects.[6] Another study found that a single 400-mg dose of cimetidine given one hour before paracetamol 1 g in fasting subjects delayed the absorption of paracetamol (for instance, there was a 37% reduction in peak salivary level and a 63% increase in time to peak level). This effect was not seen when the two drugs were given simultaneously.[7]

(b) Nizatidine

In a study in 5 healthy subjects, nizatidine 300 mg taken with paracetamol 1 g modestly increased the AUC of paracetamol in the first 3 hours by 25%. Over this time period, there was also a 4% reduction in the formation of paracetamol glucuronide, but this did reach statistical significance at 30 minutes and 45 minutes. Nizatidine 150 mg had a similar, but smaller, effect.[8]

(c) Ranitidine

In a study in 8 healthy subjects, ranitidine 300 mg twice daily for 4 days had no effect on the clearance and half-life of single 1-g intravenous and oral doses of paracetamol, given one hour after the ranitidine dose. In addition, there was no difference in the urinary excretion of the paracetamol metabolites.[9,10] Another study reported similar findings when ranitidine 300 mg was given one hour before paracetamol 1 g. However, when the two drugs were given simultaneously, the AUC_{0-3} of paracetamol was increased by 63%, and there was a 35% decrease in the AUC_{0-3} of paracetamol glucuronide, but no change occurred in sulfate levels.[11] An isolated case describes a man who noted his urine was dark 3 weeks after starting to take ranitidine 150 mg twice daily and paracetamol 1.3 to 2 g daily. He was found to have raised liver enzyme levels (alkaline phosphatase 708 units/L; AST 196 mIU/mL), which returned to normal on discontinuing ranitidine.[12]

Mechanism

Cimetidine may inhibit the oxidative metabolism of paracetamol by cytochrome P450 isoenzymes, resulting in a reduction in the hepatotoxic metabolite, see 'paracetamol', (p.149). It was suggested that cimetidine delayed paracetamol absorption by reducing gastric emptying.[7] Nizatidine may cause a minor inhibition of glucuronyltransferases.[8] Ranitidine may also inhibit paracetamol glucuronyltransferases when given simultaneously, but this was not seen when the drugs were given one hour apart.

Importance and management

Any changes in the pharmacokinetics of paracetamol with these H_2-receptor antagonists appear to be clinically unimportant. Thus, no special precaution would seem to be necessary when paracetamol is used with cimetidine, nizatidine or ranitidine. The effect of cimetidine on the oxidative metabolism of paracetamol has been investigated as a means of reducing paracetamol hepatotoxicity. However, it appears that cimetidine is not effective for this purpose.[13]

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Paracetamol (Acetaminophen) + Herbal medicines; Miscellaneous

Hibiscus extract does not appear to affect the pharmacokinetics of single-dose paracetamol to a clinically relevant extent. Kakkonto extract does not appear to affect the pharmacokinetics of a single dose of paracetamol, although *animal* studies reported an increase in paracetamol levels.

Clinical evidence, mechanism, importance and management

(a) Hibiscus

A study in 6 healthy subjects found that **Zobo** drink (***Hibiscus sabdariffa*** water extract) given 78 minutes before a single 1-g dose of paracetamol did not affect the absorption or AUC of paracetamol, but the total body clearance increased by 12%.[1] This is not expected to be clinically significant.

(b) Kakkonto

A study in 6 healthy subjects found that 5 g of Kakkonto extract, a Chinese herbal medicine containing extracts of *Puerariae*, *Ephedrae*, *Zingiberis*, *Cinnamomi*, *Glycyrrhizae*, *Paeoniae* and *Zizphi* spp. had no effects on the pharmacokinetics of a single 12-mg/kg dose of paracetamol. A further study in 19 healthy subjects found that 1.25 g of Kakkonto had no effect on the pharmacokinetics of paracetamol 150 mg (from a preparation also containing salicylamide, caffeine and promethazine methylene disalicylate). Because in *animal* studies high doses of Kakkonto for 7 days were found to significantly increase serum levels of paracetamol, the authors concluded that further investigations were required to assess safety and efficacy of concurrent use.[2]

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Paracetamol (Acetaminophen) + Hormonal contraceptives or HRT

Paracetamol clearance is increased in women taking oral hormonal contraceptives. Paracetamol also slightly increases the absorption of ethinylestradiol from the gut. HRT does not appear to interact with paracetamol.

Clinical evidence

(a) Effect of contraceptives or HRT on paracetamol

In 7 healthy women taking oral combined hormonal contraceptives (containing **ethinylestradiol**), the plasma clearance of a single 1.5-g dose of paracetamol was 64% higher and the elimination half-life 30% lower, when compared with 7 healthy women not taking oral hormonal contraceptives. The fractional clearance by glucuronidation and of the cysteine conjugate increased, but that of sulfation and the mercapturic acid conjugate were unchanged.[1] Similarly, other studies have found higher paracetamol clearances of 30 to 49%, and corresponding lower paracetamol half-lives, in women taking oral hormonal contraceptives, when compared with control subjects.[2-4]

One study found that the pharmacokinetics of a single 650-mg intravenous dose of paracetamol did not differ between women who had taken **conjugated oestrogens** for at least 3 months and control subjects.[5]

(b) Effect of paracetamol on oral contraceptives

In a study in 6 healthy women, a single 1-g oral dose of paracetamol increased the AUC of **ethinylestradiol** by 22%, and decreased the AUC of ethinylestradiol sulfate by 41%. The plasma levels of **levonorgestrel** were not affected.[6]

Mechanism

The evidence suggests that oral hormonal contraceptives increase the metabolism (both oxidation and glucuronidation) of paracetamol by the liver so that it is cleared from the body more quickly.[3] The increased absorption of the ethinylestradiol probably occurs because paracetamol reduces its metabolism by the gut wall during absorption.[6] It has been suggested that the differences between the effects of oral hormonal contraceptives and conjugated oestrogens on paracetamol may be attributable to the influence of progestogens on glucuronide and sulfate conjugation.[5] This needs confirmation.

Importance and management

The modest pharmacokinetic interaction between the oral hormonal contraceptives and paracetamol appears to be established, but its clinical importance has not been directly studied. The clinical importance of the modest increase in ethinylestradiol absorption is also uncertain, but it is likely to be minor. HRT appears not to interact with paracetamol.

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Paracetamol (Acetaminophen) + 5-HT$_3$-receptor antagonists

Tropisetron and granisetron may block the analgesic effects of paracetamol.

Clinical evidence, mechanism, importance and management

A placebo-controlled, crossover study in 26 healthy subjects found that both intravenous granisetron 3 mg and tropisetron 5 mg blocked the analgesic effect of a single 1-g oral dose of paracetamol given 90 minutes later. The pharmacokinetics of paracetamol were unaffected by the two drugs. The interaction was thought to involve the serotonergic system,[1] see *Mechanism*, under 'Opioids + Antiemetics; Ondansetron', p.178, for further explanation of this effect. It may be prudent to consider the use of other analgesics in patients given these antiemetics.

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Paracetamol (Acetaminophen) + Isoniazid

A number of reports suggest that the toxicity of paracetamol may be increased by isoniazid so that normal analgesic doses (4 g daily) may not be safe in some individuals. Pharmacokinetic studies suggest that isoniazid usually inhibits the metabolism of paracetamol, but that metabolism to toxic metabolites may be induced shortly after stopping isoniazid, or late in the isoniazid dose-interval in fast acetylators of isoniazid.

Clinical evidence

A 21-year-old woman who had been taking isoniazid 300 mg for 6 months developed marked evidence of liver damage (prolonged prothrombin time, elevated ammonia, transaminases, hyperbilirubinaemia) within about 6 hours of taking 3.25 g of paracetamol for abdominal cramping.[1]

A young woman taking isoniazid who had taken up to 11.5 g of paracetamol in a suicide attempt, developed life-threatening hepatic and renal toxicity despite the fact that her serum paracetamol levels were only 15 micromol/L 13 hours after ingestion (toxicity normally associated with levels above 26 micromol/L).[2]

Three other similar cases have been reported in patients taking isoniazid, rifampicin and pyrazinamide who had taken only 2 to 6 g of paracetamol daily.[3] Three other possible cases of this toxic interaction have also been described.[4]

However, in a pharmacokinetic study in 10 healthy subjects (including both slow and fast acetylators of isoniazid), isoniazid 300 mg daily for 7 days modestly decreased the total clearance of a single 500-mg dose of paracetamol by 15%. Moreover, the clearance of paracetamol to oxidative metabolites was *decreased*.[5] Similarly, in a further study in 10 healthy slow acetylators of isoniazid, the formation of paracetamol thioether metabolites and oxidative metabolites was reduced by 63% and 49%, respectively, by isoniazid 300 mg daily. However, one day after stopping isoniazid, the formation of thioether metabolites was *increased* by 56%, and this returned to pretreatment values 3 days after the discontinuation of isoniazid.[6] In yet another study in 10 healthy subjects taking isoniazid as prophylaxis, the formation clearance of paracetamol to *N*-acetyl-*p*-benzoquinone imine (NAPQI) was inhibited by 56% when paracetamol was given simultaneously with the daily isoniazid dose, but when the paracetamol was taken 12 hours after the isoniazid, there was no difference in NAPQI formation clearance, compared with the control phase (one to 2 weeks after isoniazid had been discontinued). However, when the results were analysed by isoniazid acetylator status, it appeared that the NAPQI

formation clearance was *increased* in fast acetylators taking paracetamol 12 hours after the isoniazid dose.[7]

Mechanism

Not established. A possible reason for the altered paracetamol metabolism is that isoniazid induces the cytochrome P450 isoenzyme CYP2E1 by stabilisation.[8] This means that while the isoniazid is still present, the metabolism of substrates such as paracetamol is inhibited. However, when isoniazid levels drop sufficiently (as may be the case late in the dosing interval in fast acetylators), metabolism may be induced resulting in a greater proportion of paracetamol being converted into toxic metabolites than would normally occur.[7]

Importance and management

Information is limited, but it would now seem prudent to consider warning patients taking isoniazid to limit their use of paracetamol because it seems that some individuals risk possible paracetamol-induced liver toxicity, even with normal recommended doses of paracetamol. Pharmacokinetic studies suggest that it is possible that the risk is greatest shortly after stopping isoniazid. The risk may also be higher if paracetamol is taken late in the isoniazid dosing interval, particularly in fast acetylators of isoniazid. More study is needed to clarify the situation.

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Paracetamol (Acetaminophen) + Opioids

Diamorphine, morphine, oxycodone, pentazocine and pethidine (meperidine) delay gastric emptying so that the rate of absorption of oral paracetamol is reduced. No pharmacokinetic interaction occurs between codeine and paracetamol, but the combination may not always result in increased analgesia.

Clinical evidence

(a) Codeine

A study in 6 healthy subjects found that paracetamol 1 g every 8 hours for 7 doses had no effect on the pharmacokinetics of a single 30-mg oral dose of codeine, or its metabolites.[1] Similarly in other studies, codeine had no effect on the pharmacokinetics of paracetamol.[2,3] Paracetamol and codeine are often given together because the combination is more effective than either drug given alone. However, note that not all studies have found this. For example, in one clinical study of surgical removal of impacted third molar teeth, there was no difference in analgesic efficacy between patients given paracetamol alone (800 mg given 3, 6, and 9 hours after surgery, then 400 mg four times daily for 2 days) and those given the same dose of paracetamol with the addition of codeine phosphate 30 mg. Moreover, patients given codeine experienced more adverse effects (nausea, dizziness, drowsiness).[4]

(b) Diamorphine, Pethidine (Meperidine) and Pentazocine

A study in 8 healthy subjects reported that the absorption of a single 20-mg/kg oral dose of paracetamol solution given 30 minutes after an intramuscular injection of either pethidine 150 mg or diamorphine 10 mg was markedly delayed and reduced. Peak plasma paracetamol levels were reduced by 31% and 74%, respectively, and delayed from 22 minutes, to 114 minutes and 142 minutes, respectively.[5] This interaction was also observed, by the same study group, in women in labour who had been given paracetamol tablets after receiving pethidine, diamorphine or pentazocine.[6]

(c) Fentanyl

An *in vitro* study found that paracetamol inhibited the oxidation of fentanyl to norfentanyl, but the concentrations of paracetamol used were greater than those found therapeutically. A potential interaction was thought possible because fentanyl is metabolised by the cytochrome P450 isoenzyme CYP3A4 and paracetamol is also partially metabolised by the CYP3A family.[7]

(d) Morphine

A study in healthy subjects, who remained in the supine position, investigated the effect of morphine syrup (4 doses of 10 mg given every 4 hours) on the absorption of paracetamol. The time to the maximum plasma paracetamol level, for conventional tablets, was increased from 51 minutes to 160 minutes by morphine, whereas the time to the maximum plasma paracetamol level for dispersible tablets was only increased from 14 minutes to 15 minutes.[8]

(e) Oxycodone

A crossover study in 10 healthy subjects investigated the effect of oxycodone 500 micrograms/kg on the absorption kinetics of a simulated paracetamol overdose (5 g). The maximum serum paracetamol level was reduced by 40%, the time to maximum level was increased by 68%, and the $AUC_{0–8}$ was 27% lower, when compared with paracetamol alone.[9]

Mechanism, importance and management

The underlying mechanism of these interactions is that the opioid analgesics delay gastric emptying so that the rate of absorption of paracetamol is reduced, but the total amount absorbed is not affected. These were largely investigational studies in healthy subjects, where paracetamol was used as a measure of gastric emptying, and any clinical relevance has not been determined. Reducing the rate of paracetamol absorption would be expected to reduce the onset of analgesic effect, but this is probably not relevant in patients who are receiving regular doses of paracetamol. However, if speed of onset of action is important, one study[8] suggested that the use of dispersible paracetamol might help to reduce the delay in reaching therapeutic plasma levels.

In paracetamol overdose, it has been suggested that when an opioid is present there may be a potential role for the use of activated charcoal beyond one-hour post-ingestion, because of the delay in the absorption of paracetamol.[9] When assessing treatment options it is also worth noting that maximum plasma levels may be delayed.

1. Somogyi A, Bochner F, Chen ZR. Lack of effect of paracetamol on the pharmacokinetics and metabolism of codeine in man. *Eur J Clin Pharmacol* (1991) 41, 379–82.
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3. Sonne J, Poulsen HE, Loft S, Døssing M, Vollmer-Larsen A, Simonsen K, Thyssen H, Lundstrøm K. Therapeutic doses of codeine have no effect on acetaminophen clearance or metabolism. *Eur J Clin Pharmacol* (1988) 35, 109–11.
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5. Nimmo WS, Heading RC, Wilson J, Tothill P, Prescott LF. Inhibition of gastric emptying and drug absorption by narcotic analgesics. *Br J Clin Pharmacol* (1975) 2, 509–13.
6. Nimmo WS, Wilson J, Prescott LF. Narcotic analgesics and delayed gastric emptying during labour. *Lancet* (1975) i, 890–3.
7. Feierman DE. The effect of paracetamol (acetaminophen) on fentanyl metabolism *in vitro*. *Acta Anaesthesiol Scand* (2000) 44, 560–3.
8. Kennedy JM, Tyers NM, Davey AK. The influence of morphine on the absorption of paracetamol from various formulations in subjects in the supine position, as assessed by TDx measurement of salivary paracetamol concentrations. *J Pharm Pharmacol* (2003) 55, 1345–50.
9. Halcomb SE, Sivilotti ML, Goklaney A, Mullins ME. Pharmacokinetic effects of diphenhydramine or oxycodone in simulated acetaminophen overdose. *Acad Emerg Med* (2005) 12, 169–72.

Paracetamol (Acetaminophen) + Probenecid

Probenecid reduces the clearance of paracetamol.

Clinical evidence, mechanism, importance and management

A metabolic study in 10 healthy subjects found that the clearance of paracetamol 1.5 g was almost halved (from 6.23 to 3.42 mL/minute per kg) when it was taken one hour after a 1-g dose of probenecid. The amount of unchanged paracetamol in the urine stayed the same, but the glucuronide metabolite fell sharply.[1] Another study in 11 subjects also found that probenecid 500 mg every 6 hours almost halved (from 329 to

178 mL/minute) the clearance of a 650-mg intravenous dose of paracetamol. The urinary excretion of the glucuronide metabolite was decreased by 68% and the excretion of the sulfate metabolite was increased by 49%.[2] These studies suggest that probenecid inhibits paracetamol glucuronidation, possibly by inhibiting glucuronyltransferases. The practical consequences of this interaction are uncertain but there seem to be no adverse reports.

1. Kamali F. The effect of probenecid on paracetamol metabolism and pharmacokinetics. *Eur J Clin Pharmacol* (1993) 45, 551–3.
2. Abernethy DR, Greenblatt DJ, Ameer B, Shader RI. Probenecid impairment of acetaminophen and lorazepam clearance: direct inhibition of ether glucuronide formation. *J Pharmacol Exp Ther* (1985) 234, 345–9.

Paracetamol (Acetaminophen) + Propranolol

Propranolol may slightly increase the bioavailability of paracetamol.

Clinical evidence, mechanism, importance and management

In a study in 10 healthy subjects, propranolol 80 mg twice daily for 4 days increased the half-life of a single 1.5-g dose of paracetamol by 25% and lowered its clearance by 14%. The partial clearance of paracetamol to its cysteine and mercapturate derivatives was decreased by 16% and 32%, respectively, and the clearance to the glucuronide conjugate was decreased by 27%, but the sulfate was not significantly affected.[1] Similarly, an earlier study found that propranolol 40 mg four times daily for one week increased the maximum plasma level of a single 1.5-g dose of paracetamol and reduced the time to peak plasma level. However, the increased rate of absorption of paracetamol was not thought to be clinically important.[2] In contrast, a study in 6 subjects found that a relatively small dose of propranolol (80 mg daily for 6 days) did not affect the pharmacokinetics of paracetamol.[3] Another study found that long-term propranolol use in patients with chronic liver disease did not influence the clearance of total or unconjugated paracetamol.[4] The changes described here appear to be small, and are therefore unlikely to be clinically significant.

1. Baraka OZ, Truman CA, Ford JM, Roberts CJC. The effect of propranolol on paracetamol metabolism in man. *Br J Clin Pharmacol* (1990) 29, 261–4.
2. Clark RA, Holdsworth CD, Rees MR, Howlett PJ. The effect on paracetamol absorption of stimulation and blockade of β-adrenoceptors. *Br J Clin Pharmacol* (1980) 10, 555–9.
3. Sanchez-Martinez V, Tucker GT, Jackson PR, Lennard MS, Bax NDS, Woods HF. Lack of effect of propranolol on the kinetics of paracetamol in man. *Br J Clin Pharmacol* (1985) 20, 548P.
4. Hayes PC, Bouchier IAD. Effect of acute and chronic propranolol administration on antipyrine and paracetamol clearance in patients with chronic liver disease. *Am J Gastroenterol* (1989) 84, 723–6.

Paracetamol (Acetaminophen) + Proton pump inhibitors

Lansoprazole modestly increased the rate, but not the extent, of absorption of a paracetamol solution. Omeprazole does not appear to have any effect on the metabolism of phenacetin (which is metabolised to paracetamol) or paracetamol.

Clinical evidence

(a) Lansoprazole

In a study in 6 healthy subjects, lansoprazole 30 mg daily for 3 days increased the peak level of paracetamol (given as a single 1-g dose in solution) by 43%, and decreased the time to peak paracetamol levels by half (from about 35 to 17.5 minutes). However, lansoprazole had no effect on the AUC and elimination half-life of paracetamol.[1]

(b) Omeprazole

In 10 healthy subjects omeprazole 20 mg daily for 8 days had no effect on the pharmacokinetics of **phenacetin**, or paracetamol derived from **phenacetin**, except that the peak plasma level of **phenacetin** was higher. There was no change in the metabolism (oxidative and conjugative) of **phenacetin** or derived paracetamol.[2] In another study in 10 subjects, omeprazole 40 mg daily for 7 days had no effect on the formation of thioether metabolites of paracetamol.[3]

Mechanism

Lansoprazole may increase the absorption of paracetamol by indirectly increasing the rate of gastric emptying.[1] Phenacetin is metabolised to paracetamol by the cytochrome P450 isoenzyme CYP1A2, and it has been suggested that omeprazole can induce CYP1A2, and possibly increase the formation of hepatotoxic metabolites of paracetamol. However, the findings here suggest that omeprazole has no important effect on CYP1A2, or on phenacetin or paracetamol metabolism.

Importance and management

The findings from these studies suggest that neither lansoprazole nor omeprazole cause any clinically important changes in the pharmacokinetics of paracetamol. No paracetamol dose adjustment appears to be needed on the concurrent use of either omeprazole or lansoprazole. Other proton pump inhibitors would also not be expected to interact, but this needs confirmation.

1. Sanaka M, Kuyama Y, Mineshita S, Qi J, Hanada Y, Enatsu I, Tanaka H, Makino H, Yamanaka M. Pharmacokinetic interaction between acetaminophen and lansoprazole. *J Clin Gastroenterol* (1999) 29, 56–8.
2. Xiaodong S, Gatti G, Bartoli A, Cipolla G, Crema F, Perucca E. Omeprazole does not enhance the metabolism of phenacetin, a marker of CYP1A2 activity, in healthy volunteers. *Ther Drug Monit* (1994) 16, 248–50.
3. Sarich T, Kalhorn T, Magee S, Al-Sayegh F, Adams S, Slattery J, Goldstein J, Nelson S, Wright J. The effect of omeprazole pretreatment on acetaminophen metabolism in rapid and slow metabolizers of *S*-mephenytoin. *Clin Pharmacol Ther* (1997) 62, 21–8.

Paracetamol (Acetaminophen) + Rifampicin (Rifampin)

Rifampicin increases the metabolism of paracetamol. An isolated report describes liver failure, which may have been due to an interaction between paracetamol and rifampicin.

Clinical evidence, mechanism, importance and management

In 10 patients taking rifampicin 600 mg daily, the metabolite to paracetamol ratio for glucuronides was twice as high than in 14 healthy control subjects. In contrast the ratio for sulfates did not differ between the two groups.[1] In a crossover study in healthy subjects, rifampicin 600 mg daily for one week, given before paracetamol 500 mg, had no effect on the formation of *N*-acetyl-*p*-benzoquinone imine (NAPQI) or the recovery of thiol metabolites formed by conjugation of NAPQI with glutathione.[2] The clinical importance of these studies awaits further clarification, but they suggest that rifampicin may reduce the efficacy of paracetamol. These studies suggest that rifampicin induces the glucuronidation of paracetamol, but that it does not increase the formation of hepatotoxic metabolites of 'paracetamol', (p.149). However, a 32-year-old woman, who had taken paracetamol 2 to 4 g daily for several weeks, and who had not responded to doxycycline or clarithromycin for suspected cat scratch fever, became confused and agitated 2 days after starting to take rifampicin 600 mg twice daily. Her INR increased from 1.1 to 5.2 and her liver enzymes became raised. Rifampicin and paracetamol were stopped, and she was treated with vitamin K and acetylcysteine, and liver function returned to normal. Paracetamol hepatotoxicity, in doses not normally associated with such effects, occurred only after the addition of rifampicin. It was suggested that rifampicin, which alone may cause hepatitis, had in this case induced the metabolism of paracetamol to hepatotoxic metabolites.[3] The general significance of this is unknown.

1. Bock KW, Wiltfang J, Blume R, Ullrich D, Bircher J. Paracetamol as a test drug to determine glucuronide formation in man. Effects of inducers and of smoking. *Eur J Clin Pharmacol* (1987) 31, 677–83.
2. Manyike PT, Kharasch ED, Kalhorn TF, Slattery JT. Contribution of CYP2E1 and CYP3A to acetaminophen reactive metabolite formation. *Clin Pharmacol Ther* (2000) 67, 275–82.
3. Stephenson I, Qualie M, Wiselka MJ. Hepatic failure and encephalopathy attributed to an interaction between acetaminophen and rifampicin. *Am J Gastroenterol* (2001) 96, 1310–1.

Paracetamol (Acetaminophen) + Sodium nitrate

An isolated report describes severe methaemoglobinaemia in a patient who had taken paracetamol after a meal consisting of 'yuke' (raw beef preserved with sodium nitrate). Both paracetamol and sodium nitrate may cause methaemoglobinaemia, so an

interaction resulting in additive effects may have occurred, but a genetic cause was also considered to be a possibility.[1] This is an isolated report and its general relevance is unknown.

1. Kobayashi T, Kawabata M, Tanaka S, Maehara M, Mishima A, Murase T. Methemoglobinemia induced by combined use of sodium nitrate and acetoaminophen. *Intern Med* (2000) 39, 860.

Paracetamol (Acetaminophen) + Sucralfate

In 6 healthy subjects, the bioavailability of paracetamol 1 g (using salivary paracetamol levels over 4 hours as a measure of paracetamol absorption) was found to be unchanged by sucralfate 1 g.[1] This suggests that paracetamol absorption is unlikely to be affected by sucralfate. No special precautions appear to be necessary if both drugs are given.

1. Kamali F, Fry JR, Smart HL, Bell GD. A double-blind placebo-controlled study to examine effects of sucralfate on paracetamol absorption. *Br J Clin Pharmacol* (1985) 19, 113–14.

Paracetamol (Acetaminophen) + Sulfinpyrazone

Sulfinpyrazone modestly increases the clearance of paracetamol.

Clinical evidence, mechanism, importance and management

In a study in 12 healthy subjects, sulfinpyrazone 200 mg given every 6 hours for one week increased the clearance of a single 1-g dose of paracetamol by 23%. There was a 26% increase in metabolic clearance of the glucuronide conjugate of paracetamol, and a 43% increase in the glutathione-derived conjugates (indicating an increased production of the hepatotoxic metabolite), but no change in sulfation.[1] It has therefore been suggested that, in patients taking sulfinpyrazone, the risk of liver damage may be increased after paracetamol overdose and perhaps during prolonged consumption,[1] but there seem to be no adverse reports. The clinical importance of these findings awaits further study.

1. Miners JO, Attwood J, Birkett DJ. Determinants of acetaminophen metabolism: effect of inducers and inhibitors of drug metabolism on acetaminophen's metabolic pathways. *Clin Pharmacol Ther* (1984) 35, 480–6.

Paracetamol (Acetaminophen) + Tobacco

Heavy, but not moderate, smoking may increase the metabolism of paracetamol. The clearance of phenacetin (which is metabolised to paracetamol) is also increased in smokers. There is some evidence that smokers are at risk of a poorer outcome after paracetamol overdose.

Clinical evidence, mechanism, importance and management

There was no difference in the clearance of a single 1-g dose of paracetamol or its metabolites in 6 otherwise healthy smokers (more than 15 cigarettes per day) and 6 healthy non-smokers in one study.[1] Similarly, another study found no difference in the pharmacokinetics of a single 650-mg intravenous dose of paracetamol in 14 otherwise healthy smokers (range 8 to 35 cigarettes per day) and 15 non-smokers.[2] In contrast, in another study, the glucuronide metabolite to paracetamol ratio was 83% higher in 9 heavy smokers (about 40 cigarettes daily), suggesting increased paracetamol metabolism, than in 14 healthy non-smokers. However, it was not higher in moderate smokers (about 10 cigarettes daily).[3] A retrospective study of patients treated for paracetamol poisoning found that there was a much higher proportion of smokers than in the general population (70% versus 31%). Moreover, smoking was independently associated with an increased risk of hepatic encephalopathy (odds ratio 2.68) and death (odds ratio 3.64) following paracetamol overdose.[4]

A study in 36 healthy Chinese subjects given a single 900-mg dose of **phenacetin** (which is metabolised to paracetamol) found that subjects who smoked cigarettes (7 to 40 daily; mean 20) had a 2.5-fold higher phenacetin apparent oral clearance, when compared with non-smokers. Paracetamol plasma levels were also moderately lower in the smokers.[5]

Cigarette smoke appears to induce the metabolism of **phenacetin** by the cytochrome P450 isoenzyme CYP1A2, and also appears to increase the metabolism of paracetamol either by stimulating a minor pathway involving CYP1A2 oxidation or by stimulating the conversion of phenacetin to compounds other than paracetamol.[5]

No interaction is established, but the above studies suggest that heavy smoking may increase the metabolism of paracetamol. The retrospective study also suggests that smoking is associated with a poorer outcome after paracetamol overdose. Further study is needed.

1. Miners JO, Attwood J, Birkett DJ. Determinants of acetaminophen metabolism: effect of inducers and inhibitors of drug metabolism on acetaminophen's metabolic pathways. *Clin Pharmacol Ther* (1984) 35, 480–6.
2. Scavone JM, Greenblatt DJ, LeDuc BW, Blyden GT, Luna BG, Harmatz JS. Differential effect of cigarette smoking on antipyrine oxidation versus acetaminophen conjugation. *Pharmacology* (1990) 40, 77–84.
3. Bock KW, Wiltfang J, Blume R, Ullrich D, Bircher J. Paracetamol as a test drug to determine glucuronide formation in man. Effects of inducers and of smoking. *Eur J Clin Pharmacol* (1987) 31, 677–83.
4. Schmidt LE, Dalhoff K. The impact of current tobacco use on the outcome of paracetamol poisoning. *Aliment Pharmacol Ther* (2003) 18, 979–85.
5. Dong SX , Ping ZZ, Xiao WZ, Shu CC, Bartoli A, Gatti G, D'Urso S, Perucca E. Effect of active and passive cigarette smoking on CYP1A2-mediated phenacetin disposition in Chinese subjects. *Ther Drug Monit* (1998) 20, 371–5.

Ziconotide + Miscellaneous

The use of ziconotide with intrathecal morphine increases the risk of neuropsychiatric adverse effects. Additive CNS depression may occur if ziconotide is given with other CNS depressants: ziconotide may increase the risk of somnolence in patients also taking baclofen, clonidine, propofol or bupivacaine. No interaction appears to occur between ziconotide and ACE inhibitors or protease inhibitors.

Clinical evidence, mechanism, importance and management

(a) Opioids

Intrathecal ziconotide appears to increase the incidence of neuropsychiatric adverse effects (confusion, paranoia, hallucinations, abnormal gait) as well as vomiting, anorexia and peripheral oedema in patients receiving *intrathecal* **morphine**.[1] Intrathecal **morphine** given to patients established on ziconotide may be better tolerated, although pruritus has been reported.[1] If an opioid and ziconotide are needed, patients should be closely monitored for adverse effects. If adverse effects occur, consideration should be given to discontinuing one or both drugs, or decreasing their doses. The US manufacturer advises against the use of *intrathecal* opiates with ziconotide as this has not been fully studied in placebo-controlled clinical studies.[2]

The UK manufacturer notes that there is no data on concurrent use of partial opioid agonists such as **buprenorphine** with ziconotide.[1]

(b) CNS depressants

The use of ziconotide may increase the risk of CNS adverse effects, including confusion and dizziness, if it is given with other CNS depressant drugs.[2] Note that respiratory depression does not appear to occur with ziconotide.[1,2] As ziconotide may cause loss of consciousness or stupor, the manufacturers recommend that, should this occur, the concurrent use of other CNS depressants should be reviewed and ziconotide discontinued until the patient regains full consciousness.[1,2] The US manufacturer notes that patients also taking antiepileptics, sedatives or diuretics are at higher risk of this loss of consciousness occurring.[2] Note that increased somnolence has been seen in patients given ziconotide with systemic **baclofen**, **clonidine**, **propofol** or **bupivacaine**.[1] See also *Opioids*, above.

(c) Miscellaneous

The manufacturers of ziconotide note that, based on limited data, ACE inhibitors (**benazepril**, **lisinopril** and **moexipril** specifically named) and protease inhibitors (**ritonavir**, **saquinavir** and **indinavir** specifically named) are not expected to affect plasma levels of ziconotide.[1]

Note that ziconotide is given intrathecally, and is therefore contraindicated with intrathecal chemotherapy. The UK manufacturers also note that only a small number of patients have received systemic chemotherapy and intrathecal ziconotide, and therefore caution is advised on concurrent use.[1]

1. Prialt (Ziconotide acetate). Eisai Ltd. UK Summary of product characteristics, March 2009.
2. Prialt (Ziconotide). Elan Pharmaceuticals Inc. US Prescribing information, October 2008.

7

Anorectics and Stimulants

This section covers the drugs used in the management of obesity (such as orlistat, rimonabant and sibutramine) as well as the older drugs, such as the amfetamines, which are now no longer widely indicated for this condition and are now more generally considered as drugs of abuse. However, it should not be forgotten that the amfetamines (largely dexamfetamine) still have a limited therapeutic role in the management of narcolepsy and refractory attention deficit hyperactivity disorder (ADHD).

Ecstasy (MDMA, methylenedioxymethamfetamine), a drug of abuse that is structurally related to amfetamine, is also included in this section. The amfetamines are sympathomimetics, a diverse group, which have a number of interactions not necessarily shared by all members of the class. The mechanism of action and classification of sympathomimetics is discussed in 'Cardiovascular drugs, miscellaneous', (p.1047). Other stimulant drugs such as atomoxetine or methylphenidate (another sympathomimetic), that have a role in ADHD, and modafinil, used in narcolepsy, are also discussed in this section.

Amfetamines + Caffeine

A man who took a mixture of amfetamines and caffeine intranasally had an ischaemic stroke, and a girl receiving dexamfetamine experienced acute onset myoclonus after taking a caffeine-containing preparation.

Clinical evidence, mechanism, importance and management

A 37-year-old man experienced an ischaemic stroke after the nasal use of amfetamines and caffeine. Three hours after he took the mixture, his blood pressure was 230/130 mmHg and pulse rate 120 bpm, but there was no neurological deficit. However, 6 hours later he had developed motor aphasia, right hemiplegia and right facial nerve palsy, and his blood pressure was 200/100 mmHg. It was thought that the nasal use of a mixture of amfetamines and caffeine caused the stroke, probably through the rapid rise in blood pressure combined with cerebral vasoconstriction.[1]

A 16-year-old girl with attention deficit hyperactivity disorder (ADHD) well controlled with **dexamfetamine** 10 mg daily, experienced a severe headache and then, on the following day, palpitations and acute onset myoclonus, which ceased spontaneously within 4 to 5 hours. The patient then revealed that she had taken *Excedrin* (paracetamol (acetaminophen), aspirin and caffeine) for headaches, both the day before and on the day of the abnormal movements; the last dose had been taken about 30 minutes before the jerking movements began. The combination of the CNS stimulant caffeine and **dexamfetamine** was thought to have caused the CNS toxicity.[2]

These appear to be the only documented cases of an interaction and so their clinical relevance is unclear. However, given the severity of the outcome, it may be prudent to consider potential caffeine intake in anyone receiving amfetamines.

1. Lambrecht GLY, Malbrain MLNG, Chew SL, Baeck E, Verbraeken H. Intranasal caffeine and amphetamine causing stroke. *Acta Neurol Belg* (1993) 93, 146–9.
2. Jafri SH, Cook JW, Reed RR, Beebe DK. Acute onset of bilateral myoclonus in a 16-year-old female. *J Miss State Med Assoc* (2004) 45, 169–72.

Amfetamines + Calcium-channel blockers

Diltiazem attenuated the increase in blood pressure caused by dexamfetamine, and isradipine had similar effects with metamfetamine. The subjective changes or changes in reaction time associated with dexamfetamine were not affected by diltiazem. However, isradipine, both alone and with metamfetamine, tended to modestly decrease cognitive performance.

Clinical evidence, mechanism, importance and management

In a placebo-controlled study in 10 healthy subjects, pretreatment with a single 60-mg dose of **diltiazem** significantly attenuated the increase in diastolic blood pressure caused by a single oral 20-mg dose of **dexamfetamine**. The increase in systolic blood pressure was also attenuated, but the effect of diltiazem wore off over the 4-hour study period. The subjective changes or changes in reaction time associated with **dexamfetamine** were not affected by **diltiazem**.[1] A placebo-controlled study in 19 **metamfetamine**-dependent subjects found that pretreatment with **isradipine** reduced intravenous metamfetamine-associated increases in all measures of blood pressure except pulse pressure, but tended to enhance the effect of metamfetamine on heart rate.[2] Furthermore, another study found that **isradipine** tended to modestly decrease cognitive performance both with and without **metamfetamine**.[3]

The clinical relevance of these effects is unclear; the interaction between dexamfetamine and diltiazem may be beneficial, but the effects of isradipine on metamfetamine may be detrimental in some subjects. More study is needed.

1. Fabian JE, Silverstone PH. Diltiazem, a calcium antagonist, partly attenuates the effects of dextroamphetamine in healthy volunteers. *Int Clin Psychopharmacol* (1997) 12, 113–20.
2. Johnson BA, Wells LT, Roache JD, Wallace C, Ait-Daoud N, Wang Y. Isradipine decreases the hemodynamic response of cocaine and methamphetamine: results from two human laboratory studies. *Am J Hypertens* (2005) 18, 813–22.
3. Johnson BA, Roache JD, Ait-Daoud N, Wallace C, Wells LT, Wang Y. Effects of isradipine on methamphetamine-induced changes in attentional and perceptual-motor skills of cognition. *Psychopharmacology (Berl)* (2005) 178, 296–302.

Amfetamines + Cannabis

Cannabis opposes the stimulant and hyperthermic effects of ecstasy, but long-term users of both drugs may potentially experience cumulative CNS impairment. A report describes severe arterial ischaemia in a patient who regularly abused amfetamines and cannabis.

Clinical evidence

A 22-year-old woman who smoked cigarettes and had regularly abused amfetamine derivatives such as **metamfetamine** ("crystal speed") and **ecstasy** (MDMA, methylenedioxymethamfetamine) together with cannabis, experienced severe arterial ischaemia leading to claudication and ulceration of the feet.[1]

A study in 18 cannabis users, 11 cannabis and **ecstasy** users, and 31 subjects who had used neither drug, found that cannabis and cannabis/ecstasy users performed similarly in most CNS tests. However, both groups combined performed less well than non-drug users on tests of memory, learning, word fluency, speed of processing and manual dexterity. Furthermore, the deficits were more closely related to cannabis than **ecstasy** usage.[2] Similar results were reported in another study.[3] A further self-rated study found that moderate cannabis use might help to improve or mask **ecstasy**-induced aggression and somatic symptoms (e.g. headache, chronic tiredness). However, heavy cannabis and **ecstasy** use appeared to be associated with problems such as paranoia or cognitive disorders, which might emerge after a period of abstinence from both drugs.[4]

Mechanism

It was suggested that the amfetamine derivatives might have induced vasculitis of the arteries with cannabis possibly adding to the effect on the microcirculation.[1] Both drugs may cause additive CNS impairment.

Importance and management

The majority of recreational **ecstasy** users also take cannabis and this combined-drug usage appears to reflect the opposing effects of the two drugs: ecstasy is a powerful stimulant whereas cannabis is a relaxant, ecstasy is hyperthermic whereas cannabis is hypothermic and ecstasy increases oxidative stress whereas cannabinoids are antioxidant. Therefore cannabis may modulate the acute reactions to **ecstasy**.[5] However, the chronic effects of each drug may be functionally damaging, so that using both drugs may be associated with a variety of psychological problems.[5,6] Furthermore, regular cannabis use seems to be necessary for the development and maintenance of symptoms of mental illness in ecstasy users.[6]

1. Leithäuser B, Langheinrich AC, Rau WS, Tillmanns H, Matthias FR. A 22-year-old woman with lower limb arteriopathy. Buerger's disease, or methamphetamine- or cannabis-induced arteritis? *Heart Vessels* (2005) 20, 39–43.
2. Croft RJ, Mackay AJ, Mills ATD, Gruzelier JGH. The relative contributions of ecstasy and cannabis to cognitive impairment. *Psychopharmacology (Berl)* (2001) 153, 373–9.
3. Fisk JE, Montgomery C, Wareing M, Murphy PN. The effects of concurrent cannabis use among ecstasy users: neuroprotective or neurotoxic? *Hum Psychopharmacol* (2006) 21, 355–66.
4. Milani RM, Parrott AC, Schifano F, Turner JJD. Pattern of cannabis use in ecstasy polydrug users: moderate cannabis use may compensate for self-rated aggression and somatic symptoms. *Hum Psychopharmacol* (2005) 20, 249–61.
5. Parrott AC, Milani RM, Gouzoulis-Mayfrank E, Daumann J. Cannabis and ecstasy/MDMA (3,4-methylenedioxymethamphetamine): an analysis of their neuropsychobiological interactions in recreational users. *J Neural Transm* (2007) 114, 959–68.
6. Sala M, Braida D. Endocannabinoids and 3,4-methylenedioxymethamphetamine (MDMA) interaction. *Pharmacol Biochem Behav* (2005) 81, 407–16.

Amfetamines + Cocaine

An ischaemic stroke occurred in a patient who was abusing amfetamine and cocaine. Convulsions and cardiovascular adverse effects occurred in an infant exposed to an amfetamine and cocaine. *In vitro*, cocaine inhibits the metabolism of ecstasy, but the clinical significance of this is unknown.

Clinical evidence, mechanism, importance and management

A 16-year-old boy developed unsteadiness and double vision 5 minutes after intranasal inhalation of a small amount of **amfetamine** 'cut' with cocaine. Cranial magnetic resonance imaging revealed a mesencephalic

lesion that was seen to have decreased 12 days later, and he became symptom-free after 3 weeks. The ischaemic lesion was thought to be due to vasospasm caused by synergistic stimulation of the sympathetic nervous system: amfetamine causes the release of adrenaline (epinephrine) and noradrenaline (norepinephrine), while cocaine prevents their reuptake.[1] An 11-month-old infant experienced apparent generalised convulsions and cardiovascular adverse effects after accidental ingestion of **ecstasy** (MDMA, methylenedioxymethamfetamine) and chronic exposure to cocaine. It was suggested that, as both drugs are neurotoxic and have similar mechanisms of action, the combination could increase the risk of serious medical consequences.[2]

An *in vitro* study showed that cocaine (a potent inhibitor of the cytochrome P450 isoenzyme CYP2D6) inhibited the CYP2D6-mediated demethylenation of **ecstasy**. Therefore, theoretically, the use of cocaine would be expected to increase plasma and CNS **ecstasy** levels[3] but it is not known if this is significant in practice.

Evidence is currently limited, but it would appear that the concurrent use of amfetamines and cocaine may have adverse CNS consequences. The clinical relevance of these reports is unclear.

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Amfetamines and related drugs + Lithium

The stimulant and/or cardiovascular effects of the amfetamines have been shown to be opposed by lithium in some, but not all studies.

Clinical evidence, mechanism, importance and management

Two depressed patients stopped abusing **metamfetamine** and cannabis, or **phenmetrazine** and 'other diet pills' because, while taking lithium carbonate, they were unable to get 'high'. Another patient complained that she felt no effects from amfetamines taken for weight reduction, including no decrease in appetite, until lithium carbonate was withdrawn.[1] A controlled study in 9 depressed patients confirmed that lithium carbonate taken for 10 days attenuated the subjective stimulant effects of **dexamfetamine** or **levamfetamine**.[2] Another study found similar results with **dexamfetamine** in schizophrenic patients.[3] However, in a further study, the stimulant effects of **amfetamine** were attenuated in only 4 of 8 subjects given lithium. However, lithium attenuated the increase in systolic blood pressure caused by amfetamine (from an average increase of 31/15 mmHg down to 20/9 mmHg).[4]

In contrast, in a placebo-controlled study in healthy subjects, lithium 1.2 g daily for 7 days did not alter the subjective or cardiovascular effects of a single 20-mg dose of **dexamfetamine**.[5] In another controlled study, in 9 subjects, the only significant effect of pretreatment with lithium 900 mg for 14 days was to attenuate the feeling of happiness induced by **dexamfetamine**.[6]

The reasons for these reactions, when they occur, are not known. One study found that pretreatment of healthy subjects with lithium for 14 days attenuated **dexamfetamine**-induced regional decreases in brain activation when performing cognitive tasks.[7] It has been suggested that amfetamines and lithium have mutually opposing pharmacological actions on dopamine and noradrenaline (norepinephrine) release and uptake at adrenergic neurones,[1,7] possibly partially due to opposing effects on the phosphoinositol second messenger system (PI-cycle).[7]

Information is contradictory, and therefore an interaction is not fully established. Nevertheless, it may be prudent to be alert for evidence of reduced amfetamine effects in the presence of lithium.

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Amfetamines + Miscellaneous

The use of amfetamines and beta blockers may have undesirable effects on blood pressure. Delavirdine and disulfiram are predicted to inhibit the metabolism of amphetamines, and drugs that increase gastrointestinal acidity are predicted to decrease the absorption of amfetamines.

Clinical evidence, mechanism, importance and management

(a) Beta blockers

The US manufacturers of some amfetamines give general warnings that the effects of adrenergic blockers are inhibited by amfetamines[1,2] and that amfetamines may antagonise the hypotensive effects of antihypertensives.[1-3] However, the UK manufacturer of **dexamfetamine** warns that the concurrent use of beta blockers may result in severe hypertension and that adrenoreceptor blocking drugs such as **propranolol** may antagonise the effects of **dexamfetamine** (a sympathomimetic).[4] This is similar to the effects seen with vasopressor sympathomimetics, see 'Beta blockers + Inotropes and Vasopressors', p.1011.

(b) Delavirdine

The NNRTI, delavirdine, is an inhibitor of CYP3A and other isoenzymes including CYP2D6 by which amfetamines are metabolised. The manufacturer suggests caution if delavirdine is used with amfetamines because the amfetamine levels may be increased.[5]

(c) Disulfiram

Studies in *animals* have indicated that disulfiram may inhibit the metabolism of amfetamines.[6] The UK manufacturer of **dexamfetamine** says that disulfiram may inhibit the metabolism and excretion of **dexamfetamine**. In addition, they contraindicate the use of **dexamfetamine** in patients with a history of alcohol abuse.[4]

(d) Drugs that affect gastric acidity

The manufacturers note that drugs or substances that increase gastrointestinal acidity (**glutamic acid hydrochloride**, **ascorbic acid**, **fruit juices** etc.) could lower the absorption of amfetamines and might therefore lower their blood levels and efficacy.[1,2]

1. Dexedrine (Dextroamphetamine sulfate). GlaxoSmithKline. US Prescribing information, July 2008.
2. Adderall XR (Mixed salts of amphetamine and dextroamphetamine). Shire US Inc. US Prescribing information, March 2009.
3. Didrex (Benzphetamine hydrochloride). Pfizer Inc. US Prescribing information, January 2006.
4. Dexedrine (Dexamfetamine sulphate). UCB Pharma Ltd. UK Summary of product characteristics, September 2008.
5. Rescriptor (Delavirdine mesylate). Pfizer Inc. US Prescribing information, May 2008.
6. Antabuse (Disulfiram). Actavis UK Ltd. UK Summary of product characteristics, September 2007.

Amfetamines + Ondansetron

Ondansetron appears to attenuate the effects of amfetamine and dexamfetamine on subjective feelings such as light-headedness, but not the effects of amfetamine on psychomotor tests. One study found that ondansetron did not affect most physiological responses to dexamfetamine, but might attenuate blood pressure increases, although another study found ondansetron had no effect on amfetamine-induced increases in blood pressure.

Clinical evidence, mechanism, importance and management

In a placebo-controlled study, when 9 healthy subjects were given **amfetamine** 15 mg, they reported an increase in subjective feelings such as light-headedness or "high" and a decrease in hunger. The use of **amfetamine** also caused an increase in systolic blood pressure and a decrease in the mean time to complete psychomotor tests. When ondansetron 4 mg was given every 12 hours for 3 doses, with the last dose 30 minutes before the amfetamine, the effects of **amfetamine** on hunger and subjective state

were diminished, but its effects on blood pressure and psychomotor performance tests were not altered.[1] These findings have also been published elsewhere.[2] In another placebo-controlled study, in 10 healthy subjects, pretreatment with ondansetron 150, 50 or 15 micrograms/kg reduced the increases in prolactin associated with intravenous **dexamfetamine** 500 micrograms/kg, but did not affect other neuroendocrine responses (increased plasma levels of cortisol and growth hormone) or most physiological responses (elevated pulse and temperature). However, the lower doses of ondansetron attenuated amfetamine-induced increases in diastolic blood pressure. Mild/moderate euphoria/activation induced by **dexamfetamine** was only minimally affected by pretreatment with ondansetron, but ondansetron did attenuate the responses in subjects with robust euphoria/activation.[3]

It is suggested that ondansetron may attenuate some catecholamine-mediated effects of **amfetamine**, but a pharmacokinetic interaction has not yet been excluded.[1,2] However, analysis of the plasma levels in 4 subjects found that ondansetron did not significantly alter mean **dexamfetamine** levels, or the time taken to reach peak dexamfetamine levels.[3]

These studies were mainly designed to establish whether or not ondansetron altered the responses to amphetamines. They suggest that no clinically relevant adverse interaction occurs, but more study is needed to establish the absence of a pharmacokinetic interaction.

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2. Silverstone PH, Johnson B, Cowen PJ. Does ondansetron attenuate amphetamine-induced behaviour in human volunteers? *Psychopharmacology (Berl)* (1992) 107, 140–1.

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Amfetamines and related drugs + Phenothiazines

The appetite suppressant and other effects of amfetamines, chlorphentermine and phenmetrazine are opposed by chlorpromazine. It seems possible that other phenothiazines will interact similarly. The antipsychotic effects of chlorpromazine can be opposed by dexamfetamine. Dexamfetamine can oppose the antipsychotic effects of chlorpromazine, and in one case dexamfetamine exacerbated a perphenazine-related withdrawal dyskinesia.

Clinical evidence

In a placebo-controlled study, 10 obese schizophrenic patients who were taking drugs including **chlorpromazine**, **thioridazine**, imipramine and chlordiazepoxide did not respond to treatment with **dexamfetamine** for obesity. The expected sleep disturbance in response to **dexamfetamine** was also not seen.[1] In a double-blind, placebo-controlled study in 76 patients, **chlorpromazine** was found to diminish the weight-reducing effect of **phenmetrazine**,[2] and, in another study, patients taking **chlorpromazine** did not experience the expected weight loss when they were given **phenmetrazine** or **chlorphentermine**.[3] Similarly, antagonism of the effects of **amfetamines** by **chlorpromazine** has been described in other reports,[4,5] and this interaction has been deliberately exploited, with success, in the treatment of 22 children poisoned with various amfetamines or related compounds (**amfetamine**, **dexamfetamine**, **metamfetamine**, **phenmetrazine**).[4]

A study in 462 patients taking **chlorpromazine** 200 to 600 mg daily found that the addition of **dexamfetamine** 10 to 60 mg daily had a detrimental effect on the control of their schizophrenic symptoms.[6]

A 9-year-old boy taking **perphenazine**, **dexamfetamine**, fluoxetine and diphenhydramine had his **perphenazine** dose tapered and then discontinued, followed by discontinuation of the fluoxetine and diphenhydramine. Two days after the perphenazine was stopped the patient began to have repeated tongue protrusions, which progressed to abnormal involuntary movements involving his upper and lower extremities. It was suspected that **dexamfetamine** was aggravating the movement disorder and so it was tapered over 2 days and stopped, resulting in an immediate and dramatic improvement.[7]

Mechanism

Not fully understood. It is known that chlorpromazine can inhibit adrenergic and dopaminergic activity, which could explain some part of the antagonism of the amfetamines, the euphoriant effects of which are said to be mediated by central dopamine receptors.

The severe extrapyramidal movement disorder might have occurred due to the patient developing dopamine supersensitivity as a result of long-term antipsychotic therapy. On antipsychotic withdrawal, an increased number of postsynaptic dopamine receptors were available to the dopamine agonist effects of continued amfetamine treatment, resulting in the extrapyramidal movement disorder, which did not subside until the dopamine agonist was withdrawn.[7]

Importance and management

Established interactions. These reports suggest that it is not beneficial to attempt to treat patients taking chlorpromazine with amfetamines, such as dexamfetamine, or other central stimulants such as phenmetrazine. Although in one study, thioridazine also appeared to interact it is not clear whether this interaction takes place with antipsychotics other than chlorpromazine. However, it seems possible that this interaction may occur with all phenothiazines, especially if the suggested mechanism is correct. Note that central stimulants are no longer recommended for the treatment of obesity.

The case of dyskinesia suggests that central stimulants may exacerbate symptoms caused by antipsychotic withdrawal. See also 'Methylphenidate + Risperidone', p.228.

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Amfetamines + Pimozide

Two studies suggest that pimozide attenuates the stimulant effects of amfetamine or dexamfetamine, but in two other studies the effects were inconsistent.

Clinical evidence, mechanism, importance and management

Pimozide, a dopamine antagonist, given in single oral doses of 5, 10 or 20 mg, or repeated doses of 5 mg daily, reduced the euphoriant effects of large (200-mg) intravenous doses of **amfetamine** in subjects with a history of amfetamine abuse. The blood pressure response to amfetamine was also reduced.[1] Similarly, a placebo-controlled study in 8 healthy subjects found that pimozide 2 mg attenuated the stimulant action of **dexamfetamine** 10 mg, but had no effect on dexamfetamine-induced anorexia.[2]

In contrast, in a placebo-controlled study, 10 healthy subjects were given either **dexamfetamine** 10 mg or 20 mg 2 hours after pimozide 1 mg or 2 mg. Pimozide was found to be inconsistent in antagonising the subjective responses to **dexamfetamine**.[3] In a further study by the same authors, pimozide 8 mg did not consistently antagonise the effects of **dexamfetamine**, although pimozide 8 mg alone did produce effects opposite to those of dexamfetamine.[4]

The results are inconsistent, and therefore more study would be beneficial to establish an interaction, and its clinical relevance.

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Amfetamines and related drugs + Protease inhibitors

A man taking ritonavir suffered a fatal serotonergic reaction after taking ecstasy (MDMA, methylenedioxymethamfetamine). A similar fatal reaction has occurred with metamfetamine and ritonavir. An isolated case of haemolytic anaemia has been reported in a patient taking indinavir and ecstasy. The effectiveness of antiretroviral therapy has been found to be reduced in users of metamfetamine.

Clinical evidence

(a) Ecstasy (MDMA, Methylenedioxymethamfetamine)

An HIV-positive man taking lamivudine and zidovudine was also given **ritonavir** 600 mg twice daily. About 2 weeks later he went to a club and took ecstasy, in a dose estimated to be about 180 mg. He soon became unwell, and when seen by a nurse in the club, was hypertonic, tachypnoeic (45 breaths per minute), tachycardic (more than 140 bpm), cyanosed and diaphoretic. He had a tonic-clonic seizure, his pulse rose to 200 bpm, he then vomited, had a cardiorespiratory arrest and died. A post mortem showed blood-alcohol levels of 24 mg% and an ecstasy level of 4.56 micrograms/mL, which was almost 10 times greater than might have been expected from the dose he had taken. The authors say that death was consistent with a severe serotonergic reaction.[1] Another report verifies that high ecstasy levels (4.05 micrograms/mL) may result in these life-threatening symptoms.[2]

A patient with AIDS, taking **ritonavir** and **saquinavir**, experienced agitation that lasted for over a day, following a small dose of ecstasy. He then experienced a nearly fatal reaction to a small dose of **sodium oxybate** (**GHB**, **gamma-hydroxybutyrate**, **γ-hydroxybutyrate**), becoming unresponsive within 20 minutes of ingestion of the drug and exhibiting a brief episode of repetitive clonic contractions.[3]

Another HIV-positive man who was well established on HAART (zidovudine, lamivudine and **indinavir**) experienced transient haemolytic anaemia thought to be a toxic reaction to taking three ecstasy tablets, the effects of which may have been potentiated by the indinavir.[4]

(b) Metamfetamine

A 49-year-old HIV-positive man taking protease inhibitors was found dead after injecting himself twice with metamfetamine as well as sniffing **amyl nitrate**. He had been taking an antiretroviral regimen of **ritonavir** 400 mg twice daily, soft gel **saquinavir** 400 mg twice daily and stavudine 40 mg twice daily for 4 months and it was considered that the protease inhibitors may have interacted with the recreational drugs. Toxicology detected metamfetamine 500 nanograms/mL in the blood (considered to be in the fatal range, especially when used with other drugs [unnamed]). Cannabinoids and traces of diazepam and nordiazepam were also found in this patient.[5]

An analysis of 133 patients who were receiving HAART, found that HAART effectively lowered viral loads in *former* metamfetamine users, but not in *active* metamfetamine users.[6]

Mechanism

Ritonavir inhibits the cytochrome P450 isoenzyme CYP2D6, which is responsible for the demethylenation of ecstasy, so concurrent use leads to a sharp rise in ecstasy plasma levels. Metamfetamine is also metabolised by CYP2D6 and its levels would therefore similarly be raised by ritonavir. Poor liver function (due to alcoholism) may have been a contributory factor in one patient,[1] and further inhibition of cytochrome P450 by nitric oxide (the metabolite of amyl nitrate) may have contributed to another case.[5] An additional factor is that ecstasy may show non-linear pharmacokinetics.[7]

It was suggested that the increase in virus load in metamfetamine users receiving HAART might be due to poor adherence or altered metabolism of the antiretroviral medications.[6] Another possible mechanism might be that metamfetamine induces increases in extracellular dopamine, which in turn might activate HIV replication.[8] In addition, metamfetamine use can undermine the general health of the user.[9]

Importance and management

Although there are few reported cases of interactions between amfetamines or related drugs and protease inhibitors, what happens is consistent with the known toxic effects and pharmacology of the drugs concerned. In addition, protease inhibitors may, theoretically, inhibit the metabolism of ecstasy via other isoenzymes (CYP3A4, CYP2B6), which could therefore also lead to increased levels.

It has been suggested that patients who are prescribed any protease inhibitor should be made aware of the potential risks of using any form of recreational drugs metabolised by CYP2D6.[5] In particular, some authors recommend that patients taking ritonavir should avoid using ecstasy and other amfetamines particularly metamfetamine.[10] Open discussions of illicit drug use would enable carers to warn patients that the use of these drugs may be even more dangerous while taking protease inhibitors. Appropriate precautions, apart from avoidance, include a reduction of the usual dose of ecstasy to about 25%, taking breaks from dancing, checking that a medical team are on site, maintaining adequate hydration by avoiding alcohol, and replenishing fluids regularly.[10]

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Amfetamines and related drugs + SSRIs

The psychological effects of ecstasy (MDMA, methylenedioxymethamfetamine) may be reduced if citalopram, fluoxetine or paroxetine have previously been given; some physiological effects such as increased heart rate may also be reduced. It seems likely that other SSRIs will also reduce or block some of the effects of ecstasy. There may be an increased risk of serotonin effects and neurotoxic reactions if amfetamines or related drugs are given with SSRIs. Fluoxetine and paroxetine may decrease the metabolism of amfetamines and ecstasy; amfetamine toxicity and phentermine toxicity have been reported.

Clinical evidence

(a) Amfetamines (unspecified or related drugs)

A man who had taken a small, unspecified, but previously tolerated dose of amfetamines developed signs of amfetamine overdosage (restlessness, agitation, hyperventilation, etc.) while taking **fluoxetine** 60 mg daily. Another man taking **fluoxetine** 20 mg daily developed symptoms of schizophrenia after taking two unspecified doses of amfetamines.[1]

A 22-year-old woman who had successfully and uneventfully taken **fluoxetine** 20 mg daily for 3 months, stopped the fluoxetine and then 8 days later took a single 30-mg tablet of **phentermine**. Within a few hours she experienced racing thoughts, stomach cramps, palpitations (pulse 84 bpm), tremors, dry eyes and diffuse hyper-reflexia. The problems had all resolved the following day after she took lorazepam 1.5 mg. The authors of this report suggested that the residual inhibitory effects of the **fluoxetine** on liver cytochrome P450 enzymes led to decreased **phentermine** metabolism, resulting in increased **phentermine** levels and sympathetic hyperstimulation. It is known that **fluoxetine** and its active metabolite have a long half-life and can persist for weeks. The authors also

alternatively wondered whether some of the symptoms might have fitted those of the serotonin syndrome.[2]

(b) Dexamfetamine

A patient who developed serotonin syndrome while taking 'venlafaxine', (p.1478), with dexamfetamine had a second episode when **citalopram** was taken with dexamfetamine.[3]

(c) Ecstasy (MDMA, Methylenedioxymethamfetamine)

A placebo-controlled psychometric study in 16 healthy subjects found that oral ecstasy 1.5 mg/kg produced an emotional state with heightened mood, increased self-confidence and extroversion, moderate derealisation and an intensification of sensory perception. Most of these effects were found to be markedly reduced by pretreatment with intravenous **citalopram** 40 mg, although their duration was prolonged by up to 2 hours.[4] Similarly, a study in 8 ecstasy users found that **fluoxetine** 20 mg daily for at least 5 days attenuated most of the positive subjective effects (e.g. arousal, elation, positive mood, vigour etc.) associated with ecstasy. In addition, heart rate but not blood pressure increases were reduced.[5] Another study found that pretreatment with oral **paroxetine** 20 mg daily for 3 days decreased both the physiological and subjective effects of a single 100-mg oral dose of ecstasy.[6]

A case report describes 2 patients taking **citalopram** 20 mg daily or **paroxetine** 20 mg daily who did not experience any effects from ecstasy after starting the SSRI. One of these patients continued to experience a 'high' from **amfetamines** whilst taking **paroxetine**.[7] However, an account of 4 ecstasy users who had taken **fluoxetine** 20 mg before taking ecstasy 100 to 250 mg, reported that they still experienced the subjective effects of euphoria, but one commented that the overall acute experience was "slightly calmer". Some of the adverse effects such as jaw clenching and insomnia were also attenuated and recovery was more rapid.[8]

When a man taking **citalopram** 60 mg daily also took unknown amounts of ecstasy he became aggressive, agitated, severely grandiose, restless and performed compulsive movements in a peculiar and joyless dance-like manner. He lacked normal movement control and said he could see little bugs. He was treated with haloperidol and chlordiazepoxide, and improved within 2 days of replacing the **citalopram** with promazine.[9]

In a placebo-controlled, randomised study, 7 healthy subjects were given ecstasy 100 mg on the last day of taking **paroxetine** 20 mg daily for 3 days. **Paroxetine** raised the maximum serum levels and AUC of ecstasy by 17% and 27%, respectively.[10] Another study also found that pretreatment with **paroxetine** resulted in similar increases in the maximum plasma levels and AUC of ecstasy (16% and 22%, respectively), and reductions in those of the metabolite, 3-methoxy-4-hydroxymethamfetamine (49% and 38%, respectively).[6]

Mechanism

Complex. It has been suggested that the psychological and neurotoxic effects of ecstasy may be caused by serotonin release in the brain.[8,11] This could potentially be blocked by serotonin reuptake inhibitors (such as citalopram) resulting in reduced ecstasy effects. However, ecstasy is also thought to inhibit serotonin reuptake,[11] so its use with the SSRIs could increase serotonin effects, which could result in neurotoxicity.[12] Other amfetamines also affect catecholamines such as dopamine, noradrenaline and serotonin in the brain, so they have the potential to interact with SSRIs, although they differ in their affinity for these neurotransmitters (for example metamfetamine primarily affects dopamine).[13]

In addition, some SSRIs (to varying degrees) inhibit the cytochrome P450 isoenzyme CYP2D6, by which amfetamine, metamfetamine and ecstasy are metabolised, so concurrent use could result in increased levels of the amfetamine.

Importance and management

The available evidence suggests that patients already taking citalopram, fluoxetine or paroxetine may not be able to get as 'high' on usual doses of ecstasy, and some adverse effects may also be reduced. Furthermore, if the proposed mechanism of interaction is correct, the same is also likely to be true if they are taking any SSRI. Also be aware of possible pharmacokinetic interactions with some SSRIs that are CYP2D6 inhibitors (e.g. fluoxetine, paroxetine), which may increase the levels of ecstasy or possibly other amfetamines. Marked decreases in the effects of these drugs could lead users to take higher doses, which might produce potentially life-threatening toxic effects, especially if plasma levels are raised due to a pharmacokinetic interaction. This interaction has been investigated for its potential to aid amfetamine abstinence,[14,15] but the results have not been promising, and the incidence of adverse effects may be increased.

There may be a risk of increased serotonergic activity with SSRIs and amfetamines, consider *Serotonin syndrome*, under 'Additive or synergistic interactions', (p.9), for further information.

The neurotoxic reactions cited seem to be isolated cases but they illustrate some of the risks attached to using anorectic, stimulant or 'recreational' drugs by patients already taking other medications, particularly antidepressant and psychotropic drugs that affect the same receptors in the CNS. Furthermore, as with the other interactions discussed here, toxic reactions may be more likely if the plasma levels of the amfetamine are increased by the SSRI.

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Amfetamines + Topiramate

Topiramate does not affect the haemodynamic response to metamfetamine, although some aspects of metamfetamine-induced positive cognitive performance may be increased and there may be a trend towards increased plasma levels of metamfetamine.

Clinical evidence, mechanism, importance and management

A placebo-controlled study in 10 metamfetamine-dependent subjects found that intravenous **metamfetamine** 15 or 30 mg was associated with increased psychomotor performance and attention. Pretreatment with topiramate 100 or 200 mg orally in two divided doses tended to enhance **metamfetamine**-induced increases in attention and concentration, but decreased perceptual motor function.[1] A further study in the same subjects found that **metamfetamine**-associated increases in haemodynamic response (blood pressure, heart rate) were not significantly affected by pretreatment with topiramate. However, there was a non-significant trend for topiramate to increase plasma **metamfetamine** levels, possibly due to alkalinisation of the urine by topiramate.[2]

These studies were primarily designed to assess the potential use of topiramate in amphetamine abuse. However, they indicate that a clinically significant pharmacokinetic interaction seems unlikely, and that concurrent use does not appear to be associated with any particular adverse effects.

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2. Johnson BA, Wells LT, Roache JD, Wallace CL, Ait-Daoud N, Dawes MA, Liu L, Wang X-Q, Javors MA. Kinetic and cardiovascular effects of acute topiramate dosing among non-treatment-seeking, methamphetamine-dependent individuals. *Prog Neuropsychopharmacol Biol Psychiatry* (2007) 31, 455–61.

Amfetamines + Urinary acidifiers or alkalinisers

The urinary excretion of amfetamines is increased by urinary acidifiers (ammonium chloride) and reduced by urinary alkalinisers (sodium bicarbonate).

Clinical evidence

A study in 6 healthy subjects given **dexamfetamine** 10 to 15 mg found that when the urine was made alkaline (pH of about 8) by giving **sodium bicarbonate**, only 3% of the original dose of amfetamine was excreted over a 16-hour period, compared with 55% when the urine was made acidic (pH of about 5) by taking **ammonium chloride**.[1] Similar results have been reported elsewhere for **amfetamine**, **dexamfetamine** and **metamfetamine**.[2-5] A further study found that the effects of **amfetamine** were increased and prolonged in subjects with alkaline urine,[6] and psychoses resulting from **amfetamine** retention in patients with alkaline urine have been described.[7]

Mechanism

Amfetamines are bases, which are excreted by the kidneys. If the urine is alkaline most of the drug exists in the unionised form, which is readily reabsorbed by the kidney tubules, so that little is lost. In acid urine, little of the drug is in the unionised form so that little can be reabsorbed and much of it is lost. For more detail on this mechanism, see 'Changes in urinary pH', (p.7).

Importance and management

A well established and well understood interaction but reports of problems in practice seem rare. Nevertheless, there is still the possibility that therapeutic doses of amfetamines may be excreted too rapidly if urinary acidifying agents are given. This interaction has been exploited to increase the clearance of amfetamines in cases of overdose, but although amfetamine excretion is increased, acidification of the urine is believed to increase the risk of acute renal failure if myoglobinuria is present.[8-10]

Care is needed to ensure that amfetamine toxicity does not develop if the urine is made alkaline with sodium bicarbonate or another urinary alkaliniser such as **acetazolamide**, or **sodium phosphate**.[8,10]. Note that sodium bicarbonate may also increase the absorption of amfetamines, by decreasing gastrointestinal acidity, and one manufacturer says that gastrointestinal alkalinising agents such as **antacids** should be avoided with amfetamines.[8]

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4. Davis JM, Kopin IJ, Lemberger L, Axelrod J. Effects of urinary pH on amphetamine metabolism. *Ann N Y Acad Sci* (1971) 179, 493–501.
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7. Änggård E, Jönsson L-E, Hogmark A-L, Gunne L-M. Amphetamine metabolism in amphetamine psychosis. *Clin Pharmacol Ther* (1973) 14, 870–80.
8. Adderall XR (Mixed salts of amphetamine and dextroamphetamine). Shire US Inc. US Prescribing information, March 2009.
9. Desoxyn (Metamfetamine hydrochloride). Ovation Pharmaceuticals, Inc. US Prescribing information, May 2007.
10. Dexedrine (Dextroamphetamine sulfate). GlaxoSmithKline. US Prescribing information, July 2008.

Amfetamines + Valproate

Valproate appears to attenuate the effects of dexamfetamine on mood changes and blood pressure.

Clinical evidence, mechanism, importance and management

In a placebo-controlled study, healthy subjects were given sodium valproate 500 mg daily for 3 days, then 1 g daily for 11 days followed by a single 25-mg dose of **dexamfetamine**. Pretreatment with valproate was found to significantly attenuate the effects of **dexamfetamine** on mood (happiness, energy, alertness) and attenuated the increases in diastolic blood pressure associated with **dexamfetamine**. The mechanism is uncertain, but may be partly due to the action of valproate on phosphoinositol cycle activity.[1]

The clinical significance of these changes is unclear, but the effects on blood pressure are, if anything, likely to be beneficial. It is unclear whether other amfetamines are affected similarly.

1. Willson MC, Bell EC, Dave S, Asghar SJ, McGrath BM, Silverstone PH. Valproate attenuates dextroamphetamine-induced subjective changes more than lithium. *Eur Neuropsychopharmacol* (2005) 15, 633–9.

Atomoxetine + Amfetamines

The use of atomoxetine in patients taking amfetamines may lead to adverse effects, such as psychosis and movement disorders.

Clinical evidence, mechanism, importance and management

A 9-year-old boy with attention deficit hyperactivity disorder (ADHD) who had been taking clonidine and amphetamine with dexamfetamine (*Adderall XR*) for several years, developed psychosis, abnormal involuntary movements and insomnia when atomoxetine was added to his treatment.[1]

The authors of the report suggested that the addition of atomoxetine to stable but moderately high doses of stimulant and alpha$_2$-adrenergic agonist medication triggered the symptoms through additive effects on noradrenaline and possibly dopamine. In addition, a pharmacokinetic interaction might have occurred as the cytochrome P450 isoenzyme CYP2D6 is involved in the metabolism of both drugs.[1]

Evidence for an interaction appears to be limited to this isolated case. However, the manufacturer recommends caution when atomoxetine is given concurrently with other drugs that affect noradrenaline, because of the potential for additive or synergistic pharmacological effects.[2] If both drugs are given, be aware that adverse CNS effects may develop, and consider reducing the doses or stopping one of the drugs should this occur.

1. Bond GR, Garro AC, Gilbert DL. Dyskinesias associated with atomoxetine in combination with other psychoactive drugs. *Clin Toxicol* (2007) 45, 182–5.
2. Strattera (Atomoxetine hydrochloride). Eli Lilly and Company Ltd. UK Summary of product characteristics, May 2009.

Atomoxetine + CYP2D6 inhibitors

Paroxetine markedly increases atomoxetine levels in extensive metabolisers of CYP2D6. Fluoxetine also raises atomoxetine levels; there is a possibility that this may increase adverse effects.

Clinical evidence

In one study, 22 healthy subjects who were extensive metabolisers of the cytochrome P450 isoenzyme CYP2D6 (most common phenotype) were given **paroxetine** 20 mg daily for 17 days, with atomoxetine 20 mg twice daily on the last 5 days. **Paroxetine** increased the AUC of atomoxetine 6.5-fold, increased its maximum plasma level by 3.5-fold, and increased its elimination half-life by 2.5-fold, when compared with atomoxetine alone. No changes in paroxetine pharmacokinetics were seen.[1] The pharmacokinetics of atomoxetine with **paroxetine** in these subjects was similar to that previously seen with atomoxetine alone in poor metaboliser subjects.[1,2]

Following a small-scale study in which atomoxetine was given with **fluoxetine** without any adverse effects, 127 children with attention deficit hyperactivity disorder were randomised to receive **fluoxetine** 20 mg daily and 46 to receive placebo. After 3 weeks atomoxetine (starting at 0.5 mg/kg daily, increasing over 5 weeks to a maximum of 1.8 mg/kg daily) was also given to both groups. The **fluoxetine** group had 3.3-fold higher peak atomoxetine levels than the placebo group. However, despite a trend towards a greater incidence of decreased appetite with the combination (20% versus 6.8%), there was no significant difference in adverse events between the two groups.[3]

Mechanism

Atomoxetine is extensively metabolised by the cytochrome P450 isoenzyme CYP2D6,[4] an isoenzyme that shows polymorphism, with up to 10%

of the population lacking an active form (poor metabolisers). Paroxetine inhibits CYP2D6, and thereby increases atomoxetine levels in those with an extensive metaboliser phenotype. It would not be expected to have any effect in poor metabolisers. Fluoxetine can similarly inhibit CYP2D6.

Importance and management

An established pharmacokinetic interaction. Paroxetine effectively changes patients from an extensive metaboliser phenotype to a poor metaboliser phenotype, markedly raising atomoxetine levels. Although the clinical relevance of this effect has not been directly assessed, the manufacturer notes that some adverse effects of atomoxetine were up to twice as frequent in poor metaboliser patients in clinical studies.[2] Both manufacturers suggest that, in patients already taking CYP2D6 inhibitors, dose adjustment and slower titration of atomoxetine may be necessary,[2,5] with the dose increased only if symptoms fail to improve and if the initial dose is well tolerated.[2] This seems a sensible precaution. Note that in the fluoxetine study, which found that the concurrent use of atomoxetine was generally well tolerated, dosage increases were made on a weekly basis, from 0.5 mg/kg to 0.8 mg/kg and then 1.2 mg/kg daily at the start of the third week.[3] The US manufacturer suggests a starting dose of atomoxetine 0.5 mg/kg daily (40 mg per day in those over 70 kg) and only increasing the dose to 1.2 mg/kg daily (or 80 mg per day) if symptoms fail to improve after 4 weeks and the initial dose is well tolerated.[2] The UK manufacturers say that the initial dose should be maintained for a minimum of 7 days before increasing it, if necessary.[5]

It would also seem prudent to be alert to the possibility of an increase in adverse effects if CYP2D6 inhibitors are added to established atomoxetine treatment, and the manufacturers specifically name fluoxetine, paroxetine, **quinidine**,[2,5] and **terbinafine**.[5] If one of these drugs is given they suggest that the clinical response and tolerability should be re-evaluated and a dose adjustment may be necessary.[5] For a list of inhibitors of CYP2D6, see 'Table 1.3', (p.6).

Extra caution may be prudent with this combination in those with epilepsy, as both atomoxetine and SSRIs may lower the seizure threshold, and this risk appears to be increased by higher atomoxetine levels.[2] Patients may also be more at risk of QT interval prolongation when atomoxetine is given with CYP2D6 inhibitors, see *Drugs that prolong the QT interval*, under 'Atomoxetine + Miscellaneous', below.

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2. Strattera (Atomoxetine hydrochloride). Eli Lilly and Company. US Prescribing information, May 2008.
3. Kratochvil CJ, Newcorn JH, Arnold LE, Duesenberg D, Emslie GJ, Quintana H, Sarkis EH, Wagner KD, Gao H, Michelson D, Biederman J. Atomoxetine alone or combined with fluoxetine for treating ADHD with comorbid depressive or anxiety symptoms. *J Am Acad Child Adolesc Psychiatry* (2005) 44, 915–24.
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5. Strattera (Atomoxetine hydrochloride). Eli Lilly and Company Ltd. UK Summary of product characteristics, May 2009.

Atomoxetine + Miscellaneous

The manufacturer of atomoxetine contraindicates the concurrent use of MAOIs. Atomoxetine is predicted to have additive effects with pressor drugs and other sympathomimetics and has been seen to potentiate the increase in heart rate and blood pressure caused by intravenous salbutamol. However, no increase in cardiovascular effects was seen when atomoxetine was given with methylphenidate. Atomoxetine also has the potential for an interaction with drugs that prolong the QT interval and drugs that lower the seizure threshold.

Atomoxetine does not alter desipramine or midazolam pharmacokinetics and would therefore not be expected to affect other substrates of CYP2D6 or CYP3A4. Antacids and omeprazole do not alter atomoxetine bioavailability.

Clinical evidence, mechanism, importance and management

(a) Antacids or Omeprazole

In a study in 20 subjects, **aluminium**/**magnesium hydroxide** (*Maalox*) and omeprazole did not affect the bioavailability of atomoxetine 40 mg.[1] No special precautions appear to be necessary on concurrent use.

(b) CYP2D6 substrates

In a study[2] in 21 subjects who were extensive metabolisers of CYP2D6 (most common phenotype), atomoxetine 40 or 60 mg twice daily for 13 days had no effect on the pharmacokinetics of a single 50-mg dose of **desipramine** given on day 4.

Desipramine is extensively metabolised by CYP2D6, and can be used as a probe drug for the assessment of the effect of drugs on this isoenzyme in extensive metabolisers (see 'Genetic factors', (p.4)). It was concluded that atomoxetine, even at the maximum recommended dose, does not cause clinically relevant inhibition of CYP2D6 *in vivo*, and so will not affect the pharmacokinetics of other CYP2D6 substrates.[2] For a list of CYP2D6 substrates, see 'Table 1.3', (p.6).

(c) CYP3A4 substrates

Atomoxetine 60 mg twice daily for 12 days was given to 6 subjects who were poor metabolisers of CYP2D6, with a single 5-mg oral dose of **midazolam** on days 6 and 12. Atomoxetine increased the maximum level and AUC of midazolam by about 16%, which was not statistically or clinically significant.[2]

Midazolam is extensively metabolised by CYP3A4, and can be used as a probe drug for assessment of the effect of drugs on this isoenzyme. Poor metabolisers of CYP2D6 were chosen for this study, because they have much higher levels of atomoxetine than extensive metabolisers of CYP2D6. It was concluded that atomoxetine, even at the maximum recommended dose, does not cause clinically relevant inhibition of CYP3A4 *in vivo*, and so will not affect the pharmacokinetics of other CYP3A4 substrates.[2] For a list of CYP3A4 substrates, see 'Table 1.4', (p.6).

(d) Drugs that lower the seizure threshold

Seizures are a potential risk with atomoxetine and caution is advised if drugs that lower the seizure threshold (such as **antidepressants**, **antipsychotics**, **mefloquine**, **bupropion**, or **tramadol**) are given concurrently.[3]

(e) Drugs that prolong the QT interval

There is potential for an increased risk of QT interval prolongation[3] when atomoxetine is given with other QT prolonging drugs (such as **antipsychotics**, class Ia and class III **antiarrhythmics**, **moxifloxacin**, **erythromycin**, **methadone**, **mefloquine**, **tricyclic antidepressants**, **lithium** or **cisapride**), drugs that cause electrolyte imbalance (such as **thiazide diuretics**), and drugs that inhibit CYP2D6 (see 'Atomoxetine + CYP2D6 inhibitors', p.225).

(f) MAOIs

The manufacturer contraindicates the concurrent use of atomoxetine with MAOIs, or within 2 weeks of stopping an MAOI,[3,4] because other drugs that affect brain monoamine levels have caused serious reactions (including symptoms of serotonin syndrome or symptoms similar to neuroleptic malignant syndrome) when taken with MAOIs.[4]

(g) Methylphenidate

In a placebo-controlled, crossover study, 12 healthy subjects were given atomoxetine 60 mg twice daily or methylphenidate 60 mg daily for 5 days, with the other drug added for the final 2 days. No additional changes in blood pressure or heart rate were seen when the drugs were given together, and concurrent use did not increase the frequency of adverse effects.[5]

(h) Pressor drugs

Atomoxetine is a sympathomimetic that acts as a noradrenaline reuptake inhibitor. As such, it causes a modest increase in pulse and/or blood pressure in many patients.[3,4] The manufacturer recommends caution if atomoxetine is given concurrently with pressor drugs (e.g. **dopamine**, **dobutamine**)[4] because of the possible additive effects on blood pressure.[3,4]

(i) Salbutamol (Albuterol)

The manufacturer notes that atomoxetine 60 mg twice daily for 5 days potentiated the increase in heart rate and blood pressure caused by an infusion of salbutamol 600 micrograms, given over 2 hours.[4] Because of this, they recommend caution when atomoxetine is used in patients receiving intravenous or oral salbutamol or other beta$_2$ agonists[3,4] (for a list, see 'Table 34.1', (p.1414)). The UK manufacturer also extends this precaution to high-dose nebulised salbutamol.[3] However, the effects on heart rate and blood pressure were not seen in another study when 21 healthy Asian subjects, who were extensive CYP2D6 metabolisers, were given salbutamol 200 to 800 micrograms daily with atomoxetine 80 mg daily, for 5 days.[4]

(j) Miscellaneous

The manufacturer recommends caution when atomoxetine is given concurrently with other drugs that affect noradrenaline, because of the potential for additive or synergistic pharmacological effects. They name antidepressants such as **imipramine**, **mirtazapine** and venlafaxine, and the decongestants **pseudoephedrine** or **phenylephrine**.[3] This would seem a sensible precaution, particularly as neurological complications have been reported in one patient given atomoxetine and 'venlafaxine', (p.1477) and a child given atomoxetine and 'dexamfetamine', (p.225).

1. DeSante KA, Long AJ, Smith PB, Thomasson HR, Sauer JM, Agbo F, Abeyratne A, Riggio AL, Sheets BA, Witcher JW. Atomoxetine absolute bioavailability and effects of food, Maalox or omeprazole on atomoxetine bioavailability. *AAPS PharmSci* (2001) 3(S1). Available at: http://www.aapsj.org/abstracts/am_abstracts2008.asp (accessed 02/02/10).
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3. Strattera (Atomoxetine hydrochloride). Eli Lilly and Company Ltd. UK Summary of product characteristics, May 2009.
4. Strattera (Atomoxetine hydrochloride). Eli Lilly and Company. US Prescribing information, May 2008.
5. Kelly RP, Yeo KP, Teng C-H, Smith BP, Lowe S, Soon D, Read HA, Wise SD. Hemodynamic effects of acute administration of atomoxetine and methylphenidate. *J Clin Pharmacol* (2005) 45, 851–55.

Dexfenfluramine or Fenfluramine + Anorectics

Fenfluramine and dexfenfluramine have generally been withdrawn worldwide because of the occurrence of serious and sometimes fatal valvular heart disease and pulmonary hypertension, which occurred when they were taken alone and when combined with phentermine. Some herbal preparations may, however, still contain fenfluramine and related drugs. There is an isolated case of cardiomyopathy attributed to the use of fenfluramine with mazindol.

Clinical evidence, mechanism, importance and management

Fenfluramine and dexfenfluramine have generally been withdrawn worldwide because of the occurrence of serious and sometimes fatal valvular heart disease (aortic, mitral, tricuspid or mixed valve disease). Pulmonary hypertension has also sometimes been seen. These serious adverse effects occurred when these drugs were taken alone, and when combined with phentermine as *Fen-phen* and *Dexfen-phen*, but not with phentermine alone.[1-6] There is also an isolated case of cardiomyopathy attributed to the use of fenfluramine with mazindol.[7] Before the withdrawal of the drug from the market, the manufacturer of fenfluramine recommended that concurrent use with other centrally-acting anorectics should be avoided.[8]

Note that some unlicensed traditional Chinese medicines have been found to contain **nitrosofenfluramine** (known to be toxic to the liver) and fenfluramine. Reports suggest that other products for weight loss may also contain undeclared fenfluramine and nitrosofenfluramine.[9]

1. Committee on Safety of Medicines/Medicines Control Agency. Fenfluramine and dexfenfluramine withdrawn. *Current Problems* (1997) 23, 13.
2. Food and Drugs Administration. FDA announces withdrawal fenfluramine and dexfenfluramine (Fen-Phen). September 15th, 1997.
3. Connolly HM, Crary JL, McGoon MD, Hensrud DD, Edwards BS, Edwards WD, Schaff HV. Valvular heart disease associated with fenfluramine-phentermine. *N Engl J Med* (1997) 337, 581–8.
4. Mark EJ, Patalas ED, Chang HT, Evans RJ, Kessler SC. Fatal pulmonary hypertension associated with short-term use of fenfluramine and phentermine. *N Engl J Med* (1997) 337, 602–6.
5. Graham DJ, Green L. Further cases of valvular heart disease associated with fenfluramine-phentermine. *N Engl J Med* (1997) 337, 635.
6. Fleming RM, Boyd LB. The longitudinal effects of fenfluramine-phentermine use. *Angiology* (2007) 58, 353–9.
7. Gillis D, Wengrower D, Witztum E, Leitersdorf E. Fenfluramine and mazindol: acute reversible cardiomyopathy associated with their use. *Int J Psychiatry Med* (1985) 15, 197–200.
8. Ponderax Pacaps (Fenfluramine). Servier Laboratories Limited. ABPI Compendium of Datasheets and Summaries of Product Characteristics 1997–8, 1307.
9. MHRA. Letter from R Woodfield, Group Manager Herbal Policy, to Herbal Interest Groups: Shubao Slimming Capsules containing fenfluramine and nitrosofenfluramine, 28 April 2004. Available at: http://www.mhra.gov.uk/home/groups/es-herbal/documents/websiteresources/con009291.pdf (accessed 02/02/10)

Levamfetamine + Phenylpropanolamine

The effects of levamfetamine were attenuated in a hyperactive child by a nasal decongestant containing chlorphenamine and phenylpropanolamine.

Clinical evidence, mechanism, importance and management

The use of **levamfetamine succinate** 42 mg daily was found to be ineffective in a 12-year-old hyperactive boy on two occasions when he took *Contac* cold capsules and *Allerest* tablets for colds. Both of these proprietary nasal decongestants contain **phenylpropanolamine** and **chlorphenamine**.[1] The reason for this interaction is not understood and there is too little information to make any statement about its general importance.

1. Huestis RD, Arnold LE. Possible antagonism of amphetamine by decongestant-antihistamine compounds. *J Pediatr* (1974) 85, 579–80.

Methylphenidate + Carbamazepine

Carbamazepine may reduce methylphenidate levels.

Clinical evidence, mechanism, importance and management

A 7-year-old boy with attention deficit disorder taking carbamazepine 1 g daily for grand mal epilepsy was referred because of unmanageable behaviour. He failed to respond to methylphenidate in doses of up to 30 mg every 4 hours, and his blood levels of both methylphenidate and its metabolites were undetectable. The authors of the report attributed this to an interaction with the carbamazepine.[1] Similarly, symptoms of attention deficit hyperactivity disorder worsened in a 13-year-old girl taking methylphenidate after she also took carbamazepine. Methylphenidate serum levels decreased markedly and the dose of methylphenidate had to be increased from 20 mg three times daily to 60 mg three times daily to regain a benefit similar to that achieved before the addition of carbamazepine.[2] However, another report describes 4 out of 7 children taking methylphenidate and carbamazepine in whom the combination was successful. Blood levels of methylphenidate were apparently not measured.[3] Despite the scarcity of the information, and the cases of apparently successful use, it would seem wise to consider carbamazepine as a possible cause if patients do not respond adequately to methylphenidate. If this occurs, consider increasing the methylphenidate dose.

Note that the manufacturer says methylphenidate should be used with caution in patients with epilepsy, as clinical experience has shown that it can cause an increase in seizure frequency in a small number of such patients. If seizure frequency increases, methylphenidate should be discontinued.[4]

1. Behar D, Schaller J, Spreat S. Extreme reduction of methylphenidate levels by carbamazepine. *J Am Acad Child Adolesc Psychiatry* (1998) 37, 1128–9.
2. Schaller JL, Behar D. Carbamazepine and methylphenidate in ADHD. *J Am Acad Child Adolesc Psychiatry* (1999) 38, 112–13.
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4. Ritalin (Methylphenidate hydrochloride). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, June 2007.

Methylphenidate + Clonidine

Much publicised fears about the serious consequences of using methylphenidate with clonidine appear to be unfounded. There is some evidence to suggest that concurrent use can be both safe and effective.

Clinical evidence, mechanism, importance and management

There have been fears about serious adverse events when methylphenidate is taken with clonidine,[1] due to reports of 3 deaths in children taking both drugs. One child died from ventricular fibrillation due to cardiac abnormalities, one from cardiac arrest attributed to an overdose of fluoxetine, and the third death was unexplained. Studies of these 3 cases and one other failed to establish any link between the use of methylphenidate with clonidine and these deaths, the final broad conclusion being that the event was largely a media-inspired scare story built on inconclusive evidence.[2,3] However, there are theoretical reasons to be concerned about combining clonidine and methylphenidate (which have opposing adrenergic effects), because missed doses, extra doses, or mistimed doses can lead to significant hypertension and/or tachycardia or hypotension and/or bradycardia.[2] These adverse responses have been reported in children given clonidine alone and in combination with methylphenidate.[4,5] Furthermore, one study suggested a potential pharmacokinetic interaction, with methylphenidate lowering clonidine plasma levels.[6]

However, over the 2 years following the initial adverse reports, there did not appear to be any more data to support an increase in deaths associated with the combination and the use of methylphenidate with clonidine appeared to be beneficial.[7] A small-scale pilot study in 24 patients suggested that the combination is both safe and effective for the treatment of attention deficit hyperactivity disorder (ADHD).[8] Similarly, a study in children with both ADHD and Tourette's syndrome found that clonidine used with methylphenidate was more effective than either drug alone, and only one child had evidence of adverse cardiac effects.[9] Furthermore, the manufacturers of one formulation of methylphenidate[1] said that, as of 2002, they were not aware of any reports describing adverse events when *Concerta XL* (methylphenidate) was used with clonidine.

1. Janssen-Cilag. Personal communication, April 2002.
2. Popper CW. Combining methylphenidate and clonidine: pharmacologic questions and news reports about sudden death. *J Child Adolesc Psychopharmacol* (1995) 5, 157–66.
3. Fenichel RR. Combining methylphenidate and clonidine: the role of post-marketing surveillance. *J Child Adolesc Psychopharmacol* (1995) 5, 155–6.
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5. Cantwell DP, Swanson J, Connor DF. Case study: adverse response to clonidine. *J Am Acad Child Adolesc Psychiatry* (1997) 36, 539–44.
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8. Connor DF, Barkley RA, Davis HT. A pilot study of methylphenidate, clonidine, or the combination in ADHD comorbid with aggressive oppositional defiant or conduct disorder. *Clin Pediatr (Phila)* (2000) 39, 15–25.
9. Tourette's Syndrome Study Group. Treatment of ADHD in children with tics: a randomized controlled trial. *Neurology* (2002) 58, 527–36.

Methylphenidate + Cocaine

Methylphenidate does not appear to alter the pharmacokinetics or physiological effects of cocaine to a clinically significant extent.

Clinical evidence, mechanism, importance and management

A placebo-controlled study in 7 otherwise healthy cocaine-dependent subjects found that methylphenidate 60 or 90 mg was well tolerated, did not significantly affect the pharmacokinetics of intravenous cocaine 20 or 40 mg, and did not have a clinically significant effect on the physiological effects of cocaine. However, some of the positive subjective effects (desire for cocaine and good drug effects) of cocaine were decreased. The results suggested that although both drugs can cause cardiovascular and CNS stimulation, in the doses studied, methylphenidate could be given to active cocaine users without any serious adverse reaction.[1]

1. Winhusen T, Somoza E, Singal BM, Harrer J, Apparaju S, Mezinskis J, Desai P, Elkashef A, Chiang CN, Horn P. Methylphenidate and cocaine: a placebo-controlled drug interaction study. *Pharmacol Biochem Behav* (2006) 85, 29–38.

Methylphenidate + Disulfiram

A psychotic episode occurred in a patient taking disulfiram when methylphenidate was also given.

Clinical evidence

A 33-year-old man who was taking disulfiram 400 mg daily, without any noticeable adverse effects, experienced a psychotic-like episode after receiving a single 36-mg dose of modified-release methylphenidate. He discontinued the methylphenidate, but continued to take the disulfiram, and when assessed 2 months later there was no clinical evidence of psychosis, anxiety or depression. After a further 3 months, the disulfiram was discontinued and he took methylphenidate without any adverse effect or recurrence of the psychotic experience.

Mechanism

It was suggested that an interaction might have occurred as disulfiram blocks dopamine-beta-hydroxylase. Low levels of this enzyme have been associated with psychotic symptoms.

Importance and management

Evidence of an interaction appears to be limited to this case report. As the effects of disulfiram persist for up to 2 weeks this interaction may occur even after the disulfiram is stopped. It has been suggested that a significant washout period should be observed before starting methylphenidate; alternatively, a non-dopaminergic drug might be preferred for the treatment of attention deficit hyperactivity disorder (ADHD) if disulfiram is being taken.[1] Note that one manufacturer of methylphenidate contraindicates its use in patients with alcoholism[2] and caution is advised in emotionally unstable patients, such as those with a history of alcoholism,[2-4] because such patients may increase the dosage on their own initiative.[3]

1. Caci H, Baylé F. A case of disulfiram-methylphenidate interaction: implications for treatment. *Am J Psychiatry* (2007) 164, 1759.
2. Concerta XL (Methylphenidate hydrochloride). Janssen-Cilag Ltd. UK Summary of product characteristics, November 2009.
3. Ritalin (Methylphenidate hydrochloride). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, June 2007.
4. Concerta (Methylphenidate hydrochloride). McNeil Pediatrics. US Prescribing information, June 2008.

Methylphenidate + Risperidone

The use of methylphenidate with risperidone may possibly increase the risk of dyskinesias. Furthermore, there may be an increased risk of adverse effects if methylphenidate is started following risperidone withdrawal.

Clinical evidence

Although clinical studies have suggested that the use of risperidone with a psychostimulant (including methylphenidate) is safe, effective, and does not increase the incidence of adverse effects,[1] a limited case series suggested that children taking a psychostimulant and an atypical antipsychotic had a higher propensity for movement abnormalities.[2] A number of case reports support this suggestion. For example, a 7-year-old boy experienced acute dyskinesia, overactivity, distress, headache, fatigue and vomiting within 8 hours of starting to take modified-release methylphenidate 36 mg in place of risperidone, which was stopped abruptly 12 hours earlier. Similar but less severe symptoms were seen 5 months later when methylphenidate was started 6 days after the end of a course of risperidone which was reduced over 4 weeks.[3] Another report describes a patient taking methylphenidate 15 mg and risperidone 1.5 mg, both three times daily, who developed acute dystonia when the methylphenidate was withdrawn. He recovered when given benzatropine.[4] A further case of extrapyramidal symptoms occurred in a child taking methylphenidate, risperidone, sertraline and tropisetron.[5]

A case report describes 3 children who developed severe behavioural adverse reactions when switching from risperidone to methylphenidate. A 5 year-old boy who had been taking risperidone 1 mg daily for 8 months became agitated, irritable, vigilant and violent when risperidone was abruptly withdrawn and methylphenidate 15 mg daily started 2 days later. The methylphenidate was discontinued and the severe behavioural reactions disappeared. After a 6-week drug-free period, methylphenidate was restarted at the same dose with beneficial effects on attention and hyperactivity. A similar reaction occurred in a 6-year-old girl when risperidone was discontinued abruptly and methylphenidate was started. Similarly, a 15-year-old girl was given risperidone 1 mg daily to alleviate the symptoms of attention deficit hyperactivity disorder (ADHD). When risperidone was stopped for one week withdrawal symptoms were not seen, but irritability and agitation were reported when methylphenidate 18 mg daily was started.[6]

Mechanism

Antipsychotics and psychostimulants have conflicting mechanisms of action in the CNS; risperidone is a combined serotonin and dopamine antagonist whereas methylphenidate is a dopamine agonist.[1,2] It has been suggested that adverse effects develop because stopping risperidone removes the dopaminergic blockade, which results in supersensitive dopamine receptors. Over-stimulation then occurs when methylphenidate, which has dopamine agonist actions, is started.[3]

Importance and management

The combination of risperidone and methylphenidate carries the risk of drug-induced dyskinesias and particular care should be taken if one of the drugs is discontinued. Slow antipsychotic withdrawal, followed by a drug-free interval has been suggested when switching from risperidone to methylphenidate.[3,6] Methylphenidate should then be initiated at a low dose and withdrawn immediately if a dyskinesia appears.[3]

1. Aman MG, Binder C, Turgay A. Risperidone effects in the presence/absence of psychostimulant medicine in children with ADHD, other disruptive behavior disorders, and subaverage IQ. *J Child Adolesc Psychopharmacol* (2004) 14, 243–54.
2. Sharp B, Perdue C. Abnormal motor movements associated with combining psychostimulants and atypical antipsychotics in children. *CNS Spectr* (2007) 12, 659–62.
3. Hollis CP, Thompson A. Acute dyskinesia on starting methylphenidate after risperidone withdrawal. *Pediatr Neurol* (2007) 37, 287–8.
4. Benjamin E, Salek S. Stimulant-atypical antipsychotic interaction and acute dystonia. *J Am Acad Child Adolesc Psychiatry* (2005) 44, 510–12. Erratum. ibid., 960.
5. Teoh L, Allen H, Kowalenko N. Drug-induced extrapyramidal reactions. *J Paediatr Child Health* (2002) 38, 95–7.
6. Sabuncuoglu O. Risperidone-to-methylphenidate switch reaction in children: three cases. *J Psychopharmacol* (2007) 21, 216–19.

Methylphenidate + St John's wort (*Hypericum perforatum*)

St John's wort may decrease the efficacy of methylphenidate in the treatment of attention-deficit hyperactivity disorder.

Clinical evidence, mechanism, importance and management

A 22-year-old man who had been successfully treated with methylphenidate 20 mg daily for attention deficit hyperactivity disorder (ADHD) for 6 months started to take St John's wort 600 mg daily. Over the next 4 months the efficacy of the methylphenidate decreased, but 3 weeks after the St John's wort was stopped, the methylphenidate became more effective. No adverse effects were seen during the concurrent use of the herbal medicine and drug.[1]

This is an isolated case report and therefore no general recommendations can be made. However, if the efficacy of methylphenidate becomes reduced, it may be worth questioning the patient about St John's wort use, and giving consideration to stopping the herb.

1. Niederhofer H. St John's wort may diminish methylphenidate's efficacy in treating patients suffering from attention deficit hyperactivity disorder. *Med Hypotheses* (2007) 68, 1189.

Modafinil + Cocaine

Modafinil does not appear to alter haemodynamic effects of cocaine, but it may blunt cocaine-induced euphoria. Modafinil reduces the peak plasma levels of cocaine.

Clinical evidence, mechanism, importance and management

In a placebo-controlled study in 7 subjects, pretreatment with modafinil 200 or 400 mg daily for 4 days did not affect the increase in blood pressure, pulse or temperature; or changes in ECG, produced by a single 30-mg intravenous dose of cocaine. However, subjective cocaine-induced euphoria was blunted.[1] A similar lack of any significant haemodynamic interaction was found in 12 cocaine-dependent subjects who were given modafinil 400 or 800 mg daily and infusions of 20 or 40 mg of cocaine.[2] No serious adverse events were reported in a study of cocaine abstinence in 30 cocaine-dependent patients given modafinil 200 to 400 mg daily for 8 weeks, when compared with 32 patients given placebo. However, modafinil increased the incidence of minor adverse events including nausea, dizziness, anxiety and tachycardia, which required a dose reduction in 6 patients.[3]

In a placebo-controlled study in 12 cocaine-dependent subjects, modafinil 400 or 800 mg daily for 7 days reduced peak plasma levels of intravenous cocaine 40 mg given over one minute. The $AUC_{0\text{-}3}$ of cocaine was reduced by about 20% by modafinil, but there were no statistically significant changes in the total AUC, clearance, or elimination half-life of cocaine.[4]

Note that the manufacturer of modafinil advises caution if modafinil is given to patients with history of drug or illicit substance abuse.[5]

1. Dackis CA, Lynch KG, Yu E, Samaha FF, Kampman KM, Cornish JW, Rowan A, Poole S, White L, O'Brien CP. Modafinil and cocaine: a double-blind, placebo-controlled drug interaction study. *Drug Alcohol Depend* (2003) 70, 29–37.
2. Malcolm R, Swayngim K, Donovan JL, DeVane CL, Elkashef A, Chiang N, Khan R, Mojsiak J, Myrick DL, Hedden S, Cochran K, Woolson RF. Modafinil and cocaine interactions. *Am J Drug Alcohol Abuse* (2006) 32, 577–87.
3. Dackis CA, Kampman KM, Lynch KG, Pettinati HM, O'Brien CP. A double-blind, placebo-controlled trial of modafinil for cocaine dependence. *Neuropsychopharmacology* (2005) 30, 205–11.
4. Donovan JL, DeVane CL, Malcolm RJ, Mojsiak J, Chiang CN, Elkashef A, Taylor RM. Modafinil influences the pharmacokinetics of intravenous cocaine in healthy cocaine-dependent volunteers. *Clin Pharmacokinet* (2005) 44, 753–65.
5. Provigil (Modafinil). Cephalon (UK) Ltd. UK Summary of product characteristics, November 2009.

Modafinil + Dexamfetamine

No pharmacokinetic interaction appears to occur between modafinil and dexamfetamine.

Clinical evidence, mechanism, importance and management

In a steady-state study, 23 healthy subjects were given modafinil 200 mg daily for 7 days, then 400 mg daily for 3 weeks. During the last week, 10 of the subjects were also given dexamfetamine 20 mg daily, 7 hours after their modafinil dose. Dexamfetamine caused no significant change in the pharmacokinetics of modafinil and the combination was well tolerated. In addition, the pharmacokinetics of dexamfetamine did not appear to be affected by modafinil, when compared with values reported in the literature.[1] Similar results were found in a single-dose study.[2] No dosage adjustments appear to be necessary on concurrent use.

1. Hellriegel ET, Arora S, Nelson M, Robertson P. Steady-state pharmacokinetics and tolerability of modafinil administered alone or in combination with dextroamphetamine in healthy volunteers. *J Clin Pharmacol* (2002) 42, 448–58.
2. Wong YN, Wang L, Hartman L, Simcoe D, Chen Y, Laughton W, Eldon R, Markland C, Grebow P. Comparison of the single-dose pharmacokinetics and tolerability of modafinil and dextroamphetamine administered alone or in combination in healthy male volunteers. *J Clin Pharmacol* (1998) 38, 971–8.

Modafinil + Methylphenidate

No pharmacokinetic interaction appears to occur between modafinil and methylphenidate.

Clinical evidence, mechanism, importance and management

In a single-dose study in healthy subjects, modafinil 200 mg and methylphenidate 40 mg were given together without any clinically relevant changes in the pharmacokinetics of either drug.[1] In a steady-state study, 30 healthy subjects were given modafinil 200 mg daily for 7 days, then 400 mg daily for 3 weeks. During the last week, 16 of the subjects were also given methylphenidate 20 mg daily, taken 8 hours after their modafinil dose. Methylphenidate caused no significant change in the pharmacokinetics of modafinil. In addition, the pharmacokinetics of methylphenidate did not appear to be affected by modafinil, when compared with values reported in the literature.[2] No dosage adjustments would appear to be necessary on concurrent use.

1. Wong YN, King SP, Laughton WB, McCormick GC, Grebow PE. Single-dose pharmacokinetics of modafinil and methylphenidate given alone or in combination in healthy male volunteers. *J Clin Pharmacol* (1998) 38, 276–82.
2. Hellriegel ET, Arora S, Nelson M, Robertson P. Steady-state pharmacokinetics and tolerability of modafinil given alone or in combination with methylphenidate in healthy volunteers. *J Clin Pharmacol* (2001) 41, 895–904.

Modafinil + Miscellaneous

The manufacturers advise caution if enzyme-inducing antiepileptics, particularly phenytoin, are given with modafinil. There is speculation, based on *in vitro* studies, about some possible interactions with other drugs, such as CYP2C19 substrates. Modafinil is a slight inducer of CYP3A4 and therefore may be expected to interact with substrates of this isoenzyme.

Clinical evidence, mechanism, importance and management

(a) CYP3A4 inducers and inhibitors

Animal studies suggest that **phenobarbital** reduces the serum levels of modafinil; both drugs are inducers of the cytochrome P450 isoenzyme

CYP3A4.[1] The manufacturers similarly suggest that this is a possibility.[2,3]

There is no clinical evidence of interactions with other potent enzyme inducers, but the manufacturers suggest that **carbamazepine**[2,3] and **rifampicin** (**rifampin**)[3] may reduce modafinil levels, see also *Phenytoin*, below. Also, inhibitors of CYP3A4 (**itraconazole** and **ketoconazole** are specifically named) are predicted to increase modafinil levels.[3] However, clinically relevant interactions with either CYP3A4 inducers or inhibitors seem unlikely because CYP3A4 is not the only cytochrome P450 isoenzyme that is involved in the metabolism of modafinil.

(b) CYP3A4 substrates

Modafinil is a minor inducer of the cytochrome P450 isoenzyme CYP3A4 *in vitro*. The manufacturers therefore predict that it may reduce the levels of drugs that are CYP3A4 substrates,[2,3] particularly those that undergo significant presystemic metabolism.[2] The UK manufacturer[2] specifically names **buspirone**, ciclosporin, midazolam, triazolam, **protease inhibitors**, and most of the **calcium-channel blockers** and **statins** [note that only some statins, namely atorvastatin, lovastatin and simvastatin, are CYP3A4 substrates]. For a list of substrates of CYP3A4, see 'Table 1.4', (p.6). Interactions have been seen with 'ciclosporin', (p.1244), and 'triazolam', (p.855).

(c) CYP2C19 substrates

In vitro, modafinil is a reversible inhibitor of CYP2C19 and it might therefore reduce the metabolism of drugs that are largely metabolised by CYP2C19. The manufacturers specifically name **propranolol**[2,3] and **omeprazole**[2] and suggest that a dose reduction may be necessary.[2,3] However, a clinically meaningful interaction with these two drugs seems unlikely, as propranolol is mainly metabolised by CYP2D6 and CYP1A2, and omeprazole has a very wide therapeutic margin. See also *Phenytoin*, below.

(d) Phenytoin

There is *in vitro* evidence to indicate that modafinil may possibly inhibit the metabolism of phenytoin by the cytochrome P450 isoenzymes CYP2C9 and CYP2C19, and so there is some reason for monitoring concurrent use for evidence of increased phenytoin effects and toxicity.[2,3] Nevertheless, modafinil did not have any clinically relevant inhibitory effect on CYP2C9 using warfarin as a substrate (see 'Coumarins + Modafinil', p.479). Note that phenytoin is also an inducer of CYP3A4, see under *CYP3A4 inducers and inhibitors*, above.

1. Moachon G, Kanmacher I, Clenet M, Matinier D. Pharmacokinetic profile of modafinil. *Drugs Today* (1996) 32 (Suppl 1), 23–33.
2. Provigil (Modafinil). Cephalon (UK) Ltd. UK Summary of product characteristics, November 2009.
3. Provigil (Modafinil). Cephalon, Inc. US Prescribing information, March 2008.

Orlistat + Anorectics

In two pharmacokinetic studies, healthy subjects were given phentermine 37.5 mg daily for 7 days or sibutramine 10 mg daily for 7 days with orlistat 120 mg three times daily for 6 or 7 days. Orlistat did not affect the bioavailability of phentermine or the active metabolites of sibutramine, and concurrent use did not appear to increase the incidence of adverse effects, or cause significant changes in vital signs (e.g. heart rate, blood pressure).[1]

1. Zhi J, Moore R, Kanitra L, Mulligan TE. Pharmacokinetic evaluation of the possible interaction between selected concomitant medications and orlistat at steady state in healthy subjects. *J Clin Pharmacol* (2002) 42, 1011–19.

Orlistat + Sucrose polyesters

A single case report suggests that the concurrent use of orlistat and sucrose polyesters (*Olestra* – used in some foods as a fat substitute) can result in additive gastrointestinal adverse effects (soft, fatty/oily stools, increased flatus and abdominal pain). In the case in question, symptoms resolved when the patient stopped eating *Olestra*-containing food while continuing to take orlistat.[1]

1. Heck AM, Calis KA, McDuffie JR, Carobene SE, Yanovski JA. Additive gastrointestinal effects with concomitant use of olestra and orlistat. *Ann Pharmacother* (2002) 36, 1003–5.

Phenmetrazine + Barbiturates

The CNS adverse effects and the weight-reducing effects of phenmetrazine are reduced by amobarbital. Psychotic episodes occurred in two patients taking barbiturates and phenmetrazine.

Clinical evidence, mechanism, importance and management

A comparative study in 50 overweight adults, of the effects of phenmetrazine 25 mg three times daily with or without **amobarbital** 30 mg three times daily, found that although the adverse CNS effects, particularly insomnia, headache and nervousness, were decreased by the presence of the barbiturate, the weight-reducing effects were also decreased (by 65%).[1]

A case report describes 2 cases of psychoses induced by the long-term use of barbiturates in combination with phenmetrazine, which resolved when the barbiturates or phenmetrazine were withdrawn.[2]

1. Hadler AJ. Phenmetrazine vs. phenmetrazine with amobarbital for weight reduction: a double-blind study. *Curr Ther Res* (1969) 11, 750–4.
2. Vinařová E, Vinař O. Psychotické epizody, vyvolané kombinací barbiturátů s fenmetrazinem. *Cesk Psychiatr* (1971) 67, 284–91.

Rimonabant + Miscellaneous

Ketoconazole doubles the AUC of rimonabant; other potent CYP3A4 inhibitors are expected to interact similarly, whereas potent CYP3A4 inducers are expected to lower rimonabant levels. Rimonabant does not appear to affect the levels of oral contraceptives, digoxin, midazolam, or warfarin, and alcohol, lorazepam, and orlistat do not appear to alter rimonabant levels.

Clinical evidence, mechanism, importance and management

(a) CYP3A4 inducers and inhibitors

Rimonabant is partly metabolised by the cytochrome P450 isoenzyme CYP3A4. **Ketoconazole**, a potent CYP3A4 inhibitor, doubles the AUC of rimonabant. The manufacturer therefore expects that other potent CYP3A4 inhibitors (they name **clarithromycin**, **itraconazole**, **nefazodone**, **ritonavir**, and **telithromycin**) will also raise rimonabant levels, and they therefore advise caution on concurrent use.[1] They similarly suggest that potent CYP3A4 inducers (such as **carbamazepine**, **phenobarbital**, **phenytoin**, **rifampicin** (**rifampin**) and **St John's wort**) may lower rimonabant plasma levels.[1] If concurrent use is necessary, monitor to ensure that rimonabant remains effective. See 'Table 1.4', (p.6), for a list of clinically relevant CYP3A4 inducers and inhibitors.

(b) Miscellaneous

Digoxin, **midazolam**, and **warfarin** were given with rimonabant in clinical studies to assess the effect of rimonabant on P-glycoprotein, CYP3A4 and CYP2C9, respectively. As rimonabant did not interact with these drugs, the manufacturer says this confirms *in vitro* evidence that it has no effect on these isoenzymes or transporter, and would not be expected to interact with other substrates of P-glycoprotein, CYP3A4 or CYP2C9. The manufacturer also notes that rimonabant had no effect on the pharmacokinetics of an oral contraceptive containing **ethinylestradiol** and **levonorgestrel**, and that **alcohol**, **lorazepam**, and **orlistat** did not affect the plasma levels of rimonabant.[1]

1. Acomplia (Rimonabant). Sanofi-Aventis. UK Summary of product characteristics, October 2007.

Sibutramine + Azoles

Ketoconazole modestly increases the steady-state levels of sibutramine and its active metabolites.

Clinical evidence, mechanism, importance and management

Twelve obese patients were given sibutramine 20 mg daily for 14 days, with **ketoconazole** 200 mg twice daily for the last 7 days. **Ketoconazole** caused moderate increases in the serum levels of sibutramine and its two metabolites (AUC and maximum serum level increases of 58% and 36%,

respectively, for metabolites M_1, and 20% and 19%, respectively, for M_2, probably by inhibition of the cytochrome P450 isoenzyme CYP3A4). Small increases in heart rates were seen (2.5 bpm at 4 hours and 1.4 bpm at 8 hours), while ECG parameters were unchanged.[1] Sibutramine alone can cause an increase in heart rate, and a rate increase of 10 bpm is an indication to withdraw the drug. Therefore, the manufacturer in the UK[2] suggests caution should be exercised when sibutramine is used with **ketoconazole**. They also suggest that, due to its ability to inhibit CYP3A4, **itraconazole** should also be used with caution.

1. Hinson JL, Leone MB, Kisiki MJ, Moult JT, Trammel JT, Faulkner RD. Steady-state interaction study of sibutramine (Meridia) and ketoconazole in uncomplicated obese subjects. *Pharm Res* (1996) 13 (9 Suppl), S116.
2. Reductil (Sibutramine hydrochloride monohydrate). Abbott Laboratories Ltd. UK Summary of product characteristics, October 2007.

Sibutramine + Food

Food may delay the time to peak plasma levels of sibutramine and its metabolites. The bioavailability of sibutramine and possibly its M_1 metabolite may be increased by food.

Clinical evidence, mechanism, importance and management

A study in 6 healthy subjects found that, compared with the fasted state, a **high-fat meal** increased the AUC and maximum plasma level of sibutramine 15 mg by about five- and threefold, respectively, and delayed the peak plasma level by 2 to 4 hours. The AUC and maximum plasma level of the M_1 metabolite was increased twofold, but the M_2 metabolite was not affected.[1] In contrast, another study found that giving a single 20-mg dose of sibutramine with a **standard breakfast** modestly reduced the peak levels of the active metabolites M_1 and M_2 by 27% and 32%, respectively, and delayed the peak levels by about 3 hours. However, the AUCs of M_1 and M_2 were not significantly altered.[2] Despite the large increases in sibutramine levels the manufacturers say that it may be given with or without food.[2,3] This is presumably because sibutramine is rapidly metabolised to its active metabolites, which are only modestly affected by food.

1. Abolfathi Z, Couture J, Vallée F, LeBel M, Tanguay M, Masson É. A pilot study to evaluate the pharmacokinetics of sibutramine in healthy subjects under fasting and fed conditions. *J Pharm Pharm Sci* (2004) 7, 345–9.
2. Meridia (Sibutramine hydrochloride monohydrate). Abbott Laboratories. US Prescribing information, May 2009.
3. Reductil (Sibutramine hydrochloride monohydrate). Abbott Laboratories Ltd. UK Summary of product characteristics, October 2007.

Sibutramine + Macrolides

Although no interaction appears to occur between sibutramine and erythromycin, the UK manufacturer still cautions the use of sibutramine with clarithromycin, erythromycin and troleandomycin.

Clinical evidence, mechanism, importance and management

Twelve obese patients were given sibutramine 20 mg daily for 14 days, with **erythromycin** 500 mg three times daily for the last 7 days. It was found that, apart from some slight and unimportant changes in the pharmacokinetics of the metabolites of sibutramine (probably caused by some inhibition of the cytochrome P450 isoenzyme CYP3A4), the pharmacokinetics of sibutramine were not significantly altered by **erythromycin**. No blood pressure changes were seen and only very small and clinically irrelevant increases in the QTc interval and heart rate occurred.[1] The extent of any interaction appears to be too small to matter,[1] and there would seem to be no reason for avoiding the concurrent use of these two drugs. Despite this, the UK manufacturer still says that caution should be exercised, probably because sibutramine is principally metabolised by CYP3A4.[2] They also extrapolate their caution to other potent CYP3A4 inhibiting macrolides, namely **clarithromycin** and **troleandomycin**.

1. Hinson JL, Leone MB, Leese PT, Moult JT, Carter FJ, Faulkner RD. Steady-state interaction study of sibutramine (Meridia) and erythromycin in uncomplicated obese subjects. *Pharm Res* (1996) 13 (9 Suppl), S116.
2. Reductil (Sibutramine hydrochloride monohydrate). Abbott Laboratories Ltd. UK Summary of product characteristics, October 2007.

Sibutramine + Miscellaneous

The manufacturers of sibutramine contraindicate its use with MAOIs and centrally acting appetite suppressants, and suggest that it should not be given with serotonergic drugs or cold and influenza remedies containing sympathomimetic agents. The plasma levels of sibutramine are moderately increased by olanzapine and omeprazole, and are predicted to be increased by grapefruit juice. No clinically relevant pharmacokinetic interactions have been seen between sibutramine and cimetidine or simvastatin, and no interaction occurs with oral contraceptives.

Clinical evidence, mechanism, importance and management

(a) Centrally acting appetite suppressants, and drugs that raise blood pressure or heart rate

The manufacturers say that the concurrent use of sibutramine and other centrally acting appetite suppressants is contraindicated.[1,2] No work appears to have been done to see what happens if sibutramine is given with sympathomimetics including certain **decongestants**, **cough**, **cold** and **allergy medications**, but the manufacturers advise caution because of the risk of raised blood pressure or heart rate. The manufacturers in the UK and US both list **ephedrine** and **pseudoephedrine**,[1,2] while in the UK **xylometazoline** is also specifically named.[2]

(b) Cimetidine

When cimetidine 400 mg twice daily was given with sibutramine 15 mg once daily to 12 healthy subjects the maximum serum levels and AUCs of the combined sibutramine metabolites were increased by 3.4% and 7.3%, respectively.[1] These changes are too small to be of clinical significance, and there is no reason for avoiding the concurrent use of these two drugs.

(c) CYP3A4 inducers

The UK manufacturer states that **carbamazepine**, **dexamethasone**, **phenobarbital**, **phenytoin** and **rifampicin** (**rifampin**) are all inducers of CYP3A4, an isoenzyme involved in the metabolism of sibutramine.[2] These drugs might therefore increase the metabolism of sibutramine resulting in a fall in its serum levels. However, this has not been studied experimentally and, at the present time, the existence, the extent and the possible clinical relevance of any such interaction is unknown. Furthermore, clinically relevant interactions occurring as a result of **dexamethasone** inducing CYP3A4 appear rare.

(d) Grapefruit juice

Grapefruit juice is predicted to interact with sibutramine by inhibiting its metabolism by the cytochrome P450 isoenzyme CYP3A4.[3] It has been suggested that, as the manufacturer of sibutramine advises caution if CYP3A4 inhibitors such as ketoconazole are given, it might also be appropriate to suggest avoidance of grapefruit juice especially as patients might consider the 'grapefruit diet' as an adjunct to weight reduction.[3] However, only modest increases in sibutramine levels were seen with the potent CYP3A4 inhibitor, 'ketoconazole', (p.230), and therefore a clinically relevant interaction with grapefruit juice would not generally be anticipated.

(e) MAOIs

There are no reports of adverse reactions between sibutramine and the MAOIs. However, sibutramine inhibits serotonin reuptake, and because the serious serotonin syndrome can occur when MAOIs and SSRIs are used together, the manufacturers contraindicate the concurrent use of sibutramine and MAOIs. They say that 14 days should elapse between stopping either drug and starting the other.[1,2] The US manufacturer includes **selegiline** in this warning.[1]

(f) Olanzapine

Olanzapine has been reported to moderately increase the AUC and maximum plasma levels of sibutramine by 63% and 47%, respectively, in healthy subjects; sibutramine had no significant effect on olanzapine pharmacokinetics.[1] However, the UK manufacturer of sibutramine contraindicates its use both with and for 2 weeks after the use of antipsychotics.[2]

(g) Omeprazole

In a study in 26 healthy subjects, omeprazole 20 mg daily for 7 days increased the maximum plasma level and AUC of sibutramine by 57% and 67%, respectively, and increased the levels of the active M_1 metabolite by 30% and 40%, respectively. The pharmacokinetics of the M_2 metabolite

were not significantly affected. Sibutramine had no significant effect on omeprazole pharmacokinetics.[1] These changes are modest, and no dosage adjustment would be expected to be necessary on concurrent use.

(h) Oral contraceptives

A crossover study in 12 subjects found that sibutramine 15 mg daily, given for 8 weeks, had no clinically significant effect on the inhibition of ovulation caused by an oral contraceptive, and it was concluded that there is no need to use alternative contraceptive methods while taking sibutramine.[1]

(i) Serotonergic drugs

Because sibutramine inhibits serotonin uptake, and because the serious serotonin syndrome has been seen when serotonergic drugs were taken with SSRIs, the manufacturers say that sibutramine should not be taken with any serotonergic drugs.[1,2] They name **dextromethorphan**, **dihydroergotamine**, **fentanyl**, **pentazocine**, **pethidine** (**meperidine**), SSRIs, **sumatriptan**, and **tryptophan**. Possible cases have been reported for sibutramine and 'SSRIs', (p.1492). The US manufacturer also includes **lithium** in their list.[1] Note that this list is not exhaustive (see MAOIs under (e) above) and a case of the serotonin syndrome has been seen when 'venlafaxine', (p.1480), was given with sibutramine. The extent of the risk with these serotonergic drugs is not known, but because of the potential severity of the reaction this warning would seem to be a prudent precaution. For more information on the serotonin syndrome, see 'Additive or synergistic interactions', (p.9).

(j) Simvastatin

In a study in 27 healthy subjects, giving simvastatin 20 mg daily in the evening and sibutramine 15 mg daily in the morning for 7 days resulted in a slight decrease in sibutramine maximum plasma levels and AUC of 14% and 21%, respectively. The plasma levels of the active M_1 and M_2 metabolites combined were not significantly affected, although the plasma levels of the M_1 metabolite were slightly reduced. Sibutramine decreased the maximum levels and AUC of simvastatin by 25% and 15%, respectively, but the AUC of the active metabolite, simvastatin acid, was increased by 7%.[1] These changes are not expected to be clinically significant.

1. Meridia (Sibutramine hydrochloride monohydrate). Abbott Laboratories. US Prescribing information, May 2009.
2. Reductil (Sibutramine hydrochloride monohydrate). Abbott Laboratories Ltd. UK Summary of product characteristics, October 2007.
3. Bailey DG, Dresser GK. Interactions between grapefruit juice and cardiovascular drugs. *Am J Cardiovasc Drugs* (2004) 4, 281–97.

8

Anthelmintics, Antifungals and Antiprotozoals

'Table 8.1', (p.234) lists the drugs covered in this section by therapeutic group and drug class. If the anti-infective is the drug causing the interaction, the interaction is generally dealt with under the affected drug. Also note that drugs such as the 5-nitroimidazoles (e.g. metronidazole), which have actions against more than one type of organism (e.g. bacteria and protozoa) are covered under Antibacterials.

(a) Amphotericin B

Intravenous amphotericin B causes important pharmacodynamic interactions via additive nephrotoxicity and myelotoxicity, and may increase the cardiotoxicity of other drugs because of amphotericin-induced hypokalaemia. No important pharmacokinetic interactions are known. Lipid formulations such as liposomal amphotericin B are less nephrotoxic than conventional amphotericin, and would therefore be expected to interact less frequently. Orally administered amphotericin B is not absorbed systemically, and no interactions are established.

(b) Azole antifungals

The most important interactions affecting and caused by the azole antifungals are those resulting from inhibition and induction of cytochrome P450 isoenzymes.

- **Fluconazole** is principally (80%) excreted unchanged in the urine, so is less affected by enzyme inducers and inhibitors than some other azoles. Fluconazole is a potent inhibitor of CYP2C9 and CYP2C19, and generally only inhibits CYP3A4 at high doses (greater than 200 mg daily). Interactions are less likely with single doses used for genital candidiasis than with longer term use.
- **Itraconazole** is extensively metabolised by CYP3A4, and its metabolism may become saturated with multiple dosing. Itraconazole and its major metabolite, hydroxy-itraconazole are potent inhibitors of CYP3A4.
- **Ketoconazole** is extensively metabolised, particularly by CYP3A4. It is also a potent inhibitor of CYP3A4.
- **Miconazole** is a potent inhibitor of CYP2C9. Because this azole is generally used topically as pessaries, cream, or an oral gel, it is less likely to cause interactions, although it should be noted that at maximum doses of the oral gel, sufficient may be absorbed to cause systemic effects, see 'warfarin', (p.438).
- **Posaconazole** is metabolised via UDP-glucuronidation, and may also be a substrate for P-glycoprotein. Posaconazole is an inhibitor of CYP3A4.
- **Voriconazole** is metabolised by CYP2C19, CYP2C9, and to a lesser extent by CYP3A4. Voriconazole is an inhibitor of CYP2C9, CYP2C19 and CYP3A4.

An number of other azole antifungals are only used topically in the form of creams or intravaginal preparations, and have not been associated with drug interactions, presumably since their systemic absorption is so low, see 'Azoles; Topical + Miscellaneous', p.251.

Fluconazole, ketoconazole and voriconazole have been associated with prolongation of the QT interval, although generally not to a clinically relevant extent. However, they may also raise the levels of other drugs that prolong the QT interval, and these combinations are often contraindicated, see 'Antihistamines + Azoles', p.665.

1. Venkatakrishnan K, von Moltke LL, Greenblatt DJ. Effects of the antifungal agents on oxidative drug metabolism: clinical relevance. *Clin Pharmacokinet* (2000) 38, 111–80.

Table 8.1 Anthelmintics, antifungals and antimalarials and other antiprotozoals

Group	*Drugs*
Anthelmintics	
Benzimidazole derivatives	Albendazole, Flubendazole, Mebendazole, Tiabendazole (Thiabendazole)
Organophosphorous compounds	Metrifonate (Metriphonate)
Other	Diethylcarbamazine, Ivermectin, Levamisole, Niclosamide, Oxamniquine, Piperazine, Praziquantel, Pyrantel
Antifungals	
Allylamines	Naftifine, Terbinafine
Azoles:	
Imidazoles	Bifonazole,* Butoconazole,* Chlormidazole,* Clotrimazole,* Econazole,* Fenticonazole,* Isoconazole,* Ketoconazole, Miconazole, Oxiconazole,* Sertaconazole,* Sulconazole,* Tioconazole*
Triazoles	Fluconazole, Itraconazole, Posaconazole, Terconazole,* Voriconazole
Echinocandins	Anidulafungin, Caspofungin, Micafungin
Polyene antibiotics	Amphotericin B, Natamycin,* Nystatin*
Other	Amorolfine,* Butenafine,* Ciclopirox,* Flucytosine, Griseofulvin, Tolnaftate*
Antimalarials	
4-aminoquinolines	Amodiaquine, Chloroquine, Hydroxychloroquine
8-aminoquinolines	Primaquine
4-methanolquinolines	Mefloquine, Quinine
Artemisinin derivatives	Artemether, Artemotil, Artesunate, Co-artemether (Artemether/Lumefantrine)
Other	Atovaquone, Doxycycline,† Halofantrine, Lumefantrine, Proguanil, Pyrimethamine/Sulfadoxine, Tetracycline†
Antiprotozoals	
Antimony compounds	Sodium stibogluconate
Arsenicals	Melarsoprol
5-nitroimidazoles†	Metronidazole, Ornidazole, Tinidazole
Nitrofuran	Furazolidone, Nifurtimox
Other	Atovaquone, Diiodohydroxyquinoline, Diloxanide furoate, Eflornithine, Mepacrine, Pentamidine, Pyrimethamine/Sulfadiazine, Suramin

*Mainly used by topical application
†Covered under Antibacterials

Albendazole with Ivermectin + Azithromycin

The combination of albendazole and ivermectin with azithromycin causes moderate changes in the pharmacokinetics of all three drugs.

Clinical evidence, mechanism, importance and management

A study in 18 healthy subjects investigated the interaction between the combination of single doses of ivermectin 200 micrograms/kg (to the nearest 3 mg) and albendazole 400 mg, with and without a single 500-mg dose of azithromycin. The combination of all three drugs increased the AUC and maximum concentration of azithromycin by 13% and 20%, respectively, and of ivermectin by 31% and 27%, respectively. In addition, the AUC and maximum concentration of albendazole sulfoxide (active metabolite of albendazole) were reduced by 16% and 14%, respectively. No serious adverse effects were reported.[1] These changes are unlikely to be of clinical significance, although the authors note that large inter-individual variability was seen in the pharmacokinetics of these drugs, suggesting that some patients may experience greater effects. Further study is needed to establish the safety and efficacy of concurrent use.

Note that a study has found no pharmacokinetic interaction between albendazole and ivermectin, see 'Albendazole + Ivermectin', p.236.

1. Amsden GW, Gregory TB, Michalak CA, Glue P, Knirsch CA. Pharmacokinetics of azithromycin and the combination of ivermectin and albendazole when administered alone and concurrently in healthy volunteers. *Am J Trop Med Hyg* (2007) 76, 1153–7.

Albendazole or Mebendazole + Antiepileptics; Enzyme-inducing

Carbamazepine, phenytoin and phenobarbital lower the plasma levels of albendazole and mebendazole.

Clinical evidence

(a) Albendazole

In one study, 32 patients with intraparenchymatous neurocysticercosis were given albendazole 7.5 mg/kg every 12 hours for 8 days. These patients were also taking either **phenytoin** 200 to 300 mg daily (9 patients), **carbamazepine** 600 to 1200 mg daily (9 patients), or **phenobarbital** 100 to 300 mg daily (5 patients) all for at least 3 months, and a control group (9 patients) who did not receive any antiepileptics. The AUCs for (+)-albendazole sulfoxide were 49%, 66%, and 61% lower than the control group for the **carbamazepine**, **phenytoin**, and **phenobarbital** groups, respectively. The maximum plasma levels of (+)-albendazole sulfoxide were 50 to 63% lower and the half-lives about 3 to 4 hours shorter. The AUCs, peak plasma levels and half-life of (–)-albendazole sulfoxide (present in much lower levels than the (+)-isomer) were similarly reduced by the antiepileptics.[1]

(b) Mebendazole

A retrospective analysis found that patients with echinococcosis taking mebendazole and **phenytoin** or **carbamazepine** tended to have lower plasma mebendazole levels than patients not taking these antiepileptics.[2] Some patients had a clinically important rise in mebendazole levels when they were switched from **phenytoin** or **carbamazepine** to valproic acid,[2] although this increase would be expected when the enzyme-inducing drug is stopped.

Mechanism

Carbamazepine, phenytoin and phenobarbital appear to induce the oxidative metabolism of albendazole by the cytochrome P450 subfamily CYP3A to roughly the same extent, resulting in significantly reduced levels of albendazole sulfoxide, the active metabolite of albendazole. Mebendazole is similarly affected.

Importance and management

The pharmacokinetic interactions between albendazole or mebendazole and enzyme-inducing antiepileptics are established, and are likely to be clinically important when these anthelmintics are used to treat systemic worm infections. It may be necessary to increase the albendazole or mebendazole dosage in patients treated for systemic worm infections and also taking phenytoin (and therefore probably **fosphenytoin**), carbamazepine or phenobarbital (and therefore **primidone**). Monitor the outcome of concurrent use.

The interactions are of no importance when these anthelmintics are used for intestinal worm infections (where their action is a local effect on the worms in the gut), which is the most common use of mebendazole in particular.

1. Lanchote VL, Garcia FS, Dreossi SAC, Takayanagui OM. Pharmacokinetic interaction between albendazole sulfoxide enantiomers and antiepileptic drugs in patients with neurocysticercosis. *Ther Drug Monit* (2002) 24, 338–45.

2. Luder PJ, Siffert B, Witassek F, Meister F, Bircher J. Treatment of hydatid disease with high oral doses of mebendazole. Long-term follow-up of plasma mebendazole levels and drug interactions. *Eur J Clin Pharmacol* (1986) 31, 443–8.

Albendazole or Mebendazole + Cimetidine

Cimetidine raises serum mebendazole levels, and prolongs the half-life of albendazole sulfoxide, the active metabolite of albendazole. In some cases cimetidine appeared to increase the effectiveness of these anthelmintics against systemic infection.

Clinical evidence

(a) Albendazole

A study in 6 healthy subjects given albendazole 20 mg/kg and cimetidine 10 mg/kg twice daily found that cimetidine significantly inhibited the metabolism of the active metabolite sulfoxide metabolite of albendazole, as indicated by an increase in its elimination half-life from 7.4 to 19 hours. Cimetidine reduced inter-individual variability in plasma albendazole sulfoxide levels but tended to decrease the maximum levels of albendazole by around 50%, although this was not statistically significant. However, the AUC of albendazole sulfoxide was not significantly altered.[1] A similar study by the same authors[2] also found that cimetidine reduced the increase in albendazole sulfoxide levels produced by 'grapefruit juice', (p.236). Another study in patients with cystic echinococcosis given albendazole 20 mg/kg daily, for three 4-week courses separated by intervals of 10 days, found that levels of the active metabolite albendazole sulfoxide were higher in bile and hydatid cyst fluid in 7 patients who also received cimetidine 10 mg/kg daily. The therapeutic benefit of the combined treatment was reported to be greater than that with albendazole alone.[3]

(b) Mebendazole

A study in 8 patients (5 with peptic ulcers and 3 with hydatid cysts) taking mebendazole 1.5 g three times daily found that cimetidine 400 mg three times daily for 30 days raised the maximum plasma mebendazole levels by 48%. The previously unresponsive hepatic hydatid cysts resolved totally.[4] However, a previous study had found smaller increases in serum mebendazole levels with cimetidine 1 g daily in divided doses, which were considered too small to be clinically useful.[5]

Mechanism

It is suggested that the interaction is caused by the enzyme inhibitory actions of cimetidine, which result in a reduction in the metabolism of mebendazole.[4] Further, cimetidine inhibits the metabolism of albendazole to its active metabolite albendazole sulfoxide.[1] However, as cimetidine may also inhibit the metabolism of albendazole sulfoxide to its inactive sulfone metabolite, any reduction in levels of albendazole sulfoxide are compensated for by its prolonged elimination half-life.[1] Cimetidine may also reduce albendazole absorption and minimise inter-patient variability by reducing gastric acidity,[1,2] but the reduction in absorption appears to be outweighed by the enzyme-inhibitory effects.

Importance and management

These pharmacokinetic interactions would appear to be established, but their clinical relevance is uncertain. Increased efficacy has been shown in some studies for systemic worm infections. There would seem to be no

reason for avoiding concurrent use, but increased monitoring for efficacy and toxicity might be prudent.

1. Schipper HG, Koopmans RP, Nagy J, Butter JJ, Kager PA, Van Boxtel CJ. Effect of dose increase or cimetidine co-administration on albendazole bioavailability. *Am J Trop Med Hyg* (2000) 63, 270–3.
2. Nagy J, Schipper HG, Koopmans RP, Butter JJ, Van Boxtel CJ, Kager PA. Effect of grapefruit juice or cimetidine coadministration on albendazole bioavailability. *Am J Trop Med Hyg* (2002) 260–3.
3. Wen H, Zhang HW, Muhmut M, Zou PF, New RRC, Craig PS. Initial observation on albendazole in combination with cimetidine for the treatment of human cystic echinococcosis. *Ann Trop Med Parasitol* (1994) 88, 49–52.
4. Bekhti A, Pirotte J. Cimetidine increases serum mebendazole concentrations. Implications for treatment of hepatic hydatid cysts. *Br J Clin Pharmacol* (1987) 24, 390–2.
5. Luder PJ, Siffert B, Witassek F, Meister F, Bircher J. Treatment of hydatid disease with high oral doses of mebendazole. Long-term follow-up of plasma mebendazole levels and drug interactions. *Eur J Clin Pharmacol* (1986) 31, 443–8.

Albendazole + Corticosteroids

Dexamethasone can raise levels of the active metabolite of albendazole, albendazole sulfoxide, by 50%, which might increase its efficacy in systemic worm infections.

Clinical evidence

In one study albendazole 15 mg/kg daily in three divided doses was given to 8 patients with cysticercosis. The plasma levels of the active metabolite of albendazole (albendazole sulfoxide) were found to be increased by about 50% by the use of **dexamethasone** 8 mg every 8 hours.[1] Another study did not detect significantly increased maximum plasma levels of albendazole sulfoxide when **dexamethasone** was given, but the AUC of albendazole sulfoxide was increased twofold, and there was a decrease in its clearance.[2]

Mechanism

Uncertain. Dexamethasone is a moderate inducer of the cytochrome P450 isoenzyme CYP3A4, and might therefore be expected to reduce levels of albendazole by increasing its metabolism to albendazole sulfoxide. Dexamethasone appears not to alter the rate of formation of albendazole sulfoxide, but decreases its elimination.[2]

Importance and management

Information about albendazole seems to be limited but the interaction would appear to be established. It would appear that albendazole can be given concurrently with dexamethasone without compromising treatment, and combined use may actually be beneficial.[3]

1. Jung H, Hurtado M, Tulio Medina M, Sanchez M, Sotelo J. Dexamethasone increases plasma levels of albendazole. *J Neurol* (1990) 237, 279–80.
2. Takayanagui OM, Lanchote VL, Marques MPC, Bonato PS. Therapy for neurocysticercosis: pharmacokinetic interaction of albendazole sulfoxide with dexamethasone. *Ther Drug Monit* (1997) 19, 51–5.
3. Sotelo J, Jung H. Pharmacokinetic optimisation of the treatment of neurocysticercosis. *Clin Pharmacokinet* (1998) 34, 503–15.

Albendazole + Diethylcarbamazine

There appears to be no pharmacokinetic interaction between albendazole and diethylcarbamazine.

Clinical evidence, mechanism, importance and management

The pharmacokinetics of single doses of diethylcarbamazine 6 mg/kg and albendazole 400 mg were not significantly different when groups of 14 amicrofilaraemic subjects given either drug alone were compared with another group of 14 subjects given both drugs.[1] This study suggests there is no pharmacokinetic interaction between these two anthelmintic drugs, and the lack of adverse events[1] suggests that concurrent use is safe.

1. Shenoy RK, Suma TK, John A, Arun SR, Kumaraswami V, Fleckenstein LL, Na-Bangchang K. The pharmacokinetics, safety and tolerability of the co-administration of diethylcarbamazine and albendazole. *Ann Trop Med Parasitol* (2002) 96, 603–14.

Albendazole + Food

Giving albendazole with a fatty meal markedly increases the levels of its active metabolite.

Clinical evidence, mechanism, importance and management

A study in Sudanese men found that giving a single 400-mg dose of albendazole with a meal resulted in a 7.9-fold higher level of the active metabolite, albendazole sulfoxide, than when albendazole was given in the fasted state.[1] Similarly, a further study in healthy subjects found that when albendazole 10 mg/kg was given with a fatty meal, rather than with water, the peak plasma levels of albendazole sulfoxide were increased by more than sixfold and the half-life decreased from 8.8 to 8.2 hours.[2] A study in 16 healthy subjects given a single 800-mg dose of albendazole after a fatty meal (representative of various foods in a Mexican diet) found that the maximum concentration and AUC of albendazole sulfoxide was increased sevenfold and eightfold, respectively.[3]

Albendazole absorption is poor, and if it is being used for systemic infections, it is advisable to take it with a meal.

1. Homeida M, Leahy W, Copeland S, Ali MMM, Harron DWG. Pharmacokinetic interaction between praziquantel and albendazole in Sudanese men. *Ann Trop Med Parasitol* (1994) 88, 551–9.
2. Nagy J, Schipper HG, Koopmans RP, Butter JJ, Van Boxtel CJ, Kager PA. Effect of grapefruit juice or cimetidine coadministration on albendazole bioavailability. *Am J Trop Med Hyg* (2002) 66, 260–3.
3. Mares SS, Jung CH, López AT, González-Esquivel DF. Influence of a Mexican diet on the bioavailability of albendazole. *Basic Clin Pharmacol Toxicol* (2005) 97, 122–4.

Albendazole + Grapefruit juice

Grapefruit juice increases the plasma levels of albendazole sulfoxide, the active metabolite of albendazole.

Clinical evidence, mechanism, importance and management

In a study in 6 healthy subjects, 250 mL of double-strength grapefruit juice increased albendazole sulfoxide peak levels by 3.2-fold and shortened its half-life by 46%. When cimetidine 10 mg/kg was also given, the effect of the grapefruit juice was diminished: the peak plasma level of albendazole sulfoxide was almost 50% lower than when albendazole was given with grapefruit juice alone. However, the peak level of albendazole sulfoxide was still 2.7-fold greater in the presence of cimetidine and grapefruit juice than that achieved when albendazole was given with water.[1]

It was suggested that grapefruit juice inhibits the metabolism of albendazole in the intestinal mucosa by the cytochrome P450 isoenzyme CYP3A4, resulting in raised albendazole levels. The addition of 'cimetidine', (p.235), may decrease this effect as cimetidine inhibits the metabolism of albendazole to its active metabolite, and the changes in gastric pH caused by cimetidine may also reduce albendazole absorption.[1]

The clinical outcome of the change in albendazole sulfoxide levels with grapefruit juice is uncertain. For systemic infections, increased absorption might be beneficial (although adverse effects may be increased), but the decrease in half-life might be detrimental. Further study is required.

1. Nagy J, Schipper HG, Koopmans RP, Butter JJ, Van Boxtel CJ, Kager PA. Effect of grapefruit juice or cimetidine coadministration on albendazole bioavailability. *Am J Trop Med Hyg* (2002) 66, 260–3.

Albendazole + Ivermectin

No pharmacokinetic interaction occurs between albendazole and ivermectin.

Clinical evidence, mechanism, importance and management

In a placebo-controlled study, 42 patients with onchocerciasis were given single doses of either ivermectin 200 micrograms/kg, albendazole 400 mg or both drugs together. The pharmacokinetics of both drugs were not significantly changed by concurrent use, and although the combination seemed to offer no advantage over ivermectin alone for the treatment on

onchocerciasis, the combination appeared safe. No dosage adjustments would be required during concurrent use.[1]

1. Awadzi K, Edwards G, Duke BOL, Opoku NO, Attah SK, Addy ET, Ardrey AE, Quarty BT. The co-administration of ivermectin and albendazole— safety, pharmacokinetics and efficacy against *Onchocerca volvulus*. *Ann Trop Med Parasitol* (2003) 97, 165–78.

Albendazole + Levamisole

Levamisole may markedly decrease the bioavailability of the active metabolite of albendazole, but albendazole has no clinically significant effects on levamisole pharmacokinetics.

Clinical evidence, mechanism, importance and management

A study in 28 healthy subjects given levamisole 2.5 mg/kg, alone or with albendazole 400 mg, found that albendazole produced a modest reduction in the AUC of levamisole but no other pharmacokinetic parameters were affected. However, the AUC of the active sulfoxide metabolite of albendazole was 75% in the presence of levamisole, when compared with historical values in subjects who had received albendazole alone.[1] An associated study in 44 patients found that levamisole with or without albendazole was not effective against *Onchocerca volvulus* infections. Both treatments caused a similar number of adverse effects.[1] The clinical relevance of these findings is unclear, but they suggest that caution is needed if a patient is given albendazole and levamisole for systemic worm infections as there may be a risk of treatment failure.

1. Awadzi K, Edwards G, Opoku NO, Ardrey AE, Favager S, Addy ET, Attah SK, Yamuah LK, Quartey BT. The safety, tolerability and pharmacokinetics of levamisole alone, levamisole plus ivermectin, and levamisole plus albendazole, and their efficacy against *Onchocerca volvulus*. *Ann Trop Med Parasitol* (2004) 98, 595–614.

Albendazole + Praziquantel

Albendazole does not alter the bioavailability of praziquantel. Praziquantel markedly increases the bioavailability of albendazole sulfoxide in fasted subjects, but has a much smaller effect when albendazole is given with a meal.

Clinical evidence, mechanism, importance and management

In a study, Sudanese men were given a single 400-mg dose of albendazole with praziquantel 40 mg/kg while fasting. The pharmacokinetics of praziquantel were not affected by albendazole, whereas the AUC of albendazole sulfoxide, the active metabolite of albendazole, was increased 4.5-fold by praziquantel. However, this difference was much less marked (only a 1.5-fold increase) when the drugs were given with food.[1] The reasons for these changes and their practical consequences are not known, but the increases in albendazole sulfoxide levels did not cause any adverse effects.[1]

In a randomised study, 23 healthy subjects were given albendazole 400 mg and ivermectin 200 micrograms/kg, with or without praziquantel 40 mg/kg. The addition of praziquantel increased the AUC and maximum plasma concentration of albendazole sulfoxide by 31% and 8%, respectively, although there was wide inter-individual variability in these results. No serious adverse effects were reported.[2]

In another randomised study, 21 children treated for giardiasis were given a single 400-mg dose of albendazole, either alone, or with a single 20-mg/kg dose of praziquantel. It was found that the pharmacokinetics of albendazole were not significantly affected by praziquantel when the drugs were given with 200 mL of milk, one hour after breakfast. There were wide inter-individual variations in the plasma levels and AUC of the active metabolite, albendazole sulfoxide, but these were similar whether albendazole was given alone or with praziquantel.[3]

If both drugs are given with food, as is advisable (see 'Albendazole + Food', p.236), any interaction is modest. On the basis of these studies, there do not seem to be any reasons why the concurrent use of these two drugs should be avoided.

1. Homeida M, Leahy W, Copeland S, Ali MMM, Harron DWG. Pharmacokinetic interaction between praziquantel and albendazole in Sudanese men. *Ann Trop Med Parasitol* (1994) 88, 551–9.
2. Na-Bangchang K, Kietinun S, Pawa KK, Hanpitakpong W, Na-Bangchang C, Lazdins J. Assessments of pharmacokinetic drug interactions and tolerability of albendazole, praziquantel and ivermectin combinations. *Trans R Soc Trop Med Hyg* (2006) 100, 335–45.
3. Pengsaa K, Na-Bangchang K, Limkittikul K, Kabkaew K, Lapphra K, Sirivichayakul C, Wisetsing P, Pojjaroen-Anant C, Chanthavanich P, Subchareon A. Pharmacokinetic investigation of albendazole and praziquantel in Thai children infected with *Giardia intestinalis*. *Ann Trop Med Parasitol* (2004) 98, 349–57.

Amodiaquine + Antihistamines

Chlorphenamine may improve the efficacy of amodiaquine, but concurrent use causes drowsiness.

Clinical evidence and mechanism

A small study in 5 children, treated unsuccessfully for acute uncomplicated falciparum malaria with amodiaquine, found that the addition of **chlorphenamine** (6 or 8 mg loading dose followed by 4 or 6 mg every 8 hours if less than 5-years-old or 5-years-old and above, respectively) improved the antimalarial efficacy and cure rate of amodiaquine. Drowsiness, after the first dose of the combination, was the only reported common adverse effect. However, no pharmacokinetic data for either drug were reported.[1]

Importance and management

The use of chlorphenamine with amodiaquine may improve the efficacy of amodiaquine; however, the mechanism of this is unclear, particularly as no pharmacokinetic data were collected. Therefore, it is unclear if this combination may increase the risk of amodiaquine adverse effects. It would seem prudent that if combination therapy with amodiaquine and chlorphenamine is indicated, patients should be advised of the increased risk of drowsiness, which would be expected with chlorphenamine alone. It seems likely that all sedating antihistamines may increase drowsiness with amodiaquine, but this does not appear to have been studied.

1. Sowunmi A, Gbotosho GP, Happi CT, Adedeji AA, Bolaji OM, Fehintola FA, Oduola AMJ. Enhancement of the antimalarial efficacy of amodiaquine by chlorpheniramine in vivo. *Mem Inst Oswaldo Cruz* (2007) 102, 417–19.

Amphotericin B + Azoles

The effects of amphotericin B and azole antifungals would be expected to be antagonistic, and there is some clinical evidence that supports this suggestion and describes increased adverse effects. An isolated study found that amphotericin B reduced the levels of itraconazole, and the combination may increase the incidence of hepatotoxicity.

Clinical evidence

There are numerous *in vitro* and *animal* studies of the potential interaction of azoles with amphotericin B, which show conflicting results from antagonism to additive or synergistic effects, some of which have been the subject of a review.[1] Many of the studies into the use of azoles with amphotericin B are investigating potential therapeutic uses and are therefore outside the scope of this monograph; however, there are some clinical reports of reduced efficacy and adverse effects, and these are discussed below.

In one study, 4 out of 6 patients did not respond to amphotericin B while also taking **ketoconazole**, whereas treatment was successful in 6 others, 5 of whom had stopped taking prophylactic **miconazole** or **ketoconazole**. The authors suggested that the numbers are too small to draw any definite conclusions, but antagonism is certainly a possibility.[2] Similarly, the antifungal effects of **miconazole** and amphotericin B were found to be antagonistic in one small study.[3] In contrast, two randomised studies, in patients with candidaemia, or HIV-positive subjects with cryptococcal meningitis, found that the use of amphotericin B with **fluconazole** may be slightly more effective than the use of **fluconazole** or amphotericin B alone.[4,5]

A comparative study found that patients given **itraconazole** and amphotericin B had serum **itraconazole** levels of less than 1 microgram/mL, whereas those given **itraconazole** alone had serum **itraconazole** levels of 3.75 micrograms/mL, which suggests that amphotericin B may reduce **itraconazole** levels.[6]

A retrospective study of **itraconazole** use found that 11 of 12 leukaemic

patients given amphotericin B and **itraconazole** had raised liver enzymes. These abnormalities resolved in 7 patients when the amphotericin B was discontinued. **Itraconazole** alone, given to another 8 patients did not cause liver enzyme abnormalities, even though it was used in high doses.[7]

Mechanism

Uncertain. In theory, the combination of an antifungal that binds to ergosterol in fungal cell membranes (amphotericin B) with one that inhibits the synthesis of ergosterol (azoles) would be expected to exert antagonistic effects.[1,8,9] *In vitro* studies with *Candida albicans* found that azole exposure may allow the generation of cells that are unaffected by subsequent exposure to amphotericin B. The degree of resistance appears to depend on concentration and the azole involved, with itraconazole causing more resistance than fluconazole.[10] Resistance of *Candida* species to amphotericin B appears to depend on the duration of pre-exposure to fluconazole and is also greater when amphotericin B is subsequently used in combination with fluconazole rather than alone.[9,11] Resistance may also depend on the organism involved and its sensitivity to azoles.[12,13]

Importance and management

Despite extensive *in vitro* and *animal* data, it is not entirely clear whether or not azoles inhibit the efficacy of amphotericin B.[8,14,15] The emergence of resistant strains of fungi and the fact that antifungal therapy for invasive fungal infections remains suboptimal, has meant that combinations of antifungals have continued to be tried. Critically ill patients are often given empirical treatment with amphotericin B, with a subsequent change to fluconazole if the organism is sensitive. The Infectious Disease Society of America advises that a combination of amphotericin B and fluconazole may be an option in selected patients.[16] However, combinations of azoles and amphotericin B should not be considered as routine practice, and until more is known it may be better to limit concurrent use to specific cases. The outcome of combined use should be well monitored for both a reduced antifungal response and an increase in adverse effects. There are a number of reviews that have usefully discussed the topic of antifungal combinations.[17-19]

The evidence for a pharmacokinetic interaction between amphotericin B and azole antifungals is poor and appears to be limited to the single study with itraconazole reported above. Similarly evidence for an adverse hepatic interaction is sparse. Amphotericin B has only rarely been associated with adverse effects on the liver, although increases in liver enzymes may occur in patients given itraconazole. Given these findings, it may be prudent to closely monitor the outcome of combined use of amphotericin and itraconazole for both a reduced antifungal response to the itraconazole, as well as an increase in adverse effects, such as a worsening of liver function tests.[7] Further study is needed to substantiate these results.

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Amphotericin B + Drugs that lower potassium levels

The concurrent use of amphotericin B with drugs that can lower potassium levels (such as loop diuretics, thiazide diuretics and corticosteroids) can lead to hypokalaemia.

Clinical evidence

(a) Corticosteroids

Four patients given amphotericin B and **hydrocortisone** 25 to 40 mg daily developed cardiac enlargement and congestive heart failure secondary to hypokalaemia. In these cases the potassium levels decreased from about 5 mmol/L pre-treatment to between 2.3 and 3 mmol/L during amphotericin therapy. The cardiac size decreased and the heart failure disappeared within 2 weeks of stopping the **hydrocortisone**. The amphotericin B was continued successfully with the addition of potassium supplements in some cases.[1] A retrospective study reported an incidence of hypokalaemia of about 18% in patients prescribed amphotericin B and **hydrocortisone**.[2]

(b) Potassium-depleting diuretics

Amphotericin B and loop diuretics or thiazides and related diuretics can lower potassium levels, and their concurrent use may increase the risk of hypokalaemia.[3] One retrospective study reported an incidence of hypokalaemia of about 36% in patients prescribed both amphotericin B and **furosemide**.[2] Conversely, potassium-sparing diuretics such as **amiloride** might reduce the incidence of hypokalaemia with amphotericin B.[4]

Mechanism

Amphotericin B causes potassium to be lost in the urine: the incidence of hypokalaemia with amphotericin B alone has been reported to be as high as 75 to 90%.[4] Potassium-depleting diuretics (such as the loop diuretics, thiazides and related diuretics) and corticosteroids can also increase potassium excretion. Corticosteroids may also cause salt and water to be retained, and occasional instances of hypernatraemia with amphotericin B have also been seen. Working in concert these could account for the hypokalaemic cardiopathy and the circulatory overload that was seen.

Importance and management

Information is limited but the interaction would seem to be established. The manufacturer of conventional amphotericin B advises that corticosteroids should not be used concurrently unless necessary to control drug reactions.[5] However, in clinical practice, it is sometimes deemed necessary to use amphotericin B with corticosteroids or diuretics or all three together. In this situation, close monitoring of the patient's fluid balance, electrolytes (especially potassium, which should be closely monitored in patients receiving amphotericin B in any case) and renal and cardiovascular parameters is required. The elderly would seem to be particularly at risk of this interaction. One small study found that giving spironolactone 100 mg twice daily with amphotericin B reduced the need for potassium supplementation, and did not result in clinically significant adverse effects.[6] Note that hypokalaemia increases the risk of adverse interactions with 'digitalis glycosides', (p.1099), and 'QT-interval prolonging drugs', (p.289).

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2. Depont F, Vargas F, Dutronc H, Giauque E, Ragnaud J-M, Galpérine T, Abouelfath A, Valentino R, Dupon M, Hérbert G, Moore N. Drug-drug interactions with systemic antifungals in clinical practice. *Pharmacoepidemiol Drug Safety* (2007) 16, 1227–33.
3. AmBisome (Liposomal Amphotericin B). Gilead Sciences Ltd. UK Summary of product characteristics, January 2009.
4. Wazny LD, Brophy DF. Amiloride for the prevention of amphotericin B–induced hypokalemia and hypomagnesemia. *Ann Pharmacother* (2000) 34, 94–7.
5. Fungizone Intravenous (Amphotericin B). E. R. Squibb & Sons Ltd. UK Summary of product characteristics, May 2006.
6. Ural AU. Comment: spironolactone prevents amphotericin B-induced hypokalaemia in neutropenic patients. *Ann Pharmacother* (2000) 34, 1488.

Amphotericin B + Pentamidine

Acute renal failure and electrolyte disturbances may develop in patients taking amphotericin B if they are also given pentamidine.

Clinical evidence, mechanism, importance and management

A retrospective study between 1985 and 1988 identified 101 patients with AIDS who had been given amphotericin B for various systemic mycoses. The patients were given amphotericin B 600 to 800 micrograms/kg daily for 7 to 10 days, then a dose three times each week for about 9 weeks. Nine patients were concurrently treated for pneumocystis pneumonia, and of these the 4 who had been given pentamidine parenterally developed acute and rapid reversible renal impairment. In all 4 cases, renal function returned to normal when the drugs were withdrawn. No renal impairment was seen in 2 others given pentamidine by inhalation or 3 given intravenous co-trimoxazole and the renal impairment was attributed to the additive nephrotoxicity of intravenous pentamidine with amphotericin.[1]

Both amphotericin B and intravenous pentamidine are known to be nephrotoxic. Reversible renal adverse effects may occur in up to 20% of patients given intravenous pentamidine alone, and, rarely, renal impairment may also occur in patients given inhaled pentamidine.[2] However, it seems likely that no toxicity occurred in the patients mentioned above when the pentamidine was given by inhalation because the serum levels achieved were low.

Close monitoring of renal function should be routine when either drug is used (daily monitoring is recommended in the case of parenteral pentamidine[2]), and it is essential that this recommendation is adhered to if both drugs are given. It may be prudent to use liposomal amphotericin B rather than conventional amphotericin B to reduce the risk of renal impairment. Anticipate the likelihood of renal impairment and consider the need to withdraw the drugs.

Note also that both drugs can cause significant electrolyte disturbances, such as hypomagnesaemia[2,3], and serum electrolytes should also be closely monitored on concurrent use.

1. Antoniskis D, Larsen RA. Acute, rapidly progressive renal failure with simultaneous use of amphotericin B and pentamidine. *Antimicrob Agents Chemother* (1990) 34, 470–2.
2. Pentacarinat (Pentamidine isetionate). Sanofi-Aventis. UK Summary of product characteristics, December 2006.
3. Atsmon J, Dolev E. Drug-induced hypomagnesaemia: scope and management. *Drug Safety* (2005), 28, 763–88.

Amphotericin B; Oral + Miscellaneous

The manufacturer of amphotericin B[1] notes that its absorption from the gastrointestinal tract is negligible, and that no interactions have been noted with amphotericin B lozenges, or other oral formulations. For a theoretical interaction with sucralfate, see 'sucralfate', (below).

1. Fungilin Lozenge, Oral Suspension, Oral Tablets (Amphotericin B). E. R. Squibb & Sons Ltd. UK Summary of product characteristics, May 2006.

Amphotericin B; Oral + Sucralfate

An *in vitro* study with amphotericin B found that it became markedly and irreversibly bound to sucralfate at the pH values found in the gut. This suggests that efficacy for intestinal candidiasis or gut decontamination might be decreased, but no study appears to have been conducted to establish this.

Clinical evidence, mechanism, importance and management

To simulate what might happen in the gut, amphotericin B 25 mg/L was mixed with sucralfate 500 mg in 40 mL of water at pH 3.5 and allowed to stand for 90 minutes at 25°C. Analysis of the solution found that the amphotericin B concentration fell rapidly and progressively over 90 minutes to about 20%. When the pH of the mixture was then raised to about 6.5 to 7 for 90 minutes, there was no change in the concentration of amphotericin B, suggesting that the interaction was irreversible.[1] The reason for this change is not known, but the suggestion is that sucralfate forms insoluble chelates with amphotericin B.[1]

It is not known how important this interaction is likely to be in practice, but the efficacy of amphotericin B for intestinal candidiasis or gut decontamination may be decreased. Separating the dosages might not be effective in some postoperative patients because their gastric function may not return to normal for up to 5 days, and some sucralfate might still be present when the next dose is given.[1] This study was conducted more than a decade ago, and nobody appears to have conducted a clinical study to establish its hypothesis. If both sucralfate and oral amphotericin B are required, it would seem prudent to monitor concurrent use carefully, being alert for any evidence of reduced effects.

1. Feron B, Adair CG, Gorman SP, McClurg B. Interaction of sucralfate with antibiotics used for selective decontamination of the gastrointestinal tract. *Am J Hosp Pharm* (1993) 50, 2550–3.

Artemether + Grapefruit juice

Grapefruit juice doubles the AUC of artemether.

Clinical evidence, mechanism, importance and management

In a crossover study, 6 healthy subjects were given a single 100-mg dose of artemether with water, after breakfast, then after a 7-day washout period the study was repeated, replacing water with 350 mL of double-strength grapefruit juice. Grapefruit juice increased the AUC of artemether by almost twofold, and increased its maximum level by more than twofold. The pharmacokinetics of the active metabolite of artemether, dihydroartemisinin, were unaffected. No ECG changes were reported on concurrent use.[1] In a further multiple-dose study, artemether 100 mg was taken with water or 350 mL of double-strength grapefruit juice, daily for 5 days. Grapefruit juice increased the AUC and maximum level of artemether twofold on both day one and day 5, but the AUC of artemether was markedly lower on day 5, due to auto-induction of its metabolism.[2] This suggests that grapefruit juice might increase the levels of artemether by inhibiting the cytochrome P450 isoenzyme CYP3A4 in the intestine, but that auto-induction does not affect this process.

The clinical relevance of the twofold increase in artemether levels seen in this study was not reported. However, based on the evidence for 'ketoconazole', (p.239), a potent inhibitor of CYP3A4, it seems unlikely to result in adverse effects or ECG changes, and the manufacturers advise that no dosage adjustments are needed when artemether/lumefantrine is used with potent CYP3A4 inhibitors.[3] The authors[2] suggest that the use of grapefruit juice might improve clinical efficacy of artemether in malaria, and might theoretically reduce recrudescence (the reappearance of a disease after a period of inactivity); however, artemether is used with lumefantrine to limit recrudescence.

1. van Agtmael MA, Gupta V, van der Wosten TH, Rutten JP, van Boxtel CJ. Grapefruit juice increases the bioavailability of artemether. *Eur J Clin Pharmacol* (1999) 55, 405–10.
2. van Agtmael MA, Gupta V, van der Graaf CAA, van Boxtel CJ. The effect of grapefruit juice on the time-dependent decline of artemether plasma levels in healthy subjects. *Clin Pharmacol Ther* (1999) 66, 408–14.
3. Riamet (Artemether/Lumefantrine). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, October 2007.

Artemether/Lumefantrine + CYP3A4 inhibitors

Ketoconazole modestly increases the AUC of both artemether and lumefantrine, and other potent inhibitors of CYP3A4 are predicted to interact similarly.

Clinical evidence, mechanism, importance and management

In a study, 16 healthy subjects were given a single dose of artemether/lumefantrine 80/480 mg with a high-fat breakfast, followed by **ketoconazole** 400 mg on day one and then 200 mg daily for 4 days.

Ketoconazole increased the AUC of artemether 2.4-fold, its metabolite dihydroartemisinin 1.7-fold, and lumefantrine 1.7-fold.[1] The maximum levels of the drugs were also increased to a similar extent. **Ketoconazole** probably increases the levels of artemether and lumefantrine by inhibiting intestinal and/or hepatic cytochrome P450 isoenzyme CYP3A4. Although a pharmacokinetic interaction with ketoconazole appears to be established, the clinical relevance of a modest, twofold increase in artemether and lumefantrine levels appears to be minimal, as no changes in ECG parameters or increases in adverse events were reported,[1] and the pharmacokinetic changes seen are within the expected intersubject variability for these drugs.[1] The manufacturer[2] therefore advises that no dosage adjustment is necessary when artemether/lumefantrine is given with **ketoconazole** or other potent inhibitors of CYP3A4, see 'Table 1.4', (p.6).

1. Lefèvre G, Carpenter P, Souppart C, Schmidli H, McClean M, Stypinski D. Pharmacokinetics and electrocardiographic pharmacodynamics or artemether-lumefantrine (Riamet®) with concomitant administration of ketoconazole in healthy subjects. *Br J Clin Pharmacol* (2002) 54, 485–92.
2. Riamet (Artemether/Lumefantrine). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, October 2007.

Artemether/Lumefantrine + Food

High-fat food and soya milk markedly increase the absorption of lumefantrine, and high-fat food moderately increases the absorption of artemether. As soon as patients can tolerate food they should be encouraged to take artemether/lumefantrine with meals.

Clinical evidence, mechanism, importance and management

In a study in healthy Chinese subjects, a single dose of artemether/lumefantrine 80/480 mg was taken after a **high-fat meal** and in the fasted state. The relative bioavailabilities of artemether and its active metabolite dihydroartemisinin were increased by more than twofold, and the bioavailability of lumefantrine was increased 16-fold by the meal.[1] Based on these data, the manufacturer notes that if 100% absorption is assumed for lumefantrine taken with a **high-fat meal**, then absorption in the fasted state is less than 10% of the dose.[2] In a clinical study in patients with malaria, intake of a **light meal** within one hour of lumefantrine increased the bioavailability by 48%, and intake of a **normal meal** increased absorption twofold, when compared with liquids alone. After 24 to 48 hours in this study, most patients were eating normally.[3]

A study in 11 healthy subjects to investigate the amount of fat required to maximise lumefantrine bioavailability found that giving increasing quantities of **soya milk** up to 500 mL) significantly increased the AUC of lumefantrine by more than fivefold. The optimum quantity of fat to obtain 90% bioavailability of lumefantrine was 1.2 g (equivalent to 36 mL of **soya milk**).[4] Artemether/lumefantrine should be taken with food. However, patients with acute uncomplicated malaria are unlikely to tolerate food. The manufacturer notes that patients should be encouraged to take artemether/lumefantrine with food as soon as this can be tolerated. Patients who remain averse to food during treatment should be closely monitored as they may be at greater risk of recrudescence (reappearance of the disease after a period of inactivity).[2] The study above[4] suggests that **soya milk** may also be an option to improve lumefantrine bioavailability in those patients unable to tolerate a full meal.

1. Bindschedler M, Degen P, Lu ZL, et al. Comparative bioavailability of benflumetol after administration of single oral doses of co-artemether under fed and fasted conditions to healthy subjects. Cited in Lefèvre G, Thomsen MS. Clinical Pharmacokinetics of artemether and lumefantrine (Riamet®). *Clin Drug Invest* (1999) 18, 467–80.
2. Riamet (Artemether/Lumefantrine). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, October 2007.
3. Ezzet F, van Vugt M, Nosten F, Looareesuwan S, White NJ. Pharmacokinetics and pharmacodynamics of lumefantrine (Benflumetol) in acute falciparum malaria. *Antimicrob Agents Chemother* (2000) 44, 697–704.
4. Ashley EA, Stepniewska K, Lindegårdh N, Annerberg A, Kham A, Brockman A, Singhasivanon P, White NJ, Nosten F. How much fat is necessary to optimize lumefantrine oral bioavailability? *Trop Med Int Health* (2007) 12, 195–200.

Atovaquone + Antiemetics

Preliminary evidence suggests that metoclopramide causes a marked decrease in atovaquone serum levels.

Clinical evidence, mechanism, importance and management

An analysis of 191 patients with AIDS, given atovaquone as part of efficacy studies, found that when normalised for plasma albumin, bodyweight, and the absence of other drugs, the expected steady-state plasma levels of atovaquone were 14.8 micrograms/mL. Steady-state atovaquone plasma levels achieved in the presence of other drugs were examined in an attempt to identify possible interactions. **Metoclopramide** was associated with a decrease in atovaquone levels of 7.2 micrograms/mL. Antiemetics other than **metoclopramide** (individual drugs not named) were not associated with any change in steady-state atovaquone serum levels.[1,2] This kind of analysis provides only the very broadest indication that a marked interaction might occur between atovaquone and **metoclopramide**, and there appears to be no further published studies to confirm this report of an interaction. However, it does highlight the need to be vigilant if **metoclopramide** is used concurrently, and the manufacturers of atovaquone[2] and atovaquone/proguanil[3] recommend caution in its use with **metoclopramide**. If an antiemetic is required in patients taking atovaquone/proguanil, they suggest that **metoclopramide** should be given only if other antiemetics are unavailable,[3] and that parasitaemia should be closely monitored.[4] In the UK, the manufacturers also say that **metoclopramide** should be given with caution to patients taking atovaquone suspension for pneumocystis pneumonia, until the interaction has been further studied.[2] The US manufacturers of atovaquone suspension do not mention **metoclopramide**.[5]

1. Sadler BM, Blum MR. Relationship between steady-state plasma concentrations of atovaquone (C_{ss}) and the use of various concomitant medications in AIDS patients with *Pneumocystis Carinii* (sic) pneumonia. IXth Int Conf AIDS & IVth STD World Congr, Berlin, 1993. 504.
2. Wellvone Oral Suspension (Atovaquone). GlaxoSmithKline UK. UK Summary of product characteristics, March 2008.
3. Malarone (Atovaquone with Proguanil hydrochloride). GlaxoSmithKline. US Prescribing information, June 2008.
4. Malarone Tablets (Atovaquone with Proguanil hydrochloride). GlaxoSmithKline UK. UK Summary of product characteristics, September 2009.
5. Mepron Suspension (Atovaquone). GlaxoSmithKline. US Prescribing information, May 2008.

Atovaquone/Proguanil + Artesunate

Artesunate does not appear to affect the pharmacokinetics of atovaquone/proguanil.

Clinical evidence, mechanism, importance and management

In a pharmacokinetic study, a single dose of atovaquone/proguanil 1 g/400 mg was given to 12 healthy subjects with and without artesunate 250 mg. No change was noted in the pharmacokinetics of either atovaquone or proguanil and no unexpected adverse events were seen.[1] Although artesunate does not therefore appear to alter the pharmacokinetics of atovaquone/proguanil, this needs confirmation in a multiple-dose study.

A study to investigate whether the addition of artesunate to atovaquone/proguanil increased the risk of cardiotoxicity found that the QT_c interval was not significantly different in those receiving all three drugs, when compared with those receiving atovaquone/proguanil alone.[2]

1. van Vugt M, Edstein MD, Proux S, Lay K, Ooh M, Looareesuwan S, White NJ, Nosten F. Absence of an interaction between artesunate and atovaquone – proguanil. *Eur J Clin Pharmacol* (1999) 55, 469–74.
2. Gupta RK, van Vugt M, Paiphun L, Slight T, Looareesuwan S, White NJ, Nosten F. Short Report: No evidence of cardiotoxicity of atovaquone-proguanil alone or in combination with artesunate. *Am J Trop Med Hyg* (2005) 73, 267–8.

Atovaquone + Co-trimoxazole

In one small study co-trimoxazole did not alter atovaquone levels, and atovaquone caused a minor decrease in co-trimoxazole levels, which was not considered clinically relevant.

Clinical evidence, mechanism, importance and management

As part of a larger study, 6 HIV-positive subjects received atovaquone 500 mg once daily, co-trimoxazole 960 mg (trimethoprim/sulfamethoxazole 160/800 mg) twice daily, or the combination, with food. There was no change in steady-state atovaquone levels but there was a minor 17% decrease in steady-state trimethoprim levels and a minor 8% decrease in sulfamethoxazole levels when both drugs were given together.[1]

This study shows there is no important pharmacokinetic interaction between atovaquone and co-trimoxazole. No dosage adjustments of either drug would be required on concurrent use.

1. Falloon J, Sargent S, Piscitelli SC, Bechtel C, LaFon SW, Sadler B, Walker RE, Kovacs JA, Polis MA, Davey RT, Lan HC, Masur H. Atovaquone suspension in HIV-infected volunteers: pharmacokinetics, pharmacodynamics, and TMP-SMX interaction study. *Pharmacotherapy* (1999) 19, 1050–6.

Atovaquone + Food

Fatty foods markedly increase the AUC of atovaquone tablets and suspension by two to threefold.

Clinical evidence

(a) Suspension

A pharmacokinetic study in 12 HIV-positive subjects, designed to determine the dose of atovaquone suspension that would achieve specific steady-state plasma levels, found that **high-fat** food increased the bioavailability of atovaquone by 40%, when compared with the fasted state.[1] In another similar study, giving atovaquone suspension with food (23 g of fat) increased the average steady-state levels by 30 to 70% with different dosage regimens (using 500 mg to 1.5 g of atovaquone).[2]

In a single-dose study in healthy subjects, a **high-fat breakfast** (21 g of fat) increased the AUC of atovaquone suspension by 2.4-fold, and an **enteral nutrition supplement** (*Sustacal Plus*, containing 28 g of fat) increased the AUC by 2.7-fold, when compared with the fasted state.[3]

(b) Tablets

In a crossover study in 18 healthy subjects a single 500-mg dose of atovaquone given after a **high-fat standard breakfast** (23 g of fat) increased the AUC by 3.3-fold, when compared with the fasted state.[4] In a further study of similar design, 2 slices of **toast** alone had no effect on the AUC of atovaquone, 2 slices of **toast with 23 g of butter** increased the AUC by threefold, and 2 slices of **toast with 56 g of butter** increased the AUC by 3.9-fold.[4]

Mechanism

Atovaquone is a highly lipophilic compound, which shows considerable inter-individual variability in absorption. Dietary fat increases the rate and extent of atovaquone absorption from both the suspension and the tablets, probably by increasing its solubility in the gut. The suspension has about a twofold higher oral bioavailability than the tablets when given with food or when fasting.

Importance and management

Established interactions of clinical importance. Atovaquone suspension used for the treatment or prevention of pneumocystis pneumonia must be taken with food, since this is likely to increase the likelihood of successful treatment and survival.[5,6] Alternatively, an enteral nutritional supplement with a high-fat content appears to be suitable.[3] In the US, the manufacturer says that, for patients with pneumocystis pneumonia, who have difficulty taking atovaquone suspension with food, parenteral treatment (with other drugs) should be considered.[6]

Similarly, atovaquone/proguanil tablets used for the treatment or prophylaxis of malaria should be taken with a milky drink or with food to maximise absorption.[7,8] Be aware that if patients are unable to tolerate food, the systemic exposure to atovaquone will be reduced.[7] In this situation, monitoring of parasitaemia to ensure efficacy would seem advisable.

1. Dixon R, Pozniak AL, Watt HM, Rolan P, Posner J. Single-dose and steady-state pharmacokinetics of a novel microfluidized suspension of atovaquone in human immunodeficiency virus-seropositive patients. *Antimicrob Agents Chemother* (1996) 40, 556–60.
2. Falloon J, Sargent S, Piscitelli SC, Bechtel C, LaFon SW, Sadler B, Walker RE, Kovacs JA, Polis MA, Davey RT, Lan HC, Masur H. Atovaquone suspension in HIV-infected volunteers: pharmacokinetics, pharmacodynamics, and TMP-SMX interaction study. *Pharmacotherapy* (1999) 19, 1050–6.
3. Freeman CD, Klutman NE, Lamp KC, Dall LH, Strayer AH. Relative bioavailability of atovaquone suspension when administered with an enteral nutrition supplement. *Ann Pharmacother* (1998) 32, 1004–7.
4. Rolan PE, Mercer AJ, Weatherley BC, Holdich T, Meire H, Peck RW, Ridout G, Posner J. Examination of some factors responsible for a food-induced increase in absorption of atovaquone. *Br J Clin Pharmacol* (1994) 37, 13–20.
5. Wellvone Oral Suspension (Atovaquone). GlaxoSmithKline UK. UK Summary of product characteristics, March 2008.
6. Mepron Suspension (Atovaquone). GlaxoSmithKline. US Prescribing information, May 2008.
7. Malarone Tablets (Atovaquone with Proguanil hydrochloride). GlaxoSmithKline UK. UK Summary of product characteristics, September 2009.
8. Malarone (Atovaquone with Proguanil hydrochloride). GlaxoSmithKline. US Prescribing information, June 2008.

Atovaquone + Macrolides

Azithromycin and erythromycin do not appear to interact with atovaquone to a clinically significant extent, and the concurrent use of azithromycin and atovaquone may be beneficial in some diseases.

Clinical evidence, mechanism, importance and management

(a) Azithromycin

In a small study in 8 HIV-positive children given azithromycin suspension 5 mg/kg daily alone, or with atovaquone suspension 30 mg/kg daily for pneumocystis pneumonia, the maximum serum concentration and $AUC_{0\text{-}24}$ of azithromycin were reduced by about 30% by atovaquone. However, due to the large inter-subject variability in azithromycin pharmacokinetics, there were insufficient patients for this reduction to be statistically significant.[1]

A study in 58 patients compared the efficacy of atovaquone 750 mg twice daily and azithromycin (500 mg on day 1 followed by 250 mg daily) with the standard treatment of clindamycin and quinine in patients with non-life threatening babesiosis (a tick-borne, malaria-like illness). The two combinations were of similar efficacy, and the frequency of adverse effects in the 40 patients taking azithromycin with atovaquone was significantly less than that in the 18 patients taking quinine and clindamycin (15% compared with 72%). However, no pharmacokinetic data was recorded.[2] There are also reports of the successful treatment of babesiosis with azithromycin and atovaquone in a further 2 patients.[3,4] Another efficacy study in HIV-positive children found that the combination of azithromycin with atovaquone was as effective as co-trimoxazole for the prophylaxis of bacterial infections, and that the adverse effect profiles were similar. However, the patients taking co-trimoxazole were known to have taken it without problem previously and this may explain differences between this study and an earlier one which reported a higher rate of adverse effects with co-trimoxazole than with atovaquone alone.[5]

Information on a possible pharmacokinetic interaction appears to be limited to one report.[1] However, the clinical studies[2-5] appear to indicate that the efficacy of either drug is not affected when used in combination. Therefore, no particular precautions appear to be necessary if both drugs are given.

(b) Erythromycin

A preliminary analysis of 191 patients with AIDS given atovaquone as part of efficacy studies, found that erythromycin was not associated with any change in steady-state atovaquone serum levels. Erythromycin was represented by fewer than 5 subjects.[6] However, note that this kind of analysis provides only the very broadest indication that interactions might or might not occur.

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2. Krause PJ, Lepore T, Sikand VK, Gadbaw J, Burke G, Telford SR, Brassard P, Pearl D, Azlanzadeh J, Christianson D, McGrath D, Spielman A. Atovaquone and azithromycin for the treatment of babesiosis. *N Engl J Med* (2000) 343, 1454–8.
3. Raju M, Salazar JC, Leopold H, Krause PJ. Atovaquone and azithromycin treatment for babesiosis in an infant. *Pediatr Infect Dis J* (2007) 26, 181–3.
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5. Hughes WT, Dankner WM, Yogev R, Huang S, Paul ME, Flores MA, Kline MW, Wei L-J, for the Pediatric AIDS Clinical Trials Group (PACTG) 254 Team. Comparison of atovaquone and azithromycin with trimethoprim-sulfamethoxazole for the prevention of serious bacterial infections in children with HIV infection. *Clin Infect Dis* (2005) 40, 136–45.
6. Sadler BM, Blum MR. Relationship between steady-state plasma concentrations of atovaquone (C_{ss}) and the use of various concomitant medications in AIDS patients with *Pneumocystis Carinii* (sic) pneumonia. IXth Int Conf AIDS & IVth STD World Congr, Berlin, 1993. 504.

Atovaquone + Miscellaneous

Preliminary evidence suggests that a number of drugs given in clinical studies do not interact with atovaquone.

Clinical evidence, mechanism, importance and management

An analysis of 191 patients with AIDS, given atovaquone as part of efficacy studies, found that when normalised for plasma albumin, bodyweight, and the absence of other drugs, the expected steady-state plasma levels of atovaquone were 14.8 micrograms/mL. Steady-state atovaquone plasma levels achieved in the presence of other drugs were examined in an attempt to identify possible interactions. **Fluconazole** and **prednisone** were associated with increases of 2.5 and 2.3 micrograms/mL, respectively, whereas **paracetamol** (**acetaminophen**), **aciclovir**, **opioids**, **antidiarrhoeals**, **cephalosporins**, **benzodiazepines** and **laxatives** were associated with decreases of greater than 3.4 micrograms/mL. **U plasma protein binders** [not defined], **clofazimine**, **antacids**, **clotrimazole**, **NSAIDs**, **ketoconazole**, **hydroxyzine**, **megestrol**, **antiemetics** (other than 'metoclopramide', (p.240)), **other systemic steroids**, and **H_2-receptor antagonists** were not associated with any change in steady-state atovaquone serum levels. **U plasma protein binders** and **clofazimine** were represented by fewer than 5 subjects.[1]

The kind of analysis described above[1] provides only the very broadest indication that interactions might or might not occur between atovaquone and these drugs; however, it would appear that no dosage adjustments are necessary when these drugs are used with atovaquone.

1. Sadler BM, Blum MR. Relationship between steady-state plasma concentrations of atovaquone (C_{ss}) and the use of various concomitant medications in AIDS patients with *Pneumocystis Carinii* (sic) pneumonia. IXth Int Conf AIDS & IVth STD World Congr, Berlin, 1993. 504.

Atovaquone + Proguanil

There appears to be no clinically relevant pharmacokinetic interaction between atovaquone and proguanil.

Clinical evidence, mechanism, importance and management

Atovaquone did not affect the pharmacokinetics of proguanil in a comparative study of 4 patients taking proguanil 200 mg twice daily for 3 days and 12 patients taking proguanil 200 mg twice daily with atovaquone 500 mg twice daily for 3 days.[1] A similar lack of interaction was seen in 18 healthy subjects given proguanil 400 mg daily with atovaquone 1 g daily for 3 days.[2]

In contrast, in a longer study, 13 healthy subjects were given a single 250/100-mg dose of atovaquone/proguanil, then, after an interval of one week, they were given daily doses for 13 days. There was no change in the AUC of atovaquone from single dose to steady state, indicating that accumulation did not occur. However, in the 9 subjects who had normal levels of the cytochrome P450 isoenzyme CYP2C19, the AUC of proguanil was modestly increased at steady state and the AUC of the active metabolite, cycloguanil, was modestly decreased. It was suggested that atovaquone may have inhibited the production of cycloguanil by CYP3A4. However, since this study had no arm with each drug alone, it is impossible to determine whether these changes in pharmacokinetics were due to an interaction or not.[3]

A pharmacokinetic interaction is not established. However, any interaction would be of little clinical relevance, since the efficacy of the combination product for malaria prophylaxis is established (up to 12 weeks). The enhanced activity of the combination may, in part, be due to proguanil lowering the effective concentration at which atovaquone collapses the mitochondrial potential in malaria parasites.[4]

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2. Gillotin C, Mamet JP, Veronese L. Lack of pharmacokinetic interaction between atovaquone and proguanil. *Eur J Clin Pharmacol* (1999) 55, 311–15.
3. Thapar MM, Ashton M, Lindegardh N, Bergqvist Y, Nivelius S, Johansson I, Bjorkman A. Time-dependent pharmacokinetics and drug metabolism of atovaquone plus proguanil (Malarone) when taken as chemoprophylaxis. *Eur J Clin Pharmacol* (2002) 58, 19–27.
4. Srivastava IK, Vaidya AB. A mechanism for the synergistic antimalarial action of atovaquone and proguanil. *Antimicrob Agents Chemother* (1999) 43, 1334–9.

Atovaquone + Rifamycins

Rifampicin reduces serum atovaquone levels by about 50%, whereas atovaquone modestly raises serum rifampicin levels. Rifabutin may interact similarly, although to a lesser extent.

Clinical evidence

(a) Rifabutin

In a study in 24 healthy subjects, when atovaquone 750 mg twice daily was given with rifabutin 300 mg daily for 14 days, there was a modest 34% decrease in the AUC of atovaquone and a small 19% decrease in rifabutin levels.[1]

(b) Rifampicin (Rifampin)

A steady-state study in 13 HIV-positive subjects found that the use of atovaquone 750 mg twice daily with rifampicin 600 mg four times daily for 14 days resulted in a more than 50% reduction in the atovaquone AUC and serum levels, but a more than 30% rise in the rifampicin AUC and serum levels.[2,3]

Mechanism

Uncertain. Atovaquone is predominantly excreted (greater than 90%) as unchanged drug in the faeces,[3,4] and would not therefore be expected to be affected by cytochrome P450 enzyme induction.

Importance and management

Although information is limited these pharmacokinetic interactions appear to be established. It seems highly likely that the efficacy of atovaquone will be reduced in the presence of rifampicin, and the combination should therefore be avoided. The effect of rifabutin is smaller than that of rifampicin, and the authors of the above report suggested that no atovaquone dosage adjustment is needed.[1] The manufacturers of atovaquone still consider that rifabutin use could result in subtherapeutic atovaquone levels in some patients,[3,4] and the UK manufacturers also advise against the concurrent use of this combination.[4]

1. Gillotin C, Grandpierre I, Sadler BM. Pharmacokinetic interaction between atovaquone (ATVQ) suspension and rifabutin (RFB). *Clin Pharmacol Ther* (1998) 63, 229.
2. Sadler BM, Caldwell P, Scott JD, Rogers M, Blum MR. Drug interaction between rifampin and atovaquone (Mepron®) in HIV+ asymptomatic volunteers. *Intersci Conf Antimicrob Agents Chemother* (1995) 35, 7.
3. Mepron Suspension (Atovaquone). GlaxoSmithKline. US Prescribing information, May 2008.
4. Wellvone Oral Suspension (Atovaquone). GlaxoSmithKline UK. UK Summary of product characteristics, March 2008.

Atovaquone + Tetracyclines

Tetracycline reduces the plasma levels of atovaquone by about 40%. Doxycycline may increase the antimalarial efficacy of atovaquone.

Clinical evidence, mechanism, importance and management

A study looking at the population pharmacokinetics of atovaquone in 24 Thai patients found that neither the oral clearance nor the volume of distribution of atovaquone were significantly affected by the concurrent use of **tetracycline**.[1] This sort of data gives only the broadest indication of whether or not an interaction occurs, and the US manufacturer of atovaquone/proguanil[2] notes that **tetracycline** may reduce plasma levels of atovaquone by about 40%. They therefore suggest that parasitaemia should be closely monitored in patients taking atovaquone/proguanil with **tetracycline**.[2,3] In the UK, the manufacturer also says that **tetracycline** should be given with caution to patients taking atovaquone suspension for pneumocystis pneumonia, until the interaction has been further studied,[4] whereas the US manufacturers of atovaquone suspension do not mention **tetracycline**.[5]

Information about other tetracyclines is largely lacking. An *in vitro* study found that **doxycycline** potentiated the antimalarial activity of atovaquone,[6] but there appears to be no information on the effect of **doxycycline** on the absorption of atovaquone.

1. Hussein Z, Eaves J, Hutchinson DB, Canfield CJ. Population pharmacokinetics of atovaquone in patients with acute malaria caused by *Plasmodium falciparum*. *Clin Pharmacol Ther* (1997) 61, 518–30.
2. Malarone (Atovaquone with Proguanil hydrochloride). GlaxoSmithKline. US Prescribing information, June 2008.
3. Malarone Tablets (Atovaquone with Proguanil hydrochloride). GlaxoSmithKline UK. UK Summary of product characteristics, September 2009.
4. Wellvone Oral Suspension (Atovaquone). GlaxoSmithKline UK. UK Summary of product characteristics, March 2008.
5. Mepron Suspension (Atovaquone). GlaxoSmithKline. US Prescribing information, May 2008.
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Azoles + Antacids

The gastrointestinal absorption of itraconazole capsules and ketoconazole are markedly reduced by antacids. Itraconazole solution, fluconazole and posaconazole appear not to be affected. Similarly, voriconazole is not expected to be affected by antacids.

Clinical evidence

(a) Fluconazole

Maalox forte (**aluminium**/**magnesium hydroxide**) 20 mL did not affect the absorption of a single 100-mg dose of fluconazole in 14 healthy subjects.[1]

(b) Itraconazole

In a randomised study, 12 healthy subjects were given 30 mL of an **aluminium**/**magnesium hydroxide** antacid suspension three times daily and before bedtime for 2 days before taking a single 200-mg dose of itraconazole capsules. The antacid reduced the peak serum level and AUC of itraconazole by 70% and 66%, respectively, and delayed absorption (time to peak level increased from 3 hours to 5.1 hours).[2] In contrast, a study in 204 liver transplant patients comparing the antifungal efficacy of itraconazole oral solution with fluconazole reported that itraconazole trough levels were not affected in 16 patients also taking 'proton pump inhibitors', (p.246), 'H_2-receptor antagonists', (p.245), or antacids.[3]

For mention of a study in which some patients needed an increase in their itraconazole dose when they took ranitidine and an antacid [not named], see 'Azoles + H_2-receptor antagonists', p.245.

(c) Ketoconazole

A haemodialysis patient did not respond to treatment with ketoconazole 200 mg daily while taking **cimetidine**, **sodium bicarbonate** 2 g daily and **aluminium [hydr]oxide** 2.5 g daily. Only when the ketoconazole dosage was increased to 200 mg four times daily did her serum levels rise. A later study in 3 healthy subjects found that when ketoconazole 200 mg was taken 2 hours after **cimetidine** 400 mg, its absorption was considerably reduced (AUC reduced by about 60%). When this was repeated with the addition of **sodium bicarbonate** 500 mg, the absorption of ketoconazole was reduced by about 95%. In contrast, when this was again repeated, but with the ketoconazole in an acidic solution, the absorption was increased by about 50%.[4]

A study in 4 patients found that the concurrent use of *Maalox* reduced the absorption of ketoconazole, but this was not statistically significant.[5] An anecdotal report suggested that giving ketoconazole 2 hours before a stomatitis cocktail containing *Maalox* seemed to prevent the cocktail reducing ketoconazole effectiveness.[6]

(d) Posaconazole

A study in 12 healthy subjects found that *Mylanta* (**aluminium**/**magnesium hydroxide**) 20 mL did not significantly affect the bioavailability of a single 200-mg dose of posaconazole, either when taken with food or when fasting.[7]

Mechanism

Ketoconazole is a poorly soluble base, which must be converted by the acid in the stomach into the soluble hydrochloride salt before it can be absorbed. Drugs that reduce gastric acidity, such as antacids, 'H_2-receptor antagonists', (p.245), and 'proton pump inhibitors', (p.246), raise the pH in the stomach so that the dissolution of the ketoconazole and its absorption are reduced. The absorption of itraconazole, and possibly posaconazole,[8] is also affected by changes in gastric pH. Fluconazole absorption is minimally affected by changes in gastric acidity.

Importance and management

The interaction of antacids with **ketoconazole** is clinically important, but not extensively documented. Advise patients to take antacids not less than 2 to 3 hours before or after ketoconazole so that absorption can take place with minimal changes in the pH of the gastric contents. Monitor to confirm that ketoconazole is effective.

Itraconazole *capsules* appear to be similarly affected, and it would therefore be prudent to separate administration. The manufacturer of itraconazole *capsules* recommend taking antacids at least two hours after itraconazole.[9] Although the manufacturers of itraconazole *solution*[10,11] do not give any specific advice regarding concurrent use of antacids, the solution is already in a soluble form and is therefore less likely to be affected.[12]

Antacids do not appear to significantly affect **posaconazole** or **fluconazole** levels. However, the manufacturers of posaconazole still consider that its absorption may be affected by drugs that affect gastric acidity, including antacids.[13] Note, they recommend avoiding concurrent administration with other acid reducing drugs[8] such as 'H_2-receptor antagonists', (p.245), and 'proton pump inhibitors', (p.246). Based on the data with 'H_2-receptor antagonists', (p.245), antacids would not be expected to affect **voriconazole** levels.

1. Thorpe JE, Baker N, Bromet-Petit M. Effect of oral antacid administration on the pharmacokinetics of oral fluconazole. *Antimicrob Agents Chemother* (1990) 34, 2032–3.
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3. Winston DJ, Busuttil RW. Randomized controlled trial of oral itraconazole solution versus intravenous/oral fluconazole for prevention of fungal infections in liver transplant recipients. *Transplantation* (2002) 74, 688–95.
4. Van der Meer JWM, Keuning JJ, Scheijgrond HW, Heykants J, Van Cutsem J, Brugmans J. The influence of gastric acidity on the bio-availability of ketoconazole. *J Antimicrob Chemother* (1980) 6, 552–4.
5. Brass C, Galgiani JN, Blaschke TF, Defelice R, O'Reilly RA, Stevens DA. Disposition of ketoconazole, an oral antifungal, in humans. *Antimicrob Agents Chemother* (1982) 21, 151–8.
6. Franklin MG. Nizoral and stomatitis cocktails may not mix. *Oncol Nurs Forum* (1991) 18, 1417.
7. Courtney R, Radwanski E, Lim J, Laughlin M. Pharmacokinetics of posaconazole coadministered with antacid in fasting or nonfasting healthy men. *Antimicrob Agents Chemother* (2004) 48, 804–8.
8. Noxafil (Posaconazole). Schering-Plough Ltd. UK Summary of product characteristics, November 2009.
9. Sporanox Capsules (Itraconazole). Janssen-Cilag Ltd. UK Summary of product characteristics, October 2009.
10. Sporanox Oral Solution (Itraconazole). Ortho Biotech. US Prescribing information, October 2007.
11. Sporanox Oral Solution (Itraconazole). Janssen-Cilag Ltd. UK Summary of product characteristics, September 2008.
12. Janssen-Cilag. Personal communication, March 2008.
13. Schering-Plough Ltd. Personal communication, March 2008.

Azoles + Cola drinks

Some cola drinks can temporarily lower the stomach pH of patients with achlorhydria or hypochlorhydria due to disease or acid-suppressing drugs. This improves the bioavailability of itraconazole and ketoconazole.

Clinical evidence

(a) Itraconazole

A study in 8 healthy subjects given itraconazole 100 mg with either 325 mL of water or *Coca-Cola* (pH 2.5) found that the peak serum itraconazole levels were more than doubled by *Coca-Cola* and the AUC of itraconazole was increased by 80%, although two of the subjects did not show this effect.[1] Another study in 30 healthy subjects compared the bioavailability of itraconazole alone or after ranitidine, both with and without a cola drink. Ranitidine reduced the absorption of itraconazole but this effect was countered by the cola drink.[2] A study in 18 fasted patients with AIDS, who absorbed itraconazole poorly, found that the absorption was restored to that of fasted healthy subjects when itraconazole was given with a cola drink.[3]

(b) Ketoconazole

In a study in 9 healthy subjects, a single 200-mg dose of ketoconazole was given after pre-treatment with omeprazole 60 mg the night before (to simulate achlorhydria), with 240 mL of water or with 240 mL of *Coca-Cola Classic*. Pre-treatment with omeprazole reduced the absorption of ketoconazole by 83%, whereas when the cola drink was also given, the absorption of ketoconazole was only reduced by 35%. However, in 2 subjects the cola drink had only minor effects on ketoconazole absorption.[4]

Mechanism

Itraconazole and ketoconazole are poorly soluble bases, which must be transformed by the acid in the stomach into a soluble hydrochloride salt. Therefore any drug or condition that reduces gastric acidity can reduce the dissolution and absorption of these antifungals. Acidic drinks, which lower the pH, can increase the absorption.

Importance and management

The interactions of itraconazole and ketoconazole with cola drinks that lower the gastric pH are established. The interaction can be exploited to

improve the absorption of these antifungals in patients with achlorhydria or hypochlorhydria, and those taking gastric acid suppressants such as 'H_2-receptor antagonists', (p.245), and 'proton pump inhibitors', (p.246), and this is recommended by some manufacturers of ketoconazole[5] and itraconazole.[6,7] For a brief mention of the use of cola to increase itraconazole levels and thereby increase ciclosporin levels, see 'Ciclosporin + Azoles', p.1226. ***Coca-Cola Classic, Pepsi*** and ***Canada Dry Ginger Ale*** can be used because they can achieve stomach pH values of less than 3, but none of the other beverages examined in one study produced such a low pH. The authors suggest that these would be less effective, although they were not actually studied. They included ***Diet Coca-Cola***, ***Diet Pepsi***, ***Diet 7-Up***, ***Diet Canada Dry Ginger Ale***, ***Diet Canada Dry Orange Juice***, ***7-Up*** and ***Canada Dry Orange Juice***.[4] The acidic drug **glutamic acid** does not appear to increase the absorption of itraconazole in fasted or fed subjects, or increase the absorption of ketoconazole in subjects pre-treated with cimetidine. See 'Azoles + Food', below, and 'Azoles + H_2-receptor antagonists', p.245, respectively.

1. Jaruratanasirikul S, Kleepkaew A. Influence of an acidic beverage (Coca-Cola) on absorption of itraconazole. *Eur J Clin Pharmacol* (1997) 52, 235–7.
2. Lange D, Pavao JH, Wu J, Klausner M. Effect of cola beverage on the bioavailability of itraconazole in the presence of H_2 blockers. *J Clin Pharmacol* (1997) 37, 535–40.
3. Hardin J, Lange D, Heykants J, Ding C, Van de Velde V, Slusser C, Klausner M. The effect of co-administration of a cola beverage on the bioavailability of itraconazole in AIDS patients. *Intersci Conf Antimicrob Agents Chemother* (1995) 35, 6.
4. Chin TWF, Loeb M, Fong IW. Effects of an acidic beverage (Coca-Cola) on absorption of ketoconazole. *Antimicrob Agents Chemother* (1995) 39, 1671–5.
5. Nizoral Tablets (Ketoconazole). Janssen-Cilag Ltd. UK Summary of product characteristics, October 2008.
6. Sporanox Capsules (Itraconazole). Janssen-Cilag Ltd. UK Summary of product characteristics, October 2009.
7. Sporanox Capsules (Itraconazole). Janssen. US Prescribing information, March 2009.

Azoles + Food

Some foods increase the absorption of itraconazole from capsules or tablets, however food decreases the absorption of itraconazole from solution. Food increases the absorption of posaconazole from suspension. Studies with ketoconazole have shown little effect of food on absorption although one found a decrease. The bioavailability of voriconazole is modestly reduced by food. Food does not appear to affect the bioavailability of fluconazole.

Clinical evidence

(a) Fluconazole

A study in 12 healthy subjects found that food had no therapeutically relevant effect on the pharmacokinetics of a single 100-mg dose of fluconazole in capsule form.[1]

(b) Itraconazole

A study in 24 patients with superficial dermatophyte, *Candida albicans* and pityriasis versicolor infections, given itraconazole 50 or 100 mg daily, found that taking the drug with or after breakfast produced higher serum levels and gave much better treatment results than taking the drug before breakfast.[2] A later study found that the relative bioavailability of itraconazole (given as a capsule) was 54% on an empty stomach, 86% after a light meal and 100% after a full meal.[1] Similar results were found in other studies using itraconazole.[3,4] Another study investigated the absorption of itraconazole in 144 healthy subjects given itraconazole 100 mg (tablets or capsules) either in the fasting state, or immediately after a bread or a rice-based meal. This study found that while a bread-based meal more than doubled the bioavailability of itraconazole, when compared with the fasting state, in contrast a rice-based meal *reduced* the bioavailability of itraconazole by 43 to 80%.[5]

Studies with itraconazole oral solution give different results. A study in 30 healthy males given itraconazole solution 200 mg daily, either on an empty stomach or with a standard breakfast, found that the bioavailability was 29% higher when itraconazole was taken in the *fasted* state.[6]

(c) Ketoconazole

A study in 10 healthy subjects found that the AUC and peak serum concentrations of a single 200-mg dose of ketoconazole tablets were *reduced* by about 40% (levels reduced from 4.1 to 2.3 micrograms/mL) when ketoconazole was given after a standardised meal.[7]

In contrast, one study found that high-carbohydrate and high-fat diets tended to reduce the rate, but not the overall amount of ketoconazole absorbed from tablets.[8] Further, a study in 8 healthy subjects found that the absorption of single 200- or 800-mg doses of ketoconazole was not altered when the ketoconazole was taken after a standardised breakfast, although the peak serum levels were delayed. The absorption of single 400- and 600-mg doses of ketoconazole were increased by about up to 50% with food, but this was not statistically significant.[9]

(d) Posaconazole

A study in 23 healthy subjects found that the maximum plasma levels and AUC of a single 400-mg dose of posaconazole oral suspension were increased 3.4- and 2.6-fold, respectively, when given with about 230 mL of a **nutritional supplement** (*Boost Plus*) rather than in the fasting state.[10] In a further study in 20 healthy subjects, single 200-mg doses of posaconazole oral suspension were given with either a high-fat meal, a non-fat breakfast, or after a 10-hour fast. The AUC of the suspension was increased fourfold by the high-fat meal, and 2.7-fold by the non-fat breakfast, when compared with fasting.[11]

(e) Voriconazole

In a study, 12 healthy subjects were given voriconazole capsules 200 mg twice daily either with food or in the fasted state (2 hours before or after food). Food delayed the oral absorption of voriconazole by about one hour and reduced the AUC by 22%.[12]

Mechanism

Not understood.

Importance and management

Itraconazole absorption from the *capsule* formulation is best when it is taken with or after food and patients should still be advised this. However, as one study[5] found a *reduction* in the bioavailability with a rice-based meal, further study may be needed to clarify if other foods may have the opposite effects to those expected. It would be prudent to be aware that the choice of food taken with the itraconazole may not always have a positive effect on its absorption and bear this in mind in case of an unexpected response to treatment. The absorption from the acidic *liquid* formulation appears to be better when it is taken at least one hour before food, and this is recommended by the manufacturers.[13]

Posaconazole absorption from the oral suspension is improved by food, and the manufacturer recommends that posaconazole should be taken with food, or with a nutritional supplement for those who cannot tolerate food.[14]

A confusing and conflicting picture is presented by the studies with **ketoconazole**, two showing no significant change in absorption with food, and one showing a decrease. However, one manufacturer of ketoconazole says that the absorption of ketoconazole is maximal when it is taken during a meal, as it depends on stomach acidity, and it should therefore always be taken with meals.[15]

The manufacturers of **voriconazole** tablets and the US manufacturers of voriconazole suspension recommend that it should be taken at least 1 hour before or at least 1 hour after a meal.[16,17] The UK manufacturer of voriconazole suspension suggests that it should be taken at least 1 hour before or at least *2* hours after a meal.[16]

There appears to be no relevant interaction between food and **fluconazole**.

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14. Noxafil (Posaconazole). Schering-Plough Ltd. UK Summary of product characteristics, November 2009.
15. Nizoral Tablets (Ketoconazole). Janssen-Cilag Ltd. UK Summary of product characteristics, October 2008.
16. VFEND (Voriconazole). Pfizer Ltd. UK Summary of product characteristics, September 2009.
17. VFEND (Voriconazole). Pfizer Inc. US Prescribing information, December 2009.

Azoles + H_2-receptor antagonists

H_2-receptor antagonists markedly reduce the gastrointestinal absorption of ketoconazole; and modestly reduce that of itraconazole (possibly halved) and posaconazole (about 40%); whereas the absorption of fluconazole and voriconazole is not significantly affected. Not all H_2-receptor antagonists have been studied, but all are expected to interact similarly.
Ketoconazole may increase the levels of ranitidine.

Clinical evidence

A. Effects of H_2-receptor antagonists on the absorption of azoles

(a) Fluconazole

In a study in 6 healthy subjects, the AUC_{0-48} of fluconazole 100 mg was reduced by only 13% by a single 400-mg dose of **cimetidine**.[1] Two other studies found that **cimetidine**[2] and **famotidine**[3] did not affect fluconazole absorption.

(b) Itraconazole

In one study, 12 healthy subjects were given **cimetidine** 400 mg twice daily or **ranitidine** 150 mg twice daily for 3 days before and after a single 200-mg dose of itraconazole. The AUC and maximum serum levels of the itraconazole were reduced, but not significantly. The largest changes were 20% reductions in the AUC and maximum serum levels with **ranitidine**.[4] A study in 204 liver transplant patients,[5] comparing the antifungal efficacy of itraconazole with fluconazole, reported that itraconazole trough levels were not affected in the 16 patients also taking H_2-receptor antagonists, 'proton pump inhibitors', (p.246), or 'antacids', (p.243).

In contrast, another study in 30 healthy subjects found that **ranitidine** 150 mg twice daily for 3 days reduced the AUC of a single 200-mg dose of itraconazole by 44%, and reduced its maximum serum levels by 52%.[6] A study of the bioavailability of itraconazole, in 12 lung transplant patients also given **ranitidine** 150 mg twice daily and an antacid four times daily, found that the serum levels of itraconazole were highly variable. Half of the patients required the dose of itraconazole to be increased from 200 to 400 mg daily to achieve satisfactory serum levels.[7]

In 12 healthy subjects, the serum levels of a single 200-mg dose of itraconazole were reduced by about 50% when they were given two doses of **famotidine** 40 mg, one dose the night before and the second dose taken one hour before itraconazole.[3] In a further study **famotidine** 20 mg twice daily was given with itraconazole 200 mg daily for 10 days to 16 patients undergoing chemotherapy for haematological malignancies. The minimum plasma levels of itraconazole were reduced by about 39%, and 8 patients did not achieve the levels considered necessary to protect neutropenic patients from fungal infections.[8]

In another study in 20 HIV-positive patients, **glutamic acid** 1360 mg, given to acidify the stomach, either with or without food did not enhance itraconazole absorption.[9]

(c) Ketoconazole

A case report describes a haemodialysis patient, who did not respond to treatment with ketoconazole 200 mg daily while taking **cimetidine**, sodium bicarbonate 2 g daily and aluminium oxide 2.5 g daily. Only when the ketoconazole dosage was increased to 200 mg four times daily did her serum levels rise. A later study in 3 healthy subjects found that when ketoconazole 200 mg was taken 2 hours after **cimetidine** 400 mg, the absorption was considerably reduced (AUC reduced by about 60%). When these two drugs were given with the addition of sodium bicarbonate 500 mg, the absorption of ketoconazole was reduced by about 95%. In contrast, when cimetidine was given with ketoconazole in an acidic solution, the absorption of ketoconazole was *increased* by about 50%.[10]

The AUC of a single 200-mg oral dose of ketoconazole was reduced by 91% in 12 fasting subjects who received **cimetidine** 300 mg two hours before ketoconazole, and then sodium bicarbonate 2 g one hour before ketoconazole. This effect was only slightly reversed by the use of **glutamic acid**.[11] Another study[2] in 24 healthy subjects found that intravenous **cimetidine** titrated to give a gastric pH of 6 or more reduced the absorption of ketoconazole by 95%. Similarly, a study[12] in 6 healthy subjects found that **ranitidine** 150 mg given 2 hours before ketoconazole 400 mg reduced its AUC by about 95%.

(d) Posaconazole

A placebo-controlled study in 12 healthy subjects found that **cimetidine** 400 mg every 12 hours, given with posaconazole 200 mg once daily for 10 days, reduced the AUC and maximum plasma levels of posaconazole by about 40%.[13]

(e) Voriconazole

A study in 12 healthy subjects found that **cimetidine** 400 mg twice daily given with voriconazole 200 mg twice daily increased the maximum plasma levels and AUC of voriconazole by about 20%, but this is not considered sufficient to warrant a dosage adjustment.[14] **Ranitidine** 150 mg twice daily had no significant effect on the AUC and maximum plasma levels of voriconazole.[14]

B. Effects of azoles on H_2-receptor antagonists

A study in 8 healthy subjects found that **itraconazole** 200 mg twice daily for 3 days increased the AUC of intravenous **cimetidine** (loading dose 0.2 mg/kg followed by an infusion of 36 mg/hour for 4 hours) by 25%.[15] A study in 12 healthy subjects found that pre-treatment with **ketoconazole** 200 mg daily for 5 days had significant effects on the pharmacokinetics of a single 150-mg dose of **ranitidine**, taken 30 minutes before ketoconazole on day 5. Ketoconazole pre-treatment increased the AUC, peak serum level and half-life of ranitidine by 74%, 78% and 56%, respectively. The effects of ranitidine on ketoconazole were not reported in this study.[16]

Mechanism

Ketoconazole is a poorly soluble base, which must be converted by the acid in the stomach into the soluble hydrochloride salt. Drugs that reduce gastric acidity, such as H_2-receptor antagonists, 'proton pump inhibitors', (p.246) or 'antacids', (p.243), raise the pH in the stomach so that the dissolution of the ketoconazole and its absorption are reduced. Conversely, anything that increases the gastric acidity increases the dissolution and the absorption (e.g. 'cola drinks', (p.243)). The absorption of itraconazole capsules, and possibly posaconazole, is similarly affected by changes in gastric pH. The absorption of fluconazole and voriconazole[17] are not affected by reductions in gastric acidity.

The slight increase in cimetidine levels in the presence of itraconazole may be due to inhibition of P-glycoprotein mediated renal tubular secretion of cimetidine,[15] and the increase in the bioavailability of ranitidine is thought to be due to inhibition of intestinal P-glycoprotein by ketoconazole.[16]

Importance and management

The interactions of the H_2-receptor antagonists with **ketoconazole** are clinically important but not extensively documented. The situation with **itraconazole** is not entirely clear, but some reduction in its absorption apparently occurs which may be of clinical significance. It would therefore be prudent to confirm that both itraconazole and ketoconazole remain effective in the presence of H_2-receptor antagonists. It has been suggested[6] that the reduction in bioavailability due to H_2-receptor antagonists can be minimised by giving itraconazole and ketoconazole with an acidic drink such as 'cola', (p.243), and this is recommended by some manufacturers.[18-20] Although there appear to be no specific studies with itraconazole *solution*, the concurrent use of drugs that affect gastric acidity, such as H_2-receptor antagonists, would *not* be expected to have a similar effect. Studies with 'omeprazole', (p.246), have found no significant reduction in the absorption of itraconazole solution. The UK manufacturer of itraconazole oral solution[21] does not give any specific advice on concurrent use of these drugs; however, the US manufacturer advises caution with concurrent use, although they expect the effect to be significantly less than that seen with itraconazole capsules.[22]

The bioavailability of **posaconazole** also appears to be reduced by cimetidine. There appear to be no data on the effects of other H_2-receptor antagonists such as ranitidine, famotidine and nizatidine. If this reduction in absorption is due to the reduction in gastric acid, then it could minimised by taking posaconazole with a cola drink, as for ketoconazole and itraconazole. However, the manufacturer currently recommends that the use of posaconazole with cimetidine or other H_2-receptor antagonists (as there are no data) be avoided if possible, unless the benefit to the patient outweighs the risk.[23] Further study is needed.

Fluconazole only interacts to a small and clinically irrelevant extent with H_2-receptor antagonists and is therefore a possible alternative to ketoconazole and itraconazole. Similarly, **voriconazole** is not significantly affected by drugs that increase gastric pH such as the H_2-receptor antagonists,[17] and no dose adjustments are necessary with concurrent use.[24]

The clinical significance of the increases in **ranitidine** bioavailability produced by ketoconazole in one isolated study[16] are unclear: however, as ranitidine has a wide therapeutic margin, dose-related toxicity arising from this interaction seems unlikely.

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18. Nizoral Tablets (Ketoconazole). Janssen-Cilag Ltd. UK Summary of product characteristics, October 2008.
19. Sporanox Capsules (Itraconazole). Janssen-Cilag Ltd. UK Summary of product characteristics, October 2009.
20. Sporanox Capsules (Itraconazole). Janssen. US Prescribing information, March 2009.
21. Sporanox Oral Solution (Itraconazole). Janssen-Cilag Ltd. UK Summary of product characteristics, September 2008.
22. Sporanox Oral Solution (Itraconazole). Ortho Biotech. US Prescribing information, October 2007.
23. Noxafil (Posaconazole). Schering-Plough Ltd. UK Summary of product characteristics, November 2009.
24. VFEND (Voriconazole). Pfizer Ltd. UK Summary of product characteristics, September 2009.

Azoles + Proton pump inhibitors

The bioavailability of ketoconazole, itraconazole capsules (but not oral solution) and posaconazole is reduced by omeprazole and/or esomeprazole. Other proton pump inhibitors are expected to behave similarly. The bioavailability of fluconazole and voriconazole do not appear to affected by the proton pump inhibitors. Esomeprazole levels may be increased by voriconazole, omeprazole levels are increased by ketoconazole, and omeprazole levels are markedly increased by fluconazole and voriconazole.

Clinical evidence

(a) Esomeprazole

Esomeprazole 40 mg daily reduced the maximum plasma levels and AUC of **posaconazole** 400 mg by 46% and 32%, respectively.[1] Based on data for omeprazole, and the known acid-lowering effect of esomeprazole,[2] the manufacturers predict that esomeprazole might also reduce the absorption of **itraconazole**[2] and **ketoconazole**,[2,3] which depend on a low pH for optimal dissolution and absorption.

Voriconazole may more than double the levels of esomeprazole.[3]

(b) Omeprazole

1. Fluconazole. A study in 12 healthy subjects found that omeprazole 20 mg daily for 7 days did not affect the pharmacokinetics of a single 100-mg dose of fluconazole, given after a standard breakfast.[4]

In another study in 18 healthy subjects, fluconazole 100 mg daily for 5 days markedly increased the peak plasma levels and AUC of a single 20-mg dose of omeprazole by 2.4- and 6.3-fold, respectively.[5]

2. Itraconazole. In a study, 11 healthy subjects were given omeprazole 40 mg daily for 14 days, with a single 200-mg dose of itraconazole [capsule] given after a standard breakfast on day 14. The AUC and maximum serum level of itraconazole were both reduced by about 65% by omeprazole.[6] In contrast, another study in 15 healthy subjects found that omeprazole 40 mg daily did not significantly affect the pharmacokinetics of single 400-mg doses of itraconazole or its metabolite hydroxy-itraconazole, but in this study itraconazole was given as an oral solution, and there was a large interpatient variation in mean serum levels.[7] Another study similarly reported that omeprazole had little effect on the pharmacokinetics of itraconazole oral solution.[8] A study in 204 liver transplant patients,[9] comparing the antifungal efficacy of itraconazole solution with fluconazole, reported that itraconazole trough levels were not affected in 16 patients also taking proton pump inhibitors, 'H_2-receptor antagonists', (p.245), or 'antacids', (p.243).

3. Ketoconazole. A three-way crossover study in 9 healthy fasting subjects found that omeprazole 60 mg reduced the AUC of ketoconazole 200 mg by about 80%.[10]

Another study was carried out in 10 healthy subjects to find the extent to which the cytochrome P450 isoenzyme CYP3A4 is involved in the metabolism (sulfoxidation) of omeprazole. This revealed that ketoconazole 100 to 200 mg, a known inhibitor of CYP3A4, reduced the formation of the omeprazole sulfone in both subjects with normal amounts of CYP2C19, and those deficient or totally lacking CYP2C19. However, the serum omeprazole levels were doubled in the subjects totally lacking or deficient in CYP2C19.[11]

4. Posaconazole. Esomeprazole reduces posaconazole levels (see under *Esomeprazole*, above). The manufacturers of posaconazole therefore consider that proton pump inhibitors such as omeprazole might interact similarly.[1]

5. Voriconazole. A study in 18 healthy subjects found that omeprazole 40 mg daily for 7 days increased the maximum plasma levels and AUC of voriconazole by 15% and 41%, respectively. Food was prohibited within one hour before and after each dose.[12] In another study, voriconazole 200 mg twice daily increased the maximum plasma levels and AUC of omeprazole 40 mg once daily by about twofold and fourfold, respectively.[13]

An isolated case report suggests that the use of omeprazole with voriconazole may have contributed to the 'unmasking' of an inherited long QT syndrome in a young female patient. In this case, the patient developed torsade de pointes and cardiac arrest (successfully resuscitated). However, voriconazole had been stopped 12 hours previously and this particular patient had many other contributing risk factors to the development of torsade de pointes, such as hypomagnesaemia and the use of other drugs that have been reported to increase the QT interval.[14]

(c) Rabeprazole

In a randomised, placebo-controlled study, 18 healthy subjects were given **ketoconazole** 400 mg before and after taking rabeprazole 20 mg daily for 7 days. Rabeprazole significantly decreased the **ketoconazole** AUC and maximum serum levels,[15] representing about a 30% reduction in its bioavailability.[16] There was no evidence that **ketoconazole** affected rabeprazole metabolism.[15]

Mechanism

Ketoconazole and itraconazole are poorly soluble bases, which must be converted by the acid in the stomach into the soluble hydrochloride salt. Drugs that reduce gastric secretions, such as proton pump inhibitors, 'H_2-receptor antagonists', (p.245), or 'antacids', (p.243), raise the pH in the stomach so that the dissolution and absorption of drugs such as itraconazole (in capsule form), ketoconazole and posaconazole are reduced. Conversely, anything that increases the gastric acidity increases their dissolution and absorption.[10]

Fluconazole and voriconazole almost certainly cause a rise in omeprazole and esomeprazole levels by inhibiting their metabolism by the cytochrome P450 isoenzymes CYP2C19 and CYP3A4. Ketoconazole only inhibits CYP3A4 and therefore causes a less marked rise in omeprazole levels, although in subjects deficient in CYP2C19, where the metabolism of omeprazole is more dependent on CYP3A4, ketoconazole has greater effects. Itraconazole would be expected to interact similarly to ketoconazole.

Importance and management

(a) Fluconazole

Fluconazole pharmacokinetics are not affected by **omeprazole**, and are unlikely to be affected by other proton pump inhibitors. However, fluconazole markedly increases omeprazole levels. The clinical relevance of these changes is uncertain, but not likely to be important for single-dose fluconazole regimens. More study is needed to establish whether it is advisable to reduce the omeprazole dose in those given both drugs longer-term. Note that these increases in omeprazole levels are of a similar magnitude to those seen with voriconazole, and some manufacturers recommend dose adjustments with hepatic impairment or long term use.

(b) Itraconazole

The interaction between itraconazole and **omeprazole** appears to be established, but it appears that this can be minimised by using an oral itraconazole solution. As with ketoconazole, giving itraconazole capsules with an acidic drink such as 'cola', (p.243), would minimise the interaction, and this is recommended by one manufacturer of itraconazole.[17] Monitor patients taking itraconazole for antifungal efficacy if proton pump inhibitors are also given. The UK manufacturer of itraconazole oral *solution*[18] does not give any specific advice on concurrent use of drugs that reduce gastric acidity, such as the proton pump inhibitors. However the US manufacturers advise caution on concurrent use, although they expect the effect to be significantly less than that seen with itraconazole capsules.[19] The effect of itraconazole on omeprazole is unknown, but it might be expected to increase omeprazole levels similarly to ketoconazole: any effect seems unlikely to be significant in the majority of patients.

(c) Ketoconazole

The interaction between ketoconazole and **omeprazole** appears to be established and of clinical importance. Direct evidence seems to be limited to this study, but other drugs that raise the gastric pH have a similar effect (see 'Azoles + Antacids', p.243 or 'H_2-receptor antagonists', (p.245)). Such a large reduction in the absorption of ketoconazole would be expected to result in the failure of treatment. Separating the dosages of the two drugs is unlikely to be the answer because the effect of omeprazole is so prolonged. An alternative would simply be to monitor for any inadequate response to ketoconazole if omeprazole or **esomeprazole** is also given and to raise the dosage if necessary. Giving ketoconazole with an acidic drink[10] such as 'cola', (p.243), appears to minimise the interaction, and is recommended by some manufacturers.[20] However, bear in mind that ketoconazole can also double omeprazole levels, although the clinical relevance of this is likely to be small for the majority of patients.

The interaction between ketoconazole and **rabeprazole** is also established, but the reduction in ketoconazole bioavailability is only moderate (30%) and it may be possible to accommodate this by raising the antifungal dosage. There seem to be no reports about ketoconazole and other proton pump inhibitors but they are expected to interact similarly. It would therefore be prudent to monitor for a reduced effect if other proton pump inhibitors are used with ketoconazole.

(d) Posaconazole

Posaconazole levels are reduced by esomeprazole, the manufacturer therefore currently recommends that concurrent use of proton pump inhibitors be avoided if possible.[1] Further study is needed.

(e) Voriconazole

The small increase in the bioavailability of voriconazole seen with **omeprazole** is not expected to be of general clinical significance, and no adjustment to the dose of voriconazole is required.[13,21] The isolated report[14] of torsade de pointes in a patient taking voriconazole with omeprazole is complicated by multiple factors that may have contributed to the development of QT prolongation. As voriconazole alone has been reported to cause QT prolongation, its general significance is unclear. The clinical importance of the marked rise in serum omeprazole levels caused by voriconazole is not established, but the manufacturers of voriconazole recommend that the omeprazole dose be halved,[13,21] although the US manufacturers restrict this to patients taking omeprazole 40 mg or more.[13] The manufacturers of omeprazole do not recommend routine omeprazole dose adjustments with the concurrent use of voriconazole, but suggest that consideration is given to reducing the dose in patients with hepatic impairment or if long-term treatment is required.[22] The increase in the levels of **esomeprazole** by voriconazole does not routinely require a dose adjustment of esomeprazole. However, patients taking esomeprazole in doses of more than 240 mg daily (e.g. for Zollinger-Ellison syndrome) may require a dose adjustment.[3]

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17. Sporanox Capsules (Itraconazole). Janssen-Cilag Ltd. UK Summary of product characteristics, October 2009.
18. Sporanox Oral Solution (Itraconazole). Janssen-Cilag Ltd. UK Summary of product characteristics, September 2008.
19. Sporanox Oral Solution (Itraconazole). Ortho Biotech. US Prescribing information, October 2007.
20. Nizoral Tablets (Ketoconazole). Janssen-Cilag Ltd. UK Summary of product characteristics, October 2008.
21. VFEND (Voriconazole). Pfizer Ltd. UK Summary of product characteristics, September 2009.
22. Losec Capsules (Omeprazole). AstraZeneca UK Ltd. UK Summary of product characteristics, February 2008.

Azoles + Rifabutin

Rifabutin levels are increased by fluconazole, posaconazole, voriconazole, possibly itraconazole (and therefore possibly also ketoconazole). Patients taking this combination are at increased risk of rifabutin toxicity, specifically uveitis.

Rifabutin markedly reduces the plasma levels of itraconazole (and therefore possibly also ketoconazole), posaconazole, and voriconazole. Rifabutin does not affect the metabolism of fluconazole.

Clinical evidence

(a) Fluconazole

Twelve HIV-positive patients were given zidovudine 500 mg daily from day 1 to 44, fluconazole 200 mg daily from days 3 to 30 and rifabutin 300 mg daily from days 17 to 44. Rifabutin did not significantly affect the pharmacokinetics of fluconazole,[1] but fluconazole increased the AUC of rifabutin by 82%, and increased the AUC of the rifabutin metabolite LM565 by 216%.[1] In another study in 10 patients with HIV infection, fluconazole 200 mg daily increased the AUC of rifabutin 300 mg daily by 76% and increased its maximum level by 91%. When the patients were also given clarithromycin 500 mg daily, the AUC of rifabutin was further increased to 152%.[2] There is some evidence that fluconazole increases the prophylactic efficacy of rifabutin against *Mycobacterium avium* complex disease, although there was also an increase in incidence of leucopenia.[3] Uveitis developed in 6 HIV-positive patients taking rifabutin 450 to 600 mg daily and fluconazole, 5 of whom were also taking clarithromycin,[4] which is also known to increase rifabutin levels, see 'Macrolides + Rifamycins', p.357. Uveitis has been attributed to the concurrent use of rifabutin and fluconazole in other reports.[5,6]

Rifabutin does not appear to significantly affect the metabolism of fluconazole.[7,8]

(b) Itraconazole

1. Itraconazole levels. In a three-period study, 6 HIV-positive patients were given itraconazole 200 mg daily for 14 days, rifabutin 300 mg daily for 10 days, and then both drugs for 14 days. It was found that the rifabutin reduced the peak plasma levels of itraconazole by 71% and reduced its AUC by 74%.[9]

2. Rifabutin levels. A 49-year-old HIV-positive man taking rifabutin 300 mg daily was also given itraconazole 600 mg daily. Because of low plasma levels after 3 weeks the itraconazole dose was increased to 900 mg daily. One week later the patient developed anterior uveitis. It was found that the itraconazole trough serum levels were normal but rifabutin trough serum levels were 153 nanograms/mL (expected to be less than 50 nanograms/mL after 24 hours). Rifabutin was stopped and the uveitis was treated. Symptoms resolved after 5 days.[10]

(c) Posaconazole

In a study in healthy subjects the concurrent use of posaconazole 200 mg daily and rifabutin 300 mg daily for 10 days increased the AUC of rifabutin by 72% and decreased the AUC of posaconazole by 51%, when compared with either drug alone.[11] Another study in 24 healthy subjects given posaconazole 200 mg daily for 10 days alone or starting on day 8 of a 17-day course of rifabutin 300 mg daily found that rifabutin reduced the maximum plasma concentration and AUC of posaconazole by 43% and 49%, respectively. Posaconazole increased the AUC and maximum concentration of rifabutin by 72% and 31%, respectively. Adverse effects (headache, back pain, leucopenia, eye abnormalities) were more common with the concurrent use of posaconazole and rifabutin, leading to 4 subjects given both drugs being withdrawn from the study.[12]

(d) Voriconazole

The manufacturers describe a study in which rifabutin 300 mg daily decreased the AUC and maximum plasma levels of voriconazole 200 mg twice daily by 79% and 67%, respectively. Increasing the dose of voriconazole to 350 mg twice daily in the presence of rifabutin gave an AUC of 68% and maximum plasma levels more or less the same as that achieved with voriconazole 200 mg twice daily alone.[13,14] At a dose of 400 mg twice daily, voriconazole increased the maximum plasma level and AUC of rifabutin 300 mg twice daily by about threefold and fourfold, respectively.[13,14]

Mechanism

Rifabutin increases the metabolism of itraconazole and voriconazole, probably, at least in part, by inducing their metabolism by the cytochrome P450 CYP3A subfamily. Ketoconazole would be expected to be similarly affected. Rifabutin is also an inducer of P-glycoprotein and so would be expected to reduce the levels of posaconazole, which is a substrate for P-glycoprotein.[15] Fluconazole is largely excreted unchanged in the urine and so it is not affected by rifabutin.

The azoles apparently increase rifabutin levels by inhibiting its metabolism, probably by CYP3A4. Raised rifabutin levels can cause uveitis.

Importance and management

The interaction between rifabutin and **fluconazole** is established, the general picture being that concurrent use can be advantageous. However, because of the increased risk of uveitis, the CSM in the UK says that full consideration should be given to reducing the dosage of rifabutin to 300 mg daily. The rifabutin should be stopped if uveitis develops and the patient referred to an ophthalmologist.[16] A later review suggests this 300 mg dose is associated with a reduced risk of uveitis and maintains efficacy.[17] The combination should be well monitored. Note that the effects of 'clarithromycin', (p.357), are additive with those of fluconazole.

Information on the interaction between **itraconazole** and rifabutin is very limited, but if both drugs are given, monitor for reduced antifungal activity, raising the itraconazole dosage as necessary, and watch for increased rifabutin levels and toxicity (in particular uveitis). Note that the manufacturers do not recommend concurrent use.[18,19]

The manufacturer of **ketoconazole** does not recommend concurrent use with enzyme inducers, such as rifabutin.[20] However, if concurrent use is necessary, it may be prudent to follow the same precautions suggested for itraconazole.

On the basis of the interaction between rifabutin and **posaconazole**, the manufacturer suggests that the combination be avoided unless the benefit to the patient outweighs the risk.[15] If the combination is used, monitor the efficacy of posaconazole and the toxicity of rifabutin, particularly full blood counts and uveitis.

The manufacturer in the US contraindicates the combination of **voriconazole** and rifabutin.[14] However, the UK manufacturer permits concurrent use if the benefits outweigh the risks.[13] If used together, the oral dose of voriconazole should be increased from 200 mg twice daily to 350 mg twice daily (and from 100 to 200 mg twice daily in patients under 40 kg). The intravenous dose should also be increased from 4 to 5 mg/kg twice daily. Importantly, the manufacturer advises careful monitoring for rifabutin adverse effects (e.g. check full blood counts, monitor for uveitis).[13]

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8. Mycobutin (Rifabutin). Pharmacia Ltd. UK Summary of product characteristics, June 2009.
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15. Noxafil (Posaconazole). Schering-Plough Ltd. UK Summary of product characteristics, November 2009.
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19. Sporanox Capsules (Itraconazole). Janssen. US Prescribing information, March 2009.
20. Nizoral Tablets (Ketoconazole). Janssen-Cilag Ltd. UK Summary of product characteristics, October 2008.

Azoles + Rifampicin (Rifampin) and/or Isoniazid

Rifampicin causes only a modest increase in fluconazole clearance; however, cases of reduced fluconazole efficacy have been reported. Rifampicin very markedly reduces itraconazole, ketoconazole, and voriconazole levels, and is predicted to have similar effects on posaconazole levels.

Fluconazole does not appear to affect rifampicin pharmacokinetics, but rifampicin levels are halved by ketoconazole.

Clinical evidence

(a) Fluconazole

1. Fluconazole levels. In a study in healthy subjects rifampicin 600 mg daily for 19 days reduced the AUC of a single 200-mg dose of oral fluconazole by 23% and decreased its half-life by 19%.[1] Similarly, a study in patients with AIDS, taking fluconazole 400 mg daily for cryptococcal meningitis found that the AUC and peak plasma level of fluconazole were reduced by 22% and 17%, respectively, in 12 patients also taking rifampicin 600 mg daily, when compared with 12 similar patients not given rifampicin. There were no significant changes in clinical outcome, although the subsequent use of a lower prophylactic dose of fluconazole 200 mg with rifampicin was found to result in levels of fluconazole below the MIC of the infecting organism.[2] Another 3 patients with AIDS, taking fluconazole 400 mg daily for cryptococcal meningitis relapsed when rifampicin was added.[3] Another report briefly states that one of 5 patients taking fluconazole needed an increased dosage or a replacement antifungal when given rifampicin,[4] and a small study found that the AUC of *intravenous* fluconazole was 52% lower in 2 patients taking rifampicin, when compared with 3 patients not taking rifampicin.[5]

2. Rifampicin (Rifampin) levels. A study in 11 patients with AIDS and cryptococcal meningitis found that fluconazole 200 mg twice daily for 14 days had no effect on the pharmacokinetics of rifampicin 300 mg daily.[6] Five patients with AIDS and tuberculosis, taking rifampicin and fluconazole, had normal rifampicin levels, when compared with 14 similar patients taking rifampicin alone, but in both groups rifampicin levels were only about 28% of those predicted.[7]

3. Hypercalcaemia. There is an isolated report of severe hypercalcaemia attributed to the use of rifampicin and fluconazole in a patient with tuberculosis and pneumocystosis.[8] The clinical relevance of this case is uncertain.

(b) Itraconazole

A patient receiving antitubercular treatment including rifampicin 600 mg and isoniazid 300 mg daily was also given itraconazole 200 mg daily. After 2 weeks of treatment his serum itraconazole levels were negligible (0.011 mg/L). Even when the itraconazole dosage was doubled the levels only reached a maximum of 0.056 mg/L. When the antitubercular drugs were stopped his serum itraconazole level increased to 3.23 mg/L with a 300 mg daily dose, and were 2.35 to 2.6 mg/L with a 200 mg daily dose.[9]

A later study in 8 other patients confirmed that itraconazole levels were reduced by rifampicin but the clinical outcome depended on the mycosis being treated. Four out of 5 patients responded to treatment for a *Cryptococcus neoformans* infection, despite undetectable itraconazole levels, apparently because of synergy between the two drugs (demonstrated *in vitro*). In contrast, 2 patients with coccidioidomycosis failed to respond, and 2 others with cryptococcosis suffered a relapse or persistence of seborrhoeic dermatitis (possibly due to *M. furfur*) while taking both drugs.[10] A further study in 6 healthy subjects found that the AUC of a single 100-mg dose of itraconazole was reduced by 80% by rifampicin 600 mg daily for 3 days.[11] Very markedly reduced serum itraconazole levels (undetectable in some instances) have been seen in other healthy subjects and patients with AIDS when they were given rifampicin.[12-14]

Retrospective review of the medical records of 2 patients given itraconazole and rifampicin indicated that itraconazole was not effective until rifampicin was stopped, based on the finding of continued weight loss while on the combination, and a clear weight gain after rifampicin was stopped.[15]

(c) Ketoconazole

1. Ketoconazole levels. A study[16] in 6 healthy subjects found that rifampicin 600 mg daily reduced the AUC of ketoconazole 200 mg by 80%. Similarly, in another patient, the serum levels of ketoconazole 200 mg daily were roughly halved by rifampicin 600 mg. After 5 months of concurrent use with rifampicin and isoniazid 300 mg daily, there was a ninefold decrease in peak serum levels and the AUC was reduced by nearly 90%.[17]

A study in a 3-year-old child who had responded poorly to treatment, found that the peak serum levels and AUC of ketoconazole were both reduced by about 65% to 80% by rifampicin and/or **isoniazid**. The interaction also occurred when the dosages were separated by 12 hours. When all three drugs were given together the ketoconazole serum levels were undetectable.[18] Other reports confirm these reports of decreased ketoconazole levels with rifampicin.[19-23]

2. Rifampicin (Rifampin) levels. A study in 6 healthy subjects found that the addition of ketoconazole 200 mg twice daily for one day then 200 mg daily for 2 days to rifampicin 600 mg daily had little effect on the peak level and AUC of rifampicin.[16] In contrast, the serum rifampicin levels of a child were roughly halved by ketoconazole, but when the rifampicin was given 12 hours after the ketoconazole, the serum levels of rifampicin were unaffected.[18] Other studies also show a reduction in rifampicin levels caused by ketoconazole,[21-23] one confirming that separation of the drugs by 12 hours minimised the interaction.[21]

(d) Voriconazole

A study investigating the steady-state pharmacokinetics of voriconazole reported a case where rifampicin was inadvertently started in a patient taking voriconazole 200 mg twice daily. The peak plasma level of voriconazole was reduced from 3.92 to 0.038 micrograms/L and the AUC of voriconazole was reduced by 99% after voriconazole was given with rifampicin (dose not stated) for 30 days.[24] The manufacturer[25] notes that rifampicin 600 mg once daily decreased the maximum plasma levels and AUC of voriconazole 200 mg twice daily by about 95%. Even doubling the dose of voriconazole to 400 mg twice daily did not give adequate exposure.[25]

Mechanism

Rifampicin is an inducer of many cytochrome P450 isoenzymes, including CYP3A4, and therefore increases the metabolism of the azole antifungals by these liver isoenzymes. However, as fluconazole (unlike ketoconazole, itraconazole and voriconazole) is mainly excreted unchanged in the urine, changes to its metabolism would not be expected to have as marked an effect as on these other azoles. Furthermore, posaconazole is a substrate for P-glycoprotein. Therefore, inducers of this transport system such as rifampicin are predicted to reduce its levels.[26]

The absorption of antitubercular drugs may be reduced in patients with AIDS and an increase in rifampicin levels may be due to increased absorption in the presence of fluconazole.[7] In contrast, it is suggested that ketoconazole impairs the absorption of rifampicin from the gut. Just how isoniazid interacts is uncertain.

Importance and management

The interaction between rifampicin and **fluconazole** appears to be established and of clinical importance. Although rifampicin has only a modest effect on fluconazole levels, the cases of relapse cited above[3] and the need for an increased dosage[4] indicate that this interaction can be clinically important. Monitor concurrent use and increase the fluconazole dosage if necessary. One study suggests that a 30% increase in the fluconazole dose may be considered for serious infections if rifampicin is also given. This may be especially important during prophylaxis of cryptococcal meningitis with lower doses of fluconazole, such as 200 mg daily.[2]

The interaction between **itraconazole** and rifampicin is established and clinically important. The effect on serum itraconazole levels can be very marked indeed. The clinical importance of this interaction can apparently depend on the mycosis being treated, and therefore if the decision is taken to use both drugs monitor the outcome closely, being alert for the need to increase the itraconazole dosage. However, note that the manufacturers do not recommend the concurrent use of itraconazole and rifampicin, as its levels are so markedly reduced.[27,28]

The interactions between **ketoconazole** and rifampicin appear to be established and of clinical importance, but there is very much less information about the interaction with isoniazid. The effects on rifampicin can apparently be avoided by giving the ketoconazole at a different time (12 hours apart seems to be effective) but this does not solve the problem of the effects on ketoconazole: because of this the manufacturer suggests that concurrent use is not recommended.[29]

The manufacturer of **posaconazole** predicts that its levels may be significantly lowered when used with rifampicin. They suggest that the combination be avoided unless the benefit to the patient outweighs the risk.[26]

Voriconazole levels are very markedly reduced by rifampicin and concurrent use is contraindicated.[25,30]

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26. Noxafil (Posaconazole). Schering-Plough Ltd. UK Summary of product characteristics, November 2009.
27. Sporanox Capsules (Itraconazole). Janssen-Cilag Ltd. UK Summary of product characteristics, October 2009.
28. Sporanox Capsules (Itraconazole). Janssen. US Prescribing information, March 2009.
29. Nizoral Tablets (Ketoconazole). Janssen-Cilag Ltd. UK Summary of product characteristics, October 2008.
30. VFEND (Voriconazole). Pfizer Ltd. UK Summary of product characteristics, September 2009.

Azoles + Sucralfate

The gastrointestinal absorption of ketoconazole is modestly reduced by sucralfate, whereas the absorption of fluconazole does not appear to be significantly affected.

Clinical evidence

(a) Fluconazole

Sucralfate 2 g was found to have no significant effect on the pharmacokinetics of a single 200-mg dose of fluconazole in 10 healthy subjects, confirming the results of an *in vitro* study.[1]

(b) Ketoconazole

A study[2] in 6 fasting healthy subjects found that sucralfate 1 g given 2 hours before ketoconazole 400 mg reduced its AUC by about 20%. Another study in fasting healthy subjects found that sucralfate 1 g given with glutamic acid hydrochloride reduced the AUC and maximum serum levels of a single 100-mg dose of ketoconazole by about 25%, but no significant changes were seen when the ketoconazole was given 2 hours after the sucralfate.[3]

Mechanism

There is *in vitro* evidence that an electrostatic interaction occurs between ketoconazole and sucralfate to form an ion pair that cannot pass through the gut wall.[4]

Importance and management

The interaction of sucralfate with ketoconazole is modest and of uncertain clinical importance. Any interaction may be minimised by taking sucralfate not less than 2 to 3 hours before or after the ketoconazole. No adjustments would be expected to be necessary of fluconazole is given with sucralfate.

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Azoles; Fluconazole + Hydrochlorothiazide

Hydrochlorothiazide modestly increases the levels of fluconazole, but this is unlikely to be clinically relevant.

Clinical evidence, mechanism, importance and management

The manufacturer notes that, in 13 healthy subjects, hydrochlorothiazide 50 mg daily increased the AUC and plasma levels of fluconazole 100 mg daily for 10 days by about 40%.[1,2] They attribute these changes to a reduction in the renal clearance of fluconazole.[2] However they say it is unlikely that a change in the fluconazole dosage will be needed in patients taking diuretics, but that the interaction should be borne in mind.[1] Any interaction is almost certainly of no relevance in a patient taking a single dose of fluconazole (e.g. for genital candidiasis).

1. Diflucan (Fluconazole). Pfizer Ltd. UK Summary of product characteristics, April 2007.
2. Diflucan (Fluconazole). Pfizer Inc. US Prescribing information, March 2008.

Azoles; Itraconazole + Grapefruit and other fruit juices

Grapefruit juice impaired the absorption of itraconazole capsules in one study, but not in another. Grapefruit juice had no effect on the absorption of itraconazole oral solution. Orange juice impaired the absorption of itraconazole capsules in one study.

Clinical evidence

(a) Capsules

In one study in 11 healthy subjects, either 240 mL of double-strength grapefruit juice or water were given with and 2 hours after a single 200-mg dose of itraconazole (*Sporanox capsules, Janssen*) immediately after a standard breakfast. Grapefruit juice unexpectedly decreased the AUC of itraconazole by 43% (range 81% reduction to 105% increase), with a similar decrease in hydroxy-itraconazole levels.[1] However, another similar study found that grapefruit juice had no effect on the pharmacokinetics of itraconazole capsules (*Itrizole, Janssen*). The only apparent differences in this study were that itraconazole was given at the lower dose of 100 mg, and that 350 mL of single-strength grapefruit juice was used.[2] Furthermore, in this study,[2] **orange juice** reduced the AUC of itraconazole by an average of 41%.

(b) Oral solution

In a study in 20 healthy subjects grapefruit juice caused a small 17% increase in the AUC of itraconazole. In this study, regular strength grapefruit juice 240 mL was given three times daily for 2 days, then together with itraconazole oral solution 200 mg on the morning of the third day in the fasted state, then again 2 hours later.[3]

Mechanism

Grapefruit juice is an inhibitor of intestinal cytochrome P450 isoenzyme CYP3A4, the major enzyme involved in itraconazole metabolism. It was therefore predicted that it would enhance itraconazole absorption, a prediction confirmed with itraconazole oral solution. However, studies with itraconazole capsules have found decreased levels and no change. The

mechanism is not known, but it has been suggested that grapefruit juice may impair the absorption of itraconazole capsules either by affecting P-glycoprotein or lowering the duodenal pH.[1]

Importance and management

Evidence is limited and somewhat conflicting. The 40% reduction in itraconazole levels from itraconazole capsules seen with grapefruit juice would be anticipated to be clinically relevant in some situations, but it was seen in only one of two single-dose studies. Similarly, the reduction in levels with orange juice might be clinically relevant. However, at present, there is insufficient evidence to recommend avoiding concurrent use. Until more is known, in the event of unexpected inefficacy or low levels of itraconazole, consider grapefruit juice or orange juice intake as a possible factor.

Itraconazole oral solution, which is better absorbed than the capsules, did not appear to be affected by grapefruit juice.

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Azoles; Topical + Miscellaneous

Butoconazole, clotrimazole, econazole and fenticonazole are absorbed very poorly from the vagina so that the risk of an interaction with other drugs given systemically is small. Similarly, econazole, oxiconazole and sertaconazole are minimally absorbed through the skin, and would not be expected to cause drug interactions. However, note that there have been a few cases of miconazole cream or pessaries and one case with econazole cream interacting with oral anticoagulants.

Clinical evidence, mechanism, importance and management

(a) Intravaginal application

The manufacturer notes that 1.3 to 2.2% of the dose of intravaginal **butoconazole** cream 2% was absorbed in a study in three women.[1]

Early studies with intravaginal **clotrimazole** revealed that only a small fraction (3 to 10% of the dose) was absorbed systemically, and that this was rapidly metabolised.[2]

A study in 14 women (5 of them healthy, 4 with relapsing vulvovaginal candidiasis, and 5 with cervical carcinoma) found that the systemic absorption of **fenticonazole** nitrate from a single 1-g pessary was very small indeed. The amount absorbed, based on the amount recovered from the urine and faeces over 5 days, ranged from 0.58 to 1.81% of the original dose.[3] **Econazole** is also poorly absorbed when given intravaginally.[4]

The risk of a clinically relevant interaction with other drugs that may be present in the body would therefore seem to be very small with these antifungals used vaginally. However, for a few reports of raised INRs in women taking oral anticoagulants while using intravaginal miconazole, see 'Coumarins and related drugs + Azoles; Miconazole', p.438.

(b) Topical application

Systemic **econazole** is known to inhibit cytochrome P450 isoenzymes, but because of the very low systemic availability after topical application the manufacturer notes that clinically relevant interactions are rare.[5] However, for a case report of raised INR in a man taking warfarin while using econazole cream see 'Coumarins + Azoles; Econazole', p.436.

The manufacturer of **oxiconazole** notes that systemic absorption is low, and in healthy subjects less than 0.3% of the applied dose was recovered in the urine after topical application of the cream.[6]

Plasma levels of **sertaconazole** were below the limit of detection (2.5 nanograms/mL) when 5 patients with interdigital tinea pedis applied sertaconazole cream 2% every 2 hours for a total of 13 doses.[7]

Based on this information the risk of a clinically relevant drug interaction with systemically administered drugs and these topical azoles would seem to be very small. However, for a case report of raised INR in a man taking warfarin while using miconazole cream for a groin infection, see 'Coumarins and related drugs + Azoles; Miconazole', p.438.

1. Gynazole 1 (Butoconazole nitrate). Ther-Rx Corp. US Prescribing information, August 2003.
2. Ritter W. Pharmacokinetic fundamentals of vaginal treatment with clotrimazole. *Am J Obstet Gynecol* (1985) 152, 945–7.
3. Novelli A, Periti E, Massi GB, Mazzei T, Periti P. Systemic absorption of 3H-fenticonazole after vaginal administration of 1 gram in patients. *J Chemother* (1991) 3, 23–7.
4. Gyno-Pevaryl Pessaries (Econazole nitrate). Janssen-Cilag Ltd. UK Summary of product characteristics, August 2008.
5. Pevaryl Topical Cream (Econazole nitrate). Janssen-Cilag Ltd. UK Summary of product characteristics, March 2008.
6. Oxistat (Oxiconazole nitrate). Pharmderm. US Prescribing information, March 2008.
7. Ertaczo (Sertaconazole nitrate). OrthoNeutrogena. US Prescribing information, November 2005.

Azoles; Voriconazole + St John's wort (*Hypericum perforatum*)

St John's wort, taken for two weeks, more than halved the AUC of a single dose of voriconazole.

Clinical evidence, mechanism, importance and management

In a study in 17 healthy subjects, a single 400-mg dose of oral voriconazole was given alone and on the first and last day of St John's wort (*Jarsin, Lichtwer Pharma*) given at a dose of 300 mg three times daily for 15 days. One day of St John's wort had no effect on the voriconazole $AUC_{0-\infty}$, but slightly increased the maximum serum level and AUC_{0-10} by 22%. However, when voriconazole was given on day 15, the AUC of voriconazole was decreased by 59% and there was a 2.4-fold increase in oral clearance.[1]

These results suggest that the short-term effect of St John's wort is to slightly enhance the absorption of voriconazole, whereas the longer-term effect is to induce absorption-limiting transport proteins and intestinal metabolism by cytochrome P450 isoenzymes.[1]

The slight increase in voriconazole absorption with a single dose of St John's wort is not clinically relevant. However, the reduction in voriconazole levels after 15 days of St John's wort could have a significant impact on clinical efficacy. For this reason, the manufacturers contraindicate concurrent use of St John's wort with voriconazole.[2,3] Patients taking voriconazole should be advised not to take St John's wort. Patients requiring voriconazole should be asked about current or recent use of St John's wort, since this may indicate the need to use an increased voriconazole dose, at least initially, while the metabolic effects of the herb decline.

1. Rengelshausen J, Banfield M, Riedel KD, Burhenne J, Mikus G, et al. Opposite effects of short-term and long-term St John's wort on voriconazole pharmacokinetics. *Clin Pharmacol Ther* (2005) 78, 25–33.
2. VFEND (Voriconazole). Pfizer Ltd. UK Summary of product characteristics, September 2009.
3. VFEND (Voriconazole). Pfizer Inc. US Prescribing information, December 2009.

Chloroquine + Antihistamines

Chlorphenamine appears to increase the levels and therapeutic efficacy of chloroquine. Promethazine appears to increase the levels of intramuscular chloroquine and its metabolites, although no increase was seen with oral chloroquine.

Clinical evidence and mechanism

(a) Chlorphenamine

A study in 8 children given chloroquine 25 mg/kg over 3 days found that the addition of chlorphenamine (8 mg as a loading dose then 4 mg three times daily for 7 days) significantly increased the AUC and peak concentration of chloroquine, when compared with 9 children given chloroquine alone. A shorter parasite clearance rate (reduced from 3.5 days to 2 days) and higher cure rate (increased from 67% to 88%) were reported with the combination.[1]

A study in 10 healthy subjects given chloroquine 10 mg/kg on days 1 and 2 and 5 mg/kg on day 3, alone or with chlorphenamine (8 mg as a single dose followed by 4 mg every 8 hours for 7 days), found that the combination of chloroquine with chlorphenamine significantly increased the peak level of chloroquine in erythrocytes by about 25% and doubled the erythrocyte AUC and half-life,when compared with chloroquine alone. Increased erythrocyte bioavailability is thought to reduce resistance to chloroquine. However, the clinical efficacy of this increase was not studied.[2]

A study in 41 children found that the adverse cardiac effects (QT prolongation, PR interval prolongation) of chloroquine with chlorphenamine were similar to that of chloroquine alone and these effects were less severe and occurred in fewer children when compared with halofantrine alone.[3]

(b) Promethazine

A study in 20 healthy subjects found that intramuscular promethazine hydrochloride 25 mg increased the AUC of intramuscular chloroquine phosphate 200 mg and its metabolites by 85%. This may be due to promethazine enhancing the absorption of chloroquine from the injection site or displacing it and its metabolites from binding sites in the blood. The initial rate of excretion of chloroquine and the total drug excreted within 3 hours was unaffected by promethazine.[4] The increased bioavailability of chloroquine may improve its therapeutic effects but could also increase toxicity. A study in 10 healthy subjects given chloroquine 10 mg/kg on days 1 and 2, and 5 mg/kg on day 3, alone or with promethazine (25 mg followed by 12.5 mg every 8 hours for 5 days), found that promethazine had no statistically significant effect on the plasma or erythrocyte bioavailability of chloroquine.[2]

See also 'Metronidazole + Chloroquine', p.359, for details of an isolated case of acute dystonia in a patient given chloroquine, promethazine and metronidazole.

Importance and management

Evidence is limited and many of the available studies were primarily designed to assess efficacy. Nevertheless, it would appear that the concurrent use of chloroquine and chlorphenamine, or possibly promethazine, may result in a significant increase in chloroquine levels. This appears to improve the efficacy of chloroquine in malaria treatment without increasing serious adverse effects, particularly cardiac toxicity, although minor adverse effects, such as sedation, may be increased by promethazine.

If the concurrent use of chloroquine and chlorphenamine or promethazine is considered desirable, it would seem prudent to advise patients of the increased risk of drowsiness.

1. Okonkwo CA, Coker HAB, Agomo PU, Ogunbanwo JA, Mafe AG, Agomo CO, Afolabi BM. Effect of chlorpheniramine on the pharmacokinetics and response to chloroquine of Nigerian children with falciparum malaria. *Trans R Soc Trop Med Hyg* (1999) 93, 306–11.
2. Gbotosho GO, Happi CT, Sijuade A, Ogundahunsi OAT, Sowunmi A, Oduola AMJ. Comparative study of interactions between chloroquine and chlorpheniramine or promethazine in healthy volunteers: a potential combination-therapy phenomenon for resuscitating chloroquine for malaria treatment in Africa. Ann Trop Med Parasitol (2008) 102, 3–9.
3. Sowunmi A, Fehintola FA, Ogundahunsi OAT, Ofi AB, Happi TC, Oduola AMJ. Comparative cardiac effects of halofantrine and chloroquine plus chlorpheniramine in children with acute uncomplicated falciparum malaria. *Trans R Soc Trop Med Hyg* (1999) 93, 78–83.
4. Ehiemua AO, Komolafe OO, Oyedeji GA, Olamijulo SK. Effect of promethazine on the metabolism of chloroquine. *Eur J Drug Metab Pharmacokinet* (1988) 13, 15–17.

Chloroquine or Hydroxychloroquine + Antacids or Kaolin

The absorption of chloroquine is moderately reduced by magnesium trisilicate and kaolin. Calcium carbonate and gerdiga may have a similar effect.
Hydroxychloroquine absorption is predicted to be similarly reduced.

Clinical evidence

Six healthy subjects were given chloroquine phosphate 1 g (equivalent to 620 mg of chloroquine base) with either **magnesium trisilicate** 1 g or **kaolin** 1 g after an overnight fast. The **magnesium trisilicate** reduced the AUC of the chloroquine by about 18% and the **kaolin** reduced it by about 29%.[1]

Related *in vitro* studies by the same authors using segments of *rat* intestine found that the absorption of chloroquine was decreased as follows: **magnesium trisilicate** 31%, **kaolin** 47%, **calcium carbonate** 52%, and **gerdiga** 36%. **Gerdiga** is a clay containing hydrated silicates with sodium and potassium carbonates and bicarbonates. It is used as an antacid and is similar to **attapulgite**.[2]

Mechanism

These antacid and antidiarrhoeal compounds adsorb chloroquine thereby reducing the amount available for absorption by the gut. Dissolution of chloroquine from tablets may also be delayed by adsorbent antacids such as **aluminium hydroxide**, **magnesium oxide** and magnesium trisilicate.[3]

Importance and management

The modest pharmacokinetic interactions between chloroquine and magnesium trisilicate or kaolin are established, but their clinical importance does not seem to have been assessed. One way to minimise any interaction is to separate the doses of the antimalarials and magnesium trisilicate or kaolin as much as possible (at least 2 to 3 hours has been effective with similar adsorption interactions) to reduce admixture in the gut. Note that one manufacturer of chloroquine[4] suggests that the concurrent use of antacids should be separated by 4 hours. There do not appear to be any clinical studies to see if other antacids behave similarly, but it may be prudent to separate the administration of any type of antacid.

The manufacturer of **hydroxychloroquine**[5] predicts that, as with chloroquine, antacids might decrease hydroxychloroquine absorption, and they recommend separating administration by 4 hours.

1. McElnay JC, Mukhtar HA, D'Arcy PF, Temple DJ, Collier PS. The effect of magnesium trisilicate and kaolin on the *in vivo* absorption of chloroquine. *J Trop Med Hyg* (1982) 85, 159–63.
2. McElnay JC, Mukhtar HA, D'Arcy PF, Temple DJ. *In vitro* experiments on chloroquine and pyrimethamine absorption in the presence of antacid constituents of kaolin. *J Trop Med Hyg* (1982) 85, 153–8.
3. Iwuagwu MA, Aloko KS. Adsorption of paracetamol and chloroquine phosphate by some antacids. *J Pharm Pharmacol* (1992) 44, 655–8.
4. Avloclor (Chloroquine phosphate). AstraZeneca UK Ltd. UK Summary of product characteristics, July 2009.
5. Plaquenil (Hydroxychloroquine sulfate). Sanofi-Aventis. UK Summary of product characteristics, May 2007.

Chloroquine + Colestyramine

Colestyramine can modestly reduce the absorption of chloroquine, but the clinical importance of this is uncertain.

Clinical evidence, mechanism, importance and management

In a study in 5 children aged 6 to 13 years, colestyramine 4 g reduced the absorption of chloroquine 10 mg/kg by about 30%. Considerable inter-individual differences were seen.[1] This reduced absorption is consistent with the way colestyramine interacts with other drugs by binding to them in the gut. The clinical importance of this isolated report is uncertain but separating the dosages is effective in minimising the interaction of colestyramine with other drugs. It is generally advised that other drugs are given 1 hour before or 4 to 6 hours after colestyramine.

1. Gendrel D, Verdier F, Richard-Lenoble D, Nardou M. Interaction entre cholestyramine et chloroquine. *Arch Fr Pediatr* (1990) 47, 387–8.

Chloroquine or Hydroxychloroquine + H_2-receptor antagonists

Cimetidine reduces the metabolism and clearance of chloroquine, but the clinical importance of this is uncertain. Hydroxychloroquine is predicted to interact with cimetidine in the same way as chloroquine. Ranitidine does not appear to interact with chloroquine.

Clinical evidence, mechanism, importance and management

Cimetidine 400 mg daily for 4 days approximately halved the clearance of a single 600-mg dose of chloroquine base in 10 healthy subjects. The elimination half-life was also prolonged from 3.11 to 4.62 days.[1] It was suggested that these effects occurred because **cimetidine** inhibits the metabolism of chloroquine by the liver. A similar study by the same authors found that **ranitidine** does not interact with chloroquine.[2] On the basis of these data for chloroquine and cimetidine, the manufacturer of **hydroxychloroquine** states that, even though specific reports have not appeared, **cimetidine** might inhibit **hydroxychloroquine** metabolism.[3]

The clinical importance of this interaction is uncertain, but it would seem prudent to be alert for any signs of chloroquine or hydroxychloroquine toxicity during concurrent use. Ranitidine would appear to be a non-interacting alternative to cimetidine.

1. Ette EI, Brown-Awala EA, Essien EE. Chloroquine elimination in humans: effect of low-dose cimetidine. *J Clin Pharmacol* (1987) 27, 813–16.

2. Ette EI, Brown-Awala EA, Essien EE. Effect of ranitidine on chloroquine disposition. *Drug Intell Clin Pharm* (1987) 21, 732–4.
3. Plaquenil (Hydroxychloroquine sulfate). Sanofi-Aventis. UK Summary of product characteristics, May 2007.

Chloroquine + Imipramine

No pharmacokinetic interaction was seen in 6 healthy subjects given single doses of chloroquine 300 mg and imipramine 50 mg.[1]

1. Onyeji CO, Toriola TA, Ogunbona FA. Lack of pharmacokinetic interaction between chloroquine and imipramine. *Ther Drug Monit* (1993) 15, 43–6.

Chloroquine + Methylthioninium chloride (Methylene blue)

Methylthioninium chloride possibly reduces the exposure to chloroquine.

Clinical evidence, mechanism, importance and management

Methylthioninium chloride 130 mg twice daily given orally to 12 healthy subjects taking a 3-day course of chloroquine tended to decrease the AUC of chloroquine by about 20% without affecting renal clearance, when compared with a control group of 12 subjects receiving chloroquine with placebo. This small reduction would not be expected to be clinically relevant.[1]

1. Rengelshausen J, Burhenne J, Fröhlich M, Tayrouz Y, Kumar Singh S, Riedel K-D, Müller O, Hoppe-Tichy T, Haefeli WE, Mikus G, Walter-Sack I. Pharmacokinetic interaction of chloroquine and methylene blue combination against malaria. *Eur J Clin Pharmacol* (2004) 60, 709–15.

Chloroquine or Hydroxychloroquine + Rifampicin (Rifampin)

A woman with discoid lupus, controlled by hydroxychloroquine, rapidly relapsed when rifampicin was started. Disease control was regained when the hydroxychloroquine dosage was doubled. Data in *mice* suggests that chloroquine may interact similarly.

Clinical evidence, mechanism, importance and management

A woman with discoid lupus, which was controlled by hydroxychloroquine 200 mg daily, was also given rifampicin, isoniazid and pyrazinamide for tuberculosis. Within 1 to 2 weeks the discoid lupus flared-up again but it rapidly responded when the hydroxychloroquine dosage was doubled. The reason for this reaction is not established but the authors of the report suggest that the rifampicin (a recognised and potent cytochrome P450 enzyme inducer) increased the metabolism and clearance of the hydroxychloroquine so that it was no longer effective.[1] It also seems possible that transport by P-glycoprotein may have a part to play. It is already known that discoid lupus flare-ups can occur within 2 weeks of stopping hydroxychloroquine,[2] which gives support to the suggested mechanisms. Neither isoniazid nor pyrazinamide is likely to have been responsible for the relapse.

This seems to be the first and only report of this interaction, but what happened is consistent with the way rifampicin interacts with many other drugs. If rifampicin is added to hydroxychloroquine, the outcome should be well monitored. Be alert for the need to increase the hydroxychloroquine dosage. Data from *mice* suggests that chloroquine may interact similarly,[3] and therefore similar precautions would seem prudent.

1. Harvey CJ, Bateman NT, Lloyd ME, Hughes GRV. Influence of rifampicin on hydroxychloroquine. *Clin Exp Rheumatol* (1995) 13, 536.
2. The Canadian Hydroxychloroquine Study Group. A randomized study of the effect of withdrawing hydroxychloroquine sulfate in systemic lupus erythematosus. *N Engl J Med* (1991) 324, 150–4.
3. Hou LJ, Raju SS, Abdulah MS, Nor NM, Ravichandran M. Rifampicin antagonizes the effect of choloroquine on chloroquine-resistant Plasmodium berghei in mice. *Jpn J Infect Dis* (2004), 198–202.

Diethylcarbamazine + Urinary acidifiers or alkalinisers

Urinary alkalinisers can reduce the loss of diethylcarbamazine in the urine, whereas urinary acidifiers can increase the loss of diethylcarbamazine in the urine.

Clinical evidence

Two studies, one in healthy subjects[1] and the other in patients with onchocerciasis,[2] found that making the urine alkaline with **sodium bicarbonate** markedly increased the retention of diethylcarbamazine. The urinary excretion of a 50-mg dose of diethylcarbamazine was about 62% and its elimination half-life 4 hours when the urine was made acidic (pH less than 5.5) by giving **ammonium chloride**, compared with about 5% and 9.6 hours, respectively, when the urine was made alkaline (pH more than 7.5) using **sodium bicarbonate**.[1]

Mechanism

In alkaline urine most of the diethylcarbamazine is non-ionised and is therefore easily reabsorbed in the kidney by simple diffusion through the lipid membrane. The opposing effect occurs with acidic urine.

Importance and management

The clinical importance of any unsought for changes in the urinary pH brought about by the use of other drugs during diethylcarbamazine treatment has not been assessed, but be aware that its pharmacokinetics and possibly the severity of its adverse effects can be changed.

One study concluded that in practice there is no advantage in making the urine alkaline in order to be able to use smaller doses of diethylcarbamazine because the severity of the adverse reactions (the Mazzotti reaction) is not reduced, and the microfilarial counts at the end of a month are not significantly different.[2]

1. Edwards G, Breckenridge AM, Adjepon-Yamoah KK, Orme M L'E, Ward SA. The effect of variations in urinary pH on the pharmacokinetics of diethylcarbamazine. *Br J Clin Pharmacol* (1981) 12, 807–12.
2. Awadzi K, Adjepon-Yamoah KK, Edwards G, Orme M L'E, Breckenridge AM, Gilles HM. The effect of moderate urine alkalinisation on low dose diethylcarbamazine therapy in patients with onchocerciasis. *Br J Clin Pharmacol* (1986) 21, 669–76.

Echinocandins + Amphotericin B

Amphotericin B does not appear to alter the pharmacokinetics of anidulafungin, caspofungin or micafungin. The pharmacokinetics of amphotericin B are not altered by caspofungin.

Clinical evidence, mechanism, importance and management

(a) Anidulafungin

The manufacturer notes that population pharmacokinetic analysis showed no difference in the pharmacokinetics of anidulafungin in 27 patients who were also given liposomal amphotericin B, when compared with data from patients receiving anidulafungin alone. This suggests that no dose adjustment of anidulafungin is required if it is given with amphotericin B.[1,2]

(b) Caspofungin

The manufacturers of caspofungin say there were no pharmacokinetic interactions between caspofungin and amphotericin B in a study in healthy subjects.[3,4] Therefore no dose adjustments are likely to be needed on concurrent use.

(c) Micafungin

The manufacturers of micafungin state that, in drug interaction studies in healthy subjects, no change in the pharmacokinetics of micafungin occurred with concurrent use of amphotericin B.[5] Therefore no dose adjustments are likely to be needed with concurrent use.

1. Eraxis (Anidulafungin). Pfizer Inc. US Prescribing information, May 2007.
2. Eclata (Anidulafungin). Pfizer Ltd. UK Summary of product characteristics, September 2007.
3. Cancidas (Caspofungin acetate). Merck Sharp & Dohme Ltd. UK Summary of product characteristics, July 2009.

4. Cancidas (Caspofungin acetate). Merck & Co., Inc. US Prescribing information, December 2009.
5. Mycamine (Micafungin sodium). Astellas Pharma US, Inc. US Prescribing information, January 2008.

Echinocandins + Azoles

No significant pharmacokinetic interaction appears to occur between anidulafungin and voriconazole, between caspofungin and itraconazole, or between micafungin and fluconazole or voriconazole. Micafungin may slightly increase itraconazole levels.

Clinical evidence, mechanism, importance and management

(a) Anidulafungin

In a crossover study in 17 healthy subjects the steady state maximum level and AUC of both anidulafungin and **voriconazole** were not significantly altered by concurrent use, when compared with either drug given with placebo. Intravenous anidulafungin was given at a dose of 200 mg on the first day, then 100 mg daily for 3 days. **Voriconazole** was given orally, at a dose of 400 mg every 12 hours on the first day, then 200 mg every 12 hours for 3 days.[1] No dosage adjustment of either drug appears to be necessary when they are used together.

(b) Caspofungin

Caspofungin 70 mg on day 1 and 50 mg for the next 13 days did not alter the pharmacokinetics of **itraconazole** 200 mg daily.[2] The pharmacokinetics of caspofungin were also unaltered. No dosage adjustment of either drug appears to be necessary when they are used together.

(c) Micafungin

A study in 35 healthy subjects found no evidence of a clinically relevant pharmacokinetic interaction when intravenous micafungin 150 mg was given daily for 14 days with oral **voriconazole** 400 mg twice daily on day 11 then 200 mg twice daily on days 12 to 14.[3]

A study in 62 patients undergoing a bone marrow or stem cell transplant found that the pharmacokinetics of both **fluconazole** 400 mg daily and micafungin 12.5 mg to 200 mg daily for 7 days were unaffected by concurrent use. No increase in adverse effects was seen with combined use, when compared with the use of fluconazole alone. An unpublished study in 30 healthy subjects also found similar results.[4]

The manufacturer states that in studies in healthy subjects, **fluconazole**, **itraconazole**, and **voriconazole** did not alter the pharmacokinetics of micafungin. Micafungin was found to increase the AUC and maximum concentration of **itraconazole** by 22% and 11%, respectively. Although this small change is unlikely to be of clinical significance, the manufacturers of micafungin recommend that patients taking both drugs should be monitored and the dose of **itraconazole** reduced as necessary.[5] No dose adjustments appear to be necessary with the concurrent use of **fluconazole** or **voriconazole** and micafungin.

1. Dowell JA, Schranz J, Baruch A, Foster G. Safety and pharmacokinetics of coadministered voriconazole and anidulafungin. *J Clin Pharmacol* (2005) 45, 1373–82.
2. Stone JA, McCrea JB, Wickersham PJ, Holland SD, Deutsch PJ, Bi S, Cicero T, Greenberg H, Waldman SA. A phase I study of caspofungin evaluating the potential for drug interactions with itraconazole, the effect of gender and the use of a loading dose regimen. *Intersci Conf Antimicrob Agents Chemother* (2000) 40, 26.
3. Keirns J, Sawamoto T, Holum M, Buell D, Wisemandle W, Alak A. Steady-state pharmacokinetics of micafungin and voriconazole after separate and concomitant dosing in healthy adults. *Antimicrob Agents Chemother* (2007) 51, 787–90.
4. Hiemenz J, Cagnoni P, Simpson D, Devine S, Chao N, Keirns J, Lau W, Facklam D, Buell D. Pharmacokinetic and maximum tolerated dose study of micafungin in combination with fluconazole versus fluconazole alone for prophylaxis of fungal infections in adult patients undergoing a bone marrow or peripheral stem cell transplant. *Antimicrob Agents Chemother* (2005) 49, 1331–6.
5. Mycamine (Micafungin sodium). Astellas Pharma US, Inc. US Prescribing information, January 2008.

Echinocandins + Ciclosporin

Ciclosporin appears to modestly increase caspofungin levels, and concurrent use may result in raised liver enzymes. Ciclosporin slightly raised anidulafungin levels in one study, without any serious adverse events. Micafungin may slightly decrease ciclosporin oral clearance in some subjects.

Clinical evidence, mechanism, importance and management

(a) Anidulafungin

Intravenous anidulafungin 200 mg on day one, then 100 mg daily for 7 days was given to 12 healthy subjects with oral ciclosporin solution (*Neoral*) 1.25 mg/kg twice daily on the last 4 days. Ciclosporin caused a small 22% increase in the steady-state AUC of anidulafungin, which was not considered to be clinically relevant. No dose-limiting toxicities or serious adverse events were noted. One subject had a mild increase in liver enzymes on day 6 (after 2 days of concurrent use), and the study drugs were withdrawn at this point.[1]

Anidulafungin is not expected to alter ciclosporin levels based on an *in vitro* study where anidulafungin had no effect on the metabolism of ciclosporin.[1]

The manufacturer states that no dosage adjustment of either drug is needed on concurrent use.[2]

(b) Caspofungin

The manufacturers report that in two studies in healthy subjects, ciclosporin (a single 4-mg/kg dose, or two 3-mg/kg doses 12 hours apart) increased the AUC of caspofungin by 35%. Moreover, 5 of 12 subjects (43%) had increases in AST and ALT of up to threefold. The liver enzymes returned to normal on discontinuation of both drugs, and during concurrent use the levels of ciclosporin were not affected.[3-5] These findings led to the exclusion of patients receiving ciclosporin from phase II/III studies of caspofungin.[5] Note that elevated liver enzymes (typically mild and rarely leading to discontinuation) are a common adverse effect of caspofungin alone.[3] More recently, four studies have reported retrospective analyses of the clinical use of caspofungin in a total of 75 patients taking ciclosporin.[6-9] No serious hepatic adverse events were found, and three reported no clinically significant elevations of liver enzymes;[6,8,9] however, one found 2 of 40 patients had discontinued treatment because of abnormalities in hepatic enzymes, possibly related to caspofungin and/or ciclosporin.[7] Another retrospective review of 54 patients with invasive aspergillosis also found that the concurrent use of caspofungin with ciclosporin for more than 7 days was an independent risk factor for elevated liver enzymes.[10]

The manufacturers say that ciclosporin and caspofungin can be used together if the potential benefit outweighs the risk. If they are used together, close monitoring of liver enzymes is recommended.[3,4]

(c) Micafungin

In a study in 27 healthy subjects, a single 5-mg/kg dose of oral ciclosporin (*Neoral*) was given alone, with a single 100-mg dose of intravenous micafungin, and on the last day of a 5-day course of intravenous micafungin 100 mg daily. Micafungin (at steady state) very slightly increased the AUC and half-life of ciclosporin and decreased the mean oral clearance by about 10%. However in five subjects, oral ciclosporin clearance was decreased by about 25% (up to about 60% in two patients with steady-state micafungin) The data suggest that in general micafungin does not have a clinically significant effect on ciclosporin clearance, although note that the potential effects on steady-state ciclosporin were not investigated. However, given the wide variability seen, until further data are available, it would appear to be prudent to monitor ciclosporin levels if micafungin is also given.[11]

1. Dowell JA, Stogniew M, Krause D, Henkel T, Weston IE. Assessment of the safety and pharmacokinetics of anidulafungin when administered with cyclosporine. *J Clin Pharmacol* (2005) 45, 227–33.
2. Eraxis (Anidulafungin). Pfizer Inc. US Prescribing information, May 2007.
3. Cancidas (Caspofungin acetate). Merck Sharp & Dohme Ltd. UK Summary of product characteristics, July 2009.
4. Cancidas (Caspofungin acetate). Merck & Co., Inc. US Prescribing information, December 2009.
5. Sable CA, Nguyen B-YT, Chodakewitz JA, DiNubile MJ. Safety and tolerability of caspofungin acetate in the treatment of fungal infections. *Transpl Infect Dis* (2002) 4, 25–30.
6. Sanz-Rodriguez C, Lopez-Duarte M, Jurado M, Lopez J, Arranz R, Cisneros JM, Martino ML, Garcia-Sanchez PJ, Morales P, Olive T, Rovira M, Solano C. Safety of the concomitant use of caspofungin and cyclosporin A in patients with invasive fungal infections. *Bone Marrow Transplant* (2004) 34, 13–20.
7. Marr KA, Hachem R, Papanicolaou G, Somani J, Arduino JM, Lipka CJ, Ngai AL, Kartsonis N, Chodakewitz J, Sable C. Retrospective study of the hepatic safety profile of patients concomitantly treated with caspofungin and cyclosporin A. *Transpl Infect Dis* (2004) 6, 110–16.
8. Glasmacher A, Cornely OA, Orlopp K, Reuter S, Blaschke S, Eichel M, Silling G, Simons B, Egerer G, Siemann M, Florek M, Schnitzler R, Ebeling P, Ritter J, Reinel H, Schutt P, Fischer H, Hahn C, Just-Nuebling G. Caspofungin treatment in severely ill, immunocompromised patients: a case-documentation study of 118 patients. *J Antimicrob Chemother* (2006) 57, 127–34.
9. Saner F, Gensicke J, Rath P, Fruhauf N, Gu Y, Paul A, Radtke A, Malagó M, Broelsch C. Safety profile of concomitant use of caspofungin and cyclosporine or tacrolimus in liver transplant patients. *Infection* (2006) 34, 328–32..

10. Morrissey CO, Slavin MA, O'Reilly MA, Daffy JR, Seymour JF, Schwarer AP, Szer J. Caspofungin as salvage monotherapy for invasive aspergillosis in patients with haematological malignancies or following allogeneic stem cell transplant: efficacy and concomitant cyclosporin A. *Mycoses* (2007) 50 (Suppl 1), 24–37.
11. Hebert MF, Townsend RW, Austin S, Balan G, Blough DK, Buell D, Keirns J, Bekersky I. Concomitant cyclosporine and micafungin pharmacokinetics in healthy volunteers. *J Clin Pharmacol* (2005) 45, 954–60.

Echinocandins + Mycophenolate

The manufacturers of caspofungin say that the pharmacokinetics of caspofungin and mycophenolate are not altered by concurrent use.[1,2] Similarly the manufacturers of micafungin found no pharmacokinetic interaction between micafungin and mycophenolate in studies in healthy subjects.[3,4] No additional precautions therefore appear to be needed with concurrent use of either caspofungin or micafungin with mycophenolate.

1. Cancidas (Caspofungin acetate). Merck Sharp & Dohme Ltd. UK Summary of product characteristics, July 2009.
2. Cancidas (Caspofungin acetate). Merck & Co., Inc. US Prescribing information, December 2009.
3. Mycamine (Micafungin sodium). Astellas Pharma US, Inc. US Prescribing information, January 2008.
4. Mycamine (Micafungin sodium). Astellas Pharma Ltd. UK Summary of product characteristics, April 2008.

Echinocandins + Rifampicin (Rifampin) or other enzyme inducers

Rifampicin modestly reduces the trough levels of caspofungin. One case of caspofungin treatment failure has been reported in a patient taking rifampicin. Other potent enzyme inducers are predicted to interact similarly.
Rifampicin does not appear to alter anidulafungin clearance or affect the pharmacokinetics of micafungin.

Clinical evidence

(a) Anidulafungin

A population pharmacokinetic analysis of anidulafungin in patients with serious fungal infections found that the clearance of anidulafungin did not differ between 27 patients also taking rifampicin (rifampin) and 77 patients taking no known interacting drugs.[1]

(b) Caspofungin

A parallel-group study in healthy subjects looked at the effects of rifampicin on the pharmacokinetics of caspofungin. In the first group, rifampicin 600 mg daily was given with intravenous caspofungin 50 mg daily, started on the same day. It was found that the trough levels and AUC of caspofungin were increased by 170% and 61%, respectively, on day one. However, after 2 weeks the AUC had returned to normal, and, when compared with subjects not taking rifampicin, there was a trend to *lower* trough levels of caspofungin. In the second group of healthy subjects in this study, rifampicin 600 mg daily was given for 14 days alone and then for a further 14 days combined with caspofungin. No significant increase in the caspofungin AUC was seen on day one of concurrent use. On both day one and day 14, the trough levels of caspofungin were reduced by about 30%, without any change in the AUC, similar to the findings on day 14 in the first group. In this second group, caspofungin did not alter the pharmacokinetics of rifampicin.[2]

A case report describes a neutropenic patient with fungaemia who did not respond to intravenous caspofungin (70 mg on the first day then 50 mg daily) while taking rifampicin 600 mg daily. Although this patient was given a standard dose of caspofungin, the authors note she weighed just 47 kg and did not show even an initial response. Susceptibility testing found that the isolate was not resistant to caspofungin. The patient was subsequently successfully treated with amphotericin B. The authors suggest that caspofungin doses of more than 70 mg daily would have been required for efficacy in their patient.[3]

(c) Micafungin

The manufacturers of micafungin state that, in drug interaction studies in healthy subjects, rifampicin did not affect the pharmacokinetics of micafungin.[4]

Mechanism

Caspofungin is a poor substrate for cytochrome P450 and is not a substrate for P-glycoprotein,[5] therefore these mechanisms are not thought to be involved in the interaction with rifampicin. It is possible that the modest effect of rifampicin on caspofungin is due to induction of tissue uptake transport proteins at steady-state.[2]

Importance and management

The UK manufacturer of caspofungin recommends that consideration should be given to increasing the dose from 50 to 70 mg daily in patients taking rifampicin,[5] whereas the US manufacturer specifically states that this dose should be used.[6] A 70-mg dose has been generally well tolerated in clinical studies.[2] However, bear in mind the case report of possible caspofungin failure, even at this dose. The manufacturers also say that a population pharmacokinetic analysis suggested that the concurrent use of other metabolic inducers (**carbamazepine**, **dexamethasone**, **efavirenz**, **nevirapine** or **phenytoin**) may result in clinically meaningful reductions in the AUC of caspofungin.[5,6] They suggest considering increasing the dose of caspofungin from 50 to 70 mg daily if it is used with these enzyme inducers. Further study is needed.

No dose adjustments anidulafungin or micafungin appear to be necessary with the concurrent use of rifampicin.

1. Dowell J, Knebel W, Ludden T, Stogniew M, Krause D, Henkel T. Population pharmacokinetic analysis of anidulafungin, an echinocandin antifungal. *J Clin Pharmacol* (2004) 44, 590–8.
2. Stone JA, Migoya EM, Hickey L, Winchell GA, Deutsch PJ, Ghosh K, Freeman A, Bi S, Desai R, Dilzer SC, Lasseter KC, Kraft WK, Greenberg H, Waldman SA. Potential for interactions between caspofungin and nelfinavir or rifampin. *Antimicrob Agents Chemother* (2004) 48, 4306–14.
3. Belmares J, Colaizzi L, Parada JP, Johnson S. Caspofungin treatment failure in a patient with invasive candidiasis and concomitant rifampicin treatment. *Int J Antimicrob Agents* (2005) 26, 264–5.
4. Mycamine (Micafungin sodium). Astellas Pharma Ltd. UK Summary of product characteristics, April 2008.
5. Cancidas (Caspofungin acetate). Merck Sharp & Dohme Ltd. UK Summary of product characteristics, July 2009.
6. Cancidas (Caspofungin acetate). Merck & Co., Inc. US Prescribing information, December 2009.

Echinocandins; Caspofungin + Nelfinavir

Nelfinavir does not have a clinically relevant effect on the pharmacokinetics of multiple doses of caspofungin.

Clinical evidence, mechanism, importance and management

In a parallel-group study, healthy subjects were given nelfinavir 1.25 g every 12 hours and intravenous caspofungin 50 mg daily, started on the same day. The AUC and trough level of caspofungin were increased by 16% and 58%, respectively, on the first day, when compared with subjects receiving caspofungin alone. However, after 2 weeks of combined use, the AUC and trough level of caspofungin were similar in both groups of patients.[1] The authors note that their previous population pharmacokinetic analysis had shown that nelfinavir might decrease the AUC and trough level of caspofungin, which in the light of the controlled study, they consider to be a spurious finding.

It appears that nelfinavir does not have a clinically significant effect on the pharmacokinetics of caspofungin, when both drugs are given in multiple doses, and therefore no dosage adjustment of caspofungin is required on concurrent use.

1. Stone JA, Migoya EM, Hickey L, Winchell GA, Deutsch PJ, Ghosh K, Freeman A, Bi S, Desai R, Dilzer SC, Lasseter KC, Kraft WK, Greenberg H, Waldman SA. Potential for interactions between caspofungin and nelfinavir or rifampin. *Antimicrob Agents Chemother* (2004) 48, 4306–14.

Echinocandins; Micafungin + Miscellaneous

Micafungin may increase the AUCs of nifedipine and sirolimus. Micafungin has no effect on the pharmacokinetics of prednisolone. Nifedipine, prednisolone, ritonavir and sirolimus do not affect the pharmacokinetics of micafungin.

Clinical evidence and mechanism

(a) Nifedipine

The manufacturers state that micafungin (at steady-state) increased the AUC and maximum concentration of nifedipine by 18% and 42%, respectively, when compared with nifedipine alone. Nifedipine did not affect the pharmacokinetics of micafungin in healthy subjects.[1]

(b) Prednisolone

Prednisolone did not affect the pharmacokinetics of micafungin in a study in healthy subjects. Similarly, both single dose and multiple dose micafungin had no effect on the pharmacokinetics of prednisolone.[1]

(c) Ritonavir

Ritonavir did not affect the pharmacokinetics of micafungin in a study in healthy subjects.[1]

(d) Sirolimus

The manufacturers report that micafungin (at steady-state) increased the AUC of sirolimus by 21%, however the maximum concentration was not affected. Sirolimus did not affect the pharmacokinetics of micafungin in healthy subjects.[1]

Importance and management

Evidence is limited to these studies reported by the manufacturer. The increase in nifedipine levels is modest and would not be expected to be clinically significant in most patients. Nevertheless, the manufacturer advises increased monitoring for adverse effects and toxicity, and as the occasional patient may be affected it would seem prudent to check that blood pressure is not excessively reduced when micafungin is started.

Similarly, and increase in the AUC of sirolimus would not generally be expected to be clinically relevant. Nevertheless, the manufacturer advises increased monitoring for adverse effects and toxicity. As a greater effect in patients cannot be excluded, consider monitoring sirolimus levels when micafungin is started.

No dosage adjustments appear to be needed in patients taking prednisolone or ritonavir with micafungin, although note that ritonavir is usually prescribed as part of a regimen with other antiretrovirals, which do not appear to have been studied with micafungin.

1. Mycamine (Micafungin sodium). Astellas Pharma US, Inc. US Prescribing information, January 2008.

Flucytosine + Amphotericin B

For some fungal infections the combination of flucytosine with amphotericin B may be more effective than flucytosine alone, but amphotericin B increases the toxicity of flucytosine.

Clinical evidence, mechanism, importance and management

The combined use of flucytosine and amphotericin B is more effective than the use of flucytosine alone in the treatment of cryptococcal meningitis, as demonstrated in an early study.[1] However, amphotericin B can cause deterioration in renal function, which reduces flucytosine elimination, and may result in raised flucytosine blood levels. In addition, amphotericin B may increase the cellular uptake of flucytosine.[2] Whatever the exact mechanism, combined use increases flucytosine bone marrow toxicity. A study of 194 patients randomised to either a 4 or 6-week course of low-dose amphotericin B (initially 0.3 mg/kg daily) and maximal dose flucytosine (150 mg/kg daily, adjusted for renal function) found that severe adverse effects were common. These included azotaemia (51 patients), blood dyscrasias (52 patients), and hepatitis (13 patients).[3]

Combined therapy is the recommended treatment for some systemic fungal infections.[4] Nevertheless, flucytosine levels and renal function should be very closely monitored when the drugs are used concurrently.

1. Bennett JE, Dismukes WE, Duma RJ, Medoff G, Sande MA, Gallis H, Leonard J, Fields BT, Bradshaw M, Haywood H, McGee ZA, Cate TR, Cobbs CG, Warner JF, Alling DW. A comparison of amphotericin B alone and combined with flucytosine in the treatment of cryptoccal meningitis. *N Engl J Med* (1979) 301, 126–31.
2. Fungizone Intravenous (Amphotericin B). E. R. Squibb & Sons Ltd. UK Summary of product characteristics, May 2006.
3. Stamm AM, Diasio RB, Dismukes WE, Shadomy S, Cloud GA, Bowles CA, Karam GH, Espinel-Ingroff A and members of the National Institute of Allergy and Infectious Diseases Mycoses Study group. Toxicity of amphotericin B plus flucytosine in 194 patients with cryptococcal meningitis. *Am J Med* (1987) 83, 236–42.
4. Pappas PG, Rex JH, Sobel JD, Filler SG, Dismukes WE, Walsh TJ, Edwards JE. IDSA Guidelines for treatment of candidiasis. *Clin Infect Dis* (2004) 38, 161–89.

Flucytosine + Antacids

Aluminium/magnesium hydroxide delays the absorption of flucytosine from the gut, but the total amount absorbed remains unaffected.[1] No additional precautions therefore appear to be needed if this antacid is given with oral flucytosine.

1. Cutler RE, Blair AD, Kelly MR. Flucytosine kinetics in subjects with normal and impaired renal function. *Clin Pharmacol Ther* (1978) 24, 333–42.

Flucytosine + Cytarabine

Some very limited evidence suggests that cytarabine may oppose the antifungal effects of flucytosine, or reduce flucytosine levels. Theoretically, their bone marrow suppressant effects might be additive.

Clinical evidence, mechanism, importance and management

A man with Hodgkin's disease treated for cryptococcal meningitis with flucytosine 100 mg/kg daily had reduced flucytosine serum and CSF levels, from a range of 30 to 40 mg/L down to undetectable levels, when he was given cytarabine intravenously. When the cytarabine was replaced by procarbazine, the flucytosine levels returned to their former values. *In vitro* tests found that cytarabine 1 mg/L completely abolished the activity of up to 50 mg/L of flucytosine against the patient's strain of *Cryptococcus*, whereas procarbazine did not.[1] In another study in a patient with acute myeloid leukaemia, the predose flucytosine level fell from 65 to 42 mg/L and the post-dose flucytosine level fell from 80 to 53 mg/L when cytarabine and daunorubicin were given. However, these levels were still within the therapeutic range. The drop in levels was attributed to an improvement in renal function rather than antagonism between the two drugs.[2]

In an *in vitro* study the antifungal effects of flucytosine against 14 out of 16 wild isolates of *Cryptococcus* were not changed in the presence of cytarabine. In the remaining two isolates, an increase in effect was seen in one and a decrease was seen the other.[2]

The evidence for any interaction is therefore very limited indeed and its general clinical importance remains uncertain. The manufacturer of flucytosine advises that strict monitoring of flucytosine levels is required if both drugs are given,[3] whereas, despite the very limited evidence, the manufacturer of cytarabine recommends avoiding concurrent use.[4] It would seem prudent to closely monitor the efficacy and clinical response to flucytosine if both drugs are needed.

Of equal concern is the fact that both drugs are bone marrow suppressants, and this effect might be additive; however, it should be standard practice to closely monitor full blood counts if either of these drugs is given, and therefore additional monitoring seems unnecessary.

1. Holt RJ. Clinical problems with 5-fluorocytosine. *Mykosen* (1978) 21, 363–9.
2. Wingfield HJ. Absence of fungistatic antagonism between flucytosine and cytarabine *in vitro* and *in vivo*. *J Antimicrob Chemother* (1987) 20, 523–7.
3. Ancotil Solution for Infusion (Flucytosine). Valeant Pharmaceuticals Ltd. UK Summary of product characteristics, November 2004.
4. Cytarabine. Pharmacia Ltd. UK Summary of product characteristics, July 2007.

Furazolidone + Miscellaneous

After 5 to 10 days of use furazolidone has MAO-inhibitory activity about equivalent to that of the non-selective MAOIs. The concurrent use of furazolidone with amfetamines or nasal decongestants (indirectly-acting sympathomimetic amines), or with tyramine-rich foods and drinks may be expected to result in a potentially serious rise in blood pressure. However, direct evidence of accidental adverse reactions of this kind does not seem to have been reported. The pressor effects of noradrenaline (norepinephrine) (a directly-acting sympathomimetic) are unchanged by furazolidone.

Clinical evidence

A study in 4 hypertensive patients found that after 6 days of treatment with furazolidone 400 mg daily, the pressor responses to **tyramine** or **dexam-**

fetamine had increased two to threefold, and after 13 days had increased by about tenfold. These responses to furazolidone were about the same as those found in 2 other patients taking the MAOI pargyline.[1] The MAO-inhibitory activity of furazolidone was confirmed by measurements taken on jejunal mucosal samples.[2]

The pressor effects of **noradrenaline** (**norepinephrine**) were unchanged by furazolidone.[1]

Mechanism

The MAO-inhibitory activity of furazolidone is not immediate and may in fact be due to a metabolite of furazolidone.[3] It develops gradually so that after 5 to 10 days of use, amfetamines and tyramine (indirectly-acting sympathomimetics) will interact with furazolidone in the same way as they do with other non-selective MAOIs.[2,4] More details of the mechanisms of this interaction are to be found elsewhere, see 'MAOIs or RIMAs + Tyramine-rich foods', p.1395 and 'MAOIs or RIMAs + Sympathomimetics; Indirectly-acting', p.1388.

Importance and management

The MAO-inhibitory activity of furazolidone after 5 to 10 days of use is established, but reports of hypertensive crises either with sympathomimetics or tyramine-containing foods or drinks appear to be lacking. This may be, in part, a reflection of the fact that furazolidone may be given for just 2 to 5 days. Notwithstanding, it would seem prudent to warn patients given furazolidone not to take any of the drugs, foods or drinks that are prohibited with non-selective MAOIs. See the appropriate monographs on 'MAOIs', (p.1370) for more detailed lists of these drugs, 'foods', (p.1395), and 'drinks', (p.1393).

No adverse interaction would be expected with many of the inotropes and vasopressors that are 'directly-acting sympathomimetics', (p.1388), such as noradrenaline (norepinephrine).

1. Pettinger WA, Oates JA. Supersensitivity to tyramine during monoamine oxidase inhibition in man. Mechanism at the level of the adrenergic neurone. *Clin Pharmacol Ther* (1968) 9, 341–4.
2. Pettinger WA, Soyangco FG, Oates JA. Inhibition of monoamine oxidase in man by furazolidone. *Clin Pharmacol Ther* (1968) 9, 442–7.
3. Stern IJ, Hollifield RD, Wilk S, Buzard JA. The anti-monoamine oxidase effects of furazolidone. *J Pharmacol Exp Ther* (1967) 156, 492–9.
4. Pettinger WA, Soyangco FG, Oates JA. Monoamine-oxidase inhibition by furazolidone in man. *Clin Res* (1966) 14, 258.

Furazolidone + Proton pump inhibitors

Omeprazole modestly reduces the serum levels of furazolidone. Other proton pump inhibitors could interact similarly.

Clinical evidence, mechanism, importance and management

A study in 18 healthy subjects found that omeprazole 20 mg twice daily for 5 days reduced the peak serum level of a single 200-mg dose of furazolidone by about 30%. Omeprazole may alter the bioavailability of furazolidone by reducing its dissolution or increasing its degradation before it reaches the intestine and/or inducing its first-pass metabolism.[1] The clinical relevance of this modest change is uncertain, as there are a large number of clinical studies describing the successful combination of furazolidone with omeprazole in regimens to eradicate *H. pylori*. However, there is some evidence that success rates are unacceptable if low-dose furazolidone (100 mg twice daily) rather than standard dose (200 mg twice daily) is used.[2] It is possible that a pharmacokinetic interaction could play a part in this finding. It may be prudent to be alert for a decrease in the effects of low doses of furazolidone if it is given with omeprazole outside of an established regimen. Other proton pump inhibitors do not appear to have been studied, but if the proposed mechanism is correct, it seems likely that they would interact similarly.

1. Calafatti SA, Ortiz RAM, Deguer M, Martinez M, Pedrazzoli J. Effect of acid secretion blockade by omeprazole on the relative bioavailability of orally administered furazolidone in healthy volunteers. *Br J Clin Pharmacol* (2001) 52, 205–9.
2. Fakheri H, Merat S, Hosseini C, Malekzadeh R. Low-dose furazolidone in triple and quadruple regimens for Helicobacter pylori eradication. *Aliment Pharmacol Ther* (2004) 19, 89–93.

Griseofulvin + Food

The rate and probably extent of griseofulvin absorption is markedly increased if it is taken with a high-fat meal.

Clinical evidence, mechanism, importance and management

A study in 5 healthy subjects found that the absorption of micronised griseofulvin 125 mg (*Fulcin*) was enhanced if it was given with a fatty meal rather than in the fasting state, as assessed by a 37% increase in griseofulvin urinary excretion.[1] Other studies similarly found that the absorption of griseofulvin at 4 and 8 hours was approximately doubled when it was taken with a high-fat meal.[2,3] A further study in 12 healthy subjects found that the higher the fat content of the meal the higher the bioavailability of griseofulvin (70% increase in bioavailability with a low-fat meal and 120% increase with a high-fat meal, when compared with fasting state absorption).[4] However, another study found that although food increased the rate of absorption of micronised and PEG-ultramicronised griseofulvin, the extent of absorption was not changed.[5] Another report suggested that giving griseofulvin with food tended to reduce the differences in the bioavailability of griseofulvin from micronised and ultramicronised tablets.[6] Enhanced absorption was also found with a formulation of griseofulvin in a **corn oil** emulsion, when compared with tablets or an aqueous suspension.[7]

This interaction is established and of clinical importance. Some manufacturers have advised that griseofulvin should be given after meals, otherwise absorption is likely to be inadequate.[8]

1. Khalafalla N, Elgholmy ZA, Khalil SA. Influence of a high fat diet on GI absorption of griseofulvin tablets in man. *Pharmazie* (1981) 36, 692–3.
2. Crounse RG. Human pharmacology of griseofulvin: the effect of fat intake on gastrointestinal absorption. *J Invest Dermatol* (1961) 37, 529–33.
3. Crounse RG. Effective use of griseofulvin. *Arch Dermatol* (1963) 87, 176–8.
4. Ogunbona FA, Smith IF, Olawoye OS. Fat contents of meals and bioavailability of griseofulvin in man. *J Pharm Pharmacol* (1985) 37, 283–4.
5. Aoyagi N, Ogata H, Kaniwa N, Ejima A. Effect of food on the bioavailability of griseofulvin from microsize and PEG ultramicrosize (GRIS-PEG) plain tablets. *J Pharmacobiodyn* (1982) 4, 120–4.
6. Bijanzadeh M, Mahmoudian M, Salehian P, Khazainia T, Eshghi L, Khosravy A. The bioavailability of griseofulvin from microsized and ultramicrosized tablets in nonfasting volunteers. *Indian J Physiol Pharmacol* (1990) 34, 157–61.
7. Bates TR, Sequeria JA. Bioavailability of micronized griseofulvin from corn oil-in-water emulsion, aqueous suspension, and commercial tablet dosage forms in humans. *J Pharm Sci* (1975) 64, 793–7.
8. Grisovin (Griseofulvin). GlaxoSmithKline UK. UK Summary of product characteristics, July 2004.

Griseofulvin + Phenobarbital

The antifungal effects of griseofulvin can be reduced or even abolished by phenobarbital.

Clinical evidence

Two epileptic children taking phenobarbital 40 mg daily did not respond to long-term treatment for tinea capitis with griseofulvin 125 mg three times daily until the barbiturate was withdrawn.[1] Five other patients similarly did not respond to griseofulvin while taking phenobarbital (3 patients were also taking phenytoin).[2-4]

Two studies, in a total of 14 healthy subjects, found that phenobarbital 30 mg three times daily reduced the serum levels of oral griseofulvin by about one-third,[5] and the absorption of griseofulvin was reduced from about 58% without phenobarbital to 41% in the presence of phenobarbital.[6]

Mechanism

Not fully understood. Initially it was thought that phenobarbital increased the metabolism and clearance of griseofulvin,[7] but it has also been suggested that phenobarbital reduces the absorption of griseofulvin from the gut.[6] It has variously been suggested that this is due to an increase in peristalsis reducing the opportunity for absorption,[6] the formation of a complex, which makes an already poorly soluble drug even less soluble and therefore less readily absorbed,[8] and a reduction in the level of intestinal bile salts leading to reduced griseofulvin solubility.[9]

Importance and management

An established interaction of clinical importance, although the evidence seems to be limited to the reports cited. If phenobarbital must be given, it has been suggested that the griseofulvin should be given in divided doses three times a day to give it a better chance of being absorbed;[6] however, griseofulvin was given in divided doses in one of the reports describing an interaction.[1] The effect of increasing the dosage of griseofulvin appears not to have been studied. An alternative, where possible, is to use a

non-interacting antiepileptic, such as sodium valproate. This proved to be successful in one of the cases cited.[1]

1. Beurey J, Weber M, Vignaud J-M. Traitement des teignes microsporiques. Interférence métabolique entre phénobarbital et griséofulvine. *Ann Dermatol Venereol* (1982) 109, 567–70.
2. Lorenc E. A new factor in griseofulvin treatment failures. *Mo Med* (1967) 64, 32–3.
3. Stepanova ZV, Sheklakova AA. Liuminal kak prichina neudachi griseoful'vinoterapii bol'nogo mikrospoviei. *Vestn Dermatol Venerol* (1975) 12, 63–5.
4. Hay RJ, Clayton YM, Moore MK, Midgely G. An evaluation of itraconazole in the management of onychomycosis. *Br J Dermatol* (1988) 119, 359–66.
5. Busfield D, Child KJ, Atkinson RM, Tomich EG. An effect of phenobarbitone on blood-levels of griseofulvin in man. *Lancet* (1963) ii, 1042–3.
6. Riegelman S, Rowland M, Epstein WL. Griseofulvin-phenobarbital interaction in man. *JAMA* (1970) 213, 426–31.
7. Busfield D, Child KJ, Tomich EG. An effect of phenobarbitone on griseofulvin metabolism in the rat. *Br J Pharmacol* (1964) 22, 137–42.
8. Abougela IKA, Bigford DJ, McCorquodale I, Grant DJW. Complex formation and other physico-chemical interactions between griseofulvin and phenobarbitone. *J Pharm Pharmacol* (1976) 28, 44P.
9. Jamali F, Axelson JE. Griseofulvin–phenobarbital interaction: a formulation-dependent phenomenon. *J Pharm Sci* (1978) 67, 466–70.

Halofantrine + Antacids

Magnesium carbonate halves the maximum plasma levels of halofantrine. Aluminium hydroxide and magnesium trisilicate seem less likely to interact.

Clinical evidence

A single-dose study in healthy subjects found that **magnesium carbonate** 1 g reduced the maximum plasma levels of halofantrine 500 mg by almost 50%. The AUC was also reduced by 28%, but this was not statistically significant. The active metabolite of halofantrine, which is equally potent, was similarly affected.[1]

Mechanism

Magnesium carbonate might decrease the absorption of halofantrine. An *in vitro* study showed that the halofantrine adsorptive capacity of various antacids was highest for magnesium carbonate, intermediate for **aluminium hydroxide**, and least for **magnesium trisilicate**.[1]

Importance and management

The pharmacokinetic interaction between halofantrine and magnesium carbonate appears to be established. Its clinical importance does not seem to have been assessed, but the authors note that the clinical efficacy of halofantrine is related to peak levels, and therefore they consider that magnesium carbonate might affect antimalarial efficacy.[1] One way to minimise the interaction is to separate the dosages of halofantrine and magnesium carbonate as much as possible (at least 2 to 3 hours has worked with other drugs that interact with antacids in this way) to reduce admixture in the gut. There do not appear to be any studies to see if other antacids behave similarly, but the *in vitro* data with aluminium hydroxide and magnesium trisilicate (see Mechanism, above) suggest that they are less likely to interact.[1]

1. Aideloje SO, Onyeji CO, Ugwu NC. Altered pharmacokinetics of halofantrine by an antacid, magnesium carbonate. *Eur J Pharm Biopharm* (1998) 46, 299–303.

Halofantrine + Miscellaneous

Halofantrine prolongs the QT interval and therefore should not be used with other drugs that can prolong the QT interval because of the increased risk of cardiac arrhythmias. The concurrent and sequential use of halofantrine and mefloquine markedly increased the risk of clinically important increases in the QT interval.

Pyrimethamine/sulfadoxine and tetracycline have been shown to increase halofantrine levels. *In vitro* studies suggest that diltiazem, erythromycin, ketoconazole, mefloquine, quinine, and quinidine might also increase the toxicity of halofantrine. Fatty food markedly increases halofantrine levels. Grapefruit juice has a similar effect.

Clinical evidence, mechanism, importance and management

(a) CYP3A4 inhibitors

A study in *animals* found that **ketoconazole** roughly doubled the AUC of halofantrine and inhibited its metabolism to the equipotent metabolite, desbutylhalofantrine.[1] In *in vitro* studies, **ketoconazole** markedly inhibited the metabolism of halofantrine by CYP3A4.[2,3] It has been suggested that the rise in halofantrine levels could reasonably be expected to increase toxicity.[2,3] Other CYP3A4 inhibitors, such as **diltiazem** and **erythromycin**, also inhibited the metabolism of halofantrine *in vitro*,[3] which is in line with their known clinical effects on other CYP3A4 substrates. It would therefore seem prudent to be cautious if any of these drugs, or other known CYP3A4 inhibitors (see 'Table 1.4', (p.6), for a list), are given with halofantrine, as raised halofantrine levels may increase its adverse cardiac effects, see *Drugs that prolong the QT interval*, below. *In vitro* studies[2,3] also found that **quinine** and **quinidine** had moderate inhibitory effects on halofantrine metabolism by CYP3A4, but note that these drugs are not known to be clinically significant inhibitors of this isoenzyme. Probably of more importance is the potential for additive cardiac effects, see *Drugs that prolong the QT interval*, below.

(b) Drugs that prolong the QT interval

Halofantrine, in therapeutic doses, can prolong the QT interval in the majority of patients, causing ventricular arrhythmias in a very small number. By 1993, worldwide, 14 cases of cardiac arrhythmias associated with halofantrine had been reported, and 8 patients were known to have died. In order to reduce the likelihood of arrhythmias, in 1994 the CSM in the UK advised that halofantrine should not be taken with drugs that may induce arrhythmias. They named **chloroquine**, **mefloquine**, **quinine**, **tricyclic antidepressants**, **antipsychotics**, **certain antiarrhythmics**, **terfenadine** and **astemizole**, as well as drugs causing electrolyte disturbances.[4] Although not listed, it would seem prudent to avoid other drugs that prolong the QT interval. For a list, see 'Table 9.2', (p.290)'.

Animal studies found that although **mefloquine** alone did not significantly alter the QTc interval, it enhanced the effects of halofantrine by increasing blood levels.[5] Similarly, a study in patients with malaria found that the risk of clinically relevant QT prolongation was increased twofold when halofantrine was used after **mefloquine** failure (7 of 10 patients), when compared with use as primary treatment (18 of 51 patients). However, the authors note that their population had longer baseline QT intervals than the average population, which may have made them more susceptible to the effects of halofantrine[6] The manufacturers of **mefloquine**[7,8] contraindicate the concurrent use of halofantrine, and the sequential use of halofantrine after **mefloquine** treatment.

(c) Food

A study in 6 healthy subjects found that the maximum plasma levels and AUC of a single 250-mg dose of halofantrine were increased by about 6.6-fold and 2.9-fold, respectively, when given with a **fatty meal** rather than in a fasting state. The AUC of the metabolite desbutylhalofantrine was also increased.[9] *Animal* data suggest that **fats** may reduce the presystemic metabolism of halofantrine.[1] As this is likely to increase the risk of halofantrine-induced arrhythmias (see *Drugs that prolong the QT interval*, above), halofantrine should not be taken with **meals**, but should be taken on an empty stomach.[4]

(d) Grapefruit juice or Orange juice

A crossover study in 12 healthy subjects given halofantrine 500 mg with 250 mL of either water, orange juice or grapefruit juice (standard strength), found that grapefruit juice increased the AUC and peak plasma levels of halofantrine by 2.8-fold and 3.2-fold, respectively. The QTc interval increased by 17 milliseconds with halofantrine, and by 31 milliseconds when grapefruit juice was also given. Orange juice did not affect the pharmacokinetics or pharmacodynamics of halofantrine.[10] These data suggest that grapefruit juice should be avoided by patients taking halofantrine due to the increased risk of arrhythmias.[10]

(e) Pyrimethamine/Sulfadoxine

In a preliminary study in healthy subjects, pyrimethamine/sulfadoxine (*Fansidar*) raised the AUC_{0-6} and peak plasma levels of halofantrine by about 60%, without changing the overall AUC. This might lead to an increased incidence of arrhythmias,[11] see *Drugs that prolong the QT interval*, above.

(f) Tetracyclines

A study in 8 healthy subjects found that **tetracycline** 500 mg twice daily for 7 days increased the maximum plasma levels, AUC and elimination half-life of a single 500-mg dose of halofantrine by 146%, 99%, and 73%, respectively. Increases in the major metabolite of halofantrine also occurred in the presence of **tetracycline**.[12] As both halofantrine and **tetracycline** are excreted into the bile, competition for this elimination route may result in increased plasma levels. There may be an increased risk of halofantrine toxicity if it is used with higher doses of tetracycline.[12]

1. Khoo S-M, Porter CJH, Edwards GA, Charman WN. Metabolism of halofantrine to its equipotent metabolite, desbutylhalofantrine, is decreased when orally administered with ketoconazole. *J Pharm Sci* (1998) 87, 1538–41.
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3. Baune B, Flinois JP, Furlan V, Gimenez F, Taburet AM, Becquemont L, Farinotti R. Halofantrine metabolism in microsomes in man: major role of CYP 3A4 and CYP 3A5. *J Pharm Pharmacol* (1999) 51, 419–26.
4. Committee on Safety of Medicines/Medicines Control Agency. Cardiac arrhythmias with halofantrine (Halfan). *Current Problems* (1994) 20, 6.
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7. Lariam (Mefloquine hydrochloride). Roche Products Ltd. UK Summary of product characteristics, August 2009.
8. Lariam (Mefloquine hydrochloride). Roche Pharmaceuticals. US Prescribing information, September 2008.
9. Milton K, Edwards G, Ward SA, Orme ML'E, Breckenridge AM. Pharmacokinetics of halofantrine in man: effects of food and dose size. *Br J Clin Pharmacol* (1989) 28, 71–7.
10. Charbit B, Becquemont L, Lepère B, Peytavin G, Funck-Brentano C. Pharmacokinetic and pharmacodynamic interaction between grapefruit juice and halofantrine. *Clin Pharmacol Ther* (2002) 72, 514–23.
11. Hombhanje FW. Effect of a single dose of Fansidar™ on the pharmacokinetics of halofantrine in healthy volunteers: a preliminary report. *Br J Clin Pharmacol* (2000) 49, 283–4.
12. Bassi PU, Onyeji CO, Ukponmwan OE. Effects of tetracycline on the pharmacokinetics of halofantrine in healthy volunteers. *Br J Clin Pharmacol* (2004) 58, 52–5.

Hydroxyquinoline (Oxyquinoline) + Zinc oxide

The presence of zinc oxide inhibits the therapeutic effects of hydroxyquinoline in ointments.

Clinical evidence

The observation that a patient had an allergic reaction to hydroxyquinoline in ointments with a paraffin base, but not a zinc oxide base, prompted further study of a possible incompatibility. The subsequent study in 13 patients confirmed that zinc oxide reduces the eczematogenic (allergic) properties of the hydroxyquinoline. However, it also inhibits its antibacterial and antimycotic effects, and appears to stimulate the growth of *Candida albicans*.[1]

Mechanism

It seems almost certain that the zinc ions and hydroxyquinoline form chelates, which have little or no antibacterial properties.[1,2]

Importance and management

The documentation is limited but the reaction appears to be established. There is no point in using zinc oxide to reduce the allergic properties of hydroxyquinoline if, at the same time, the therapeutic effects disappear.

1. Fischer T. On 8-hydroxyquinoline-zinc oxide incompatibility. *Dermatologica* (1974) 149, 129–35.
2. Albert A, Rubbo SD, Goldacre RJ, Balfour BG. The influence of chemical constitution on antibacterial activity. Part III: A study of 8-hydroxyquinoline (oxine) and related compounds. *Br J Exp Pathol* (1947) 28, 69–87.

Ivermectin + Food

The bioavailability of ivermectin is significantly increased by food.

Clinical evidence, mechanism, importance and management

In a study, 11 subjects were given ivermectin 30 mg after overnight fasting three times a week for one week and then a single 30-mg dose of ivermectin 20 minutes after a **high-fat breakfast**. The AUC and maximum plasma levels of ivermectin were increased by around 2.6-fold and threefold, respectively, by food.[1] The manufacturers recommend that ivermectin is taken on a empty stomach with water.[2]

1. Guzzo CA, Furtek CI, Porras AG, Chen C, Tipping R, Clineschmidt CM, Sciberras DG, Hsieh JY-K, Lasseter KC,. Safety, tolerability, and pharmacokinetics of escalating high doses of ivermectin in healthy adult subjects. *J Clin Pharmacol* (2002) 42, 1122–33.
2. Stromectol (Ivermectin). Merck & Co., Inc. US Prescribing information, September 2008.

Ivermectin + Levamisole

Levamisole may markedly increase the bioavailability of ivermectin. Ivermectin does not alter the pharmacokinetics of levamisole.

Clinical evidence, mechanism, importance and management

A study in 28 healthy subjects given levamisole 2.5 mg/kg, alone or with ivermectin 200 micrograms/kg, found that ivermectin had no effect on the AUC or maximum plasma level of levamisole. However, the AUC of ivermectin was twofold higher in patients given levamisole, when compared with historical values in subjects who had received ivermectin alone.[1] An associated study in 44 patients with *Onchocerca volvulus* infections found that levamisole given with ivermectin was neither macrofilaricidal nor more effective against microfilariae and adult worms than ivermectin alone. In addition, patients taking both drugs had a higher incidence of pruritus, arthralgia and fever than those taking ivermectin alone.[1] Concurrent use need not be avoided, but it would seem prudent to be alert for an increase in adverse effects if both drugs are thought to be necessary.

1. Awadzi K, Edwards G, Opoku NO, Ardrey AE, Favager S, Addy ET, Attah SK, Yamuah LK, Quartey BT. The safety, tolerability and pharmacokinetics of levamisole alone, levamisole plus ivermectin, and levamisole plus albendazole, and their efficacy against *Onchocerca volvulus*. *Ann Trop Med Parasitol* (2004) 98, 595–614.

Ivermectin + Orange juice

Orange juice modestly reduces the bioavailability of ivermectin.

Clinical evidence, mechanism, importance and management

A study in 16 healthy subjects found that the AUC and peak plasma levels of a single 150-micrograms/kg dose of ivermectin were reduced by 36% and 39%, respectively, when the ivermectin was given with orange juice (750 mL over 4 hours) rather than with water. The mechanism for the reduced bioavailability is not known but it does not seem related to P-glycoprotein activity.[1] The clinical relevance of these changes is uncertain, although with an AUC decrease of this size, a reduction in the efficacy of ivermectin given for systemic infections may be a possibility. Further study is needed.

1. Vanapalli SR, Chen Y, Ellingrod VL, Kitzman D, Lee Y, Hohl RJ, Fleckenstein L. Orange juice decreases the oral bioavailability of ivermectin in healthy volunteers. *Clin Pharmacol Ther* (2003) 73, P94.

Ivermectin + Praziquantel

No clinically significant pharmacokinetic interaction appears to occur between praziquantel and ivermectin.

Clinical evidence, mechanism, importance and management

In a pharmacokinetic study, 23 healthy subjects were given a single dose of praziquantel 40 mg/kg alone or with single doses of a combination of albendazole 400 mg and ivermectin 200 micrograms/kg. The pharmacokinetics of ivermectin and praziquantel were not significantly affected by concurrent use, except for a small 10% reduction in praziquantel volume of distribution. No serious adverse effects were reported.[1] Modest effects were seen on the pharmacokinetics of albendazole, see 'Albendazole + Praziquantel', p.237.

From this study it would appear that the concurrent use of ivermectin and praziquantel has no clinically significant effects on the pharmacokinetics of either drug. No additional precautions appear to be necessary if both drugs are given.

1. Na-Bangchang K, Kietinun S, Pawa KK, Hanpitakpong W, Na-Bangchang C, Lazdins J. Assessments of pharmacokinetic drug interactions and tolerability of albendazole, praziquantel and ivermectin combinations. *Trans R Soc Trop Med Hyg* (2006) 100, 335–45.

Lumefantrine + CYP2D6 substrates

The manufacturer of artemether/lumefantrine[1] notes that *in vitro* data indicate that lumefantrine significantly inhibits CYP2D6. As a consequence, they contraindicate the use of co-artemether in patients taking any drug that is metabolised by CYP2D6, and they give flecainide, metoprolol, imipramine, amitriptyline, clomipramine as examples (for a list of CYP2D6 substrates, see 'Table 1.3', (p.6)). These contraindications seem unnecessarily restrictive, especially since none of the drugs they give as examples are contraindicated with other established inhibitors of CYP2D6. Until more is known, it would be prudent to closely monitor the effects of any CYP2D6 substrate in patients for whom artemether/lumefantrine is considered the antimalarial drug of choice.

1. Riamet (Artemether/Lumefantrine). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, October 2007.

Mefloquine + Ampicillin

Ampicillin modestly increases the plasma levels of mefloquine and reduces its half-life.

Clinical evidence, mechanism, importance and management

In a study, 8 healthy subjects were given ampicillin 250 mg four times daily for 5 days, with a single 750-mg dose of mefloquine on day 2. The maximum plasma level and 5-day AUC of mefloquine were increased by 34% and 49%, respectively, although the $AUC_{0-\infty}$ was not significantly increased. Ampicillin reduced the half-life of mefloquine from 17.7 to 15.3 days. No increase in adverse events was seen. These pharmacokinetic effects may be due to an increase in mefloquine bioavailability, possibly due to a reduction in its enterohepatic recycling.[1] The clinical relevance of these changes is uncertain, but the authors consider that the changes in elimination are unlikely to be clinically significant, since these occur after the resolution of malaria.[1]

1. Karbwang J, Na Bangchang K, Back DJ, Bunnag D. Effect of ampicillin on mefloquine pharmacokinetics in Thai males. *Eur J Clin Pharmacol* (1991) 40, 631–3.

Mefloquine + Artemisinin derivatives

Artemether pretreatment may modestly reduce mefloquine levels, whereas artemisinin does not affect the pharmacokinetics of mefloquine. If mefloquine is given shortly after artesunate its levels are lowered, but giving mefloquine two days in to artesunate treatment appears to raise mefloquine levels. The levels of lumefantrine were modestly reduced by mefloquine pretreatment, but the levels of artemether and of mefloquine were not affected. No adverse effects on the QT interval were seen.

Clinical evidence, mechanism, importance and management

(a) Artemether

In a study, 15 patients with acute uncomplicated falciparum malaria were given a single 750-mg dose of mefloquine, either alone or 24 hours after a single 300-mg dose of artemether. The AUC of mefloquine was reduced by 27%, when compared with 7 patients receiving mefloquine alone. However, the addition of artemether improved the rate of parasite clearance, and cure rates were similar between the groups.[1] Another study in 8 healthy subjects found the pharmacokinetics of single doses of artemether 300 mg and mefloquine 750 mg were not significantly affected by concurrent use. No serious adverse effects were reported.[2]

(b) Artemether/Lumefantrine

In a study, 42 healthy subjects were given 6 doses of artemether/lumefantrine 80/480 mg over 60 hours, starting 12 hours after a short course of mefloquine (3 doses totalling 1 g given over 12 hours). The pharmacokinetics of mefloquine and artemether were unaffected by sequential use, but the maximum plasma concentrations and AUC of lumefantrine were reduced by 29% and 41%, respectively. However, given that the plasma levels of lumefantrine are usually highly variable, these changes were not thought large enough to affect the efficacy of treatment.[3]

In another study, similar sequential use of these drugs did not affect the QT interval, and drug levels were also considered adequate for treatment.[4] The authors considered that adverse effects on the QT interval are unlikely to occur if artemether/lumefantrine is given after mefloquine prophylaxis or treatment.

These data indicate that sequential use of mefloquine then artemether/lumefantrine is unlikely to require any special precautions. The manufacturer of artemether/lumefantrine notes that prolongation of the QT interval was seen in about 5% of patients in clinical studies, although they say this could be disease related. They state that, due to the limited data on safety and efficacy, artemether/lumefantrine should not be given concurrently with any other antimalarial unless there is no other treatment option.[5]

(c) Artemisinin

Another study in patients with falciparum malaria found no significant pharmacokinetic interaction between artemisinin and mefloquine. In this study, patients received mefloquine 750 mg alone or artemisinin 500 mg daily for 3 days with a single 750-mg dose of mefloquine either on day 1 or day 4. There was no difference in overall efficacy between treatments, although those given artemisinin with mefloquine on the first day of treatment had the fastest parasite clearance rates.[6]

(d) Artesunate

A study, in 20 patients with acute uncomplicated falciparum malaria given mefloquine (750 mg followed after 6 hours by 500 mg), found that the levels of mefloquine were reduced by 27% and its clearance rate was increased 2.6-fold when the doses of mefloquine were given 6 and 12 hours after artesunate 200 mg. However, the patients who received the combination had shorter fever clearance and parasite clearance times than those given mefloquine alone, although the cure rate was lower for combined treatment (66%) than for mefloquine alone (75%). To prevent the pharmacokinetic interaction resulting in a reduction in its efficacy, the authors of this study recommended that mefloquine should be given when artesunate and its metabolites have cleared the circulation (the authors suggest possibly 24 hours after a dose).[7] This suggestion is supported by a study looking at the efficacy of mefloquine with artesunate, which found that the AUC of mefloquine was about 30% higher in 22 children given mefloquine on day 2 of artesunate treatment, when compared with 24 children given mefloquine on day 0 (before artesunate was started). Both groups were given mefloquine without food.[8]

In a more recent study, 179 patients with falciparum malaria were given a single 4-mg/kg dose of artesunate with a single 15-mg/kg dose of mefloquine taken either with, 8 hours, or 24 hours after the artesunate dose, found that the pharmacokinetics of mefloquine and artesunate were not affected by the timing of the doses.[9] Another pharmacokinetic study in 25 healthy subjects also found no evidence of an interaction when a single 250-mg dose of mefloquine was given at the same time as artesunate 200 mg daily for 3 days.[10]

The combined use of artesunate and mefloquine is one of the recommended treatment options in the WHO guidelines for the treatment of uncomplicated falciparum malaria, and for uncomplicated vivax malaria in selected areas.[11]

(e) Other artemisinin derivatives

In a single-dose crossover study, 10 healthy subjects were given either mefloquine 750 mg, dihydroartemisinin 300 mg (exact derivative not specified) or both drugs together. The pharmacokinetics of the drugs were unchanged on concurrent use, except for the rate of absorption of mefloquine, which was increased. Also the activity of these drugs against *Plasmodium falciparum* was synergistic, rather than additive.[12] A study in 12 patients with acute uncomplicated falciparum malaria, given either two doses of dihydroartemisinin (exact derivative not specified) 300 mg 24 hours apart, with a single 750-mg dose of mefloquine either 6 hours after the first dose of dihydroartemisinin or with the last dose of dihydroartemisinin, found no evidence of a pharmacokinetic interaction.[13]

1. Na-Bangchang K, Karbwang J, Molunto P, Banmairuroi V, Thanavibul A. Pharmacokinetics of mefloquine, when given alone and in combination with artemether, in patients with uncomplicated falciparum malaria. *Fundam Clin Pharmacol* (1995) 9, 576–82.
2. Na-Bangchang K, Karbwang J, Ubalee R, Thanavibul A, Saenglertsilapachai S. Absence of significant pharmacokinetic and pharmacodynamic interactions between artemether and quinoline antimalarials. *Eur J Drug Metab Pharmacokinet* (2000) 25 171–8.
3. Lefèvre G, Bindschedler M, Ezzet F, Schaeffer N, Meyer I, Thomsen MS. Pharmacokinetic interaction trial between co-artemether and mefloquine. *Eur J Pharm Sci* (2000) 10, 141–51.

4. Bindschedler M, Lefèvre G, Ezzet F, Schaeffer N, Meyer I, Thomsen MS. Cardiac effects of co-artemether (artemether/lumefantrine) and mefloquine given alone or in combination to healthy volunteers. *Eur J Clin Pharmacol* (2000) 56, 375–81.
5. Riamet (Artemether/Lumefantrine). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, October 2007.
6. Svensson USH, Alin MH, Karlsson MO, Bergqvist Y, Ashton M. Population pharmacokinetic and pharmacodynamic modelling of artemisinin and mefloquine enantiomers in patients with falciparum malaria. *Eur J Clin Pharmacol* (2002) 58, 339–51.
7. Karbwang J, Na Bangchang K, Thanavibul A, Back DJ, Bunnag D, Harinasuta T. Pharmacokinetics of mefloquine alone or in combination with artesunate. *Bull WHO* (1994) 72, 83–7.
8. Price R, Simpson JA, Teja-Isavatharm P, Than MM, Luxemburger C, Heppner DG, Chongsuphajaisiddhi T, Nosten F, White NJ. Pharmacokinetics of mefloquine combined with artesunate in children with acute falciparum malaria. *Antimicrob Agents Chemother* (1999) 43, 341–6.
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10. Davis TME, England M, Dunlop A-M, Page-Sharp M, Cambon N, Keller TG, Heidecker JL, Ilett K. Assessment of the effect of mefloquine on artesunate pharmacokinetics in healthy male volunteers. *Antimicrob Agents Chemother* (2007) 51, 1099–1101.
11. World Health Organization. Guidelines for the treatment of malaria 2006. Available at: http://www.who.int/malaria/docs/TreatmentGuidelines2006.pdf (accessed 29/01/10).
12. Na-Bangchang K, Tippawangkosol P, Thanavibul A, Ubalee R, Karbwang J. Pharmacokinetic and pharmacodynamic interactions of mefloquine and dihydroartemisinin. *Int J Clin Pharmacol Res* (1999) 19, 9–17.
13. Thuy le TD, Hung le N, Hung NC, Na-Bangchang K. Pharmacokinetics of mefloquine with dihydroartemisinin as 2-day regimens in patients with uncomplicated falciparum malaria. *Southeast Asian J Trop Med Public Health* (2007) 38, 205–12.

Mefloquine + Azoles

Ketoconazole increased the AUC of mefloquine by 79%. The clinical relevance of this is uncertain, but an increase in adverse events is possible.

Clinical evidence, mechanism, importance and management

In a study in healthy subjects a single 500-mg dose of mefloquine, given on day 5 of a 10-day course of ketoconazole 400 mg daily, increased the mefloquine AUC by 79%, the maximum level by 64% and the half-life by 34%, when compared to mefloquine alone. A 28% decrease in the AUC of the carboxylic metabolite was also seen. No significant adverse effects were reported.[1] It is probable that ketoconazole inhibits the metabolism of mefloquine by cytochrome P450 isoenzyme CYP3A4. Although the clinical relevance of this increase in mefloquine levels is not known, it seems possible that it could increase the risk of adverse effects in some patients. Until more is known, it may be prudent to be cautious in the use of mefloquine in patients taking ketoconazole.

Note that many azoles have inhibitory effects on CYP3A4, see under 'azole antifungals', (p.233). If the suggested mechanism is correct, these azoles may interact similarly, although there are no clinical reports of an interaction.

1. Ridtitid W, Wongnawa M, Mahatthanatrakul W, Raungsri N, Sunbhanich M. Ketoconazole increases plasma concentrations of antimalarial mefloquine in healthy human volunteers. *J Clin Pharm Ther* (2005) 30, 285–90.

Mefloquine + Cimetidine

The levels of mefloquine may be modestly increased and/or its elimination modestly reduced by cimetidine.

Clinical evidence, mechanism, importance and management

A single 500-mg dose of mefloquine was given to 10 healthy subjects before and after they took cimetidine 400 mg twice daily for 28 days. Cimetidine had no effect on the AUC or serum levels of mefloquine, but the mefloquine half-life increased by 50% (from 9.6 to 14.4 days) and the oral clearance decreased by almost 40%.[1] In another study mefloquine was given to 6 healthy subjects and 6 patients with peptic ulcers, before and after cimetidine 400 mg twice daily for 3 days. In contrast to the first study, cimetidine increased the maximum plasma levels of mefloquine by about 42% and 20% and increased the AUC by about 37% and 32%, in the healthy subjects and patients, respectively. The elimination half-life was increased, but not to a significant extent.[2]

The findings of the first study suggest that cimetidine (a recognised enzyme inhibitor) reduces the metabolism of the mefloquine by the liver,[1] whereas the second study suggests that cimetidine may increase the rate of mefloquine absorption without significantly inhibiting its elimination.[2]

These two studies produced different findings, and an interaction is therefore not established. Nevertheless, the changes seen in both studies were modest, and unlikely to be clinically relevant in most patients taking lower doses of chloroquine for malaria prophylaxis. With higher doses of mefloquine used to treat malaria, to be on the safe side, prescribers should be alert for any evidence of increased mefloquine adverse effects (e.g. dizziness, nausea, vomiting, and abdominal pain) and psychiatric or neurological reactions during concurrent use. Note that the CSM in the UK say that any patient given mefloquine [for malaria prophylaxis] should be informed about its neurological adverse effects, and advised that, if these occur, they should seek medical advice about the use of alternative antimalarials before the next dose is due.[3]

1. Sunbhanichi M, Ridtitid W, Wongnawa M, Akesiripong S, Chamnongchob P. Effect of cimetidine on an oral single-dose mefloquine pharmacokinetics in humans. *Asia Pac J Pharmacol* (1997) 12, 51–5.
2. Kolawole JA, Mustapha A, Abudu-Aguye I, Ochekpe N. Mefloquine pharmacokinetics in healthy subjects and in peptic ulcer patients after cimetidine administration. *Eur J Drug Metab Pharmacokinet* (2000) 25, 165–70.
3. Committee on Safety of Medicines/Medicines Control Agency. Mefloquine (Lariam) and neuropsychiatric reactions. *Current Problems* (1996) 22, 6.

Mefloquine + Metoclopramide

Although metoclopramide increases the rate of absorption and peak levels of a single-dose of mefloquine, the gastrointestinal adverse effects of mefloquine are possibly reduced.

Clinical evidence, mechanism, importance and management

When 7 healthy subjects took a 10-mg dose of metoclopramide 15 minutes before a single 750-mg dose of mefloquine, the absorption half-life of the mefloquine was reduced from 3.2 to 2.4 hours and the peak blood levels were raised by 31%. However, although the rate of absorption was increased, the total amount absorbed was unchanged. A possible reason for these changes is that metoclopramide increases gastric emptying causing mefloquine to reach the small intestine more quickly, which would increase the rate of absorption. Despite these changes, the toxicity of mefloquine (e.g. dizziness, nausea, vomiting, and abdominal pain) was noted to be reduced.[1] The modest increase in peak levels is probably not clinically relevant, especially with prophylactic mefloquine doses.

1. Na Bangchang K, Karbwang J, Bunnag D, Harinasuta T, Back DJ. The effect of metoclopramide on mefloquine pharmacokinetics. *Br J Clin Pharmacol* (1991) 32, 640–1.

Mefloquine + Miscellaneous

An isolated report describes cardiopulmonary arrest in a patient taking mefloquine with propranolol. The WHO have issued a warning about the concurrent use of mefloquine with antiarrhythmics, antihistamines, beta blockers, calcium-channel blockers, digoxin, phenothiazines, pimozide, tricyclic antidepressants and some related antimalarials.

Clinical evidence, mechanism, importance and management

The WHO[1] warns, that the use of mefloquine with **antiarrhythmics**, **beta blockers**, **calcium-channel blockers**, **antihistamines**, **antidepressants** (class not specified, the manufacturers specify **tricyclic antidepressants**[2]), **digoxin**, **pimozide** and **phenothiazines** may increase the risk of arrhythmias.[1] The manufacturers of mefloquine also give these warnings, pointing out that the interactions are theoretical, and that clinically significant QTc prolongation has not been found with mefloquine alone.[2,3] Note that, of the classes mentioned, class Ic and class III antiarrhythmics, sotalol, astemizole and terfenadine are most frequently associated with QT-prolongation, and these drugs are therefore likely to present the greatest risk.[1] No formal studies on the possible adverse effects of combining any of the above drugs with mefloquine seem to have been done. One 1990 review[4] and the US prescribing information[3] briefly mention a single case of cardiopulmonary arrest (with full recovery[3]) when a patient taking **propranolol** was given a single dose[4] of mefloquine. It has been suggested that the concurrent use of beta blockers and mefloquine may also lead to bradycardia, which is an uncommon adverse effect of mefloquine,[2,3] and a known effect of the beta blockers. However, there do not appear to be any reports of an adverse interaction in the literature. It remains to be confirmed whether the effects of mefloquine and these other drugs on cardiac function are normally additive, and whether the outcome

is clinically important, although a case has been reported of the successful use of digoxin and sotalol in the treatment of mefloquine-induced atrial flutter with AV 1:1 conduction.[5] Until more is known it would seem prudent to follow the cautionary advice issued by the WHO and the manufacturers of mefloquine. Drugs that may prolong the QT interval are listed in 'Table 9.2', (p.290). Note that some quinolones can prolong the QT interval, and may also increase the risk of convulsions if given with mefloquine, see 'Mefloquine + Quinolones' p.263.

For mention that halofantrine should not be used with or after mefloquine, because of a clinically significant lengthening of the QT interval, which may be due to a pharmacokinetic interaction, see 'Halofantrine + Miscellaneous', p.258, and for mention of adverse cardiac effects when mefloquine is given with chloroquine, quinine, or quinidine, see 'Mefloquine + Quinine and related drugs', below.

1. WHO. Guidelines for the treatment of malaria 2006. Available at: http://www.who.int/malaria/docs/TreatmentGuidelines2006.pdf (accessed 29/01/10).
2. Lariam (Mefloquine hydrochloride). Roche Products Ltd. UK Summary of product characteristics, August 2009.
3. Lariam (Mefloquine hydrochloride). Roche Pharmaceuticals. US Prescribing information, September 2008.
4. Anon. Mefloquine for malaria. *Med Lett Drugs Ther* (1990) 31, 13–14.
5. Fonteyne W, Bauwens A, Jordaens L. Atrial flutter with 1:1 conduction after administration of the antimalarial drug mefloquine. *Clin Cardiol* (1996) 19, 967–8.

Mefloquine + Primaquine

Although one study suggested that primaquine can increase both the peak serum levels and adverse effects of mefloquine, other studies have generally found no important interaction.

Clinical evidence

A preliminary report of a randomised, crossover study, in 14 healthy subjects given mefloquine 1 g, found that the addition of primaquine 15 or 30 mg raised the peak serum levels of mefloquine by 48% and 29%, respectively. Those taking the larger dose of primaquine had a transient increase in peak primaquine serum levels, and its conversion to its inactive carboxyl metabolite was also increased. Significant CNS symptoms were also experienced by those taking the larger dose of primaquine.[1]

However, these results contrast with another single-dose study in 8 healthy subjects, who were given mefloquine 750 mg with primaquine 45 mg. No increased adverse effects attributable to concurrent use were seen, and mefloquine pharmacokinetics (including the peak level) were not altered by primaquine.[2] Similarly, in a study in patients with malaria, there was no change in mefloquine pharmacokinetics when it was given with primaquine.[3] In another group in this study, the only difference in mefloquine pharmacokinetics was an 11% shorter terminal elimination half-life in those taking primaquine with mefloquine and pyrimethamine/sulfadoxine, when compared with those taking mefloquine with pyrimethamine/sulfadoxine.[3] Similarly, in another study in children given mefloquine with pyrimethamine/sulfadoxine, the addition of primaquine had no effect on the pharmacokinetics of mefloquine, and there were no serious adverse effects.[4]

The pharmacokinetics of a single 45-mg dose of primaquine were not altered by a single 10-mg/kg oral dose of mefloquine in healthy subjects.[5]

Mechanism

In vitro studies suggest that primaquine is a potent inhibitor of mefloquine metabolism.[6]

Importance and management

The bulk of the evidence suggests there is no important alteration in the pharmacokinetics or effect of mefloquine when it is given with primaquine. After treatment of vivax malaria, primaquine is used to eradicate hepatic parasites, so producing a radical cure, and the manufacturer of mefloquine specifically advises this.[7,8]

1. Macleod CM, Trenholme GM, Nora MV, Bartley EA, Frischer H. Interaction of primaquine with mefloquine in healthy males. *Intersci Conf Antimicrob Agents Chemother* (1990) 30, 213.
2. Karbwang J, Na Bangchang K, Thanavibul A, Back DJ, Bunnag D. Pharmacokinetics of mefloquine in the presence of primaquine. *Eur J Clin Pharmacol* (1992) 42, 559–60.
3. Karbwang J, Back DJ, Bunnag D, Breckenridge AM. Pharmacokinetics of mefloquine in combination with sulfadoxine-pyrimethamine and primaquine in male Thai patients with falciparum malaria. *Bull WHO* (1990) 68, 633–8.
4. Singhasivanon V, Chongsuphajaisiddhi T, Sabchareon A, Attanath P, Webster HK, Edstein MD, Lika ID. Pharmacokinetic study of mefloquine in Thai children aged 5–12 years suffering from uncomplicated falciparum malaria treated with MSP or MSP plus primaquine. *Eur J Drug Metab Pharmacokinet* (1994) 19, 27–32.
5. Edwards G, McGrath CS, Ward SA, Supanaranond W, Pukrittayakamee S, Davis TM, White NJ. Interactions among primaquine, malaria infection and other antimalarials in Thai subjects. *Br J Clin Pharmacol* (1993) 35, 193–8.
6. Na Bangchang K, Karbwang J, Back DJ. Mefloquine metabolism by human liver microsomes. Effect of other antimalarial drugs. *Biochem Pharmacol* (1992) 43, 1957–61.
7. Lariam (Mefloquine hydrochloride). Roche Products Ltd. UK Summary of product characteristics, August 2009.
8. Lariam (Mefloquine hydrochloride). Roche Pharmaceuticals. US Prescribing information, September 2008.

Mefloquine + Pyrimethamine/Sulfadoxine

Pyrimethamine/sulfadoxine caused a modest increase in exposure to mefloquine in healthy subjects, but had no effect on mefloquine exposure in patients.

Clinical evidence, mechanism, importance and management

In healthy subjects, a comparison of the pharmacokinetic parameters of a single 750-mg dose of mefloquine, given alone or in combination with pyrimethamine/sulfadoxine, found that the only difference was a 33% increase in mean residence time and 27% increase in the half-life of mefloquine.[1] However, in a further study in patients with malaria, there was no difference in any pharmacokinetic parameter of mefloquine 750 mg between 15 patients taking mefloquine alone and 16 patients taking mefloquine with pyrimethamine/sulfadoxine.[2] In both of these studies there was considerable inter-individual variability in the pharmacokinetics of mefloquine.[1,2] In another study in healthy subjects, the mefloquine AUC was increased by a non-significant 13% when mefloquine was given as a combination tablet containing mefloquine, sulfadoxine and pyrimethamine when compared with mefloquine given alone.[3]

These studies suggest that, at the most, a small increase in exposure to mefloquine may occur when it is given with pyrimethamine/sulfadoxine. It would seem that this is unlikely to be clinically relevant, especially in view of the inter-individual variability in mefloquine pharmacokinetics.

1. Karbwang J, Bunnag D, Breckenridge AM, Back DJ. The pharmacokinetics of mefloquine when given alone or in combination with sulphadoxine and pyrimethamine in Thai male and female subjects. *Eur J Clin Pharmacol* (1987) 32, 173–7.
2. Karbwang J, Back DJ, Bunnag D, Breckenridge AM. Pharmacokinetics of mefloquine in combination with sulfadoxine-pyrimethamine and primaquine in male Thai patients with falciparum malaria. *Bull WHO* (1990) 68, 633–8.
3. Schwartz DE, Weidekamm E, Ranalder UB, Dubach UC, Forgo I, Weber B. Absence of pharmacokinetic interaction between Fansidar and mefloquine. *Trans R Soc Trop Med Hyg* (1986) 80, 1001–2.

Mefloquine + Quinine and related drugs

Mefloquine serum levels may possibly be increased by quinine. In theory, there is an increased risk of convulsions if mefloquine is given with quinine, quinidine, or chloroquine.

Clinical evidence, mechanism, importance and management

Mefloquine 750 mg was given to 7 healthy subjects either alone, or followed 24 hours later by quinine 600 mg. The combination did not affect the pharmacokinetics of either drug, but the number of adverse effects and the period of prolongation of the QT interval was greater with the combination, although no symptomatic cardiotoxicity was seen.[1] This absence of a change in pharmacokinetics is contrary to earlier *in vitro* data and unpublished clinical observations,[2] which suggested that quinine may inhibit the metabolism of mefloquine, thereby raising its serum levels. Another study in 13 patients with uncomplicated falciparum malaria given quinine dihydrochloride 10 mg/kg as a one-hour infusion and simultaneous oral mefloquine 15 mg/kg found no evidence of a pharmacokinetic interaction, but postural hypotension was common. The QTc interval was prolonged by 12%, although no clinically significant cardiovascular interaction was reported.[3]

The manufacturers of mefloquine and the WHO say that mefloquine should not be given with quinine or related compounds (e.g. **quinidine**, **chloroquine**) since this could increase the risk of ECG abnormalities and

convulsions.[4-6] They suggest that patients initially given intravenous quinine for 2 to 3 days should delay mefloquine until at least 12 hours after the last dosing of quinine to minimise interactions leading to adverse events.[4,5] However, there seem to be no documented adverse reports of this interaction leading to convulsions.

1. Na-Bangchang K, Tan-Ariya P, Thanavibul A, Reingchainam S, Shrestha SB, Karbwang J. Pharmacokinetic and pharmacodynamic interactions of mefloquine and quinine. *Int J Clin Pharmacol Res* (1999) 19, 73–82.
2. Na Bangchang K, Karbwang J, Back DJ. Mefloquine metabolism by human liver microsomes. Effect of other antimalarial drugs. *Biochem Pharmacol* (1992) 43, 1957–61.
3. Supanaranond W, Suputtamongkol Y, Davis TME, Pukrittayakamee S, Teja-Isavadharm P, Webster HK, White NJ. Lack of a significant adverse cardiovascular effect of combined quinine and mefloquine therapy for uncomplicated malaria. *Trans R Soc Trop Med Hyg* (1997) 91, 694–6.
4. Lariam (Mefloquine hydrochloride). Roche Products Ltd. UK Summary of product characteristics, August 2009.
5. Lariam (Mefloquine hydrochloride). Roche Pharmaceuticals. US Prescribing information, September 2008.
6. World Health Organization. Guidelines for the treatment of malaria 2006. Available at: http://www.who.int/malaria/docs/TreatmentGuidelines2006.pdf (accessed 29/01/10).

Mefloquine + Quinolones

Three non-epileptic patients had convulsions when they were given mefloquine and a quinolone. Also, some quinolones, such as moxifloxacin, prolong the QT interval and concurrent use with mefloquine might theoretically result in additive effects.

Clinical evidence, mechanism, importance and management

A large scale survey in India of the adverse effects of mefloquine identified 3 cases of convulsions out of a total of 150 patients also taking **ciprofloxacin**, **ofloxacin** or **sparfloxacin**. All 3 patients were not epileptic, and had no family history of epilepsy. All were being treated for fever, which was due to *Plasmodium vivax* in one case, *P. falciparum* in the second, and was not established in the third. None of the patients had severe or complicated malaria, which suggests that the convulsions were not solely a result of the disease state. The **ofloxacin** was given 2 days before the mefloquine, and the other two quinolones were given together with the mefloquine.[1] The reason for the seizures is not known, but seizures are among the recognised adverse effects of both mefloquine and these quinolones. These adverse, apparently additive, effects are rare, but prescribers should be aware of the potential increased risk of convulsions when prescribing these drugs together.

Some quinolones may cause clinically relevant prolongation of the QT interval, see 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290. Although mefloquine alone has not been shown to cause a clinically relevant lengthening of the QT interval, caution has still been recommended when it is combined with some other drugs that may prolong the QT interval, see 'Mefloquine + Miscellaneous', p.261. It would therefore be prudent to extend this caution to these quinolones.

1. Mangalvedhekar SS, Gogtay NJ, Wagh VR, Waran MS, Mane D, Kshirsager NA. Convulsions in non-epileptics due to mefloquine-fluoroquinolone co-administration. *Natl Med J India* (2000) 13, 47.

Mefloquine + Rifampicin (Rifampin)

Rifampicin significantly reduces the plasma concentrations of mefloquine.

Clinical evidence, mechanism, importance and management

In a crossover study, 7 healthy subjects were given rifampicin 600 mg daily for 7 days with a single 500-mg dose of mefloquine on day 7. The maximum plasma level of mefloquine was reduced by 19% and its AUC was decreased by 68%. Rifampicin, a potent enzyme-inducer, was thought to have lowered mefloquine levels by inducing the cytochrome P450 isoenzyme CYP3A4 in the liver and gut wall, thereby increasing mefloquine metabolism. The clinical relevance of this reduction in mefloquine levels is uncertain, but the authors suggest that simultaneous use of rifampicin and mefloquine should be avoided to prevent treatment failure and the risk of *Plasmodium falciparum* resistance to mefloquine.[1] Until more is known, this would seem a sensible precaution.

1. Ridtitid W, Wongnawa M, Mahatthanatrakul W, Chaipol P, Sunbhanich M. Effect of rifampicin on plasma concentrations of mefloquine in healthy volunteers. *J Pharm Pharmacol* (2000) 52, 1265–9.

Mefloquine + Tetracycline

Mefloquine serum levels are modestly increased by tetracycline.

Clinical evidence, mechanism, importance and management

In a study in 20 healthy Thai men, the maximum serum levels of a single 750-mg dose of mefloquine were increased by 38% (from 1.16 to 1.6 mg/mL) by tetracycline 250 mg four times daily for one week. The AUC was increased by 30% and the half-life reduced from 19.3 to 14.4 days, without any evidence of an increase in adverse effects. It is suggested that mefloquine levels are increased because its enterohepatic recycling is reduced by competition with tetracycline for biliary excretion.[1] The authors of the report concluded that concurrent use of mefloquine and tetracycline may be valuable for treating multi-drug resistant falciparum malaria because higher mefloquine levels are associated with a more effective response. However, more study is needed to confirm these findings. There seems to be no reason for avoiding concurrent use.

1. Karbwang J, Na Bangchang K, Back DJ, Bunnag D, Rooney W. Effect of tetracycline on mefloquine pharmacokinetics in Thai males. *Eur J Clin Pharmacol* (1992) 43, 567–9.

Metrifonate + Antacids or H_2-receptor antagonists

The pharmacokinetics of metrifonate do not appear to affected by an antacid containing aluminium/magnesium hydroxide, or by pretreatment with cimetidine or ranitidine.

Clinical evidence, mechanism, importance and management

(a) Antacids

A single-dose study in healthy subjects found that the AUC and maximum level of metrifonate and its pharmacologically active metabolite were not altered by the concurrent use of an **aluminium/magnesium hydroxide**-containing antacid.[1] Therefore no special precautions seem necessary with concurrent use.

(b) H_2-receptor antagonists

In a study in healthy subjects the AUC and maximum level of metrifonate and its pharmacologically active metabolite were not altered by pretreatment with either **cimetidine** or **ranitidine**.[1] Based on these results it seems unlikely that other H_2-receptor antagonists will interact with metrifonate.

1. Heinig R, Boettcher M, Herman-Gnjidic Z, Pierce CH. Effects of magnesium/aluminium hydroxide–containing antacid, cimetidine or ranitidine on the pharmacokinetics of metrifonate and its metabolite DDVP. *Clin Drug Invest* (1999) 17, 67–77.

Piperazine + Chlorpromazine

An isolated case of convulsions in a child was attributed to the use of piperazine followed by chlorpromazine.

Clinical evidence, mechanism, importance and management

A child given piperazine for pin worms developed convulsions when chlorpromazine was given several days later.[1] In a subsequent *animal* study using piperazine and chlorpromazine 4.5 or 10 mg/kg, many of the *animals* died from respiratory arrest after severe clonic convulsions.[1] However, a later *animal* study did not confirm these findings[2] and it is by no means certain whether the adverse reaction in the child was due to an interaction or not. Given that both drugs may cause convulsions, there is probably enough evidence to warrant caution if they are used concurrently.

1. Boulos BM, Davis LE. Hazard of simultaneous administration of phenothiazine and piperazine. *N Engl J Med* (1969) 280, 1245–6.
2. Armbrecht BH. Reaction between piperazine and chlorpromazine. *N Engl J Med* (1970) 282, 1490–1.

Praziquantel + Antiepileptics; Enzyme-inducing

Phenytoin, phenobarbital and carbamazepine markedly reduce the serum levels of praziquantel. Fosphenytoin would be expected to interact similarly.

Clinical evidence

(a) Carbamazepine, Phenobarbital or Phenytoin

A comparative study of patients taking long-term phenytoin or carbamazepine and healthy subjects (10 in each group), both given a single 25-mg/kg oral dose of praziquantel, found that phenytoin and carbamazepine reduced the AUC of praziquantel by about 74% and 90%, respectively, and reduced its maximum serum levels by 76% and 92%, respectively, when compared with the healthy subjects.[1] Another study also reported low praziquantel levels (maximum levels of 42 to 540 nanograms/mL with undetectable trough levels) in patients given praziquantel 15 mg/kg daily 3 times daily for 15 days and also taking phenytoin (4 patients) or phenobarbital (8 patients). However, in this study praziquantel was still found to be very effective for neurocysticercosis, with all patients showing a marked improvement.[2]

(b) Phenytoin/Phenobarbital and Cimetidine

A patient with neurocysticercosis taking phenytoin and phenobarbital for a seizure disorder had no response to praziquantel (four courses in doses of up to 50 mg/kg daily). Praziquantel 50 mg/kg daily and dexamethasone 12 mg daily were started, and, after one week, cimetidine 400 mg four times daily was added. The patient's serum praziquantel levels more than doubled with the addition of cimetidine (maximum serum levels raised from 350 nanograms/mL to 826 nanograms/mL) and the AUC rose about fourfold, and became similar to that found in control subjects taking praziquantel alone. The patient showed marginal improvement, and continued to slowly improve over the following 4 months.[3]

Mechanism

Not established. Praziquantel appears to be metabolised by the cytochrome P450 isoenzymes CYP1A2, CYP2C19 and CYP3A4.[4] These antiepileptics and 'dexamethasone', (p.265), have cytochrome P450 enzyme-inducing effects and can therefore increase the metabolism of praziquantel. 'Rifampicin (Rifampin)', (p.266), another potent inducer of cytochrome P450, also markedly reduces praziquantel levels. Conversely, 'cimetidine', (p.265), an enzyme inhibitor, appears to oppose this effect. However, the fact that praziquantel was still effective in one study suggests that praziquantel metabolites might be active.[2]

Importance and management

Direct information appears to be limited to the reports cited, but the pharmacokinetic interactions appear to be established. However, the clinical relevance of the interaction is uncertain. When treating systemic worm infections such as neurocysticercosis some authors advise increasing the praziquantel dosage from 25 mg/kg to 50 mg/kg if potent enzyme inducers such as carbamazepine or phenytoin are being used, in order to reduce the risk of treatment failure.[1] A 45 mg/kg daily dose was effective in one study in 11 patients taking antiepileptics, despite low praziquantel levels,[2] but a 50 mg/kg daily dose was not effective in another case.[3] The recommended dose for the treatment of neurocysticercosis is 50 mg/kg daily in 3 divided doses.[5] Adding cimetidine may reduce the effect of enzyme-inducing antiepileptics. However, the authors of the case above[3] were not sure whether the improvement they saw was in fact due to the cimetidine or simply part of the natural history of the disease. It is clear that 'cimetidine', (p.265), alone can markedly increase praziquantel levels. One Canadian manufacturer of praziquantel advises that the reduction in praziquantel levels may also occur with **fosphenytoin**.[6] As fosphenytoin is a prodrug of phenytoin, this seems a reasonable prediction, and similar precautions should be considered.

Note that the interaction with enzyme-inducing antiepileptics is of no importance when praziquantel is used for intestinal worm infections (where its action is a local effect on the worms in the gut).

1. Bittencourt PRM, Gracia CM, Martins R, Fernandes AG, Diekmann HW, Jung W. Phenytoin and carbamazepine decrease oral bioavailability of praziquantel. *Neurology* (1992) 42, 492–6.
2. Na-Bangchang K, Vanijanonta S, Karbwang J. Plasma concentrations of praziquantel during the therapy of neurocysticerosis with praziquantel, in the presence of antiepileptics and dexamethasone. *Southeast Asian J Trop Med Public Health* (1995) 26, 120–3.
3. Dachman WD, Adubofour KO, Bikin DS, Johnson CH, Mullin PD, Winograd M. Cimetidine-induced rise in praziquantel levels in a patient with neurocysticercosis being treated with anticonvulsants. *J Infect Dis* (1994) 169, 689–91.
4. Li X-Q, Björkman A, Andersson TB, Gustafsson LL, Masimirembwa CM. Identification of human cytochrome P_{450}s that metabolise anti-parasitic drugs and predictions of in vivo hepatic clearance from in vitro data. *Eur J Clin Pharmacol* (2003) 59, 429–42.
5. Sweetman SC, ed. Martindale: The complete drug reference. 36th ed. London: Pharmaceutical Press; 2009. p. 154.
6. Biltricide (Praziquantel). Bayer Inc. Canadian Prescribing information, November 2007.

Praziquantel + Azoles

Ketoconazole increases praziquantel levels. Miconazole increases the bioavailability of praziquantel in *rats*, and other azoles are also predicted to interact.

Clinical evidence

In a randomised, crossover study, 10 healthy subjects were given a single dose of praziquantel 20 mg/kg alone or after pretreatment with **ketoconazole** 400 mg daily for 5 days. **Ketoconazole** significantly increased the AUC and maximum plasma levels of praziquantel by 93% and 102%, respectively. The total clearance was decreased by 58% but the half-life was only slightly prolonged. No adverse effects were reported with praziquantel alone; however, mild headache and gastrointestinal adverse effects (including nausea and vomiting) were reported when patients were pretreated with **ketoconazole**.[1]

A study in *rats* has reported that **miconazole** also increases praziquantel bioavailability.[2]

Mechanism

Praziquantel is metabolised by the cytochrome P450 isoenzyme CYP3A4, which is potently inhibited by ketoconazole. Concurrent use therefore decreases praziquantel metabolism, resulting in raised levels. All azoles inhibit this isoenzyme (although the extent varies, see under 'azoles', (p.233)), and would therefore be expected to interact.

Importance and management

Information on this interaction is limited, but it is in line with the known metabolism of praziquantel and the inhibitory effects of ketoconazole. All azoles inhibit this isoenzyme (although the extent varies, see under 'azoles', (p.233)), and would therefore be expected to interact similarly. Although there is no direct information, it is possible that concurrent use may lead to an improved clinical outcome, as has been reported for 'cimetidine', (p.265), which also raises praziquantel levels. However, the study with ketoconazole found that concurrent use increased adverse effects, and so it would seem prudent to monitor for praziquantel adverse effects if an azole is also given.

1. Ridtitid W, Ratsamemonthon K, Mahatthanatrakul W, Wongnawa M. Pharmacokinetic interaction between ketoconazole and praziquantel in healthy volunteers. *J Clin Pharm Ther* (2007) 32, 585–93.
2. Diekmann HW, Scheidereit M, Overbosch D. Inhibitory effects of cimetidine ketoconazole and miconazole on the metabolism of praziquantel. *Acta Leiden* (1989) 57, 217–28.

Praziquantel + Chloroquine

Chloroquine reduces the bioavailability of praziquantel.

Clinical evidence

A single 40-mg/kg oral dose of praziquantel was given to 8 healthy subjects alone, and 2 hours after chloroquine 600 mg. Chloroquine reduced the AUC and maximum serum levels of praziquantel by 65% and 59%, respectively. There were large individual variations in levels, and one subject was not affected.

Mechanism

Not understood.

Importance and management

Evidence is limited, but the effect appears to be established. The result of this interaction could be that some patients will not achieve high enough

serum praziquantel levels to treat systemic worm infections such as schistosomiasis. After taking chloroquine, the praziquantel serum levels of 4 out of the 8 subjects (50%) did not reach the threshold of 0.3 micrograms/mL for about 6 hours (which is required to effectively kill schistosomes), compared with only 2 of 8 (25%) during the control period. The authors conclude that an increased dosage of praziquantel should be considered if chloroquine is given (they do not suggest how much), particularly in anyone who does not respond to initial treatment with praziquantel.[1] More study of this interaction is needed.

Note that this interaction is of no importance when praziquantel is used for intestinal worm infections (where its action is a local effect on the worms in the gut).

1. Masimirembwa CM, Naik YS, Hasler JA. The effect of chloroquine on the pharmacokinetics and metabolism of praziquantel in rats and in humans. *Biopharm Drug Dispos* (1994) 15, 33–43.

Praziquantel + Cimetidine

Cimetidine can double the serum levels of praziquantel, and may improve its efficacy in neurocysticercosis.

Clinical evidence

In a randomised, crossover study, 8 healthy subjects were given three 25-mg/kg oral doses of praziquantel at 2-hourly intervals with cimetidine 400 mg given 1 hour before each dose of praziquantel. Cimetidine roughly doubled the praziquantel serum levels and AUC.[1,2] A further study in patients with neurocysticercosis found that this short regimen of praziquantel with cimetidine (which increased plasma levels of praziquantel by about threefold), had similar efficacy to the traditional regimen of 50 mg/kg daily in divided doses for 15 days.[3] Of the 6 patients receiving praziquantel with cimetidine, the clinical cure rate was 83%, compared with only 50% in 6 patients receiving praziquantel alone.[3]

Mechanism

Uncertain. An *in vitro* study has shown praziquantel to be a substrate for several cytochrome P450 isoenzymes including CYP1A2, CYP2C19 and CYP3A4.[4] Cimetidine, a potent inhibitor of cytochrome P450, probably inhibits the metabolism of praziquantel.

Importance and management

Direct information appears to be limited to the reports cited, but the interaction appears to be established. It is clear that cimetidine can markedly increase praziquantel levels, and the authors say that concurrent use can reduce treatment for neurocysticercosis from 2 weeks to 1 day.[1,3] One case report suggests that the concurrent use of cimetidine contributed to the resolution of refractory neurocysticercosis in a patient treated with high-dose praziquantel 100 mg/kg daily, although no pharmacokinetic data for praziquantel were reported.[5]

Cimetidine has been tried to reverse the effects of 'antiepileptics', (p.264), and 'corticosteroids', (below), which reduce praziquantel levels.

1. Jung H, Medina R, Castro N, Corona T, Sotelo J. Pharmacokinetic study of praziquantel administered alone and in combination with cimetidine in a single-day therapeutic regimen. *Antimicrob Agents Chemother* (1997) 41, 1256–9.
2. Castro N, Gonzàlez-Esquivel D, Medina R, Sotelo J, Jung H. The influence of cimetidine on plasma levels of praziquantel after a single day therapeutic regimen. *Proc West Pharmacol Soc* (1997) 40, 33–4.
3. Castro N, González-Esquivel DF, López M, Jung H. Análisis comparativo de la influencia de los alimentos y la cimetidina en los niveles plasmáticos de prazicuantel. *Rev Invest Clin* (2003) 55, 655–61.
4. Li X-Q, Björkman A, Andersson TB, Gustafsson LL, Masimirembwa CM. Identification of human cytochrome P_{450}s that metabolise anti-parasitic drugs and predictions of in vivo hepatic clearance from in vitro data. *Eur J Clin Pharmacol* (2003) 59, 429–42.
5. Yee T, Barakos JA, Knight RT. High-dose praziquantel with cimetidine for refractory neurocysticercosis: a case report with clinical and MRI follow-up. *West J Med* (1999), 170, 112–15.

Praziquantel + Corticosteroids

The continuous use of dexamethasone can halve serum praziquantel levels and may reduce its efficacy.

Clinical evidence

Eight patients with parenchymal brain cysticercosis taking praziquantel 50 mg/kg (in three divided doses every 8 hours) had a 50% reduction in the praziquantel steady-state serum levels (from 3.13 to 1.55 micrograms/mL) when given **dexamethasone** 8 mg every 8 hours.[1] Another patient with recurrent neurocysticercosis, who did not respond to praziquantel 50 mg/kg daily, was successfully treated with high-dose praziquantel 100 mg/kg daily, **dexamethasone** 12 mg daily and cimetidine 800 mg daily. As dexamethasone was thought to reduce the plasma levels of praziquantel, 'cimetidine', (above), was added to try to reverse this effect, as it has been reported to increase the bioavailability of praziquantel.[2] However, some patients have responded well to praziquantel, despite low serum levels.[3]

Mechanism

Uncertain. It has been suggested that dexamethasone is an inducer of the cytochrome P450 isoenzyme CYP3A4, and might therefore reduce levels of praziquantel, which is, in part, metabolised by this route. Potent CYP3A4 inducers such as 'phenytoin', (p.264), and 'rifampicin (rifampin)', (p.266), also significantly reduce the levels of praziquantel. Conversely, 'cimetidine', (above), an inhibitor of cytochrome P450, may reverse this effect.

Importance and management

Information seems to be limited but the pharmacokinetic interaction would appear to be established. However, the extent to which it affects the clinical outcome of treatment for systemic worm infections such as cysticercosis is unknown as the optimum praziquantel levels required are still uncertain, and it is also possible that the metabolites of praziquantel might be active.[3] The authors of one report suggest that dexamethasone should not be given continuously with praziquantel but only used transiently to resolve inflammatory reactions to praziquantel treatment.[1] Alternatively, limited information suggests the addition of cimetidine may allow dexamethasone to be used.[2]

Intravenous **methylprednisolone** has also been used for acute corticosteroid therapy with praziquantel, and oral **prednisone** has been used long-term to prevent further tissue damage associated with inflammation[4,5] but the effect of these corticosteroids on the plasma levels of praziquantel do not appear to have been studied.

The interaction with dexamethasone is of no importance when praziquantel is used for intestinal worm infections (where its action is a local effect on the worms in the gut).

1. Vazquez ML, Jung H, Sotelo J. Plasma levels of praziquantel decrease when dexamethasone is given simultaneously. *Neurology* (1987) 37, 1561–2.
2. Yee T, Barakos JA, Knight RT. High-dose praziquantel with cimetidine for refractory neurocysticercosis: a case report with clinical and MRI follow-up. *West J Med* (1999) 170, 112–15.
3. Na-Bangchang K, Vanijanonta S, Karbwang J. Plasma concentrations of praziquantel during the therapy of neurocysticerosis with praziquantel, in the presence of antiepileptics and dexamethasone. *Southeast Asian J Trop Med Public Health* (1995) 26, 120–3.
4. Sotelo J, Jung H. Pharmacokinetic optimisation of the treatment of neurocysticercosis. *Clin Pharmacokinet* (1998) 34, 503–15.
5. Silva LCS, Maciel PE, Ribas JGR, Souza-Pereira SR, Antunes CM, Lambertucci JR. Treatment of schistosomal myeloradiculopathy with praziquantel and corticosteroids and evaluation by magnetic resonance imaging: a longitudinal study. *Clin Infect Dis* (2004) 39, 1618–24.

Praziquantel + Food

Food increases the bioavailability of praziquantel.

Clinical evidence, mechanism, importance and management

The maximum plasma levels and AUC of a single 1.8-g dose of praziquantel were increased by 243% and 180% when it was given immediately after a **high-fat** meal and by 515% and 271% after a **high-carbohydrate** meal, respectively.[1] In another study in healthy Sudanese men, when praziquantel was given with food, the AUC was 2.6-fold higher than when it was given in the fasted state.[2]

A further study in patients with neurocysticercosis found that taking praziquantel 25 mg/kg every 2 hours for 3 doses with a **high-carbohydrate** diet increased the plasma levels of praziquantel, and provided an adequate clinical alternative to the traditional regimen of 50 mg/kg daily in divided doses for 15 days.[3] In 6 patients who took praziquantel with food, the clinical cure rate was 83%, compared with only 50% in 6 patients who took praziquantel while fasting.[3]

On the basis of the above studies, if praziquantel is used for systemic worm infections, administration with **food** is advisable, and this is recommended by the manufacturers.[4]

1. Castro N, Medina R, Sotelo J, Jung H. Bioavailability of praziquantel increases with concomitant administration of food. *Antimicrob Agents Chemother* (2000) 44, 2903–4.
2. Homeida M, Leahy W, Copeland S, Ali MM, Harron DWG. Pharmacokinetic interaction between praziquantel and albendazole in Sudanese men. *Ann Trop Med Parasitol* (1994) 88, 551–9.
3. Castro N, González-Esquivel DF, López M, Jung H. Análisis comparativo de la influencia de los alimentos y la cimetidina en los niveles plasmáticos de prazicuantel. *Rev Invest Clin* (2003) 55, 655–61.
4. Biltricide (Praziquantel). Bayer HealthCare Pharmaceuticals Inc. US Prescribing information, August 2007.

Praziquantel + Grapefruit juice

Grapefruit juice increases the AUC of praziquantel.

Clinical evidence, mechanism, importance and management

In a randomised, crossover study in 18 healthy subjects a single 1.8-g dose of praziquantel was given with 250 mL of **grapefruit juice** or water. Grapefruit juice increased maximum plasma level and AUC of praziquantel by about 63% and 90%, respectively, when compared with water.[1] The authors suggested that grapefruit juice probably increased the absorption of praziquantel. The clinical effect of this interaction has not been assessed: it may lead to improved efficacy, but it may also lead to an increase in praziquantel adverse effects (e.g. headache, diarrhoea, dizziness, and drowsiness). Until more is known it may be prudent to be alert for an increase in praziquantel adverse effects in patients that drink grapefruit juice. When compared with other studies, the authors noted that the effect of grapefruit juice was comparable to that of 'cimetidine', (p.265), and less than that of 'food', (p.265).

1. Castro N, Jung H, Medina R, González-Esquivel D, Lopez M, Sotelo J. Interaction between grapefruit juice and praziquantel in humans. *Antimicrob Agents Chemother* (2002) 46, 1614–16.

Praziquantel + Rifampicin (Rifampin)

Rifampicin markedly reduces the levels, and therefore probably the efficacy, of praziquantel.

Clinical evidence, mechanism, importance and management

A study in 10 subjects found that pretreatment with rifampicin 600 mg daily for 5 days markedly reduced the AUC and maximum level of a single 40-mg/kg dose of praziquantel. Seven of the subjects had undetectable praziquantel levels (less than 12.5 nanograms/mL), and the other 3 had an 85% reduction in the AUC of praziquantel. The same subjects were then given three doses of praziquantel 25 mg/kg at intervals of 8 hours, alone, and after pretreatment with rifampicin, as above. In this multiple-dose study, 5 of the 10 subjects had undetectable praziquantel levels, and the remainder had an 80% reduction in AUC.[1] Praziquantel is metabolised by various cytochrome P450 isoenzymes including CYP3A4, and it is likely that rifampicin induced the metabolism of praziquantel by this isoenzyme. Although efficacy has not been assessed, the authors concluded that the levels of praziquantel after rifampicin pretreatment were less than those considered necessary for anthelmintic activity. They therefore recommend that the combination should be avoided,[1] a stance which is also taken by one of the manufacturers of praziquantel.[2]

1. Ridtitid W, Wongnawa M, Mahatthanatrakul W, Punyo J, Sunbhanich M. Rifampin markedly decreases plasma concentrations of praziquantel in healthy volunteers. *Clin Pharmacol Ther* (2002) 72, 505–13.
2. Biltricide (Praziquantel). Bayer HealthCare Pharmaceuticals Inc. US Prescribing information, August 2007.

Primaquine + Food

Food slightly increases the bioavailability of primaquine.

Clinical evidence, mechanism, importance and management

A study in 20 healthy subjects found that giving a single 30-mg dose of primaquine with food (two bread rolls and 30 g of butter) increased the AUC and maximum plasma concentration of primaquine by 14% and 26%, respectively when compared to administration in the fasting state. These small increases are unlikely to increase the risk of adverse effects.[1] Primaquine should usually be taken with a meal to minimise gastrointestinal adverse effects such as abdominal cramps, and it appears that this advice may also slightly improve the bioavailability.

1. Cuong BT, Binh VQ, Dai B, Duy DN, Lovell CM, Rieckmann KH, Edstein MD. Does gender, food or grapefruit juice alter the pharmacokinetics of primaquine. *Br J Clin Pharmacol* (2006) 61, 682–9.

Primaquine + Grapefruit juice

Grapefruit juice may increase the levels of primaquine, which may be significant in some individuals.

Clinical evidence, mechanism, importance and management

A study in 20 healthy subjects found that 300 mL of grapefruit juice (concentrated grapefruit juice diluted to 50%) increased the mean AUC and maximum plasma concentration of primaquine by 19% and 23%, respectively. These changes are relatively minor; however, the authors note that although some individuals showed no interaction, some had up to a twofold increase in primaquine bioavailability.[1]

Evidence is limited to the study, and the general significance of this interaction is unclear. The authors of this study suggest that it may be prudent to avoid drinking grapefruit juice while taking primaquine, due to a lack of further information, particular on the effects of more concentrated juice, and also due to the unpredictability of this interaction.[1] This would appear to be sensible advice until further evidence is available.

1. Cuong BT, Binh VQ, Dai B, Duy DN, Lovell CM, Rieckmann KH, Edstein MD. Does gender, food or grapefruit juice alter the pharmacokinetics of primaquine. *Br J Clin Pharmacol* (2006) 61, 682–9.

Primaquine + Mepacrine (Quinacrine)

Theoretically, mepacrine would be expected to elevate the serum levels of primaquine, because it increased the levels of a formerly used drug pamaquine, which is structurally similar, but there do not seem to be any reports confirming or disproving this.

Clinical evidence, mechanism, importance and management

Patients given pamaquine (a formerly used antimalarial that was a predecessor of primaquine, and almost identical in structure), had grossly elevated pamaquine plasma levels when they were also given mepacrine.[1,2] The reason is unknown. On theoretical grounds primaquine might be expected to interact with mepacrine similarly, but there seem to be no reports confirming that a clinically important interaction actually takes place. However, the US manufacturer contraindicates the concurrent use of primaquine with mepacrine and also the use of primaquine in patients who have recently taken mepacrine.[3]

1. Zubrod CG, Kennedy TJ, Shannon JA. Studies on the chemotherapy of the human malarias. VIII. The physiological disposition of pamaquine. *J Clin Invest* (1948) 27 (Suppl), 114–120.
2. Earle DP, Bigelow FS, Zubrod CG, Kane CA. Studies on the chemotherapy of the human malarias. IX. Effect of pamaquine on the blood cells of man. *J Clin Invest* (1948) 27, (Suppl), 121–9.
3. Primaquine phosphate. Sanofi-Aventis. US Prescribing information, January 2008.

Primaquine + Quinine

Quinine does not appear to affect the pharmacokinetics of primaquine.

Clinical evidence, mechanism, importance and management

In a study in 7 subjects, quinine 10 mg/kg three times daily had no effect on the pharmacokinetics of a single 45-mg dose of primaquine, except for a 50% increase in the AUC of the carboxyprimaquine metabolite. The combination was effective for the treatment of malaria with no complications and no adverse effects reported.[1]

Usually quinine is used only for the treatment of falciparum malaria, and

primaquine is used only to eliminate the liver stages of vivax and ovale malarias, and therefore the drugs are generally unlikely to be taken together. However, quinine may be used when the infective species is unknown or the infection mixed, when subsequent primaquine may then be required. The limited data from the above study suggest that no special precautions would be required in this situation.

1. Edwards G, McGrath CS, Ward SA, Supanaranond W, Pukrittayakamee S, Davis TM, White NJ. Interactions among primaquine, malaria infection and other antimalarials in Thai subjects. *Br J Clin Pharmacol* (1993) 35, 193–8.

Proguanil + Antacids

The absorption of proguanil is markedly reduced by magnesium trisilicate, and therefore the efficacy of proguanil may be reduced. Other antacids such as aluminium hydroxide may interact similarly.

Clinical evidence

Magnesium trisilicate reduced the AUC of a 200-mg dose of proguanil by about 65% in 8 healthy subjects, as assessed by salivary proguanil levels.[1]

Mechanism

In vitro tests showed that magnesium trisilicate adsorbed proguanil. Two other antacids, **aluminium hydroxide** and light **magnesium carbonate** also adsorbed proguanil, but to a lesser extent.[1]

Importance and management

The interaction between proguanil and magnesium trisilicate appears to be established, but its clinical importance does not seem to have been assessed. Given the extent of the reduction in levels, the antimalarial effects of proguanil might be expected to be reduced. One way to minimise the interaction is to separate the dosage of proguanil and magnesium trisilicate as much as possible (2 to 3 hours has been shown to be sufficient with other drugs that interact with antacids in this way) to reduce admixture in the gut; this is also suggested by the manufacturers of proguanil.[2] There do not appear to be any clinical studies to see if other antacids behave similarly, but *in* vitro *studies* suggest aluminium hydroxide and magnesium carbonate may. Therefore similar precautions for these antacids may be prudent.

1. Onyeji CO, Babalola CP. The effect of magnesium trisilicate on proguanil absorption. *Int J Pharmaceutics* (1993) 100, 249–52.
2. Paludrine (Proguanil hydrochloride). AstraZeneca UK Ltd. UK Summary of product characteristics, April 2005.

Proguanil + Chloroquine

Chloroquine appears to increase the incidence of mouth ulcers in those taking proguanil by 50%. Both drugs were given as antimalarial prophylaxis.

Clinical evidence, mechanism, importance and management

Following the observation that mouth ulcers appeared to be common in those taking prophylactic antimalarials, an extensive study was undertaken in 628 servicemen in Belize. Of those taking proguanil 200 mg daily, 24% developed mouth ulcers, and in those also taking chloroquine base 150 to 300 mg weekly, 37% developed mouth ulcers. The incidence of diarrhoea was also increased from 63% among those who did not develop ulcers to 83% in those that did develop ulcers (any treatment). The reasons are not understood. The authors of the study suggested that these two drugs should not be given together unnecessarily for prophylaxis against *Plasmodium falciparum*.[1] However, chloroquine plus proguanil is an established prophylactic regimen that is commonly recommended in regions where there is some chloroquine resistance.

1. Drysdale SF, Phillips-Howard PA, Behrens RH. Proguanil, chloroquine, and mouth ulcers. *Lancet* (1990) 1, 164.

Proguanil + Cimetidine or Omeprazole

There is some evidence that omeprazole and cimetidine can moderately reduce the production of cycloguanil, the active metabolite of proguanil.

Clinical evidence

(a) Cimetidine

In one study, 4 patients with peptic ulcer disease and 6 healthy subjects were given a single 200-mg dose of proguanil on the last day of a 3-day course of cimetidine 400 mg twice daily. In both groups the half-life and AUC of proguanil were significantly increased, but only the healthy subjects had an increase in the maximum serum concentration (of 89%). In both groups these pharmacokinetic changes resulted in lower levels of the active metabolite, cycloguanil.[1] This decrease in cycloguanil levels supported the findings of an earlier study, which had found a 30% decrease in the urinary recovery of cycloguanil when proguanil and cimetidine were given together.[2]

(b) Omeprazole

A steady-state study in 12 healthy subjects taking proguanil 200 mg daily found that omeprazole 20 mg daily roughly halved the AUC of cycloguanil, the active metabolite of proguanil.[3] However, an earlier study found that omeprazole 20 mg had no effect on the urinary recovery of cycloguanil (or proguanil) following a single 200-mg dose of proguanil.[2]

Mechanism

Cimetidine and omeprazole increase the gastric pH, which may lead to an increase in the absorption of proguanil. Cimetidine[1,2] and omeprazole[3] are also thought to inhibit the metabolism of proguanil, due to their inhibitory effects on the cytochrome P450 isoenzyme CYP2C19.

Importance and management

Evidence is limited, but roughly in line with the known pharmacokinetic effects of these drugs. The differences between the healthy subjects and patients with peptic ulcer disease seen in one study may have been because the disease itself alters the effects of the cimetidine in some way.[1] Patients with peptic ulcer disease are also likely to have an increased gastric pH, which will lead to altered proguanil absorption. The clinical relevance of all these findings is still unclear, although the implication is that decreased cycloguanil levels may lead to inadequate malaria prophylaxis. However, a subsequent clinical study reported that subjects who were lacking or had low levels of CYP2C19 (and who therefore had relatively low cycloguanil levels) did not have an increased risk of failure of proguanil prophylaxis.[4] Similarly, treatment of malaria with proguanil was as effective in 62 patients who were lacking or had low levels of CYP2C19 as in 33 patients with normal levels of this isoenzyme, independent of cycloguanil levels.[5] This suggests that any interaction with omeprazole or cimetidine via this mechanism would be unlikely to be clinically relevant, and therefore dosage adjustments would not be expected to be necessary in patients given proguanil with cimetidine or omeprazole.

1. Kolawole JA, Mustapha A, Abdul-Aguye I, Ochekpe N, Taylor RB. Effects of cimetidine on the pharmacokinetics of proguanil in healthy subjects and in peptic ulcer patients. *J Pharm Biomed Anal* (1999) 20, 737–43.
2. Somogyi AA, Reinhard HA, Bochner F. Effects of omeprazole and cimetidine on the urinary metabolic ratio of proguanil in healthy volunteers. *Eur J Clin Pharmacol* (1996) 50, 417–19.
3. Funck-Bretano C, Becquemont L, Lenevu A, Roux A, Jaillon P, Beaune P. Inhibition by omeprazole of proguanil metabolism: mechanism of the interaction *in vitro* and prediction of *in vivo* results from the *in vitro* experiments. *J Pharmacol Exp Ther* (1997) 280, 730–8.
4. Mberu EK, Wansor T, Sato H, Nishikawa Y, Watkins WM. Japanese poor metabolizers of proguanil do not have an increased risk of malaria chemoprophylaxis breakthrough. Trans R Soc Trop Med Hyg. 1995 Nov-Dec;89(6):658–9.
5. Kaneko A, Bergqvist Y, Takechi M, Kalkoa M, Kaneko O, Kobayakawa T, Ishizaki T, Bjorkman A. Intrinsic efficacy of proguanil against falciparum and vivax malaria independent of the metabolite cycloguanil. *J Infect Dis* (1999) 179; 974–9.

Proguanil + Fluvoxamine

The conversion of proguanil to its active metabolite is markedly inhibited by fluvoxamine in patients who have normal levels of CYP2C19. However, there is some evidence this may not be of any clinical relevance.

Clinical evidence

Twelve healthy subjects, 6 of whom had normal levels of CYP2C19 and 6 of whom were lacking or deficient in CYP2C19, were given proguanil 200 mg daily for 8 days, followed by fluvoxamine 100 mg for 8 days, with a single 200-mg dose of proguanil on day 6. In the subjects with normal CYP2C19 levels it was found that fluvoxamine reduced the total clearance of proguanil by about 40%. The partial clearance of proguanil via its two metabolites was also reduced, by 85% for cycloguanil, and by 89% for 4-chlorophenylbiguanide. The concentrations of these two metabolites in the plasma were hardly detectable while fluvoxamine was being taken. No pharmacokinetic interaction occurred in any of the subjects lacking or deficient in CYP2C19.[1]

Mechanism

Proguanil, which is thought to be a prodrug, is metabolised to its active metabolite, cycloguanil, by the cytochrome P450 isoenzyme CYP2C19. This isoenzyme is inhibited by fluvoxamine, which prevents proguanil from being activated.[2]

Importance and management

Information appears to be limited to the studies cited, the purpose of which was to confirm that fluvoxamine is an inhibitor of CYP2C19. However, they also demonstrate that proguanil, which is a prodrug, will not be effectively converted into its active form in patients who have normal levels of CYP2C19 (extensive metabolisers) if fluvoxamine is also being taken, making them effectively poor metabolisers (i.e. like those subjects lacking or deficient in CYP2C19). There are as yet no reports of treatment failures due to this interaction, but if the activity of proguanil is virtually abolished by fluvoxamine, as the authors suggest,[2] then proguanil would also be expected to be ineffective in the proportion of the population that are poor metabolisers. However, a subsequent clinical study reported that subjects who were poor metabolisers of proguanil did not have an increased risk of failure of proguanil prophylaxis.[3] Similarly, treatment of malaria with proguanil was as effective in 62 patients who were CYP2C19 poor metabolisers as in 33 patients who were extensive metabolisers, independent of cycloguanil levels.[4] This suggests any interaction with fluvoxamine may not be clinically relevant.

1. Jeppesen U, Rasmussen BB, Brøsen K. Fluvoxamine inhibits the CYP2C19-catalyzed bioactivation of chloroguanide. *Clin Pharmacol Ther* (1997) 62, 279–86.
2. Rasmussen BB, Nielsen TL, Brøsen K. Fluvoxamine inhibits the CYP2C19-catalysed metabolism of proguanil in vitro. *Eur J Clin Pharmacol* (1998) 54, 735–40.
3. Mberu EK, Wansor T, Sato H, Nishikawa Y, Watkins WM. Japanese poor metabolizers of proguanil do not have an increased risk of malaria chemoprophylaxis breakthrough. *Trans R Soc Trop Med Hyg* (1995) 89, 658–9.
4. Kaneko A, Bergqvist Y, Takechi M, Kalkoa M, Kaneko O, Kobayakawa T, Ishizaki T, Bjorkman A. Intrinsic efficacy of proguanil against falciparum and vivax malaria independent of the metabolite cycloguanil. *J Infect Dis* (1999) 179; 974–9.

Pyrantel + Piperazine

Piperazine is expected to oppose the anthelmintic actions of pyrantel.

Clinical evidence, mechanism, importance and management

Pyrantel acts as an anthelmintic because it depolarises the neuromuscular junctions of some intestinal nematodes causing the worms to contract. This paralyses the worms so that they are dislodged by peristalsis and expelled in the faeces. Piperazine also paralyses nematodes but it does so by causing hyperpolarisation of the neuromuscular junctions. These two pharmacological actions oppose one another, as was shown in two *in vitro* pharmacological studies. Strips of whole *Ascaris lumbricoides,* which contracted when exposed to pyrantel, failed to do so when also exposed to piperazine.[1] Parallel electrophysiological studies using *Ascaris* cells confirmed that the depolarisation due to pyrantel (which causes the paralysis) was opposed by piperazine.[1]

In practical terms this means that piperazine does not add to the anthelmintic effect of pyrantel on *Ascaris* as might be expected, but opposes it. For this reason it is recommended that concurrent use should be avoided, but direct clinical evidence confirming that combined use is ineffective seems to be lacking.

It seems reasonable to extrapolate the results of these studies on *Ascaris lumbricoides* (roundworm) to the other gastrointestinal parasites for which pyrantel is used, i.e. *Enterobius vermicularis* (threadworm or pinworm), *Ancylostoma duodenale*, *Necator americanus* (hookworm) and *Trichostrongylus* spp. However, this does not appear to have been studied.

1. Aubry ML, Cowell P, Davey MJ, Shevde S. Aspects of the pharmacology of a new anthelmintic: pyrantel. *Br J Pharmacol* (1970) 38, 332–44.

Pyrimethamine ± Sulfadoxine + Artemisinin derivatives

Artemether raises pyrimethamine plasma levels, but this does not appear to cause an increase in adverse effects. Artesunate does not appear to affect the pharmacokinetics of pyrimethamine or sulfadoxine.

Clinical evidence, mechanism, importance and management

(a) Artemether

In a crossover study, 8 healthy subjects were given a single-dose of either artemether 300 mg, pyrimethamine 100 mg, or both drugs together. Although there were large inter-individual variations in the pharmacokinetics of pyrimethamine, its maximum plasma level was raised by 44%. As there was no corresponding increase in adverse effects the authors suggest that the interaction may be of benefit.[1] More study is warranted to confirm this result.

(b) Artesunate

A study in 16 healthy subjects found that artesunate (200 mg on day 1 then 100 mg daily for 4 days) had no significant effects on the pharmacokinetics of pyrimethamine/sulfadoxine 75 mg/1500 mg taken on day 1. However, the pharmacokinetics of artesunate were not investigated in this study.[2] No particular dose adjustments of pyrimethamine/sulfadoxine appear to be required if artesunate is also given. Note that artesunate combined with pyrimethamine/sulfadoxine is one of the artemisinin-based combinations recommended by the WHO for the treatment of malaria.[3]

1. Tan-ariya P, Na-Bangchang K, Ubalee R, Thanavibul A, Thipawangkosol P, Karbwang J. Pharmacokinetic interaction or artemether and pyrimethamine in healthy male Thais. *Southeast Asian J Trop Med Public Health* (1998) 29, 18–23.
2. Minzi OMS, Gupta A, Haule AF, Kagashe GAB, Massele AY, Gustafsson LL. Lack of impact of artesunate on the disposition pharmacokinetics of sulfadoxine/pyrimethamine when the two drugs are concomitantly administered. *Eur J Clin Pharmacol* (2007) 63, 457–62.
3. World Health Organization. Guidelines for the treatment of malaria 2006. Available at: http://www.who.int/malaria/docs/TreatmentGuidelines2006.pdf (accessed 29/01/10).

Pyrimethamine + Co-trimoxazole or Sulfonamides

Serious pancytopenia and megaloblastic anaemia have occasionally occurred in patients given pyrimethamine with either co-trimoxazole or other sulfonamides.

Clinical evidence

A woman taking pyrimethamine 50 mg weekly as malaria prophylaxis, developed petechial haemorrhages and widespread bruising within 10 days of starting to take co-trimoxazole (trimethoprim 320 mg with sulfamethoxazole 800 mg) daily for a urinary-tract infection. She was found to have gross megaloblastic changes and pancytopenia in addition to being obviously pale and ill. After withdrawal of the two drugs she responded rapidly to hydroxocobalamin and folic acid. She was subsequently given chloroquine for malaria prophylaxis.[1]

Similar cases have been described in other patients taking pyrimethamine with co-trimoxazole,[2-4] **sulfafurazole (sulfisoxazole)**,[5] or other sulfonamides.[6]

Mechanism

Uncertain, but a reasonable surmise can be made. Pyrimethamine and **trimethoprim** are both **folate antagonists** and both selectively inhibit the actions of the enzyme dihydrofolate reductase, which leads to the eventual synthesis of the nucleic acids needed for the production of new cells. This may result in folate deficiency and the development of megaloblastic anaemia. The sulfonamides inhibit another part of the same synthetic chain. The adverse reactions seen would seem to reflect a gross reduction of the normal folate metabolism caused by the combined actions of both

drugs. Megaloblastic anaemia and pancytopenia are among the adverse effects of both pyrimethamine and, more rarely, co-trimoxazole.

Importance and management

Information seems to be limited to the reports cited, but the interaction appears to be established. Its incidence is unknown. Pyrimethamine is usually given with a sulfonamide for toxoplasmosis (sulfadiazine) and malaria (sulfadoxine). Caution should be used in prescribing these combinations, especially in the presence of other drugs, such as 'folate antagonists', (below), or disease states that may predispose to folate deficiency. Note that the manufacturer of sulfadoxine/pyrimethamine (*Fansidar*), which is indicated for the prophylaxis and treatment of malaria, recommends that with the concurrent use of folate antagonists, such as other sulfonamides, trimethoprim, co-trimoxazole and some antiepileptics, should be avoided.[7] When high-dose pyrimethamine is used for the treatment of toxoplasmosis, the manufacturers recommend that all patients should receive a folate supplement, preferably calcium folinate, to reduce the risk of bone marrow depression.[8,9]

1. Fleming AF, Warrell DA, Dickmeiss H. Co-trimoxazole and the blood. *Lancet* (1974) ii, 284–5.
2. Ansdell VE, Wright SG, Hutchinson DBA. Megaloblastic anaemia associated with combined pyrimethamine and co-trimoxazole administration. *Lancet* (1976) ii, 1257.
3. Malfatti S, Piccini A. Anemia megaloblastica pancitopenica in corso di trattamento con pirimetamina, trimethoprim e sulfametossazolo. *Haematologica* (1976) 61, 349–57.
4. Borgstein A, Tozer RA. Infectious mononucleosis and megaloblastic anaemia associated with Daraprim and Bactrim. *Cent Afr J Med* (1974) 20, 185.
5. Waxman S, Herbert V. Mechanism of pyrimethamine-induced megaloblastosis in human bone marrow. *N Engl J Med* (1969) 280, 1316–19.
6. Weißbach G. Auswirkungen kombinierter Behandlung der kindlichen Toxoplasmose mit Pyrimethamin (Daraprim) und Sulfonamiden auf Blut und Knochenmark. *Z Arztl Fortbild (Berl)* (1965) 59, 10–22.
7. Fansidar (Sulfadoxine/Pyrimethamine). Roche Pharmaceuticals. US Prescribing information, August 2004.
8. Daraprim (Pyrimethamine). GlaxoSmithKline UK. UK Summary of product characteristics, December 2005.
9. Daraprim (Pyrimethamine). GlaxoSmithKline. US Prescribing information, March 2003.

Pyrimethamine ± Sulfonamides + Drugs that affect folate metabolism

Serious pancytopenia and megaloblastic anaemia may occur in patients given pyrimethamine and/or sulfonamides with other drugs that inhibit folate metabolism.

Clinical evidence, mechanism, importance and management

Pyrimethamine is known to inhibit folate metabolism, which is associated with a risk of adverse effects (in particular anaemias and pancytopenia). Pyrimethamine is usually given with a sulfonamide for toxoplasmosis (sulfadiazine) and malaria (sulfadoxine), which is known to increase the risk of additive haematological toxicity even further. The manufacturer of sulfadoxine/pyrimethamine (*Fansidar*), recommends that the concurrent use of folate antagonists (they name other sulfonamides, trimethoprim and some antiepileptics) should be avoided.[1] This seems a prudent precaution, as adverse haematological effects have been seen with the use of pyrimethamine and 'sulfonamides', (p.268), and folate deficiency is a known adverse effect of a number of 'antiepileptics', (p.596). Other drugs known to be folate antagonists include methotrexate and pemetrexed, but note that these drugs are often given with folate supplements to limit their toxicity. If the concurrent use of pyrimethamine and a drug that inhibits folate metabolism cannot be avoided it would seem prudent to consider the use of a folate supplement, preferably folinic acid.

1. Fansidar (Sulfadoxine/Pyrimethamine). Roche Pharmaceuticals. US Prescribing information, August 2004.

Pyrimethamine ± Sulfadoxine + Zidovudine

Pyrimethamine does not appear to alter zidovudine pharmacokinetics, and zidovudine does not appear to alter the prophylactic efficacy of pyrimethamine/ sulfadoxine for toxoplasmosis. However, the combination of pyrimethamine and zidovudine may increase the risk of myelosuppression.

Clinical evidence, mechanism, importance and management

The addition of pyrimethamine (200 mg loading dose then 50 mg daily) and folinic acid 10 mg daily to zidovudine had no effect on zidovudine pharmacokinetics, based on data from 10 HIV-positive patients for whom zidovudine pharmacokinetics were available before and after starting pyrimethamine. Of 26 patients receiving the combination, 5 developed leucopenia and one discontinued treatment because of anaemia.[1]

A study in patients with AIDS found that zidovudine 250 mg four times daily did not adversely affect the prevention of toxoplasma encephalitis with pyrimethamine/sulfadoxine (*Fansidar*), one tablet twice weekly for up to 8 months.[2] *In vitro* and *animal* data have shown that the combination of zidovudine and pyrimethamine caused synergistic decreases in lymphocyte and neutrophil numbers.[3]

The manufacturers of pyrimethamine note that the concurrent use of zidovudine may increase the risk of bone marrow depression.[4,5] They say that if signs of folate deficiency develop, then pyrimethamine should be discontinued and folinic acid given. Note that the prophylactic use of a folate supplement, preferably folinic acid, is recommended for all patients with toxoplasmosis taking high-dose pyrimethamine, to reduce the risk of bone marrow suppression.[4,5]

1. Jacobson JM, Davidian M, Rainey PM, Hafner R, Raasch RH, Luft BJ. Pyrimethamine pharmacokinetics in human immunodeficiency virus-positive patients seropositive for *Toxoplasma gondii*. *Antimicrob Agents Chemother* (1996) 40, 1360–5.
2. Eljaschewitsch J, Schürmann D, Pohle HD, Ruf B. Zidovudine does not antagonize Fansidar in preventing toxoplasma encephalitis in HIV infected patients. 7th International Conference on AIDS; Science Challenging AIDS, Florence, Italy, 1991. Abstract W.B.2334.
3. Freund YR, Dabbs J, Creek MR, Phillips SJ, Tyson CA, MacGregor JT. Synergistic bone marrow toxicity of pyrimethamine and zidovudine in murine *in vivo* and *in vitro* models: mechanism of toxicity. *Toxicol Appl Pharmacol* (2002) 181, 16–26.
4. Daraprim (Pyrimethamine). GlaxoSmithKline UK. UK Summary of product characteristics, December 2005.
5. Daraprim (Pyrimethamine). GlaxoSmithKline. US Prescribing information, March 2003.

Quinine + Artemether/Lumefantrine

No clinically significant pharmacokinetic interaction appears to occur between quinine and co-artemether. Quinine-induced QTc prolongation may be enhanced by artemether.

Clinical evidence, mechanism, importance and management

In a placebo-controlled study in healthy subjects, 6 doses of artemether/lumefantrine 80/480 mg were given to 14 subjects, over a period of 60 hours, followed 2 hours after the last dose by intravenous quinine 10 mg/kg (to a maximum of 600 mg) over 2 hours. Another two groups, each containing 14 subjects, received quinine or artemether/lumefantrine, with placebo. The pharmacokinetics of lumefantrine and quinine were unaffected by combined use but the AUC and plasma levels of artemether and its active metabolite dihydroartemisinin appeared to be lower when artemether/lumefantrine was given with quinine. However, the levels of artemether before quinine use in this group were also lower, and this reduction in artemether levels in the presence of quinine was not considered clinically significant. The transient prolongation of the QTc interval noted with quinine (average and peak increases of 3 and 6 milliseconds, respectively) was slightly greater when quinine was given after artemether/lumefantrine (average and peak increases 7 milliseconds and 15 milliseconds, respectively).[1] Both quinine and artemether are known to prolong the QT interval. In general, it is advised that the concurrent use of drugs that prolong the QT interval should be avoided (see also 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290). However, the authors of this study considered that the modest increased risk of QTc prolongation was outweighed by the potential benefit of the combined treatment in complicated or multidrug-resistant falciparum malaria.[1] If the combination is used, close cardiac monitoring is recommended.[2]

1. Lefèvre G, Carpenter P, Souppart C, Schmidli H, Martin JM, Lane A, Ward C, Amakye D. Interaction trial between artemether-lumefantrine (Riamet®) and quinine in healthy subjects. *J Clin Pharmacol* (2002) 42, 1147–58.
2. Riamet (Artemether/Lumefantrine). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, October 2007.

Quinine + Colestyramine

A single-dose study suggests that colestyramine may not alter the pharmacokinetics of quinine.

Clinical evidence, mechanism, importance and management

In a study in 8 healthy subjects, colestyramine 8 g did not alter the pharmacokinetics of quinine 600 mg. The authors warn that this lack of interaction may have been because only single doses were used, and suggest continuing to separate the administration of the two drugs until a lack of interaction is demonstrated in a multiple dose study.[1] It is usually recommended that other drugs are taken 1 hour before or 4 to 6 hours after colestyramine.

1. Ridtitid W, Wongnawa M, Kleekaew A, Mahatthanatrakul W, Sunbhanich M. Cholestyramine does not significantly decrease the bioavailability of quinine in healthy volunteers. *Asia Pac J Pharmacol* (1998) 13, 123–7.

Quinine + Fluvoxamine

Fluvoxamine has no effect on the pharmacokinetics of quinine.

Clinical evidence, mechanism, importance and management

In a study in healthy subjects, fluvoxamine 25 mg was given both 12 hours and 1 hour before a single 500-mg dose of quinine hydrochloride, followed by a further 4 doses of fluvoxamine, given every 12 hours.[1] Fluvoxamine had no effect on the apparent oral clearance of quinine and caused a minor 6% increase in the AUC of 3-hydroxyquinine, with no effect on the AUC of various other metabolites.[1,2]

Fluvoxamine is a known inhibitor of the cytochrome P450 isoenzymes CYP1A2 and to some extent CYP2C19, and it appears that this has little effect on the pharmacokinetics of quinine. No dose adjustments are necessary on concurrent use.

1. Mirghani RA, Helllgren U, Westerberg PA, Ericsson O, Bertilsson L, Gustafsson LL. The roles of cytochrome P450 3A4 and 1A2 in the 3-hydroxylation of quinine in vivo. *Clin Pharmacol Ther* (1999) 66, 454–60.
2. Mirghani RA, Hellgren U, Bertilsson L, Gustafsson LL, Ericsson Ö. Metabolism and elimination of quinine in healthy volunteers. *Eur J Clin Pharmacol* (2003) 59, 423–7.

Quinine + Food

A study in 7 healthy subjects found that neither a low nor a high-salt diet affected the pharmacokinetics of a single 600-mg dose of quinine sulfate.[1]

1. Newton P, Simpson A, Wanwimolruk S, Maliakal P, Villegas L, Kuypers D, White NJ. Oral quinine pharmacokinetics and dietary salt intake. *Eur J Clin Pharmacol* (2001) 57, 111–13.

Quinine + Grapefruit juice

Grapefruit juice had no effect on the pharmacokinetics of quinine in healthy subjects. An isolated case of torsade de pointes has been reported following the excessive intake of grapefruit juice and quinine-containing tonic water in a patient with a history of long QT syndrome.

Clinical evidence, mechanism, importance and management

In a study in 10 healthy subjects, 200 mL of full-strength grapefruit juice, half-strength grapefruit juice, or orange juice was given twice daily for 11 doses with a single 600-mg dose of quinine sulfate, given on day 6 with the last dose of fruit juice. There were no significant differences in the pharmacokinetics of quinine between the three treatments, although the maximum level of the 3-hydroxymetabolite was slightly reduced (by 19%) with full-strength grapefruit juice compared with orange juice or half-strength grapefruit juice.[1] An isolated report describes a diabetic patient with a history of long QT syndrome who was found to have torsade de pointes arrhythmia after admission to hospital with polydipsia. It was discovered that because of the polydipsia, she had been drinking excessive quantities of grapefruit juice and quinine-containing tonic water. Two days after discontinuing these drinks, the torsade de pointes disappeared.[2]

Grapefruit juice is a known inhibitor of intestinal cytochrome P450 isoenzyme CYP3A4, and it appears that this has little effect on the pharmacokinetics of quinine, in healthy human subjects. It would seem that, in general, patients taking quinine may safely drink grapefruit juice if they wish.[1] The case report introduces an element of caution, but it should be noted that its clinical relevance is unclear because the patient did not take quinine without grapefruit juice, and so the arrhythmia may have been caused by the use of quinine in a patient with long QT syndrome, and not an interaction.

1. Ho PC, Chalcroft SC, Coville PF, Wanwimolruk S. Grapefruit juice has no effect on quinine pharmacokinetics. *Eur J Clin Pharmacol* (1999) 55, 393–8.
2. Hermans K, Stockman D, Van den Branden F. Grapefruit and tonic: A deadly combination in a patient with the long QT syndrome. *Am J Med* (2003) 114, 511–12.

Quinine + H_2-receptor antagonists

The clearance of quinine is reduced by cimetidine, but not ranitidine.

Clinical evidence, mechanism, importance and management

In a study in 6 healthy subjects **cimetidine** 200 mg three times daily and 400 mg at night for one week reduced the clearance of quinine by 27%, increased its half-life from 7.6 to 11.3 hours, and increased its AUC by 42%. Peak quinine levels were unchanged. No interaction was seen when **cimetidine** was replaced by **ranitidine** 150 mg twice daily.[1] The probable reason for this effect is that **cimetidine** (a recognised enzyme inhibitor) reduces the hepatic metabolism of quinine by the cytochrome P450 isoenzyme CYP3A4. **Ranitidine** does not inhibit hepatic enzymes and therefore does not interact. It therefore seems likely that other H_2-receptor antagonists (that also lack enzyme-inhibitory effects) will not interact, although this needs confirmation.

The clinical importance of the modest interaction between cimetidine and quinine is uncertain, but prescribers should be alert for any evidence of quinine adverse effects if cimetidine is also given.

1. Wanwimolruk S, Sunbhanich M, Pongmarutai M and Patamasucon P. Effects of cimetidine and ranitidine on the pharmacokinetics of quinine. *Br J Clin Pharmacol* (1986) 22, 346–50.

Quinine + Isoniazid

A study in 9 healthy subjects found that the clearance of a single 600-mg dose of quinine sulfate was not significantly affected by pretreatment with isoniazid 300 mg daily for one week.[1] No additional precautions therefore seem necessary if quinine is given with isoniazid; however, bear in mind that isoniazid is usually used in combination with 'rifampicin (rifampin)', (p.271), which may reduce the efficacy of quinine.

1. Wanwimolruk S, Kang W, Coville PF, Viriyayudhakorn S, Thitiarchakul S. Marked enhancement by rifampicin and lack of effect of isoniazid on the elimination of quinine in man. *Br J Clin Pharmacol* (1995) 40, 87–91.

Quinine + Ketoconazole

Ketoconazole modestly decreases the clearance of quinine.

Clinical evidence, mechanism, importance and management

In a study in healthy subjects ketoconazole 100 mg twice daily was given for 3 days with a single 500-mg dose of quinine hydrochloride one hour after the second dose of ketoconazole. Ketoconazole decreased the apparent oral clearance of quinine by 31% and decreased the AUC of the major metabolite 3-hydroxyquinine by 30%,[1] with increases in the AUCs of various other metabolites.[2]

Ketoconazole inhibits the cytochrome P450 isoenzyme CYP3A4, which is responsible for the metabolism of quinine to its major metabolite 3-hydroxyquinine. CYP3A5 may possibly also play some part.[3] This pharmacokinetic interaction would appear to be established, but of unknown clinical relevance. The modest increase in 3-hydroxyquinine levels seen is probably unlikely to be of much significance.

1. Mirghani RA, Helllgren U, Westerberg PA, Ericsson O, Bertilsson L, Gustafsson LL. The roles of cytochrome P450 3A4 and 1A2 in the 3-hydroxylation of quinine in vivo. *Clin Pharmacol Ther* (1999) 66, 454–60.

2. Mirghani RA, Hellgren U, Bertilsson L, Gustafsson LL, Ericsson Ö. Metabolism and elimination of quinine in healthy volunteers. *Eur J Clin Pharmacol* (2003) 59, 423–7.
3. Allqvist A, Miura J, Bertilsson L, Mirghani RA. Inhibition of CYP3A4 and CYP3A5 catalyzed metabolism of alprazolam and quinine by ketoconazole as racemate and four different enantiomers. *Eur J Clin Pharmacol* (2007) 63, 173–9.

Quinine + Miscellaneous

Urinary alkalinisers can reduce the urinary excretion of quinine in man, and antacids can reduce the absorption of quinine in *animals*.

Clinical evidence, mechanism, importance and management

(a) Antacids

Aluminium/magnesium hydroxide gel reduces the absorption of quinine from the gut of *rats* and reduces quinine blood levels by 50 to 70%.[1] This appears to occur because **aluminium hydroxide** slows gastric emptying, and because **magnesium hydroxide** forms an insoluble precipitate with quinine, both of which reduce quinine absorption. However, there seem to be no clinical reports of a reduction in the therapeutic effectiveness of quinine due to the concurrent use of antacids.

(b) Urinary alkalinisers

The excretion of unchanged quinine is virtually halved (from 17.4% to 8.9%) if the urine is alkalinised. This is because in alkaline urine more of the quinine exists in the non-ionised (lipid soluble) form, which is more easily reabsorbed by the kidney tubules.[2] However, there seem to be no reports of adverse effects arising from changes in excretion due to this interaction, and no special precautions seem to be necessary.

1. Hurwitz A. The effects of antacids on gastrointestinal drug absorption. II. Effect of sulfadiazine and quinine. *J Pharmacol Exp Ther* (1971) 179, 485–9.
2. Haag HB, Larson PS, Schwartz JJ. The effect of urinary pH on the elimination of quinine in man. *J Pharmacol Exp Ther* (1943) 79, 136–9.

Quinine + Rifampicin (Rifampin)

Rifampicin induces the metabolism of quinine, which may result in subtherapeutic quinine levels.

Clinical evidence

A study in 9 healthy subjects found that the clearance of a single 600-mg dose of quinine sulfate was increased more than sixfold by pretreatment with rifampicin 600 mg daily for 2 weeks. The elimination half-life of quinine was decreased from about 11 hours to 5.5 hours.[1] In another study, in patients with uncomplicated falciparum malaria, quinine sulfate 10 mg/kg three times daily was given either alone (30 patients) or with rifampicin 15 mg/kg daily (29 patients) for 7 days. Peak plasma levels of quinine during monotherapy were attained within 2 days of treatment and remained within the therapeutic range for the 7-day treatment period. Levels of the main metabolite of quinine, 3-hydroxyquinine, followed a similar pattern. In patients taking quinine with rifampicin, quinine was more extensively metabolised and, after the second day of treatment, quinine levels were sharply reduced to below therapeutic levels. Although patients who received rifampicin with quinine had shorter parasite clearance times than those who received quinine alone (suggesting rifampicin may enhance the antimalarial activity of quinine) recrudescence rates (the reappearance of the disease after a period of inactivity) were 5 times higher suggesting increased resistance to quinine treatment.[2]

A report describes a patient with myotonia, controlled with quinine, whose symptoms worsened within 3 weeks of starting to take rifampicin for the treatment of tuberculosis. Peak quinine levels were found to be low, but rose again when the rifampicin was stopped. Control of the myotonia was regained 6 weeks later.[3]

Mechanism

Acute malaria reduces the metabolic clearance of quinine (by a reduction in hepatic mixed function oxidase activity, mainly the cytochrome P450 isoenzyme CYP3A4) and recovery from malaria is associated with a sharp decline in quinine levels. Rifampicin induces the cytochrome P450 isoenzymes and this probably antagonised their inhibition by acute malaria, resulting in increased quinine metabolism.

Importance and management

Although there is limited evidence, this interaction would appear to of clinical importance. The authors of one of the studies[2] suggest that rifampicin should not be given with quinine for the treatment of malaria. Increased quinine doses should be considered if the concurrent use of rifampicin is considered essential.

1. Wanwimolruk S, Kang W, Coville PF, Viriyayudhakorn S, Thitiarchakul S. Marked enhancement by rifampicin and lack of effect of isoniazid on the elimination of quinine in man. *Br J Clin Pharmacol* (1995) 40, 87–91.
2. Pukrittayakamee S, Prakongpan S, Wanwimolruk S, Clemens R, Looareesuwan S, White NJ. Adverse effect of rifampin on quinine efficacy in uncomplicated falciparum malaria. *Antimicrob Agents Chemother* (2003) 47, 1509–13.
3. Osborn JE, Pettit MJ, Graham P. Interaction between rifampicin and quinine: case report. *Pharm J* (1989) 243, 704.

Quinine + Tetracyclines

Doxycycline does not appear to alter the pharmacokinetics of quinine. Tetracycline increases quinine levels leading to improved efficacy in malaria.

Clinical evidence, mechanism, importance and management

(a) Doxycycline

In a study in 13 patients with acute falciparum malaria, the addition of intravenous doxycycline to intravenous quinine did not affect the pharmacokinetics of quinine, when compared with 13 patients taking quinine alone.[1] In contrast, *in vitro*, doxycycline appears to be a potent inhibitor of quinine metabolism.[2] However, given the above evidence from their use in patients, no special precautions would seem to be necessary on concurrent use, and the combination is one of the treatments recommended in the WHO guidelines for the treatment of malaria.[3]

(b) Tetracycline

A study in patients with acute falciparum malaria found that the levels of quinine 600 mg every 8 hours were about doubled by tetracycline 250 mg every 6 hours, when compared with quinine alone. Quinine levels were above the MIC for malaria with the combination but not with quinine alone. Two of 8 patients treated with quinine alone had malaria recrudescence (the reappearance of the disease after a period of inactivity) compared with none of 8 patients receiving the combination.[4] *In vitro* tetracycline is also a potent inhibitor of quinine metabolism.[2] The authors considered that this pharmacokinetic interaction might be part of the explanation why the combination has been found to be more effective than quinine alone.[4] Quinine with tetracycline is one of the combinations recommended by WHO for the treatment of malaria.[3]

1. Couet W, Laroche R, Floch JJ, Istin B, Fourtillan JB, Sauniere JF. Pharmacokinetics of quinine and doxycycline in patients with acute falciparum malaria: a study in Africa. *Ther Drug Monit* (1991) 13, 496–501.
2. Zhao X-J, Ishizaki T. A further interaction study of quinine with clinically important drugs by human liver microsomes: determinations of inhibition constant (K_i) and type of inhibition. *Eur J Drug Metab Pharmacokinet* (1999) 24, 272–8.
3. World Health Organization. Guidelines for the treatment of malaria 2006. Available at: http://www.who.int/malaria/docs/TreatmentGuidelines2006.pdf (accessed 29/01/10).
4. Karbwang J, Molunto P, Bunnag D, Harinasuta T. Plasma quinine levels in patients with falciparum malaria given alone or in combination with tetracycline with or without primaquine. *Southeast Asian J Trop Med Public Health* (1991) 22, 72–6.

Quinine + Tobacco

Quinine pharmacokinetics and efficacy were unchanged by smoking in one study. In contrast, in another study, otherwise healthy smokers appeared to clear quinine from the body much more quickly than non-smokers; however, quinine metabolism is reduced in patients with falciparum malaria, which may negate this effect.

Clinical evidence

A comparative study found that in 10 smokers (averaging 17 cigarettes daily) the AUC of a single 600-mg dose of quinine sulfate was reduced by 44%, the clearance was increased by 77% and the half-life was shortened (from 12 to 7.5 hours), when compared with 10 non-smokers.[1] In contrast, in a study in patients with uncomplicated falciparum malaria taking quinine sulfate 10 mg/kg three times daily for 7 days, there was no significant

difference in fever clearance time, parasite clearance time, and cure rate between 10 regular smokers and 12 non-smokers. In addition pharmacokinetic parameters did not differ significantly between the smokers and non-smokers.[2]

Mechanism

Tobacco smoke contains polycyclic aromatic compounds and other substances, which are potent inducers of the liver enzymes that metabolise quinine. It is not yet clear which cytochrome P450 isoenzymes are affected. Smoking induces CYP1A, but the formation of the major metabolite of quinine, 3-hydroxyquinine, is catalysed by CYP3A, which suggests that other metabolic pathways of quinine are affected by smoking.[3]

Importance and management

Information seems to be limited but the pharmacokinetic interaction would appear to be established in healthy subjects. However, the clinical study in patients with falciparum malaria suggests that any pharmacokinetic differences are more limited probably due to the additional effect the disease has on quinine metabolism, and that smoking status does not appear to affect the clinical outcome of quinine treatment for malaria. The systemic clearance of quinine in acute falciparum malaria may be reduced by up to two-thirds, when compared with healthy subjects, as malaria reduces hepatic microsomal enzyme activity. The authors say that this reduction in the clearance of quinine outweighs the possible effects of smoking-induced clearance.[2]

1. Wanwimolruk S, Wong SM, Coville PF, Viriyayudhakorn S, Thitiarchakul S. Cigarette smoking enhances the elimination of quinine. *Br J Clin Pharmacol* (1993) 36, 610–14.
2. Pukrittayakamee S, Pitisuttithum P, Zhang H, Jantra A, Wanwimolruk S, White NJ. Effects of cigarette smoking on quinine pharmacokinetics in malaria. *Eur J Clin Pharmacol* (2002) 58, 315–19.
3. Wanwimolruk S, Wong S-M, Zhang H, Coville PF, Walker RJ. Metabolism of quinine in man: identification of a major metabolite, and effects of smoking and rifampicin pretreatment. *J Pharm Pharmacol* (1995) 47, 957–63.

Terbinafine + H_2-receptor antagonists

Although cimetidine modestly increases the AUC of terbinafine no clinically relevant interactions appear to have been reported. Limited evidence suggests that ranitidine does not interact with terbinafine.

Clinical evidence, mechanism, importance and management

In a study in 12 healthy subjects **cimetidine** 400 mg twice daily for 5 days increased the AUC of a single 250-mg dose of terbinafine by 34% and reduced its clearance by 30%.[1] The likely reason is that **cimetidine** (a known enzyme inhibitor) reduces the metabolism of terbinafine by the liver. However, it seems that this modest increase in the serum levels of terbinafine is of little or no clinical relevance. This is supported by a large scale post-marketing survey of patients taking terbinafine that found no interactions were reported in patients also taking **cimetidine** or **ranitidine** (number unknown).[2] The UK manufacturer of terbinafine recommends that the dose of terbinafine may need adjusting (presumably reduced) if drugs that inhibit cytochrome P450 are given,[3] but the evidence available suggests that this will not be necessary with cimetidine. Evidence regarding an interaction with other H_2-receptor antagonists is lacking, but there seems to be no reason to suspect that they will interact.

1. Jensen JC. Pharmacokinetics of Lamisil® in humans. *J Dermatol Treat* (1990) 1 (Suppl 2), 15–18.
2. Hall M, Monka C, Krupp P, O'Sullivan D. Safety of oral terbinafine. Results of a postmarketing surveillance study in 25 884 patients. *Arch Dermatol* (1997) 133, 1213–19.
3. Lamisil Tablets (Terbinafine hydrochloride). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, September 2008.

Terbinafine + Miscellaneous

Terbinafine may raise the levels of drugs that are substrates of CYP2D6.

Clinical evidence, mechanism, importance and management

In vitro studies suggest that terbinafine is an inhibitor of the cytochrome P450 isoenzyme CYP2D6. It may therefore be expected to increase the plasma levels of other drugs that are substrates of this enzyme. The manufacturers specifically mention tricyclic antidepressants,[1] SSRIs,[1] **beta blockers**,[1,2] **antiarrhythmics** (including class Ia,[1] Ib,[1] and Ic[1,2]) and **MAO-B inhibitors**.[1,2] Of these predictions the tricyclics have been seen to interact markedly (see 'Tricyclic antidepressants + Terbinafine', p.1515) and the SSRI paroxetine has been seen to interact modestly (see 'SSRIs + Terbinafine', p.1493). Note that only some beta blockers would be expected to interact, as they are not all substrates for CYP2D6 (see 'Table 22.1', (p.995)), and only some antiarrhythmics would be expected to interact (namely **flecainide**, **mexiletine** and **propafenone**, which are known clinically relevant CYP2D6 substrates). There appear to be no reported interactions between **selegiline** or **rasagiline** and CYP2D6 inhibitors, so the clinical relevance of this prediction is unclear.

Until more is known it would seem wise to be aware of the possibility of an increase in adverse effects if any of these drugs is given with terbinafine and consider a dose reduction if necessary. See 'Table 1.3', (p.6), for a list of drugs that are known to be clinically relevant substrates of CYP2D6.

1. Lamisil Tablets (Terbinafine hydrochloride). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, September 2008.
2. Lamisil (Terbinafine hydrochloride) Novartis Pharmaceuticals Corp. US Prescribing information, November 2005.

Terbinafine + Rifampicin (Rifampin)

The plasma levels of terbinafine are reduced by rifampicin.

Clinical evidence, mechanism, importance and management

A study in 12 healthy subjects found that rifampicin 600 mg daily for 6 days halved the AUC of terbinafine and roughly doubled its clearance.[1] Rifampicin is a potent enzyme inducer, which increases the metabolism of many drugs. Be alert, therefore, for the need to increase the dosage of terbinafine if rifampicin is given.

1. Jensen JC. Pharmacokinetics of Lamisil® in humans. *J Dermatol Treat* (1990) 1 (Suppl 2), 15–18.

9

Antiarrhythmics

This section is mainly concerned with the class I antiarrhythmics, which also possess some local anaesthetic properties, and with class III antiarrhythmics. Antiarrhythmics that fall into other classes are dealt with under 'beta blockers', (p.995), 'digitalis glycosides', (p.1077), and 'calcium-channel blockers', (p.1025). Some antiarrhythmics that do not fit into the Vaughan Williams classification (see 'Table 9.1', (below)) are also included in this section (e.g. adenosine). Interactions in which the antiarrhythmic drug is the affecting substance, rather than the drug whose activity is altered, are dealt with elsewhere.

Predicting interactions between two antiarrhythmics

It is difficult to know exactly what is likely to happen if two antiarrhythmics are used together. The hope is always that a combination will work better than just one drug, and many studies have confirmed that hope, but sometimes the combinations are unsafe. Predicting unsafe combinations is difficult, but there are some very broad general rules that can be applied if the general pharmacology of the drugs is understood.

If drugs with similar effects are used together, whether they act on the myocardium itself or on the conducting tissues, the total effect is likely to be increased (additive). The classification of the antiarrhythmics in 'Table 9.1', (below) helps to predict what is likely to happen, but remember that the classification is not rigid, and therefore drugs in one class can share some characteristics with others. The following sections deal with some examples.

(a) Combinations of antiarrhythmics from the same class

The drugs in class Ia can prolong the QT interval; combining drugs from this class would be expected to have an increased effect on the QT interval. This prolongation carries the risk of causing torsade de pointes arrhythmias (see the monograph, 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290). It would also be expected that the negative inotropic effects of quinidine would be additive with procainamide or any of the other drugs within class Ia. Therefore, for safety, it is sometimes considered best to avoid drugs that fall into the same subclass or only to use them together with caution.

(b) Combinations of antiarrhythmics from different classes

Class III antiarrhythmics such as amiodarone can also prolong the QT interval; they would therefore be expected to interact with drugs in other classes that do the same, namely class Ia drugs (see 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290). Verapamil is a class IV antiarrhythmic, and has negative inotropic effects; it can therefore interact with other drugs with similar effects, such as sotalol, which is a class III antiarrhythmic. For safety, always consider the whole drug profile and take care with any two drugs, from any class, that share a common pharmacological action.

Table 9.1 Antiarrhythmics (modified Vaughan Williams classification)

Class I: Membrane stabilising drugs (a) Ajmaline, Cibenzoline,* Disopyramide, Hydroquinidine, Procainamide, Quinidine (b) Aprindine, Lidocaine, Mexiletine, Tocainide (c) Flecainide, Propafenone Class I, but not easily fitting the above subgroups – Moracizine
Class II: Beta blocker activity Atenolol, Bretylium,† Propranolol
Class III: Inhibitors of depolarisation Amiodarone, Azimilide, Bretylium,† Cibenzoline,* Dofetilide, Dronedarone, Ibutilide, Sotalol
Class IV: Calcium-channel blocker activity Cibenzoline,* Diltiazem, Verapamil
Drugs not fitting into this classification Adenosine

*Cibenzoline has class Ia, and also some class III and IV activity

†Bretylium has class II and III activity

Adenosine + Dipyridamole

Dipyridamole reduces the bolus dose of adenosine necessary to convert supraventricular tachycardia to sinus rhythm by about fourfold. Profound bradycardia occurred in one patient taking dipyridamole when an adenosine infusion was given for myocardial stress testing.

Clinical evidence

(a) Adenosine bolus for supraventricular tachycardia

Adenosine by rapid intravenous bolus (10 to 200 micrograms/kg in stepwise doses) was found to restore sinus rhythm in 10 of 14 episodes of tachycardia in 7 patients with supraventricular tachycardia (SVT). The mean dose required was 8.8 mg, compared with only 1 mg in two patients also taking oral dipyridamole.[1] Another study in 6 patients found that dipyridamole (560 microgram/kg intravenous bolus, followed by a continuous infusion of 5 micrograms/kg/minute) reduced the minimum effective bolus dose of intravenous adenosine required to stop the SVT from 68 micrograms/kg to 17 micrograms/kg in 5 patients. In the other patient, dipyridamole alone stopped the SVT.[2]

Other studies in healthy subjects have clearly shown that dipyridamole reduces the dose of adenosine required to produce an equivalent cardiovascular effect by fourfold[3] or even six- to sixteenfold.[4] A brief report describes a woman with paroxysmal SVT who lost ventricular activity for 18 seconds when given adenosine 6 mg intravenously. She was also taking dipyridamole [dose unstated], which was considered to have contributed to the loss of ventricular function.[5] Another report describes 3 of 4 patients who had heart block of 3, 9 and 21-second duration, respectively, when given adenosine 3 to 6 mg by central venous bolus. The patient with the most profound heart block was also receiving dipyridamole, which was thought to have contributed to the reaction.[6]

(b) Adenosine infusion for myocardial stress testing

A 79-year-old woman taking a combination of low-dose aspirin and extended-release dipyridamole (*Aggrenox*) became profoundly bradycardic (36 bpm), dizzy and almost fainted 2 minutes after the start of an adenosine infusion for radionuclide myocardial imaging. Adenosine was stopped, and she recovered within 2 minutes. The last dose of *Aggrenox* had been taken 12 hours previously.[7] However, note that bradycardia is a known adverse effect of adenosine.[8,9]

Mechanism

Not fully understood. Part of the explanation is that dipyridamole increases plasma levels of endogenous adenosine by inhibiting its uptake into cells.[2,4,10]

Importance and management

An established interaction. Patients will need much less adenosine to treat arrhythmias while taking dipyridamole. It has been suggested that the initial dose of adenosine should be reduced by twofold[5] or fourfold.[2] The UK manufacturers actually advise the avoidance of adenosine in patients taking dipyridamole. If it must be used for supraventricular tachycardia in a patient taking dipyridamole, they recommend that the adenosine dose should be reduced about fourfold.[8]

The UK manufacturers advise the avoidance of adenosine for stress testing in patients taking dipyridamole. If adenosine is considered necessary, they suggest that the dipyridamole should be stopped 24 hours before testing, or the dose of adenosine should be greatly reduced.[9] This may be insufficient for extended-release dipyridamole preparations: the authors of the above report recommend stopping dipyridamole several days before testing.[7] Xanthines, such as intravenous aminophylline, have been used to terminate persistent adverse effects resulting from the use of adenosine infusions in myocardial imaging, see 'Adenosine + Xanthines', below.

1. Watt AH, Bernard MS, Webster J, Passani SL, Stephens MR, Routledge PA. Intravenous adenosine in the treatment of supraventricular tachycardia: a dose-ranging study and interaction with dipyridamole. *Br J Clin Pharmacol* (1986) 21, 227–30.
2. Lerman BB, Wesley RC, Belardinelli L. Electrophysiologic effects of dipyridamole on atrioventricular nodal conduction and supraventricular tachycardia. Role of endogenous adenosine. *Circulation* (1989) 80, 1536–43.
3. Biaggioni I, Onrot J, Hollister AS, Robertson D. Cardiovascular effects of adenosine infusion in man and their modulation by dipyridamole. *Life Sci* (1986) 39, 2229–36.
4. Conradson T-BG, Dixon CMS, Clarke B, Barnes PJ. Cardiovascular effects of infused adenosine in man: potentiation by dipyridamole. *Acta Physiol Scand* (1987) 129, 387–91.
5. Mader TJ. Adenosine: adverse interactions. *Ann Emerg Med* (1992) 21, 453.
6. McCollam PL, Uber WE, Van Bakel AB. Adenosine-related ventricular asystole. *Ann Intern Med* (1993) 118, 315–16.
7. Littmann L, Anderson JD, Monroe MH. Adenosine and Aggrenox: a hazardous combination. *Ann Intern Med* (2002) 137, W1.
8. Adenocor (Adenosine). Sanofi-Aventis. UK Summary of product characteristics, March 2009.
9. Adenoscan (Adenosine). Sanofi-Aventis. UK Summary of product characteristics, May 2008.
10. German DC, Kredich NM, Bjornsson TD. Oral dipyridamole increases plasma adenosine levels in human beings. *Clin Pharmacol Ther* (1989) 45, 80–4.

Adenosine + Nicotine

Nicotine appears to enhance the effects of adenosine, but the clinical relevance of this is unclear.

Clinical evidence, mechanism, importance and management

In 10 healthy subjects, **nicotine chewing gum** 2 mg (approximately equal to one cigarette) increased the circulatory effects of a 70 micrograms/kg per minute infusion of adenosine. The 5.5 bpm increase in heart rate due to nicotine was further increased to 14.9 bpm by adenosine, and the 7 mmHg diastolic blood pressure rise due to nicotine was reduced to 1.1 mmHg by adenosine.[1] In another study, in 7 healthy subjects, **nicotine chewing gum** 2 mg increased chest pain and the duration of AV block when it was given with intravenous bolus doses of adenosine.[2] What this means in practical terms is uncertain, but be aware that the effects of adenosine may be modified to some extent by nicotine-containing products (**tobacco smoking**, **nicotine gum**, etc.).

1. Smits P, Eijsbouts A, Thien T. Nicotine enhances the circulatory effects of adenosine in human beings. *Clin Pharmacol Ther* (1989) 46, 272–8.
2. Sylvén C, Beerman B, Kaijser L, Jonzon B. Nicotine enhances angina pectoris-like chest pain and atrioventricular blockade provoked by intravenous bolus of adenosine in healthy volunteers. *J Cardiovasc Pharmacol* (1990) 16, 962–5.

Adenosine + Xanthines

Caffeine and theophylline can inhibit the effects of adenosine infusions used in conjunction with radionuclide myocardial imaging. Aminophylline has been used to terminate persistent adverse effects of adenosine infusions, but adenosine may still be effective for terminating supraventricular tachycardia in patients taking xanthines.

Clinical evidence

(a) Adenosine bolus for supraventricular tachycardia

It is usually considered that an adenosine bolus for the termination of paroxysmal supraventricular tachycardia will be ineffective in patients taking xanthines. However, one case describes a man taking **theophylline** (serum level 8 nanograms/mL) in whom adenosine 9 mg terminated supraventricular tachycardia. Two previous adenosine doses, one of 3 mg and one of 6 mg had not been effective.[1] Another report found that high adenosine doses, of 400 to 800 micrograms/kg (usual dose 50 to 200 micrograms/kg), were required to revert supraventricular tachycardia in a preterm infant receiving **theophylline**.[2]

(b) Adenosine infusion

Experimental studies in healthy subjects, on the way xanthine drugs possibly interact with adenosine, have found that **caffeine** and **theophylline** reduced the increased heart rate and the changes in blood pressure caused by infusions of adenosine,[3-6] and attenuated adenosine-induced vasodilatation.[7,8] **Theophylline** also attenuated adenosine-induced respiratory effects and chest pain.[5,6] Similarly, an adenosine infusion antagonised the haemodynamic effects of a single dose of **theophylline** in healthy subjects, but did not reduce the metabolic effects (reductions in plasma potassium and magnesium).[5]

Mechanism

Caffeine and theophylline have an antagonistic effect on adenosine receptors.[9] They appear to have opposite effects on the circulatory system: caffeine and theophylline cause vasoconstriction whereas adenosine infusions generally cause vasodilatation.[3] Consequently their concurrent use is likely to result in an interaction.

Importance and management

Adenosine bolus injections for the termination of paroxysmal supraventricular tachycardia may still be effective in patients receiving xanthines. The usual dose schedule should be followed. However, note that adenosine has induced bronchospasm. The US manufacturers[10,11] state that adenosine preparations, whether used for supraventricular tachycardia or myocardial imaging, should be avoided in patients with bronchoconstriction or bronchospasm (e.g. asthma), and used cautiously in those with obstructive pulmonary disease not associated with bronchospasm (e.g. emphysema, bronchitis). The UK manufacturers similarly recommend that the product used for supraventricular tachycardia[12] should be avoided in asthma, and warn that adenosine may precipitate or aggravate bronchospasm. They also contraindicate the use of adenosine for diagnostic imaging[13] in both asthma and other obstructive pulmonary disease associated with bronchospasm. Whether an adenosine bolus can stop theophylline-induced supraventricular tachycardia appears not to have been studied.

The manufacturers of adenosine also state that theophylline, aminophylline and other xanthines should be avoided for 24 hours before using an adenosine infusion in conjunction with radionuclide myocardial imaging, and that xanthine-containing drinks (tea, coffee, chocolate, cola drinks etc.) should be avoided for at least 12 hours before imaging.[13] In a recent study in 70 patients, measurable caffeine serum levels were found in 74% of patients after 12 hours of self-reported abstention from caffeine-containing products. Patients with caffeine serum levels of at least 2.9 mg/L had significantly fewer stress symptoms (chest tightness, chest pain, headache, dyspnoea, nausea, dizziness) than those with lower serum levels. The authors suggest that a 12-hour abstention from caffeine-containing products may be insufficient, and could result in false-negative results.[14] Xanthines, such as intravenous aminophylline, have been used to terminate persistent adverse effects of adenosine infusion given for myocardial imaging.[13]

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Ajmaline + Miscellaneous

An isolated report describes cardiac failure in a patient given ajmaline with lidocaine. Quinidine causes a very considerable increase in ajmaline levels, whereas phenobarbital appears to cause an increase in ajmaline clearance.

Clinical evidence, mechanism, importance and management

(a) Lidocaine

A woman had a marked aggravation of her existing cardiac failure when she was given ajmaline orally and lidocaine intravenously for repeated ventricular tachycardias.[1] The general relevance of this isolated case is uncertain.

(b) Phenobarbital

The clearance of intravenous ajmaline was almost twice as high in 3 patients also taking phenobarbital when compared with 5 patients who were not taking phenobarbital. Therefore the clinical effects of ajmaline would be expected to be diminished in those taking phenobarbital.[2] The clinical relevance of this interaction does not appear to have been established. Nevertheless, it would seem prudent to monitor concurrent use to ensure ajmaline remains effective.

(c) Quinidine

A single-dose study[3] in 4 healthy subjects found that the concurrent use of quinidine 200 mg with ajmaline 50 mg increased the AUC of ajmaline 10- to 30-fold and increased its maximum plasma concentration from 18 nanograms/mL to 141 nanograms/mL. Another single-dose study in 5 healthy subjects found that the metabolism of ajmaline was inhibited by quinidine, possibly because the quinidine becomes competitively bound to the enzymes that metabolise ajmaline.[4] This marked rise in ajmaline levels is likely to increase its adverse effects, and concurrent use should probably be avoided.

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Amiodarone + Anaesthesia

There is some evidence that the presence of amiodarone possibly increases the risk of complications (atropine-resistant bradycardia, hypotension, decreased cardiac output) during general anaesthesia. All of these cases were with fentanyl-based anaesthesia, but other studies have shown no problems with fentanyl-based anaesthesia.

Clinical evidence

(a) Evidence for complications

Several case reports[1-4] and two studies[5,6] suggest that severe intra-operative complications (atropine-resistant bradycardia, myocardial depression, hypotension) may occur in patients receiving amiodarone. One of the studies, a comparative retrospective review of patients (16 receiving amiodarone 300 to 800 mg daily and 30 controls) having operations under anaesthesia (mainly open-heart surgery), found that the incidence of slow nodal rhythm, complete heart block or pacemaker dependency rose from 17% in controls to 66% in amiodarone-treated patients. Intra-aortic balloon pump augmentation (reflecting poor cardiac output) was 50% in the amiodarone group compared with 7% in the control group, and a state of low systemic vascular resistance with normal to high cardiac output occurred in 13% of the amiodarone-treated patients, but not in the control patients. Overall there were 3 fatalities; all of these patients had received amiodarone and had been on cardiopulmonary bypass during surgery. **Fentanyl** was used for all of the patients, often combined with diazepam, and sometimes also **isoflurane**, **enflurane** or **halothane**.[5]

Another study of 37 patients receiving amiodarone (mean dose about 250 mg daily) found no problems in 8 patients undergoing non-cardiac surgery. Of the 29 patients undergoing cardiac surgery, 52% had postoperative arrhythmias and 24% required a pacemaker, which was not considered exceptional for the type of surgery. However, one patient having coronary artery bypass surgery had fatal vasoplegia (a hypotensive syndrome), which was considered to be amiodarone-related. This occurred shortly after he was taken off cardiopulmonary bypass. Anaesthesia in all patients was **fentanyl**-based.[6] It was suggested in one case report that serious hypotension in 2 patients taking amiodarone undergoing surgery may have been further compounded by the presence of an **ACE inhibitor**.[3] For interactions between ACE inhibitors and anaesthetics see 'Anaesthetics, general + ACE inhibitors or Angiotensin II receptor antagonists', p.102.

(b) Evidence for no complications

The preliminary report of a study in 21 patients taking amiodarone (mean dose 538 mg daily) and undergoing defibrillator implantation suggested that haemodynamic changes during surgery were not significantly different from those in matched controls not taking amiodarone.[7] Similarly, another study found no difference in haemodynamic status or pacemaker

dependency between patients taking short-term amiodarone 600 mg daily for one week then 400 mg daily for 2 weeks before surgery and a control group not taking amiodarone, during valve replacement surgery with **thiopental-fentanyl** anaesthesia.[8] In a double-blind study, there was no significant difference in haemodynamic instability during **fentanyl-isoflurane** anaesthesia between patients randomised to receive short-term amiodarone (3.4 g over 5 days or 2.2 g over 24 hours) or placebo before cardiac surgery. In this study, haemodynamic instability was assessed by fluid balance, use of dopamine or other vasopressors, and use of a phosphodiesterase inhibitor or intra-aortic balloon pump.[9]

A case report describes the successful use of epidural anaesthesia with **fentanyl** then **chloroprocaine** during labour and caesarean section in a woman who had been taking amiodarone long-term. The only haemodynamic change of possible note was that the patient had a drop in systemic vascular resistance from high to almost normal levels shortly after receiving **fentanyl** during the first stage of labour, and again when **fentanyl** was given for postoperative pain relief.[10] Another case report describes the successful use of epidural anaesthesia using incremental doses of lidocaine 2% with adrenaline and **fentanyl** 100 micrograms for caesarean section in a woman receiving high-dose amiodarone (1600 mg daily) for fetal supraventricular tachycardia.[11]

Mechanism

In vitro and *in vivo* studies in *animals* suggest that amiodarone has additive cardiodepressant and vasodilator effects with volatile anaesthetics such as halothane, enflurane and isoflurane.[2,12] The manufacturer notes that fentanyl is a substrate for the cytochrome P450 isoenzyme CYP3A4, and that amiodarone might inhibit CYP3A4, thereby increasing the toxicity of fentanyl.[13]

Importance and management

The assessment of this interaction is complicated by the problem of conducting studies in anaesthesia, most being retrospective and using matched controls. The only randomised study used short-term amiodarone to assess its safety in the prevention of post-operative atrial fibrillation, and its findings may not be relevant to patients taking long-term amiodarone.[9] It appears that potentially severe complications may occur in some patients taking amiodarone who undergo general anaesthesia, including bradycardia unresponsive to atropine, hypotension, conduction disturbances, and decreased cardiac output. It has been suggested that anaesthetists should take particular care in patients taking amiodarone who undergo surgery on cardiopulmonary bypass.[14] Amiodarone persists in the body for many weeks, which usually means it cannot be withdrawn before surgery, especially if there are risks in delaying surgery,[6] or the amiodarone is being used for serious arrhythmias.[14] A possible pharmacokinetic interaction exists between fentanyl and amiodarone, which could contribute to the interactions seen, and further study is needed on this.

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13. Cordarone X (Amiodarone hydrochloride). Sanofi-Aventis. UK Summary of product characteristics, March 2009.
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Amiodarone + Beta blockers

The concurrent use of amiodarone and beta blockers can be beneficial; however, hypotension, bradycardia, ventricular fibrillation and asystole have been seen in a few patients given amiodarone with propranolol, metoprolol or sotalol (for sotalol, see also 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290). Torsade de pointes developed in two patients taking amiodarone and atenolol, but other factors may have contributed to the development of the arrhythmia. Amiodarone may inhibit the metabolism of beta blockers metabolised by CYP2D6, such as metoprolol, which might be a factor in the interaction.

Clinical evidence

(a) Case reports of problems

A 64-year-old woman with hypertrophic cardiomyopathy taking amiodarone 1.2 g daily and **atenolol** 50 mg daily had her **atenolol** replaced by **metoprolol** 100 mg daily. Within 3 hours she complained of dizziness, weakness and blurred vision. On examination she was found to be pale and sweating with a pulse rate of 20 bpm. Her systolic blood pressure was 60 mmHg. Atropine 2 mg did not produce chronotropic or haemodynamic improvement. She responded to isoprenaline (isoproterenol).[1] In a review of torsade de pointes in patients taking amiodarone long-term, two elderly patients developed torsade de pointes 3 and 5 weeks after **atenolol** 25 mg daily was added. Bradycardia was observed in one patient and hypokalaemia probably contributed to the arrhythmia in the other patient.[2] Severe hypotension has been reported in another patient taking **sotalol** when intravenous amiodarone (total dose 250 mg) was given.[3] Another report describes cardiac arrest in one patient taking amiodarone, and severe bradycardia and ventricular fibrillation (requiring defibrillation) in another, within 1.5 hours and 2 hours of starting to take **propranolol**.[4]

(b) Clinical studies showing benefits

In contrast to the above case reports, a placebo-controlled study to assess the efficacy of amiodarone in preventing atrial fibrillation in elderly patients undergoing open-heart surgery found that in the amiodarone group, atrial fibrillation occurred in 12 of 77 patients (16%) also receiving beta blockers (about 80% were taking **metoprolol** and about 10% **atenolol** and the rest taking unnamed drug) and in 15 of 43 (35%) who did not receive or tolerate beta blockers. The combination of amiodarone and beta blockers may be associated with a lower risk of cerebrovascular accidents and ventricular tachycardia.[5] An analysis of data from two large clinical studies of the use of amiodarone for post-myocardial infarction arrhythmias found that the combination of unnamed beta blockers and amiodarone was beneficial (reduced cardiac deaths, arrhythmic deaths and resuscitated cardiac arrest) compared with either drug alone, or neither drug. Discontinuation of amiodarone because of excessive bradycardia was no more frequent when beta blockers were also given, although more patients taking amiodarone discontinued beta blockers than those taking placebo.[6] Similarly, in the analysis of another study in ischaemic heart failure, the benefits of **carvedilol** were still apparent in those patients already receiving amiodarone, and the combination was not associated with a greater incidence of adverse effects (worsened heart failure, hypotension or dizziness, bradycardia or atrioventricular block) than either drug alone.[7]

(c) Pharmacokinetics

In one study, 10 elderly patients (9 with symptomatic atrial fibrillation and one with an implanted defibrillator and frequent ventricular tachycardia) taking **metoprolol** (mean daily dose 119 mg) were also given amiodarone 1.2 g daily for 6 days. The **metoprolol** AUC and plasma levels were increased by about 80% and 75%, respectively, by the amiodarone, the extent varying by CYP2D6 genotype.[8] None of the patients included in the study were poor metabolisers (that is, those lacking CYP2D6).

In another study in 120 patients with cardiac arrhythmias taking **metoprolol**, the concurrent use of amiodarone in an average dose of 170 mg daily for one month in 30 patients increased the **metoprolol** serum concentration to dose ratio. Furthermore, the **metoprolol** dose was higher in those patients receiving **metoprolol** alone.[9] In another study by the same authors in patients with heart failure receiving **carvedilol**, it was found that the serum concentration to dose ratio for ***R*-carvedilol** was not affected by amiodarone given for 14 days. However, the serum concentration to

dose ratio for ***S*-carvedilol** and the serum ***S*- to *R*-carvedilol** ratio was significantly lower in the group given **carvedilol** alone than in the group given **carvedilol** and amiodarone,[10] suggesting that amiodarone inhibits the metabolism of ***S*-carvedilol**.

Mechanism

Not understood. The clinical picture is that of excessive beta-blockade, and additive pharmacodynamic effects are possible. Bradycardia associated with beta blockers and amiodarone can induce early after-depolarisations and facilitate torsade de pointes.[2] In addition, amiodarone and its metabolite, desethylamiodarone, increase the levels of metoprolol by inhibiting its metabolism by the cytochrome P450 isoenzyme CYP2D6.[8,9] Other beta blockers that are also substrates of CYP2D6, and which could therefore be similarly affected, include carvedilol and propranolol. However, the study with carvedilol suggests that other factors (e.g. other isoenzymes (CYP2C9), P-glycoprotein) may also be involved.[10]

Importance and management

The reports of adverse reactions cited here emphasise the need for caution when amiodarone is used with beta blockers. The manufacturers of amiodarone recommend that the combination should not be used[11] or used with caution[12] because potentiation of negative chronotropic properties and conduction-slowing effects may occur. However, the concurrent use of beta blockers and amiodarone is not uncommon and may be therapeutically useful. The authors of one of the analyses suggest that post-myocardial infarction, if possible, beta blockers should be continued in patients for whom amiodarone is indicated.[6] A pharmacokinetic interaction between amiodarone and beta blockers that are substrates of CYP2D6, such as metoprolol, also appears to be established. Although this interaction with other moderate inhibitors of CYP2D6 is generally not thought to be clinically relevant (e.g. see 'Beta blockers + SSRIs', p.1019), it is possible that this pharmacokinetic interaction plays some part in the adverse reactions sometimes seen, or even in the clinical benefits.[5,8]

Note that the concurrent use of sotalol presents a greater risk than that of other beta blockers, as it may prolong the QT interval. See also 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290, for more information.

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Amiodarone + Calcium-channel blockers

Increased cardiac depressant effects would be expected if amiodarone is used with diltiazem or verapamil. One case of sinus arrest and serious hypotension occurred in a woman taking diltiazem when she was given amiodarone.

Clinical evidence, mechanism, importance and management

A woman with compensated congestive heart failure, paroxysmal atrial fibrillation and ventricular arrhythmias was taking furosemide and **diltiazem** 90 mg every 6 hours. Four days after amiodarone 600 mg every 12 hours was added, she developed sinus arrest and a life-threatening low cardiac output state (systolic blood pressure 80 mmHg) with oliguria. **Diltiazem** and amiodarone were stopped and she was treated with pressor drugs and ventricular pacing. She had previously had no problems when taking **diltiazem** or **verapamil** alone, and later she took amiodarone 400 mg daily alone without incident. This reaction is thought to be caused by the additive effects of both drugs on myocardial contractility, and on sinus and atrioventricular nodal function.[1] Before this isolated case report was published, another author predicted this interaction with **diltiazem** or **verapamil** on theoretical grounds, and warned of the risks if dysfunction of the sinus node (bradycardia or sick sinus syndrome) is suspected, or if partial AV block exists.[2] The manufacturers state that amiodarone should not be used,[3] or used with caution,[4] with certain calcium-channel blockers (**diltiazem**, **verapamil**) because potentiation of negative chronotropic properties and conduction-slowing effects may occur. Note that **diltiazem** has been used for rate control in patients developing postoperative atrial fibrillation despite the use of prophylactic amiodarone.[5] There do not appear to be any reports of adverse effects attributed to the use of amiodarone with the dihydropyridine class of calcium-channel blockers (e.g. **nifedipine**), which typically have little or no negative inotropic activity at usual doses.

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Amiodarone + Chloroquine

In theory the concurrent use of chloroquine and amiodarone may increase the risk of torsade de pointes, but there appears to be no published cases of an interaction.
106 Clinical evidence, mechanism, importance and management

Some UK manufacturers of amiodarone and chloroquine contraindicate the concurrent use of these drugs because of the risk of torsade de pointes,[1,2] whereas another warns of an increased risk of arrhythmias.[3] Chloroquine may cause arrhythmias and ECG changes when used alone, particularly in high doses[2,3] and for prolonged periods (e.g. for rheumatoid arthritis);[2] however, chloroquine is not generally considered a high risk for causing cardiovascular toxicity, especially when given at the correct dose and administered appropriately.[4] There appears to be only one isolated report of QT prolongation in a patient taking chloroquine, but this was secondary to long term use (17 years) for systemic lupus erythematosus,[5] and no published cases of an interaction with amiodarone. Furthermore, the US manufacturers of amiodarone and chloroquine do not include any warnings about QT prolongation on concurrent use.[6,7] An interaction is therefore not established.

1. Cordarone X (Amiodarone hydrochloride). Sanofi-Aventis. UK Summary of product characteristics, March 2009.
2. Avloclor (Chloroquine phosphate). AstraZeneca UK Ltd. UK Summary of product characteristics, July 2009.
3. Nivaquine Syrup (Chloroquine sulphate). Sanofi-Aventis. UK Summary of product characteristics, September 2008.
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6. Cordarone (Amiodarone hydrochloride). Wyeth Pharmaceuticals Inc. US Prescribing information, August 2009.
7. Aralen (Chloroquine phosphate). Sanofi-Aventis U.S LLC. US Prescribing information, September 2008.

Amiodarone + Cimetidine

Cimetidine possibly causes a modest rise in the serum levels of amiodarone in some patients.

Clinical evidence, mechanism, importance and management

The preliminary report of one study in 12 patients noted that the mean serum levels of amiodarone 200 mg twice daily rose by an average of 38%, from 1.4 micrograms/mL to 1.93 micrograms/mL, when cimetidine 1.2 g daily was given for a week. The desethylamiodarone levels rose by 54%. However, these increases were not statistically significant (possibly due to the small sample size), and only 8 of the 12 patients had any rise.[1]

It is possible that cimetidine (a non-specific enzyme inhibitor) may reduce the metabolism of amiodarone leading to the increased levels seen.

Information seems to be limited to this study but this interaction may be clinically important in some patients. Monitor the effects when cimetidine is started, being alert for amiodarone adverse effects (e.g. bradycardia, taste disturbances, tremor, nausea). Remember that amiodarone has a very long half-life of 25 to 100 days, so that the results of the one-week study cited here may possibly not adequately reflect the magnitude of this interaction. There does not appear to have been anything further published on this.

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Amiodarone + Colestyramine

Colestyramine appears to reduce the serum levels of amiodarone.

Clinical evidence

In a study in 11 patients, 4 doses of colestyramine 4 g were given at one-hour intervals starting 1.5 hours after a single 400-mg dose of amiodarone. The serum amiodarone levels measured 7.5 hours later were reduced by about 50%.[1] In a further study, the amiodarone half-life was shorter in 3 patients given colestyramine 4 g daily after discontinuing long-term amiodarone (23.5, 29 and 32 days, respectively) compared with the half-life in 8 patients discontinuing amiodarone and not given colestyramine (35 to 58 days).[1]

Mechanism

This interaction probably occurs because colestyramine binds with amiodarone in the gut, thereby reducing its absorption. It may also affect the enterohepatic recirculation of amiodarone.[1] This is consistent with the way colestyramine interacts with other drugs.

Importance and management

Information is very limited but a reduced response to amiodarone may be expected. Separating the dosages to avoid admixture in the gut would reduce or prevent any effects on absorption from the gut, but not the effects due to reduced enterohepatic recirculation. Monitor concurrent use closely for amiodarone efficacy and consider an alternative to colestyramine, or raise the amiodarone dosage if necessary.

1. Nitsch J, Luderitz B. Beschleunigte elimination von Amiodaron durch Colestyramin. *Dtsch Med Wochenschr* (1986) 111, 1241–44.

Amiodarone + Co-trimoxazole

Some predict that co-trimoxazole (trimethoprim with sulfamethoxazole) increases the risk of QT prolongation and ventricular arrhythmias with amiodarone, but clinical evidence for this is sparse.

Clinical evidence, mechanism, importance and management

The UK manufacturer of amiodarone contraindicates the concurrent use of co-trimoxazole (trimethoprim with sulfamethoxazole), as they state that it prolongs the QT interval and increases the risk of torsade de pointes.[1] However, one UK manufacturer of co-trimoxazole similarly states that concurrent use increases the risk of ventricular arrhythmias, but does not specifically contraindicate concurrent use.[2] Co-trimoxazole is not generally associated with causing significant QT interval prolongation and torsade de pointes, and only three isolated cases appear to have been reported for co-trimoxazole alone,[3-5] of these, one was in a 90-year-old woman,[3] and another was in a patient genetically predisposed to QT prolongation.[4] Furthermore, the US manufacturer[6] of amiodarone and one other UK manufacturer[7] of co-trimoxazole make no mention of any possible interaction. An interaction is therefore not established.

1. Cordarone X (Amiodarone hydrochloride). Sanofi-Aventis. UK Summary of product characteristics, March 2009.
2. Co-trimoxazole Tablets. Actavis UK Ltd. UK Summary of product characteristics, October 2009.
3. Lopez JA, Harold JG, Rosenthal MC, Oseran DS, Schapira JN, Peter T. QT prolongation and torsades de pointes after administration of trimethoprim-sulfamethoxazole. *Am J Cardiol* (1987) 59, 376–7.
4. Sesti F, Abbott GW, Wei J, Murray KT, Saksena S, Schwartz PJ, Priori SG, Roden DM, George AL, Goldstein SAN. A common polymorphism associated with antibiotic-induced cardiac arrhythmia. *Proc Natl Acad Sci U S A* (2000) 97, 10613–18.
5. Owens RC. Risk assessment for antimicrobial agent-induced QTc interval prolongation and torsades de pointes. *Pharmacotherapy* (2001) 21, 301–19.
6. Cordarone (Amiodarone hydrochloride). Wyeth Pharmaceuticals Inc. US Prescribing information, August 2009.
7. Septrin Tablets (Trimethoprim with Sulfamethoxazole). GlaxoSmithKline UK. UK Summary of product characteristics, July 2009.

Amiodarone + Disopyramide

The risk of QT interval prolongation and torsade de pointes is increased if amiodarone is given with disopyramide.

Clinical evidence

A brief report describes 2 patients who developed torsade de pointes when they were given amiodarone with disopyramide. Their QT intervals became markedly prolonged to somewhere between 500 and 600 milliseconds.[1] In another study, 2 patients who had been taking disopyramide 300 mg daily for a number of months developed prolonged QT intervals, increasing from 450 milliseconds to 640 milliseconds and from 390 milliseconds to 680 milliseconds respectively, and developed torsade de pointes 2 days and 5 days respectively, after starting amiodarone 800 mg daily.[2] However, one early report also described the successful and apparently safe use of amiodarone 100 to 600 mg daily with disopyramide 300 to 500 mg daily,[3] although the results of long-term follow-up were not reported in all cases.

Mechanism

Amiodarone is a class III antiarrhythmic and can prolong the QT interval. Disopyramide is a class Ia antiarrhythmic and also prolongs the QT interval. Their additive effects can result in the development of torsade de pointes.

Importance and management

An established and potentially serious interaction. In general, class Ia antiarrhythmics such as disopyramide (see 'Table 9.2', (p.290)) should be avoided or used with great caution with amiodarone because of their additive effects in delaying conduction. The manufacturers of amiodarone contraindicate[4] or urge caution[5] if it is used with class Ia antiarrhythmics. If amiodarone is started in a patient taking disopyramide, they suggest the dose of disopyramide should be reduced by 30 to 50% several days after the addition of amiodarone, and that the continued need for disopyramide should be monitored, and withdrawal attempted. If disopyramide is given to a patient already taking amiodarone, the initial dose of disopyramide should be about half of the usual recommended dose.[5]

See also 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290, and for the interactions of other class Ia antiarrhythmics with amiodarone see 'Procainamide + Amiodarone', p.306, and 'Quinidine + Amiodarone', p.312.

1. Tartini R, Kappenberger L, Steinbrunn W. Gefährliche Interaktionen zwischen Amiodaron und Antiarrhythmika der Klass I. *Schweiz Med Wochenschr* (1982) 112, 1585–87.
2. Keren A, Tzivoni D, Gavish D, Levi J, Gottlieb S, Benhorin J, Stern S. Etiology, warning signs and therapy of torsade de pointes. A study of 10 patients. *Circulation* (1981) 64, 1167–74.
3. James MA, Papouchado M, Vann Jonec J. Combined therapy with disopyramide and amiodarone: a report of 11 cases. *Int J Cardiol* (1986) 13, 248–52.
4. Cordarone X (Amiodarone hydrochloride). Sanofi-Aventis. UK Summary of product characteristics, March 2009.
5. Cordarone (Amiodarone hydrochloride). Wyeth Pharmaceuticals Inc. US Prescribing information, August 2009.

Amiodarone + Grapefruit juice

Grapefruit juice inhibited the metabolism of oral amiodarone, and *decreased* its effects on the PR and QTc interval.

Clinical evidence

A single 17-mg/kg oral dose of amiodarone was given to 11 healthy subjects on two occasions, once with water and once with grapefruit juice (300 mL taken three times on the same day). Grapefruit juice completely inhibited the metabolism of amiodarone to its major metabolite *N*-desethylamiodarone and increased the amiodarone AUC by 50% and increased its peak serum level by 84%. The effect of amiodarone on the PR and QTc intervals was *decreased*.[1]

Mechanism

It is likely that grapefruit juice inhibits the cytochrome P450 isoenzyme CYP3A4 in the intestinal mucosa, thus inhibiting the formation of *N*-desethylamiodarone from oral, but probably not intravenous, amiodarone.

Importance and management

The interaction between amiodarone and grapefruit juice appears to be established, but its clinical consequences remain to be determined. *N*-desethylamiodarone is known to be active, so this could possibly result in decreased activity. In addition, high amiodarone concentrations may increase toxicity. Conversely, a reduction in QT prolongation is potentially beneficial.[1] However, further study is needed to establish any beneficial effect. The US manufacturer recommends that grapefruit juice should not be taken during treatment with oral amiodarone.[2]

1. Libersa CC, Brique SA, Motte KB, Caron JF, Guédon-Moreau LM, Humbert L, Vincent A, Devos P, Lhermitte MA. Dramatic inhibition of amiodarone metabolism induced by grapefruit juice. *Br J Clin Pharmacol* (2000) 49, 373–8.
2. Cordarone (Amiodarone hydrochloride). Wyeth Pharmaceuticals Inc. US Prescribing information, August 2009.

Amiodarone + Haloperidol

A retrospective study describes QT prolongation on the concurrent use of amiodarone and haloperidol.

Clinical evidence, mechanism, importance and management

A retrospective analysis identified 49 patients who were given amiodarone (mean daily dose 771 mg) with haloperidol (mean daily dose 11 mg) and a total of 381 instances of concurrent use (classified as haloperidol administration by any route within 24 hours of amiodarone administration by any route). Most patients were already taking amiodarone when haloperidol (intravenous haloperidol in 96% of patients) was given, with a mean increase in the QTc interval of 9.8 milliseconds. No ventricular arrhythmias were reported.[1] Both drugs are known to prolong the QT interval, and concurrent use is contraindicated by the UK manufacturers of amiodarone and haloperidol.[2,3] In contrast, the US manufacturer of amiodarone does not contraindicate the use of haloperidol, but advises that the concurrent use of amiodarone and any QT-prolonging drugs should only be undertaken after careful risk assessment.[4] For a further discussion of the risks of QT prolongation and the concurrent use or two or more QT-prolonging drugs, see 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290.

1. Bush SE, Hatton RC, Winterstein AG, Thomson MR, Woo GW. Effects of concomitant amiodarone and haloperidol on Q-Tc interval prolongation. Am J Heath Syst Pharm (2008) 65, 2232–6.
2. Cordarone X (Amiodarone hydrochloride). Sanofi-Aventis. UK Summary of product characteristics, March 2009.
3. Haldol Tablets (Haloperidol). Janssen-Cilag Ltd. UK Summary of product characteristics, October 2009.
4. Cordarone (Amiodarone hydrochloride). Wyeth Pharmaceuticals Inc. US Prescribing information, August 2009.

Amiodarone + Lithium

Hypothyroidism developed very rapidly in two patients taking amiodarone when lithium was added.

Clinical evidence, mechanism, importance and management

A patient who had taken amiodarone 400 mg daily for more than a year developed acute manic depression. He was given lithium 600 mg daily (salt unknown), but within 2 weeks he developed clinical signs of hypothyroidism, which were confirmed by clinical tests. He made a complete recovery within 3 weeks of stopping amiodarone while continuing lithium.[1] Similarly, another patient rapidly developed hypothyroidism, when taking amiodarone with lithium (dose and salt unknown). It resolved when the amiodarone was stopped.[1] Both lithium and amiodarone on their own can cause hypothyroidism (amiodarone can also cause hyperthyroidism). In these two cases the effects appear to have been additive, and very rapid.

These two cases appear to be the first and only reports of this interaction. Its general importance is therefore still uncertain. Note that lithium has been tried for the treatment of amiodarone-induced hyperthyroidism,[2,3] and regular monitoring of thyroid status is recommended throughout amiodarone treatment.[4,5] It would therefore seem prudent to be extra vigilant for any signs of hypothyroidism (lethargy, weakness, depression, weight gain, hoarseness) in any patient given both drugs.

Lithium therapy has rarely been associated with cardiac QT prolongation, and consequently the UK manufacturer of amiodarone contraindicates combined use.[4] However, note that QT-prolongation associated with lithium is usually as a result of lithium toxicity. See also 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290.

1. Ahmad S. Sudden hypothyroidism and amiodarone-lithium combination: an interaction. *Cardiovasc Drugs Ther* (1995) 9, 827–8.
2. Dickstein G, Shechner C, Adawi F, Kaplan J, Baron E, Ish-Shalom S. Lithium treatment in amiodarone-induced thyrotoxicosis. *Am J Med* (1997) 102, 454–8.
3. Boeving A, Cubas ER, Santos CM, de Carvalho GA, Graf H. O uso de carbonato de lítio no tratamento da tireotoxicose induzida por amiodarona. *Arq Bras Endocrinol Metabol* (2005) 49, 991–5.
4. Cordarone X (Amiodarone hydrochloride). Sanofi-Aventis. UK Summary of product characteristics, March 2009.
5. Cordarone (Amiodarone hydrochloride). Wyeth Pharmaceuticals Inc. US Prescribing information, August 2009.

Amiodarone + Macrolides

Torsade de pointes occurred in a man taking amiodarone when he was also given intravenous erythromycin. QT prolongation occurred in another patient when azithromycin was added to long-term amiodarone.

Clinical evidence

A 76-year-old man taking amiodarone 200 mg daily had a prolonged QT interval and a syncopal episode with torsade de pointes 24 hours after starting a course of intravenous **erythromycin lactobionate** (1 g every 6 hours). This occurred on rechallenge.[1] Marked QT prolongation and increased QT dispersion occurred when **azithromycin** was given to a patient taking amiodarone long-term, and resolved when the **azithromycin** was stopped.[2]

Mechanism

Amiodarone alone can prolong the QT interval and increase the risk of torsade de pointes. Of the macrolides, *intravenous* erythromycin is known to prolong the QT interval, and there is also some evidence that clarithromycin may prolong the QT interval.[3] Amiodarone and these macrolides may therefore have additive effects on the QT interval.

Importance and management

In general the concurrent use of two or more drugs that prolong the QT interval should be avoided, because this increases the risk of torsade de pointes arrhythmias (see also 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290). For this reason, the UK manufacturer of amiodarone contraindicates the concurrent use of *intravenous* erythromycin.[4] The authors of the above report suggest that the combination of azithromycin and amiodarone should be used with caution,[2] and this should probably also apply to **clarithromycin** until more is known. The US manufacturer recommends that a careful risk assessment should be undertaken if amiodarone is to be given with a macrolide.[5]

1. Nattel S, Ranger S, Talajic M, Lemery R, Roy D. Erythromycin-induced long QT syndrome: concordance with quinidine and underlying cellular electrophysiologic mechanism. *Am J Med* (1990) 89, 235–8.

2. Samarendra P, Kumari S, Evans SJ, Sacchi TJ, Navarro V. QT prolongation associated with azithromycin/amiodarone combination. *Pacing Clin Electrophysiol* (2001) 24, 1572–4.
3. Lee KL, Man-Hong J, Tang SC, Tai Y-T. QT-prolongation and torsades de pointes associated with clarithromycin. *Am J Med* (1998) 104, 395–6.
4. Cordarone X (Amiodarone hydrochloride). Sanofi-Aventis. UK Summary of product characteristics, March 2009.
5. Cordarone (Amiodarone hydrochloride). Wyeth Pharmaceuticals Inc. US Prescribing information, August 2009.

Amiodarone + Metronidazole

An isolated report describes QT interval prolongation and torsade de pointes in a patient given metronidazole and amiodarone.

Clinical evidence, mechanism, importance and management

An elderly patient taking metronidazole 500 mg three times daily for antibacterial-associated colitis and amiodarone (as an initial bolus of 450 mg followed by 900 mg daily) for paroxysmal atrial fibrillation developed marked QTc interval prolongation and torsade de pointes. Metronidazole and amiodarone were withdrawn and defibrillation was required to restore sinus rhythm. The QTc interval gradually decreased to normal over 6 days.[1]

It was suggested that metronidazole may have inhibited the metabolism of amiodarone by the cytochrome P450 isoenzyme CYP3A4 resulting in higher levels which are associated with QT interval prolongation and torsade de pointes.[1] However, some pharmacokinetic studies have found that metronidazole is not an inhibitor of CYP3A4/5 and suggest that increases in plasma levels of CYP3A4 substrates in the presence of metronidazole are not the result of CYP3A4 inhibition.[2] Furthermore, amiodarone was not given alone, so it is unclear if the effects seen were as a result of an interaction, of simply an adverse effect of the amiodarone. No general conclusions can be drawn from this isolated case.

1. Kounas SP, Letsas K, Sideris A, Efraimidis M, Kardaras F. QT interval prolongation and torsades de pointes due to a coadministration of metronidazole and amiodarone. *Pacing Clin Electrophysiol* (2005) 28, 472–3.
2. Roedler R, Neuhauser MM, Penzak SR. Does metronidazole interact with CYP3A substrates by inhibiting their metabolism through this metabolic pathway? Or should other mechanisms be considered? *Ann Pharmacother* (2007) 41, 653–8.

Amiodarone + Orlistat

Orlistat modestly reduces the absorption of amiodarone.

Clinical evidence, mechanism, importance and management

A randomised, placebo-controlled study in 16 healthy subjects found that orlistat 120 mg three times daily reduced the AUC and peak serum level of a single 1.2-g dose of amiodarone by 23% and 27%, respectively. Levels of its active metabolite, desethylamiodarone, were similarly reduced. The half-life and time to maximum serum level were not significantly altered. It was suggested that orlistat, which inhibits dietary fat absorption, may also reduce the absorption of amiodarone, which is a lipophilic drug.[1]

Although this modest reduction in amiodarone levels is unlikely to be clinically relevant, the manufacturer of orlistat recommends clinical and ECG monitoring during concurrent use.[2]

1. Zhi J, Moore R, Kanitra L, Mulligan TE. Effects of orlistat, a lipase inhibitor, on the pharmacokinetics of three highly lipophilic drugs (amiodarone, fluoxetine, and simvastatin) in healthy volunteers. *J Clin Pharmacol* (2003) 43, 428–35.
2. Xenical (Orlistat). Roche Products Ltd. UK Summary of product characteristics, March 2009.

Amiodarone + Oxygen

High-dose oxygen may increase the risks of amiodarone-induced postoperative adult respiratory distress syndrome.

Clinical evidence, mechanism, importance and management

A retrospective review of 20 patients who underwent cardiac surgery found that pulmonary complications were more common in those receiving amiodarone (73% versus 25%). Moreover, the incidence of pulmonary complications in patients taking amiodarone was higher in those exposed to 100% oxygen (6 of 7) than those not exposed to this concentration of oxygen (2 of 4).[1]

Four other patients taking amiodarone (without preoperative amiodarone pulmonary toxicity), developed postoperative toxicity, and 2 patients died. The common intraoperative factor in the 4 patients was exposure to high inspired oxygen concentrations.[2] A further two reports describe 3 patients taking amiodarone who developed acute onset unilateral adult respiratory distress syndrome after receiving 100% oxygen ventilation of one lung during surgery.[3,4]

Life-threatening pulmonary complications occurred in 4 patients with diagnosed amiodarone pulmonary toxicity who subsequently underwent cardiothoracic surgery: 2 patients died. These 4 patients were compared with 13 other patients taking amiodarone (only one of whom had preoperative amiodarone pulmonary toxicity) who were undergoing similar surgery and who did not develop pulmonary complications. The comparison indicated that *preoperative* amiodarone pulmonary toxicity appears to be a risk factor in the development of pulmonary complications, but other additional factors could include pump-oxygenator time and oxygen toxicity.[5]

The UK manufacturer of amiodarone suggests caution in patients receiving high-dose oxygen,[6] and the US manufacturer recommends that the determinants of oxygen delivery to the tissues should be closely monitored.[7] Others have suggested that the concentration of oxygen should be maintained at the lowest possible level consistent with adequate oxygenation.[1,3,4]

1. Duke PK, Ramsay MAE, Herndon JC, Swygert TH, Cook AO. Acute oxygen induced amiodarone pulmonary toxicity after general anaesthesia. *Anesthesiology* (1991) 75, A228.
2. Kay GN, Epstein AE, Kirklin JK, Diethelm AG, Graybar G, Plumb VJ. Fatal postoperative amiodarone pulmonary toxicity. *Am J Cardiol* (1988) 62, 490–2.
3. Herndon JC, Cook AO, Ramsay AE, Swygert TH, Capehart J. Postoperative unilateral pulmonary edema: possible amiodarone pulmonary toxicity. *Anesthesiology* (1992) 76, 308–12.
4. Saussine M, Colson P, Alauzen M, Mary H. Postoperative acute respiratory distress syndrome. A complication of amiodarone associated with 100 percent oxygen ventilation. *Chest* (1992) 102, 980–1.
5. Nalos PC, Kass RM, Gang ES, Fishbein MC, Mandel WJ, Peter T. Life-threatening postoperative pulmonary complications in patients with previous amiodarone pulmonary toxicity undergoing cardiothoracic operations. *J Thorac Cardiovasc Surg* (1987) 93, 904–12.
6. Cordarone X (Amiodarone hydrochloride). Sanofi-Aventis. UK Summary of product characteristics, March 2009.
7. Cordarone (Amiodarone hydrochloride). Wyeth Pharmaceuticals. US prescribing information, August 2009.

Amiodarone + Protease inhibitors

A case report describes increased amiodarone levels in a patient given indinavir. Other protease inhibitors are predicted to interact similarly.

Clinical evidence

A patient taking amiodarone 200 mg daily was also given zidovudine, lamivudine, and **indinavir** for 4 weeks, as post HIV-exposure prophylaxis after a needlestick injury. Amiodarone serum levels increased, from 0.9 mg/L before antiretroviral prophylaxis, to 1.3 mg/L during prophylaxis, and gradually decreased to 0.8 mg/L during the 77 days after stopping prophylaxis. Although the reference range for amiodarone levels is not established, these levels were not outside those usually considered to achieve good antiarrhythmic control.[1]

Mechanism

Protease inhibitors such as indinavir are inhibitors of cytochrome P450 enzymes and pharmacokinetic interactions are therefore possible. It was considered that the increase in serum amiodarone in this case was due to decreased metabolism of amiodarone, although no decrease in the serum levels of desethylamiodarone were observed.[1]

Importance and management

Although in the case cited the interaction was not clinically relevant, the authors considered that it could be important in patients with higher initial amiodarone levels. They recommend monitoring amiodarone if indinavir is also given.[1] In general the UK manufacturers of protease inhibitors suggest that they may increase amiodarone levels, and contraindicate concurrent use. The exception is **atazanavir**/**ritonavir**,[2] where caution and increased monitoring, including taking amiodarone levels, where possible, is recommended. Similarly the US manufacturers of the protease inhibitors generally contraindicate concurrent use. The exceptions are **amprenavir**,[3] **atazanavir**,[4] **darunavir**/**ritonavir**,[5] **fosamprenavir**[6] and **lopinavir**/**ritonavir**,[7] where the manufacturers recommend increased

monitoring, including taking amiodarone levels, where possible. Amiodarone adverse effects include bradycardia, taste disturbances, tremor and nausea.

1. Lohman JJHM, Reichert LJM, Degen LPM. Antiretroviral therapy increases serum concentrations of amiodarone. *Ann Pharmacother* (1999) 33, 645–6.
2. Reyataz (Atazanavir sulfate). Bristol-Myers Squibb Pharmaceuticals Ltd. UK Summary of product characteristics, July 2009.
3. Agenerase (Amprenavir). GlaxoSmithKline. US Prescribing information, May 2005.
4. Reyataz (Atazanavir sulfate). Bristol-Myers Squibb. US Prescribing information, November 2009.
5. Prezista (Darunavir ethanolate). Tibotec, Inc. US Prescribing information, June 2009.
6. Lexiva (Fosamprenavir calcium). GlaxoSmithKline. US Prescribing information, September 2009.
7. Kaletra (Lopinavir with Ritonavir). Abbott Laboratories. US Prescribing information, April 2009.

Amiodarone + Quinolones

Torsade de pointes has been reported in two patients taking amiodarone and levofloxacin. Post-marketing surveillance identified two similar cases with amiodarone and sparfloxacin. An increased risk of this arrhythmia would also be expected if amiodarone is used with gatifloxacin or moxifloxacin.

Clinical evidence, mechanism, importance and management

Torsade de pointes occurred in a patient taking **levofloxacin** and amiodarone.[1] The same authors subsequently encountered a second case of this reaction.[2] The Adverse Events Reporting System database of the FDA in the US was reviewed for cases of torsade de pointes associated with quinolones up until May 2001. In total, 37 cases of torsade de pointes were identified, and 19 occurred in patients also taking other drugs known to prolong the QT interval. Of the 19 cases, 4 cases were noted in patients taking amiodarone and a quinolone (unspecified, but **ciprofloxacin**, **gatifloxacin**, **levofloxacin**, **moxifloxacin**, and **ofloxacin** were assessed).[3] These 4 cases possibly include the two with **levofloxacin** mentioned above.

During post-marketing surveillance of **sparfloxacin** in France over a period of 8 months (about 750 000 patients) serious adverse cardiovascular effects were reported in 7 patients. All 7 patients had underlying risk factors including 3 patients who were also receiving amiodarone. Of these, 2 patients had documented QT prolongation and ventricular tachycardia.[4]

Amiodarone can prolong the QT interval and increase the risk of torsade de pointes. Of the quinolones used clinically, **gatifloxacin**, **moxifloxacin**, and **sparfloxacin** are known to prolong the QT interval (see 'Table 9.2', (p.290)). There is also evidence that **levofloxacin** may prolong the QT interval.[2,3]

In general the concurrent use of two or more drugs that prolong the QT interval should be avoided, because this increases the risk of torsade de pointes arrhythmias (see also 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290). The quinolones that prolong the QT interval should probably be avoided in patients taking amiodarone: moxifloxacin is specifically contraindicated.[5] **Ciprofloxacin** appears to have less effect on the QT interval.[3] Nevertheless, in the UK the manufacturer of amiodarone suggests that the concurrent use of any quinolone should be avoided.[5]

1. Iannini PB, Kramer H, Circiumaru I, Byazrova E, Doddamani S. QTc prolongation associated with levofloxacin. *Intersci Conf Antimicrob Agents Chemother* (2000) 40, 477.
2. Iannini P. Quinolone-induced QT interval prolongation: a not-so-unexpected class effect. *J Antimicrob Chemother* (2001) 47, 893–4.
3. Frothingham R. Rates of torsades de pointes associated with ciprofloxacin, ofloxacin, levofloxacin, gatifloxacin, and moxifloxacin. *Pharmacotherapy* (2001) 21, 1468–72.
4. Jaillon P, Morganroth J, Brumpt I, Talbot G, and the Sparfloxacin Safety Group. Overview of electrocardiographic and cardiovascular safety data for sparfloxacin. *J Antimicrob Chemother* (1996) 37 (Suppl A), 161–7.
5. Cordarone X (Amiodarone hydrochloride). Sanofi-Aventis. UK Summary of product characteristics, March 2009.

Amiodarone + Rifampicin (Rifampin)

A case report suggests that rifampicin may decrease the serum levels of amiodarone and its metabolite *N*-desethylamiodarone.

Clinical evidence, mechanism, importance and management

A woman with congenital heart disease, and atrial and ventricular arrhythmias managed by an implanted cardioverter defibrillator, epicardial pacing and amiodarone 400 mg daily, experienced deterioration in the control of her condition. She developed palpitations and experienced a shock from the defibrillator. Her amiodarone serum levels were 40% lower than 2 months previously, and her *N*-desethylamiodarone levels were undetectable. It was noted that 5 weeks earlier rifampicin 600 mg daily had been started to treat an infection of the pacing system. The amiodarone dose was doubled, but the palpitations continued. Amiodarone and *N*-desethylamiodarone levels increased after rifampicin was discontinued.[1] Rifampicin is a potent enzyme inducer and it may have increased the metabolism and clearance of amiodarone. Evidence appears to be limited to this case, but it is in line with the way both drugs are known to interact with other substances. An interaction would therefore seem to be established. It would be prudent to monitor concurrent use for amiodarone efficacy, taking amiodarone and metabolite levels, where possible.

1. Zarembski DG, Fischer SA, Santucci PA, Porter MT, Costanzo MR, Trohman RG. Impact of rifampin on serum amiodarone concentrations in a patient with congenital heart disease. *Pharmacotherapy* (1999) 19, 249–51.

Amiodarone + Sertraline

In an isolated report, a slight to moderate rise in plasma amiodarone levels was attributed to the concurrent use of sertraline.

Clinical evidence, mechanism, importance and management

A depressed patient taking amiodarone 200 mg twice daily had his treatment with carbamazepine 200 mg twice daily and sertraline 100 mg daily stopped, just before ECT treatment. After 4 days it was noted that his plasma amiodarone levels had fallen by nearly 20%. The authors of the report drew the conclusion that while taking all three drugs, the amiodarone levels had become slightly raised due to the enzyme inhibitory effects of the sertraline, despite the potential enzyme-inducing activity of the carbamazepine.[1] The patient had no changes in his cardiac status while amiodarone levels were reduced. Furthermore, a change of 20% would usually be considered to be within the normal fluctuation of drug levels. Therefore an interaction, particularly a clinically relevant interaction, seems unlikely.

1. DeVane CL, Gill HS, Markowitz JS, Carson WH. Awareness of potential drug interactions may aid avoidance. *Ther Drug Monit* (1997) 19, 366–7.

Amiodarone + Tolvaptan

Tolvaptan does not appear to affect the pharmacokinetics of amiodarone.

Clinical evidence, mechanism, importance and management

In a study in 17 patients with stable arrhythmias taking amiodarone 200 mg daily, single 30- or 90-mg doses of tolvaptan had no effect on the AUC or maximum plasma concentrations of amiodarone or its metabolite, desethylamiodarone. The pharmacokinetics of tolvaptan did not appear to differ, when compared with historical control data. No clinically relevant ECG changes were reported on concurrent use.[1]

Therefore, no amiodarone dose adjustment would be expected to be needed on the concurrent use of tolvaptan.

1. Shoaf SE, Elizari MV, Wang Z, Sekar K, Grinfeld LR, Barbagelata NA, Lerman J, Bramer SL, Trongé J, Orlandi C. Tolvaptan administration does not affect steady state amiodarone concentrations in patients with cardiac arrhythmias. *J Cardiovasc Pharmacol Ther* (2005) 10, 165–71.

Amiodarone + Trazodone

Two reports describe the development of torsade de pointes in patients taking trazodone and amiodarone; in one case trazodone was added to amiodarone, and in the other case amiodarone was added to trazodone.

Clinical evidence, mechanism, importance and management

A 74-year-old woman with a pacemaker, taking nifedipine, furosemide, aspirin and amiodarone 200 mg daily, began to have dizzy spells but no loss of consciousness soon after starting trazodone (initially 50 mg and

eventually 150 mg daily by the end of 2 weeks). Both the amiodarone and trazodone were stopped when she was hospitalised. She had a prolonged QTc interval and recurrent episodes of torsade de pointes, which were controlled by increasing the ventricular pacing rate. The QTc interval shortened and she was later discharged taking amiodarone without the trazodone, with an ECG similar to that seen 4 months before hospitalisation.[1] In a review of torsade de pointes in patients taking amiodarone long-term, one elderly female patient who had taken trazodone 50 mg daily for 2 years developed torsade de pointes 2 months after amiodarone 200 mg daily was added. The authors noted that hypokalaemia in this patient may have contributed to the arrhythmia.[2]

No general conclusions can be drawn from this apparent interaction, but prescribers should be aware of these cases. The manufacturer notes that trazodone does have the potential to be arrhythmogenic.[3]

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2. Antonelli D, Atar S, Freedberg NA, Rosenfeld T. Torsade de pointes in patients on chronic amiodarone treatment: contributing factors and drug interactions. *Isr Med Assoc J* (2005) 7,163–5.
3. Molipaxin Capsules (Trazodone hydrochloride). Sanofi-Aventis. UK Summary of product characteristics, August 2009.

Aprindine + Amiodarone

Serum aprindine levels can be increased by amiodarone.

Clinical evidence, mechanism, importance and management

The serum aprindine levels of 2 patients rose, accompanied by signs of toxicity (e.g. nausea, ataxia), when they were also given amiodarone. One of them, taking aprindine 100 mg daily, had a progressive rise in trough serum levels from 2.3 mg/L to 3.5 mg/L over a 5-week period, when given 1.2 g and later 600 mg of amiodarone daily. Even when the aprindine dose was reduced, serum levels remained higher than before amiodarone was started.[1] The authors say that those taking both drugs generally need less aprindine than those taking aprindine alone. This interaction has been briefly reported elsewhere.[2]

The reason for the rise in aprindine levels is not understood. Nevertheless it would seem prudent to monitor the effects of concurrent use and reduce the dose of aprindine as necessary.

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Azimilide + Miscellaneous

Ketoconazole (a CYP3A4 inhibitor) did not alter the pharmacokinetics of azimilide to a clinically relevant extent, and azimilide did not affect the pharmacokinetics of omeprazole (a CYP2C19 substrate) to a clinically relevant extent. Interactions with other CYP3A4 inhibitors and CYP2C19 substrates are therefore considered unlikely.

A case report describes QT prolongation in a patient given azimilide and ciprofloxacin. Azimilide does not appear to interact to a clinically relevant extent with digoxin or food, and its antiarrhythmic effects are unaffected by isoprenaline (isoproterenol).

Clinical evidence, mechanism, importance and management

(a) Ciprofloxacin

A patient with a history of myocardial infarction and with an implanted cardioverter-defibrillator (ICD) who was taking several drugs including azimilide 125 mg daily, was admitted to hospital because of worsening heart failure. On day 6 he developed a urinary-tract infection and was given ciprofloxacin 250 mg twice daily, but after 2 doses he developed QTc interval prolongation (increase from 470 milliseconds on admission to 754 milliseconds) and multiple episodes of torsade de pointes followed by ICD shocks. Azimilide and ciprofloxacin were withdrawn and he was given metoprolol but he also required ICD reprogramming. It was suggested that this occurred as a result of the additive effects of both drugs on the QT interval.[1]

(b) Digoxin

A study in 18 healthy subjects found that the concurrent use of azimilide and digoxin had only minor effects on the pharmacokinetics of both drugs (azimilide renal clearance increased by 36%, digoxin maximum serum level and AUC increased by 21% and 10%, respectively). In this study, azimilide 175 mg was given orally daily for 4 days then 100 mg on day 5 and digoxin was given as a loading dose of 750 micrograms on day one then as 250 micrograms daily for 4 days. Azimilide alone increased the QTc: this effect was decreased by 2 to 4% by digoxin. These effects are unlikely to be clinically relevant.[2]

(c) Food

A study in 30 healthy subjects given azimilide in the fasted state or after a high-fat meal found that the high-fat meal decreased the maximum serum levels of azimilide by 19%, but the extent of absorption was the same. Azimilide may be given without regard to meal times.[3]

(d) Isoprenaline (Isoproterenol)

In a placebo-controlled study, patients with cardiovascular disorders were given an infusion of isoprenaline, titrated from 0.5 micrograms/minute up to a maximum of 4 micrograms/minute until the heart rate reached 125% of baseline (up to a maximum 120 bpm). This dose of isoprenaline was then given again, but with an infusion of azimilide, as a loading dose of 4.5 mg/kg over 15 minutes followed by a continuous infusion of 0.625 mg/kg per hour. It was found that azimilide maintained its class III antiarrhythmic effect in the presence of isoprenaline, and at increased heart rate.[4]

(e) Ketoconazole

In a randomised, placebo-controlled study, 21 healthy subjects were given ketoconazole 200 mg daily with a single 125-mg dose of azimilide on day 8. Ketoconazole affected the AUC, maximum blood levels, half-life and clearance of azimilide by less than 20%. Azimilide is partly metabolised by the cytochrome P450 isoenzyme CYP3A4, which is inhibited by ketoconazole. The minor changes in azimilide pharmacokinetics with ketoconazole are not considered to be clinically important, and clinically significant pharmacokinetic interactions with other CYP3A4 inhibitors are not expected.[5]

(f) Omeprazole

In a randomised, placebo-controlled study, 40 healthy subjects (extensive metabolisers of the cytochrome P450 isoenzyme CYP2C19, that is, those that have normal levels of this isoenzyme) were given azimilide 125 mg every 12 hours for 3 days, then daily for 5 days. Azimilide reduced the AUC of a single 20-mg dose of omeprazole given on day 8 by 12%, which is not clinically relevant. There was no change in the metabolite-to-parent AUC suggesting that azimilide had no effect on the metabolism of omeprazole by CYP2C19.[6]

The authors note that *in vitro* studies suggested that of the cytochrome P450 isoenzymes, azimilide had the lowest inhibitory concentration against CYP2C19. On this basis they suggest that azimilide is also unlikely to interact with drugs metabolised by CYP1A2, CYP2C9, CYP2D6 and CYP3A4.[6]

1. Kaźmierczak J, Peregud-Pogorzelska M, Rzeuski R. QT interval prolongation and torsades de pointes due to a coadministration of ciprofloxacin and azimilide in a patient with implantable cardioverter–defibrillator. *Pacing Clin Electrophysiol* (2007) 30, 1043–6.
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Bretylium + Miscellaneous

The pressor effects of adrenaline (epinephrine) and noradrenaline (norepinephrine) are increased in the presence of bretylium. Amfetamine and protriptyline antagonise the blood pressure lowering effect of bretylium.

Clinical evidence

(a) Adrenaline (Epinephrine) or Noradrenaline (Norepinephrine)

In 4 healthy subjects, a dose of bretylium sufficient to produce postural hypotension enhanced the pressor effect of noradrenaline. A similar effect was found with adrenaline.[1]

(b) Amfetamine

When 7 patients with hypertension, taking bretylium 600 mg to 4 g daily were given a single 25-mg dose of amphetamine, 6 patients had a rise in blood pressure.[2]

(c) Protriptyline

An experimental study found that protriptyline can return the blood pressure to normal in patients taking bretylium, without reducing its antiarrhythmic efficacy.[3]

Mechanism

Animal studies have shown that bretylium reduces blood pressure via its blocking effects on adrenergic neurones similar to guanethidine.[4,5] Bretylium therefore enhances the effects of directly-acting sympathomimetics such as noradrenaline (norepinephrine), and is antagonised by drugs with indirect sympathomimetic activity such as the amfetamines and tricyclic antidepressants.

Importance and management

Although documentation is limited, based on the known pharmacology of bretylium, these interactions would appear to be established. The use of bretylium is limited to the short-term control of ventricular arrhythmias. In this situation, if directly-acting sympathomimetics such as noradrenaline (norepinephrine) are required to reverse bretylium-induced hypotension, this should be undertaken with caution since their effects may be enhanced.

Bretylium is no longer used for the treatment of hypertension, therefore the interactions with amfetamines and tricyclics are unlikely to be of much general relevance.

1. Laurence DR, Nagle RE. The interaction of bretylium with pressor agents. *Lancet* (1961) i, 593–4.
2. Wilson R, Long C. Action of bretylium antagonised by amphetamine. *Lancet* (1960) ii, 262.
3. Woosley RL, Reele SB, Roden DM, Nies AS, Oates JA. Pharmacological reversal of hypotensive effect complicating antiarrhythmic therapy with bretylium. *Clin Pharmacol Ther* (1982) 32, 313–21.
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Cibenzoline (Cifenline) + H_2-receptor antagonists

Cimetidine increases the plasma levels of cibenzoline. Ranitidine does not interact with cibenzoline.

Clinical evidence, mechanism, importance and management

In a study in 12 healthy subjects, **cimetidine** 1.2 g daily raised the maximum plasma levels of a single 160-mg dose of cibenzoline by 27%, increased its AUC by 44%, and prolonged its half-life by 30%. **Ranitidine** 300 mg daily had no effect.[1] The probable reason for the rise in cibenzoline levels is that **cimetidine**, an enzyme inhibitor, reduces the metabolism of the cibenzoline by the liver, whereas **ranitidine**, which is not an enzyme inhibitor, does not affect cibenzoline metabolism. The clinical importance of this interaction is not known but be alert for increased cibenzoline adverse effects.

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Disopyramide + Antacids

There is some inconclusive evidence that aluminium phosphate may possibly cause a small reduction in the absorption of disopyramide.

Clinical evidence, mechanism, importance and management

In a study in 10 patients, a single 11-g dose of an **aluminium phosphate** antacid had no statistically significant effect on the pharmacokinetics of a single 200-mg oral dose of disopyramide. However the antacid appeared to reduce the absorption of disopyramide to some extent in individual subjects.[1] The clinical importance of this interaction is uncertain, but probably small.

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Disopyramide + Azoles

Ketoconazole increased the levels of disopyramide *in vitro*. Other azole antifungals would be expected to interact similarly.

Clinical evidence, mechanism, importance and management

An *in vitro* study[1] found that **ketoconazole** inhibits the metabolism of disopyramide, although there do not appear to be any case reports or clinical studies of an interaction. Disopyramide is metabolised by the cytochrome P450 isoenzyme CYP3A4, of which ketoconazole is an inhibitor. Therefore concurrent use would be expected to increase disopyramide levels and adverse effects. The UK manufacturer of **ketoconazole** contraindicates the concurrent use of disopyramide, as this increase in disopyramide levels may increase the risk of developing QT prolongation and torsade de pointes.[2] As **itraconazole** is also a potent inhibitor of CYP3A4, the UK manufacturer[3] contraindicates its concurrent use in patients taking disopyramide for non-life threatening indications, whereas the US manufacturer advises caution during concurrent use.[4] Other azole antifungals inhibit CYP3A4 to varying degrees (see 'azole antifungals', (p.233)) and therefore they would also be expected to interact with disopyramide. If the concurrent use of disopyramide and an azole is necessary, it would seem prudent to monitor the patient for an increase in disopyramide adverse effects (such as dry mouth, blurred vision, urinary retention and nausea).

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2. Nizoral Tablets (Ketoconazole). Janssen-Cilag Ltd. UK Summary of product characteristics, October 2008.
3. Sporanox Capsules (Itraconazole). Janssen-Cilag Ltd. UK Summary of product characteristics, October 2009.
4. Sporanox (Itraconazole). Ortho-McNeil-Janssen Pharmaceuticals, Inc. US Prescribing information, March 2009.

Disopyramide + Beta blockers

Severe bradycardia has been described after the use of disopyramide with beta blockers including practolol, pindolol, and metoprolol; in some cases this was fatal. Atenolol modestly decreased disopyramide clearance in one study. Oral propranolol and disopyramide have been given together without any increase in negative inotropic effects or pharmacokinetic changes in healthy subjects.

A patient given disopyramide and intravenous sotalol developed asystole. For more information on the effects of giving sotalol with disopyramide, see 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290.

Clinical evidence

Two patients with supraventricular tachycardia (180 bpm) were given, firstly intravenous **practolol** (20 mg and 10 mg, respectively) and shortly afterwards with disopyramide (150 mg and 80 mg, respectively). The first patient rapidly developed sinus bradycardia of 25 bpm, lost consciousness and became profoundly hypotensive. He did not respond to 600 micrograms of atropine, but later his heart rate increased to 60 bpm while a temporary pacemaker was being inserted.[1] He was successfully treated with disopyramide 150 mg alone for a later episode of tachycardia. The second patient also developed severe bradycardia and asystole, despite the use of atropine. He was resuscitated with adrenaline (epinephrine) but later died.[1]

Severe bradycardia has been reported in another patient, also given intravenous **practolol** and then disopyramide.[2] Another patient developed severe bradycardia and died when given **pindolol** 5 mg and disopyramide

250 mg (both orally) for supraventricular tachycardia.[3] Another patient taking oral disopyramide 250 mg twice daily developed asystole when given a total of 60 mg of intravenous **sotalol**.[4]

A patient with hypertrophic obstructive cardiomyopathy and paroxysmal atrial fibrillation taking disopyramide 450 mg daily developed hypotension, bradycardia and cardiac conduction disturbances 5 days after starting **metoprolol** 50 mg daily.[5]

Atenolol 100 mg daily has been shown to increase the steady-state disopyramide levels from 3.46 micrograms/mL to 4.25 micrograms/mL and reduce the clearance of disopyramide by 16% in healthy subjects and patients with ischaemic heart disease.[6] None of the subjects developed any adverse reactions or symptoms of heart failure, apart from one of the subjects who had transient first degree heart block.[6]

In contrast, studies in healthy subjects have found that the negative inotropic effects were no greater when oral **propranolol** and disopyramide were used concurrently,[7] nor were the pharmacokinetics of either drug affected.[8]

Mechanism

Not understood. Both disopyramide and the beta blockers can depress the contractility and conductivity of the heart muscle.

Importance and management

An interaction between disopyramide and beta blockers is established. It seems to occur rarely, but is potentially very serious; fatalities have been reported. The US manufacturers of disopyramide suggest that the combination of disopyramide and beta blockers should generally be avoided, except in the case of life-threatening arrhythmias unresponsive to a single drug.[9]

Note that the concurrent use of sotalol presents a greater risk than that of other beta blockers, as it may prolong the QT interval. See also 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290.

1. Cumming AD, Robertson C. Interaction between disopyramide and practolol. *BMJ* (1979) 2, 1264.
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3. Pedersen C, Josephsen P, Lindvig K. Interaktion mellem disopyramid og pindolol efter oral indgift. *Ugeskr Laeger* (1983) 145, 3266.
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6. Bonde J, Bødtker S, Angelo HR, Svendsen TL, Kampmann JP. Atenolol inhibits the elimination of disopyramide. *Eur J Clin Pharmacol* (1986) 28, 41–3.
7. Cathcart-Rake WF, Coker JE, Atkins FL, Huffman DH, Hassanein KM, Shen DD, Azarnoff DL. The effect of concurrent oral administration of propranolol and disopyramide on cardiac function in healthy men. *Circulation* (1980) 61, 938–45.
8. Karim A, Nissen C, Azarnoff DL. Clinical pharmacokinetics of disopyramide. *J Pharmacokinet Biopharm* (1982) 10, 465–94.
9. Norpace (Disopyramide). Pfizer Inc. US Prescribing information, September 2006.

Disopyramide + H_2-receptor antagonists

Cimetidine may slightly increase the serum levels of oral disopyramide, but does not affect the pharmacokinetics of intravenous disopyramide. Ranitidine appears not to interact with disopyramide.

Clinical evidence, mechanism, importance and management

In a study in 7 healthy subjects, oral **cimetidine** 400 mg twice daily for 14 days did not alter the pharmacokinetics of a single 150-mg intravenous dose of disopyramide.[1] Another study, in 6 healthy subjects, found that a single 400-mg dose of **cimetidine** increased the AUC of a single 300-mg oral dose of disopyramide by 9% and increased the maximum serum levels by 19%, but did not significantly affect the metabolism of disopyramide. **Ranitidine** 150 mg was found not to interact significantly.[2]

The reasons for the slight increase in disopyramide levels are not known, but the authors of the report suggest that **cimetidine** may have increased disopyramide absorption.[2] **Cimetidine** is only a weak inhibitor of disopyramide metabolism *in vitro*.[3] The changes described are unlikely to be clinically important, but this should probably be confirmed in a more clinically realistic situation, using multiple oral doses of both drugs.

1. Bonde J, Pedersen LE, Nygaard E, Ramsing T, Angelo HR, Kampmann JP. Stereoselective pharmacokinetics of disopyramide and interaction with cimetidine. *Br J Clin Pharmacol* (1991) 31, 708–10.
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3. Echuzen H, Kawasaki H, Chiba K, Tani M. Ishizaki T. A potent inhibitory effect of erythromycin and other macrolide antibiotics on the mono-N-dealkylation metabolism of disopyramide with human liver microsomes. *J Pharmacol Exp Ther* (1993) 264, 1425–31.

Disopyramide + Macrolides

Erythromycin appears to raise disopyramide levels; concurrent use has led to QT prolongation, cardiac arrhythmias and heart block. The concurrent use of clarithromycin and disopyramide has led to torsade de pointes, ventricular fibrillation and severe hypoglycaemia, and the concurrent use of azithromycin and disopyramide has led to ventricular fibrillation.

Clinical evidence

(a) Azithromycin

A patient taking disopyramide 150 mg three times daily developed ventricular tachycardia requiring cardioversion 11 days after starting azithromycin 250 mg daily.[1] Her disopyramide level was found to have risen from 2.6 micrograms/mL to 11.1 micrograms/mL.

(b) Clarithromycin

A 74-year-old woman who had been taking disopyramide 200 mg twice daily for 7 years collapsed with ventricular fibrillation 6 days after starting to take omeprazole 40 mg, metronidazole 800 mg and clarithromycin 500 mg daily. After successful resuscitation, her QTc interval, which had never previously been above 440 milliseconds, was found to have risen to 625 milliseconds. Her disopyramide plasma level was also elevated (4.6 micrograms/mL) and the half-life was markedly prolonged (40 hours). The QTc interval normalised as her plasma disopyramide levels fell.[2] A 76-year old woman taking disopyramide developed torsade de pointes when given clarithromycin 200 mg twice daily. Hypokalaemia (potassium 2.8 mmol/L) probably contributed to this case.[3]

An episode of torsade de pointes occurred in another elderly woman taking disopyramide 5 days after starting clarithromycin 250 mg twice daily.[4]

A haemodialysis patient, receiving disopyramide 50 mg daily because of paroxysmal atrial fibrillation, was hospitalised with hypoglycaemic coma after also taking clarithromycin 600 mg daily. Serum disopyramide levels increased from 1.5 to 8 micrograms/mL during treatment with clarithromycin. QT and QTc intervals were prolonged, but torsade de pointes did not occur.[5] Hypoglycaemic coma has also been reported in another patient taking disopyramide with clarithromycin.[6]

(c) Erythromycin

A woman with ventricular ectopy taking disopyramide (300 mg alternating with 150 mg every 6 hours) developed new arrhythmias (ventricular asystoles and later torsade de pointes) within 36 hours of starting erythromycin lactobionate 1 g intravenously every 6 hours, and cefamandole. Her QTc interval had increased from 390 to 600 milliseconds and her serum disopyramide level was found to be 16 micromol/L. The problem resolved when the disopyramide was stopped and bretylium given, but returned again when disopyramide was restarted. It resolved again when the erythromycin was stopped.[7] Another patient with ventricular tachycardia, well controlled over 5 years with disopyramide 200 mg four times daily, developed polymorphic ventricular tachycardia within a few days of starting erythromycin 500 mg four times daily. His QTc interval had increased from 430 milliseconds to 630 milliseconds and serum disopyramide levels were found to be elevated at 30 micromol/L. The problem resolved when both drugs were withdrawn and antiarrhythmics given.[7]

Mechanism

Not fully established. An *in vitro* study using human liver microsomes indicated that erythromycin inhibits the metabolism (mono-*N*-dealkylation) of disopyramide which, *in vivo*, would be expected to reduce its loss from the body and increase its serum levels.[8] Clarithromycin probably does the same. The increased serum levels of disopyramide can result in adverse effects such as QT prolongation and torsade de pointes, and may result in enhanced insulin secretion and hypoglycaemia.[5,6] Both intravenous

erythromycin[9] and clarithromycin[10] alone have been associated with prolongation of the QT interval and torsade de pointes. Therefore, disopyramide and macrolides may have additive effects on the QT interval in addition to the pharmacokinetic interaction.

Importance and management

An established interaction, although it is probably rare. Even so the effects of concurrent use should be well monitored if clarithromycin or erythromycin is added to disopyramide, being alert for the development of raised plasma disopyramide levels and prolongation of the QT interval. The manufacturer of disopyramide[11] recommends avoiding the combination of disopyramide and macrolides that inhibit the cytochrome P450 isoenzyme CYP3A, and this would certainly be prudent in situations where close monitoring is not possible. Although direct clinical information is lacking, *in vitro* studies with human liver microsomes[8] indicate that **josamycin** is likely to interact similarly, and **telithromycin** might also be expected to interact in the same way. See also 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290.

1. Granowitz EV, Tabor KJ, Kirchhoffer JB. Potentially fatal interaction between azithromycin and disopyramide. *Pacing Clin Electrophysiol* (2000) 23, 1433–5.
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5. Iida H, Morita T, Suzuki E, Iwasawa K, Toyo-oka T, Nakajima T. Hypoglycemia induced by interaction between clarithromycin and disopyramide. *Jpn Heart J* (1999) 40, 91–6.
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11. Rythmodan Capsules (Disopyramide). Sanofi-Aventis. UK Summary of product characteristics, February 2009.

Disopyramide + Phenobarbital

Serum disopyramide levels are reduced by phenobarbital.

Clinical evidence

In a study in 16 healthy subjects, phenobarbital 100 mg daily for 21 days reduced the half-life and AUC of a single 200-mg dose of disopyramide by about 35%. The apparent metabolic clearance more than doubled, and the fraction recovered in the urine as metabolite increased. There were no significant differences seen between subjects who smoked and non-smoking subjects.[1]

Mechanism

It seems probable that phenobarbital (a known enzyme inducer) increases the metabolism of disopyramide by the liver, and thereby increases its loss from the body.

Importance and management

This interaction between phenobarbital and disopyramide appears to be established, but its clinical importance is uncertain. The extent to which it would reduce the control of arrhythmias by disopyramide is unknown, but monitor the effects and, where possible, the serum levels of disopyramide if phenobarbital is added or withdrawn. The manufacturer of disopyramide[2] recommends avoiding using it in combination with inducers of the cytochrome P450 subfamily CYP3A, such as phenobarbital. Other **barbiturates** would be expected to interact similarly.

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2. Rythmodan Capsules (Disopyramide). Sanofi-Aventis. UK Summary of product characteristics, February 2009.

Disopyramide + Phenytoin

Serum disopyramide levels are reduced by phenytoin and may fall below therapeutic levels.

Clinical evidence

Eight patients with ventricular tachycardia taking disopyramide 600 mg to 2 g daily had a 54% fall in their serum disopyramide levels (from a mean of 3.99 micrograms/mL to 1.82 micrograms/mL) when they were also given phenytoin 200 to 600 mg daily for a week. Two of the patients who responded to disopyramide and underwent Holter monitoring had a 53- and 2000-fold increase in ventricular premature beat frequency as a result of this interaction.[1]

In other reports, 3 patients who had low levels of disopyramide and high levels of its metabolite were noted to be taking phenytoin,[2] and one patient taking phenytoin required an unusually high dose of disopyramide.[3] A marked fall in serum disopyramide levels (75% in one case) was seen in 2 patients who took phenytoin 300 to 400 mg daily for up to 2 weeks.[4] Pharmacokinetic studies[3,5] in a total of 12 healthy subjects confirm this interaction. In addition, one healthy patient with epilepsy, taking phenytoin, had a disopyramide AUC and elimination half-life that were 50% lower than those in control subjects.[5]

Mechanism

Phenytoin, which is a known enzyme-inducer, increases the metabolism of the disopyramide by the liver. Although the major metabolite (*N*-dealkyldisopyramide) also possesses antiarrhythmic activity, the net effect is a reduction in arrhythmic control.[1]

Importance and management

The interaction between disopyramide and phenytoin is established and of clinical importance. Some loss of arrhythmic control can occur during concurrent use. Disopyramide adverse effects (e.g. dry mouth, blurred vision, urinary retention and nausea), because of the potential for high metabolite levels, and the antiarrhythmic response should be well monitored. An increase in the dose of disopyramide may be necessary. The interaction appears to resolve fully within 2 weeks of withdrawing the phenytoin. Note that the manufacturer of disopyramide[6] recommends avoiding using it in combination with inducers of the cytochrome P450 subfamily CYP3A, such as phenytoin.

1. Matos JA, Fisher JD, Kim SG. Disopyramide-phenytoin interaction. *Clin Res* (1981) 29, 655A.
2. Aitio M-L, Vuorenmaa T. Enhanced metabolism and diminished efficacy of disopyramide by enzyme induction? *Br J Clin Pharmacol* (1980) 9, 149–152.
3. Nightingale J, Nappi JM. Effect of phenytoin on serum disopyramide concentrations. *Clin Pharm* (1987) 6, 46–50.
4. Kessler JM, Keys PW, Stafford RW. Disopyramide and phenytoin interaction. *Clin Pharm* (1982) 1, 263–4.
5. Aitio M-L, Mansury L, Tala E, Haataja M, Aitio A. The effect of enzyme induction on the metabolism of disopyramide in man. *Br J Clin Pharmacol* (1981) 11, 279–85.
6. Rythmodan Capsules (Disopyramide). Sanofi-Aventis. UK Summary of product characteristics, February 2009.

Disopyramide + Protease inhibitors

Disopyramide levels may be increased by ritonavir. Other protease inhibitors may interact similarly.

Clinical evidence, mechanism, importance and management

Direct, published evidence (from case reports or clinical studies) of an interaction between disopyramide and the protease inhibitors appears to be lacking; however, a review of protease inhibitor interactions reports that **ritonavir** may increase the plasma levels of disopyramide more than threefold.[1] Furthermore, the manufacturer of ritonavir states that cardiac adverse effects have been reported on the concurrent use of disopyramide.[2]

Disopyramide is partially metabolised by the cytochrome P450 isoenzyme CYP3A4, of which **ritonavir** is a potent inhibitor, and therefore concurrent use would be expected to result in raised disopyramide levels, which may increase the risk of arrhythmias and other adverse effects, Note that the protease inhibitors as a group are inhibitors of CYP3A4, to varying degrees, and may be expected to interact similarly.

An interaction between the protease inhibitors and disopyramide is therefore considered to be established, despite the general lack of direct data. The manufacturer of disopyramide states that concurrent use is not recommended, because the outcome of concurrent use is not known.[3] They also state that as the protease inhibitors (they name **ritonavir**, **indinavir** and **saquinavir**) are substrates of CYP3A4, they may compete with disopyramide for metabolism by CYP3A4, possibly resulting in increased serum levels of these drugs.[3] However, note that drug interactions by this mechanism do not generally result in a clinically relevant interaction. Other known inhibitors of CYP3A4, such as some macrolides (see 'Disopyramide + Macrolides', p.284) have been reported to increase disopyramide levels and this has resulted in serious adverse effects. It would therefore seem prudent to monitor any patient taking both disopyramide and a protease inhibitor for an increase in disopyramide adverse effects (such as dry mouth, blurred vision, urinary retention and nausea).

1. Burger DM, Hoetelmans RMW, Koopmans PP, Meenhorst PL, Mulder JW, Hekster YA, Beijnen JH. Clinically relevant drug interactions with antiretroviral agents. *Antivir Ther* (1997) 2, 149–165.
2. Norvir Soft Capsules (Ritonavir). Abbott Laboratories Ltd. UK Summary of product characteristics, October 2009.
3. Rythmodan Capsules (Disopyramide). Sanofi-Aventis. UK Summary of product characteristics, February 2009.

Disopyramide + Quinidine

Disopyramide serum levels may be slightly raised by quinidine. Both drugs prolong the QT interval, and this effect may be additive on combined use.

Clinical evidence, mechanism, importance and management

In a study in 16 healthy subjects, quinidine 200 mg four times daily increased the peak serum levels of a single 150-mg dose of disopyramide by 20% from 2.68 micrograms/mL to 3.23 micrograms/mL. The effect was smaller (14%) when disopyramide 150 mg four times daily was given. Serum quinidine levels were decreased by 26%. However, there was no change in the half-life of either drug. Both quinidine and disopyramide caused a slight lengthening of the QTc interval, and when quinidine was added to disopyramide additional lengthening of the QT interval occurred. The frequency of adverse effects such as dry mouth, blurred vision, urinary retention and nausea were also somewhat increased.[1]

The mechanism of the effect on serum levels is not understood. If both drugs are given, the antimuscarinic adverse effects of disopyramide may be increased; consider decreasing the disopyramide dose if these are troublesome. Disopyramide and quinidine are both class Ia antiarrhythmics that prolong the QT interval, and, in general, such combinations should be avoided (see also 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290).

1. Baker BJ, Gammill J, Massengill J, Schubert E, Karin A, Doherty JE. Concurrent use of quinidine and disopyramide: evaluation of serum concentrations and electrocardiographic effects. *Am Heart J* (1983) 105, 12–15.

Disopyramide + Rifampicin (Rifampin)

The plasma levels of disopyramide can be reduced by rifampicin.

Clinical evidence

In a study in 11 patients with tuberculosis, rifampicin for 14 days approximately halved the plasma levels of a single 200- or 300-mg dose of disopyramide.[1] The disopyramide AUC was reduced by about two-thirds and the half-life was reduced from 5.9 to 3.25 hours. A woman who had been taking rifampicin for 2 weeks started taking disopyramide 100 mg every 8 hours but only achieved a subtherapeutic level of 0.9 micromol/L. The dose of disopyramide was increased to 300 mg every 8 hours, and the rifampicin was discontinued. Three days after discontinuing rifampicin the disopyramide level was 3.6 micromol/L and after 5 days it was 8.1 micromol/L. The patient was eventually stabilised taking disopyramide 250 mg every 8 hours.[2]

Mechanism

The most probable explanation is that rifampicin (a well-known enzyme inducer) increases the metabolism of the disopyramide by the liver so that it is cleared from the body much more quickly.

Importance and management

Information seems to be limited to these studies, but they indicate that the dosage of disopyramide will need to be increased in most patients taking rifampicin. Note that the manufacturer of disopyramide[3] recommends avoiding using it in combination with inducers of the cytochrome P450 subfamily CYP3A, such as rifampicin.

1. Aitio M-L, Mansury L, Tala E, Haataja M, Aitio A. The effect of enzyme induction on the metabolism of disopyramide in man. *Br J Clin Pharmacol* (1981) 11, 279–85.
2. Staum JM. Enzyme induction: rifampin-disopyramide interaction. *DICP Ann Pharmacother* (1990) 24, 701–3.
3. Rythmodan Capsules (Disopyramide). Sanofi-Aventis. UK Summary of product characteristics, February 2009.

Disopyramide + Verapamil

Profound hypotension and collapse has occurred in a small number of patients taking verapamil who were also given disopyramide.

Clinical evidence, mechanism, importance and management

A group of clinicians who had used single 400-mg oral doses of disopyramide successfully and with few adverse effects for reverting acute supraventricular arrhythmias, reported 5 cases of profound hypotension and collapse. Three of the patients developed severe epigastric pain. All 5 had previous myocardial disease and/or were taking myocardial depressants, either beta blockers or verapamil in small quantities [not specified].[1]

On the basis of this report, reports of studies in *animals*,[2] and from the known risks associated with the concurrent use of beta blockers (see 'Disopyramide + Beta blockers', p.283), the UK manufacturer warns about combining disopyramide and other drugs [such as verapamil] that may have additive negative inotropic effects.[3] However, they do point out that in some specific circumstances combinations of antiarrhythmic drugs may be beneficial; they specifically name verapamil for the control of atrial fibrillation).[3] However, the US manufacturer advises that until more data is available, disopyramide should not be given within 48 hours before or 24 hours after verapamil.[4]

1. Manolas EG, Hunt D, Dowling JT, Luxton M, Vohra J. Collapse after oral administration of disopyramide. *Med J Aust* (1979) 1, 20.
2. Lee JT, Davy J-M, Kates RE. Evaluation of combined administration of verapamil and disopyramide in dogs. *J Cardiovasc Pharmacol* (1985) 7, 501–7.
3. Rythmodan Capsules (Disopyramide). Sanofi-Aventis. UK Summary of product characteristics, February 2009.
4. Norpace (Disopyramide). Pfizer Inc. US Prescribing information, September 2006.

Dofetilide + Antacids

Antacids (aluminium/magnesium hydroxide) appear not to interact with dofetilide.

Clinical evidence, mechanism, importance and management

A study in 12 healthy subjects found that pretreatment with **aluminium/magnesium hydroxide** (*Maalox*) 30 mL, given 10 hours, 2 hours and 0.5 hours before dofetilide, did not affect the pharmacokinetics of a single 500-microgram dose of dofetilide, or the dofetilide-induced change in QTc interval.[1] No special precautions appear to be necessary.

1. Vincent J, Gardner MJ, Baris B, Willavize SA. Concurrent administration of omeprazole and antacid does not alter the pharmacokinetics and pharmacodynamic of dofetilide in healthy subjects. *Clin Pharmacol Ther* (1996) 59, 182.

Dofetilide + Diuretics

Hydrochlorothiazide and hydrochlorothiazide/triamterene modestly increase dofetilide plasma exposure. Concurrent use increased the QT interval prolongation seen with dofetilide alone.

Clinical evidence

The manufacturer notes that the concurrent use of dofetilide 500 micrograms twice daily with **hydrochlorothiazide** 50 mg daily for 7 days increased the dofetilide AUC by 14% and increased the QTc interval by 48 milliseconds.[1] Similar results were seen with the same dose of dofetilide given with **hydrochlorothiazide**/**triamterene** 50/100 mg daily (18% increase in AUC, and 38 millisecond increase in QTc).[1]

Mechanism

Triamterene might be expected to increase dofetilide plasma levels by competing for its renal tubular secretion (see 'Dofetilide + Miscellaneous', below), but the effect of its combination with hydrochlorothiazide was no greater than with hydrochlorothiazide alone. Why hydrochlorothiazide should increase dofetilide levels is unclear. An increase in dofetilide levels would be expected to increase the QT interval, but the increase seen here was much greater than expected by the change in plasma levels. The manufacturer suggests that a reduction in serum potassium could have contributed to the extent of QT prolongation.[1] This makes sense for hydrochlorothiazide (a potassium-depleting diuretic), but the combination with triamterene (a potassium-sparing diuretic) might therefore have been expected to have less effect on the QT interval.

Importance and management

On the basis of the above findings, the manufacturer contraindicates the use of dofetilide with hydrochlorothiazide alone or in combination with triamterene.[2] Given the increase in QT interval, a risk factor for torsade de pointes, this appears a prudent precaution. Further study is needed. Any diuretic that depletes serum potassium (such as the **loop diuretics**) might be expected to increase the risk of QT prolongation and torsade de pointes with dofetilide, and serum potassium should be monitored.[2]

1. Pfizer Global Pharmaceuticals. Personal Communication, June 2004.
2. Tikosyn (Dofetilide). Pfizer Labs. US Prescribing information, November 2006.

Dofetilide + H_2-receptor antagonists

Cimetidine markedly increases plasma dofetilide levels, and increases dofetilide-induced QT prolongation and the risk of torsade de pointes. Dofetilide appears not to interact with ranitidine.

Clinical evidence

A placebo-controlled study in 24 healthy subjects found that **cimetidine** 400 mg twice daily given with dofetilide 500 micrograms twice daily for 7 days decreased the renal clearance of dofetilide by 44%, increased its AUC by 58%, and increased its peak blood levels by 50%, without significantly altering the QTc interval.[1] In a further study it was found that **cimetidine** 100 mg twice daily or 400 mg twice daily for 4 days reduced the renal clearance of a single 500-microgram dose of dofetilide by 13% and 33%, respectively. In addition, the respective **cimetidine** doses increased the QTc interval by 22% and 33%. Conversely, **ranitidine** 150 mg twice daily did not significantly affect the pharmacokinetics or pharmacodynamics of dofetilide.[2]

Mechanism

At least 50% of a dofetilide dose is eliminated unchanged in the urine by an active renal tubular secretion mechanism.[3,4] Drugs that inhibit this mechanism, such as cimetidine, increase dofetilide plasma levels.[2,3] There is a linear relationship between plasma dofetilide concentrations and prolongation of the QT interval, which increases the risk of torsade de pointes.[3]

Importance and management

An established interaction. Because of the likely increased risk of torsade de pointes, the manufacturer contraindicates the use of cimetidine in patients taking dofetilide. This would seem to be a prudent precaution. This applies equally to cimetidine at non-prescription doses, and patients taking dofetilide should be warned to avoid this. No special precautions appear to be necessary with ranitidine.

1. Vincent J, Gardner MJ, Apseloff G, Baris B, Willavize S, Friedman HL. Cimetidine inhibits renal elimination of dofetilide without altering QTc activity on multiple dosing in healthy subjects. *Clin Pharmacol Ther* (1998) 63, 210.
2. Abel S, Nichols DJ, Brearly CJ, Eve MD. Effect of cimetidine and ranitidine on pharmacokinetics and pharmacodynamics of a single dose of dofetilide. *Br J Clin Pharmacol* (2000) 49, 64–71.
3. Tikosyn (Dofetilide). Pfizer Labs. US Prescribing information, November 2006.
4. Rasmussen HS, Allen MJ, Blackburn KJ, Butrous GS, Dalrymple HW. Dofetilide, a novel class III antiarrhythmic agent. *J Cardiovasc Pharmacol* (1992) 20 (Suppl 2), S96–S105.

Dofetilide + Ketoconazole

Ketoconazole markedly increases the plasma levels of dofetilide. This is likely to be associated with an increased risk of dofetilide-induced QT prolongation and torsade de pointes.

Clinical evidence

The manufacturer of dofetilide notes that ketoconazole 400 mg daily, given with dofetilide 500 micrograms twice daily for 7 days, increased the dofetilide peak levels by 53% in men and 97% in women, and increased the AUC by 41% in men and 69% in women.[1] Ketoconazole decreased the renal clearance of dofetilide by 31% and the non-renal clearance by 40%, resulting in a reduction in total clearance of 35%.[2]

Mechanism

Ketoconazole may inhibit the active renal tubular secretion mechanism by which dofetilide is eliminated, so reducing its loss from the body.[1,2] Ketoconazole also inhibits the metabolism of dofetilide[2] by the cytochrome P450 isoenzyme CYP3A4. Both of these mechanisms contribute to the increase in dofetilide plasma levels. There is a linear relationship between plasma dofetilide concentrations and prolongation of the QT interval, which increases the risk of torsade de pointes.[1]

Importance and management

An established interaction. Because of the likely increased risk of torsade de pointes, the manufacturer contraindicates the use of ketoconazole in patients taking dofetilide. This would seem to be a prudent precaution.

1. Tikosyn (Dofetilide). Pfizer Labs. US Prescribing information, November 2006.
2. Tikosyn (Dofetilide). Pfizer US Pharmaceuticals. Product monograph, March 2002. Available at http://www.tikosyn.com/pdf/Tikosyn_Product_Monograph.pdf (accessed 29/01/10).

Dofetilide + Miscellaneous

The manufacturer of dofetilide cautions about the use of various drugs that may have the potential to increase dofetilide plasma levels, so increasing the risk of QT prolongation and arrhythmias. Use with other drugs that prolong the QT interval should be avoided.

Clinical evidence, mechanism, importance and management

(a) Drugs that affect renal secretion

At least 50% of a dofetilide dose is eliminated unchanged in the urine by an active renal tubular secretion mechanism.[1,2] Some drugs that inhibit this mechanism have been shown to increase dofetilide plasma levels (e.g. see 'Dofetilide + H_2-receptor antagonists', above). The manufacturer contraindicates their concurrent use since there is a linear relationship between plasma dofetilide concentrations and prolongation of the QT interval, which is a risk factor for torsade de pointes.[1] The manufacturer also contraindicates the use of other drugs that may inhibit the renal mechanism by which dofetilide is eliminated, such as **prochlorperazine** and **megestrol**,[1] although these have not been directly studied. Furthermore, the manufacturer suggests[1] that there is a potential for dofetilide plasma levels to be increased by other drugs undergoing active renal secretion (e.g. **amiloride**, **metformin** and **triamterene**), but this needs confirmation in direct studies (see also 'Dofetilide + Diuretics', p.286). Until then, these drugs should be used cautiously with dofetilide.

(b) Inhibitors of hepatic metabolism

Dofetilide is partially metabolised by the liver, primarily by the cytochrome P450 isoenzyme CYP3A4.[3] The manufacturer suggests[1] that there is a potential for dofetilide plasma levels to be increased by inhibitors of CYP3A4, and this has been shown for ketoconazole (see 'Dofetilide + Ketoconazole', p.287). They recommend caution with other CYP3A4 inhibitors and specifically name **macrolides**, **azoles**, **protease inhibitors**, **amiodarone**, **diltiazem**, **grapefruit juice**, and **nefazodone**. They also name **SSRIs**, **cannabinoids**, **norfloxacin**, **quinine** and **zafirlukast**, but with the exception of the SSRI **fluvoxamine** (and possibly **fluoxetine**), these drugs do not usually appear to cause clinically relevant interactions by this mechanism.

(c) Other drugs that prolong the QT interval

Dofetilide is a class III antiarrhythmic that prolongs the QT interval and can cause torsade de pointes arrhythmia. In general, use of two or more drugs that prolong the QT interval should be avoided. See also 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290.

(d) Other drugs

Studies in healthy subjects have shown that **amlodipine**, **glibenclamide**, and **HRT** (**conjugated oestrogens** plus **medroxyprogesterone**) do not affect the pharmacokinetics of dofetilide.[1] The pharmacokinetics of **propranolol** 40 mg twice daily and **oral contraceptives** are not affected by dofetilide.[1]

1. Tikosyn (Dofetilide). Pfizer Inc. US prescribing information, November 2006.
2. Rasmussen HS, Allen MJ, Blackburn KJ, Butrous GS, Dalrymple HW. Dofetilide, a novel class III antiarrhythmic agent. *J Cardiovasc Pharmacol* (1992) 20 (Suppl 2), S96–S105.
3. Walker DK, Alabaster CT, Congrave GS, Hargreaves MB, Hyland R, Jones BC, Reed LJ, Smith DA. Significance of metabolism in the disposition and action of the antidysrhythmic drug, dofetilide. *In vitro* studies and correlation with *in vivo* data. *Drug Metab Dispos* (1996) 24, 447–55.

Dofetilide + Omeprazole

Omeprazole appears not to interact with dofetilide.

Clinical evidence, mechanism, importance and management

A study in 12 healthy subjects found that pretreatment with omeprazole 40 mg (10 or 2 hours before dofetilide) did not affect the pharmacokinetics of a single 500-microgram dose of dofetilide or the dofetilide-induced change in QTc interval.[1] No special precautions appear to be necessary.

1. Vincent J, Gardner MJ, Baris B, Willavize SA. Concurrent administration of omeprazole and antacid does not alter the pharmacokinetics and pharmacodynamic of dofetilide in healthy subjects. *Clin Pharmacol Ther* (1996) 59, 182.

Dofetilide + Phenytoin

The concurrent use of dofetilide and phenytoin does not affect the pharmacokinetics of either drug.

Clinical evidence, mechanism, importance and management

In a placebo-controlled study, 24 healthy subjects were given phenytoin, to achieve steady-state plasma levels of 8 to 20 micrograms/mL, and then dofetilide 500 micrograms twice daily. No changes in phenytoin pharmacokinetics or cardiac effects were seen.[1] Another study by the same researchers in 24 subjects given dofetilide 500 micrograms every 12 hours found that phenytoin 300 mg daily did not have a clinically important effect on either the pharmacokinetics of dofetilide or on its cardiovascular pharmacodynamics (QTc, PR, QRS, RR intervals).[2] These findings confirm those of an *in vitro* study[3] showing that dofetilide did not inhibit the cytochrome P450 isoenzyme CYP2C9, thus suggesting that dofetilide is unlikely to affect the metabolism of phenytoin. No additional precautions therefore seem necessary on concurrent use.

1. Vincent J, Gardner M, Scavone J, Ashton H, Willavize S, Friedman HL. The effect of dofetilide on the steady-state PK and cardiac effects of phenytoin in healthy subjects. *Clin Pharmacol Ther* (1997) 61, 233.
2. Gardner MJ, Ashton HM, Willavize SA, Friedman HL, Vincent J. The effects of phenytoin on the steady-state PK and PD of dofetilide in healthy subjects. *Clin Pharmacol Ther* (1997) 61, 205.
3. Walker DK, Alabaster CT, Congrave GS, Hargreaves MB, Hyland R, Jones BC, Reed LJ, Smith DA. Significance of metabolism in the disposition and action of the antidysrhythmic drug, dofetilide. *In vitro* studies and correlation with *in vivo* data. *Drug Metab Dispos* (1996) 24, 447–55.

Dofetilide + Theophylline

The concurrent use of theophylline and dofetilide does not appear to affect the pharmacokinetics of either drug.

Clinical evidence, mechanism, importance and management

Studies in healthy subjects found that the concurrent use of theophylline 450 mg every 12 hours and dofetilide 500 micrograms every 12 hours did not alter the steady-state pharmacokinetics of either drug.[1,2] In addition, the increase in the QTc interval was no greater with the combination than with dofetilide alone.[1] No additional precautions appear to be necessary if both drugs are given. Aminophylline does not appear to have been studied, but it would be expected to behave in much the same way as theophylline.

1. Gardner MJ, Ashton HM, Willavize SA, Vincent J. The effects of concomitant dofetilide therapy on the pharmacokinetics and pharmacodynamics of theophylline. *Clin Pharmacol Ther* (1996) 59, 181.
2. Gardner MJ, Ashton HM, Willavize SA, Vincent J. The effects of orally administered theophylline on the pharmacokinetics and pharmacodynamics of dofetilide. *Clin Pharmacol Ther* (1996) 59, 182.

Dofetilide + Trimethoprim

Trimethoprim markedly increases the plasma levels of dofetilide. This is likely to be associated with an increased risk of dofetilide-induced QT prolongation and torsade de pointes.

Clinical evidence, mechanism, importance and management

The manufacturer of dofetilide notes that trimethoprim 160 mg (in combination with sulfamethoxazole 800 mg) twice daily given with dofetilide 500 micrograms twice daily for 4 days increased the peak levels of dofetilide by 93% and increased its AUC by 103%.[1] Trimethoprim inhibits the active renal tubular secretion mechanism by which dofetilide is eliminated, so reducing its loss from the body. There is a linear relationship between plasma dofetilide concentrations and prolongation of the QT interval, which increases the risk of torsade de pointes.[1] For this reason, the manufacturer contraindicates the use of trimethoprim in patients taking dofetilide. This would seem to be a prudent precaution.

1. Tikosyn (Dofetilide). Pfizer Labs. US Prescribing information, November 2006.

Dofetilide + Verapamil

Verapamil transiently increases dofetilide plasma levels and QTc prolongation, and has been associated with an increased risk of torsade de pointes.

Clinical evidence

A study in 12 healthy subjects found that verapamil 80 mg three times daily given with dofetilide 500 micrograms twice daily for 3 days caused a 42% increase in the peak plasma levels of dofetilide (from 2.4 nanograms/mL to 3.43 nanograms/mL). There was a 26% increase in the AUC_{0-4}, which was associated with a transient simultaneous increase in the QTc interval of 20 milliseconds for dofetilide alone and 26 milliseconds for the combination. However, the AUC_{0-8} was not significantly different.[1] The manufacturer notes that an analysis of clinical study data for dofetilide revealed a higher occurrence of torsade de pointes when verapamil was used with dofetilide.[2]

Mechanism

Verapamil is postulated to interact with dofetilide by increasing its rate of absorption by increasing hepatic blood flow.[1] There is a linear relationship

between plasma dofetilide concentrations and prolongation of the QT interval, which is a risk factor for torsade de pointes.[2]

Importance and management

The use of verapamil with dofetilide appears to be associated with a transient increase in dofetilide plasma concentrations, and an increased risk of torsade de pointes. For this reason, the combination is contraindicated.

1. Johnson BF, Cheng SL, Venitz J. Transient kinetic and dynamic interactions between verapamil and dofetilide, a class III antiarrhythmic. *J Clin Pharmacol* (2001) 41, 1248–56.
2. Tikosyn (Dofetilide). Pfizer Labs. US Prescribing information, November 2006.

Dronedarone + Miscellaneous

Dronedarone exposure is increased by diltiazem, grapefruit juice, ketoconazole (17-fold increase) and verapamil, all CYP3A4 inhibitors. Other CYP3A4 inhibitors would be expected to interact similarly. Dronedarone exposure is decreased by rifampicin (rifampin), a CYP3A4 inducer, and other CYP3A4 inducers would be expected to interact similarly. Dronedarone increases the exposure to simvastatin, diltiazem, nifedipine and verapamil, all CYP3A4 substrates: other CYP3A4 substrates (such as tacrolimus, sirolimus and other calcium-channel blockers) are predicted to interact similarly. Dronedarone is also predicted to increase the exposure to CYP2D6 substrates (such as the tricyclics). Pantoprazole and losartan do not appear to affect the pharmacokinetics of dronedarone and dronedarone does not appear to affect the pharmacokinetics of oral hormonal contraceptives, theophylline, warfarin or losartan.

Clinical evidence, mechanism, importance and management

(a) Calcium-channel blockers

Dronedarone exposure was increased by about 40 to 70% by **diltiazem** and **verapamil**.[1] Dronedarone is primarily metabolised by the cytochrome P450 isoenzyme CYP3A4, of which diltiazem and verapamil are both inhibitors. Exposure to **diltiazem**, **nifedipine** and **verapamil** was increased by 40 to 50% by dronedarone.[1] Dronedarone is a moderate inhibitor of the cytochrome P450 isoenzyme CYP3A4, by which these drugs are metabolised. Concurrent use therefore raises their levels. Note that other calcium-channel blockers are also substrates for CYP3A4 and would therefore be expected to interact similarly. Note that additive bradycardia and cardiac depression may also occur with the concurrent use of dronedarone and calcium-channel blockers that affect heart rate, such as **verapamil** or **diltiazem**. This is similar to the interaction of amiodarone with **verapamil** or **diltiazem**, see 'Amiodarone + Calcium-channel blockers', p.277.

(b) CYP2D6 substrates

Dronedarone is an inhibitor of the cytochrome P450 isoenzyme CYP2D6 and as such may increase exposure to drugs metabolised by this route. This has been seen with metoprolol, see 'Beta blockers + Dronedarone', p.1005). Other CYP2D6 substrates (the manufacturers name the **tricyclic antidepressants** and **SSRIs**) may be expected to interact similarly.[1] For a list of CYP2D6 substrates, see 'Table 1.3', (p.6).

(c) CYP3A4 inducers

Rifampicin (**rifampin**) decreased dronedarone exposure by 80% and its use with dronedarone should be avoided.[1] Dronedarone is primarily metabolised by the cytochrome P450 isoenzyme CYP3A4 and the concurrent use of other CYP3A4 inducers is also not recommended. The manufacturer of dronedarone specifically names **carbamazepine**, **phenobarbital**, **phenytoin** and **St John's wort**.[1] For a list of CYP3A4 inducers, see 'Table 1.4', (p.6).

(d) CYP3A4 inhibitors

The AUC and maximum plasma concentration of dronedarone were increased 17-fold and 9-fold, respectively, by repeated doses of **ketoconazole**.[1] Dronedarone is primarily metabolised by the cytochrome P450 isoenzyme CYP3A4, of which ketoconazole is a potent inhibitor. Concurrent use therefore leads to raised dronedarone levels. The manufacturer of dronedarone contraindicates its use with potent CYP3A4 inhibitors, and specifically names the azoles **itraconazole**, **ketoconazole** and **voriconazole**, **ciclosporin**, the macrolides **clarithromycin** and **telithromycin**, **nefazodone** and **ritonavir**. However, note that **ciclosporin** is not usually considered to be a potent CYP3A4 inhibitor. For a list of CYP3A4 inhibitors, see 'Table 1.4', (p.6).

Grapefruit juice also increased the AUC and maximum plasma concentration of dronedarone 3-fold and 2.5-fold, respectively, and the manufacturers state that it should be avoided in patients taking dronedarone.[1]

(e) CYP3A4 substrates

The plasma concentrations of **sirolimus**, **tacrolimus** and other CYP3A4 substrates with a narrow therapeutic index, may be increased by dronedarone, particularly after oral administration. As such, the manufacturer recommends that plasma concentrations are monitored and doses adjusted accordingly.[1] Note that dronedarone has a modest effect on the pharmacokinetics of the calcium-channel blockers, which are CYP3A4 substrates (see *Calcium-channel blockers*, above). For a list of CYP3A4 substrates see 'Table 1.4', (p.6).

(f) Digoxin

The manufacturer of dronedarone states that the exposure to digoxin was increased 2.5-fold by dronedarone.[1] Digoxin is a substrate of the drug transporter protein P-glycoprotein, which is inhibited by dronedarone. Furthermore, both drugs can cause bradycardia, and additive bradycardia and AV block may possibly occur on concurrent use. Because of this, the manufacturer advises that the need for digoxin should be reviewed and if considered necessary, the digoxin dose should be halved and plasma levels monitored closely. The patient should also be monitored for any signs of digoxin toxicity[1] (e.g. bradycardia, nausea, vomiting). This is similar to the interaction of digoxin and amiodarone, to which dronedarone is structurally related. Consider also 'Digoxin and related drugs + Amiodarone', p.1081.

Digoxin may be used as a probe drug to assess the effects of other drugs on P-glycoprotein, and therefore the manufacturers of dronedarone suggest that it may raise the levels of other P-glycoprotein substrates.

(g) Hormonal contraceptives

The manufacturers of dronedarone state that, in healthy subjects, the concentrations of **ethinylestradiol** and **levonorgestrel** (given as an oral combined hormonal contraceptive) were not affected by the concurrent use of dronedarone.[1]

(h) Statins

The manufacturers of dronedarone state that the exposure to **simvastatin** and its active metabolite, simvastatin acid, was increased fourfold and twofold, respectively, by dronedarone.[1] Dronedarone is an inhibitor of the cytochrome P450 isoenzyme CYP3A4, which is involved in the metabolism of **simvastatin** and some other statins. This interaction is similarly to that seen with amiodarone, which is structurally related to dronedarone. Until more is known it may be prudent to follow the recommendations given for the use of amiodarone with the statins. See 'Statins + Amiodarone', p.1320.

(i) Warfarin

The exposure to *S*-warfarin was increased by 20% when healthy subjects were also given dronedarone 600 mg twice daily (note this is higher than the recommended dose of 400 mg twice daily). The exposure to *R*-warfarin was unaffected and there was no clinically significant increase in INR.[1] In addition, in clinical studies in patients with atrial fibrillation or atrial flutter, no excessive risk of bleeding (compared with placebo) was observed when dronedarone was given with oral anticoagulants (drugs not specified).[1]

(j) Other drugs

The manufacturer of dronedarone states that the pharmacokinetics of dronedarone were not affected by **pantoprazole**, the steady-state exposure to **theophylline** was not affected by dronedarone, and no interaction has been seen between **losartan** and dronedarone.[1]

1. Multaq (Dronedarone). Sanofi-Aventis U.S. LLC. US Prescribing Information, July 2009.

Drugs that prolong the QT interval + Drugs that lower potassium levels

The combined use of drugs that can cause hypokalaemia (e.g. amphotericin B, corticosteroids, thiazide and loop diuretics, and stimulant laxatives) and drugs that prolong the QT interval (e.g. class Ia and class III antiarrhythmics; see 'Table 9.2', p.290)

Table 9.2 Drugs causing QT prolongation and torsade de pointes

High risk	*Some risk*
Amisulpride	Clarithromycin (increase in QTc interval less than 5 milliseconds; rare case reports of torsade de pointes)
Antiarrhythmics, class Ia (ajmaline, cibenzoline, disopyramide, hydroquinidine, procainamide, quinidine)	Chlorpromazine (rare case reports of torsade de pointes)
Antiarrhythmics, class III (amiodarone, azimilide, cibenzoline, dofetilide,† dronedarone, ibutilide,† sotalol†)	Erythromycin oral (see also high risk)
Arsenic trioxide (40% of patients had a QTc interval greater than 500 milliseconds)	Gatifloxacin (increase in QTc interval less than 10 milliseconds)
Artemisinin derivatives (artemisinin, artemether/lumefantrine - 5% of patients had an asymptomatic prolongation of QTc intervals by greater than 30 milliseconds, with an actual QTc of greater than 450 milliseconds in males and greater than 470 milliseconds in females)	Levofloxacin (rare case reports of torsade de pointes)
Astemizole† (if metabolism inhibited)	Lithium (greater risk if levels raised)
Cisapride† (if metabolism inhibited)	Methadone (in doses greater than 100 mg)
Droperidol†	Moxifloxacin (increase in QTc interval less than 10 milliseconds)
Erythromycin intravenous (see also some risk)	Pentamidine intravenous (case reports of torsade de pointes)
Halofantrine†	Quinine (greater risk with higher doses and intravenous use)
Haloperidol (also increased in high doses and with intravenous use)	Spiramycin
Ketanserin (30% of patients had an increase of greater than 30 milliseconds in a clinical trial)	Tricyclics (prolongation of QTc interval greater than 10 milliseconds, most notable risk occurs with clomipramine, risk with other tricyclics largely seems to be in overdose)
Mesoridazine†	
Pimozide†	
Ranolazine (dose-related QTc interval prolonged by up to 15 milliseconds, or more if metabolism inhibited)	
Sertindole†	
Sparfloxacin (10 millisecond increase in clinical trials)	
Terfenadine† (if metabolism inhibited)	
Thioridazine†	

†indicates drug suspended/restricted in some countries because of this effect
This list is not exhaustive

should be well monitored because hypokalaemia increases the risk of torsade de pointes. There appear to be only a few reports of this interaction, for example, see 'Beta blockers + Potassium-depleting drugs', p.1016. Note that stimulant laxatives only tend to cause hypokalaemia in cases of misuse or overuse.

Drugs that prolong the QT interval + Other drugs that prolong the QT interval

The concurrent use of more than one drug that prolongs the QT interval increases the risk of torsade de pointes, which may lead to life-threatening ventricular arrhythmias. The risk varies with different combinations of drugs that prolong the QT interval, and with the presence of other risk factors for this effect.

Clinical evidence, mechanism, importance and management

If the QT interval on the ECG becomes excessively prolonged, ventricular arrhythmias can develop, in particular a type of polymorphic tachycardia known as torsade de pointes. On the ECG this arrhythmia can appear as an intermittent series of rapid spikes during which the heart fails to pump effectively, the blood pressure falls and the patient will feel dizzy and may possibly lose consciousness. Usually the condition is self-limiting but it may progress and degenerate into ventricular fibrillation, which can cause sudden death.

There are a number of reasons why QT interval prolongation can occur. These include:

- increasing age
- female sex
- congenital long QT syndrome
- cardiac disease
- thyroid disease
- some metabolic disturbances (hypocalcaemia, hypokalaemia, hypomagnesaemia)

Another important cause is the use of various QT-prolonging drugs including some antiarrhythmics, antipsychotics, antihistamines, antimalarials and others.[1,2] These drugs all appear to cause this effect by blocking the rapid component of the delayed rectifier (repolarisation) potassium channel.

At what degree of prolongation of corrected QT (QTc) interval torsade de pointes is likely to develop is uncertain. However a QTc interval exceeding 500 milliseconds is generally considered of particular concern, but this is not an exact figure. In addition, there is uncertainty about what constitutes an important change in QTc interval from baseline, although, in general, increases of 30 to 60 milliseconds should raise concern, and increases of over 60 milliseconds raise clear concerns about the potential for arrhythmias. Because of these uncertainties, many drug manufacturers and regulatory agencies contraindicated the concurrent use of drugs known to prolong the QT interval, and a 'blanket' warning was often issued because the QT prolonging effects of the drugs are expected to be additive. Regulatory guidance for the assessment of risk of a non-antiarrhythmic drug states that drugs causing an increase in mean

QT/QTc interval of around 5 milliseconds or less do not appear to cause torsade de pointes. Data on drugs causing mean increases of around 5 milliseconds and less than 20 milliseconds are inconclusive, and some drugs causing this have been associated with proarrhythmic risk. Drugs with an increase of more than 20 milliseconds have a substantially increased likelihood of being proarrhythmic.[3,4] The extent of the drug-induced prolongation usually depends on the dose of the drug and the particular drugs in question.

'Table 9.2', (p.290) is a list of drugs that are known to prolong the QT interval and cause torsade de pointes. Note that this list is not exhaustive of all the drugs that have ever been reported to be associated with QT interval prolongation and torsade de pointes. For some of the drugs listed, QT prolongation is a fairly frequent effect when the drug is used alone, and it is well accepted that use of these drugs requires careful monitoring (e.g. a number of the antiarrhythmics). For other drugs, QT prolongation is rare, but because of the relatively benign indications for these drugs, the risk-benefit ratio is considered poor, and use of these drugs has been severely restricted or discontinued (e.g. astemizole, terfenadine, cisapride). For others there is less clear evidence of the risk of QT prolongation (e.g. clarithromycin, chlorpromazine). Drugs that have only been associated with isolated cases of torsade de pointes, and drugs that are commonly considered to cause QT prolongation, but for which there does not appear to be any published evidence to support this effect (e.g. **chloroquine**), are not usually included in this table. Specific reports of additive QT-prolonging effects with or without torsade de pointes are covered in individual monographs.

Drugs that do not themselves prolong the QT interval, but potentiate the effect of drugs that do (e.g. by pharmacokinetic mechanisms, lowering serum potassium, or by causing bradycardia) are not included in 'Table 9.2', (p.290). The interactions of these drugs (e.g. azole antifungals with cisapride, astemizole, or terfenadine, and potassium-depleting diuretics with sotalol) are dealt with in individual monographs. However, note that some drugs, for example the macrolide antibacterials, may cause QT prolongation by dual mechanisms: they appear to have both the intrinsic ability to prolong the QT interval, and they may inhibit the metabolism of drugs that prolong the QT interval.[5]

General references discussing the problems of QT-prolongation are given below.[6-15]

The consensus of opinion is that the concurrent use of drugs that have a high risk of prolonging the QTc interval should be avoided because of the risk of additive effects, leading to the possible development of serious and potentially life-threatening torsade de pointes. However, under certain circumstances (e.g. in the treatment of life-threatening arrhythmias) concurrent use may be unavoidable. In this situation close ECG monitoring, and a careful consideration of other risk factors present is essential. With drugs that have some risk of prolonging the QTc interval, some caution is appropriate, particularly in patients with other risk factors for QTc prolongation.

1. Zeltzer D, Justo D, Halkin A, Prokhorov V, Heller K, Viskin S. Torsade de pointes due to noncardiac drugs. Most patients have easily identifiable risk factors. *Medicine* (2003) 82, 282–90.
2. Benoit SR, Mendelsohn AB, Nourjah P, Staffa JA, Graham DJ. Risk factors for prolonged QTc among US adults: Third National Health and Nutrition Survey. *Eur J Cardiovasc Prev Rehabil* (2005) 12, 363–8.
3. European Medicines Agency. Note for guidance on the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. November 2005. Available at: http://www.emea.europa.eu/pdfs/human/ich/000204en.pdf (accessed 29/01/10).
4. US Food and Drug Administration. Guidance for Industry: E14 Clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. October 2005. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073153.pdf (accessed 29/01/10).
5. Shaffer D, Singer S, Korvick J, Honig P. Concomitant risk factors in reports of torsades de pointes associated with macrolide use: review of the United States Food and Drug Administration Adverse Event Reporting System. *Clin Infect Dis* (2002) 35, 197–200.
6. Committee on Safety of Medicines/Medicines Control Agency. Drug-induced prolongation of the QT interval. *Current Problems* (1996) 22, 2.
7. Thomas SHL. Drugs, QT interval abnormalities and ventricular arrhythmias. *Adverse Drug React Toxicol Rev* (1994) 13, 77–102.
8. De Ponti F, Poluzzi E, Montanaro N. QT-interval prolongation by non-cardiac drugs: lessons to be learned from recent experience. *Eur J Clin Pharmacol* (2000) 56, 1–18.
9. Haverkamp W, Breithardt G, Camm AJ, Janse MJ, Rosen MR, Antzelevitch C, Escande D, Franz M, Malik M, Moss A, Shah R. The potential for QT prolongation and pro-arrhythmia by non-anti-arrhythmic drugs: clinical and regulatory implications. Report on a policy conference of the European Society of Cardiology. *Cardiovasc Res* (2000) 47, 219–33.
10. Bednar MM, Harrigan EP, Anziano RJ, Camm AJ, Ruskin JN. The QT interval. *Prog Cardiovasc Dis* (2001) 43 (Suppl 1): 1–45.
11. Kao LW, Furbee RB. Drug-induced Q–T prolongation. *Med Clin North Am* (2005) 89, 1125–44.
12. Glassman AH, Bigger JT. Antipsychotic drugs: prolonged QTc interval, torsade de pointes, and sudden death. *Am J Psychiatry* (2001) 158, 1774–82.
13. Stöllberger C, Huber JO, Finsterer J. Antipsychotic drugs and QT prolongation. *Int Clin Psychopharmacol* (2005) 20, 243–51.
14. Committee on Safety of Medicines/Medicines Control Agency. Risk of QT interval prolongation with methadone. *Current Problems* (2006) 31, 6.
15. Committee on Safety of Medicines/Medicines Control Agency. Cardiac arrhythmias associated with antipsychotic drugs. *Current Problems* (2006) 31, 9.

Flecainide + Amiodarone

Serum flecainide levels are increased by amiodarone. An isolated report describes a patient taking amiodarone who developed torsade de pointes when given flecainide.

Clinical evidence

Amiodarone (1.2 g daily for 10 to 14 days then 600 mg daily) was given to 7 patients taking oral flecainide 200 to 500 mg daily. The trough plasma levels of flecainide were increased by about 50%, and the flecainide dose was reduced by one-third (averaging a reduction from 325 to 225 mg daily) to keep the flecainide levels constant. Observations in two patients suggest that the interaction begins soon after the amiodarone is added, and it takes 2 weeks or more to develop fully.[1]

Other authors have reported this interaction, and suggest reducing the flecainide dose by between one-third to one-half when amiodarone is added.[2-5] Another study found that amiodarone raised steady-state flecainide plasma levels by 37% in extensive CYP2D6 metabolisers (that is, those with normal levels of this isoenzyme), and by 55% in poor CYP2D6 metabolisers (that is, those lacking this isoenzyme).[6] In a later report of this study the authors concluded that these differences were not clinically important, and that CYP2D6 phenotype does not affect the extent of the interaction between flecainide and amiodarone.[7]

An isolated report describes a patient taking amiodarone who developed torsade de pointes when also given flecainide.[8]

Mechanism

Amiodarone inhibits the cytochrome P450 isoenzyme CYP2D6 by which flecainide is metabolised, so that the flecainide is metabolised by the liver more slowly. Other mechanisms may also be involved.[7]

Importance and management

An established interaction, but the documentation is limited. Reduce the flecainide dosage by one-third to one-half if amiodarone is added.[1-5,7] Monitor for flecainide adverse effects (dizziness, nausea, and tremor) and, where possible, consider monitoring flecainide levels. There seems to be no need to treat extensive metabolisers differently from poor metabolisers.[7] Remember that the interaction may take 2 weeks or more to develop fully, and also that amiodarone is cleared from the body exceptionally slowly so that this interaction may persist for some weeks after it has been withdrawn.

1. Shea P, Lal R, Kim SS, Schechtman K, Ruffy R. Flecainide and amiodarone interaction. *J Am Coll Cardiol* (1986) 7, 1127–30.
2. Leclercq JF, Coumel P. La flécaïnide: un nouvel antiarythmique. *Arch Mal Coeur* (1983) 76, 1218–29.
3. Fontaine G, Frank R, Tonet JL. Association amiodarone-flécaïnide dans le traitement des troubles du rythme ventriculaires graves. *Arch Mal Coeur* (1984) 77, 1421.
4. Leclercq JF, Coumel P. Association amiodarone-flécaïnide dans le traitement des troubles du rythme ventriculaires graves. Résponse. *Arch Mal Coeur* (1984) 77, 1421–2.
5. Leclercq JF, Denjoy I, Mentré F, Coumel P. Flecainide acetate dose-concentration relationship in cardiac arrhythmias: influence of heart failure and amiodarone. *Cardiovasc Drugs Ther* (1990) 4, 1161–65.
6. Funck-Brentano C, Kroemer HK, Becquemont L, Bühl K, Eichelbaum M, Jaillon P. The interaction between amiodarone and flecainide is genetically determined. *Circulation* (1992) 86, (Suppl I), I–720.
7. Funck-Brentano C, Becquemont L, Kroemer HK, Bühl K, Knebel NG, Eichelbaum M, Jaillon P. Variable disposition kinetics and electrocardiographic effects of flecainide during repeated dosing in humans: contribution of genetic factors, dose-dependent clearance, and interaction with amiodarone. *Clin Pharmacol Ther* (1994) 55, 256–69.
8. Andrivet P, Beaslay V, Canh VD. Torsades de pointe with flecainide-amiodarone therapy. *Intensive Care Med* (1990) 16, 342–3.

Flecainide + Antiepileptics; Enzyme-inducing

Limited data suggests that carbamazepine, phenytoin or phenobarbital may modestly increase flecainide clearance. Primidone and fosphenytoin may interact similarly.

Clinical evidence, mechanism, importance and management

Preliminary findings of a controlled study in 6 patients with epilepsy taking **phenytoin** or **phenobarbital** found that the pharmacokinetics of a single 2-mg/kg intravenous dose of flecainide were not generally different from those in a group of 7 healthy subjects not taking these antiepileptics. However, a 25 to 30% shorter flecainide half-life and decreased urinary clearance of unchanged drug were noted.[1] The manufacturer notes there is limited data indicating similar changes in flecainide elimination associated with **carbamazepine**.[2]

These changes are modest and the authors of the first study suggest that an adjustment of the flecainide dose may not be required in those also taking **phenytoin** or **phenobarbital**. These findings probably also apply to **primidone**, which is, in part, metabolised to phenobarbital, and **fosphenytoin**, a prodrug of phenytoin.

1. Pentikäinen PJ, Halinen MO, Hiepakorpi S, Chang SF, Conard GJ, McQuinn RL. Pharmacokinetics of flecainide in patients receiving enzyme inducers. *Acta Pharmacol Toxicol (Copenh)* (1986) 59 (Suppl 5), 91.
2. Tambocor (Flecainide acetate). Meda Pharmaceuticals. UK Summary of product characteristics, October 2007.

Flecainide + Antihistamines

There are no published cases of an interaction between flecainide and non-sedating antihistamines, but it has been suggested that the concurrent use of mizolastine or terfenadine may increase the risk of ventricular arrhythmias.

Clinical evidence, mechanism, importance and management

The UK manufacturer of flecainide advises avoiding the concurrent use of **mizolastine** and **terfenadine** due to an increased risk of ventricular arrhythmias.[1] Similarly, the manufacturer of **mizolastine**[2] contraindicates its use with drugs known to prolong the QT interval, and gives the examples of class I and III antiarrhythmics. Note that, of the class 1 antiarrhythmics, only the class 1a antiarrhythmics are generally considered to cause QT prolongation: flecainide is a class 1c antiarrhythmic.

Terfenadine and possibly mizolastine can cause QT prolongation, but usually only when their levels are raised; however flecainide is not known to affect their metabolism. There appear to be no published reports of an interaction between these drugs, and therefore an interaction is not established.

1. Tambocor (Flecainide acetate). Meda Pharmaceuticals. UK Summary of product characteristics, October 2007.
2. Mizollen (Mizolastine). Sanofi-Aventis. UK Summary of product characteristics, March 2009.

Flecainide + Benziodarone

A single case report describes ECG changes in a patient taking flecainide with benziodarone.

Clinical evidence, mechanism, importance and management

A 71-year-old woman who had undergone kidney transplantation 7 years earlier and who was taking amlodipine, losartan, furosemide, chlortalidone, calcitriol, aspirin, prednisone, ciclosporin, cyclophosphamide and insulin was also taking flecainide, which controlled her paroxysmal atrial fibrillation. Atorvastatin was then restarted for hypercholesterolaemia and benziodarone 100 mg daily (because of intolerance to allopurinol) was added to treat hyperuricaemia. Three days later she presented with asthenia and poor overall condition and later an ECG showed a number of ECG changes including QTc interval prolongation of 482 milliseconds (22% increase) and PR interval prolongation of 203 milliseconds (18% increase). Creatinine levels were about 127 micromol/L, creatine phosphokinase 354 units/L and urea 155 mg/dL. Atorvastatin was stopped because of mild rhabdomyolysis and flecainide and benziodarone were both discontinued because an interaction was also suspected. Symptoms resolved within 48 hours, with the ECG then becoming similar to baseline. Flecainide was restarted and the dose gradually increased to 100 mg daily.[1]

It was suggested that benziodarone may inhibit the cytochrome P450 isoenzyme CYP2D6, which is concerned with the metabolism of flecainide.[1] Note that benziodarone is chemically related to amiodarone, which has a similar effect, see 'Flecainide + Amiodarone', p.291. Mild renal impairment in the patient may also have contributed to reduced flecainide elimination.

This is an isolated case and more study is needed to establish an interaction. Nevertheless, because of the similarities to amiodarone, monitoring may be prudent if flecainide and benziodarone are given concurrently.

1. Gormaz CL, Page JCG, Fuentes FL. Pharmacological interaction between flecainide and benziodarone. *Rev Esp Cardiol* (2003) 56, 631–2.

Flecainide + Cimetidine

Cimetidine can increase flecainide plasma levels.

Clinical evidence

In a study in 8 healthy subjects, cimetidine 1 g daily for a week increased the AUC of a single 200-mg dose of flecainide by 28%. The fraction of flecainide excreted unchanged in the urine was increased by 20%, but the total renal clearance was not altered.[1] In another study, in 11 patients, cimetidine 1 g daily for 5 days almost doubled the plasma levels of flecainide 200 mg daily measured 2 hours after the morning dose.[2]

Mechanism

Uncertain, but it is thought that the cimetidine reduces the hepatic metabolism of flecainide.[1,2]

Importance and management

An established but not extensively documented interaction. The clinical importance appears not to have been assessed, but be alert for the need to reduce the flecainide dose if cimetidine is added. Flecainide adverse effects include dizziness, nausea, and tremor. Caution is recommended in patients with renal impairment, as the interaction is likely to be enhanced.[1]

1. Tjandra-Maga TB, Van Hecken A, Van Melle P, Verbesselt R, De Schepper PJ. Altered pharmacokinetics of oral flecainide by cimetidine. *Br J Clin Pharmacol* (1986) 22, 108–110.
2. Nitsch J, Köhler U, Neyses L, Lüderitz B. Flecainid-Plasmakonzentraionen bei Hemmung des hepatischen Metabolismus durch Cimetidin. *Klin Wochenschr* (1987) 65 (Suppl IX), 250.

Flecainide + Colestyramine

An isolated report describes reduced plasma flecainide levels in a patient given colestyramine. However, small studies have not found an interaction.

Clinical evidence, mechanism, importance and management

A patient taking flecainide 100 mg twice daily had unusually low trough plasma levels (100 nanograms/mL) while taking colestyramine 4 g three times daily. When he stopped taking the colestyramine his plasma flecainide levels rose. However, a later study in 3 healthy subjects given flecainide 100 mg daily and colestyramine 4 g three times daily, found little or no evidence of an interaction (steady-state flecainide levels of 63.1 nanograms/mL and 59.1 nanograms/mL without and with colestyramine, respectively). *In vitro* studies also did not find any binding between flecainide and colestyramine that might result in reduced absorption from the gut.[1] The authors however postulate that the citric acid contained in the colestyramine formulation might have altered the urinary pH, which could have increased the renal clearance of the flecainide.[1]

Information seems to be limited to this preliminary report. Its general importance seems to be minor, nevertheless the outcome of concurrent use should be monitored so that any unusual cases can be identified. Note that it is generally recommended that other drugs should be given one hour before or 4 to 6 hours after colestyramine.

1. Stein H, Hoppe U. Is there an interaction between flecainide and cholestyramine? *Naunyn Schmiedebergs Arch Pharmacol* (1989) 339 (Suppl), R114.

Flecainide + Food

The absorption of flecainide is not significantly altered if it is taken with food in adults, but it may possibly be reduced by milk in infants.

Clinical evidence, mechanism, importance and management

In a study in healthy adult subjects, food had no significant effect on the rate or extent of absorption of a single 200-mg dose of flecainide.[1]

A premature baby being treated for refractory atrio-ventricular tachycardia with high doses of flecainide (40 mg/kg daily or 25 mg every 6 hours) developed flecainide toxicity (seen as ventricular tachycardia) when his **milk feed** was replaced by **dextrose 5%**. His serum flecainide levels approximately doubled. It was concluded that the **milk** had reduced flecainide absorption.[2] **Milk**-fed infants may therefore possibly need a reduced dose of flecainide if **milk** intake is reduced or stopped, but more study is needed to establish an interaction. Nevertheless, it would be prudent to monitor the effects of altering **milk** intake. Adult patients may take flecainide without regard to meals.

1. Tjandra-Maga TB, Verbesselt R, Van Hecken A, Mullie A, De Schepper PJ. Flecainide: single and multiple oral dose kinetics, absolute bioavailability and effect of food and antacid in man. *Br J Clin Pharmacol* (1986) 22, 309–16.
2. Russell GAB, Martin RP. Flecainide toxicity. *Arch Dis Child* (1989) 64, 860–2.

Flecainide + Protease inhibitors

Ritonavir may increase the levels of flecainide. A number of ritonavir-boosted protease inhibitors are predicted to interact similarly.

Clinical evidence, mechanism, importance and management

Direct evidence (from case reports or clinical studies) of an interaction between flecainide and the protease inhibitors is lacking; however, a review of protease inhibitor interactions reports that the plasma levels of flecainide may be increased by **ritonavir**.[1] Flecainide is metabolised by the cytochrome P450 isoenzyme CYP2D6, of which ritonavir is an inhibitor, leading to an increase in flecainide levels, which may increase the risk of arrhythmias and other adverse effects. As a result the manufacturers of **ritonavir** contraindicate its use with flecainide.[2,3] **Ritonavir** is commonly used to boost the activity of other protease inhibitors, until more is known, it may be prudent to avoid or use caution on the use of **ritonavir**-boosted protease inhibitors: the manufacturers of **fosamprenavir**,[4,5] **saquinavir**[6,7] and **tipranavir**,[8,9] all of which should be given with ritonavir, contraindicate the concurrent use of flecainide. Similarly, the UK manufacturer of **indinavir** contraindicates the concurrent use of flecainide.[10]

If the concurrent use of flecainide and a protease inhibitor is necessary, it would be prudent to closely monitor patients for an increase in flecainide adverse effects (such as dizziness, nausea, and tremor), adjusting the dose as necessary.

1. Burger DM, Hoetelmans RMW, Koopmans PP, Meenhorst PL, Mulder JW, Hekster YA, Beijnen JH. Clinically relevant drug interactions with antiretroviral agents. *Antivir Ther* (1997) 2, 149–165.
2. Norvir Soft Capsules (Ritonavir). Abbott Laboratories Ltd. UK Summary of product characteristics, October 2009.
3. Norvir (Ritonavir). Abbott Laboratories. US Prescribing information, November 2009.
4. Telzir (Fosamprenavir calcium). ViiV Healthcare UK Ltd. UK Summary of product characteristics, May 2009.
5. Lexiva (Fosamprenavir calcium). GlaxoSmithKline. US Prescribing information, September 2009.
6. Invirase Film-coated Tablets (Saquinavir mesilate). Roche Products Ltd. UK Summary of product characteristics, January 2009.
7. Invirase (Saquinavir mesylate). Roche Laboratories Inc. US Prescribing information, July 2007.
8. Aptivus Soft Capsules (Tipranavir). Boehringer Ingelheim Ltd. UK Summary of product characteristics, June 2009.
9. Aptivus (Tipranavir). Boehringer Ingelheim Pharmaceuticals, Inc. US Prescribing information, June 2009.
10. Crixivan (Indinavir sulphate). Merck Sharp & Dohme Ltd. UK Summary of product characteristics, October 2008.

Flecainide + Quinidine or Quinine

Quinidine and quinine cause a modest reduction in the clearance of flecainide.

Clinical evidence, mechanism, importance and management

(a) Quinidine

In a study in 6 healthy subjects, a single 50-mg oral dose of quinidine given the night before a single 150-mg intravenous dose of flecainide decreased the flecainide clearance by 23%. The flecainide half-life was increased by 22% and its AUC by 28%.[1] In another study, 5 patients who were extensive CYP2D6 metabolisers (that is, those with normal levels of this isoenzyme) and taking long-term flecainide were given quinidine 50 mg every 6 hours for 5 days. The plasma levels and clearance of *S*-(+)-flecainide were unchanged, but plasma levels of *R*-(−)-flecainide increased by about 15% and its clearance reduced by 15%. The effects of the flecainide were slightly but not significantly increased.[2] Quinidine inhibits the cytochrome P450 isoenzyme CYP2D6, which is concerned with the metabolism of flecainide. Therefore concurrent use may modestly decrease flecainide metabolism and increase its levels. The clinical importance of this interaction is uncertain, but it is probably minor.

(b) Quinine

In a study, 10 healthy subjects were given three 500-mg doses of quinine over 24 hours then a single 150-mg intravenous infusion of flecainide (given over 30 minutes). Quinine increased the AUC of flecainide by 21% and reduced its systemic clearance by 17%. Renal clearance remained unchanged. The increases in the PR and QRS intervals caused by flecainide were slightly, but not significantly, increased by quinine.[3] The evidence suggests that quinine reduces the metabolism of flecainide. The clinical importance of this interaction is uncertain but it is probably minor.

1. Munafo A, Buclin T, Tuto D, Biollaz J. The effect of a low dose of quinidine on the disposition of flecainide in healthy volunteers. *Eur J Clin Pharmacol* (1992) 43, 441–3.
2. Birgersdotter UM, Wong W, Turgeon J, Roden DM. Stereoselective genetically-determined interaction between chronic flecainide and quinidine in patients with arrhythmias. *Br J Clin Pharmacol* (1992) 33, 275–80.
3. Munafo A, Reymond-Michel G, Biollaz J. Altered flecainide disposition in healthy volunteers taking quinine. *Eur J Clin Pharmacol* (1990) 38, 269–73.

Flecainide + SSRIs

Paroxetine slightly increases flecainide levels, and an isolated case report describes raised flecainide levels and adverse effects in a patient taking paroxetine. Escitalopram and fluoxetine are predicted to interact similarly.

Clinical evidence, mechanism, importance and management

(a) Escitalopram

Although studies *in vitro* did not reveal an inhibitory effect of escitalopram on CYP2D6, limited clinical data for 'desipramine', (p.1513), and 'metoprolol', (p.1019), suggest a modest inhibitory effect.[1] The UK manufacturer of escitalopram recommends caution if it is given with drugs that are mainly metabolised by this enzyme, and that have a narrow therapeutic index. They specifically name flecainide.[1]

(b) Fluoxetine

The manufacturers of fluoxetine warn that drugs predominantly metabolised by CYP2D6, and which have a narrow therapeutic index, should be initiated at or adjusted to the low end of their dose range in patients taking fluoxetine. This will also apply if fluoxetine has been taken in the previous 5 weeks because of its long elimination half-life.[2,3] They specifically mention flecainide.[2,3]

(c) Paroxetine

In a study, 21 healthy Korean subjects with differing levels of the cytochrome P450 isoenzyme CYP2D6 were given paroxetine 20 mg daily for 7 days with a single 200-mg dose of flecainide on day 15. Paroxetine slightly increased the AUC of flecainide, by 29%, in the extensive metabolisers (that is, those with normal levels of CYP2D6) and by 17% in the intermediate metabolisers (those with reduced levels of CYP2D6), but did not significantly affect the AUC in poor metabolisers (that is, those with low levels or lacking in CYP2D6), when compared with a single dose of flecainide alone. The pharmacokinetics of flecainide alone did not differ significantly between the different metaboliser groups.[4]

A case report describes a 69-year-old patient who had been stable taking paroxetine 40 mg daily for at least 5 years, who developed confusion and paranoia about 2 weeks after starting to take flecainide 100 mg twice daily. On admission she had a flecainide plasma concentration of 1360 micrograms/L (therapeutic range 200 to 1000 micrograms/L). The symptoms resolved 3 days after paroxetine was stopped and the flecainide dose was reduced to 50 mg twice daily.[5]

Flecainide is metabolised by the cytochrome P450 isoenzyme CYP2D6. This route of metabolism can be inhibited by paroxetine, a moderate inhibitor of CYP2D6, resulting in raised flecainide levels. However, this

interaction is not apparent in the small percentage of the population who lack this isoenzyme.

The limited data available suggest a modest interaction may occur between flecainide and paroxetine; however its clinical significance does not appear to have been assessed. The slight increase in flecainide levels seen may be of clinical significance in some patients, such as those with renal impairment. It would seem prudent to be alert for an increase in flecainide adverse effects (such as dizziness, nausea, and tremor) if paroxetine is also given, and consider a flecainide dose reduction if necessary.

1. Cipralex (Escitalopram oxalate). Lundbeck Ltd. UK Summary of product characteristics, October 2008.
2. Prozac (Fluoxetine hydrochloride). Eli Lilly and Company Ltd. UK Summary of product characteristics, February 2009.
3. Prozac (Fluoxetine hydrochloride). Eli Lilly and Company. US Prescribing information, October 2009.
4. Lim KS, Cho J-Y, Jang I-J, Kim B-H, Kim J, Jeon JY, Tae Y-M, Yi S, Eum S, Shin S-G, Yu K-S. Pharmacokinetic interaction of flecainide and paroxetine in relation to the CYP2D6*10 allele in healthy Korean subjects. Br J Clin Pharmacol (2008) 66, 660–6.
5. Tsao YY, Gugger JJ. Delirium in a patient with toxic flecainide plasma concentrations: the role of a pharmacokinetic drug interaction with paroxetine. Ann Pharmacother (2009) 43, 1366–9.

Flecainide + Thiazide diuretics

An isolated report describes cardiotoxicity in a patient taking flecainide, which was associated with an electrolyte imbalance caused by bendroflumethiazide.

Clinical evidence, mechanism, importance and management

A patient taking **bendroflumethiazide** developed syncope, weakness and fatigue 2 months after starting flecainide. He also had ECG changes (marked QRS widening) and gross hyponatraemia and hypokalaemia, which was consistent with flecainide cardiotoxicity exacerbated by electrolyte disturbances. The symptoms resolved when the electrolyte balance was corrected.

Flecainide acts by a use-dependent block of sodium channels and hypertonic sodium salts have been used to reverse flecainide toxicity. Data in *animals* suggest flecainide may reduce salt absorption in the bowel.[1] This report suggests hyponatraemia as well as hypokalaemia may contribute to flecainide toxicity.

Although this appears to be the only report of an interaction, it serves as a reminder that electrolytes should be carefully controlled in patients taking flecainide, and this is particularly important when other drugs that may cause electrolyte disturbances, such as the thiazides, are given.

1. Khavandi A, Walker PR. Flecainide cardiotoxicity precipitated by electrolyte imbalance. Caution with thiazide diuretics. *Emerg Med J* (2007) 24, e26.

Flecainide + Tobacco

Tobacco smokers need larger doses of flecainide than non-smokers to achieve the same therapeutic effects.

Clinical evidence

Prompted by the chance observation that smokers appeared to have a reduced pharmacodynamic response to flecainide than non-smokers, a meta-analysis[1] was undertaken of the findings of 7 pre-marketing pharmacokinetic studies and 5 multicentre efficacy studies in which flecainide had been studied and in which the smoking habits of the subjects or patients had been also been recorded. In the pharmacokinetic studies, the clearance of flecainide was found to be about 50% higher in smokers than in non-smokers. In the efficacy studies, average clinically effective flecainide doses were found to be 338 mg daily for smokers and 288 mg daily for non-smokers, while trough plasma concentrations of flecainide were 1.74 nanograms/mL and 2.18 nanograms/mL per mg dose for the smokers and non-smokers, respectively. This confirmed that smokers needed higher doses of flecainide to achieve the same steady-state serum levels.[1]

Mechanism

The probable reason for this interaction is that some components of tobacco smoke stimulate the cytochrome P450 enzymes in the liver concerned with the *O*-dealkylation of flecainide, so that it is cleared from the body more quickly.[1]

Importance and management

An established interaction. Smokers seem likely to need higher doses of flecainide than non-smokers, but the way in which this interaction was identified suggests that in practice no specific action needs to be taken to accommodate it. It may be most relevant if a patient taking flecainide abruptly stops smoking. In this situation be alert for flecainide adverse effects (e.g. dizziness, nausea, tremor), and be aware that it is likely that the dose of flecainide will need to be reduced.

1. Holtzman JL, Weeks CE, Kvam DC, Berry DA, Mottonen L, Ekholm BP, Chang SF, Conard GJ. Identification of drug interactions by meta-analysis of premarketing trials: the effect of smoking on the pharmacokinetic and dosage requirements for flecainide acetate. *Clin Pharmacol Ther* (1989) 46, 1–8.

Flecainide + Urinary acidifiers or alkalinisers

The excretion of flecainide is increased if the urine is made acidic (e.g. with ammonium chloride) and reduced if the urine is made alkaline (e.g. with sodium bicarbonate).

Clinical evidence

Six healthy subjects were given a single 300-mg oral dose of flecainide on two occasions. On the first occasion flecainide was taken after **ammonium chloride** 1 g orally every 3 hours, and 2 g at bedtime, for a total of 21 hours to make the urine acidic (pH range 4.4 to 5.4). On the second occasion flecainide was taken after **sodium bicarbonate** 4 g every 4 hours for a total of 21 hours (including night periods) to make the urine alkaline (pH range 7.4 to 8.3). Over the next 32 hours, 44.7% of unchanged flecainide appeared in the acidic urine, but only 7.4% in alkaline urine.[1] This compares with 25% found by other researchers when urinary pH was not controlled.[1] A later similar study from the same research group broadly confirmed these findings; the elimination half-life of the flecainide was 10.7 hours in acidic urine and 17.6 hours in alkaline urine.[2] Another study also confirmed the effect of urinary pH on the excretion of flecainide, and found that the fluid load and the urinary flow rate had little effect on flecainide excretion.[3]

In a study in healthy adult subjects, three 15-mL doses of *Aldrox* (280 mg of **aluminium hydroxide** per 5 mL) had no significant effect on the rate or extent of absorption of a single 200-mg dose of flecainide.[4]

Mechanism

In alkaline urine at pH 8, much of the flecainide exists in the kidney tubules in the non-ionised form (non-ionised fraction 0.04), which is more readily reabsorbed. In acidic urine at pH 5 more exists in the ionised form (non-ionised fraction 0.0001), which is less readily reabsorbed and is therefore lost in the urine.[3]

Importance and management

Established interactions, but their clinical importance is uncertain. The effects of these changes on the subsequent control of arrhythmias by flecainide in patients seem not to have been studied, but the outcome should be well monitored if patients are given drugs that alter urinary pH to a significant extent (such as ammonium chloride, sodium bicarbonate). Large doses of some **antacids** may possibly do the same, but one study suggests that aluminium hydroxide may not interact in this way.

1. Muhiddin KA, Johnston A, Turner P. The influence of urinary pH on flecainide excretion and its serum pharmacokinetics. *Br J Clin Pharmacol* (1984) 17, 447–51.
2. Johnston A, Warrington S, Turner P. Flecainide pharmacokinetics in healthy volunteers: the influence of urinary pH. *Br J Clin Pharmacol* (1985) 20, 333–8.
3. Hertrampf R, Gundert-Remy U, Beckmann J, Hoppe U, Elsäβer W, Stein H. Elimination of flecainide as a function of urinary flow rate and pH. *Eur J Clin Pharmacol* (1991) 41, 61–3.
4. Tjandra-Maga TB, Verbesselt R, Van Hecken A, Mullie A, De Schepper PJ. Flecainide: single and multiple oral dose kinetics, absolute bioavailability and effect of food and antacid in man. *Br J Clin Pharmacol* (1986) 22, 309–16.

Flecainide + Verapamil

Although flecainide and verapamil have been used together successfully, serious and potentially life-threatening cardiogenic shock and asystole have been seen in a few patients, because the cardiac depressant effects of the two drugs can be additive.

Clinical evidence

A man with triple coronary vessel disease taking flecainide 200 mg daily for recurrent ventricular tachycardia, developed severe cardiogenic shock within 2 days of increasing the flecainide dose to 300 mg daily and within one day of starting verapamil 80 mg daily. His blood pressure fell to 60/40 mmHg and he had an idioventricular rhythm of 88 bpm.[1] Another patient with atrial flutter and fibrillation was given digitalis and verapamil 120 mg three times daily. He was also given flecainide 150 mg daily for 10 days, but 3 days after the dose was raised to 200 mg daily he fainted, and later developed severe bradycardia (15 bpm) and asystoles of up to 14 seconds. He later died.[1]

Another report describes atrioventricular block when a patient with a pacemaker took digoxin, flecainide and verapamil.[2]

Two earlier studies in patients[3] and healthy subjects[4] had found that the pharmacokinetics of flecainide and verapamil were only minimally affected by concurrent use, but the PR interval was increased by both drugs. Furthermore, additive depressant effects were seen on heart contractility and AV conduction, although no serious adverse responses occurred.

Mechanism

Flecainide and verapamil have little or no effects on the pharmacokinetics of each other,[3,4] but they can apparently have additive depressant effects on the heart (negative inotropic and chronotropic) in both patients and healthy subjects.[1,3,4] Verapamil alone[5,6] and flecainide alone[7,8] have been responsible for asystole and cardiogenic shock in a few patients. In the cases cited above[1-3] the cardiac depressant effects were particularly serious because the patients already had compromised cardiac function.

Importance and management

An established interaction, but the incidence of serious adverse effects is probably not great. The additive cardiac depressant effects are probably of little importance in many patients, but may represent 'the last straw' in a few who have seriously compromised cardiac function. The authors of one of the reports cited[1] advise careful monitoring if both drugs are used and emphasise the potential hazards of combining **class Ic antiarrhythmics** and verapamil.

1. Buss J, Lasserre JJ, Heene DL. Asystole and cardiogenic shock due to combined treatment with verapamil and flecainide. *Lancet* (1992) 340, 546.
2. Tworek DA, Nazari J, Ezri M, Bauman JL. Interference by antiarrhythmic agents with function of electrical cardiac devices. *Clin Pharm* (1992) 11, 48–56.
3. Landau S, Hogan C, Butler B, Somberg J. The combined administration of verapamil and flecainide. *J Clin Pharmacol* (1988) 28, 909.
4. Holtzman JL, Finley D, Mottonen L, Berry DA, Ekholm BP, Kvam DC, McQuinn RL, Miller AM. The pharmacodynamic and pharmacokinetic interaction between single doses of flecainide acetate and verapamil: effects on cardiac function and drug clearance. *Clin Pharmacol Ther* (1989) 46, 26–32.
5. Perrot B, Danchin N, De La Chaise AT. Verapamil: a cause of sudden death in a patient with hypertrophic cardiomyopathy. *Br Heart J* (1984) 51, 532–4.
6. Cohen IL, Fein A, Nabi A. Reversal of cardiogenic shock and asystole in a septic patient with hypertrophic cardiomyopathy on verapamil. *Crit Care Med* (1990) 18, 775–6.
7. Forbes WP, Hee TT, Mohiuddin SM, Hillman DE. Flecainide-induced cardiogenic shock. *Chest* (1988) 94, 1121.
8. Echt DS, Liebson PR, Mitchell LB, Peters RW, Obias-Manno D, Barker AH, Arensberg D, Baker A, Friedman L, Greene HL, Huther ML, Richardson DW, CAST investigators. Mortality and morbidity in patients receiving encainide, flecainide or placebo. *N Engl J Med* (1991) 324, 781–8.

Ibutilide + Amiodarone

Two reports describe the successful use of ibutilide and amiodarone for cardioversion. Both ibutilide and amiodarone can prolong the QT interval, and concurrent use would be expected to result in additive effects.

Clinical evidence, mechanism, importance and management

Intravenous ibutilide 2 mg has been used for cardioversion of atrial fibrillation or flutter in 70 patients taking long-term amiodarone. The QT interval was further prolonged (from 371 to 479 milliseconds). Only one patient had an episode of non-sustained torsade de pointes. Ibutilide was effective within 30 minutes of infusion in 39% of patients with atrial flutter, and 54% of patients with fibrillation.[1] A further report also found the use of ibutilide in 46 patients receiving amiodarone for atrial flutter and fibrillation as effective and safe as use of ibutilide alone (in 28 patients).[2]

The authors of one report[1] suggest that ibutilide may be useful for cardioversion in those already taking amiodarone. However, it is generally recommended that the concurrent use of two drugs that prolong the QT interval should be avoided. The manufacturer of ibutilide specifically recommends that other class III antiarrhythmics should not be given within 4 hours of an ibutilide infusion, and that ibutilide should not be given within five half-lives of these antiarrhythmics.[3] The concern is that a prolongation of the QT interval is associated with an increased risk of torsade de pointes, which is potentially life-threatening. See 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290.

1. Glatter K, Yang Y, Chatterjee K, Modin G, Cheng J, Kayser S, Scheinman MM. Chemical cardioversion of atrial fibrillation or flutter with ibutilide in patients receiving amiodarone therapy. *Circulation* (2001) 103, 253–7.
2. Fragakis N, Papadopoulos N, Papanastasiou S, Kozirakis M, Maligkos G, Tsaritsaniotis E, Katsaris G. Efficacy and safety of ibutilide for cardioversion of atrial flutter and fibrillation in patients receiving amiodarone or propafenone. *Pacing Clin Electrophysiol* (2005) 28, 954–61.
3. Corvert (Ibutilide fumarate). Pharmacia & Upjohn. US Prescribing information, February 2006.

Ibutilide + Calcium-channel blockers

Calcium-channel blockers (predominantly non-dihydropyridine type) have not altered the safety or efficacy of ibutilide in clinical studies.

Clinical evidence, mechanism, importance and management

Retrospective analysis of three clinical studies found that calcium-channel blockers did not alter the ECG effects (QT prolongation) or the efficacy of ibutilide. In these three studies, 68 of the 130 patients taking ibutilide were also taking calcium-channel blockers. The report did not specify which calcium-channel blockers were used, except to say that only 12 of the 68 (19%) were taking a dihydropyridine-type.[1]

In vitro studies have shown that **nifedipine** (a dihydropyridine) attenuated the effects of ibutilide.[2] The findings of the above report[1] suggest that this may not be clinically important. However, since so few patients were taking a dihydropyridine, an effect specific to dihydropyridines cannot be excluded. Further study is needed.

1. Wood MA, Gilligan DM, Brown-Mahoney C, Nematzadeh F, Stambler BS, Ellenbogen KA. Clinical and electrophysiologic effects of calcium channel blockers in patients receiving ibutilide. *Am Heart J* (2002) 143, 176–80.
2. Lee KS, Lee EW. Ionic mechanism of ibutilide in human atrium: evidence for a drug-induced Na^+ current through a nifedipine inhibited inward channel. *J Pharmacol Exp Ther* (1998) 286, 9–22.

Ibutilide + Class Ic antiarrhythmics

Some evidence suggests that patients taking ibutilide have a less marked increase in QT interval, without a change in efficacy, when they are also given propafenone or flecainide.

Clinical evidence, mechanism, importance and management

The increase in QTc interval after intravenous ibutilide 2 mg was less in patients taking **propafenone** (5 patients) or **flecainide** (1 patient) than in 85 other patients who had taken ibutilide alone (34 milliseconds versus 65 milliseconds). The effect appeared to be dose-related, with higher propafenone doses causing the largest attenuation in the ibutilide-induced QT prolongation. The efficacy of ibutilide was unaltered.[1] In another study, 71 patients with atrial fibrillation or atrial flutter receiving either **propafenone** 300 to 900 mg daily or **flecainide** 100 to 300 mg daily underwent cardioversion with a single intravenous dose of ibutilide 1 mg over 10 minutes, followed if necessary by a further dose after an interval of 10 minutes. Torsade de pointes occurred in one patient with profound sinus node suppression after cardioversion, but the mean increase in the QT interval in response to ibutilide was attenuated (20 ± 54 milliseconds compared to reported range of 47 to 90 milliseconds) without a decrease in efficacy. However, the authors note that the risk of sustained torsade de pointes in this study appears to be similar to that seen in other studies of ibutilide.[2] In a further study in 100 patients with atrial fibrillation, undergoing elective cardioversion with either intravenous ibutilide (1 mg with a further 1 mg if required), or oral **propafenone** 600 mg plus intravenous ibutilide, cardioversion was achieved in 41% of 51 patients given ibutilide alone and about 71% of 49 patients given ibutilide and **propafenone**. Increases in the QTc interval were similar in both groups, but one case of torsade de pointes requiring electrical cardioversion occurred in one patient given ibutilide and **propafenone**.[3] A further report also found that the

use of ibutilide in 30 patients receiving **propafenone** for atrial flutter and fibrillation was as effective and safe as use of ibutilide alone (in 28 patients).[4]

Ibutilide, a class III antiarrhythmic, is known to increase the QT interval, so increasing the risk of torsade de pointes. Class Ic antiarrhythmics such as **propafenone** and **flecainide** generally shorten the QT interval. It is possible that class Ic antiarrhythmics may usefully attenuate the risk of torsade de pointes with ibutilide,[1] and ibutilide may be useful in restoring sinus rhythm in patients taking class Ic antiarrhythmics.[2,3] However, the cases of torsade de pointes add a note of caution, and further study is needed.

1. Reiffel JA, Blitzer M. The actions of ibutilide and class Ic drugs on the slow sodium channel: new insights regarding individual pharmacologic effects elucidated through combination therapies. *J Cardiovasc Pharmacol Ther* (2000) 5, 177–81.
2. Hongo RH, Themistoclakis S, Raviele A, Bonso A, Rossillo A, Glatter A, Yang Y, Scheinman MM. Use of ibutilide in cardioversion of patients with atrial fibrillation or atrial flutter treated with Class IC agents. *J Am Coll Cardiol* (2004) 44, 864–8.
3. Korantzopoulos P, Kolettis TM, Papathanasiou A, Naka KK, Kolios P, Leontaridis I, Dragangigos A, Katsouras CS, Goudenvenos JA. Propafenone added to ibutilide increases conversion rates of persistent atrial fibrillation. *Heart* (2006) 92, 631–4.
4. Fragakis N, Papadopoulos N, Papanastasiou S, Kozirakis M, Maligkos G, Tsaritsaniotis E, Katsaris G. Efficacy and safety of ibutilide for cardioversion of atrial flutter and fibrillation in patients receiving amiodarone or propafenone. *Pacing Clin Electrophysiol* (2005) 28, 954–61.

Ibutilide + Miscellaneous

Ibutilide can prolong the QT interval, therefore caution has been advised about the concurrent use of other drugs that can do the same. Ibutilide is reported not to interact with beta blockers or digoxin.

Clinical evidence, mechanism, importance and management

No specific drug interaction studies appear to have been undertaken with ibutilide, which is a class III antiarrhythmic, but because it can prolong the QT interval it has been recommended that other drugs that can do the same should be administered with caution, because of the potential additive effects.[1] The manufacturer of ibutilide[2] specifically recommends that class Ia and other class III antiarrhythmics should not be given within 4 hours of an ibutilide infusion, and that ibutilide should not be given within five half-lives of these antiarrhythmics (but see also, 'Ibutilide + Amiodarone', p.295). The concern is that a prolongation of the QT interval is associated with an increased risk of torsade de pointes, which is potentially life-threatening. The manufacturer of ibutilide specifically names **phenothiazines**, **tricyclic** and **tetracyclic antidepressants**, and **antihistamines**.[2] For further discussion of QT prolongation, and for further examples of drugs that prolong the QT interval, see also 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290.

The concurrent use of **beta blockers** and **digoxin** during clinical studies is reported not to affect the safety or efficacy of ibutilide;[1,2] however, note that **sotalol** is known to prolong the QT interval.

Ibutilide is said not to affect the cytochrome P450 isoenzymes CYP3A4 or CYP2D6 and so metabolic interactions with drugs affected by these enzymes would not be expected.[1]

1. Cropp JS, Antal EG, Talbert RL. Ibutilide: a new Class III antiarrhythmic agent. *Pharmacotherapy* (1997) 17, 1–9.
2. Corvert (Ibutilide fumarate). Pharmacia & Upjohn. US Prescribing information, February 2006.

Lidocaine + Amiodarone

One man receiving intravenous lidocaine had a seizure about two days after starting to take amiodarone. Another man with sick sinus syndrome taking amiodarone had a sinoatrial arrest during placement of a pacemaker under local anaesthesia with lidocaine. There is conflicting evidence as to whether or not amiodarone affects the pharmacokinetics of intravenous lidocaine.

Clinical evidence

An elderly man taking digoxin, enalapril, amitriptyline and temazepam was treated for monomorphic ventricular tachycardia, firstly with procainamide, later replaced by a 2 mg/minute infusion of lidocaine, to which oral amiodarone 600 mg twice daily was added. After 12 hours his lidocaine level was 5.4 mg/L (reference range 1.5 to 5 mg/L), but 53 hours later he developed a seizure and his lidocaine level was found to have risen to 12.6 mg/L. A tomography brain scan found no abnormalities that could have caused the seizure and it was therefore attributed to the toxic lidocaine levels.[1]

An elderly man with long standing brady-tachycardia was successfully treated for atrial flutter firstly with a temporary pacemaker (later withdrawn) and 600 mg amiodarone daily. Ten days later, and 25 minutes after a permanent pacemaker was inserted under local anaesthesia with 15 mL of 2% lidocaine, severe sinus bradycardia and long sinoatrial arrest developed. He was effectively treated with atropine plus isoprenaline, and cardiac massage.[2]

Six patients with symptomatic cardiac arrhythmias took part in a two-phase study. Initially, lidocaine 1 mg/kg was given intravenously over 2 minutes. In phase I, loading doses of amiodarone 500 mg daily for 6 days were given, followed by the same lidocaine dose. After 19 to 21 days, when the total cumulative amiodarone dose was 13 g, the same lidocaine dose was given again (phase II). The lidocaine AUC increased by about 20% and the systemic clearance decreased by about 20%. The elimination half-life and distribution volume at steady-state were unchanged. The pharmacokinetic parameters of lidocaine in phase II were the same as those in phase I, indicating that the interaction occurs early in the loading phase of amiodarone use.[3] This is in contrast to an earlier study, in which the pharmacokinetics of a bolus dose of lidocaine 1 mg/kg over 2 minutes were not altered in 10 patients who had taken amiodarone 200 to 400 mg daily (following a loading dose of 800 or 1200 mg) for 4 to 5 weeks.[4]

Mechanism

An *in vitro* study found that amiodarone may competitively inhibit lidocaine metabolism and *vice versa*. The interaction *in vivo* may be due to inhibition of the cytochrome P450 isoenzyme CYP3A4 by amiodarone and/or its main metabolite desethylamiodarone.[4] CYP3A4 is partially involved in the metabolism of lidocaine.

The authors of the report describing the sinoatrial arrest suggest that this occurred because of a synergistic depression by both drugs of the sinus node.

Importance and management

A pharmacokinetic interaction between lidocaine and amiodarone is not established. However, in the study that did find an interaction, the effects were slight, and would not be expected to be clinically relevant. The two reports of adverse interactions and the study in patients with arrhythmias illustrate the importance of good monitoring if both drugs are used as there is the possibility of a pharmacodynamic interaction. The manufacturer of some topical lidocaine preparations notes that although specific interaction studies of topical lidocaine with class III antiarrhythmics such as amiodarone have not been undertaken, caution and close monitoring is also important with topical lidocaine products especially if large doses are applied.[5,6]

1. Siegmund JB, Wilson JH, Imhoff TE. Amiodarone interaction with lidocaine. *J Cardiovasc Pharmacol* (1993) 21, 513–15.
2. Keidar S, Grenadier E, Palant A. Sinoatrial arrest due to lidocaine injection in sick sinus syndrome during amiodarone administration. *Am Heart J* (1982) 104, 1384–5.
3. Ha HR, Candinas R, Steiger B, Meyer UA, Follath F. Interactions between amiodarone and lidocaine. *J Cardiovasc Pharmacol* (1996) 28, 533–9.
4. Nattel S, Talajic M, Beaudoin D, Matthews C, Roy D. Absence of pharmacokinetic interaction between amiodarone and lidocaine. *Am J Cardiol* (1994) 73, 92–4.
5. Xylocaine Spray (Lidocaine). AstraZeneca UK Ltd. UK Summary of product characteristics, March 2008.
6. EMLA Cream (Lidocaine with Prilocaine). AstraZeneca UK Ltd. UK Summary of product characteristics, September 2009.

Lidocaine + Atropine

Atropine delays the absorption of lidocaine, but does not significantly alter its peak levels.

Clinical evidence, mechanism, importance and management

A study in 4 healthy subjects found that the absorption of a single 400-mg oral dose of lidocaine was delayed when it was given at the same time as intramuscular atropine 600 micrograms. Peak plasma lidocaine levels were reduced by atropine but not to a significant extent. Atropine probably delayed lidocaine absorption by inhibition of gastric emptying.[1]

These pharmacokinetic changes are relatively minor, and would not be expected to alter the clinical effects of lidocaine.

1. Adjepon-Yamoah KK, Scott DB, Prescott LF. The effect of atropine on the oral absorption of lidocaine in man. *Eur J Clin Pharmacol* (1974) 7, 397–400.

Lidocaine + Barbiturates

Plasma lidocaine levels following slow intravenous injection may be modestly lowered by phenobarbital and other barbiturates.

Clinical evidence

In a study, 7 patients with epilepsy were given a single 2-mg/kg dose of lidocaine by slow intravenous injection (rate about 100 mg over 15 minutes), firstly while taking their usual antiepileptic drugs and sedatives (including phenytoin, barbiturates, phenothiazines, benzodiazepines) and secondly after taking only **phenobarbital** 300 mg daily for 4 weeks. The same lidocaine dose was also given to 6 control subjects who had not received any drugs. When compared with the levels in the 6 control subjects, plasma lidocaine levels were somewhat lower when the patients took their standard antiepileptic treatment (18% and 29% lower at 30 and 60 minutes, respectively). When plasma lidocaine levels achieved during the **phenobarbital** phase were compared with those achieved during the standard antiepileptic treatment they were found to be 10 to 25% higher, suggesting that the effect of combined treatment caused a greater reduction in lidocaine levels than **phenobarbital**.[1]

Mechanism

Not fully understood. One suggestion is that the barbiturates increase the activity of the liver microsomal enzymes, thereby increasing the rate of metabolism of the lidocaine.[1]

Importance and management

Direct information is very limited. It may be necessary to increase the dose of lidocaine to achieve the desired therapeutic response in patients taking phenobarbital or other barbiturates.

1. Heinonen J, Takki S, Jarho L. Plasma lidocaine levels in patients treated with potential inducers of microsomal enzymes. *Acta Anaesthesiol Scand* (1970) 14, 89–95.

Lidocaine + Beta blockers

The plasma levels of lidocaine after intravenous, and possibly oral, use can be increased by propranolol. Isolated cases of toxicity attributed to this interaction have been reported. Nadolol and penbutolol possibly interact similarly, but there is uncertainty about metoprolol. Atenolol and pindolol appear not to interact.

Clinical evidence

(a) Atenolol

A study in 7 healthy subjects pretreated with oral atenolol 50 mg daily for a week found that it did not affect the clearance of lidocaine after oral or intravenous use.[1]

(b) Metoprolol

In 6 healthy subjects, pretreatment with metoprolol 100 mg twice daily for 2 days did not affect the pharmacokinetics of a single intravenous dose of lidocaine.[2] Similarly, another study in 7 healthy subjects did not find any changes in the pharmacokinetics of a single oral or intravenous dose of lidocaine after pretreatment with metoprolol 100 mg every 12 hours for a week.[1] In contrast, another study found that the clearance of a single intravenous dose of lidocaine was reduced by 31% by pretreatment with metoprolol 50 mg every 6 hours for a day.[3]

(c) Nadolol

A study in 6 healthy subjects receiving 30-hour infusions of lidocaine at a rate of 2 mg/minute found that pretreatment with nadolol 160 mg daily for 3 days raised the steady-state plasma lidocaine levels by 28% (from 2.1 to 2.7 micrograms/mL) and reduced its plasma clearance by 17%.[4]

(d) Penbutolol

In 7 healthy subjects, pre-treatment with penbutolol 60 mg daily significantly increased the volume of distribution of a single 100-mg intravenous dose of lidocaine, thus prolonging its elimination half-life. However, the reduction in clearance of lidocaine was not statistically significant.[5]

(e) Pindolol

A study in 8 healthy subjects found that pretreatment with intravenous pindolol 23 micrograms/kg did not affect the clearance of intravenous lidocaine.[6]

(f) Propranolol

A study in 6 healthy subjects receiving 30-hour infusions of lidocaine at a rate of 2 mg/minute found that pretreatment with propranolol 80 mg every 8 hours for 3 days raised the steady-state plasma lidocaine levels by 19% (from 2.1 to 2.5 micrograms/mL) and reduced its plasma clearance by 16%.[4] Other similar studies have found a 23 to 30% increase in steady-state serum lidocaine levels and a 15 to 46% reduction in plasma clearance due to the concurrent use of propranolol.[3,6,7] Two cases of lidocaine toxicity attributed to a lidocaine-propranolol interaction[8] were revealed by a search of the adverse drug reaction file of the FDA in the US in 1981. A further case of lidocaine toxicity (seizures) has been described in a man taking propranolol after the accidental *oral* ingestion of lidocaine for oesophageal anaesthesia. High serum levels of lidocaine were detected.[9]

(g) Unnamed beta blockers

A matched study in 51 cardiac patients taking a variety of beta blockers (including **propranolol**, **metoprolol**, **timolol**, **pindolol**) found no significant differences in either total or free concentrations of lidocaine during a lidocaine infusion, but there was a trend towards increased bradycardia with the concurrent use of a beta blocker.[10]

Mechanism

Not fully agreed. There is some debate about whether the increased serum lidocaine levels largely occur because of the decreased cardiac output caused by the beta blockers, which decreases the flow of blood through the liver thereby reducing the metabolism of the lidocaine,[4] or because of direct liver enzyme inhibition.[11] An *in vitro* study in *animal* tissue found that propranolol significantly decreased the binding of lidocaine to liver tissue, so that concurrent use may increase the free fraction of lidocaine excreted by the liver. Further study of this *in vitro* model is required.[12] There may also be a pharmacodynamic interaction, with an increased risk of myocardial depression.[10]

Importance and management

The interaction between lidocaine and propranolol is established and possibly of some clinical relevance. Monitor the effects of concurrent use and reduce the intravenous lidocaine dose if necessary to avoid toxicity. The situation with other beta blockers is less clear. Nadolol appears to interact like propranolol, but it is uncertain whether metoprolol interacts or not. Atenolol and pindolol are reported not to cause a pharmacokinetic interaction. It has been suggested that a higher intravenous loading dose (but not a higher maintenance dose) of lidocaine may be needed if penbutolol is used.[5] The suggestion has been made that a significant pharmacokinetic interaction is only likely to occur with non-selective beta blockers without intrinsic sympathomimetic activity[11] e.g. nadolol or propranolol. Aside from the pharmacokinetic interactions, a pharmacodynamic interaction is possible, and so it would be prudent to monitor the effects of concurrent use with any beta blocker.

Note that local anaesthetic preparations of lidocaine often contain adrenaline (epinephrine), which may interact with beta blockers, see 'Beta blockers + Inotropes and Vasopressors', p.1011.

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Lidocaine + Cocaine

Limited evidence suggests intravenous lidocaine use in patients with cocaine-associated myocardial infarction is not associated with significant toxicity.

Clinical evidence, mechanism, importance and management

A retrospective study, covering a 6-year period in 29 hospitals, identified 29 patients (27 available for review) who received lidocaine for prophylaxis or treatment of cocaine-associated myocardial infarction. No patient exhibited bradycardia, sustained ventricular tachycardia or ventricular fibrillation, and no patients died.[1]

Both lidocaine and cocaine exhibit class I antiarrhythmic effects and are proconvulsants. Lidocaine may potentiate the cardiac and CNS adverse effects of cocaine. Therefore the use of lidocaine for cocaine-associated myocardial infarction is controversial. The lack of adverse effects in this study may have been due to delays of more than 5 hours between last exposure to cocaine and the use of lidocaine. These authors[1] and others[2,3] consider that the cautious use of lidocaine does not appear to be contraindicated in patients with cocaine-associated myocardial infarction who require an antiarrhythmic. However, extra care should be taken in patients who receive lidocaine shortly after cocaine.[1]

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Lidocaine + Dextromethorphan

Intravenous lidocaine does not affect the pharmacokinetics of dextromethorphan.

Clinical evidence, mechanism, importance and management

Although *in vitro* data suggested that lidocaine inhibited oxidative metabolism reactions mediated by the cytochrome P450 isoenzyme CYP2D6, a later *in vivo* study in 16 patients found that, while being given an infusion of lidocaine (serum level range 3.2 to 55.9 micromol/L), the metabolism of a single 30-mg dose of dextromethorphan remained unchanged. All of the patients were extensive CYP2D6 metabolisers (that is, those with normal levels of this isoenzyme). Dextromethorphan is also used as a probe drug for CYP2D6 activity, and it was therefore concluded that lidocaine is unlikely to affect the metabolism of drugs that are extensively metabolised by this isoenzyme.[1]

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Lidocaine + Disopyramide

***In vitro* studies suggest that disopyramide can increase the levels of unbound lidocaine, but it is not known whether their combined effects have a clinically important cardiac depressant effect in practice.**

Clinical evidence, mechanism, importance and management

An *in vitro* study using serum taken from 9 patients receiving intravenous lidocaine for severe ventricular arrhythmias found that there was an average 20% increase in the free (unbound) fraction of lidocaine when disopyramide in a concentration of 14.7 micromol/L was added.[1] This appears to occur because disopyramide can displace lidocaine from its binding sites on plasma proteins (alpha-1-acid glycoprotein).

The importance of this possible displacement interaction in clinical practice is uncertain. The suggestion made by the authors[1] is that, although lidocaine has only a minor cardiac depressant effect, a transient 20% increase in levels of free and active lidocaine plus the negative inotropic effects of the disopyramide might possibly be hazardous in patients with reduced cardiac function.

1. Bonde J, Jensen NM, Burgaard P, Angelo HR, Graudal N, Kampmann JP, Pedersen LE. Displacement of lidocaine from human plasma proteins by disopyramide. *Pharmacol Toxicol* (1987) 60, 151–5.

Lidocaine + Erythromycin

Erythromycin may markedly increase the levels of oral lidocaine, but it causes only a minor increase in the levels of intravenous lidocaine.

Clinical evidence

In a randomised, crossover study, 9 healthy subjects were given erythromycin 500 mg three times daily or placebo daily for 4 days. Erythromycin increased the AUC and peak plasma levels of a single 1-mg/kg *oral* dose of lidocaine by 50% and 40%, respectively. Erythromycin also markedly increased the AUC of the main metabolite of lidocaine, monoethylglycinexylidide (MEGX) by 60%.[1]

In a similar study,[2] erythromycin had no effect on the AUC or peak plasma level of a single 1.5-mg/kg *intravenous* dose of lidocaine, but still increased the AUC of MEGX by 70%. In yet another study, erythromycin ethylsuccinate 600 mg three times daily for 5 doses had a minor effect on the pharmacokinetics of a single 1-mg/kg *intravenous* dose of lidocaine (an 18% decrease in clearance), and caused a 33% increase in the AUC of MEGX. There was no difference in the results from the 10 healthy subjects and the 20 patients with biopsy proven cirrhosis who were entered into the study.[3]

In another study, 9 healthy subjects were given fluvoxamine 100 mg daily alone or with erythromycin 500 mg three times daily for 5 days, with a single *intravenous* dose of lidocaine 1.5 mg/kg on day 6. The clearance of lidocaine was reduced 41% by fluvoxamine and 53% by concurrent fluvoxamine and erythromycin.[4] The same study was repeated in 8 healthy subjects who were given a single *oral* dose of lidocaine 1 mg/kg on day 6. The AUC and peak levels of lidocaine were increased by 305% and 220% by fluvoxamine and by 360% and 250% by concurrent fluvoxamine and erythromycin. The half-life of lidocaine was increased by fluvoxamine and fluvoxamine with erythromycin from 2.4 hours, to 3.1 hours and 3.8 hours, respectively. Fluvoxamine alone and fluvoxamine with erythromycin decreased the peak levels of MEGX by 50% and 30%, respectively.[5]

Mechanism

Erythromycin is an inhibitor of the cytochrome P450 isoenzyme CYP3A4, an isoenzyme partially involved in the metabolism of lidocaine. Erythromycin appears to markedly reduce the first-pass metabolism of oral lidocaine so that its plasma levels rise.[1] The increase in the main metabolite monoethylglycinexylidide (MEGX) could be due to either an increase in the production of this metabolite, or the inhibition of its further metabolism. Fluvoxamine is an inhibitor of CYP1A2, which is also involved in lidocaine metabolism. Lidocaine clearance is reduced by fluvoxamine and further decreased by the concurrent use of erythromycin.

Importance and management

Information regarding an interaction between *oral* lidocaine and erythromycin seems limited, and as lidocaine is not usually given orally the practical importance is minor. However, lidocaine is used for oro-pharyngeal topical anaesthesia, and there have been cases of toxicity after accidental ingestion. Thus, in a patient taking erythromycin, the toxicity of *oral* lidocaine may be markedly increased.

There appears to be more evidence regarding the interaction between *intravenous* lidocaine and erythromycin; however, some studies suggest that no increase in exposure occurs, and in others, only moderate pharmacokinetic changes were found. Therefore the increase in *intravenous* lidocaine

levels would not be expected to be clinically relevant. However, further study is required to assess the significance of the increase in MEGX during prolonged intravenous lidocaine infusions.

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5. Isohanni MH, Neuvonen PJ, Olkkola KT. Effect of fluvoxamine and erythromycin on the pharmacokinetics of oral lidocaine. *Basic Clin Pharmacol Toxicol* (2006) 99, 168–72.

Lidocaine + Fluvoxamine

Fluvoxamine reduces the clearance of intravenous lidocaine. The bioavailability of oral lidocaine is increased by fluvoxamine.

Clinical evidence

In a study, 9 healthy subjects were given fluvoxamine 100 mg daily alone, or with erythromycin 500 mg three times daily for 5 days, with a single *intravenous* dose of lidocaine 1.5 mg/kg on day 6. The clearance of lidocaine was reduced 41% by fluvoxamine and 53% by concurrent fluvoxamine and erythromycin.[1] The same study was repeated in 8 healthy subjects, who were given a single *oral* dose of lidocaine 1 mg/kg on day 6. The AUC and peak levels of lidocaine were increased by 305% and 220%, respectively, by fluvoxamine and by 360% and 250%, respectively, by concurrent fluvoxamine and erythromycin. The half-life of lidocaine was increased by fluvoxamine and fluvoxamine with erythromycin, from 2.4 hours, to 3.1 hours and 3.8 hours, respectively. Fluvoxamine alone and fluvoxamine with erythromycin decreased the peak levels of the main metabolite of lidocaine, monoethylglycinexylidide (MEGX) by 50% and 30%, respectively.[2]

Mechanism

The cytochrome P450 isoenzymes CYP1A2 and CYP3A4 are involved in the first-pass metabolism of lidocaine. An *in vitro* study found that fluvoxamine (a CYP1A2 inhibitor) was a more potent inhibitor of lidocaine metabolism than erythromycin (a CYP3A4 inhibitor).[3] Therefore fluvoxamine decreases the clearance of lidocaine, and erythromycin has a modest additional effect.

Importance and management

Information regarding an interaction between *oral* lidocaine and fluvoxamine seems limited, and as lidocaine is not usually given orally the practical importance is minor. However, lidocaine is used for oro-pharyngeal topical anaesthesia, and there have been cases of toxicity after accidental ingestion. Thus, in a patient taking fluvoxamine, the toxicity of *oral* lidocaine may be markedly increased.

Similarly, the evidence for an interaction between *intravenous* lidocaine and fluvoxamine is also limited; however, what is known suggests that the exposure to intravenous lidocaine will only be modestly increased, and possibly not of clinical relevance. However, further study is required to assess the significance of the decrease in MEGX during prolonged intravenous lidocaine infusions.

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Lidocaine + H_2-receptor antagonists

Cimetidine modestly reduces the clearance of intravenous and possibly oral lidocaine, and raises its serum levels in some patients. Ranitidine appears to have minimal effects on lidocaine clearance.

Clinical evidence

(a) Cimetidine

In one study, 15 patients were given a 1-mg/kg intravenous loading dose of lidocaine followed by a continuous infusion of 2 or 3 mg/minute over 26 hours. At 6 hours the patients started taking oral cimetidine (initial dose 300 mg intravenously, then 300 mg every 6 hours). After 26 hours (20 hours after cimetidine was started) the serum levels of lidocaine were 30% higher (5.6 micrograms/mL) than in a control group of 6 patients (4.3 micrograms/mL). The most substantial rise in levels occurred in the first 6 hours after cimetidine was started. Six patients developed toxic serum lidocaine levels (over 5 micrograms/mL) and two (with levels of 10 and 11 micrograms/mL) experienced lethargy and confusion attributed to lidocaine toxicity, which disappeared when the lidocaine was stopped.[1]

In a study, patients with suspected myocardial infarction were given a 2 mg/minute infusion of lidocaine, and then, 11 to 20 hours later, two 300-mg oral doses of cimetidine 4 hours apart. Serum lidocaine levels, taken 24 hours after the initial cimetidine dose, had risen by 28%, and unbound levels had risen by 18%. In three of these patients whose diagnosis of myocardial infarction was subsequently confirmed, rises in total and unbound lidocaine serum levels of 24% and 9% occurred.[2] In contrast, a study in 6 patients with suspected myocardial infarction given lidocaine infusions, followed later by a cimetidine infusion, did not find a significant increase in the plasma accumulation of lidocaine.[3]

Studies in healthy subjects[4,5] have similarly found that oral cimetidine 300 mg four times daily increases the peak levels of intravenous lidocaine (by 50%) and/or decreases its clearance (by 30%), and adverse effects (light-headedness, paraesthesia), developed.[4] However, other studies in healthy subjects have found that cimetidine 300 mg four times daily has no effect on intravenous lidocaine clearance.[6,7]

Cimetidine pretreatment increased the *oral* bioavailability of lidocaine by 35% in healthy subjects, and reduced the apparent oral clearance by 42%.[8] Another study found that 2 days of cimetidine pretreatment increased the AUC of lidocaine by 52% after the aerosol application of lidocaine 120 mg (12 sprays of *Xylocaine* 10%) to the oropharynx.[9]

An 89-year-old man with congestive heart failure taking oral cimetidine had two seizures 10 to 15 minutes after accidental *oral* ingestion of lidocaine solution for oesophageal anaesthesia. He had a high serum lidocaine level of 7.8 micrograms/mL.[10]

(b) Ranitidine

A study in 10 healthy subjects given 150 mg ranitidine twice daily for 5 days found that it increased the systemic clearance of lidocaine by 9%, but did not alter its oral clearance.[11] In two other studies, ranitidine 150 mg twice daily for 1 to 2 days did not change the clearance of intravenous lidocaine.[6,12]

Mechanism

Not established. It seems possible that the metabolism of lidocaine is reduced both by a fall in blood flow to the liver and by direct inhibition of the activity of the liver microsomal enzymes. As a result its clearance is reduced and its serum levels rise.

Importance and management

The interaction between intravenous lidocaine and cimetidine is well studied and established, but the effects appear modest. Nevertheless, some studies report an increase in the adverse effects of lidocaine. The interaction may possibly be of less importance in patients following a myocardial infarction because of the increased amounts of alpha-1-acid glycoprotein, which alters the levels of bound and free lidocaine.[2] Nevertheless, it would seem prudent to monitor all patients closely for evidence of toxicity (e.g. bradycardia, hypotension, pins and needles) and, where possible, check serum lidocaine levels. A reduced infusion rate may be needed. Ranitidine would appear to be a suitable alternative to cimetidine.

For interactions of cimetidine and lidocaine, when lidocaine was used as a local anaesthetic, see 'Anaesthetics, local + H_2-receptor antagonists', p.123.

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Lidocaine + Itraconazole

Itraconazole may markedly increase the plasma levels of oral lidocaine, but not intravenous lidocaine or inhaled lidocaine.

Clinical evidence

In a randomised, crossover study, 9 healthy subjects were given either itraconazole 200 mg daily or placebo for 4 days. Itraconazole increased the AUC and peak plasma levels of a single 1-mg/kg oral dose of lidocaine by 75% and 55%, respectively. Itraconazole did not affect the concentration of the main metabolite of lidocaine, monoethylglycinexylidide (MEGX).[1] In similar studies, itraconazole had no effect on the AUC and peak plasma levels of lidocaine or MEGX after 1.5-mg/kg intravenous[2] or nebulised[3] doses of lidocaine.

Mechanism

Itraconazole is an inhibitor of the cytochrome P450 isoenzyme CYP3A4, which is partially involved in the metabolism of lidocaine. Itraconazole appears to markedly reduce the first-pass metabolism of oral lidocaine so that its plasma levels rise.[1]

Importance and management

Information about an interaction between itraconazole and lidocaine seems to be limited, and as lidocaine is not usually given orally the practical importance of any interaction is minor. However, lidocaine is used for oro-pharyngeal topical anaesthesia, and there have been cases of toxicity after accidental ingestion. There is also a possibility of accidental oral ingestion during inhalation of lidocaine. In patients taking itraconazole, the toxicity of oral lidocaine may be markedly increased. Be alert for lidocaine adverse effects (e.g. bradycardia, hypotension, pins and needles).

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Lidocaine + Mexiletine

Mexiletine may increase the toxicity of lidocaine.

Clinical evidence, mechanism, importance and management

A patient with cardiomyopathy taking mexiletine 300 mg twice daily developed lidocaine CNS toxicity within one hour of receiving a total of 600 mg of oral lidocaine for oesophageal burning. Her lidocaine concentration was raised at 26.9 micrograms/mL.[1] Similarly, involuntary motion and muscular stiffness occurred in a man taking oral mexiletine after he received an intravenous infusion of lidocaine for one day.[2] Studies in *animals* have shown that the concurrent use of mexiletine and intravenous lidocaine results in a decrease in the total clearance of lidocaine and an increase in its plasma levels. It appeared that this was due to mexiletine displacing the tissue binding of lidocaine and reducing its distribution.[3] Mexiletine is an oral lidocaine analogue, so it is perhaps not surprising the two drugs may interact. The combination should be used with caution, especially during the initial stages of treatment. Where possible, lidocaine levels should be closely monitored. Note that, when lidocaine is used topically, particularly in large doses, additive systemic toxicity may occur in patients also receiving mexiletine and caution with this combination is therefore advised.[4-6]

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4. EMLA Cream (Lidocaine with Prilocaine). AstraZeneca UK Ltd. UK Summary of product characteristics, September 2009.
5. Versatis Medicated Plaster (Lidocaine). Grunenthal Ltd. UK Summary of product characteristics, September 2009.
6. Xylocaine Spray (Lidocaine). AstraZeneca UK Ltd. UK Summary of product characteristics, March 2008.

Lidocaine + Omeprazole

Omeprazole does not appear to alter the pharmacokinetics of intravenous lidocaine.

Clinical evidence, mechanism, importance and management

In a study in 10 healthy subjects, omeprazole 40 mg daily for one week did not affect the AUC or half-life of a single 1-mg/kg intravenous dose of lidocaine or those of its main metabolite methylglycinexylidine.[1] This study suggests that no special precautions are required during concurrent use.

1. Noble DW, Bannister J, Lamont M, Andersson T, Scott DB. The effect of oral omeprazole on the disposition of lignocaine. *Anaesthesia* (1994) 49, 497–500.

Lidocaine + Opioids

Morphine given as an intravenous bolus does not alter the levels of lidocaine given as a continuous intravenous infusion. A case of respiratory depression has been reported when intravenous lidocaine was given to a patient who had been given fentanyl and morphine.

Clinical evidence, mechanism, importance and management

A double-blind study in 10 patients who were receiving continuous lidocaine infusions during suspected myocardial infarction found that a 10-mg intravenous bolus dose of **morphine sulfate** did not significantly alter the steady-state serum levels of lidocaine.[1] However, in one case, respiratory depression occurred within 5 minutes of giving intravenous lidocaine for an episode of ventricular tachycardia in a patient who had been given spinal **fentanyl** and **morphine**: the last dose of opioid had been given 4 hours previously. Naloxone successfully reversed this.[2] This appears to be an isolated case, and its clinical relevance is unknown.

For a report of respiratory depression with a local anaesthetic injection of lidocaine and alphaprodine, see 'Opioids + Local anaesthetics', p.191.

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Lidocaine + Phenytoin

The incidence of central toxic adverse effects may be increased following the concurrent intravenous infusion of lidocaine and phenytoin. Sinoatrial arrest has been reported in one patient. Phenytoin may slightly reduce the levels of intravenous lidocaine, and markedly reduce the levels of oral lidocaine.

Clinical evidence

A study in 5 patients with suspected myocardial infarction, given lidocaine 0.5 to 3 mg/minute intravenously for at least 24 hours, followed by additional intravenous injections or infusions of phenytoin, found that the

plasma levels of both drugs remained unchanged but the incidence of adverse effects (vertigo, nausea, nystagmus, diplopia, impaired hearing) were unusually high.[1] However, in another study, lidocaine 2 mg/kg was given intravenously to 7 patients with epilepsy taking their usual antiepileptics (including phenytoin, barbiturates, phenothiazines, benzodiazepines), and to 6 control subjects. Plasma lidocaine levels were 27% and 43% lower in the patients at 30 and 60 minutes, respectively.[2] Another study found that the clearance of intravenous lidocaine was slightly greater in patients taking antiepileptics than in healthy subjects (850 mL/minute compared with 770 mL/minute) but this difference was not statistically significant.[3] Other studies in patients with epilepsy and healthy subjects have found that phenytoin halves the bioavailability of *oral* lidocaine.[3,4]

Sinoatrial arrest occurred in a man with heart block following a suspected myocardial infarction, after he received intravenous lidocaine 1 mg/kg over one minute, followed 3 minutes later by phenytoin 250 mg given over 5 minutes. The patient lost consciousness and his blood pressure could not be measured, but he responded to a 200-microgram dose of isoprenaline (isoproterenol).[5]

Mechanism

Phenytoin and lidocaine appear to have additive cardiac depressant actions. The reduced lidocaine serum levels are possibly due to liver enzyme induction; when lidocaine is given orally the marked reduction in levels results from the stimulation of hepatic first-pass metabolism by phenytoin.[3,4] In addition, patients taking antiepileptics including phenytoin had higher plasma concentrations of alpha-1-acid glycoprotein, which may result in a lower free fraction of lidocaine in the plasma.[6]

Importance and management

Information regarding an interaction between intravenous lidocaine and phenytoin is limited and its importance is not well established. However, the case of sinoatrial arrest emphasises the need to exercise caution when giving two drugs that have cardiac depressant actions.

The reduction in the serum levels of intravenous lidocaine in patients taking antiepileptics, including phenytoin, is small and appears not to be of any clinical significance. The reduction in the bioavailability of oral lidocaine is larger, but as lidocaine is not usually given orally, the practical importance of this interaction would also seem to be small.

1. Karlsson E, Collste P, Rawlins MD. Plasma levels of lidocaine during combined treatment with phenytoin and procainamide. *Eur J Clin Pharmacol* (1974) 7, 455–9.
2. Heinonen J, Takki S, Jarho L. Plasma lidocaine levels in patients treated with potential inducers of microsomal enzymes. *Acta Anaesthesiol Scand* (1970) 14, 89–95.
3. Perucca E, Richens A. Reduction of oral bioavailability of lignocaine by induction of first pass metabolism in epileptic patients. *Br J Clin Pharmacol* (1979) 8, 21–31.
4. Perucca E, Hedges A, Makki KA, Richens A. A comparative study of antipyrine and lignocaine disposition in normal subjects and in patients treated with enzyme-inducing drugs. *Br J Clin Pharmacol* (1980) 10, 491–7.
5. Wood RA. Sinoatrial arrest: an interaction between phenytoin and lignocaine. *BMJ* (1971) i, 645.
6. Routledge PA, Stargel WW, Finn AL, Barchowsky A, Shand DG. Lignocaine disposition in blood in epilepsy. *Br J Clin Pharmacol* (1981) 12, 663–6.

Lidocaine + Procainamide

An isolated case of delirium has been described in a patient given intravenous lidocaine with procainamide.

Clinical evidence, mechanism, importance and management

A man with paroxysmal tachycardia, taking oral procainamide 1 g every 5 hours and receiving increasing doses of lidocaine by intravenous infusion (550 mg within 3.5 hours), became restless, noisy and delirious when given a further 250 mg intravenous dose of procainamide.[1] The symptoms disappeared within 20 minutes of discontinuing the lidocaine. The reason for this reaction is not understood but the symptoms suggest that the neurotoxic effects of the two drugs might be additive. Other studies in patients have found that lidocaine plasma levels are unaffected by intravenous or oral procainamide.[2] If both drugs are given it would be prudent to be alert for CNS adverse effects, and, where possible, consider stopping one of the drugs if these become troublesome.

1. Ilyas M, Owens D, Kvasnicka G. Delirium induced by a combination of anti-arrhythmic drugs. *Lancet* (1969) ii, 1368–9.
2. Karlsson E, Collste P, Rawlins MD. Plasma levels of lidocaine during combined treatment with phenytoin and procainamide. *Eur J Clin Pharmacol* (1974) 7, 455–9.

Lidocaine + Propafenone

Propafenone has minimal effects on the pharmacokinetics of intravenous lidocaine, but the severity and duration of the CNS adverse effects of lidocaine are increased by propafenone.

Clinical evidence, mechanism, importance and management

Twelve healthy subjects, who had been taking propafenone 225 mg every 8 hours for 4 days, were given a continuous infusion of lidocaine 2 mg/kg per hour for 22 hours. Propafenone increased the AUC of lidocaine by 7% and reduced its clearance by 7%. One poor metaboliser of propafenone (that is, a subject lacking the cytochrome P450 isoenzyme CYP2D6) had an increase in lidocaine clearance. Increases in the PR and QRS intervals of 10 to 20% were also seen. Combined use increased the severity and duration of adverse effects (lightheadedness, dizziness, paraesthesia, lethargy, somnolence). One subject withdrew from the study as a result.[1] In another study, the concurrent use of lidocaine (100 mg bolus then a 2 mg/minute infusion) and propafenone (1 or 2 mg/kg infusion) produced a minor additional negative inotropic effect (which was not statistically significant) and reversed the prolongation in atrial and ventricular refractoriness produced by propafenone alone.[2]

There would therefore appear to be no marked or important pharmacokinetic interaction between these two drugs, but the increased CNS adverse effects may be poorly tolerated by some individuals, and cardiac depressant effects may be additive.

1. Ujhelyi MR, O'Rangers EA, Fan C, Kluger J, Pharand C, Chow MSS. The pharmacokinetic and pharmacodynamic interaction between propafenone and lidocaine. *Clin Pharmacol Ther* (1993) 53, 38–48.
2. Feld GK, Nademanee K, Singh BN, Kirsten E. Hemodynamic and electrophysiologic effects of combined infusion of lidocaine and propafenone in humans. *J Clin Pharmacol* (1987) 27, 52–9.

Lidocaine + Protease inhibitors

Ritonavir may increase levels of lidocaine more than threefold. Other protease inhibitors may interact similarly.

Clinical evidence, mechanism, importance and management

Direct evidence (from case reports or clinical studies) of an interaction between lidocaine and the protease inhibitors is lacking; however, a review of protease inhibitor interactions reports that the plasma levels of lidocaine may be increased more than threefold by **ritonavir**.[1] The same review also states that **indinavir**, **nelfinavir** and **saquinavir** may interact similarly. Lidocaine is metabolised by the cytochrome P450 isoenzyme CYP3A4, of which ritonavir is a potent inhibitor. Concurrent use therefore raises lidocaine levels. All protease inhibitors are, to varying degrees, inhibitors of this isoenzyme, and would therefore be expected to raise lidocaine levels.

Evidence for an interaction between lidocaine and protease inhibitors is limited, but a rise in lidocaine levels would be expected from the known pharmacology of these drugs. A threefold increase in the levels of lidocaine would be expected to increase the risk of lidocaine adverse effects, including arrhythmias. The manufacturer of **darunavir**[2] contraindicates its concurrent use with lidocaine. Similarly, the manufacturers of **indinavir**,[3] **nelfinavir**[4] and **tipranavir**[5,6] contraindicate the concurrent use of drugs with a narrow therapeutic range that are metabolised by CYP3A4, which could reasonably be expected to include lidocaine.

If the concurrent use of lidocaine and a protease inhibitor cannot be avoided, it would seem prudent to monitor the outcome of concurrent use closely for lidocaine adverse effects (e.g. light-headedness, paraesthesia), monitoring lidocaine levels if possible. Reduce the lidocaine dose as necessary.

1. Burger DM, Hoetelmans RMW, Koopmans PP, Meenhorst PL, Mulder JW, Hekster YA, Beijnen JH. Clinically relevant drug interactions with antiretroviral agents. *Antivir Ther* (1997) 2, 149–165.
2. Prezista (Darunavir ethanolate). Janssen-Cilag Ltd. UK Summary of product characteristics, October 2009.
3. Crixivan (Indinavir sulphate). Merck Sharp & Dohme Ltd. UK Summary of product characteristics, October 2008.
4. Viracept (Nelfinavir mesilate). Roche Products Ltd. UK Summary of product characteristics, July 2008.
5. Aptivus Soft Capsules (Tipranavir). Boehringer Ingelheim Ltd. UK Summary of product characteristics, June 2009.
6. Aptivus (Tipranavir). Boehringer Ingelheim Pharmaceuticals, Inc. US Prescribing information, June 2009.

Lidocaine + Rifampicin (Rifampin)

Rifampicin slightly increases the clearance of intravenous lidocaine.

Clinical evidence, mechanism, importance and management

In a study in 10 healthy subjects, rifampicin 600 mg daily for 6 days increased the clearance of a 50-mg intravenous dose of lidocaine by 15%. In addition, plasma concentrations of the main metabolite of lidocaine, monoethylglycinexylidide (MEGX) increased by 34%, although this did not reach statistical significance.[1] Using cultured human hepatocytes it was found that rifampicin increases the metabolism of lidocaine, probably because it induces the cytochrome P450 isoenzyme CYP3A4, which is partially concerned with the metabolism of lidocaine to MEGX.[2] These modest changes in lidocaine pharmacokinetics are unlikely to be of much importance, particularly as the intravenous lidocaine dose is usually titrated to effect.

1. Reichel C, Skodra T, Nacke A, Spengler U, Sauerbruch T. The lignocaine metabolite (MEGX) liver function test and P-450 induction in humans. *Br J Clin Pharmacol* (1998) 46, 535–9.
2. Li AP, Rasmussen A, Xu L, Kaminski DL. Rifampicin induction of lidocaine metabolism in cultured human hepatocytes. *J Pharmacol Exp Ther* (1995) 274, 673–7.

Lidocaine + Tobacco

Tobacco smoking reduces the bioavailability of oral, but not intravenous, lidocaine.

Clinical evidence, mechanism, importance and management

A study in 9 subjects found that the bioavailability of oral lidocaine was markedly lower in smokers. The AUC of lidocaine was almost 70% lower in the 4 smokers than in the 5 non-smokers. However, when the lidocaine was given intravenously only moderate differences were seen.[1] The reduced lidocaine AUC in the smokers probably occurs due to liver enzyme induction caused by components of tobacco smoke. With oral lidocaine this could result in increased first-pass hepatic clearance. In the case of intravenous lidocaine, first-pass clearance is bypassed, and the enzyme induction was opposed by a smoking-related decrease in hepatic flow. In practical terms this interaction is unlikely to be of much importance as lidocaine is not usually given orally.

1. Huet P-M, Lelorier J. Effects of smoking and chronic hepatitis B on lidocaine and indocyanine green kinetics. *Clin Pharmacol Ther* (1980) 28, 208–15.

Lidocaine + Tocainide

A report describes a tonic-clonic seizure in a man during the period when his treatment was being changed from intravenous lidocaine to oral tocainide.

Clinical evidence, mechanism, importance and management

An elderly man taking furosemide and co-trimoxazole experienced a tonic-clonic seizure while his treatment with intravenous lidocaine was being changed to oral tocainide, although the serum levels of both antiarrhythmics remained within their therapeutic ranges. The patient became progressively agitated and disorientated about 8 hours after starting oral tocainide 600 mg every 6 hours while still receiving lidocaine 2 mg/minute intravenously. About one hour later he had a seizure. The patient subsequently tolerated each drug separately, at concentrations similar to those that preceded the seizure, without problems.[1] A study in *animals*[2] found that tocainide reduces the lidocaine serum levels at which seizures occur by about 45%. Tocainide is no longer widely available, but the US manufacturer previously noted that the concurrent use of lidocaine and tocainide may cause an increased incidence of adverse effects, including CNS adverse reactions such as seizure, because the two drugs have similar pharmacodynamic effects.[3] Great care must therefore be exercised if tocainide is given during lidocaine use. Note that, when lidocaine is used topically, particularly at large doses, additive systemic toxicity may occur in patients also receiving tocainide and caution with this combination is therefore also advised.[4]

1. Forrence E, Covinsky JO, Mullen C. A seizure induced by concurrent lidocaine-tocainide therapy — Is it just a case of additive toxicity? *Drug Intell Clin Pharm* (1986) 20, 56–9.
2. Schuster MR, Paris PM, Kaplan RM, Stewart RD. Effect on the seizure threshold in dogs of tocainide/lidocaine administration. *Ann Emerg Med* (1987) 16, 749–51.
3. Tonocard (Tocainide). AstraZeneca. US Prescribing information, September 2000.
4. Versatis Medicated Plaster (Lidocaine). Grunenthal Ltd. UK Summary of product characteristics, September 2009.

Mexiletine + Amiodarone

Amiodarone does not affect the clearance of mexiletine; concurrent use can be clinically useful.

Clinical evidence, mechanism, importance and management

In 10 patients the clearance of mexiletine was found to be unchanged when assessed after 1, 3 and 5 months of the concurrent use of amiodarone. In addition, the clearance of mexiletine did not differ between these patients and 155 other patients not taking amiodarone.[1]

Torsade de pointes has been described in a patient taking amiodarone and mexiletine (a class Ib antiarrhythmic).[2] The manufacturers of mexiletine say that this seems to be an isolated case.[3] The two drugs have been used together successfully.[4,5]

Class Ib antiarrhythmics are usually associated with shortening of the QT interval, and could therefore be expected to reduce QT prolongation and the risk of torsade de pointes seen with amiodarone. This has been seen with sotalol in *animals* (see 'Mexiletine + Beta blockers', p.303) and quinidine (see 'Mexiletine + Quinidine', p.304).

1. Yonezawa E, Matsumoto K, Ueno K, Tachibana M, Hashimoto H, Komamura K, Kamakura S, Miyatake K, Tanaka K. Lack of interaction between amiodarone and mexiletine in cardiac arrhythmia patients. *J Clin Pharmacol* (2002) 42, 342–6.
2. Tartini R, Kappenberger L, Steinbrunn W. Gefährliche Interaktionen zwischen Amiodaron und Antiarrhythmika der Klasse I. *Schweiz Med Wochenschr* (1982) 112, 1585–7.
3. Boehringer Ingelheim. Personal Communication, July 1995.
4. Waleffe A, Mary-Rabine L, Legrand V, Demoulin JC, Kulbertus HE. Combined mexiletine and amiodarone treatment of refractory recurrent ventricular tachycardia. *Am Heart J* (1980) 100, 788–93.
5. Hoffmann A, Follath F, Burckhardt D. Safe treatment of resistant ventricular arrhythmias with a combination of amiodarone and quinidine or mexiletine. *Lancet* (1983) i, 704–5.

Mexiletine + Antacids, Atropine or Metoclopramide

The rate of absorption of mexiletine is slowed by atropine, and hastened by metoclopramide, but the extent of the absorption is unaltered.

Clinical evidence, mechanism, importance and management

In a study in healthy subjects, the antacid almasilate (*Gelusil*), given one hour before a single 400-mg dose of mexiletine, resulted in a slight delay in absorption (time to maximum concentration prolonged from 1.7 hours to 2.9 hours), but had no effect on the extent of absorption.[1]

A study in 8 healthy subjects found that a single 600-microgram dose of intravenous atropine reduced the rate of absorption of a single 400-mg oral dose of mexiletine, but the mexiletine AUC remained unaffected. Intravenous metoclopramide 10 mg hastened the absorption of mexiletine but similarly did not affect the AUC. Metoclopramide may reverse the effect of diamorphine on plasma mexiletine levels. See 'Mexiletine + Opioids', p.303.

The achievement of steady-state mexiletine levels depends on the extent of absorption, not on its rate, and therefore it seems very unlikely that these drugs will affect the antiarrhythmic effects of mexiletine during long-term use.[2] However, these drugs may cause variations in the antiarrhythmic effects of initial oral mexiletine doses, which may be a problem if rapid control of the arrhythmia is essential. In general, no special precautions would appear necessary.

1. Herzog P, Holtermüller KH, Kasper W, Meinertz T, Trenk D, Jähnchen E. Absorption of mexiletine after treatment with gastric antacids. *Br J Clin Pharmacol* (1982) 14, 746–7.
2. Wing LMH, Meffin PJ, Grygiel JJ, Smith KJ, Birkett DJ. The effect of metoclopramide and atropine on the absorption of orally administered mexiletine. *Br J Clin Pharmacol* (1980) 9, 505–9.

Mexiletine + Beta blockers

The concurrent use of mexiletine and beta blockers can be clinically useful. Mexiletine may reduce the QT-prolonging effects of sotalol.

Clinical evidence, mechanism, importance and management

A study in 4 patients found that a combination of mexiletine and **propranolol** 240 mg daily was more effective in blocking ventricular premature depolarisation (VPD) and ventricular tachycardia than mexiletine alone, and did not increase adverse effects. Plasma mexiletine concentrations were not significantly altered by **propranolol**.[1] Similar efficacy was reported for **metoprolol** with mexiletine.[2] Success in decreasing VPDs was noted in 30% of 44 patients taking mexiletine and a beta blocker [unspecified] compared with only 14% of 185 subjects taking mexiletine alone.[3] A study in *animals* found that mexiletine reduced the QT prolonging effect of **sotalol** and reduced the risk of torsade de pointes.[4] This is in line with the known effects of mexiletine, and a similar effects would be expected clinically.

1. Leahey EB, Heissenbuttel RH, Giardina E-GV, Bigger JT. Combined mexiletine and propranolol treatment of refractory ventricular tachycardia. *BMJ* (1980) 281, 357–8.
2. Ravid S, Lampert S, Graboys TB. Effect of the combination of low-dose mexiletine and metoprolol on ventricular arrhythmia. *Clin Cardiol* (1991) 14, 951–5.
3. Bigger JT. The interaction of mexiletine with other cardiovascular drugs. *Am Heart J* (1984) 107, 1079–85.
4. Chézalveil-Guilbert F, Davy J-M, Poirier J-M, Weissenburger J. Mexiletine antagonizes effects of sotalol on QT interval duration and its proarrhythmic effects in a canine model of torsade de pointes. *J Am Coll Cardiol* (1995) 26, 787–92.

Mexiletine + Fluconazole

Fluconazole does not affect the pharmacokinetics of mexiletine.

Clinical evidence, mechanism, importance and management

Six healthy subjects were given a single 200-mg dose of mexiletine before and after taking fluconazole 200 mg daily for 7 days. Two of the subjects were given fluconazole 400 mg daily for a further 7 days. No significant changes in the pharmacokinetics of mexiletine were seen.[1] The clinical outcome of concurrent use in patients was not studied, but there appear to be no adverse reports in the literature. No special precautions appear to be necessary if these drugs are used concurrently.

1. Ueno K, Yamaguchi R, Tanaka K, Sakaguchi M, Morishima Y, Yamauchi K, Iwai A. Lack of a kinetic interaction between fluconazole and mexiletine. *Eur J Clin Pharmacol* (1996) 50, 129–31.

Mexiletine + H_2-receptor antagonists

The pharmacokinetics of mexiletine are not altered by cimetidine or ranitidine. Cimetidine can reduce the gastric adverse effects of mexiletine.

Clinical evidence, mechanism, importance and management

The peak and trough plasma mexiletine levels of 11 patients were unaltered when they were given **cimetidine** 300 mg four times daily for a week, and the frequency and severity of the ventricular arrhythmias for which they were being treated remained unchanged. Moreover the gastric adverse effects of mexiletine were reduced in half of the patients.[1] This study in patients confirms the findings of two other studies using **cimetidine** or **ranitidine** in healthy subjects.[2,3] There would seem to be no problems associated with giving these drugs concurrently, and some advantages.

1. Klein AL, Sami MH. Usefulness and safety of cimetidine in patients receiving mexiletine for ventricular arrhythmia. *Am Heart J* (1985) 109, 1281–6.
2. Klein A, Sami M, Selinger K. Mexiletine kinetics in healthy subjects taking cimetidine. *Clin Pharmacol Ther* (1985) 37, 669–73.
3. Brockmeyer NH, Breithaupt H, Ferdinand W, von Hattingberg M, Ohnhaus EE. Kinetics of oral and intravenous mexiletine: lack of effect of cimetidine and ranitidine. *Eur J Clin Pharmacol* (1989) 36, 375–8.

Mexiletine + Omeprazole

Omeprazole does not appear to affect the pharmacokinetics of mexiletine.

Clinical evidence, mechanism, importance and management

A crossover study in 9 healthy Japanese men found that when they were given mexiletine 200 mg after taking omeprazole 40 mg daily for 8 days, the serum concentration and AUC of mexiletine were unchanged. It was concluded that omeprazole does not affect the metabolism of mexiletine,[1] and no special precautions would seem to be needed if these drugs are used concurrently.

1. Kusumoto M, Ueno K, Tanaka K, Takeda K, Mashimo K, Kameda T, Fujimura Y, Shibakawa M. Lack of pharmacokinetic interaction between mexiletine and omeprazole. *Ann Pharmacother* (1998) 32, 182–4.

Mexiletine + Opioids

The absorption of mexiletine is reduced following myocardial infarction, and very markedly reduced and delayed if diamorphine or morphine is used concurrently. Other opioids may interact similarly.

Clinical evidence

A pharmacokinetic study found that the mean plasma levels of mexiletine (400 mg orally followed by 200 mg 2 hours later) in the first 3 hours were more than 50% lower in 6 patients who had suffered a myocardial infarction and who had been given **diamorphine** 5 to 10 mg or **morphine** 10 to 15 mg than in 4 patients who had not been given opioids. In addition, the $AUC_{0\text{-}8}$ was 39% lower in those who had received opioids.[1]

In a further study about the prophylactic use of mexiletine, the same authors found that plasma mexiletine levels 3 hours after the first oral dose were 31% lower in 10 patients who had received opioids than in 6 patients who had not received opioids. These patients were from a subset that were subsequently shown not to have had a myocardial infarction.[1] In another similar study of mexiletine in acute myocardial infarction, the use of **diamorphine** was associated with low plasma mexiletine levels at 3 hours, and a possible reduction in the efficacy of mexiletine. In this study, pretreatment with intravenous metoclopramide tended to reduce the effect of **diamorphine** on mexiletine absorption,[2] although this was not noted in the other report.[1]

Mechanism

The reduced absorption of mexiletine would seem to result from inhibition of gastric emptying by diamorphine and morphine. Other mechanisms probably contribute to the delayed clearance of mexiletine.

Importance and management

An established interaction although information is limited. The delay and reduction in the absorption of mexiletine would seem to limit the value of oral mexiletine during the first few hours after a myocardial infarction, particularly if morphine or diamorphine are used. The manufacturer suggests that a higher loading dose of oral mexiletine may be preferable in this situation. Alternatively, an intravenous dose of mexiletine may be given. In addition, they note that it may be necessary to titrate the dose against therapeutic effects and adverse effects.[3] There seems to be no information about other opioids, but if the mechanism of interaction is correct, then other opioids would be expected to interact similarly.

1. Pottage A, Campbell RWF, Achuff SC, Murray A, Julian DC, Prescott LF. The absorption of oral mexiletine in coronary care patients. *Eur J Clin Pharmacol* (1978) 13, 393–9.
2. Smyllie HC, Doar JW, Head CD, Leggett RJ. A trial of intravenous and oral mexiletine in acute myocardial infarction. *Eur J Clin Pharmacol* (1984) 26, 537–42.
3. Mexitil (Mexiletine). Boehringer Ingelheim Ltd. UK Summary of product characteristics, May 2003.

Mexiletine + Phenytoin

Plasma mexiletine levels are reduced by phenytoin. Fosphenytoin may be expected to interact similarly.

Clinical evidence

The observation that 3 patients had unusually low plasma mexiletine levels while taking phenytoin prompted a pharmacokinetic study in 6 healthy subjects. After taking phenytoin 300 mg daily for a week, the mean AUC and half-life of a single 400-mg dose of mexiletine were reduced by an average of about 50% (half-life reduced from 17.2 hours to 8.4 hours).[1]

Mechanism

The most likely explanation for the reduction in mexiletine levels is that phenytoin increases the metabolism of mexiletine by the cytochrome P450 isoenzyme CYP1A2.

Importance and management

Information seems to be limited to this report but the interaction appears to be established. It seems likely that the reduction in mexiletine levels will be clinically important in some individuals. Monitor for mexiletine efficacy, and, where possible, monitor mexiletine levels. Raise the dose if necessary. There seems to be no information about **fosphenytoin**, but as it is a prodrug of phenytoin, it seems likely that it will interact similarly.

1. Begg EJ, Chinwah PM, Webb C, Day RO, Wade DN. Enhanced metabolism of mexiletine after phenytoin administration. *Br J Clin Pharmacol* (1982) 14, 219–23.

Mexiletine + Propafenone

Propafenone raises mexiletine serum levels in some patients.

Clinical evidence, mechanism, importance and management

In one study in healthy subjects, propafenone reduced mexiletine clearance and increased plasma mexiletine concentrations in CYP2D6 extensive metabolisers (that is, those with normal levels of this isoenzyme), but had no effect in CYP2D6 poor metabolisers (that is, those lacking this isoenzyme). Propafenone effectively turned the extensive metabolisers into poor metabolisers. Mexiletine did not affect propafenone pharmacokinetics. In this study, overall changes in ECG parameters were minor during the concurrent use of mexiletine and propafenone.[1]

The authors suggested that the increased levels of mexiletine occurred because propafenone is an inhibitor of CYP2D6, and inhibits the metabolism of mexiletine by this pathway.[1] Although the use of the combination was not associated with significant ECG changes, the potentiation of drug effects could predispose to proarrhythmias in patients with ischaemic heart disease. The authors suggest that slow dose titration of the combination may decrease the risk of adverse effects.[1] If propafenone is given to a patient taking mexiletine it would seem prudent to monitor the outcome of concurrent use (e.g. for nausea, tremor, hypotension), and decrease the dose of mexiletine if necessary.

1. Labbé L, O'Hara G, Lefebvre M, Lessard É, Gilbert M, Adedoyin A, Champagne J, Hamelin B, Turgeon J. Pharmacokinetic and pharmacodynamic interaction between mexiletine and propafenone in human beings. *Clin Pharmacol Ther* (2000) 68, 44–57.

Mexiletine + Protease inhibitors

Ritonavir appears to increase the levels of mexiletine levels. Tipranavir would be expected to interact similarly.

Clinical evidence, mechanism, importance and management

Direct evidence (from case reports or clinical studies) of an interaction between mexiletine and the protease inhibitors appears to be lacking; however, a review of protease inhibitor interactions reports that plasma levels of mexiletine may be increased 1.5- to 3-fold by **ritonavir**.[1] Mexiletine is primarily metabolised by the cytochrome P450 isoenzyme CYP2D6, of which **ritonavir** is an inhibitor. Concurrent use would therefore be expected to result in raised mexiletine levels, which may increase the risk of arrhythmias and other adverse effects. The manufacturer of ritonavir reports that cardiac adverse effects have been reported on concurrent use.[2] **Tipranavir** also inhibits CYP2D6 and would also be expected to interact with mexiletine in this way. The other protease inhibitors do not significantly affect CYP2D6 and would not be expected to increase mexiletine levels alone; however, they are usually given with low-dose **ritonavir** as a pharmacological booster. Therefore, until more is known, it would seem prudent to monitor any patient taking mexiletine with **ritonavir**, **tipranavir** or any **ritonavir**-boosted protease inhibitor for an increase in mexiletine adverse effects (such as nausea, tremor, hypotension), and titrate the mexiletine dose slowly, according to clinical response.

1. Burger DM, Hoetelmans RMW, Koopmans PP, Meenhorst PL, Mulder JW, Hekster YA, Beijnen JH. Clinically relevant drug interactions with antiretroviral agents. *Antivir Ther* (1997) 2, 149–165.
2. Norvir Soft Capsules (Ritonavir). Abbott Laboratories Ltd. UK Summary of product characteristics, October 2009.

Mexiletine + Quinidine

Mexiletine appears to limit the quinidine-induced increase in QT interval and the concurrent use of these drugs can be clinically useful. Quinidine raises mexiletine serum levels in some patients.

Clinical evidence, mechanism, importance and management

Mexiletine and quinidine given concurrently (in lower doses) were reported to be more effective than either drug alone,[1,2] and the incidence of adverse effects was reduced. Mexiletine limited the quinidine-induced increase in QT interval,[1] and may prevent ventricular tachycardias in response to quinidine, which may be due to a prolonged ventricular refractory period.[3] Two studies[4,5] in healthy subjects have found that quinidine reduces the metabolism and excretion of mexiletine in CYP2D6 extensive metabolisers (that is, those with normal levels of this isoenzyme). The total clearance of mexiletine was reduced by 24%.[5] Quinidine had no effect on mexiletine metabolism in CYP2D6 poor metabolisers (that is, those lacking this isoenzyme).

Quinidine is an inhibitor of CYP2D6, and inhibits the metabolism of mexiletine by this pathway. However, the effects appear modest and a clinically relevant adverse pharmacokinetic interaction seems unlikely.

1. Duff HJ, Roden D, Primm RK, Oates JA, Woosley RL. Mexiletine in the treatment of resistant ventricular arrhythmias: enhancement of efficacy and reduction of dose-related side effects by combination with quinidine. *Circulation* (1983) 67, 1124–8.
2. Giardina E-GV, Wechsler ME. Low dose quinidine-mexiletine combination therapy versus quinidine monotherapy for treatment of ventricular arrhythmias. *J Am Coll Cardiol* (1990) 15, 1138–45.
3. Bonavita GJ, Pires LA, Wagshal AB, Cuello C, Mittleman RS, Greene TO, Huang SKS. Usefulness of oral quinidine-mexiletine combination therapy for sustained ventricular tachyarrhythmias as assessed by programmed electrical stimulation when quinidine monotherapy has failed. *Am Heart J* (1994) 127, 847–51.
4. Broly F, Vandamme N, Caron J, Libersa C, Lhermitte M. Single-dose quinidine treatment inhibits mexiletine oxidation in extensive metabolizers of debrisoquine. *Life Sci* (1991) 48, PL-123–128.
5. Turgeon J, Fiset C, Giguère R, Gilbert M, Moerike K, Rouleau JR, Kroemer HK, Eichelbaum M, Grech-Bélanger O, Bélanger PM. Influence of debrisoquine phenotype and of quinidine on mexiletine disposition in man. *J Pharmacol Exp Ther* (1991) 259, 789–98.

Mexiletine + Quinolones

Ciprofloxacin slightly reduces the clearance of mexiletine, but this is unlikely to be clinically relevant. Mexiletine may reduce sparfloxacin-induced QT prolongation.

Clinical evidence, mechanism, importance and management

(a) Ciprofloxacin

A study in healthy subjects found that the oral clearance of a single dose of mexiletine was reduced by about 8 to 20% when it was given on day 3 of a 5-day course of ciprofloxacin 750 mg twice daily. This was due to a decrease in the metabolic clearance of mexiletine, which presumably occurred because ciprofloxacin inhibits the cytochrome P450 isoenzyme CYP1A2, which is involved in the metabolism of mexiletine.[1] It is unlikely that changes of this magnitude would be clinically relevant.

(b) Other quinolones

An *animal* study found that mexiletine may reduce the QT-prolonging effect of **sparfloxacin**.[2] This is in line with the known effects of mexiletine, and this effect would be expected to be replicated clinically, both with **sparfloxacin**, and other quinolones that prolong the QT interval (e.g. **gatifloxacin**, **moxifloxacin** and possibly **levofloxacin**).

1. Labbé L, Robitaille NM, Lefez C, Potvin D, Gilbert M, O'Hara G, Turgeon J. Effects of ciprofloxacin on the stereoselective disposition of mexiletine in man. *Ther Drug Monit* (2004) 26, 492–8.
2. Takahara A, Sugiyama A, Satoh Y, Hashimoto K. Effects of mexiletine on the canine model of sparfloxacin-induced long QT syndrome. *Eur J Pharmacol* (2003) 476, 115–22.

Mexiletine + Rifampicin (Rifampin)

The clearance of mexiletine is increased by rifampicin.

Clinical evidence, mechanism, importance and management

In a study in 8 healthy subjects, rifampicin 600 mg daily for 10 days reduced the half-life of a single 400-mg dose of mexiletine by 40% (from 8.5 hours to 5 hours) and the AUC fell by 39%.[1] The probable reason for these pharmacokinetics changes is that the rifampicin (a known, potent enzyme-inducer) increases the metabolism and clearance of mexiletine. It seems likely that the mexiletine dosage will need to be increased during concurrent use. Monitor concurrent use well.

1. Pentikäinen PJ, Koivula IH, Hiltunen HA. Effect of rifampicin treatment on the kinetics of mexiletine. *Eur J Clin Pharmacol* (1982) 23, 261–6.

Mexiletine + SSRIs

Fluvoxamine markedly increases the AUC of mexiletine by inhibiting CYP1A2. Fluoxetine and paroxetine might also be expected to interact, by inhibiting CYP2D6, but sertraline seems unlikely to interact.

Clinical evidence, mechanism, importance and management

In a study in 6 healthy subjects, **fluvoxamine** 50 mg twice daily for 7 days increased the AUC of a single 200-mg dose of mexiletine by 55%, and decreased its clearance by 37%.[1] It is likely that **fluvoxamine** increases the AUC of mexiletine by inhibiting the cytochrome P450 isoenzyme CYP1A2, which is partially responsible for the metabolism of mexiletine.[1] Many adverse effects of mexiletine are dose related, and therefore concurrent use should be monitored for adverse effects (e.g. nausea, tremor, hypotension), and the mexiletine dose reduced as necessary.

In an *in vitro* study using human liver microsomes, **paroxetine**, **fluoxetine**, and **sertraline** extensively inhibited the metabolism of mexiletine. Using a model to predict *in vivo* interactions, it was suggested that both **fluoxetine** and **paroxetine** may interact with mexiletine to a clinically relevant extent, whereas **sertraline** is less likely to interact.[2] This *in vitro* finding is supported by the interactions of these SSRIs with known CYP2D6 substrates (e.g. see 'Tricyclic and related antidepressants + SSRIs', p.1513). However, note that quinidine (a potent CYP2D6 inhibitor) had only modest effects on mexiletine metabolism (see 'Mexiletine + Quinidine', p.304), and therefore **fluoxetine** and **paroxetine**, which are modest CYP2D6 inhibitors see unlikely to interact to a clinically relevant extent. Nevertheless, until more is known it may be prudent to be alert for mexiletine adverse effects (e.g. nausea, tremor, hypotension) in patients given **fluoxetine** or **paroxetine**. If they develop, consider an interaction as a possible cause.

1. Kusumoto M, Ueno K, Oda A, Takeda K, Mashimo K, Takaya K, Fujimura Y, Nishihori T, Tanaka K. Effect of fluvoxamine on the pharmacokinetics of mexiletine in healthy Japanese men. *Clin Pharmacol Ther* (2001) 69, 104–7.
2. Hara Y, Nakajima M, Miyamoto K-I, Yokoi T. Inhibitory effects of psychotropic drugs on mexiletine metabolism in human liver microsomes: prediction of *in vivo* drug interactions. *Xenobiotica* (2005) 35, 549–60.

Mexiletine + Tobacco

Tobacco smoking reduces the elimination half-life of mexiletine but does not affect its absorption and distribution.

Clinical evidence, mechanism, importance and management

A study in 14 healthy subjects (6 smokers and 8 non-smokers) found that cigarette smoking had no effect on the absorption or distribution of a single 200-mg dose of mexiletine. However, smoking significantly reduced the elimination half-life of mexiletine from 11.1 hours to 7.2 hours. Cigarette smoking was also found to induce the conjugation of mexiletine with glucuronic acid and the hydroxylation of mexiletine to hydroxymethylmexiletine but had no effect on the formation of *p*-hydroxymexiletine.[1]

It seems likely that some constituents of tobacco smoke induced the metabolism of mexiletine, leading to the reduction in half-life seen. The clinical significance of this effect is not known, but as mexiletine is titrated to effect it would seem that any interaction would automatically be accounted for in smokers. If a patient taking mexiletine stops smoking, it may be prudent to be alert for mexiletine adverse effects (e.g. nausea, tremor, hypotension), and decrease the dose of mexiletine, according to clinical response.

1. Grech-Bélanger O, Gilbert M, Turgeon J, LeBlanc P-P. Effects of cigarette smoking on mexiletine kinetics. Clin Pharmacol Ther 1985) 37, 638–43.

Mexiletine + Urinary acidifiers or alkalinisers

Large changes in urinary pH caused by acidifying or alkalinising drugs can have a marked effect on the plasma levels of mexiletine in some patients.

Clinical evidence

In 4 healthy subjects, a single 200-mg intravenous dose of mexiletine was given, once when the urine was acidic (pH 5) after administration of **ammonium chloride**, and once when the urine was alkaline (pH 8) after administration of **sodium bicarbonate**. The plasma elimination half-life was significantly shorter when the urine was acidic (2.8 hours) compared with when it was alkaline (8.6 hours). In addition, the percentage of mexiletine excreted unchanged in the urine was 58% in acidic urine and less than 1% in alkaline urine.[1] Similar results were found in another study.[2] A further study in patients with uncontrolled urinary pHs (range 5.04 to 7.86) given mexiletine orally for 5 days found that the plasma concentration of mexiletine correlated with urine pH. In addition, it was predicted that a normal variation in pH could cause more than a 50% variation in plasma mexiletine levels.[3] A later comprehensive pharmacokinetic study in 5 healthy subjects found that the renal clearance of mexiletine was 4 mL/minute in alkaline urine (pH 8) compared with 168 mL/minute in acidic urine (pH 5.2). In two subjects, this resulted in an increase in mexiletine plasma concentrations of 61% and 96%, but in the other three subjects the increase was less than 20%. Non-renal clearance (metabolic clearance) increased in the three subjects with little change in plasma concentrations, but was unaffected in the two subjects with marked changes in plasma concentrations.[4]

Mechanism

Mexiletine is a basic drug, which undergoes greater reabsorption by the kidneys when in the non-ionised form in alkaline urine. Mexiletine is also extensively cleared from the body by liver metabolism and only about 10% is excreted unchanged in the urine at physiological pH, although this is variable. Any changes in the renal clearance of mexiletine that occur as a result of urinary pH changes might therefore be expected to be compensated for by an increase in metabolic clearance, but this does not seem to occur in all patients.[4]

Importance and management

Although changes in urinary pH can affect the amount of mexiletine lost in the urine, the effect of diet or the concurrent use of alkalinisers (sodium bicarbonate, **acetazolamide**) or acidifiers (ammonium chloride etc.) on the plasma concentrations of mexiletine does not appear to be predictable. There appear to be no reports of adverse interactions but concurrent use should be monitored. The UK manufacturer of mexiletine recommends that the concomitant use of drugs that markedly acidify or alkalinise the urine should be avoided.[5]

1. Kiddie MA, Kaye CM, Turner P, Shaw TRD. The influence of urinary pH on the elimination of mexiletine. *Br J Clin Pharmacol* (1974) 1, 229–32.
2. Beckett AH, Chidomere EC. The distribution, metabolism and excretion of mexiletine in man. *Postgrad Med J* (1977) 53 (Suppl 1), 60–6.
3. Johnston A, Burgess CD, Warrington SJ, Wadsworth J, Hamer NAJ. The effect of spontaneous changes in urinary pH on mexiletine plasma concentrations and excretion during chronic administration to healthy volunteers. *Br J Clin Pharmacol* (1979) 8, 349–52.
4. Mitchell BG, Clements JA, Pottage A, Prescott LF. Mexiletine disposition: individual variation in response to urine acidification and alkalinisation. *Br J Clin Pharmacol* (1983) 16, 281–4.
5. Mexitil (Mexiletine). Boehringer Ingelheim Ltd. UK Summary of product characteristics, May 2003.

Moracizine + Cimetidine

Cimetidine increases the AUC of moracizine. Moracizine does not affect the pharmacokinetics of cimetidine.

Clinical evidence, mechanism, importance and management

In a study in 8 healthy subjects, cimetidine 300 mg four times daily for 7 days halved the clearance of a single 500-mg dose of moracizine and increased both its half-life and AUC by 39%. It is believed that these pharmacokinetic changes occur because cimetidine reduces moracizine metabolism by the liver.[1] Despite the increase in plasma moracizine levels, the PR and QRS intervals were not further prolonged. It has been suggested that this effect may occur because some of the metabolites of moracizine, whose production is inhibited by cimetidine, could also be pharmacologically active. Moracizine is reported not to affect the pharmacokinetics of cimetidine. Concurrent use should be well monitored for moracizine adverse effects (e.g. dizziness, abdominal pain, blurred vision), but measuring plasma moracizine levels may be of limited value because of the potential effects of the moracizine metabolites.

1. Biollaz J, Shaheen O, Wood AJJ. Cimetidine inhibition of ethmozine metabolism. *Clin Pharmacol Ther* (1985) 37, 665–8.

Moracizine + Diltiazem

A pharmacokinetic interaction occurs between moracizine and diltiazem resulting in increased systemic availability of moracizine and decreased systemic availability of diltiazem.

Clinical evidence, mechanism, importance and management

After 16 healthy subjects took both diltiazem 60 mg and moracizine 250 mg every 8 hours for 7 days, the maximum plasma concentration of moracizine was increased by 89%, the AUC was increased by 121%, and clearance was decreased by 54%. In addition, the maximum plasma concentration and AUC of diltiazem decreased by 36% and its clearance was increased by 52%. The AUCs for the diltiazem metabolites were not significantly affected. No clinically significant changes in ECG parameters were seen. However, the frequency of adverse events (e.g. headache, dizziness, paraesthesia) was greater on concurrent use (76%) than with either drug alone (54% and 45% for moracizine and diltiazem, respectively).[1]

Diltiazem probably inhibits the hepatic metabolism of moracizine while moracizine increases that of diltiazem. The clinical significance of this interaction is not known. However, particular caution is advised if diltiazem and moracizine are given concurrently, in light of the increase in adverse events. Dose adjustments may also be required to obtain optimum therapeutic responses.[1]

1. Shum L, Pieniaszek HJ, Robinson CA, Davidson AF, Widner PJ, Benedek IH, Flamenbaum W. Pharmacokinetic interactions of moricizine and diltiazem in healthy volunteers. *J Clin Pharmacol* (1996) 36, 1161–8.

Moracizine + Propranolol

Moracizine appears not to interact adversely with propranolol.

Clinical evidence, mechanism, importance and management

In controlled studies, the efficacy and tolerability of the combination of propranolol and moracizine was compared with either drug alone in patients with ventricular arrhythmias. The combination was well tolerated, with no evidence of any adverse interactions, nor any beneficial interactions. However, the dose of propranolol used was fairly low at 120 mg daily.[1,2]

1. Pratt CM, Butman SM, Young JB, Knoll M, English LD. Antiarrhythmic efficacy of Ethmozine® (moricizine HCl) compared with disopyramide and propranolol. *Am J Cardiol* (1987) 60, 52F–58F.

2. Butman SM, Knoll ML, Gardin JM. Comparison of ethmozine to propranolol and the combination for ventricular arrhythmias. *Am J Cardiol* (1987) 60, 603–7.

Pirmenol + Cimetidine

In a study in 8 healthy subjects, cimetidine 300 mg four times daily for 8 days had no significant effect on the pharmacokinetics of a single 150-mg oral dose of pirmenol.[1] No clinically important pharmacokinetic interaction would therefore be expected in patients given both drugs.

1. Stringer KA, Lebsack ME, Cetnarowski-Cropp AB, Goldfarb AL, Radulovic LL, Bockbrader HN, Chang T, Sedman AJ. Effect of cimetidine administration on the pharmacokinetics of pirmenol. *J Clin Pharmacol* (1992) 32, 91–4.

Pirmenol + Rifampicin (Rifampin)

Rifampicin markedly increases the clearance of pirmenol.

Clinical evidence, mechanism, importance and management

In a study in 12 healthy subjects, rifampicin 600 mg daily for 14 days markedly affected the pharmacokinetics of a single 150-mg dose of pirmenol.[1] The apparent plasma clearance increased sevenfold and the AUC decreased by 83%.[1] The probable reason for these pharmacokinetic changes is that rifampicin increases the hepatic metabolism of pirmenol. Monitor concurrent use well and anticipate the need to increase the dose of pirmenol if rifampicin is used concurrently. However, note that, with such a large reduction in pirmenol exposure it is possible that dose increases will be ineffective, and alternative antiarrhythmics should be considered.

1. Stringer KA, Cetnarowski AB, Goldfarb AB, Lebsack ME, Chang TS, Sedman AJ. Enhanced pirmenol elimination by rifampin. *J Clin Pharmacol* (1988) 28, 1094–7.

Procainamide + Amiodarone

When procainamide and amiodarone are used together the QT interval prolonging effects are increased. Serum procainamide levels are increased by about 60% and procainamide metabolite levels are increased by about 30% by amiodarone.

Clinical evidence

In a study, 12 patients were stabilised taking procainamide (2 to 6 g daily, or about 900 mg every 6 hours). When amiodarone (600 mg loading dose every 12 hours for 5 to 7 days, then 600 mg daily) was also given their mean serum procainamide levels rose by 57% (from 6.8 to 10.6 micrograms/mL) and their serum levels of the metabolite *N*-acetylprocainamide (NAPA) rose by 32% (from 6.9 to 9.1 micrograms/mL). Procainamide levels increased by more than 3 micrograms/mL in 6 of the patients. The increases usually occurred within 24 hours, but in other patients they occurred as late as 4 or 5 days. Toxicity was seen in 2 patients. Despite lowering the procainamide doses by 20%, serum procainamide levels were still higher (at 7.7 micrograms/mL) than before the amiodarone was started.[1]

In another study, intravenous procainamide was given once before (at a mean dose of 13 mg/kg), and once during (at a 30% reduced dose: mean 9.2 mg/kg) the use of amiodarone 1.6 g daily for 7 to 14 days. Amiodarone decreased the clearance of procainamide by 23% and increased its elimination half-life by 38%. Both drugs prolonged the QRS and QTc intervals, and the extent of prolongation was significantly greater with the combination than with either drug alone.[2]

Mechanism

The mechanism behind the pharmacokinetic interaction is not understood. The QT prolonging effects of the two drugs appear to be additive.

Importance and management

Information about an interaction between procainamide and amiodarone appears to be limited to these studies, but the interaction would seem to be established and clinically important. The authors of the pharmacokinetic studies, suggest that the dose of procainamide may need to be reduced by 20 to 50%. They also suggest that serum levels should be monitored and patients observed for adverse effects.[1,2] Remember that the interaction can develop within 24 hours.

Note that the concurrent use of two drugs that prolong the QT interval, such as amiodarone and procainamide, should generally be avoided. For

further discussion, see also 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290.

1. Saal AK, Werner JA, Greene HL, Sears GK, Graham EL. Effect of amiodarone on serum quinidine and procainamide levels. *Am J Cardiol* (1984) 53, 1264–7.
2. Windle J, Prystowsky EN, Miles WM, Heger JJ. Pharmacokinetic and electrophysiologic interactions of amiodarone and procainamide. *Clin Pharmacol Ther* (1987) 41, 603–10.

Procainamide + Antacids or Antidiarrhoeals

There is some inconclusive evidence that aluminium phosphate may possibly cause a small reduction in the absorption of procainamide. Kaolin-pectin appears to modestly reduce the bioavailability of procainamide.

Clinical evidence, mechanism, importance and management

A single 11-g dose of an **aluminium phosphate** antacid modestly reduced the AUC of a single 750-mg oral dose of procainamide by about 15%.[1] The clinical importance of this interaction is uncertain, but probably small.

In a study in 4 healthy subjects, **kaolin-pectin** was found to reduce the peak saliva concentrations and AUC of a single 250-mg dose of procainamide by about 30%. **Kaolin-pectin** and **magnesium trisilicate** absorbed procainamide *in vitro*.[2] The clinical importance of this is also uncertain, but the effects appear to be relatively modest. The same *in vitro* study found that *Simeco* (**co-dried aluminium hydroxide**/**magnesium carbonate** with **magnesium hydroxide** and **simeticone**) and *Pepto-Bismol* (**bismuth salicylate**) did not adsorb procainamide[2] which suggests that they are unlikely to interact, but this needs confirmation.

1. Albin H, Vincon G, Bertolaso D, Dangoumau J. Influence du phosphate d'aluminium sur la biodisponibilité de la procaïnamide et du disopyramide. *Therapie* (1981) 36, 541–6.
2. Al-Shora HI, Moustafa MA, Niazy EM, Gaber M, Gouda MW. Interactions of procainamide, verapamil, guanethidine and hydralazine with adsorbent antacids and antidiarrhoeal mixtures. *Int J Pharmaceutics* (1988) 47, 209–13.

Procainamide + Beta blockers

The pharmacokinetics of procainamide are only slightly altered by propranolol and metoprolol. Both sotalol and procainamide have QT-interval prolonging effects, which may be additive if they are used together.

Clinical evidence, mechanism, importance and management

Preliminary results of a study in 6 healthy subjects found that long-term treatment with **propranolol** (period and dose not stated) increased the procainamide half-life from 1.71 to 2.66 hours and reduced the plasma clearance by 16%.[1] A later study in 8 healthy subjects found that the pharmacokinetics of a single 500-mg dose of procainamide were only slightly altered by **propranolol** 80 mg three times daily or **metoprolol** 100 mg twice daily. The procainamide half-life of 1.9 hours increased to 2.2 hours with **propranolol**, and to 2.3 hours with **metoprolol**, but no significant changes in total clearance occurred. No changes in the AUC of the metabolite *N*-acetylprocainamide were seen.[2] It seems unlikely that a clinically important adverse pharmacokinetic interaction normally occurs between these drugs.

A clinical study describes the successful use of procainamide with **sotalol**.[3] However, both **sotalol** and procainamide can prolong the QT interval, and there may be an increased risk of torsade de pointes arrhythmias if they are used together, see 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290.

1. Weidler DJ, Garg DC, Jallad NS, McFarland MA. The effect of long-term propranolol administration on the pharmacokinetics of procainamide in humans. *Clin Pharmacol Ther* (1981) 29, 289.
2. Ochs HR, Carstens G, Roberts G-M, Greenblatt DJ. Metoprolol or propranolol does not alter the kinetics of procainamide. *J Cardiovasc Pharmacol* (1983) 5, 392–5.
3. Dorian P, Newman D, Berman N, Hardy J, Mitchell J. Sotalol and type IA drugs in combination prevent recurrence of sustained ventricular tachycardia. *J Am Coll Cardiol* (1993) 22, 106–13.

Procainamide + H_2-receptor antagonists

Serum procainamide levels can be increased by cimetidine and toxicity may develop, particularly in those who have a reduced renal clearance, such as the elderly. Ranitidine and famotidine appear to interact with procainamide only minimally or not at all.

Clinical evidence

(a) Cimetidine

In one study, 36 elderly patients (aged 65 to 90 years) taking sustained-release oral procainamide every 6 hours had rises in mean steady-state serum levels of procainamide and its metabolite *N*-acetylprocainamide of 55% and 36%, respectively, after taking cimetidine 300 mg every 6 hours for 3 days. This was tolerated in 24 patients with serum procainamide and *N*-acetylprocainamide levels of less than 12 mg/L and less than 15 mg/L, respectively, without adverse effects. However, 9 patients had some mild adverse effects (nausea, weakness, malaise, PR interval increases of less than 20%), with serum procainamide and *N*-acetylprocainamide levels between 10 and 15 mg/L and 10 and 20 mg/L, respectively. Three patients experienced severe procainamide toxicity (e.g. ventricular rate above 150 bpm for between 30 seconds and 5 minutes) with serum procainamide and *N*-acetylprocainamide levels greater than 14 mg/L and 16 mg/L, respectively. These adverse effects were dealt with by stopping one or both drugs and symptoms resolved within 12 to 24 hours.[1] Another report describes an elderly man who developed procainamide toxicity after taking cimetidine 1.2 g daily. His procainamide dose was roughly halved (from 937.5 mg every 6 hours to 500 mg every 6 hours) to bring his serum procainamide and *N*-acetylprocainamide levels into the accepted therapeutic range.[2]

Four studies in healthy subjects have found that cimetidine increases the AUC of procainamide by 24 to 43%, and decreases its renal clearance by 31 to 40%,[3-6] these changes occurring even with single doses of cimetidine.[5] An increase in the steady-state levels of procainamide of 43% has been seen when cimetidine 1.2 g daily was also given.[6]

(b) Famotidine

In a study in 8 healthy subjects, famotidine 40 mg daily for 5 days did not affect the pharmacokinetics or pharmacodynamics of a single 5-mg/kg intravenous dose of procainamide.[7]

(c) Ranitidine

One study[8] found that ranitidine 150 mg twice daily for one day reduced the absorption of procainamide from the gut by 10% and reduced its renal excretion by 19%, increasing the procainamide and *N*-acetylprocainamide AUC by about 14%. Another study found no change in the steady-state pharmacokinetics of procainamide when ranitidine 150 mg twice daily was also given, except that ranitidine delayed the time to maximum plasma concentration (from 1.4 to 2.7 hours).[6] In a further study, in 13 healthy subjects, ranitidine 150 mg twice daily for 4 days caused no significant changes in the mean pharmacokinetics of oral procainamide 1 g. However, it appeared that subjects had either a modest 20% increase or decrease in procainamide clearance, with the direction of change related to their baseline procainamide clearance: the higher the baseline clearance the greater the decrease caused by ranitidine.[9]

Mechanism

Procainamide levels are increased because cimetidine reduces its renal excretion by about one-third or more, but the precise mechanism for this is uncertain. One suggestion is that it interferes with the active secretion of procainamide by the kidney tubules.[3,4]

Importance and management

The interaction between procainamide and cimetidine is established. Concurrent use should be undertaken with care because the safety margin of procainamide is low. Reduce the procainamide dosage as necessary. This is particularly important in the elderly because they have a reduced ability to clear both drugs. Ranitidine and famotidine appear not to interact to a clinically important extent, but it should be appreciated that what is known is based on studies in healthy subjects rather than patients.

1. Bauer LA, Black D, Gensler A. Procainamide-cimetidine drug interaction in elderly male patients. *J Am Geriatr Soc* (1990) 38, 467–9.
2. Higbee MD, Wood JS, Mead RA. Case report. Procainamide-cimetidine interaction. A potential toxic interaction in the elderly. *J Am Geriatr Soc* (1984) 32, 162–4.
3. Somogyi A, McLean A, Heinzow B. Cimetidine-procainamide pharmacokinetic interaction in man: evidence of competition for tubular secretion of basic drugs. *Eur J Clin Pharmacol* (1983) 25, 339–45.
4. Christian CD, Meredith CG, Speeg KV. Cimetidine inhibits renal procainamide clearance. *Clin Pharmacol Ther* (1984) 36, 221–7.

5. Lai MY, Jiang FM, Chung CH, Chen HC, Chao PDL. Dose dependent effect of cimetidine on procainamide disposition in man. *Int J Clin Pharmacol Ther Toxicol* (1988) 26, 118–21.
6. Rodvold KA, Paloucek FP, Jung D, Gallastegui J. Interaction of steady-state procainamide with H_2-receptor antagonists cimetidine and ranitidine. *Ther Drug Monit* (1987) 9, 378–83.
7. Klotz U, Arvela P, Rosenkranz B. Famotidine, a new H_2-receptor antagonist, does not affect hepatic elimination of diazepam or tubular secretion of procainamide. *Eur J Clin Pharmacol* (1985) 28, 671–5.
8. Somogyi A, Bochner F. Dose and concentration dependent effect of ranitidine on procainamide disposition and renal clearance in man. *Br J Clin Pharmacol* (1984) 18, 175–81.
9. Rocci ML, Kosoglou T, Ferguson RK, Vlasses PH. Ranitidine-induced changes in the renal and hepatic clearances of procainamide are correlated. *J Pharmacol Exp Ther* (1989) 248, 923–8.

Procainamide + Para-aminobenzoic acid (PABA)

A single case report found that para-aminobenzoic acid (PABA) increased the serum levels of procainamide and reduced the serum levels of the procainamide metabolite *N*-acetylprocainamide. In contrast, a later pharmacokinetic study in healthy subjects found that PABA had no effect on serum procainamide levels, and increased serum *N*-acetylprocainamide levels.

Clinical evidence, mechanism, importance and management

A 61-year-old man who had sustained ventricular tachycardia, which did not respond adequately to oral procainamide, was found to be a fast acetylator of procainamide, which resulted in particularly high serum levels of the procainamide metabolite (*N*-acetylprocainamide) in relation to his procainamide levels. When he was also given para-aminobenzoic acid (PABA) 1.5 g every 6 hours for 30 hours, to suppress the production of this metabolite, the serum level of procainamide increased, that of *N*-acetylprocainamide decreased, and control of his arrhythmia improved.[1] However, a later study in 10 healthy subjects, who were also fast acetylators of procainamide, found that PABA did not significantly affect the pharmacokinetics of procainamide. In addition, although PABA inhibited the production of *N*-acetylprocainamide, it also inhibited its renal excretion, so that the AUC and elimination half-life were increased. This suggests that PABA may in fact not be useful for increasing the efficacy and safety of procainamide.[2]

These contradictory findings are difficult to explain, but neither report suggests that concurrent use need be avoided.

1. Nylen ES, Cohen AI, Wish MH, Lima JL, Finkelstein JD. Reduced acetylation of procainamide by para-aminobenzoic acid. *J Am Coll Cardiol* (1986) 7, 185–7.
2. Tisdale JE, Rudis MI, Padhi ID, Svensson CK, Webb CR, Borzak S, Ware JA, Krepostman A, Zarowitz BJ. Inhibition of N-acetylation of procainamide by para-aminobenzoic acid in humans. *J Clin Pharmacol* (1995) 35, 902–10.

Procainamide + Probenecid

In a study in 6 healthy subjects, the pharmacokinetics of a single 750-mg intravenous dose of procainamide and its effects on the QT interval were not altered by pretreatment with probenecid 2 g.[1] No special precautions appear to be necessary on concurrent use.

1. Lam YWF, Boyd RA, Chin SK, Chang D, Giacomini KM. Effect of probenecid on the pharmacokinetics and pharmacodynamics of procainamide. *J Clin Pharmacol* (1991) 31, 429–32.

Procainamide + Quinidine

A single case report describes a patient who developed a marked increase in his procainamide levels when he was also given quinidine. The combination prolongs the QT interval, and should generally be avoided because of the increased risk of torsade de pointes.

Clinical evidence

A man with sustained ventricular tachycardia taking high-dose intravenous procainamide 2 g every 8 hours had a 70% increase in his steady-state plasma procainamide levels, from 9.1 nanograms/mL to 15.4 nanograms/mL, when he also took quinidine gluconate 324 mg every 8 hours. The procainamide half-life increased from 3.7 hours to 7.2 hours and its clearance fell from 27 L/hour to 16 L/hour. His QTc interval increased by 30 milliseconds, to 678 milliseconds.[1] In another study in patients with ventricular arrhythmias, quinidine was given with procainamide. The doses were adjusted, based in part on the QT interval. The QTc interval was longer when both drugs were given (499 milliseconds) than with each drug alone (quinidine 470 milliseconds, procainamide 460 milliseconds) despite reducing the doses when both drugs were given (mean quinidine dose reduced by 28%; mean procainamide dose reduced by 32%).[2]

Mechanism

It has been suggested that the quinidine interferes with one or more of the renal pathways by which procainamide is cleared from the body.[1]

Importance and management

Information on the possible pharmacokinetic interaction between procainamide and quinidine seems to be limited to this report. Both quinidine and procainamide are class Ia antiarrhythmics and prolong the QT interval, an effect that is increased by concurrent use. Such combinations should generally be avoided because of the increased risk of torsade de pointes. For further discussion of this effect, see 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290.

1. Hughes B, Dyer JE, Schwartz AB. Increased procainamide plasma concentrations caused by quinidine: a new drug interaction. *Am Heart J* (1987) 114, 908–9.
2. Kim SG, Seiden SW, Matos JA, Waspe LE, Fisher JD. Combination of procainamide and quinidine for better tolerance and additive effects for ventricular arrhythmias. *Am J Cardiol* (1985) 56, 84–8.

Procainamide + Quinolones

Ofloxacin and levofloxacin cause moderate increases in the serum levels of procainamide, whereas ciprofloxacin has a lesser effect. However, the ECG appears to be unaltered in studies in healthy subjects given these quinolones with procainamide. An increased risk of torsade de pointes would be expected if procainamide is used with gatifloxacin, moxifloxacin, or sparfloxacin, and possibly levofloxacin.

Clinical evidence

Nine healthy subjects were given a single 1-g oral dose of procainamide alone, then again with the fifth dose of **ofloxacin** (400 mg twice daily for five doses). **Ofloxacin** increased the AUC of procainamide by 27%, increased its maximum plasma levels by 21% (from 4.8 to 5.8 micrograms/mL) and reduced its total clearance by 22%, whereas the pharmacokinetics of the active metabolite of procainamide, *N*-acetylprocainamide, were not significantly altered.[1] In another study, 10 healthy subjects were given **levofloxacin** 500 mg daily or **ciprofloxacin** 500 mg twice daily, with a single 15-mg/kg intravenous dose of procainamide on day 5. **Levofloxacin** increased the AUC of procainamide by 21% and prolonged its half-life by about 19% (from 2.7 to 3.2 hours). The clearance of procainamide was reduced by 17% (range 4 to 46%) with renal clearance reduced by 26% (range 11 to 58%). The pharmacokinetics of *N*-acetylprocainamide were similarly affected. **Ciprofloxacin** caused only minor changes in procainamide and *N*-acetylprocainamide pharmacokinetics, although the renal clearance of procainamide was reduced by 15% (range 3 to 26%).[2]

Despite these pharmacokinetic changes, no ECG changes were detected. However, these studies[1,2] involved only single doses of procainamide with average maximum serum levels (about 4 to 6 micrograms/mL) at the lower end of the therapeutic range for procainamide, although in one study individual levels of up to 8.5 micrograms/mL were found.[1]

The QTc interval in an elderly patient with atrial fibrillation increased from 450 to 464 milliseconds 3 days after she was given a single intravenous dose of procainamide and also started taking **levofloxacin** 500 mg daily. Procainamide levels on day 3 were subtherapeutic (1.8 micrograms/mL). On day 4 the QTc interval had increased to 568 milliseconds, she developed polymorphic ventricular tachycardia, and by the evening the QTc interval had further increased to 577 milliseconds. **Levofloxacin** was discontinued on day 5 and the QTc interval returned to normal within 48 hours.[3] This effect was attributed to

levofloxacin, and an interaction with procainamide was not considered.

An analysis of the Adverse Events Reporting System database of the FDA in the US looked at cases of torsade de pointes associated with quinolones reported up until May 2001. The quinolones included in the analysis were **ciprofloxacin**, **ofloxacin**, **levofloxacin**, **gatifloxacin**, and **moxifloxacin**, and in total there were 37 cases identified, of which 19 occurred in patients also taking other drugs known to prolong the QT interval. One of these 19 cases was noted in a patient taking procainamide with a quinolone [unspecified].[4]

Mechanism

The probable reason for the pharmacokinetic interaction is that levofloxacin, ofloxacin and to a lesser extent ciprofloxacin, inhibit the secretion of unchanged procainamide by the kidney tubules via renal drug transporters. Levofloxacin also appears to inhibit the secretion of *N*-acetylprocainamide. Some quinolones can prolong the QT interval, and these effects may be additive with the QT-prolonging effects of procainamide.

Importance and management

These results suggest that ofloxacin and levofloxacin affect the pharmacokinetics of procainamide to a modest extent; ciprofloxacin has lesser effects. The large interpatient variation found in these studies suggests it is possible that many patients will not experience a clinically significant interaction. However, in slow acetylators of procainamide, in whom renal clearance contributes to a larger fraction of total clearance, and those receiving higher doses of procainamide (serum levels greater than 10 micrograms/mL), the use of ofloxacin or levofloxacin could result in a clinically relevant effect. Therefore, it would be prudent to monitor the outcome if procainamide is given with these quinolones.

Evidence for an interaction between QT-prolonging quinolones and procainamide is limited. Of the quinolones used clinically, gatifloxacin, moxifloxacin, **sparfloxacin** and possibly levofloxacin prolong the QT interval (see 'Table 9.2', (p.290)) and would be expected to increase the risk of torsade de pointes when used with procainamide. The concurrent use of two drugs that prolong the QT interval should generally be avoided, or undertaken with caution. For a further discussion of QT prolongation, see 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290.

1. Martin DE, Shen J, Griener J, Raasch R, Patterson JH, Cascio W. Effects of ofloxacin on the pharmacokinetics and pharmacodynamics of procainamide. *J Clin Pharmacol* (1996) 36, 85–91.
2. Bauer LA, Black DJ, Lill JS, Garrison J, Raisys VA, Hooton TM. Levofloxacin and ciprofloxacin decrease procainamide and *N*-acetylprocainamide renal clearances. *Antimicrob Agents Chemother* (2005) 49, 1649–51.
3. Samaha FF. QTc interval prolongation and polymorphic ventricular tachycardia in association with levofloxacin. *Am J Med* (1999) 107, 528–9.
4. Frothingham R. Rates of torsades de pointes associated with ciprofloxacin, ofloxacin, levofloxacin, gatifloxacin, and moxifloxacin. *Pharmacotherapy* (2001) 21, 1468–72.

Procainamide + Sucralfate

Sucralfate does not appear to affect the absorption of procainamide.

Clinical evidence, mechanism, importance and management

In 4 healthy subjects, sucralfate 1 g taken 30 minutes before a single 250-mg dose of procainamide reduced the mean maximum salivary level of procainamide by 5.3%, but did not significantly affect either the AUC or the rate of absorption.[1] These results suggest that a clinically significant interaction between sucralfate and procainamide is unlikely.

1. Turkistani AAA, Gaber M, Al-Meshal MA, Al-Shora HI, Gouda MW. Effect of sucralfate on procainamide absorption. *Int J Pharmaceutics* (1990) 59, R1–R3.

Procainamide + Trimethoprim

Trimethoprim causes a marked increase in the plasma levels of procainamide and its active metabolite, *N*-acetylprocainamide.

Clinical evidence

Eight healthy subjects were given procainamide 500 mg every 6 hours for 3 days. The concurrent use of trimethoprim 200 mg daily increased the $AUC_{0\text{-}12}$ of procainamide and its active metabolite, *N*-acetylprocainamide (NAPA), by 63% and 51%, respectively. The renal clearance of procainamide and NAPA decreased by 47% and 13%, respectively. The QTc prolonging effects of procainamide were increased to a significant, but slight, extent by trimethoprim.[1] Another study found that trimethoprim 200 mg daily reduced the renal clearance of a single 1-g dose of procainamide and NAPA by 45% and 26%, respectively. The QTc interval was increased by 30 milliseconds to 430 milliseconds.[2]

Mechanism

Trimethoprim decreases the renal clearance of both procainamide and its active metabolite by competing for active tubular secretion. It may also cause a small increase in the conversion of procainamide to *N*-acetylprocainamide.[1]

Importance and management

An established interaction but its documentation is limited. The need to reduce the procainamide dose should be anticipated if trimethoprim is given to patients already taking stable doses of procainamide. In practice the effects may be greater than those found in the studies cited because the renal excretion of procainamide is slower in the elderly than in young healthy subjects. Remember too that the daily dose of trimethoprim in **co-trimoxazole** (trimethoprim 160 mg with sulfamethoxazole 800 mg) may equal or exceed the doses used in the studies cited.

1. Kosoglou T, Rocci ML, Vlasses PH. Trimethoprim alters the disposition of procainamide and N-acetylprocainamide. *Clin Pharmacol Ther* (1988) 44, 467–77.
2. Vlasses PH, Kosoglou T, Chase SL, Greenspon AJ, Lottes S, Andress E, Ferguson RK, Rocci ML. Trimethoprim inhibition of the renal clearance of procainamide and N-acetylprocainamide. *Arch Intern Med* (1989) 149, 1350–3.

Propafenone + Azoles

An isolated case report describes a man taking propafenone who had a seizure two days after taking ketoconazole. Limited evidence suggests ketoconazole may inhibit the metabolism of propafenone.

Clinical evidence

A man who had been taking captopril and hydrochlorothiazide for 6 years and propafenone 300 mg daily for 4 years, without problems, and without any history of convulsive episodes, experienced a tonic-clonic seizure while watching television. It was later found that he had started to take **ketoconazole** 2 days previously for the treatment of a candidal infection.[1] The preliminary results of a study in 12 healthy subjects given a single 300-mg dose of propafenone with or without **ketoconazole** 200 mg found that the increase in propafenone AUC with **ketoconazole** was greater in those with lower cytochrome P450 isoenzyme CYP2D6 activity.[2]

Mechanism

The authors of the case report postulate that the ketoconazole may have inhibited the metabolism of the propafenone so that this patient, in effect, may have developed an overdose.[1] However, convulsions with propafenone, even in overdose, are extremely rare.[3] Ketoconazole is an inhibitor of the cytochrome P450 isoenzyme CYP3A4, by which propafenone is metabolised. Propafenone is also extensively metabolised by CYP2D6 but it was suggested that if CYP2D6 activity is low, propafenone metabolism may be shifted to the CYP3A4 pathway increasing the possibility of an interaction with ketoconazole.[2]

Importance and management

The general importance of this interaction is uncertain. As of 2006, there had been no other cases reported to the manufacturer of propafenone.[4] As available data suggest that an interaction can occur, it would seem prudent to keep this interaction in mind during concurrent use. There seems to be nothing documented about the effects of other azole antifungals, but as they can all affect CYP3A4 (to a greater or lesser extent, see

'Azoles', (p.233)) it would be prudent to consider the possibility of an interaction if any of them are given with propafenone.

1. Duvelleroy Hommet C, Jonville-Bera AP, Autret A, Saudeau D, Autret E, Fauchier JP. Une crise convulsive chez un patient traité par propafénone et kétoconazole. *Therapie* (1995) 50, 164–5.
2. Munoz CE, Ito S, Bend JR, Tesoro A, Freeman D, Spence JD, Bailey DG. Propafenone interaction with CYP3A4 inhibitors in man. *Clin Pharmacol Ther* (1997) 61, 154.
3. Arythmol (Propafenone hydrochloride). Abbott Laboratories Ltd. UK Summary of product characteristics, January 2010.
4. Abbott Laboratories. Personal communication, April 2006.

Propafenone + Barbiturates

Phenobarbital increases the metabolism of propafenone and reduces its serum levels.

Clinical evidence, mechanism, importance and management

In a preliminary report of a study in 7 non-smoking subjects, **phenobarbital** 100 mg daily for 3 weeks reduced the levels of a single 300-mg dose of propafenone by 26 to 87% and reduced its AUC by 10 to 89%. The intrinsic clearance of propafenone was increased by 11 to 84%. The results in a further 4 heavy smokers were similar.[1] These changes probably occur because **phenobarbital** (a potent enzyme inducer) increases the metabolism of propafenone. The clinical importance of this interaction awaits assessment, but check that propafenone remains effective if **phenobarbital** is added (the increases seen suggest that it may be ineffective in some patients in the presence of phenobarbital), and monitor to ensure that toxicity does not occur if **phenobarbital** is stopped. If the suggested mechanism is correct, other barbiturates would be expected to interact similarly.

1. Chan GL-Y, Axelson JE, Kerr CR. The effect of phenobarbital on the pharmacokinetics of propafenone in man. *Pharm Res* (1988) 5, S153.

Propafenone + Cimetidine

Cimetidine appears to interact minimally with propafenone.

Clinical evidence, mechanism, importance and management

A study in 12 healthy subjects (10 extensive metabolisers and 2 poor metabolisers of propafenone) given propafenone 225 mg every 8 hours found that the concurrent use of cimetidine 400 mg every 8 hours caused some changes in the pharmacokinetics and pharmacodynamics of the propafenone, with wide intersubject variability. Raised mean peak and steady-state plasma levels were seen (24% and 22%, respectively), but these did not reach statistical significance. A slight increase in the QRS duration also occurred.[1] However, none of the changes were considered clinically important.

1. Pritchett ELC, Smith WM, Kirsten EB. Pharmacokinetic and pharmacodynamic interactions of propafenone and cimetidine. *J Clin Pharmacol* (1988) 28, 619–24.

Propafenone + Erythromycin

Limited evidence suggests that erythromycin may inhibit the metabolism of propafenone.

Clinical evidence, mechanism, importance and management

The preliminary results of a study in 12 healthy subjects given a single 300-mg dose of propafenone with or without erythromycin 250 mg found that the increase in the AUC of propafenone with erythromycin was greater in those with lower cytochrome P450 isoenzyme CYP2D6 activity. It was suggested[1] that low CYP2D6 activity shifts propafenone metabolism to the CYP3A4/1A2-mediated *N*-depropylpropafenone pathway increasing the interaction with erythromycin, which is an inhibitor of CYP3A4. This appears to be the only documentation of a possible interaction with erythromycin and its clinical significance is not certain. More study is needed.

1. Munoz CE, Ito S, Bend JR, Tesoro A, Freeman D, Spence JD, Bailey DG. Propafenone interaction with CYP3A4 inhibitors in man. *Clin Pharmacol Ther* (1997) 61, 154.

Propafenone + Grapefruit juice

Limited evidence suggests that grapefruit juice may inhibit the metabolism of propafenone.

Clinical evidence, mechanism, importance and management

Preliminary results of a study in 12 healthy subjects given a single 300-mg dose of propafenone with or without 250 mL of grapefruit juice found that the increase in the AUC of propafenone with grapefruit juice was greater in those with lower cytochrome P450 isoenzyme CYP2D6 activity. It was suggested[1] that in the presence of low CYP2D6 activity a greater proportion of propafenone is eliminated by metabolism by CYP3A4 and CYP1A2 and the effect of grapefruit juice is increased as it is an inhibitor of CYP3A4. The clinical significance of this finding is not certain. Further study is needed.

1. Munoz CE, Ito S, Bend JR, Tesoro A, Freeman D, Spence JD, Bailey DG. Propafenone interaction with CYP3A4 inhibitors in man. *Clin Pharmacol Ther* (1997) 61, 154.

Propafenone + Protease inhibitors

Ritonavir may increase the levels of propafenone. Other protease inhibitors may interact similarly.

Clinical evidence, mechanism, importance and management

Direct evidence (from case reports or clinical studies) of an interaction between propafenone and the protease inhibitors appears to be lacking; however, a review of protease inhibitor interactions reports that the plasma levels of propafenone may be increased by **ritonavir**.[1] Similarly, **indinavir**, **nelfinavir** and **saquinavir** may increase plasma levels of propafenone.[1]

Propafenone is metabolised by the cytochrome P450 isoenzymes CYP2D6 and CYP3A4, of which **ritonavir** is an inhibitor, to its active metabolites, 5-hydroxypropafenone and *N*-depropylpropafenone. Concurrent use may therefore lead to an increase in propafenone levels and a possible increase in adverse effects such arrhythmias.

Evidence for an interaction between **ritonavir** and propafenone is limited, but what is said to occur is in line with the known pharmacokinetics of these drugs. Because of the risk of serious adverse effects, the manufacturers of **ritonavir** contraindicate concurrent use.[2,3] The UK manufacturer of propafenone also contraindicates concurrent use, but limits this to the use of high-dose ritonavir (800 to 1200 mg daily).[4] **Tipranavir** is also an inhibitor of CYP2D6 and CYP3A4, and its use with propafenone is similarly contraindicated.[5,6]

Most other protease inhibitors inhibit CYP3A4 but do not significantly affect CYP2D6, and would not be expected to interact with propafenone to the same extent as ritonavir. However, some patients may have reduced or low levels of CYP2D6 (poor metabolisers). In these patients, metabolism of propafenone by CYP3A4 may be of more importance and a more significant interaction with the other protease inhibitors is possible (see also 'Propafenone + Azoles', p.309). The manufacturers of **fosamprenavir**,[7] **indinavir**,[8] and **saquinavir**[9,10] contraindicate their use with propafenone. The US manufacturer of **darunavir** recommends caution and monitoring propafenone levels, where possible.[11] Other manufacturers of protease inhibitors do not appear to specifically mention the possibility of an interaction with propafenone. As low-dose ritonavir is commonly used with other protease inhibitors as a pharmacological booster, it would seem prudent to avoid the concurrent use of propafenone with ritonavir-boosted protease inhibitors if possible. However if concurrent use is necessary, it would be prudent to closely monitor for an increase in propafenone adverse effects.

1. Burger DM, Hoetelmans RMW, Koopmans PP, Meenhorst PL, Mulder JW, Hekster YA, Beijnen JH. Clinically relevant drug interactions with antiretroviral agents. *Antivir Ther* (1997) 2, 149–165.
2. Norvir Soft Capsules (Ritonavir). Abbott Laboratories Ltd. UK Summary of product characteristics, October 2009.
3. Norvir (Ritonavir). Abbott Laboratories. US Prescribing information, November 2009.
4. Arythmol (Propafenone hydrochloride). Abbott Laboratories Ltd. UK Summary of product characteristics, January 2010.
5. Aptivus Soft Capsules (Tipranavir). Boehringer Ingelheim Ltd. UK Summary of product characteristics, June 2009.
6. Aptivus (Tipranavir). Boehringer Ingelheim Pharmaceuticals, Inc. US Prescribing information, June 2009.
7. Telzir (Fosamprenavir calcium). ViiV Healthcare UK Ltd. UK Summary of product characteristics, May 2009.

8. Crixivan (Indinavir sulphate). Merck Sharp & Dohme Ltd. UK Summary of product characteristics, October 2008.
9. Invirase Film-coated Tablets (Saquinavir mesilate). Roche Products Ltd. UK Summary of product characteristics, January 2009.
10. Invirase (Saquinavir mesylate). Roche Laboratories Inc. US Prescribing information, July 2007.
11. Prezista (Darunavir ethanolate). Tibotec, Inc. US Prescribing information, June 2009.

Propafenone + Quinidine

Quinidine doubles the plasma levels of propafenone and halves the levels of its active metabolite in some patients. This interaction has been utilised clinically.

Clinical evidence

Nine patients taking propafenone for frequent isolated ventricular ectopic beats, firstly had their dose reduced to 150 mg every 8 hours and then 4 days later the steady-state pharmacokinetics of propafenone were determined at this new dose. Quinidine was then added at a dose of 50 mg every 8 hours, and after a further 4 days the steady-state plasma propafenone levels in 7 CYP2D6 extensive metabolisers (that is, those with normal levels of this isoenzyme) had more than doubled from 408 nanograms/mL to 1100 nanograms/mL, and concentrations of the metabolite 5-hydroxypropafenone had approximately halved. However, the ECG intervals and arrhythmia frequency were unaltered. The steady-state plasma propafenone levels remained unchanged in the other 2 patients with low levels of CYP2D6 (poor metabolisers).[1]

The same research group conducted a similar study in healthy subjects, which confirmed that quinidine increased the plasma levels of propafenone in extensive but not poor metabolisers. In addition, it was found that quinidine increased the extent of the beta-blockade caused by the propafenone in extensive metabolisers to approach that seen in poor metabolisers.[2] Another study found that the inhibition of propafenone metabolism by low-dose quinidine also occurs in Chinese as well as Caucasian patients.[3] [CYP2D6 shows pronounced interethnic differences in expression.] A further study found that combining low-dose quinidine (150 mg daily) with standard doses of propafenone in patients with atrial fibrillation resulted in a similar control of the arrhythmia as increasing the propafenone dose, but caused less gastrointestinal adverse effects.[4]

Mechanism

Quinidine inhibits the 5-hydroxylation of propafenone by the cytochrome P450 isoenzyme CYP2D6 in the liver of extensive metabolisers so that it is cleared more slowly. Its plasma levels are doubled as a result, but the overall antiarrhythmic effects remain effectively unchanged, possibly because the production of its active metabolite (5-hydroxypropafenone) is simultaneously halved.[1] Quinidine increases the beta-blocking effects of propafenone in extensive metabolisers because only the parent drug, and not the metabolites, has beta-blocking activity.[2]

Importance and management

Quinidine appears to raise propafenone levels, and may also affect the beta-blocking properties of propafenone in some patients. In one study the concurrent use of propafenone and quinidine was said to have an effect similar to increasing the propafenone dose.[4] More study is needed to clarify the importance of CYP2D6 metaboliser status.

1. Funck-Brentano C, Kroemer HK, Pavlou H, Woosley RL, Roden DM. Genetically-determined interaction between propafenone and low dose quinidine: role of active metabolites in modulating net drug effect. *Br J Clin Pharmacol* (1989) 27, 435–44.
2. Mörike K, Roden D. Quinidine-enhanced β-blockade during treatment with propafenone in extensive metabolizer human subjects. *Clin Pharmacol Ther* (1994) 55, 28–34.
3. Fan C, Tang M, Lau C-P, Chow M. The effect of quinidine on propafenone metabolism in Chinese patients. *Clin Invest Med* (1998) (Suppl) S12.
4. Lau C-P, Chow MSS, Tse H-F, Tang M-O, Fan C. Control of paroxysmal atrial fibrillation recurrence using combined administration of propafenone and quinidine. *Am J Cardiol* (2000) 86, 1327–32.

Propafenone + Rifampicin (Rifampin)

Propafenone serum levels and therapeutic effects can be markedly reduced by rifampicin.

Clinical evidence

A man with ventricular arrhythmias successfully treated with propafenone had a marked fall in his plasma propafenone level from 993 nanograms/mL to 176 nanograms/mL within 12 days of starting to take rifampicin 450 mg twice daily. Levels of the two active metabolites of propafenone were altered; 5-hydroxypropafenone levels were reduced from 195 nanograms/mL to 64 nanograms/mL and *N*-depropylpropafenone levels were increased from 110 nanograms/mL to 192 nanograms/mL. His arrhythmias returned, but 2 weeks after stopping the rifampicin his arrhythmias had disappeared and the propafenone and its 5-hydroxy and *N*-depropyl metabolites had returned to acceptable levels (1411 nanograms/mL, 78 nanograms/mL and 158 nanograms/mL respectively).[1]

In a study in young healthy subjects, rifampicin 600 mg daily for 9 days reduced the bioavailability of a single 300-mg oral dose of propafenone from 30% to 10% in CYP2D6 extensive metabolisers (that is, those with normal levels of this isoenzyme), and from 81% to 48% in those with low levels of CYP2D6 (poor metabolisers). QRS prolongation decreased during enzyme induction. In contrast, in this study, rifampicin had no substantial effect on the pharmacokinetics of propafenone given intravenously.[2] Similar findings were reported in a further study by the same research group, in healthy elderly subjects.[3]

There is a report of rifampicin 600 mg daily being used to increase the metabolism of propafenone (as well as digoxin and warfarin) in a case of multiple drug overdosage in a 16-year-old female. She had ingested 15 tablets each containing propafenone 300 mg (equivalent to 90 mg/kg) but levels of propafenone were not obtained. Other treatments including gastric lavage, activated charcoal, cardiac pacing and plasma exchange were also used so the contribution of rifampicin treatment to the patient's recovery is not known.[4]

Mechanism

Propafenone is extensively metabolised by the cytochrome P450 isoenzyme CYP2D6, although CYP1A2 and CYP3A4 are also involved. Rifampicin induces the metabolism of propafenone by CYP1A2 and CYP3A4, and increases the phase II glucuronidation of propafenone. The effect of rifampicin on gastrointestinal clearance of propafenone was greater than that of its hepatic clearance.[2,3]

Importance and management

An established and clinically relevant metabolic drug interaction. The dose of oral propafenone is likely to need increasing during the concurrent use of rifampicin.[3] Alternatively, the authors of the case report[1] advise the use of another antibacterial, where possible, because of the probable difficulty in adjusting the propafenone dose.

1. Castel JM, Cappiello E, Leopaldi D, Latini R. Rifampicin lowers plasma concentrations of propafenone and its antiarrhythmic effect. *Br J Clin Pharmacol* (1990) 30, 155–6.
2. Dilger K, Greiner B, Fromm MF, Hofmann U, Kroemer HK, Eichelbaum M. Consequences of rifampicin treatment on propafenone disposition in extensive and poor metabolizers of CYP2D6. *Pharmacogenetics* (1999) 9, 551–9.
3. Dilger K, Hofmann U, Klotz U. Enzyme induction in the elderly: Effect of rifampin on the pharmacokinetics and pharmacodynamics of propafenone. *Clin Pharmacol Ther* (2000) 67, 512–20.
4. Unal S, Bayrakci B, Yasar U, Karagoz T. Successful treatment of propafenone, digoxin and warfarin overdosage with plasma exchange therapy and rifampicin. *Clin Drug Invest* (2007) 27, 505–8.

Propafenone + SSRIs

In general, the SSRIs would be expected to inhibit the metabolism of propafenone, but the extent of this interaction varies by drug; fluoxetine and paroxetine would be expected to have the greatest effect, although fluvoxamine may also have a significant effect in some patients.

Clinical evidence

In a study in healthy subjects **fluoxetine** 20 mg daily for 10 days decreased the oral clearance of a single 400-mg dose of propafenone by 34% for both the *R*- and *S*-enantiomers. The peak plasma levels were increased by 39% for *S*-propafenone and by 71% for *R*-propafenone. However, there were no differences in the changes to the PR and QRS intervals.[1]

A case report describes an elderly woman who had been taking propafenone 900 mg daily for more than 10 years for paroxysmal atrial fibrilla-

tion, who experienced chest tightness and dizziness 3 months after starting to take **citalopram** 10 mg daily, increased after one month to 20 mg daily. The episodes became more frequent in the following months and she had several falls but no acute coronary event was diagnosed. She was given amlodipine, glyceryl trinitrate patches and warfarin, but after a fall she became delirious. Amlodipine and glyceryl trinitrate were discontinued and her dose of propafenone was reduced to 450 mg daily and **citalopram** was continued at 20 mg daily. The patient recovered well without any further symptoms during a one-year follow-up.[2]

Mechanism

Fluoxetine is an inhibitor of the cytochrome P450 isoenzyme CYP2D6, which is responsible for the metabolism of propafenone to its primary active metabolite 5-hydroxypropafenone. *In vitro* data have shown that, of the SSRIs, fluoxetine is the most potent inhibitor of propafenone 5-hydroxylation, followed by **paroxetine**. **Sertraline** and **fluvoxamine** have less effect on propafenone 5-hydroxylation, and citalopram has slight or no effects.[3] Although **fluvoxamine** only moderately inhibited propafenone 5-hydroxylation it did inhibit propafenone *N*-dealkylation[3] by inhibiting CYP1A2. This isoenzyme has only a minor role in the metabolism of propafenone, but it may assume greater importance in patients with low levels of CYP2D6 (poor metabolisers).[3]

Importance and management

Evidence for an interaction between **fluoxetine** and propafenone is limited. The study suggests that fluoxetine increases the peak propafenone levels without affecting the ECG, but as the overall propafenone exposure was not assessed, and as it was only a single-dose study, it is difficult to assess the clinical relevance of the interaction on the long-term use of both drugs. As with 'quinidine', (p.311), inhibition of 5-hydroxylation would be expected to increase the beta-blocking effects of propafenone, although note that fluoxetine is a less potent inhibitor of CYP2D6 than quinidine, and therefore its effects would be smaller. Until more is known, it would be prudent to use caution when giving fluoxetine with propafenone, monitoring for an increase in propafenone adverse effects (e.g. hypotension, bradycardia, dizziness, dry mouth) and consider decreasing the dose of propafenone if these become troublesome.

Evidence regarding an interaction with the other SSRIs is even more sparse. **Paroxetine** generally interacts in the same way as fluoxetine, and therefore similar precautions to those given for fluoxetine would be appropriate. **Fluvoxamine** would not generally be expected to interact, except for in patients who have low levels of CYP2D6. As it is unlikely that these patients will be known, it would seem prudent to monitor concurrent use in the same way as for fluoxetine.

The *in vitro* study with propafenone suggests that other SSRIs (**citalopram** (and therefore probably **escitalopram**) and **sertraline**) tend to have more minor, if any, effects on CYP2D6, and this is supported by the known clinical effects of these drugs on other CYP2D6 substrates (e.g. see 'Beta blockers + SSRIs', p.1019). Nevertheless, a modest increase in propafenone levels is possible, and the case report with citalopram reinforces this. Therefore, if propafenone adverse effects (e.g. hypotension, bradycardia, dizziness, dry mouth) develop in a patient taking one of these SSRIs, it may be prudent to consider an interaction as a possible cause.

1. Cai WM, Chen B, Zhou Y, Zhang YD. Fluoxetine impairs the CYP2D6-mediated metabolism of propafenone enantiomers in healthy Chinese volunteers. *Clin Pharmacol Ther* (1999) 66, 516–21.
2. Garcia A. Adverse effects of propafenone after long-term therapy with the addition of citalopram. Am J Geriatr Pharmacother (2008) 6, 96–9.
3. Hemeryck A, De Vriendt C, Belpaire FM. Effect of selective serotonin reuptake inhibitors on the oxidative metabolism of propafenone: *in vitro* studies using human liver microsomes. *J Clin Psychopharmacol* (2000) 20, 428–34.

Quinidine + Amiloride

A single study found that the antiarrhythmic activity of quinidine can be opposed by amiloride.

Clinical evidence

A study in 10 patients with inducible sustained ventricular tachycardia was carried out to see whether a beneficial interaction occurred between quinidine and amiloride. Patients were given oral quinidine until their trough serum levels reached 10 micromol/L, or the maximum well-tolerated dose was reached. After electrophysiological studies, oral amiloride 5 mg twice daily was started, and increased up to 10 mg twice daily (if serum potassium levels remained normal) for 3 days. The electrophysiological studies were then repeated. Unexpectedly, 7 of the 10 patients demonstrated adverse responses while taking both drugs. Three developed sustained ventricular tachycardia and 3 others had somatic adverse effects (hypotension, nausea, diarrhoea), which prevented further studies being undertaken. One patient had 12 episodes of sustained ventricular tachycardia while taking both drugs. Amiloride had no effect on quinidine levels.[1]

Mechanism

Not understood. The combination of quinidine and amiloride increased the QRS interval, but did not prolong the QT interval more than quinidine alone.

Importance and management

So far the evidence seems to be limited to this single study but it suggests that amiloride can oppose the antiarrhythmic activity of quinidine. The full clinical implications of this interaction are not known, but it would clearly be prudent to consider monitoring to confirm that the quinidine continues to be effective if amiloride is given.

1. Wang L, Sheldon RS, Mitchell B, Wyse DG, Gillis AM, Chiamvimonvat N, Duff HJ. Amiloride-quinidine interaction: adverse outcomes. *Clin Pharmacol Ther* (1994) 56, 659–67.

Quinidine + Amiodarone

The QT interval prolonging effects of quinidine and amiodarone are increased when they are used together, and torsade de pointes has occurred. Amiodarone increases quinidine levels.

Clinical evidence

In a study, 11 patients were stabilised taking quinidine in daily doses of 1.2 to 4.2 g. When they were also given amiodarone (600 mg every 12 hours for 5 to 7 days, then 600 mg daily) their mean serum quinidine levels rose by an average of 32%, from 4.4 to 5.8 micrograms/mL and 3 of them had a substantial increase of 2 micrograms/mL. Signs of toxicity (diarrhoea, nausea, vomiting, hypotension) were seen in some patients, and the quinidine dose was reduced in 9 patients, by an average of 37%. Despite the dose reduction, the quinidine serum levels were still higher at 5.2 micrograms/mL than before the amiodarone was started.[1]

A test in a healthy subject found that 3 days after amiodarone 600 mg was added to quinidine 1.2 g daily, the serum quinidine levels doubled and the relative QT interval was prolonged from 1 (no drugs) to 1.2 (quinidine alone) to 1.4 (quinidine plus amiodarone).[2] This report also described 2 patients with minor cardiac arrhythmias who developed QT prolongation and torsade de pointes when given both drugs.[2] A Russian study of the use of the combination in atrial fibrillation reported that one of 52 patients had a 50% increase in the QT interval resulting in torsade de pointes and subsequently ventricular fibrillation, which required repeated defibrillation over 6 hours.[3] A 76-year-old man taking quinidine and amiodarone had a number of episodes of loss of consciousness, and subsequently QT prolongation and torsade de pointes, which stopped when the quinidine was discontinued.[4]

Successful and uneventful concurrent use has been described in a report of 4 patients taking quinidine (dose not stated) and amiodarone 200 mg five times weekly.[5] Another report describes the successful use of a short course of quinidine to convert chronic atrial fibrillation to sinus rhythm in 9 of 15 patients taking long-term amiodarone. Patients were hospitalised and continuously monitored. No proarrhythmias occurred and the QT interval remained within acceptable limits.[6]

Mechanism

The mechanism behind the pharmacokinetic interaction is not understood. The QT prolonging effects of the two drugs would be expected to be additive.

Importance and management

An established and clinically important pharmacokinetic and pharmacodynamic interaction. The pharmacokinetic component appears to occur in most patients, and to develop rapidly. The study suggests that the dose of

quinidine may need to be reduced by 30 to 50% or more to keep quinidine at its pre-amiodarone level. Where possible, quinidine levels should be monitored.

The use of amiodarone with quinidine further prolongs the QT interval and increases the risk of torsade de pointes. The concurrent use of two drugs that prolong the QT interval should generally be avoided. For further discussion, see 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290.

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Quinidine + Antacids or Urinary alkalinisers

Large rises in urinary pH due to the concurrent use of some antacids, diuretics or alkaline salts can cause quinidine retention, which could lead to quinidine toxicity, but there seems to be only one case on record of an adverse interaction (with an aluminium/magnesium hydroxide antacid). Aluminium hydroxide alone appears not to interact with quinidine.

Clinical evidence

In a study in 4 subjects, the renal clearance of oral quinidine 200 mg every 6 hours was reduced by an average of 50% (from 53 to 26 mL/minute) when their urine was made alkaline (i.e. changed from pH 6 to 7, up to pH 7 to 8) with **sodium bicarbonate** and **acetazolamide** 500 mg twice daily. Below pH 6 their urinary quinidine level averaged 115 mg/L, whereas when urinary pH values rose above 7.5 the average urinary quinidine level was only 13 mg/L. The quinidine urinary excretion rate decreased from 103 micrograms/minute to 31 micrograms/minute. In 6 other subjects the rise in serum quinidine levels was reflected in a prolongation of the QT interval. Raising the urinary pH from about 6 to 7.5 in one individual increased serum quinidine levels from about 1.6 micrograms/mL to 2.6 micrograms/mL.[1]

A patient taking quinidine who took eight *Mylanta* tablets daily (**aluminium hydroxide** gel 200 mg, **magnesium hydroxide** 200 mg and simeticone 20 mg) for a week, with a little over one litre of fruit juice (orange and grapefruit) each day developed a threefold increase in serum quinidine levels (from 8 mg/L to 25 mg/L) and toxicity. However, note that the 'grapefruit juice', (p.317) may have contributed. In 6 healthy subjects, this dose of *Mylanta* for 3 days produced consistently alkaline urine in 4 subjects; the addition of fruit juice produced consistently alkaline urine in a further subject.[2]

In 4 healthy subjects, 30 mL of **aluminium hydroxide** gel (*Amphogel*) given with, and one hour after, a single 200-mg dose of quinidine sulphate had no effect on serum quinidine levels, AUC or excretion (urine pH ranged from 5 to 6.2).[3] Two similar single-dose studies in healthy subjects found that the absorption and elimination of 400 mg of quinidine sulfate[4] or 648 mg of quinidine gluconate[5] was unaffected by 30 mL **aluminium hydroxide** gel, although the change in quinidine AUC did vary from a decrease of 18% to an increase of 35% in one study.[5] Urinary pH was unaffected in both studies.[4,5]

Mechanism

Quinidine is excreted unchanged in the urine. In acid urine much of the quinidine excreted by the renal tubules is in the ionised (lipid-insoluble) form, which is unable to diffuse freely back into the cells and so is lost in the urine. In alkaline urine more of the quinidine is in the non-ionised (lipid-soluble) form, which freely diffuses back into the cells and is retained. In this way the pH of the urine determines how much quinidine is lost or retained and thereby governs the serum levels. *In vitro* data suggest that changes in pH and adsorption effects within the gut due to antacids could also affect the absorption of quinidine.[6,7]

Importance and management

An established interaction, but with the exception of the one isolated case cited,[2] there seem to be no reports of problems in patients given quinidine and antacids or urinary alkalinisers. However, in the case quinidine was given with grapefruit juice, which may potentially have had an effect of its own, see 'Quinidine + Grapefruit juice', p.317. Nevertheless it would be prudent to monitor the effects if drugs that can markedly change urinary pH are started or stopped. Avoid concurrent use, or reduce the quinidine dose as necessary.

It is difficult to predict which antacids, if any, are likely to increase the serum levels of quinidine. As noted above, aluminium hydroxide gel and magnesium hydroxide (*Mylanta*) alkalinises urine and may interact. Similarly, magnesium and aluminium hydroxide (*Maalox*) can raise the urinary pH by about 0.9 and could possibly interact.[8] Magnesium hydroxide (*Milk of magnesia*) and **calcium carbonate-glycine** (*Titralac*) raise the urinary pH by about 0.5, so that a smaller effect is likely.[8] Aluminium hydroxide gel (*Amphogel*) and **dihydroxyaluminium glycinate** (*Robalate*) are reported to have no effect on urinary pH,[8] and the studies above confirm aluminium hydroxide gel does not generally interact.

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Quinidine + Antiepileptics

Serum quinidine levels can be reduced by phenytoin, phenobarbital or primidone. Fosphenytoin would be expected to interact similarly. Quinidine does not affect the metabolism of mephenytoin.

Clinical evidence

A man taking long-term **primidone** 500 mg daily was given quinidine sulfate 300 mg every 4 hours, but only attained a plasma quinidine level of 0.8 micrograms/mL with an estimated half-life of 5 hours. When **primidone** was discontinued, his quinidine level rose to 2.4 micrograms/mL and the half-life was 12 hours. **Phenobarbital** 90 mg daily was then started, and the quinidine level fell to 1.6 micrograms/mL with a half-life of 7.6 hours.

In another case, a woman required doses of quinidine sulfate of up to 800 mg every 4 hours to achieve therapeutic levels while taking **phenytoin**. When the **phenytoin** was stopped, quinidine toxicity occurred, and the dose was eventually halved. Further study was then undertaken in 4 healthy subjects. After taking either **phenytoin** (in doses adjusted to give levels of 10 to 20 micrograms/mL) or **phenobarbital** for 4 weeks the elimination half-life of a single 300-mg dose of quinidine sulfate was reduced by about 50% and the total AUC was reduced by about 60%.[1] Similar results were found with **phenytoin** in another study in 3 healthy subjects.[2] Other cases have also been reported with **phenytoin**, **primidone**, **pentobarbital** and **phenobarbital**.[3-6] In one case, when **phenytoin** was given with quinidine to a patient with recurrent ventricular tachycardia the quinidine levels fell by 44%.[3] In another report quinidine levels increased from a mean of 0.8 micrograms.mL to 2.2 micrograms/mL, 15 days after **pentobarbital** was discontinued.[4] Interestingly, in this case the patient was also taking digoxin, and stopping phenobarbital precipitated digoxin toxicity by causing an increase in quinidine levels.

A 3-year-old child taking both **phenobarbital** and **phenytoin** needed to take quinidine 300 mg every 4 hours to achieve therapeutic serum quinidine levels, and had an estimated quinidine half-life of only 1.4 hours.[5] Difficulty in achieving adequate serum quinidine levels was also reported in a woman taking **phenytoin** and **primidone**. Her quinidine half-life was 2.7 hours, about half that usually seen in adults.[6]

In a study in 10 healthy subjects, quinidine 200 mg had no effect on the metabolism (4-hydroxylation) of **mephenytoin** 100 mg.[7]

Mechanism

The evidence suggests that phenytoin, primidone or phenobarbital (all known enzyme-inducers) increase the hepatic metabolism of quinidine and thereby reduce its levels.[2]

Importance and management

Established interactions of clinical importance although the documentation is limited. The concurrent use of phenytoin (and therefore probably the prodrug, **fosphenytoin**), primidone, phenobarbital or any other barbiturate need not be avoided, but be alert for the need to increase the quinidine dose. If the antiepileptics are withdrawn the quinidine dose may need to be reduced to avoid quinidine toxicity. Where possible, quinidine serum levels should be monitored.

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Quinidine + Aspirin

A patient and two healthy subjects given quinidine and aspirin had a two- to threefold increase in bleeding times. The patient developed petechiae and gastrointestinal bleeding.

Clinical evidence, mechanism, importance and management

A patient with a prolonged history of paroxysmal atrial tachycardia was given quinidine 800 mg daily and aspirin 325 mg twice daily. After a week he developed generalised petechiae and blood in his faeces. His prothrombin and partial prothrombin times were normal but the template bleeding time was more than 35 minutes (reference range 2 to 10 minutes). Further study in 2 healthy subjects found that quinidine 975 mg daily given alone for 5 days and aspirin 650 mg three times daily given alone for 5 days prolonged bleeding times by 125% and 163% respectively; given together for 5 days the bleeding times were prolonged by 288%.[1] The underlying mechanism for this increase in bleeding time is not totally understood but it is believed to be the outcome of the additive effects of the two drugs, both of which can reduce platelet aggregation,[1] although with quinidine this antiplatelet effect usually only occurs as the result of a hypersensitivity reaction.

This seems to be the only study of this adverse interaction, and its general importance is uncertain.

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Quinidine + Azoles

Itraconazole increases the plasma levels of quinidine, and a case report suggests that ketoconazole may also raise quinidine levels. Other azoles are predicted to interact similarly. An isolated report describes QT prolongation in a patient taking hydroquinidine and itraconazole.

Clinical evidence

(a) Itraconazole

In a randomised, crossover study, 9 healthy subjects were given a single 100-mg dose of quinidine sulfate on the final day of a 4-day course of either itraconazole 200 mg daily or placebo. Itraconazole caused a 60% increase in the peak plasma quinidine levels, a 2.4-fold increase in its AUC, a 60% increase in its elimination half-life and a 50% decrease in its renal clearance.[1] Similarly, another study in 6 healthy subjects found that itraconazole 100 mg daily for 6 days reduced the total clearance of a single 200-mg dose of quinidine sulfate by 61%, increased its elimination half-life by 35%, and decreased its renal clearance by 60%.[2]

An isolated report describes QT prolongation after itraconazole was given to an elderly patient taking **hydroquinidine**. The QT interval returned to normal after hydroquinidine was withdrawn.[3]

(b) Ketoconazole

An elderly man with chronic atrial fibrillation, taking quinidine sulfate 300 mg four times daily, was also given ketoconazole 200 mg daily, for candidal oesophagitis after antineoplastic therapy. Within 7 days his plasma quinidine levels had risen from a range of 1.4 to 2.7 mg/L up to 6.9 mg/L (reference range 2 to 5 mg/L) but there was no evidence of toxicity. The elimination half-life of quinidine was found to be 25 hours (reference range in healthy subjects 6 to 7 hours). The quinidine dose was reduced to 200 mg twice daily, but it needed to be increased to the former dose by the end of a month, even though ketoconazole was continued at the same dose.[4]

Mechanism

The most likely explanation for the rises in quinidine levels is that itraconazole and ketoconazole inhibit the metabolism of quinidine by the cytochrome P450 isoenzyme CYP3A4 in the gut wall and liver. Itraconazole may also inhibit the active secretion of quinidine by the renal tubules.[1,2] In the case with ketoconazole, it is unclear why the quinidine dose was subsequently returned to normal. Hydroquinidine is structurally related to quinidine and may interact similarly.

Importance and management

Direct information regarding an interaction between itraconazole and quinidine appears to be limited to these studies, but what is known suggests that this interaction is clinically important. The authors of one report advise that concurrent use of these drugs should therefore be well monitored and the dose of quinidine reduced accordingly.[1]

The isolated case with ketoconazole suggests that it may interact similarly, and other azoles (including **voriconazole**, **posaconazole** and possibly **fluconazole**) would also be expected to raise quinidine levels. Because of the risk of torsade de pointes with raised quinidine levels, the concurrent use of these azoles is generally contraindicated. Note that, a large proportion of **miconazole** oral gel (both prescription and non-prescription doses) may be swallowed, and therefore adequate systemic absorption may occur to produce an interaction.

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Quinidine + Calcium-channel blockers

A few patients have had increases in their quinidine levels when stopping nifedipine, but in others no interaction has occurred. In contrast, one study suggests that quinidine serum levels may be slightly raised by nifedipine. Nifedipine levels may be modestly raised by quinidine.

Verapamil reduces the clearance of quinidine and in one patient the quinidine levels doubled and quinidine toxicity developed. Acute hypotension has also been seen in three patients taking quinidine when they were given verapamil intravenously. Felodipine and nisoldipine appear not to interact, and the situation with diltiazem is unclear.

Clinical evidence

(a) Diltiazem

A study in 10 healthy subjects given quinidine 600 mg twice daily and diltiazem 120 mg daily for 7 days found that concurrent use did not affect the pharmacokinetics of either drug.[1] These findings contrast with a crossover study in 12 healthy subjects. In this study, a single 60-mg dose of diltiazem was given before and after quinidine 100 mg twice daily for 5 doses, and a single 200-mg dose of quinidine was given before and after diltiazem 90 mg twice daily for 5 doses. The pharmacokinetics of diltiazem were unaffected by quinidine, but the AUC of quinidine was increased by 51% by diltiazem.[2] When quinidine was given after diltiazem pretreatment, there were significant increases in QTc and PR intervals, and a significant decrease in heart rate and diastolic blood pressure. Pretreatment with quinidine did not significantly alter the effects of diltiazem.[2]

(b) Felodipine

In a study in 12 healthy subjects, felodipine 10 mg daily for 3 days was found to have no clinically significant effect on the pharmacokinetics or haemodynamic and ECG effects of a single 400-mg dose of quinidine. Felodipine did cause a modest 22% decrease in the AUC of the quinidine metabolite 3-hydroxyquinidine.[3]

(c) Nifedipine

1. Nifedipine serum levels. In a study in 10 healthy subjects quinidine sulfate 200 mg every 8 hours increased the AUC of nifedipine by 37%, and heart rates were significantly increased. Quinidine levels were unchanged.[4] Another study found that quinidine had a modest inhibitory effect on the metabolism of nifedipine (half-life prolonged by 40%).[5] A further study in 12 healthy subjects found that the AUC of a single 20-mg dose of nifedipine was increased 16% by quinidine 200 mg and its clearance was reduced by 17%, but these modest changes were not considered clinically relevant.[6]

2. Quinidine serum levels. The quinidine serum levels of 2 patients taking quinidine sulfate 300 or 400 mg every 6 hours and nifedipine 10 or 20 mg every 6 or 8 hours doubled (from a range of 2 to 2.5 micrograms/mL up to 4.6 micrograms/mL and from 1.6 to 1.8 micrograms/mL up to 3.5 micrograms/mL, respectively) when the nifedipine was withdrawn. The increased serum quinidine levels were reflected in a prolongation of the QTc interval. However, in the first patient there had been no change in quinidine levels when nifedipine was initially added. Further, 4 other patients did not develop this interaction.[7] Two other reports[8,9] describe a similar response: the quinidine serum level doubled in one patient when the nifedipine was stopped,[8] and in the other it was found difficult to achieve adequate serum quinidine levels when nifedipine was added, even when the quinidine dosage was increased threefold. When the nifedipine was withdrawn, the quinidine levels rose once again.[9]

A study in 12 patients found no significant change in serum quinidine levels in the group as a whole when nifedipine was given, but one patient had a 41% decrease in quinidine levels.[10] Two other studies in healthy subjects found that the quinidine AUC was unchanged by nifedipine.[3,4]

A further study in 12 healthy subjects found that the AUC of a single 200-mg oral dose of quinidine sulfate was increased by 16% by nifedipine 20 mg. The quinidine clearance was reduced by 14% and the maximum serum level was raised by almost 20%. These modest changes were not considered clinically relevant.[6]

(d) Nisoldipine

An open, crossover study in 20 healthy subjects found that nisoldipine 20 mg had no effect on the bioavailability of quinidine gluconate 648 mg.[11]

(e) Verapamil

In a study in 6 healthy subjects, verapamil 80 mg three times daily for 3 days, decreased the clearance of a single 400-mg dose of quinidine sulfate by 32% and increased the half-life was by 35% (from 6.87 to 9.29 hours).[12]

A patient given quinidine gluconate 648 mg every 6 hours had an increase in serum quinidine levels from 2.6 micrograms/mL to 5.7 micrograms/mL after taking verapamil 80 mg every 8 hours for a week. He became dizzy and had blurred vision and was found to have atrioventricular block (heart rate 38 bpm) and a systolic blood pressure of 50 mmHg. In a subsequent study in this patient it was found that verapamil halved quinidine clearance and almost doubled its serum half-life.[13]

Three other patients given quinidine orally developed marked hypotension when given intravenous verapamil 2.5 or 5 mg (blood pressure reduced from 130/70 mmHg to 80/50 mmHg, systolic pressure reduced from 140 mmHg to 85 mmHg, and mean arterial pressure reduced from 100 mmHg to 60 mmHg, in the 3 patients respectively). In two of the patients, after quinidine was discontinued, the same dose of verapamil did not cause a reduction in blood pressure.[14]

Mechanism

Suggestions for how nifedipine could alter quinidine levels include changes in cardiovascular haemodynamics,[7] and effects on metabolism.[10] Quinidine possibly inhibits the metabolism of nifedipine by competing for metabolism by the cytochrome P450 isoenzyme CYP3A4.[5] The interaction with verapamil is probably due to an inhibitory effect of verapamil on the metabolism of quinidine (inhibition of cytochrome P450 isoenzyme CYP3A).[12,15] The marked hypotension observed may be related to the antagonistic effects of the two drugs on catecholamine-induced alpha-receptor induced vasoconstriction.[14]

Importance and management

The results of studies of the interaction between quinidine and **nifedipine** are somewhat contradictory, so that the outcome of concurrent use is uncertain. However, the increase in QTc interval seen in some patients suggests that some caution would be prudent. The increases in quinidine levels seen in the studies are generally modest, but the case reports suggest that greater increases may occur in some patients. Monitor concurrent use for quinidine adverse effects (e.g. nausea, diarrhoea, tinnitus) and decrease the dose accordingly. The increases in nifedipine levels are also modest, nevertheless, it would seem prudent to monitor for nifedipine adverse effects (e.g. greater than desired reductions in blood pressure, flushing, oedema) and reduce the nifedipine dose as necessary.

What is known about the interaction between quinidine and **verapamil** suggests that a reduction in the dose of the quinidine may be needed to avoid toxicity. If the verapamil is given intravenously, use with caution and be alert for evidence of acute hypotension. Monitor the effects of concurrent use closely. There is actually a fixed dose preparation containing verapamil and quinidine (*Cordichin*) available in Germany, which is used for the management of atrial fibrillation.

No interaction apparently occurs between quinidine and **felodipine** or **nisoldipine**. The situation with **diltiazem** is as yet uncertain but be alert for the need to reduce the quinidine dose.

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Quinidine + Colesevelam

In a study in 25 subjects, a single 4.5-g dose of colesevelam had no significant effect on the pharmacokinetics of a single 324-mg dose

of quinidine [gluconate].[1] This suggests that colesevelam does not reduce the absorption of quinidine. No special precautions appear to be needed during concurrent use.

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Quinidine + Co-phenotrope (Atropine/Diphenoxylate)

Co-phenotrope slightly reduced the rate, but not the extent, of absorption of a single dose of quinidine.

Clinical evidence, mechanism, importance and management

In one study, 8 healthy subjects were given a single 300-mg dose of quinidine sulfate alone and after taking two tablets of co-phenotrope (atropine sulfate 25 micrograms, diphenoxylate 2.5 mg; *Lomotil*) at midnight on the evening before and another two tablets the next morning an hour before the quinidine.[1] It was found that the maximum plasma quinidine levels were reduced by 21% (from 2.1 to 1.65 micrograms/mL) by the co-phenotrope, the time to maximum level was prolonged from 0.89 hours to 1.21 hours, and there was a slight increase in elimination half-life from 5.7 hours to 6.8 hours. While these results were statistically significant, the changes were relatively small and it seems doubtful if they are clinically relevant, particularly as the extent of absorption was unchanged. However it needs to be emphasised that because the quinidine formulation used was an immediate-release preparation, these results may not necessarily apply to sustained-release preparations, and also may not apply if multiple doses of quinidine are used.

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Quinidine + Diazepam

A single-dose study suggests that diazepam does not affect the pharmacokinetics of quinidine.

Clinical evidence, mechanism, importance and management

A comparative study in 8 healthy subjects found that the pharmacokinetics of a single 250-mg dose of quinidine sulfate was unaltered by a single 10-mg dose of diazepam.[1] This suggests that no dose adjustment of quinidine is likely to be needed in patients given diazepam, but this ideally needs confirmation by further studies using multiple doses of both drugs.

1. Rao BR, Rambhau D. Absence of a pharmacokinetic interaction between quinidine and diazepam. *Drug Metabol Drug Interact* (1995) 12, 45–51.

Quinidine + Diclofenac

Diclofenac inhibits the metabolism (*N*-oxidation) of quinidine but does not affect other pharmacokinetic parameters.

Clinical evidence, mechanism, importance and management

In an open study, 6 healthy subjects were given a single 200-mg dose of quinidine sulfate before and on day 5 of a 6-day course of diclofenac 100 mg daily. Diclofenac reduced the *N*-oxidation of quinidine by 33%, but no other pharmacokinetic changes were found.[1] Diclofenac is a substrate for, and therefore a possible competitive inhibitor of the cytochrome P450 isoenzyme CYP2C9. These results suggest that CYP2C9 does not appear to have a major role in quinidine metabolism,[1] and so clinically relevant changes in quinidine pharmacokinetics with diclofenac would seem unlikely.

1. Damkier P, Hansen LL, Brøsen K. Effect of diclofenac, disulfiram, itraconazole, grapefruit juice and erythromycin on the pharmacokinetics of quinidine. *Br J Clin Pharmacol* (1999) 48, 829–38.

Quinidine + Disulfiram

Disulfiram does not affect the pharmacokinetics of quinidine.

Clinical evidence, mechanism, importance and management

In an open study, 6 healthy subjects were given a single 200-mg dose of quinidine sulfate before and on day 5 of a 6-day course of disulfiram 200 mg daily. There were no changes in quinidine pharmacokinetics during disulfiram use.[1] Disulfiram is thought to be an inhibitor of the cytochrome P450 isoenzyme CYP2E1, but this isoenzyme does not appear to have a major role in quinidine metabolism.[1] Disulfiram therefore seems unlikely to have a clinically relevant effect on the pharmacokinetics of quinidine.

1. Damkier P, Hansen LL, Brøsen K. Effect of diclofenac, disulfiram, itraconazole, grapefruit juice and erythromycin on the pharmacokinetics of quinidine. *Br J Clin Pharmacol* (1999) 48, 829–38.

Quinidine + Erythromycin

Erythromycin can increase quinidine levels and cause a small further increase in the QTc interval.

Clinical evidence

Preliminary results of a randomised, placebo-controlled study in 12 subjects found that when a single 400-mg dose of quinidine was given after oral erythromycin 500 mg three times daily for 5 days, the AUC of the QTc interval was prolonged by about 6%.[1] In a parallel study by the same group, peak levels of quinidine were increased by 39% (from 587 nanograms/mL to 816 nanograms/mL), and the AUC was increased by 62% by day 5 of the erythromycin phase. Peak levels of the main metabolite of quinidine, 3-hydroxyquinidine, were significantly reduced.[2] Another study in 6 healthy subjects found that oral erythromycin 250 mg four times daily for 6 days reduced the total clearance of a single 200-mg dose of quinidine sulfate by 34% and increased its maximum serum concentration by 39%.[3]

A 74-year-old man with a history of cardiac disease (coronary artery bypass graft surgery, ventricular tachycardia) taking quinidine sulfate 200 mg every 6 hours and several other drugs, including mexiletine, was hospitalised with suspected infection of his implantable cardioverter defibrillator. Within 2 days of starting erythromycin lactobionate 500 mg every 6 hours and ceftriaxone 1 g daily, both intravenously, his trough serum quinidine levels had risen by about 50% from about 2.8 mg/L to 4.2 mg/L. On day 7, metronidazole 500 mg every 8 hours was added and the erythromycin dosage was doubled, and the patient experienced an episode of torsade de pointes. By day 12 his serum quinidine levels had further risen to 5.8 mg/L, whereupon the quinidine dosage was reduced by 25%. Because an interaction between quinidine and erythromycin had by then been suspected, the antibacterials were replaced by doxycycline and ciprofloxacin. By day 21, the quinidine serum levels had fallen to their former levels. The patient had a prolonged QTc interval of 504 milliseconds on admission, and this did not change.[4]

A 95-year-old man developed QT interval prolongation, torsade de pointes, with a subsequent cardiac arrest when given quinidine and erythromycin, both orally.[5]

Mechanism

Not fully understood, but erythromycin inhibits the metabolism of quinidine,[2] possibly by inhibition of the cytochrome P450 isoenzyme CYP3A4,[3] thereby reducing its clearance from the body and increasing its effects. There are also a number of cases on record of prolongation of the QT interval and torsade de pointes associated with the use of intravenous erythromycin alone.[6] Therefore, quinidine and erythromycin may have additive effects on the QT interval in addition to the pharmacokinetic interaction.

Importance and management

Information about this interaction appears to be limited to these reports, but it would appear to be established. If erythromycin is essential in a patient taking quinidine, the effects of concurrent use should be well moni-

tored, being alert for the development of raised plasma quinidine levels. Monitor for quinidine adverse effects (e.g. nausea, diarrhoea, tinnitus). The concurrent use of two drugs that prolong the QT interval should usually be undertaken with great caution. For further discussion, see 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290).

1. Stanford RH, Geraets DR, Lee H-C, Min DI. Effect of oral erythromycin on quinidine pharmacodynamics in healthy volunteers. *Pharmacotherapy* (1997) 17, 1111.
2. Stanford RH, Park JM, Geraets Dr, Min DI, Lee H-C. Effect of oral erythromycin on quinidine pharmacokinetics in healthy volunteers. *Pharmacotherapy* (1998) 18, 426–7.
3. Damkier P, Hansen LL, Brøsen K. Effect of diclofenac, disulfiram, itraconazole, grapefruit juice and erythromycin on the pharmacokinetics of quinidine. *Br J Clin Pharmacol* (1999) 48, 829–38.
4. Spinler SA, Cheng JWM, Kindwall KE, Charland SL. Possible inhibition of hepatic metabolism of quinidine by erythromycin. *Clin Pharmacol Ther* (1995) 57, 89–94.
5. Lin JC, Quasny HA. QT prolongation and development of torsades de pointes with the concomitant administration of oral erythromycin base and quinidine. *Pharmacotherapy* (1997) 17, 626–30.
6. Gitler B, Berger LS, Buffa SD. Torsades de pointes induced by erythromycin. *Chest* (1994) 105, 368–72.

Quinidine + Fluvoxamine

Fluvoxamine appears to inhibit the metabolism and clearance of quinidine.

Clinical evidence, mechanism, importance and management

In a study, 6 healthy subjects were given a single 200-mg dose of quinidine sulfate before and on day 5 of a 6-day course of fluvoxamine 100 mg daily. The total apparent oral clearance of quinidine was reduced by 29%, and *N*-oxidation and 3-hydroxylation were reduced by 33% and 44%, respectively. The renal clearance and elimination half-life of quinidine were unchanged.[1] It was concluded that fluvoxamine inhibited the metabolism of quinidine by the cytochrome P450 isoenzyme CYP3A4, although a role for CYP1A2 and CYP2C19 was not excluded. The clinical relevance of these findings is unclear. However, it would seem prudent to monitor concurrent use for quinidine adverse effects (e.g. nausea, diarrhoea, tinnitus). More study is needed to assess the effect of multiple dosing and to establish the clinical significance of this interaction.

1. Damkier P, Hansen LL, Brøsen K. Effect of fluvoxamine on the pharmacokinetics of quinidine. *Eur J Clin Pharmacol* (1999) 55, 451–6.

Quinidine + Grapefruit juice

Grapefruit juice delays the absorption of quinidine and reduces its metabolism to some extent, but no clinically relevant adverse interaction seems to occur.

Clinical evidence, mechanism, importance and management

In one study, 12 healthy subjects were given quinidine sulfate 400 mg orally on two occasions, once with 240 mL of water and once with grapefruit juice. The pharmacokinetics of the quinidine were unchanged, except that its absorption was delayed (the time to reach maximum plasma concentrations was doubled from 1.6 hours to 3.3 hours) by grapefruit juice for reasons that are not understood. The AUC of the quinidine metabolite, 3-hydroxyquinidine was decreased by one-third, suggesting that grapefruit juice inhibits the metabolism of quinidine. No important changes in the QTc interval were seen.[1]

Similarly, another study in 6 healthy subjects found the total clearance of a single 200-mg dose of quinidine sulfate was reduced by 15% by 250 mL of grapefruit juice, with no change in its maximum level. There was a small reduction in metabolite formation suggesting only minor inhibition of metabolism.[2]

Grapefruit is known to inhibit the cytochrome P450 isoenzyme CYP3A4, which is involved with the metabolism of quinidine, so it seems likely that any interaction would occur via this pathway.[1,2] The effects of grapefruit juice appear to be modest, and these studies suggest that it is not usually necessary for patients on quinidine to avoid grapefruit juice. However, grapefruit juice may have contributed to raised quinidine levels and toxicity in a woman who took an antacid and one litre of fruit juice daily for a week, see 'Quinidine + Antacids or Urinary alkalinisers', p.313. It may therefore be prudent to be alert for an increase in quinidine adverse effects (e.g. nausea, diarrhoea, tinnitus), and consider avoiding grapefruit if these become troublesome.

1. Min DI, Ku Y-M, Geraets DR, Lee H-C. Effect of grapefruit juice on the pharmacokinetics and pharmacodynamics of quinidine in healthy volunteers. *J Clin Pharmacol* (1996) 36, 469–76.
2. Damkier P, Hansen LL, Brøsen K. Effect of diclofenac, disulfiram, itraconazole, grapefruit juice and erythromycin on the pharmacokinetics of quinidine. *Br J Clin Pharmacol* (1999) 48, 829–38.

Quinidine + H_2-receptor antagonists

Quinidine serum levels can rise and toxicity may develop in some patients when they take cimetidine. An isolated case of ventricular bigeminy (a form of arrhythmia) occurred in a patient taking quinidine and ranitidine.

Clinical evidence

In a study in 6 healthy subjects, **cimetidine** 300 mg four times daily for 7 days prolonged the elimination half-life of a single 400-mg dose of quinidine sulfate by 55%, from 5.8 to 9 hours, and decreased its clearance by 37%. Peak plasma levels were raised by 21%. These changes were reflected in ECG changes, with 51% and 28% increases in the mean areas under the QT and QTc time curves, respectively, but these were not considered to be statistically significant.[1]

A later study in healthy subjects, prompted by the observation of 2 patients who developed toxic quinidine levels when given **cimetidine**, found essentially the same effects. The AUC and half-life of quinidine were increased by 15% and 23%, respectively, and the clearance was decreased by 25% by **cimetidine** 300 mg four times daily.[2] A further study in 4 healthy subjects found that **cimetidine** 300 mg four times daily for 5 days prolonged the elimination half-life of quinidine by 54% and decreased its total clearance by 36%.[3,4] In one study, the addition of **cimetidine** prolonged the QT interval by 30% more than the effect of quinidine alone.[4] A case report describes marked increases in both quinidine and digitoxin concentrations in a woman also given **cimetidine**.[5] Similarly, quinidine levels increased by up to 50%, without causing any adverse effects, when a man taking quinidine was given **cimetidine**.[6]

Ventricular bigeminy (a form of arrhythmia) occurred when a man taking quinidine was given **ranitidine**. His serum quinidine levels remained unchanged.[7]

Mechanism

It was originally suggested that the cimetidine inhibits the metabolism of the quinidine by the liver so that it is cleared more slowly.[2] However, further data suggest that cimetidine successfully competes with quinidine for its excretion by the kidneys.[8]

Importance and management

The interaction between quinidine and cimetidine is established and of clinical importance. The incidence is unknown. Be alert for changes in the response to quinidine if cimetidine is started or stopped. Ideally the quinidine serum levels should be monitored (consider monitoring in response to adverse effects such as hypotension, tinnitus and diarrhoea) and reduce the quinidine dose as necessary. Reductions of 25% (oral) and 35% (intravenous) have been suggested.[3] Those at greatest risk are likely to be patients with impaired renal function, patients with impaired liver function, the elderly, and those with serum quinidine levels already at the top end of the therapeutic range.[2] The situation with ranitidine is uncertain.

1. Hardy BG, Zador IT, Golden L, Lalka D, Schentag JJ. Effect of cimetidine on the pharmacokinetics and pharmacodynamics of quinidine. *Am J Cardiol* (1983) 52, 172–5.
2. Kolb KW, Garnett WR, Small RE, Vetrovec GW, Kline BJ, Fox T. Effect of cimetidine on quinidine clearance. *Ther Drug Monit* (1984) 6, 306–12.
3. MacKichan JJ, Boudoulas H, Schaal SF. Effect of cimetidine on quinidine bioavailability. *Biopharm Drug Dispos* (1989) 10, 121–5.
4. Boudoulas H, MacKichan JJ, Schaal SF. Effect of cimetidine on the pharmacodynamics of quinidine. *Med Sci Res* (1988) 16, 713–14.
5. Polish LB, Branch RA, Fitzgerald GA. Digitoxin-quinidine interaction: potentiation during administration of cimetidine. *South Med J* (1981) 74, 633–4.
6. Farringer JA, McWay-Hess K, Clementi WA. Cimetidine–quinidine interaction. *Clin Pharm* (1984) 3, 81–3.

7. Iliopoulou A, Kontogiannis D, Tsoutsos D, Moulopoulos S. Quinidine-ranitidine adverse reaction. *Eur Heart J* (1986) 7, 360.
8. Hardy BG, Schentag JJ. Lack of effect of cimetidine on the metabolism of quinidine: effect on renal clearance. *Int J Clin Pharmacol Ther Toxicol* (1988) 26, 388–91.

Quinidine + Kaolin-pectin

There is some evidence that kaolin-pectin can reduce the absorption of quinidine and lower its serum levels.

Clinical evidence, mechanism, importance and management

When 4 healthy subjects were given 30 mL of kaolin-pectin (*Kaopectate*), after a single 100-mg dose of oral quinidine sulfate, the maximal salivary quinidine concentration was reduced by 54% and its AUC was reduced by 58%, without any effect on the rate of absorption.[1] There is a correlation between salivary and serum concentrations after single (but not repeated) doses of quinidine.[2] This is consistent with *in vitro* data showing that quinidine is adsorbed onto kaolin and pectin.[1,3] Documentation appears to be limited to these two studies, but be alert for the need to increase the quinidine dose if kaolin-pectin is used concurrently.

1. Moustafa MA, Al-Shora HI, Gaber M, Gouda MW. Decreased bioavailability of quinidine sulphate due to interactions with adsorbent antacids and antidiarrhoeal mixtures. *Int J Pharmaceutics* (1987) 34, 207–11.
2. Narang PK, Carliner NH, Fisher ML, Crouthamel WG. Quinidine saliva concentrations: absence of correlation with serum concentrations at steady state. *Clin Pharmacol Ther* (1983) 34, 695–702.
3. Bucci AJ, Myre SA, Tan HSI, Shenouda LS. In vitro interaction of quinidine with kaolin and pectin. *J Pharm Sci* (1981) 70, 999–1002.

Quinidine + Laxatives

Quinidine plasma levels can be reduced by the anthraquinone laxative senna.

Clinical evidence, mechanism, importance and management

In a study in 7 patients with cardiac arrhythmias taking sustained-release quinidine bisulfate 500 mg every 12 hours, **senna** reduced plasma quinidine levels, measured 12 hours after the last dose of quinidine, by about 25%.[1] The modest reduction in quinidine levels might be of clinical importance in patients whose plasma levels are barely adequate to control their arrhythmia.

1. Guckenbiehl W, Gilfrich HJ, Just H. Einfluß von Laxantien und Metoclopramid auf die Chindin-Plasmakonzentration während Langzeittherapie bei Patienten mit Herzrhythmusstörugen. *Med Welt* (1976) 27, 1273–6.

Quinidine + Lidocaine

A single case report describes a man taking quinidine who had sinoatrial arrest when he was given intravenous lidocaine.

Clinical evidence, mechanism, importance and management

A man with Parkinson's disease was given quinidine 300 mg every 6 hours for the control of ventricular ectopic beats. After receiving two doses he was given lidocaine as well, initially as a bolus of 80 mg, followed by an infusion of 4 mg/minute because persistent premature ventricular beats developed. Within 2.5 hours the patient complained of dizziness and weakness, and was found to have sinus bradycardia, sinoatrial arrest and an atrioventricular escape rhythm. Normal sinus rhythm resumed when the lidocaine was stopped. Whether quinidine was a contributing factor in this reaction is uncertain.[1] However, this case emphasises the need to exercise caution when giving two drugs that have cardiac depressant actions.

1. Jeresaty RM, Kahn AH, Landry AB. Sinoatrial arrest due to lidocaine in a patient receiving quinidine. *Chest* (1972) 61, 683–5.

Quinidine + Metoclopramide

Metoclopramide has been seen to both modestly increase quinidine levels and modestly decrease quinidine exposure.

Clinical evidence

A study of a possible interaction between quinidine and metoclopramide was prompted by the case of a patient who was taking sustained-release quinidine (*Quinidex*) and whose arrhythmia became uncontrolled when metoclopramide was added. In a crossover study, 9 healthy subjects were given metoclopramide 10 mg every 6 hours, for 24 hours before and 48 hours after a single 600- or 900-mg oral dose of quinidine sulfate or quinidine alone. It was found that metoclopramide caused a mean 10% decrease in the AUC of quinidine, although two subjects had decreases of 23% and 28%, respectively. The elimination rate constant was unaffected.[1]

Another study, in patients taking sustained-release quinidine bisulfate 500 mg every 12 hours, found that metoclopramide 10 mg three times daily increased the mean plasma levels measured 3.5 hours after the last dose of quinidine by almost 20%, from 1.6 to 1.9 micrograms/mL, and increased the levels at 12 hours by about 16%, from 2.4 to 2.8 micrograms/mL.[2]

Mechanism

Not understood. Metoclopramide alters both the gastric emptying time and gastrointestinal motility, which can affect quinidine absorption.

Importance and management

Direct information seems to be limited to these studies using different quinidine preparations. The outcome of concurrent use is uncertain, but any effect generally seems small in most patients.

1. Yuen GJ, Hansten PD, Collins J. Effect of metoclopramide on the absorption of an oral sustained-release quinidine product. *Clin Pharm* (1987) 6, 722–5.
2. Guckenbiehl W, Gilfrich HJ, Just H. Einfluß von Laxantien und Metoclopramid auf die Chindin-Plasmakonzentration während Langzeittherapie bei Patienten mit Herzrhythmusstörugen. *Med Welt* (1976) 27, 1273–6.

Quinidine + Omeprazole

Omeprazole does not appear to alter the pharmacokinetics or QT-interval prolonging effects of quinidine.

Clinical evidence, mechanism, importance and management

In a study in 8 healthy subjects, omeprazole 40 mg daily for one week had no effect on the pharmacokinetics of a single 400-mg dose of quinidine sulfate. In addition, the corrected QT interval was not significantly changed.[1] There would not appear to be the need for any special precautions during concurrent use.

1. Ching MS, Elliott SL, Stead CK, Murdoch RT, Devenish-Meares S, Morgan DJ, Smallwood RA. Quinidine single dose pharmacokinetics and pharmacodynamics are unaltered by omeprazole. *Aliment Pharmacol Ther* (1991) 5, 523–31.

Quinidine + Protease inhibitors

In theory, the protease inhibitors may increase the levels of quinidine. Quinidine does not affect indinavir levels.

Clinical evidence

In a study in which quinidine sulphate 200 mg was given to 10 healthy subjects, followed one hour later by a single 400-mg dose of **indinavir**, the pharmacokinetics of **indinavir** were not significantly affected.[1]

Direct evidence (from case reports or clinical studies) of an interaction between quinidine and the other protease inhibitors appears to be lacking; however, a review of protease inhibitor interactions reports that plasma levels of quinidine may be increased by **ritonavir**. The same review states that **nelfinavir** and **saquinavir** may interact similarly.[2]

Mechanism

Quinidine is metabolised by the cytochrome P450 isoenzyme CYP3A4, of which nelfinavir, ritonavir and saquinavir are all inhibitors. Note that the protease inhibitors are all inhibitors of CYP3A4, to varying degrees, and therefore may be expected to interact similarly.

Importance and management

Clinical evidence of an interaction between quinidine and protease inhibitors is lacking; however, in theory, all protease inhibitors could raise quinidine levels. Raised levels of quinidine may increase the risk of arrhythmias and other adverse effects. The manufacturers of **ritonavir** contraindicate concurrent use with quinidine,[3,4] and for this reason, many of the manufacturers contraindicate the concurrent use of ritonavir-boosted protease inhibitors with quinidine. However, the UK manufacturers of **lopinavir**[5] and **saquinavir**[6] caution concurrent use and recommend monitoring of quinidine levels, where available. Note that quinidine adverse effects include nausea, diarrhoea, and tinnitus. In the US, most manufacturers advise caution and close monitoring of quinidine levels, with the exception of the manufacturers of **nelfinavir**,[7] **saquinavir**[8] and **tipranavir**,[9] who contraindicate the concurrent use of quinidine.

No dose adjustment of **indinavir** appears to be needed if the concurrent use of quinidine is necessary.

1. McCrea J, Woolf E, Sterrett A, Matthews C, Deutsch, Yeh KC, Waldman S, Bjornsson T. Effects of ketoconazole and other p-450 inhibitors on the pharmacokinetics of indinavir. *Pharm Res* (1996) 13 (9 Suppl), S485.
2. Burger DM, Hoetelmans RMW, Koopmans PP, Meenhorst PL, Mulder JW, Hekster YA, Beijnen JH. Clinically relevant drug interactions with antiretroviral agents. *Antivir Ther* (1997) 2, 149–165.
3. Norvir Soft Capsules (Ritonavir). Abbott Laboratories Ltd. UK Summary of product characteristics, October 2009.
4. Norvir (Ritonavir). Abbott Laboratories. US Prescribing information, November 2009.
5. Kaletra Tablets (Lopinavir with Ritonavir). Abbott Laboratories Ltd. UK Summary of product characteristics, November 2009.
6. Invirase Film-coated Tablets (Saquinavir mesilate). Roche Products Ltd. UK Summary of product characteristics, January 2009.
7. Viracept (Nelfinavir mesylate). Agouron Pharmaceuticals, Inc. US Prescribing information, September 2008.
8. Invirase (Saquinavir mesylate). Roche Laboratories Inc. US Prescribing information, July 2007.
9. Aptivus (Tipranavir). Boehringer Ingelheim Pharmaceuticals, Inc. US Prescribing information, June 2009.

Quinidine + Quinolones

Ciprofloxacin does not normally appear to interact with quinidine to a clinically relevant extent. An increased risk of torsade de pointes might be expected if quinidine is used with gatifloxacin, moxifloxacin, or sparfloxacin, and possibly levofloxacin.

Clinical evidence, mechanism, importance and management

In a study in 7 healthy subjects, **ciprofloxacin** 750 mg daily for 6 days did not significantly affect the pharmacokinetics of a single 400-mg oral dose of quinidine sulfate, and QRS and QTc prolongation were not significantly changed. The decrease in clearance ranged from a decrease of 10% to an increase of 20%, with a mean 1% increase, which is unlikely to be clinically relevant.[1] However an isolated case report describes a woman who started taking quinidine gluconate 324 mg every 8 hours while she was taking **ciprofloxacin** and metronidazole. Her first trough serum quinidine level was 6.3 micrograms/mL, which was slightly above the reference range of 2 to 5 micrograms/mL, but she had no evidence of toxicity. Quinidine was continued unchanged, and her next trough serum quinidine level was only 2.3 micrograms/mL, 3 days after finishing the course of antibacterials. This effect was tentatively attributed to the possible enzyme inhibitory effects of **ciprofloxacin** and metronidazole. This case is far from clear and so no firm conclusions can be reached.[2] There would seem to be little reason for avoiding concurrent use.

Some quinolones can prolong the QT interval, and would be expected to increase the risk of torsade de pointes when used with quinidine. Of the quinolones used clinically, **gatifloxacin**, **moxifloxacin**, and **sparfloxacin** are known to prolong the QT interval (see 'Table 9.2', (p.290)). There is also evidence that **levofloxacin** may prolong the QT interval (see 'Amiodarone + Quinolones', p.281). The concurrent use of two drugs that prolong the QT interval should usually be avoided, or undertaken with great caution. For further discussion, see also 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290.

1. Bleske BE, Carver PL, Annesley TM, Bleske JRM, Morady F. The effect of ciprofloxacin on the pharmacokinetic and ECG parameters of quinidine. *J Clin Pharmacol* (1990) 30, 911–15.
2. Cooke CE, Sklar GE, Nappi JM. Possible pharmacokinetic interaction with quinidine: ciprofloxacin or metronidazole? *Ann Pharmacother* (1996) 30, 364–6.

Quinidine + Rifamycins

The serum levels and therapeutic effects of quinidine can be markedly reduced by rifampicin.

Clinical evidence

It was noted that the control of ventricular arrhythmia deteriorated in a patient taking quinidine sulfate 800 mg daily within a week of **rifampicin** 600 mg daily being started. His serum quinidine level fell from 4 micrograms/mL to 0.5 micrograms/mL, and remained low despite doubling the quinidine dose to 1.6 g daily. The **rifampicin** was discontinued, and quinidine levels gradually increased over a week. Some signs of quinidine toxicity then occurred, and the quinidine dose was reduced back to 800 mg daily.[1] Further study in 4 healthy subjects found that **rifampicin** 600 mg daily for 7 days reduced the mean half-life of a single 6-mg/kg oral dose of quinidine sulfate by about 62% (from 6.1 hours to 2.3 hours) and reduced the AUC by 83%.[2] Similar findings were reported in 4 other subjects receiving the same dose of quinidine intravenously.[2]

Another case report describes a patient taking **rifampicin** who did not achieve adequate serum quinidine levels despite daily doses of quinidine of up to 3.2 g. When the **rifampicin** was stopped, ultimately, a reduced quinidine dose of 1.8 g daily achieved a serum level of 2 micrograms/mL, reflecting a 44% decrease in dose and a 43% increase in level.[3] In a further case, a patient taking quinidine and digoxin was given **rifampicin**: the quinidine levels fell, resulting in a fall in digoxin levels.[4]

Mechanism

Rifampicin is a potent enzyme-inducer, which markedly increases the metabolism of the quinidine by 3-hydroxylation and *N*-oxidation, thereby reducing its levels and effects.[5] It has been suggested that two of the quinidine metabolites (3-hydroxyquinidine and 2-oxoquinidinone) may be active, which might, to some extent, offset the effects of this interaction.[4]

Importance and management

An established and clinically important interaction, although documentation is limited. The dose of quinidine will need to be increased if rifampicin is given concurrently. Monitor the serum levels. Doubling the dose may not be sufficient.[2,4] An equivalent dosage reduction will be needed if the rifampicin is stopped. There does not seem to be any information regarding the other rifamycins, **rifabutin** (a weak enzyme inducer) and **rifapentine** (a moderate enzyme inducer). However, the manufacturers and the CSM in the UK warn that **rifabutin** may possibly reduce the effects of a number of drugs, including quinidine.[6,7]

1. Ahmad D, Mathur P, Ahuja S, Henderson R, Carruthers G. Rifampicin-quinidine interaction. *Br J Dis Chest* (1979) 73, 409–11.
2. Twum-Barima Y, Carruthers SG. Quinidine-rifampin interaction. *N Engl J Med* (1981) 304, 1466–9.
3. Schwartz A, Brown JR. Quinidine-rifampin interaction. *Am Heart J* (1984) 107, 789–90.
4. Bussey HI, Merritt GJ, Hill EG. The influence of rifampin on quinidine and digoxin. *Arch Intern Med* (1984) 144, 1021–3.
5. Damkier P, Hansen LL, Brøsen K. Rifampicin treatment greatly increases the apparent oral clearance of quinidine. *Pharmacol Toxicol* (1999) 85, 257–62.
6. Mycobutin (Rifabutin). Pharmacia Ltd. UK Summary of product characteristics, June 2009.
7. Committee on the Safety of Medicines/Medicines Control Agency. Revised indication and drug interactions of rifabutin. *Current Problems* (1997) 23, 14.

Quinidine + Sucralfate

An isolated report describes a marked reduction in serum quinidine levels, which was attributed to the concurrent use of sucralfate.

Clinical evidence, mechanism, importance and management

An elderly woman was found to have subtherapeutic levels of warfarin, digoxin and sustained-release quinidine (serum quinidine level 0.31 micromol/L), even though they were given 2 hours apart from sucralfate. On hospitalisation, a variety of other medications were then started for chest pain (glyceryl trinitrate, diltiazem, pethidine (meperidine), promethazine), and on day 4 the sucralfate was stopped. On day 5, her serum quinidine level was 5.55 micromol/L.[1] The patient denied non-compliance, and the suggestion was that sucralfate can bind with quinidine within

the gut and reduce its absorption. This isolated case appears to be the only report of an interaction between quinidine and sucralfate and its general importance is unclear.

1. Rey AM, Gums JG. Altered absorption of digoxin, sustained-release quinidine, and warfarin with sucralfate administration. *DICP Ann Pharmacother* (1991) 25, 745–6.

Tocainide + Antacids or Urinary alkalinisers

Raising the pH of the urine (e.g. with some antacids, diuretics or alkaline salts) can modestly reduce the clearance of tocainide.

Clinical evidence

The preliminary findings of a study suggested that when 5 healthy subjects took 30 mL of an unnamed antacid four times daily for 48 hours before and 58 hours after a single 600-mg dose of tocainide, the urinary pH rose from 5.9 to 6.9, the total clearance of tocainide fell by 28%, the peak serum levels fell by 19% from 4.2 to 3.4 micrograms/mL, the AUC rose by 33% and the half-life was prolonged from 13.2 to 15.4 hours.[1]

Mechanism

Tocainide is a weak base so that its loss in the urine will be affected by the pH of the urine. Alkalinisation of the urine increases the number of non-ionised molecules available for passive reabsorption, thereby reducing the urinary loss and raising the serum levels.

Importance and management

An established interaction of uncertain but probably limited clinical importance. There seem to be no reports of adverse reactions in patients as a result of this interaction, but be alert for any evidence of increased tocainide effects if other drugs are given that can raise the urinary pH significantly (e.g. **sodium bicarbonate** and **acetazolamide**). Reduce the tocainide dosage if necessary. Of the antacids, **aluminium/magnesium hydroxide** (*Maalox*) can raise urinary pH by about 0.9 whereas **magnesium hydroxide** (*Milk of magnesia*) and **calcium carbonate-glycine** (*Titralac*) raise the pH by about 0.5. **Aluminium hydroxide** (*Amphogel*) and **dihydroxyaluminium glycinate** (*Robalate*) are reported to have no effect on urinary pH.[2]

1. Meneilly GP, Scavone JM, Meneilly GS, Wei JY. Tocainide: pharmacokinetic alterations during antacid-induced urinary alkalinization. *Clin Pharmacol Ther* (1987) 41, 178.
2. Gibaldi M, Grundhofer B, Levy G. Effect of antacids on pH of urine. *Clin Pharmacol Ther* (1974) 16, 520–5.

Tocainide + H_2-receptor antagonists

There is some evidence that cimetidine can reduce the bioavailability and serum levels of tocainide. Ranitidine appears not to interact with tocainide.

Clinical evidence, mechanism, importance and management

In a preliminary report of a study in 11 healthy subjects, 4 days of treatment with **cimetidine** [dose not stated] had a small effect on the pharmacokinetics of tocainide 500 mg given intravenously over 15 minutes, which was not considered to be clinically important.[1] In another study, in 7 healthy subjects, **cimetidine** 300 mg four times daily for 2 days reduced the AUC of a single 400-mg oral dose of tocainide by about one-third. The peak serum levels were also reduced, from about 2.8 micrograms/mL to 1.7 micrograms/mL, but no changes in the half-life or renal clearance occurred.[2] The reasons for these modest changes, and their clinical importance are uncertain, but be alert for evidence of a reduced response to tocainide in the presence of **cimetidine**. **Ranitidine** 150 mg twice daily has been found not to interact.[2]

1. Price BA, Holmes GI, Antonello J, Yeh KC, Demetriades J, Irvin JD, McMahon FG. Intravenous tocainide (T) maintains safe therapeutic levels when administered concomitantly with cimetidine (C). *Clin Pharmacol Ther* (1987), 41, 237.
2. North DS, Mattern AL, Kapil RP, Lalonde RL. The effect of histamine-2 receptor antagonists on tocainide pharmacokinetics. *J Clin Pharmacol* (1988) 28, 640–3.

Tocainide + Phenobarbital

Phenobarbital does not appear to alter the pharmacokinetics of tocainide.

Clinical evidence, mechanism, importance and management

In a study in 6 healthy subjects, phenobarbital 100 mg daily for 15 days did not alter the AUC of a single 600-mg dose of tocainide. In addition, the percentage of the dose excreted unchanged in the urine and as the glucuronide metabolite did not differ.[1] Phenobarbital at this dose does not appear to alter the metabolism of tocainide. No tocainide dose adjustment appears to be necessary if phenobarbital is also given.

1. Elvin AT, Lalka D, Stoeckel K, du Souich P, Axelson JE, Golden LH, McLean AJ. Tocainide kinetics and metabolism: effects of phenobarbital and substrates of glucuronyl transferase. *Clin Pharmacol Ther* (1980) 28, 652–8.

Tocainide + Rifampicin (Rifampin)

Rifampicin decreases the half-life and AUC of tocainide.

Clinical evidence, mechanism, importance and management

In a study in 8 healthy subjects, rifampicin 300 mg twice daily for 5 days reduced the AUC of a single 600-mg oral dose of tocainide by almost 30% and similarly reduced the half-life, from 13.2 hours to 9.4 hours.[1]

This response is consistent with the well-known enzyme-inducing effects of rifampicin. Information is limited to this single dose study, but the interaction would seem to be established, although its clinical importance is probably modest. Be alert for any evidence of a reduction in tocainide serum levels and effects if rifampicin is also given. Increase the dosage as necessary, remembering to reduce the tocainide dosage if the rifampicin is withdrawn.

1. Rice TL, Patterson JH, Celestin C, Foster JR, Powell JR. Influence of rifampin on tocainide pharmacokinetics in humans. *Clin Pharm* (1989) 8, 200–205.

10

Antibacterials

This section deals with interactions where the effects of the antibacterial are altered. In many cases the antibacterial drugs interact by affecting other drugs, and these interactions are dealt with elsewhere in this publication. Some of the macrolides and the quinolones are potent enzyme inhibitors; the macrolides exert their effects on the cytochrome P450 isoenzyme CYP3A4, whereas many quinolones inhibit CYP1A2. Rifampicin (rifampin) is a potent non-specific enzyme inducer and therefore lowers the levels of many drugs.

Many of the interactions covered in this section concern absorption interactions, such as the ability of the tetracyclines and quinolones to chelate with divalent cations. More information on the mechanism of these interactions can be found in 'Drug absorption interactions', (p.3).

Many monographs concern the use of multiple antibacterials. One of the great difficulties with these interactions is the often poor correlation between *in vitro* and *in vivo* studies, so that it is difficult to get a thoroughly reliable indication of how antibacterial drugs will behave together in clinical practice. Two antibacterials may actually be less effective than one on its own, because, in theory, the effects of a bactericidal drug, which requires actively dividing cells for it to be effective, may be reduced by a bacteriostatic drug. However, in practice this seems to be less important than might be supposed and there are relatively few well-authenticated clinical examples.

The antibacterials covered in this section are listed in 'Table 10.1', (below).

Table 10.1 Antibacterials

Group	*Drugs*
Aminoglycosides	Amikacin, Astromicin, Dibekacin, Dihydrostreptomycin, Framycetin, Gentamicin, Isepamicin, Kanamycin, Micronomicin, Neomycin, Netilmicin, Paromomycin, Sisomicin, Streptomycin, Tobramycin
Antimycobacterials and related drugs	Aminosalicylic acid (PAS), Capreomycin, Clofazimine, Cycloserine, Dapsone, Ethambutol, Ethionamide, Isoniazid, Methaniazide, Protionamide, Pyrazinamide, Rifabutin, Rifampicin (Rifampin), Rifamycin, Rifapentine, Rifaximin
Carbapenems	Biapenem, Doripenem, Ertapenem, Faropenem, Imipenem, Meropenem, Panipenem
Cephalosporins	Cefaclor, Cefadroxil, Cefalexin, Cefaloglycin, Cefaloridine, Cefalotin, Cefamandole, Cefapirin, Cefatrizine, Cefazolin, Cefbuperazone, Cefcapene, Cefdinir, Cefditoren, Cefepime, Cefetamet, Cefixime, Cefmenoxime, Cefmetazole, Cefminox, Cefodizime, Cefonicid, Cefoperazone, Ceforanide, Cefotaxime, Cefotetan, Cefotiam, Cefoxitin, Cefpiramide, Cefpirome, Cefpodoxime, Cefprozil, Cefradine, Cefsulodin, Ceftazidime, Cefteram, Ceftezole, Ceftibuten, Ceftizoxime, Ceftriaxone, Cefuroxime, Flomoxef, Latamoxef
Macrolides	Azithromycin, Clarithromycin, Dirithromycin, Erythromycin, Flurithromycin, Josamycin, Midecamycin, Rokitomycin, Roxithromycin, Spiramycin, Telithromycin, Troleandomycin
Penicillins	Amoxicillin, Ampicillin, Azidocillin, Azlocillin, Bacampicillin, Benzylpenicillin (Penicillin G), Carbenicillin, Carindacillin, Ciclacillin, Clometocillin, Cloxacillin, Dicloxacillin, Flucloxacillin, Mecillinam, Meticillin, Mezlocillin, Nafcillin, Oxacillin, Phenethicillin, Phenoxymethylpenicillin (Penicillin V), Piperacillin, Pivampicillin, Pivmecillinam, Procaine benzylpenicillin (Procaine penicillin), Propicillin, Sulbenicillin, Temocillin, Ticarcillin
Polypeptides	Bacitracin, Colistimethate sodium, Colistin, Polymyxin B, Teicoplanin, Vancomycin
Quinolones	Cinoxacin, Ciprofloxacin, Enoxacin, Fleroxacin, Flumequine, Gatifloxacin, Gemifloxacin, Grepafloxacin, Levofloxacin, Lomefloxacin, Moxifloxacin, Nadifloxacin, Nalidixic acid, Norfloxacin, Ofloxacin, Oxolinic Acid, Pazufloxacin, Pefloxacin, Pipemidic Acid, Rosoxacin, Rufloxacin, Sparfloxacin, Temafloxacin, Tosufloxacin, Trovafloxacin
Sulfonamides	Co-trimoxazole, Phthalylsulfathiazole, Sulfadiazine, Sulfadimidine (Sulfamethazine), Sulfafurazole (Sulfisoxazole), Sulfaguanidine, Sulfamerazine, Sulfamethizole, Sulfamethoxazole, Sulfametopyrazine, Sulfametrole
Tetracyclines	Chlortetracyline, Demeclocycline, Doxycycline, Lymecycline, Methacycline, Minocycline, Oxytetracycline, Rolitetracycline, Tetracycline, Tigecycline
Miscellaneous	Aztreonam, Carumonam, Chloramphenicol, Cilastatin, Clindamycin, Daptomycin, Fosfomycin, Fusidic acid, Lincomycin, Linezolid, Loracarbef, Methenamine, Metronidazole, Mupirocin, Nitrofurantoin, Novobiocin, Pristinamycin, Quinupristin/Dalfopristin, Retapamulin, Spectinomycin, Trimethoprim, Vancomycin

Aminoglycosides + Amphotericin B

One study in children suggested that amphotericin B decreased the clearance of amikacin and gentamicin. The concurrent use of aminoglycosides and amphotericin B can result in nephrotoxicity.

Clinical evidence, mechanism, importance and management

A study found that **amikacin** or **gentamicin** clearance was impaired in 12 of 17 children given amphotericin B. Serum creatinine increased by 50% or more in 3 of the children, but there was no significant increase in creatinine levels in 7 others. As a result, the aminoglycoside dose was decreased or the dose interval lengthened in 7 children.[1]

The renal function of 4 patients receiving moderate doses of **gentamicin** deteriorated when they were given amphotericin B. Both drugs are known to be nephrotoxic and it is suggested, on the basis of what was seen, that combined use may have had additive nephrotoxic effects.[2] A further retrospective analysis found that the use of **amikacin** tended to increase amphotericin B-related nephrotoxicity.[3]

A study assessing the risk factors for nephrotoxicity with aminoglycosides (**tobramycin** and **gentamicin**) enrolled 1489 patients, 157 of whom developed clinical nephrotoxicity. Of these patients 118 had no immediately identifiable cause (such as acute renal failure) and further evaluation of other risk factors found that the concurrent use of amphotericin B significantly increased the risk of nephrotoxicity.[4]

The nephrotoxicity of various combinations of antibiotics was assessed in 171 patients with cancer (139 given a combination of aminoglycoside with penicillin or cephalosporin; 32 given amphotericin B or vancomycin with other antibacterials). The highest nephrotoxicity (based on changes in urea and electrolytes) was found in patients receiving amphotericin B with an aminoglycoside and a cephalosporin.[5]

Two other studies did not find that aminoglycosides increased the risk of amphotericin B-associated toxicity (defined as a 100% or greater increase in serum creatinine),[6,7] although in one of the studies[7] the frequency of concurrent aminoglycoside use may have been too low to identify any evidence of increased nephrotoxic risk.

A case report describes hypomagnesemic tetany, which developed in a patient who had received **gentamicin** for 9 days, followed immediately by an 8-day course of amphotericin B. Intravenous magnesium replacement resulted in immediate resolution of the tetany. The authors suggested that the hypomagnesemia had occurred due to the additive magnesium-lowering effects of **gentamicin** and amphotericin B.[8]

Aminoglycosides are generally considered to be nephrotoxic, and therefore it is generally recommended that other nephrotoxic drugs (such as amphotericin B) should be avoided. However, concurrent use may be essential. Renal function and drug levels should be routinely monitored during the use of an aminoglycoside, and it may be prudent to increase the frequency of such monitoring in the presence of amphotericin B. Lipid formulations of amphotericin B are less nephrotoxic than the conventional formulation.[9] One manufacturer notes there was significantly less nephrotoxicity in patients receiving an aminoglycoside with liposomal amphotericin B (*Ambisome*) compared with aminoglycosides and conventional amphotericin B.[10]

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3. Harbath S, Pestotnik SL, Lloyd JF, Burke JP, Samore MH. The epidemiology of nephrotoxicity associated with conventional amphotericin B therapy. *Am J Med* (2001) 111, 528–34.
4. Bertino JS, Booker LA, Franck PA, Jenkins PL, Franck KR, Nafziger AN. Incidence of and significant risk factors for aminoglycoside-associated nephrotoxicity in patients dosed by using individualized pharmacokinetic monitoring. *J Infect Dis* (1993) 167, 173–9.
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6. Fisher MA, Talbot GH, Maislin G, McKeon BP, Tynan KP, Strom BL. Risk factors for amphotericin B-associated nephrotoxicity. *Am J Med* (1989) 87, 547–52.
7. Zager RA, O'Quigley J, Zager BK, Alpers CE, Shulman HM, Gamelin LM, Stewart P, Thomas ED. Acute renal failure following bone marrow transplantation: a retrospective study of 272 patients. *Am J Kidney Dis* (1989) 13, 210–16.
8. Davies SV, Murray JA. Amphotericin B, aminoglycosides and hypomagnesaemic [sic] tetany. *BMJ* (1986) 292, 1395–6.
9. Dupont B. Overview of the lipid formulations of amphotericin B. *J Antimicrob Chemother* (2002) 49, (Suppl S1) 31–6.
10. AmBisome (Liposomal Amphotericin B). Gilead Sciences Ltd. UK Summary of product characteristics, January 2009.

Aminoglycosides + Carbapenems

No pharmacokinetic interaction of importance appears to occur between the aminoglycosides and the carbapenems.

Clinical evidence, mechanism, importance and management

The suspicion that low **tobramycin** levels in one patient might have been due to an interaction with **imipenem** with **cilastatin** was not confirmed in a later *in vitro* study.[1] It has also been suggested that the nephrotoxic effects of **imipenem** and the **aminoglycosides** might possibly be additive.[2] However, a study in healthy subjects given single intravenous doses of **imipenem** and **amikacin** found there was a transient increase in **imipenem** levels but no effects on other pharmacokinetic parameters of either drug.[3] In a study in 12 healthy subjects the concurrent use of **tobramycin** and **biapenem** did not alter the pharmacokinetics of either drug.[4] There would seem to be no reason for avoiding concurrent use.

1. Ariano RE, Kassum DA, Meatherall RC, Patrick WD. Lack of in vitro inactivation of tobramycin by imipenem/cilastatin. *Ann Pharmacother* (1992) 26, 1075–7.
2. Albrecht LM, Rybak MJ. Combination imipenem-aminoglycoside therapy. *Drug Intell Clin Pharm* (1986) 20, 506.
3. Adamis G, Papaionnou MG, Giamarellos-Bourboulis EJ, Gargalianos P, Kosmidis J, Giamarellou H. Pharmacokinetic interactions of ceftazidime, imipenem and aztreonam with amikacin in healthy volunteers. *Int J Antimicrob Agents* (2004) 23, 144–9.
4. Muralidharan G, Buice R, Depuis E, Carver A, Friederici D, Kinchelow T, Kinzig M, Kuye O, Sorgel F, Yacobi A, Mayer P. Pharmacokinetics of biapenem with and without tobramycin in healthy volunteers. *Pharm Res* (1993) 10 (10 Suppl), S-396.

Aminoglycosides + Cephalosporins

The nephrotoxic effects of gentamicin and tobramycin can be increased by cefalotin. Nephrotoxicity may also occur when other aminoglycosides are given with cephalosporins.

Clinical evidence

(a) Cefaloridine

Acute renal failure has been reported in a patient given **gentamicin** and cefaloridine.[1] One study reported an increase in the incidence of nephrotoxicity when cefaloridine was given with **gentamicin** (or other unnamed aminoglycosides), although other factors such as excessive dose or pre-existing renal impairment were also associated with the increase in cephalosporin nephrotoxicity in most cases.[2]

(b) Cefalotin

A randomised, double-blind study[3] in patients with sepsis found the following incidence of definite nephrotoxicity;

- **gentamicin** with **cefalotin** 30.4% (7 of 23 patients),
- **tobramycin** with **cefalotin** 20.8% (5 of 24),
- **gentamicin** with methicillin 10% (2 of 20),
- **tobramycin** with methicillin 4.3% (1 of 23).

A very considerable number of studies and case reports confirm an increase in the incidence of nephrotoxicity when **gentamicin**[2,4-14] or **tobramycin**[15,16] are used with **cefalotin**. However, some other studies have found no increase in nephrotoxicity with the combination.[17-20]

(c) Other cephalosporins

The nephrotoxicity of various combinations of antibacterials was assessed in 171 patients with cancer. In those receiving an aminoglycoside with a third generation cephalosporin, the most nephrotoxic combinations were found to be **gentamicin** with **cefotaxime** (although another study did not find this combination to be nephrotoxic[21]) and **amikacin** with **ceftriaxone**, where 5 of 20 and 5 of 13 patients, respectively, had increased serum creatinine. The following combinations were found to be safer: **amikacin** with **cefoxitin** or **ceftazidime**; **gentamicin** with **cefoxitin**; and **netilmicin** with **cefotaxime**.[22]

Another study assessing the risk factors for nephrotoxicity with aminoglycosides (**tobramycin** and **gentamicin**) enrolled 1489 patients, 157 of whom developed clinical nephrotoxicity. Of these patients 118 had no immediately identifiable cause (such as acute renal failure) and further evaluation of other risk factors found that the concurrent use of cephalosporins (including **cefazolin**, **cefotaxime**, **cefoxitin**, **cefamandole**, **cefuroxime**, **ceftriaxone**, and **ceftazidime**) significantly increased the risk of nephrotoxicity.[23]

Other adverse effects have also been reported. Hypokalaemia has also been described in patients taking cytotoxic drugs for leukaemia when they were given **gentamicin** and **cefalexin**,[24] and a study in healthy subjects found that **ceftazidime** may increase the levels of **amikacin**.[25]

In contrast, some studies have reported no adverse interactions between;

- **amikacin** and **cefepime**[26]
- **gentamicin** and **cefuroxime**,[27] or **cefazolin**,[20]
- **tobramycin** and **cefuroxime**,[28] **cefotaxime**,[29] **ceftazidime**[30] or **cefazolin**.[20]

Mechanism

Uncertain. The nephrotoxic effects of gentamicin and tobramycin are well documented, and some (mostly older) cephalosporins are known to be nephrotoxic, especially in high dose. However, it appears that doses that are well tolerated separately can become nephrotoxic when given together.[11]

Importance and management

The interaction between gentamicin and cefalotin is very well documented and potentially serious: there is less information about tobramycin with cefalotin, but they appear to interact similarly. The risk of nephrotoxicity is probably greatest if high doses of cefalotin are used in those with some existing renal impairment. One study suggests that short courses of treatment are sometimes justified,[12] but renal function should be very closely monitored and doses kept to a minimum. The combination of any aminoglycoside and cefalotin is probably best avoided in high-risk patients wherever possible.

The interaction between other aminoglycosides or cephalosporins is less well documented, but what is known suggests that they can, on occasion, interact similarly. Risk factors for this interaction are said to include raised aminoglycoside trough levels, decreased albumin, male gender, advanced age, increased length of treatment, liver disease or ascites, and some other diseases, including leukaemia,[23,31] although their significance in practice has been questioned.[23] It seems likely that the routine monitoring of renal function that is advised with aminoglycosides should be adequate to detect any interaction, but if renal impairment develops the contribution of an interaction should be considered.

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16. Klastersky J, Hensgens C, Debusscher L. Empiric therapy for cancer patients: comparative study of ticarcillin-tobramycin, ticarcillin-cephalothin, and cephalothin-tobramycin. *Antimicrob Agents Chemother* (1975) 7, 640–45.
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Aminoglycosides + Clindamycin

Three cases of acute renal failure have been tentatively attributed to the use of gentamicin with clindamycin, and another report identified the combination as a risk factor for nephrotoxicity. However, other reports note no increased risk of nephrotoxicity when gentamicin or tobramycin was given with clindamycin.

Clinical evidence, mechanism, importance and management

Acute renal failure has been reported in 3 patients with normal renal function when they were given **gentamicin** 3.9 to 4.9 mg/kg daily and clindamycin 0.9 to 1.8 mg/kg daily for 13 to 18 days. They recovered within 3 to 5 days of discontinuing the antibacterials[1] but in one patient acute renal failure only developed after the clindamycin was stopped. The reasons for the renal failure are not known, but given the long courses of **gentamicin** involved, the possibility that renal impairment occurred as an adverse effect of the aminoglycoside alone cannot be excluded. However, one report identified the concurrent use of clindamycin as one of several factors that increased the risk of aminoglycoside-associated nephrotoxicity.[2]

The use of clindamycin with an aminoglycoside seems to be a fairly commonly used combination, especially following abdominal trauma. A study assessing the risk factors for nephrotoxicity with aminoglycosides (**tobramycin** and **gentamicin**) enrolled 1489 patients, 157 of whom developed clinical nephrotoxicity. Of these patients 118 had no immediately identifiable cause (such as acute renal failure) and further evaluation of other risk factors found that the concurrent use of clindamycin was not significantly associated with increased risk of nephrotoxicity.[3] This suggests that treatment with the combination is without nephrotoxic risk above and beyond that seen with an aminoglycoside alone. A short report has also indicated that the combination of **tobramycin** and clindamycin is not nephrotoxic.[4]

As renal function should be routinely monitored during the use of aminoglycosides, no additional precautions would be expected to be necessary if clindamycin is also given.

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Aminoglycosides + Loop diuretics

The concurrent use of aminoglycosides and etacrynic acid should be avoided because their damaging actions on the ear can be additive. Even sequential use may not be safe. Bumetanide and piretanide have been shown to interact similarly in *animals*. Although some patients have developed nephrotoxicity and/or ototoxicity

while taking furosemide and an aminoglycoside, it has not been established that this was as a result of an interaction.

Clinical evidence

(a) Bumetanide

There seem to be no clinical reports of an interaction between aminoglycosides and bumetanide, but ototoxicity has been described in *animals* given **kanamycin** and bumetanide.[1,2]

(b) Etacrynic acid

Four patients with renal impairment became permanently deaf after they were given intramuscular **kanamycin** 1 to 1.5 g and intravenous etacrynic acid 50 to 150 mg. One patient also received **streptomycin**, and another also received oral **neomycin**. Deafness took between 30 minutes and almost 2 weeks to develop. In some cases deafness developed despite the doses being given on separate days, and in all cases it appeared irreversible.[3] A patient receiving **gentamicin** rapidly developed deafness when furosemide was replaced by intravenous etacrynic acid.[4]

There are other reports describing temporary, partial or total permanent deafness as a result of giving intravenous etacrynic acid with **gentamicin**,[5] intramuscular **kanamycin**,[5-7] oral **neomycin**,[8] or **streptomycin**.[6,9]

(c) Furosemide

An analysis of three, controlled, randomised, studies found that furosemide did not increase either aminoglycoside-induced nephrotoxicity, or ototoxicity: the aminoglycosides used were **amikacin**, **gentamicin**, and **tobramycin**. Nephrotoxicity developed in 20% (10 of 50 patients) given furosemide and 17% (38 of 222) not given furosemide. Auditory toxicity developed in 22% (5 of 23) given furosemide and 24% (28 of 119) not given furosemide.[4] Other clinical studies similarly suggest that furosemide does not increase aminoglycoside-associated renal damage.[10,11]

In contrast, a study assessing the risk factors for nephrotoxicity with aminoglycosides (**tobramycin** and **gentamicin**) enrolled 1489 patients, 157 of whom developed clinical nephrotoxicity. Of these patients 118 had no immediately identifiable cause (such as acute renal failure) and further evaluation of other risk factors found that the concurrent use of furosemide increased the risk of nephrotoxicity.[12] A clinical study evaluating a possible interaction also found that furosemide increased aminoglycoside-induced renal damage,[13] and there are clinical reports claiming that concurrent use results in ototoxicity, but usually only small numbers of patients were involved and control groups were not included.[14-18] A retrospective study of neonates suggested the possibility of increased ototoxicity but no firm conclusions could be drawn.[19]

Studies in patients and healthy subjects have found that furosemide reduces the renal clearance of **gentamicin**[20,21] and can cause a rise in both serum **gentamicin**[21] and **tobramycin** levels.[22] In contrast, a study in 6 healthy subjects found that although the AUC of a single parenteral 1-mg/kg dose of **gentamicin** was not affected by the administration of a single 0.25-mg/kg dose of furosemide, its clearance was increased during the first 3 hours The authors suggest that the observed increased clearance may reduce the nephrotoxic potential of this combination in patients with normal renal function.[23]

Ototoxicity has been described in *animals* given **kanamycin** and furosemide.[1,2]

(d) Piretanide

A study in 6 healthy subjects found that although the AUC of a single parenteral 1-mg/kg dose of **gentamicin** was not affected by the use of a single 0.1-mg/kg dose of piretanide, its clearance was increased during the first 3 hours. The authors suggest that the observed increased clearance may reduce the nephrotoxic potential of this combination in patients with normal renal function.[23]

Ototoxicity has been described in *animals* given **kanamycin** and piretanide.[24]

Mechanism

Aminoglycosides or etacrynic acid alone can damage the ear and cause deafness, the site of action of the aminoglycosides being the hair cell and that of etacrynic acid the stria vascularis. It appears that the effects of concurrent use are additive. Other loop diuretics can similarly damage hearing. *Animal* studies have shown that intramuscular neomycin can cause a fivefold increase in the concentration of etacrynate in cochlear tissues, and it is possible that the aminoglycoside has some effect on the tissues, which allows the etacrynic acid to penetrate more easily.[25] Similar results have been found with gentamicin.[26]

Importance and management

The interaction between etacrynic acid and the aminoglycosides is well established and well documented. The concurrent or sequential use of etacrynic acid with parenteral aminoglycosides should be avoided because permanent deafness may result. Patients with renal impairment seem to be particularly at risk, most likely because the drugs are less rapidly cleared. Most of the reports describe deafness after intravenous use, but it has also been seen when etacrynic acid is given orally alone.[9] If it is deemed absolutely necessary to use etacrynic acid and an intravenous aminoglycoside, minimal doses should be used and the effects on hearing should be monitored continuously. Not every aminoglycoside has been implicated, but their ototoxicity is clearly established and they may be expected to interact in a similar way. For this reason the same precautions should be used.

Although there is ample evidence of an adverse interaction between furosemide and aminoglycosides in *animals*,[2,27] the weight of clinical evidence suggests that furosemide does not normally increase either the nephrotoxicity or ototoxicity of the aminoglycosides. Nevertheless as there is still some uncertainty about the safety of concurrent use it would be prudent to monitor for any evidence of changes in aminoglycoside serum levels, and renal or hearing impairment. The authors of the major study cited[4] suggest that an interaction may possibly occur if high dose infusions of furosemide are used. The same precautions would seem to be appropriate with bumetanide and piretanide. Note that it is generally advised that aminoglycosides should not be used with other drugs that may cause ototoxicity or nephrotoxicity, such as etacrynic acid and furosemide, but in some cases concurrent use may be unavoidable.

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Aminoglycosides + Magnesium compounds

A neonate with elevated serum magnesium levels had a respiratory arrest when given gentamicin.

Clinical evidence

An infant born to a woman whose pre-eclampsia had been treated with magnesium sulfate was found to have muscle weakness and a serum magnesium concentration of 1.77 mmol/L. The neonate was given ampicillin 100 mg/kg intravenously and **gentamicin** 2.5 mg/kg intramuscularly every 12 hours, starting 12 hours after birth. Soon after the second dose of **gentamicin** she stopped breathing and needed intubation. The **gentamicin** was stopped and the child improved.[1] *Animal* studies support this interaction.[1]

Mechanism

Magnesium ions and the aminoglycosides have neuromuscular blocking activity, which can be additive (see also 'Neuromuscular blockers + Magnesium compounds', p.139 and 'Neuromuscular blockers + Aminoglycosides', p.127). In the case cited here it seems that it was enough to block the actions of the respiratory muscles.

Importance and management

Direct information about this interaction is very limited, but it is well supported by the recognised pharmacological actions of magnesium and the aminoglycosides, and their interactions with conventional neuromuscular blockers. The aminoglycosides as a group should be avoided in hypermagnesaemic infants needing antibacterial treatment. If this is not possible, the effects on respiration should be closely monitored.

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Aminoglycosides + Miconazole

A report describes a reduction in tobramycin levels, which was attributed to the use of miconazole.

Clinical evidence, mechanism, importance and management

In 9 patients undergoing bone marrow transplantation intravenous miconazole significantly lowered the peak serum **tobramycin** levels, from 9.1 micrograms/mL to 6.7 micrograms/mL. Six patients needed **tobramycin** dose adjustments.[1] Miconazole was stopped in 4 patients, and **tobramycin** pharmacokinetic parameters returned to normal 4 to 8 days later. The reasons for this interaction are not understood. Although the use of **tobramycin** should be well monitored it would be prudent to increase the frequency in patients also given systemic miconazole (note that miconazole oral gel can have significant systemic absorption). There does not appear to be any information about other aminoglycosides and azole antifungals.

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Aminoglycosides + NSAIDs

There are conflicting reports as to whether or not serum gentamicin and amikacin levels are raised by indometacin or ibuprofen in premature infants.

Clinical evidence

(a) Amikacin

A study in 10 preterm infants with gestational ages ranging from 25 to 34 weeks, who were given amikacin, found that the use of **indometacin** 200 micrograms/kg every 8 hours, for up to 3 doses, caused a rise in the serum levels of amikacin. Trough and peak levels of amikacin were raised by 28% and 17%, respectively.[1]

In another study, preterm infants were given amikacin 20 mg/kg every 36 hours (gestational age less than 30 weeks) or every 24 hours (gestational age 30 to 31 weeks) with either **ibuprofen lysine** 10 mg/kg within 6 hours of birth, then a further 5 mg/kg dose 24 and 48 hours later, or placebo. The half-life of amikacin was increased from 12.4 hours to 16.4 hours and its clearance was reduced by 40% in infants who also received intravenous **ibuprofen lysine**.[2] Reductions in amikacin clearance, independent of gestational age were found by the same authors in another study in which preterm infants with gestational ages of between 24 and 34 weeks were given amikacin and **ibuprofen**.[3]

In contrast, another study in preterm infants given amikacin found no changes in its pharmacokinetics when **ibuprofen** or **indometacin** were given.[4]

(b) Gentamicin

A study in 10 preterm infants with gestational ages ranging from 25 to 34 weeks, who were given gentamicin, found that the use of **indometacin** 200 micrograms/kg every 8 hours, for up to 3 doses, caused a rise in the serum levels of gentamicin. Trough and peak levels of gentamicin were raised by 48% and 33%, respectively.[1] A later study[5] confirmed that **indometacin** (200 micrograms/kg given intravenously at 0 hours, then 100 micrograms/kg given at 12 hours and then 36 hours) decreased the clearance of 3-mg/kg daily doses of gentamicin by 23% in preterm infants weighing less than 1250 g.

In contrast, 8 out of 13 infants had no increase in their serum gentamicin levels when they were given **indometacin** 200 to 250 micrograms/kg every 12 hours for 3 doses. Of the remaining 5, slight to moderate rises occurred in 4, and a substantial rise occurred in just one.[6] In another study no significant changes in serum gentamicin levels were seen in 31 preterm newborns given parenteral **indometacin** 200 micrograms/kg every 12 hours for 3 doses.[7]

Mechanism

Aminoglycosides are excreted by renal filtration, which can be inhibited by indometacin or ibuprofen. This may result in the retention of the aminoglycoside.

Importance and management

Information seems to be limited to these conflicting studies, although supporting evidence for indometacin comes from the fact that it also causes the retention of digoxin in premature infants. The authors of one of the studies[6] suggest that the different results may be because aminoglycoside serum levels were lower in their study before the indometacin was given, and also because they measured the new steady-state levels after 40 to 60 hours instead of 24 hours. Whatever the explanation, concurrent use should be very closely monitored because toxicity is associated with raised aminoglycoside serum levels. It has been suggested that the aminoglycoside dose should be reduced before giving indometacin and aminoglycoside levels and renal function should be well monitored during concurrent use.[1] It has also been suggested that the dose interval of amikacin should be increased by at least 6 to 8 hours if ibuprofen lysine is also given during the first days of life.[2] Other aminoglycosides possibly behave similarly. This interaction does not seem to have been studied in adults.

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Aminoglycosides + Penicillins

The use of piperacillin is reported to be a risk factor for aminoglycoside-associated nephrotoxicity. A reduction in serum aminoglycoside levels can occur if aminoglycosides and penicillins are

given to patients with severe renal impairment. No pharmacokinetic interaction of importance appears to occur with intravenous aminoglycosides and penicillins in those with normal renal function.
The serum levels of oral phenoxymethylpenicillin can be halved by oral neomycin.

Clinical evidence

A. Intravenous or intramuscular aminoglycosides

(a) Patients with renal impairment

A study in 6 patients with renal failure requiring dialysis, who were receiving intravenous **carbenicillin** 8 to 15 g daily in 3 to 6 divided doses, found that in the presence of the penicillin, serum **gentamicin** levels did not exceed 4 micrograms/mL. When the **carbenicillin** was stopped, serum **gentamicin** levels rose.[1]

Other reports similarly describe unusually low **gentamicin** levels in patients with impaired renal function, given **carbenicillin**,[2-5] **piperacillin**,[6] or **ticarcillin**.[3,5,7] The half-life of **gentamicin** has been reported to be reduced by **carbenicillin** or **piperacillin** by about one-half or one-third.[3,6,8] Similarly, unusually low **tobramycin** levels have been reported in patients with impaired renal function, who were given **carbenicillin**,[1] **piperacillin**[9] or **ticarcillin**.[7]

In 3 patients receiving long-term haemodialysis, **piperacillin** doubled the clearance of **tobramycin** 2 mg/kg, and reduced its half-life from 73 hours to 22 hours.[10] In one patient, the half-life of **tobramycin** was reduced from an expected 70 hours to 10.5 hours, and the serum level of **tobramycin** was unexpectedly low, when **piperacillin** was given.[9]

In contrast one study found that **piperacillin** or **piperacillin** with **tazobactam** did not affect the pharmacokinetics of **tobramycin** in subjects with renal impairment.[11] Similarly, **piperacillin** 4 g every 12 hours did not affect the pharmacokinetics of **netilmicin** 2 mg/kg in 3 patients receiving long-term haemodialysis.[10]

(b) Patients with normal renal function

A patient with normal renal function was given **gentamicin** 80 mg intravenously, with and without **carbenicillin** 4 g. The serum **gentamicin** concentration profiles in both cases were very similar.[2] No interaction was seen in 10 patients given **tobramycin** with **piperacillin**,[12] or in another 10 healthy subjects given daily **gentamicin** and **piperacillin** with **tazobactam**.[13] Only minimal pharmacokinetic changes were seen in 9 healthy subjects given **tobramycin** and **piperacillin** with **tazobactam**,[14] and 18 patients with cystic fibrosis (adults and children) given **tobramycin** with **ticarcillin**.[15] However, a study assessing the risk factors for nephrotoxicity with aminoglycosides (**tobramycin** and **gentamicin**) enrolled 1489 patients, 157 of whom developed clinical nephrotoxicity. Of these patients 118 had no immediately identifiable cause (such as acute renal failure) and further evaluation of other risk factors found that the concurrent use of **piperacillin**, but not **ticarcillin** or **carbenicillin** increased the risk of nephrotoxicity.[16]

B. Oral aminoglycosides

In 5 healthy subjects the serum concentrations of a 250-mg oral dose of **phenoxymethylpenicillin** were reduced by more than 50% after they took **neomycin** 3 g four times daily for 7 days. Normal penicillin pharmacokinetics were not seen until 6 days after the **neomycin** was withdrawn.[17]

Mechanism

The nephrotoxic effects of gentamicin and tobramycin are well documented. The reason why piperacillin but not carbenicillin or ticarcillin appears to increase the risk of nephrotoxicity in patients with normal renal function is not clear. One suggestion is that sodium loading may protect the kidney from tobramycin toxicity and piperacillin has only 40% as much sodium as ticarcillin.[16]

In vitro, the amino groups on the aminoglycosides and the beta-lactam ring on the penicillins interact chemically to form biologically inactive amides.[18] It has been suggested that this reaction may also occur in the plasma, causing a drop in the levels of active antibacterial.[8] The interaction occurs in those with poor renal function as the drugs persist in the plasma for longer, allowing a greater time for inactivation. This therefore means that the drug is lost more rapidly than has been accounted for by the renal function, and consequently lower than expected levels of the antibacterial result. However, the lack of interaction found in one study led to the conclusion that reported interactions in renal impairment may be due to *in vitro* inactivation after sample collection.[11]

In the case of phenoxymethylpenicillin, the levels are probably lowered because oral neomycin can cause a reversible malabsorption syndrome (histologically similar to nontropical sprue).

Importance and management

The concurrent use of piperacillin and aminoglycosides is reported to be a risk factor for nephrotoxicity in patients with normal renal function.[16,19] The nephrotoxic effects of gentamicin and tobramycin are well documented. Risk factors for nephrotoxicity include raised aminoglycoside trough levels, decreased albumin, male gender, advanced age, increased length of treatment, liver disease or ascites, and some other diseases, including leukaemia,[16,19] although their significance in practice has been questioned.[16] Renal function should be monitored if an aminoglycoside is given, but it may be prudent to increase the frequency of this monitoring if piperacillin is also given.

Other reports suggest that a pharmacokinetic interaction between parenteral aminoglycosides and piperacillin or other penicillins, resulting in reduced levels of the aminoglycoside, seems to occur in patients with renal impairment. In those cases where concurrent use is thought necessary, it has been recommended that the serum levels of both antibacterials are closely monitored.[1] However, note that antibacterial inactivation can continue in the assay sample, and one author[20] suggests that rapid assay is necessary, while others[11] note the importance of protecting samples against further inactivation. There would seem to be no reason for avoiding concurrent use in patients with normal renal function because no significant *in vivo* inactivation appears to occur. Moreover there is good clinical evidence that concurrent use is valuable, especially in the treatment of Pseudomonas infections.[2,21]

Evidence for an interaction between oral neomycin and penicillins seems limited to the report about phenoxymethylpenicillin, and its clinical significance is unclear. It seems possible that oral **kanamycin** and **paromomycin** might interact similarly, but this needs confirmation.

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Aminoglycosides + Polygeline (*Haemaccel*)

The incidence of acute renal failure appears to be increased in cardiac surgical patients given polygeline (*Haemaccel*) with gentamicin.

Clinical evidence

The observation of a differing incidence of acute renal failure in patients undergoing coronary artery bypass surgery in two similar units, prompted a retrospective review of patient records. This showed that the only management differences were related to antibacterial prophylaxis and the bypass prime content (i.e. the solution used to prime the cardiopulmonary bypass circuit). Acute renal failure was defined as a more than 50% rise in serum creatinine on the first postoperative day in those patients whose creatinine was also greater than 120 micromol/L. Four groups of patients were identified, and the incidence of renal failure was as follows:

Group A: (polygeline plus **gentamicin** and flucloxacillin) 31% (28 of 91 patients);

Group B: (polygeline plus cefalotin)12% (9 of 72 patients);

Group C: (crystalloid plus **gentamicin** and flucloxacillin) 7% (4 of 57 patients);

Group D: (crystalloid plus cefalotin) 2% (1 of 47 patients).

Polygeline (*Haemaccel*) 1 litre, which is a urea linked gelatin colloid with a calcium concentration of 6.25 micromol/L, was used for groups A and B, with crystalloid - Hartmann's solution or Ringer's injection (calcium concentration 2 mmol/L) to make up the rest of the prime volume of 2 litres. Groups C and D received only crystalloid (no polygeline) in the prime. Albumin 100 mL was used in groups B and D.[1] However, the study has been criticised because other drugs that affect renal function (such as ACE inhibitors, cimetidine, NSAIDs or clonidine), which may have been taken by the patients were not considered.[2] This criticism has been refuted because of the large sample size involved.[3]

Mechanism

Not fully understood. It is thought that the relatively high calcium content of the polygeline may have potentiated gentamicin-associated nephrotoxicity. Hypercalcaemia has been shown in *animals* to increase aminoglycoside-induced nephrotoxicity.[4]

Importance and management

Information appears to be limited to this clinical study and *animal* studies, but the evidence available suggests that a clinically important adverse interaction occurs between these drugs. The incidence of acute renal failure in cardiac surgery patients is normally about 3 to 5%[5] which is low compared with the 31% shown by those given polygeline and gentamicin. The authors of the study advise avoidance of these two drugs. More study is needed.

1. Schneider M, Valentine S, Clarke GM, Newman MAJ, Peakcock J. Acute renal failure in cardiac surgical patients potentiated by gentamicin and calcium. *Anaesth Intensive Care* (1996) 24, 647–50.
2. Bolsin S, Jones S. Acute renal failure potentiated by gentamicin and calcium. *Anaesth Intensive Care* (1997) 25, 431–2.
3. Schneider M, Clarke GM, Valentine SJ, Peakcock J. Acute renal failure potentiated by gentamicin and calcium; reply. *Anaesth Intensive Care* (1997) 25, 432.
4. Elliott WC, Patchin DS, Jones DB. Effect of parathyroid hormone activity on gentamicin nephrotoxicity. *J Lab Clin Med* (1987) 109, 48–54.
5. Hilberman M, Myers BD, Carrie BJ, Derby G, Jamison RL, Stinson EB. Acute renal failure following cardiac surgery. *J Thorac Cardiovasc Surg* (1979) 77, 880–8.

Aminoglycosides + Vancomycin

The nephrotoxicity of the aminoglycosides appears to be potentiated by vancomycin.

Clinical evidence, mechanism, importance and management

A retrospective review of 105 patients who had received an aminoglycoside with vancomycin for at least 5 days found that nephrotoxicity occurred in 27% of the patients. Of these, 6 had no other identifiable cause for nephrotoxicity.[1] A study assessing the risks factors for nephrotoxicity with aminoglycosides (**tobramycin** and **gentamicin**) enrolled 1489 patients, 157 of whom developed clinical nephrotoxicity. Of these patients 118 had no immediately identifiable cause (such as acute renal failure) and further evaluation of other risk factors found that the concurrent use of vancomycin increased the risk of nephrotoxicity.[2]

A number of other studies,[3-9] including those where patients have had individualised pharmacokinetic monitoring,[3] and those using both once daily and multiple daily dosing,[4] have all found that vancomycin independently increases the risk of nephrotoxicity in patients receiving aminoglycosides. In one meta-analysis of 8 studies, the incidence of nephrotoxicity with the combination was 4.3% greater than with aminoglycosides alone and 13.3% greater than with vancomycin alone.[8]

Risk factors are said to include vancomycin peak and trough levels,[1,6] aminoglycoside trough levels,[1,3,6] decreased albumin concentrations,[2] male gender,[1-3] advanced age,[1-3] increased length of treatment,[1-3] liver disease or ascites,[1,2] as well as a large number of other disease states (such as leukaemia,[2] peritonitis[1] or neutropenia),[1] although their significance in practice has been questioned.[2]

The concurrent use of these antibacterials is therapeutically useful, but the risk of increased nephrotoxicity should be borne in mind. Therapeutic drug monitoring and regular assessment of renal function is warranted, as is recommended with the use of either drug alone.

1. Pauly DJ, Musa DM, Lestico MR, Lindstrom MJ, Hetsko CM. Risk of nephrotoxicity with combination vancomycin-aminoglycoside antibiotic therapy. *Pharmacotherapy* (1990) 10, 378–82.
2. Bertino JS, Booker LA, Franck PA, Jenkins PL, Franck KR, Nafziger AN. Incidence of and significant risk factors for aminoglycoside-associated nephrotoxicity in patients dosed by using individualized pharmacokinetic monitoring. *J Infect Dis* (1993) 167, 173–9.
3. Streetman DS, Nafziger AN, Destache CJ, Bertino JS. Individualized pharmacokinetic monitoring results in less aminoglycoside-associated nephrotoxicity and fewer associated costs. *Pharmacotherapy* (2001) 21, 443–51.
4. Rybak MJ, Abate BJ, Kang SL, Ruffing MJ, Lerner SA, Drusano GL. Prospective evaluation on the effect of an aminoglycoside dosing regimen on rates of observed nephrotoxicity and ototoxicity. *Antimicrob Agents Chemother* (1999) 43, 1549–55.
5. Farber BF, Moellering RC. Retrospective study of the toxicity of preparations of vancomycin from 1974 to 1981. *Antimicrob Agents Chemother* (1983) 23, 138–41.
6. Cimino MA, Rotstein C, Slaughter RL, Emrich LJ. Relationship of serum antibiotic concentrations to nephrotoxicity in cancer patients receiving concurrent aminoglycoside and vancomycin therapy. *Am J Med* (1987) 83, 1091–7.
7. Rybak MJ, Frankowski JJ, Edwards DJ, Albrecht LM. Alanine aminopeptidase and β_2-microglobulin excretion in patients receiving vancomycin and gentamicin. *Antimicrob Agents Chemother* (1987) 31, 1461–4.
8. Goetz MB, Sayers J. Nephrotoxicity of vancomycin and aminoglycoside therapy separately and in combination. *J Antimicrob Chemother* (1993) 32, 325–34.
9. Rybak MJ, Albrecht LM, Boike SC, Chandrasekar PH. Nephrotoxicity of vancomycin, alone and with an aminoglycoside. *J Antimicrob Chemother* (1990) 25, 679–87.

Aminoglycosides + Verapamil

Verapamil appears to protect the kidney from damage caused by gentamicin.

Clinical evidence, mechanism, importance and management

In a comparative study, 9 healthy subjects were given **gentamicin** alone (2 mg/kg loading dose, followed by doses every 8 hours to achieve a peak concentration of 5.5 mg/L and a trough concentration of 0.5 mg/L), and 6 other subjects were given the same dose of **gentamicin** with sustained-release verapamil 180 mg twice daily. The **gentamicin** AUCs of the two groups were virtually the same but the 24-hour urinary excretion of alanine aminopeptidase (AAP) was modestly reduced, by 18%, in the group given verapamil. The reduction in AAP excretion was particularly marked during the first 6 days.[1] The significance of urinary AAP is that this enzyme is found primarily in the brush border membranes of the proximal renal tubules, and its excretion is an early and sensitive marker of renal damage. Thus it seems that verapamil may modestly protect the kidneys from damage by **gentamicin**, but using a drug as potentially toxic as verapamil to provide this protection, when the risks of renal toxicity can be minimised by carefully controlling the **gentamicin** dose, is unwarranted. Information about other aminoglycosides and other calcium-channel blockers seems to be lacking.

1. Kazierad DJ, Wojcik GJ, Nix DE, Goldfarb AL, Schentag JJ. The effect of verapamil on the nephrotoxic potential of gentamicin as measured by urinary enzyme excretion in healthy volunteers. *J Clin Pharmacol* (1995) 35, 196–201.

Aminoglycosides; Amikacin + Dopamine

Dopamine probably does not alter the clearance of amikacin in premature infants.

Clinical evidence, mechanism, importance and management

A retrospective review of the amikacin levels achieved in 240 premature infants found that the median amikacin clearance in infants given dopamine was lower than in infants who did not receive dopamine. However, when the birth weight, gestational age, or use of non-selective COX inhibitors was considered, the change in clearance caused by dopamine was no longer significant.[1] The requirement for dopamine may indicate other medical issues that also have an impact on the clearance of amikacin, and it is therefore essential that doses of amikacin for such infants are individualised.

1. Allegaert K, Debeer A, Cossey V, Rayyan M, Devlieger H. Dopamine is not an independent risk factor for reduced amikacin clearance in extremely low-birth-weight infants. *Pediatr Crit Care Med* (2006) 7, 143–6.

Aminoglycosides; Tobramycin + Sucralfate

An *in vitro* study with tobramycin found that it became markedly and irreversibly bound to sucralfate at the pH values found in the gut. This suggests that the efficacy of tobramycin in gut decontamination might be decreased.

Clinical evidence, mechanism, importance and management

To simulate what might happen in the gut, tobramycin 50 mg/mL was mixed with sucralfate 500 mg in 40 mL of water at pH 3.5 and allowed to stand for 90 minutes at 25°C. Analysis of the solution showed that the tobramycin concentration fell rapidly and progressively over 90 minutes to about 1%. When the pH of the mixture was then raised to 6.5 to 7 for 90 minutes, there was no change in the concentration of tobramycin, suggesting that the interaction was irreversible.[1] The reason for this change is not known, but the authors of the study suggest that sucralfate forms insoluble chelates with tobramycin.[1]

It is not known how important this interaction is likely to be in practice, but the efficacy of tobramycin in gut decontamination may be decreased. Separating the doses of tobramycin and sucralfate might not be effective in some postoperative patients because their gastric function may not return to normal for up to 5 days, and some sucralfate might still be present when the next dose is given.[1] More study is needed to find out whether this interaction is clinically important, but in the meanwhile it would seem prudent to monitor concurrent use carefully, being alert for any evidence of reduced effects.

1. Feron B, Adair CG, Gorman SP, McClurg B. Interaction of sucralfate with antibiotics used for selective decontamination of the gastrointestinal tract. *Am J Hosp Pharm* (1993) 50, 2550–3.

Aminosalicylic acid + Antacids

An aluminium/magnesium hydroxide antacid had no significant effect on the pharmacokinetics of aminosalicylic acid in one study.

Clinical evidence, mechanism, importance and management

In a study, 12 healthy subjects were given a single 6-g dose of aminosalicylic acid with cycloserine, ethionamide and clofazimine, after an overnight fast, or with 15 mL of maximum strength ***Mylanta***, containing **aluminium/magnesium hydroxide** 400/400 mg and **simeticone** 40 mg/5 mL. The antacid had no significant effect on the pharmacokinetics of aminosalicylic acid.[1] No adjustments to the timing of dosing would therefore appear to be necessary if both drugs are given.

1. Peloquin CA, Zhu M, Adam RD, Singleton MD, Nix DE. Pharmacokinetics of para-aminosalicylic acid granules under four dosing conditions. *Ann Pharmacother* (2001) 35, 1332–8.

Aminosalicylic acid + Diphenhydramine

Diphenhydramine can cause a small reduction in the absorption of aminosalicylic acid from the gut.

Clinical evidence, mechanism, importance and management

A study in 9 healthy subjects[1] found that diphenhydramine 50 mg given intramuscularly 10 minutes before a 2-g oral dose of aminosalicylic acid, reduced the mean peak serum aminosalicylic acid levels by about 15%. This effect may occur because diphenhydramine reduces peristalsis in the gut, which in some way reduces aminosalicylic acid absorption. The extent to which diphenhydramine or any other anticholinergic drug diminishes the therapeutic response to long-term treatment with aminosalicylic acid is uncertain, but it is probably small.

1. Lavigne J-G, Marchand C. Inhibition of the gastrointestinal absorption of p-aminosalicylate (PAS) in rats and humans by diphenhydramine. *Clin Pharmacol Ther* (1973) 14, 404–12.

Aminosalicylic acid + Food

A high-fat meal increases the extent of absorption of aminosalicylic acid. Orange juice appears to have no significant effect on the pharmacokinetics of aminosalicylic acid.

Clinical evidence, mechanism, importance and management

In a study, 12 healthy subjects were given a single 6-g dose of aminosalicylic acid with cycloserine, ethionamide and clofazimine, after an overnight fast, with **orange juice** or a high-fat meal. The high-fat meal increased the maximum aminosalicylic acid plasma level and AUC by 50% and 70%, respectively, when compared with an overnight fast, although there was wide inter-individual variation in the effects of the meal. **Orange juice** had no significant effect on the pharmacokinetics of aminosalicylic acid.[1]

1. Peloquin CA, Zhu M, Adam RD, Singleton MD, Nix DE. Pharmacokinetics of para-aminosalicylic acid granules under four dosing conditions. *Ann Pharmacother* (2001) 35, 1332–8.

Aminosalicylic acid + Probenecid

The plasma levels of aminosalicylic acid can be raised up to fourfold by probenecid.

Clinical evidence, mechanism, importance and management

In a study in 7 patients, probenecid 500 mg every 6 hours increased the plasma levels of aminosalicylic acid 4 g by as much as fourfold.[1] Similar results are described in three other reports.[2-4]

The reasons for this effect are uncertain but it seems probable that probenecid successfully competes with aminosalicylic acid for active excretion by the kidney tubules, which results in the increased aminosalicylic acid levels.

The documentation of this interaction is old but it appears to be established. Such large increases in plasma aminosalicylic acid levels would be expected to lead to toxicity. It also seems possible that the dose of aminosalicylic acid could be reduced without losing the required therapeutic response, but this needs confirmation. Monitoring aminosalicylic acid levels, where possible, would probably be useful. Concurrent use should be undertaken with caution.

1. Boger WP, Pitts FW. Influence of *p*-(Di-n-propylsulfamyl)-benzoic acid, 'Benemid' on para-aminosalicylic acid (PAS) plasma concentrations. *Am Rev Tuberc* (1950) 61, 862–7.
2. Carr DT, Karlson AG, Bridge EV. Concentration of PAS and tuberculostatic potency of serum after administration of PAS with and without Benemid. *Proc Staff Meet Mayo Clin* (1952) 27, 209–15.
3. Breitenbucher RB, Amatuzio DS, Falk A. The effect of probenecid (Benemid) in enhancing para-aminosalicylic acid concentrations in the blood. *Am Rev Tuberc* (1952) 66, 228–32.
4. McLeod JA, Turnbull FWA, Crofton JW. The use of Benemid to enhance blood-levels of sodium para-aminosalicylate (PAS). *Tubercle* (1953) 34, 152–5.

Antibacterials + Immunoglobulins

One *animal* study found that for severe infections antibacterials were less effective in the presence of high-dose immunoglobulin, but this was not seen in less severe infections.

Clinical evidence, mechanism, importance and management

A study in an *animal* model of severe group B streptococcal infection found the following mortalities: 51% with **benzylpenicillin** 200 mg/kg alone, 88% with immunoglobulin and benzylpenicillin, and 100% with immunoglobulin 2 g/kg alone. A smaller dose of immunoglobulin 0.5 g/kg was not associated with an increase in mortality.[1] Roughly similar results were found when the penicillin was replaced by **ceftriaxone**.[1]

In another study using a 1000-fold smaller inoculum of group B streptococci, there was no difference in mortality between **benzylpenicillin** 200 mg/kg daily alone and **benzylpenicillin** with immunoglobulin 0.25 to 2 g/kg, and there was some evidence of a lower incidence of bacteraemia with the combination.[1,2]

Immunoglobulins are used with antibacterials in the successful prevention of infections in clinical practice, and no special precautions appear to be needed in this situation. However, their clinical use for treating established infection is unclear, and the above findings suggest that some caution is warranted.

1. Kim KS. High-dose intravenous immune globulin impairs antibacterial activity of antibiotics. *J Allergy Clin Immunol* (1989) 84, 579–88.
2. Kim KS. Efficacy of human immunoglobulin and penicillin G in treatment of experimental group B streptococcal infection. *Pediatr Res* (1987) 21, 289–92.

Aztreonam + Other antibacterials

There appear to be no clinically significant pharmacokinetic interactions between aztreonam and amikacin, cefradine, clindamycin, gentamicin, metronidazole or nafcillin.

Clinical evidence, mechanism, importance and management

A study in healthy subjects given a single 1-g intravenous dose of aztreonam found that its maximum levels were reduced by 13% and 10% when it was given with **gentamicin** 80 mg and **metronidazole** 500 mg, respectively. Serum bound aztreonam fell by 5% when it was given with **nafcillin** 500 mg and increased by 5% when it was given with **cefradine** 1 g. When aztreonam 1 g and **clindamycin** 600 mg were given together, their renal excretion was increased by 5% and 11%, respectively. None of these changes was statistically significant.[1] Another study in healthy subjects found that the AUC of a 1-g intravenous dose of aztreonam was reduced by 22% by **amikacin** 500 mg, and the AUC of **amikacin** was increased by 27% by aztreonam.[2] These changes are modest and unlikely to be clinically significant in most patients.

1. Creasey WA, Adamovics J, Dhruv R, Platt TB, Sugerman AA. Pharmacokinetic interaction of aztreonam with other antibiotics. *J Clin Pharmacol* (1984) 24, 174–80.
2. Adamis G, Papaioannou MG, Giamarellos-Bourboulis EJ, Gargalianos P, Kosmidis J, Giamarellou H. Pharmacokinetic interactions of ceftazidime, imipenem and aztreonam with amikacin in healthy volunteers. *Int J Antimicrob Agents* (2004) 23, 144–9.

Carbapenems + Probenecid

Probenecid increases the AUC of doripenem and meropenem, but does not appear to interact with ertapenem to a clinically relevant extent.

Clinical evidence, mechanism, importance and management

(a) Doripenem

Probenecid increased the AUC of doripenem by 75% and prolonged its plasma elimination half-life by 53%. The manufacturer does not recommend the concurrent use of doripenem with probenecid.[1]

(b) Ertapenem

The use of probenecid with ertapenem is reported to decrease the renal clearance of unbound ertapenem by about 50%, probably because probenecid inhibits the renal tubular secretion of ertapenem. Probenecid slightly increased the elimination half-life and AUC of ertapenem and therefore concurrent use is considered unlikely to increase the effects of ertapenem.[2]

(c) Meropenem

In 6 healthy subjects probenecid 1 g given orally 2 hours before meropenem and 500 mg given orally 1.5 hours after meropenem, increased the AUC of meropenem 500 mg by 43%.[3] Another study in 6 healthy subjects found that probenecid 1.5 g in divided doses the day before meropenem and 500 mg one hour before meropenem increased the AUC of meropenem 1 g by up to 55% and increased its half-life by 33% (from 0.98 to 1.3 hours).[4] In both studies the serum levels of meropenem were modestly increased. This is possibly because meropenem and probenecid compete for active kidney tubular secretion.[5,6] The manufacturers say that because the potency and duration of meropenem are adequate without probenecid, they do not recommend concurrent use.[5,6]

1. Doribax (Doripenem). Ortho-McNeil Pharmaceuticals Inc. US Prescribing information, May 2009.
2. Nix DE, Majumdar AK, DiNubile MJ. Pharmacokinetics and pharmacodynamics of ertapenem: an overview for clinicians. *J Antimicrob Chemother* (2004) 53 (Suppl S2), ii23–ii28.
3. Ishida Y, Matsumoto F, Sakai O, Yoshida M, Shiba K. The pharmacokinetic study of meropenem: effect of probenecid and hemodialysis. *J Chemother* (1993) 5 (Suppl 1), 124–6.
4. Bax RP, Bastain W, Featherstone A, Wilkinson DM, Hutchison M, Haworth SJ. The pharmacokinetics of meropenem in volunteers. *J Antimicrob Chemother* (1989) 24 (Suppl A), 311–20.
5. Meronem (Meropenem). AstraZeneca UK Ltd. UK Summary of product characteristics, July 2007.
6. Merrem (Meropenem). AstraZeneca. US Prescribing information, July 2009.

Cephalosporins + Acetylcysteine

Acetylcysteine does not alter the pharmacokinetics of cefpodoxime or cefadroxil.

Clinical evidence, mechanism, importance and management

The pharmacokinetics of a single 200-mg dose of **cefpodoxime proxetil** are minimally affected by a single 200-mg dose of acetylcysteine.[1] Similarly, the pharmacokinetics of a single 1-g dose of **cefadroxil** are not significantly altered by acetylcysteine.[2] These interactions are unlikely to be of clinical importance.

1. Kees F, Wellenhofer M, Bröhl K, Grobecker H. Bioavailability of cefpodoxime proxetil with co-administered acetylcysteine. *Arzneimittelforschung* (1996) 46, 435–8.
2. Barkworth MF, Mangold B, Rehm KD, Schmieder G, Töberich H, Vinchenzo A, Weber J, Rübartsch C. Ermittlung der bioverfügbarkeit von cefadroxil bei gleichzeitiger gabe von N-acetylcystein. *Arzneimittelforschung* (1991) 41, 839–43.

Cephalosporins + Antacids

No clinically significant interactions appear to occur between an aluminium/magnesium hydroxide antacid and cefaclor AF, cefalexin, cefetamet pivoxil, cefixime or cefprozil; between *Alka-Seltzer* and cefixime; or between ceftibuten and *Mylanta*. In contrast, antacids reduce the bioavailability of cefpodoxime proxetil.

Clinical evidence, mechanism, importance and management

(a) Cefaclor

A study with cefaclor AF (a formulation with a slow rate of release) found that an **aluminium/magnesium hydroxide** antacid (*Maalox*) given one hour after the cefaclor AF to fed subjects reduced the AUC by 18%.[1] This reduction is small and unlikely to be clinically important.

(b) Cefalexin

An **aluminium/magnesium hydroxide** antacid (*Maalox*) given as 8 doses of 10 mL on day one and 2 doses of 10 mL on day 2, had only small and therapeutically unimportant effects on the pharmacokinetics of cefalexin 1 g.[2]

(c) Cefetamet pivoxil

Cefetamet pivoxil 1 g was given to 18 healthy subjects after breakfast with or without 80 mL of an **aluminium/magnesium hydroxide** antacid (*Maalox 70*) given the evening before, 2 hours before, and after breakfast. The pharmacokinetics of the cefetamet were unaffected by the antacid.[3]

(d) Cefixime

An **aluminium/magnesium hydroxide** antacid (*Maalox*) and ***Alka-Seltzer*** (aspirin, calcium phosphate, citric acid and **sodium bicarbonate**) do not significantly affect the absorption of cefixime,[4,5]

(e) Cefpodoxime proxetil

A study in 10 healthy subjects found that 10 mL of an **aluminium/magnesium hydroxide** antacid (*Maalox*) reduced the bioavailability of cefpodoxime proxetil by about 40%. This was considered to be due to reduced dissolution at increased gastric pH values.[6] These results confirm the findings of a previous study with **sodium bicarbonate** and **aluminium hydroxide**.[7] It has been recommended that cefpodoxime is given at least 2 hours after antacids.[6]

(f) Cefprozil

An **aluminium/magnesium hydroxide** antacid (*Maalox*) does not affect the bioavailability of cefprozil.[8]

(g) Ceftibuten

In 18 healthy subjects, 60 mL of an antacid containing **aluminium/magnesium hydroxide** plus **simeticone** (*Mylanta II*) was found not to affect the pharmacokinetics of ceftibuten 400 mg.[9]

1. Satterwhite JH, Cerimele BJ, Coleman DL, Hatcher BL, Kisicki J, DeSante KA. Pharmacokinetics of cefaclor AF: effects of age, antacids and H_2-receptor antagonists. *Postgrad Med J* (1992) 68 (Suppl 3), S3–S9.
2. Deppermann K-M, Lode H, Höffken G, Tschink G, Kalz C, Koeppe P. Influence of ranitidine, pirenzepine, and aluminum magnesium hydroxide on the bioavailability of various antibiotics, including amoxicillin, cephalexin, doxycycline and amoxicillin-clavulanic acid. *Antimicrob Agents Chemother* (1989) 33, 1901–1907.
3. Blouin RA, Kneer J, Ambros RJ, Stoeckel K. Influence of antacid and ranitidine on the pharmacokinetics of oral cefetamet pivoxil. *Antimicrob Agents Chemother* (1990) 34, 1744–8.
4. Petitjean O, Brion N, Tod M, Montagne A, Nicolas P. Étude de l'interaction pharmacocinétique entre le céfixime et deux antiacides. Résultats préliminaires. *Presse Med* (1989) 18, 1596–8.
5. Healy DP, Sahai JV, Sterling LP, Racht EM. Influence of an antacid containing aluminum and magnesium on the pharmacokinetics of cefixime. *Antimicrob Agents Chemother* (1989) 33, 1994–7.
6. Saathoff N, Lode H, Neider K, Depperman KM, Borner K, Koeppe P. Pharmacokinetics of cefpodoxime proxetil and interactions with an antacid and an H_2 receptor antagonist. *Antimicrob Agents Chemother* (1992) 36, 796–800.
7. Hughes GS, Heald DL, Barker KB, Patel RK, Spillers CR, Watts KC, Batts DH, Euler AR. The effects of gastric pH and food on the pharmacokinetics of a new oral cephalosporin, cefpodoxime proxetil. *Clin Pharmacol Ther* (1989) 46, 674–85.
8. Shyu WC, Wilber RB, Pittman KA, Barbhaiya RH. Effect of antacid on the bioavailability of cefprozil. *Antimicrob Agents Chemother* (1992) 36, 962–5.
9. Radwanski E, Nomeir A, Cutler D, Affrime M, Lin C-C. Pharmacokinetic drug interaction study: administration of ceftibuten concurrently with the antacid Mylanta double-strength liquid or with ranitidine. *Am J Ther* (1998) 5, 67–72.

Cephalosporins + Calcium-channel blockers

Nifedipine increases the levels of cefixime. The pharmacokinetics of cefpodoxime proxetil are not affected by nifedipine or diltiazem.

Clinical evidence, mechanism, importance and management

In 8 healthy subjects the AUC and peak serum levels of a single 200-mg dose of **cefixime** were increased by about 70% and 50%, respectively, when **cefixime** was taken 30 minutes after a 20-mg dose of **nifedipine**. The rate of absorption was also increased. One suggested reason for this interaction is that the **nifedipine** increases the absorption of the **cefixime** by affecting the carrier system across the epithelial wall of the gut.[1] It seems doubtful if this increased **cefixime** bioavailability is clinically important (the combination was well-tolerated) and no particular precautions would seem to be necessary on concurrent use.

In 12 healthy subjects, the pharmacokinetics of a single 200-mg dose of **cefpodoxime proxetil** were found to be unchanged by single doses of either **diltiazem** 60 mg or **nifedipine** 20 mg.[2] No special precautions would seem necessary during concurrent use.

Information about other cephalosporins and calcium-channel blockers seems to be lacking, but there seems to be no particular reason to suspect an interaction.

1. Duverne C, Bouten A, Deslandes A, Westphal J-F, Trouvin J-H, Farinotti R, Carbon C. Modification of cefixime bioavailability by nifedipine in humans: involvement of the dipeptide carrier system. *Antimicrob Agents Chemother* (1992) 36, 2462–7.
2. Deslandes A, Camus F, Lacroix C, Carbon C, Farinotti R. Effects of nifedipine and diltiazem on pharmacokinetics of cefpodoxime following its oral administration. *Antimicrob Agents Chemother* (1996) 40, 2879–81.

Cephalosporins + Colestyramine

Colestyramine binds with cefadroxil and cefalexin in the gut, which delays their absorption.

Clinical evidence

In 4 subjects, the peak serum levels of a 500-mg oral dose of **cefadroxil** were reduced and delayed when it was taken with 10 g of colestyramine, but the total amount absorbed was not affected.[1] Similar results were found in a study involving **cefalexin** and colestyramine.[2]

Mechanism

Colestyramine is an ion-exchange resin, which binds with these two cephalosporins in the gut. This prevents the early and rapid absorption of the antibacterial, but as the colestyramine/cephalosporin complex passes along the gastrointestinal tract, the antibacterial is progressively released and eventually virtually all of it becomes available for absorption.[1]

Importance and management

Direct information seems to be limited to the studies cited. The clinical significance is uncertain, but as the total amount of antibacterial absorbed is not reduced this interaction is probably of little importance. Information about other cephalosporins seems to be lacking.

1. Marino EL, Vicente MT and Dominguez-Gil A. Influence of cholestyramine on the pharmacokinetic parameters of cefadroxil after simultaneous administration. *Int J Pharmaceutics* (1983) 16, 23–30.
2. Parsons RL, Paddock GM. Absorption of two antibacterial drugs, cephalexin and co-trimoxazole, in malabsorption syndromes. *J Antimicrob Chemother* (1975) 1 (Suppl), 59–67.

Cephalosporins + Food

The bioavailabilities of cefadroxil, cefalexin, cefdinir, cefixime, cefprozil, and cefradine are not affected by food. Cefaclor may be given without regard to food but absorption of an extended-release preparation may be increased by food. The bioavailabilities of cefetamet pivoxil and cefuroxime axetil may be increased by food.

Clinical evidence, mechanism, importance and management

(a) Cefaclor

A study in 18 healthy subjects, the bioavailability and AUC of a single 250-mg capsule of cefaclor was unchanged when it was given after an overnight fast or within 30 minutes of different meals. The rate of absorption and its maximum plasma levels were decreased: a low-fat vegetarian diet produced the smallest decrease in maximum plasma levels (26%) and a high-fat non-vegetarian diet produced the largest decrease (47%), when compared with the levels achieved after an overnight fast. However, therapeutic efficacy (measured by time levels were above MIC_{50}) was not significantly altered.[1] In a further study, healthy subjects were given a single 500-mg dose of cefaclor as an extended-release tablet. The rate of absorption was decreased by food but compared with the fasting state, the maximum levels were increased; by 52% for rice-based diets, by 33% for low-fat-vegetarian food, by 29% for high-fat non-vegetarian food, by 13% for high-fat-vegetarian food, and by 7% for low-fat non-vegetarian food. Compared with the fasting state, all the diets increased the time above MIC_{90}, with a significant increase of almost 42% with low-fat vegetarian (wheat-based) food.[2] The manufacturer of immediate-release cefaclor capsules states that total absorption is the same whether the drug is given with or without food,[3] but for the extended-release preparation, as absorption is enhanced by food, the manufacturer recommends that this preparation should be taken with meals.[4]

(b) Cefadroxil

The manufacturers of cefadroxil state that the bioavailability of cefadroxil is unaffected by food so it may be taken either with meals or on an empty stomach.[5]

(c) Cefalexin

The manufacturers of cefalexin state that it is acid stable and may be given without regard to meals.[6]

(d) Cefdinir

In 6 healthy subjects, the pharmacokinetics of a single 100-mg dose of cefdinir were unaltered by a normal-protein diet, a high-protein diet, or a normal-protein diet supplemented with L-phenylalanine 7.5 g/day for 12 days.[7]

(e) Cefetamet pivoxil

A study found that the bioavailability of cefetamet pivoxil was up to 25% higher when it was given 10 minutes after a standard breakfast rather than in the fasting state.[8,9] In another study, healthy subjects were given oral cefetamet pivoxil hydrochloride 1 g (equivalent to 693 mg of cefetamet free acid) either: 1 hour before food with 200 mL of water; with a standard breakfast and a cup of tea or coffee; or one hour after breakfast with 200 mL of water. The cefetamet maximum plasma levels were 5.5 micrograms/mL, 5.47 micrograms/mL and 6.57 micrograms/mL, respectively, and the AUCs, compared to the fasting state were decreased by 6% when taken with breakfast and increased by 13% when taken one hour

after breakfast. The time to reach maximum plasma levels was increased from 3.3 hours when given before food to 4.3 hours when given with food, and to 4.1 hours when given one hour after food.[10] It was thought possible that the amount of fluid taken with cefetamet may have affected absorption, but a study in which cefetamet 1 g was given under fasting conditions with either 250 or 450 mL of water found that increasing fluid intake did not affect absorption. Further, the absorption when taken with food, with or without 200 mL of water was similar. These changes are modest. Nevertheless, the authors recommended that cefetamet pivoxil should be taken within an hour of a meal to improve absorption. The delay in absorption was not considered to be of significance.[10]

(f) Cefixime

A study in healthy subjects given a single 400-mg dose of cefixime, either in the fasting state or immediately after a standard breakfast found that the time to peak serum levels was increased from about 3.8 hours to 4.8 hours when cefixime was given with food, probably because of delayed gastric emptying. The cefixime serum levels, AUC and 24-hour urinary recovery were similar for fasted and fed states.[11] Cefixime may be given without regard to meals.[11,12]

(g) Cefpodoxime proxetil

In a study in healthy subjects, cefpodoxime proxetil 400 mg tablets were given with 180 mL of water after an overnight fast, or either one hour before, with, or 2 hours after the start of a high-fat meal. Dosing one hour before the meal was similar to dosing in the fasting state. However, when cefpodoxime was taken with, or 2 hours after the meal its peak plasma levels were increased by about 45% and 46%, respectively, when compared with the peak levels achieved in the fasting state. The AUC was also increased, by 40%. The rate of cefpodoxime absorption was not greatly affected by food.[13] Studies with a 200-mg dose of cefpodoxime have also found that food increases the extent, but not the rate, of cefpodoxime absorption.[14] However, the extent of the food effect appears to be greater with the 400 mg dose. This is possibly because the bioavailability of the 400-mg tablets is less than that of the 200-mg tablets, so food may have a greater effect on the higher strength preparation.[13] In another study by the same authors the AUC and urinary excretion of cefpodoxime proxetil 200 mg given as a suspension were higher (11% and 14%, respectively) when taken with a high-fat meal rather than in the fasting state. Maximum plasma levels were not affected by a high-fat meal but the time to achieve maximum levels was prolonged.[15]

The manufacturers state that the bioavailability of cefpodoxime proxetil 100 mg tablets and suspension is increased by food.[16,17] The studies[13-15] suggest the increased bioavailability of the tablets, but possibly not that of the suspension, when given with food may be clinically significant.

(h) Cefprozil

A study in healthy subjects found that, although food caused slight changes in the rate of absorption of a 1-g dose of cefprozil its pharmacokinetics (including total absorption) were not significantly affected.[18]

(i) Cefradine

A study in healthy subjects given cefradine 500 mg in the fasting state or immediately after a meal found the time to peak levels was increased from 0.8 hours to 2 hours by food. Peak serum levels of cefradine were reduced by 45% when it was given after food. However, the half-life and AUC were not affected.[19] The manufacturer states that cefradine may be given without regard to meals.[20]

(j) Cefuroxime axetil

A study in healthy subjects given cefuroxime axetil 500 mg intravenously or oral doses of 125 mg to 1 g with or without food found that 36% and 52% of a 500-mg oral dose was absorbed in the fasting and fed states respectively.[21] In another study in healthy subjects, a single 1-g dose of cefuroxime axetil was given 2 hours before or 35 minutes after a standard cooked breakfast. The bioavailability of cefuroxime was markedly enhanced by food.[22] The manufacturer notes that optimum absorption of cefuroxime axetil occurs when it is given after a meal.[23] This is probably because of delayed gastric emptying and transit which allowed more complete dissolution and absorption.[22]

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Cephalosporins + H_2-receptor antagonists

Ranitidine and famotidine reduce the bioavailability of cefpodoxime proxetil. Ranitidine with sodium bicarbonate reduces the bioavailability of cefuroxime axetil. No clinically significant pharmacokinetic interactions appear to occur between cefaclor AF and cimetidine, or between cefetamet pivoxil, cefalexin or ceftibuten and ranitidine.

Clinical evidence

(a) Cefaclor

A study using cefaclor AF (a formulation with a slow rate of release) found that **cimetidine** 800 mg taken the previous night reduced its maximum plasma concentration by 12%.[1]

(b) Cefalexin

Ranitidine 150 mg for 3 doses had only small and therapeutically unimportant effects on the pharmacokinetics of cefalexin 1 g.[2] In another study in healthy subjects, **ranitidine** 150 mg for 3 doses prolonged the time to attain peak serum levels of a single 500-mg dose of cefalexin from 1.19 hours to 1.48 hours. Other pharmacokinetic parameters were not significantly affected. Similar results were found when **omeprazole** was given instead of ranitidine.[3]

(c) Cefetamet pivoxil

In 18 healthy subjects, **ranitidine** 150 mg twice daily for 4 days did not affect the pharmacokinetics of cefetamet pivoxil 1 g given after breakfast.[4]

(d) Cefpodoxime proxetil

A study in 10 healthy fasted subjects found that **famotidine** 40 mg reduced the bioavailability of cefpodoxime proxetil by about 40%.[5] This confirms the findings of a previous study with **ranitidine**.[6]

(e) Ceftibuten

In 18 healthy subjects **ranitidine** 150 mg every 12 hours for 3 days raised the maximum plasma levels and AUC of ceftibuten by 23% and 16%, respectively. However these values lie within the normal ranges seen in healthy subjects.[7]

(f) Cefuroxime axetil

Ranitidine 300 mg with sodium bicarbonate 4 g reduced the AUC of cefuroxime axetil 1 g by 43% when the combination was given to fasted subjects. However, when cefuroxime was given after food, its bioavailability was higher, and minimally affected by **ranitidine** plus sodium bicarbonate (10% reduction in AUC) .[8]

Mechanism

The reduction in the bioavailability of some of the cephalosporins is thought to be due to reduced dissolution at increased gastric pH values.[5]

Importance and management

In most cases the interactions between the cephalosporins and H_2-receptor antagonists are not clinically significant. The clinical importance of the interaction with cefpodoxime has not been studied, but the manufacturer recommends that cefpodoxime is given at least 2 hours before H_2-receptor antagonists.[9] As it is thought that a change in gastric pH is responsible for this interaction it would seem likely that **proton pump inhibitors** will interact similarly.

As long as cefuroxime is taken with food (as is recommended[10]), any interaction is minimal. The bioavailability of cefetamet pivoxil,[4] and cefpodoxime proxetil,[5,6] are also enhanced by food so it is probable that any interaction with drugs that raise gastric pH may be similarly minimised.

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9. Orelox Tablets (Cefpodoxime proxetil). Sanofi-Aventis. UK Summary of product characteristics, December 2006.
10. Zinnat Tablets (Cefuroxime axetil). GlaxoSmithKline UK. UK Summary of product characteristics, July 2008.

Cephalosporins + Loop diuretics

The nephrotoxic effects of cefaloridine and possibly cefalotin or cefacetrile appear to be increased by furosemide. Cefradine brain levels are reduced by furosemide. No important interactions appear to occur between furosemide and cefoxitin, ceftazidime, ceftriaxone, or cefuroxime.

Clinical evidence

(a) Nephrotoxicity

Nine out of 36 patients who developed acute renal failure while taking **cefaloridine** had also been taking a diuretic: furosemide was used in 7 cases. Other factors such as patient age and drug dose may also have been involved. The authors of this report related their observations to previous *animal* studies, which showed that potent diuretics such as furosemide and etacrynic acid enhanced the incidence and extent of tubular necrosis.[1] Several other reports describe nephrotoxicity in patients given both **cefaloridine** and furosemide.[2-4] There is a possibility that this effect also occurs with **cefalotin** and **cefacetrile** because *animal* studies found an increase in nephrotoxicity,[5,6] and there is a single report describing nephrotoxicity in one patient taking **cefalotin** with furosemide.[2] **Cefoxitin** seems to be relatively free of nephrotoxicity alone or with furosemide.[7]

(b) Changes in serum levels and clearance

A clinical study[8] found that furosemide 80 mg increased the serum half-life of **cefaloridine** by 25%, and in another study **cefaloridine** clearance was reduced by furosemide.[9] A further study found that brain concentrations of **cefradine** are markedly reduced by furosemide.[10] In a study in 6 healthy subjects, furosemide 40 mg, given one hour before a 1-g intramuscular dose of **ceftazidime**, raised the serum **ceftazidime** levels by about 20 to 40% over 8 hours and increased its AUC by 28%. Furosemide given 3 hours before **ceftazidime** had much smaller effects.[11] The serum half-lives of intravenous **cefoxitin** and **cefuroxime** were not affected by oral furosemide.[12] **Ceftriaxone** does not appear to interfere with the diuretic effects of furosemide.[13]

Mechanism

Cefaloridine is nephrotoxic, but why this should be increased by furosemide is not understood. It may possibly be related to a reduction in its clearance.[9]

Importance and management

The interaction between cefaloridine and furosemide is not well-established, but there is enough evidence to suggest that concurrent use should be undertaken with care. Age and/or renal impairment may possibly be predisposing factors. Renal function should be checked frequently if both drugs are given. A pharmacokinetic study suggests that the development of this adverse interaction may possibly depend on the time relationship of drug use, and it has been recommended that furosemide should be avoided for 3 or 4 hours before the cefaloridine.[14] There seems to be no evidence about other loop diuretics, but it seems possible that they will interact similarly.

Although the manufacturers of ceftazidime issue a caution about the use of high doses of cephalosporins with other nephrotoxic drugs, they say that clinical experience has not shown this to be a problem with ceftazidime at the recommended doses.[15] The rest of the information about other cephalosporins and furosemide is fairly sparse. Most appear not to interact adversely, with a few possible exceptions, namely cefalotin (nephrotoxicity in a single case[2] and *animal* studies[5]) and cefacetrile (nephrotoxicity in *animal* studies[6]). Care is clearly prudent with these two cephalosporins.

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Cephalosporins + Metoclopramide or Propantheline

The pharmacokinetics of cefprozil and cefpodoxime proxetil are minimally affected by propantheline and metoclopramide.

Clinical evidence, mechanism, importance and management

(a) Cefpodoxime

In 12 healthy subjects, the pharmacokinetics of a single 200-mg dose of cefpodoxime proxetil were not significantly altered when it was given 30 minutes after a single dose of metoclopramide 10 mg or propantheline 30 mg.[1]

(b) Cefprozil

A study in 15 healthy subjects who received a single 30-mg dose of metoclopramide or a single 30-mg dose of propantheline 30 minutes before a single 1 g dose of cefprozil, found that the pharmacokinetics of cefprozil were only minimally affected by these drugs.[2]

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Cephalosporins + NSAIDs

The biliary excretion of ceftriaxone is increased by diclofenac. The clearance of ceftazidime is significantly reduced by indometacin in neonates Cefadroxil does not alter the pharmacokinetics of diclofenac.

Clinical evidence, mechanism, importance and management

(a) Diclofenac

The pharmacokinetics of diclofenac 100 mg daily were unaffected by either **cefadroxil** 2 g daily (8 patients) or doxycycline 100 mg daily (7 patients) for one week.[1] No special precautions are needed while taking either of these drugs and diclofenac.

A pharmacokinetic study in 8 patients who had undergone cholecystectomy and who had a T-drain in the common bile duct, found that diclofenac 50 mg every 12 hours increased the excretion of intravenous **ceftriaxone** 2 g in the bile by about fourfold and roughly halved the urinary excretion.[2] The clinical importance of this is uncertain, but probably small.

(b) Indometacin

A study found that the prenatal use of indometacin reduced the clearance of **ceftazidime** 25 mg/kg by 18% in 12 premature neonates (born at about 29 weeks) who were 10 days old. Further, in similar neonates who had not received indometacin, the clearance of **ceftazidime** increased over the first 10 days of life, but this was not seen when indometacin had been given.[3] A further study by the same authors intended to establish an appropriate dose of **ceftazidime** for premature neonates. This study found that in 25 subjects who had received indometacin prenatally, the clearance of **ceftazidime** was reduced by 31% and therefore the authors suggest that additional dose reductions are required. However, note that the effect of indometacin was cancelled out in neonates who had also received betamethasone prenatally.[4] *Animal* studies have shown that indometacin reduces **ceftazidime** excretion by decreasing its glomerular filtered load.[5]

The dose of **ceftazidime** in preterm infants in the first week of life is normally based on chronological age and glomerular filtration rate, although some have suggested that the gestational age should be taken into account.[4] Additional dose adjustments are recommended in preterm infants who are also given indometacin.[3,4]

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Cephalosporins + Probenecid

The serum levels of many cephalosporins are raised by probenecid. Possible exceptions include ceforanide, ceftazidime, ceftriaxone and latamoxef. The rise in serum levels may possibly increase the risk of nephrotoxicity with some cephalosporins such as cefaloridine and cefalotin.

Clinical evidence

Ten healthy subjects given a single 500-mg oral dose of **cefradine** or **cefaclor** developed markedly raised serum antibacterial concentrations when they were also given probenecid (500 mg doses taken 25, 13 and 2 hours before the antibacterial). Peak serum levels of the antibacterial were very roughly doubled.[1] Similar results were obtained in another study in healthy subjects given **cefradine** orally or intramuscularly.[2]

Although some cephalosporins do not appear to interact with probenecid, in general, most have their clearance reduced, their serum levels raised and sometimes their half-lives prolonged by probenecid, see 'Table 10.2', (p.334).

Mechanism

Probenecid inhibits the excretion of most cephalosporins by the renal tubules by successfully competing for the excretory mechanisms. A fuller explanation of this mechanism is set out in 'Drug excretion interactions', (p.7). Thus the cephalosporin is retained in the body and its serum levels rise. The extent of the rise cannot always be fully accounted for by this mechanism alone and it is suggested that some change in tissue distribution may sometimes have a part to play.[1]

Importance and management

An extremely well-documented interaction. The serum levels of many (but not all) cephalosporins will be higher if probenecid is given, but no special precautions are normally needed. The interaction has been used clinically; however, elevated serum levels of some cephalosporins, in particular cefaloridine and cefalotin, might possibly increase the risk of nephrotoxicity.

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Cephalosporins; Cefalexin + Pirenzepine

Pirenzepine (50 mg for 4 doses) had only small and therapeutically unimportant effects on the pharmacokinetics of a 1-g dose of cefalexin.[1]

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Cephalosporins; Cefalotin + Colistin

Renal failure has been attributed to the concurrent use of cefalotin and colistin.

Clinical evidence, mechanism, importance and management

Four patients developed acute renal failure, which appeared to be reversible, during treatment with colistin. Three were given cefalotin concurrently and the fourth had previously been taking this antibacterial.[1] An increase in renal toxicity associated with the concurrent use of these drugs has been described in another report.[2] The reason for this reaction is not

Table 10.2 Effect of probenecid on the pharmacokinetics of the cephalosporins

Drug	*Route*	*Effect of probenecid*	*Refs*
Cefacetrile	Intramuscular	Mean serum half-life increased from 52 minutes to 90 minutes	1
Cefaclor	Oral	Serum level approximately doubled; renal excretion inhibited; renal excretion after 4 hours reduced by 61%	2,3
Cefadroxil	Oral	Probenecid 500 mg every 8 hours for 5 doses increased the half-life of cefadroxil from 1.13 hours to 1.63 hours and reduced its renal excretion by 58%; probenecid slightly increased and prolonged cefadroxil serum levels	4
Cefalexin	Oral	Reduced clearance	5
Cefaloglycin	Oral	Increased peak serum levels and duration of antibacterial activity	6
Cefaloridine	Intramuscular/Intravenous	Plasma levels increased by 20%. Clearance reduced by 24% (intravenous); increased serum levels; prolonged antibacterial activity (intramuscular)	7,8
Cefalotin	Intravenous	Plasma levels increased by 70%. Clearance reduced by 59%	7
Cefamandole	Intramuscular	Peak serum levels almost doubled; half-life prolonged from 1.1 hours to 2 hours	9
Cefazedone	Intravenous	AUC increased more than threefold; elimination half-life increased from 1.58 hours to 4.44 hours; total clearance reduced by 68%	10
Cefazolin	Intramuscular/Intravenous	At 6 hours serum levels of intramuscular dose doubled; after intravenous dose elimination half-life increased from 1.6 hours to 2.7 hours and mean serum level after 24 hours was increased from 1.1 mg/L to 2 mg/L; therapeutic levels at steady-state maintained by once daily rather than three times daily dose regimen	11-13
Cefditoren	Oral	Increased plasma half-life; decreased excretion and renal clearance	14
Cefmenoxime	Intravenous	Renal clearance of cefmenoxime reduced from 159 mL/minute to 66 mL/minute; AUC almost doubled	15
Cefmetazole	Intravenous	Mean AUC increased by about 58%; clearance reduced by about 36%; half-life increased from 1.5 hours to 2.27 hours	16
Cefonicid	Intramuscular	Probenecid 1 g increased the maximum levels of cefonicid 500 mg by 52%, increased the AUC twofold, increased the half-life from 3.5 hours to 7.5 hours, reduced elimination rates and decreased renal clearance	17
Ceforanide	Intramuscular	No significant effect	18
Cefotaxime	Intramuscular/Intravenous	Oral probenecid 500 mg every 6 hours for 24 hours before, and 1 g 30 minutes before, intravenous cefotaxime 1 g reduced renal clearance by about half and almost doubled its AUC. Delayed excretion and increased plasma levels due to effects on renal tubular transfer. Clearance of cefotaxime and also its metabolites decreased by probenecid	19-21
Cefoxitin	Intramuscular/Intravenous	Serum half-life increased from 39 minutes to 129 minutes and clearance halved (intravenous); greater increase in AUC when probenecid given 1 hour before rather than with cefoxitin (intravenous); increasing dose of probenecid from 1 to 2 g increased AUC of cefoxitin (intramuscular)	21-23
Cefprozil	Oral	Significant increase in half-life and maximum levels, AUC approximately doubled, and clearance decreased by about 60%	24
Cefradine	Oral/Intramuscular	Serum levels approximately doubled. Peak levels delayed (from 1 to 2 hours oral and from 1 to 1.5 hours intramuscular); half-lives prolonged	2,25
Ceftazidime	Intravenous	Probenecid 500 mg every 6 hours for 24 hours before and 1 g immediately before a single intravenous dose of ceftazidime 1 g did not significantly affect ceftazidime clearance. Pharmacokinetics of single 50-mg/kg dose of ceftazidime in patients with cystic fibrosis not affected by pre-treatment with probenecid 2 g	19,26
Ceftizoxime	Intramuscular/Intravenous	AUC increased by 49% (both routes); half-life increased from 1.7 hours to 2.3 hours (intravenous) and 1.9 hours to 2.8 hours (intramuscular)	27
Ceftriaxone	Intravenous	No significant effect	28
Cefuroxime	Intravenous	AUC increased by 44 to 50%; half-life prolonged by 63%; clearance decreased by 29%	29
Latamoxef	Intravenous	Probenecid 500 mg every 6 hours for 24 hours before and 1 g immediately before a single 1-g intravenous dose of latamoxef did not significantly affect latamoxef clearance	19

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Continued

Table 10.2 Effect of probenecid on the pharmacokinetics of the cephalosporins (continued)

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known. What is known suggests that renal function should be closely monitored if these drugs are given concurrently or sequentially.

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Cephalosporins; Cefdinir + Iron compounds

Ferrous sulfate markedly reduces the absorption of cefdinir.

Clinical evidence

When 6 healthy subjects were given **ferrous sulfate** (1050 mg of *Fero-Gradumet*, sustained release, equivalent to 210 mg of elemental iron) with cefdinir 200 mg the AUC of cefdinir was reduced by 93%. When **ferrous sulfate** was taken 3 hours after cefdinir, the absorption of cefdinir remained unchanged for 3 hours and then rapidly fell, the total AUC over 12 hours being reduced by 36%.[1] There have been a small number of reported cases of maroon or red stools in children who have taken cefdinir with iron supplements.[2,3] One of these cases occurred in a child who was receiving an iron-containing infant formula.[3]

Mechanism

It is believed that iron compounds chelate with cefdinir in the gut to produce a poorly absorbed complex, which may discolour the stools.

Importance and management

An established interaction of clinical importance. Avoid ferrous sulfate and other iron compounds while taking cefdinir. The manufacturer advises separating the administration of cefdinir and iron preparations by at least 2 hours, but notes that although iron-containing vitamin supplements may interact, iron-fortified infant formula may be taken with cefdinir.[4] Parents should be advised about the potential discoloration of the stools. There is no information to suggest that other cephalosporins interact in this way.

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Cephalosporins; Cefotaxime + Penicillins

Azlocillin and mezlocillin may reduce the clearance of cefotaxime.

Clinical evidence, mechanism, importance and management

A patient with renal failure developed encephalopathy with focal motor status and generalised convulsions when given cefotaxime 2 g every 8 hours and **azlocillin** 5 g every 8 hours (high-dose).[1] In a study in subjects with either normal or impaired renal function, the clearance of a single dose of cefotaxime was reduced by 40 to 50% by **azlocillin** regardless of renal function.[2]

When 8 healthy subjects were given intravenous cefotaxime 30 mg/kg and **mezlocillin** 50 mg/kg together over 30 minutes the pharmacokinetics of the **mezlocillin** were unchanged but the clearance of the cefotaxime was reduced by about 40%. However, in a series of 5 patients with end-stage renal disease no significant decrease in cefotaxime clearance was seen when **mezlocillin** was given.[3]

Doses of cefotaxime may need to be reduced in the presence of either **azlocillin** or **mezlocillin**. One report suggests a dose reduction of cefotaxime is advisable if the glomerular filtration rate is 20 to 40 mL/minute and **azlocillin** is also given.[2]

There seems to be no information about other penicillins.

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3. Rodondi LC, Flaherty JF, Schoenfeld P, Barriere SL, Gambertoglio JG. Influence of coadministration on the pharmacokinetics of mezlocillin and cefotaxime in healthy volunteers and in patients with renal failure. *Clin Pharmacol Ther* (1989) 45, 527–34.

Cephalosporins; Cefotaxime + Phenobarbital

A 30-month study noted a very marked increase in drug-induced reactions in children in intensive care who were given high-dose phenobarbital and beta-lactam antibacterials (mainly cefotaxime). Twenty-four out of 49 children developed drug-induced reactions, which were mainly exanthematous skin reactions.[1] The reasons for this reaction are not known. It would seem prudent to consider this interaction in patients who develop skin reactions while taking both drugs.

1. Harder S, Schneider W, Bae ZU, Bock U, Zielen S. Unerwünschte Arzneimittelreaktionen bei gleichzeitiger Gabe von hochdosiertem Phenobarbital und Betalaktam-Antibiotika. *Klin Padiatr* (1990) 202, 404–7.

Chloramphenicol + Cimetidine

Isolated reports describe fatal aplastic anaemia in two patients given intravenous chloramphenicol and cimetidine.

Clinical evidence, mechanism, importance and management

Pancytopenia and aplastic anaemia developed in a man taking cimetidine 1.2 g daily, within 18 days of being given intravenous chloramphenicol 1 g every 6 hours. It proved to be fatal.[1] Another patient, similarly treated, developed fatal aplastic anaemia after 19 days.[2] A drug interaction with cimetidine was suspected because the onset of pancytopenia was more rapid than in previous cases where chloramphenicol alone induced aplastic anaemia. This effect may occur because the bone marrow depressant effects of the two drugs are additive. There are at least 8 other cases of aplastic anaemia following the use of parenteral chloramphenicol in the absence of cimetidine.[2] The general importance of these observations is uncertain, but the authors of one of the reports suggest that these drugs should be used together with caution.

1. Farber BF, Brody JP. Rapid development of aplastic anemia after intravenous chloramphenicol and cimetidine therapy. *South Med J* (1981) 74, 1257–8.
2. West BC, DeVault GA, Clement JC, Williams DM. Aplastic anemia associated with parenteral chloramphenicol: review of 10 cases, including the second case of possible increased risk with cimetidine. *Rev Infect Dis* (1988) 10, 1048–51.

Chloramphenicol + Dapsone

Dapsone does not significantly affect the pharmacokinetics of oral chloramphenicol.

Clinical evidence, mechanism, importance and management

A comparison of the pharmacokinetics of oral chloramphenicol in 8 healthy subjects and 8 patients with uncomplicated lepromatous leprosy found that the half-life of a single 500-mg dose of chloramphenicol was prolonged from 4.3 hours to 6.4 hours in patients with leprosy, possibly due to changes in liver function. The elimination half-life of chloramphenicol was further increased, to about 8 hours, when the subjects were also given dapsone 100 mg daily for 8 days. However, this latter increase was not statistically significant. Although there was no clinically significant interaction between dapsone and chloramphenicol, the disposition of chloramphenicol may be altered in leprosy.[1]

1. Garg SK, Kumar B, Shukla VK, Bakaya V, Lal R, Kaur S. Pharmacokinetics of aspirin and chloramphenicol in normal and leprotic patients before and after dapsone therapy. *Int J Clin Pharmacol* (1988) 26, 204–5.

Chloramphenicol + Other antibacterials

An old report suggests that the use of chloramphenicol may antagonise the effects of ampicillin in bacterial meningitis. In contrast, no antagonism and even additive antibacterial effects have been described in other infections. Chloramphenicol levels have been markedly lowered by rifampicin (rifampin) in a small number of children.

Clinical evidence

(a) Antibacterial antagonism

A study in 264 patients (adults, and children over 2 months old) with acute bacterial meningitis found that when they were given **ampicillin** 150 mg/kg daily alone, the case-fatality ratio was 4.3% compared with 10.5% in comparable subjects given a combination of **ampicillin**, chloramphenicol 100 mg/kg daily (up to 4 g), and **streptomycin** 40 mg/kg daily (up to 2 g). The neurological sequelae (hemiparesis, deafness, cranial nerve palsies) were also markedly increased by the combined use of these drugs.[1] Antibacterial antagonism was clearly seen in a 10-week-old infant with *Salmonella enteritidis* meningitis, who was given chloramphenicol and **ceftazidime**.[2]

However, in contrast a report claims that antibacterial antagonism was not seen in 65 of 66 patients given chloramphenicol and **benzylpenicillin** for bronchitis or bronchopneumonia.[3] **Ampicillin** with chloramphenicol is more effective than chloramphenicol alone in the treatment of typhoid,[4] and in a study of 700 patients, **procaine benzylpenicillin** with chloramphenicol was shown to be more effective than chloramphenicol alone in the treatment of gonorrhoea (failure rates of 1.8% compared with 8.5%).[5]

(b) Pharmacokinetic interactions

In a study in premature and full-term neonates, infants and small children, it was found that the presence of **penicillin** markedly raised chloramphenicol levels.[6]

Two children, aged 2 and 5 years, with *Haemophilus influenzae* meningitis, were given chloramphenicol 100 mg/kg daily in four divided doses by infusion over 30 minutes. Within 3 days of starting **rifampicin** (**rifampin**) 20 mg/kg daily their peak serum chloramphenicol levels were reduced by 86% and 64%, respectively, and only returned to the therapeutic range when the chloramphenicol dose was increased to 125 mg/kg daily.[7]

Two other children, of 5 and 18 months, with *Haemophilus influenzae* infections, are also reported to have shown reductions of 75% and 94%, respectively, in serum chloramphenicol levels when given **rifampicin** 20 mg/kg daily for 4 days. These reductions occurred despite 20 to 25% increases in the chloramphenicol dose.[8]

Mechanism

By no means fully understood. Chloramphenicol inhibits bacterial protein synthesis and can change an actively growing bacterial colony into a static one. Thus the effects of a bactericide, such as penicillin, which interferes with cell wall synthesis, are blunted, and the death of the organism occurs more slowly. This would seem to explain the antagonism seen with some organisms.

It is thought that rifampicin (rifampin), a potent enzyme inducer, markedly increases the metabolism of chloramphenicol by the liver, thereby lowering its serum levels.[7,8]

Importance and management

Proven cases of antibacterial antagonism of chloramphenicol by penicillins in patients seem to be few in number, and there is insufficient evidence to impose a general prohibition, because, depending on the organism, penicillins and chloramphenicol have been used together with clear advantage.

So far only four cases of an interaction between rifampicin (rifampin)

and chloramphenicol appear to have been reported. However, the evidence is of good quality and in line with the way rifampicin interacts with other drugs, so this interaction should be taken seriously. There is a risk that chloramphenicol levels will become subtherapeutic. The authors of the second report point out that raising the chloramphenicol dose may possibly expose the patient to a greater risk of bone marrow aplasia. They suggest delaying rifampicin prophylaxis in patients with invasive *Haemophilus influenzae* infections until the end of chloramphenicol treatment.

1. Mathies AW, Leedom JM, Ivler D, Wehrle PF, Portnoy B. Antibiotic antagonism in bacterial meningitis. *Antimicrob Agents Chemother* (1967) 7, 218–24.
2. French GL, Ling TKW, Davies DP, Leung DTY. Antagonism of ceftazidime by chloramphenicol in vitro and in vivo during treatment of gram negative meningitis. *BMJ* (1985) 291, 636–7.
3. Ardalan P. Zur Frage des Antagonismus von Penicillin und Chloramphenicolus klinischer Sicht. *Prax Pneumol* (1969) 23, 772–6.
4. De Ritis R, Giammanco G, Manzillo G. Chloramphenicol combined with ampicillin in treatment of typhoid. *BMJ* (1972) 4, 17–18.
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6. Windorfer A, Pringsheim W. Studies on the concentrations of chloramphenicol in the serum and cerebrospinal fluid of neonates, infants and small children. *Eur J Pediatr* (1977) 124, 129–38.
7. Prober CG. Effect of rifampin on chloramphenicol levels. *N Engl J Med* (1985) 312, 788–9.
8. Kelly HW, Couch RC, Davis RL, Cushing AH, Knott R. Interaction of chloramphenicol and rifampin. *J Pediatr* (1988) 112, 817–20.

Chloramphenicol + Paracetamol (Acetaminophen)

Although there is limited evidence to suggest that paracetamol may affect chloramphenicol pharmacokinetics its validity has been criticised.

Clinical evidence, mechanism, importance and management

Three studies report alterations in the pharmacokinetics of chloramphenicol by paracetamol. The first was conducted in 6 adults in intensive care after an observation that the half-life of chloramphenicol was prolonged by paracetamol in children with kwashiorkor. The addition of 100 mg of intravenous paracetamol increased the half-life of chloramphenicol in the adults from 3.25 hours to 15 hours.[1] However, this study has been criticised because of potential errors in the method used to calculate the half-life,[2] the unusual doses used,[2,3] and because the pharmacokinetics of the chloramphenicol with and without paracetamol were calculated at different times after the administration of chloramphenicol.[4] It has also been pointed out that malnutrition (e.g. kwashiorkor) can increase the elimination rate and AUC of chloramphenicol independently of paracetamol.[2]

The second study demonstrated a different interaction, in that the clearance of chloramphenicol was *increased* and the half-life *reduced* by paracetamol.[5] This study has also been criticised as it does not account for the fact that chloramphenicol clearance increases over the duration of a treatment course, which suggests that the changes seen in the pharmacokinetics of chloramphenicol may be independent of the paracetamol.[6] The authors later admit this as a possibility.[7] The third study found no differences in the pharmacokinetics of chloramphenicol after the first dose, but at steady state, the AUC and peak serum levels of chloramphenicol were lower in children who also received paracetamol.[8]

Three other studies do not support the existence of a pharmacokinetic interaction between chloramphenicol and paracetamol.[2-4]

The clinical significance of these reports is unclear, and clinical evidence of toxicity or treatment failure of chloramphenicol appears to be lacking. It would seem prudent to remain aware of the potential for interaction, especially in malnourished patients, but routine monitoring would appear unnecessary without further evidence.

1. Buchanan N, Moodley GP. Interaction between chloramphenicol and paracetamol. *BMJ* (1979) 2, 307–308.
2. Kearns GL, Bocchini JA, Brown RD, Cotter DL, Wilson JT. Absence of a pharmacokinetic interaction between chloramphenicol and acetaminophen in children. *J Pediatr* (1985) 107, 134–9.
3. Rajpurohit R, Krishnaswamy K. Lack of effect of paracetamol on the pharmacokinetics of chloramphenicol in adult human subjects. *Indian J Pharm* (1984) 16, 124–8.
4. Stein CM, Thornhill DP, Neill P, Nyazema NZ. Lack of effect of paracetamol on the pharmacokinetics of chloramphenicol. *Br J Clin Pharmacol* (1989) 27, 262–4.
5. Spika JS, Davis DJ, Martin SR, Beharry K, Rex J, Aranda JV. Interaction between chloramphenicol and acetaminophen. *Arch Dis Child* (1986) 61, 1121–4.
6. Choonara IA. Interaction between chloramphenicol and acetaminophen. *Arch Dis Child* (1987) 62, 319.
7. Spika JS, Aranda JV. Interaction between chloramphenicol and acetaminophen. *Arch Dis Child* (1987) 62, 1087–8.
8. Bravo ME, Horwitz I, Contreras C, Olea I, Arancibia A. Influencia del paracetamol en la farmacocinética del cloramfenicol en pacientes con fiebre tifoídea. *Rev Chil Pediatr* (1987) 58, 117–20.

Chloramphenicol + Phenobarbital

Studies in children have found that phenobarbital can markedly reduce serum chloramphenicol levels. There is a single report, in one adult, of markedly increased serum phenobarbital levels caused by chloramphenicol.

Clinical evidence

(a) Effects on chloramphenicol

A study in a group of infants and children (aged one month to 12 years) given chloramphenicol 25 mg/kg every 6 hours found that 6 of them, also taking phenobarbital, had reduced serum chloramphenicol levels, when compared with 17 control patients. The peak levels were lowered by 34%, from 25.3 to 16.6 micrograms/mL, and the trough levels were lowered by 44%, from 13.4 to 7.5 micrograms/mL.[1] Two children aged 3 and 7 months were given chloramphenicol 100 mg/kg daily, initially intravenously, and later orally for *Haemophilus influenzae* meningitis. The chloramphenicol levels halved over the first 2 days of treatment, while the children were receiving phenobarbital 10 mg/kg daily to prevent convulsions. One child had serum chloramphenicol levels of only 5 micrograms/mL even though the initial doses used were expected to give levels of 15 to 25 micrograms/mL.[2]

Another study confirmed that this interaction occurred in 20 neonates, but no statistically significant effect was found in 40 infants.[3] Decreased chloramphenicol levels have been described in a single case report of a child who was also taking phenytoin and phenobarbital. The serum chloramphenicol levels were 35.1 micrograms/mL before the antiepileptics were started, 19.1 micrograms/mL after 2 days of phenytoin, and 13.2 micrograms/mL a month after the addition of phenobarbital.[4] For more information on the interaction of chloramphenicol with phenytoin see 'Phenytoin + Chloramphenicol', p.633.

(b) Effects on phenobarbital

A man admitted to hospital on numerous occasions for pulmonary complications associated with cystic fibrosis, had average serum phenobarbital levels of 33 micrograms/mL while taking phenobarbital 200 mg daily and oral chloramphenicol 600 mg every 6 hours. One week after the antibacterial was withdrawn, his serum phenobarbital levels were 24 micrograms/mL even though the phenobarbital dose was increased from 200 to 300 mg daily.[5]

Mechanism

Phenobarbital is a potent liver enzyme inducer, which can increase the metabolism and clearance of chloramphenicol (clearly demonstrated in *rats*[6]), so that its serum levels fall and its effects are reduced. Chloramphenicol inhibits the metabolism of the phenobarbital (also demonstrated in *animals*[7]) so that the effects of the barbiturate are increased.

Importance and management

This interaction appears to be established. The documentation is limited but what happened is consistent with the recognised enzyme-inducing actions of phenobarbital and the inhibitory actions of chloramphenicol. Concurrent use should be well monitored to ensure that chloramphenicol serum levels are adequate, and that phenobarbital levels do not become too high (indicators of toxicity include drowsiness, ataxia or dysarthria). Make appropriate dose adjustments as necessary.

1. Krasinski K, Kusmiesz H, Nelson JD. Pharmacologic interactions among chloramphenicol, phenytoin and phenobarbital. *Pediatr Infect Dis* (1982) 1, 232–5.
2. Bloxham RA, Durbin GM, Johnson T, Winterborn MH. Chloramphenicol and phenobarbitone—a drug interaction. *Arch Dis Child* (1979) 54, 76–7.
3. Windorfer A, Pringsheim W. Studies on the concentrations of chloramphenicol in the serum and cerebrospinal fluid of neonates, infants, and small children. *Eur J Pediatr* (1977) 124, 129–38.
4. Powell DA, Nahata MC, Durrell DC, Glazer JP, Hilty MD. Interactions among chloramphenicol, phenytoin, and phenobarbital in a pediatric patient. *J Pediatr* (1981) 98, 1001–1003.
5. Koup JR, Gibaldi M, McNamara P, Hilligoss DM, Colburn WA, Bruck E. Interaction of chloramphenicol with phenytoin and phenobarbital. Case report. *Clin Pharmacol Ther* (1978) 24, 571–5.

6. Bella DD, Ferrari V, Marca G,Bonanomi L. Chloramphenicol metabolism in the phenobarbital-induced rat. Comparison with thiamphenicol. *Biochem Pharmacol* (1968) 17, 2381–90.
7. Adams HR. Prolonged barbiturate anesthesia by chloramphenicol in laboratory animals. *J Am Vet Med Assoc* (1970) 157, 1908–13.

Clindamycin or Lincomycin + Food

The serum levels of lincomycin are markedly reduced (by up to two-thirds) if taken in the presence of food, but clindamycin is not significantly affected. Cyclamate sweeteners can also reduce the absorption of lincomycin.

Clinical evidence

In a study in 10 healthy subjects the mean peak serum levels of a single 500-mg oral dose of lincomycin were about 3 micrograms/mL when taken 4 hours before **breakfast**, 2 micrograms/mL when taken 1 hour before breakfast, and less than 1 microgram/mL when taken after breakfast. The mean total amounts of lincomycin recovered from the urine were 40.4 mg, 23.8 mg, and 8.9 mg, respectively.[1]

Reduced serum lincomycin levels due to the presence of **food** have been described in other reports,[2,3] but the absorption of clindamycin is not affected.[3,4]

Sodium cyclamate, an artificial sweetener found in diet foods, drinks and some pharmaceuticals, can also markedly reduce the absorption of lincomycin. The AUC of lincomycin 500 mg was reduced by about 75% by 1 Molar equivalent of **sodium cyclamate** (said to be an amount equal to only part of a bottle of diet drink, but exact quantity not stated).[5]

Mechanism

Not understood.

Importance and management

The food interaction with lincomycin is well established and of clinical importance. Lincomycin should not be taken with food or within several hours of eating a meal if adequate serum levels are to be achieved. An alternative is clindamycin, a synthetic derivative of lincomycin, which has the same antibacterial spectrum but is not affected by food.

1. McCall CE, Steigbigel NH, Finland M. Lincomycin: activity *in vitro* and absorption and excretion in normal young men. *Am J Med Sci* (1967) 254, 144–55.
2. Kaplan K, Chew WH, Weinstein L. Microbiological, pharmacological and clinical studies of lincomycin. *Am J Med Sci* (1965) 250, 137–46.
3. McGehee RF, Smith CB, Wilcox C, Finland M. Comparative studies of antibacterial activity in vitro and absorption and excretion of lincomycin and clinimycin. *Am J Med Sci* (1968) 256, 279–92.
4. Wagner JG, Novak E, Patel NC, Chidester CG, Lummis WL. Absorption, excretion and half-life of clinimycin in normal adult males. *Am J Med Sci* (1968) 256, 25–37.
5. Wagner JG. Aspects of pharmacokinetics and biopharmaceutics in relation to drug activity. *Am J Pharm Sci Support Public Health* (1969) 141, 5–20.

Clindamycin or Lincomycin + Kaolin

Kaolin-pectin can markedly reduce the absorption of lincomycin. The rate but not the extent of clindamycin absorption is altered by kaolin.

Clinical evidence

In 8 healthy subjects about 85 mL of *Kaopectate* (kaolin-pectin) reduced the absorption of lincomycin 500 mg by about 90%. Giving the *Kaopectate* 2 hours before the antibacterial had little or no effect on its absorption, whereas when *Kaopectate* was given 2 hours after lincomycin, the absorption was reduced by about 50%. The absorption rate of clindamycin is markedly prolonged by kaolin, but the extent of its absorption remains unaffected.[1]

Mechanism

It seems probable that the lincomycin becomes adsorbed onto the kaolin, thereby reducing its bioavailability. The kaolin also coats the lining of the gut and acts as a physical barrier to absorption.[2]

Importance and management

Information seems to be limited to this study, but the interaction between lincomycin and kaolin appears to be established and of clinical importance. For good absorption and a good antibacterial response separate their administration as much as possible, ideally giving the kaolin at least 2 hours before the antibacterial. Clindamycin appears to be a suitable alternative to lincomycin. However, note that marked diarrhoea is an indication that lincomycin or clindamycin should be stopped immediately. This is because it may be a sign of pseudomembranous colitis, which can be fatal.

1. Albert KS, DeSante KA, Welch RD, DiSanto AR. Pharmacokinetic evaluation of a drug interaction between kaolin-pectin and clindamycin. *J Pharm Sci* (1978) 67, 1579–82.
2. Wagner JG. Design and data analysis of biopharmaceutical studies in man. *Can J Pharm Sci* (1966) 1, 55–68.

Clofazimine + Miscellaneous

The bioavailability of a single dose of clofazimine is increased by a high-fat meal, and slightly decreased by orange juice and an aluminium/magnesium hydroxide antacid.

Clinical evidence, mechanism, importance and management

In a randomised, crossover study healthy subjects received a single 200-mg dose of clofazimine after a 12 hour fast (13 subjects), with 240 mL of **orange juice** (15 subjects), with a high-fat meal (15 subjects) or with 15 mL of an **aluminium**/**magnesium hydroxide** and **simeticone**-containing antacid given 9 hours before the clofazimine, at the time of dosing, and four times daily for the subsequent day. The high-fat meal increased the AUC and maximum plasma levels of clofazimine by 98% and 146%, respectively. The **orange juice** reduced the AUC and maximum plasma levels of clofazimine by 13% and 7%, respectively, and the **antacid** reduced the AUC and maximum plasma levels of clofazimine by 16% and 35%, respectively. There was wide inter-individual variation in each of the study groups.[1]

The clinical significance of the findings of this single-dose study with food is unclear; clofazimine has a half-life after repeated doses of about 70 days. The manufacturer advises that clofazimine is taken with meals.[2] The changes in clofazimine levels caused by the **antacid** and **orange juice** are small, and unlikely to be clinically relevant.

1. Nix DE, Adam RD, Auclair B, Krueger TS, Godo PG, Peloquin CA. Pharmacokinetics and relative bioavailability of clofazimine in relation to food, orange juice and antacid. *Tuberculosis (Edinb)* (2004) 84, 365–73.
2. Lamprene (Clofazimine). Novartis Pharmaceuticals Corporation. US Prescribing information, September 1998.

Colistin + Sucralfate

An *in vitro* study with colistin sulfate found that it became markedly and irreversibly bound to sucralfate at the pH values found in the gut.

Clinical evidence, mechanism, importance and management

To simulate what might happen in the gut, colistin sulfate 50 mg/L was mixed with sucralfate 500 mg in 40 mL of water at pH 3.5 and allowed to stand for 90 minutes at 25°C. Analysis of the solution showed that the colistin concentration fell rapidly and progressively over 90 minutes to about 40%. When the pH of the mixture was then raised to 6.5 to 7 for 90 minutes, there was no change in the concentration of colistin, suggesting that the interaction was irreversible.[1] The reason for this change is not known, but the suggestion is that sucralfate forms insoluble chelates with colistin.[1]

It is not known how important this interaction is likely to be in practice, but the efficacy of colistin in gut decontamination and gut infections may be decreased. Separating the doses might not be effective in some postoperative patients because their gastric function may not return to normal for up to 5 days, and some sucralfate might still be present when the next dose is given.[1] More study is needed to find out whether this interaction is clinically important, but in the meanwhile it would seem prudent to monitor concurrent use carefully, being alert for any evidence of reduced effects.

1. Feron B, Adair CG, Gorman SP, McClurg B. Interaction of sucralfate with antibiotics used for selective decontamination of the gastrointestinal tract. *Am J Hosp Pharm* (1993) 50, 2550–3.

Co-trimoxazole + Azithromycin

Azithromycin does not alter the pharmacokinetics of co-trimoxazole.

Clinical evidence, mechanism, importance and management

A study in 12 healthy subjects given co-trimoxazole (trimethoprim and sulfamethoxazole) 960 mg daily for 7 days found that a single 1.2-g dose of azithromycin given on day 7 did not alter the pharmacokinetics of either trimethoprim or sulfamethoxazole to a clinically relevant extent.[1]

1. Amsden GW, Foulds G, Thakker K. Pharmacokinetic study of azithromycin with fluconazole and cotrimoxazole (trimethoprim-sulfamethoxazole) in healthy volunteers. *Clin Drug Invest* (2000) 20, 135–42.

Co-trimoxazole + Azoles

Fluconazole, but not ketoconazole inhibits the metabolism of sulfamethoxazole to its hydroxylamine metabolite.

Clinical evidence, mechanism, importance and management

Ten healthy subjects were given co-trimoxazole (sulfamethoxazole 800 mg with trimethoprim 160 mg) either alone or one hour after either **fluconazole** 150 mg or **ketoconazole** 200 mg. **Ketoconazole** had no effect on the urinary recovery of sulfamethoxazole or its metabolites. However, **fluconazole** significantly inhibited the formation of sulfamethoxazole hydroxylamine and also inhibited the oxidation of sulfamethoxazole to its 5-methylhydroxy- and 5-methylhydroxy acetate metabolites. The amount of unchanged sulfamethoxazole or its *N*-acetyl or glucuronide metabolites were not affected by **fluconazole**.[1] Another study in HIV-positive patients given co-trimoxazole (sulfamethoxazole 800 mg with trimethoprim 160 mg daily) found that **fluconazole** 200 mg daily decreased the AUC, urinary recovery, and formation clearance of sulfamethoxazole hydroxylamine by 37%, 53% and 61% respectively.[2] As the hydroxylamine metabolite is possibly one of the causes of sulfamethoxazole toxicity, the concurrent use of **fluconazole** may be associated with reduced rates of sulfamethoxazole toxicity.[1,2]

Evidence about other azoles appears to be lacking, but they would, in general, be expected to interact similarly.

1. Gill HJ, Maggs JL, Madden S, Pirmohamed M, Park BK. The effect of fluconazole and ketoconazole on the metabolism of sulphamethoxazole. *Br J Clin Pharmacol* (1996) 42, 347–53.
2. Winter HR, Trapnell CB, Slattery JT, Jacobson M, Greenspan DL, Hooton TM, Unadkat JD. The effect of clarithromycin, fluconazole, and rifabutin on sulfamethoxazole hydroxylamine formation in individuals with human immunodeficiency virus infection (AATG 283). *Clin Pharmacol Ther* (2004) 76, 313–22.

Co-trimoxazole + Cimetidine

Cimetidine has no significant effect on the pharmacokinetics of co-trimoxazole.

Clinical evidence, mechanism, importance and management

In a placebo-controlled study, 6 healthy subjects were given cimetidine 400 mg every 6 hours for 6 days, with a single 960-mg dose of co-trimoxazole (trimethoprim with sulfamethoxazole) on day 6. Although trimethoprim levels were consistently higher in the presence of cimetidine, the slight difference was not statistically significant. Cimetidine had no effect on the pharmacokinetics of sulfamethoxazole.[1]

1. Rogers HJ, James CA, Morrison PJ, Bradbrook ID. Effect of cimetidine on oral absorption of ampicillin and co-trimoxazole. *J Antimicrob Chemother* (1980) 6, 297–300.

Co-trimoxazole + Kaolin-pectin

Kaolin-pectin can cause a small but probably clinically unimportant reduction in trimethoprim levels, and has no effect on sulfamethoxazole pharmacokinetics.

Clinical evidence, mechanism, importance and management

Co-trimoxazole suspension (trimethoprim 160 mg with sulfamethoxazole 800 mg) was given to 8 healthy subjects, with and without 20 mL of kaolin-pectin suspension. Kaolin-pectin reduced the AUC and the maximum serum levels of trimethoprim by about 12% and 20%, respectively. Changes in the sulfamethoxazole pharmacokinetics were not statistically significant.[1] The probable reason for this reduction in the trimethoprim AUC is that trimethoprim is adsorbed onto the kaolin-pectin, which reduces the amount available for absorption. However, the reduction is small and unlikely to be clinically relevant.

1. Gupta KC, Desai NK, Satoskar RS, Gupta C, Goswami SN. Effect of pectin and kaolin on bioavailability of co-trimoxazole suspension. *Int J Clin Pharmacol Ther Toxicol* (1987) 25, 320–1.

Co-trimoxazole + Prilocaine/Lidocaine cream

Methaemoglobinaemia developed in a baby treated with co-trimoxazole when *Emla* (prilocaine/lidocaine) cream was applied to his skin. Other drugs that cause methaemoglobinaemia are predicted to have similar effects.

Clinical evidence, mechanism, importance and management

A 12-week-old child, given co-trimoxazole for 2 months for pyelitis, was given 5 g of *Emla* cream (prilocaine 25 mg and lidocaine 25 mg per gram) applied to the back of his hands and the cubital regions. Unfortunately his operation was delayed, and 5 hours later, just before the operation began, his skin was noted to be pale and his lips had a brownish cyanotic colour. This was found to be due to the presence of 28% methaemoglobin (reference range less than 3%).[1] The authors of the report suggest that prilocaine together with sulfamethoxazole (both known to cause methaemoglobin formation) suppressed the activity of two enzymes (NADH-dehydrogenase and NADP-diaphorase), which normally keep blood levels of methaemoglobin to a minimum.[1] A study in 20 children[2] confirmed that *Emla* cream can increase methaemoglobin levels, although levels *decreased* in 6 of them. However, the maximum increase was 1.2% (from 0.7 to 1.9%), and the highest value was 2%, which was still within the reference range. Another study found similar small increases in methaemoglobin levels, and found that these remained elevated after 24 hours. The authors concluded that daily application of prilocaine with lidocaine may lead to accumulation, and a greater risk of toxicity.[3]

The case report appears to be unusual, but it has been suggested that there may be a special risk of methaemoglobinaemia with *Emla* in children with pre-existing anaemia, reduced renal excretion of the metabolites of prilocaine, or the concurrent use of sulfonamides.[3] It would seem prudent to keep *Emla* contact time to a minimum in these patients. Note that the UK and US manufacturers advise that *Emla* should not be applied to the skin of infants who are under the age of 12 months who are receiving treatment with methaemoglobin-inducing drugs. They specifically name the **sulfonamides**.[4] In addition, the manufacturers name a number of other drugs that they suggest may cause methaemoglobinaemia. This includes **aminosalicylic acid**, **benzocaine**, **chloroquine**, **dapsone**, **metoclopramide**, **nitrates**, **nitrofurantoin**, **nitroprusside**, **paracetamol** (**acetaminophen**), **phenacetin**, **phenobarbital**, **phenytoin**, and **primaquine**.[4,5]

1. Jakobson B, Nilsson A. Methemoglobinemia associated with a prilocaine-lidocaine cream and trimethoprim-sulphamethoxazole. A case report. *Acta Anaesthesiol Scand* (1985) 29, 453–55.
2. Engberg G, Danielson K, Henneberg S, Nilsson A. Plasma concentrations of prilocaine and lidocaine and methaemoglobin formation in infants after epicutaneous application of a 5% lidocaine-prilocaine cream (Emla). *Acta Anaesthesiol Scand* (1987) 31, 624–8.
3. Frayling IM, Addison GM, Chattergee K, Meakin G. Methaemoglobinaemia in children treated with prilocaine-lignocaine cream. *BMJ* (1990) 301, 153–4.
4. EMLA Cream (Lidocaine with Prilocaine). AstraZeneca. US Prescribing information, May 2005.
5. EMLA Cream (Lidocaine with Prilocaine). AstraZeneca UK Limited. UK Summary of product characteristics, September 2009.

Co-trimoxazole or Trimethoprim + Rifamycins

The pharmacokinetics of trimethoprim are not significantly affected by rifabutin, and probably not by rifampicin (rifampin). Trimethoprim does not affect the pharmacokinetics of rifampicin.

Rifabutin does not affect the pharmacokinetics of sulfamethoxazole, but significantly increases exposure to its hydroxylamine

metabolite and as a result may increase adverse reactions to sulfamethoxazole in HIV-positive patients.
A significant reduction in co-trimoxazole levels and a decrease in prophylactic efficacy has been seen in HIV-positive patients taking rifampicin. Limited evidence suggests that co-trimoxazole can increase rifampicin levels.

Clinical evidence, mechanism, importance and management

(a) Rifabutin

Twelve HIV-positive patients taking co-trimoxazole (sulfamethoxazole and trimethoprim; strength not stated) twice daily for 7 days were also given rifabutin 300 mg daily for a further 14 days. The sulfamethoxazole component remained unaffected by rifabutin but the trimethoprim AUC was decreased by 22%. This small reduction is not expected to be clinically significant.[1] However, another study in HIV-positive patients given co-trimoxazole (sulfamethoxazole 800 mg with trimethoprim 160 mg daily) found that although rifabutin 300 mg daily had minimal effects on the disposition of sulfamethoxazole and its acetylated metabolite, it significantly increased the AUC, urinary recovery and formation clearance of its hydroxylamine metabolite by about 50%. As the hydroxylamine metabolite may be one of the factors associated with adverse reactions to sulfamethoxazole in HIV-positive patients, concurrent rifabutin may increase the rate of adverse reactions.[2]

(b) Rifampicin (Rifampin)

No significant pharmacokinetic interaction seems to occur when healthy subjects are given trimethoprim 240 mg daily with rifampicin 900 mg daily (both in divided doses). After 4 to 5 days, less trimethoprim is recovered in the urine, as more is metabolised before excretion due to the enzyme-inducing effects of rifampicin, but this does not appear to be of clinical importance.[3,4] Another study also notes that no clinically significant pharmacokinetic interaction occurs between trimethoprim and rifampicin.[5]

However, a case-control study of the efficacy of co-trimoxazole in preventing toxoplasmosis in HIV-positive patients found a link between rifampicin use and co-trimoxazole failure,[6] which prompted the authors to conduct a pharmacokinetic study. When rifampicin 600 mg daily was given to 10 HIV-positive patients with co-trimoxazole 960 mg daily, it was found that the AUCs of trimethoprim and sulfamethoxazole were reduced by 56% and 28%, respectively. These changes are sufficient to reduce the efficacy of co-trimoxazole treatment.[7] It would therefore seem prudent to consider this interaction when giving rifampicin to HIV-positive patients taking co-trimoxazole prophylaxis.

In one study, 15 patients with tuberculosis, who had taken rifampicin 450 mg daily for at least 15 days, were given co-trimoxazole (trimethoprim 320 mg and sulfamethoxazole 800 mg every 12 hours) for 5 to 10 days. Rifampicin levels were measured at five time points over 6 hours before and during co-trimoxazole treatment. At 4 and 6 hours, rifampicin levels were significantly higher (27% and 56%, respectively) during co-trimoxazole use, but peak levels were only increased by about 18%. Concurrent use did not result in any increase in adverse effects.[8]

1. Lee BL, Lampiris H, Colborn DC, Lewis RC, Narang PK, Sullam P. The effect of rifabutin (RBT) on the pharmacokinetics (PK) of trimethoprim-sulfamethoxazole (TMP-SMX) in HIV-infected patients. *Intersci Conf Antimicrob Agents Chemother* (1995) 35, 7.
2. Winter HR, Trapnell CB, Slattery JT, Jacobson M, Greenspan DL, Hooton TM, Unadkat JD. The effect of clarithromycin, fluconazole, and rifabutin on sulfamethoxazole hydroxylamine formation in individuals with human immunodeficiency virus infection (AACTG 283). *Clin Pharmacol Ther* (2004) 76, 313–22.
3. Buniva G, Palminteri R, Berti M. Kinetics of a rifampicin-trimethoprim combination. *Int J Clin Pharmacol Biopharm* (1979) 17, 256–9.
4. Emmerson AM, Grüneberg RN, Johnson ES. The pharmacokinetics in man of a combination of rifampicin and trimethoprim. *J Antimicrob Chemother* (1978) 4, 523–31.
5. Acocella G, Scotti R. Kinetic studies on the combination rifampicin-trimethoprim in man. *J Antimicrob Chemother* (1976) 2, 271–77.
6. Ribera E, Fernandez-Sola A, Juste C, Rovira A, Romero FJ, Armandas-Gil L, Ruiz I, Ocaña I, Pahissa A. Comparison of high and low doses of trimethoprim-sulfamethoxazole for primary prevention of toxoplasmic encephalitis in human immunodeficiency virus-infected patients. *Clin Infect Dis* (1999) 29, 1461–6.
7. Ribera E, Pou L, Fernandez-Sola A, Campos F, Lopez RM, Ocaña I, Ruiz I, Pahissa A. Rifampin reduces concentrations of trimethoprim and sulfamethoxazole in serum in human immunodeficiency virus infected patients. *Antimicrob Agents Chemother* (2001) 45, 3238–41.
8. Bhatia RS, Uppal R, Malhi R, Behera D, Jindal SK. Drug interaction between rifampicin and co-trimoxazole in patients with tuberculosis. *Hum Exp Toxicol* (1991) 10, 419–21.

Co-trimoxazole + Salbutamol (Albuterol)

Salbutamol reduces the rate but increases the extent of sulfamethoxazole absorption.

Clinical evidence, mechanism, importance and management

In 6 healthy subjects, oral salbutamol 4 mg four times daily for 2 weeks had no effect on the pharmacokinetics of a single 400-mg oral dose of sulfamethoxazole (given as co-trimoxazole), although the absorption rate constant was reduced by about 40% and the extent of absorption over 72 hours was increased by 23%.[1] A possible reason for these effects is that salbutamol stimulates the beta receptors in the gut, causing relaxation, which allows an increased contact time, and therefore increased absorption of sulfamethoxazole.[1] The clinical significance of this interaction is unknown, but it seems unlikely to be of importance. No interaction would be expected with inhaled salbutamol.

1. Adebayo GI, Ogundipe TO. Effects of salbutamol on the absorption and disposition of sulphamethoxazole in adult volunteers. *Eur J Drug Metab Pharmacokinet* (1989) 14, 57–60.

Cycloserine + Ethionamide

Neurotoxic adverse effects may be potentiated by the concurrent use of cycloserine and ethionamide.

Clinical evidence, mechanism, importance and management

Three cases of encephalopathy have been reported in patients taking antimycobacterial regimens that included ethionamide (and in 2 cases, isoniazid): in one case symptoms occurred during the concurrent use of ethionamide and cycloserine. All 3 patients recovered after the withdrawal of either ethionamide (and isoniazid) or cycloserine, and treatment with nicotinamide and other vitamin B compounds.[1] The manufacturers note that the concurrent use of ethionamide can potentiate the neurotoxic adverse effects of cycloserine.[2,3] The US manufacturer of ethionamide notes that convulsions have been reported in patients also taking cycloserine and they recommend special care with treatment regimens that include both drugs.[4]

1. Swash M, Roberts AH, Murnaghan DJ. Reversible pellagra-like encephalopathy with ethionamide and cycloserine. *Tubercle* (1972) 53, 132–6.
2. Cycloserine. King Pharmaceuticals Ltd. UK Summary of product characteristics, March 2007.
3. Seromycin (Cycloserine). Eli Lilly and Company. US Prescribing information, April 2005.
4. Trecator (Ethionamide). Wyeth Pharmaceuticals Inc. US Prescribing information, November 2007.

Cycloserine + Isoniazid

The adverse CNS effects of cycloserine are increased by isoniazid.

Clinical evidence, mechanism, importance and management

A report describes both an increase and a decrease in serum cycloserine levels in some subjects, which were apparently caused by isoniazid; however, the mean level of cycloserine was not significantly changed. Only one out of 11 patients taking cycloserine alone developed adverse effects (drowsiness, dizziness, unstable gait), but when isoniazid was added, 9 of the 11 developed these effects.[1] The manufacturers recommend monitoring for these adverse effects if both drugs are given and adjusting the doses as necessary to manage them.[2,3]

1. Mattila MJ, Nieminen E, Tiitinen H. Serum levels, urinary excretion, and side-effects of cycloserine in the presence of isoniazid and p-aminosalicylic acid. *Scand J Respir Dis* (1969) 50, 291–300.
2. Cycloserine. King Pharmaceuticals Ltd. UK Summary of product characteristics, March 2007.
3. Seromycin (Cycloserine). Eli Lilly and Company. US Prescribing information, April 2005.

Cycloserine + Miscellaneous

Orange juice and an aluminium/magnesium hydroxide-containing antacid do not affect the pharmacokinetics of cycloserine, but a high-fat meal delays its absorption.

Clinical evidence, mechanism, importance and management

(a) Antacids

A study in 12 healthy subjects found that the bioavailability of a single 500-mg dose of cycloserine was not affected by 15 mL of an antacid containing **aluminium/magnesium hydroxide** and **simeticone** (*Mylanta*) was given 9 hours before the cycloserine, at the same time as the cycloser-

ine, immediately after meals, and at bedtime on both the dosing day and the following day.[1]

(b) Food

A study in 12 healthy subjects found that the bioavailability of a single 500-mg dose of cycloserine was not significantly affected by 240 mL of **orange juice**.[1] When cycloserine 500 mg was given 15 minutes after the start of a high-fat meal, which was completed within 30 minutes, its AUC was not affected, but its maximum serum levels were reduced by about 16% and the time to maximum levels was increased from 45 minutes to 3.5 hours. The authors suggest that, in patients with relatively low plasma levels or patients receiving once rather than twice daily doses, it is possible that the delay in absorption could result in increased periods of sub-inhibitory levels.[1] However, there is no evidence to suggest that this is clinically significant.

1. Zhu M, Nix DE, Adam RD, Childs JM, Peloquin CA. Pharmacokinetics of cycloserine under fasting conditions and with high-fat meal, orange juice, and antacids. *Pharmacotherapy* (2001) 21, 891–7.

Dapsone + Antacids

The absorption of dapsone is unaltered by an antacid containing aluminium/magnesium hydroxide and/or simeticone.

Clinical evidence, mechanism, importance and management

A study to see whether changes in gastric pH might affect the absorption of dapsone found that when a single 100-mg dose of dapsone was taken with the second of 11 doses of **aluminium/magnesium hydroxide** and **simeticone** (*Mylanta II*), given every hour, the absorption of the dapsone remained unchanged. The mean gastric pH rose from 2.3 before using the antacid, to 4.5 or higher while taking dapsone and the antacid.[1] In another study, 8 subjects were given a single 100-mg dose of dapsone as a liquid oral preparation followed immediately by 12.5 mL of an **aluminium/magnesium hydroxide** antacid (*Maalox TC*). The peak plasma levels of dapsone were increased by about 11% and the time to peak levels was reduced from 1.9 hours to 1.3 hours. However, the dapsone AUC and elimination rate were not affected.[2] No special precautions would therefore seem to be needed if *Mylanta II*, *Maalox TC* or any other similar antacid is used with dapsone. See also 'NRTIs + Dapsone', p.946, for a discussion of the effects of the buffer in didanosine tablets on dapsone absorption.

1. Breen GA, Brocavich JM, Etzel JV, Shah V, Schaefer P, Forlenza S. Evaluation of effects of altered gastric pH on absorption of dapsone in healthy volunteers. *Antimicrob Agents Chemother* (1994) 38, 2227–9.
2. Mirochnick M, Breña A, McNamara ER, Clarke D, Pelton S. Effect of antacid on dapsone absorption. *Pediatr AIDS HIV Infect* (1993) 4, 13–16.

Dapsone + Clarithromycin

Clarithromycin does not alter the metabolism of dapsone.

Clinical evidence, mechanism, importance and management

A study in 12 healthy subjects given single 100-mg doses of dapsone before and after taking clarithromycin 1 g twice daily for 10 days, found that the clearance of dapsone was unchanged. Of equal importance was finding that the AUC of the *N*-hydroxylation metabolite of dapsone, which appears to be responsible for its haematological toxicity (methaemoglobinaemia), was also unchanged.[1]

In another study, 11 HIV-positive patients were given dapsone 100 mg daily then clarithromycin 500 mg twice daily for 2 weeks. Clarithromycin had no effect on dapsone clearance or on the production of the hydroxylamine metabolite of dapsone.[2] These results suggest that the cytochrome P450 isoenzyme CYP3A4, which is inhibited by clarithromycin, is not involved in dapsone metabolism.[2]

Clarithromycin would not be expected to alter the toxicity of dapsone, and no special precautions are required during concurrent use.

1. Occhipinti DJ, Choi A, Deyo K, Danziger LH, Fischer JH. Influence of rifampin and clarithromycin on dapsone (D) disposition and methemoglobin concentrations. *Clin Pharmacol Ther* (1995) 57, 163.
2. Winter HR, Trapnell CB, Slattery JT, Jacobson M, Greenspan DL, Hooton TM, Unadkat JD. The effect of clarithromycin, fluconazole, and rifabutin on dapsone hydroxylamine formation in individuals with human immunodeficiency virus infection (AACTG 283). *Clin Pharmacol Ther* (2004) 76, 579–87.

Dapsone + Clofazimine

Dapsone can reduce the anti-inflammatory effects of clofazimine. Clofazimine does not affect the pharmacokinetics of dapsone.

Clinical evidence, mechanism, importance and management

Fourteen out of 16 patients with severe recurrent erythema nodosum leprosum (ENL) did not respond adequately when given dapsone and clofazimine and needed additional treatment with corticosteroids. When the dapsone was stopped the patients responded to clofazimine alone, and in some instances the ENL was controlled by smaller doses.[1] Further evidence of this interaction comes from a laboratory study, which suggests that the actions of clofazimine may be related to its ability to inhibit neutrophil migration (resulting in decreased numbers of neutrophils in areas of inflammation), whereas dapsone can have the opposite effect.[1] Although the information is very limited, it would seem prudent to avoid the concurrent use of dapsone and clofazimine in the treatment of ENL. The authors of this report[1] are at great pains to emphasise that what they describe only relates to the effects of dapsone on the anti-inflammatory effects of clofazimine, and not to the beneficial effects of concurrent use when treating drug-resistant *Mycobacterium leprae*.

A study in patients taking clofazimine and dapsone[2] and 4 other studies in patients also taking isoniazid or rifampicin suggest that clofazimine does not affect the pharmacokinetics of dapsone.[3-6] However, one earlier study[7] found that clofazimine transiently increased the renal excretion of dapsone in 9 of 17 patients with leprosy who had recently discontinued dapsone.

1. Imkamp FMJH, Anderson R, Gatner EMS. Possible incompatibility of dapsone with clofazimine in the treatment of patients with erythema nodosum leprosum. *Lepr Rev* (1982) 53, 148–9.
2. George J, Balakrishnan S, Bhatia VN. Drug interaction during multidrug regimens for treatment of leprosy. *Indian J Med Res* (1988) 87, 151–6.
3. Venkatesan K, Mathur A, Girdhar BK, Bharadwaj VP. The effect of clofazimine on the pharmacokinetics of rifampicin and dapsone in leprosy. *J Antimicrob Chemother* (1986) 18, 715–18.
4. Pieters FAJM, Woonink F, Zuidema J. Influence of once-monthly rifampicin and daily clofazimine on the pharmacokinetics of dapsone in leprosy patients in Nigeria. *Eur J Clin Pharmacol* (1988) 34, 73–6.
5. Venkatesan K, Bharadwaj VP, Ramu R, Desikan KV. Study on drug interactions. *Lepr India* (1980) 52, 229–35.
6. Balakrishnan S, Seshadri PS. Drug interactions— the influence of rifampicin and clofazimine on the urinary excretion of DDS. *Lepr India* (1981) 53, 17–22.
7. Grabosz JAJ, Wheate HW. Effect of clofazimine on the urinary excretion of DDS (Dapsone). *Int J Lepr* (1975) 43, 61–2.

Dapsone + Drugs that affect gastric pH

Cimetidine raises serum dapsone levels, and may reduce methaemoglobinaemia due to the hydroxylamine metabolite of dapsone. Cimetidine, ranitidine and omeprazole do not appear to affect the outcome of dapsone prophylaxis against pneumocystis pneumonia. The absorption of dapsone does not appear to be altered by nizatidine-induced increases in gastric pH.

Clinical evidence, mechanism, importance and management

In 7 healthy subjects **cimetidine** 400 mg three times daily for 3 days increased the AUC of a single 100-mg dose of dapsone by 40%.[1] The probable reason for this effect is that the **cimetidine** (a known non-specific enzyme inhibitor) inhibits the metabolism of the dapsone by the liver. Although this might be expected to increase the risk of haematological adverse effects of dapsone by raising its serum levels, **cimetidine** also apparently markedly reduces the production of the hydroxylamine metabolite of dapsone (the AUC fell by more than half). Dapsone hydroxylamine appears to be responsible for the methaemoglobinaemia and haemolysis that may occur with dapsone.[1] These findings were later confirmed in 6 patients taking long-term dapsone 75 to 350 mg daily who were given **cimetidine** 1.2 g daily for 2 weeks. Steady-state serum dapsone levels rose by about 47%, accompanied by a fall in serum methaemoglobin levels from 7.1% to 5.2% (reference range less than 2%) in the first week.[2] Similar findings were reported in a further 3-month study in 8 patients.[3] However, a sustained decrease in methaemoglobin was not seen, with levels returning to baseline at week 12, despite the continued use of **cimetidine**.[3] Another report based on a small number of patients, comparing those given **cimetidine**, **ranitidine** or **omeprazole** with those not tak-

ing acid suppression, found no difference in the outcome of dapsone prophylaxis for pneumocystis pneumonia in HIV-positive patients.[4] A study in healthy subjects found that the increase in pH produced by **nizatidine** did not result in any clinically significant changes in the rate or extent of dapsone absorption.[5] It would therefore seem that no additional precautions are needed if H_2-receptor antagonists or proton pump inhibitors are given to patients taking dapsone. Consider also 'Dapsone + Antacids', p.341.

1. Coleman MD, Scott AK, Breckenridge AM, Park BK. The use of cimetidine as a selective inhibitor of dapsone *N*-hydroxylation in man. *Br J Clin Pharmacol* (1990) 30, 761–7.
2. Coleman MD, Rhodes LE, Scott AK, Verbov JL, Friedmann PS, Breckenridge AM, Park BK. The use of cimetidine to reduce dapsone-dependent methaemoglobinaemia in dermatitis herpetiformis patients. *Br J Clin Pharmacol* (1992) 34, 244–9.
3. Rhodes LE, Tingle MD, Park BK, Chu P, Verbov JL, Friedmann PS. Cimetidine improves the therapeutic/toxic ratio of dapsone in patients on chronic dapsone therapy. *Br J Dermatol* (1995) 132, 257–62.
4. Huengsberg M, Castelino S, Sherrard J, O'Farrell N, Bingham J. Does drug interaction cause failure of PCP prophylaxis with dapsone? *Lancet* (1993) 341, 48.
5. Itokazu GA, Fischer JH, Manitpisitkul P, Hariharan R, Danziger LH. Lack of effect of nizatidine-induced elevation of gastric pH on the oral bioavailability of dapsone in healthy volunteers. *Pharmacotherapy* (2002) 22, 1420–5.

Dapsone + Fluconazole

Fluconazole decreases the production of the toxic metabolite of dapsone, and might therefore reduce the incidence of adverse reactions to dapsone.

Clinical evidence, mechanism, importance and management

Twelve HIV-positive patients were given dapsone 100 mg daily for 2 weeks and then in random order either fluconazole 200 mg daily, rifabutin 300 mg daily or fluconazole with rifabutin, each for 2 weeks. Dapsone pharmacokinetics were unaffected by fluconazole. However, fluconazole inhibited the production of the *N*-hydroxylamine metabolite of dapsone (AUC, urinary recovery, and formation clearance reduced by about 50%).[1]

Hydroxylamine is assumed to be responsible for the haematological toxicity of dapsone (methaemoglobinaemia). The findings of this study suggest that the production of this metabolite is mediated by the cytochrome P450 isoenzyme CYP2C9, which fluconazole inhibits.

On the basis of these results, fluconazole would not be expected to alter the efficacy of dapsone, but might reduce its toxicity. Further study is needed to assess this potential.

1. Winter HR, Trapnell CB, Slattery JT, Jacobson M, Greenspan DL, Hooton TM, Unadkat JD. The effect of clarithromycin, fluconazole, and rifabutin on dapsone hydroxylamine formation in individuals with human immunodeficiency virus infection (AACTG 283). *Clin Pharmacol Ther* (2004) 76, 579–87.

Dapsone + Probenecid

The serum levels of dapsone can be markedly raised by probenecid.

Clinical evidence

Twelve patients with quiescent tuberculoid leprosy were given dapsone 300 mg with probenecid 500 mg, and 5 hours later another 300-mg dose of dapsone. At 4 hours, the dapsone serum levels were raised by about 50%. The urinary excretion of dapsone and its metabolites were reduced.[1]

Mechanism

Not fully examined. It seems probable that the probenecid inhibits the renal excretion of dapsone by the kidney.

Importance and management

The documentation is very limited. It is likely that the probenecid will raise the serum levels of dapsone given long-term. The importance of this is uncertain, but the extent of the rise and evidence that the haematological toxicity of dapsone may be related to dapsone levels[2] suggests that it may well have some clinical importance. It would therefore seem prudent to monitor for dapsone adverse effects if probenecid is also given.

1. Goodwin CS, Sparell G. Inhibition of dapsone excretion by probenecid. *Lancet* (1969) ii, 884–5.
2. Ellard GA, Gammon PT, Savin JA, Tan RS-H. Dapsone acetylation in dermatitis herpeti-

Dapsone + Proguanil

No pharmacokinetic interaction appears to occur between dapsone and proguanil, and they have been successfully used together for malaria prophylaxis.

Clinical evidence, mechanism, importance and management

A study in 6 healthy subjects found that proguanil 200 mg daily had no effect on the pharmacokinetics of dapsone 10 mg daily, nor on its principal metabolite, monoacetyldapsone. The authors of this report are extremely cautious because, despite this lack of a pharmacokinetic interaction at these doses, they say that increased dapsone toxicity cannot be ruled out.[1] However, dapsone 25 mg was successfully used with proguanil 200 mg daily for malaria prophylaxis in the Vietnam war,[2] and the same regimen, but with the dapsone dose every third day was successful as prophylaxis against proguanil-resistant falciparum malaria in Papua New Guinea.[1] Moreover, a different dose (dapsone 4 or 12.5 mg with proguanil 200 mg daily), was well tolerated over a period of 80 days when used as malaria prophylaxis in Thailand.[3]

1. Edstein MD, Rieckmann KH. Lack of effect of proguanil on the pharmacokinetics of dapsone in healthy volunteers. *Chemotherapy* (1993) 39, 235–41.
2. Black RH. Malaria in the Australian army in South Vietnam. Successful use of a proguanil-dapsone combination for chemoprophylaxis of chloroquine-resistant falciparum malaria. *Med J Aust* (1973) 1, 1265–70.
3. Shanks GD, Edstein MD, Suriyamongkol V, Timsaad S, Webster HK. Malaria prophylaxis using proguanil/dapsone combinations on the Thai-Cambodian border. *Am J Trop Med Hyg* (1992) 46, 643–8.

Dapsone + Pyrimethamine

Pyrimethamine does not significantly affect the pharmacokinetics of dapsone.

Clinical evidence, mechanism, importance and management

A study in 7 healthy subjects given single doses of dapsone 100 mg, pyrimethamine 25 mg, or both drugs together found that the peak plasma levels of dapsone fell by 17%, its half-life was unchanged, and the apparent volume of distribution was increased by 26% (from 1.53 to 1.93 L/kg). The pharmacokinetics of pyrimethamine were not affected by dapsone.[1] In another study HIV-positive patients were given dapsone 200 mg weekly (the maximum tolerated dose) either alone or with pyrimethamine 25 mg weekly. In contrast to the earlier study, there was a *decrease* in the volume of distribution of dapsone when it was given with pyrimethamine, although dapsone levels were not significantly altered.[2] Furthermore, the tolerability of once-weekly dapsone with pyrimethamine was found to be similar to that of once-weekly dapsone alone.[2]

1. Ahmad RA, Rogers HJ. Pharmacokinetics and protein binding interactions of dapsone and pyrimethamine. *Br J Clin Pharmacol* (1980) 10, 519–24.
2. Falloon J, Lavelle J, Ogata-Arakaki D, Byrne A, Graziani A, Morgan A, Amantea MA, Ownby K, Polis M, Davey RT, Kovacs JA, Lane HC, Masur H, MacGregor RR. Pharmacokinetics and safety of weekly dapsone and dapsone plus pyrimethamine for prevention of pneumocystis pneumonia. *Antimicrob Agents Chemother* (1994) 38, 1580–7.

Dapsone + Rifamycins

Rifampicin (rifampin) increases the urinary excretion of dapsone, lowers its serum levels and increases the risk of toxicity (methaemoglobinaemia). Similarly, rifabutin increases the clearance of dapsone, and may also increase its toxicity.

Clinical evidence

(a) Rifabutin

Twelve HIV-positive patients were given dapsone 100 mg daily for 2 weeks and then, in random order, either rifabutin 300 mg daily, fluconazole 200 mg daily, or fluconazole with rifabutin, each for 2 weeks. Rifabutin alone increased the clearance of dapsone by 67%. When combined with fluconazole, rifabutin increased the clearance of dapsone by 38%, which shows that fluconazole (a known enzyme inhibitor) partially attenuates the enzyme-inducing effects of rifabutin. Rifabutin increased the formation clearance of dapsone by 92%, which was again attenuated by

fluconazole. Rifabutin did not affect the AUC of the hydroxylamine metabolite of dapsone, which is thought to be associated with dapsone toxicity.[1]

Similarly, in a population analysis of 60 HIV-positive children, 7 of whom were also receiving rifabutin, factors associated with increased dapsone clearance included rifabutin use. It was suggested that dapsone clearance was increased by 38 to 50% in these children.[2]

(b) Rifampicin (Rifampin)

A study in 7 patients with leprosy given single doses of dapsone 100 mg and rifampicin 600 mg, alone or together, found that while the pharmacokinetics of rifampicin were not significantly changed, the half-life of dapsone was roughly halved and the AUC was reduced by about 20%.[3] Other studies in patients given both drugs for several days, similarly found reduced dapsone serum levels and an increased urinary excretion.[4-8] Likewise, a study in HIV-positive adults also found lowered dapsone levels in the presence of rifampicin.[9] Another study in 12 healthy subjects given a single 100-mg dose of dapsone before and after taking rifampicin 600 mg daily for 10 days, found that the clearance of dapsone was increased more than 3.5-fold (from 2.01 to 7.17 L/hour). Of equal importance was the finding that the production of the hydroxylamine metabolite of dapsone, which appears to be responsible for the haematological toxicity (methaemoglobinaemia), was markedly increased. The 24-hour AUC of methaemoglobin was increased by more than 60%,[10] suggesting that this interaction increases dapsone toxicity.

Mechanism

Rifampicin and rifabutin increase the metabolism and clearance of dapsone. Rifampicin also increases the blood levels of the toxic hydroxylamine metabolite of dapsone. Similarly, rifabutin increased the formation of this metabolite, although increases in the AUC were not seen.

Importance and management

The interaction between dapsone and rifampicin is established but of uncertain clinical importance. Concurrent use should be well monitored to confirm that treatment is effective. It may be necessary to raise the dose of dapsone. It has been pointed out that there is the risk of treatment failures for pneumocystis pneumonia as well as for leprosy.[11] Also be alert for any evidence of methaemoglobinaemia.

Although there is less information, rifabutin appears to interact similarly to rifampicin. When dapsone is given with rifabutin, the dose of dapsone may need to be increased, but this may increase exposure to the potentially toxic hydroxylamine metabolite.[1]

1. Winter HR, Trapnell CB, Slattery JT, Jacobson M, Greenspan DL, Hooton TM, Unadkat JD. The effect of clarithromycin, fluconazole, and rifabutin on dapsone hydroxylamine formation in individuals with human immunodeficiency virus infection (AACTG 283). *Clin Pharmacol Ther* (2004) 76, 579–87.
2. Mirochnick M, Cooper E, Capparelli E, McIntosh K, Lindsey J, Xu J, Jacobus D, Mofenson L, Bonagura VR, Nachman S, Yogev R, Sullivan JL, Spector SA. Population pharmacokinetics of dapsone in children with human immunodeficiency virus infection. *Clin Pharmacol Ther* (2001) 70, 24–32.
3. Krishna DR, Appa Rao AVN, Ramanakar TV, Prabhakar MC. Pharmacokinetic interaction between dapsone and rifampicin in leprosy patients. *Drug Dev Ind Pharm* (1986) 12, 443–59.
4. Balakrishnan S, Seshadri PS. Drug interactions – the influence of rifampicin and clofazimine on the urinary excretion of DDS. *Lepr India* (1981) 53, 17–22.
5. Peters JH, Murray JF, Gordon GR, Gelber RH, Laing ABG, Waters MFR. Effect of rifampin on the disposition of dapsone in Malaysian leprosy patients. *Fedn Proc* (1977) 36, 996.
6. George J, Balakrishnan S, Bhatia VN. Drug interaction during multidrug regimens for treatment of leprosy. *Indian J Med Res* (1988) 87, 151–6.
7. Pieters FAJM, Woonink F, Zuidema J. Influence of once-monthly rifampicin and daily clofazimine on the pharmacokinetics of dapsone in leprosy patients in Nigeria. *Eur J Clin Pharmacol* (1988) 34, 73–6.
8. Venkatesan K, Bharadwaj VP, Ramu G, Desikan KV. Study on drug interactions. *Lepr India* (1980) 52, 229–35.
9. Gatti G, Merighi M, Hossein J, Travaini S, Casazza R, Karlsson M, Cruciani M, Bassetti D. Population pharmacokinetics of dapsone administered biweekly to human immunodeficiency virus-infected patients. *Antimicrob Agents Chemother* (1996) 40, 2743–8.
10. Occhipinti DJ, Choi A, Deyo K, Danziger LH, Fischer JH. Influence of rifampin and clarithromycin on dapsone (D) disposition and methemoglobin concentrations. *Clin Pharmacol Ther* (1995) 57, 163.
11. Jorde UP, Horowitz HW, Wormser GP. Significance of drug interactions with rifampin in *Pneumocystis carinii* pneumonia prophylaxis. *Arch Intern Med* (1992) 152, 2348.

Dapsone + Trimethoprim

The serum levels of both dapsone and trimethoprim are possibly raised by concurrent oral use. Both increased efficacy and dapsone toxicity have been seen. Topical dapsone levels are also raised by trimethoprim given as co-trimoxazole.

Clinical evidence

Eighteen patients with AIDS, treated for pneumocystis pneumonia and taking dapsone 100 mg daily, were compared with 30 other patients taking dapsone with trimethoprim 20 mg/kg daily. Trimethoprim raised dapsone levels by 40% (from 1.5 to 2.1 micrograms/mL), at 7 days (steady-state). Dapsone toxicity (methaemoglobinaemia) was also increased.[1] Trimethoprim plasma levels were 48% higher in the 30 patients also taking dapsone when compared with another group of 30 patients given co-trimoxazole (trimethoprim with sulfamethoxazole), but the incidence of toxicity was higher in the co-trimoxazole group.[1] However, a later study by the same authors in 8 asymptomatic HIV-positive patients given dapsone 100 mg daily and trimethoprim 200 mg every 12 hours found that the steady-state pharmacokinetics of each drug was unaffected by the other, although the single dose pharmacokinetics indicated higher serum levels than at steady state for both drugs.[2]

A study in 17 patients with acne vulgaris who applied dapsone 5% gel topically, and took co-trimoxazole (trimethoprim with sulfamethoxazole) 960 mg twice daily, found no significant change in the pharmacokinetics of either trimethoprim or sulfamethoxazole. In contrast, the AUC and maximum plasma level of dapsone were increased by 45% and 39%, respectively. Further, the AUC and maximum plasma level of dapsone hydroxylamine, the metabolite responsible for the haematological adverse effects, were increased by 145% and 113%, respectively. However, these parameters were still lower than would be expected after an oral dose of dapsone 100 mg.[3]

Mechanism

Not understood. Dapsone and trimethoprim appear to have mutually inhibitory effects on clearance.

Importance and management

Information is limited. The difference between the results of the two studies using oral dapsone may be because the first was in patients with AIDS and pneumocystis pneumonia and the second was in asymptomatic HIV-positive patients whose drug metabolism may possibly be different. Concurrent use appears to be an effective form of treatment, but be alert for evidence of increased dapsone toxicity (methaemoglobinaemia). No adverse effects would be expected if topical dapsone is given with oral trimethoprim or co-trimoxazole.

1. Lee BL, Medina I, Benowitz NL, Jacob P, Wofsy CB, Mills J. Dapsone, trimethoprim, and sulfamethoxazole plasma levels during treatment of pneumocystis pneumonia in patients with acquired immunodeficiency syndrome (AIDS). *Ann Intern Med* (1989) 110, 606–11.
2. Lee BL, Safrin S, Makrides V, Gambertoglio JG. Zidovudine, trimethoprim, and dapsone pharmacokinetic interactions in patients with human immunodeficiency virus infection. *Antimicrob Agents Chemother* (1996) 40, 1231–6.
3. Thiboutot DM, Willmer J, Sharata H, Halder R, Garrett S. Pharmacokinetics of dapsone gel, 5% for the treatment of acne vulgaris. *Clin Pharmacokinet* (2007) 46, 697–712.

Dapsone + Ursodeoxycholic acid (Ursodiol)

A single case suggests that the effectiveness of dapsone in the treatment of dermatitis herpetiformis may be reduced by ursodeoxycholic acid.

Clinical evidence, mechanism, importance and management

A 61-year-old man taking dapsone 50 mg daily for dermatitis herpetiformis started taking ursodeoxycholic acid 450 mg twice daily for cholecystitis. Two weeks later the dermatitis herpetiformis worsened and the dose of dapsone was increased to 150 mg daily. However, his condition did not improve, so ursodeoxycholic acid was stopped and, as his condition improved, the dapsone dose was reduced to 100 mg, and then 50 mg daily. Two months later ursodeoxycholic acid was restarted and there was again an exacerbation of the dermatitis herpetiformis.[1] This case appears to have also been published elsewhere.[2] The general importance of this isolated report is unknown, but consider the possibility of reduced dapsone effects if ursodeoxycholic acid is also given.

1. Stroubou E, Dawn G, Forsyth A. Ursodeoxycholic acid causing exacerbation of dermatitis herpetiformis. *J Am Acad Dermatol* (2001) 45, 319–20.
2. Schmutz J-L, Barbaud A, Trechot PH. Interaction acide ursodéoxycholique-dapsone. *Ann Dermatol Venereol* (2003) 130, 391.

Daptomycin + Aminoglycosides

The pharmacokinetics of daptomycin are not altered by gentamicin or tobramycin. The pharmacokinetics of tobramycin are not altered by daptomycin.

Clinical evidence, mechanism, importance and management

(a) Gentamicin

In a crossover study in 11 healthy subjects who were given intravenous daptomycin 6 mg/kg daily for 3 days with 1 mg/kg gentamicin given every 8 hours starting after the second dose of daptomycin, there were no clinically significant changes in the pharmacokinetics of daptomycin.[1] No daptomycin dose adjustment therefore seems necessary on concurrent use.

(b) Tobramycin

In a crossover study, 6 healthy subjects were given daptomycin 2 mg/kg, tobramycin 1 mg/kg, or both drugs together. There was no change in the pharmacokinetics of either drug.[2] No dose adjustment of either drug would be expected to be necessary on concurrent use.

1. DeRyke CA, Sutherland C, Zhang B, Nicolau DP, Kuti JL. Serum bactericidal activities of high-dose daptomycin with and without coadministration of gentamicin against isolates of *Staphylococcus aureus* and *Enterococcus* species. *Antimicrob Agents Chemother* (2006) 50, 3529–3534.
2. Woodworth JR, Nyhart EH, Wolny JD, Brier GL, Black HR. Tobramycin and daptomycin disposition when co-administered to healthy volunteers. *J Antimicrob Chemother* (1994) 33, 655–9.

Daptomycin + Miscellaneous

The use of statins, probably fibrates and possibly ciclosporin with daptomycin may increase the risk of muscle toxicity. Daptomycin does not appear to interact with warfarin, but its use may result in falsely elevated prothrombin times. NSAIDs may reduce daptomycin excretion and concurrent use may increase the risks of renal impairment. Probenecid and aztreonam do not appear to affect the pharmacokinetics of daptomycin.

Clinical evidence, mechanism, importance and management

(a) Drugs causing myopathy

The US manufacturers describe a study in 20 healthy subjects taking **simvastatin** 40 mg daily, in which the addition of daptomycin 4 mg/kg per day for 14 days did not result in an increase in adverse effects, when compared with subjects given placebo. In contrast, in a phase III study of patients with bacteraemia, 5 out of 22 patients who were currently, or had recently, been taking a **statin** developed raised creatinine phosphokinase levels.[1] Furthermore, a case report describes a patient who was given daptomycin 6.5 mg/kg daily, who developed muscle pain and a raised creatinine phosphokinase level (20 771 units/L). He had been taking **simvastatin**, but this had been discontinued when the daptomycin was started.[2] It is difficult to know whether this was a result of an interaction as another case of rhabdomyolysis (creatinine phosphokinase 21 243 units/L) was attributed to the use of daptomycin alone: the patient was taking no other drugs known to cause myopathy (fibrates and statins specifically mentioned).[3] A review of patients with Gram-positive complicated skin and skin structure infections found that musculoskeletal pain or myalgia occurred in up to 0.4% of patients. In patients with similar infections treated with daptomycin the incidence of myopathy was slightly higher, at 0.2 to 0.9%,[4] suggesting that daptomycin may modestly increase the risk of muscle toxicity.

The manufacturers note that experience of the concurrent use of daptomycin with statins is limited, and therefore the use of a statin should be suspended if daptomycin is given,[1,5] unless the benefits of concurrent use outweigh the risks, in which case the patient's creatine kinase should be monitored more frequently than weekly.[5] See also 'muscle toxicity', (p.1313), for further guidance on monitoring for statin-associated myopathy, and risk factors for muscle toxicity. The UK manufacturers give the same guidance for **fibrates** and **ciclosporin**, both of which have been associated with myopathy.[1]

(b) NSAIDs

The UK manufacturers note that NSAIDs (including coxibs) may reduce the renal excretion of daptomycin and have additive detrimental effects on renal function if used with daptomycin.[5] They advise caution on concurrent use, which in practice probably means keeping a close eye on renal function and monitoring for possible daptomycin adverse effects.

(c) Warfarin

The US manufacturers describe a study in 16 healthy subjects in which daptomycin 6 mg/kg daily for 5 days did not affect either the pharmacokinetics or the INR in response to a single 25-mg dose of warfarin. The pharmacokinetics of daptomycin were also unchanged.[1] However, as experience is limited the manufacturers advise monitoring the INR for the first few days of concurrent use. Note that daptomycin causes a concentration-dependent false prolongation of the prothrombin time.[1,5] This only appears to occur with recombinant thromboplastin reagents. Blood for INR testing should therefore be drawn during the daptomycin trough (i.e. immediately before the next dose). If a raised INR is found it is recommended that the INR should be re-tested, and alternative methods of monitoring should be considered.[1]

(d) Miscellaneous

The US manufacturers[1] briefly mention a small study in which daptomycin was given with **aztreonam** without any significant change in the pharmacokinetics of either drug. They also mention a study in which **probenecid** did not alter the pharmacokinetics of daptomycin.

1. Cubicin (Daptomycin). Cubist Pharmaceuticals, Inc. US Prescribing information, August 2008.
2. Echevarria K, Datta P, Cadena J, Lewis JS. Severe myopathy and possible hepatotoxicity related to daptomycin. *J Antimicrob Chemother* (2005) 55, 599–600.
3. Kazory A, Dibadj, K, Weiner ID. Rhabdomyolysis and acute renal failure in a patient treated with daptomycin. *J Antimicrob Chemother* (2006) 57, 578–9.
4. Fenton C, Keating GM, Curran MP. Daptomycin. *Drugs* (2004) 64, 445–55.
5. Cubicin (Daptomycin). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, July 2009.

Ethambutol + Antacids

Aluminium hydroxide and aluminium/magnesium hydroxide can cause a small reduction in the absorption of ethambutol in some patients.

Clinical evidence, mechanism, importance and management

A study in 13 patients with tuberculosis, given a single 50-mg/kg dose of ethambutol, found that when they were also given three 1.5-g doses of **aluminium hydroxide gel** (at the same time and 15 and 30 minutes later) their peak serum ethambutol levels were delayed and reduced. The average urinary excretion of ethambutol over a 10-hour period was reduced by about 15%, but there were marked variations between individual patients. In some patients there was no interaction, and the absorption of ethambutol was even increased in others.[1] No interaction was seen in 6 healthy subjects similarly treated.[1] A further study in 14 healthy subjects found that 30 mL of an **aluminium/magnesium hydroxide** antacid decreased the AUC and maximum serum levels of a 25-mg/kg dose of ethambutol by 10% and 29%, respectively.[2]

The reason for this interaction is not understood, but **aluminium hydroxide** can affect gastric emptying. The reduction in absorption is generally small and variable, and it seems doubtful if it will have a significant effect on the treatment of tuberculosis. However, the authors of the second study suggest avoiding giving antacids at the same time as ethambutol,[2] and the US manufacturer states that **aluminium hydroxide**-containing antacids should not be taken until 4 hours after a dose of ethambutol.[3]

1. Mattila MJ, Linnoila M, Seppälä T, Koskinen R. Effect of aluminium hydroxide and glycopyrrhonium on the absorption of ethambutol and alcohol in man. *Br J Clin Pharmacol* (1978) 5, 161–6.
2. Peloquin CA, Bulpitt AE, Jaresko GS, Jelliffe RW, Childs JM, Nix DE. Pharmacokinetics of ethambutol under fasting conditions, with food, and with antacids. *Antimicrob Agents Chemother* (1999) 43, 568–72.
3. Myambutol (Ethambutol). X-Gen Pharmaceuticals Inc. US Prescribing information, May 2007.

Ethambutol + Food

The pharmacokinetics of ethambutol given with a high-fat breakfast were only slightly different to its pharmacokinetics when it is

given in the fasting state.[1] Therefore ethambutol may be given without regard to meals.

1. Peloquin CA, Bulpitt AE, Jaresko GS, Jelliffe RW, Childs JM, Nix DE. Pharmacokinetics of ethambutol under fasting conditions, with food, and with antacids. *Antimicrob Agents Chemother* (1999) 43, 568–72.

Ethambutol + Rifabutin

Rifabutin does not appear to affect the pharmacokinetics of ethambutol.

Clinical evidence, mechanism, importance and management

Ten healthy subjects were given a single 1.2-g dose of ethambutol before and after taking rifabutin 300 mg daily for a week. No clinically relevant changes in the pharmacokinetics of ethambutol were seen.[1] Although 5 of the subjects experienced moderate to severe chills, and one had transient thrombocytopenia, these reactions are unlikely to have been due to an interaction. No special precautions would appear to be necessary during concurrent use.

1. Breda M, Benedetti MS, Bani M, Pellizzoni C, Poggesi I, Brianceschi G, Rocchetti M, Dolfi L, Sassella D, Rimoldi R. Effect of rifabutin on ethambutol pharmacokinetics in healthy volunteers. *Pharmacol Res* (1999) 40, 351–6.

Ethionamide + Isoniazid

Isoniazid may contribute to acute psychotic reactions associated with ethionamide, but evidence for this is limited.

Clinical evidence, mechanism, importance and management

Acute psychotic reactions occurring during treatment with either isoniazid or ethionamide are reported to be uncommon.[1] Acute mania occurred in a patient taking streptomycin, isoniazid and prednisolone for 4 months, and ethionamide and pyrazinamide for 27 days. It was thought that ethionamide was probably responsible for the psychotic reaction but that isoniazid and prednisolone may have potentiated the reaction.[2] In another patient, ethionamide was considered to be responsible for psychological changes, which resolved when the drug was stopped. However, the contribution of alcohol and other concurrent drugs such as isoniazid was not ruled out.[3] One study in patients found that ethionamide 750 mg increased the serum levels of a single 10-mg/kg dose of isoniazid at 4 hours but not at one or 10 hours, but this was not considered to be of therapeutic significance[4] and the toxic symptoms reported with the combination[5,6] were considered not to be due to increased isoniazid levels.[4]

A clinically significant interaction therefore seems unlikely, but as both drugs can, rarely, cause psychotic reactions these tentative reports cannot entirely be dismissed.

1. Sharma GS, Gupta PK, Jain NK, Shanker A, Nanawati V. Toxic psychosis to isoniazid and ethionamide in a patient with pulmonary tuberculosis. *Tubercle* (1979) 60, 171–2.
2. Narang RK. Acute psychotic reaction probably caused by ethionamide. *Tubercle* (1972) 137–8.
3. Lansdown FS, Beran M, Litwak T. Psychotoxic reaction during ethionamide therapy. *Am Rev Respir Dis* (1967) 95,1053–5.
4. Tiitinen H. Isoniazid and ethionamide serum levels and inactivation in Finnish subjects. *Scand J Respir Dis* (1969) 50, 110–24.
5. Brouet G, Marche J, Rist N, Chevallier J, LeMeur G. Observations on the antituberculous effectiveness of alpha-ethyl-thioisonicotinamide in tuberculosis in humans. *Am Rev Tuberc* (1959) 79, 6–18.
6. Trendelenburg F. Antibakterielle chemotherapie der tuberkulose. *Fortschr Arzneimittelforsch* (1964) 7, 193–303.

Ethionamide + Miscellaneous

A study in 12 healthy subjects found that the bioavailability of a single 500-mg dose of ethionamide was not significantly affected by food, orange juice or antacids, when compared with ethionamide bioavailability under fasting conditions. It was suggested that ethionamide may be given with food if tolerance is a problem.[1] The US manufacturer of ethionamide advises that it may be taken without regard to meals.[2]

1. Auclair B, Nix DE, Adam RD, James GT, Peloquin CA. Pharmacokinetics of ethionamide administered under fasting conditions or with orange juice, food, or antacids. *Antimicrob Agents Chemother* (2001) 45, 810–4.
2. Trecator (Ethionamide). Wyeth Pharmaceuticals Inc. US Prescribing information, November 2007.

Fosfomycin + Cimetidine

In a study in 9 healthy subjects, the pharmacokinetics of a 50-mg dose of fosfomycin were not significantly altered by two 400 mg doses of cimetidine, given the night before and 30 minutes before the fosfomycin.[1]

1. Bergan T, Mastropaolo G, Di Mario F, Naccarato R. Pharmacokinetics of fosfomycin and influence of cimetidine and metoclopramide on the bioavailability of fosfomycin trometamol. New Trends in Urinary Tract Infections (eds Neu and Williams) Int Symp Rome 1987, p 157–66. Published in 1988.

Fosfomycin + Metoclopramide

Metoclopramide reduces fosfomycin bioavailability.

Clinical evidence, mechanism, importance and management

Metoclopramide 20 mg given to 9 healthy subjects 30 minutes before fosfomycin 50 mg/kg reduced the peak serum levels of fosfomycin by 42% and reduced the AUC by 27%. These changes appear to occur because metoclopramide speeds the transit through the gut, so that less time is available for good absorption. However, despite these reductions, the urinary concentrations of fosfomycin remained above the minimum levels required for common urinary pathogens for at least 36 hours after the dose.[1] This suggests that the interaction is unlikely to be clinically important.

1. Bergan T, Mastropaolo G, Di Mario F, Naccarato R. Pharmacokinetics of fosfomycin and influence of cimetidine and metoclopramide on the bioavailability of fosfomycin trometamol. New Trends in Urinary Tract Infections (eds Neu and Williams) Int Symp Rome 1987, p 157–66. Published in 1988.

Fusidic acid + Colestyramine

***In vitro* studies have shown that colestyramine can bind with sodium fusidate in the gut, thereby reducing its activity,[1] and *in vivo animal* studies have shown peak fusidate levels are decreased by 33 to 77% by colestyramine,[2] but whether this also occurs clinically has not been confirmed. It is generally recommended that other drugs are given one hour before or 4 to 6 hours after colestyramine.**

1. Johns WH, Bates TR. Drug-cholestyramine interactions. I: Physicochemical factors affecting *in vitro* binding of sodium fusidate to cholestyramine. *J Pharm Sci* (1972) 61, 730–5.
2. Johns WH, Bates TR. Drug-cholestyramine interactions. II: Influence of cholestyramine on GI absorption of sodium fusidate. *J Pharm Sci* (1972) 61, 735–9.

Isoniazid + Aminosalicylic acid

Isoniazid levels are raised by aminosalicylic acid.

Clinical evidence, mechanism, importance and management

A study found that aminosalicylic acid significantly increased the plasma levels of isoniazid at 4 and 6 hours after administration by 32% and 114%, respectively in fast acetylators of isoniazid, and by 21% and 39%, respectively in slow acetylators of isoniazid. The half-life of isoniazid was increased from 1.32 hours to 2.89 hours in the fast acetylators and from 3.05 hours to 4.27 hours in the slow acetylators (see 'Genetic factors', (p.4), for more information about acetylator status). The effects were probably due to the inhibition of isoniazid metabolism by aminosalicylic acid.[1] There seem to be no reports of isoniazid toxicity arising from this interac-

tion, but the manufacturers of isoniazid warn that adverse effects are more likely in the presence of aminosalicylic acid.[2]

1. Hanngren Å, Borgå O, Sjöqvist F. Inactivation of isoniazid (INH) in Swedish tuberculous patients before and during treatment with para-aminosalicylic acid (PAS). *Scand J Respir Dis* (1970) 51, 61–9.
2. Isoniazid Tablets. UCB Pharma Ltd. UK Summary of product characteristics, July 2009.

Isoniazid + Antacids

The absorption of isoniazid from the gut is modestly reduced by aluminium hydroxide, slightly reduced by magaldrate, and not affected by aluminium/magnesium hydroxide tablets or didanosine chewable tablets.

Clinical evidence

Aluminium hydroxide (*Amphojel*) 45 mL was given to 10 patients with tuberculosis at 6 am, 7 am and 8 am, followed immediately by isoniazid and any other medication they were receiving. The plasma isoniazid levels at one hour were decreased, and peak plasma levels occurring between one and 2 hours after the dose were reduced by about 25%, when adjusted for different doses.[1] The effect of **magaldrate** (hydrated magnesium aluminate) was smaller,[1] and in another well-controlled study **aluminium/magnesium hydroxide** (*Mylanta*) had no effect on isoniazid plasma levels.[2]

Didanosine chewable tablets contain antacids (**aluminium/magnesium hydroxide**) in the formulation, but it has been shown that they do not affect the bioavailability of isoniazid.[3]

Mechanism

Aluminium hydroxide delays gastric emptying,[4,5] causing retention of the isoniazid in the stomach. As isoniazid is largely absorbed from the intestine, this explains the slight decrease in plasma isoniazid concentrations. Aluminium hydroxide also appears to inhibit the absorption of isoniazid.

Importance and management

Information on this interaction is limited, and it is not established. The clinical importance of the modest reductions in isoniazid levels with aluminium hydroxide in one study is uncertain, but likely to be small. Aluminium/magnesium hydroxide did not interact, and neither did didanosine chewable tablets.

1. Hurwitz A, Schlozman DL. Effects of antacids on gastrointestinal absorption of isoniazid in rat and man. *Am Rev Respir Dis* (1974) 109, 41–7.
2. Peloquin CA, Namdar S, Dodge AA, Nix DE. Pharmacokinetics of isoniazid under fasting conditions, with food, and with antacids. *Int J Tuberc Lung Dis* (1999) 3, 703–710.
3. Gallicano K, Sahai J, Zaror-Behrens G, Pakuts A. Effect of antacids in didanosine tablet on bioavailability of isoniazid. *Antimicrob Agents Chemother* (1994) 38, 894–7.
4. Vats TS, Hurwitz A, Robinson RG, Herrin W. Effects of antacids on gastric emptying in children. *Pediatr Res* (1973) 7, 340.
5. Hava M, Hurwitz A. The relaxing effect of aluminium and lanthanum on rat and human gastric smooth muscle in vitro. *Eur J Pharmacol* (1973) 22, 156–61.

Isoniazid + Chlorpromazine

A study in 11 patients found that the half-life of isoniazid was increased by 41% when a single 300-mg dose of chlorpromazine was given one hour before a single 5 mg/kg intravenous dose of isoniazid.[1] The clinical relevance of this finding is unclear.

1. Matilla MJ, Takki S. Half-lives of isoniazid and salicylic acid in serum and their modification by different drugs in psychiatric patients. *Ann Med Exp Biol Fenn* (1969) 47, 124–8.

Isoniazid + Disulfiram

In most patients the concurrent use of isoniazid and disulfiram is uneventful, but difficulties in co-ordination, with changes in mental status, behaviour, and drowsiness have been reported in a small number of patients.

Clinical evidence

Seven patients with tuberculosis who had been taking isoniazid for at least 30 days, without problems, experienced adverse reactions within 2 to 8 days of starting to take disulfiram 500 mg daily. Among the symptoms were dizziness, disorientation, a staggering gait, insomnia, irritability and querulous behaviour, listlessness, and lethargy. One patient became hypomanic. Most of the patients were also taking chlordiazepoxide, and other drugs included aminosalicylic acid, streptomycin and phenobarbital. The adverse reactions decreased or disappeared when the disulfiram was either reduced to 250 or 125 mg daily, or withdrawn. These 7 patients represented less than one-third of those who received both drugs.[1] As disulfiram is known to inhibit the metabolism of chlordiazepoxide,[2] another 4 patients were given only isoniazid and disulfiram. Although their reaction was not as severe, all 4 developed drowsiness and depression.[1]

In contrast, another report describes the concurrent use of both drugs, without problems, in 200 patients.[3] A retrospective study in patients taking isoniazid-containing regimens for tuberculosis found no difference in the rate of toxicity in 13 patients taking disulfiram, when compared with a large group of patients not taking disulfiram. However, the small number of patients taking disulfiram in this study limits the strength of the negative finding.[4] Another patient taking disulfiram with isoniazid and rifampicin (rifampin) also did not experience any problems.[5]

Mechanism

Not understood. One idea is that some kind of synergy occurs between the two drugs because both can produce similar adverse effects if given in high doses. The authors of one report[1] speculate that isoniazid and disulfiram together inhibit two of three biochemical pathways concerned with the metabolism of dopamine. This leaves a third pathway open, catalysed by COMT (catechol-*O*-methyl transferase), which produces a number of methylated products of dopamine. These methylated products may possibly have been responsible for the mental and physical reactions seen.

Importance and management

Information about this interaction appears to be limited to the reports cited. Its incidence is uncertain but apparently quite small. Two-thirds of the patients in one study, and at least 200 other patients did not experience an interaction. It would therefore seem that concurrent use need not be avoided, but the response should be monitored. If marked changes in mental status occur, or there is unsteady gait, the manufacturers recommend that the disulfiram should be withdrawn.[6]

1. Whittington HG, Grey L. Possible interaction between disulfiram and isoniazid. *Am J Psychiatry* (1969) 125, 1725–9.
2. Antabuse (Disulfiram). Actavis UK Ltd. UK Summary of product characteristics, September 2007.
3. McNichol RW, Ewing JA, Faiman MD, eds. Disulfiram (Antabuse), a unique medical aid to sobriety: history, pharmacology, research, clinical use. Springfield Ill: Thomas; 1987 p. 47–90.
4. Burman WJ, Terra M, Breese P, Cohn D, Reves R. Lack of toxicity from concomitant directly observed disulfiram and isoniazid-containing therapy for active tuberculosis. *Int J Tuberc Lung Dis* (2002) 6, 839–42.
5. Rothstein E. Rifampin with disulfiram. *JAMA* (1972) 219, 1216.
6. Antabuse (Disulfiram). Odyssey Pharmaceuticals, Inc. US Prescribing information, December 2003.

Isoniazid + Etanercept

A case report describes a patient who developed optic neuritis while taking isoniazid and etanercept.

Clinical evidence, mechanism, importance and management

A case report describes a patient with rheumatoid arthritis who developed latent tuberculosis, and was given isoniazid and pyridoxine. Five days after starting to take these drugs, he also started treatment with subcutaneous etanercept twice weekly. Approximately 2 months later he experienced a reduction in visual acuity, which was attributed to optic neuritis. After stopping treatment with etanercept and isoniazid, and starting a corticosteroid, his condition improved. The authors of the case report considered that the combination of isoniazid and etanercept were causative factors in his optic neuritis, although either drug alone may have caused this adverse

effect.[1] No particular precautions are warranted on the basis of this isolated case.

1. Noguera-Pons R, Borrás-Blasco J, Romero-Crespo I, Antón-Torres R, Navarro-Ruiz A, González-Ferrandez JA. Optic neuritis with concurrent etanercept and isoniazid therapy. *Ann Pharmacother* (2005) 39, 2131–5.

Isoniazid + Ethambutol

Ethambutol does not appear to affect isoniazid levels. However, it seems that the optic neuropathy caused by ethambutol may be increased by isoniazid.

Clinical evidence, mechanism, importance and management

In 10 patients with tuberculosis, the mean serum levels of a 300-mg dose of isoniazid were not significantly changed by a single 20-mg/kg dose of ethambutol.[1] The possible effects of concurrent use over a period of time were not studied. However, there is some evidence that the optic neuropathy caused by ethambutol may be increased by isoniazid, and any effects resolve more slowly after the use of isoniazid.[2-5] One group of authors recommends that both ethambutol and isoniazid should be stopped immediately if severe optic neuritis occurs. They further recommend that isoniazid should be stopped if less severe optic neuritis does not improve within 6 weeks after stopping ethambutol.[6]

1. Singhal KC, Varshney DP, Rathi R, Kishore K, Varshney SC. Serum concentration of isoniazid administered with and without ethambutol in pulmonary tuberculosis patients. *Indian J Med Res* (1986) 83, 360–2.
2. Renard G, Morax PV. Nevrite optique au cours des traitements antituberculeux. *Ann Ocul (Paris)* (1977) 210, 53–61.
3. Karmon G, Savir H, Zevin D, Levi J. Bilateral optic neuropathy due to combined ethambutol and isoniazid treatment. *Ann Ophthalmol* (1979) 11, 1013–17.
4. Garret CR. Optic neuritis in a patient on ethambutol and isoniazid evaluated by visual evoked potentials: Case report. *Mil Med* (1985) 150, 43–6.
5. Jimenez-Lucho VE, del Busto R, Odel J. Isoniazid and ethambutol as a cause of optic neuropathy. *Eur J Respir Dis* (1987) 71, 42–5.
6. Sivakumaran P, Harrison AC, Marschner J, Martin P. Ocular toxicity from ethambutol: a review of four cases and recommended precautions. *N Z Med J* (1998) 111, 428–30.

Isoniazid + Fluconazole

A double-blind, crossover study in 16 healthy subjects (8 fast and 8 slow acetylators of isoniazid) found that fluconazole 400 mg daily for a week had no clinically significant effect on the pharmacokinetics of isoniazid.[1] No special precautions would appear necessary during concurrent use.

1. Buss DC, Routledge PA, Hutchings A, Brammer KW, Thorpe JE. The effect of fluconazole on the acetylation of isoniazid. *Hum Exp Toxicol* (1991) 10, 85–6.

Isoniazid + Food

The absorption of isoniazid is reduced by food. See also 'Isoniazid + Food; Cheese or Fish', below, for toxic reactions between isoniazid and specific foods.

Clinical evidence

In 9 healthy subjects the mean peak serum levels of isoniazid 10 mg/kg were delayed, and reduced by 79%,when isoniazid was given with breakfast rather than when fasting. The AUC was reduced by 43%.[1] In another study in 14 healthy subjects given isoniazid with a full fat breakfast, the maximum serum levels of isoniazid were decreased by 51%, its absorption was delayed, and its AUC was decreased by 12%.[2] Similar results have been found in other studies.[3,4]

Mechanism

Uncertain. Food delays gastric emptying so that absorption further along the gut is also delayed, but the reduction in absorption is not understood.

Importance and management

Information is limited but the interaction seems to be established. For maximum absorption isoniazid should be taken without food, hence the manufacturer's guidance to take it at least 30 minutes before or 2 hours after food.[5]

1. Melander A, Danielson K, Hanson A, Jansson L, Rerup C, Scherstén B, Thulin T, Wåhlin E. Reduction of isoniazid bioavailability in normal men by concomitant intake of food. *Acta Med Scand* (1976) 200, 93–7.
2. Peloquin CA, Namdar S, Dodge AA, Nix DE. Pharmacokinetics of isoniazid under fasting conditions, with food, and with antacids. *Int J Tuberc Lung Dis* (1999) 3, 703–710.
3. Männisto P, Mäntylä R, Klinge R, Nykänen S, Koponen A, Lamminsivu U. Influence of various diets on the bioavailability of isoniazid. *J Antimicrob Chemother* (1982) 10, 427–34.
4. Zwolska Z, Niemirowska-Mikulska H, Augustynowicz-Kopeć E. Wpływ pożywienia na biologiczną dostępność izoniazydu (INH) u zdrowych ochotników. *Pneumonol Alergol Pol* (1998) 66, 412–21.
5. Isoniazid Tablets. UCB Pharma Ltd. UK Summary of product characteristics, July 2009.

Isoniazid + Food; Cheese or Fish

Patients taking isoniazid who eat some foods, particularly fish from the scombroid family (tuna, mackerel, salmon) that are not fresh, may experience an exaggerated histamine poisoning reaction. Cheese has also been implicated in this reaction, but the adverse effects may be due to the weak MAOI effects of isoniazid rather than histamine poisoning.

Clinical evidence

Three months after starting to take isoniazid 300 mg daily, a woman experienced a series of unpleasant reactions 10 to 30 minutes after eating cheese. These reactions included chills, headache (sometimes severe), itching of the face and scalp, slight diarrhoea, flushing of the face (and on one occasion the whole body), variable and mild tachycardia, and a bursting sensation in the head. Blood pressure measurements showed only a modest rise (from her normal blood pressure of 95/65 mmHg to 110/80 mmHg). No physical or biochemical abnormalities were found.[1]

Headache, dizziness, blurred vision, tachycardia, flushing and itching of the skin, redness of the eyes, burning sensation of the body, difficulty in breathing, abdominal colic, diarrhoea, vomiting, sweating and wheezing have all been described after other patients taking isoniazid ate cheese.[2-6] Certain tropical fish, including **tuna** (**skipjack** or **bonito**; ***Katsuwanus pelamis***),[7-11] ***Sardinella (Amblygaster) sirm***,[12] ***Rastrigella kanagurta***,[13] **saury** (**skipper** or **bill-fish**)[14] and others[15] are also implicated. There are a few hundred cases of this reaction on record.

Mechanism

The reaction appears to be an exaggeration of the histamine poisoning that can occur after eating some foods, such as members of the scombroid family of fish (tuna, mackerel, salmon, etc), if they are not fresh and adequately refrigerated. These fish (and some cheeses) have a high histidine content and under poor storage circumstances the histidine is decarboxylated by bacteria to produce unusually large amounts of histamine. Normally this is inactivated by histaminase in the body, but isoniazid is a potent inhibitor of this enzyme, which means that the histamine is absorbed largely unchanged and histamine poisoning develops.[16] Histamine survives all but very prolonged cooking. Tuna fish can contain 180 to 500 mg histamine per 100 g, other types of fish may contain as little as 0.5 to 7.5 mg.[10]

Alternatively, it has been suggested that the cases of reactions to cheese are caused by tyramine content and the weak MAOI properties of isoniazid. See 'MAOIs or RIMAs + Tyramine-rich foods', p.1395, for more details of the mechanism of this interaction.

Importance and management

An established interaction of clinical importance. With the exception of one patient who appeared to have had a cerebrovascular accident,[9] the reactions experienced by the others were unpleasant and alarming but usually not serious or life-threatening. They required little or no treatment, although 'scombroid poisoning' in the absence of isoniazid is sometimes more serious. Two reports say that treatment with antihistamines can be effective.[10,15] Isoniazid has been in use since 1956 and there is little need to now introduce any general dietary restrictions, but if any of these reactions are experienced, examine the patient's diet and advise the avoidance of any probable offending foodstuffs. Very mature cheese and fish of the scombroid family (tuna, mackerel, salmon and other varieties of dark meat fish) that are not fresh are to be treated with suspicion, but the likely histamine or tyramine content of food cannot be assessed without undertak-

ing a detailed analysis. See 'Table 32.2', (p.1394), and 'Table 32.3', (p.1396), for a list of tyramine-rich foods and drinks.

1. Smith CK, Durack DT. Isoniazid and reaction to cheese. *Ann Intern Med* (1978) 88, 520–1.
2. Uragoda CG, Lodha SC. Histamine intoxication in a tuberculous patient after ingestion of cheese. *Tubercle* (1979) 60, 59–61.
3. Lejonc JL, Gusmini D, Brochard P. Isoniazid and reaction to cheese. *Ann Intern Med* (1979) 91, 793.
4. Hauser MJ, Baier H. Interactions of isoniazid with foods. *Drug Intell Clin Pharm* (1982) 16, 617–18.
5. Toutoungi M, Carroll R, Dick P. Isoniazide (INH) and tyramine-rich food. *Chest* (1986) 89 (Suppl 6), 540S.
6. Carvalho ACC, Manfrin M, Gore RP, Capone S, Scalvini A, Armellini A, Giovine T, Carosi G, Matteelli A. Reaction to cheese during TB treatment. *Thorax* (2004) 59, 635.
7. Uragoda CG, Kottegoda SR. Adverse reactions to isoniazid on ingestion of fish with a high histamine content. *Tubercle* (1977) 58, 83–9.
8. Uragoda CG. Histamine poisoning in tuberculous patients after ingestion of tuna fish. *Am Rev Respir Dis* (1980) 121, 157–9.
9. Senanayake N, Vyravanathan S, Kanagasuriyam S. Cerebrovascular accident after a 'skipjack' reaction in a patient taking isoniazid. *BMJ* (1978) 2, 1127–8.
10. Senanayake N, Vyravanathan S. Histamine reactions due to ingestion of tuna fish (*Thunnus argentivittatus*) in patients on antituberculosis therapy. *Toxicon* (1981) 19, 184–5.
11. Morinaga S, Kawasaki A, Hirata H, Suzuki S, Mizushima Y. Histamine poisoning after ingestion of spoiled raw tuna in a patient taking isoniazid. *Intern Med* (1997) 36, 198–200.
12. Uragoda CG. Histamine poisoning in tuberculous patients on ingestion of tropical fish. *J Trop Med Hyg* (1978) 81, 243–5.
13. Uragoda CG. Histamine intoxication with isoniazid and a species of fish. *Ceylon Med J* (1978) 23, 109–10.
14. Miki M, Ishikawa T, Okayama H. An outbreak of histamine poisoning after ingestion of the ground saury paste in eight patients taking isoniazid in a tuberculous ward. *Intern Med* (2005) 44, 1133–6.
15. Diao Y *et al*. Histamine like reaction in tuberculosis patients taking fishes containing much of histamine under treatment with isoniazid in 277 cases. *Zhonghua Jie He He Hu Xi Xi Ji Bing Za Zhi* (1986) 9, 267–9, 317–18.
16. O'Sullivan TL. Drug-food interaction with isoniazid resembling anaphylaxis. *Ann Pharmacother* (1997) 31, 928–9.

Isoniazid + H_2-receptor antagonists

Cimetidine and ranitidine do not appear to affect the pharmacokinetics of isoniazid.

Clinical evidence, mechanism, importance and management

In 13 healthy subjects, **cimetidine** 400 mg or **ranitidine** 300 mg, three times daily, for 3 days had no effect on the pharmacokinetics of a single 10-mg/kg dose of isoniazid. The absorption and the metabolism of isoniazid were both unchanged.[1] No special precautions would appear to be necessary on concurrent use. Although data about other H_2-receptor antagonists appears to be lacking, based on this study, they would not be expected to interact with isoniazid.

1. Paulsen O, Höglund P, Nilsson L-G, Gredeby H. No interaction between H_2 blockers and isoniazid. *Eur J Respir Dis* (1986) 68, 286–90.

Isoniazid + Laxatives

Sodium sulfate and castor oil used as laxatives can cause a modest reduction in isoniazid absorption.

Clinical evidence, mechanism, importance and management

In an experimental study of the possible effects of laxatives on isoniazid absorption, healthy subjects were given 10 to 20 g of oral **sodium sulfate** or 20 g of **castor oil** (doses sufficient to provoke diarrhoea). Absorption, measured by the amount of isoniazid excreted in the urine, was decreased by 50% with **castor oil** and by 41% with **sodium sulfate** at 4 hours. However, serum levels of isoniazid were relatively unchanged. The overall picture was that while these laxatives can alter the pattern of absorption, they do not seriously impair the total amount of drug absorbed.[1]

1. Mattila MJ, Takki S, Jussila J. Effect of sodium sulphate and castor oil on drug absorption from the human intestine. *Ann Clin Res* (1974) 6, 19–24.

Isoniazid + Pethidine (Meperidine)

An isolated case report describes hypotension and lethargy in a patient after he took isoniazid with pethidine.

Clinical evidence, mechanism, importance and management

A patient became lethargic and his blood pressure fell from 124/68 mmHg to 84/50 mmHg within 20 minutes of being given pethidine 75 mg intramuscularly. An hour before, he had been given isoniazid. There was no evidence of fever or cardiac arrhythmias, and his serum electrolytes, glucose levels and blood gases were normal. His blood pressure returned to normal over the next 3 hours. He had previously had both pethidine and isoniazid separately without incident. He was subsequently uneventfully given intravenous morphine sulfate 4 mg every 2 to 4 hours.[1] The authors of the report attribute this reaction to the MAO-inhibitory properties of the isoniazid and equate it with the severe and potentially fatal interaction between MAOIs and pethidine (see 'MAOIs or RIMAs + Opioids; Pethidine (Meperidine)', p.1381), but in reality this reaction was mild and lacked many of the characteristics of the more serious reaction. Moreover, isoniazid possesses only mild MAO-inhibitory properties and does not normally interact to the same extent as the non-selective MAOIs.

There is too little evidence to advise against concurrent use, but bear this interaction in mind in case of an unexpected response to treatment.

1. Gannon R, Pearsall W, Rowley R. Isoniazid, meperidine, and hypotension. *Ann Intern Med* (1983) 99, 415.

Isoniazid + Prednisolone

Prednisolone can lower isoniazid levels.

Clinical evidence, mechanism, importance and management

Isoniazid 10 mg/kg daily was given to 26 patients with tuberculosis. The 13 slow acetylators of isoniazid had a 23% fall in plasma isoniazid levels when they were given **prednisolone** 20 mg, while the 13 fast acetylators had a 38% fall over 8.5 hours (see 'Genetic factors', (p.4), for an explanation of acetylator status). The reasons for these changes are not understood but changes in the metabolism, and/or the excretion of the isoniazid by the kidney, are possibilities. Despite these changes the response to treatment was excellent.[1] In another group of 49 patients (including both slow and fast acetylators of isoniazid), rifampicin 12 mg/kg largely counteracted the isoniazid-lowering effects of **prednisolone**.[1]

None of these interactions were of clinical importance, but the authors point out that if the dose of isoniazid had been lower, its effects might have been reduced. Be aware of the possibility of a reduced response during concurrent use, and raise the isoniazid dose if necessary. There seems to be no information about other corticosteroids.

1. Sarma GR, Kailasam S, Nair NGK, Narayana ASL, Tripathy SP. Effect of prednisolone and rifampin on isoniazid metabolism in slow and rapid inactivators of isoniazid. *Antimicrob Agents Chemother* (1980) 18, 661–6.

Isoniazid + Propranolol

Propranolol causes a small reduction in the clearance of isoniazid.

Clinical evidence, mechanism, importance and management

In 6 healthy subjects, the clearance of a single 600-mg intravenous dose of isoniazid was reduced by 21%, from 16.4 to 13 L/hour, by propranolol 40 mg three times daily for 3 days.[1] It is suggested that propranolol reduces the clearance of isoniazid by inhibiting its metabolism (acetylation) by the liver.[1] However, as the increase in isoniazid levels is likely to be only modest this interaction is probably of little clinical importance.

1. Santoso B. Impairment of isoniazid clearance by propranolol. *Int J Clin Pharmacol Ther Toxicol* (1985) 23, 134–6.

Isoniazid + Pyrazinamide

A study in 19 patients with tuberculosis found that pyrazinamide did not affect serum levels of isoniazid.[1]

1. Levy D, Duysak S, Zylberberg B, Haapanen J, Russell WF, Middlebrook G. Effect of pyrazinamide on antimicrobially active serum isoniazid. *Dis Chest* (1960) 38, 148–51.

Isoniazid + Quinolones

Ciprofloxacin may cause a slight increase in the bioavailability of isoniazid, and pefloxacin may increase both the absorption and excretion of isoniazid.

Clinical evidence, mechanism, importance and management

(a) Ciprofloxacin

In a single-dose study, ciprofloxacin 500 mg was found to increase the absorption of isoniazid 300 mg by about 15%. The time to reach maximum plasma levels was increased from 3 hours to 4 hours. The rate of elimination and plasma half-life of isoniazid were not significantly affected.[1] In a very similar study, measurement of the salivary and urinary levels of isoniazid also found that ciprofloxacin increased the absorption of isoniazid, although the time to reach maximum salivary levels of isoniazid was shortened from 4 hours to 3 hours.[2] The urinary excretion was also increased by 38% in the presence of ciprofloxacin. The effects on isoniazid absorption may be due to inhibition of gastric motility and emptying by ciprofloxacin.[1] However, these effects are modest and unlikely to be clinically significant.

(b) Pefloxacin

In a study in 6 healthy subjects a single 400-mg dose of pefloxacin increased the maximum salivary levels and AUC of a single 300-mg dose of isoniazid almost twofold, indicating increased absorption. The time to reach maximum saliva concentrations was reduced from 5 hours to 4 hours. The excretion of isoniazid was also increased by 38%, as measured by an increased recovery from the urine.[3] The clinical relevance of the increased salivary levels of isoniazid is unclear. The authors suggest that concurrent use may lead to increased isoniazid toxicity. Therefore, until more is known, if patients develop isoniazid adverse effects (e.g. nausea, vomiting, constipation), while taking pefloxacin, consider this interaction as a possible cause.

1. Ofoefule SI, Obodo CE, Orisakwe OE, Ilondu NA, Afonne OJ, Maduka SO, Anusiem CA, Agbasi PU. Some plasma pharmacokinetic parameters of isoniazid in the presence of a fluoroquinolone antibacterial agent. *Am J Ther* (2001) 8, 243–6.
2. Ofoefule SI, Obodo CE, Orisakwe OE, Afonne JO, Ilondu NA, Agbasi PU, Anusiem CA, Maduka SO, Ilo CE. Salivary and urinary excretion and plasma-saliva concentration ratios of isoniazid in the presence of co-administered ciprofloxacin. *Am J Ther* (2002) 9, 15–18.
3. Ofoefule SI, Onyeagba OE, Orisakwe OE. Effects of pefloxacin on urinary and salivary concentrations of isoniazid in six healthy female volunteers. *Am J Ther* (2000) 7, 313–16.

Isoniazid + Rifamycins

The concurrent use of a rifamycin and isoniazid is common and therapeutically valuable, but there is evidence that the incidence of hepatotoxicity may be increased, particularly in slow acetylators of isoniazid. One study suggests the bioavailability of rifampicin may be reduced by isoniazid but other studies found no pharmacokinetic interaction. Rifabutin and rifampicin do not alter the pharmacokinetics of isoniazid.

Clinical evidence, mechanism, importance and management

(a) Rifabutin

In 6 healthy subjects, rifabutin 300 mg daily for 7 days, had no significant effect on the pharmacokinetics of a single 300-mg dose of isoniazid or its metabolite acetylisoniazid.[1] Two of the 6 subjects were rapid acetylators of isoniazid (see 'Genetic factors', (p.4), for more information about acetylator status).

Although both drugs have been effectively used together in the treatment of tuberculosis, it is not clear whether concurrent use increases the incidence of hepatotoxicity, as occurs with isoniazid and rifampicin (see below). However, as regular monitoring of liver function is required for both isoniazid and rifabutin, no additional monitoring seems necessary on concurrent use. The manufacturer of rifabutin notes that haematological reactions of rifabutin could be increased by isoniazid, but, again, as regular monitoring of white blood cell and platelet counts is advised,[2] no additional monitoring seems necessary.

(b) Rifampicin (Rifampin)

Most studies have shown that the serum levels and half-lives of isoniazid and rifampicin are not significantly affected by concurrent use,[3-6] even in those with hepatic impairment.[6] There was also no difference[4] between rapid and slow acetylators of isoniazid, (see 'Genetic factors', (p.4), for more information about acetylator status). One single-dose study in healthy subjects found that isoniazid 12 mg/kg reduced the AUC of rifampicin 10 mg/kg by about 25%.[7] There is some evidence that the incidence and severity of hepatotoxicity rises if both drugs are given together.[8] Reports from India suggest that the incidence can be as high as 8 to 10%, while much lower figures of 2 to 3% are reported in the US.[9] There is one case report that appears to prove that hepatotoxicity can arise rapidly from the use of both drugs. The patient tolerated both drugs individually, but hepatotoxicity reappeared on concurrent use.[10]

The reasons for the hepatotoxicity are not fully understood but rifampicin or isoniazid alone can cause liver damage by their own toxic action. One suggestion is that the rifampicin alters the metabolism of isoniazid, resulting in the formation of hydrazine, which has proven to be hepatotoxic.[9-11] Higher plasma levels of hydrazine are said to occur in slow acetylators of isoniazid,[9] but this effects was not found in one study.[12] There has been at least one fatality caused by this combination.[13] The manufacturers of rifampicin advise that caution is particularly needed in patients with impaired liver function, the elderly, malnourished patients, and children under 2 years of age. In patients with normal pre-treatment liver function, after baseline LFTs, further tests are only needed if fever, vomiting, or jaundice occur, or if the patient deteriorates.[14] However, one of the manufacturers of isoniazid suggests that liver function tests should be reviewed monthly in patients receiving both drugs.[15]

1. Breda M, Painezzola E, Benedetti MS, Efthymiopoulos C, Carpentieri M, Sassella D, Rimoldi R. A study of the effects of rifabutin on isoniazid pharmacokinetics and metabolism in healthy volunteers. *Drug Metabol Drug Interact* (1993) 10, 323–40.
2. Mycobutin (Rifabutin). Pharmacia Ltd. UK Summary of product characteristics, June 2009.
3. Boman G. Serum concentration and half-life of rifampicin after simultaneous oral administration of aminosalicylic acid or isoniazid. *Eur J Clin Pharmacol* (1974) 7, 217–25.
4. Sarma GR, Kailasam S, Nair NGK, Narayana ASL, Tripathy SP. Effect of prednisolone and rifampin on isoniazid metabolism in slow and rapid inactivators of isoniazid. *Antimicrob Agents Chemother* (1980) 18, 661–6.
5. Venho VMK, Koskinen R. The effect of pyrazinamide, rifampicin and cycloserine on the blood levels and urinary excretion of isoniazid. *Ann Clin Res* (1971) 3, 277–80.
6. Acocella G, Bonollo L, Garimoldi M, Mainardi M, Tenconi LT. Kinetics of rifampicin and isoniazid administered alone and in combination to normal subjects and patients with liver disease. *Gut* (1972) 13, 47–53.
7. Immanuel C, Gurumurthy P, Ramachandran G, Venkatesan P, Chandrasekaran V, Prabhakar R. Bioavailability of rifampicin following concomitant administration of ethambutol or isoniazid or pyrazinamide or a combination of the three drugs. *Indian J Med Res* (2003) 118, 109–14.
8. Steele MA, Burk RF, DesPrez RM. Toxic hepatitis with isoniazid and rifampin. A meta-analysis. *Chest* (1991) 99, 465–71.
9. Gangadharam PRJ. Isoniazid, rifampin and hepatotoxicity. *Am Rev Respir Dis* (1986) 133, 963–5.
10. Askgaard DS, Wilcke T, Døssing M. Hepatotoxicity caused by the combined action of isoniazid and rifampicin. *Thorax* (1995) 50, 213–14.
11. Pessayre D, Bentata M, Degott C, Nouel O, Miguet J-P, Rueff B, Benhamou J-P. Isoniazid-rifampin fulminant hepatitis. A possible consequence of the enhancement of isoniazid hepatotoxicity by enzyme induction. *Gastroenterology* (1977) 72, 284–9.
12. Jenner PJ, Ellard GA. Isoniazid-related hepatotoxicity: a study of the effect of rifampicin administration on the metabolism of acetylisoniazid in man. *Tubercle* (1989) 70, 93–101.
13. Lenders JWM, Bartelink AKM, van Herwaarden CLA, van Haelst UJGM, van Tongeren JHM. Dodelijke levercelnecrose na kort durende toediening van isoniazide en rifampicine aan een patiënt die reeds werd behandeld met anti-epileptica. *Ned Tijdschr Geneeskd* (1983) 127, 420–3.
14. Rifadin for Infusion (Rifampicin). Sanofi-Aventis. UK Summary of product characteristics, March 2009.
15. Isoniazid Ampoules. Cambridge Laboratories. UK Summary of product characteristics, April 2002.

Isoniazid + Salicylates

Isoniazid prolongs the half-life of salicylate in patients given aspirin.

Clinical evidence, mechanism, importance and management

In 8 patients it was found that the half-life of isoniazid was reduced by 14% when a single 2-g dose of sodium salicylate was given one hour before a single 5 mg/kg intravenous dose of isoniazid. This is unlikely to be clinically relevant. Further analysis in 10 patients found that the half-life of salicylate was almost doubled when a 2 g dose of aspirin was given with isoniazid 600 mg. A further dose of isoniazid was given 4 hours later.[1] The clinical relevance of this increase in the half-life of salicylate is unclear, but it seems likely to be small, particularly with antiplatelet doses of aspirin.

1. Matilla MJ, Takki S. Half-lives of isoniazid and salicylic acid in serum and their modification by different drugs in psychiatric patients. *Ann Med Exp Biol Fenn* (1969) 47, 124–8.

Isoniazid + SSRIs and related antidepressants

A few reports suggest that no important interaction occurs between isoniazid and the SSRIs or nefazodone. However, adverse reactions have been seen during concurrent use and one report found an increased discontinuation rate in patients taking an SSRI with isoniazid.

Clinical evidence

Two HIV-positive patients taking **fluoxetine** 20 mg daily were also given isoniazid. One of them tolerated the use of both drugs, but the other developed vomiting and diarrhoea, and after 10 days the **fluoxetine** was stopped.[1]

A woman who had been hospitalised for serious depression was given **nefazodone** 300 mg daily. A few days later she began to take isoniazid 300 mg daily, and was later discharged on an increased **nefazodone** dose of 400 mg daily. She was reported to have had no problems while taking both drugs over a 5-month period.[2]

A woman with tuberculosis taking isoniazid 300 mg daily presented with depression, and was given **sertraline** 50 mg daily, later raised to 150 mg daily, without problems. She responded well and was reported to have taken both drugs together for 8 months without problems.[2]

A retrospective review of HIV-positive patients who were taking either an SSRI, isoniazid, or both, found that the rate of discontinuation of the SSRI was higher in those also taking isoniazid (7 of 10 patients) than in the group of patients taking an SSRI alone (2 of 14). It is unclear why this rate was increased; little mention is made of the influence of other drugs or medical conditions.[3]

Mechanism

In theory isoniazid could interact with the SSRIs[4] because it has some weak MAO inhibitory activity. However, isoniazid rarely interacts like the non-selective MAOIs. This is because isoniazid seems to lack activity on mitochondrial MAO even though it has activity on plasma MAO. Therefore no adverse interaction would usually be expected.

Importance and management

Direct information about the concurrent use of isoniazid and SSRIs seems to be limited, but the case reports cited here[1,2,4] would suggest that the concurrent use of isoniazid and these SSRIs is normally without problems. However, also be aware that one report suggests the possibility of an increase in adverse effects with the combination of SSRIs and isoniazid.[3]

1. Judd FK, Mijch AM, Cockram A, Norman TR. Isoniazid and antidepressants: is there cause for concern? *Int Clin Psychopharmacol* (1994) 9, 123–5.
2. Malek-Ahmadi P, Chavez M, Contreras SA. Coadministration of isoniazid and antidepressant drugs. *J Clin Psychiatry* (1996) 57, 550.
3. Doyle ME, Hicks D, Aronson NE. Selective serotonin reuptake inhibitors and isoniazid: evidence of a potential adverse interaction. *Mil Med* (2001) 166, 1054–6.
4. Evans ME, Kortas KJ. Potential interaction between isoniazid and selective serotonin-reuptake inhibitors. *Am J Health-Syst Pharm* (1995) 52, 2135–6.

Linezolid + Antacids

A study in healthy subjects found that *Maalox 70mVal* suspension 10 mL (aluminium/magnesium hydroxide) did not affect the pharmacokinetics of a single 600-mg dose of linezolid.[1]

1. Grunder G, Zysset-Aschmann Y, Vollenweider F, Maier T, Krähenbühl S, Drewe J. Lack of pharmacokinetic interaction between linezolid and antacid in healthy volunteers. *Antimicrob Agents Chemother* (2006) 50, 68–72.

Linezolid + Aztreonam

In a single-dose study in healthy subjects, the pharmacokinetics of intravenous aztreonam 1 g and intravenous linezolid 375 mg were not affected by concurrent use. Therefore dose alterations are unlikely to be needed if both drugs are given.[1]

1. Sisson TL, Jungbluth GL, Hopkins NK. A pharmacokinetic evaluation of concomitant administration of linezolid and aztreonam. *J Clin Pharmacol* (1999) 39, 1277–82.

Linezolid + Dextromethorphan

There is no important pharmacokinetic interaction between linezolid and dextromethorphan, but one case of concurrent use resulted in serotonin syndrome.

Clinical evidence, mechanism, importance and management

In a study in 14 healthy subjects, two 20-mg doses of dextromethorphan given 4 hours apart, before and during the use of linezolid 600 mg every 12 hours, had no effect on linezolid pharmacokinetics. The AUC and maximum level of the dextromethorphan metabolite, dextrorphan was decreased by 30%, but this was not considered sufficient to warrant any dosing alterations. There was no evidence of serotonin syndrome, as measured by changes in body temperature, alertness and mental performance.[1] However, the manufacturer describes one case where the concurrent use of linezolid and dextromethorphan resulted in serotonin syndrome.[2] Linezolid has mild reversible MAOI activity, and serotonin syndrome has been described when dextromethorphan was taken by patients also taking antidepressant MAOIs, see 'MAOIs or RIMAs + Dextromethorphan', p.1375. If the concurrent use of linezolid and dextromethorphan is considered necessary, it would seem prudent to monitor for symptoms of serotonin syndrome. See under 'Additive or synergistic interactions', (p.9), for more information about serotonin syndrome.

1. Hendershot PE, Antal EJ, Welshman IR, Batts DH, Hopkins NK. Linezolid: pharmacokinetic and pharmacodynamic evaluation of coadministration with pseudoephedrine HCl, phenylpropanolamine HCl, and dextromethorphan HBr. *J Clin Pharmacol* (2001) 41, 563–72.
2. Zyvox (Linezolid). Pharmacia Ltd. UK Summary of product characteristics, September 2009.

Linezolid + Diphenhydramine

A single case report describes delirium in a patient receiving linezolid and diphenhydramine.

Clinical evidence

A case report describes a patient taking linezolid 600 mg twice daily, with metronidazole, aztreonam and diphenhydramine to treat a rash caused by previous antibacterials. The patient developed delirium, with aggression and hallucinations 2 days after starting to take the diphenhydramine. The symptoms of delirium resolved 2 to 3 days after the diphenhydramine was withdrawn. Metronidazole was also stopped at the same time.[1]

Mechanism

There are several factors that could account for the delirium seen in this patient. Linezolid may have enhanced the antimuscarinic action of diphenhydramine resulting in the symptoms seen. In addition, psychotic disorders including hallucinations are a very rare adverse effect of metronidazole,[2] and can also occur due to sepsis.

Importance and management

Evidence for an interaction between diphenhydramine and linezolid appears to be limited to this isolated case, the reasons for which are not established. As such, no general recommendations can be made.

1. Serio RN. Acute delirium associated with combined diphenhydramine and linezolid use. *Ann Pharmacother* (2004) 38, 62–5.
2. Flagyl Tablets (Metronidazole). Winthrop Pharmaceuticals UK Ltd. UK Summary of product characteristics, August 2008.

Linezolid + Food

Linezolid modestly increases the blood pressure response to oral tyramine. The bioavailability of linezolid is not affected by enteral feeds or food.

Clinical evidence, mechanism, importance and management

(a) Enteral feeds

In a study, 9 patients receiving enteral feeds were given a single 600-mg dose of linezolid as a suspension via a nasogastric tube or gastric tube. The

rate and extent of linezolid absorption was not significantly different from that found in another 6 patients not receiving enteral feeds. No dose adjustments are therefore thought to be required if linezolid is given with enteral feeds.[1]

(b) Food

A study in healthy subjects found that the plasma levels following a single 375-mg oral dose of a linezolid tablet were 23% higher when given to fasted subjects than when it was taken immediately after a high-fat meal. However, the AUCs were not significantly different, indicating that the extent of absorption was not affected by food.[2] Another study in healthy subjects found that food delayed the rate but not the extent of absorption and distribution of linezolid into tissues.[3] The manufacturer of linezolid states that both the oral suspension and the film-coated tablets may be taken with or without food.[4]

(c) Tyramine-rich food

In a pharmacodynamic study in healthy subjects, the dose of oral tyramine required to raise the systolic blood pressure by 30 mmHg was decreased by a factor of about 3.5 (from a range of 300 to 600 mg without linezolid to 100 to 200 mg with linezolid) when the subjects were pretreated with linezolid 625 mg twice daily for 4 to 7 days. This increase in the pressor response to tyramine was similar to that seen with moclobemide 150 mg three times daily.[5] Further, another placebo-controlled study in healthy subjects found that single doses of linezolid 600 mg and moclobemide 300 mg also caused similar increases in the pressor response to intravenous tyramine, as measured by amount of tyramine required to raise the systolic blood pressure by 30 mmHg.[6]

Linezolid is a weak, non-selective inhibitor of MAO. As a consequence, it can inhibit the breakdown of tyramine by MAO in the gut, and can also potentiate the effect of tyramine at nerve endings, therefore causing an increase in blood pressure (see *Mechanism*, under 'MAOIs or RIMAs + Tyramine-rich foods', p.1395). However, the extent of this rise was similar to that for moclobemide, which is much less than that seen with antidepressant MAOIs.

The manufacturers of linezolid recommend that patients should avoid large amounts of tyramine-rich foods and drinks[4,7] and should not consume more than 100 mg of tyramine per meal.[7] For a list of the possible tyramine-content of various foods and drinks, see 'Table 32.2', (p.1394), 'Table 32.3', (p.1396) and 'Table 32.4', (p.1397), but note that these amounts are only a guide. The manufacturers advice is in line with the dietary restrictions recommended for RIMAs rather than the more stringent dietary recommendations required in patients taking non-selective MAOIs.

1. Nguyen M, Beringer P, Wong-Beringer A, Louie S, Gill M, Gurevitch A. Effect of continuous enteral feedings (TF) on oral bioavailability (F) of linezolid (LZD) in hospitalized patients. Abstracts of the 43rd Annual Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, Il, 2003, 43, 36.
2. Welshman IR, Sisson TA, Jungbluth GL, Stalker D, Hopkins NK. Linezolid absolute bioavailability and the effect of food on oral bioavailability. *Biopharm Drug Dispos* (2001) 22, 91–7.
3. Islinger F, Dehghanyar P, Sauermann R, Burger C, Kloft C, Muller M, Joukhader C. The effect of food on plasma and tissue concentrations of linezolid after multiple doses. *Int J Antimicrob Agents* (2006) 27, 108–12.
4. Zyvox (Linezolid). Pharmacia Ltd. UK Summary of product characteristics, September 2009.
5. Antal EJ, Hendershot PE, Batts DH, Sheu W-P, Hopkins NK, Donaldson KM. Linezolid, a novel oxazolidinone antibiotic: assessment of monoamine oxidase inhibition using pressor response to oral tyramine. *J Clin Pharmacol* (2001) 41, 552–62.
6. Cantarini MV, Painter CJ, Gilmore EM, Bolger C, Watkins CL, Hughes AM. Effect of oral linezolid on the pressor response to intravenous tyramine. *Br J Clin Pharmacol* (2004) 58, 470–5.
7. Zyvox (Linezolid). Pharmacia & Upjohn. US Prescribing information, July 2008.

Linezolid + Mirtazapine

Serotonin syndrome has been reported in patients taking linezolid with mirtazapine.

Clinical evidence

A patient taking linezolid 600 mg twice daily developed delirium, confusion and visual hallucinations 2 weeks after starting to take mirtazapine 15 or 30 mg daily and gabapentin 300 mg at night. Gabapentin was stopped and the delirium resolved. About 4 weeks later the delirium recurred and then resolved when the patient discontinued mirtazapine. Mirtazapine was restarted without recurrence of delirium. The patient subsequently took mirtazapine 15 mg daily with linezolid 600 mg twice daily without adverse effects.[1] See 'Linezolid + SSRIs', p.353, for mention of a case of serotonin syndrome in a patient taking mirtazapine, citalopram and linezolid.

Mechanism

Not fully understood. Linezolid has weak MAOI effects, and serotonin syndrome is known to occur when MAOIs are given with 'tricyclics', (p.1391) and 'SSRIs', (p.1384), which are related to mirtazapine.

Importance and management

Information on the interaction between linezolid and mirtazapine appears to be limited, but it is in line with the way both drugs are known to interact. If linezolid is used with a drug with serotonergic actions, including mirtazapine it would seem prudent to monitor for symptoms of serotonin syndrome, which may take several weeks to manifest. See 'serotonin syndrome', (p.9), for further details on the development and management of this syndrome.

1. Aga VM, Barklage NE, Jefferson JW. Linezolid, a monoamine oxidase inhibiting antibiotic, and antidepressants. *J Clin Psychiatry* (2003) 64, 609–11.

Linezolid + Miscellaneous

Linezolid is predicted to interact with a number of drugs (e.g. salbutamol, buspirone, inotropes and vasopressors, triptans) in the same way as the MAOIs. The concurrent use of linezolid and gentamicin does not affect the pharmacokinetics of either drug.

Clinical evidence, mechanism, importance and management

Linezolid is a weak, reversible, non-selective inhibitor of MAOI. It is therefore expected to share the interactions of the antidepressant MAOIs, although the magnitude of any interaction is likely to be smaller. The UK manufacturer of linezolid[1] contraindicates its use with a number of drugs, unless facilities are available for close observation and monitoring of blood pressure. Similarly, the US manufacturer advises that patients should only receive linezolid with these drugs if they are observed for signs of 'serotonin syndrome', (p.9).[2]

The drugs mentioned include:

- Beta agonist bronchodilators; consider 'MAOIs or RIMAs + Sympathomimetics; Beta-agonist bronchodilators', p.1387.
- Buspirone; consider 'MAOIs or RIMAs + Buspirone', p.1374.
- Inotropes and vasopressors (e.g. adrenaline (epinephrine), noradrenaline (norepinephrine), dopamine, dobutamine); consider 'MAOIs or RIMAs + Sympathomimetics; Directly-acting', p.1388.
- Triptans; consider 'Triptans + MAOIs', p.688.

The manufacturers also contraindicate the concurrent use of linezolid with or within 2 weeks of taking any other drug that inhibits MAO-A or MAO-B.[1] They specifically name the non-selective MAOIs **isocarboxazid** and **phenelzine**.[1,2] The UK manufacturer includes the RIMA, moclobemide, and the MAO-B inhibitor, selegiline.[1] See 'MAOIs + MAOIs or RIMAs', p.1378, and see 'MAO-B inhibitors + MAOIs or RIMAs', p.807.

The US manufacturer of linezolid notes that the pharmacokinetics of neither linezolid or gentamicin are altered when the two drugs are given together.[2]

1. Zyvox (Linezolid). Pharmacia Ltd. UK Summary of product characteristics, September 2009.
2. Zyvox (Linezolid). Pharmacia & Upjohn. US Prescribing information, July 2008.

Linezolid + Nasal decongestants

In one study the use of linezolid with phenylpropanolamine or pseudoephedrine resulted in additive hypertensive effects.

Clinical evidence

In a placebo-controlled study, 14 healthy patients were given two 60-mg doses of **pseudoephedrine** or two 25-mg doses of **phenylpropanolamine** 4 hours apart, with and without linezolid. The mean maximum blood pressure rise was 11 mmHg with placebo, 15 mmHg with linezolid, 18 mmHg with **pseudoephedrine** and 14 mmHg with **phenylpropanolamine**. When the subjects were given linezolid with **pseudoephedrine** the rise was 32 mmHg, which was similar to the 38 mmHg rise seen with linezolid plus **phenylpropanolamine**. However, these rises were transient, resolving in about 2 hours. No effects were seen on linezolid pharmacokinetics.[1]

Mechanism

Linezolid acts as a weak MAO-inhibitor, which allows the accumulation of some noradrenaline at adrenergic nerve endings associated with arterial blood vessels. Pseudoephedrine and phenylpropanolamine, both indirectly-acting sympathomimetics, can release these above-normal amounts of noradrenaline resulting in blood vessel constriction and a rise in blood pressure.

Importance and management

Evidence for an interaction between linezolid and phenylpropanolamine or pseudoephedrine appears to be limited to this report, but given what is known about the way non-selective MAOIs interact with these drugs (see 'MAOIs or RIMAs + Sympathomimetics; Indirectly-acting', p.1388) an interaction appears to be established. However, it should be said that the evidence available indicates that blood pressure rises are unlikely to be of the proportions seen with the antidepressant MAOIs, which result in hypertensive crises. The manufacturers of linezolid[2,3] contraindicate the use of pseudoephedrine and phenylpropanolamine with linezolid unless there are facilities available for close observation of the patient and monitoring of blood pressure. The UK manufacturer additionally advises careful dose titration if concurrent use is undertaken.

Pseudoephedrine and phenylpropanolamine are present in some cough and cold remedies, which can be bought without prescription. Patients should be told to avoid these preparations while taking linezolid. There appears to be no direct information about **ephedrine**, but it would be expected to interact similarly.

1. Hendershot PE, Antal EJ, Welshman IR, Batts DH, Hopkins NK. Linezolid: pharmacokinetic and pharmacodynamic evaluation of coadministration with pseudoephedrine HCl, phenylpropanolamine HCl, and dextromethorphan HBr. *J Clin Pharmacol* (2001) 41, 563–72.
2. Zyvox (Linezolid). Pharmacia Ltd. UK Summary of product characteristics, September 2009.
3. Zyvox (Linezolid). Pharmacia & Upjohn. US Prescribing information, July 2008.

Linezolid + Pethidine (Meperidine)

A single case report describes serotonin syndrome, which developed when a patient was given pethidine and linezolid.

Clinical evidence, mechanism, importance and management

A case report describes a 27-year old man who developed serotonin syndrome after receiving linezolid and pethidine. He developed myoclonus and paranoid ideations, with an elevated temperature, respiratory rate, heart rate and blood pressure 2 hours after receiving the third dose of linezolid, and half an hour after receiving pethidine for amphotericin-associated rigors. His neuropsychiatric symptoms resolved within 2 hours of stopping the pethidine.[1]

The UK manufacturer of linezolid[2] (a drug with weak, reversible, non-selective MAOI activity) contraindicates its use with pethidine, unless facilities are available for close observation and monitoring of blood pressure, because of the possibility of serious reactions, similar to those that have occurred with antidepressant MAOIs and pethidine, see 'MAOIs or RIMAs + Opioids; Pethidine (Meperidine)', p.1381. Similarly, the US manufacturer advises that patients should only receive linezolid with pethidine if they are observed for signs of 'serotonin syndrome', (p.9).[3]

1. Das PK, Warkentin DI, Hewko R, Forrest DL. Serotonin syndrome after concomitant treatment with linezolid and meperidine. Clin Infect Dis (2008) 46, 264–5.
2. Zyvox (Linezolid). Pharmacia Ltd. UK Summary of product characteristics, September 2009.
3. Zyvox (Linezolid). Pharmacia & Upjohn. US Prescribing information, July 2008.

Linezolid + Rifampicin (Rifampin)

The serum levels of intravenous linezolid are reduced by intravenous rifampicin.

Clinical evidence, mechanism, importance and management

A 31-year-old woman was given intravenous rifampicin 300 mg every 8 hours and linezolid 600 mg every 12 hours for an MRSA infection. During rifampicin treatment her linezolid peak and trough levels were 7.29 micrograms/mL and 2.04 micrograms/mL, respectively. However, when the rifampicin was stopped the linezolid peak and trough levels were higher, at 12.46 micrograms/mL and 5.03 micrograms/mL, respectively.[1]

In an earlier study, healthy subjects were given a single 600-mg dose of intravenous linezolid either alone or with a single 600-mg dose of intravenous rifampicin. This study also found that rifampicin reduced the serum levels of linezolid by 10%, 20% and 35% at 6 hours, 9 hours and 12 hours, respectively.[2]

The manufacturers of linezolid report the findings of a study in 16 healthy subjects who took linezolid 600 mg twice daily for 5 doses with or without rifampicin 600 mg daily for 8 days. There was a reduction in linezolid maximum plasma levels and AUC of 21% and 32%, respectively.[3,4]

Linezolid is not metabolised by the cytochrome P450 enzyme system so the reduction in levels is unlikely to be due to increased metabolism associated with rifampicin enzyme induction. The reduction in linezolid serum levels may be attributable to the induction of P-glycoprotein by rifampicin, resulting in increased excretion of linezolid.[1,2]

The clinical significance of this interaction is unclear and the concurrent use of rifampicin and linezolid is not established. The available evidence suggests that, where possible, linezolid levels should be monitored if both drugs are given. If this is not possible it would seem prudent to monitor concurrent use closely to ensure that the antibacterial treatment is effective.

1. Gebhart BC, Barker BC, Markewitz BA. Decreased serum linezolid levels in a critically ill patient receiving concomitant linezolid and rifampin. *Pharmacotherapy* (2007) 27, 476–9.
2. Egle H, Trittler R, Kümmerer K, Lemmen SW. Linezolid and rifampicin: drug interaction contrary to expectations? *Clin Pharmacol Ther* (2005) 77,451–3.
3. Zyvox (Linezolid). Pharmacia & Upjohn. US Prescribing information, July 2008.
4. Zyvox (Linezolid). Pharmacia Ltd. UK Summary of product characteristics, September 2009.

Linezolid + SNRIs

Serotonin syndrome has been reported in patients taking linezolid with venlafaxine or duloxetine.

Clinical evidence

(a) Duloxetine

A case report describes a 55-year old woman taking duloxetine 60 mg daily who developed changes in her mental status including confusion, restlessness and abnormal movements 3 hours after receiving linezolid 600 mg. She was also tachycardic, with a low grade fever, hyperreflexic and unable to stay awake. Serotonin syndrome was suspected, and duloxetine was withheld. Her symptoms improved over the subsequent 12 hours.[1]

(b) Venlafaxine

An 85-year-old man taking venlafaxine 150 mg daily was given ciprofloxacin, rifampicin and linezolid 600 mg twice daily for a hip prosthesis infection. After 20 days he was found to be confused and disorientated, and 4 days later he was also drowsy, and suffering myoclonic jerks. Linezolid and venlafaxine were stopped and the symptoms resolved over 2 days.[2] Other cases of serotonin syndrome in patients taking venlafaxine and linezolid have also been reported,[3,4] including a case in which the patient continued to take venlafaxine, but at half the original dose.[3] A further case report describes a 7-year-old boy taking venlafaxine and methylphenidate who was given linezolid for osteomyelitis. He took all three drugs (doses not stated) for several days without any alterations in vital signs or evidence of serotonin syndrome.[5]

Mechanism

Not fully understood. Linezolid has weak MAOI effects, and serotonin syndrome is known to occur when MAOIs are given with 'venlafaxine', (p.1383).

Importance and management

Information on the interaction between linezolid and duloxetine or venlafaxine appears to be limited, but it is in line with the way both drugs are known to interact. If linezolid is used with a drug with serotonergic actions, including duloxetine and venlafaxine it would seem prudent to monitor for symptoms of serotonin syndrome, which may take several weeks to manifest. See 'serotonin syndrome', (p.9), for further details on the development and management of this syndrome.

1. Strouse TB, Kerrihard TN, Forscher CA, Zakowski P. Serotonin syndrome precipitated by linezolid in a medically ill patient on duloxetine. *J Clin Psychopharmacol* (2006) 26, 681–3.

2. Jones SL, Athan E, O'Brien D. Serotonin syndrome due to co-administration of linezolid and venlafaxine. *J Antimicrob Chemother* (2004) 54, 289–90.
3. Bergeron L, Boulé M, Perreault S. Serotonin toxicity associated with concomitant use of linezolid. *Ann Pharmacother* (2005) 39, 956–61.
4. Packer S, Berman SA, Serotonin syndrome precipitated by the monoamine oxidase inhibitor linezolid. *Am J Psychiatry* (2007) 164, 346–7.
5. Hammerness P, Parada H, Abrams A. Linezolid: MAOI activity and potential drug interactions. *Psychosomatics* (2002) 43, 248–9.

Linezolid + SSRIs

Serotonin syndrome has been reported in patients taking linezolid with SSRIs.

Clinical evidence

In an analysis of phase III studies, changes in vital signs did not differ between patients given linezolid and comparator drugs (i.e. antibacterials) when either were used with drugs known to interact with MAOIs, including unnamed SSRIs.[1,2] However, a number of case reports describe serotonin syndrome in patients given linezolid and an SSRI. These are described in the sections below.

(a) Citalopram

A case report describes an 85-year-old woman taking citalopram who developed tremor, confusion, dysarthria, hyperreflexia, agitation, and restlessness after linezolid was started. Citalopram was stopped and the symptoms resolved over 72 hours.[3] There are several other similar case reports of this interaction between linezolid and citalopram,[4-8] including one patient who was given citalopram 40 mg daily and mirtazapine 30 mg daily, whose symptoms resolved 2 days after stopping linezolid,[6] and one patient who received citalopram 40 mg daily and continued to show signs of serotonin syndrome 10 days after the end of a 12 day course of linezolid, which were partially resolved by cyproheptadine.[8]

(b) Escitalopram

A patient taking escitalopram 10 mg daily was also given intravenous linezolid 600 mg twice daily. After 3 days of concurrent therapy, she experienced two seizures. She also demonstrated mental status changes, agitation, and diarrhoea. Other causes of the seizures could not be ruled out, but the authors consider this case was highly suggestive of serotonin syndrome.[8]

(c) Fluoxetine

One patient taking fluoxetine had a transient episode of asymptomatic hypertension after one dose of linezolid, but since this patient had no other symptoms of serotonin syndrome, it was not considered an interaction.[2] However, a 4-year-old girl given fluoxetine 5 mg daily developed symptoms of serotonin syndrome 2 days after starting linezolid 140 mg every 12 hours, and after a procedure for which she was given fentanyl 200 micrograms. Fentanyl may have been a contributing factor.[9]

A further case report describes a 23-year old patient who received 6 doses of linezolid 600 mg whilst also taking fluoxetine 80 mg daily and developed abdominal pain, and unsteady gait. His symptoms were attributed to serotonin syndrome, and improved after the linezolid was stopped.[10]

A woman who was given linezolid 18 days after stopping fluoxetine developed serotonin syndrome, and required treatment with cyproheptadine.[11]

(d) Paroxetine

Paroxetine has also been implicated in the development of serotonin syndrome.[12,13] In one case paroxetine was stopped 3 days before linezolid was started.[12] In the other case, an elderly patient was given linezolid 600 mg every 12 hours, 21 days after amitriptyline 10 mg daily, paroxetine 20 mg daily and alprazolam 500 micrograms daily were started.[13]

(e) Sertraline

A woman taking sertraline 100 mg daily developed serotonin syndrome (incoordination, confusion and hypertension) 4 days after starting to take linezolid 600 mg twice daily. Her symptoms subsided 4 days after linezolid was withdrawn. She then required a further course of linezolid, and, despite stopping sertraline on day one, she again exhibited symptoms likely to be those of serotonin syndrome on day 9. The linezolid was stopped and cyproheptadine was given, and her symptoms resolved.[14] Other cases have also been published:[5,15,16] in one case symptoms resolved within one day of discontinuing linezolid and sertraline.[5]

Mechanism

Not fully understood. Linezolid has weak MAOI effects, and serotonin syndrome is known to occur when MAOIs are given with 'SSRIs', (p.1384). In the case of the patient taking linezolid with amitriptyline and paroxetine, it is possible that an interaction between amitriptyline and paroxetine contributed to the development of serotonin syndrome.

Importance and management

Information on the interaction between linezolid and the SSRIs, appears to be limited, but what is known suggests that the interaction is probably rare. The manufacturers of linezolid say that concurrent use of SSRIs should be avoided unless patients are closely observed[17] (for serotonin syndrome[18]) and have their blood pressure monitored.[17] If linezolid is used with a drug with serotonergic actions it would seem prudent to monitor for symptoms of serotonin syndrome, which may take several weeks to manifest. Note that in some cases, serotonin syndrome has occurred several days after stopping the SSRI. Consideration should be given to allowing a washout period after stopping the SSRI if clinically appropriate. See 'serotonin syndrome', (p.9), for further details on the development and management of this syndrome.

1. Hartman CS, Leach TS, Todd WM, Hafkin B. Lack of drug-interaction with combination of linezolid and monoamine oxidase inhibitor-interacting medications. *Pharmacotherapy* (2000) 20, 1230.
2. Rubinstein E, Isturiz R, Standiford HC, Smith LG, Oliphant TH, Cammarata S, Hafkin B, Le V, Remington J. Worldwide assessment of linezolid's clinical safety and tolerability: comparator-controlled phase III studies. *Antimicrob Agents Chemother* (2003) 47, 1824–31.
3. Tahir N. Serotonin syndrome as a consequence of drug-resistant infections: an interaction between linezolid and citalopram. *J Am Med Dir Assoc* (2004) 5, 111–13.
4. Bernard L, Stern R, Lew D, Hoffmeyer P. Serotonin syndrome after concomitant treatment with linezolid and citalopram. *Clin Infect Dis* (2003) 36, 1197.
5. Hachem RY, Hicks K, Huen A, Raad I. Myelosuppression and serotonin syndrome associated with concurrent use of linezolid and selective serotonin reuptake inhibitors in bone marrow transplant recipients. *Clin Infect Dis* (2003) 37, 37: e8–e11.
6. DeBellis RJ, Schaefer OP, Liquori M, Volturo GA. Linezolid-associated serotonin syndrome after concomitant treatment with citalopram and mirtazepine [sic] in a critically ill bone marrow transplant recipient. *J Intensive Care Med* (2005) 20, 351–3.
7. Bergeron L, Boulé M, Perreault S. Serotonin toxicity associated with concomitant use of linezolid. *Ann Pharmacother* (2005) 39, 956–61.
8. Lorenz RA, Vandenberg AM, Canepa EA. Serotonergic antidepressants and linezolid: a retrospective chart review and presentation of cases. Int J Psychiatry Med (2008) 38, 81–90.
9. Thomas CR, Rosenberg M, Blythe V, Meyer WJ. Serotonin syndrome and linezolid. *J Am Acad Child Adolesc Psychiatry* (2004) 43, 790.
10. Steinberg M, Morin AK. Mild serotonin syndrome associated with concurrent linezolid and fluoxetine. *Am J Health-Syst Pharm* (2007) 64, 59–62.
11. Morales N, Vermette H. Serotonin syndrome associated with linezolid treatment after discontinuation of fluoxetine. *Psychosomatics* (2005) 46, 274–5.
12. Wigen CL, Goetz MB. Serotonin syndrome and linezolid. *Clin Infect Dis* (2002) 34, 1651–2.
13. Morales-Molina JA, Mateu-de Antonio J, Grau Cerrato S, Marín-Casino M. Probable síndrome serotoninérgico por interacción entre amitriptilina, paroxetina y linezolid. *Farm Hosp* (2005) 29, 1–2.
14. Clark DB, Andrus MR, Byrd DC. Drug interactions between linezolid and selective serotonin reuptake inhibitors: case report involving sertraline and review of the literature. *Pharmacotherapy* (2006) 26, 269–76.
15. Lavery S, Ravi H, McDaniel WW, Pushkin YR. Linezolid and serotonin syndrome. *Psychosomatics* (2001) 42, 432–4.
16. Sola CL, Bostwick JM, Hart DA, Lineberry TW. Anticipating potential linezolid-SSRI interactions in the general hospital setting: an MAOI in disguise. *Mayo Clin Proc* (2006) 81, 330–4.
17. Zyvox (Linezolid). Pharmacia Ltd. UK Summary of product characteristics, September 2009.
18. Zyvox (Linezolid). Pharmacia & Upjohn. US Prescribing information, July 2008.

Linezolid + Tricyclic antidepressants

Serotonin syndrome has been reported in a patient taking linezolid with amitriptyline and paroxetine and is also predicted to occur if linezolid is given with any tricyclic antidepressant.

Clinical evidence, mechanism, importance and management

In an analysis of phase III studies, changes in vital signs did not differ between patients given linezolid and comparator drugs (i.e. antibacterials) when either were used with drugs known to interact with MAOIs, including unnamed cyclic antidepressants.[1,2] A case report describes serotonin syndrome in an elderly patient taking linezolid 600 mg every 12 hours, 21 days after amitriptyline 10 mg daily, paroxetine 20 mg daily and alprazolam 500 micrograms daily were started.[3] However, it seems possible that an interaction between amitriptyline and paroxetine, or between paroxetine and linezolid contributed to the development of serotonin syndrome in this case.

Information on an interaction between linezolid and the tricyclics is limited and inconclusive. However, both drugs have caused serotonin syndrome when given with other serotonergic drugs. The manufacturers of linezolid say that concurrent use of tricyclic antidepressants should be

avoided unless patients are closely observed[4] (for serotonin syndrome[5]) and have their blood pressure monitored.[4] If linezolid is used with a drug with serotonergic actions it would seem prudent to monitor for symptoms of serotonin syndrome, which may take several weeks to manifest. See 'serotonin syndrome', (p.9), for further details on the development and management of this syndrome.

1. Hartman CS, Leach TS, Todd WM, Hafkin B. Lack of drug-interaction with combination of linezolid and monoamine oxidase inhibitor-interacting medications. *Pharmacotherapy* (2000) 20, 1230.
2. Rubinstein E, Isturiz R, Standiford HC, Smith LG, Oliphant TH, Cammarata S, Hafkin B, Le V, Remington J. Worldwide assessment of linezolid's clinical safety and tolerability: comparator-controlled phase III studies. *Antimicrob Agents Chemother* (2003) 47, 1824–31.
3. Morales-Molina JA, Mateu-de Antonio J, Grau Cerrato S, Marín-Casino M. Probable síndrome serotoninérgico por interacción entre amitriptilina, paroxetina y linezolid. *Farm Hosp* (2005) 29, 1–2.
4. Zyvox (Linezolid). Pharmacia Ltd. UK Summary of product characteristics, September 2009.
5. Zyvox (Linezolid). Pharmacia & Upjohn. US Prescribing information, July 2008.

Linezolid + Vitamins

The pharmacokinetics of linezolid are not affected by either vitamin C or vitamin E.

Clinical evidence, mechanism, importance and management

In a study, healthy subjects were given vitamin C 1 g daily or vitamin E 800 units daily for 8 days with a single 600-mg dose of linezolid on day 6. As *in vitro* studies have indicated that endogenous reactive oxygen species (ROS) may affect linezolid clearance, it was considered possible that antioxidant supplements may affect the balance of ROS and linezolid clearance. However, the study found that antioxidants (vitamins C and E) given in doses far higher than the recommended daily intake did not affect linezolid pharmacokinetics. Therefore no dose adjustments are considered necessary during concurrent use.[1]

1. Gordi T, Tan LH, Hong C, Hopkins NJ, Francom SF, Slatter JG, Antal EJ. The pharmacokinetics of linezolid are not affected by concomitant intake of the antioxidant vitamins C and E. *J Clin Pharmacol* (2003) 43, 1161–7.

Loracarbef + Acetylcysteine

A study in healthy subjects found that acetylcysteine 200 mg had no effect on the absorption of loracarbef 400 mg.[1]

1. Roller S, Lode H, Stelzer I, Deppermann KM, Boeckh M, Koeppe P. Pharmacokinetics of loracarbef and interaction with acetylcysteine. *Eur J Clin Microbiol Infect Dis* (1992) 11, 851–5.

Loracarbef + Food

Food reduces the maximum plasma levels of loracarbef, but does not alter its bioavailability.

Clinical evidence, mechanism, importance and management

Loracarbef 400 mg was given to 12 healthy subjects either in a fasting state or following a standard breakfast. Food slowed the rate of absorption, but not the total bioavailability of loracarbef.[1] In another study, food was found to decrease the maximum plasma levels of a single 200-mg dose of loracarbef and increase the time to achieve maximum levels but the AUC of loracarbef was not significantly affected by food.[2] In a crossover study 24 healthy subjects received a single 200-mg dose of loracarbef after an overnight fast, a vegetarian low-fat breakfast, a vegetarian high-fat breakfast, a non-vegetarian low-fat breakfast, and a non-vegetarian high-fat breakfast. There was no significant difference between the pharmacokinetics of loracarbef observed after each of the four different meals. There was, however, a significant decrease in the maximum plasma level of loracarbef between the fed state and the fasted state, ranging from a 43% decrease with a high-fat vegetarian meal, to a 59% decrease with a low-fat non-vegetarian meal.[3] Loracarbef should be taken one hour before or 2 hours after food.[4]

1. Roller S, Lode H, Stelzer I, Deppermann KM, Boeckh M, Koeppe P. Pharmacokinetics of loracarbef and interaction with acetylcysteine. *Eur J Clin Microbiol Infect Dis* (1992) 11, 851–5.
2. DeSante KA, Zeckel ML. Pharmacokinetic profile of loracarbef. *Am J Med* (1992) 92 (Suppl 6A), 16S–19S.
3. Bapujee AT, Singh T, Ahmed T, Monif T, Saha N, Sharma PL. The effect of four different types of diet on the bioavailability of loracarbef. *Eur J Drug Metab Pharmacokinet* (2007) 32, 205–11.
4. Lorabid (Loracarbef). Monarch Pharmaceuticals, Inc. US Prescribing information, September 2002.

Loracarbef + Probenecid

Probenecid increases the half-life of loracarbef by about 50% but the clinical importance of this is unknown.[1]

1. Force RW, Nahata MC. Loracarbef: a new orally administered carbacephem antibiotic. *Ann Pharmacother* (1993) 27, 321–9.

Macrolides + Antacids

Aluminium/magnesium hydroxide antacids may reduce the peak levels of azithromycin, and aluminium/magnesium hydroxide (with simeticone) can prolong the absorption of erythromycin. Aluminium/magnesium hydroxide antacids do not appear to significantly alter the pharmacokinetics of clarithromycin, roxithromycin or telithromycin.

Clinical evidence, mechanism, importance and management

In 10 healthy subjects the peak serum levels, but not the total absorption, of **azithromycin** was reduced by 30 mL of *Maalox* (**aluminium**/**magnesium hydroxide**).[1] It is suggested therefore that **azithromycin** should not be given at the same time as antacids, but should be taken at least one hour before or 2 hours after.[2,3]

In 8 healthy subjects 30 mL of *Mylanta* (**aluminium**/**magnesium hydroxide** and [**simeticone**]) had no significant effect on the AUC, peak serum concentration, or time to peak serum concentration of **erythromycin stearate** 500 mg, but the mean elimination rate constant was more than doubled. It was suggested that the effect on elimination may be due to a possible prolonging of absorption, although the reason for this effect is unclear.[4] However, an *in vitro* study has suggested that the release and absorption of **erythromycin stearate** may be slowed in the presence of some antacids, including **aluminium** and **magnesium hydroxides**, **aluminium** and **magnesium trisilicates**, and **simeticone** because of adsorption of **erythromycin** by the antacids.[5] The clinical relevance of this is uncertain, but likely to be small.

Aluminium/magnesium hydroxide antacids are reported not to affect the pharmacokinetics of **clarithromycin**,[6] **roxithromycin**,[7] or **telithromycin**.[8,9]

1. Foulds G, Hilligoss DM, Henry EB, Gerber N. The effects of an antacid or cimetidine on the serum concentrations of azithromycin. *J Clin Pharmacol* (1991) 31, 164–7.
2. Hopkins S. Clinical toleration and safety of azithromycin. *Am J Med* (1991) 91 (Suppl 3A), 40S–45S.
3. Zithromax (Azithromycin). Pfizer Ltd. UK Summary of product characteristics, March 2008.
4. Yamreudeewong W, Scavone JM, Paone RP, Lewis GP. Effect of antacid coadministration on the bioavailability of erythromycin stearate. *Clin Pharm* (1989) 8, 352–4.
5. Arayne MS, Sultana N. Erythromycin-antacid interaction. *Pharmazie* (1993) 48, 599–602.
6. Zündorf H, Wischmann L, Fassenbender M, Lode H, Borner K, Koeppe P. Pharmacokinetics of clarithromycin and possible interaction with H_2 blockers and antacids. *Intersci Conf Antimicrob Agents Chemother* (1991) 31, 185.
7. Boeckh M, Lode H, Höffken G, Daeschlein S, Koeppe P. Pharmacokinetics of roxithromycin and influence of H_2-blockers and antacids on gastrointestinal absorption. *Eur J Clin Microbiol Infect Dis* (1992) 11, 465–8.
8. Ketek (Telithromycin). Sanofi-Aventis. US Prescribing information, June 2009.
9. Ketek (Telithromycin). Sanofi-Aventis. UK Summary of product characteristics, June 2009.

Macrolides + Azoles

Moderate pharmacokinetic interactions appear to occur between several of the azoles and macrolides but many of these are unlikely to be of clinical significance. However, clarithromycin may almost double itraconazole levels, and ketoconazole may almost double telithromycin levels.

Clinical evidence, mechanism, importance and management

(a) Azithromycin

1. Fluconazole. Single doses of fluconazole 800 mg and azithromycin 1.2 g were given to 18 healthy subjects alone and together without any significant change in the pharmacokinetics of either drug.[1]

2. Voriconazole. In healthy subjects, azithromycin 500 mg daily for 3 days had no significant effect on the AUC and maximum plasma levels of voriconazole 200 mg twice daily.[2]

(b) Clarithromycin

1. Fluconazole. Twenty healthy subjects were given clarithromycin 500 mg twice daily for 8 days. Fluconazole 400 mg daily was added on day 5, followed by 200 mg daily on days 6 to 8. The fluconazole increased the minimum plasma levels of the clarithromycin by 33% and the $AUC_{0\text{-}12}$ by 18%.[3] These relatively small changes in the pharmacokinetics of clarithromycin are almost certainly of little or no clinical importance.

2. Itraconazole. A study in 8 patients with AIDS, taking itraconazole 200 mg daily, found that when clarithromycin 500 mg twice daily for 14 days was also given, the maximum serum levels and the AUC of the itraconazole were increased by 90% and 92%, respectively.[4] A report of 3 patients who took clarithromycin with itraconazole describes clarithromycin and itraconazole levels above the expected values in each of the patients. In one patient the clarithromycin plasma level was more than double the expected upper level, and the itraconazole level was almost ninefold the expected level.[5] Both clarithromycin and itraconazole are known to be metabolised by the hepatic cytochrome P450 isoenzyme CYP3A4 and it is therefore probable that competition for metabolism leads to a reduction in the clearance of itraconazole. The first report does not comment on the outcome of this almost twofold increase in itraconazole levels, but none of the three patients in the second report experienced signs or symptoms of either clarithromycin or itraconazole toxicity.[5] However, it would seem prudent to be alert for the need to reduce its dosage. More study is needed.

3. Posaconazole. The manufacturer of posaconazole notes that it is metabolised by UDP glucuronidation, and is a substrate for P-glycoprotein, and suggests that inhibitors of these pathways, (they name clarithromycin) may increase posaconazole plasma levels.[6] The clinical relevance of any interaction has not been established.

(c) Erythromycin

1. Itraconazole. The manufacturer of itraconazole notes that the peak plasma levels and AUC of a single 200-mg dose of itraconazole were increased by 44% and 36%, respectively, by a single 1-g dose of erythromycin ethyl succinate.[7] However, no dose adjustments are recommended.

2. Posaconazole. The manufacturer of posaconazole notes that it is metabolised by glucuronidation, and is a substrate for P-glycoprotein, and suggests that inhibitors of these pathways, (they name erythromycin) may increase posaconazole plasma levels.[6] The clinical relevance of any interaction has not been established.

3. Voriconazole. In healthy subjects, erythromycin 1 g twice daily for 7 days had no significant effect on the AUC and maximum plasma levels of voriconazole 200 mg twice daily.[2]

(d) Telithromycin

In a study in which healthy subjects were given either telithromycin 800 mg daily, **ketoconazole** 800 mg daily or both drugs together, it was found that the AUC and peak plasma levels of telithromycin were increased by 95% and 51%, respectively. It may be prudent to monitor for telithromycin adverse effects on concurrent use. In a further related study, healthy subjects were given **itraconazole** 200 mg daily, telithromycin 800 mg daily, or both drugs together. **Itraconazole** was found to increase the AUC and peak plasma levels of telithromycin by 54% and 22%, respectively. No serious adverse effects were reported in either study and telithromycin did not increase the QTc intervals observed with either **ketoconazole** or **itraconazole** alone.[8,9] Another study[10] by the same authors, in subjects aged 60 years or older and with a creatinine clearance of 30 mL/minute or more, found that, when **ketoconazole** was given, levels of telithromycin were increased but were only slightly higher than those found in younger healthy subjects[8] in the earlier study.

1. Amsden GW, Foulds G, Thakker K. Pharmacokinetic study of azithromycin with fluconazole and cotrimoxazole (trimethoprim-sulfamethoxazole) in healthy volunteers. *Clin Drug Invest* (2000) 20, 135–42.
2. Purkins L, Wood N, Ghahramani P, Kleinermans D, Layton G, Nichols D. No clinically significant effect of erythromycin or azithromycin on the pharmacokinetics of voriconazole in healthy male volunteers. *Br J Clin Pharmacol* (2003) 56, 30–6.
3. Gustavson LE, Shi H, Palmer RN, Siepman NC, Craft JC. Drug interaction between clarithromycin and fluconazole in healthy subjects. *Clin Pharmacol Ther* (1996) 59, 185.
4. Hardin TC, Summers KS, Rinaldi MG, Sharkey PK. Evaluation of the pharmacokinetic interaction between itraconazole and clarithromycin following chronic oral dosing in HIV-infected patients. *Pharmacotherapy* (1997) 17, 195.
5. Auclair B, Berning SE, Huitt GA, Peloquin CA. Potential interaction between itraconazole and clarithromycin. *Pharmacotherapy* (1999) 19, 1439–44.
6. Noxafil (Posaconazole). Schering-Plough Ltd. UK summary of product characteristics, November 2009.
7. Sporanox Capsules (Itraconazole). Janssen. US Prescribing information, March 2009.
8. Shi J, Montay G, Leroy B, Bhargava V. Effects of ketoconazole and itraconazole on the pharmacokinetics of telithromycin, a new ketolide antibiotic. *Intersci Conf Antimicrob Agents Chemother* (2002) 42, 28.
9. Shi J, Montay G, Leroy B, Bhargava VO. Effects of itraconazole or grapefruit juice on the pharmacokinetics of telithromycin. *Pharmacotherapy* (2005) 25, 42–51.
10. Shi J, Chapel S, Montay G, Hardy P, Barrett JS, Sica D, Swan SK, Noveck R, Leroy B, Bhargava VO. Effect of ketoconazole on the pharmacokinetics and safety of telithromycin and clarithromycin in older subjects with renal impairment. *Int J Clin Pharmacol Ther* (2005) 43, 123–33.

Macrolides + Food

Food appears to halve the absorption of azithromycin from the capsule formulation, but does not alter the AUC of azithromycin tablets or suspension. The pharmacokinetics of telithromycin are not altered by food.

Clinical evidence, mechanism, importance and management

(a) Azithromycin

A review by the manufacturers briefly mentions that food reduced the absorption of azithromycin by about half.[1] It is suggested therefore that azithromycin *capsules* should not be given at the same time as food, but should be taken at least one hour before or 2 hours after a meal.[1,2] However, the US manufacturers note that a high-fat meal increased the maximum levels of azithromycin *tablets* by 23%, and had no effect on the AUC.[3] Similarly, food increased the maximum levels of azithromycin *suspension* by 56%, without altering the AUC.[3] Azithromycin suspension[2,3] and tablets[3] may therefore be taken without regard to food.

(b) Telithromycin

In a crossover study, 18 healthy subjects were given a single 800-mg dose of telithromycin after an overnight fast, or at the end of a high-fat breakfast. There was no clinically significant change in the pharmacokinetics of telithromycin when taken with food.[4] Telithromycin can therefore be taken alone, or with food.[5]

1. Hopkins S. Clinical toleration and safety of azithromycin. *Am J Med* (1991) 91 (Suppl 3A), 40S–45S.
2. Zithromax (Azithromycin). Pfizer Ltd. UK Summary of product characteristics, March 2008.
3. Zithromax (Azithromycin). Pfizer Inc. US Prescribing information, January 2009.
4. Bhargava V, Lenfant B, Perret C, Pascual M-H, Sultan E, Montay G. Lack of effect of food on the bioavailability of a new ketolide antibacterial, telithromycin. *Scand J Infect Dis* (2002) 34, 823–6.
5. Ketek (Telithromycin). Sanofi-Aventis. UK Summary of product characteristics, June 2009.

Macrolides + Grapefruit juice

Grapefruit juice modestly increases the bioavailability of erythromycin, but does not affect the bioavailability of clarithromycin or telithromycin.

Clinical evidence

(a) Clarithromycin

In a study, 12 healthy subjects were given a single 500-mg dose of clarithromycin and 240 mL of either water or freshly squeezed grapefruit juice with and 2 hours after clarithromycin. Grapefruit juice increased the time to peak levels of both clarithromycin and its metabolite, 14-hydroxyclarithromycin, from about 82 minutes to 148 minutes and from about 85 minutes to 172 minutes, respectively, but it did not affect the extent of clarithromycin absorption and had no significant effects on any other pharmacokinetic parameters.[1]

(b) Erythromycin

A study in 6 healthy subjects given a single 400-mg dose of erythromycin with either water or grapefruit juice found that grapefruit juice increased the AUC and maximum plasma level of erythromycin by about 49% and

52%, respectively. The time to achieve maximum levels and the half-life of erythromycin were not affected.[2]

(c) Telithromycin

A study in 16 healthy subjects given telithromycin 800 mg daily found that grapefruit juice did not affect telithromycin pharmacokinetics.[3]

Mechanism

Some components of grapefruit juice, possibly flavonoids such as naringenin, or a psoralen, dihydroxybergamottin, may inhibit the activity of the cytochrome P450 isoenzyme CYP3A4 in the gut.[1] The levels of drugs metabolised by CYP3A4, such as the macrolides, may therefore be raised by grapefruit juice. Erythromycin levels, but not those of clarithromycin or telithromycin appear to be affected by grapefruit juice. It has been suggested that a drug with low or variable bioavailability may be more likely to have its levels increased by grapefruit juice and it has been suggested that this may partly explain why the pharmacokinetics of clarithromycin (bioavailability of about 55%) and telithromycin (bioavailability of about 60%) are not significantly affected.[1]

Importance and management

Information is very limited but it would appear that there is unlikely to be a clinically significant interaction between grapefruit juice and either clarithromycin or telithromycin. The increased bioavailability of erythromycin was found in a single-dose study and it has been suggested that more prolonged administration of erythromycin with grapefruit juice could increase levels further and potentially increase the risk of adverse effects.[4] More study is needed to establish this.

1. Cheng KL, Nafziger AN, Peloquin CA, Amsden GW. Effect of grapefruit juice on clarithromycin pharmacokinetics. *Antimicrob Agents Chemother* (1998) 42, 927–9.
2. Kanazawa S, Ohkubo T, Sugawara K. The effects of grapefruit juice on the pharmacokinetics of erythromycin. *Eur J Clin Pharmacol* (2001) 56, 799–803.
3. Shi J, Montay G, Leroy B, Bhargava VO. Effects of itraconazole or grapefruit juice on the pharmacokinetics of telithromycin. *Pharmacotherapy* (2005) 25, 42–51.
4. Amory JK, Amory DW. Oral erythromycin and the risk of sudden death. *N Engl J Med* (2005) 352, 302–3.

Macrolides + H_2-receptor antagonists

Cimetidine doubled the levels of erythromycin in one single-dose study, and a single case report describes reversible deafness, which was attributed to this interaction. No clinically significant interaction appears to occur when cimetidine is given with azithromycin or clarithromycin, or when ranitidine is given with clarithromycin, roxithromycin, or telithromycin.

Clinical evidence

(a) Cimetidine

A 64-year-old woman was admitted to hospital with cough, dyspnoea and pleuritic pain and was found to have an atypical pneumonia and renal impairment. All her antihypertensive treatment (methyldopa, propranolol, co-amilofruse) was stopped, due to hypotension, and her treatment for duodenal ulcer was changed from ranitidine 150 mg twice daily to cimetidine 400 mg at night. She was then given amoxicillin 500 mg three times daily and **erythromycin** stearate 1 g four times daily. Two days later she complained of 'fuzzy hearing' and audiometry showed a bilateral hearing loss. The **erythromycin** was stopped and her hearing returned to normal after 5 days.[1] This prompted a study of this possible interaction in 8 healthy subjects, which found that cimetidine 400 mg twice daily increased the AUC of a single 250-mg dose of **erythromycin** by 73%. Maximum serum **erythromycin** levels were doubled.[1]

The pharmacokinetics of **azithromycin** were not affected by a single 800-mg dose of cimetidine in one study,[2] and although cimetidine prolongs the absorption of **clarithromycin**, this is unlikely to be of clinical significance.[3]

(b) Ranitidine

The pharmacokinetics of **clarithromycin**,[4] **roxithromycin**[5] and **telithromycin**[6,7] are reported to be unaffected by ranitidine.

Mechanism

Cimetidine is known to inhibit the *N*-demethylation of erythromycin so that it is metabolised and cleared from the body more slowly and its serum levels rise. Deafness is known to be one of the adverse effects of erythromycin,[1] which usually occurs with high-doses or intravenous use, and was probably exacerbated by renal impairment[4] in the patient described above.

Importance and management

Clinical information about an interaction between cimetidine and erythromycin seems to be limited to this case and the associated single-dose study. The manufacturers note that, with erythromycin alone, reversible hearing loss has been reported, usually in patients with renal impairment and those receiving high doses[8] (greater than 4 g daily[9]) and usually when given by the intravenous route.[9] If deafness were to occur, the management would seem to be similar (withdraw the erythromycin) regardless of whether or not cimetidine was present, so no additional precautions seem necessary.

There is evidence that azithromycin and clarithromycin do not interact with cimetidine, and ranitidine does not interact with clarithromycin, roxithromycin or telithromycin. No interaction would be expected between the macrolides and other non-enzyme inducing H_2-receptor antagonists.

1. Mogford N, Pallett A, George C. Erythromycin deafness and cimetidine treatment. *BMJ* (1994) 309, 1620.
2. Foulds G, Hilligoss DM, Henry EB, Gerber N. The effects of an antacid or cimetidine on the serum concentrations of azithromycin. *J Clin Pharmacol* (1991) 31, 164–7.
3. Amsden GW, Cheng KL, Peloquin CA, Nafziger AN. Oral cimetidine prolongs clarithromycin absorption. *Antimicrob Agents Chemother* (1998) 42, 1578–80.
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6. Ketek (Telithromycin). Sanofi-Aventis. US Prescribing information, June 2009.
7. Ketek (Telithromycin). Sanofi-Aventis. UK Summary of product characteristics, June 2009.
8. PCE (Erythromycin particles in tablets). Abbott Laboratories. US Prescribing information, November 2008.
9. Erymax Capsules (Erythromycin). Cephalon Ltd. UK Summary of product characteristics, January 2009.

Macrolides + Penicillins

Although there is *in vitro* evidence of antagonism between erythromycin and penicillins, this combination has been used successfully to treat community-acquired pneumonia.

Clinical evidence, mechanism, importance and management

Some *in vitro* evidence suggests that antagonism may occur between erythromycin (a bacteriostatic drug) and penicillins (bactericidal drugs) when they are used against staphylococci[1] and *Streptococcus pneumoniae*.[2] However, another study has suggested that this *in vitro* antagonism against *S. pneumoniae* between 'penicillin' and erythromycin is minimal and dependent on the interpretative criteria applied.[3] Clinical evidence for this interaction is apparently lacking, and the combination is generally used successfully for pneumonia.[4] In the UK, the combination of amoxicillin and erythromycin or another macrolide (e.g. azithromycin or clarithromycin) has been recommended by the British Thoracic Society (BTS) for adult patients with non-severe community-acquired pneumonia who require hospital admission.[5] In addition, the BTS has recommended an intravenous combination of a beta-lactamase stable antibacterial such as co-amoxiclav (amoxicillin with clavulanic acid) with a macrolide (erythromycin or clarithromycin) for severe community-acquired pneumonia in hospitalised patients.[6]

1. Manten A. Synergism and antagonism between antibiotic mixtures containing erythromycin. *Antibiot Chemother* (1954) 4, 1228–33.
2. Johansen HK, Jensen TG, Dessau RB, Lundgren B, Frimodt-Møller N. Antagonism between penicillin and erythromycin against Streptococcus pneumoniae in vitro and in vivo. *J Antimicrob Chemother* (2000) 46, 973–80.
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Macrolides + Rifamycins

The concurrent use of rifabutin and azithromycin does not appear to affect the levels of either drug, but a very high incidence of neutropenia was seen in one study of the combination. Both rifabutin and rifampicin markedly reduce clarithromycin levels. Clarithromycin increases the levels of rifabutin and the combination is associated with an increased risk of uveitis and neutropenia. Rifampicin (rifampin) greatly reduces telithromycin levels and concurrent use is not recommended.

Clinical evidence

(a) Rifabutin

1. Neutropenia. A study in 12 healthy subjects was designed to investigate the safety and possible interactions between rifabutin 300 mg daily, and **azithromycin** 250 mg daily or **clarithromycin** 500 mg twice daily, over 14 days. The subjects were matched against 18 healthy controls who received either of the macrolides or rifabutin alone. The study had to be abandoned after 10 days because 14 patients developed neutropenia; 2 taking rifabutin alone, and all 12 of those taking rifabutin with a macrolide. Eight subjects developed a fever, 5 required colony simulating factors, and 3 required hospitalisation.[1]

2. Pharmacokinetics. In a randomised study[2] investigating a possible regimen for the prophylaxis of *Mycobacterium avium* complex (MAC) disease, 12 HIV-positive patients were given **clarithromycin** 500 mg daily, to which rifabutin 300 mg daily was added on day 15. By day 42 the **clarithromycin** AUC had fallen by 44%, and the levels of the metabolite, 14-hydroxyclarithromycin, had risen by 57%. A further 14 patients were given rifabutin 300 mg daily with **clarithromycin** 500 mg every 12 hours from day 15. After 28 days the AUC of the rifabutin had increased by 99%, and the AUC of the active metabolite, 25-*O*-desacetyl-rifabutin, had increased by 375%. Another group of patients with lung disease due to MAC were given **clarithromycin** 500 mg twice daily. When rifabutin 600 mg was added the **clarithromycin** levels fell by 63% (from 5.4 to 2 micrograms/mL).[3] Limited information from a randomised study in healthy subjects suggested similar results.[1] Fluconazole appears to further increase the effects of clarithromycin on rifabutin.[4] One study suggests that there is no pharmacokinetic interaction between **azithromycin** and rifabutin.[1]

3. Uveitis or arthralgias. Uveitis, and in some cases pseudojaundice, aphthous stomatitis and an arthralgia syndrome have been described in patients taking both **clarithromycin** 1 to 2 g daily and rifabutin 300 to 600 mg daily.[5-8] The authors of a study in which patients with pulmonary *Mycobacterium avium* complex disease were given rifabutin 600 mg daily with clarithromycin 500 mg twice daily (15 patients) or azithromycin 600 mg daily (11 patients) considered that overall there was a high incidence of adverse events, which included 2 patients in the clarithromycin group who developed uveitis requiring discontinuation of both drugs.[9]
Reports suggest that uveitis develops between 27 to 370 days after taking the combination.[6,7] The reaction appears to be dose-dependent. In patients taking rifabutin 600 mg with clarithromycin the incidence of uveitis was 14% in patients weighing more than 65 kg, 45% in those weighing between 55 and 65 kg and 64% in those weighing less than 55 kg. The risk of developing uveitis was reduced from a mean of 43% to 13% when the dose of rifabutin was reduced to 300 mg daily.[10] The presence of fluconazole does not appear to affect the development of uveitis in patients taking clarithromycin with rifabutin,[6,7,10] but it has been suggested that this was because only small doses (50 mg) were used.[7]
Uveitis did not develop in 8 patients taking rifabutin and **azithromycin** 500 mg daily,[7] although cases of uveitis have been reported in patients taking rifabutin, fluconazole, and **azithromycin** 1.2 g weekly but they have been attributed to an interaction between rifabutin and fluconazole.[11]
See 'Azoles + Rifabutin', p.247.

(b) Rifampicin (Rifampin)

Patients with lung disease due to MAC were given **clarithromycin** 500 mg twice daily. When rifampicin 600 mg daily was added, the mean serum levels of **clarithromycin** fell by almost 90% (from 5.4 to 0.7 micrograms/mL).[3] Similar results are reported in two further studies.[12,13]

The manufacturer of **telithromycin** notes that rifampicin reduces its AUC and maximum serum levels by 86% and 79%, respectively.[14]

Two cases of cholestatic jaundice have been reported in patients taking rifampicin with **troleandomycin**.[15,16]

Mechanism

Both rifabutin and rifampicin (rifampin) are known enzyme inducers, which can increase the metabolism of other drugs by the liver, thereby reducing their serum levels. Rifampicin is recognised as being the more potent inducer. Rifabutin is also a substrate for the cytochrome P450 isoenzyme CYP3A4. Both clarithromycin and fluconazole are inhibitors of CYP3A4 and it is probable that clarithromycin and fluconazole exert additive effects resulting in greater inhibition of rifabutin metabolism than occurs with either drug alone.[4]

The reason for the uveitis is not known, but based on *animal* studies it has been suggested that it is associated with effective treatment of MAC and is due to release of a mycobacterial protein, rather than a toxic effect of the drugs.[17] It has been suggested that lower body-weight and concurrent clarithromycin may result in toxic rifabutin serum levels, although concurrent fluconazole, which increases rifabutin levels, does not appear to be a factor.[10] The hepatotoxicity seen with rifampicin and troleandomycin is probably due to additive effects as both drugs are known to be hepatotoxic.

Importance and management

(a) Rifabutin and Rifampicin: Pharmacokinetics

Direct information appears to be limited to the reports cited but the interactions would appear to be established. What is not entirely clear is whether these interactions result in treatment failures because of the potentially subtherapeutic clarithromycin serum levels. Because of the lack of information, be alert for evidence of reduced efficacy if clarithromycin and rifampicin are used.

Although rifabutin can lower clarithromycin levels, the efficacy of this combination for MAC infection is established, although not without risk, see *Uveitis*, below. Clarithromycin raises rifabutin levels and therefore increases the risks of adverse effects. Concurrent use may therefore be desirable, but monitoring for adverse effects is necessary.

Due to a pharmacokinetic interaction the UK manufacturers recommend that telithromycin should not be given during and for 2 weeks after the use of rifampicin.[14]

(b) Rifabutin: Neutropenia

Information regarding neutropenia with macrolides and rifamycins is very limited but what is known suggests that white cell counts should be monitored closely if rifabutin is given with azithromycin or clarithromycin. Rifabutin is known to cause polyarthritis on rare occasions, but in conjunction with clarithromycin it appears to happen at much lower doses.[8] Careful monitoring is necessary.

(c) Rifabutin: Uveitis

The CSM in the UK has warned about the need to be aware of the increased risk of uveitis with clarithromycin and rifabutin. If uveitis occurs the CSM recommends that rifabutin should be stopped and the patient should be referred to an ophthalmologist. Because of the increased risk of uveitis they also say that consideration should be given to reducing the dose of rifabutin to 300 mg daily in the presence of macrolides.[18] A review and a case-control study also suggest that this dose is associated with a reduced risk of uveitis and maintains efficacy.[10,19] A similar suggestion has been made by others.[9]

1. Apseloff G, Foulds G, LaBoy-Goral L, Willavize S, Vincent J. Comparison of azithromycin and clarithromycin in their interactions with rifabutin in healthy volunteers. *J Clin Pharmacol* (1998) 38, 830–5.
2. Hafner R, Bethel J, Power M, Landry B, Banach M, Mole L, Standiford HC, Follansbee S, Kumar P, Raasch R, Cohn D, Mushatt D, Drusano G. Tolerance and pharmacokinetic interactions of rifabutin and clarithromycin in human immunodeficiency virus-infected volunteers. *Antimicrob Agents Chemother* (1998) 42, 631–9.
3. Wallace RJ, Brown BA, Griffith DE, Girard W, Tanaka K. Reduced serum levels of clarithromycin in patients treated with multidrug regimens including rifampin or rifabutin for *Mycobacterium avium-M. intracellulare* infection. *J Infect Dis* (1995) 171, 747–50.
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6. Becker K, Schimkat M, Jablonowski H, Häussinger D. Anterior uveitis associated with rifabutin medication in AIDS patients. *Infection* (1996) 24, 34–6.
7. Kelleher P, Helbert M, Sweeney J, Anderson J, Parkin J, Pinching A. Uveitis associated with rifabutin and macrolide therapy for *Mycobacterium avium intracellulare* infections in AIDS patients. *Genitourin Med* (1996) 72, 419–21.
8. Le Gars L, Collon T, Picard O, Kaplan G, Berenbaum F. Polyarthralgia-arthritis syndrome induced by low doses of rifabutin. *J Rheumatol* (1999) 26, 1201–2.
9. Griffith DE, Brown BA, Girard WM, Wallace RJ. Adverse events associated with high-dose rifabutin in macrolide-containing regimens for the treatment of *Mycobacterium avium* complex lung disease. *Clin Infect Dis* (1995) 21, 594–8.
10. Shafran SD, Singer J, Zarowny DP, Deschênes J, Phillips P, Turgeon F, Aoki FY, Toma E, Miller M, Duperval R, Lemieux C, Schlech WF, for the Canadian HIV Trials Network Protocol 010 Study Group. Determinants of rifabutin-associated uveitis in patients treated with rifabutin, clarithromycin, and ethambutol for *Mycobacterium avium* complex bacteremia: a multivariate analysis. *J Infect Dis* (1998) 177, 252–5.
11. Havlir D, Torriani F, Dubé M. Uveitis associated with rifabutin prophylaxis. *Ann Intern Med* (1994) 121, 510–12.
12. Yamamoto F, Harada S, Mitsuyama T, Harada Y, Kitahara Y, Yoshida M, Nakanishi Y. Concentration of clarithromycin and 14-R-hydroxyclarithromycin in plasma of patients with *Mycobacterium avium* complex infection, before and after the addition of rifampicin. *Jpn J Antibiot* (2004) 57, 124–33.
13. Taki H, Ogawa K, Nakagawa T, Kashima K, Tarumi O, Saitou Y, Yamada N, Tano M, Nikai T. Clinical analysis of drug interaction between rifampicin and clarithromycin which are used for treating pulmonary *Mycobacterium avium* complex infection. *Kekkaku* (2007) 82, 641–6.
14. Ketek (Telithromycin). Sanofi-Aventis. UK Summary of product characteristics, June 2009.
15. Piette F, Peyrard P. Ictère bénin médicamenteux lors d'un traitement associant rifampicine-triacétyloléandomycine. *Nouv Presse Med* (1979) 8, 368–9.
16. Givaudan JF, Gamby T, Privat Y. Ictère cholestatique après association rifampicine-troléandomycine: une nouvelle observation. *Nouv Presse Med* (1979) 8, 2357.
17. Opremcak EM, Cynamon M. Uveitogenic activity of rifabutin and clarithromycin in the *Mycobacterium avium*-infected beige mice. Am Soc Microbiol 2nd Nat Conf. Human retroviruses and related infections. Washington DC, Jan 29—Feb 2 1995, 74.
18. Committee on Safety of Medicines. Rifabutin (Mycobutin) – uveitis. *Current Problems* (1994) 20, 4.
19. Committee on Safety of Medicines/Medicines Control Agency. Revised indications and drug interactions of rifabutin. *Current Problems* (1997) 23, 14.

Macrolides; Azithromycin + Ceftriaxone

A study in healthy subjects found that there did not appear to be a pharmacokinetic interaction between steady-state intravenous azithromycin and ceftriaxone: the combination was well-tolerated.[1]

1. Chiu LM, Menhinick AM, Johnson PW, Amsden GW. Pharmacokinetics of intravenous azithromycin and ceftriaxone when administered alone and concurrently to healthy volunteers. *J Antimicrob Chemother* (2002) 50, 1075–9.

Macrolides; Azithromycin + Chloroquine

A study in which healthy subjects were given azithromycin 1 g daily for 3 days either alone or with chloroquine base 600 mg daily on days 1 and 2, and 300 mg on day 3, found no pharmacokinetic interaction.[1]

1. Cook JA, Randinitis EJ, Bramson CR, Wesche DL. Lack of a pharmacokinetic interaction between azithromycin and chloroquine. *Am J Trop Med Hyg* (2006) 74, 407–12.

Macrolides; Clarithromycin + Disulfiram

Fatal toxic epidermal necrolysis and fulminant hepatitis occurred in a patient taking disulfiram and clarithromycin.

Clinical evidence, mechanism, importance and management

A 47-year-old man who had taken disulfiram 250 mg daily for about a month, with clarithromycin 500 mg twice daily and paracetamol 500 mg three times daily for one week, developed fatal toxic epidermal necrolysis and fulminant hepatitis. He had not drunk alcohol for several weeks and although he was taking paracetamol, the dose was below the toxic range and therefore an interaction between disulfiram and clarithromycin was considered probable.[1]

Disulfiram alone may cause hepatic toxicity, possibly as the result of hypersensitivity or toxic metabolites. It was suggested that inhibition of the cytochrome P450 isoenzyme CYP3A4 by clarithromycin could have resulted in the accumulation of toxic metabolites of disulfiram. Hepatocellular damage is uncommon in patients receiving clarithromycin alone, but may occur in patients with underlying disease. Both clarithromycin and disulfiram alone may cause adverse skin reactions, but neither has been reported to cause toxic epidermal necrolysis. The reason why this should occur on concurrent use is not understood.[1] Information seems to be limited to this single report, so no general conclusions can be drawn.

1. Masiá M, Guliérrez F, Jimeno A, Navarro A, Borrás J, Matarredona J, Martín-Hidalgo A. Fulminant hepatitis and fatal toxic epidermal necrolysis (Lyell disease) coincident with clarithromycin administration in an alcoholic patient receiving disulfiram therapy. *Arch Intern Med* (2002) 162, 474–6.

Macrolides; Erythromycin + Carbimazole

An isolated case describes torsade de pointes in an elderly patient taking carbimazole and oral erythromycin.

Clinical evidence

A 75-year-old woman with known mild mitral stenosis taking digoxin, furosemide, warfarin and carbimazole was given oral erythromycin 250 mg four times daily for a urinary tract infection. Three days later she experienced presyncopal episodes, and 4 days later she was admitted to hospital with syncope and self-terminating episodes of torsade de pointes. She completed the 7-day course of erythromycin on the day before admission. Five days after admission, when the QT interval was back to normal, she was inadvertently rechallenged with erythromycin, given as prophylaxis before permanent pacemaker insertion. After two doses of erythromycin 500 mg given at an interval of 6 hours, she developed torsade de pointes associated with a prolonged QT interval (QTc 612 milliseconds). The QT interval returned to normal 4 days after erythromycin was discontinued.[1]

Mechanism

QT prolongation and torsade de pointes are rare with oral erythromycin. Carbimazole is rapidly metabolised to thiamazole which is the active form of the drug. Thiamazole inhibits cytochrome P450 isoenzymes including CYP3A4 and it may therefore have inhibited the metabolism of erythromycin resulting in higher than normal levels. In addition, hypothyroidism can cause torsade de pointes, and therefore mild hypothyroidism induced by carbimazole could have contributed.[1] Furthermore, bradycardia (heart rate less than 60 bpm) may also have contributed to the development of torsade de pointes.

Importance and management

It was suggested that the combination of oral erythromycin and carbimazole could lead to torsade de pointes in susceptible individuals. In this case, female sex, presence of valvular heart disease, bradycardia, hypokalaemia, and hypothyroidism may all have been contributory factors.[1] See also, 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290.

1. Koh TW. Risk of torsades de pointes from oral erythromycin with concomitant carbimazole (methimazole) administration. *PACE* (2001) 24, 1575–6.

Macrolides; Erythromycin + Sucralfate

Sucralfate does not appear to affect the pharmacokinetics of erythromycin.

Clinical evidence, mechanism, importance and management

In 6 healthy subjects the pharmacokinetics (elimination rate constant, half-life, AUC) of a single 400-mg dose of erythromycin ethylsuccinate were not significantly altered by a single 1-g dose of sucralfate. It was concluded that the therapeutic effects of erythromycin are unlikely to be affected by concurrent use.[1]

1. Miller LG, Prichard JG, White CA, Vytla B, Feldman S, Bowman RC. Effect of concurrent sucralfate administration on the absorption of erythromycin. *J Clin Pharmacol* (1990) 30, 39–44.

Macrolides; Erythromycin + Urinary acidifiers or alkalinisers

In the treatment of urinary tract infections, the antibacterial activity of erythromycin is maximal in alkaline urine and minimal in acidic urine.

Clinical evidence

Urine taken from 7 subjects receiving erythromycin 1 g every 8 hours, was tested against 5 genera of Gram-negative bacilli (*Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa* and *Serratia* sp.) both before and after treatment with **acetazolamide** or **sodium bicarbonate**, given to alkalinise the urine. A direct correlation was found between the activity of the antibacterial and the pH of the urine. In general, acidic urine had little or no antibacterial activity, whereas alkalinised urine had activity.[1]

Clinical studies have confirmed the increased antibacterial effectiveness of erythromycin in the treatment of bacteriuria when the urine is made alkaline.[2,3]

Mechanism

The pH of the urine does not apparently affect the way the kidney handles erythromycin (most of it is excreted actively rather than passively) but it does have a direct influence on the way the antibacterial affects the microorganisms. Mechanisms suggested include effects on bacterial cell receptors, the induction of active transport mechanisms on bacterial cell walls, and changes in ionisation of the antibacterial, which enables it to enter the bacterial cell more effectively.

Importance and management

An established interaction, which can be exploited. Should erythromycin be used to treat urinary tract infections its efficacy can be maximised by making the urine alkaline (for example with acetazolamide or sodium bicarbonate). Treatment with urinary acidifiers will minimise the activity of the erythromycin for urinary tract infections and should be avoided. There is no evidence that the efficacy of erythromycin in other infections is affected by urinary acidifiers or alkalinisers.

1. Sabath LD, Gerstein DA, Loder PB, Finland M. Excretion of erythromycin and its enhanced activity in urine against gram-negative bacilli with alkalinization. *J Lab Clin Med* (1968) 72, 916–23.
2. Zinner SH, Sabath LD, Casey JI, Finland M. Erythromycin and alkalinisation of the urine in the treatment of urinary-tract infections due to gram-negative bacilli. *Lancet* (1971) i, 1267–8.
3. Zinner SH, Sabath LD, Casey JI, Finland M. Erythromycin plus alkalinization in treatment of urinary infections. *Antimicrob Agents Chemother* (1969) 9, 413–16.

Methenamine + Urinary acidifiers or alkalinisers

Urinary alkalinisers (e.g. potassium or sodium citrate) and those antacids that can raise the urinary pH above 5.5 inhibit its activation of methenamine.

Clinical evidence, mechanism, importance and management

Methenamine and methenamine mandelate are only effective as urinary antiseptics if the pH is about 5.5 or lower, when formaldehyde is released. This is normally achieved by giving urinary acidifiers such as ammonium chloride, ascorbic acid,[1,2] or sodium acid phosphate. In the case of methenamine hippurate, the acidification of the urine is achieved by the presence of hippuric acid. The concurrent use of substances that raise the urinary pH such as **acetazolamide**, **sodium bicarbonate**, **potassium** or **sodium citrate** is clearly contraindicated. **Potassium citrate mixture BPC** has been shown to raise the pH by more than 1 at normal therapeutic doses, thereby making the urine sufficiently alkaline to interfere with the activation of methenamine to formaldehyde.[3] Some **antacids** (containing magnesium, aluminium or calcium as well as sodium bicarbonate, as mentioned above) can also cause a significant rise in the pH of the urine.[4]

1. Strom JG, Jun HW. Effect of urine pH and ascorbic acid on the rate of conversion of methenamine to formaldehyde. *Biopharm Drug Dispos* (1993) 14, 61–9.
2. Nahata MC, Cummins BA, McLeod DC, Schondelmeyer SW, Butler R. Effect of urinary acidifiers on formaldehyde concentration and efficacy with methenamine therapy. *Eur J Clin Pharmacol* (1982) 22, 281–4.
3. Lipton JH. Incompatibility between sulfamethizole and methenamine mandelate. *N Engl J Med* (1963) 268, 92.
4. Blondheim SH, Alkan WJ, Brunner D, eds. Frontiers of Internal Medicine. 1974. Basel: Karger; 1975 p. 404–8.

Metronidazole + Barbiturates

Phenobarbital markedly increases the metabolism of metronidazole and treatment failure has been reported in both adults and children.

Clinical evidence

A woman with vaginal trichomoniasis was given metronidazole on several occasions over the course of a year, but the infection flared up again as soon as it was stopped. When it was realised that she was also taking **phenobarbital** 100 mg daily, the metronidazole dose was doubled to 500 mg three times daily, and she was cured after a 7-day course.[1] A pharmacokinetic study found that the clearance of metronidazole was increased by **phenobarbital** (half-life 3.5 hours compared with the normal half-life of 8 to 9 hours).[1]

A retrospective study in children who had not responded to metronidazole for giardiasis or amoebiasis found that 80% of them had been taking long-term **phenobarbital**. In a prospective study in 36 children the normal recommended metronidazole dose had to be increased about threefold to 60 mg/kg to achieve a cure. The half-life of metronidazole in 15 other children taking **phenobarbital** was found to be 3.5 hours, compared with the normal half-life of 8 to 9 hours.[2]

Other studies in patients with Crohn's disease and healthy subjects have found that **phenobarbital** reduces the AUC of metronidazole by about one-third,[3] and increases the clearance of metronidazole by 50%.[4]

Mechanism

Phenobarbital is a known, potent liver-enzyme inducer, which increases the metabolism and clearance of metronidazole from the body.

Importance and management

An established and clinically important interaction. Monitor the effects of concurrent use and anticipate the need to increase the metronidazole dose two to threefold if phenobarbital is given. All of the barbiturates are potent liver enzyme inducers and would therefore be expected to interact similarly.

1. Mead PB, Gibson M, Schentag JJ, Ziemniak JA. Possible alteration of metronidazole metabolism by phenobarbital. *N Engl J Med* (1982) 306, 1490.
2. Gupte S. Phenobarbital and metabolism of metronidazole. *N Engl J Med* (1983) 308, 529.
3. Eradiri O, Jamali F, Thomson ABR. Interaction of metronidazole with phenobarbital, cimetidine, prednisone, and sulfasalazine in Crohn's disease. *Biopharm Drug Dispos* (1988) 9, 219–27.
4. Loft S, Sonne J, Poulsen HE, Petersen KT, Jørgensen BG, Døssing M. Inhibition and induction of metronidazole and antipyrine metabolism. *Eur J Clin Pharmacol* (1987) 32, 35–41.

Metronidazole + Chloroquine

An isolated report describes acute dystonia in one patient, which was attributed to an interaction between metronidazole and chloroquine.

Clinical evidence, mechanism, importance and management

A patient was given a 7-day course of metronidazole and ampicillin, following a laparoscopic investigation. She developed acute dystonic reactions (facial grimacing, coarse tremors, and an inability to maintain posture) on day 6, within 10 minutes of being given chloroquine phosphate (equivalent to 200 mg of base) and intramuscular promethazine 25 mg. The dystonic symptoms started to subside within 15 minutes of being given diazepam 5 mg intravenously, and had completely resolved within 2 hours.[1]

The authors of the report attribute the dystonia to an interaction between metronidazole and chloroquine as she had taken both drugs alone without

adverse effect. However, they do not fully assess the possible contribution of **promethazine**, which is known to cause dystonias. It is therefore possible that the reaction seen was an adverse effect of the **promethazine**, or perhaps even an interaction between **promethazine** and chloroquine, which, very rarely, has been associated with movement disorders. No general recommendations can therefore be made from this single report.

1. Achumba JI, Ette EI, Thomas WOA, Essien EE. Chloroquine-induced acute dystonic reactions in the presence of metronidazole. *Drug Intell Clin Pharm* (1988) 22, 308–10.

Metronidazole and related drugs + Cimetidine

Cimetidine reduces the metabolism of tinidazole, and possibly also metronidazole.

Clinical evidence

(a) Metronidazole

In 6 healthy subjects, the half-life of a 400-mg intravenous dose of metronidazole was increased from 6.2 hours to 7.9 hours by cimetidine 400 mg twice daily for 6 days. The total plasma clearance of metronidazole was reduced by almost 30%.[1] However, in another study in 6 patients with Crohn's disease, cimetidine 600 mg twice daily for 7 days was found not to affect either the AUC or the half-life of metronidazole,[2] and no evidence of an interaction was found in a further study in 6 healthy subjects.[3]

(b) Tinidazole

In a study in 6 healthy subjects, cimetidine 400 mg twice daily for 7 days raised the peak serum levels of a single 600-mg dose of tinidazole by 21%, increased the 24-hour AUC by 40% and increased the half-life by 47%, from 7.66 to 11.23 hours.[4]

Mechanism

Cimetidine is a well known enzyme inhibitor, which probably inhibits the metabolism of the metronidazole and tinidazole by the liver.

Importance and management

Evidence for an interaction between metronidazole or tinidazole and cimetidine appears to be limited to these studies. With metronidazole, only one study found an interaction, but the effects were modest, and unlikely to be clinically relevant. Similarly the effects of cimetidine on tinidazole are small, and probably not of any clinical importance.

1. Gugler R, Jensen JC. Interaction between cimetidine and metronidazole. *N Engl J Med* (1983) 309, 1518–19.
2. Eradiri O, Jamali F, Thomson ABR. Interaction of metronidazole with phenobarbital, cimetidine, prednisone, and sulfasalazine in Crohn's disease. *Biopharm Drug Dispos* (1988) 9, 219–27.
3. Loft S, Døssing M, Sonne J, Dalhof K, Bjerrum K, Poulsen HE. Lack of effect of cimetidine on the pharmacokinetics and metabolism of a single oral dose of metronidazole. *Eur J Clin Pharmacol* (1988) 35, 65–8.
4. Patel RB, Shah GF, Raval JD, Gandhi TP, Gilbert RN. The effect of cimetidine and rifampicin on tinidazole kinetics in healthy human volunteers. *Indian Drugs* (1986) 23, 338–41.

Metronidazole + Diosmin

Diosmin reduces the metabolism of metronidazole to some extent.

Clinical evidence, mechanism, importance and management

A single 800-mg dose of metronidazole was given to 12 healthy subjects following 9 days of treatment with diosmin 500 mg daily. The metronidazole AUC and maximum plasma concentrations were raised by 27% and 25%, respectively.[1] This interaction is thought to occur because of an inhibitory effect of diosmin on metronidazole metabolism by hepatic enzymes, and inhibition of P-glycoprotein. The increase in metronidazole levels is similar to that seen with other drugs (e.g. 'cimetidine', (above)), and are not considered to be clinically significant. Therefore no clinically significant pharmacokinetic interaction is likely to occur if metronidazole is given with diosmin.

1. Rajnarayana K, Reddy MS, Krishna DR. Diosmin pretreatment affects bioavailability of metronidazole. *Eur J Clin Pharmacol* (2003) 58, 803–807.

Metronidazole + Disulfiram

Acute psychoses and confusion can be caused by the concurrent use of metronidazole and disulfiram.

Clinical evidence, mechanism, importance and management

In a double-blind study in 58 hospitalised chronic alcoholics taking disulfiram, 29 patients were also given metronidazole 750 mg daily for a month, then 250 mg daily thereafter. Six of the 29 subjects in the group receiving metronidazole developed acute psychoses or confusion. Five of the 6 had paranoid delusions and in 3 visual and auditory hallucinations were also seen. The symptoms persisted for 2 to 3 days after the drugs were withdrawn, but had disappeared after about 2 weeks and did not reappear when disulfiram alone was restarted.[1] Similar reactions have been described in two other reports.[2,3]

The reason for this interaction is not understood, but it appears to be established. Concurrent use should be avoided or very well monitored. Withdrawing the drugs appears to resolve any adverse effects.

1. Rothstein E, Clancy DD. Toxicity of disulfiram combined with metronidazole. *N Engl J Med* (1969) 280, 1006–7.
2. Goodhue WW. Disulfiram-metronidazole (well-identified) toxicity. *N Engl J Med* (1969) 280, 1482–3.
3. Scher JM. Psychotic reaction to disulfiram. *JAMA* (1967) 201,1051.

Metronidazole + Mebendazole

A case-control study identified the concurrent use of metronidazole and mebendazole as a risk factor in an outbreak of Stevens-Johnson syndrome/toxic epidermal necrolysis.

Clinical evidence, mechanism, importance and management

A case control study was conducted in an attempt to identify risk factors associated with an outbreak of Stevens-Johnson syndrome/toxic epidermal necrolysis that occurred amongst Filipino workers in Taiwan. The risk of developing this serious condition was significantly higher in workers who had taken both metronidazole and mebendazole sometime in the preceding 6 weeks (odds ratio of 9.5). In addition, there was an increase in risk with higher doses of metronidazole.[1]

The information is limited to this report, which does not establish an interaction. However, Stevens-Johnson syndrome/toxic epidermal necrolysis is a serious condition, and therefore, the manufacturer of mebendazole states that the concurrent use of mebendazole and metronidazole should be avoided.[2] Caution would certainly seem appropriate if both drugs are considered essential.

1. Chen K-T, Twu S-J, Chang H-J, Lin R-S. Outbreak of Stevens-Johnson syndrome/toxic epidermal necrolysis associated with mebendazole and metronidazole use among Filipino laborers in Taiwan. *Am J Public Health* (2003) 93, 489–92.
2. Vermox (Mebendazole). Janssen-Cilag Ltd. UK Summary of product characteristics, May 2009.

Metronidazole + Miscellaneous

The absorption of metronidazole is unaffected by kaolin-pectin, but it is slightly reduced by an aluminium hydroxide antacid and colestyramine.

Clinical evidence, mechanism, importance and management

In 5 healthy subjects, the bioavailability of a single 500-mg dose of metronidazole was not significantly changed by 30 mL of a **kaolin-pectin** antidiarrhoeal mixture. However, a 15% reduction in metronidazole bioavailability occurred with 30 mL of an **aluminium hydroxide**/**simeticone** suspension, and a 21% reduction occurred with a single 4-g dose of

colestyramine.[1] The clinical importance of these reductions is small, and no special precautions seem necessary on concurrent use.

1. Molokhia AM, Al-Rahman S. Effect of concomitant oral administration of some adsorbing drugs on the bioavailability of metronidazole. *Drug Dev Ind Pharm* (1987) 13, 1229–37.

Metronidazole + Prednisone

Prednisone modestly decreases the AUC of metronidazole.

Clinical evidence, mechanism, importance and management

In 6 patients with Crohn's disease the AUC of metronidazole 250 mg twice daily was reduced by 31% by prednisone 10 mg twice daily for 6 days. It was suggested that this occurred because prednisone induces the metabolism of metronidazole by liver enzymes.[1]

Information appears to be limited to this report and the interaction is probably of only limited clinical importance. Information about other corticosteroids is lacking.

1. Eradiri O, Jamali F, Thomson ABR. Interaction of metronidazole with phenobarbital, cimetidine, prednisone, and sulfasalazine in Crohn's disease. *Biopharm Drug Dispos* (1988) 9, 219–27.

Metronidazole and related drugs + Rifampicin (Rifampin)

Rifampicin modestly increases the clearance of metronidazole and tinidazole.

Clinical evidence

(a) Metronidazole

Intravenous metronidazole 500 mg or 1 g was given to 10 healthy subjects before and after they took rifampicin 450 mg daily for 7 days. Rifampicin reduced the AUC of metronidazole by 33% and increased its clearance by 44%. Results were the same with both metronidazole doses.[1]

(b) Tinidazole

In a study in 6 healthy subjects, rifampicin 600 mg daily for 7 days reduced the peak serum levels of a single 600-mg dose of tinidazole by 22%, reduced its $AUC_{0\text{-}24}$ by 30% and reduced its half-life by 27% (from 7.66 to 5.6 hours).[2]

Mechanism

This interaction almost certainly occurs because rifampicin (a well-recognised and potent enzyme inducer) increases the metabolism of metronidazole and tinidazole by the liver.

Importance and management

The clinical significance of these interactions appear not to have been studied. A 30% reduction in metronidazole exposure would not be expected to be of much clinical significance and there do not appear to be any reports of an interaction in practice. The effect of rifampicin on tinidazole is smaller, and a clinically relevant reduction in the effects of tinidazole seems unlikely.

1. Djojosaputro M, Mustofa SS, Donatus IA, Santoso B. The effects of doses and pre-treatment with rifampicin on the elimination kinetics of metronidazole. *Eur J Pharmacol* (1990) 183, 1870–1.
2. Patel RB, Shah GF, Raval JD, Gandhi TP, Gilbert RN. The effect of cimetidine and rifampicin on tinidazole kinetics in healthy human volunteers. *Indian Drugs* (1986) 23, 338–41.

Metronidazole + Sucralfate

Sucralfate does not alter the pharmacokinetics of metronidazole.

Clinical evidence, mechanism, importance and management

Because oral triple therapy to eradicate *Helicobacter pylori* using sucralfate instead of bismuth has yielded inconsistent results, a 5-day study was undertaken in 14 healthy subjects to investigate whether sucralfate interacts with metronidazole. It was found that sucralfate 2 g twice daily had no effect on the pharmacokinetics of a single 400-mg dose of metronidazole.[1] Sucralfate would therefore not be expected to alter the effects of metronidazole.

1. Amaral Moraes ME, De Almeida Pierossi M, Moraes MO, Bezerra FF, Ferreira De Silva CM, Dias HB, Muscará MN, De Nucci G, Pedrazzoli J. Short-term sucralfate administration does not alter the absorption of metronidazole in healthy male volunteers. *Int J Clin Pharmacol Ther* (1996) 34, 433–7.

Nitrofurantoin + Antacids

Magnesium trisilicate reduces the absorption of nitrofurantoin. Aluminium hydroxide is reported not to interact with nitrofurantoin. Whether other antacids interact adversely is uncertain.

Clinical evidence

In 6 healthy subjects, **magnesium trisilicate** 5 g in 150 mL of water reduced the absorption of a single 100-mg oral dose of nitrofurantoin by more than 50%. The time during which the concentration of nitrofurantoin in the urine was at, or above 32 micrograms/mL (a level stated to be the minimum inhibitory concentration) was also reduced.[1] The amounts of nitrofurantoin adsorbed by other antacids during *in vitro* tests were as follows: **magnesium trisilicate** and **charcoal** 99%, **bismuth subcarbonate** and **talc** 50 to 53%, **kaolin** 31%, **magnesium oxide** 27%, **aluminium hydroxide** 2.5% and **calcium carbonate** 0%.[1]

A crossover study in 6 healthy subjects confirmed that **aluminium hydroxide gel** does not affect the absorption of nitrofurantoin from the gut (as measured by its excretion into the urine).[2] Another study, in 10 healthy subjects, found that an antacid containing **aluminium/magnesium hydroxide** and **magnesium carbonate** reduced the absorption of nitrofurantoin by 22%.[3]

Mechanism

Antacids can, to a greater or lesser extent, adsorb nitrofurantoin onto their surfaces, as a result less is available for absorption by the gut and for excretion into the urine.

Importance and management

Information appears to be limited to these reports. There seems to be nothing in the literature confirming that a clinically important interaction occurs between nitrofurantoin and antacids. One reviewer offers the opinion that common antacid preparations are unlikely to interact with nitrofurantoin.[4]

It is not yet known whether magnesium trisilicate significantly reduces the antibacterial effectiveness of nitrofurantoin but the response should be monitored. While it is known that the antibacterial action of nitrofurantoin is increased by drugs that acidify the urine (so that reduced actions would be expected if the urine were made more alkaline by antacids) this again does not seem to have been confirmed. The results of the *in vitro* studies suggest that the possible effects of the other antacids are quite small, and aluminium hydroxide is reported not to interact.

1. Naggar VF, Khalil SA. Effect of magnesium trisilicate on nitrofurantoin absorption. *Clin Pharmacol Ther* (1979) 25, 857–63.
2. Jaffe JM, Hamilton B, Jeffers S. Nitrofurantoin-antacid interaction. *Drug Intell Clin Pharm* (1976) 10, 419–20.
3. Männistö P. The effect of crystal size, gastric content and emptying rate on the absorption of nitrofurantoin in healthy human volunteers. *Int J Clin Pharmacol Biopharm* (1978) 16, 223–8.
4. D'Arcy PF. Nitrofurantoin. *Drug Intell Clin Pharm* (1985) 19, 540–7.

Nitrofurantoin + Antigout drugs

On theoretical grounds the toxicity of nitrofurantoin may possibly be increased, and its efficacy in urinary tract infections decreased, by probenecid and sulfinpyrazone.

Clinical evidence, mechanism, importance and management

A study of the way the kidneys handle nitrofurantoin found that intravenous **sulfinpyrazone** 2.5 mg/kg reduced the secretion of nitrofurantoin by the renal tubules by about 50%.[1] This reduction would be expected to reduce its urinary antibacterial efficacy, and the higher serum levels might lead to increased systemic toxicity, but there do not seem to be any reports

suggesting that this represents a real problem in practice. The same situation would also seem likely with **probenecid**, but there do not appear to be any reports confirming this interaction.

The clinical importance of both of these interactions is therefore uncertain, but it would seem prudent to be alert for any evidence of reduced antibacterial efficacy and increased systemic toxicity if either **sulfinpyrazone** or **probenecid** is used with nitrofurantoin.

1. Schirmeister J, Stefani F, Willmann H, Hallauer W. Renal handling of nitrofurantoin in man. *Antimicrob Agents Chemother* (1965) 5, 223–6.

Nitrofurantoin + Antimuscarinics or Diphenoxylate

Diphenoxylate and antimuscarinic drugs such as propantheline can double the absorption of nitrofurantoin in some patients.

Clinical evidence, mechanism, importance and management

In 6 healthy subjects **propantheline** 30 mg given 45 minutes before nitrofurantoin approximately doubled the absorption of nitrofurantoin 100 mg (as measured by the urinary excretion).[1] In another study, **diphenoxylate** 200 mg daily for 3 days nearly doubled nitrofurantoin absorption in 2 out of 6 men.[2] **Atropine** 500 micrograms given subcutaneously 30 minutes before a single 100-mg dose of nitrofurantoin had little effect on the bioavailability of nitrofurantoin, but the absorption and excretion into the urine was delayed.[3]

It was suggested that the reduced gut motility caused by these drugs allows the nitrofurantoin to dissolve more completely so that it is absorbed by the gut more easily. Whether this is of any clinical importance is uncertain but it could possibly increase the incidence of dose-related adverse reactions. So far there appear to be no reports of any problems arising from concurrent use.

1. Jaffe JM. Effect of propantheline on nitrofurantoin absorption. *J Pharm Sci* (1975) 64, 1729–30.

2. Callahan M, Bullock FJ, Braun J, Yesair DW. Pharmacodynamics of drug interactions with diphenoxylate (Lomotil®). *Fedn Proc* (1974) 33, 513.

3. Männistö P. The effect of crystal size, gastric content and emptying rate on the absorption of nitrofurantoin in healthy human volunteers. *Int J Clin Pharmacol Biopharm* (1978) 16, 223–8.

Nitrofurantoin + Azoles

In an isolated case hepatic and pulmonary toxicity occurred when nitrofurantoin was given with fluconazole, but not with itraconazole.

Clinical evidence, mechanism, importance and management

A 73-year-old man who had taken nitrofurantoin 50 mg daily for 5 years was given **fluconazole** 150 mg weekly for onychomycosis. At the start of treatment with **fluconazole** his hepatic enzyme levels were slightly raised, and 3 weeks later they were increased more than twofold. Two months after starting **fluconazole** the patient's hepatic enzyme levels had increased fivefold and he had fatigue, dyspnoea on exertion, pleuritic pain, burning tracheal pain, and a cough. Bilateral pulmonary disease was confirmed by chest X-rays, and pulmonary function tests suggested nitrofurantoin toxicity. Both **fluconazole** and nitrofurantoin were discontinued, and hepatic and lung function gradually improved.[1]

Either **fluconazole** or nitrofurantoin could have caused the liver toxicity. However, it was considered that both the lung and liver toxicity may have been due to an interaction between nitrofurantoin and **fluconazole**, possibly due to increased nitrofurantoin concentrations resulting from competition with **fluconazole** for renal tubular secretion.

Some 2 years earlier the patient had received pulse **itraconazole** (less than 1% excreted in the urine as active drug) with nitrofurantoin without raised liver enzymes or any other adverse effects.[1]

Information appears to be limited to this report, but bear it in mind in the event of increased nitrofurantoin adverse effects. More study is needed.

1. Linnebur SA, Parnes BL. Pulmonary and hepatic toxicity due to nitrofurantoin and fluconazole treatment. *Ann Pharmacother* (2004) 38, 612–16.

Nitrofurantoin + Metoclopramide

Metoclopramide reduces the absorption of nitrofurantoin.

Clinical evidence, mechanism, importance and management

In 10 healthy subjects the urinary excretion of a 100-mg dose of nitrofurantoin was approximately halved by pretreatment with a 10-mg intramuscular dose of metoclopramide and a 10-mg oral dose of metoclopramide given 30 minutes before the nitrofurantoin.[1]

It is thought that metoclopramide increases the gastric emptying rate, thus decreasing nitrofurantoin absorption. The practical importance of this is uncertain, and there seem to be no reports of an interaction in practice.

1. Männistö P. The effect of crystal size, gastric content and emptying rate on the absorption of nitrofurantoin in healthy human volunteers. *Int J Clin Pharmacol Biopharm* (1978) 16, 223–8.

Nitrofurantoin + Pyridoxine (Vitamin B_6)

Paraesthesias occurred in an elderly woman who had taken pyridoxine for several years and several courses of nitrofurantoin over a 10-year period.

Clinical evidence, mechanism, importance and management

A 73-year-old woman with a 10-year history of recurrent urinary-tract infections treated with nitrofurantoin 100 mg twice daily for 3 to 10 days, two to three times each year and who also took conjugated oestrogens, calcium and magnesium, and a vitamin B complex (including pyridoxine 100 mg for 5 years), reported tingling and burning sensation of the distal lower extremity and alternate sensations of hot and cold in both feet 3 weeks after taking a 6-day course of nitrofurantoin. She also had abdominal discomfort. Her pyridoxine levels were 88.6 nanograms/mL (reference range 2 to 26 nanograms/mL). No evidence of peripheral sensory motor neuropathy, lower motor neurone dysfunction, myopathic dysfunction, or abdominal problems was found, but one year after symptoms developed she still had paraesthesias of the distal lower extremity.[1]

Nitrofurantoin may cause neuropathy after both short- or long-term treatment and occurs more frequently in women and the elderly. Pyridoxine, particularly in high doses may cause sensory neuropathy. Either drug could have caused the paraesthesias. However, it has been suggested that concurrent use of nitrofurantoin with other neurotoxic medications may increase the potential for neurotoxicity. The reason for the elevated pyridoxine levels is unclear, but they may have contributed to the neuropathy.

Information appears to be limited to this report, but bear it in mind in the event of unexpected toxicity.

1. Lacerna RA, Chien C. Paresthesias developing in an elderly patient after chronic usage of nitrofurantoin and vitamin B_6. *J Am Geriatr Soc* (2003) 51, 1822–3.

Nitroxoline + Antacids

The antibacterial effects of nitroxoline have been found to be reduced *in vitro* by magnesium and calcium ions because they form chelates with the nitroxoline.[1] In the absence of any direct clinical information it would seem prudent to monitor concurrent use for any evidence that its antibacterial effects are reduced. In many interactions with antacids, separating administration by 2 to 3 hours is effective in minimising the extent of the effects.

1. Pelletier C, Prognon P, Bourlioux P. Roles of divalent cations and pH in mechanism of action of nitroxoline against *Escherichia coli* strains. *Antimicrob Agents Chemother* (1995) 707–13.

Novobiocin + Rifampicin (Rifampin)

Rifampicin reduces the half-life of novobiocin.

Clinical evidence, mechanism, importance and management

When 10 healthy subjects were given novobiocin 1 g daily for 13 days with rifampicin 600 mg daily, the novobiocin half-life was reduced from

5.85 hours to 2.66 hours and its AUC was reduced by almost 50%. There were no significant changes to the half-life or AUC of rifampicin. The serum novobiocin and rifampicin levels were not significantly altered and the trough serum levels of both antibacterials when given alone or concurrently remained in excess of the MIC for 90% of the strains of MRSA tested.[1] No special precautions would therefore seem to be necessary during concurrent use.

1. Drusano GL, Townsend RJ, Walsh TJ, Forrest A, Antal EJ, Standiford HC. Steady-state serum pharmacokinetics of novobiocin and rifampin alone and in combination. *Antimicrob Agents Chemother* (1986) 30, 42–5.

Penicillins + Acacia or Guar gum

The absorption of amoxicillin may be significantly reduced when given with or 2 hours after acacia. Guar gum causes a small reduction in the absorption of phenoxymethylpenicillin.

Clinical evidence, mechanism, importance and management

(a) Acacia

In healthy subjects the maximum serum levels and AUC of a single 500-mg dose of **amoxicillin** were reduced by 73% and 79%, respectively, when given with acacia (gum arabic: amount not stated) and by 56% and 49%, respectively, when given 2 hours after acacia. The pharmacokinetics of **amoxicillin** were not significantly affected when it was given 4 hours after acacia. Acacia is used in pharmaceutical preparations as a suspending, demulcent and emulsifying agent. Concurrent administration with **amoxicillin** could result in subtherapeutic levels of the antibacterial, but whether or not this would occur with the amount of acacia in a dose of a preparation containing it as an excipient is not known. In some countries acacia is given to patients with chronic renal failure. The authors suggest that if **amoxicillin** is used to treat urinary tract infections in patients also treated with acacia, it should be given 4 hours before or after the acacia.[1]

(b) Guar gum

In 10 healthy subjects, guar gum 5 g (*Guarem*, 95% guar gum) reduced the absorption of a single 1980-mg dose of **phenoxymethylpenicillin** (penicillin V). Peak serum penicillin levels were reduced by 25% and the AUC_{0-6} was reduced by 28%.[2] The reasons are not understood. The clinical significance of this interaction is uncertain, but the reduction in serum levels is only small. It would clearly only be important if the reduced amount of penicillin absorbed was inadequate to control infection The effect of guar gum on other penicillins seems not to have been studied.

1. Eltayeb IB, Awad AI, Elderbi MA, Shadad SA. Effect of gum arabic on the absorption of a single oral dose of amoxicillin in healthy Sudanese volunteers. *J Antimicrob Chemother* (2004) 54, 577–8.
2. Huupponen R, Seppälä P, Iisalo E. Effect of guar gum, a fibre preparation, on digoxin and penicillin absorption in man. *Eur J Clin Pharmacol* (1984) 26, 279–81.

Penicillins + Allopurinol

The incidence of skin rashes in patients taking either ampicillin or amoxicillin is increased by allopurinol.

Clinical evidence

A retrospective search through the records of 1324 patients, 67 of whom were taking allopurinol and **ampicillin**, found that 15 of them (22%) developed a skin rash compared with 94 (8%) of the patients not taking allopurinol.[1] The types of rash were not defined. Another study found that 35 out of 252 patients (14%) taking allopurinol and **ampicillin** developed a rash, compared with 251 out of 4434 (6%) taking **ampicillin** alone.[2] A parallel study revealed that 8 out of 36 patients (22%) taking **amoxicillin** and allopurinol developed a rash, whereas only 52 out of 887 (6%) did so when taking **amoxicillin** alone.[2]

A case report describes a patient who developed erythema multiforme shortly after starting **amoxicillin** and allopurinol and who was found to have both allopurinol hypersensitivity and type IV amoxicillin hypersensitivity.[3]

In contrast, one study did not find that the incidence of penicillin-related rashes was increased by allopurinol, and the authors suggested that this contrasting finding may be because exposure to penicillins was shorter in their study.[4]

Mechanism

Not understood. One suggestion is that the hyperuricaemia was responsible.[1] Another is that hyperuricaemic individuals may possibly have an altered immunological reactivity.[5]

Importance and management

An established interaction of limited importance. There would seem to be no strong reason for avoiding concurrent use, but prescribers should recognise that the development of a rash is by no means unusual. Whether this also occurs with penicillins other than ampicillin or amoxicillin is uncertain, and does not seem to have been reported.

1. Boston Collaborative Drug Surveillance Programme. Excess of ampicillin rashes associated with allopurinol or hyperuricemia. *N Engl J Med* (1972) 286, 505–7.
2. Jick H, Porter JB. Potentiation of ampicillin skin reactions by allopurinol or hyperuricemia. *J Clin Pharmacol* (1981) 21, 456–8.
3. Pérez A, Cabrerizo S, de Barrio M, Díaz MP, Herrero T, Tornero P, Baeza ML. Erythema-multiforme-like eruption from amoxicillin and allopurinol. *Contact Dermatitis* (2001) 44, 113–14.
4. Sonntag MR, Zoppi M, Fritschy D, Maibach R, Stocker F, Sollberger J, Buchli W, Hess T, Hoigné R. Exantheme unter haufig angewandten Antibiotika und antibakteriellen Chemotherapeutika (Penicilline, speziell Aminopenicilline, Cephalosporine und Cotrimoxazol) sowie Allopurinol. *Schweiz Med Wochenschr* (1986) 116, 142–5.
5. Fessel WJ. Immunologic reactivity in hyperuricemia. *N Engl J Med* (1972) 286, 1218.

Penicillins + Antacids

Aluminium/magnesium hydroxide and aluminium hydroxide do not significantly affect the bioavailability of amoxicillin or amoxicillin with clavulanic acid (co-amoxiclav). Antacids may reduce the absorption of the hydrochloride salt of pivampicillin.

Clinical evidence, mechanism, importance and management

(a) Amoxicillin or Co-amoxiclav

The pharmacokinetics of amoxicillin 1 g, and both amoxicillin and clavulanic acid (given as co-amoxiclav 625 mg), were not significantly altered by 10 doses of **aluminium/magnesium hydroxide** (*Maalox*) 10 mL, with the last dose given 30 minutes before amoxicillin.[1] Another study found that four 40-mg doses of **aluminium hydroxide** (*Aludrox*) given at 20 minute intervals had no effect on the pharmacokinetics of either amoxicillin or clavulanic acid (given as co-amoxiclav 750 mg with the second dose of antacid).[2]

There would seem to be no reason for avoiding the concurrent use of antacids and amoxicillin or co-amoxiclav.

(b) Pivampicillin

The UK manufacturers of pivampicillin[3] used to recommend that, because antacids may decrease pivampicillin absorption, concurrent use should be avoided. This warning relates to a hydrochloride salt formulation, which needs acidic conditions for optimal absorption, whereas the basic salt formulation should not be affected by any pH change.[4]

1. Deppermann K-M, Lode H, Höffken G, Tschink G, Kalz C, Koeppe P. Influence of ranitidine, pirenzepine, and aluminium magnesium hydroxide on the bioavailability of various antibacterials, including amoxicillin, cephalexin, doxycycline, and amoxicillin-clavulanic acid. *Antimicrob Agents Chemother* (1989) 33, 1901–7.
2. Staniforth DH, Clarke HL, Horton R, Jackson D, Lau D. Augmentin bioavailability following cimetidine, aluminum hydroxide and milk. *Int J Clin Pharmacol Ther Toxicol* (1985) 23, 145–7.
3. Pondocillin (Pivampicillin). Leo Laboratories Ltd. ABPI Compendium of Datasheets and Summaries of Product Characteristics, 1998–99, 625–6.
4. Leo Laboratories Limited. Personal communication, March 1995.

Penicillins + Catha (Khat)

Chewing khat reduces the absorption of ampicillin and, to a lesser extent, amoxicillin, but the effects are minimal 2 hours after khat chewing stops.

Clinical evidence, mechanism, importance and management

A study in 8 healthy Yemeni male subjects found that chewing khat reduced the absorption of oral **ampicillin** from the gut.[1] When **ampicillin** 500 mg was taken with 250 mL water 2 hours before, just before khat chewing started, or midway through a 4-hour chewing session, the amounts of unchanged **ampicillin** in the urine fell by 46%, 41% and 49%, respectively. Even when **ampicillin** was taken 2 hours after a chewing

session had stopped, the amount of drug excreted unchanged in the urine fell by 12%. A parallel series of studies with **amoxicillin** 500 mg found much smaller reductions. The equivalent reductions were 14%, 9%, 22% and 13%. A similar study found that chewing khat resulted in variable reduction in the bioavailability of **amoxicillin** 500 mg, which was maximal (22%) when it was given midway during the 4-hour chewing period.[2]

The reasons for this interaction are not known, but the authors of the reports suggest that tannins from the khat might form insoluble and non-absorbable complexes with these penicillins, and possibly also directly reduce the way the gut absorbs them.[1]

Khat (the leaves and stem tips of *Catha edulis*) is chewed in some African and Arabian countries for its stimulatory properties. The authors of one of the studies concluded that both **ampicillin** and **amoxicillin** should be taken 2 hours after khat chewing to ensure that maximum absorption occurs.[1]

1. Attef OA, Ali A-AA, Ali HM. Effect of Khat chewing on the bioavailability of ampicillin and amoxycillin. *J Antimicrob Chemother* (1997) 39, 523–5.
2. Abdel Ghani YM, Etman MA, Nada AH. Effect of khat chewing on the absorption of orally administered amoxycillin. *Acta Pharm* (1999) 49, 43–50.

Penicillins + Chloroquine

Chloroquine reduces the absorption of ampicillin, but does not affect the absorption of ampicillin from bacampicillin.

Clinical evidence

In 7 healthy subjects, chloroquine 1 g reduced the absorption (as measured by excretion in the urine) of a single 1-g dose of oral **ampicillin** by about one-third (from 29 to 19%).[1] Another study by the same author demonstrated that the absorption of **ampicillin** from **bacampicillin** tablets was unaffected by chloroquine.[2]

Mechanism

A possible reason for the reduction in absorption is that the chloroquine irritates the gut so that the ampicillin is moved through more quickly, thereby reducing the time for absorption.

Importance and management

Information appears to be limited to the studies cited, which used large doses of chloroquine (1 g) when compared with those usually used for malarial prophylaxis (300 mg base weekly) or for rheumatic diseases (150 mg daily). The reduction in the ampicillin absorption is also only moderate. The general clinical importance of this interaction therefore seems likely to be small. However, one report suggests separating the dosing by not less than 2 hours.[1] An alternative would be to use bacampicillin (an ampicillin pro-drug), which does not appear to interact with chloroquine.[2] More study is needed to confirm and evaluate the importance of this interaction.

1. Ali HM. Reduced ampicillin bioavailability following oral coadministration with chloroquine. *J Antimicrob Chemother* (1985) 15, 781–4.
2. Ali HM. The effect of Sudanese food and chloroquine on the bioavailability of ampicillin from bacampicillin tablets. *Int J Pharmaceutics* (1981) 9, 185–90.

Penicillins + Food

The absorption of many penicillins is not significantly affected by food. The exceptions are ampicillin (food may reduce its levels by up to 50%), cloxacillin, and possibly pivampicillin and phenoxymethylpenicillin.

Clinical evidence, mechanism, importance and management

(a) Dietary fibre

In 10 healthy subjects the AUC of a single 500-mg oral dose of **amoxicillin** was found to be 12.17 micrograms/mL per hour when the subjects consumed a low-fibre diet (7.8 g of insoluble fibre daily) but only 9.65 micrograms/mL per hour when the subjects consumed a high-fibre diet (36.2 g of insoluble fibre daily); a difference of about 20%. Peak serum levels were the same and occurred at 3 hours.[1] The clinical relevance of these changes is likely to be minimal.

(b) Enteral and parenteral feeds

A single 250-mg intravenous dose of **ampicillin** was given to 7 healthy subjects 2 hours into a 12-hour infusion of parenteral nutrition or 4 hours after an enteral meal. The parenteral nutrition was of two types, one with and one without amino acids, calcium and phosphorus, both without lipids, and of similar calorific content and volume to the enteral feed. None of the three regimens altered the pharmacokinetics of intravenous **ampicillin**.[2] Note that the **ampicillin** was given in a separate limb to the parenteral nutrition.

(c) Food

1. Amoxicillin and Co-amoxiclav. When amoxicillin was taken after food, its serum levels were reduced by about 50% and its urinary excretion was reduced, when compared with the fasted state.[3] However, in another study in 16 healthy subjects, a standard breakfast had no effect on the AUC of a single 500-mg dose of amoxicillin.[4] Similarly, a crossover study in 18 healthy subjects given co-amoxiclav (amoxicillin 500 mg with **clavulanic acid** 250 mg), either 2 hours before or with a fried breakfast, found that the breakfast had no significant effect on the pharmacokinetics of amoxicillin or **clavulanic acid**. Moreover, a further study in 43 healthy subjects found that taking co-amoxiclav with food tended to minimise the incidence (but not the severity) of gastrointestinal adverse effects (watery stools, nausea and vomiting).[5] It would therefore be beneficial to take co-amoxiclav with a meal.

2. Ampicillin. When a single 500-mg dose of ampicillin was taken immediately after food, its serum levels were reduced by about 50% and its urinary excretion was reduced.[3] In 16 healthy subjects, a standard breakfast reduced the AUC of a single 500-mg dose of ampicillin by 31%.[4] Another study found ampicillin absorption was delayed and the total absorption reduced when it was taken with food. Urinary excretion of ampicillin was about 30% of a dose when given on an empty stomach and about 20% when given with food.[6] It is recommended that ampicillin is taken one hour before food or on an empty stomach to optimise absorption.

3. Bacampicillin. When 6 healthy subjects took a 1.6-g dose of bacampicillin either 35 minutes after breakfast or 2 hours before breakfast, its AUC was 26% lower with the post-breakfast dose, but this difference was not statistically significant.[7] On the basis of other work that also suggests that no important interaction occurs with food,[8,9] the manufacturers say that bacampicillin can be given without regard to the time of food intake.

4. Flucloxacillin. A study in children given flucloxacillin 12.5 mg/kg as either tablets or mixture found that while the absorption depended on both the formulation and age of the child, there was no difference in levels achieved when given to a subject when fasting or with a breakfast.[10] However, it is recommended that flucloxacillin is taken one hour before food or on an empty stomach to optimise absorption. The presence of food is reported to reduce the rate and extent of absorption of the related drug **cloxacillin**,[11] and therefore it may be prudent to follow the advice given for flucloxacillin.

5. Pivampicillin. A study in healthy subjects found the absorption of pivampicillin was delayed when it was given with food, but the amount absorbed was not affected. The urinary excretion of ampicillin following pivampicillin was about 60% of the dose when taken with or without food.[6] However, another study in which pivampicillin 350 mg was given in the fasting state or with a standardised cooked breakfast found that food both delayed and reduced the absorption of pivampicillin by almost 50%.[12]

6. Pivmecillinam. The manufacturer of pivmecillinam states that the tablets should preferably be taken with or immediately after a meal.[13]

(d) Milk

The peak levels and the AUCs of oral **phenoxymethylpenicillin** and *oral* **benzylpenicillin** were reduced by 40 to 60% in infants and children when they were given with milk.[14] It is recommended that **phenoxymethylpenicillin** is taken one hour before food or on an empty stomach to optimise absorption.

Co-amoxiclav (**amoxicillin** 500 mg with **clavulanic acid** 250 mg) was given to 16 healthy subjects at the same time as the second of four 200-mL glasses of milk (taken at 20 minute intervals). Although the bioavailability of the **amoxicillin** and **clavulanic acid** tended to be decreased, and the time to peak levels delayed, the changes did not reach statistical significance.[15] No special precautions would seem to be necessary.

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Penicillins + H_2-receptor antagonists

Cimetidine does not adversely affect the bioavailability of ampicillin or co-amoxiclav, but the bioavailability of oral benzylpenicillin may be increased in some subjects. Ranitidine does not affect the pharmacokinetics of amoxicillin, but may possibly reduce the bioavailability of bacampicillin.

Clinical evidence, mechanism, importance and management

(a) Amoxicillin and Co-amoxiclav

Cimetidine 200 mg, given three times daily the day before and with a single 200-mg dose of co-amoxiclav (amoxicillin with clavulanic acid), had no significant effect on the bioavailability of amoxicillin or clavulanic acid.[1] Another study found that **ranitidine** (300 mg given the day before and 150 mg given with the antibacterial) had no effect on the pharmacokinetics of a single 1-g dose of amoxicillin.[2]

(b) Ampicillin

In a placebo-controlled study in 6 healthy subjects, **cimetidine** 400 mg every 6 hours for 6 days had no effect on the pharmacokinetics of a single 500-mg dose of ampicillin given on day 6.[3]

(c) Bacampicillin

One small study suggested that when bacampicillin was given with **ranitidine** 300 mg and **sodium bicarbonate** 4 g, the AUC was reduced by 78% when the drugs were given with breakfast and by 55% when the drugs were given without food.[4] However, these results have been criticised because the study only included 6 subjects and because of differences in methodology between the compared groups.[5] The findings remain unconfirmed, and their clinical significance is uncertain.

(d) Benzylpenicillin

A study using a 600-mg *oral* dose of benzylpenicillin found that **cimetidine** raised the benzylpenicillin serum levels by about threefold in one subject, but did not significantly affect benzylpenicillin levels in another 4 subjects.[5] The clinical significance of these findings is unclear, especially as benzylpenicillin is more usually given parenterally.

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Penicillins + Miscellaneous

Aspirin, indometacin, phenylbutazone, sulfaphenazole and sulfinpyrazone prolong the half-life of benzylpenicillin. Some sulfonamides reduce oxacillin blood levels. Pirenzepine does not affect the pharmacokinetics of amoxicillin, and chlorothiazide, sulfamethizole and sulfamethoxypyridazine do not affect the half-life of benzylpenicillin.

Clinical evidence, mechanism, importance and management

Studies in patients given different drugs for 5 to 7 days showed the following increases in the half-life of **benzylpenicillin**: **aspirin** 63%, **indometacin** 22%, **phenylbutazone** 139%, **sulfaphenazole** 44% and **sulfinpyrazone** 65%. It seems likely that competition between these drugs and **benzylpenicillin** for excretion by the kidney tubules caused these increases.[1] Changes in the half-life of benzylpenicillin with **chlorothiazide**, **sulfamethizole** and **sulfamethoxypyridazine** were not significant.[1]

In healthy subjects, **sulfamethoxypyridazine** 3 g given 8 hours before a 1-g dose of oral **oxacillin** reduced the 6-hour urinary recovery by 55%. **Sulfaethidole** 3.9 g given 3 hours before the **oxacillin** reduced the 6-hour urinary recovery by 42%.[2]

Pirenzepine 50 mg given three times daily on the day before and with a single 1-g dose of **amoxicillin** had no significant effect on the pharmacokinetics of the antibacterial.[3]

None of the interactions listed appears to be adverse, and no particular precautions would seem necessary during concurrent use of these drugs and the penicillins. The importance of the interaction between **oxacillin** and the sulfonamides is uncertain, but it can easily be avoided by choosing alternative drugs.

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Penicillins + Nifedipine

Nifedipine increases the absorption of amoxicillin from the gut. Nafcillin increases the clearance of nifedipine.

Clinical evidence, mechanism, importance and management

(a) Amoxicillin

In 8 healthy subjects when amoxicillin 1 g was given 30 minutes after a 20-mg nifedipine capsule, the peak serum amoxicillin levels were raised by 33%, the bioavailability was raised by 21% and the absorption rate was raised by 70%.[1] The authors speculate that the uptake of amoxicillin through the gut wall is increased by nifedipine in some way.[1] There would seem to be no good reason for avoiding concurrent use as overall the bioavailability was not significantly altered.

(b) Nafcillin

In a randomised, placebo-controlled study, 9 healthy subjects were given a single 10-mg nifedipine capsule after a 5-day course of nafcillin 500 mg four times daily. The nifedipine AUC was decreased by 63% and its clearance was increased by 145%, but the effect of these changes on nifedipine pharmacodynamics was not assessed. It was suggested that nafcillin is an inducer of cytochrome P450 isoenzymes, and increased the metabolism of nifedipine.[2] The clinical significance of these changes is unclear, but it may be prudent to be alert for any decrease in the efficacy of nifedipine.

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Penicillins + Probenecid

Probenecid reduces the excretion of the penicillins.

Clinical evidence

(a) Amoxicillin

In 10 healthy subjects a single 3-g dose of amoxicillin was given with or without probenecid 1 g. Two hours after administration, the serum levels of amoxicillin taken with probenecid were 55% higher than those with amoxicillin alone, and they remained higher for up to 18 hours.[1] Similar results were found in another study.[2] Amoxicillin 3 g twice daily plus placebo, amoxicillin 1 g twice daily plus probenecid 1 g twice daily, and amoxicillin 1 g twice daily plus probenecid 500 mg four times daily were given to 6 patients to treat bronchiectasis. The maximum serum concentration and half-life of both high- and low-dose amoxicillin were similar, but in the regimens containing probenecid the clearance of amoxicillin was reduced by two-thirds, when compared with amoxicillin given alone.[3]

(b) Amoxicillin with clavulanic acid

A crossover study in 16 healthy subjects found that probenecid, 1 g given 12 hours and one hour before a single 500-mg dose of amoxicillin, with or without 250 mg of clavulanic acid, had no significant effects on the pharmacokinetics of clavulanic acid. However, the AUC of amoxicillin was increased by 89% and 77% when given with clavulanic acid and alone, respectively, and the maximum plasma level of amoxicillin was increased by 54% and 29% when given with clavulanic acid and alone, respectively.[4]

(c) Benzylpenicillin

Four healthy subjects were given infusions of benzylpenicillin at three different rates, either alone or with probenecid (as a separate infusion), at rates to provide low and high plasma levels. An infusion rate of probenecid 83 mg/hour, corresponding to a daily dose of 2 g was found to produce about 90% inhibition of the tubular excretion of benzylpenicillin (at plasma levels of 25 mg/L). Doses of probenecid above 2 g daily did not have a significantly greater effect.[5]

(d) Mezlocillin

A study in healthy subjects found that probenecid 1 g, given one hour before an intramuscular injection of mezlocillin, increased the peak serum levels and AUC of mezlocillin by 65% and decreased the total clearance, renal clearance and apparent volume of distribution by 38%, 52%, and 35%, respectively.[6]

(e) Nafcillin

A study in 5 healthy subjects given 500 mg of intravenous nafcillin sodium with probenecid, 1 g given orally the previous night and 2 hours before the antibacterial, found that the urinary recovery of nafcillin was reduced from 30% to 17%, and its AUC was approximately doubled.[7]

(f) Piperacillin with Tazobactam

In 10 healthy subjects probenecid 1 g given one hour before a single infusion of piperacillin 3 g with tazobactam 375 mg caused a decrease of about 25% in the clearance of both components. The half-life of tazobactam was increased by 72%.[8] A study in 8 healthy subjects found that oral probenecid 1 g, given one hour before an intramuscular injection of piperacillin 1 g, increased both the peak plasma level and terminal half-life of piperacillin by 30% and increased its AUC by 60%. The apparent volume of distribution of piperacillin was reduced by 20% and renal clearance was reduced by 40%.[9]

(g) Pivampicillin

In a crossover study, healthy subjects were given either pivampicillin 350 mg every 8 hours or a tablet of MK-356 (approximately 350 mg of pivampicillin with 200 mg of probenecid). Peak ampicillin levels of 4 to 5 micrograms/mL were found about one hour after administration of the first and last dose of both treatments suggesting that probenecid did not affect the elimination of the ampicillin metabolite of pivampicillin. Administration of MK-356 (pivampicillin 700 mg with probenecid 400 mg) twice daily indicated that peak serum levels of ampicillin were increased and elimination rate slowed following successive doses.[10]

(h) Procaine benzylpenicillin

A study in patients given intramuscular procaine benzylpenicillin 2.4 or 4.8 g with or without probenecid 2 g found the peak serum levels were higher in patients given probenecid, but because of wide interpatient variation, possibly associated with differences in the release of penicillin from the injection sites; the exact potentiating effect of probenecid could not be determined.[11] However, another study in men and women given procaine benzylpenicillin 2.4 g and 4.8 g, respectively (for uncomplicated gonorrhoea), found treatment failure after one week in 15.4% of men and 10.4% of women. Failure rates were reduced to 1.8% and 3.7%, respectively, when oral probenecid 1 g was given with the penicillin.[12]

(i) Ticarcillin

Probenecid, either 500 mg twice daily, 1 g daily, or 2 g daily was added to ticarcillin 3 g every 4 hours, which was being given to treat infections in adult cystic fibrosis patients. In all cases the clearance of ticarcillin was reduced: by about 27% with the 500-mg dose regimen, by about 32% with the 1-g dose regimen and by about 43% with the 2-g dose regimen.[13]

Mechanism

In each case the penicillin competes with the probenecid for excretion by the renal tubules, although with nafcillin, non-renal clearance may also play a part.

Importance and management

In the case of amoxicillin, benzylpenicillin, nafcillin and ticarcillin the effects of probenecid are of clinical significance. The presence of clavulanic acid does not alter the interaction of amoxicillin with probenecid. In the case of the ticarcillin study the authors suggest that a 12-hourly dosing regimen could be used if probenecid is given concurrently, which has implications for home treatment. When piperacillin with tazobactam is given with probenecid the changes are not thought to provide any benefit in terms of dose reduction or alteration of the dose interval. Note that this is generally considered to be a beneficial interaction, but bear in mind that, in some cases, such as in renal impairment, the increase in penicillin levels may be undesirably large.

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Penicillins + Tetracyclines

Data from the 1950s suggested that the tetracyclines can reduce the effectiveness of penicillins in the treatment of pneumococcal meningitis and probably scarlet fever. It is uncertain whether a similar interaction occurs with other infections. This interaction may possibly be important only with those infections where a rapid kill is essential.

Clinical evidence

When **chlortetracycline** originally became available it was tested as a potential treatment for meningitis. In patients with pneumococcal meningitis it was found that intramuscular **benzylpenicillin** 600 mg every 2 hours was more effective than the same regimen of penicillin with intravenous **chlortetracycline** 500 mg every 6 hours. Out of 43 patients given penicil-

lin alone, 70% recovered, compared with only 20% in another group of 14 essentially similar patients who had received both antibacterials.[1]

Another report about the treatment of pneumococcal meningitis with intramuscular or intravenous **penicillin** and intravenous tetracyclines (**chlortetracycline**, **oxytetracycline**, **tetracycline**) confirmed that the mortality was much lower in those given only penicillin, rather than the combination of penicillin and a tetracycline.[2] In the treatment of scarlet fever (Group A beta-haemolytic streptococci), no difference was seen in the initial response to treatment with penicillin (oral **procaine benzylpenicillin**) and **chlortetracycline** or the penicillin alone, but spontaneous reinfection occurred more frequently in those who had received both antibacterials.[3]

Mechanism

The generally accepted explanation is that bactericides such as the penicillins, which inhibit bacterial cell wall synthesis, require cells to be actively growing and dividing to be maximally effective, a situation that will not occur in the presence of bacteriostatic antibacterials, such as the tetracyclines.

Importance and management

Documentation is limited, but this is an apparently important interaction when treating pneumococcal meningitis and probably scarlet fever. However, the use of these antibacterials for such severe infections has largely been superseded. It has not been shown to occur when treating pneumococcal pneumonia.[4] It has been suggested that antagonism, if it occurs, may only be significant when it is essential to kill bacteria rapidly,[4] i.e. in serious infections such as meningitis or in neutropenic patients. Any penicillin and any tetracycline would be expected to behave in this way. The manufacturers of some tetracyclines (including doxycycline and oxytetracycline) advise that their use with penicillins should be avoided.[5-7]

Note that, the macrolides, which are also bacteriostatic would be expected to attenuate the action of penicillins, but this does not seem to occur in practice. See 'Macrolides + Penicillins', p.356.

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Penicillins + Valproate

An isolated report describes hyperammonaemic encephalopathy in an elderly patient during treatment with valproate and pivmecillinam.

Clinical evidence, mechanism, importance and management

There is a report of hyperammonaemic encephalopathy which developed in a 72-year-old woman taking valproate monotherapy for partial epilepsy after she started treatment with **pivmecillinam** 600 mg daily. She recovered after discontinuation of valproate and use of cefuroxime instead of **pivmecillinam**.[1] Valproate may reduce serum carnitine,[1] for reasons that are not well understood.[2] Valproate-induced hyperammonaemic encephalopathy may be due to reduced carnitine levels.[1]

Pivmecillinam and **pivampicillin** are hydrolysed to release mecillinam or ampicillin, respectively, as well as pivalic acid and formaldehyde. One of the potential problems of these drugs is that the pivalic acid can react with carnitine to form pivaloyl-carnitine, which is excreted in the urine, and so the body can become depleted of carnitine. Carnitine deficiency also manifests as muscle weakness and cardiomyopathy.

The risks of carnitine deficiency due to **pivmecillinam** or **pivampicillin** seem to be small in healthy adults, but the manufacturer of **pivmecillinam** issues a warning about long-term or frequently repeated treatment.[3]

The authors of the report advise caution if **pivmecillinam** is added to treatment with valproate.[1] Although this appears to be the only report of an adverse effect due to the combined effects of **pivmecillinam** and valproate on carnitine levels, the manufacturer of **pivmecillinam** advises its avoidance with valproic acid or valproate.[3] **Pivampicillin** is likely to have a similar effect and should therefore probably also be avoided.

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3. Selexid (Pivmecillinam hydrochloride). Leo Laboratories Ltd. UK Summary of product characteristics, January 2008.

Penicillins; Amoxicillin + Amiloride

Amiloride can cause a small reduction in the absorption of amoxicillin.

Clinical evidence, mechanism, importance and management

When 8 healthy subjects were given amiloride 10 mg followed 2 hours later by a single 1-g oral dose of amoxicillin, the bioavailability and maximum serum levels of amoxicillin were reduced by 27% and 25%, respectively, and the time to reach maximum levels was delayed from 1 hour to 1.56 hours. When amoxicillin was given intravenously its bioavailability was unchanged by amiloride.[1] A second study in which amiloride and amoxicillin were delivered directly to the jejunum found that amiloride had no effect on the jejunal permeability of amoxicillin.[2]

It is thought that the absorption of beta lactams like amoxicillin depends on a dipeptide carrier system in the cells lining the intestine (brush border membrane). This system depends on the existence of a pH gradient between the outside and inside of the cells, which is maintained by a Na-H exchanger. As this exchanger is inhibited by amiloride the reduced absorption seen in the first study would seem to be explained.

This reported reduction in the absorption of the amoxicillin is only small and unlikely to have very much clinical relevance. There seems to be no information about other penicillins.

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Penicillins; Cloxacillin + Proguanil

Proguanil may reduce the bioavailability of cloxacillin.

Clinical evidence, mechanism, importance and management

A pharmacokinetic study in healthy subjects given cloxacillin 500 mg with or without proguanil 200 mg found that the total amount of cloxacillin excreted in the urine over 12 hours was reduced by up to 48% by proguanil. The time to maximum excretion and the half-life of cloxacillin were increased by 23% and 34%, respectively. The reasons why cloxacillin absorption is reduced by proguanil are not known, but it has been suggested that it may be due to adsorption of cloxacillin on to proguanil in the gut, formation of a drug-complex, increased gastric motility or increased beta-lactam ring hydrolysis leading to reduced cloxacillin bioavailability.[1] The clinical implications of the interaction are unknown.

1. Babalola CP, Iwheye GB, Olaniyi AA. Effect of proguanil interaction on bioavailability of cloxacillin. *J Clin Pharm Ther* (2002) 27, 461–4.

Penicillins; Dicloxacillin + Rifampicin (Rifampin)

Rifampicin increases the oral clearance of dicloxacillin and reduces its plasma levels.

Clinical evidence, mechanism, importance and management

A study in 18 healthy subjects found that rifampicin 600 mg daily for 10 days decreased the maximum plasma level of a single 1-g dose of dicloxacillin by 27% and increased its mean oral clearance by 26%. The

mean absorption time increased from 0.71 hours to 1.34 hours. Rifampicin increased the formation clearance, maximum level and AUC of the 5-hydroxymetabolite of dicloxacillin by 135%, 119%, and 59%, respectively. Dicloxacillin is a substrate of P-glycoprotein and it was suggested that the effects of rifampicin on dicloxacillin were due to induction of both intestinal P-glycoprotein and dicloxacillin metabolism.[1] The changes in the levels of dicloxacillin are modest, and unlikely to be clinically relevant.

1. Putnam WS, Woo JM, Huang Y, Benet LZ. Effect of the *MDR1* C3435T variant and P-glycoprotein induction on dicloxacillin pharmacokinetics. *J Clin Pharmacol* (2005) 45, 411–21.

Penicillins; Flucloxacillin + Paracetamol (Acetaminophen)

A case report describes severe acidosis in a critically ill patient receiving paracetamol and flucloxacillin.

Clinical evidence, mechanism, importance and management

A case report describes a patient with sepsis and renal impairment who was admitted to an intensive care unit with a high anion gap (42 mmol/L) metabolic acidosis which was tentatively attributed to treatment with flucloxacillin and paracetamol. He had received 8 g of paracetamol and 16 g of flucloxacillin over the 4 days before admission. The patient was diagnosed with pyroglutamic acidaemia, which is defined as a high anion gap acidosis resulting from excess production of 5-oxoproline. It was suggested that the depletion of glutathione by paracetamol, and further inhibition of the production of glutathione from 5-oxoproline by flucloxacillin had contributed to this patients condition. Note that this patient was also receiving carbamazepine, phenobarbital and phenytoin, which the authors suggest may also have reduced glutathione stores.[1]

This is not an unusual combination of drugs, and the clinical significance of this case, in a patient with serious medical problems, to other patients is unclear.

1. Peter JV, Rogers N, Murty S, Gerace R, Mackay R, Peake SL. An unusual cause of severe metabolic acidosis. *Med J Aust* (2006) 185, 223–5.

Penicillins; Piperacillin with Tazobactam + Vancomycin

Vancomycin does not interact to a clinically relevant extent with piperacillin and tazobactam.

Clinical evidence, mechanism, importance and management

A randomised, crossover study in 9 healthy subjects found that infusions of vancomycin 500 mg and piperacillin 3 g with tazobactam 375 mg had little or no effect on the pharmacokinetics of any of the antibacterials, except that the piperacillin AUC was slightly raised, by about 7%. It was concluded that no dose adjustments are needed if these drugs are given together.[1]

1. Vechlekar D, Sia L, Lanc R, Kuye O, Yacobi A, Faulkner R. Pharmacokinetics of piperacillin/tazobactam (Pip/Taz) IV with and without vancomycin IV in healthy adult male volunteers. *Pharm Res* (1992) 9 (10 Suppl), S-322.

Protionamide + Other antimycobacterials

Protionamide appears to be very hepatotoxic and this effect is possibly increased by the concurrent use of rifampicin (rifampin) or rifandin. Protionamide does not affect the pharmacokinetics of either dapsone or rifampicin.

Clinical evidence

In a study of 39 patients with leprosy, 39% became jaundiced after treatment for 24 to 120 days with **dapsone** 100 mg daily, protionamide 300 mg daily and **rifandin** [isopiperazinylrifamycin SV] 300 to 600 mg monthly. Laboratory evidence of liver damage occurred in 56% of patients, and despite the withdrawal of the drugs from all the patients, 2 of them died.[1] All the patients except two had previously taken **dapsone** alone for 3 to 227 months without reported problems.[1] In another group of patients with leprosy, 22% (11 of 50) had liver damage after treatment with **dapsone** 100 mg and protionamide 300 mg given daily, and **rifampicin** (rifampin) 900 mg, protionamide 500 mg and **clofazimine** 300 mg given monthly over a period of 30 to 50 days. One patient died.[1] Most of the patients recovered within 30 to 60 days after withdrawing the treatment. Jaundice, liver damage and deaths have occurred in other patients with leprosy given **rifampicin** and protionamide or **ethionamide**.[2-4]

Protionamide does not affect the pharmacokinetics of either **dapsone** or **rifampicin**.[5]

Mechanism

Although not certain, it seems probable that the liver damage was primarily caused by the protionamide, and possibly exacerbated by the rifampicin (rifampin) or the rifandin.

Importance and management

This serious and potentially life-threatening hepatotoxic reaction to protionamide is established, but the part played by the other drugs, particularly the rifampicin (rifampin), is uncertain. Strictly speaking this may not be an interaction. If protionamide is given the liver function should be very closely monitored in order to detect toxicity as soon as possible. This monitoring is probably sufficient to detect any adverse interaction.

1. Baohong J, Jiakun C, Chenmin W, Guang X. Hepatotoxicity of combined therapy with rifampicin and daily prothionamide for leprosy. *Lepr Rev* (1984) 55, 283–9.
2. Lesobre R, Ruffino J, Teyssier L, Achard F, Brefort G. Les ictères au cours du traitement par la rifampicine. *Rev Tuberc Pneumol (Paris)* (1969) 33, 393–403.
3. Report of the Third Meeting of the Scientific Working Group on Chemotherapy of Leprosy (THELEP) of the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases. *Int J Lepr* (1981) 49, 431–6.
4. Cartel J-L, Millan J, Guelpa-Lauras C-C, Grosset JH. Hepatitis in leprosy patients treated by a daily combination of dapsone, rifampin, and a thioamide. *Int J Lepr* (1983) 51, 461–5.
5. Mathur A, Venkatesan K, Girdhar BK, Bharadwaj VP, Girdhar A, Bagga AK. A study of drug interactions in leprosy — 1. Effect of simultaneous administration of prothionamide on metabolic disposition of rifampicin and dapsone. *Lepr Rev* (1986) 57, 33–7.

Pyrazinamide + Antacids

In 14 healthy subjects, 30 mL of *Mylanta* (aluminium/magnesium hydroxide) given 9 hours before, with, and after a single 30-mg/kg dose of pyrazinamide decreased the time to peak absorption by 17%, but had no effect on other pharmacokinetic parameters.[1] This change is not clinically important.

1. Peloquin CA, Bulpitt AE, Jaresko GS, Jelliffe RW, James GT, Nix DE. Pharmacokinetics of pyrazinamide under fasting conditions, with food, and with antacids. *Pharmacotherapy* (1998) 18, 1205–11.

Pyrazinamide + Antigout drugs

Pyrazinamide commonly causes hyperuricaemia and may therefore reduce the uricosuric effect of benzbromarone and probenecid, however benzbromarone may have modest efficacy in reducing the hyperuricaemia caused by pyrazinamide. Allopurinol is unlikely to be effective against pyrazinamide-induced hyperuricaemia, and may exacerbate the situation.

Clinical evidence and mechanism

(a) Allopurinol

It is thought that pyrazinamide is hydrolysed in the body to pyrazinoic acid, which appears to be responsible for its hyperuricaemic effect. Pyrazinoic acid is oxidised by the enzyme xanthine oxidase to 5-hydroxypyrazoic acid.[1] As allopurinol is an inhibitor of xanthine oxidase, its presence increases pyrazinoic acid concentrations[2] thereby probably worsening pyrazinamide-induced hyperuricaemia.[3]

(b) Benzbromarone

In 5 subjects with hyperuricaemia and gout a single dose of pyrazinamide completely abolished the uricosuric effect of a single 160-mg dose of benzbromarone.[4] Other authors also briefly mention the same finding.[5] However in another study, when 10 patients taking pyrazinamide 35 mg/kg daily for tuberculosis were given benzbromarone 50 mg daily for 8 to

10 days, uric acid levels were reduced by an average of 24%, and returned to normal in 4 patients.[6] It is unclear from these studies whether or not pyrazinamide abolishes the uricosuric effects of benzbromarone.

(c) Probenecid

The interactions of probenecid and pyrazinamide and their effects on the excretion of uric acid are complex and intertwined. Probenecid increases the secretion of uric acid into the urine, apparently by inhibiting its reabsorption from the kidney tubules.[7] Pyrazinamide on the other hand decreases the secretion of uric acid into the urine by one-third to one-half,[8] resulting in a rise in the serum levels of urate in the blood, thereby causing hyperuricaemia.[8,9] The result of using probenecid and pyrazinamide together is not however merely the simple sum of these two effects. This is because pyrazinamide additionally decreases the metabolism of the probenecid and prolongs its uricosuric effects, and the effect of pyrazinamide is reduced. Also, probenecid inhibits the secretion of pyrazinamide, increasing its effects.[10]

Importance and management

Pyrazinamide commonly causes hyperuricaemia, and would be expected to antagonise the effects of uricosuric drugs such as benzbromarone. Benzbromarone may have modest efficacy in reducing hyperuricaemia caused by pyrazinamide, but further study is necessary to establish this.

If probenecid were to be used to treat the hyperuricaemia caused by pyrazinamide, the normal uricosuric effects of probenecid would be diminished, and larger doses would be required. Allopurinol would appear to be unsuitable for treating pyrazinamide-induced hyperuricaemia as it potentially exacerbates the situation.

Note that pyrazinamide should be used with caution[11] or is contraindicated[12] in patients with a history of gout. Baseline serum uric acid levels should be established in all patients given pyrazinamide.[12] If hyperuricaemia accompanied by gouty arthritis occurs (without liver dysfunction[12]), pyrazinamide should be stopped.[11,12]

1. Weiner IM, Tinker JP. Pharmacology of pyrazinamide: metabolic and renal function studies related to the mechanism of drug-induced urate retention. *J Pharmacol Exp Ther* (1972) 180, 411–34.
2. Lacroix C, Guyonnaud C, Chaou M, Duwoos H, Lafont O. Interaction between allopurinol and pyrazinamide. *Eur Respir J* (1988) 807–11.
3. Urban T, Maquarre E, Housset C, Chouaid C, Devin E, Lebeau B. Hypersensibilité à l'allopurinol. Une cause possible d'hépatite et d'éruption cutanéo-muqueuse chez un patient sous antituberculeux. *Rev Mal Respir* (1995) 12, 314–16.
4. Sinclair DS, Fox IH. The pharmacology of hypouricemic effect of benzbromarone. *J Rheumatol* (1975) 2, 437–45.
5. Sorensen LB, Levinson DJ. Clinical evaluation of benzbromarone. *Arthritis Rheum* (1976) 19, 183–90.
6. Kropp R. Zur urikosurischen Wirkung von Benzbromaronum an Modell der pyrizinamidbedingten Hyperurikämie. *Med Klin* (1970) 65, 1448–50.
7. Meisel AD, Diamond HS. Mechanism of probenecid-induced uricosuria: inhibition of reabsorption of secreted urate. *Arthritis Rheum* (1977) 20, 128.
8. Cullen JH, LeVine M, Fiore JM. Studies of hyperuricemia produced by pyrazinamide. *Am J Med* (1957) 23, 587–95.
9. Shapiro M, Hyde L. Hyperuricemia due to pyrazinamide. *Am J Med* (1957) 23, 596–9.
10. Yü T-F, Perel J, Berger L, Roboz J, Israili ZH, Dayton PG. The effect of the interaction of pyrazinamide and probenecid on urinary uric acid excretion in man. *Am J Med* (1977) 63, 723–8.
11. Rifater Tablets (Rifampicin, Isoniazid and Pyrazinamide). Sanofi-Aventis. UK Summary of product characteristics, March 2009.
12. Rifater (Rifampin, Isoniazid and Pyrazinamide). Sanofi-Aventis. US Prescribing information, April 2008.

Pyrazinamide + Food

In 14 subjects a high-fat breakfast approximately doubled the time to peak absorption of a single 30-mg/kg dose of pyrazinamide but had no effect on other pharmacokinetic parameters.[1] It would therefore seem that pyrazinamide may be taken without regard to meals.

1. Peloquin CA, Bulpitt AE, Jaresko GS, Jelliffe RW, James GT, Nix DE. Pharmacokinetics of pyrazinamide under fasting conditions, with food, and with antacids. *Pharmacotherapy* (1998) 18, 1205–11.

Quinolones + Antacids or Calcium compounds

The serum levels of many of the quinolone antibacterials can be reduced by aluminium and magnesium antacids. Calcium compounds interact to a lesser extent, and bismuth compounds interact only minimally.

Clinical evidence

There is a wealth of information about the interaction between quinolones and antacids and for simplicity this is summarised in 'Table 10.3', (p.370). This table shows what happens to the maximum serum levels (C_{max}) and the relative bioavailabilities (%) when the quinolones listed have been given at the same time as antacids, and when separated by time intervals (e.g. –2 h; two hours before the antacid).

Mechanism

It is believed that certain of the quinolone functional groups (3-carboxyl and 4-oxo) form insoluble chelates with aluminium and magnesium ions within the gut, which reduces their absorption.[1-3] The stability of the chelate formed seems to be an important factor in determining the degree of interaction.[3] It has been suggested from *animal* studies that adsorption of quinolones by aluminium hydroxide re-precipitated in the small intestine may be a factor in the reduced bioavailability of quinolones.[4] See also 'Quinolones + Iron or Zinc compounds', p.378.

Importance and management

The interactions between quinolones and antacids are generally well documented, well established and, depending on the particular quinolone and antacid concerned, of clinical importance. The risk is that the serum levels of the antibacterial may fall below minimum inhibitory concentrations (i.e. become subtherapeutic, particularly against organisms such as staphylococci and *Pseudomonas aeruginosa*[5]), resulting in treatment failures.[6] From a review of the use of levofloxacin, it has been suggested that the low levels of quinolones which occur as a result of this interaction may contribute to the development of resistance.[7] The overall picture is that the aluminium/magnesium antacids interact to a greater extent than the calcium compounds, and bismuth compounds hardly at all.

Possible alternatives to the antacids, which do not appear to interact with the quinolones, include the 'H_2-receptor antagonists', (p.377) and 'omeprazole', (p.380).

(a) Aluminium/magnesium antacids

'Table 10.3', (p.370) shows that the aluminium/magnesium antacids can greatly reduce the bioavailabilities of the quinolones. Separating their administration to reduce the admixture of the two drugs in the gut minimises the interaction, a very broad rule-of-thumb being that the quinolones should be taken at least 2 hours before and not less than 4 to 6 hours after the antacid.[1,8-14] The only obvious exception is **fleroxacin**, which appears to interact minimally.

(b) Bismuth compounds

As can be seen from 'Table 10.3', (p.370), bismuth compounds have little or no effect on the bioavailability of **ciprofloxacin**. Information about other quinolones appears to be lacking. However, using **ciprofloxacin** as a guide it would seem that any interaction is likely only to be of minimal clinical importance, and no action appears to be necessary.

(c) Calcium compounds

Information about the interactions with calcium carbonate is more limited than with the aluminium/magnesium antacids, but 'Table 10.3', (p.370) shows that the bioavailabilities of **ciprofloxacin**, **norfloxacin**, and to a lesser extent **gemifloxacin**, can be reduced. Other calcium compounds, for example those used as phosphate binders, are likely to interact similarly. These reductions are less than those seen with the aluminium/magnesium antacids, but using **ciprofloxacin** as a guide a very broad rule-of-thumb would be to separate the drug administration by about 2 hours to minimise this interaction.[15,16] This is clearly not necessary with **levofloxacin**,[17] **lomefloxacin**,[18] **moxifloxacin**[19] or **ofloxacin**,[20] nor probably with some of the other quinolones that have yet to be studied, but in the absence of direct information a 2-hour separation errs on the side of caution.

(d) Sodium antacids

Sodium bicarbonate does not interact significantly with **norfloxacin**[21] but information about other quinolones appears to be lacking. However, bear in mind that in the case of **ciprofloxacin** an excessive rise in urinary pH

Table 10.3 The effect of antacids on the pharmacokinetics of quinolone antibacterials

Quinolone (*mg:time*[*])	*Antacid or other coadministered drug*	*Maximum level (micrograms/mL)*		*Relative bioavailability (%)*[†]	*Refs*
		alone	*with*		
Ciprofloxacin					
250	$Mg(OH)_2$ + $Al(OH)_3$	3.69	less than 1.25	NR	1
500	$Mg(OH)_2$ + $Al(OH)_3$	2.6	0.88	NR	2
500: +24 h	$Mg(OH)_2$ + $Al(OH)_3$	1.7	0.1	NR	3
500: +24 h	$Mg(OH)_2$ + $Al(OH)_3$	1.9	0.13	9.5	4
750: –2 h	$Mg(OH)_2$ + $Al(OH)_3$	3.01	3.96	107	5
+0.08 h		3.42	0.68	15.1	
+2 h		3.42	0.88	23.2	
+4 h		3.01	2.62	70	
+6 h		2.63	2.64	108.5	
750:+0.08 h	$Al(OH)_3$	3.2	0.6	15.4	6
750	$Al(OH)_3$	2.3	0.8	NR	7
200	$Al(OH)_3$	1.3	0.2	12	8
250	$CaCO_3$	3.69	3.42 (ns)	NR	1
500	$CaCO_3$	1.53	1.37 (ns)	94 (ns)	9
500	$CaCO_3$	2.9	1.8	58.8	10
750:+0.08 h	$CaCO_3$	3.2	1.7	64.5	6
500:+2 h	$CaCO_3$	1.25	1.44	102.4	11
500	Mg citrate	2.4	0.6	21	12
500	Bismuth salicylate (subsalicylate)	3.8	2.9	83.8	13
750	Bismuth salicylate (subsalicylate)	2.95	2.57	87	14
500	Tripotassium dicitratobismuthate			100	12
400	Polycarbophil calcium	2.66	0.95	48	15
750	Calcium acetate	3.77	1.9	0.49	16
Enoxacin					
200	$Al(OH)_3$	2.26	0.46	15.4	17
400:+0.5 h	$Mg(OH)_2$ + $Al(OH)_3$	3.17	0.95	26.8	18
+2 h		3.17	1.95	52.3	
+8 h		3.17	2.88	82.7	
200	$Al(OH)_3$	2.3	0.5	15.8	8
Fleroxacin					
200	$Al(OH)_3$	2.4	1.8	82.8	8
Garenoxacin					
600	$Mg(OH)_2$ + $Al(OH)_3$	9.3	3.8	42	19
+4 h		9.3	7.9	84	
+2 h		9.3	7.7	78	
-2 h		9.3	11		
-4 h		9.3	9.4 (ns)	ns	
Gatifloxacin					
200	$Al(OH)_3$	1.71	0.75	45.9	20
400	$Mg(OH)_2$ + $Al(OH)_3$	3.8	1.2	35.6	21
400:–2 h		3.8	2.1	57.9	
+2 h		3.4	3.3	82.5	
+4 h		3.4	3.5 (ns)	100 (ns)	
Gemifloxacin					
320:+3 h	$Mg(OH)_2$ + $Al(OH)_3$	0.91	0.75	85.9	22
–0.17 h		0.91	0.13	16.8	
–2 h		0.91	0.99	101.2	
320	$CaCO_3$	1.13	0.9	77	23
320:–2 h		1.13	1.13	93	
+2 h		1.11	1.01	90	
Grepafloxacin					
200	$Al(OH)_3$	NR	NR	60	24

Continued

Table 10.3 The effect of antacids on the pharmacokinetics of quinolone antibacterials (continued)

Quinolone	*Antacid or other*	*Maximum level (micrograms/mL)*		*Relative*	*Refs*
(mg:time)*	*coadministered drug*	*alone*	*with*	*bioavailability (%)†*	
Levofloxacin					
100	$Al(OH)_3$	1.82	0.64	56.3	25, 26
100	$Al(OH)_3$	1.8	0.6	54.8	8
100	MgO	1.82	1.13	78.2	25, 26
100	$CaCO_3$	1.45	1.12	96.7	25, 26
750:–2 h	$CaCO_3$	9.7	8.8	ns	27
Lomefloxacin					
200	$Mg(OH)_2 + Al(OH)_3$	1.91	1.03	59.2	28
200	$Al(OH)_3$	2.2	1.0	65.2	8
NR:+2 h	$Mg(OH)_2 + Al(OH)_3$	2.85	2.67 (ns)	88.2	29
–2 h		2.85	2.16	80.4	
–4 h		2.85	2.67 (ns)	90.1	
400	$Mg(OH)_2 + Al(OH)_3$	3.25	1.31	52.1	30
400:+12 h		3.25	3.66 (ns)		
–4 h		3.25	3.69 (ns)		
400	$CaCO_3$	4.72	4.08	97.9 (ns)	31
Moxifloxacin					
400	$Mg(OH)_2 + Al(OH)_3$	2.57	1	74	32
400	Calcium lactate gluconate + $CaCO_3$	2.71	2.29	97.6	33
Norfloxacin					
200	$Al(OH)_3$	1.45	less than 0.01	2.7	17
400:+0.08 h	$Mg(OH)_2 + Al(OH)_3$	1.64	0.08	9 (based on urinary recovery)	34
–2 h		1.64	1.25	81.3	
200	$Al(OH)_3$	1.5	less than 0.1	3	8
400	$Al(OH)_3$	1.51	1.09	71.2 (from saliva)	35
400	Mg trisilicate	1.51	0.43	19.3 (from saliva)	35
400	$CaCO_3$	1.64	0.56	37.5	34
400	$CaCO_3$	1.51	1.08	52.8 (from saliva)	35
400	Bismuth salicylate (subsalicylate)			89.7 (ns)	36
400	Sodium bicarbonate	1.4	1.47	104.9 (ns)	35
Ofloxacin					
200	$Al(OH)_3$	3.23	1.31	52.1	17
200	$Al(PO)_4$			93.1 (ns)	37
200	$MgO + Al(OH)_3$	1.97	1.1	62	38
200:+24 h	$Mg(OH)_2 + Al(OH)_3$	2.6	0.7	30.8	4
400:+2 h	$Mg(OH)_2 + Al(OH)_3$	3.7	2.6	79.2	39
–2 h		3.7	3.8 (ns)	101.9 (ns)	
+24 h		3.7	3.5 (ns)	95.3 (ns)	
600	$Mg(OH)_2 + Al(OH)_3$	8.11	6.13	NR	40
200	$Al(OH)_3$	3.2	1.3	52.1	8
400:+2 h	$CaCO_3$	3.2	3.3 (ns)	103.6 (ns)	39
–2 h		3.2	3.3 (ns)	97.9 (ns)	
+24 h		3.2	3.5 (ns)	95.9 (ns)	
Pefloxacin					
400	$Mg(OH)_2 + Al(OH)_3$	5.14	1.95	44.2	41
400	$Mg(OH)_2 + Al(OH)_3$	3.95	1.25	NR	42
400	$Mg(OH)_2 + Al(OH)_3$	5.1	2	45.7	43
Rufloxacin					
400:+0.08 h	$Mg(OH)_2 + Al(OH)_3$	3.74	2.12	59.7	44
–4 h		3.74	3.97 (ns)	84.7	
Sparfloxacin					
400:–2 h	$Mg(OH)_2 + Al(OH)_3$	1.09	0.94	82.8	45
+2 h		1.09	0.77	77.2	
–4 h		1.09	1.17	93.4	

Continued

Table 10.3 The effect of antacids on the pharmacokinetics of quinolone antibacterials (continued)

Quinolone	*Antacid or other*	*Maximum level (micrograms/mL)*		*Relative*	*Refs*
(mg:time)*	*coadministered drug*	*alone*	*with*	*bioavailability (%)†*	
200	$Al(OH)_3$	1.09	1.17	94.7	8, 46
Tosufloxacin					
150	$Al(OH)_3$	0.3	0.1	29.2	8
300	$Al(OH)_3$	0.88	0.52	68	47
Trovafloxacin					
300:–2 h	$Mg(OH)_2$ + $Al(OH)_3$	2.8	2.5	71.7	48
+0.5 h		2.8	1.1	33.7	

*Time interval between intake of quinolone and the other drug: - and + indicate that the quinolone was administered before and after, respectively, intake of the other drug.
†Calculated from AUC data.
NR = not reported; h = hour; ns = not significant.

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Continued

Table 10.3 The effect of antacids on the pharmacokinetics of quinolone antibacterials (continued)

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(which can be caused by antacids like sodium bicarbonate) may possibly result in urinary crystalluria and kidney damage.[22]

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Quinolones + Antineoplastics

The absorption of ciprofloxacin and ofloxacin can be reduced by some cytotoxic antineoplastics. Production of the active metabolite of cyclophosphamide may be reduced by ciprofloxacin.

Clinical evidence

(a) Ciprofloxacin

Six patients with newly diagnosed haematological malignancies (5 with acute myeloid leukaemia and one with non-Hodgkin's lymphoma) were given ciprofloxacin 500 mg twice daily to control possible neutropenic infections. It was found that, after 13 days of chemotherapy, their mean maximum serum ciprofloxacin levels had fallen by 46% (from 3.7 to 2 mg/L) and the $AUC_{0\text{-}4}$ was reduced by 47%. There were large individual differences between the patients. The antineoplastics used were **cyclophosphamide**, **cytarabine**, **daunorubicin**, **doxorubicin**, **mitoxantrone** and **vincristine**.[1]

A study in 8 patients who received a course of CHOP (**cyclophosphamide**, **doxorubicin**, prednisolone and **vincristine**) found that oral ciprofloxacin, 1 g given in the evening and 500 mg given on the morning before intravenous **cyclophosphamide** was given, reduced the AUC of the active metabolite of **cyclophosphamide** by 32%.[2]

For mention that methotrexate toxicity has occurred in 2 patients during treatment with ciprofloxacin, see 'Methotrexate + Antibacterials; Ciprofloxacin', p.745.

(b) Ofloxacin

Ten patients with non-Hodgkin's lymphoma, hairy cell leukaemia or acute myeloid leukaemia were given ofloxacin 400 mg at breakfast time for antibacterial prophylaxis during neutropenia. Blood samples were taken 3 days before chemotherapy began and then at 2 to 3 days, 5 to 7 days, and 8 to 10 days. The maximum serum ofloxacin levels were reduced by 18% two to three days after the chemotherapy but none of the other pharmacokinetic measurements were changed by the antineoplastic treatment. The serum levels had returned to normal by 5 to 7 days. At all times serum levels exceeded the expected MICs of the gram-negative potential pathogens. The antineoplastics used were **cyclophosphamide**, **cytarabine**, **doxorubicin**, **etoposide**, **ifosfamide** (with mesna), **vincristine**.[3]

Mechanism

Uncertain. The reduction in serum levels seems to result from a reduction in the absorption of the quinolones by the small intestine, possibly related to the damaging effect cytotoxic antineoplastics have on the rapidly divid-

ing cells of the intestinal mucosa. It was suggested that the production of the active metabolite of cyclophosphamide may have been inhibited by ciprofloxacin.

Importance and management

Direct information is limited, but the reports of reduced serum levels are consistent with the way cytotoxic antineoplastics can reduce the absorption of some other drugs; however, the authors suggest that these changes are probably clinically unimportant, because the serum levels achieved are likely to be sufficient to treat most infections. If the suggested mechanism of interaction is correct, no interaction should occur if quinolones are given parenterally. Nothing appears to be documented about any of the other quinolones.

The significance of the reduction in the active metabolite of cyclophosphamide seen in one study is unclear; however the authors suggest that a reduction in the therapeutic efficacy of cyclophosphamide may result and this combination should therefore be avoided. It has also been suggested that this interaction was a high-risk factor for relapse in patients undergoing bone marrow transplantation when ciprofloxacin was given as prophylaxis during cyclophosphamide use.[4]

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Quinolones + Chinese herbal medicines

Sho-saiko-to, Rikkunshi-to and Sairei-to do not interact with ofloxacin, and Hotyu-ekki-to, Rikkunshi-to and Juzen-taiho-to do not interact with levofloxacin.

Clinical evidence, mechanism, importance and management

The bioavailability and urinary recovery of a single 200-mg oral dose of **ofloxacin** were not significantly altered in 7 healthy subjects by three Chinese herbal medicines (**Sho-saiko-to**, **Rikkunshi-to** or **Sairei-to**).[1] The bioavailability and renal excretion of a single 200-mg oral dose of **levofloxacin** was not affected in 8 healthy subjects given single 2.5-g doses of **Hotyu-ekki-to**, **Rikkunshi-to** or **Juzen-taiho-to**.[2] There would therefore seem to be no reason for avoiding concurrent use. Information about other quinolones is lacking. The ingredients of these herbal medicines are detailed in 'Table 10.4', (p.375).

1. Hasegawa T, Yamaki K, Nadai M, Muraoka I, Wang L, Takagi K, Nabeshima T. Lack of effect of Chinese medicines on bioavailability of ofloxacin in healthy volunteers. *Int J Clin Pharmacol Ther* (1994) 32, 57–61.
2. Hasegawa T, Yamaki K-I, Muraoka I, Nadai M, Takagi K, Nabeshima T. Effects of traditional Chinese medicines on pharmacokinetics of levofloxacin. *Antimicrob Agents Chemother* (1995) 39, 2135–7.

Quinolones + Dairy products

Dairy products reduce the bioavailability of ciprofloxacin and norfloxacin, and to a minor extent, gatifloxacin, but not enoxacin, lomefloxacin, moxifloxacin, ofloxacin and probably not fleroxacin.

Clinical evidence

(a) Ciprofloxacin

A study in 7 healthy subjects found that 300 mL of **milk** or **yoghurt** reduced the peak plasma levels of a single 500-mg dose of ciprofloxacin by 36% and 47%, respectively, and reduced its AUC by 33% and 36%, respectively.[1] In another study 300 mL of **milk** reduced the AUC of ciprofloxacin 500 mg by about 30%.[2]

(b) Enoxacin

A study found that **milk** and a standard breakfast had no effect on enoxacin absorption.[3]

(c) Fleroxacin

In a study, a fat and liquid calcium meal had no clinically significant effect on the pharmacokinetics of fleroxacin.[4] In another study, **milk** had no effect on fleroxacin pharmacokinetics.[2]

(d) Gatifloxacin

In one study 200 mL of **milk** reduced the AUC of gatifloxacin 200 mg by about 15%.[5]

(e) Lomefloxacin

Milk had no effect on the pharmacokinetics of lomefloxacin.[6]

(f) Moxifloxacin

A study found that the rate of absorption of a single 400-mg dose of moxifloxacin was slightly delayed by 250 g of **yoghurt**. The maximum plasma level of moxifloxacin was reduced by about 15%, but its bioavailability was unaffected.[7]

(g) Norfloxacin

A study found that 300 mL of **milk** or **yoghurt** reduced the absorption and the peak plasma levels of a single 200-mg dose of norfloxacin by roughly 50%.[8]

(h) Ofloxacin

A study in 21 healthy subjects found that 8 oz (about 250 mL) of **milk** had no clinically significant effects on the absorption of 300 mg of ofloxacin.[9] Another study confirmed the lack of a significant interaction between ofloxacin and both **milk** and **yoghurt**.[10]

Mechanism

The proposed reason for these changes is that the calcium in milk and yoghurt or other dairy products combines with the ciprofloxacin and norfloxacin to produce insoluble chelates. Compare also 'Quinolones + Antacids or Calcium compounds', p.369.

Importance and management

The effect of these changes to ciprofloxacin and norfloxacin pharmacokinetics on the control of infection is uncertain but until the situation is clear patients should be advised not to take these dairy products within one to 2 hours of either ciprofloxacin or norfloxacin to prevent admixture in the gut. The slight reduction in gatifloxacin levels is probably not clinically relevant.

Enoxacin, lomefloxacin, moxifloxacin, ofloxacin and probably fleroxacin do not appear to interact with dairy products to a clinically relevant extent, and they may therefore provide a useful alternative to the interacting quinolones.

1. Neuvonen PJ, Kivistö KT, Lehto P. Interference of dairy products with the absorption of ciprofloxacin. *Clin Pharmacol Ther* (1991) 50, 498–502.
2. Hoogkamer JFW, Kleinbloesem CH. The effect of milk consumption on the pharmacokinetics of fleroxacin and ciprofloxacin in healthy volunteers. *Drugs* (1995) 49 (Suppl 2), 346–8.
3. Lehto P, Kivistö KT. Effects of milk and food on the absorption of enoxacin. *Br J Clin Pharmacol* (1995) 39, 194–6.
4. Bertino JS, Nafziger AN, Wong M, Stragand L, Puleo C. Effects of a fat- and calcium-rich breakfast on pharmacokinetics of fleroxacin administered in single and multiple doses. *Antimicrob Agents Chemother* (1994) 38, 499–503.
5. Shiba K, Kusajima H, Momo K. The effects of aluminium hydroxide, cimetidine, ferrous sulfate, green tea and milk on pharmacokinetics of gatifloxacin in healthy humans. *J Antimicrob Chemother* (1999) 44 (Suppl A), 141.
6. Lehto PL, Kivistö KT. Different effects of products containing metal ions on the absorption of lomefloxacin. *Clin Pharmacol Ther* (1994) 56, 477–82.
7. Stass H, Kubitza D. Effects of dairy products on the oral bioavailability of moxifloxacin, a novel 8-methoxyfluoroquinolone, in healthy volunteers. *Clin Pharmacokinet* (2001) 40 (Suppl 1) 33–8.
8. Kivistö KT, Ojala-Karlsson P, Neuvonen PJ. Inhibition of norfloxacin absorption by dairy products. *Antimicrob Agents Chemother* (1992) 36, 489–91.
9. Dudley MN, Marchbanks CR, Flor SC, Beals B. The effect of food or milk on the absorption kinetics of ofloxacin. *Eur J Clin Pharmacol* (1991) 41, 569–71.
10. Neuvonen PJ, Kivistö KT. Milk and yoghurt do not impair the absorption of ofloxacin. *Br J Clin Pharmacol* (1992) 33, 346–8.

Quinolones + Didanosine

An extremely marked reduction in the serum levels of ciprofloxacin occurs if it is given at the same time as didanosine tablets, because of an interaction with the antacid buffers in the didanos-

Table 10.4 Herbs contained in some Chinese herbal remedies[1,2]

Herb (plant part)	*Amounts of herbs in the medicines (mg/2.5 g)*				
	Hotyu-ekki-to	**Rikkunshi-to**	**Juzen-taiho-to**	**Sho-saiko-to**	**Sairei-to**
Atractylodis lanceae (rhizome)	278	248	175		125
Ginseng (root)	278	248	175	188	125
Glycyrrhizae (root)	104	662	688	125	83
Aurantii nobilis (pericarp)	139	124			
Zizyphi (fruit)	139	124		188	125
Zingiberis (rhizome)	635	631		63	42
Astragali (root)	278		175		
Angelicae (root)	208		175		
Bupleuri (root)	139			438	292
Cimicifugae (rhizome)	669				
Hoelen		248	175		125
Pinelliae (tuber)		248		313	208
Cinnamomi (cortex)			175		83
Rehmanniae (root)			175		
Paeoniae (root)			175		
Cnidii (rhizome)			175		
Scutellariae (root)				188	125
Alismatis (rhizome)					208
Polyporus					125

1. Hasegawa T, Yamaki K, Nadai M, Muraoka I, Wang L, Takagi K, Nabeshima T. Lack of effect of Chinese medicines on bioavailability of ofloxacin in healthy volunteers. *Int J Clin Pharmacol Ther* (1994) 32, 57-61.
2. Hasegawa T, Yamaki K-I, Muraoka I, Nadai M, Takagi K, Nabeshima T. Effects of traditional Chinese medicines on pharmacokinetics of levofloxacin. *Antimicrob Agents Chemother* (1995) 39, 2135-7.

ine formulation. Other quinolones are expected to interact similarly. Didanosine enteric-coated capsules do not interact with ciprofloxacin.

Clinical evidence

When 12 healthy subjects were given **ciprofloxacin** 750 mg with two didanosine placebo tablets (i.e. all of the antacid additives but no didanosine), the **ciprofloxacin** AUC and maximum serum levels were reduced by 98% and 93%, respectively.[1] The antacids in this formulation were dihydroxyaluminium sodium carbonate and magnesium hydroxide.

Other studies have looked at whether separating administration affects this interaction. When 16 HIV-positive patients were given **ciprofloxacin** 1.5 g daily 2 hours before didanosine tablets, the AUC of **ciprofloxacin** was reduced by only 26%.[2] Another study in just one subject found that when **ciprofloxacin** 500 mg was given 2 hours after taking two didanosine placebo tablets the **ciprofloxacin** serum levels were reduced below minimal inhibitory concentrations, but giving the **ciprofloxacin** 2 hours before the didanosine placebo tablets resulted in normal blood levels.[3]

The enteric-coated capsule formulation of didanosine (which does not contain antacids) does not interact with **ciprofloxacin**.[4]

Mechanism

Didanosine is extremely acid labile at pH values below 3, so one of the formulations contains buffering agents (dihydroxyaluminium sodium carbonate and magnesium hydroxide) to keep the pH as high as possible to minimise the acid-induced hydrolysis. Ciprofloxacin forms insoluble non-absorbable chelates with these metallic ions in the buffer so that its bioavailability is markedly reduced. See also 'Quinolones + Antacids or Calcium compounds', p.369.

Importance and management

Direct information is limited to these reports but the interaction between buffered didanosine and ciprofloxacin appears to be clinically important. Such drastic reductions in serum ciprofloxacin levels mean that minimal inhibitory concentrations are unlikely to be achieved. Ciprofloxacin should be given at least 2 hours before or 6 hours after didanosine tablets (see 'Quinolones + Antacids or Calcium compounds', p.369). Other quinolone antibacterials that interact with antacids are also expected to interact with didanosine tablets, but so far reports are lacking. Didanosine enteric-coated capsules do not interact.

1. Sahai J, Gallicano K, Oliveras L, Khaliq S, Hawley-Foss N, Garber G. Cations in the didanosine tablet reduce ciprofloxacin bioavailability. *Clin Pharmacol Ther* (1993) 53, 292–7.
2. Knupp CA, Barbhaiya RH. A multiple-dose pharmacokinetic interaction study between didanosine (Videx®) and ciprofloxacin (Cipro®) in male subjects seropositive for HIV but asymptomatic. *Biopharm Drug Dispos* (1997) 18, 65–77.
3. Sahai J. Avoiding the ciprofloxacin-didanosine interaction. *Ann Intern Med* (1995) 123, 394–5.
4. Damle BD, Mummaneni V, Kaul S, Knupp C. Lack of effect of simultaneously administered didanosine encapsulated enteric bead formulation (Videx EC) on oral absorption of indinavir, ketoconazole, or ciprofloxacin. *Antimicrob Agents Chemother* (2002) 46, 385–91.

Quinolones + Enteral feeds or Food

The absorption of ciprofloxacin can be reduced by enteral feeds. Moxifloxacin and ofloxacin are similarly affected, but the extent of the interaction is smaller. No interaction is seen with garenoxacin or gatifloxacin and enteral feeds.
Apart from dairy products most foods delay but do not reduce the absorption of ciprofloxacin, enoxacin, gemifloxacin, lomefloxacin, ofloxacin or sparfloxacin. A high-fat/high-calcium breakfast did not reduce ciprofloxacin levels. Calcium-fortified orange juice significantly reduces the absorption of ciprofloxacin, but not gatifloxacin or levofloxacin.

Clinical evidence

A. Enteral feeds

(a) Ciprofloxacin

When ciprofloxacin 750 mg was given to 13 fasted subjects with *Ensure* its oral bioavailability was reduced by 28% and its mean maximum serum levels were reduced by 48%. In this study the subjects were given 120 mL of the study liquid (*Ensure* or water) and this was repeated at 30-minute intervals for 5 doses. The ciprofloxacin was crushed and mixed with the second dose of the study liquid and the cup rinsed with another 60 mL of the study liquid.[1]

Other enteral feeds given orally (*Osmolite*, *Pulmocare*, and *Resource*) similarly reduced the bioavailability and maximum serum levels of ciprofloxacin by about one-quarter to one-third in two other studies.[2,3] One comparative study found that *Ensure* reduced the AUC of ciprofloxacin by 40% in men but by only 15% in women.[4]

In a study of 26 hospitalised patients, ciprofloxacin bioavailability was reduced by 53% and 67% by *Jevity* or *Sustacal*, respectively, when given via gastrostomy or jejunostomy tubes. Despite this, the serum levels achieved with gastrostomy tubes were roughly equivalent to those seen in subjects taking tablets orally.[5] In another study in patients given *Jevity* or *Osmolite*, the 4 patients with a nasoduodenal tube achieved a ciprofloxacin AUC that was about double that seen in the 3 patients with a nasogastric tube or a gastrostomy tube.[6] In contrast, in another study in healthy subjects, there was no difference in the bioavailability of ciprofloxacin when it was given alone or when it was given with *Osmolite* via a nasogastric tube.[7]

The bioavailability of ciprofloxacin 750 mg every 12 hours in 5 patients with severe gram-negative intra-abdominal infections was reduced by 47% when it was added to enteral feeding with *Nutrison* or *Nutrison E+* and given via nasogastric or nasoduodenal tubes. The serum levels were similar to those found in another 7 patients given ciprofloxacin with these enteral feeds and also to those found when the 5 original patients were given intravenous ciprofloxacin 400 mg every 12 hours.[8] In another study, in 12 intensive care patients, the AUC of ciprofloxacin 400 mg given by intravenous infusion was similar to that found after a dose of 750 mg given via nasogastric tube during enteral feeding with *Normo-Réal fibres*.[9]

(b) Garenoxacin

In a randomised crossover study, 18 healthy subjects received a single 600-mg dose of garenoxacin via a nasogastric tube, alone or 2 hours after the start of a 6-hour nasogastric feed of *Osmolite*. The pharmacokinetics of garenoxacin were not altered by the enteral feed.[10]

(c) Gatifloxacin

In a crossover study, 12 healthy subjects were given a single 400-mg dose of gatifloxacin alone, or with *Ensure* 120 mL given every 30 minutes for 5 doses, starting 30 minutes before the gatifloxacin. The AUC and maximum plasma levels of gatifloxacin were reduced by 26% and 45%, respectively, in the presence of *Ensure*.[11]

A randomised study in critically ill patients found no significant difference in the bioavailability of gatifloxacin given as a single 400-mg dose either nasogastrically or intravenously with two enteral feed schedules. Seven patients received continuous enteral feeds, and 8 patients received feeds interrupted for 2 hours before and after the administration of the gatifloxacin. In this study 5 different enteral feeds were given (*Glucerna*, *Impact*, *Jevity*, *Promote*, *and Pulmocare*) at rates ranging from 30 mL/hour to 75 mL/hour. There was significant variation in the bioavailability of gatifloxacin, most likely due to the critical illnesses of the patients.[12]

(d) Moxifloxacin

In a study in 12 healthy subjects, the oral bioavailability of a single 400-mg dose of moxifloxacin was decreased by 9% when it was given to as a suspension of a crushed tablet via a nasogastric tube with either water or *Isosource Energy*. This decrease was in comparison with oral administration of an uncrushed tablet with water. Maximum plasma levels were decreased by 5% and 12% after nasogastric administration with water and *Isosource Energy*, respectively.[13]

(e) Ofloxacin

The oral bioavailability of ofloxacin 400 mg was reduced by 10% when it was given to 13 healthy subjects with *Ensure*. The mean maximum serum ofloxacin levels were reduced by 36%. In this study the subjects were given 120 mL of the study liquid (*Ensure* or water) and this was repeated at 30-minute intervals for 5 doses. The ofloxacin was crushed and mixed with the second dose of the study liquid and the cup rinsed with another 60 mL of the study liquid.[1] Only small reductions in the AUCs of ofloxacin were seen in another study (11% in men, 13% in women) with *Ensure*.[4]

B. Food

Food delayed the absorption of **ciprofloxacin** and **ofloxacin** in 10 subjects, but their bioavailabilities remained unchanged.[14] A study in 12 healthy subjects found that standard or high-fat breakfasts did not affect the absorption of **ciprofloxacin**.[15] Another study in healthy subjects found that a standard breakfast reduced the bioavailability of a single 300-mg dose of **ofloxacin** by about 18%, but this was not considered clinically significant.[16] Other studies suggest that food delays the absorption of **ofloxacin**[17] and **lomefloxacin**[18] but the bioavailability is unchanged. Food also has no effect on the absorption of **enoxacin**, but high-carbohydrate meals delayed the peak serum levels by almost an hour.[19] The pharmacokinetics of **gemifloxacin** 320 mg or 640 mg[20] or **sparfloxacin** 200 mg[21] were not significantly affected when they were given to healthy subjects with high-fat or standard meals, although the absorption of **sparfloxacin** was slightly delayed.

C. Calcium-fortified foods

Calcium-fortified orange juice decreased the AUC of **ciprofloxacin** by 38% and decreased its maximum plasma level by 41%, when compared with water.[22] However, in another study, a high-fat/high-calcium breakfast did not affect the absorption of **ciprofloxacin**.[15]

The AUC of **gatifloxacin** was reduced by only 12% by calcium-fortified orange juice.[23] Similarly, in two studies, orange juice, calcium-fortified orange juice,[24] or a breakfast of calcium-fortified orange juice and cereal with or without milk[25] were found to decrease the bioavailability of **levofloxacin**. However, the **levofloxacin** AUC was decreased by less than 16%, an amount that rarely proves to be clinically significant.

Mechanism

Not fully understood. The quinolone antibacterials can form insoluble chelates with divalent ions, which reduces their absorption from the gut. Enteral feeds such as those used above contain at least two divalent ions, calcium and magnesium. However, an *in vitro* study found no evidence of chelate formation with ciprofloxacin, **levofloxacin** or ofloxacin and calcium or magnesium, and therefore suggested that either other divalent cations may be involved, or that the quinolones may be adsorbed onto other metal ions, proteins or fat in the enteral feed.[26]

It has also been suggested that alteration in pH as well as the presence of cations are required to form chelates with ciprofloxacin and while this helps explain the lack of effect of high calcium in a high-fat breakfast,[15] it does not explain the significant effect with enteral feeds or calcium-fortified orange juice. The differences seen in men and women are possibly due to a slower gastric emptying rate in men, which increases the exposure of the quinolone to the enteral feed.[4]

Importance and management

The interaction between ciprofloxacin and enteral feeds is established. No treatment failures have been reported but it may be clinically important. For example, if patients receiving enteral feeds were to be switched from parenteral to oral ciprofloxacin, there could be a significant reduction in serum ciprofloxacin levels. The authors of one study recommend that in patients with severe infections, such a switch from parenteral to nasogastric administration of ciprofloxacin should be restricted to those whose plasma ciprofloxacin levels can be routinely monitored. However, some have found the reduced levels with enteral feeding still provide adequate antibacterial levels,[8,27] but be alert for any evidence that ciprofloxacin is less effective and raise the dose as necessary. Use of enteral feeds with lower concentrations of divalent ions or even stopping tube feeding for a short period of time have been suggested as methods to try to improve ciprofloxacin absorption.[27] The authors of one *in vitro* study suggest that *Ensure* should be given at least 2 hours before or after fluoroquinolones.[26]

The interaction between ofloxacin or moxifloxacin and enteral feeds is much smaller and probably not clinically important but this needs confirmation. Garenoxacin and gatifloxacin appear not to interact. There are no specific reports about other quinolones but be alert for this interaction with any of them.

Apart from ‘dairy products’ (p.374), quinolones can be given with food

without any decrease in levels. However, calcium-fortified foods may cause significant interactions with ciprofloxacin.

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Quinolones + H_2-receptor antagonists

Cimetidine can increase the serum levels of some quinolones (intravenous enoxacin or fleroxacin and oral clinafloxacin or pefloxacin). Famotidine can reduce the serum levels of norfloxacin, and ranitidine can reduce the absorption of enoxacin.

Clinical evidence and mechanism

(a) Ciprofloxacin

Neither **cimetidine**[1,2] nor **ranitidine**[3,4] appear to have a clinically important effect on the pharmacokinetics of ciprofloxacin.

(b) Clinafloxacin

Cimetidine 300 mg four times daily for 4 days increased the maximum serum levels of clinafloxacin by 15% and increased its AUC by 44%.[5]

(c) Enoxacin

The plasma levels of a 400-mg intravenous dose of enoxacin were higher when **cimetidine** 300 mg four times daily was given concurrently. Renal clearance and systemic clearance were reduced by 26% and 20%, respectively, and the elimination half-life was increased by 30%.[6]

In one study, **ranitidine** 150 mg twice daily did not affect the pharmacokinetics of a single 400-mg intravenous dose of enoxacin.[6] However, in another study, **ranitidine** 50 mg given intravenously 2 hours before a single 400-mg oral dose of enoxacin reduced the absorption of the enoxacin by 26 to 40%,[7,8] which seemed to be related to changes in gastric pH caused by **ranitidine**.[8]

(d) Fleroxacin

Cimetidine decreases the total clearance of fleroxacin by about 25%, without much effect on renal clearance, and increases its elimination half-life by 32%.[9]

(e) Gatifloxacin

Cimetidine does not alter the pharmacokinetics of gatifloxacin.[10]

(f) Levofloxacin

Cimetidine reduces the clearance of levofloxacin by about 25% and increased its AUC by almost 30%,[11] whereas **ranitidine** does not affect the pharmacokinetics of levofloxacin.[12]

(g) Lomefloxacin

Ranitidine does not affect the pharmacokinetics of lomefloxacin.[13,14]

(h) Moxifloxacin

Ranitidine does not affect the pharmacokinetics of moxifloxacin.[15]

(i) Norfloxacin

Famotidine given 8 hours before norfloxacin significantly reduced its maximum serum concentrations in 6 healthy subjects, but the AUC and urinary recovery rate were unchanged.[16]

(j) Ofloxacin

Cimetidine does not alter the pharmacokinetics of ofloxacin.[17]

(k) Pefloxacin

Cimetidine increases the AUC of intravenous pefloxacin by about 40%. It increases the half-life from 10.3 hours to 15.3 hours and the clearance of pefloxacin was reduced by almost 30%.[18]

(l) Sparfloxacin

Cimetidine does not alter the pharmacokinetics of sparfloxacin.[19]

(m) Tosufloxacin

Famotidine does not alter the pharmacokinetics of tosufloxacin.[20]

(n) Trovafloxacin

Cimetidine does not alter the pharmacokinetics of trovafloxacin.[21]

Importance and management

Although the pharmacokinetic changes seen in some of these studies are moderate, none has been shown to affect the outcome of treatment and they are probably only of minor clinical relevance.

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Quinolones + Iron or Zinc compounds

Ferrous fumarate, ferrous gluconate, ferrous sulfate and other iron compounds can reduce the absorption of ciprofloxacin, gatifloxacin, levofloxacin, moxifloxacin, norfloxacin, ofloxacin, sparfloxacin from the gut. Serum levels of the antibacterial may become subtherapeutic as a result. Limited evidence suggests that fleroxacin is not affected, lomefloxacin is only minimally affected and gemifloxacin is not affected when dosing is separated. Zinc appears to interact like the iron compounds. No interaction appears to occur with iron-ovotransferrin.

Clinical evidence

(a) Ciprofloxacin

The absorption of ciprofloxacin is markedly reduced by iron and zinc compounds. Several studies have clearly demonstrated reductions in the AUC and maximum serum levels of 30 to 90% with **ferrous fumarate**,[1] **ferrous gluconate**,[2] **ferrous sulfate**,[2-5] **iron-glycine sulfate**,[6] ***Centrum Forte***[2] (a multi-mineral preparation containing iron, magnesium, zinc, calcium, copper and manganese) and with ***Stresstabs 600-with-zinc***[4] (a multivitamin-with-zinc preparation). However **iron-ovotransferrin** has been found to have no significant effect on the absorption of ciprofloxacin.[7]

(b) Fleroxacin

A study in 12 subjects found that **ferrous sulfate** (equivalent to 100 mg of elemental iron) had no significant effect on the pharmacokinetics of fleroxacin.[8]

(c) Gatifloxacin

A study in 6 healthy subjects found that **ferrous sulfate** 160 mg given with gatifloxacin 200 mg decreased the maximum serum levels and AUC of gatifloxacin by 49% and 29%, respectively.[9]

A case report describes a woman who did not respond to treatment with gatifloxacin for hospital acquired pneumonia when it was given at the same time as a multivitamin preparation containing iron, magnesium and **zinc**. When administration was separated by 6 hours her clinical signs improved.[10]

(d) Gemifloxacin

In a study in 27 healthy subjects, gemifloxacin 320 mg was given either 3 hours before or 2 hours after **ferrous sulfate** 325 mg. The pharmacokinetics of gemifloxacin were not significantly altered in either case.[11]

(e) Levofloxacin

Ferrous sulfate has been found to reduce the bioavailability of levofloxacin by 79%.[12]

(f) Lomefloxacin

When lomefloxacin 400 mg was given with **ferrous sulfate** (equivalent to 100 mg of elemental iron), the lomefloxacin maximum serum levels were reduced by about 28% and the AUC was reduced by about 14%.[13]

(g) Moxifloxacin

In 12 healthy subjects **ferrous sulfate** (equivalent to 100 mg of elemental iron) reduced the AUC and maximum plasma levels of a single 400-mg dose of moxifloxacin by 39% and 59%, respectively. The rate of absorption was reduced (time to maximum plasma level increased from a mean of one hour to 2.79 hours).[14]

(h) Norfloxacin

In 8 healthy subjects **ferrous sulfate** reduced the AUC and maximum serum levels of a single 400-mg dose of norfloxacin by 73% and 75%, respectively.[5] **Ferrous sulfate** caused a 51% reduction in the AUC of norfloxacin in another study,[15,16] and a 97% reduction in bioavailability in a further single-dose study.[17] The same authors also found that both **ferrous sulfate** and **zinc sulfate** reduced the urinary recovery of norfloxacin by 55% and 56%, respectively.[18]

(i) Ofloxacin

In 8 healthy subjects **ferrous sulfate** (equivalent to 100 mg of elemental iron) reduced the AUC and maximum serum levels of a single 400-mg dose of ofloxacin by 25% and 36%, respectively.[5] In 9 healthy subjects **ferrous sulfate** 1050 mg decreased the absorption of ofloxacin 200 mg by 11%.[19] In 12 healthy subjects elemental iron 200 mg (in the form of an **iron-glycine-sulfate** complex) reduced the bioavailability of ofloxacin 400 mg by 36%.[6]

(j) Sparfloxacin

In a single-dose study in 6 subjects, **ferrous sulfate** 525 mg (equivalent to 170 mg of elemental iron) reduced the AUC of sparfloxacin 200 mg by 27%.[15,16]

Mechanism

It is believed that the quinolones form a complex with iron and zinc (by chelation between the metal ion and the 4-oxo and adjacent carboxyl groups), which is less easily absorbed by the gut. However, a study in *rats* using oral iron and intravenous ciprofloxacin suggested that the interaction may not be entirely confined to the gut.[20] This needs further study. Iron-ovotransferrin differs from other iron preparations in being able to combine directly with the transferrin receptors of intestinal cells, and appears to release little iron into the gut to interact with the quinolones.

Importance and management

The interactions between the quinolones and iron compounds are established and would appear to be of clinical importance because the serum antibacterial levels can become subtherapeutic. In descending order the extent of the interaction appears to be: norfloxacin, levofloxacin, ciprofloxacin, moxifloxacin, gatifloxacin, ofloxacin/sparfloxacin, then least affected, lomefloxacin.

None of these quinolones should be taken at the same time as any iron preparation that contains substantial amounts of iron (e.g. ferrous sulfate, ferrous gluconate, ferrous fumarate, iron-glycine sulfate). As the quinolones are rapidly absorbed, taking them 2 hours before the iron should minimise the risk of admixture in the gut and largely avoid this interaction. Information about other quinolones seems to be lacking but the same precautions should be taken with all of them except fleroxacin, which appears not to interact, and lomefloxacin, which seems to interact only minimally.

Iron-ovotransferrin does not interact with ciprofloxacin and is not expected to interact with any of the quinolones (see 'Mechanism') but this awaits confirmation.

There seems to be very little data about the interactions between zinc compounds and quinolones, but zinc appears to interact like iron and therefore the same precautions suggested for iron should be followed.

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Quinolones + NSAIDs

A number of cases of convulsions have been seen in Japanese patients given fenbufen with enoxacin, and there is also one possible case involving ofloxacin. Normally no interaction seems to occur with most quinolones and NSAIDs, except where there is a predisposition to convulsive episodes. Isolated cases of convulsions, other neurological toxicity or skin eruptions have been seen when ciprofloxacin was given with indometacin, mefenamic acid or naproxen. These appear to be very rare events.

Clinical evidence

(a) Ciprofloxacin

As of 1995 the manufacturer of ciprofloxacin had, on record, two confirmed spontaneous reports of convulsions in patients taking ciprofloxacin and an NSAID; one with **mefenamic acid** and the other with **naproxen**.[1] These appear to be the only medically validated reports of an interaction between ciprofloxacin and an NSAID by 1995.[1]

A woman taking chloroquine 250 mg and **naproxen** 1 g daily developed dizziness, anxiety and tremors within a week of starting to take ciprofloxacin 1 g daily. The symptoms largely resolved when the chloroquine was stopped; it was not known if she also stopped the naproxen. Two months after chloroquine was discontinued, and while she was still taking ciprofloxacin, **indometacin** was started. This time she developed pain in her feet and became extremely tired. The pain partially subsided and the fatigue vanished when the ciprofloxacin was stopped. Later she was found to have some axonal demyelination, compatible with drug-induced polyneuropathy.[2]

A study in 8 healthy subjects found that the pharmacokinetics of ciprofloxacin were unaffected by treatment with **fenbufen** for 3 days.[3] Another study, in 12 healthy subjects, found that the concurrent use of single doses of ciprofloxacin and **fenbufen** produced no evidence, using EEG recordings, of increased CNS excitatory effects.[4]

(b) Enoxacin

A total of 17 Japanese patients have been identified, with apparently no previous history of seizures, who in the 1986 to 1987 period developed convulsions when given **fenbufen** 400 mg to 1.2 g daily with enoxacin 200 to 800 mg.[5] Two case reports of this interaction have been published.[6,7] An 87-year-old Japanese woman taking enoxacin 200 mg also had convulsions after receiving a single 50-mg intravenous dose of **flurbiprofen**.[8]

(c) Levofloxacin

A study in 24 healthy subjects found plasma levels of single 125-mg and 500-mg doses of levofloxacin were increased by about 13%, 6.5 hours after they were given **fenbufen** 600 mg. No changes in CNS activity were found.[9]

(d) Ofloxacin

One patient taking **fenbufen** 800 mg had involuntary movements of the neck and upper extremities after taking ofloxacin 600 mg.[5] In 10 healthy subjects the pharmacokinetics of ofloxacin 200 mg twice daily were unchanged by **ketoprofen** 100 mg daily for 3 days.[10] The incidence of psychotic adverse effects (euphoria, hysteria, psychosis) in 151 patients taking ofloxacin were not increased by the concurrent use of NSAIDs (**aspirin**, **diclofenac**, **indometacin**, **dipyrone**).[11]

(e) Pefloxacin

In 10 healthy subjects the pharmacokinetics of pefloxacin 400 mg twice daily were not affected by **ketoprofen** 100 mg daily for 3 days.[10]

(f) Sparfloxacin

A 62-year-old woman developed drug eruptions (erythematous papules), which were attributed to sparfloxacin hypersensitivity induced by **mefenamic acid**.[12]

Mechanism

Not fully understood. Convulsions have occurred in a few patients taking quinolones alone, some of whom had epilepsy and some of whom did not, see 'Antiepileptics + Quinolones', p.598. Experiments in *mice* have shown that quinolones competitively inhibit the binding of GABA to its receptors.[13] GABA is an inhibitory transmitter in the CNS, which is believed to be involved in the control of convulsive activity. Enoxacin and fenbufen are known to affect the GABA receptor site in the hippocampus and frontal cortex of *mice*, which is associated with convulsive activity.[14] It could be that, if and when an interaction occurs, the NSAID simply lowers the amount of quinolone needed to precipitate convulsions in already susceptible individuals.

Importance and management

The interaction between enoxacin and fenbufen is established, but it seems to be uncommon. Nevertheless, it would seem prudent to avoid fenbufen with enoxacin. There are very many alternatives.

Reports of adverse interactions between other quinolones and NSAIDs are extremely rare. The general warning about convulsions with quinolones and NSAIDs issued by the CSM in the UK[15] seems to be an extrapolation from the interaction between enoxacin and fenbufen, and from some *animal* experiments. In addition to the data cited above, an epidemiological study of 856 users of quinolones (ciprofloxacin, enoxacin, nalidixic acid) and a range of NSAIDs found no cases of convulsions.[16] The overall picture would therefore seem to be that although a potential for interaction exists, the risk is very small indeed and normally there would seem to be little reason for most patients taking quinolones to avoid NSAIDs. Patients with epilepsy are a possible exception and it would seem prudent to avoid quinolones and NSAIDs wherever possible in these patients.

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Quinolones + Omeprazole

Omeprazole has no clinically important effect on the pharmacokinetics of ciprofloxacin, garenoxacin, gemifloxacin, lomefloxacin, ofloxacin or trovafloxacin.

Clinical evidence, mechanism, importance and management

A single-dose study found that omeprazole 20 or 80 mg had no significant effect on the pharmacokinetics of single doses of **ofloxacin** 400 mg, **ciprofloxacin** 500 mg or **lomefloxacin** 250 or 400 mg.[1] Another study in 27 subjects found that omeprazole 40 mg daily for 3 days did not affect the pharmacokinetics of a single 1-g dose of an extended-release formulation of **ciprofloxacin** (*Depomed*).[2] Omeprazole 40 mg caused an 18% reduction in the AUC of a single 300-mg dose of **trovafloxacin** and a 32% reduction in the maximum serum levels, but this was considered not to be of clinical significance.[3] A randomised, crossover study in 12 healthy subjects found that the maximum serum levels and AUC of a single 320-mg dose of **gemifloxacin** were increased by 11% and 10%, respectively, by omeprazole 40 mg daily for 4 days. The confidence intervals indicated that the respective increases were unlikely to exceed 36% and 43%, and it was concluded that these two drugs could be given together without any need for dose adjustments.[4] In a study in 12 healthy subjects, slow-release omeprazole 40 mg daily did not affect the pharmacokinetics of a single 600-mg dose of **garenoxacin** and concurrent use did not increase adverse effects.[5]

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Quinolones + Opioids

Morphine modestly reduces the AUC of trovafloxacin, but this is not considered to be clinically significant. Trovafloxacin did not alter the effects or pharmacokinetics of morphine. Oxycodone does not appear to significantly affect the pharmacokinetics of either levofloxacin or gatifloxacin. It has been suggested that opiates decrease oral ciprofloxacin levels, but good evidence for this appears to be lacking.

Clinical evidence, mechanism, importance and management

(a) Ciprofloxacin

In one non-randomised study[1] the levels of oral ciprofloxacin were only 1.3 mg/L in the presence of intramuscular **papaveretum**, compared to 3.22 mg/L in a control group not receiving **papaveretum**. The authors say that this means the peak ciprofloxacin levels in the **papaveretum** group would not reach the MIC of a number of gut pathogens. They name *Bacteroides fragilis* (but it should be noted that the levels of the control group also did not reach the MIC of this organism), and *Enterococcus faecalis*, many strains of which are only moderately susceptible to ciprofloxacin anyway. Further, the **papaveretum** group in this study had only 4 patients, and, as the authors note, the control group was not matched.[1] Based on this rather slim evidence, some have suggested that the concurrent use of opioids and ciprofloxacin as pre-medication should be avoided.[2-4]

(b) Gatifloxacin

In 12 healthy subjects, the pharmacokinetics of gatifloxacin 400 mg were not significantly altered by **oxycodone** 5 mg every 4 hours.[5]

(c) Levofloxacin

In 8 healthy subjects, the pharmacokinetics of oral levofloxacin 500 mg were not significantly altered by **oxycodone** 5 mg every 4 hours.[6]

(d) Trovafloxacin

An intravenous infusion of **morphine** 150 micrograms/kg given with oral trovafloxacin 200 mg to 18 healthy subjects caused a 36% reduction in the trovafloxacin AUC and a 46% reduction in the maximum serum levels. These levels were considered sufficient for prophylaxis of infection, and remained above the MICs of the most likely organisms to cause post-surgical infections. The bioavailability and effects of **morphine** were not significantly changed by trovafloxacin.[7]

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Quinolones + Opioids; Methadone

An isolated case describes sedation, confusion and respiratory depression, which was attributed to the inhibition of methadone metabolism by ciprofloxacin.

Clinical evidence

A woman taking methadone 140 mg daily for 6 years, to manage pain due to chronic intestinal pseudo-obstruction, was admitted to hospital because of a urinary tract infection and given ciprofloxacin 750 mg twice daily. Two days later she became sedated and confused. Ciprofloxacin was replaced with co-trimoxazole and the patient recovered within 48 hours. She was treated with ciprofloxacin for recurrent urinary-tract infections a further three times and on each occasion the patient became sedated, with her normal alertness regained on discontinuing ciprofloxacin. On the last occasion, when the venlafaxine that she had also been taking was replaced by fluoxetine, she also developed respiratory depression, which was reversed with naloxone.[1]

Mechanism

The cytochrome P450 isoenzymes CYP1A2, CYP2D6 and CYP3A4 are involved in the metabolism of methadone. Ciprofloxacin is a potent inhibitor of CYP1A2 and possibly has some effect on CYP3A4. It is therefore probable that the confusion and sedation seen in the patient were due to the inhibition of methadone metabolism. The use of 'fluoxetine', (p.1489), and the fact that the patient was a smoker, may also have contributed.

Importance and management

This seems to be the only report of this interaction but it would appear to be of clinical importance. Care is needed if ciprofloxacin and methadone are given concurrently, especially if there are other factors present, such as smoking or the use of other enzyme inhibitors, which may also contribute to the interaction. Be alert for the need to change the methadone dose. Consider also 'Quinolones + Opioids', above.

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Quinolones + Other antibacterials

There appear to be few documented cases of clinically relevant interactions between the quinolones and other antibacterials. How-

ever, note that clindamycin may antagonise the effects of ciprofloxacin on *Staphylococcus aureus*. Further, *in vitro* studies have demonstrated antagonistic antibacterial effects when nitrofurantoin and nalidixic acid are used together, and other quinolones are also said to antagonise the effects of nitrofurantoin.

Clinical evidence, mechanism, importance and management

(a) Aminoglycosides

A study found that a single 100-mg intravenous dose of **tobramycin** had no effect on the pharmacokinetics of **pefloxacin**, and **pefloxacin** did not affect the pharmacokinetics of **tobramycin**.[1] Similarly no pharmacokinetic interaction was found between **pefloxacin** and **amikacin**.[2]

(b) Cephalosporins

A study found that a single 2-g intravenous dose of **ceftazidime** had no effect on the pharmacokinetics of **pefloxacin**, and **pefloxacin** did not affect the pharmacokinetics of **ceftazidime**.[1]

In a study in 11 healthy subjects, the pharmacokinetics of **cefotaxime** and **ofloxacin** were similar, whether given alone or in combination, and the antimicrobial effect of the combination was additive for *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Enterobacter cloacae* and *Klebsiella pneumoniae*, but not for *Pseudomonas aeruginosa*.[3]

(c) Clindamycin

One study found that the pharmacokinetics of intravenous **ciprofloxacin** 200 mg were not affected by intravenous clindamycin 600 mg and there is evidence that combined use may possibly enhance the antibacterial activity, particularly against *Staphylococcus aureus* and *Streptococcus pneumoniae*.[4] However, another study found that the serum bactericidal activity of **ciprofloxacin** against *Staphylococcus aureus* was completely antagonised by clindamycin, if the strains were susceptible to the latter.[5]

(d) Macrolides

A study designed to assess the potential interaction between **trovafloxacin** and **azithromycin** found no significant alteration in the pharmacokinetics of either drug.[6]

(e) Metronidazole

A study found that a single 400-mg oral dose of metronidazole had no effect on the pharmacokinetics of **pefloxacin**, and similarly **pefloxacin** did not affect the pharmacokinetics of metronidazole.[1] In other studies no interaction was found between **ciprofloxacin** or **ofloxacin** (both 200 mg intravenously) and metronidazole 500 mg intravenously;[7] and metronidazole with **ciprofloxacin** orally.[8]

A further study, investigating the use of metronidazole 500 mg intravenously and **ciprofloxacin** 200 mg intravenously, also did not find any significant pharmacokinetic changes, although metronidazole reduced the **ciprofloxacin** volume of distribution by 20%.[4] This is not expected to be clinically significant.

(f) Nitrofurantoin

The antibacterial activity of **nalidixic acid** can be attenuated by sub-inhibitory concentrations of nitrofurantoin. In 44 out of 53 strains of *Escherichia coli*, *Salmonella* and *Proteus*, antagonism was shown.[9] Another study confirmed these findings.[10] Whether this similarly occurs if both antibacterials are given to patients is uncertain, but the advice that concurrent use should be avoided when treating urinary tract infections seems sound.[9] Active division of bacteria is required for the bactericidal activity of quinolones such as nalidixic acid, and the presence of a bacteriostatic drug such as nitrofurantoin may inhibit its action.[11] Other quinolone antibacterials (not named) and nitrofurantoin have been found to be antagonistic *in vitro*, although the clinical significance of this is unknown.[12,13]

(g) Penicillins

A single-dose study in 6 healthy subjects found that intravenous **azlocillin** 60 mg/kg reduced the clearance of intravenous **ciprofloxacin** 4 mg/kg by 35%. The pharmacokinetics of **azlocillin** were not affected.[14] Another study found that when a single 4-g intravenous dose of **piperacillin** was given with **pefloxacin** 400 mg the pharmacokinetics of both drugs were unchanged.[1] In 6 healthy subjects the absorption of **ofloxacin** 400 mg was not altered by **amoxicillin** 3 g.[15]

In another study, in 12 healthy subjects, the serum bacterial activity of **ciprofloxacin** with **piperacillin** against a variety of organisms was found to be additive, rather than antagonistic or synergistic despite the fact that the clearance of **ciprofloxacin** was reduced by 24%.[16]

(h) Rifampicin (Rifampin)

1. Ciprofloxacin. A single-dose study in 5 healthy subjects found that ciprofloxacin 500 mg decreased the peak serum levels of rifampicin 600 mg by 12%, and prolonged its half-life from 3.5 hours to 3.8 hours.[17] In a further study, ciprofloxacin did not affect the percentage of rifampicin recovered in the urine, but it did increase its initial rate of excretion.[18] In 12 elderly patients (aged 67 to 95 years), ciprofloxacin 750 mg and rifampicin 300 mg, both given every 12 hours for 2 weeks, did not significantly affect the pharmacokinetics of either drug.[19] This is confirmed by other pharmacokinetic studies, one of which also reported that combined use provided excellent serum bactericidal activity against *Staphylococcus aureus* strains, although activity was modestly lower than rifampicin alone.[5,20,21] No special precautions would seem necessary if rifampicin is given with ciprofloxacin.

2. Fleroxacin. A study in 13 healthy subjects found that rifampicin 600 mg daily for a week increased the clearance of fleroxacin 400 mg daily by 15%. However, the fleroxacin levels remained above the MIC_{90} of methicillin-sensitive strains of *Staphylococcus aureus* and *Staphylococcus epidermidis* for at least 24 hours.[22]

3. Gatifloxacin. A study in 22 healthy subjects who took a single 400-mg dose of gatifloxacin alone, or with a combined preparation containing rifampicin 400 mg, isoniazid 300 mg and pyrazinamide 1.6 g, found that the AUC of gatifloxacin was increased by 10% when taken with the combined preparation. In addition, the AUC and maximum plasma concentration of rifampicin were reduced by 14% and 27%, respectively, by gatifloxacin.[23] The effect of these changes on the efficacy of treatment is unclear, but it seems likely to be small.

4. Moxifloxacin. A study in 19 patients who were nearing the end of treatment for tuberculosis with rifampicin 450 mg daily and isoniazid 600 mg daily found that the maximum plasma levels and AUC of moxifloxacin 400 mg daily for 5 days were reduced by 32% and 31%, respectively, when it was taken with the antimycobacterials, compared with when it was taken alone. It was also noted that the MIC of moxifloxacin against fast growing bacilli was achieved in only one patient taking moxifloxacin with the antimycobacterials, compared with 9 of 19 patients taking moxifloxacin alone.[24]Another study in healthy subjects found that the AUC of moxifloxacin 400 mg daily, given for 4 days alone, and then with rifampicin 600 mg daily for 10 days was reduced by 27% by rifampicin. There was no significant difference between the maximum plasma moxifloxacin levels achieved in each treatment period.[25] The clinical significance of these findings is unclear, but it seems likely to be small.

5. Pefloxacin. A study in 8 healthy subjects found that rifampicin 900 mg daily for 10 days decreased the half-life and $AUC_{0\text{-}12}$ of pefloxacin 400 mg twice daily by about 30%, due to a 35% increase in total plasma clearance.[26] Despite these changes the serum pefloxacin levels still remained well above the MIC (0.5 mg/L) for 90% of strains of methicillin-sensitive *Staphylococcus aureus* and *Staphylococcus epidermidis*.[26] A single-dose study in 5 healthy subjects found that pefloxacin 500 mg increased the AUC of a single 600-mg dose of rifampicin about twofold.[27] In a further study the urinary recovery of rifampicin was increased from 16% of the dose to 20% by pefloxacin.[28] No special precautions would seem necessary if rifampicin is given with pefloxacin.

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Quinolones + Phosphate binders

The bioavailability of ciprofloxacin is markedly reduced by lanthanum. Other quinolones are likely to interact similarly. Sevelamer reduced the bioavailability of ciprofloxacin by 48% in one study.

Clinical evidence, mechanism, importance and management

(a) Lanthanum

In a randomised, crossover study, 12 healthy subjects received a single 750-mg dose of oral **ciprofloxacin** alone, or on the second day of a 2-day course of lanthanum 1 g three times daily. Lanthanum reduced the AUC and maximum plasma levels of **ciprofloxacin** by 54% and 56%, respectively.[1] It seems likely that **ciprofloxacin** forms an insoluble chelate with lanthanum within the gut, which reduces its absorption. Such a reduction in bioavailability may lead to subtherapeutic levels and hence reduced efficacy. It is therefore recommended that quinolones are not taken within 2 hours of lanthanum.[2]

(b) Sevelamer

In a crossover study in 15 healthy subjects, the AUC of **ciprofloxacin** was reduced by 39% and its relative oral bioavailability was reduced by 48% when a single 750-mg dose of **ciprofloxacin** was taken with sevelamer 2.8 g. The reduction was variable.[3] The mechanism of the interaction is unknown. Based on the results of this study, sevelamer should not be given at the same time as **ciprofloxacin** because the efficacy of **ciprofloxacin** might be reduced in some patients. Note that the manufacturers of sevelamer suggest that, when giving any other oral drug for which a reduction in the bioavailability could have a clinically significant effect on safety or efficacy, the drug should be given at least one hour before or 3 hours after sevelamer.[4,5] Until more is known it would seem prudent to apply this advice to all quinolones.

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Quinolones + Pirenzepine

In 10 healthy subjects, four doses of pirenzepine 50 mg delayed the absorption of ciprofloxacin and ofloxacin, but their bioavailabilities remained unchanged.[1] The delayed absorption is unlikely to be of clinical significance.

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Quinolones + Probenecid

Probenecid increases the serum levels and/or decreases the urinary excretion of cinoxacin, ciprofloxacin, clinafloxacin, enoxacin, fleroxacin, levofloxacin, nalidixic acid and norfloxacin. Moxifloxacin, sparfloxacin, and probably ofloxacin, appear not to interact with probenecid.

Clinical evidence

(a) Cinoxacin

A study in 6 healthy subjects found that probenecid 500 mg three times daily roughly doubled the serum levels of a 3-hour intravenous infusion of cinoxacin. The renal clearance of cinoxacin was also reduced from 68% to 46% during and for the 4 hours after the infusion.[1]

(b) Ciprofloxacin

In one study, probenecid 1 g, given 30 minutes before ciprofloxacin 500 mg, was found to reduce the renal clearance of ciprofloxacin by up to 50%. Other pharmacokinetic parameters (maximum serum levels, AUC) were unchanged and no accumulation of ciprofloxacin appeared to occur, probably due to an increase in extra-renal elimination.[2]

Another study found that the renal clearance of ciprofloxacin was reduced by 64% by probenecid. However, in contrast to the other study cited, the AUC of ciprofloxacin was increased by 74% and the AUC of its 2-aminoethylamino metabolite was increased by 234%. As a consequence, levels of ciprofloxacin in tears, sweat and saliva were also increased, but probenecid had no direct effect on ciprofloxacin distribution into these fluids.[3]

(c) Clinafloxacin

Probenecid 1 g, given one hour before a single 400-mg dose of clinafloxacin, reduced the total and renal clearance of clinafloxacin by 24% and 36%, respectively, raised its AUC by 32%, and increased its elimination half-life from 6.3 hours to 7 hours.[4]

(d) Enoxacin

In one subject, the renal clearance of enoxacin 600 mg was approximately halved, and the half-life increased from 3.5 hours to 4.5 hours by a single 2.5-g dose of probenecid.[5]

(e) Fleroxacin

A study in 6 healthy subjects given a single 200-mg dose of fleroxacin, followed by 500 mg of probenecid 30 minutes, 12 hours, 24 hours and 36 hours later, found that the AUC of fleroxacin was increased by 37% and its urinary excretion was decreased by 22%.[6] Another study found that probenecid increased the AUC of fleroxacin 400 mg by 26% (not statistically significant), and had no effect on fleroxacin urinary excretion.[7]

(f) Levofloxacin

A study in 12 healthy subjects found that although probenecid reduced the renal clearance of a single 500-mg oral dose of levofloxacin by about one-third and increased its AUC and half-life by similar amounts, the 72-hour urinary levofloxacin excretion was unaltered.[8]

(g) Moxifloxacin

A study in 12 healthy subjects found that probenecid had no clinically significant effects on the pharmacokinetics of a single 400-mg dose of moxifloxacin.[9]

(h) Nalidixic acid

Two subjects, acting as their own controls, took nalidixic acid 500 mg with and without probenecid 500 mg. The peak serum levels of nalidixic

acid were unaffected at 2 hours, but at 8 hours the levels were increased threefold by probenecid.[10]

Another study in 5 women with urinary tract infections treated with nalidixic acid found that probenecid increased the maximum serum nalidixic acid levels and AUC by 43% and 74%, respectively.[11]

(i) Norfloxacin

In 5 subjects the mean 12-hour urinary recovery of norfloxacin 200 mg was reduced by about half when they were given probenecid 1 g. Norfloxacin serum concentrations were unaffected.[12]

(j) Ofloxacin

A study in 8 healthy subjects found that probenecid 500 mg increased the AUC of a single 200-mg dose of ofloxacin by 16% and decreased the total body clearance by 14%. Other pharmacokinetic parameters were not significantly affected.[13]

(k) Sparfloxacin

In 6 healthy subjects, probenecid 1.5 g did not significantly affect the clearance, the AUC or the half-life of sparfloxacin 200 mg.[14]

Mechanism

The likely explanation for this interaction is that probenecid successfully competes with some quinolones for tubular excretion, so that their renal elimination is reduced. Some quinolones are more dependent on glomerular filtration than tubular excretion for elimination, and thus are unaffected by competition for tubular excretion.[7]

Importance and management

Established interactions, but their clinical importance seems not to have been assessed. The increased levels and decreased renal excretion of clinafloxacin caused by probenecid are not considered large enough to warrant dose adjustment,[4] and most of the changes seen with the other quinolones were of a similar magnitude. However, caution has been advised if probenecid is given with quinolones to patients with impaired renal function, or in the presence of other drugs that may also compete for renal excretion (such as some penicillins or cephalosporins).[3,4] Moxifloxacin, sparfloxacin, and probably ofloxacin, appear not to interact, and so may be useful alternatives in some situations.

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Quinolones + Sucralfate

Sucralfate causes a marked reduction in the absorption of ciprofloxacin, enoxacin, gemifloxacin, lomefloxacin, moxifloxacin, ofloxacin, norfloxacin and sparfloxacin, but causes only a modest reduction in fleroxacin levels.

Clinical evidence

(a) Ciprofloxacin

In a study in 8 healthy subjects sucralfate 1 g four times daily reduced the AUC and maximum serum concentration of ciprofloxacin 500 mg by 88% and 90%, respectively.[1] A study in 12 healthy subjects found that a 1-g dose of sucralfate given 6 hours and 2 hours before a single 750-mg dose of ciprofloxacin, reduced the ciprofloxacin AUC by about 30%. In 3 subjects there were little or no changes in the AUC of ciprofloxacin but a decrease of more than 50% was seen in 4 others.[2] A related study in 12 healthy subjects found that the bioavailability of ciprofloxacin 750 mg was reduced by 7%, 20%, and 95%, respectively, when sucralfate was given 6 hours before, 2 hours before, or at the same time as, the ciprofloxacin.[3]

A patient given sucralfate 1 g four times daily had serum ciprofloxacin levels that were 85 to 90% lower than 5 other patients who were not taking sucralfate.[4] A single dose study found a 96% reduction in the AUC of ciprofloxacin following a 2-g dose of sucralfate.[5] Oral sucralfate does not alter the effects of ciprofloxacin on aerobic bacteria in the gut.[6]

(b) Enoxacin

In 8 healthy subjects when sucralfate 1 g was given 2 hours before or with enoxacin 400 mg the bioavailability of the enoxacin was reduced by 54% and 88%, respectively,. When sucralfate was given 2 hours after enoxacin its bioavailability was not affected.[7]

(c) Fleroxacin

In 20 healthy subjects, sucralfate 1 g every 6 hours reduced the bioavailability of fleroxacin 400 mg by 24%.[8]

(d) Gemifloxacin

In a study in 27 healthy subjects, gemifloxacin 320 mg was given either 3 hours before or 2 hours after sucralfate 2 g. The pharmacokinetics of gemifloxacin were not significantly altered when sucralfate was given after the gemifloxacin, probably due to its rapid absorption. However, when sucralfate was given 3 hours before gemifloxacin, its AUC and maximum plasma levels were decreased by 53% and 69%, respectively.[9]

(e) Levofloxacin

The pharmacokinetics of levofloxacin are unaffected by sucralfate taken 2 hours after the quinolone.[10]

(f) Lomefloxacin

A study in 12 subjects found that when lomefloxacin 400 mg was given 2 hours after sucralfate 1 g the lomefloxacin AUC and maximum serum concentration were reduced by about 25% and 30%, respectively.[11] Another study in 8 healthy subjects found that when lomefloxacin 400 mg was given with sucralfate 1 g, the lomefloxacin AUC was reduced by 51%.[12]

(g) Moxifloxacin

In 12 healthy subjects, a total of five doses of sucralfate 1 g, given at the same time as a single 400-mg dose of moxifloxacin and then 5, 10, 15, and 24 hours after the dose, reduced the AUC and maximum serum concentration of moxifloxacin by 40% and 29%, respectively.[13]

(h) Norfloxacin

A study in 8 healthy subjects found that sucralfate 1 g four times daily reduced the AUC of a single 400-mg dose of norfloxacin by 98%, when taken with the sucralfate, and by 42% when taken 2 hours after the sucralfate.[14] Another study found a reduction of 91% in the AUC of norfloxacin 400 mg when it was taken with sucralfate 1 g, but no reduction when norfloxacin was taken 2 hours before sucralfate.[15]

(i) Ofloxacin

A single-dose study found that sucralfate (dose not stated) reduced the maximum serum levels and AUC of a single 200-mg dose of ofloxacin by about two-thirds.[16] Another study found a reduction in the maximum serum levels and the AUC of ofloxacin of 70% and 61%, respectively, when ofloxacin 400 mg was taken with sucralfate 1 g, but no reduction when the ofloxacin was taken 2 hours before sucralfate.[15] Food reduced the extent of the interaction but it was still marked.[17]

(j) Sparfloxacin

In a study in 15 healthy subjects, sucralfate 1 g four times daily reduced the maximum serum levels, the AUC and the relative bioavailability of sparfloxacin 400 mg daily by 39%, 47%, and 44%, respectively.[18] In a study assessing staggered dosing of sucralfate 1.5 g on the pharmacokinet-

ics of sparfloxacin 300 mg, the AUC of sparfloxacin was unaffected when sucralfate was given 4 hours after the quinolone, but was decreased by 34% when sucralfate was given 2 hours after the quinolone, and by 51% when sucralfate was given at the same time as the quinolone.[19]

Mechanism

The aluminium hydroxide component of sucralfate (about 200 mg in each gram) forms an insoluble chelate between the cation and the 4-keto and 3-carboxyl groups of the quinolone, which reduces its absorption. See 'Quinolones + Antacids or Calcium compounds', p.369, for more on this mechanism.

Importance and management

Established and clinically important interactions. Because it seems probable that serum ciprofloxacin, enoxacin, gemifloxacin, levofloxacin, lomefloxacin, moxifloxacin, ofloxacin, norfloxacin and sparfloxacin levels will be reduced to subtherapeutic concentrations if given with sucralfate, separate the doses as much as possible (by 2 hours or more), giving the quinolone first. The manufacturer of ciprofloxacin advises that it should be given one to 2 hours before, or 4 hours after, sucralfate.[20] The study with moxifloxacin suggested that sucralfate should not be given for 2 hours before or 4 hours after the quinolone, but more study is needed to confirm both these findings and the effectiveness of separating the doses; however, the UK manufacturer of moxifloxacin advises separating administration by 6 hours,[21] whereas the US manufacturer of moxifloxacin recommends that it is taken at least 4 hours before or 8 hours after sucralfate.[22] The interaction with fleroxacin is only modest (bioavailability reduced by 24%) and probably not clinically important, but some separation of the doses may reduce the interaction further. This needs confirmation. **Pefloxacin** interacts with antacids containing aluminium hydroxide (see 'Quinolones + Antacids or Calcium compounds', p.369) and is therefore likely to interact with sucralfate.

The 'H_2-receptor antagonists', (p.377) and 'omeprazole', (p.380) do not interact with the quinolones and may therefore be alternatives to sucralfate in some situations.

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Quinolones; Ciprofloxacin + Chloroquine

Chloroquine may modestly reduce ciprofloxacin levels.

Clinical evidence, mechanism, importance and management

A study in 5 healthy subjects who were given a single 500-mg dose of ciprofloxacin alone, or with a single 600-mg dose of chloroquine found that the maximum plasma level of ciprofloxacin was reduced by 18% by chloroquine, and was below the minimum inhibitory concentration for *Plasmodium falciparum*.[1] The same or a very similar study is reported elsewhere.[2] The authors of these reports suggest that the reduction in ciprofloxacin bioavailability may have implications for the management of infections resistant to chloroquine. More study is needed to establish the clinical relevance of this small decrease in ciprofloxacin levels.

For details of a possible interaction between a NSAID and ciprofloxacin in a patient also taking chloroquine, see 'Quinolones + NSAIDs', p.379.

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Quinolones; Ciprofloxacin + Pancreatic enzymes

The pharmacokinetics of ciprofloxacin are not affected by pancreatic enzyme supplements.

Clinical evidence, mechanism, importance and management

Six patients with cystic fibrosis, chronically infected with *Pseudomonas aeruginosa* and who had received a range of drugs including ceftazidime, tobramycin, ticarcillin and salbutamol, demonstrated no significant changes in the pharmacokinetics of a single 250-mg dose of ciprofloxacin when it was given with standard doses of pancreatic enzymes (seven *Pancrease* capsules).[1] Another study in 12 patients with cystic fibrosis found that giving pancreatic enzyme supplements 30 minutes before a single 750-mg dose of ciprofloxacin did not alter the pharmacokinetics of ciprofloxacin.[2] No special precautions would seem to be necessary during concurrent use.

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Quinolones; Ciprofloxacin + Paracetamol (Acetaminophen)

Paracetamol does not alter the pharmacokinetics of ciprofloxacin, but ciprofloxacin may delay and reduce maximum paracetamol levels.

Clinical evidence, mechanism, importance and management

In a study in 10 healthy subjects, a single 500-mg dose of paracetamol had no effect on the pharmacokinetics of a single 500-mg dose of ciprofloxacin.[1] The maximum salivary concentration of a single 1-g dose of paracetamol was reduced by 30% by a single 500-mg dose of ciprofloxacin, and the time to reach maximum salivary levels was delayed from 0.7 hours to 1.43 hours. However, there was no significant change in the AUC of paracetamol in salivary samples. The authors of one study suggest that administration of ciprofloxacin and paracetamol should be separated to avoid a delayed onset of action of paracetamol.[2] However, unless analge-

sia is urgently required, this interaction seems unlikely to be clinically relevant, as the exposure to paracetamol did not appear to be affected.

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Quinolones; Ciprofloxacin + Phenazopyridine

Phenazopyridine appears to increase the bioavailability of ciprofloxacin.

Clinical evidence, mechanism, importance and management

A study in 23 healthy subjects given a single 500-mg dose of ciprofloxacin either alone or with phenazopyridine 200 mg found that phenazopyridine increased the AUC and mean residence time of ciprofloxacin by about 30%. The time to achieve maximum plasma levels was increased from 1 hours to 1.5 hours.[1] If anything, this seems likely to be a beneficial, rather than adverse, interaction.

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Quinolones; Ciprofloxacin + Ursodeoxycholic acid (Ursodiol)

An isolated report describes a reduction in serum ciprofloxacin levels in a patient taking ursodeoxycholic acid.

Clinical evidence, mechanism, importance and management

A man with metastatic colon cancer had unusually low serum levels of ciprofloxacin following oral dosing; his only other medication was ursodeoxycholic acid 300 mg twice daily for gallstones. Despite the low antibacterial serum levels the bacteraemia cleared. Several months later, when he was readmitted to hospital, both drugs were again given, initially staggered, and then later together. When taken together the AUC of ciprofloxacin was reduced by 50% by ursodeoxycholic acid.[1] The reason for this interaction is not understood.

This seems to be the first and only report of an interaction between a quinolone and ursodeoxycholic acid and its importance is uncertain. More study is needed to establish this interaction, its importance, and its mechanism.

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Quinolones; Levofloxacin + Antiretrovirals

There appears to be no clinically important pharmacokinetic interaction between levofloxacin and efavirenz, nelfinavir or zidovudine.

Clinical evidence, mechanism, importance and management

A study in HIV-positive patients who were taking zidovudine and lamivudine with either **efavirenz** or **nelfinavir**, found that levofloxacin 500 mg daily for 4 days did not affect the steady-state pharmacokinetics of either **efavirenz** 600 mg daily or **nelfinavir** 750 mg three times daily. The pharmacokinetics of levofloxacin during the concurrent use of **efavirenz** or **nelfinavir** were unaffected, except for the time to reach maximum levels, which was increased from a range of 0.9 to 1.7 hours in control subjects, to 3.3 hours with **efavirenz**. This may have occurred as a result of delayed gastric emptying caused by the **efavirenz**. A clinically important interaction between levofloxacin and either **efavirenz** or **nelfinavir** is unlikely.[1]

A double-blind study in 16 HIV-positive patients taking **zidovudine** with levofloxacin 350 mg every 8 hours or placebo, did not find any changes in the pharmacokinetics of either drug.[2] No dose adjustments would therefore be expected to be necessary if both drugs are given.

1. Villani P, Viale P, Signorini L, Cadeo B, Marchetti F, Villani A, Fiocchi C, Regazzi MB, Carosi G. Pharmacokinetic evaluation of oral levofloxacin in human immunodeficiency virus-infected subjects receiving concomitant antiretroviral therapy. *Antimicrob Agents Chemother* (2001) 45, 2160–2.
2. Chien SC, Chow AT, Rogge MC, Williams RR, Hendrix CW. Pharmacokinetics and safety of oral levofloxacin in human immunodeficiency virus-infected individuals receiving concomitant zidovudine. *Antimicrob Agents Chemother* (1997) 41, 1765–9.

Quinolones; Lomefloxacin + Furosemide

Furosemide causes a small rise in the serum levels of lomefloxacin. The pharmacokinetics and diuretic effects of furosemide are not changed by lomefloxacin.

Clinical evidence, mechanism, importance and management

A study in 8 healthy subjects found that when a single 200-mg dose of lomefloxacin was taken with furosemide 40 mg, the AUC of lomefloxacin was increased by 12%. The maximum serum levels and the half-life of lomefloxacin were also increased, but not to a statistically significant extent.[1] The suggested reason for the interaction is that there is some competition between the two drugs for excretion by the renal tubules. No significant changes were seen in the pharmacokinetics of furosemide nor in its diuretic effects.[1] The small rise in the serum levels of lomefloxacin is almost certainly too small to be important and there would seem to be no reason for avoiding concurrent use. Information about other quinolone antibacterials appears to be lacking.

1. Sudoh T, Fujimura A, Shiga T, Sasaki M, Harada K, Tateishi T, Ohashi K, Ebihara A. Renal clearance of lomefloxacin is decreased by furosemide. *Eur J Clin Pharmacol* (1994) 46, 267–9.

Quinolones; Moxifloxacin + Itraconazole

A study in healthy subjects found that itraconazole 200 mg daily for 9 days did not affect the pharmacokinetics of a single 200-mg dose of moxifloxacin given on day 7. No clinically relevant changes were found in the pharmacokinetics of itraconazole.[1] No dose adjustments would seem to be necessary during concurrent use.

1. Stass H, Nagelschmitz J, Moeller J-G, Delesen. Pharmacokinetics of moxifloxacin are not influenced by a 7-day pre-treatment with 200 mg oral itraconazole given once a day in healthy subjects. *Int J Clin Pharmacol Ther* (2004) 42, 23–9.

Quinolones; Ofloxacin + Cetraxate

A single-dose study found that cetraxate (dose not stated) did not affect the pharmacokinetics of a single 200-mg dose of ofloxacin.[1] No dose adjustments would seem to be necessary on concurrent use.

1. Shiba K, Yoshida M, Kachi M, Shimada J, Saito A, Sakai N. Effects of peptic ulcer-healing drugs on the pharmacokinetics of new quinolone (OFLX). 17th Int Congr Chemother, June 1991, Berlin, Abstract 415.

Quinupristin/Dalfopristin + Miscellaneous

Quinupristin/dalfopristin modestly increases the levels of intravenous midazolam, a substrate for CYP3A4. The manufacturers therefore predict that quinupristin/dalfopristin will raise the levels of a number of other CYP3A4 substrates.

Clinical evidence, mechanism, importance and management

The manufacturers report a study in which quinupristin/dalfopristin raised the levels of an intravenous bolus dose of midazolam by 33 to 38%.[1,2] These effects are relatively modest, but oral doses of midazolam may be increased to a greater extent. Be alert for increased and/or prolonged sedation when both drugs are given. This study also suggests that quinupristin/dalfopristin is a moderate inhibitor of the cytochrome P450 isoenzyme CYP3A4, and this is supported by other studies in which the levels of

CYP3A4 substrates were raised by quinupristin/dalfopristin (consider also, 'Calcium-channel blockers + Quinupristin/Dalfopristin', p.1042). The manufacturers therefore predict that quinupristin/dalfopristin will raise the levels of other drugs metabolised by CYP3A4, including some antiarrhythmics (**disopyramide**, **lidocaine**, **quinidine**), antiretrovirals (such as **delavirdine**, **indinavir**, **nevirapine**, **ritonavir**), **astemizole**, **carbamazepine**, **cisapride**, **methylprednisolone**, **paclitaxel**, and **vinca alkaloids** (the US manufacturer specifically mentions **vinblastine**).[1] It would therefore be prudent to be alert for increased adverse effects when these drugs are given with quinupristin/dalfopristin. However, the manufacturers also advise that the concurrent use of quinupristin/dalfopristin with drugs that are metabolised by CYP3A4 and which may prolong the QTc interval should be avoided.[1,2] This would be expected to include **astemizole** and **cisapride**.

The manufacturers also name **diazepam** and the **statins** (the US manufacturer specifically mentions **lovastatin**) in their list of drugs that may have their levels raised by quinupristin/dalfopristin.[1,2] However, note that diazepam is not usually affected by CYP3A4 inhibitors, and the statins are not all metabolised by this route, see 'Lipid-regulating drugs', (p.1313). For a further list of CYP3A4 substrates, see 'Table 1.4', (p.6).

The manufacturers also note that when healthy subjects were given **rifampicin** and quinupristin/dalfopristin the pharmacokinetics of both drugs were unchanged. However, the AUC of the sum of quinupristin and its active metabolites was increased by 43%.[2] The clinical relevance of this finding is unclear.

1. Synercid (Quinupristin/Dalfopristin). DSM Pharmaceuticals, Inc. US Prescribing information, November 2007.
2. Synercid (Quinupristin/Dalfopristin). Monarch Pharmaceuticals Ireland Ltd. UK Summary of product characteristics, March 2005.

Retapamulin + Azoles

Ketoconazole increases the plasma levels and AUC of topical retapamulin. Other azoles may interact similarly.

Clinical evidence, mechanism, importance and management

The manufacturers note that the AUC and maximum plasma level of topical retapamulin ointment 1% applied to the abraded skin of healthy subjects was increased by 81% when they also took ketoconazole 200 mg twice daily.[1,2] However, this interaction is not expected to be clinically significant, and no dose adjustment of retapamulin is recommended due to its low systemic exposure following topical application.[1,2] Other azoles would be expected to interact similarly, or to a lesser extent.

1. Altargo (Retapamulin). GlaxoSmithKline UK. UK Summary of product characteristics, May 2007.
2. Altabax (Retapamulin). GlaxoSmithKline. US Prescribing information, May 2009.

Rifampicin (Rifampin) + Aminosalicylic acid

The serum levels of rifampicin are approximately halved if aminosalicylic acid granules containing bentonite are given.

Clinical evidence

In 30 patients with tuberculosis, the serum levels of rifampicin 10 mg/kg were reduced by more than 50% at 2 hours (from 6.06 to 2.91 micrograms/mL) by aminosalicylate.[1,2] Later studies in 6 healthy subjects found that this interaction was not due to the aminosalicylic acid itself but to the **bentonite**, which was the main excipient of the granules.[3] The rifampicin AUC was statistically unchanged in the presence of sodium aminosalicylate tablets (no **bentonite**), whereas it was reduced by more than 37% in the presence of **bentonite** from aminosalicylate granules.[3]

Other studies confirm this marked reduction in serum rifampicin levels in the presence of **bentonite** in aminosalicylic acid granules.[4]

Mechanism

The bentonite excipient in the aminosalicylic acid granules adsorbs the rifampicin onto its surface so that much less is available for absorption, which results in reduced serum levels.[3] Bentonite is a naturally occurring mineral (montmorillonite) consisting largely of hydrate aluminium silicate, and is similar to kaolin.

Importance and management

A well documented and clinically important interaction. Separating the administration of the two drugs by 8 to 12 hours to prevent their mixing in the gut has been suggested as an effective way to prevent this interaction.[1] Based on this interaction with rifampicin, one UK manufacturer of **rifabutin** gives the same administration advice.[5] An alternative is to give aminosalicylic acid preparations that do not contain bentonite.

1. Boman G, Hanngren Å, Malmborg A-S, Borgå O, Sjöqvist F. Drug Interaction: decreased serum concentrations of rifampicin when given with P.A.S. *Lancet* (1971) i, 800.
2. Boman G, Borgå O, Hanngren Å, Malmborg A-S and Sjöqvist F. Pharmacokinetic interactions between the tuberculostatics rifampicin, para-aminosalicylic acid and isoniazid. *Acta Pharmacol Toxicol (Copenh)* (1970) 28 (Suppl 1), 15.
3. Boman G, Lundgren P, Stjernström G. Mechanism of the inhibitory effect of PAS granules on the absorption of rifampicin: adsorption of rifampicin by an excipient, bentonite. *Eur J Clin Pharmacol* (1975) 8, 293–9.
4. Boman G. Serum concentration and half-life of rifampicin after simultaneous oral administration of aminosalicylic acid or isoniazid. *Eur J Clin Pharmacol* (1974) 7, 217–25.
5. Mycobutin (Rifabutin). Pharmacia Ltd. UK Summary of product characteristics, June 2009.

Rifampicin (Rifampin) + Antacids

The absorption of rifampicin can be reduced by up to about one-third by antacids.

Clinical evidence

When 5 healthy subjects took a single 600-mg dose of rifampicin with various antacids the absorption of rifampicin was reduced. The antacids caused a fall in the urinary excretion of rifampicin as follows:

- 15 or 30 mL of **aluminium hydroxide gel** 29 to 31%;
- 2 or 4 g of **magnesium trisilicate** 31 to 36%;
- 2 g of **sodium bicarbonate** 21%.[1]

Three groups of 15 patients with tuberculosis were given a single oral dose of rifampicin 10 to 12 mg/kg, isoniazid 300 mg and ethambutol 20 mg/kg either alone or with about 20 mL of antacid. A 'significant number' of patients had peak rifampicin concentrations below 6.5 micrograms/mL (serum level quoted as necessary to achieve adequate lung concentrations) in the group receiving *Aludrox* (**aluminium hydroxide**), but no significant effect was noted in the group receiving *Gelusil* (**aluminium hydroxide** with **magnesium trisilicate**).[2] However, in a further study in 14 healthy subjects, 30 mL of *Mylanta* (**aluminium**/**magnesium hydroxide**) given 9 hours before, with and after rifampicin had no effect on rifampicin pharmacokinetics.[3]

Mechanism

It has been suggested that the rise in stomach pH caused by these antacids reduces the dissolution of the rifampicin and thereby inhibits its absorption. In addition, aluminium ions may form less soluble chelates with rifampicin, and magnesium trisilicate can adsorb rifampicin, both of which would also be expected to reduce bioavailability.[1]

Importance and management

Direct information seems to be limited to these reports. The effects of 20 to 35% reductions in rifampicin absorption do not appear to have been assessed, but if antacids are given it would be prudent to be alert for any evidence that treatment is less effective than expected. The US manufacturers of rifampicin advise giving rifampicin one hour before antacids.[4]

1. Khalil SAH, El-Khordagui LK, El-Gholmy ZA. Effect of antacids on oral absorption of rifampicin. *Int J Pharmaceutics* (1984) 20, 99–106.
2. Gupta PR, Mehta YR, Gupta ML, Sharma TN, Jain D, Gupta RB. Rifampicin-aluminium antacid interaction. *J Assoc Physicians India* (1988) 36, 363–4.
3. Peloquin CA, Namdar R, Singleton MD, Nix DE. Pharmacokinetics of rifampin under fasting conditions, with food, and with antacids. *Chest* (1999) 115, 12–18.
4. Rifadin (Rifampicin). Sanofi-Aventis US LLC. US Prescribing information, March 2007.

Rifampicin (Rifampin) + Barbiturates

Phenobarbital possibly modestly increases the clearance of rifampicin. The effect of rifampicin on phenobarbital levels is

unknown, but rifampicin markedly increases the clearance of another barbiturate hexobarbital.

Clinical evidence, mechanism, importance and management

In one study, the serum levels of rifampicin were reduced by 20 to 40% in 12 of 15 patients taking **phenobarbital** 100 mg daily.[1] In another study, although **phenobarbital** 100 mg daily for 7 days reduced the mean half-life of a single 600-mg dose of rifampicin by 15%, this was not statistically significant. However, in a further 5 patients with cirrhosis of the liver, **phenobarbital** reduced the half-life of rifampicin by a mean of 2.2 hours.[2]

The effect of rifampicin on **phenobarbital** levels does not appear to have been studied, but rifampicin markedly increased the clearance of another barbiturate **hexobarbital**, which is used as a marker of drug metabolism.[3-6]

The evidence for an interaction between rifampicin and the barbiturates is limited. Both rifampicin and the barbiturates are potent liver enzyme inducers. The outcome of their effects when combined is not clear from the available data, but a reduction in the levels of both drugs seems possible. Concurrent use need not be avoided, but be alert for a reduced response to both the barbiturate and rifampicin.

1. de Rautlin de la Roy Y, Beauchant G, Breuil K, Patte F. Diminution du taux sérique de rifampicine par le phénobarbital. *Presse Med* (1971) 79, 350.
2. Acocella G, Bonollo L, Mainardi M, Margaroli P, Nicolis FB. Kinetic studies on rifampicin. III. Effect of phenobarbital on the half-life of the antibiotic. *Tijdschr Gastroenterol* (1974) 17, 151–8.
3. Breimer DD, Zilly W, Richter E. Influence of rifampicin on drug metabolism: differences between hexobarbital and antipyrine. *Clin Pharmacol Ther* (1977) 21, 470–81.
4. Zilly W, Breimer DD, Richter E. Induction of drug metabolism in man after rifampicin treatment measured by increased hexobarbital and tolbutamide clearance. *Eur J Clin Pharmacol* (1975) 9, 219–27.
5. Zilly W, Breimer DD, Richter E. Stimulation of drug metabolism by rifampicin in patients with cirrhosis or cholestasis measured by increased hexobarbital and tolbutamide clearance. *Eur J Clin Pharmacol* (1977) 11, 287–93.
6. Smith DA, Chandler MHH, Shedlofsky SI, Wedlund PJ, Blouin RA. Age-dependent stereoselective increase in the oral clearance of hexobarbitone isomers caused by rifampicin. *Br J Clin Pharmacol* (1991) 32, 735–9.

Rifampicin (Rifampin) + Clofazimine

Clofazimine does not affect the pharmacokinetics of rifampicin and rifampicin does not affect the bioavailability of clofazimine.

Clinical evidence, mechanism, importance and management

Clofazimine 100 mg daily, given to 15 patients with leprosy taking rifampicin 600 mg daily and dapsone 100 mg daily, had no effect on the pharmacokinetics of rifampicin.[1] A single-dose study found that the bioavailability of clofazimine remained unaltered when rifampicin was given, although a reduction in the rate of absorption was seen.[2] No special precautions would seem to be necessary on concurrent use.

1. Venkatesan K, Mathur A, Girdhar BK, Bharadwaj VP. The effect of clofazimine on the pharmacokinetics of rifampicin and dapsone in leprosy. *J Antimicrob Chemother* (1986) 18, 715–18.
2. Mehta J, Gandhi IS, Sane SB, Wamburkar MN. Effect of clofazimine and dapsone on rifampicin (Lositril) pharmacokinetics in multibacillary and paucibacillary leprosy cases. *Indian J Lepr* (1985) 57, 297–310.

Rifampicin (Rifampin) + Food

Food delays and reduces the absorption of rifampicin from the gut.

Clinical evidence

The absorption of a single 10-mg/kg dose of rifampicin was reduced when it was given to 6 healthy subjects with a standard Indian breakfast (125 g wheat, 10 g visible fat, 350 g vegetables). The AUC after 8 hours was reduced by 26% and the peak plasma levels were delayed, and reduced by about 30% (from 11.84 micrograms/mL at 2 hours to 8.35 micrograms/mL at 4 hours).[1] In another study, a high-fat breakfast reduced the maximum serum level of rifampicin 600 mg by 36% and delayed the absorption, but the AUC was not significantly altered.[2]

Mechanism

Not understood.

Importance and management

An established interaction. Rifampicin should be taken on an empty stomach (at least 30 minutes before a meal, or 2 hours after a meal) to ensure rapid and complete absorption.

1. Polasa K, Krishnaswamy K. Effect of food on bioavailability of rifampicin. *J Clin Pharmacol* (1983) 23, 433–7.
2. Peloquin CA, Namdar R, Singleton MD, Nix DE. Pharmacokinetics of rifampin under fasting conditions, with food, and with antacids. *Chest* (1999) 155, 12–18.

Rifampicin (Rifampin) + Probenecid

Probenecid increased rifampicin levels in one study, but not in another.

Clinical evidence, mechanism, importance and management

A study in 6 healthy subjects given probenecid 2 g, before and after a single 300-mg dose of rifampicin, found that probenecid increased the mean peak serum rifampicin levels by 86%. At 4, 6, and 9 hours after the dose the increases were 118%, 90%, and 102%, respectively.[1] However, subsequent studies in patients taking either rifampicin 600 mg daily, or rifampicin 300 mg daily given 30 minutes after a 2-g dose of probenecid, found that the probenecid group achieved serum rifampicin levels that were only about half of those achieved in patients taking rifampicin 600 mg alone, suggesting that no interaction occurred.[2] The reasons for these discordant results are not understood, although it has been suggested that erratic rifampicin absorption may have played a part.[2] The interaction is not proven, but it seems possible that some patients will experience a rise in rifampicin levels. Consider this interaction as a possible cause if rifampicin adverse effects are troublesome.

1. Kenwright S, Levi AJ. Impairment of hepatic uptake of rifamycin antibiotics by probenecid, and its therapeutic implications. *Lancet* (1973) ii, 1401–5.
2. Fallon RJ, Lees AW, Allan GW, Smith J, Tyrrell WF. Probenecid and rifampicin serum levels. *Lancet* (1975) ii, 792–4.

Sulfonamides + Local anaesthetics

Para-aminobenzoic acid, derived from certain local anaesthetics, can reduce the effects of the sulfonamides and allow the development of local and even generalised infections. However, it should be noted that the limited evidence for this interaction is from the 1940s.

Clinical evidence

Four patients taking sulfonamides developed local infections in areas where **procaine** had been injected before diagnostic taps for meningitis, or draining procedures in empyema. Extensive cellulitis of the lumbar region occurred in one case, and abscesses appeared at the puncture sites in another. However, it should be noted that lumbar punctures were being done at least daily and up to four times a day in the 3 patients with meningitis.[1]

An *in vitro* study demonstrated that the amount of **procaine** in the pleural fluid after anaesthesia for thoracentesis was sufficient to inhibit the antibacterial activity of 0.005% **sulfapyridine** against type III pneumococci.[2] Another *in vitro* study found that some local anaesthetics derived from para-aminobenzoic acid (PABA) inhibited the bacteriostatic activity of **sulfapyridine** and **sulfathiazole** but some other local anaesthetics not derived from PABA did not affect the antibacterial activity of these sulfonamides.[3] Other studies in *animals* confirm that both *in vitro*[4-6] and *in vivo*[7] antagonism can occur between sulfonamides and local anaesthetics that are hydrolysed to **PABA**.

Mechanism

The ester type of local anaesthetic is hydrolysed within the body to produce para-aminobenzoic acid (PABA). Sulfonamides work by inhibiting bacterial DNA synthesis by competitively inhibiting folate production. The PABA competes with the sulfonamides, so higher PABA concentrations effectively dilute the effects of the sulfonamides.

Importance and management

Clinical examples of this interaction seem to be few and of poor quality (note that the patients were given repeated lumbar punctures, up to four times daily in some instances). It should also be noted that the supporting evidence (human, *animal* and *in vitro* studies) dates back to the mid-1940s with nothing more recent apparently on record. Local anaesthetics of the ester type that are hydrolysed to para-aminobenzoic acid (e.g. tetracaine, procaine, benzocaine) present the greatest risk of a reaction, whereas those of the amide type (bupivacaine, cinchocaine, lidocaine, mepivacaine and prilocaine) would not be expected to interact adversely. The evidence seems to be too slim to preclude concurrent use of these drugs, but it is perhaps worth considering this interaction if high or repeated doses of the local anaesthetic are used. However, note that high doses or prolonged use of these ester-type anaesthetics are best avoided given their toxicity when used in this manner.

1. Peterson OL, Finland M. Sulfonamide inhibiting action of procaine. *Am J Med Sci* (1944) 207, 166–75.
2. Boroff DA, Cooper A, Bullowa JGM. Inhibition of sulfapyridine by procaine in chest fluids after procaine anesthesia. *Proc Soc Exp Biol Med* (1941) 47,182–3.
3. Keltch AK, Baker LA, Krahl ME, Clowes GHA. Anti-sulfapyridine and anti-sulfathiazole effect of local anaesthetics derived from p-aminobenzoic acid. *Proc Soc Exp Biol Med* (1941) 47, 533–8.
4. Casten D, Fried JJ, Hallman FA. Inhibitory effect of procaine on the bacteriostatic activity of sulfathiazole. *Surg Gynecol Obstet* (1943) 76, 726–8.
5. Powell HM, Krahl ME, Clowes GHA. Inhibition of chemotherapeutic action of sulfapyridine by local anesthetics. *J Indiana State Med Assoc* (1942) 35, 62–3.
6. Walker BS, Derow MA. The antagonism of local anesthetics against the sulfonamides. *Am J Med Sci* (1945) 210, 585–8.
7. Pfeiffer CC, Grant CW. The procaine-sulfonamide antagonism: an evaluation of local anesthetics for use with sulfonamide therapy. *Anesthesiology* (1944) 5, 605–14.

Sulfonamides; Sulfafurazole (Sulfisoxazole) + Laxatives

Sodium sulfate and castor oil used as laxatives can cause a modest reduction in sulfafurazole absorption.

Clinical evidence, mechanism, importance and management

In an experimental study of the possible effects of laxatives on the absorption of sulfafurazole, healthy subjects were given 10 to 20 g of oral **sodium sulfate** or 20 g of **castor oil** (doses sufficient to provoke diarrhoea). Absorption, measured by the amount of sulfafurazole excreted in the urine, was decreased by 50% with **castor oil**, and by 33% with **sodium sulfate** at 4 hours. However, serum levels of the drugs were relatively unchanged. The overall picture was that while these laxatives can alter the pattern of absorption, they do not seriously impair the total amount of drug absorbed.[1]

1. Mattila MJ, Takki S, Jussila J. Effect of sodium sulphate and castor oil on drug absorption from the human intestine. *Ann Clin Res* (1974) 6, 19–24.

Tetracyclines + Antacids

The serum levels and therefore the therapeutic effectiveness of the tetracyclines can be markedly reduced or even abolished by antacids containing aluminium, bismuth, calcium or magnesium. Other antacids, such as sodium bicarbonate, may also reduce the bioavailability of some tetracyclines. Even intravenous doxycycline levels can be reduced by antacids.

Clinical evidence

(a) Aluminium-containing antacids

A study in 5 patients and 6 healthy subjects found that within 48 hours of starting to take about 10 mL of aluminium hydroxide gel (*Amphogel*) every 6 hours with **chlortetracycline** 500 mg the serum levels of the antibacterial were reduced by 80 to 90%. One patient had a recurrence of her urinary tract infection, which only subsided when the antacid was withdrawn, and one patient maintained **chlortetracycline** levels despite antacid use.[1] Similar results were obtained in other studies.[2,3]

Further studies have found similar interactions with other tetracyclines:

- 30 mL of aluminium hydroxide reduced **oxytetracycline** serum levels by more than 50%,[3]
- 20 mL of aluminium hydroxide caused a 75% reduction in **demeclocycline** serum levels,[4]
- 15 mL of aluminium hydroxide caused a 100% reduction in serum **doxycycline** levels,[5,6]
- 30 mL of aluminium/magnesium hydroxide (*Maalox*) caused a 90% reduction in **tetracycline** serum levels.[7]

Intravenous doxycycline also appears to be affected. The mean serum levels of an intravenous dose of **doxycycline** were found to be reduced by 36% when 30 mL of aluminium hydroxide was taken four times daily, for 2 days before and after the antibacterial.[8]

(b) Bismuth-containing antacids

Bismuth subsalicylate reduces the absorption of **tetracycline** by 34%[9] and reduces the maximum serum levels of **doxycycline** by 50%.[10] It has been suggested the excipient *Veegum* (magnesium aluminium silicate) in some bismuth subsalicylate formulations enhances this effect.[11] Bismuth carbonate similarly interacts with the tetracyclines *in vitro*.[12] An observation that patients given metronidazole, with bismuth and **tetracycline** taken at the same time, experienced a *Helicobacter pylori* eradication rate greater than that achieved with metronidazole and bismuth has led to the suggestion that the reduced absorption of **tetracycline** may not be as clinically relevant in the treatment of this disorder.[13]

(c) Calcium-containing antacids

There seem to be no direct clinical studies with calcium-containing antacids, but a clinically important interaction seems almost a certainty, based on *in vitro* studies with calcium carbonate,[12] calcium in milk, (see 'Tetracyclines + Food', p.390), dicalcium phosphate,[14] and calcium as an excipient in tetracycline capsules.[15]

(d) Magnesium-containing antacids

Magnesium sulfate certainly interacts with **tetracycline**, but in the only clinical study available[16] the amount of magnesium was much higher than would normally be found in the usual dose of antacid. It has been suggested the excipient *Veegum* (magnesium aluminium silicate) enhances the effect of some bismuth subsalicylate formulations on **tetracycline** absorption,[11] and in one study, 30 mL of aluminium/magnesium hydroxide (*Maalox*) caused a 90% reduction in **tetracycline** serum levels.[7]

(e) Sodium-containing antacids

In 8 subjects, sodium bicarbonate 2 g reduced the absorption of a 250-mg capsule of **tetracycline** by 50%. However, if the **tetracycline** was dissolved before administration, the absorption was unaffected by sodium bicarbonate.[17] Another study stated that sodium bicarbonate 2 g had an insignificant effect on **tetracycline** absorption.[7]

Mechanism

The tetracyclines bind with aluminium, bismuth, calcium, magnesium and other metallic ions to form compounds (chelates), which are much less soluble and therefore much less readily absorbed by the gut.[18] Because doxycycline undergoes enterohepatic recirculation, even intravenous doxycycline is affected, although less so than oral. It has also been suggested that the antacids reduce gastric acidity and thereby decrease the absorption of tetracyclines,[17] but studies demonstrating the lack of a significant interaction with 'H_2-receptor antagonists', (p.390), suggest that this is not the case. The reduced absorption with bismuth compounds may be because they adsorb tetracyclines.[9] The interaction of some tetracycline preparations with sodium bicarbonate is unexplained.

Importance and management

Extremely well-documented, and well-established interactions. Their clinical importance depends on how much the serum tetracycline levels are lowered, but with normal antacid doses the reductions cited above (50 to 100%) are large enough to mean that many organisms will not be exposed to minimum inhibitory concentrations (MIC) of antibacterial. As a general rule none of the aluminium, bismuth, calcium or magnesium-containing antacids should be given at the same time as the tetracycline antibacterials. If they must be used, separate the doses by 2 to 3 hours or more to prevent their admixture in the gut. This also applies to **quinapril** formulations containing substantial quantities of magnesium (such as *Accupro*), although the interaction is less pronounced (see 'Tetracyclines + Quinapril', p.392), and to **didanosine** tablets that are formulated with antacid.[19] The enteric-coated capsule formulation (which does not contain antacids) is not expected to interact.[20]

Patients should be warned about taking any antacids and indigestion preparations at the same time as tetracyclines. Instead of using antacids to minimise the gastric irritant effects of the tetracyclines it is usually recommended that tetracyclines are taken after food; however, it is not entirely clear how much this affects their absorption (see 'Tetracyclines + Food', p.390). H_2-receptor antagonists may be suitable non-interacting alternatives to antacids in some situations, see 'Tetracyclines + H_2-receptor antagonists', p.390.

1. Waisbren BA, Hueckel JS. Reduced absorption of aureomycin caused by aluminum hydroxide gel (*Amphojel*). *Proc Soc Exp Biol Med* (1950) 73, 73–4.
2. Seed JC, Wilson CE. The effect of aluminum hydroxide on serum aureomycin concentrations after simultaneous oral administration. *Bull Johns Hopkins Hosp* (1950) 86, 415–8.
3. Michel JC, Sayer RJ, Kirby WMM. Effect of food and antacids on blood levels of aureomycin and terramycin. *J Lab Clin Med* (1950) 36, 632–4.
4. Scheiner J, Altemeier WA. Experimental study of factors inhibiting absorption and effective therapeutic levels of declomycin. *Surg Gynecol Obstet* (1962) 114, 9–14.
5. Rosenblatt JE, Barrett JE, Brodie JL, Kirby WMM. Comparison of in vitro activity and clinical pharmacology of doxycycline with other tetracyclines. *Antimicrob Agents Chemother* (1966) 6, 134–41.
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17. Barr WH, Adir J, Garrettson L. Decrease of tetracycline absorption in man by sodium bicarbonate. *Clin Pharmacol Ther* (1971) 12, 779–84.
18. Albert A, Rees CW. Avidity of the tetracyclines for the cations of metals. *Nature* (1956) 177, 433–4.
19. Videx Tablets (Didanosine). Bristol-Myers Squibb Pharmaceuticals Ltd. UK Summary of product characteristics, August 2008.
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Tetracyclines + Antiepileptics; Enzyme-inducing

The serum levels of doxycycline are reduced and may fall below the accepted minimum inhibitory concentration in patients receiving long-term treatment with barbiturates, phenytoin or carbamazepine. Other tetracyclines do not appear to be affected.

Clinical evidence

A study in 14 patients taking **phenytoin** 200 to 500 mg daily, **carbamazepine** 300 mg to 1 g daily, or both, found that the half-life of **doxycycline** was approximately halved from 15.1 hours in patients not taking antiepileptics, to 7.2 hours in patients taking **phenytoin**, 8.4 hours in patients taking **carbamazepine**, and 7.4 hours in patients taking both drugs.[1]

Similar results were found in 16 other patients taking various combinations of **phenytoin**, **carbamazepine**, **primidone** or **phenobarbital**. The serum **doxycycline** levels of almost all of them fell below 0.5 micrograms/mL during the 12- to 24-hour period following their last dose of **doxycycline** 100 mg.[2] Other studies confirm this interaction between some **barbiturates** (**amobarbital**, **pentobarbital**, **phenobarbital**) and **doxycycline**.[3,4]

Tetracycline, **methacycline**, **oxytetracycline**, **demeclocycline** and **chlortetracycline** levels were not significantly affected by various combinations of **phenytoin**, **carbamazepine**, **primidone** or **phenobarbital**.[2]

Mechanism

Uncertain. These antiepileptics and barbiturates are known enzyme inducers and it seems probable that they increase the metabolism of the doxycycline by the liver, thereby increasing its clearance from the body.

Importance and management

The interactions between doxycycline and the enzyme-inducing antiepileptics are established, but the clinical significance of the reduction in levels does not seem to have been studied. Serum doxycycline levels below 0.5 micrograms/mL are less than the minimum inhibitory concentration (MIC) quoted by the authors, so that it seems likely that the antibacterial will be less effective. To accommodate this potential problem it has been suggested that the doxycycline dose could be doubled.[2] Alternatively any of the tetracyclines that are reported not to be affected by these antiepileptics (tetracycline, methacycline, oxytetracycline, demeclocycline and chlortetracycline) may provide a suitable alternative.[2]

1. Penttilä O, Neuvonen PJ, Aho K, Lehtovaara R. Interaction between doxycycline and some antiepileptic drugs. *BMJ* (1974) 2, 470–2.
2. Neuvonen PJ, Penttilä O, Lehtovaara R, Aho K. Effect of antiepileptic drugs on the elimination of various tetracycline derivatives. *Eur J Clin Pharmacol* (1975) 9, 147–54.
3. Neuvonen PJ, Penttilä O. Interaction between doxycycline and barbiturates. *BMJ* (1974) 1, 535–6.
4. Alestig K. Studies on the intestinal excretion of doxycycline. *Scand J Infect Dis* (1974) 6, 265–71.

Tetracyclines + Colestipol

Colestipol can reduce the absorption of tetracycline by about a half. Information about other tetracyclines is lacking but it seems likely that they will interact similarly.

Clinical evidence

In 9 healthy subjects, colestipol 30 g taken either in 180 mL of water or orange juice reduced the absorption of a single 500-mg dose of oral **tetracycline** by about 55%, as measured by recovery in the urine.[1]

Mechanism

Colestipol binds to bile acids in the gut and can also bind with some drugs, thereby reducing their availability for absorption. An *in vitro* study found a 30% binding with tetracycline.[2] The presence of citrate ions in the orange juice, which can also bind to colestipol, appears not to have a marked effect on the binding of the tetracycline.

Importance and management

An established interaction. Direct information seems to be limited to the report cited, but it is consistent with the way colestipol interacts with other drugs. In practice up to 30 g of colestipol is given daily in single or twice daily, in divided doses, and tetracycline 250 to 500-mg is given every 6 hours. As other drugs need to be given one hour before or 4 hours after colestipol it may be difficult to avoid some mixing in the gut. It seems very probable that a clinically important interaction will occur, but the extent to which the efficacy of tetracycline is affected seems not to have been determined. Advise patients to separate the doses as much as possible. Monitor the outcome well. Information about other tetracyclines is lacking but it also seems likely that they will interact similarly, but those that can be given less often may prove easier to administer, although note that doxycycline undergoes enterohepatic recirculation and therefore separating doses may not be completely effective.

1. Friedman H, Greenblatt DJ, LeDuc BW. Impaired absorption of tetracycline by colestipol is not reversed by orange juice. *J Clin Pharmacol* (1989) 29, 748–51.
2. Ko H, Royer ME. *In vitro* binding of drugs to colestipol hydrochloride. *J Pharm Sci* (1974) 63, 1914–20.

Tetracyclines + Diuretics

It has been recommended by some that the concurrent use of tetracyclines and diuretics should be avoided because of their association with rises in blood urea nitrogen levels.

Clinical evidence, mechanism, importance and management

A retrospective study of patient records as part of the Boston Collaborative Drug Surveillance Program showed that an association existed between tetracycline use with diuretics (not named) and rises in blood urea nitrogen (BUN) levels.[1] It was suggested that tetracyclines should be avoided in patients taking diuretics when alternative antibacterials could be substitut-

ed.[1] However, the results of this study have been much criticised as the authors could not exclude physician bias,[1,2] they did not define what was meant by 'clinically significant rise in BUN',[2] they did not state whether or not this rise affected patient outcomes,[2] they did not measure creatinine levels,[3] they did not specify which diuretics were involved,[2] and they did not adequately consider the fact that diuretics are known to cause rises in BUN.[4] The patients most affected also had the highest levels of BUN before starting tetracyclines. Tetracyclines alone are known to cause rises in BUN, especially where a degree of renal impairment exists, although it has been suggested that **doxycycline** is less prone to this effect.[4] It would seem that tetracyclines and diuretics may be used together safely, although it would be wise to give thought to the patient's renal function.

1. Boston Collaborative Drug Surveillance Program. Tetracycline and drug-attributed rises in blood urea nitrogen. *JAMA* (1972) 220, 377–9.
2. Tannenberg AM. Tetracyclines and rises in urea nitrogen. *JAMA* (1972) 221, 713.
3. Dijkhuis HJPM, van Meurs AJ. Tetracycline and BUN level. *JAMA* (1973) 223, 441.
4. Alexander MR. Tetracyclines and rises in urea nitrogen. *JAMA* (1972) 221, 713–14.

Tetracyclines + Food

The calcium in food can complex with tetracycline to reduce its absorption. This is particularly notable with dairy products, which can reduce the absorption of the tetracyclines by up to 80%, thereby reducing or even abolishing their therapeutic effects. Doxycycline and minocycline are less affected by dairy products (25 to 30% reduction) and lymecycline is not affected by milk. Orange juice and coffee do not interact with tetracycline.

Clinical evidence

(a) Dairy products

1. Demeclocycline. In 4 subjects given dairy products the serum levels of a 300-mg dose of demeclocycline were 70 to 80% lower, when compared with subjects who took demeclocycline with a meal containing no dairy products. The dairy products used were either 8 oz (about 250 mL) of **fresh pasteurized milk**, 8 oz of **buttermilk** or 4 oz of **cottage cheese**.[1]

2. Doxycycline. The plasma doxycycline levels were reduced by 20%, from 1.79 micrograms/mL to 1.45 micrograms/mL, 2 hours after a single 100-mg oral dose was taken with 240 mL of **milk**.[2] Another study, in 9 healthy subjects, found a 30% reduction in the absorption of doxycycline 200 mg, and a 24% reduction in its peak serum levels when it was taken with 300 mL of **fresh milk**.[3] However, two other studies suggest that the absorption of doxycycline 200 mg is unaffected by milk,[4,5] although in one study the half-life was almost halved and its clearance increased.[5]

3. Lymecycline. In 10 healthy subjects the absorption of lymecycline 300 mg twice daily has not been shown to be significantly affected by 300 g of **milk**.[6]

4. Methacycline. In one study 300 mL of **milk** reduced the absorption of methacycline 300 mg by about 63%.[4]

5. Minocycline. In one study about 180 mL (6 oz) of **homogenised milk** reduced the absorption of minocycline 100 mg by 27%.[7]

6. Oxytetracycline. In one study 300 mL of **milk** reduced the absorption of oxytetracycline 500 mg by about 64%.[4]

7. Tetracycline. In one study about 180 mL (6 oz) of **homogenised milk** reduced the absorption of tetracycline hydrochloride 250 mg by 65%.[7] In another study the absorption of tetracycline 500 mg was reduced by about 50% by 300 mL of **milk**.[4] The addition of 16 mL **evaporated milk** to tea and coffee reduced the bioavailability of a single 250-mg dose of tetracycline by about 40 to 50%.[8]

(b) Other calcium-containing foods or drinks

A study in 9 healthy subjects found that 200 mL of **orange juice** or **coffee** (milk content, if any, unstated) did not significantly affect the bioavailability of a single 250-mg dose of **tetracycline**. This is despite the fact that **orange juice** contains 35 to 70 mg calcium per 100 mL.[9]

Tetracycline 250 mg was given to 9 healthy subjects with 200 mL of water on an empty stomach. The **tetracycline** bioavailability was compared with its administration after a standard meal (two slices of bread, ham, tomato, and water, containing 145 mg calcium) and a Mexican meal (two tortillas, beans, two eggs, tomato and water, containing 235 mg calcium). The cumulative amounts of tetracycline excreted in the urine at 72 hours were about 151 mg (fasting), 90 mg (standard meal) and 68 mg (Mexican meal).[10] Another study in 23 healthy subjects also found a reduction in the maximum **tetracycline** plasma levels and AUC when it was taken with food.[11] A brief report describes a 14% reduction in the bioavailability of **minocycline** when 12 healthy subjects took **minocycline** with a standard meal, although there was wide inter-individual variation in the findings.[12] The absorption of a 300-mg dose of **demeclocycline** was not affected when it was given with a meal not containing dairy products,[1] and **doxycycline** seems to be minimally affected by food not containing dairy products.[2]

Mechanism

The tetracyclines have a strong affinity for the calcium ions that are found in abundance in dairy products and some foodstuffs. The tetracycline/calcium chelates formed are much less readily absorbed from the gastrointestinal tract and as a result the serum tetracycline levels achieved are much lower. Some tetracyclines have a lesser tendency to form chelates, which explains why their serum levels are reduced to a smaller extent.[13]

Orange juice appears not to interact, despite its calcium content, because at the relevant pH values in the gut, the calcium is bound to components within the orange juice (citric, tartaric and ascorbic acids) and is not free to combine with the tetracycline.[9]

Importance and management

Well documented and very well established interactions of clinical importance. Reductions in serum tetracycline levels of 50 to 80% caused by calcium-rich foods are sufficiently large to reduce or even abolish their antibacterial effects. For this reason tetracyclines should not be taken with milk or dairy products such as yoghurt or cheese. Separate the ingestion of these foods and tetracycline as much as possible. In the case of iron, which interacts by the same mechanism, 2 to 3 hours is enough. Doxycycline[3,14] and minocycline[7] are not affected as much by dairy products (reductions of about 25 to 30%), and lymecycline appears unaffected, and in this respect they may have some advantages over the other tetracyclines.

It is usual to recommend that tetracyclines are taken one hour before or 2 hours after food (which would be expected to contain at least some calcium), to minimise admixture in the gut and thereby reduce the effects of the interaction. The separation is something of a compromise, because food can help to minimise the gastric irritant effects of the tetracyclines.

1. Scheiner J, Altemeier WA. Experimental study of factors inhibiting absorption and effective therapeutic levels of declomycin. *Surg Gynecol Obstet* (1962) 114, 9–14.
2. Rosenblatt JE, Barrett JE, Brodie JL, Kirby WMM. Comparison of in vitro activity and clinical pharmacology of doxycycline with other tetracyclines. *Antimicrob Agents Chemother* (1966) 6, 134–41.
3. Meyer FP, Specht H, Quednow B, Walther H. Influence of milk on bioavailability of doxycycline — new aspects. *Infection* (1989) 17, 245–6.
4. Mattila MJ, Neuvonen PJ, Gothoni G, Hackman CR. Interference of iron preparations and milk with the absorption of tetracyclines. *Int Congr Ser* (1972) 254, 128–33.
5. Saux M-C, Mosser J, Pontagnier H, Leng B. Pharmacokinetic study of doxycycline polyphosphate after simultaneous ingestion of milk. *Eur J Drug Metab Pharmacokinet* (1983) 8, 43–9.
6. Ericson S, Gnarpe H. Lymecycline and concurrent ingestion of milk. *J Int Med Res* (1979) 7, 471–2.
7. Leyden JJ. Absorption of minocycline hydrochloride and tetracycline hydrochloride. Effect of food, milk, and iron. *J Am Acad Dermatol* (1985) 12, 308–12.
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9. Jung H, Rivera O, Reguero MT, Rodríguez JM, Moreno-Esparza R. Influence of liquids (coffee and orange juice) on the bioavailability of tetracycline. *Biopharm Drug Dispos* (1990) 11, 729–34.
10. Cook HJ, Mundo CR, Fonseca L, Gasque L, Moreno-Esparza R. Influence of the diet on bioavailability of tetracycline. *Biopharm Drug Dispos* (1993) 14, 549–53.
11. Spénard J, Aumais C, Massicotte J, Brunet J-S, Tremblay C, Grace M, Lefebvre M. Effects of food and formulation on the relative bioavailability of bismuth biskalcitrate, metronidazole, and tetracycline given for *Helicobacter pylori* eradication. *Br J Clin Pharmacol* (2005) 60, 374–7.
12. Meyer FP. Minocycline for acne. Food reduces minocycline's bioavailability. *BMJ* (1996) 312, 1101.
13. Albert A, Rees CW. Avidity of the tetracyclines for the cations of metals. *Nature* (1956) 177, 433–4.
14. Siewert M, Blume H, Stenzhorn G, Kieferndorf U, Lenhard G. Zur Qualitätsbeurteilung von doxycyclinhaltigen ertigarzneimitteln. 3. Mitteilung: Vergleichende Bioverfügbarkeitsstudie unter Berücksichtigung einer Einnahme mit Milch. *Pharm Ztg* (1990) 3, 96–102.

Tetracyclines + H_2-receptor antagonists

Cimetidine reduces the absorption of tetracycline but does not appear to affect its serum levels. Ranitidine does not appear to affect the bioavailability of doxycycline. Information about other tetra-

cyclines and H_2-receptor antagonists is lacking, but there would seem to be no reason to suspect that they will interact.

Clinical evidence, mechanism, importance and management

A study in 5 subjects found that **cimetidine** 200 mg three times daily and 400 mg at bedtime for 3 days reduced the absorption of a single 500-mg dose of a **tetracycline** capsule by about 30%, but had no effect on absorption when the **tetracycline** was given as a solution.[1] However, when **tetracycline** as either a tablet or a suspension was given to 6 subjects with **cimetidine** 1.6 g daily for 6 days, no changes in the plasma levels of **tetracycline** were seen.[2] Similar results were found in another study.[3]

In 10 healthy subjects, the bioavailability of **doxycycline** 200 mg was not altered by three 150-mg doses of **ranitidine**.[4]

No special precautions would seem necessary with either combination. Information about other tetracyclines seems to be lacking, but there would seem to be no reason to suspect that they will interact.

1. Cole JJ, Charles BG, Ravenscroft PJ. Interaction of cimetidine with tetracycline absorption. *Lancet* (1980) ii, 536.
2. Fisher P, House F, Inns P, Morrison PJ, Rogers HJ, Bradbrook ID. Effect of cimetidine on the absorption of orally administered tetracycline. *Br J Clin Pharmacol* (1980) 9, 153–8.
3. Garty M, Hurwitz A. Effect of cimetidine and antacids on gastrointestinal absorption of tetracycline. *Clin Pharmacol Ther* (1980) 28, 203–7.
4. Deppermann K-M, Lode H, Höffken G, Tschink G, Kalz C, Koeppe P. Influence of ranitidine, pirenzepine, and aluminum magnesium hydroxide on the bioavailability of various antibiotics, including amoxicillin, cephalexin, doxycycline, and amoxicillin-clavulanic acid. *Antimicrob Agents Chemother* (1989) 33, 1901–7.

Tetracyclines + Iron compounds

The absorption of both the tetracyclines and iron compounds is markedly reduced by concurrent use, leading to reduced serum levels of the tetracyclines. Their therapeutic effectiveness may be reduced or even abolished.

Clinical evidence

(a) Effect on tetracyclines

An investigation in 10 healthy subjects given single oral doses of tetracyclines found that **ferrous sulfate** 200 mg decreased the serum antibacterial levels as follows: **doxycycline** 200 mg, 80 to 90%; **methacycline** 300 mg, 80 to 85%; **oxytetracycline** 500 mg, 50 to 60% and **tetracycline** 500 mg, 40 to 50%.[1] Another study in two groups of 8 healthy subjects found that **ferrous sulfate** 300 mg reduced the absorption of **tetracycline** and **minocycline** by 81% and 77%, respectively.[2]

Other studies found that in some instances iron caused the tetracycline serum levels to fall below minimum bacterial inhibitory concentrations.[3,4] If the iron was given 3 hours before or 2 hours after most tetracyclines the serum levels were not significantly reduced.[3-5] However, even when the iron was given up to 11 hours after **doxycycline**, serum concentrations were still lowered by 20 to 45%.[5] In contrast to this, another study found that four doses of **ferrous sulfate** (each equivalent to 80 mg of elemental iron) starting 11.5 hours after doxycycline did not affect the absorption of a 200-mg dose of **doxycycline**, and only reduced the AUC of a 100-mg dose of **doxycycline** by 17%.[6]

In 22 patients, an **iron polymaltose** complex, equivalent to 100 mg elemental iron, had no clinically significant effect on the pharmacokinetics of a single 500-mg dose of **tetracycline**.[7]

(b) Effect on iron

When **ferrous sulfate** 250 mg (equivalent to 50 mg of elemental iron) was given with **tetracycline** 500 mg, the absorption of iron was reduced by up to 78% in healthy subjects, and up to 65% in those with depleted iron stores.[8,9]

There was no change in the iron uptake into erythrocytes in 22 patients when an **iron polymaltose** complex, equivalent to 100 mg elemental iron, was given with a single 500-mg dose of **tetracycline**.[10]

Mechanism

The tetracyclines have a strong affinity for iron and form poorly soluble tetracycline/iron chelates, which are much less readily absorbed by the gut, and as a result the serum tetracycline levels achieved are much lower.[11,12] There is also less free iron available for absorption. Separating the administration of the two prevents their admixture.[3,4] However, doxycycline undergoes enterohepatic recycling, which could affect any attempt to keep the iron and antibacterial apart, although the significance of the enterohepatic recycling has been said to be minimal.[6] Even when given intravenously the half-life of doxycycline is reduced.[5] The different extent to which iron compounds interact with the tetracyclines appears to be a reflection of their ability to liberate ferrous and ferric ions, which are free to combine with the tetracycline.[13]

Importance and management

The interactions between the tetracyclines and iron compounds are well-documented, well-established, and of clinical importance. The 30 to 90% reductions in serum tetracycline levels that are caused by iron are so large that tetracycline levels may fall below the MIC.[4] However, the extent of the reductions depends on a number of factors.

- *the particular tetracycline used:* tetracycline and oxytetracycline in the study cited above were the least affected.[1]
- *the time-interval between the administration of the two drugs:* giving the iron 3 hours before or 2 to 3 hours after the antibacterial is satisfactory with tetracycline itself,[3] but one study found that even 11 hours was inadequate for doxycycline.
- *the particular iron preparation used:* with tetracycline the reduction in serum levels with ferrous sulfate was 80 to 90%, with **ferrous fumarate**, **succinate** and **gluconate**, 70 to 80%; with **ferrous tartrate**, 50%; and with **ferrous sodium edetate**, 30%. This was with doses containing equivalent amounts of elemental iron.[13] The small studies with **iron polymaltose** indicate that this preparation may have minimal interaction with tetracycline.

The interaction can therefore be accommodated by separating the doses as much as possible. It would also seem logical to choose one of the iron preparations causing minimal interference, but it seems unlikely that there will be a clinically significant difference between those that are commonly available (i.e. sulfate, fumarate and gluconate).

Only tetracycline, oxytetracycline, methacycline, minocycline and doxycycline have been shown to interact with iron, but it seems reasonable to expect that the other tetracyclines will behave in a similar way.

1. Neuvonen PJ, Gothoni G, Hackman R, Björksten K. Interference of iron with the absorption of tetracyclines in man. *BMJ* (1970) 4, 532–4.
2. Leyden JJ. Absorption of minocycline hydrochloride and tetracycline hydrochloride. Effect of food, milk, and iron. *J Am Acad Dermatol* (1985) 12, 308–12.
3. Mattila MJ, Neuvonen PJ, Gothoni G, Hackman CR. Interference of iron preparations and milk with the absorption of tetracyclines. *Int Congr Ser* (1972) 254, 128–33.
4. Gothoni G, Neuvonen PJ, Mattila M, Hackman R. Iron-tetracycline interaction: effect of time interval between the drugs. *Acta Med Scand* (1972) 191, 409–11.
5. Neuvonen PJ, Penttilä O. Effect of oral ferrous sulphate on the half-life of doxycycline in man. *Eur J Clin Pharmacol* (1974) 7, 361–3.
6. Venho VMK, Salonen RO, Mattila MJ. Modification of the pharmacokinetics of doxycycline in man by ferrous sulphate or charcoal. *Eur J Clin Pharmacol* (1978) 14, 277–80.
7. Potgieter MA, Pretorius SG, Jacobs YL, Venter C, Venter JL, Geisser P. Effect of an oral iron(III)-hydroxide polymaltose complex on tetracycline pharmacokinetics in patients with iron deficiency anaemia. *Arzneimittelforschung* (2007) 57, 385–91.
8. Heinrich HC, Oppitz KH, Gabbe EE. Hemmung der Eisenabsorption beim Menschen durch Tetracyclin. *Klin Wochenschr* (1974) 52, 493–8.
9. Heinrich HC, Oppitz KH. Tetracycline inhibits iron absorption in man. *Naturwissenschaften* (1973) 60, 524–5.
10. Potgieter MA, Potgieter JH, Venter C, Venter JL, Geisser P. Effect of oral tetracycline on iron absorption from iron(III)-hydroxide polymaltose complex in patients with iron deficiency anaemia. *Arzneimittelforschung* (2007) 57, 376–84.
11. Albert A, Rees CW. Avidity of the tetracyclines for the cations of metals. *Nature* (1956) 177, 433–4.
12. Albert A, Rees C. Incompatibility of aluminium hydroxide and certain antibiotics. *BMJ* (1955) 2, 1027–8.
13. Neuvonen PJ, Turakka H. Inhibitory effect of various iron salts on the absorption of tetracycline in man. *Eur J Clin Pharmacol* (1974) 7, 357–60.

Tetracyclines + Kaolin-pectin

Kaolin-pectin reduces the absorption of tetracycline by about 50%.

Clinical evidence, mechanism, importance and management

Healthy subjects were given **tetracycline** 250 mg as a solution or as a capsule, with and without 30 mL of kaolin-pectin (*Kaopectate*). The absorption of both formulations was reduced by about 50% by the kaolin-pectin. Even when the kaolin-pectin was given 2 hours before or after the **tetracycline**, the drug absorption was still reduced by about 20%.[1] The likely reason for this interaction is that **tetracycline** becomes adsorbed onto the kaolin-pectin so that less is available for absorption.

If these two drugs are given together, consider separating the doses by at least 2 hours to minimise admixture in the gut. It may even then be necessary to increase the **tetracycline** dose. Information about other tetracyclines is lacking, but be aware that they may interact similarly.

1. Gouda MW. Effect of an antidiarrhoeal mixture on the bioavailability of tetracycline. *Int J Pharmaceutics* (1993) 89, 75–7.

Tetracyclines + Lanthanum

The bioavailability of tetracyclines is expected to be reduced by lanthanum, as concurrent use may result in the formation of insoluble chelates (as with other polyvalent cations). As a result, it is recommended that tetracyclines (the manufacturer names tetracycline and doxycycline) are not taken within 2 hours of a dose of lanthanum.[1]

1. Fosrenol (Lanthanum carbonate hydrate). Shire Pharmaceuticals Ltd. UK Summary of product characteristics, July 2008.

Tetracyclines + Metoclopramide

In 4 patients, metoclopramide 20 mg was found to double the rate of absorption and slightly reduce the maximum serum levels of a single 500-mg dose of tetracycline.[1] This appears to be of little clinical importance.

1. Nimmo J. The influence of metoclopramide on drug absorption. *Postgrad Med J* (1973) 49 (July Suppl), 25–8.

Tetracyclines + Quinapril

The absorption of tetracycline is reduced by the magnesium carbonate excipient in some quinapril formulations.

Clinical evidence

Quinapril, formulated as *Accupro*, contains **magnesium carbonate** as an excipient (250 mg in a 40 mg quinapril capsule, 47 mg in a 5 mg capsule). A pharmacokinetic study in 12 healthy subjects investigating the potential interaction between the **magnesium carbonate** in these capsules and **tetracycline** found that single doses of both strengths of *Accupro* capsules markedly reduced the absorption of **tetracycline**. The 5 mg and 40 mg *Accupro* capsules reduced the **tetracycline** AUC by 28% and 37%, respectively, and the maximum serum levels were reduced by 25% and 34%, respectively.[1]

Mechanism

The reason for these reductions in tetracycline levels is that the magnesium carbonate and the tetracycline form a less soluble chelate in the gut which is less well absorbed (see 'Tetracyclines + Antacids', p.388).

Importance and management

An established interaction but the extent of the reduction is only moderate and its clinical importance is uncertain. However, the authors of the study and the manufacturers[2] recommend that the concurrent use of *Accupro* and tetracycline should be avoided.[1] Other tetracyclines would be expected to behave similarly. One possible way to accommodate this interaction (as with the antacid interaction) is to separate the doses as much as possible (by about 2 to 3 hours) to minimise admixture in the gut.

Quinapril, formulated as *Quinil* tablets, contains **magnesium oxide**, and, based on the interaction with magnesium carbonate, the manufacturer advises that *Quinil* tablets should not be taken with tetracycline.[3]

1. Parke Davis Ltd. Effect of magnesium-containing quinapril tablets on the single-dose pharmacokinetics of tetracycline in healthy volunteers, protocol 906–237. Data on file, Report RR 764–00872.
2. Accupro (Quinapril hydrochloride). Pfizer Ltd. UK Summary of product characteristics, June 2009.
3. Quinil (Quinapril hydrochloride). Tillomed Laboratories Ltd. UK Summary of product characteristics, May 2004.

Tetracyclines + Sucralfate

On theoretical grounds the absorption of tetracycline may possibly be reduced by sucralfate, but clinical confirmation of this appears to be lacking.

Clinical evidence, mechanism, importance and management

The manufacturers of sucralfate point out that it may reduce the bioavailability of **tetracycline**, probably because the two become bound together in the gut, thereby reducing absorption. It is suggested that they should be given 2 hours apart to minimise their admixture in the gut.[1] There do not appear to be any clinical reports in the literature confirming this potential interaction.

However, the formation of a **tetracycline**-sucralfate acid complex has been investigated in *animal* and *in vitro* studies and this indicates that the interaction may be clinically useful for *Helicobacter pylori* eradication because of direct delivery of **tetracycline** to the gastric mucosa for extended periods of time.[2-5]

1. Antepsin Suspension (Sucralfate). Chugai Pharma UK Ltd. UK Summary of product characteristics, November 2007.
2. Higo S, Ori K, Takeuchi H, Yamamoto H, Hino T, Kawashima Y. A novel evaluation method of gastric mucoadhesive property *in vitro* and the mucoadhesive mechanism of tetracycline-sucralfate acidic complex for eradication of *Helicobacter pylori*. *Pharm Res* (2004) 21, 413–9.
3. Higo S, Takeuchi H, Yamamoto H, Hino T, Kawashima Y. The acidic complexation of tetracycline with sucralfate for its mucoadhesive preparation. *Drug Dev Ind Pharm* (2004) 30, 715–24.
4. Yokel RA, Dickey KM, Goldberg AH. Selective adherence of a sucralfate-tetracycline complex to gastric ulcers: implications for the treatment of *Helicobacter pylori*. *Biopharm Drug Dispos* (1995) 16, 475–9.
5. Higo S, Takeuchi H, Yamamoto H, Hino T, Kawashima Y. Slow release of tetracycline from a mucoadhesive complex with sucralfate for eradication of *Helicobacter pylori*. Chem Pharm Bull (2008) 56, 1412–16.

Tetracyclines + Thiomersal

Patients taking tetracyclines who use contact lens solutions containing thiomersal may experience an inflammatory ocular reaction.

Clinical evidence, mechanism, importance and management

The observation that 2 patients had ocular reactions (red eye, irritation, blepharitis) when they used a 0.004% thiomersal-containing contact lens solution while taking a tetracycline, prompted further study of this interaction. A questionnaire revealed another 9 similar cases that suddenly began shortly after patients who had used thiomersal-containing solutions for 6 months without problem started to take a tetracycline. In each case the reaction cleared when the thiomersal or the tetracycline was stopped. The same reaction was also clearly demonstrated in *rabbits*.[1] The reasons are not understood. It would seem prudent to avoid the concurrent use of these compounds.

1. Crook TG, Freeman JJ. Reactions induced by the concurrent use of thimerosal and tetracycline. *Am J Optom Physiol Opt* (1983) 60, 759–61.

Tetracyclines + Zinc compounds

The absorption of tetracycline can be reduced by as much as 50% by zinc sulphate. Doxycycline interacts minimally with zinc.

Clinical evidence

When **tetracycline** 500 mg was given to 7 subjects either alone or with zinc sulfate 200 mg (equivalent to 45 mg of elemental zinc) the **tetracycline** serum concentrations and AUC were reduced by about 30 to 40%.[1] This study was repeated with **doxycycline** 200 mg and zinc, but **doxycycline** absorption was not affected.[1] A reduction in **tetracycline** absorption

of more than 50% has been seen in other studies when zinc was given concurrently.[2,3]

Tetracycline appears to cause minimal reductions in zinc concentrations.[2]

Mechanism

Zinc (like iron, calcium, magnesium and aluminium) forms a relatively stable and poorly absorbed chelate with tetracycline in the gut, which results in a reduction in the amount of antibacterial available for absorption.[4,5]

Importance and management

An established and moderately well documented interaction of clinical importance. Separate the administration of tetracycline and zinc compounds as much as possible to minimise admixture in the gut. In the case of 'iron', (p.391), which interacts by the same mechanism, 2 to 3 hours is usually enough. Alternatively it would seem that doxycycline is less affected, so it may be a useful alternative.[1] Other tetracyclines would be expected to interact like tetracycline itself, but this needs confirmation. The small reduction in serum zinc concentrations is likely to be of little practical importance.[2]

1. Penttilä O, Hurme H, Neuvonen PJ. Effect of zinc sulphate on the absorption of tetracycline and doxycycline in man. *Eur J Clin Pharmacol* (1975) 9, 131–4.
2. Andersson K-E, Bratt L, Dencker H, Kamme C, Lanner E. Inhibition of tetracycline absorption by zinc. *Eur J Clin Pharmacol* (1976) 10, 59–62.
3. Mapp RK, McCarthy TJ. The effect of zinc sulphate and of bicitropeptide on tetracycline absorption. *S Afr Med J* (1976) 50, 1829–30.
4. Albert A, Rees CW. Avidity of the tetracyclines for the cations of metals. *Nature* (1956) 177, 433–4.
5. Doluisio JT, Martin AN. Metal complexation of the tetracycline hydrochlorides. *J Med Chem* (1963) 16, 16.

Tetracyclines; Doxycycline + Rifampicin (Rifampin)

Rifampicin may cause a marked reduction in doxycycline levels, which has led to treatment failures in some cases.

Clinical evidence

In 7 patients, rifampicin 10 mg/kg daily caused a considerable reduction in the serum levels of doxycycline 200 mg daily. The reduction was very marked in 4 patients but not significant in the other 3 patients. The AUC of doxycycline was reduced by 54%, its clearance was approximately doubled, and its half-life was reduced from about 14 hours to 9 hours.[1,2]

Five patients with brucellosis taking doxycycline 200 mg daily had a reduction in the doxycycline half-life from about 14.5 hours to 8 hours when they took rifampicin 200 mg daily.[3] Another study, in 20 patients treated for brucellosis, found that the mean AUC of doxycycline was nearly 60% lower in the presence of rifampicin, when compared with streptomycin. There were no treatment failures in the patients taking doxycycline and streptomycin, but two treatment failures occurred in the 10 patients taking doxycycline and rifampicin.[4]

A meta-analysis of 6 studies involving 544 patients with brucellosis found a significantly higher numbers of relapses and lower numbers of initial cures if doxycycline was given with rifampicin rather than streptomycin.[5]

Mechanism

Not established, but it seems almost certain that the rifampicin (a known potent enzyme inducer) increases the metabolism of the doxycycline thereby reducing its levels.

Importance and management

The interaction between doxycycline and rifampicin is established and of clinical importance. Monitor the effects of concurrent use and increase the doxycycline dose as necessary. No clinically important adverse interaction appears to occur between doxycycline and streptomycin.

1. Garraffo R, Dellamonica P, Fournier JP, Lapalus P, Bernard E, Beziau H, Chichmanian RM. Effet de la rifampicine sur la pharmacocinétique de la doxycycline. *Pathol Biol (Paris)* (1987) 35, 746–9.
2. Garraffo R, Dellamonica P, Fournier JP, Lapalus P, Bernard E. The effect of rifampicin on the pharmacokinetics of doxycycline. *Infection* (1988) 16, 297–8.
3. Bessard G, Stahl JP, Dubois F, Gaillat J, Micoud M. Modification de la pharmacocinetique de la doxycycline par l'administration de rifampicine chez l'homme. *Med Mal Infect* (1983) 13, 138–41.
4. Colmenero JD, Fernández-Gallardo LC, Agúndez JAG, Sedeño J, Benítez J, Valverde E. Possible implications of doxycycline-rifampin interaction for the treatment of brucellosis. *Antimicrob Agents Chemother* (1994) 38, 2798–2802.
5. Solera J, Martínez-Alfaro E, Sáez L. Metaanálisis sobre la eficacia de la combinación de rifampicina y doxiciclina en el tratamiento de la brucelosis humana. *Med Clin (Barc)* (1994) 102, 731–8.

Tetracyclines; Doxycycline + Simeticone

A study in 8 healthy subjects found that [simeticone] 2.25 g did not alter the bioavailability of a single 200-mg dose of doxycycline.[1]

1. Bistue C, Perez P, Becquart D, Vinçon G, Albin H. Effet du diméticone sur la biodisponibilité de la doxycycline. *Therapie* (1987) 42, 13–16.

Tetracyclines; Minocycline + Ethinylestradiol

There is some evidence that ethinylestradiol may accentuate the facial pigmentation that can be caused by minocycline.

Clinical evidence

Two teenage sisters with severe acne vulgaris, taking minocycline 50 mg four times daily for 14 days then 50 mg twice daily thereafter, developed dark-brown pigmentation in their acne scars when they took *Dianette* (cyproterone acetate and ethinylestradiol) for about 15 months.[1] The type of pigmentation was not identified because they both declined to have a biopsy, but in other cases it has been found to consist of haemosiderin, iron, melanin and a metabolic degradation product of minocycline.[1] Two other reports describe facial pigmentation in patients taking minocycline, two of whom were taking oral hormonal contraceptives containing ethinylestradiol.[2,3] Other young women who have developed minocycline pigmentation may also have been taking oral hormonal contraceptives because they fall into the right age-group, but this is not specifically stated in any of the reports.

Mechanism

Not understood. It seems possible that the facial pigmentation (melasma, chloasma) that can occur with hormonal contraceptives may have been additive with the effects of the minocycline.[1]

Importance and management

Evidence is very limited but it has been suggested that all patients given long-term minocycline treatment should be well screened for the development of pigmentation, particularly if they are taking other drugs such as the hormonal contraceptives that are known to induce hyperpigmentation.[1] Remember also that very rarely contraceptive failure has been associated with the use of minocycline and other tetracyclines, see 'Combined hormonal contraceptives + Antibacterials; Tetracyclines', p.1173.

1. Eedy DJ, Burrows D. Minocycline-induced pigmentation occurring in two sisters. *Clin Exp Dermatol* (1991) 16, 55–7.
2. Ridgeway HA, Sonnex TS, Kennedy CTC, Millard PR, Henderson WJ, Gold SC. Hyperpigmentation associated with oral minocycline. *Br J Dermatol* (1982) 107, 95–102.
3. Prigent F, Cavelier-Balloy B, Tollenaere C, Civatte J. Pigmentation cutanée induite par la minocycline: deux cas. *Ann Dermatol Venereol* (1986) 113, 227–33.

Tetracyclines; Minocycline + Phenothiazines

An isolated report describes black galactorrhoea, which was attributed to an interaction between minocycline and perphenazine.

Clinical evidence, mechanism, importance and management

A woman taking minocycline 100 mg twice daily for 4 years to control pustulocystic acne, and also taking **perphenazine**, amitriptyline and diphenhydramine, developed irregular darkly pigmented macules in the areas of acne scarring and later began to produce droplets of darkly col-

oured milk. The milk was found to contain macrophages filled with positive iron-staining particles, assumed to be haemosiderin. The situation resolved when the drugs were withdrawn: the galactorrhoea within a week and the skin staining over 6 months.[1] Galactorrhoea is a known adverse effect of the phenothiazines and is due to an elevation of serum prolactin levels caused by the blockade of dopamine receptors in the hypothalamus. The dark colour appeared to be an adverse effect of the **minocycline**, which can cause haemosiderin to be deposited in cells, and in this instance to be scavenged by the macrophages that were then secreted in the milk. The general significance of this isolated case is unknown, but it seems likely to be small.

1. Basler RSW, Lynch PJ. Black galactorrhea as a consequence of minocycline and phenothiazine therapy. *Arch Dermatol* (1985) 121, 417–18.

Tetracyclines; Oxytetracycline + Pyridostigmine

When oxytetracycline 500 mg every 8 hours was given with pyridostigmine 30 mg every 8 hours the pharmacokinetics of both drugs were unchanged. There was an increase in erythrocyte cholinesterase activity when pyridostigmine was given with oxytetracycline, but the clinical significance of this finding is unclear.[1] It would appear that no dose adjustments are necessary on concurrent use.

1. Johnston A, Hedges A, Turner P. A study of the interaction between oxytetracycline and pyridostigmine. *Hum Toxicol* (1988) 7, 263–6.

Trimethoprim + Food or Guar gum

Guar gum and food can modestly reduce the absorption of trimethoprim suspension.

Clinical evidence, mechanism, importance and management

In a study over a 24-hour period, 12 healthy subjects were given a single 3-mg/kg oral dose of a trimethoprim suspension with food, with or without guar gum. The mean peak serum levels were reduced by food and by food given with 5 g of guar gum by 21% and 15%, respectively. Food, both with guar gum and alone, reduced the AUC of trimethoprim by about 22%.[1] The greatest individual reductions in peak serum levels and AUC were 44% and 36%, respectively with food, and 48% and 38%, respectively, with food and guar gum.[1] The reasons are not understood but it may be due to adsorption of the trimethoprim onto the food and guar gum.

The clinical importance of this interaction is uncertain but a modest reduction in absorption can occur in some individuals. However, trimethoprim is generally taken without regard to food, so this interaction would not appear to be significant in most patients.

1. Hoppu K, Tuomisto J, Koskimies O and Simell O. Food and guar decrease absorption of trimethoprim. *Eur J Clin Pharmacol* (1987) 32, 427–9.

Vancomycin + Colestyramine

Colestyramine may bind with vancomycin in the gut.

Clinical evidence, mechanism, importance and management

Colestyramine binds with vancomycin within the gut, thereby reducing its biological activity (about tenfold according to *in vitro* studies). The combination of vancomycin and colestyramine used to be used in antibacterial-associated colitis (now no longer recommended) and to overcome this interaction it was suggested that a vancomycin dose of 2 g daily should be used, and that administration of vancomycin and colestyramine should be separated as much as possible to minimise their admixture in the gut.[1] It is usually recommended that other drugs should be taken one hour before or 4 to 6 hours after colestyramine.

1. Taylor NS, Bartlett JG. Binding of *Clostridium difficile* cytotoxin and vancomycin by anion-exchange resins. *J Infect Dis* (1980) 141, 92–7.

Vancomycin + Indometacin

Indometacin reduces the renal clearance of vancomycin in premature neonates. This interaction does not appear to have been studied in adults.

Clinical evidence, mechanism, importance and management

In 6 premature neonates with patent ductus arteriosus given indometacin, the half-life of vancomycin 15 to 20 mg/kg given intravenously over one hour was found to be 24.6 hours, compared with only 7 hours in 5 other premature neonates without patent ductus arteriosus who were not given indometacin.[1] A second study, which included 4 premature infants who received vancomycin within 2 weeks of receiving indometacin for patent ductus arteriosus, suggested that only one of these infants had reduced vancomycin clearance as a result of indometacin use. This infant had received indometacin 4 days before starting vancomycin, and a 36-hour interval was required between doses to attain target vancomycin levels.[2] The reason for this effect is uncertain but it seems possible that the indometacin reduces the renal clearance of vancomycin. The authors of the first report suggest that the usual vancomycin maintenance dose should be halved if indometacin is also being used. If vancomycin therapeutic drug monitoring is possible it would be advisable to take levels and adjust the vancomycin dose and/or dosing interval accordingly. It is not known whether indometacin has the same effect on vancomycin in adults.

1. Spivey JM, Gal P. Vancomycin pharmacokinetics in neonates. *Am J Dis Child* (1986) 140, 859.
2. Asbury WH, Darsey EH, Rose WB, Murphy JE, Buffington DE, Capers CC. Vancomycin pharmacokinetics in neonates and infants: a retrospective evaluation. *Ann Pharmacother* (1993) 27, 490–6.

Vancomycin + Miscellaneous

The risk of nephrotoxicity and ototoxicity with vancomycin may possibly be increased if it is given with other drugs with similar toxic effects. There is some evidence to suggest that dobutamine, dopamine and furosemide can markedly reduce vancomycin serum levels following cardiac surgery.

Clinical evidence, mechanism, importance and management

A retrospective evaluation of the records of 18 critically ill patients in intensive care units following cardiac surgery, suggested that drugs with important haemodynamic effects (**dopamine**, **dobutamine**, **furosemide**) may lower the serum levels of vancomycin. It was noted that withdrawal of the interacting drugs was followed by an increase in the minimum steady-state serum levels of vancomycin, from 8.79 mg/L to 13.3 mg/L, despite no major changes in body-weight or estimated renal clearance. This resulted in a mean dose reduction of 4.26 mg/kg per day.

It is suggested that this interaction occurs because these drugs increase cardiac output, which increases the renal clearance of vancomycin, and therefore reduces its serum levels.[1] The clinical implication is that in this particular situation creatinine clearance is not as good a predictor of vancomycin clearance and consequently dose. Good therapeutic drug monitoring is needed to ensure that serum vancomycin levels are optimal. More confirmatory study is needed.

In addition, vancomycin is both potentially nephrotoxic and ototoxic, and its manufacturer therefore advises that it should be avoided with other drugs that have nephrotoxic potential, because the effects could be additive. They list **amphotericin B**, **aminoglycosides**, **bacitracin**, **colistin**, **polymyxin B** and **cisplatin**. They also list **etacrynic acid** and **furosemide** as potentially aggravating ototoxicity.[2] However, a review of 494 patients receiving **amphotericin B**, 57% of whom also received treatment with vancomycin, did not identify this combination as a risk factor for the development of nephrotoxicity.[3] In contrast, there is some evidence to suggest that additive nephrotoxicity can occur with the **aminoglycosides** (see 'Aminoglycosides + Vancomycin', p.327). The general warning issued by

the manufacturers to monitor carefully therefore seems a reasonable precaution.

1. Pea F, Porreca L, Baraldo M, Furlanut M. High vancomycin dosage regimens required by intensive care unit patients cotreated with drugs to improve haemodynamics following cardiac surgical procedures. *J Antimicrob Chemother* (2000) 45, 329–35.
2. Vancomycin hydrochloride. Hospira UK Ltd. UK Summary of product characteristics, January 2008.
3. Harbarth S, Pestotnik SL, Lloyd JF, Burke JP, Samore MH. The epidemiology of nephrotoxicity associated with conventional amphotericin B therapy. *Am J Med* (2001) 111, 528–34.

Vancomycin + Theophylline

Theophylline appears not to interact with vancomycin in premature infants.

Clinical evidence, mechanism, importance and management

Five premature infants (mean gestational age of 25 weeks and weighing 1.1 kg) were given theophylline (serum levels of 6.6 mg/L) for apnoea of prematurity. It was found that the pharmacokinetics of vancomycin 20 mg/kg given every 12 to 18 hours for suspected sepsis were unchanged by the presence of the theophylline, when compared with previously published data on the pharmacokinetics of vancomycin in neonates.[1] There seems to be no other clinical reports about vancomycin with theophylline or aminophylline (which is metabolised to theophylline), and nothing to suggest that vancomycin has any effect on the serum levels of theophylline.

1. Ilagan NB, MacDonald JL, Liang K-C, Womack SJ. Vancomycin pharmacokinetics in low birth weight preterm neonates on therapeutic doses of theophylline. *Pediatr Res* (1996) 39, 74A.

11

Anticholinesterases

The anticholinesterase drugs (or cholinesterase inhibitors) can be classified as **centrally-acting, reversible inhibitors** such as donepezil (used in the treatment of Alzheimer's disease), **reversible inhibitors with poor CNS penetration**, such as neostigmine (used in the treatment of myasthenia gravis), or **irreversible inhibitors**, such as ecothiopate and metrifonate. Note that organophosphorus insecticides are also potent cholinesterase inhibitors.

The centrally-acting anticholinesterases and the reversible anticholinesterases form the basis of this section, and these are listed in 'Table 11.1', (see below). Interactions where the anticholinesterases are affecting other drugs are covered elsewhere in the publication.

Centrally-acting anticholinesterases share a number of common pharmacodynamic interactions. The effects of anticholinesterases are expected to be additive with other cholinergic drugs or depolarising neuromuscular blockers, such as suxamethonium (succinylcholine) and antagonistic with antimuscarinic drugs or competitive (non-depolarising) neuromuscular blockers, such as tubocurarine, see 'Anticholinesterases; Centrally acting + Other drugs that affect acetylcholine', p.401. The concurrent use of anticholinesterases and drugs that slow the heart rate, such as beta blockers, some calcium-channel blockers and some antiarrhythmics may increase the risk of bradycardia, arrhythmias or syncope. Anticholinesterases may have the potential to exacerbate or induce extrapyramidal symptoms and so may possibly increase the risk of adverse effects with antipsychotics (see 'Anticholinesterases; Centrally acting + Antipsychotics', p.397).

Due to their differing pharmacokinetic characteristics, the centrally-acting anticholinesterases have slightly different interaction profiles. Tacrine is metabolised by the cytochrome P450 isoenzyme CYP1A2, and so interacts with fluvoxamine, a potent inhibitor of this isoenzyme (see 'Anticholinesterases; Centrally acting + SSRIs', p.402), whereas there is no evidence to suggest the other centrally acting anticholinesterases do. On the other hand, donepezil and galantamine are metabolised by the cytochrome P450 isoenzymes CYP3A4 and CYP2D6, and so they may interact with ketoconazole (see 'Anticholinesterases; Centrally acting + CYP3A4 inducers or inhibitors', p.400) and quinidine (see 'Anticholinesterases; Centrally acting + Quinidine', p.402), respectively, whereas tacrine would not be expected to do so. Rivastigmine, which is metabolised by conjugation, seems relatively free of *pharmacokinetic* interactions. Consideration of concurrent drug use would therefore seem to be an important factor in the choice of a centrally-acting anticholinesterase.

Table 11.1 Anticholinesterase drugs; reversible

Centrally-acting inhibitors used principally for Alzheimer's disease	*Inhibitors with poor CNS penetration used principally for myasthenia gravis*
Donepezil	Ambenonium
Galantamine	Distigmine
Rivastigmine	Edrophonium (mainly used diagnostically)
Tacrine	Neostigmine
	Physostigmine
	Pyridostigmine (also used for glaucoma)

Anticholinesterases + Miscellaneous

A number of drugs can affect myasthenia gravis, often by increasing muscular weakness. This is, strictly speaking, a drug-disease interaction, but such effects may be expected to oppose the actions of the drugs used to treat myasthenia gravis. A number of drugs (e.g. chlorpromazine, methocarbamol, and propafenone) are clearly contraindicated in patients with myasthenia, and, as this is not strictly a drug interaction, they are not dealt with here. A number of case reports (see 'Table 11.2', (p.398)) describe the worsening or unmasking of myasthenia gravis with a range of different drugs. The evidence for many of these interactions is very sparse indeed, and in some instances they are simply rare and isolated cases. It would therefore be wrong to exaggerate their importance, but it would nevertheless be prudent to be alert for any evidence of worsening myasthenia if any of the drugs listed are added to established treatment.

Anticholinesterases + Ranitidine

In 10 patients with myasthenia gravis receiving long-term pyridostigmine, ranitidine 150 mg slightly reduced the renal clearance of pyridostigmine, but this was not statistically significant. Pyridostigmine plasma levels were unchanged.[1]

1. Eiermann, Sommer N, Winne D, Schumm F, Maier U, Breyer-Pfaff U. Renal clearance of pyridostigmine in myasthenic patients and volunteers under the influence of ranitidine and pirenzepine. *Xenobiotica* (1993) 23, 1263–75.

Anticholinesterases; Centrally acting + Amiodarone

The risk of adverse effects, including bradycardia, may be increased if a centrally-acting anticholinesterase is given with amiodarone.

Clinical evidence, mechanism, importance and management

An analysis of the French Pharmacovigilance Database for adverse drug reactions involving centrally-acting cholinesterases (**donepezil**, **galantamine** and **rivastigmine**) up to March 2006 found 45 potential drug interactions between centrally-acting anticholinesterases and amiodarone. Eleven of these interactions were thought to have caused adverse reactions [probably bradycardia]. Inhibitors of the cytochrome P450 isoenzyme CYP3A4, such as amiodarone, were also involved in pharmacokinetic interactions with **donepezil** and **galantamine**, which are substrates of this isoenzyme. However, the extent to which the plasma concentrations of donepezil and galantamine were raised is unknown.[1]

It would appear that the effects of these centrally-acting anticholinesterases on heart rate can be additive with those of amiodarone. Be alert for bradycardia if amiodarone is given with **donepezil**, **galantamine** or **rivastigmine**. The effects of **tacrine** do not appear to have been studied, but it would also be expected to slow the heart rate, and therefore may have additive effects with amiodarone.

1. Tavassoli N, Sommet A, Lapeyre-Mestre M, Bagheri H, Montrastruc J-L. Drug interactions with cholinesterase inhibitors: an analysis of the French Pharmacovigilance Database and a comparison of two national drug formularies (Vidal, British National Formulary). *Drug Safety* (2007) 30, 1063–71.

Anticholinesterases; Centrally acting + Antipsychotics

No pharmacokinetic interaction appears to occur between risperidone and donepezil or galantamine, and the pharmacokinetics of thioridazine are not affected by donepezil. However, adverse effects such as movement disorders and neuroleptic malignant syndrome have occurred in patients given centrally-acting anticholinesterases with antipsychotics.

Clinical evidence, mechanism, importance and management

(a) Donepezil

1. Olanzapine. A 78-year-old man who had been taking olanzapine for 10 years experienced fatigue, progressive weakness, confusion, lethargy and severe muscle stiffness within a week of starting to take donepezil. He was diagnosed as having a variant of neuroleptic malignant syndrome secondary to an interaction between the two drugs.[1]

2. Risperidone. In a randomised, crossover study, 24 healthy subjects were given risperidone 500 micrograms twice daily with donepezil 5 mg daily. Although donepezil caused slight changes in the levels of risperidone and its metabolite, 9-hydroxyrisperidone, they were not considered clinically relevant. Concurrent use did not increase adverse effects.[2] In one study, 16 patients with schizophrenia taking risperidone were given donepezil 5 mg daily for 7 days without any alteration in their risperidone and 9-hydroxyrisperidone levels. The pharmacokinetics of donepezil were similar in the risperidone-treated patients and healthy controls taking donepezil alone.[3] However, a case report describes the emergence of parkinsonian symptoms in an 80-year-old woman after she was given donepezil 5 mg daily, with risperidone 1 mg daily added 12 days later. Risperidone was discontinued and she recovered without treatment.[4] Another report describes extrapyramidal adverse effects in a 79-year-old woman taking donepezil and risperidone.[5]

3. Thioridazine. In a crossover study, 11 healthy subjects were given donepezil 5 mg daily for 16 days, with a single 50-mg dose of thioridazine on the final day. Although donepezil did not affect the pharmacokinetics of thioridazine or its effects on the QT interval, thioridazine, either alone or in combination with donepezil, was poorly tolerated, and resulted in postural hypotension and increases in heart rate.[6] It would therefore seem prudent to use an alternative antipsychotic wherever possible.

4. Tiapride. Severe parkinsonism developed in a 79-year-old woman taking tiapride 25 mg twice daily and donepezil 3 mg daily, after the dose of donepezil was increased to 5 mg daily. Both tiapride and donepezil were discontinued and, on the following day, her gait disturbance began to improve: in 10 days, she could walk without assistance and the rigidity had disappeared. It was suggested that the two drugs had caused an acetylcholine/dopamine imbalance in the striatum resulting in the symptoms.[7]

(b) Galantamine

In a randomised, crossover study, 16 patients over 60 years of age were given a 14-day dose escalation of galantamine, after which they were given galantamine 12 mg twice daily with **risperidone** 500 micrograms twice daily, both for 13 doses. Although galantamine caused slight changes in the levels of **risperidone** and its metabolite, 9-hydroxyrisperidone, their combined level (the active moiety) was unchanged. The combination was well tolerated so no additional precautions would seem to be necessary on concurrent use.[8]

(c) Rivastigmine

A 58-year-old man receiving low-dose **olanzapine** and rivastigmine developed neuroleptic malignant syndrome 4 months after starting olanzapine and 6 weeks after his dose of rivastigmine was doubled to 6 mg twice daily. The patient fully recovered once the **olanzapine** was discontinued. **Olanzapine** was considered to be the probable cause of the patient's neuroleptic malignant syndrome, but it was suggested that rivastigmine might have contributed, possibly due to an acetylcholine/dopamine imbalance.[9]

In a study in 65 patients with Alzheimer's disease, 10 vascular dementia patients, and 15 mixed dementia patients, the patients were randomised to receive rivastigmine, **risperidone**, or both drugs together, for 20 weeks. No significant adverse events were reported on concurrent use.[10] However, a patient taking multiple drugs including **quetiapine**, **risperidone** and rivastigmine experienced acute dystonia, which resolved over the next 48 hours after rivastigmine was discontinued and benzatropine given. Three days later, rivastigmine was restarted and the dystonia-like symptoms returned within 2 hours of her morning dose.[11]

(d) Tacrine

An isolated report describes an 87-year-old man with dementia, who started taking **haloperidol** 5 mg daily for symptoms of agitation and paranoia. Doses of greater than 5 mg were noted to cause extrapyramidal symptoms. After 10 days, tacrine 10 mg four times daily was added. Within 72 hours he developed severe parkinsonian symptoms, which

Table 11.2 Case reports of drugs aggravating or unmasking myasthenia gravis

Drug	*Effect seen*	*Refs*
Acetazolamide 500 mg intravenously	Aggravation of muscular weakness in patients with myasthenia gravis taking unnamed anticholinesterases.	1
Ampicillin up to 1.5 g daily	Aggravation of myasthenic symptoms in 2 patients taking pyridostigmine.	2
Aspirin	Mild aggravation of myasthenic symptoms in a patient taking neostigmine.	3
Beta blockers	See Beta blockers + Anticholinesterases.	
Chloroquine	Persisting myasthenic symptoms, including muscular weakness, attributed to prior chloroquine use. Development of myasthenic symptoms in 3 patients, one who took chloroquine in overdose.	4-7
Ciprofloxacin	Aggravation of myasthenic symptoms in a patient taking pyridostigmine, and unmasking of myasthenia in one patient.	8, 9
Dipyridamole* 75 mg three times daily	Aggravation of myasthenic symptoms in a patient taking distigmine.	10
Erythromycin 500 mg intravenously	Precipitation of a myasthenic crisis in an undiagnosed 15-year-old girl.	11
Imipenem/cilastatin 500 mg four times daily	Aggravation of myasthenic symptoms in a patient taking pyridostigmine.	12
Interferons	Development of myasthenia gravis in patients given interferon-alfa (4 patients), interferon-beta (2 patients) and peginterferon-alfa 2a (1 patient), and aggravation of myasthenic symptoms in 1 patient given interferon- beta.	13-19
Ketoprofen 50 mg daily	Aggravation of myasthenic symptoms in a patient taking neostigmine.	3
Lithium carbonate 600 mg daily	Unmasking of myasthenia in one patient.	20
Norfloxacin*	Aggravation of myasthenic symptoms in a patient taking pyridostigmine.	21
Oxytetracycline	Transient aggravation of myasthenic symptoms in one patient taking pyridostigmine.	22, 23
Penicillamine	Aggravation of myasthenic symptoms in numerous patients taking anticholinesterases. Amitriptyline and imipramine also implicated in 2 cases.	24-27
Phenytoin 100 mg three times daily	Aggravation of myasthenic symptoms in an untreated patient.	28
Procainamide* 250 mg	Serious aggravation of myasthenic symptoms in a patient taking pyridostigmine. Two other less severe cases also reported.	29, 30
Quinidine* up to 970 mg daily	Mild aggravation of myasthenic symptoms in one patient taking pyridostigmine and another taking neostigmine. Development of myasthenic symptoms in 2 undiagnosed patients.	30-32
Rolitetracycline	Aggravation of myasthenic symptoms in 4 patients, two patients taking various anticholinesterases (cases originally reported elsewhere).	22, 23, 33

*Drugs that should be used with caution in myasthenia gravis.

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Continued

Table 11.2 Case reports of drugs aggravating or unmasking myasthenia gravis (continued)

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30. Kornfeld P, Horowitz SH, Genkins G, Papatestas AE. Myasthenia gravis unmasked by antiarrhythmic agents. *Mt Sinai J Med* (1976) 43, 10–14.
31. Stoffer SS, Chandler JH. Quinidine-induced exacerbation of myasthenia gravis in patient with Graves' disease. *Arch Intern Med* (1980) 140, 283–4.
32. Weisman SJ. Masked myasthenia gravis. *JAMA* (1949) 141, 917–18.
33. Gibbels E. Weitere Beobachtungen zur Nebenwirkung intravenöser Reverin-Gaben bei Myasthenia gravis pseudoparalytica. *Dtsch Med Wochenschr* (1967) 92, 1153–4.

resolved within 8 hours of stopping both drugs.[12] Another isolated report describes a woman taking **haloperidol** 10 mg daily who similarly developed a disabling parkinsonian syndrome within one week of starting tacrine 10 mg four times daily.[13] One possible reason is that the haloperidol blocked the dopamine receptors in striatum, thereby increasing striatal acetylcholine activity, which was further increased by the tacrine.[2] It is not clear whether patients given other dopamine receptor blocking drugs and tacrine would similarly show this reaction.

1. Warwick TC, Moningi V, Jami P, Lucas K, Molokwu O, Moningi S. Neuroleptic malignant syndrome variant in a patient receiving donepezil and olanzapine. Nat Clin Pract Neurol (2008) 4, 170–4.
2. Zhao Q, Xie C, Pesco-Koplowitz L, Jia X, Parier J-L. Pharmacokinetic and safety assessments of concurrent administration of risperidone and donepezil. *J Clin Pharmacol* (2003) 43, 180–6.
3. Reyes JF, Preskorn SH, Khan A, Kumar D, Cullen EI, Perdomo CA, Pratt RD. Concurrent administration of donepezil HCl and risperidone in patients with schizophrenia: assessment of pharmacokinetic changes and safety following multiple oral doses. *Br J Clin Pharmacol* (2004) 58, 50–7.
4. Liu H-C, Lin S-K, Sung S-M. Extrapyramidal side-effect due to drug combination of risperidone and donepezil. *Psychiatry Clin Neurosci* (2002) 54, 479.
5. Magnuson TM, Keller BK, Burke WJ. Extrapyramidal side effects in a patient treated with risperidone plus donepezil. *Am J Psychiatry* (1998) 155, 1458–9.
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7. Arai M. Parkinsonism onset in a patient concurrently using tiapride and donepezil. *Intern Med* (2000) 39, 863.
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11. Pavlis CJ, Kutscher EC, Carnahan RM, Kennedy WK, Van Gerpen S, Schlenker E. Rivastigmine-induced dystonia. *Am J Health-Syst Pharm* (2007) 64, 2468–70.
12. McSwain ML, Forman LM. Severe parkinsonian symptom development on combination treatment with tacrine and haloperidol. *J Clin Psychopharmacol* (1995) 15, 284.
13. Maany I. Adverse interaction of tacrine and haloperidol. *Am J Psychiatry* (1996) 153, 1504.

Anticholinesterases; Centrally acting + Azoles

Ketoconazole modestly increases the levels of donepezil. Galantamine levels are also increased by ketoconazole. Other azoles may interact similarly.

Clinical evidence, mechanism, importance and management

(a) Donepezil

Donepezil 5 mg daily was given to 18 healthy subjects with **ketoconazole** 200 mg daily, which is a specific and potent inhibitor of the cytochrome P450 isoenzyme CYP3A4. After one week of concurrent use, the maximum plasma levels and AUC of donepezil were increased by about 36%. Donepezil had no effect on the pharmacokinetics of **ketoconazole**.[1] None of the increases in donepezil levels were considered to be clinically relevant, and the authors suggest that no dose modifications will be required with **ketoconazole** or other CYP3A4 inhibitors.[1] Despite this, the UK manufacturer recommends that donepezil should be used with care with CYP3A4 inhibitors (which, to a greater or lesser extent, would be expected to include all azoles) and they specifically name **itraconazole**.[2]

(b) Galantamine

The manufacturers of galantamine note that **ketoconazole** increased the bioavailability of galantamine by 30%, probably by inhibiting the cytochrome P450 isoenzyme CYP3A4, by which galantamine is metabolised.[3,4] The UK manufacturer therefore predicts that **ketoconazole** may increase the incidence of nausea and vomiting with galantamine, and suggests that, based on tolerability, a reduction in the maintenance dose can be considered.[3] Note that, all azoles, to a greater or lesser extent, inhibit this isoenzyme, and therefore, until more is known, similar caution would seem prudent.

1. Tiseo PJ, Perdomo CA, Friedhoff LT. Concurrent administration of donepezil HCl and ketoconazole: assessment of pharmacokinetic changes following single and multiple doses. *Br J Clin Pharmacol* (1998) 46 (Suppl 1), 30–34.
2. Aricept (Donepezil hydrochloride). Eisai Ltd. UK Summary of product characteristics, May 2009.
3. Reminyl Tablets (Galantamine hydrobromide). Shire Pharmaceuticals Ltd. UK Summary of product characteristics, September 2009.
4. Razadyne ER (Galantamine hydrobromide). Ortho-McNeil-Janssen Pharmaceuticals, Inc. US Prescribing information, April 2008.

Anticholinesterases; Centrally acting + Calcium-channel blockers

The risk of adverse effects, including bradycardia, may be increased if donepezil, galantamine or rivastigmine are given concurrently with calcium-channel blockers.

Clinical evidence, mechanism, importance and management

An analysis of the French Pharmacovigilance Database for adverse drug reactions involving centrally-acting anticholinesterases (**donepezil**, **galantamine** and **rivastigmine**) up to March 2006 found 40 potential drug interactions between centrally-acting anticholinesterases and calcium-channel blockers. Fifteen of these were thought to have caused adverse reactions [probably bradycardia]. CYP3A4 inhibitors such as **diltiazem** and **verapamil** were also involved in pharmacokinetic drug interactions with **donepezil** and **galantamine**, which are substrates of this isoenzyme. The extent to which the plasma concentrations of donepezil and galantamine were raised is unknown.[1] However, as the effects of the potent CYP3A4 inhibitor ketoconazole was only modest (see 'Anticholinesterases; Centrally acting + Azoles', p.399) the effects of the modest CYP3A4 inhibitors **diltiazem** and **verapamil** would not be expected to be clinically relevant.

It would appear that the effects of these centrally-acting anticholinesterases on heart rate can be additive with those of the calcium-channel blockers. Although not stated in the report, only the calcium-channel blockers that have effects on heart rate (that is, **diltiazem** and **verapamil**) would be expected to be implicated. Be alert for bradycardia if either of these calcium-channel blockers is given with **donepezil**, **galantamine** or **rivastigmine**. The effects of **tacrine** do not appear to have been studied, but it would also be expected to slow the heart rate, and therefore may have additive effects with amiodarone.

1. Tavassoli N, Sommet A, Lapeyre-Mestre M, Bagheri H, Montrastruc J-L. Drug interactions with cholinesterase inhibitors: an analysis of the French Pharmacovigilance Database and a comparison of two national drug formularies (Vidal, British National Formulary). *Drug Safety* (2007) 30, 1063–71.

Anticholinesterases; Centrally acting + CYP3A4 inducers or inhibitors

Potent inhibitors of CYP3A4 may raise donepezil levels and inducers of CYP3A4 may lower donepezil levels. Galantamine levels are also predicted to be increased by potent CYP3A4 inhibitors such as ritonavir, but the moderate CYP3A4 inhibitor, erythromycin, only slightly increased the bioavailability of galantamine.

Clinical evidence, mechanism, importance and management

(a) Donepezil

Ketoconazole, a potent inhibitor of the cytochrome P450 isoenzyme CYP3A4, modestly increases donepezil levels, see 'Anticholinesterases; Centrally acting + Azoles', p.399, but this was not considered to be clinically relevant. Despite this, the UK manufacturer suggests that CYP3A4 inhibitors (they specifically name **erythromycin**) could inhibit the metabolism of donepezil and should be used with care. Furthermore, both the US and UK manufacturers suggest that inducers of CYP3A4 (including **carbamazepine**, **dexamethasone**, **phenobarbital**, **phenytoin** and **rifampicin**) may lower donepezil levels.[1,2] The UK manufacturer says, that as the magnitude of the effect is unknown, such drug combinations should be used with care.[1] Note that, dexamethasone does not usually cause clinically relevant interactions as a result of this effect.

(b) Galantamine

Based on the interaction of ketoconazole, a potent CYP3A4 inhibitor, and galantamine (see 'Anticholinesterases; Centrally acting + Azoles', p.399), the manufacturers of galantamine predict that other potent CYP3A4 inhibitors (the UK manufacturers name **ritonavir**) may increase the AUC of galantamine.[3,4] As a consequence patients may experience an increased incidence of nausea and vomiting, and, based on tolerability, it is suggested that a decrease in the galantamine maintenance dose could be considered.[4] Until the extent of the interaction with ritonavir is known, this seems prudent.

Erythromycin, a moderate CYP3A4 inhibitor, only increased galantamine bioavailability by about 10%,[3,4] and so a clinically significant interaction would not be expected.

1. Aricept (Donepezil hydrochloride). Eisai Ltd. UK Summary of product characteristics, May 2009.
2. Aricept (Donepezil hydrochloride). Eisai Inc. US Prescribing information, November 2006.
3. Razadyne ER (Galantamine hydrobromide). Ortho-McNeil-Janssen Pharmaceuticals, Inc. US Prescribing information, April 2008.
4. Reminyl Tablets (Galantamine hydrobromide). Shire Pharmaceuticals Ltd. UK Summary of product characteristics, September 2009.

Anticholinesterases; Centrally acting + Diazepam

Rivastigmine and tacrine do not appear to affect the pharmacokinetics of diazepam.

Clinical evidence, mechanism, importance and management

In a small study, **tacrine** 20 mg every 6 hours did not affect the pharmacokinetics of a single 2-mg dose of diazepam, when compared with diazepam alone.[1] Similarly the manufacturers of **rivastigmine** say that no pharmacokinetic interaction has been seen with diazepam in healthy subjects.[2,3] No diazepam dose adjustments would seem necessary if **tacrine** or **rivastigmine** are also given.

1. deVries TM, Siedlik P, Smithers JA, Brown RR, Reece PA, Posvar EL, Sedman AJ, Koup JR, Forgue ST. Effect of multiple-dose tacrine administration on single-dose pharmacokinetics of digoxin, diazepam, and theophylline. *Pharm Res* (1993) 10 (10 Suppl), S-333.
2. Exelon (Rivastigmine hydrogen tartrate). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, November 2009.
3. Exelon (Rivastigmine tartrate). Novartis Pharmaceuticals Corp. US Prescribing information, June 2006.

Anticholinesterases; Centrally acting + H_2-receptor antagonists

Cimetidine possibly increases the effects of tacrine. Cimetidine does not appear to significantly affect the pharmacokinetics of donepezil or galantamine, and ranitidine does not affect the bioavailability of galantamine.

Clinical evidence, mechanism, importance and management

Centrally-acting anticholinesterases may be expected to increase gastric acid secretion due to increased cholinergic activity, but it is not clear whether this would oppose the actions of the H_2-receptor antagonists.

(a) Donepezil

In a crossover study, donepezil 5 mg daily was given to 18 healthy subjects with **cimetidine** 800 mg daily. It was found that after one week of concurrent use the maximum plasma levels and AUC of donepezil were increased by 13% and 10%, respectively. Donepezil had no effect on the pharmacokinetics of **cimetidine**.[1] The changes in the pharmacokinetics of donepezil were not considered to be clinically relevant.[1]

(b) Galantamine

When a single 4-mg dose of galantamine was given on day 2 of a 3-day course of **cimetidine** 800 mg daily, the bioavailability of galantamine was increased by about 16%,[2] which would not be expected to be clinically significant. **Ranitidine** 300 mg daily had no effect on galantamine bioavailability.[2]

(c) Tacrine

In a study in 10 healthy, elderly subjects, **cimetidine** 300 mg four times daily for 2 days decreased the clearance of a single 40-mg dose of tacrine by 30%, and increased its AUC and maximum plasma level by 39% and 35%, respectively.[3] The manufacturer of tacrine says that **cimetidine** increased the AUC and the maximum plasma level of tacrine by about 64% and 54%, respectively.[4] The reason for these changes is not established, but it seems probable that **cimetidine** (a well-recognised liver enzyme inhibitor) reduces the metabolism of tacrine by the cytochrome P450 isoenzyme CYP1A2. An increase in both the beneficial effects and possibly adverse effects of tacrine (nausea, vomiting, diarrhoea) seems possible: one patient had to be withdrawn from the study mentioned above due to nausea and vomiting.[3] If the suggested mechanism of interaction is correct, the other H_2-receptor antagonists would not be expected to interact in this way.

1. Tiseo PJ, Perdomo CA, Friedhoff LT. Concurrent administration of donepezil HCl and cimetidine: assessment of pharmacokinetic changes following single and multiple doses. *Br J Clin Pharmacol* (1998) 46 (Suppl 1), 25–29.
2. Razadyne ER (Galantamine hydrobromide). Ortho-McNeil-Janssen Pharmaceuticals, Inc. US Prescribing information, April 2008.
3. Forgue ST, Reece PA, Sedman AJ, deVries TM. Inhibition of tacrine oral clearance by cimetidine. *Clin Pharmacol Ther* (1996) 59, 444–9.
4. Cognex (Tacrine hydrochloride). Sciele Pharma, Inc. US Prescribing information, June 2006.

Anticholinesterases; Centrally acting + HRT

A small study suggests that HRT can almost double the plasma levels of tacrine. Limited evidence suggests that oestrogens do not affect rivastigmine pharmacokinetics.

Clinical evidence, mechanism, importance and management

Observational results from a multicentre study of women with Alzheimer's disease receiving **tacrine** or placebo suggested that women receiving HRT (**conjugated oestrogens**, **estradiol** or **estrone sulfate**) and tacrine performed better on both cognitive and clinical assessments than women receiving tacrine alone or placebo. However, the subgroup of patients receiving HRT was not randomised and these patients were somewhat younger and better educated.[1] Following these observations, a randomised, crossover, placebo-controlled study was undertaken in 10 healthy women who were given HRT (**estradiol** 2 mg with **levonorgestrel** 250 micrograms daily) with a single 40-mg dose of **tacrine** on day 10. The HRT increased the mean **tacrine** AUC by 60%, increased the mean peak plasma level of tacrine by 46% and reduced the tacrine clearance by 31%. The AUC of one individual was increased threefold. These pharmacoki-

netic changes are thought to occur because HRT reduces the metabolism of **tacrine** to its main metabolite (1-hydroxytacrine) by the cytochrome P450 isoenzyme CYP1A2.[2] The importance of this interaction is uncertain, but increased **tacrine** levels would be expected to increase its adverse effects. Therefore it would seem prudent to be alert for the need to use a smaller **tacrine** dose in patients given HRT. More study of this interaction is needed.

In contrast, HRT did not enhance the response to **rivastigmine** in menopausal women with Alzheimer's disease.[3] **Rivastigmine** metabolism is minimally affected by the major cytochrome P450 isoenzymes and analysis of population data from 70 subjects found that oestrogens did not affect **rivastigmine** pharmacokinetics.[4]

1. Schneider LS, Farlow MR, Henderson VW, Pogoda JM. Effects of estrogen replacement therapy on response to tacrine in patients with Alzheimer's disease. *Neurology* (1996) 46, 1580–4.
2. Laine K, Palovaara S, Tapanainen P, Manninen P. Plasma tacrine concentrations are significantly increased by concomitant hormone replacement therapy. *Clin Pharmacol Ther* (1999) 66, 602–8.
3. Rigaud AS, André G, Vellas B, Touchon J, Pere JJ; French Study Group. No additional benefit of HRT on response to rivastigmine in menopausal women with AD. *Neurology* (2003) 60, 148–50.
4. Exelon (Rivastigmine tartrate). Novartis Pharmaceuticals Corp. US Prescribing information, June 2006.

Anticholinesterases; Centrally acting + Memantine

Memantine does not appear to attenuate the anticholinesterase effects of donepezil, galantamine, rivastigmine or tacrine, nor affect the pharmacokinetics of donepezil, galantamine or rivastigmine.

Clinical evidence, mechanism, importance and management

(a) Donepezil

In a study, 19 healthy subjects were given memantine 10 mg before and on the last day of taking donepezil (5 mg daily for 7 days then 10 mg daily for 22 days). The pharmacokinetics of both drugs were not significantly affected by concurrent use, and the effects of donepezil on anticholinesterase were also unaffected.[1] Furthermore, a one-year efficacy and safety study reported that the combination is well tolerated and beneficial.[2]

(b) Galantamine

A study in 15 healthy subjects found that the concurrent use of extended-release galantamine 16 mg daily with memantine 10 mg twice daily for 12 days did not affect the pharmacokinetics of galantamine and generally did not increase the incidence of adverse effects, although dizziness may have been more common.[3] Furthermore, a review of efficacy studies suggested that the effects of galantamine on anticholinesterase are unaffected by memantine, and that the combination is safe and generally well tolerated.[4]

(c) Rivastigmine

In vitro and *in vivo* studies demonstrate that the inhibition of cholinesterase by rivastigmine is not affected by the concurrent use of memantine.[5] A study in 16 patients with mild to moderate Alzheimer's disease taking rivastigmine 1.5 to 6 mg twice daily for 2 months or more found that memantine, increased in a gradual step-up approach to 10 mg twice daily, did not affect the pharmacokinetics of rivastigmine. The combination was well tolerated with adverse events being mild to moderate.[6]

(d) Tacrine

An *in vitro* study in *rats* suggested that memantine does not attenuate the anticholinesterase effects of tacrine at therapeutic concentrations.[7] Note that this study also found a lack of attenuation with donepezil and galantamine, which has subsequently been proven in clinical use.

1. Periclou AP, Ventura D, Sherman T, Rao N, Abramowitz WT. Lack of pharmacokinetic or pharmacodynamic interaction between memantine and donepezil. *Ann Pharmacother* (2004) 38, 1389–94.
2. Tariot PN, Farlow MR, Grossberg GT, Graham SM, McDonald S, Gergel I, for the Memantine Study Group. Memantine treatment in patients with moderate to severe Alzheimer Disease already receiving donepezil: a randomized controlled trial. *JAMA* (2004) 291, 317–24.
3. Yao C, Raoufinia A, Gold M, Nye JS, Ramael S, Padmanabhan M, Walschap Y, Verhaeghe T, Zhao Q. Steady-state pharmacokinetics of galantamine are not affected by addition of memantine in healthy subjects. *J Clin Pharmacol* (2005) 45, 519–28.
4. Grossberg GT, Edwards KR, Zhao Q. Rationale for combination therapy with galantamine and memantine in Alzheimer's disease. *J Clin Pharmacol* (2006) 46, 17S–26S.
5. Exelon (Rivastigmine tartrate). Novartis Pharmaceuticals Corp. US Prescribing information, June 2006.
6. Shua-Haim J, Smith J, Picard F, Sedek G, Athalye S, Pommier F, Lefèvre G. Steady-state pharmacokinetics of rivastigmine in patients with mild to moderate Alzheimer's disease not affected by co-administration of memantine: an open-label, crossover, single-centre study. Clin Drug Investig (2008) 28, 361–74.
7. Wenk GL, Quack G, Moebius H-J, Danysz W. No interaction of memantine with anticholinesterase inhibitors approved for clinical use. *Life Sci* (2000) 66, 1079–83.

Anticholinesterases; Centrally acting + Other drugs that affect acetylcholine

The effects of centrally-acting anticholinesterases (e.g. donepezil) are expected to be additive with those of other anticholinesterases (e.g. neostigmine) and cholinergics (e.g. pilocarpine). The effects of centrally-acting anticholinesterases and drugs with antimuscarinic effects are expected to be antagonistic, but case reports have described the opposite effect.

Clinical evidence, mechanism, importance and management

Anticholinesterases raise acetylcholine levels: some are more selective for raising acetylcholine levels in the brain (e.g. **donepezil**), whereas others (e.g. **neostigmine**, **pyridostigmine**) have a more generalised effect, see 'Table 11.1', (p.396). Therefore, if both drugs are given together their effects may be expected to be additive. Similarly, additive effects may be expected if anticholinesterases are given with cholinergic drugs, such as **bethanechol** or **pilocarpine**, which mimic the effects of acetylcholine, and depolarising neuromuscular blockers such as **suxamethonium** (**succinylcholine**), which act like acetylcholine to cause depolarisation. In contrast, competitive (non-depolarising) neuromuscular blockers (e.g. **tubocurarine**) compete with acetylcholine for receptors on the motor endplate of the neuromuscular junction and anticholinesterases such as neostigmine can oppose or reverse this blockade. See 'Neuromuscular blockers + Anticholinesterases', p.128, for reports of these interactions.

Drugs with **antimuscarinic** (anticholinergic) effects, which block the actions of acetylcholine, such as **atropine**, would be expected to oppose the actions of the anticholinesterases, and the findings of one long-term study suggested that concurrent use of these centrally-acting anticholinesterases and antimuscarinics may cause a greater rate of decline in cognitive function in patients with Alzheimer's disease.[1] Similar effects were found in another study in which urinary antimuscarinics (**oxybutynin**, **tolterodine**) were taken with **donepezil**, **rivastigmine**, **galantamine** or **tacrine**, although those with the lowest initial functional ability did not demonstrate any decline.[2] In another study, no decline in mental status was seen in patients taking centrally-acting anticholinesterases and antimuscarinics.[3]

In addition, an analysis of the French Pharmacovigilance Database for adverse drug reactions involving centrally-acting anticholinesterases (**donepezil**, **galantamine** and **rivastigmine**) up to March 2006 found 118 potential drug-drug interactions with antimuscarinic drugs. Of these, 24 were thought to have caused adverse drug reactions,[4] although the exact nature of the adverse effects due to antimuscarinic drugs was not stated.

Case reports also describe an interaction between centrally-acting anticholinesterases and antimuscarinics. Two patients taking **donepezil** and one taking **rivastigmine** were given **tolterodine** (a urinary antimuscarinic). One patient (taking **donepezil**) developed confusion, while the other two developed delusional states. This is the opposite effect to the predicted interaction (where the anticholinesterase may be expected to oppose the antimuscarinic effects of **tolterodine**). The authors suggest that the combination causes 'cholinergic neurogenic hypersensitivity' similar to that seen as a withdrawal reaction to anticholinesterases.[5] In contrast, a case report describes the successful use of **tolterodine** 6 mg daily in a patient taking **donepezil** 10 mg daily. The authors of this report suggest that, despite the predictions of an interaction, a trial of an **antimuscarinic** for urinary incontinence may be worthwhile in patients taking centrally-acting anticholinesterases.[6]

Seizures have occurred in 2 patients taking the irreversible anticholinesterase, **metrifonate**, after antimuscarinics were started and then abruptly discontinued. One patient took **hyoscyamine** for about 10 days and then experienced a generalised tonic-clonic seizure approximately 36 hours after the hyoscyamine was stopped. Another patient taking metrifonate 60 mg daily for 6 weeks experienced seizures after she was prescribed **doxepin** cream for pruritus, which was applied liberally for 5 days.[7]

The authors suggested that, in both cases, excess cholinergic stimulation

resulting in seizures was due to the abrupt discontinuation of the antimuscarinic and continued use of metrifonate.[7] It would therefore appear that the outcome of concurrent use is uncertain, but it would certainly be prudent to monitor the concurrent use of **donepezil**, **galantamine**, **rivastigmine** or **tacrine** and any cholinergic or antimuscarinic drug.

1. Lu C, Tune LE. Chronic exposure to anticholinergic medications adversely affects the course of Alzheimer disease. *Am J Geriatr Psychiatry* (2003) 11, 458–61.
2. Sink KM, Thomas J, Xu H, Craig B, Kritchevsky S, Sands LP. Dual use of bladder anticholinergics and cholinesterase inhibitors: long-term functional and cognitive outcomes. J Am Geriatr Soc (2008) 56, 847–53.
3. Bottiggi KA, Salazar JC, Yu L, Caban-Holt AM, Ryan M, Schmitt FA. Concomitant use of medications with anticholinergic properties and acetylcholinesterase inhibitors: impact on cognitive and physical functioning in Alzheimer disease. *Am J Geriatr Psychiatry* (2007) 15, 357–9.
4. Tavassoli N, Sommet A, Lapeyre-Mestre M, Bagheri H, Montrastruc J-L. Drug interactions with cholinesterase inhibitors: an analysis of the French Pharmacovigilance Database and a comparison of two national drug formularies (Vidal, British National Formulary). *Drug Safety* (2007) 30, 1063–71.
5. Edwards KR, O'Connor JT. Risk of delirium with concomitant use of tolterodine and acetylcholinesterase inhibitors. *J Am Geriatr Soc* (2002) 50, 1165–6.
6. Siegler EL, Reidenberg M. Treatment of urinary incontinence with anticholinergics in patients taking cholinesterase inhibitors for dementia. *Clin Pharmacol Ther* (2004) 75, 484–8.
7. Piecoro LT, Wermeling DP, Schmitt FA, Ashford JW. Seizures in patients receiving concomitant antimuscarinics and acetylcholinesterase inhibitor. *Pharmacotherapy* (1998) 18, 1129–32.

Anticholinesterases; Centrally acting + Quinidine

Quinidine inhibits the metabolism of galantamine and is predicted to inhibit the metabolism of donepezil. Quinidine does not affect the metabolism of tacrine.

Clinical evidence, mechanism, importance and management

(a) Donepezil

In vitro study has shown that quinidine (an inhibitor of the cytochrome P450 isoenzyme CYP2D6) inhibits donepezil metabolism[1,2] and, as no clinical information is available, the manufacturer suggests care with the combination:[1] increased donepezil levels and adverse effects are theoretically possible.

(b) Galantamine

A study in 8 healthy subjects given a single 10-mg dose of galantamine found that almost 20% of a dose of galantamine is excreted in the urine as *O*-demethylgalantamine glucuronide. Four of the 8 subjects were then given quinidine 250 mg twice daily for 2 days, with a single 15-mg dose of galantamine on day 2. Quinidine abolished the excretion of *O*-demethylgalantamine glucuronide in 3 subjects, and substantially reduced it in the fourth. The cumulative urinary recovery of unchanged galantamine increased by 60% in the presence of quinidine.[3] Quinidine is a known potent inhibitor of the cytochrome P450 isoenzyme CYP2D6, by which galantamine is metabolised. Concurrent use therefore decreases the metabolism of galantamine. This would be expected to result in raised levels of galantamine, but this does not appear to have been assessed in this study. A population pharmacokinetic analysis of a database of 852 patients with Alzheimer's disease, showed that the clearance of galantamine was decreased by about 25 to 33% by CYP2D6 inhibitors including 7 patients receiving quinidine.[4] Consequently the UK manufacturer of galantamine suggests that the concurrent use of quinidine may result in increased adverse effects (mainly nausea and vomiting), and, if this occurs, a reduction in the maintenance dose of galantamine should be considered.[5] This seems prudent.

(c) Tacrine

In a study in 11 healthy subjects, quinidine 83 mg every 8 hours did not affect the clearance of a single 40-mg dose of tacrine.[6] As quinidine inhibits the cytochrome P450 isoenzyme CYP2D6 in the liver, it was concluded that CYP2D6 does not have an important role to play in the metabolism of tacrine. No tacrine dose adjustments would be expected to be necessary if quinidine is also given.

1. Aricept (Donepezil hydrochloride). Eisai Ltd. UK Summary of product characteristics, May 2009.
2. Aricept (Donepezil hydrochloride). Eisai Inc. US Prescribing information, November 2006.
3. Bachus R, Bickel U, Thomsen T, Roots I, Kewitz H. The *O*-demethylation of the antidementia drug galanthamine is catalysed by cytochrome P450 2D6. *Pharmacogenetics* (1999) 9, 661–8.
4. Razadyne ER (Galantamine hydrobromide). Ortho-McNeil-Janssen Pharmaceuticals, Inc. US Prescribing information, April 2008.
5. Reminyl Tablets (Galantamine hydrobromide). Shire Pharmaceuticals Ltd. UK Summary of product characteristics, September 2009.
6. deVries TM, O'Connor-Semmes RL, Guttendorf RJ, Reece PA, Posvar EL, Sedman AJ, Koup JR, Forgue ST. Effect of cimetidine and low-dose quinidine on tacrine pharmacokinetics in humans. *Pharm Res* (1993) 10 (10 Suppl), S-337.

Anticholinesterases; Centrally acting + SSRIs

Fluvoxamine markedly increases the levels of tacrine, and increases its adverse effects. Paroxetine and fluoxetine may increase donepezil and galantamine levels. Sertraline does not appear to have a pharmacokinetic interaction with donepezil, and concurrent use seems generally well tolerated, although there may be an increase in gastrointestinal adverse effects, and one report describes hepatotoxicity. Rivastigmine and fluoxetine appear not to interact.

Clinical evidence, mechanism, importance and management

(a) Donepezil

Two case reports suggest that donepezil and **paroxetine** may interact, in one case with an increase in gastrointestinal adverse effects, and the other with increased CNS effects. These adverse effects were thought to occur because **paroxetine** may inhibit donepezil metabolism by the cytochrome P450 isoenzyme CYP2D6.[1] A further report describes a patient taking **paroxetine** for 6 months who developed hypertonic limbs and severe gait disorders when donepezil 5 to 10 mg daily was also given.[2] The manufacturer of donepezil logically predicts that **fluoxetine** could also inhibit the metabolism of donepezil, and until more information is available, they suggest care should be taken on the concurrent use of donepezil and CYP2D6 inhibitors.[3]

In a crossover study, 16 healthy subjects were given **sertraline** (50 mg daily increasing after 5 days to 100 mg daily) with donepezil 5 mg daily for 15 days. The pharmacokinetics of both drugs were not significantly altered by concurrent use, and, although there was some indication that gastrointestinal adverse effects may have been increased, overall adverse effects were not changed.[4] Another study similarly found that the concurrent use of donepezil and **sertraline** was well tolerated with a relatively low incidence of adverse effects, although diarrhoea was significantly more common with concurrent use than with donepezil alone.[5] A case report describes an 83-year-old woman taking **sertraline** 200 mg daily, who developed drug-induced cholestatic jaundice within 10 days of starting donepezil 5 mg daily. The authors suggest that although this reaction could have been in response to either drug, it may also have been precipitated by their concurrent use. The general significance of this report is unclear.[6]

(b) Galantamine

The manufacturers[7,8] note that an interaction study found that **paroxetine** 20 mg daily for 16 days increased the bioavailability of galantamine by about 40%, by inhibiting galantamine metabolism by the cytochrome P450 isoenzyme CYP2D6. The UK manufacturer warns about the increased risk of galantamine adverse effects (in particular nausea and vomiting) if **paroxetine** is added, and suggests a reduction in the galantamine dose, based on tolerability.[7] They also predict that other SSRIs that are potent inhibitors of CYP2D6 e.g. **fluoxetine** may interact similarly.[7] A population pharmacokinetic analysis of a database of 852 patients with Alzheimer's disease showed that the clearance of galantamine was decreased by about 25 to 33% by the concurrent use of CYP2D6 inhibitors including **fluoxetine** (48 patients) and **fluvoxamine** (14 patients),[8] although it should be noted that **fluvoxamine** is only a weak inhibitor of CYP2D6. Thus far there appear to be no reports of adverse reactions with any of these drugs.

(c) Rivastigmine

The manufacturers of rivastigmine report that in studies in healthy subjects no pharmacokinetic interaction was seen between rivastigmine and **fluoxetine**.[9,10] No dose adjustment of either drug would appear necessary with concurrent use.

(d) Tacrine

Fluvoxamine is an inhibitor of cytochrome P450 isoenzyme CYP1A2, the main isoenzyme involved in the metabolism of tacrine. An *in vitro* study showed that **fluvoxamine** is a potent inhibitor of tacrine metabolism, and it was therefore predicted that **fluvoxamine** may dramatically increase ta-

crine plasma levels in patients.[11] This prediction was confirmed in a placebo-controlled study in 13 healthy subjects who had an eightfold increase in the mean AUC of a single 40-mg dose of tacrine after taking **fluvoxamine** 100 mg for 6 days. A very large increase in the AUC of the hydroxylated metabolites of tacrine, and an eightfold fall in the clearance of tacrine were also seen. No subjects had any adverse effects when they took tacrine after placebo, but 5 had adverse effects (nausea, vomiting, sweating, and diarrhoea) when they took tacrine after **fluvoxamine**.[12] Another pilot study in one individual found that the total clearance of tacrine was reduced about tenfold and its half-life increased tenfold by **fluvoxamine** 100 mg daily.[13] A further study by the same authors, in 18 healthy subjects, found that the clearance of tacrine was reduced by about 85% by **fluvoxamine** 50 or 100 mg.[14] It is likely that standard tacrine doses will be poorly tolerated in the presence of **fluvoxamine** because of cholinergic adverse effects, and a decrease in tacrine dose is probably necessary.[14] Other SSRIs such as **fluoxetine**, **paroxetine**, or **sertraline** may be suitable alternatives, as they seem unlikely to inhibit tacrine metabolism (they do not inhibit CYP1A2 to a clinically relevant extent).

1. Carrier L. Donepezil and paroxetine: possible drug interaction. *J Am Geriatr Soc* (1999) 47, 1037.
2. Carcenac D, Martin-Hunyadi C, Kiesmann M, Demuynck-Roegel C, Alt M, Kuntzmann F. Syndrome extrapyramidal sous donepezil. *Presse Med* (2000) 29, 992–3.
3. Aricept (Donepezil hydrochloride). Eisai Ltd. UK Summary of product characteristics, May 2009.
4. Nagy CF, Kumar D, Perdomo CA, Wason S, Cullen EI, Pratt RD. Concurrent administration of donepezil HCl and sertraline HCl in healthy volunteers: assessment of pharmacokinetic changes and safety following single and multiple oral doses. *Br J Clin Pharmacol* (2004) 58 (Suppl 1), 25–33.
5. Finkel SI, Mintzer JE, Dysken M, Krishnan KRR, Burt T, McRae T. A randomized, placebo-controlled study of the efficacy and safety of sertraline in the treatment of the behavioral manifestations of Alzheimer's disease in outpatients treated with donepezil. *Int J Geriatr Psychiatry* (2004) 19, 9–18.
6. Verrico MM, Nace DA, Towers AL. Fulminant chemical hepatitis possibly associated with donepezil and sertraline therapy. *J Am Geriatr Soc* (2000) 48, 1659–63.
7. Reminyl Tablets (Galantamine hydrobromide). Shire Pharmaceuticals Ltd. UK Summary of product characteristics, September 2009.
8. Razadyne ER (Galantamine hydrobromide). Ortho-McNeil-Janssen Pharmaceuticals, Inc. US Prescribing information, April 2008.
9. Exelon (Rivastigmine hydrogen tartrate). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, November 2009.
10. Exelon (Rivastigmine tartrate). Novartis Pharmaceuticals Corp. US Prescribing information, June 2006.
11. Becquemont L, Le Bot MA, Riche C, Beaune P. Influence of fluvoxamine on tacrine metabolism in vitro: potential implication for the hepatotoxicity in vivo. *Fundam Clin Pharmacol* (1996) 10, 156–7.
12. Becquemont L, Ragueneau I, Le Bot MA, Riche C, Funck-Brentano C, Jaillon P. Influence of the CYP1A2 inhibitor fluvoxamine on tacrine pharmacokinetics in humans. *Clin Pharmacol Ther* (1997) 61, 619–27.
13. Larsen JT, Hansen LL, Brøsen K. Tacrine-fluvoxamine interaction study in healthy volunteers. *Eur J Clin Pharmacol* (1997) 52 (Suppl), A136.
14. Larsen JT, Hansen LL, Spigset O, Brøsen K. Fluvoxamine is a potent inhibitor of tacrine metabolism in vivo. *Eur J Clin Pharmacol* (1999) 55, 375–82.

Anticholinesterases; Centrally acting + Tobacco

Smoking tobacco reduces the plasma levels of tacrine and increases the clearance of rivastigmine.

Clinical evidence, mechanism, importance and management

A comparative study in 7 tobacco smokers and 4 non-smokers found that the AUC of a single 40-mg dose of **tacrine** in the smokers was about 10% of that in the non-smokers. The elimination half-life in the smokers was also reduced, to about two-thirds of that in non-smokers. The increase in **tacrine** metabolism in smokers is thought to occur because some of the components of tobacco smoke increase the activity of the cytochrome P450 isoenzyme CYP1A2 in the liver, by which **tacrine** is metabolised.[1] In practical terms it would appear that smokers are likely to need larger doses of **tacrine** than non-smokers, although this needs confirmation in multiple-dose studies. Theoretically, other centrally acting anticholinesterases (**donepezil**, **galantamine**, **rivastigmine**) would not be expected to interact in this way, as they are not metabolised by CYP1A2. However, the US manufacturer[2] notes that population pharmacokinetic analysis (75 smokers and 549 non-smokers) showed that nicotine use increases **rivastigmine** clearance by 23%, and so other mechanisms may have a part to play.

One observational study has suggested that patients with Alzheimer's disease who are smokers may be more likely to have an improved response to the digit symbol substitution test (a psychomotor test) when taking centrally-acting anticholinesterases than non-smokers; however, this was not associated with improved functional ability.[3] Furthermore, smoking may also increase the risk of dementia and cognitive decline.[4]

1. Welty D, Pool W, Woolf T, Posvar E, Sedman A. The effect of smoking on the pharmacokinetics and metabolism of Cognex® in healthy volunteers. *Pharm Res* (1993) 10 (10 Suppl), S-334.
2. Exelon (Rivastigmine tartrate). Novartis Pharmaceuticals Corp. US Prescribing information, June 2006.
3. Connelly PJ, Prentice NP. Current smoking and response to cholinesterase inhibitor therapy in Alzheimer's disease. *Dementia Geriatr Cogn Disord* (2005) 19, 11–14.
4. Duron E, Hanon O. Vascular risk factors, cognitive decline, and dementia. Vasc Health Risk Manag (2008) 4, 363–81.

Anticholinesterases; Centrally acting + Tricyclic antidepressants

The tricyclics may affect the outcome of using a centrally-acting anticholinesterase.

Clinical evidence, mechanism, importance and management

A population pharmacokinetic analysis of a database of 852 patients with Alzheimer's disease found that the clearance of galantamine was decreased by about 25 to 33% by the concurrent use of inhibitors of the cytochrome P450 isoenzyme CYP2D6, which was said to include 17 patients receiving amitriptyline.[1] However, note that amitriptyline is more usually considered a substrate, rather than an inhibitor of this isoenzyme. Further, the effects of a reduction in clearance of galantamine of this magnitude do not appear to have been studied.

Also, note that amitriptyline and other tricyclic antidepressants have antimuscarinic adverse effects, which might affect the actions of the centrally-acting anticholinesterases, see 'Anticholinesterases; Centrally acting + Other drugs that affect acetylcholine', p.401.

1. Razadyne ER (Galantamine hydrobromide). Ortho-McNeil-Janssen Pharmaceuticals, Inc. US Prescribing information, April 2008.

Donepezil + Ginkgo (*Ginkgo biloba*)

Ginkgo does not appear to affect the pharmacokinetics or effects of donepezil.

Clinical evidence, mechanism, importance and management

In a pharmacokinetic study, 14 elderly patients with Alzheimer's disease were given donepezil 5 mg daily for at least 20 weeks, after which ginkgo extract 90 mg daily was also given for a further 30 days. Concurrent use did not affect the pharmacokinetics or cholinesterase activity of donepezil, and cognitive function appeared to be unchanged.[1] Therefore, over the course of 30 days, concurrent use appears neither beneficial nor detrimental.

1. Yasui-Furukori N, Furukori H, Kaneda A, Kaneko S, Tateishi T. The effects of *Ginkgo biloba* extracts on the pharmacokinetics and pharmacodynamics of donepezil. *J Clin Pharmacol* (2004) 44, 538–42.

Tacrine + Ibuprofen

An isolated report describes a woman taking tacrine who became delirious when she also started to take ibuprofen.

Clinical evidence, mechanism, importance and management

A 71-year-old diabetic woman with probable Alzheimer's disease developed delirium while taking tacrine 40 mg four times daily. The symptoms included delusions, hallucinations, and fluctuating awareness. She was also bradycardic, diaphoretic and dizzy.[1] She was eventually stabilised with tacrine 20 mg four times daily, and continued this for 8 months without problems, but became delirious again 2 weeks after starting to take ibuprofen 600 mg daily. The delirium resolved when both drugs were withdrawn. The reasons for this reaction are unknown. This is the first and only report of this apparent interaction and its general importance is probably small, especially as the patient had previously experienced delirium with tacrine alone.

1. Hooten WM, Pearlson G. Delirium caused by tacrine and ibuprofen interaction. *Am J Psychiatry* (1996) 153, 842.

Tacrine + Quinolones

Enoxacin possibly increases the effects of tacrine.

Clinical evidence, mechanism, importance and management

In vitro studies with human and *rat* liver microsomes found that **enoxacin**, a specific inhibitor of the cytochrome P450 isoenzyme CYP1A2, significantly inhibited all known routes by which tacrine is metabolised.[1] A reasonable conclusion to be drawn from this is that the effects of tacrine (both beneficial and adverse) would be increased by **enoxacin**, but this interaction does not appear to have been studied in patients or healthy subjects. The same study also suggested that **enoxacin** possibly inhibits the production of the hepatotoxic metabolites of tacrine.[1]

Other quinolones vary in the extent to which they inhibit CYP1A2 (see 'Theophylline + Quinolones', p.1452), so that any interaction with other quinolones would be expected to reflect this variation.

1. Madden S, Woolf TF, Pool WF, Park BK. An investigation into the formation of stable, protein-reactive and cytotoxic metabolites from tacrine *in vitro*. Studies with human and rat liver microsomes. *Biochem Pharmacol* (1993) 46, 13–20.

12

Anticoagulants

The blood clotting process

When blood is lost or clotting is initiated in some other way, a complex cascade of biochemical reactions is set in motion, which ends in the formation of a network or clot of insoluble protein threads enmeshing the blood cells. These threads are produced by the polymerisation of the molecules of fibrinogen (a soluble protein present in the plasma) into threads of insoluble fibrin. The penultimate step in the chain of reactions requires the presence of an enzyme, thrombin, which is produced from its precursor prothrombin, already present in the plasma. This is initiated by factor III (tissue thromboplastin), and subsequently involves various factors including activated factor VII, IX, X, XI and XII, and is inhibited by antithrombin III. Platelets are also involved in the coagulation process. Fibrinolysis is the mechanism of dissolution of fibrin clots, which can be promoted with thrombolytics. For further information on platelet aggregation and clot dissolution, see 'Antiplatelet drugs and thrombolytics', (p.813).

Mode of action of the anticoagulants

Anticoagulants may be divided into direct anticoagulants, which have an immediate effect, and the indirect anticoagulants, which inhibit the formation of coagulation factors, so have a delayed effect as they do not inactivate coagulation factors already formed. See 'Table 12.1', (below), for a list.

(a) Direct anticoagulants

The direct anticoagulants include **heparin**, which principally enhances the effect of antithrombin III, thereby inhibiting the effect of thrombin (factor IIa) and activated factor X (factor Xa). **Low-molecular-weight heparins** are salts of fragments of heparin and act similarly, except that they have a greater effect on factor Xa than factor IIa. They have a longer duration of action than heparin and usually require less monitoring. The **heparinoids** (such as **danaparoid**) are similar. A more recent introduction is the synthetic polysaccharide **fondaparinux**, which is an inhibitor of factor Xa.

The other group of direct anticoagulants are the **thrombin inhibitors**, which bind to the active thrombin site. These include recombinant forms or synthetic analogues of **hirudin** such as bivalirudin and lepirudin. They also include **argatroban**, which is given intravenously, and the oral thrombin inhibitors, **dabigatran etexilate**, the prodrug of dabigatran, and **rivaroxaban**. Melagatran and its oral prodrug **ximelagatran** act similarly, but have been withdrawn because of liver toxicity.

(b) Indirect anticoagulants

The indirect anticoagulants inhibit the vitamin K-dependent synthesis of factors VII, IX, X and II (prothrombin) in the liver, and may also be referred to as **vitamin K antagonists**. The most commonly used are the **coumarins**, principally warfarin, but also acenocoumarol and phenprocoumon. Their target site of action is vitamin K epoxide reductase complex subunit 1 (VKORC1), and increasing evidence suggests that genetic polymorphisms in VKORC1 affect dose-requirements. The **indanediones** such as phenindione are now less frequently used. For many decades, the indirect anticoagulants have had the advantage over direct anticoagulants as they are orally active. They are often therefore referred to as **oral anticoagulants**, but this term has become misleading with the development of direct-acting oral anticoagulants, such as dabigatran and rivaroxaban, which have different monitoring requirements and interactions.

Table 12.1 Anticoagulants

Route of administration	*Class*	*Drugs*
Parenteral anticoagulants	**Activated Factor X inhibitor**	Fondaparinux sodium
	Heparins	
	Heparin	Heparin calcium, Heparin sodium
	Low-molecular weight heparins	Bemiparin, Certoparin, Dalteparin, Enoxaparin, Nadroparin, Parnoparin, Reviparin, Tinzaparin
	Heparinoids	Danaparoid, Dermatan sulphate, Pentosan polysulfate, Suleparoid, Sulodexide
	Thrombin inhibitors, direct	
	Hirudin analogues and recombinant hirudins	Bivalirudin, Desirudin, Lepirudin
	Synthetic thrombin inhibitors	Argotroban
Oral anticoagulants	**Activated Factor X inhibitor**	Rivaroxaban
	Thrombin inhibitors, direct	Dabigatran etexilate
	Vitamin K antagonists	
	Coumarins	Acenocoumarol, Dicoumarol, Ethyl biscoumacetate, Phenprocoumon, Warfarin
	Indanediones	Fluindione, Phenindione

Coagulation tests

During anticoagulant therapy the aim is to give protection against intravascular clotting, without too great a risk of bleeding. To achieve this, doses of heparin and oral anticoagulants should be individually titrated until the desired response is attained. With the coumarin and indanedione oral anticoagulants, this procedure normally takes several days because they do not act directly on the blood clotting factors already in circulation, but on the rate of synthesis of new factors by the liver. The successful titration is determined by one of a number of different but closely related laboratory tests, see 'Table 12.2', (below), and under the subsections, below. Note that routine monitoring of the anticoagulant effect is not required for low-molecular-weight heparins or heparinoids, except in patients at increased risk of bleeding such as those with renal impairment; or those who are overweight. Also, note that these tests cannot be used to monitor the anticoagulant effect of fondaparinux or the direct thrombin inhibitors, but these drugs do not require routine anticoagulant monitoring.

(a) Prothrombin time

The prothrombin time test (PT, Pro-Time, tissue factor induced coagulation time) is the most common coagulation test employed in clinical situations. It measures the time taken for a fibrin clot to form in a citrated plasma sample containing calcium ions and tissue thromboplastin. The PT is usually reported as the International Normalised Ratio (INR).

1. International normalised ratio (INR). The INR was adopted by the WHO in 1982 to standardise (using the International Sensitivity Index) oral anticoagulant therapy to take into account the sensitivities of the different thromboplastins used in laboratories across the world. The formula for calculating the INR is as follows:
INR = (patient's prothrombin time in seconds/mean normal prothrombin time in seconds)^{ISI}
The PT values obtained from the patient's sample are compared to a control, and this gives the INR. The higher the INR, the higher the PT value so if the patient's ratio is 2, this means the PT (and therefore clotting) is twice as long as the normal plasma. The British Corrected Ratio is essentially the same, but was calculated to a standard British thromboplastin.

2. Quick Value. The Quick Value is expressed as a percentage; the lower the value, the longer the blood takes to coagulate. Therefore as the Quick Value increases, the corresponding INR value gets smaller and vice versa.

(b) Activated partial thromboplastin time

The activated partial thromboplastin time (aPTT) is the second most common method for monitoring anticoagulant therapy, measuring all the clotting factors in the intrinsic pathway as opposed to the PT test, which measures the extrinsic pathway.

(c) Other methods of assessing clotting

Other tests used, which in some instances offer more sensitivity to specific aspects of therapy, include the prothrombin-proconvertin ratio (PP), the thrombotest, the thrombin clotting time test (TCT) the activated clotting time (ACT or activated coagulation time), the platelet count and the bleeding time test. The use of the most appropriate test will depend on the situation and the desired result.

Anticoagulant interactions

Stable oral anticoagulant therapy is difficult to achieve even during close monitoring. For example, in one controlled study in patients with atrial fibrillation, only 61% of INR values were within the target range of 2 to 3, despite monitoring the INR monthly and adjusting the warfarin dose appropriately.[1] A large number of factors can influence levels of coagulation, including diet, disease (fever, diarrhoea, heart failure, thyroid dysfunction), and the use of other drugs. It must therefore be remembered that it is particularly difficult to ascribe a change in INR specifically to a drug interaction in a single case report, and single case reports or a few isolated reports for widely used drugs do not prove that an interaction occurs. Nevertheless, either the addition or the withdrawal of drugs may upset the balance in a patient already well stabilised on an anticoagulant. Some drugs are well known to increase the activity of the anticoagulants and can cause bleeding if the dose of the anticoagulant is not reduced appropriately. Others reduce the activity and return the prothrombin time to normal. Both situations are serious and may be fatal, although excessive hypoprothrombinaemia manifests itself more obviously and immediately as bleeding and is usually regarded as the more serious. The interaction mechanism may be pharmacodynamic or pharmacokinetic: pharmacokinetic mechanisms are particularly well established and important for coumarin anticoagulants.

(a) Metabolism of the coumarins

The coumarins, warfarin, phenprocoumon and acenocoumarol, are racemic mixtures of *S*- and *R*-enantiomers. The *S*-enantiomers of these coumarins have several times more anticoagulant activity than the *R*-enantiomers. Reports suggest for example, that *S*-warfarin is three to five times more potent a vitamin K antagonist than *R*-warfarin. The *S*-enantiomer of warfarin is metabolised primarily by the cytochrome P450 isoenzyme CYP2C9. The metabolism of *R*-warfarin is more complex, but this enantiomer is primarily metabolised by CYP1A2, CYP3A4, CYP2C19 and CYP2C8. *S*-warfarin is eliminated in the bile and *R*-warfarin is excreted in the urine as inactive metabolites. There is much more known about the metabolism of warfarin compared with other anticoagulants, but it is established that *S*-phenprocoumon and *S*-acenocoumarol are also substrates for CYP2C9 and that they differ from warfarin in their hepatic metabolism, and stereospecific potency.[2]

It makes sense to assume therefore, that an inhibitor of CYP2C9 (e.g. fluconazole, see 'Coumarins + Azoles; Fluconazole', p.437) is likely to increase the concentration of the coumarin and enhance the anticoagulant effect. Drugs that induce CYP2C9 (e.g. rifampicin, see 'Coumarins + Antibacterials; Rifamycins', p.424) reduce plasma levels of the coumarins by increasing their clearance, and reduce the anticoagulant effect.

Genetic differences in the genes for these cytochrome P450 isoenzymes may have an important influence on drug metabolism of the coumarins. For example, different versions of the gene encoding CYP2C9 exist and the enzymatic activity of the most clinically important CYP2C9 variants, CYP2C9*2 and CYP2C9*3, is significantly reduced. Studies have suggested an association between patients possessing one or more of these variants and a low-dose requirement of warfarin. Similar observations have been made with the CYP2C9*3 variant and acenocoumarol.

While the metabolism of the coumarins, especially warfarin, are well

Table 12.2 Coagulation tests

Test	*Normal range*	*Therapeutic/diagnostic range*
Activated partial thromboplastin time	20 to 39 seconds after reagents added	1.5 to 2.5 x control
Bleeding time	1 to 9 minutes depending on method used	Critical value greater than 15 minutes
International normalised ratio	0.9 to 1.2	2 to 4 depending on indication for anticoagulation
Plasma thrombin time test	10 to 15 seconds	Greater than 15 seconds
Prothrombin-proconvertin ratio	70 to 130%	10 to 30%
Prothrombin time	10 to 15 seconds	1 to 2 x control
Quick value	70 to 130%	10 to 20%
Thrombin clotting time	70 to 120 seconds	150 to 600 seconds depending on indication for anticoagulation
Thrombotest	100%	10 to 20%

known, the numerous interaction pathways and the variability in patient responses makes the clinical consequences of affecting their metabolism less accurate to predict than with other drugs.

(b) Other mechanisms for anticoagulant interactions

Some drugs, such as colestyramine (see 'Coumarins and related drugs + Bile-acid binding resins', p.443) may prevent the absorption of the coumarins and reduce their bioavailability. See also 'Drug absorption interactions', (p.3). An increased risk of bleeding can occur if anticoagulants are given with other drugs that also impair coagulation by other mechanisms such as those drugs with an antiplatelet effect (see 'Coumarins and related drugs + Clopidogrel', p.448. Coumarins and indanediones act as vitamin K antagonists, and so dietary intake of vitamin K can also reduce or abolish their effects. Protein-binding displacement is another possible drug interaction mechanism but this usually plays a minor role compared with other mechanisms.[3] Consider also'Protein-binding displacement', (p.3).

Bleeding and its treatment

When prothrombin times become excessive, bleeding can occur. In order of decreasing frequency the bleeding shows itself as ecchymoses, blood in the urine, uterine bleeding, black faeces, bruising, nose-bleeding, haematoma, gum bleeding, coughing and vomiting blood.

Vitamin K is an antagonist of the coumarin and indanedione oral anticoagulants. The British Society for Haematology has given advice on the appropriate course of action if bleeding occurs in patients taking warfarin, and this is readily available in summarised form in the British National Formulary.

If the effects of heparin are excessive it is usually sufficient just to stop the heparin, but protamine sulfate is a specific antidote if a rapid effect is required. Protamine sulfate only partially reverses the effect of low-molecular-weight heparins.

There is currently no known specific antidote for fondaparinux, or for the direct thrombin inhibitors.

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Coumarins + ACE inhibitors

There is a single, isolated and unexplained case of melaena attributed to an interaction between acenocoumarol and fosinopril. No other ACE inhibitor studied has so far been shown to interact to a clinically relevant extent with the coumarins.

Clinical evidence

(a) Benazepril

In healthy subjects benazepril 20 mg daily for 7 days did not affect the steady-state plasma levels of either **warfarin** or **acenocoumarol**. The anticoagulant activity of **acenocoumarol** was not altered. The effects of **warfarin** were slightly reduced, as demonstrated by a mean reduction in PT of about 4%, but this is not enough to be clinically important.[1]

(b) Cilazapril

In 26 patients taking long-term **acenocoumarol** or **phenprocoumon**, cilazapril 2.5 mg daily for 3 weeks had no effect on the thrombotest times or coagulation factors II, VII and X.[2]

(c) Enalapril

Enalapril 20 mg for 5 days did not affect the anticoagulant effects of **warfarin** 2.5 to 7.5 mg daily, according to a brief summary of unpublished data cited in a review.[3]

(d) Fosinopril

A 74-year-old patient stabilised on **acenocoumarol**, **enalapril**, piretanide, and digoxin had the piretanide and **enalapril** switched to furosemide and fosinopril. Eleven days later, he presented with dark faeces (melaena) and had a low haemoglobin level. Fosinopril and acenocoumarol were stopped, and then **enalapril** and acenocoumarol were restarted. On gastrointestinal endoscopy, no explanation for the melaena was found, and his haemoglobin level had returned to normal 15 days later. This case was attributed to possible potentiation of the effect of acenocoumarol by fosinopril.[4]

(e) Moexipril

In 10 healthy subjects, the pharmacokinetics and pharmacodynamics of a single 50-mg dose of **warfarin** were not altered when it was given with the first dose of moexipril 15 mg daily for 6 days.[5]

(f) Ramipril

In 8 healthy subjects, ramipril 5 mg daily for 7 days had no effect on the steady-state pharmacokinetics or anticoagulant effects of **phenprocoumon**.[6] Similarly, ramipril 5 mg daily for 3 weeks did not alter the anticoagulant effects of **acenocoumarol** or **phenprocoumon** in patients stabilised on these anticoagulants, when compared with placebo.[7]

(g) Temocapril

In 24 healthy subjects, temocapril 20 mg daily for 2 weeks had no effect on the steady-state pharmacokinetics or pharmacodynamics of **warfarin**.[8] The absence of an interaction between **warfarin** and temocapril was also shown in another study.[9]

(h) Trandolapril

In a study in 19 healthy subjects,[10] **trandolapril** 2 mg daily for 13 days did not affect the pharmacodynamics of a single 25-mg dose of **warfarin** given on day 8.

Mechanism, importance and management

No important pharmacokinetic or pharmacodynamic interaction has been demonstrated for any ACE inhibitor and coumarin anticoagulant. Contrasting with all this evidence, there is a single, unexplained and isolated case of melaena attributed to an interaction between acenocoumarol and fosinopril. There seems to be no other evidence that fosinopril normally interacts with the oral anticoagulants and so this case report is unlikely to be of general significance. No special precautions would therefore seem necessary if any of these coumarin anticoagulants and ACE inhibitors are used concurrently.

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Coumarins and related drugs + Alcohol

The effects of the coumarins are unlikely to be changed in those with normal liver function who drink small or moderate amounts of alcoholic beverages such as wine or spirits. A non-significant trend has been reported of an increased risk of serious bleeding in patients taking warfarin with a history of binge drinking.

Clinical evidence

(a) Patients and subjects free from liver disease

In a study in 8 healthy subjects anticoagulated with **warfarin**, the daily consumption of one pint (about 560 mL) of Californian white table wine for a 3-week period at meal times had no significant effects on either the serum **warfarin** levels or the anticoagulant response.[1]

Other studies in both patients[2,3] and healthy subjects[4,5] taking either **warfarin**[2,3,5] or **phenprocoumon**[4] have very clearly confirmed the absence of an interaction with wine,[3,5] gin,[4] or alcohol 40%.[2] In one of these studies the subjects were given almost 600 mL of a table wine (alcohol 12%) or 300 mL of a fortified wine (alcohol 20%) without adverse effects on coagulation.[5] Moreover, in men randomised to receive low-dose **warfarin** in a post-coronary artery bypass graft study, there was no significant difference in the incidence of an INR above 2 between 323 non-drinkers, 181 light drinkers (one to 6 drinks weekly), 75 moderate drinkers (7 to 13 drinks weekly) and 46 heavy drinkers (14 drinks or more weekly).[6]

In contrast to the above studies, a 58-year-old man stabilised on **warfarin** experienced a sharp rise in his INR to 8 when he started to drink half a can of light beer (5.35 g of alcohol) every other day. In the previous 5 months he had an INR in the range of 1.9 to 2.5 with a stable **warfarin** dose, and no other explanation for the change in INR was found. He stopped taking the alcohol, and was eventually restabilised on the original dose of **warfarin**.[7] In a prospective, longitudinal study of patients taking **warfarin**, there was a slight statistically significant increased risk of self-reported bleeding events in patients who had increased their alcohol consumption in the previous week (35 bleeds in 245 weeks, none of which were major; odds ratio 1.24).[8]

In a case-control study of risk factors for excessive anticoagulation, self-reported alcohol use (ranging from one drink every other day to 2 drinks daily) was actually associated with an 80% *lower* risk of an INR greater than 6 with **warfarin**.[9]

(b) Chronic alcoholics or those with liver disease

In one study, 15 alcoholics who had been drinking heavily (250 g of ethanol or more daily) for at least 3 months and 11 control subjects (minimal social drinkers or non-drinkers) were given a single 40-mg dose of **warfarin**. The half-life of **warfarin** was lower in the alcoholics (26.5 hours versus 41.1 hours), but a comparison of the prothrombin times with those of healthy subjects found no differences.[10]

One patient with liver cirrhosis had marked fluctuations in prothrombin times and **warfarin** levels associated with weekend binge drinking of vodka.[2] Another patient with abnormal liver function had a fall in plasma **warfarin** levels and effect when he stopped drinking 50 mL of whiskey daily. When rechallenged with alcohol, **warfarin** levels and effect rose, and he had a nosebleed.[11] In contrast, a large retrospective cohort study did not find a significantly increased risk of serious bleeding in 140 patients with a history of alcoholic binge drinking who were taking **warfarin**. The

relative risk was 1.3 (0.8 to 1.9) compared with patients who had no record of alcohol abuse.[12]

Mechanism

It seems probable that, as in *rats*,[13] continuous heavy drinking stimulates the hepatic enzymes concerned with the metabolism of warfarin, leading to more rapid elimination.[10,14] The fluctuations in prothrombin times in those with liver impairment[2,11] may possibly occur because sudden large amounts of alcohol exacerbate the general dysfunction of the liver and this might affect the way it metabolises warfarin. Alcohol may also change the ability of the liver to synthesise clotting factors.[15] Constituents of beer other than alcohol may affect warfarin metabolism.[7]

Importance and management

The absence of an interaction between warfarin or phenprocoumon and alcohol in those free from liver disease is well documented and well established. It appears to be quite safe for patients taking oral anticoagulants to drink small or moderate amounts of wine or spirits (e.g. drinking within the generally accepted healthy daily limits). Even much less conservative amounts (up to 8 oz/250 mL of spirits[4] or a pint of wine (about 560 mL) daily[1]) do not create problems with anticoagulant control, so that there appears to be a good margin of safety even for the less than abstemious. Only warfarin and phenprocoumon appear to have been investigated, but other coumarin anticoagulants would be expected to behave similarly. The single case of increased INR in a patient who started to drink beer is unexplained, and therefore, further study with beer is needed to throw light on this possible interaction.

On the other hand, those who drink heavily may possibly need above-average doses of the coumarin, while limited evidence suggests that those with liver damage who binge drink may experience marked fluctuations in their prothrombin times. It might be prudent to avoid anticoagulation in this type of patient unless they can abstain from drinking. Nevertheless, although one cohort study in patients taking warfarin found a slight trend towards serious bleeding events in patients with a history of binge drinking, this was not significant, and other risk factors for bleeding were more important (highly variable prothrombin time ratio, or prothrombin time ratio greater than 2).[12]

Some sources also say that the indanedione **phenindione** may interact with alcohol, but there seems no direct evidence available to support this prediction.

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4. Waris E. Effect of ethyl alcohol on some coagulation factors in man during anticoagulant therapy. *Ann Med Exp Biol Fenn* (1963) 41, 45–53.
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Coumarins + Aliskiren

Aliskiren did not alter the pharmacodynamics or pharmacokinetics of a single dose of acenocoumarol, nor does it appear to interact with warfarin. Warfarin does not increase the levels of aliskiren.

Clinical evidence, mechanism, importance and management

(a) Acenocoumarol

In a well-controlled study in 18 healthy subjects, aliskiren 300 mg daily for 10 days did not alter the anticoagulant effect of a single 10-mg dose of acenocoumarol given on day 8. No significant changes in the pharmacokinetics of either *R*- and *S*-acenocoumarol were reported.[1] This study suggests that no acenocoumarol dose adjustment or additional monitoring would be expected to be needed if aliskiren is used in patients taking acenocoumarol.

(b) Warfarin

In a placebo-controlled, crossover study in 15 healthy subjects, aliskiren 150 mg daily for 11 days did not alter the pharmacodynamics of a single dose of warfarin given on day 8. In addition, there was no change in the AUC or half-life of *R*- and *S*-warfarin.[2] However, the manufacturer says that there were technical difficulties with this study, which was considered deficient.[3] They therefore state in their product information that the effects of aliskiren on warfarin pharmacokinetics have not been evaluated.[4] Nevertheless, aliskiren did not interact with acenocoumarol, which has very similar metabolism to warfarin; therefore no interaction with warfarin would be anticipated.

The US manufacturers state that warfarin does not increase the levels of aliskiren.[5]

1. Huang H-LA, Vaidyanathan S, Yeh C-M, Bizot M-N, Dieterich HA, Dole WP, Howard D. Effect of aliskiren, an oral direct renin inhibitor, on the pharmacokinetics and pharmacodynamics of a single dose of acenocoumarol in healthy volunteers. Curr Med Res Opin (2008) 24, 2449–56.
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3. Personal communication. Novartis, October 2008.
4. Rasilez (Aliskiren hemifumarate). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, April 2009.
5. Tekturna (Aliskiren hemifumarate). Novartis. US Prescribing information, December 2007.

Coumarins + Allopurinol

A number of studies and case reports suggest that allopurinol does not alter the pharmacokinetics or pharmacodynamics of warfarin. Nevertheless, a few case reports suggest that allopurinol might have increased the effect of warfarin, and similar cases have been reported with phenprocoumon. Allopurinol increased the half-life of dicoumarol in some healthy subjects, but there do not appear to be any reports of a clinically significant interaction.

Clinical evidence

(a) Dicoumarol

In 6 healthy subjects, allopurinol 2.5 mg/kg twice daily for 14 days increased the mean half-life of a single 4-mg/kg dose of dicoumarol from 51 hours to 153 hours, with large inter-individual variation.[1] In another similar study, only one of 3 healthy subjects had an increase in their dicoumarol half-life (from 13 hours to 17 hours) when they were also given allopurinol.[2]

(b) Phenprocoumon

Two patients, who had been stabilised on phenprocoumon for a few weeks, developed prolonged bleeding times, with haematuria in one of them, within 4 to 5 weeks of starting to take allopurinol 300 mg daily.[3]

(c) Warfarin

In a study in 8 healthy subjects, the half-life of a single 25-mg dose of warfarin was not altered by pretreatment with allopurinol 100 mg twice daily for 10 days.[2] Similarly, in 6 subjects, the elimination of a single 50-mg dose of warfarin was not altered by allopurinol 100 mg three times daily for 2 to 4 weeks, although one subject had a 30% reduction in the elimination of warfarin after 4 weeks.[4] No change was seen in the prothrombin ratios of 2 patients taking warfarin who took allopurinol 100 mg three times daily for 3 weeks.[4] In contrast, one patient stabilised on warfarin had a 42% increase in his prothrombin ratio after taking allopurinol 100 mg daily for 2 days.[5]

In a retrospective study[6] of the adverse effects of allopurinol in 1835 patients, 3 patients were identified who had developed excessive anticoagulation while taking warfarin and allopurinol. One of them developed extensive intrapulmonary haemorrhage and had a prothrombin time of

71 seconds. An increase in prothrombin time to 42 seconds was reported in an 82-year-old woman who had started taking warfarin 11 days previously, when she was also started on both allopurinol 300 mg daily and 'indometacin', (p.486). The precise role of the allopurinol in this case is unclear.[7]

Mechanism

It has been suggested that, as in *rats*, allopurinol inhibits the metabolism of the anticoagulants by the liver, thereby prolonging their effects and half-lives.[1,2,5] There is a wide individual variability in the effects of allopurinol on drug metabolism,[4] so that only a few individuals are affected.

Importance and management

Documentation for an interaction between allopurinol and the coumarins is poor, and a pharmacokinetic interaction is not established. There appear to be few case reports of any important interaction. Nevertheless, consider increased monitoring of the anticoagulant effect in any patient taking a coumarin with allopurinol.

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Coumarins + Alpha blockers

Tamsulosin does not appear to alter the pharmacokinetics or anticoagulant effect of acenocoumarol, and alfuzosin, doxazosin and terazosin do not appear to affect the response to warfarin.

Clinical evidence, mechanism, importance and management

(a) Alfuzosin

The UK manufacturer of alfuzosin reports that no pharmacodynamic or pharmacokinetic interaction was seen in healthy subjects given alfuzosin with **warfarin**.[1] The US manufacturer reports that in 6 healthy subjects, alfuzosin 5 mg twice daily for 6 days did not affect the pharmacological response to a single 25-mg dose of **warfarin**.[2] No warfarin dose adjustment would be expected to be needed on concurrent use.

(b) Doxazosin

The manufacturer of doxazosin reports that doxazosin has no effect on the protein binding of **warfarin** *in vitro*, and that no adverse effects have been reported with anticoagulants (unspecified).[3] No warfarin dose adjustment would be expected to be needed on concurrent use.

(c) Tamsulosin

In a double-blind, placebo-controlled, crossover study in 12 healthy subjects, tamsulosin 400 micrograms daily for 9 days had no effect on the pharmacokinetics or anticoagulant effects of a single 10-mg dose of **acenocoumarol** given on day five.[4] However, the UK manufacturer of tamsulosin states that **warfarin** might increase the elimination rate of tamsulosin.[5] The US manufacturer states that the findings of an *in vitro* metabolic interaction study between tamsulosin and **warfarin** were equivocal, and that they have not done a definitive drug interaction study; they therefore recommend caution with concurrent use.[6] Nevertheless, there do not appear to be any published cases of problems with the concurrent use of tamsulosin and **warfarin**, and the clinical study with **acenocoumarol**, which is metabolised in a similar way to **warfarin**, suggests that an interaction is unlikely.

(d) Terazosin

In a retrospective study of 26 men stabilised on **warfarin**, starting terazosin had no effect on their INRs. The patients had stable INRs for a least 2 consecutive measurements before receiving terazosin, and an INR taken within 14 days (9 patients) or 30 days (17 patients) of starting the terazosin.[7] Another study in 29 patients taking **warfarin** found that starting terazosin did not have a significant effect on anticoagulation.[8] Terazosin was used as a control comparator drug in these studies because of its lack of interaction with **warfarin**.[7,8] No warfarin dose adjustment would be expected to be needed on concurrent use.

1. Xatral (Alfuzosin hydrochloride). Sanofi-Aventis. UK Summary of product characteristics, February 2009.
2. Uroxatral (Alfuzosin hydrochloride extended-release tablets). Sanofi-Aventis US LLC. US Prescribing information, June 2009.
3. Cardura (Doxazosin mesilate). Pfizer Ltd. UK Summary of product characteristics, August 2009.
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5. Tabphyn™ (Tamsulosin hydrochloride). ProStrakan. UK Summary of product characteristics, August 2008.
6. Flomax (Tamsulosin hydrochloride). Astellas Pharma Inc. US Prescribing information, December 2009.
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Coumarins + 5-Alpha reductase inhibitors

Dutasteride and finasteride have no clinically significant effect on the pharmacokinetics or pharmacodynamics of warfarin.

Clinical evidence, mechanism, importance and management

In a study in 23 healthy subjects, dutasteride 500 micrograms daily taken with **warfarin** for 35 days had no effect on the pharmacokinetics of *S*- or *R*-warfarin, and the prothrombin time was unaffected by dutasteride.[1]

Similarly, the manufacturer of finasteride briefly notes that no clinically meaningful interaction was seen with **warfarin**.[2,3]

Therefore, no warfarin dose adjustment would be expected to be necessary on concurrent use of these 5-alpha reductase inhibitors.

1. Avodart (Dutasteride). GlaxoSmithKline. US Prescribing information, June 2008.
2. Proscar (Finasteride). Merck Sharp & Dohme Ltd. UK Summary of product characteristics, March 2008.
3. Proscar (Finasteride). Merck & Co., Inc. US Prescribing information, March 2007.

Coumarins + 5-Aminosalicylates

A single case report describes reduced warfarin effects in a patient given mesalazine. Another single case report describes a marked reduction in the response to warfarin when mesalazine was switched to sulfasalazine.

Clinical evidence

A woman stabilised on **warfarin** 5 mg daily, with INRs between 2 and 3, started taking **mesalazine** 800 mg three times daily for the treatment of a caecal ulcer. Four weeks later she presented to hospital with left leg pain, which was diagnosed as an acute popliteal vein thrombosis, and at the same time it was found that her prothrombin time and INR had fallen to 11.3 seconds and 0.9, respectively. The patient was treated with intravenous heparin. Over the next 10 days INRs of up to 1.7 were achieved by increasing the doses of **warfarin** up to 10 mg daily, but a satisfactory INR of 2.1 was only reached when the **mesalazine** was stopped. The report says that serum **warfarin** levels were not detectable during the use of **mesalazine**.[1] A 37-year-old woman taking **warfarin** 30 mg weekly with stable INRs between 2 and 3 in the previous 2 years (and also taking beclometasone, salbutamol, aspirin, azathioprine,and ethinyloestradiol with norgestrel), had her treatment for arthritis and ulcerative colitis changed from **mesalazine** to **sulfasalazine** 1 g four times daily. The day after the change her INR was found to be subtherapeutic (1.5) and she needed numerous increases in the **warfarin** doses over the next 6 weeks, eventually needing **warfarin** 75 mg weekly before acceptable INRs were achieved. During this period she developed a new deep vein thrombosis. When the **sulfasalazine** was later stopped and the **mesalazine** restarted, her **warfarin** dose was only 45 mg weekly.[2]

Mechanism

Not understood. Sulfasalazine is broken down in the colon to a sulfonamide, sulfapyridine, and 5-aminosalicylic acid (mesalazine). Some sulfon-

amides (see 'Coumarins and related drugs + Antibacterials; Sulfonamides and/or Trimethoprim', p.425) are known inhibitors of warfarin metabolism, and increase the effects of warfarin. In contrast, in the case with sulfasalazine, a marked decrease was noted.

Importance and management

Not established. The case of a reduction in effect of warfarin on starting mesalazine appears to be the first and only report of an interaction, which suggests that it is unlikely to be of general importance. Similarly, the case when mesalazine was switched to sulfasalazine is an unexplained and isolated case, and its validity has been debated.[3,4] There are no other reports in the literature and this possible interaction also seems unlikely to be of general importance. Consider these cases in the event of an unexpected response to treatment.

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Coumarins and related drugs + Amiodarone

The anticoagulant effects of warfarin, phenprocoumon and acenocoumarol are increased by amiodarone and bleeding may occur. The interaction may be maximal in 2 to 7 weeks, and may persist long after the amiodarone has been withdrawn. Amiodarone-induced thyrotoxicosis may also alter the INR in patients taking warfarin.

Clinical evidence

A. Inhibition of coumarin metabolism

(a) Acenocoumarol

A number of retrospective studies[1-4] have found that patients stabilised on acenocoumarol require a dose reduction when they are given amiodarone, the combined range in these studies being 4 to 69%. In a prospective study, 10 patients stabilised on acenocoumarol were given amiodarone 600 mg daily for a week, then 400 mg daily. Eight of the 10 patients had a decrease in prothrombin time after a mean of 4 days of amiodarone. Six patients required a decrease in their acenocoumarol dose of 60% while taking amiodarone 600 mg daily, but by the third week of taking amiodarone 400 mg daily the effects had diminished, and only a 33% reduction in dose was necessary.[5] A couple of case reports of the interaction have also been published.[6,7]

(b) Phenprocoumon

Amiodarone appears to increase the effects of **phenprocoumon**, with one case series in 7 patients reporting that a 9 to 59% phenprocoumon dose reduction was required within 1 to 3 weeks of starting amiodarone.[8] Conversely, an early study in 12 patients stabilised on **phenprocoumon** and given amiodarone 400 mg to 1 g daily did not find any interaction.[9]

(c) Warfarin

In the one of the first reports of an interaction between amiodarone and warfarin, 5 out of 9 patients who were stabilised on warfarin developed signs of bleeding (4 had microscopic haematuria and one had diffuse ecchymoses) within 3 to 4 weeks of starting to take amiodarone (dose not stated). All 9 had increases in their prothrombin times averaging 21 seconds. It was necessary to decrease the warfarin dose by an average of one-third (range 16 to 45%) to return their prothrombin times to the therapeutic range. The effects of amiodarone persisted for 6 to 16 weeks in 4 of the patients from whom it was withdrawn.[10]

Since then numerous other case reports have described a prolongation in prothrombin times and/or bleeding in patients taking warfarin and also given amiodarone (maintenance doses of 100 to 800 mg daily, sometimes with initial higher loading doses).[11-20] One patient died of haemorrhage.[15] Warfarin dose reductions varied between about 25 to 60%,[13,15,17,20] with only a few patients not needing a reduction.[13] In one retrospective study, the required dose of warfarin was related to the amiodarone maintenance dose, leading to the recommendation that the warfarin dose should be reduced by 40% for a daily maintenance dose of amiodarone of 400 mg, by 35% for 300 mg, by 30% for 200 mg and by 25% for 100 mg.[20] Other studies have also found that amiodarone use was associated with a lower required warfarin dose.[21,22] One 80-week study reported that a clinically significant interaction defined as an INR above 5 was most likely in the first 12 weeks of concurrent use, and was minimal thereafter.[23] Conversely, one large cohort study found no significant increased risk of haemorrhage with the concurrent use of warfarin and amiodarone,[24] but it is possible that the patients were on stable therapy, or that the interaction was anticipated and managed accordingly.

A few pharmacokinetic studies have shown that amiodarone decreased the clearance of warfarin by 44 to 55% in patients,[16,25] and by 20 to 37% in healthy subjects given a single dose of warfarin after taking amiodarone for 3 to 4 days.[26,27] In the two studies in healthy subjects, amiodarone caused a similar decrease in the clearance of both *R*- and *S*-warfarin.[26,27] However, a recent study in patients concluded that amiodarone had a much greater effect on *S*-warfarin than on *R*-warfarin.[28]

B. Thyrotoxicosis (Hyperthyroidism)

The INR of a patient stabilised on **warfarin** and amiodarone was noted to increase from about 2 to 5.5 after he developed amiodarone-induced thyrotoxicosis.[29] Another three well-described cases of this potential interaction have been reported.[30]

Mechanism

Amiodarone inhibits the metabolism of warfarin, probably because it, and/or its metabolite desethylamiodarone,[31] inhibit the cytochrome P450 isoenzymes CYP2C9, CYP3A4 and CYP1A2 (see 'metabolism of the coumarins', (p.405)).

Thyrotoxicosis, which can be caused by amiodarone, potentiates the effect of warfarin, see 'Coumarins and related drugs + Thyroid and Antithyroid compounds', p.513. As a result less warfarin would be required to prolong the prothrombin time.[29,30]

Importance and management

The potentiating effect of amiodarone on coumarin anticoagulants is a well documented, established and clinically important interaction. It appears to occur in most patients.[10,13,17] It would seem prudent to adjust the doses of the coumarin anticoagulants based on INR measurements. Some recommend that the dose of warfarin should initially be reduced by 25%[17] or 50%[13] when amiodarone is added to established anticoagulant treatment, with increased INR monitoring until a new steady-state is achieved. The potentiation of coumarins starts within a few days and is usually maximal by 2 to 7 weeks.[17,20,28] The final reduction in warfarin dose required may depend on the amiodarone maintenance dose: average warfarin dose reductions of 25% have been required for amiodarone 100 mg daily, 30 to 35% for amiodarone 200 mg daily, 35% for amiodarone 300 mg daily, 40 to 50% for amiodarone 400 mg daily, and 65% for amiodarone 600 mg daily.[16,20] These suggested reductions are broad generalisations and individual patients may need more or less.[4,32] If established amiodarone therapy is withdrawn in a patient taking warfarin, it is likely that the dose of warfarin will need increasing gradually over the first few months after amiodarone is stopped. This is because amiodarone has such a long half-life. If warfarin is required in a patient on established amiodarone therapy, a lower initial dose of warfarin should be used.

Similar advice applies to acenocoumarol and phenprocoumon, and probably also other coumarins. Some recommend an initial reduction in acenocoumarol dose of 50% when amiodarone is added,[1] whereas others recommend that the INR should be closely monitored, and the dose of acenocoumarol only reduced in response to an increase in INR.[32]

In patients stabilised on a coumarin and amiodarone, the possibility of amiodarone-induced thyroid dysfunction should be considered if an abrupt increase in INR occurs,[29,30] see 'Coumarins and related drugs + Thyroid and Antithyroid compounds', p.513.

Some sources say that the metabolism of the indanedione **phenindione** is inhibited by amiodarone, but this appears to be an extrapolation from the known interaction with warfarin. There seems no clinical evidence available to support this prediction.

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Coumarins and related drugs + Anabolic steroids or Androgens

Increased anticoagulant effects and bleeding have been seen in patients taking a coumarin or the indanedione, phenindione, and an anabolic steroid or testosterone.

Clinical evidence

(a) Anabolic steroids

Six patients stabilised on **warfarin** or **phenindione** were given **oxymetholone** 15 mg daily. One patient developed extensive subcutaneous bleeding and another had haematuria. After 15 to 30 days all 6 patients had thrombotests of less than 5%, which returned to the therapeutic range within a few days of **oxymetholone** being withdrawn.[1] Other similar cases have been reported with **oxymetholone** and **warfarin**,[2-4] or **acenocoumarol**.[5] In 3 of the reports[1,3,4] the interaction was severe enough to discontinue the **oxymetholone**. In one patient[2] the **warfarin** dose was reduced by 59%, and in another[5] the **acenocoumarol** dose was reduced by 66 to 75%. Similarly increased anticoagulant effects and bleeding have been described in studies and case reports involving:

- **dicoumarol** with **norethandrolone**,[6]
- **dicoumarol** with **stanozolol**,[7]
- **phenindione** with **methandienone**,[8]
- **phenindione** with **ethylestrenol**,[9]
- **warfarin** with **methandienone**[2,8,10,11] (62% to 73% decrease in dose required in 3 cases[2] and 38% in 7 others[8]),
- **warfarin** with **stanozolol**[12-15] (40% and 64% decrease in dose required in 2 patients and about a 70% increase required after stopping stanozolol[12]).

In a pharmacokinetic study in 15 healthy subjects, the concurrent use of **warfarin** and **oxandrolone** 5 or 10 mg twice daily increased the *S*-warfarin AUC by 2.65-fold and doubled its half-life, and had similar effects on *R*-warfarin.[16] Microscopic haematuria occurred in 9 subjects and gingival bleeding in one. An 80 to 85% decrease in the dose of **warfarin** was necessary to maintain a target INR of 1.5.

(b) Androgens

A 58-year-old man receiving **methyltestosterone** replacement therapy 37.5 mg daily required a maintenance dose of **phenprocoumon** of just 0.94 mg daily compared with control subjects who required 2.62 mg daily.[17] One report notes that 3 patients receiving **warfarin** and *Sustanon* (containing four combined esters of **testosterone**) had no changes in their anticoagulant requirements,[4] whereas another report describes a woman who had a 78% and a 65% increase in prothrombin times on two occasions when using a 2% **testosterone propionate** vaginal ointment twice daily. She needed a 25% reduction in her **warfarin** dose.[18]

Mechanism

Not understood. One study found that norethandrolone did not alter the metabolism of dicoumarol, and did not alter the plasma levels of vitamin-K dependent clotting factors.[6] However, a more recent study of oxandrolone and warfarin suggests a pharmacokinetic basis for this interaction.[16]

Importance and management

The interactions between warfarin and the anabolic steroids are well documented, well established and clinically important. The effect develops rapidly, possibly within 2 to 3 days. Most, if not all, patients are affected.[1,6] If concurrent use cannot be avoided, the dose of the anticoagulant should be appropriately reduced. In a few cases, where patients have been able to be stabilised on the combination, up to 75% reductions in anticoagulant dose have been required, and the study with oxandrolone[16] suggests that an 85% reduction in the dose of warfarin might be necessary. After withdrawal of the interacting drug the anticoagulant dose will need to be increased.

It seems probable that all the coumarin and indanedione anticoagulants will interact with any 17-alkyl substituted anabolic steroid; effects have been seen on acenocoumarol, dicoumarol and phenindione. The situation with testosterone and other non 17-alkylated steroids is not clear as there are only case reports, which are conflicting. Until more is known it would seem prudent to increase the frequency of INR monitoring if these drugs are given with coumarins or indanediones.

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Coumarins + Angiotensin II receptor antagonists

None of the angiotensin II receptor antagonists appear to interact with warfarin to a clinically relevant extent.

Clinical evidence

(a) Candesartan

In healthy subjects stabilised on individualised doses of **warfarin**, candesartan cilexetil 16 mg daily for 10 days reduced the trough serum levels of **warfarin** by 7%, but this had no effect on prothrombin times.[1]

(b) Eprosartan

No clinically relevant changes in anticoagulation occurred in 18 healthy subjects stabilised on **warfarin** with INRs between 1.3 and 1.6 when they were given eprosartan 300 mg twice daily for 7 days.[2]

(c) Irbesartan

Warfarin 2.5 to 10 mg daily was given to 16 healthy subjects for 2 weeks, with irbesartan 300 mg or a placebo daily for a further week. There was no evidence that irbesartan affected the pharmacokinetics or pharmacodynamics of **warfarin**.[3]

(d) Losartan

In a placebo-controlled, randomised, crossover study, 10 healthy subjects were given losartan 100 mg daily for 13 days with a single 30-mg dose of **warfarin** on day 7. The pharmacokinetics of **warfarin** (both *R*- and *S*-enantiomers) and its anticoagulant effects were not altered. Losartan, given alone for one week, also had no effect on prothrombin times.[4]

(e) Olmesartan

In a study in 24 healthy subjects given **warfarin** titrated to a Quick value of between 1.4 and 1.8 for 2 weeks, the addition of olmesartan 40 mg daily for a further 7 days had no effect on the pharmacokinetics of either *R*- or *S*-warfarin. There was also no change in Quick value or partial prothrombin time.[5]

(f) Telmisartan

Telmisartan 120 mg daily for 10 days was given to 12 healthy subjects stabilised on **warfarin**, with INRs of between 1.2 and 1.8. A small 11% decrease in the mean trough plasma **warfarin** concentration occurred, but the anticoagulation effect remained unchanged.[6]

(g) Valsartan

In a study in 12 healthy subjects, valsartan 160 mg daily was given for 7 days with **warfarin** 10 mg daily for the first 3 days. **Warfarin** had no effect on the pharmacokinetics of valsartan. Valsartan caused a small increase in prothrombin time of about 12%, which was not considered clinically important. **Warfarin** pharmacokinetics were not assessed.[7,8]

Mechanism

In vitro, various angiotensin II antagonists have some cytochrome P450 isoenzyme CYP2C9 inhibitory activity,[9] and it is therefore possible that they might reduce warfarin metabolism.

Importance and management

Despite the reported *in vitro* inhibitory effects on CYP2C9 reported for some angiotensin II antagonists, the available pharmacokinetic and pharmacodynamic studies show that the angiotensin II receptor antagonists (candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan) do not interact with warfarin to a clinically relevant extent. The lack of any published evidence to the contrary suggests that no warfarin dose adjustments should be needed if these drugs are given together.

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Coumarins + Antacids

There is some evidence that the absorption of dicoumarol may be increased by magnesium hydroxide. Aluminium hydroxide does not interact with either warfarin or dicoumarol, and magnesium hydroxide does not interact with warfarin.

Clinical evidence

(a) Dicoumarol

In a study in 6 healthy subjects, **magnesium hydroxide** (*Milk of Magnesia*) 15 mL, taken with and 3 hours after a single dose of dicoumarol, was found to raise the peak plasma levels and AUC of dicoumarol by 75% and 50%, respectively. Conversely, **aluminium hydroxide** (*Amphogel*) 30 mL did not alter dicoumarol levels.[1]

(b) Warfarin

In a study in 6 healthy subjects, **aluminium/magnesium hydroxide** (*Maalox*) 30 mL, given with and for four 2-hourly doses after warfarin, had no effect on the plasma warfarin levels or on the anticoagulant response.[2] Similarly, neither **aluminium hydroxide** (*Amphogel*) 30 mL nor **magnesium hydroxide** (*Milk of Magnesia*) 15 mL, taken with and 3 hours after a single 75-mg dose of warfarin, had any effect on warfarin peak levels or AUC.[1]

Mechanism

It is suggested that dicoumarol forms a more readily absorbed chelate with magnesium so that its effects are increased.[1,3] An *in vitro* study suggested that the absorption of warfarin may be decreased by **magnesium trisilicate**,[4] where as another *in vitro* study found no effect.[5]

Importance and management

No special precautions need be taken if aluminium or magnesium hydroxide antacids are given to patients taking warfarin, or if aluminium hydroxide is given to those taking dicoumarol. Despite the evidence of increased absorption of dicoumarol with magnesium hydroxide, there seems to be no direct clinical evidence of any important adverse interaction for this combination, or indeed between any coumarin and an antacid.

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Coumarins + Antibacterials

Altered (usually enhanced) response to anticoagulation with a coumarin has been reported with virtually every class of antibacterial. While some such as sulfamethoxazole, clearly have a pharmacokinetic interaction, for others there is no clear explanation for why an interaction might be expected. Theoretical mechanisms include reduced intestinal bacterial production of vitamin K_2 substances, or reduced enterohepatic recycling. Possible confounding mechanisms include a reduction in dietary vitamin K_1

intake because of illness, or the effect of fever or infection on coagulation or drug metabolism.

Clinical evidence and mechanism

Various studies have implicated antibacterials in general as being a risk factor for over-anticoagulation. For example, in a large prospective cohort study, INR levels of greater than 7 were recorded in 31 patients. When compared with 100 patients with stable INRs, these 31 patients were more likely to have been treated with an antibacterial (not specified) in the previous 4 weeks (odds ratio 6.2), and more likely to have an intercurrent illness (odds ratio 4.48).[1] Various mechanisms may be responsible for these findings, and these are discussed below.

(a) Confounding effects relating to the infection

1. Dietary factors. Patients taking coumarins and related drugs are advised to maintain a constant dietary intake of vitamin K_1 as sustained changes in intake of vitamin K_1-rich foods, such as green leafy vegetables, causes clinically relevant changes in anticoagulation. See 'Coumarins and related drugs + Food; Vitamin K_1-rich', p.464. It is therefore possible that patients who stop eating for more than a day or so could develop over-anticoagulation. The same could happen with a reduced appetite leading to a sustained reduction in intake of vitamin K_1-rich foods.

2. Fever. Fever might possibly be a confounding factor in reports of interactions between antibacterials and warfarin, because it might increase the catabolism of vitamin K-dependent coagulation factors by producing a hypermetabolic state. However, in one cohort study, there was no difference in the frequency of fever between patients who developed over-anticoagulation (INR greater than 6) while taking antibacterials and those who did not develop over-anticoagulation while taking antibacterials.[2]

3. Reduced metabolism. There is some evidence from *animal* studies that infection can down regulate cytochrome P450 isoenzymes, which might result in reduced drug metabolism.[3] Whether the metabolism of warfarin is different during an acute infection does not appear to have been studied.

(b) Effects relating to the antibacterial

1. Direct anticoagulant effects. Cephalosporins and related beta lactams with an *N*-methylthiotetrazole or similar side-chain can occasionally cause enough hypoprothrombinaemia for bleeding to occur when they are used alone, and this effect might therefore be additive with coumarins, although there is not that much evidence to support this, see 'Coumarins and related drugs + Antibacterials; Cephalosporins and related drugs', p.415.

2. Intestinal production of vitamin K_2 substances by bacteria. The activity of intestinal microflora produces menaquinones (vitamin K_2 substances). Suppression of the microflora might therefore result in reduced vitamin K_2, and hence reduced synthesis of vitamin-K dependent clotting factors. There is some evidence from studies in healthy subjects receiving vitamin-K_1 restricted diets and taking warfarin that giving menaquinones (an extract of bacterially synthesised material) decreases the response to warfarin.[4] In addition, natto, a fermented soya bean product which is a rich source of bacterially-derived menaquinones, markedly inhibits the effect of warfarin (see 'Coumarins + Food; Soya bean products', p.463). It is therefore possible that antibacterials that decimate gut microflora might increase the effect of warfarin by reducing vitamin K_2 levels. However, this effect might be important only if vitamin-K_1 intake from dietary sources is also reduced.

3. Protein-binding displacement. Many drugs can displace warfarin from protein-binding sites leading to an increase in unbound (active) concentrations of warfarin. However, any effect is transient, as the unbound warfarin is quickly metabolised. The exception to this is if the metabolism of warfarin is markedly inhibited at the same time. On rare example of a drug that is known to interact by both these mechanisms is phenylbutazone, see 'Coumarins and related drugs + NSAIDs; Phenylbutazone and related drugs', p.488. Altered protein binding has not clearly been shown to be an important mechanism in any interaction between warfarin and an antibacterial, but it is often suggested as one.

4. Reduced or increased metabolism. Sulfamethoxazole clearly inhibits the metabolism of warfarin by the cytochrome P450 isoenzyme CYP2C9, so enhancing its effect. Some macrolides such as erythromycin inhibit CYP3A4, and therefore have a minor inhibitory effect on *R*-warfarin, which would, on its own, be unlikely to be of any clinical relevance. Conversely, rifampicin (rifampin), see 'Coumarins + Antibacterials; Rifamycins', p.424, is a well established inducer of drug metabolism, and clearly reduces the effect of warfarin. Nafcillin (see 'Coumarins + Antibacterials; Penicillins', p.421) also appears to markedly reduce the effects of warfarin. Most other antibacterial classes have no clinically relevant effect on warfarin pharmacokinetics.

Importance and management

All these factors in their own right might affect the intensity of anticoagulation. Therefore, a few case reports of an enhanced response to warfarin on starting a specific antibacterial does not necessarily imply that the antibacterial has a direct interaction with warfarin. Conversely, demonstration of a lack of a specific interaction between an antibacterial and warfarin in a controlled study does not mean that a patient prescribed that drug for an infection will not have a change in coagulation status. Therefore, if a patient is unwell enough to require an antibacterial, it may be prudent to increase monitoring of coagulation status even if no specific drug interaction is expected. Monitor within 3 days of starting the antibacterial. The expectation of an interaction should not exclude the use of an antibacterial if it is considered clinically appropriate.

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Coumarins and related drugs + Antibacterials; Aminoglycosides

Limited data suggest that no clinically significant interaction occurs between dicoumarol or warfarin and oral neomycin or paromomycin in most patients. However, individual patients have shown some alteration in anticoagulant effect (usually increases) when given oral neomycin and parenteral streptomycin, and a marked increased risk of hospitalisation for bleeding has been reported in patients taking acenocoumarol and phenprocoumon and given neomycin.

Clinical evidence

(a) Neomycin

Six out of 10 patients taking **warfarin** who were given oral neomycin (2 g daily[1] or 4 g daily[2]) over a 3-week period had a gradual increase in their prothrombin times averaging 5.6 seconds.[1,2] Similarly, in patients taking an unnamed anticoagulant, 2 of 5 given oral neomycin with bacitracin had a fall in their prothrombin-proconvertin concentration from a range of 10 to 30% to less than 6%. This suggests an *increase* in anticoagulant effect.

Five of 7 patients taking unnamed anticoagulants had no change in their mean daily dose of anticoagulant when given oral **neomycin** 1 to 2 g daily for 18 weeks. Of the remaining two, one required an increase of about 100%, and one required a small 27% decrease.[3]

In a retrospective cohort study,[4] the relative risk of hospitalisation for bleeding in patients taking **acenocoumarol** or **phenprocoumon** and given neomycin was very high (relative risk 43). However, as the incidence of concurrent use was low (only 25 patients), the confidence interval was very broad (range 6 to 308).

(b) Paromomycin

The concurrent use of oral **paromomycin** 2 g daily with **dicoumarol** or **warfarin** did not alter anticoagulant requirements in 2 subjects.[5]

(c) Streptomycin

One of 3 patients given parenteral **streptomycin** 500 mg twice daily, and 2 patients given parenteral **streptomycin** 500 mg twice daily with 1 million units of penicillin daily had a fall in their prothrombin-proconvertin concentration from a range of 10 to 30% down to 6 to 9%. This suggests an *increase* in anticoagulant effect.[6]

Mechanism

Not understood. One idea is that these antibacterials increase the effects of these coumarins by diminishing the bacterial population in the gut, there-

by reducing their production of vitamin K_2 substances, see 'Coumarins + Antibacterials', p.413. Another suggestion is that these antibacterials decrease the vitamin K_1 absorption as part of a general antibacterial-induced malabsorption syndrome.[7]

Importance and management

A sparsely documented interaction. The data implies that, rarely, an increased risk of bleeding may occur if aminoglycosides are given with coumarins but common experience seems to confirm that normally no interaction of any significance occurs. The data relating to acenocoumarol and phenprocoumon and neomycin need confirming.

One manufacturer of **gentamicin** suggests that concurrent use with oral anticoagulants may decrease thrombin levels,[8] which would be expected to increase the risk of bleeding, but there appears to be little evidence to suggest that this usually occurs. However, occasionally vitamin K deficiency and/or spontaneous bleeding is seen after the prolonged use of broad-spectrum antibacterials in association with a totally inadequate diet, starvation or some other condition in which the intake of vitamin K is very limited.[9,10] Under these circumstances the effects of the vitamin-K antagonist anticoagulants (both coumarins and **indanediones**) would be expected to be significantly increased and appropriate precautions should be taken.

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Coumarins + Antibacterials; Aminosalicylic acid and/or Isoniazid

A report attributes bleeding in a patient taking warfarin to the concurrent use of isoniazid. Another report describes a markedly increased anticoagulant response in a patient taking warfarin when the dose was doubled and aminosalicylic acid and isoniazid were started.

Clinical evidence

A man who had recently started to take **warfarin** 10 mg daily and isoniazid 300 mg daily began to bleed (haematuria, bleeding gums) within 10 days of accidentally doubling his dose of isoniazid. His prothrombin time had increased from about 26 seconds to 53 seconds.[1] Another patient taking digoxin, potassium chloride, docusate, diazepam and **warfarin** 2.5 mg daily, was also given aminosalicylic acid 12 g, isoniazid 300 mg and pyridoxine 100 mg daily, and at the same time the warfarin dose was doubled to 5 mg daily. His prothrombin time increased from 18 seconds to 130 seconds over 20 days but no signs of bleeding were seen.[2]

Mechanism

Not understood. It seems possible that isoniazid may inhibit the metabolism of the coumarin anticoagulants, because *in vitro* study in human liver microsomes has shown that it inhibits *S*-warfarin 7-hydroxylation by the cytochrome P450 isoenzyme CYP2C9,[3] but this needs confirmation *in vivo*. Isoniazid increased the anticoagulant effects of dicoumarol in *dogs*[4] but not of warfarin in *rabbits*.[5] Two patients taking isoniazid, aminosalicylic acid and streptomycin (but not taking anticoagulants) developed haemorrhage, which was attributed to the effects of isoniazid alone.[6]

Importance and management

These two isolated cases of possible interactions are far from conclusive, and the interactions of warfarin with isoniazid and aminosalicylic acid are not established. Nevertheless, given that the *in vitro* data suggest that isoniazid might inhibit warfarin metabolism, some caution might be appropriate. If this is the case, similar caution may also need to be extended to other coumarins that are metabolised in the same way as warfarin, such as **acenocoumarol**. Further study is needed.

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Coumarins and related drugs + Antibacterials; Cephalosporins and related drugs

Cephalosporins and related beta lactams with an *N*-methylthiotetrazole or similar side-chain can occasionally cause bleeding when they are used alone. These effects could therefore be additive with those of the coumarins. Some studies and cases of raised INRs and bleeding have been reported with both warfarin and acenocoumarol.

Of the cephalosporins not having an *N*-methylthiotetrazole or related side-chain, a few cases of over-anticoagulation have been reported for cefixime and cefaclor with coumarins and phenindione, and an increased risk of haemorrhage has been reported in patients taking coumarins with cefuroxime and cefradine.

Clinical evidence

(a) Cephalosporins with N-methylthiotetrazole or similar side-chains

Note that cephalosporins with N-methylthiotetrazole or similar side-chains can cause bleeding alone. For example, serious bleeding following the use of **cefamandole** (in the absence of an anticoagulant) has been described in 3 out of 37 patients in one report,[1] and a further report highlights a further 16 cases.[2] Other similar cephalosporins and related beta lactams that have been reported to cause hypoprothrombinaemia when used alone include **cefoperazone**,[3-7] **cefotetan**,[8] **ceftriaxone**,[9] **cefalotin**,[10] **cefazolin**,[11-13] and **latamoxef**.[14,15] The incidence is very variable: in some instances only isolated cases have been reported whereas a 15% bleeding rate was found in one study[15] with **latamoxef** alone, 22% in another[14], but only 8% with **cefoxitin** alone.[14] These cephalosporins might therefore worsen the risk of bleeding by simple addition if given with coumarin or **indanedione** anticoagulants. In addition, some of them may also inhibit platelet function.[16]

1. Cefamandole or cefazolin. Two patients who had received prophylactic cefamandole before cardiac valve replacement developed unusually high prothrombin times, with bleeding in one case, within 48 hours of an initial dose of **warfarin** 10 mg. Because of this, the records of a total of 60 other patients who had undergone heart valve replacement surgery were reviewed. They had been given prophylactic antibacterials before the chest incision was made, and every 6 hours thereafter for about 72 hours. The 44 patients given cefamandole 2 g showed a much greater anticoagulant response than the 16 patients given vancomycin 500 mg. Fourteen of the cefamandole group had a prothrombin time greater than 32 seconds after the initial **warfarin** dose, compared with only one of the vancomycin group.[17] In a later randomised study by the same workers, the prothrombin times as a percentage of activity after 3 days of concurrent use with **warfarin** were cefamandole 29%, cefazolin 38%, and vancomycin 51%. This suggests that cefamandole had a much greater effect on anticoagulant response than vancomycin.[18]

2. Cefonicid. In a study in 9 patients stabilised on **warfarin**, there was no change in prothrombin times when they were given intravenous cefonicid 2 g daily for 7 days.[19] In contrast, a later study identified 9 patients taking **acenocoumarol** who had increased INRs within 3 to 8 days of being given cefonicid. They needed a reduction in the anticoagulant dose of about

one-third to one-half.[20] Another patient stabilised on **acenocoumarol**, with a prothrombin index of 28% bled 2 days after starting cefonicid 1 g daily and had a prothrombin index of less than 5%.[21]

3. Cefotiam. Severe haemorrhage has been reported in 3 patients taking **acenocoumarol** with cefotiam. One developed an abdominal haematoma and an INR of 10.4 within 2 days. Another had gastrointestinal bleeding and melaena after one day of concurrent use. The third died from intracranial haemorrhage on the day she started cefotiam.[22]

(b) Cephalosporins without N-methylthiotetrazole or similar side-chains

1. Cefaclor. Over the period 1979 to 1997, there had been 3 cases of raised INRs with or without clinical bleeding in patients taking **acenocoumarol**, **warfarin** or an unknown anticoagulant and cefaclor reported to the CSM in the UK.[23] No cases seem to have been published.

2. Cefixime. Cefixime has also been implicated in a handful of cases of bleeding and/or increased INRs in patients taking **warfarin** or the indanedione **phenindione**, but the evidence is inconclusive.[24] No cases seem to have been published.

3. Cefradine. In a retrospective cohort study, the relative risk of hospitalisation for bleeding in patients taking **acenocoumarol** or **phenprocoumon** and also taking cefradine was very high (relative risk 43). This equated to 1 major bleed per 100 cefradine dispensings during coumarin use.[25]

4. Cefuroxime. In a retrospective case-control study,[26] there was a moderate increased risk of hospitalisation for haemorrhage in acutely ill elderly patients who had received cefuroxime prior to admission (odds ratio 1.62). A retrospective review of the effect of antibacterials on INR in children taking **warfarin** mentions that a 2-and-a-half-year-old child had an INR of 6.7 five days after starting oral cefuroxime.[27]

(c) Unnamed cephalosporins

In a prospective study of the effect of antibacterials on anticoagulation, none of the 36 patients taking **warfarin** and prescribed an oral cephalosporin (not named) experienced a change in their INR.[28] Conversely, a mean INR rise of 1.2 was reported in 12 children taking **warfarin** and receiving cephalosporins.[27] In a large analysis of claims data, use of cephalosporins (unnamed) with **warfarin** was associated with a very slight increase in risk of haemorrhage of 1.16, which was statistically significant.[29]

Mechanism

Cephalosporins with an *N*-methylthiotetrazole side-chain can, like the oral anticoagulants, act as vitamin K antagonists to reduce the production of some blood clotting factors. They can therefore cause bleeding on their own, which would be expected to be additive when used with an anticoagulant. Some of these cephalosporins may also inhibit platelet function.[16]

Ceftriaxone seems to act similarly although it has an *N*-methylthio*triazine* ring instead, as does cefazolin, which has an *N*-methylthiadiazolethiol side-chain. **Aztreonam** can also increase the prothrombin time.[30-33]

Importance and management

Most cephalosporins and related beta lactams do not normally cause bleeding so would not be expected to have an additive interaction with the oral anticoagulants. In contrast, cephalosporins with the *N*-methylthiotetrazole or similar side-chains appear to increase the risk of bleeding, and might therefore interact. Both **cefamandole** and to a lesser extent **cefazolin** have been shown to increase the response to warfarin, and cases of over-anticoagulation have been reported for **cefonicid** and **cefotiam**. All other cephalosporins and related beta-lactams with the *N*-methylthiotetrazole or similar side-chains might be expected to interact similarly, but have not so far been reported to specifically interact with anticoagulants. These include **cefalotin**, **cefmenoxime**, **cefmetazole**, **cefminox**, **cefoperazone**, **ceforanide**, **cefotetan**, **cefpiramide**, **ceftriaxone**, and **latamoxef**. **Aztreonam** has also been predicted to interact similarly, although, again there are no reports. Patients most at risk seem to be those whose intake of vitamin K is restricted (poor diet, malabsorption syndromes, etc.) and those with renal impairment. The use of an anticoagulant represents just another factor that may precipitate bleeding.

A possible solution to the problem is to use a non-interacting cephalosporin. Alternatively the outcome should be closely monitored, particularly in the early stages of treatment, adjusting the anticoagulant dosage if necessary. Excessive hypoprothrombinaemia can be controlled with vitamin K. Although they do not an *N*-methylthiotetrazole side-chain, the manufacturers of **cefixime** and **cefaclor** have a few cases of over-anticoagulation on record, and an increased risk of haemorrhage has been reported for cefradine and cefuroxime.

Even with non-interacting cephalosporins, if a patient is unwell enough to require an antibacterial, it may be prudent to increase monitoring of coagulation status (see 'Coumarins + Antibacterials', p.413). Monitor within 3 days of starting the antibacterial.

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Coumarins + Antibacterials; Chloramphenicol

There is some limited evidence to suggest that the anticoagulant effects of acenocoumarol and dicoumarol can be increased by oral chloramphenicol. An isolated report attributes a marked rise in the INR of a patient taking warfarin to the use of chloramphenicol eye drops.

Clinical evidence

A study in 4 patients found that the half-life of **dicoumarol** was increased on average from 8 hours to 25 hours when they were given oral chloramphenicol 2 g daily for 5 to 8 days.[1]

Three out of 9 patients taking an unnamed anticoagulant had a fall in their prothrombin-proconvertin values from a range of 10 to 30% down to less than 6% (suggesting an increased anticoagulant effect) when given oral chloramphenicol 1 to 2 g daily for 4 to 6 days. One patient had a smaller reduction.[2] In early clinical experience with **acenocoumarol**, one of 3 patients taking chloramphenicol had greater sensitivity to the anticoagulant.[3]

An isolated report describes an 83-year-old woman stabilised on **warfarin** who had a rise in her INR to about 8.9 from her normal range of 1.9 to 2.8 within 2 weeks of starting to use eye drops containing chloramphenicol 5 mg/mL, dexamethasone sodium phosphate 1 mg/mL and tetrahydrozoline hydrochloride 0.25 mg/mL. She used one drop in each eye four times daily.[4] Hypoprothrombinaemia and bleeding have also been described in patients given intramuscular,[5] intravenous,[5] or oral[6] chloramphenicol in the absence of an anticoagulant.

Mechanism

Uncertain. One suggestion is that the chloramphenicol inhibits the liver enzymes concerned with the metabolism of the anticoagulants so that their effects are prolonged and increased.[4] An *in vitro* study with human liver microsomes found that chloramphenicol did not inhibit the hydroxylation of *S*-warfarin, but it did inhibit *R*-warfarin metabolism, probably by the cytochrome P450 isoenzyme CYP3A4.[7] Another suggestion is that the antibacterial diminishes the gut bacteria thereby decreasing a source of vitamin K, but it is doubtful if these bacteria are normally an important source of the vitamin except in exceptional cases where dietary levels are very inadequate.[8] A third suggestion is that chloramphenicol blocks the production of prothrombin by the liver.[5] See also 'Coumarins + Antibacterials', p.413.

Importance and management

The documentation for the interaction between anticoagulants and oral chloramphenicol is very sparse and poor (the best being the pharmacokinetic report about dicoumarol) so that this interaction is by no means adequately established. There would therefore appear to be little reason for avoiding concurrent use, but it would seem prudent to monitor prothrombin times if oral chloramphenicol is started in patients taking a coumarin, being alert for the need to reduce the anticoagulant dose.

The report about an apparent interaction between warfarin and topical chloramphenicol is surprising because the amount of chloramphenicol absorbed from eye drops is relatively small and because, despite the very widespread use of warfarin and chloramphenicol for very many years, this report appears to be the only one. This suggests that any such interaction is very unlikely indeed.

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Coumarins + Antibacterials; Clindamycin

Two isolated cases of a marked increase in INR and/or bleeding have been attributed to an interaction with clindamycin. However, a report found no cases of a serious increase in INR in patients taking acenocoumarol or phenprocoumon with clindamycin.

Clinical evidence, mechanism, importance and management

A 47-year-old woman with multiple medical problems stabilised on **warfarin** (and also taking azathioprine, captopril, furosemide, insulin, captopril, prednisone, levothyroxine, valproic acid and zolpidem) had all her teeth removed under general anaesthetic. Sixteen days later she needed a dental abscess drained and was given oral clindamycin 300 mg four times daily with ibuprofen 600 mg for any discomfort. On day 17 she needed a suture to stop some bleeding and her INR was found to be 3.5. By day 20 she had developed more severe oral bleeding, which needed emergency room treatment. Her INR was found to have risen to 13 and her haematocrit decreased to 18%. She was treated successfully with a blood transfusion and vitamin K.[1]

A retrospective review of the effect of antibacterials on INR in children taking **warfarin** mentions that an INR of 8.5 was noted in a 4-year-old child, 6 days after clindamycin was started.[2]

These appear to be isolated cases, from which no general conclusions should be drawn because the whole picture is so uncertain. Note that in a cohort study, none of 37 patients stabilised on **acenocoumarol** or **phenprocoumon** developed over-anticoagulation (an INR greater than 6) when they were given clindamycin.[3] However, if a patient is unwell enough to require an antibacterial, it may be prudent to increase monitoring of coagulation status even if no specific drug interaction is expected. Monitor within 3 days of starting the antibacterial (see also 'Coumarins + Antibacterials', p.413).

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Coumarins + Antibacterials; Linezolid

Linezolid had only minor effects on the pharmacokinetics and anticoagulant activity of single-dose warfarin in one study.

Clinical evidence, mechanism, importance and management

Linezolid 600 mg twice daily was given to 13 healthy subjects for 5 days followed by a single 25-mg dose of **warfarin**. The pharmacokinetics of **warfarin** with linezolid were within 20% of those seen with **warfarin** alone, and the INR was minimally affected (about a 10% increase in maximal INR).[1] These effects were not considered to be clinically relevant.

However, if a patient is unwell enough to require an antibacterial, it may be prudent to increase monitoring of coagulation status even if no specific drug interaction is expected. Monitor within 3 days of starting the antibacterial. See also 'Coumarins + Antibacterials', p.413.

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Coumarins + Antibacterials; Macrolides

Most controlled studies suggest that macrolides do not cause clinically relevant changes in the pharmacokinetics or anticoagulant effects of warfarin. There is less information about other anticoagulants, but two retrospective studies of acenocoumarol and phenprocoumon have variously shown an increased risk (azithromycin, clarithromycin), a non-significant increased risk (erythromycin) or no increased risk of bleeding (clarithromycin, erythromycin, roxithromycin). Furthermore, a number of case reports describe marked increases in INRs and/or bleeding in patients taking coumarins and macrolides.

Clinical evidence

(a) Azithromycin

There are no studies of the effect of azithromycin on the pharmacokinetics of coumarins. One pharmacodynamic study and two retrospective studies suggest that no interaction occurs with warfarin. However, two retrospective studies and at least 7 published case reports suggest an interaction might occur with coumarins. These are discussed below.

1. Acenocoumarol or Phenprocoumon. In a retrospective cohort study, the relative risk of hospitalisation for bleeding in patients taking acenocoumarol or phenprocoumon and given azithromycin was 4.1. This only just reached statistical significance (confidence interval range, 1 to 16.2), and represented one major bleed per 1250 azithromycin dispensings.[1]

2. Warfarin. The manufacturer notes that, in healthy subjects, a 5-day course of azithromycin (500 mg on day one then 250 mg daily for 4 days) did not affect the prothrombin time response to a single 15-mg dose of warfarin.[2,3]

A retrospective study of 26 patients stabilised on warfarin found no evidence that the use of azithromycin had any effect on their INRs. The patients had stable INRs for a least 2 consecutive measurements before receiving azithromycin, and an INR taken within 14 days (9 patients) or 30 days (17 patients) of starting the azithromycin.[4] The same finding was reported in another similar smaller study in 17 patients.[5] A major disadvantage of these 2 retrospective studies is the small numbers of patients who had an INR measurement within 7 days of starting azithromycin.

In contrast, in another retrospective study of 32 patients stabilised on warfarin, there was a mean increase in INR of 0.51 after starting azithromycin (5 patients had an INR of greater than 4, and one patient had an INR greater than 5). The patients had stable INRs for a least 2 consecutive measurements before receiving azithromycin, and an INR taken within 3 to 15 days of starting the azithromycin.[6] Moreover, there are now a number of published case reports suggesting that azithromycin might potentiate the activity of warfarin.[7-14] In one of these cases, a 57-year-old woman stabilised on warfarin with an INR ranging from 1.75 to 3.03 in the previous 3 months took a 5-day course of azithromycin (500 mg on day one, then 250 mg daily for 4 days) for a possible upper respiratory tract infection. Two days after completing the azithromycin, a routine INR was found to be 8.32. She had no signs or symptoms of bleeding. During the infection she had a fever on the second day, and she reduced her 'smoking', (p.514), from one pack of cigarettes daily to one pack over 3 days.[11] In other cases, a rise in INR of 40% to sixfold occurred within 1 to 7 days of starting azithromycin.[7-10,12,13] Three patients had bleeding complications,[8,9,12] and 4 required vitamin K administration.[8-10,12] Most of these patients had possible confounding factors such as recent increases in warfarin dose,[9,10] other concurrent antibacterials,[10,13] fever and decreased appetite,[7,12] or complex disease states and heart failure.[8-10,12]

The manufacturers[15] say that as of December 1998, they had received 47 reports (40 in the US, 7 elsewhere in the world, including 2 in the UK) of possible interactions between azithromycin and warfarin. A 2004 report from the Australian Adverse Drug Reactions Advisory Committee said they had received 3 reports of interactions between warfarin and azithromycin,[16] which presumably includes the 2 published cases.[10]

(b) Clarithromycin

There are no studies of the effect of clarithromycin on the pharmacokinetics of coumarins. However, there are at least 13 cases of increased INRs in published reports, and one cohort study suggesting that the use of clarithromycin is associated with an increased risk of bleeding in patients taking coumarins. Conversely, in another cohort study the increased risk was small and not significant. These are discussed below.

1. Acenocoumarol or Phenprocoumon. The INR of a 75-year-old woman stabilised on acenocoumarol rose from 2.1 to 9 within a week of starting to take clarithromycin 250 mg twice daily.[17] Five patients stabilised on acenocoumarol had a mean increase in their INRs from about 2.5 to 5.5 when they took clarithromycin.[18] The largest increase was from 1.95 to 7.01.

A 70-year-old woman stabilised on phenprocoumon developed a marked increase in prothrombin time from a range of 140 to 180 seconds up to 304 seconds, but no bleeding, within 4 days of starting to take clarithromycin 500 mg daily. The phenprocoumon was stopped and phytomenadione given. When the antibacterial was withdrawn she was restabilised on the original dose of phenprocoumon.[19]

In one cohort study in patients taking acenocoumarol or phenprocoumon, clarithromycin significantly increased the risk of over-anticoagulation (INR greater than 6: relative risk of 11.7 range 3.6 to 37.8). The risk was highest during the first 3 days of concurrent use.[20] However, in another retrospective cohort study[1] by the same research group, the relative risk of hospitalisation for haemorrhage in patients taking acenocoumarol or phenprocoumon and clarithromycin was just 1.8, and was not statistically significant (range 0.4 to 7).

2. Warfarin. In 1992 the CSM in the UK notified prescribers in the UK of a case of a woman taking warfarin for mitral valve disease who suffered a fatal cerebrovascular bleed 3 days after starting to take clarithromycin.[21] Her INR was above 10. A further patient stabilised on warfarin had a suprachoroidal haemorrhage 7 days after starting clarithromycin 250 mg twice daily, with permanent vision loss. Her INR was 8.2. She had a normal INR (2.3) three days before starting clarithromycin, and also 3 days after starting clarithromycin (2.9).[22]

Other patients taking warfarin have been found to have INRs ranging from 5.6 to 90.3 within 4 to 12 days of starting, or 5 to 14 days of finishing, a course of clarithromycin.[23-26] None of these patients had bleeding complications. In a brief report in 2004, the Adverse Drug Reactions Advisory Committee of Australia state that they had received 6 reports of interactions between clarithromycin and warfarin (median INR of 7.6), two of which were symptomatic.[16]

(c) Dirithromycin

In a study in 15 healthy subjects the pharmacokinetics and pharmacodynamics of a single 0.5-mg/kg dose of warfarin were not altered when it was given on day 10 of a 14-day course of dirithromycin 500 mg daily.[27]

(d) Erythromycin

Erythromycin caused a minor inhibition of warfarin metabolism in three pharmacokinetic studies. There are also quite a few case reports that describe this interaction. These are discussed below.

1. Acenocoumarol or Phenprocoumon. Haematuria occurred in a patient stabilised on acenocoumarol on the last day of a 14-day course of erythromycin.[28] Another patient stabilised on acenocoumarol with an INR in the range of 3 to 4.5 was found to have an INR of 15 a week after starting to take erythromycin ethylsuccinate 1.5 g daily but no bleeding was seen.[29]

Conversely, in one cohort study in patients taking acenocoumarol or phenprocoumon, no cases of over-anticoagulation (INR greater than 6) occurred in patients taking erythromycin (78 patients received this antibacterial).[20] Note that this study did show an increase for *clarithromycin*, see above. In yet another retrospective cohort study[1] by the same research group, the relative risk of hospitalisation for haemorrhage in patients taking acenocoumarol or phenprocoumon and erythromycin was 4.2, but this was not statistically significant (confidence interval range 0.6 to 30).

2. Warfarin. A study in 12 healthy subjects found that the clearance of a single 1-mg/kg dose of warfarin was reduced by an average of 14% (range 0 to about 30%) when taken on day 5 of an 8-day course of erythromycin 250 mg every 6 hours. This change was greatest in those subjects with relatively slow warfarin clearance rates.[30] In another similar study, warfarin 0.5 mg/kg, given on day 10 of a 14-day course of erythromycin 250 mg four times daily increased the AUC of *S*-warfarin by 11% and of *R*-warfarin by 12%. The INR increased by 10%.[27] Similar effects were seen in another study in 8 patients stabilised on warfarin and who did not have infections. In these patients, erythromycin 333 mg three times daily for 7 days caused a mean 10% increase in the prothrombin time ratio, which was maximal by day 2 to 5. There was also a mean 9% increase in the total plasma warfarin level, which was similar for the *S*- and *R*-enantiomers, and was maximal by day 7. No patient had a prothrombin time ratio above the therapeutic range and none required a reduction in warfarin dose.[31]

In contrast to the modest effects in the above studies, various case reports have demonstrated a marked increase in INR. For example, an elderly woman taking warfarin developed haematuria and bruising within a week of starting to take erythromycin stearate 500 mg four times daily for a chest infection. Her prothrombin time had risen to 64 seconds (prothrombin time ratio about 5.5). Within the previous month she had started taking digoxin and quinidine, and had her warfarin dose increased because of a decrease in prothrombin time.[32] At least 10 other cases of bleeding and/or an increase in prothrombin time or INR have been described in patients taking warfarin with erythromycin (as the base, ethylsuccinate, stearate, or lactobionate).[14,33-40] In addition, in a brief report in 2004, the Adverse Drug Reactions Advisory Committee of Australia stated that they had received 19 reports of interactions between erythromycin and warfarin (median INR of 9.7), only 4 of which were symptomatic.[16]

There is also a case report of sulfonamide-induced bullous haemorrhagic eruption in a patient taking warfarin, 'co-trimoxazole', (p.425), and erythromycin, in which the authors considered an interaction between warfarin and erythromycin may have contributed to the haemorrhagic component.[41]

(e) Midecamycin diacetate

The pharmacokinetics of a single 8-mg oral dose of acenocoumarol were not significantly changed when it was taken on day 4 of a 9-day course of midecamycin diacetate 800 mg twice daily.[42]

(f) Roxithromycin

Roxithromycin did not alter the pharmacokinetics or effect of warfarin in one study. However, there are at least 2 published cases of interactions with coumarins, and one report reviewing 16 cases. These are discussed below.

1. Acenocoumarol. A 79-year-old man stabilised on acenocoumarol developed an abdominal wall haematoma 2 days after starting to take roxithromycin 150 mg twice daily for a lung infection.[43] Six days later, on admission to hospital, his INR was found to be 5.9. Conversely, in one cohort study in patients taking acenocoumarol or phenprocoumon, no cases of over-anticoagulation (INR greater than 6) occurred in patients treated with roxithromycin (only 14 patients received this antibacterial).[20] Note that this study did show an increase for *clarithromycin*, see above.

2. Phenprocoumon. A 75-year-old man taking phenprocoumon developed a marked increase in prothrombin time but no bleeding when he was given roxithromycin 300 mg daily for 5 days. The phenprocoumon was stopped and phytomenadione given. When the antibacterial was withdrawn he was restabilised on the original dose of phenprocoumon.[19] For mention of a cohort study in patients stabilised on phenprocoumon or acenocoumarol showing no increased risk of over-anticoagulation with roxithromycin, see *Acenocoumarol*, above.

3. Warfarin. In a study in which warfarin was given at a daily dose sufficient to maintain the thrombotest percentages at 10 to 20%, there was no difference in warfarin dose or AUC between 10 subjects given roxithromycin 150 mg twice daily for 2 weeks and 11 subjects given placebo. The dose of warfarin and the AUC of warfarin increased by about 10% in both the roxithromycin group and the placebo group, which was taken as indicating that steady state had not been achieved. Serum roxithromycin levels were unchanged by warfarin.[44] In contrast, during the 1992 to 1995 period The Centre for Adverse Reactions Monitoring of New Zealand (ADRAC) received 7 reports of a possible interaction with roxithromycin resulting in increased warfarin effects, and, during the same period, the Adverse Drug Reactions Advisory Committee of Australia received 9 similar reports. Review of the 16 cases found that 7 patients had clinical symptoms of over-anticoagulation, and the other 9 were asymptomatic and detected by routine testing.[45] In a 2004 update from ADRAC, it was noted that they now had on record 56 cases of an interaction between roxithromycin and warfarin, with 27 cases being symptomatic. The median INR was 8.8, and the median time to onset was 6 days. One fatality occurred in a 79-year-old woman who started taking warfarin and roxithromycin at the same time. By day 8, she had an INR of 11.6, and subsequently died from widespread bleeding.[16]

(g) Telithromycin

In a placebo-controlled, crossover study in healthy subjects, telithromycin 800 mg daily for 7 days did not alter the pharmacodynamics of a single-dose of warfarin 25 mg given on day 4. There was a small 20% increase in the AUC of *R*-warfarin, and a 5% increase in the AUC of *S*-warfarin,[46] effects which the manufacturer does not consider to be clinically relevant.[47,48]

Conversely, a 73-year-old man taking warfarin for a metallic valve replacement started taking telithromycin 800 mg daily for 5 days for a cough. On the last day of treatment he developed haemoptysis and was found to have an INR of 11. His INR 10 days before telithromycin was started was 3.1. The telithromycin was stopped and he was subsequently restabilised on warfarin.[49] Moreover, Health Canada reported that from May 2003 to September 2004 they had received 7 reports of suspected coagulation disorder interactions with telithromycin, 6 with warfarin and one with an unspecified oral anticoagulant. The INR was increased in 6 of the reports and decreased in the seventh.[50] A case of a rectal sheath haematoma with an INR rise to 6 occurred 6 days after starting telithromycin 800 mg daily in a patient stabilised on acenocoumarol.[51]

(h) Unspecified macrolides

In a prospective study of the effect of antibacterials on anticoagulation, the INR increased by an estimated 0.319 when 35 patients taking warfarin also took an oral macrolide (not named).[52] In a retrospective review of the effect of antibacterials on INR in children taking warfarin, the mean INR increase in 18 children who had received a macrolide was just 0.9, and a large part of this was due to two children who had marked INR rises with erythromycin and azithromycin.[14]

Mechanism

Erythromycin, clarithromycin and telithromycin are known inhibitors of the cytochrome P450 isoenzyme CYP3A4. However, this isoenzyme has only a minor role in the 'metabolism of warfarin', (p.405), specifically the less active *R*-isomer of warfarin. Consequently, only minor increases in the levels of warfarin have been seen in pharmacokinetic studies, which would generally not be expected to be clinically relevant. However, it is possible that even these small changes might be important in a very few patients, particularly those with a low prothrombin complex activity.[30] Other macrolides (azithromycin, dirithromycin, roxithromycin) have much less effect on CYP3A4 than erythromycin or clarithromycin, and consequently would be expected to have even less effect on the pharmacokinetics of warfarin or acenocoumarol, which is borne out in the few studies available. Nevertheless, cases of interactions have been reported for nearly all these macrolides. Moreover, one cohort study found that clarithromycin increased the risk of an interaction and erythromycin did not. It is possible that there is some other, as yet unidentified, mechanism involved. Alternatively, it is equally possible that the relatively few cases just represent idiosyncratic effects attributable to other factors, such as those secondary to being acutely ill, and not to any interaction (see also 'Coumarins + Antibacterials', p.413).

Importance and management

The minor pharmacokinetic interaction with erythromycin and warfarin is established, but would not generally be expected to be clinically relevant. This is borne out by the relatively few published reports of an interaction (11 published case reports worldwide and 19 cases reported to the Adverse Drug Reactions Advisory Committee of Australia). Other macrolides would be even less likely to inhibit the metabolism of warfarin or acenocoumarol than erythromycin, and this is borne out by studies with dirithromycin, midecamycin and roxithromycin. Nevertheless, cases of important interactions have been reported for most of the other macrolides (azithromycin, clarithromycin, roxithromycin, and telithromycin). Moreover, one cohort study found an increased risk of over-anticoagulation with clarithromycin but not with erythromycin. Taken together, the available evidence suggests that, occasionally and unpredictably the effects of warfarin, acenocoumarol or phenprocoumon may be markedly increased by the macrolides. It would therefore be prudent to increase monitoring in all patients when they are first given any macrolide antibacterial. There is some evidence that this may be particularly important in those who clear warfarin and other anticoagulants slowly and who therefore only need low doses. The elderly in particular would seem to fall into this higher risk category. With azithromycin, bear in mind that, because of its long half-life, the interaction may possibly not become apparent until a couple of days after a short course of azithromycin has been stopped.

If a patient is unwell enough to require an antibacterial, it may be prudent to increase monitoring of coagulation status even if no specific drug interaction is expected, see also 'Coumarins + Antibacterials', p.413. Monitor within 3 days of starting the antibacterial.

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Coumarins + Antibacterials; Metronidazole and related drugs

Limited evidence suggests that metronidazole may cause a marked increase in INR, without bleeding, and increase the risk of haemorrhage in patients also taking warfarin. A few case reports support these findings. One early study found that metronidazole increased the half-life of a single dose of warfarin by one-third and increased its effects. Nimorazole and tinidazole may interact similarly.

Clinical evidence

(a) Metronidazole

In 8 healthy subjects, metronidazole 250 mg three times daily for one week increased the half-life of a single 1.5-mg/kg dose of **warfarin** by about one-third (from 35 to 46 hours), and increased the prothrombin time from a mean of 100 seconds to 142 seconds. When the warfarin enantiomers were given separately, the anticoagulant effects of *S*-warfarin were virtually doubled and the half-life increased by 60%, but the response to *R*-warfarin was only affected in one subject.[1] In a retrospective cohort study, 32 patients taking **warfarin** had an INR reading before and during concurrent metronidazole use. In these patients, the mean INR increased from 2.2 to a maximum of 4.3 by day 8. Fourteen of the 32 patients had an INR above 4, but no bleeding events were recorded.[2] In a large analysis of claims data, the use of metronidazole with **warfarin** was associated with an increased risk of haemorrhage (odds ratio of 1.6).[3]

Bleeding has been seen in 2 patients taking **warfarin** and metronidazole.[4,5] One of them had severe pain in one leg, ecchymoses, and haemorrhage of both legs, and an increase in her prothrombin time from 17 to 19 seconds, up to 147 seconds within 17 days of starting metronidazole.[4] A further report describes 3 elderly patients taking **warfarin**, who developed raised INRs after being given intravenous metronidazole.[6] In the first patient, the INR on admission was 4.6, and so warfarin was stopped. The next day metronidazole was given for about 24 hours, and on day 4 the INR had reached 10.3. In the second patient the INR on admission was 4.9 and so the warfarin was stopped. Later that day metronidazole was started, and the INR was reduced to 1.7 with fresh frozen plasma. Nevertheless by day 5 the INR had reached 6 (metronidazole had been stopped on day 2). In the third patient the INR on admission was 4 and so the warfarin was stopped. Later that day metronidazole was given, and the INR was reduced to 2.1 with fresh frozen plasma. Nevertheless by day 5 (while still receiving metronidazole) the INR had reached 10. In another case, an elderly woman taking **warfarin** developed a profuse nosebleed after a fall with an INR of 8 nine days after starting metronidazole and levofloxacin (which may also interact, see 'Coumarins + Antibacterials; Quinolones', p.422). She was found to have an intracerebral haemorrhage.[7] A cohort study describes one patient taking **warfarin** who had severe bleeding and was found to have an INR of 4.5 two days after starting metronidazole.[8]

(b) Nimorazole

A 66-year-old man who had been taking **phenprocoumon** for 15 years with an INR around 2.5 was diagnosed with carcinoma of the glottis.[9] He received radiotherapy 6 times a week with nimorazole 2.5 g given 1.5 hours before the radiotherapy as a radiosensitiser. At the 16th dose, he had haemoptysis, on the 17th dose continuous haematuria, and then on the 22nd dose his INR was found to be 7.5. Fluconazole (which is also known to interact, see 'Coumarins + Azoles; Fluconazole', p.437), had been started 4 days previously. When the patient had recovered and restarted **phenprocoumon**, he was rechallenged with nimorazole before his last 5 days of radiotherapy, with an INR increase from 3.7 to 5.3.

Mechanism

In the early study, it was suggested that metronidazole probably inhibits the activity of the enzymes responsible for the metabolism (ring oxidation) of the more potent isomer *S*-warfarin, but not *R*-warfarin.[1] Reduction of protein binding coupled with reduced metabolism was suggested by other authors.[6] Nimorazole may act similarly. Note also that infection may affect coagulation status, see 'Coumarins + Antibacterials', p.413.

Importance and management

The interaction between metronidazole and warfarin appears to be established and clinically important, although the documentation is limited. Monitor the INR when both drugs are used and adjust the warfarin dose accordingly. Nothing seems to be documented about other anticoagulants but it would be prudent to expect other coumarins to behave similarly. The single case with nimorazole suggests that caution may also be warranted with this drug, and therefore probably all 5-nitroimidazoles, including **tinidazole**. Note that, if a patient is unwell enough to require an antibacterial, it may be prudent to increase monitoring of coagulation status even if no specific drug interaction is expected, see also 'Coumarins + Antibacterials', p.413. Monitor within 3 days of starting the antibacterial.

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Coumarins + Antibacterials; Penicillins

Isolated cases of increased prothrombin times and/or bleeding in patients taking coumarins have been seen in patients given amoxicillin (with or without clavulanic acid), intravenous benzylpenicillin, or pheneticillin. There is also some evidence that phenoxymethylpenicillin (penicillin V) does not increase the risk of bleeding in patients taking coumarins.
In contrast, several cases of markedly *reduced* warfarin effects have been seen with nafcillin. Similarly, dicloxacillin may cause a modest reduction in warfarin effects, and an isolated case of thrombosis has been reported.

Clinical evidence

(a) Amoxicillin ± Clavulanic acid

An 81-year-old woman taking **acenocoumarol** 3 mg daily (INR 2.5 to 4) developed bruising and an increased INR of 7.1 within a week of starting amoxicillin 500 mg every 8 hours.[1] In another case, a man stabilised on **warfarin** (INR 2 to 3) had an INR of 5.7 and developed a rectus sheath haematoma 3 days after completing a 7-day-course of co-amoxiclav (amoxicillin with clavulanic acid).[2] In one case, an 85-year-old woman taking **warfarin** was found collapsed at home one week after completing a course of co-amoxiclav. She had an INR of greater than 10 and widespread haemorrhage, and died shortly afterwards.[3] Two cases of raised INRs have been reported in patients who took prophylactic single 3-g doses of amoxicillin before dental treatment.[3] Other possible cases of an interaction between **warfarin** and amoxicillin[4,5] and amoxicillin with clavulanic acid[5,6] have been reported.

In one case control study, use of co-amoxiclav was found to be associated with an increased risk of an INR of greater than 6 (odds ratio 4.1; range 0.9 to 19.2) in patients stabilised on either **acenocoumarol** or **phenprocoumon**. Amoxicillin alone was associated with a smaller increased risk (odds ratio 1.7; range 0.6 to 4.7).[7] Conversely, in a population-based cohort study in similar patients conducted by the same research group, the risk of over-anticoagulation (INR greater than or equal to 6) was greater for amoxicillin alone than amoxicillin plus an enzyme inhibitor. The relative risk for amoxicillin alone was 10.5 (range 5.1 to 21.7) and for amoxicillin plus an enzyme inhibitor was 5.1 (range 1.9 to 13.9).[8] The increased risk was observed in the early stages of concurrent use but was greater after 4 or more days of treatment.[8] In two further cohort studies by this same research group, the relative risk of hospitalisation for bleeding in patients taking **acenocoumarol** or **phenprocoumon** and given co-amoxiclav was 7 and 4.4, respectively,[9,10] and was 3.1 for amoxicillin alone.[10] Nevertheless, they estimated that the individual risk of major bleeding was low at 1 per 1000 co-amoxiclav dispensings.[10] In another retrospective study of paediatric patients taking **warfarin**, the mean INR increased by 0.8 in 20 children given amoxicillin and in 25 children given co-amoxiclav.[5]

In contrast to these reports of increased anticoagulation, a very brief report states that in an audit of an anticoagulant clinic, 5 patients who had taken amoxicillin had an unspecified decrease in prothrombin time.[11]

(b) Benzylpenicillin

One patient stabilised on **warfarin** (prothrombin time 20 seconds) was found to have an increased prothrombin time of 32 seconds 8 days after starting intravenous benzylpenicillin [14.4 g] daily for subacute bacterial endocarditis. The benzylpenicillin was continued, and the warfarin dose reduced for 18 days. However, the prothrombin time dropped below the therapeutic range, and the warfarin dose was increased back to the original dose, still with continuation of the benzylpenicillin for a further 3 weeks.[12]

In a retrospective cohort study,[10] the relative risk of hospitalisation for bleeding in patients taking **acenocoumarol** or **phenprocoumon** and given benzathine benzylpenicillin was 5.8, but it was not statistically significant (range 0.8 to 41.5).

(c) Dicloxacillin

In a controlled study in 7 patients stabilised on **warfarin** and without infections, dicloxacillin 500 mg four times daily for 7 days reduced the mean prothrombin time by 1.9 seconds. One patient had a 5.6 second reduction.[13] This study was conducted because the authors had noted a case of a patient receiving **warfarin** who had a decrease in prothrombin time when dicloxacillin was started.[13] Another patient stabilised on **warfarin** had a 17% fall in prothrombin times within 4 to 5 days of starting dicloxacillin 500 mg four times daily, with a documented 20 to 25% reduction in both *S*- and *R*-warfarin levels.[14] In a retrospective review, 7 other patients similarly treated were also identified as having a 17% reduction in prothrombin times.[14] In yet another case, a patient who had previously required **warfarin** 10 mg daily subsequently needed an increased dosage of 15 mg daily while taking dicloxacillin 4 g daily long-term.[15] However, another case report suggested a greater effect of dicloxacillin: a patient taking dicloxacillin 500 mg every 6 hours required an increase in **warfarin** dose from a range of 35 to 40 mg weekly up to 50 to 60 mg weekly, with INRs still being subtherapeutic (about 1.5).[16] Moreover, when a woman taking **warfarin** was given dicloxacillin 500 mg four times daily she developed a heart valve thrombosis, suggesting inadequate anticoagulation. Her INR was 1.4, and an increased **warfarin** dose was required for 3 weeks after she stopped dicloxacillin.[17]

(d) Flucloxacillin

In one cohort study in patients taking **acenocoumarol** or **phenprocoumon**, no cases of over-anticoagulation (INR greater than 6) occurred in patients taking flucloxacillin (25 patients received this antibacterial).[8] Note that this study did find an increase for *amoxicillin*, see above. In another cohort study[10] by the same research group, the relative risk of hospitalisation for bleeding in patients taking **acenocoumarol** or **phenprocoumon** and given flucloxacillin was slightly increased at 2.2 but this was not statistically significant (range 0.7 to 6.9).

(e) Nafcillin

The prothrombin time of a 29-year-old patient stabilised on **warfarin** fell from a range of 20 to 25 seconds down to 16 seconds five days after intravenous nafcillin 2 g every 4 hours was started for endocarditis.[18] Over the next 2 weeks the prothrombin time ranged between 14 and 17 seconds despite an eventual doubling of the **warfarin** dose, and heparin was substituted. In this patient the half-life of a single 30-mg dose of **warfarin** was 11 hours when nafcillin was taken, 17 hours four days after stopping nafcillin, and 44 hours eight months after the nafcillin was discontinued. A case report describes a 39-year-old man taking warfarin 32 mg weekly, who required an eventual 2.75-fold dose increase to 88 mg weekly when his antibacterial for septic arthritis was changed from intravenous cefazolin to intravenous nafcillin 2 g every 4 hours. When the nafcillin was discontinued, he was eventually stabilised on **warfarin** 42 to 48 mg weekly.[19] At least 10 other cases of this **warfarin** resistance have been reported with high-dose nafcillin.[15,20-24]

(f) Pheneticillin

In one cohort study[8] in patients taking **acenocoumarol** or **phenprocoumon**, one case of over-anticoagulation (INR greater than 6) occurred in a group of 219 patients taking pheneticillin, giving a calculated relative risk of 0.9. In a further cohort study by the same research group,[10] the relative risk of hospitalisation for bleeding in patients taking **acenocoumarol** or **phenprocoumon** and given pheneticillin was 4.6.

(g) Phenoxymethylpenicillin (Penicillin V)

When 10 patients taking an unnamed anticoagulant were given intravenous phenoxymethylpenicillin calcium [187.5 mg] four times daily for 4 days, none had a change in their prothrombin-proconvertin value.[25] For mention that, in another study no patients taking penicillins including phenoxymethylpenicillin had an increase in INR see under *Unspecified penicillins*, below. However, in a retrospective cohort study,[10] the relative risk of hospitalisation for bleeding in patients taking **acenocoumarol** or **phenprocoumon** and given phenoxymethylpenicillin was 4.7, but it was not statistically significant (range 0.7 to 33.2).

(h) Unspecified penicillins

In one analysis of patients taking **warfarin** with antibacterials, there was no association between use of penicillins (**phenoxymethylpenicillin** (**penicillin V**) and broad-spectrum penicillins) and an increase in INR. The estimated change in INR was 0.117 in 109 patients given the combination.[26]

Mechanism

Not understood. The interaction between nafcillin and warfarin is possibly due to increases in the metabolism of warfarin by the liver. Dicloxacillin also possibly reduces serum warfarin levels.[14] Other penicillins (ampicillin,[27] benzylpenicillin,[27,28] carbenicillin,[29-34] methicillin,[27] ticarcillin[35]) have caused increased bleeding times when given alone, principally due to platelet inhibition,[27-29] which might be additive with the effects of the anticoagulants. Broad-spectrum antibacterials may decrease the gut flora and thereby possibly decrease production of vitamin K. Other factors relating to the disease may be important, see 'Coumarins + Antibacterials' p.413.

Importance and management

The reduced effect of warfarin with **dicloxacillin** and **nafcillin** appears to be established. If these penicillins are used, increase monitoring of the INR and anticipate the need to increase the warfarin dose. Some patients taking nafcillin have been warfarin resistant, and needed heparin treatment.

Documented reports of interactions between the coumarins and other penicillins are relatively rare, bearing in mind how frequently these drugs are used, so that the broad picture is that no clinically relevant interaction normally occurs with most other penicillins. This lack of interaction was supported by one clinical study.[26] However, in one case-control study, co-amoxiclav increased the risk of bleeding, and the authors recommended avoiding this combination,[7] although a later cohort study by the same authors just recommended increased monitoring with amoxicillin or co-amoxiclav.[8] In yet another study, they estimated that the individual risk of major bleeding was low at 1 per 1000 co-amoxiclav dispensings.[10]

Although there appear to be no reports of an interaction, if the mechanism of the interaction is correct, the **indanediones** are also likely to be affected. However, these interactions may be due to a number of different factors, and these are discussed in detail in the monograph 'Coumarins + Antibacterials', p.413. Therefore concurrent use should be monitored, so that the very occasional and unpredictable cases (increases or decreases in the anticoagulant effects) can be identified and handled accordingly.

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Coumarins + Antibacterials; Quinolones

Quinolones have, at most, a small, clinically insignificant effect on the pharmacokinetics and pharmacodynamics of warfarin. However, isolated cases of increased effects and even bleeding have been reported in patients taking a coumarin with a quinolone and retrospective studies suggest that there may be an increased risk of over-anticoagulation in patients taking acenocoumarol or phenprocoumon with norfloxacin and ciprofloxacin, and warfarin with gatifloxacin or levofloxacin.

Clinical evidence

(a) Ciprofloxacin

In a randomised, placebo-controlled study in 32 patients stabilised on **warfarin** and without infections, ciprofloxacin 750 mg twice daily for 12 days had no clinically relevant effect on measures of anticoagulation. There was a mean increase in prothrombin time ratio of just 3% (range 0 to 6%), with a 10 to 13% decrease in the levels of clotting factors II and VII. In this study, ciprofloxacin had no effect on *S*-warfarin levels, but did slightly increase *R*-warfarin levels by 14.7%.[1] Similarly, ciprofloxacin had no clinically relevant effects on **warfarin** anticoagulation in a range of other studies, including two studies in a total of 16 patients without infections given ciprofloxacin 500 mg twice daily for 7 or 10 days,[2,3] a single-dose study with a controlled-release formulation of ciprofloxacin.[4]

In contrast, there are reports where ciprofloxacin has apparently been responsible for moderate to markedly increased prothrombin times and/or bleeding in patients taking **warfarin**. There have been around almost 100 cases reported, in individual case reports,[5-11] and to the FDA in the US,[12] Health Canada[13] and the Australia Adverse Drug Reactions Advisory Committee.[14] In addition this interaction has resulted in at least two fatalities.[13,15] Data, mainly from the reports to the FDA in the US, suggests that the median prothrombin time increase was 38 seconds, the INR 10, and the median time to detection after starting ciprofloxacin was 5.5 days. Hospitalisation was reported in 15 cases, bleeding in 25 cases and death in one case.[12]

In a population-based cohort study,[16] there were no cases of over-anticoagulation (INR greater than 6) in patients taking **acenocoumarol** or **phenprocoumon** with ciprofloxacin (just 19 patients received ciprofloxacin). However, in another cohort study by the same research group,[17] the relative risk of hospitalisation for bleeding in patients taking **acenocoumarol** or **phenprocoumon** and given ciprofloxacin was significant (3.2, range 1.3 to 7.7).

(b) Clinafloxacin

Clinafloxacin 200 mg twice daily for 14 days had no effect on the steady-state levels of *S*-warfarin in healthy subjects, but the levels of the less active enantiomer *R*-warfarin were increased by 32% and the mean INR was increased by 13%.[18]

(c) Enoxacin

When a single 25-mg dose of **warfarin** was given to 6 healthy subjects on day 8 of a 14-day course of enoxacin 400 mg twice daily, the pharmacokinetics of *S*-warfarin were not altered, but the clearance of *R*-warfarin was decreased by 32% and its elimination half-life was prolonged from 36.8 hours to 52.2 hours. The overall anticoagulant response to the **warfarin** was unaltered.[19] Another report about one patient taking **warfarin**

also suggested that the use of enoxacin does not alter the prothrombin time ratio.[20]

(d) Fleroxacin

The pharmacokinetics of *R*- and *S*-warfarin, the prothrombin time and factor VII clotting time were unaffected when 12 healthy subjects were given a single 25-mg dose of **warfarin** on day 4 of a 9-day course of fleroxacin 400 mg daily.[21]

(e) Gatifloxacin

Gatifloxacin 400 mg daily for 11 days had no effect on the pharmacokinetics of a single 25-mg dose of **warfarin**, nor was the prothrombin time altered.[22] In contrast, in a review of 94 patients taking **warfarin** and given antibacterials for community-acquired pneumonia, 22 of the 40 patients (55%) taking gatifloxacin had INRs greater than 3 during or within 48 hours after stopping gatifloxacin, compared with 20 of 54 patients (37%) taking ceftriaxone and/or azithromycin. In the gatifloxacin group, 38% needed a **warfarin** dose adjustment, compared with 18% of patients taking other antibacterials. There was no difference in infection severity between the two groups.[23] In another retrospective analysis, 8 of 38 patients taking warfarin had an INR of greater than 4 after taking gatifloxacin, and 4 were subsequently treated with vitamin K. This was higher than the incidence with levofloxacin.[24] For the period February 2001 to January 2004, Health Canada had received 13 reports of suspected coagulation disorders associated with gatifloxacin and **warfarin**, all of which were considered serious, and 2 of which were fatal.[13] There is also a case of an INR which was too high to be determined in a patient taking numerous drugs including warfarin, and who had been taking gatifloxacin 400 mg daily.[25]

(f) Gemifloxacin

A double-blind, randomised, placebo-controlled study found that healthy subjects taking fixed doses of **warfarin** and with INRs in the range of 1.3 to 1.8 had no INR changes when they were given gemifloxacin 320 mg daily for 7 days.[26]

(g) Levofloxacin

In a study[27] in 15 healthy subjects given a single 30-mg dose of **warfarin** on day 4, levofloxacin 500 mg twice daily for 9 days had no effect on the pharmacokinetics or pharmacodynamics of *R*- and *S*-warfarin. In an uncontrolled prospective study, 18 patients stabilised on **warfarin** were given a course of levofloxacin for various infections. There was no difference in the mean INR obtained before levofloxacin and the first INR taken a median of 5 days after levofloxacin was started (2.61 versus 2.74). However, 4 patients had an increase in INR (to a range of 3.89 to 4.2) and 3 had a decrease in INR (to a range of 1.39 to 1.84) outside of the therapeutic range (2 to 3), and required **warfarin** dose adjustments. Only 7 patients had INRs that were therapeutic (range 2 to 3) throughout the study (before, during, and after levofloxacin) and did not require an adjustment in **warfarin** dose.[28] Similar findings were reported in two other retrospective analyses of patients taking **warfarin** with levofloxacin,[29,30] whereas just one of 54 patients taking **warfarin** had an INR above 4 after taking levofloxacin in another retrospective analysis.[24] In a retrospective case-control study,[31] there was no significant increased risk of hospitalisation for haemorrhage in acutely ill elderly patients taking **warfarin** who had received levofloxacin before admission (odds ratio 1.21).

Cases of an interaction have also been reported. Two elderly patients taking **warfarin** were found to have increased INRs (of 5.7 and 7.9) on routine testing shortly after stopping levofloxacin 500 mg daily.[32] Nine other cases of modest to markedly increased INRs have been reported in patients stabilised on **warfarin** who were given courses of levofloxacin 500 mg daily for 5 to 10 days (or unstated);[33-35] bleeding complications (epistaxis, haemopericardium) occurred in some of these cases,[34,35] and one patient died.[35] Moreover, for the period November 1997 to January 2004, Health Canada had received 16 reports of suspected coagulation disorders associated with levofloxacin and **warfarin**, 14 of which were considered serious, and one of which was fatal.[13]

One study assessed the impact of pre-emptively reducing the **warfarin** dose by 10 to 20% in patients starting levofloxacin. In 10 patients who had a **warfarin** dose reduction, there was no change in mean INR before and after levofloxacin. However, 4 patients developed a *sub-therapeutic* INR, including two with borderline low INR values beforehand. In 13 patients who had no pre-emptive **warfarin** dose reduction, the INR increased from a mean of about 2.5 to about 4. Note that most of the patients had little change in their INR, but one patient had a marked increase in INR requiring oral vitamin K.[36]

(h) Moxifloxacin

The pharmacokinetics of *R*- and *S*-warfarin were not altered when a single 25-mg dose of **warfarin** was given on day 5 of an 8-day course of moxifloxacin 400 mg daily in healthy subjects. The prothrombin time increased by 3% (0 to 6%), which is not clinically relevant.[37]

In contrast, there are at least 3 reports of raised INRs in patients taking **warfarin** and given moxifloxacin.[38-40] In one of these, 5 patients taking **warfarin** had INRs raised to 5.7 to 12.8 within 4 to 12 days of starting moxifloxacin, with one case of haemorrhage.[40] For the period October 2000 to January 2004, Health Canada had received 12 reports of suspected coagulation disorders associated with moxifloxacin and **warfarin**, 11 of which were considered serious.[13] Similarly, in February 2006, the Australia Adverse Drug Reactions Advisory Committee stated they had received one report of a suspected interaction between **warfarin** and moxifloxacin. In this patient the INR rose from around 2 to greater than 10, four days after starting moxifloxacin.[14]

(i) Nalidixic acid

A patient stabilised on **warfarin** (prothrombin ratio 2), developed a purpuric rash and bruising within 6 days of starting nalidixic acid 500 mg four times daily. Her prothrombin ratio had risen to 3.46.[41] Another patient, previously well controlled on **warfarin**, developed a prothrombin time of 60 seconds 10 days after starting nalidixic acid 1 g three times daily.[42] The INR of an 84-year-old woman taking **warfarin** rose from 1.9 to 9.6 when nalidixic acid was added.[43] Similarly, a patient taking **acenocoumarol** developed hypoprothrombinaemia after receiving nalidixic acid 1 g daily.[44]

(j) Norfloxacin

In a study[45] in 10 healthy subjects, norfloxacin 400 mg twice daily for 9 days was found not to alter either the pharmacokinetics or anticoagulant effects of a single 30-mg dose of **warfarin** given on day 4.

In contrast, a 91-year-old woman taking **warfarin** and digoxin developed a brain haemorrhage within 11 days of starting to take norfloxacin (precise dose not stated). Her prothrombin times had risen from 21.6 to 36.5 seconds. At this time, the manufacturers of norfloxacin were said to have 6 other reports of an interaction between **warfarin** and norfloxacin on file.[46] In a population-based cohort study, patients taking **acenocoumarol** or **phenprocoumon** were found to have an increased risk of over-anticoagulation (INR greater than or equal to 6) during norfloxacin treatment (relative risk 9.8). The risk was greatest during the first 3 days of treatment.[16] In another cohort study by this same research group,[47] the relative risk of hospitalisation for bleeding in patients taking **acenocoumarol** or **phenprocoumon** and given norfloxacin was 5.9. However, in yet another similar cohort study by the same research group,[17] the relative risk of hospitalisation for bleeding in these patients was just 2.2 and this did not reach statistical significance (range 0.7 to 6.7).

Furthermore, for the period December 1986 to January 2004, Health Canada had received 6 reports of suspected coagulation disorders associated with norfloxacin and **warfarin**, 4 of which were considered serious.[13] Similarly, in February 2006, the Australia Adverse Drug Reactions Advisory Committee stated they had received 11 reports of a suspected interaction between **warfarin** and norfloxacin.[14]

(k) Ofloxacin

Ofloxacin 200 mg daily for 7 days did not significantly affect the prothrombin times of 7 healthy subjects stabilised on **phenprocoumon**.[48] In a population-based cohort study,[16] there were no cases of over-anticoagulation (INR greater than 6) in patients taking **acenocoumarol** or **phenprocoumon** with ofloxacin (33 received ofloxacin). Nevertheless, in another similar cohort study by the same research group,[17] the relative risk of hospitalisation for bleeding in these patients was just 2.8 and this did not reach statistical significance (range 0.7 to 11.3). Furthermore, for the period December 1990 to January 2004, Health Canada had not received any reports of suspected coagulation disorders associated with ofloxacin and **warfarin**.[13]

In contrast, a woman who had recently started to take **warfarin** 5 mg daily, had a marked increase in her INR (from 2.5 to 4.4) within 2 days of starting to take ofloxacin 200 mg three times daily.[49] Two days later her INR had risen to 5.8. Another patient stabilised on **warfarin** developed gross haematuria and a prothrombin time of 78 seconds 5 days after starting to take ofloxacin 400 mg twice daily.[50]

(l) Pefloxacin

A patient had a marked increase in the effects of **acenocoumarol** (Quick time reduced from 26% to less than 5%) within 5 days of starting to take pefloxacin 800 mg daily and rifampicin 1.2 g daily.[51] Rifampicin is an

enzyme inducer, which normally causes a reduction in the effects of acenocoumarol (see 'Coumarins + Antibacterials; Rifamycins', below), so the findings in this case are surprising.

Mechanism

Uncertain. It is not clear what other factors might have been responsible in those cases where the effects of the anticoagulants were increased. Factors relating to acute infection rather than the antibacterial used to treat it may be responsible for increased INRs, see also 'Coumarins + Antibacterials', p.413. However, one study that controlled for severity of infection indicated this was not the case and that an interaction between the quinolone and anticoagulant probably occurs.[23] *In vitro* experiments[52,53] have shown that nalidixic acid can displace warfarin from its binding sites on human plasma albumin, but this mechanism on its own is almost certainly not the full explanation. In a single-dose study enoxacin was shown to inhibit the metabolism of the less potent *R*-warfarin isomer, without affecting the anticoagulant response.[19] This effect may become important if accumulation of the *R*-warfarin isomer (which is cleared slowly) occurred during prolonged dosing.[3] Other quinolones may have a similar effects. It has also been suggested that fluoroquinolones may suppress vitamin K-producing gut bacteria with resultant potentiation of anticoagulant effects,[49] see also 'Coumarins + Antibacterials', p.413.

Importance and management

The minor pharmacokinetic interaction between ciprofloxacin and warfarin in patients taking warfarin would appear to be established, but unlikely to be clinically relevant. Similarly, no other quinolone has been shown to have a clinically significant interaction with warfarin in a controlled prospective study. Despite this, there are numerous published case reports of marked over-anticoagulation with many of the quinolones, and other known unpublished cases reported to regulatory authorities. In addition, for levofloxacin there is some information from uncontrolled studies supporting an interaction in some patients. Nevertheless, given the widespread use of warfarin and quinolones, these interactions would appear to be rare.

The overall picture is that no adverse interaction normally occurs between the quinolones and coumarins, but rarely and unpredictably increased anticoagulant effects and even bleeding can occur with some of them. There is no need to avoid using any of the quinolones with the coumarins, and, in one study, pre-emptive warfarin dose reduction resulted in sub-therapeutic INRs in some patients given levofloxacin, and was considered unnecessary.[36] Monitoring the INR within 3 to 5 days of starting the quinolone was considered reasonable. Note that, if a patient is unwell enough to require an antibacterial, it may be prudent to increase monitoring of coagulation status even if no specific drug interaction is expected, see also 'Coumarins + Antibacterials', p.413.

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Coumarins + Antibacterials; Rifamycins

The anticoagulant effects of warfarin are markedly reduced by rifampicin (rifampin), with two to fivefold increases in dose needed to maintain efficacy in a number of case reports. Acenocoumarol and phenprocoumon are similarly affected.

Clinical evidence

(a) Acenocoumarol

The dose of acenocoumarol needed to be markedly increased in 18 patients who were given rifampicin 450 mg twice daily for 7 days to maintain the Quick value within the therapeutic range. The effect was apparent 5 to 8 days after starting the rifampicin, and had not reached a maximum at 14 days, at which point a mean 76% increase in the acenocoumarol dose

was needed.[1] In another study, the Quick time of a single dose of acenocoumarol, measured 35 hours after the dose, was reduced by 44% when rifampicin 10 mg/kg daily was given for 2 weeks.[2] In one 73-year-old, a sixfold increase in the dose of acenocoumarol was insufficient to maintain a therapeutic INR after starting rifampicin for endocarditis.[3]

(b) Phenprocoumon

In a study in healthy subjects, rifampicin 600 mg daily for 14 days increased the clearance of a single dose of phenprocoumon 2.2-fold.[4] Similarly, two patients stabilised on phenprocoumon required the dose to be doubled while taking rifampicin 600 mg daily (and isoniazid with or without ethambutol). In one case, the patient developed severe gross haematuria 3 months after rifampicin had been discontinued because the phenprocoumon dose had not been reduced.[5]

(c) Warfarin

In one controlled study in 8 healthy subjects, rifampicin 600 mg daily for 21 days reduced the steady-state plasma warfarin levels by 85% (range 64% to 100%). In addition, rifampicin abolished the anticoagulant effect of warfarin (the prothrombin time averaged 27% of normal during warfarin alone, and 85% of normal when rifampicin was taken).[6] Similar findings were seen in two other single-dose warfarin studies.[7,8] One of these measured the isomers of warfarin separately and found that rifampicin increased the clearance of *R*-warfarin threefold and *S*-warfarin twofold.[8] This interaction has also been described in a number of case reports.[9-14] In these reports the dose of warfarin was doubled[9,11] or even tripled[11] to accommodate this interaction, and reduced by an equivalent amount over two[10] to three weeks[12] following withdrawal of the rifampicin. In one well-described case, a threefold increase in warfarin dose from 5 to 15 mg daily over 4 months failed to achieve a therapeutic INR during the long-term use of rifampicin, and eventually a fivefold increase in dose (25 mg daily) attained an INR of 1.7 and 1.9. A gradual 70% dose reduction over 4 to 5 weeks was required when the rifampicin was discontinued.[14] In yet another case, a five to sixfold increase in warfarin dose was not sufficient to maintain the INR in the therapeutic range, and enoxaparin was used instead of warfarin.[15]

A retrospective study[16] similarly found that the concurrent use of enzyme inducers (including rifampicin) significantly influenced the total weekly warfarin dose; further analysis found that an average additional amount of warfarin required in patients taking these drugs was 17.2 mg weekly.

Mechanism

Rifampicin is a potent non-specific liver enzyme inducer, which increases the metabolism and clearance of the anticoagulants from the body, thereby reducing their effects.[8] Other mechanisms may also be involved.[12] See also 'Coumarins + Antibacterials', p.413.

Importance and management

The interaction between rifampicin and the coumarins is very well documented, clinically important, and occurs in most patients. A marked reduction in the anticoagulant effects may be expected within one week of starting the rifampicin, and persisting for about 2 to 5 weeks after the rifampicin has been withdrawn. With warfarin there is evidence that the dose may need to be markedly increased (two to fivefold) over a number of weeks to accommodate this interaction, and reduced slowly by an equivalent amount following withdrawal of the rifampicin. Warfarin dose titrations should be carried out with close monitoring. Bridging therapy with heparin or a LMWH might be appropriate until the warfarin dose is restabilised.

There does not seem to be any information regarding the other rifamycins, **rifabutin** (a weak enzyme inducer) and **rifapentine** (a moderate enzyme inducer). However, the manufacturers and the CSM in the UK warn that rifabutin may possibly reduce the effects of a number of drugs, including oral anticoagulants.[17,18]

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Coumarins and related drugs + Antibacterials; Sulfonamides and/or Trimethoprim

Co-trimoxazole (sulfamethoxazole with trimethoprim) modestly inhibits the metabolism of *S*-warfarin, and a number of case reports show that the anticoagulant effects of the coumarins can be markedly increased. Case reports suggest that sulfafurazole, sulfadoxine, and sulfamethizole may have similar effects. Two cohort studies have suggested that trimethoprim alone may be associated with an increased risk of over-anticoagulation. Anecdotal evidence suggests that phenindione might not interact with co-trimoxazole, but sulfaphenazole has been reported to increase the effects of phenindione.

Clinical evidence

(a) Co-trimoxazole (Sulfamethoxazole with Trimethoprim)

1. Coumarins. Six out of 20 patients taking **warfarin** had an increase in their prothrombin ratios (to about 4 to 6) within 2 to 6 days of starting to take co-trimoxazole 960 mg twice daily.[1] One patient had a gastrointestinal haemorrhage and needed to be given vitamin K. The **warfarin** was temporarily withdrawn from 5 patients and the dose was reduced in one patient to control excessive hypoprothrombinaemia.[1]

Similarly, an increase in the effects of **warfarin**, with or without bleeding complications, in patients given co-trimoxazole has been described in a number of other case reports.[2-17] In a retrospective study of 16 patients stabilised on **warfarin**, there was a mean increase in INR of 1.75 after starting co-trimoxazole (7 patients had an INR of greater than 4, and 5 patients had an INR greater than 5). The patients had stable INRs for a least two consecutive measurements before receiving co-trimoxazole, and an INR was taken within 3 to 15 days of starting the co-trimoxazole.[18] In one study in healthy subjects, co-trimoxazole 480 mg four times daily for 8 days increased the prothrombin time after a single dose of **warfarin** by 50%, but no change in the half-life of **warfarin** was seen.[19] However, a later similar study by the same research group, in which **warfarin** was given as its separate isomers, co-trimoxazole increased the AUC of *S*-warfarin by 22% and caused a 5% decrease in AUC of *R*-warfarin.[20]

In a population based cohort study[21] in patients taking **acenocoumarol** or **phenprocoumon**, co-trimoxazole was associated with an increased risk of over-anticoagulation (INR greater than or equal to 6); the adjusted relative risk of over-anticoagulation was noted to be 20.1 (range 10.7 to 37.9). The risk was increased in the first 3 days of use (relative risk 16.6), but was greatest after 4 days of concurrent use (relative risk 23.2). In two other cohort studies by this same research group, the relative risk of hospitalisation for bleeding in patients taking **acenocoumarol** or **phenprocoumon** and given co-trimoxazole was lower at 6.2 and 5.1, respectively.[22,23]

In a study looking at management of the interaction, the risk of both moderate and severe over-anticoagulation with co-trimoxazole was markedly lower in patients who had their dose of anticoagulant reduced before receiving the antibacterials (preventive dose reduction) compared with those who did not (mean dose reduction 15% for **acenocoumarol** and 18% for **phenprocoumon**). Nevertheless, all patients who had taken co-trimoxazole spent significantly more time with subtherapeutic INRs in the 6 weeks after the antibacterial, although this tended to be less in patients

who had a preventive dose reduction, and less if the preventive dose reduction was less than 20%.[24] In another study of preventive **warfarin** dose reduction (10 to 20%) in patients also taking co-trimoxazole,[25] none of 8 patients had a subtherapeutic INR and none had an INR of greater than 6, although 2 patients had a INR between 4 and 6. However, in the control group with no preventive dose reduction, 4 out of 9 patients had an INR greater than 6, with values ranging from 7.1 to 17.4.

2. Indanediones. In one anecdotal report, the author noted that in several years experience of the use of **phenindione** in an anticoagulant clinic serving 1 000 patients, he had not come across a clinically important case of anticoagulant potentiation with co-trimoxazole.[26] Nothing else seems to have been published on the combination, but note that another sulphonamide, sulfaphenazole, potentiated the effect of **phenindione**, see *Sulfaphenazole*, below.

(b) Sulfadoxine

A 19-year-old with a valve replacement and taking **warfarin** presented with melaena and coughing up blood about a week after self-medicating with *Fansidar* (sulfadoxine with pyrimethamine). He had not had his anticoagulant control monitored.[27]

(c) Sulfafurazole (Sulfisoxazole)

A man taking digitalis, diuretics, antacids and **warfarin** was later given sulfafurazole 500 mg every 6 hours. After 9 days, his prothrombin time had risen from 20 seconds to 28 seconds, and after 14 days he bled (haematuria, haemoptysis, gum bleeding). His prothrombin time had risen to 60 seconds.[28]

Another patient who had recently started taking **warfarin** developed haematuria and had a prolonged prothrombin time 7 days after also starting sulfafurazole.[29]

(d) Sulfamethizole

The half-life of **warfarin** was increased by over 40% (from 65 to 93 hours) in 2 patients taking sulfamethizole 1 g four times daily for a week.[30]

(e) Sulfaphenazole

Sixteen patients given single oral doses of **phenindione** and sulfaphenazole 500 mg had prothrombin time increases after 24 hours of 16.8 seconds, compared with 10.3 seconds in 12 other patients who took **phenindione** alone.[31]

(f) Trimethoprim

Trimethoprim with sulfamethoxazole (co-trimoxazole) is known to interact with coumarins, see *Co-trimoxazole*, above. However, there appear to be no controlled studies of the effect of trimethoprim alone on these drugs, and no case reports of any interaction. In one cohort study,12 patients taking **warfarin** had a small INR increase of about 0.36 when given trimethoprim, but this was not statistically significant.[32] In another cohort study in patients taking **acenocoumarol** or **phenprocoumon**, the use of trimethoprim was associated with an increased risk of over-anticoagulation (INR greater than or equal to 6). The adjusted relative risk of over-anticoagulation was noted to be 5.6 (range 1.3 to 23.1), and the greatest risk was in the first 3 days of concurrent use. The risk from trimethoprim alone in this study was less than that for co-trimoxazole.[21] However, a further cohort study by this same research group, the relative risk of hospitalisation for bleeding in patients taking **acenocoumarol** or **phenprocoumon** and given trimethoprim was just 1.3, and it was not statistically significant (0.3 to 5.4).[23]

Mechanism

Not fully understood. Sulfamethoxazole is a known inhibitor of the cytochrome P450 isoenzyme CYP2C9, by which *S*-warfarin in predominantly metabolised. The finding that co-trimoxazole (sulfamethoxazole with trimethoprim) caused a modest 22% increase in *S*-warfarin levels supports this mechanism.[20,33] Acenocoumarol and phenprocoumon are also metabolised by CYP2C9 and might be expected to be similarly affected. Plasma protein binding displacement has been suggested as a mechanism,[34,35] but on its own it does not provide an adequate explanation because the interaction is sustained.[21,33] Sulfonamides can drastically reduce the intestinal bacterial synthesis of vitamin K, but this is not normally an essential source of the vitamin unless dietary sources are exceptionally low,[33,36] see also 'Coumarins + Antibacterials', p.413.

Importance and management

The interaction between co-trimoxazole and the coumarins is well documented and well established. The incidence appears to be high. If bleeding is to be avoided the INR should be well monitored and the warfarin, acenocoumarol, or phenprocoumon dose should be reduced. Some consider that a pre-emptive warfarin dose reduction of about 10 to 20% reduces the risk of over-anticoagulation without increasing the risk of subtherapeutic INRs.[25] However, others suggest that co-trimoxazole should be avoided in patients taking coumarins, because they found that management of the interaction (either preventive or reactive dose reduction) resulted in an increased period of under-anticoagulation after the antibacterial. They suggest that an alternative antibacterial to co-trimoxazole is always available.[24]

Anecdotal evidence suggests that co-trimoxazole may not interact with phenindione, but note that sulfaphenazole did, so some caution is still appropriate.

The other interactions are poorly documented. However, it would seem prudent to follow the precautions suggested for co-trimoxazole if any sulfonamide is given with a coumarin or indanedione.

The relative silence in the literature for trimethoprim alone would suggest that, in practice, any interaction, if it occurs, is of only minor importance, and the anticoagulant dose probably needs little or no adjustment. However, note that two cohort studies have shown some increased risk when trimethoprim was given with warfarin, acenocoumarol or phenprocoumon so an interaction cannot entirely be dismissed.

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Coumarins + Antibacterials; Teicoplanin or Vancomycin

An isolated case report describes a marked reduction in the effects of warfarin, which was attributed to the use of teicoplanin, although this could equally be explained by rifampicin treatment. Vancomycin possibly causes a small increase in the effects of warfarin, and may increase the risk of over-anticoagulation with acenocoumarol or phenprocoumon.

Clinical evidence, mechanism, importance and management

(a) Teicoplanin

A 60-year-old woman taking digoxin, furosemide and **warfarin** (INR 3.5 to 5) developed a fever after mitral valve replacement surgery and was given rifampicin 450 mg twice daily and teicoplanin 400 mg twice daily. Within 3 days her INR began to fall and by day 6 the anticoagulant effect was completely lost. Despite progressive **warfarin** increases to 10, 15, and then 20 mg daily, her INR stayed between 1.2 and 1.6, even when rifampicin was stopped, and remained low for a further 20 days, at which point the teicoplanin was also stopped.[1] Some of this resistance to **warfarin** was undoubtedly due to the rifampicin (a known and potent inducer of **warfarin** metabolism) but as the INRs remained depressed for a further 20 days after rifampicin was withdrawn the authors suggested that the teicoplanin had its own part to play. However, rifampicin has been shown is several cases to decrease the effects of warfarin for three or more weeks after its withdrawal (see 'Coumarins + Antibacterials; Rifamycins' p.424), so an interaction with teicoplanin would seem doubtful.

(b) Vancomycin

In a retrospective review of 60 patients undergoing heart valve replacement surgery and receiving prophylactic antibacterials, 44 patients given cefamandole had a much greater anticoagulant response to their first dose of **warfarin** than 16 patients given **vancomycin**.[2] In a later prospective study by the same workers, in patients taking warfarin with an antibacterial, after 3 days the prothrombin times as a percentage of activity were as follows: cefamandole 29%, cefazolin 38%, and **vancomycin** 51%, suggesting that 'cefamandole', (p.415), had a much greater effect on the anticoagulant response than **vancomycin**.[3]

In a cohort study, the use of **vancomycin** was associated with an increased risk of over-anticoagulation (an INR greater than 6) in patients stabilised on **acenocoumarol** or **phenprocoumon**. The relative risk was 13.6; however, the confidence interval was very large (1.7 to 107), so it is not possible to draw any firm conclusions from this.[4]

If a patient is unwell enough to require antibacterial therapy, it may be prudent to increase the monitoring of coagulation status even if no specific drug interaction is expected, see also 'Coumarins + Antibacterials', p.413.

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Coumarins and related drugs + Antibacterials; Tetracyclines

Isolated cases suggest that doxycycline and tetracycline can increase the effects of coumarins. Similarly, some small studies (none controlled) suggest that chlortetracycline (alone or with oxytetracycline), doxycycline, or the tetracyclines as a class may increase the risks of over-anticoagulation, but there appear to be no studies of the effect of tetracyclines on the pharmacokinetics of coumarins. However, the related antibacterial, tigecycline, increased the AUC of warfarin, and has been found to increase the prothrombin time when given alone.

Clinical evidence

There are no controlled studies of the effect of any tetracycline on the pharmacokinetics or pharmacodynamics of warfarin or other coumarins, although there are data for tigecycline, a new glycylcycline antibacterial structurally related to the tetracyclines.

(a) Chlortetracycline

Six out of 9 patients taking an unnamed anticoagulant had a fall in their prothrombin-proconvertin concentration from a range of 10 to 30% to less than 6% when given chlortetracycline 250 mg four times a day for 4 days. Although the anticoagulant effects were increased, there was no evidence of bleeding.[1] In one early study of **dicoumarol** and **ethyl biscoumacetate**, the authors briefly comment that 4 cases of the concurrent use of chlortetracycline and oxytetracycline increased the prothrombin response.[2]

(b) Doxycycline

A woman stabilised on **warfarin** developed menorrhagia after taking doxycycline 100 mg twice daily for 10 days, and her prothrombin time ratio had increased from about 2 to 4.4.[3] Two other patients stabilised on **acenocoumarol** or **warfarin** developed markedly increased prothrombin ratios (3.82 and 4.09, respectively) with bruising, haematomas and bleeding when they took doxycycline.[4] Another patient with multiple medical problems, taking **warfarin** developed peritoneal bleeding and an INR of 7.2 (previously 2.6) 6 days after starting doxycycline 100 mg twice daily.[5] Yet another patient taking **warfarin** had an INR increase from 2.3 to 6.5 with prominent bruising when given doxycycline.[6]

In a population-based cohort study in patients taking **acenocoumarol** or **phenprocoumon**, doxycycline was found to increase the risk of over-anticoagulation (INR greater than or equal to 6) with an adjusted relative risk of 4.3 (range 1.8 to 10.4). The risks were greatest after 4 or more days of concurrent use.[7] In two other cohort studies by this same research group, the relative risk of hospitalisation for bleeding in patients taking **acenocoumarol** or **phenprocoumon** and given doxycycline was 4.2 and 2.4, respectively.[8,9] Nevertheless, they estimated that the individual risk of major bleeding was low at one per 2000 doxycycline dispensings.[9]

(c) Oxytetracycline

In one early study of **dicoumarol** and **ethyl biscoumacetate**, the authors briefly comment that 4 cases of the concurrent use of chlortetracycline and **oxytetracycline** increased the prothrombin response.[2]

(d) Tetracycline

In one analysis of haemorrhagic events in patients taking **dicoumarol** and antibacterials, one patient out of 20 who received tetracycline had a bleeding event.[10] A patient stabilised on **warfarin** had a marked increase in INR (from about 2 to 7.7) 6 weeks after starting to take tetracycline 250 mg four times daily. Warfarin was withheld for a few days, and then restarted at a 40% lower dose. The INR decreased over the following months, broadly in parallel with decreases in the tetracycline dose.[11] A patient taking **warfarin** bled (right temporal lobe haematoma) and had an extended prothrombin time a week after starting to take tetracycline and nystatin.[12] Another patient taking **warfarin** also bled (epistaxis, haematemesis, melaena) 3 weeks after starting to take tetracycline and nystatin.[12]

In a retrospective cohort study, the relative risk of hospitalisation for bleeding in patients taking **acenocoumarol** or **phenprocoumon** and given tetracycline was 8.7. However, the incidence of concurrent use was low so the confidence interval was very broad (range 1.2 to 62).[9]

(e) Tigecycline

The manufacturer notes that, in healthy subjects, intravenous tigecycline 100 mg then 50 mg every 12 hours decreased the clearance of *R*-warfarin by 40% and *S*-warfarin by 23% after a single 25-mg dose of **warfarin**. The AUCs of *R*- and *S*-warfarin were increased by 68% and 29%, respectively. However, the INR was not affected.[13,14]

(f) Unnamed tetracyclines

In a prospective study of the effect of antibacterials on anticoagulation, there was an estimated 0.53 increase in the INR in 9 patients taking warfarin and a tetracycline (unnamed). The effect with tetracyclines was greater than the effect of other antibacterials studied (penicillins, cephalosporins, macrolides).[15]

Mechanism

Not understood. Tetracyclines, in the absence of anticoagulants, can reduce prothrombin activity,[16] and both hypoprothrombinaemia and bleeding have been described.[17,18] It seems possible that very occasionally the anticoagulant and the tetracycline have additive hypoprothrombinaemic effects. In clinical studies, tigecycline alone has commonly caused a prolonged prothrombin time (incidence 1 to 10%) or uncommonly caused an increased INR (incidence 0.1 to 1%).[13] It is also possible that antibacterials can diminish the intestinal flora of the gut thereby depleting the body of vitamin K_2, although this might be clinically important only where normal dietary intake of vitamin K_1 is extremely low, see 'Coumarins + Antibacterials', p.413. There appear to be no data on the effect of tetracyclines on the pharmacokinetics of coumarins. Although tigecycline decreased the clearance of warfarin, the mechanism for this is unclear, and is not thought to be as a result of decreased cytochrome P450 metabolism.[13,14]

Importance and management

A relatively sparsely documented interaction, bearing in mind that the tetracyclines have been in very widespread use for many years. It can therefore reasonably be concluded that normally any changes are of little clinical relevance. As a few patients have unpredictably had increased anticoagulant effects and even bleeding, bear the possibility of an interaction in mind when a tetracycline is first added to established anticoagulant treatment with a coumarin. Moreover, if a patient is unwell enough to require an antibacterial, it may be prudent to increase monitoring of coagulation status even if no specific drug interaction is expected, see also 'Coumarins + Antibacterials', p.413. Monitor within 3 days of starting the antibacterial.

Because tigecycline decreased the clearance of warfarin, and because tigecycline alone may cause an increase in INR, it is recommended that the INR be closely monitored if patients taking warfarin are given tigecycline.[13,14]

There appears to be no information about the **indanediones**, but if the mechanism suggested is correct they may also interact like the coumarins.

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Coumarins + Anticholinesterases; Centrally acting

Donepezil, galantamine, rivastigmine and tacrine do not appear to alter the pharmacokinetics or effects of warfarin.

Clinical evidence, mechanism, importance and management

(a) Donepezil

In an open-label, crossover study, 12 healthy men were given donepezil 10 mg daily for 19 days with a single 25-mg dose of **warfarin** on day 14. The pharmacokinetics of *R*- and *S*-warfarin and the prothrombin times were unchanged by the presence of the donepezil, and vital signs, ECG and laboratory tests were unaltered.[1] Therefore, no special precautions are needed on concurrent use.

(b) Galantamine

The manufacturers say that galantamine 24 mg daily had no effect on the pharmacokinetics of *R*- and *S*-warfarin after a single 25-mg dose of **warfarin**. In addition, galantamine did not alter the prothrombin time.[2,3] Therefore, no special precautions are needed on concurrent use.

(c) Rivastigmine

The manufacturers of rivastigmine[4,5] say that no pharmacokinetic interaction has been noted between rivastigmine and **warfarin** in healthy subjects. In addition, rivastigmine did not affect the increase in prothrombin time seen with **warfarin**. Therefore, no special precautions are needed on concurrent use.

(d) Tacrine

In a study in 10 patients stabilised on **warfarin,** the addition of tacrine 20 mg four times daily for 5 days had no significant effect on prothrombin times.[6] Therefore, no special precautions are needed on concurrent use.

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Coumarins + Antidiabetics; Alpha-glucosidase inhibitors

Miglitol and voglibose do not appear to alter the pharmacokinetics or effects of warfarin. There are isolated cases of reduced or increased INRs in patients given warfarin and acarbose.

Clinical evidence, mechanism, importance and management

(a) Acarbose

A 66-year-old man taking fosinopril, hydrochlorothiazide, diphenhydramine, insulin, glipizide and **warfarin** started taking acarbose to improve the control of his diabetes. Four days before starting acarbose his INR was 3.09, but after 2 weeks (25 mg acarbose daily for week one and then 50 mg daily for week 2) his INR had *risen* to 4.85. The **warfarin** was temporarily stopped, then it was reintroduced at a lower dose, and finally the acarbose was withdrawn, resulting in an INR of 2.84. No bleeding was seen.[1] In contrast, in 1997, the manufacturer had on record 2 other cases of patients taking **warfarin** whose INRs were *reduced* when acarbose was added. One of them stopped taking the acarbose, whereupon her INR

returned to its previous value. The other patient needed an increased **warfarin** dose.[2]

These appear to be the only cases on record, and therefore the general picture is that usually no interaction occurs, but in isolated cases some changes in **warfarin** requirements occur. Bear this potential interaction in mind if anticoagulant control alters in a patient taking acarbose.

(b) Miglitol

In a double-blind, randomised, placebo-controlled study, 24 healthy subjects were given miglitol 100 mg three times daily for 7 days, with a single 25-mg oral dose of **warfarin** on day 4. Neither the pharmacokinetics nor the pharmacodynamics of *R*- or *S*-warfarin were affected by the miglitol.[3] No special precautions would therefore appear to be needed if these two drugs are used concurrently.

(c) Voglibose

Twelve healthy male subjects were given individually adjusted doses of **warfarin** to give Quick values of 30 to 40%, and then from day 11 to 15 they were also given voglibose 5 mg three times daily. It was found that the voglibose had no effect on the pharmacokinetics of **warfarin** nor on its anticoagulant effects.[4] No special precautions would therefore appear to be needed if these two drugs are used concurrently.

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4. Fuder H, Kleist P, Birkel M, Ehrlich A, Emeklibas S, Maslak W, Stridde E, Wetzelsberger N, Wieckhorst G, Lücker PW. The α-glucosidase inhibitor voglibose (AO-128) does not change pharmacodynamics or pharmacokinetics of warfarin. *Eur J Clin Pharmacol* (1997) 53, 153–7.

Coumarins + Antidiabetics; Biguanides

One patient had a marked increase in the effects of phenprocoumon when she stopped taking metformin for a short period, and there is some evidence that metformin increases the metabolism of phenprocoumon.
One patient taking warfarin developed haematuria with a therapeutic prothrombin time three months after starting phenformin. Another patient developed metformin-induced lactic acidosis after warfarin-induced bleeding caused renal obstruction.

Clinical evidence

(a) Phenprocoumon

The Quick value of a 58-year-old woman stabilised on **metformin** 1.7 g twice daily and phenprocoumon 3 to 4.5 mg daily fell from a range of 20 to 30% down to 0% when she stopped taking the **metformin** while on holiday. Despite the increased anticoagulant effect no signs of bleeding were observed, and she was eventually restabilised on the original doses of both drugs.[1] This case prompted a further observational study in 13 patients with type 2 diabetes. It was found that the 7 patients taking **metformin** 1.1 to 3 g daily were less well anticoagulated than those taking only 400 mg to 1 g of **metformin**, even though the mean phenprocoumon dose was slightly higher in those taking the higher **metformin** dose (2.57 mg daily versus 2.27 mg daily).[1] In another study, the half-life of phenprocoumon was reduced by about one-third (from 123 to 85 hours) by **metformin** 1.7 g daily.[1]

(b) Warfarin

An elderly woman taking warfarin 5 mg daily and **metformin** 1 g twice daily developed fatigue, epistaxis, haematuria and gingival bleeding, with an INR of 16.9, which was treated with vitamin K. The following morning, she was given **metformin**, then she was found to have a retroperitoneal haematoma and bilateral perinephric blood with obstruction of both renal collecting systems. Over the next 8 hours, she developed progressive metabolic acidosis and suffered a cardiopulmonary arrest. Her **metformin** level was 7.3 micrograms/mL (therapeutic range 1 to 2 micrograms/mL). It was suggested that **metformin** accumulation occurred because of renal impairment caused by the site of renal bleeding secondary to the excessive effects of warfarin. This then resulted in metabolic acidosis.[2]

Haematuria occurred in a patient taking warfarin 3 months after **phenformin** was started. Her prothrombin values were normal.[3] **Phenformin** may have increased fibrinolysis to the point where it was additive with the effects of the warfarin.

Mechanism

Metformin possibly reduces the effects of phenprocoumon by altering blood flow to the liver and interfering with enterohepatic circulation.

Importance and management

The information about a biguanide interaction with warfarin appears to be limited to these isolated reports, none of which definitively suggest that the biguanide altered anticoagulant effects. In general no interaction would be expected between metformin or phenformin and warfarin.

There is some evidence that a small increase in the dose of phenprocoumon may be necessary if metformin is given, but it seems likely that this can be managed with routine anticoagulant monitoring.

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Coumarins + Antidiabetics; Exenatide

Exenatide does not affect the response to warfarin.

Clinical evidence, mechanism, importance and management

In a controlled study in 15 healthy subjects, subcutaneous exenatide 5 micrograms twice daily for 2 days then 10 micrograms twice daily for 9 days had no effect on the pharmacokinetics of a single dose of **warfarin** 25 mg given on day 4. There was a slight 12% decrease in the maximum INR (1.72 versus 1.95).[1] Given the lack of a pharmacokinetic interaction, and slight decrease in anticoagulant effect, no **warfarin** dose adjustments are likely to be needed when exenatide is started.

1. Soon D, Kothare PA, Linnebjerg H, Park S, Yuen E, Mace KF, Wise SD. Effect of exenatide on the pharmacokinetics and pharmacodynamics of warfarin in healthy Asian men. *J Clin Pharmacol* (2006) 46, 1179–87.

Coumarins + Antidiabetics; Nateglinide or Repaglinide

Nateglinide and repaglinide do not appear to interact with warfarin, and nateglinide does not interact with acenocoumarol.

Clinical evidence, mechanism, importance and management

(a) Nateglinide

In a randomised, double-blind study, 11 healthy subjects were given nateglinide 120 mg three times daily for 5 days, with a single 10-mg dose of **acenocoumarol** on day 3. Nateglinide had no effect on the tolerability, pharmacokinetics or anticoagulant activity of **acenocoumarol**.[1]

In another study,12 healthy subjects were given nateglinide 120 mg three times daily for 4 days with a single 30-mg dose of **warfarin** on day 2. No pharmacokinetic or pharmacodynamic interaction was noted.[2] No dose adjustments would therefore be expected to be necessary if nateglinide is taken with either acenocoumarol or warfarin.

(b) Repaglinide

In a double-blind, placebo-controlled study in 28 healthy subjects who were stabilised on **warfarin**, repaglinide did not alter the anticoagulant effects of **warfarin** or the steady-state warfarin pharmacokinetics.[3] Therefore, no **warfarin** dose adjustment would be expected to be necessary on concurrent use.

1. Sunkara G, Bigler H, Wang Y, Smith H, Prasad P, McLeod J, Ligueros-Saylan M. The effect of nateglinide on the pharmacokinetics and pharmacodynamics of acenocoumarol. *Curr Med Res Opin* (2004) 20, 41–8.
2. Anderson DM, Shelley S, Crick N, Buraglio M. No effect of the novel antidiabetic agent nateglinide on the pharmacokinetics and anticoagulant properties of warfarin in healthy volunteers. *J Clin Pharmacol* (2002) 42, 1358–65.
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Coumarins + Antidiabetics; Pioglitazone or Rosiglitazone

Pioglitazone does not appear to alter the pharmacokinetics or anticoagulant effect of warfarin or phenprocoumon, and rosiglitazone does not affect the pharmacokinetics of warfarin. However, there is one isolated report of two patients who required markedly increased warfarin doses after starting to take pioglitazone or rosiglitazone.

Clinical evidence

(a) Pioglitazone

In a study, pioglitazone 45 mg daily for 7 days did not alter the steady-state pharmacokinetics of **warfarin** and there was no significant change in prothrombin time.[1,2] Similar results were noted with **phenprocoumon**.[2] The US manufacturer also briefly mentions that pioglitazone had no effect on prothrombin time when it was given to patients stabilised on **warfarin**.[1]

However, there is an isolated report of an 84-year old woman (who had been on a stable maintenance dose of **warfarin** for the previous year) who, 12 weeks after starting to take pioglitazone 15 mg daily, had a subtherapeutic INR of 1.2. The patient denied any recent changes in diet or medication, including non-prescription and herbal medicines. An INR of 2.3 was eventually reached after her **warfarin** dose was increased by 88% from 8.5 mg to 16 mg weekly. A therapeutic INR was subsequently maintained at a similar dose over the following 18 months.[3]

(b) Rosiglitazone

The manufacturer briefly notes that rosiglitazone has been found to have no clinically relevant effect on the steady-state pharmacokinetics of **warfarin**.[4]

However, there is an isolated report of a 76-year-old man (who had been taking a stable dose of **warfarin** for the previous 18 months) who, 4 weeks after starting to take rosiglitazone 4 mg daily, had a subtherapeutic INR of 1.1. The patient denied any recent changes in diet or medication, including non-prescription and herbal medicines. An INR of 1.9 was eventually reached after increasing the **warfarin** dose by 75% from 24 mg weekly to 42 mg weekly. A therapeutic INR was subsequently maintained at a similar dose over the following 12 months.[3]

Mechanism

In vitro, troglitazone (the first thiazolidinedione, which has now been withdrawn) significantly inhibited the metabolism (7-hydroxylation) of *S*-warfarin by the cytochrome P450 isoenzyme CYP2C9; however, pioglitazone and rosiglitazone only slightly inhibited this activity.[5] Any inhibitory activity would be expected to increase warfarin effects, whereas the two cases suggest reduced effects. The authors suggest that the weak CYP3A4-inducing effect of pioglitazone might explain the interaction.[3] However, as CYP3A4 is only a minor enzyme in 'warfarin metabolism', (p.405), and controlled pharmacokinetic studies have not shown an effect on warfarin pharmacokinetics, this explanation is unlikely.

Importance and management

Controlled studies have found no interaction between pioglitazone and warfarin or phenprocoumon, or between rosiglitazone and warfarin. This suggests that coumarin dose adjustments are unlikely to be needed when these antidiabetics are also given. Nevertheless, one report describes two patients who required increases in warfarin doses 4 to 12 weeks after starting pioglitazone or rosiglitazone. The general relevance of these two cases is uncertain, and such effects are likely to be picked up by routine INR monitoring.

1. Actos (Pioglitazone hydrochloride). Takeda Pharmaceutical Company Ltd. US Prescribing information, August 2008.
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4. Avandia (Rosiglitazone maleate). GlaxoSmithKline. US Prescribing information, February 2009.
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Coumarins + Antidiabetics; Sitagliptin and Vildagliptin

Sitagliptin and vildagliptin do not appear to alter the pharmacokinetics or anticoagulant effect of warfarin.

Clinical evidence, mechanism, importance and management

In a controlled study in 15 healthy subjects, vildagliptin 100 mg daily for six days had no effect on the pharmacokinetics of *R*- and *S*-warfarin when a single dose of **warfarin** 25 mg was given on day 2. Similarly, the anticoagulant effect (prothrombin time and INR) of **warfarin** was not altered by vildagliptin.[1]

The manufacturers state that in a study, multiple dose sitagliptin did not meaningfully affect the pharmacokinetics of *S*- or *R*-warfarin after a single dose of **warfarin**,[2,3] and the anticoagulant effect (INR) was not altered.[2]

Given the lack of a pharmacokinetic or pharmacodynamic interaction, no **warfarin** dose adjustments are likely to be needed on starting these antidiabetics.

1. He Y-L, Sabo R, Riviere G-J, Sunkara G, Leon S, Ligueros-Saylan M, Rosenberg M, Dole WP, Howard D. Effect of the novel oral dipeptidyl peptidase IV inhibitor vildagliptin on the pharmacokinetics and pharmacodynamics of warfarin in healthy subjects. *Curr Med Res Opin* (2007) 23, 1131–8.
2. Januvia (Sitagliptin phosphate). Merck & Co., Inc. US Prescribing information, March 2009.
3. Januvia (Sitagliptin phosphate monohydrate). Merck Sharp & Dohme Ltd. UK Summary of product characteristics, November 2009.

Coumarins and related drugs + Antidiabetics; Sulfonylureas

Dicoumarol inhibits the metabolism of tolbutamide and increases its effects; cases of hypoglycaemic coma have been reported. Chlorpropamide may be similarly affected. Although isolated cases of interactions (raised prothrombin times, bleeding or hypoglycaemia) have been seen in patients taking other sulfonylureas and other coumarins, in general, no important interaction appears to occur. There also appears to be no interaction between phenindione and tolbutamide.

Clinical evidence

A. Coumarins

(a) Chlorpropamide

1. Acenocoumarol. A woman with normal renal function had an increase in the half-life of chlorpropamide to 88 hours (normally about 36 hours) when she took acenocoumarol.[1]

2. Dicoumarol. A 67-year-old non-diabetic man taking chlorpropamide for Parkinson's disease developed severe hypoglycaemia about 3 months after starting dicoumarol. He had high chlorpropamide levels with a half-life of 80 to 90 hours. Dicoumarol was withdrawn, and 3 weeks later his chlorpropamide half-life was 30 hours.[2] This observation prompted further study in 3 other patients and 2 non-diabetics. Dicoumarol doubled the serum chlorpropamide levels within 3 to 4 days and also more than doubled the half-life.[2]

(b) Glibenclamide (Glyburide)

1. Phenprocoumon. A small study in 4 subjects reported that the pharmacokinetics of glibenclamide were unchanged by phenprocoumon.[3] Similarly, the plasma levels and half-life of single doses of phenprocoumon did not differ between patients with type 2 diabetes managed by diet alone (12 patients) and those taking glibenclamide (9 patients).[4]

2. Warfarin. There do not appear to be any controlled studies on the effect of glibenclamide on the pharmacokinetics of warfarin, although *in vitro* data suggest that an effect is possible because glibenclamide inhibited *S*-warfarin hydroxylation (a 7 to 37% *in vivo* inhibition was predicted).[5] Moreover, an isolated report describes increased warfarin effects (INR increased from 2.3 to 6.6 with haematomas) in a patient given glibenclamide.[6]

(c) Glibornuride

Phenprocoumon, given to 3 subjects for 4 days, slightly increased the half-life of a single 25-mg dose of glibornuride by 29%.[7] The plasma lev-

els and half-life of a single dose of **phenprocoumon** did not differ between patients with type 2 diabetes managed by diet alone (12 patients) and those taking glibornuride (12 patients).[4]

(d) Glimepiride

In healthy subjects, glimepiride 4 mg daily caused only minor, clinically unimportant changes in the prothrombin times (about 10% decrease in mean maximum prothrombin time) in response to single 25-mg doses of **warfarin**. In addition, glimepiride had no effect on the pharmacokinetics of *R*- and *S*-warfarin.[8]

(e) Tolbutamide

1. Dicoumarol. Dicoumarol has been found to increase the serum levels of tolbutamide, prolong its half-life (more than threefold), and reduce blood-glucose levels in both diabetics[9,10] and healthy subjects.[9-12] This may become excessive in a few patients and hypoglycaemic coma has been described in 3 diabetics,[9,13,14] and one non-diabetic.[15]

Two patients taking dicoumarol had marked increases in prothrombin times (a rise from 33 to 60 seconds) within 2 days of starting to take tolbutamide, but no bleeding occurred. However, no increases were seen in 3 other patients taking dicoumarol when they started tolbutamide.[16] Conversely, the half-life of dicoumarol was approximately halved in 2 out of 4 healthy subjects given tolbutamide, but the hypoprothrombinaemic effects were unchanged.[12] However, in a retrospective study there was no difference in the initial or average dose of dicoumarol between 15 patients taking tolbutamide and 24 control subjects taking insulin.[17]

2. Phenprocoumon. In 3 subjects, phenprocoumon, given for one week, did not alter the half-life of a single intravenous dose of tolbutamide 1 g.[10] Similarly, there was no difference in monthly tolbutamide levels, taken over a year, between 7 patients taking tolbutamide alone and 2 patients also taking phenprocoumon.[18]

The plasma levels and half-life of single doses of phenprocoumon did not differ between patients with type 2 diabetes managed by diet alone (12 patients) and those taking tolbutamide (10 patients).[4]

3. Warfarin. Giving warfarin for one week did not alter the half-life of a single intravenous dose of tolbutamide 1 g in 2 subjects.[10] Similarly, giving warfarin for a week did not alter serum tolbutamide levels in 2 patients with diabetes.[10] In a retrospective study, there was no difference in the initial or average dose of warfarin between 42 patients taking tolbutamide and 54 control subjects taking insulin.[17]

(f) Unspecified sulfonylureas

In a retrospective study, the initial rate of warfarin anticoagulation was faster (threefold faster rise in INR) in 6 patients also taking sulfonylurea antidiabetics than in 160 control patients and 16 patients with diabetes not taking sulfonylureas.[19] The findings of this study require confirmation in a controlled, prospective study.

B. Indanediones

In early studies, phenindione given for 6 days did not affect the half-life of a single dose of **tolbutamide** in a few subjects.[9,10] Similarly, the average plasma levels of **tolbutamide** in 3 patients taking phenindione were not different from 4 patients not taking phenindione.[9]

Mechanism

Dicoumarol appears to increase the effects of tolbutamide by inhibiting its metabolism by the liver.[9,11] This may also be true for chlorpropamide.[2] The increase in the anticoagulant effects of dicoumarol by tolbutamide may, in part, be due to a plasma protein binding interaction. In the case of phenprocoumon there seem to be several different mutually opposing processes going on, which cancel each other out.[12] There is no clear explanation for most of the isolated cases.

Importance and management

Information is patchy and very incomplete. The effect of dicoumarol on tolbutamide has been the most thoroughly investigated, and the interaction is clinically important. Increased blood-glucose lowering effects may be expected if dicoumarol is given to patients taking tolbutamide, and there is a risk of hypoglycaemic coma. Whether tolbutamide alters the anticoagulant response to dicoumarol is unclear. Avoid concurrent use unless the outcome can be well monitored and dose adjustments made. The same precautions should be taken with dicoumarol and chlorpropamide, but information is limited to one study.

Information on other interactions is limited to isolated cases, and these are therefore of doubtful general significance.

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13. Spurny OM, Wolf JW, Devins GS. Protracted tolbutamide-induced hypoglycemia. *Arch Intern Med* (1965) 115, 53–6.
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Coumarins + Antihistamines

Findings from a retrospective review suggest that the anticoagulant effects of acenocoumarol may be reduced by loratadine, ebastine, or cetirizine. Conversely, an isolated report describes bleeding and a markedly raised INR in an elderly man taking acenocoumarol and cetirizine.

Clinical evidence, mechanism, importance and management

A retrospective review of patients taking **acenocoumarol** with **loratadine**, **ebastine**, or **cetirizine** found that INRs were decreased during concurrent use, but no thromboembolic event was noted. The authors consider that temporary increases in the anticoagulant dose might be required in patients taking both drugs.[1]

In contrast, there is a case report of an 88-year-old man taking **acenocoumarol** for a deep vein thrombosis who developed acute and severe epistaxis after a fall. He had started to take **cetirizine** 10 mg daily for allergic rhinitis 3 days before the fall.[2] His INR was found to have risen from 1.5 to 14. The **cetirizine** concentration was found to be particularly high, possibly because of some degree of renal impairment, and it was thought that these high levels may have displaced **acenocoumarol** from its plasma protein binding sites. However, this mechanism on its own is now largely discredited as an explanation for interactions between anticoagulants and highly protein-bound drugs.

Information is limited, and given the widespread use of these drugs, any consistent clinically significant interaction might have been expected to have come to light by now. No specific precautions seem necessary if these drugs are given in combination, but bear the interaction in mind in the case of an unexpected response to treatment.

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Coumarins + Antineoplastics; Miscellaneous cytotoxics

A number of case reports describe an increase in the effects of warfarin, accompanied by bleeding in some cases, caused by antineoplastic regimens including carboplatin, chlormethine, cyclophosphamide, doxorubicin, etoposide, ifosfamide with mesna, methotrexate, paclitaxel, procarbazine, vincristine or vindesine, and gemcitabine alone. Conversely, a decrease in the effects of warfarin has been seen in individual cases with cyclophosphamide alone and mitotane alone, and no change in warfarin effect has been seen in one patient while receiving busulfan, cyclophosphamide, cytarabine, and melphalan each given alone.

Clinical evidence

(a) Busulfan

A man well stabilised on **warfarin** had no change in his anticoagulant response while taking busulfan for 6 weeks.[1]

(b) Carboplatin

The INR of a man taking **warfarin** increased from a baseline range of 1.15 to 2.11 up to 12.6 within 16 days of a first course of chemotherapy with carboplatin and etoposide.[2]

(c) Cyclophosphamide

A woman taking **warfarin** had a marked rise in her prothrombin time when her treatment with cyclophosphamide was withdrawn, suggesting that cyclophosphamide reduced the anticoagulant response.[3] Another patient had an increase in anticoagulant effect of **warfarin** while taking a combination regimen containing cyclophosphamide, see *ProMace-Mopp*, below. In contrast, a man well stabilised on **warfarin** had no change in anticoagulant response while taking cyclophosphamide for 6 weeks.[1]

(d) Cytarabine

A man well stabilised on **warfarin** had no change in anticoagulant response while taking cytarabine for 6 weeks.[1]

(e) Etoposide

The INR of a man taking **warfarin** increased from a baseline range of 1.15 to 2.11 up to 12.6 within 16 days of a first course of chemotherapy with carboplatin and etoposide.[2] Another elderly man taking **warfarin** had a marked increase in prothrombin times (prolongation of 8 to 15 seconds) on two occasions when he took etoposide 500 mg and **vindesine** 5 mg.[4] Another patient had an increase in anticoagulant effect of **warfarin** while taking a combination regimen containing cyclophosphamide, see *ProMace-Mopp*, below.

(f) Gemcitabine

A 63-year-old man needed a reduction in his weekly **warfarin** dose from 59.23 mg to 50.75 mg in order to keep his INR at about 2.5 during 2 cycles of gemcitabine. When the gemcitabine was stopped his **warfarin** dose had to be increased again.[5] The manufacturers have information on 4 cases of suspected interactions between gemcitabine and **warfarin**, and one with **phenprocoumon** (reported by December 2000). Based on 724 reports of the concurrent use of gemcitabine and **anticoagulants**, this represents an incidence of the suspected interaction of 0.8%, which is low if there were a specific interaction.[6]

(g) Hydroxycarbamide

A man well stabilised on **warfarin** had no change in anticoagulant response while taking hydroxycarbamide for 6 weeks.[1]

(h) Ifosfamide

Three patients taking **warfarin** had a marked and very rapid increase in their INRs when given ifosfamide; with **mesna** and **cisplatin** with **etoposide**; or **doxorubicin**; or **doxorubicin** with **vincristine**.[7]

(i) Melphalan

A man well stabilised on **warfarin** had no change in anticoagulant response while taking melphalan for 6 weeks.[1]

(j) Mitotane

A patient who started to take mitotane 4 g [daily] for adrenal carcinoma was also given warfarin (5 mg and 2.5 mg on alternate days) 2 days later for a deep vein thrombosis. This patient required several increases in her warfarin dose to 12.5 mg daily over 4-month period to maintain a therapeutic prothrombin time of about 22 seconds. A few weeks later she was found to have an increase in her prothrombin time to 27.1 seconds, so her warfarin dose was decreased to 10 mg daily. However, 3 months later she was admitted to hospital with haematemesis and gingival bleeding, and her prothrombin time was found to be 74.6 seconds. She was found to have a haemorrhage of a tumour in the right posterior fossa, and she died that day.[8]

(k) Paclitaxel

A woman who had been stable on **warfarin** for 2 months had an INR increase from 3 to 5.2 on the day after receiving paclitaxel and **carboplatin**. A rise in INR occurred on each subsequent cycle of chemotherapy.[9]

(l) ProMace-Mopp

The prothrombin times of an elderly man given **warfarin** increased by 50 to 100% in the middle of three cycles of treatment with ProMace-Mopp (**cyclophosphamide**, **doxorubicin**, **etoposide**, **chlormethine**, **vincristine**, **procarbazine**, **methotrexate** and prednisone), and he developed a subconjunctival haemorrhage during the first cycle.[10]

Mechanism

Not well understood. Coagulation control can be altered by many factors in severely ill patients with cancer including altered diet due to lack of appetite, and nausea and vomiting caused by antineoplastics. Antineoplastics that cause gastrointestinal toxicity might also alter the absorption of warfarin. The authors of the case report of an interaction with paclitaxel suggest that the likely mechanism of action is displacement of warfarin from protein binding sites by paclitaxel. However, altered protein binding has not clearly been shown to be an important mechanism in warfarin interactions, as any effect is usually transient.

Importance and management

These are isolated cases, and no specific drug interaction is established for any of the cytotoxic antineoplastics covered here. Nevertheless, other factors due to the disease or patient might alter the response to anticoagulants. Therefore, the anticoagulant doses may need adjustment. Note that, from a disease perspective, when treating venous thromboembolic disease in patients with cancer, warfarin is generally inferior (higher risk of major bleeds and recurrent thrombosis) to low-molecular-weight heparins.

Note that some cytotoxic antineoplastics do have specific interactions with coumarins, see 'Coumarins + Azathioprine or Mercaptopurine', p.436, and 'Coumarins + Fluorouracil and related prodrugs', p.460.

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Coumarins + Aprepitant

Aprepitant modestly reduces warfarin levels and slightly decreases the INR in healthy subjects. It is expected to interact similarly with acenocoumarol. Fosaprepitant, a prodrug of aprepitant, would be expected to interact similarly.

Clinical evidence, mechanism, importance and management

In a double-blind study, healthy subjects were stabilised on **warfarin** and then given either aprepitant (125 mg on day one, then 80 mg daily on days 2 and 3) or placebo. On day 3, there was no change in **warfarin** lev-

els. However, by day 8 (5 days after stopping aprepitant) there was a 34% decrease in trough *S*-warfarin levels, and a 14% decrease in INR in the aprepitant group.[1]

Aprepitant is a moderate inducer of the cytochrome P450 isoenzyme CYP2C9, by which *S*-warfarin is metabolised. The manufacturer recommends that, in patients taking **warfarin**, the INR should be monitored closely for 2 weeks, particularly at 7 to 10 days,[2] after each 3-day course of aprepitant,[2,3] and this seems a prudent precaution. The UK manufacturer[3] similarly recommends caution with **acenocoumarol**, which is also metabolised by CYP2C9. **Fosaprepitant**, a prodrug of aprepitant, is expected to interact similarly, and the manufacturers recommend similar advice to manage the interaction.[4,5]

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Coumarins + Aromatase inhibitors

The anticoagulant effects of warfarin and acenocoumarol can be markedly reduced by aminoglutethimide. An isolated case of thromboembolism has been loosely attributed to an interaction between letrozole and warfarin. However, anastrozole and letrozole do not affect the pharmacokinetics of warfarin, and exemestane would not be expected to interact.

Clinical evidence

(a) Aminoglutethimide

In a study in 9 patients being treated for breast cancer, aminoglutethimide 125 mg twice daily increased the clearance of a single-dose of *R*- or *S*-warfarin by 41% with marked variability between individuals (range 15 to 103%). Aminoglutethimide 250 mg four times daily increased the clearance of **warfarin** by 91%. The effects of the interaction had developed fully by 14 days. Both enantiomers of **warfarin** were equally affected.[1]

One 79-year-old woman taking aminoglutethimide 250 mg four times daily was resistant to **warfarin** requiring a dose of 17.5 to 20 mg daily. Two weeks after the aminoglutethimide was stopped, the required dose of **warfarin** gradually declined, eventually reaching a level of 3.75 and 5 mg on alternate days (about a fourfold reduction).[2] Another patient stabilised on **warfarin** gradually needed about a threefold increase in the **warfarin** dose after starting aminoglutethimide 250 mg four times a day.[2] The increased requirement persisted for 2 weeks after the aminoglutethimide was stopped, and then declined. A study briefly mentions a patient who needed greatly increased doses of **warfarin** after starting aminoglutethimide.[3] Three patients taking **acenocoumarol** needed a doubled dose to maintain adequate anticoagulation when they took aminoglutethimide 250 mg four times daily for 3 to 4 weeks.[4]

(b) Anastrozole

In a well-controlled study in 16 healthy men,[5] anastrozole (7 mg loading dose followed by 1 mg daily for a further 10 days) had no effect on the pharmacokinetics or pharmacodynamics of a single dose of **warfarin** given on day 3.

(c) Letrozole

The manufacturers report that letrozole had no clinically relevant effect on the pharmacokinetics of **warfarin**.[6,7]

A 72-year-old woman with breast cancer developed deep vein thrombosis while taking tamoxifen. **Warfarin** was started and the tamoxifen was switched to letrozole. Five months later she developed a pulmonary thromboembolism, and her INR was noted to be subtherapeutic. The authors suggested that the low INR may be due to an interaction between **warfarin** and letrozole; however, they also note that many other factors may have contributed to this patient developing a pulmonary embolism, such as a possible adverse effect of letrozole, obesity and related immobility, and therefore the exact cause is unknown.[8]

Mechanism

Uncertain. The most likely explanation is that aminoglutethimide, like glutethimide, stimulates the activity of the liver enzymes concerned with the metabolism of the coumarin anticoagulants, thereby reducing their levels and efficacy. Alternatively, it has been suggested that aminoglutethimide may affect blood steroid levels, which in turn might affect coagulation.[2] Letrozole is not reported to be an inducer of the cytochrome P450 isoenzymes CYP2C9 or CYP3A4, which are involved in the metabolism of coumarin anticoagulants.

Importance and management

The interaction of warfarin and acenocoumarol with aminoglutethimide is established and clinically important. Monitor the effects of adding aminoglutethimide to patients already taking these drugs and increase the anticoagulant dose as necessary. Up to four times the dose may be needed. The extent of the effects would appear to be related to the dose of aminoglutethimide used. Monitor the INR and reduce the anticoagulant dose accordingly if aminoglutethimide is withdrawn. Information about other coumarins is lacking but it would be prudent to apply the same precautions with any of them.

Conversely, controlled studies have shown no interaction between anastrozole or letrozole and warfarin, and the isolated case report does not firmly implicate an interaction with warfarin. Overall, this suggests that coumarin dose adjustments are unlikely to be needed when these aromatase inhibitors are used. There appears to be no published information of an interaction with **exemestane**. The US manufacturers state that it does not inhibit CYP2C9 or CYP3A4, therefore it is unlikely to have any significant pharmacokinetic interaction with warfarin.[9]

Note that tamoxifen also interacts with warfarin and possibly other coumarin anticoagulants in some patients, see 'Coumarins + Tamoxifen or Toremifene', p.511, for further information.

Consider also that, from a disease perspective, when treating venous thromboembolic disease in patients with cancer, warfarin is generally inferior (higher risk of major bleeds and recurrent thrombosis) to low-molecular-weight heparins.[10]

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Coumarins + Ascorbic acid (Vitamin C)

Although two isolated cases have been reported in which the effects of warfarin were reduced by ascorbic acid, four subsequent prospective studies have not found any interaction.

Clinical evidence

In a woman recently stabilised on **warfarin** 7.5 mg daily, who began to simultaneously take ascorbic acid (dose not stated) with her warfarin, the prothrombin time fell steadily from 23 seconds, to 19, 17, and then 14 seconds, with no response to an increase in the dose of **warfarin** to 10 mg, 15 mg, and finally 20 mg daily. The prothrombin time returned to 28 seconds within 2 days of stopping the ascorbic acid.[1] Another woman recently stabilised on warfarin 5 mg daily had a recurrence of acute thrombophlebitis with a prothrombin time of 12 seconds. She was unusually resistant to the actions of **warfarin** and required 25 mg daily before a significant increase in prothrombin times was achieved. On questioning, she had been taking massive amounts of ascorbic acid (about 16 g daily) for several weeks. She was eventually stabilised on warfarin 10 mg daily.[2]

In contrast, in prospective studies, no changes in the effects of **warfarin** were seen:

- in 5 patients given ascorbic acid 1 g daily for a fortnight,[3]
- in 11 patients (some taking **dicoumarol**) given ascorbic acid 4 g daily for 2 weeks,[4]
- in 14 patients given ascorbic acid 3 g then 5 g daily for one week or 5 patients given 10 g daily for one week:[5] a mean fall of 18% in total plasma **warfarin** concentrations was seen at all doses,
- in a 10-week study, where the proportion of patients requiring a change in **warfarin** dose did not differ between 84 patients given ascorbic acid (dose unstated) and 96 control patients (31 patients versus 18 patients required a dose reduction, and 7 versus 13 required a dose increase, respectively).[6]

Mechanism

Not understood. One *animal* study has demonstrated this interaction[7] and others have not,[8,9] but none of them has provided any definite clues about why it ever occurs. One suggestion is that high doses of ascorbic acid can cause diarrhoea, which might prevent adequate absorption of the anticoagulant.

Importance and management

Four clinical studies in patients stabilised on warfarin have not found that ascorbic acid alters the anticoagulant effect of warfarin, even using very large doses of ascorbic acid (up to 10 g daily), even though there are two isolated reports of reduced warfarin efficacy. All these data are from the 1970s, and nothing further seems to have been published. Coumarin dose adjustments are therefore unlikely to be needed when ascorbic acid is also used.

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Coumarins and related drugs + Aspirin or other Salicylates

Antiplatelet doses of aspirin (75 to 325 mg daily) increase the risk of bleeding when given with warfarin by about 1.5 to 2.5-fold, although, in most studies the absolute risks have been small. The overall benefits of concurrent use outweigh the risks in certain patient groups; however, for some warfarin indications, there is not enough data to assess this. In addition to increased bleeding, high doses of aspirin (4 g daily or more) can increase prothrombin times.

Clinical evidence

A. Analgesic-dose aspirin

In a pharmacological study in patients stabilised on **acenocoumarol**, aspirin 2.4 g daily for one week increased faecal blood loss from an average of 1.1 mL to 4.7 mL. While taking aspirin, 11 of 17 patients required a 29% reduction in their **acenocoumarol** dose from a mean of 3.1 mg to 2.2 mg. One patient required a slight increase of 0.5 mg, and the remaining 5 required a dose reduction of less than 0.5 mg.[1]

In another study in healthy subjects, aspirin 1.95 g daily for 11 days had no effect on the prothrombin time response to a single dose of **warfarin** given on day 4. When 11 healthy subjects were stabilised on **dicoumarol** or **warfarin** and given aspirin 1.95 g daily, 7 had no significant change in prothrombin time activity, and 4 had a slight reduction (of 5 to 10% points). Two subjects had signs of bleeding, but neither had a reduction in prothrombin time activity. A further 4 subjects stabilised on **warfarin** received a higher dose of aspirin (3.9 g daily), and all 4 had a reduction in prothrombin time activity of 6 to 12% points and signs of bleeding occurred. The bleeding time was significantly prolonged by the combination of aspirin 1.95 g daily and **warfarin** than by **warfarin** alone (10.3 minutes versus 4 minutes).[2] In a study in 12 healthy subjects stabilised on **warfarin**, aspirin 2.6 g daily for one week reduced the mean prothrombin concentrations by about 2.75%.[3] In two further studies in healthy subjects, aspirin 6 g daily moderately prolonged prothrombin times,[4,5] and in one study this effect tended to be reversed by vitamin K.[4]

In contrast, in another study in 10 patients, adding aspirin 3 g daily to **warfarin** for 2 weeks had no effect on prothrombin times (20.9 seconds versus 21.2 seconds).[6]

B. Antiplatelet-dose aspirin

In a study in healthy subjects, low-dose aspirin 75 mg daily doubled the normal blood loss from the gastric mucosa. However, concurrent **warfarin** (dose individualised to achieve an INR of 1.4 to 1.6) did not increase the gastric mucosal bleeding any further.[7]

In a large population-based, retrospective case control-study using records from the UK General Practice Research Database from 2000 to 2005, the use of **warfarin** with aspirin was associated with a marked increased risk of gastrointestinal bleeding when compared with either drug alone (rate ratio of 6.48 for concurrent use compared with 1.94 for **warfarin** and 1.39 for aspirin).[8] This study did not specify the indication for concurrent use. In a similar retrospective cohort study from the Netherlands, the use of **acenocoumarol** or **phenprocoumon** with antithrombotic salicylates (not specified) was associated with an increased risk of major bleeding (relative risk 3).[9]

(a) Atrial fibrillation

In a large study in patients with atrial fibrillation, the cumulative incidence of bleeding events after 3 years was no different in those receiving fixed low-dose **warfarin** 1.25 mg daily with aspirin 300 mg daily (24.4%) than with fixed low-dose **warfarin** alone (24.7%) or aspirin 300 mg daily alone (30%).[10] This study also contained an adjusted-dose **warfarin**-only group, which proved more effective than the other group, so the study was terminated early. Other studies have found similar results.[11]

In another study, the combination of adjusted dose **fluindione** (INR 2 to 2.6) with aspirin 100 mg daily was associated with a much higher incidence of haemorrhagic complications than **fluindione** alone (13.1% versus 1.2%). The overall balance of benefit to risk could not be assessed because of the low incidence of the primary endpoint (ischaemic events).[12]

(b) Myocardial infarction

1. Primary prevention. In a large primary prevention study in men at high risk of ischaemic heart disease, the incidence of haematuria was twofold higher in those receiving both low-dose aspirin 75 mg daily and low-intensity **warfarin** (INR 1.5) than in those receiving low-dose aspirin alone, or low-intensity **warfarin** alone. Similarly, the incidence of minor episodes of bleeding (nose bleeds, bruising, rectal bleeding, pink/red urine) was 1.27-fold higher in those receiving the combination than in those receiving low-dose aspirin alone, or low-intensity **warfarin** alone (49% versus 38% and 39%, respectively), although the difference was not statistically significant. There was no difference in incidence of major and intermediate episodes of bleeding.[13]

2. Secondary prevention. In a meta-analysis of randomised, controlled studies[14] in patients following myocardial infarction or acute coronary syndrome, intensive **warfarin** (INR greater than 2) with aspirin 80 to 325 mg daily was associated with 2.5-fold increased risk of major bleeding, when compared with aspirin alone, although the actual incidence was low (1.5% versus 0.6%). This analysis excluded studies of coronary stenting. In another similar meta-analysis, the concurrent use of aspirin and **warfarin** (INR 2 to 3) was associated with a 2.3 odds ratio of a major bleed, when compared with aspirin alone.[15] The number needed to treat to cause one major bleed was 100. This compared with a number needed to treat to avoid one major adverse event (death, myocardial infarction or stroke) of 33.

Similarly, in an observational cohort study of elderly survivors of acute myocardial infarction, the rate of bleeding was higher in patients receiving **warfarin** with aspirin (0.08 per patient year), than in patients receiving aspirin alone (0.03 per patient-year).[16] Using lower intensity **warfarin** with the low-dose aspirin was still associated with more major bleeding than aspirin alone (1.77 in one study, although this is less than higher intensity **warfarin**; 2.3 as mentioned above). Nevertheless, low-intensity **warfarin** with low-dose aspirin does not appear to be any more effective than aspirin alone.[15,17]

(c) Peripheral arterial disease

In a meta-analysis of studies of patients with peripheral arterial disease, the concurrent use of **oral anticoagulants** with aspirin increased the risk of major bleeding about twofold when compared with aspirin alone, and appeared to be associated with increased mortality.[18]

In one open-label, randomised, clinical study, patients with peripheral arterial disease were assigned to take an antiplatelet alone (1081 patients taking aspirin, clopidogrel or ticlopidine) or to take an antiplatelet with **warfarin** or **acenocoumarol** (1080 patients, target INR of 2 to 3). The risk of life-threatening bleeding was 3.4-fold higher with the concurrent use of an anticoagulant and an antiplatelet than with the antiplatelet alone (4% versus 1.2%), and moderate and minor bleeding were also increased (relative risk of 2.8 and 3.6, respectively).[19]

(d) Prosthetic heart valves

In one randomised study in patients with artificial heart valves, the risk of bleeding episodes requiring blood transfusion or hospitalisation was much higher among those taking aspirin 500 mg daily and **warfarin** (14%), when compared with those taking **warfarin** and dipyridamole 400 mg daily (4%), and compared with a non-randomised control group taking **warfarin** alone (5%). Bleeding was mainly gastrointestinal or cerebral. All of those with intracerebral bleeding died.[20]

A further study found that aspirin 1 g daily, given with **unnamed anticoagulants**, was associated with a threefold higher incidence of bleeding episodes than those taking anticoagulants alone (13.9 per 100 patients per year versus 4.7 per 100 patients per year).[21,22] However, in another study there was no difference in haemorrhagic risk between patients receiving aspirin 500 mg daily and **acenocoumarol** or **acenocoumarol** alone.[23]

More recent studies have used lower doses of aspirin. In one study in patients stabilised on **warfarin** with a target INR of 3.0 to 4.5, the addition of aspirin 100 mg daily increased the risk of any bleeding 1.55-fold, when compared with placebo (35% versus 22% per year), mainly due to an increase in minor haematuria, nosebleeds and bruising. However, the risk was more than offset by the overall reduction in mortality.[24]

The preliminary report of a meta-analysis of these four studies, concluded that the concurrent use of **oral anticoagulants** and aspirin (100 mg to 1 g daily) significantly reduced mortality and embolic complications in patients with prosthetic heart valves, with an estimated increased odds ratio of major bleeds of 1.7 and of total bleeds of 1.98. Nevertheless the overall picture was that the benefits possibly outweighed the problems.[25] In a subsequent meta-analysis,[26] which excluded one non-randomised study,[20] but included two other randomised controlled studies, the risk of major bleeding for the combination of **warfarin** and aspirin was 1.53. For the two studies using low-dose aspirin (100 mg daily), there did not appear to be an excess risk of major bleeding.[26] Another analysis of these studies provided essentially the same risk of increased major bleeding with the combination.[27]

Mechanism

Aspirin has a direct irritant effect on the stomach lining and can cause gastrointestinal bleeding, even in doses as low as 75 mg daily.[28] It also decreases platelet aggregation and prolongs bleeding times. At low doses of aspirin, this increases the risk of haemorrhage with warfarin without elevating the INR. In addition, large doses of aspirin (4 g daily or more) alone are known to have a direct hypoprothrombinaemic effect, which is reversible by vitamin K.[4,5] This effect of aspirin can be additive with the effects of the anticoagulant.

Importance and management

The interaction of aspirin at high doses and warfarin is not well documented, but is clinically important. It is usual to avoid normal analgesic and anti-inflammatory doses of aspirin while taking any coumarin anticoagulant, although only dicoumarol, acenocoumarol and warfarin appear to have been investigated. Patients should be told that many non-prescription analgesic, antipyretic, cold and influenza preparations may contain substantial amounts of aspirin. Warn them that it may be listed as acetylsalicylic acid. Paracetamol is a safer analgesic substitute (but not entirely without problems, see 'Coumarins and related drugs + Paracetamol (Acetaminophen)', p.492).

The effect of low-dose aspirin, used for its antiplatelet effects, with warfarin has been far more extensively studied. Overall, the evidence shows that the combination is still associated with an increased risk of bleeding over either drug alone, and, from controlled studies, this is in the region of 1.5- to 2.5-fold, although two population studies have suggested that the risk might be greater in the primary care setting.[8,9] Nevertheless, the absolute risk is small. A twofold increased risk of haematuria and a slight increased risk of minor bleeding of 1.27 was still seen in the study using the lowest dose of warfarin (INR 1.5) with just 75 mg of aspirin a day.[13] In certain patient groups the benefits of concurrent use have been clearly shown to outweigh this increased risk of bleeding, such as patients with prosthetic heart valves at high risk of thromboembolism. In these patients, those who are at risk of gastrointestinal bleeding should additionally receive gastroprotection such as proton pump inhibitors. In addition, in the long-term, aspirin doses should be limited to no more than 81 mg daily.[29] However, in many of the common indications for warfarin, such as atrial fibrillation, there is insufficient evidence to answer the question of whether the combination should be used.[27]

For a review of the risk of bleeding when using warfarin with dual antiplatelet therapy such as low-dose aspirin and clopidogrel, see 'Coumarins and related drugs + Clopidogrel', p.448.

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Coumarins + Azathioprine or Mercaptopurine

A number of cases of a marked decrease in the effects of warfarin have been seen with azathioprine and mercaptopurine. A decrease in the effects of acenocoumarol has also been seen with mercaptopurine, and a decrease in the effects of phenprocoumon has been seen with azathioprine.

Clinical evidence

(a) Azathioprine

In a survey of 103 patients with antiphospholipid syndrome taking **warfarin**, the use of azathioprine appeared to increase **warfarin** requirements. Twelve of 26 patients (46%) requiring more than 10 mg of **warfarin** daily were taking azathioprine when compared with 15 of 77 patients (19%) requiring less than 10 mg **warfarin** daily.[1] There are a number of case reports of an interaction between coumarins and azathioprine. In one case, a woman who was resistant to **warfarin**, needing 14 to 17 mg daily while taking azathioprine, began to bleed (epistaxis, haematemesis) when the azathioprine was stopped. She was restabilised on **warfarin** 5 mg daily.[2] Reduced **warfarin** effects were seen in 2 other patients taking azathioprine,[3,4] one of whom had a marked fall in serum **warfarin** levels during azathioprine treatment.[4] Two women with systemic lupus erythematosus taking **phenprocoumon**[5] and a third taking **warfarin**[6] had marked falls in their INRs during treatment with azathioprine. Another woman needed an almost fourfold increase in the dose of **warfarin** when she was given azathioprine.[7] In a retrospective analysis of patients with antiphospholipid syndrome admitted to hospital with serious bleeding, 3 patients taking azathioprine had a serious bleed, and in two of these cases the bleed occurred when their azathioprine dose was reduced.[8] In another case, a patient required about double the **warfarin** dose when her azathioprine dose was increased from 150 mg daily to 200 mg daily. Four weeks after the azathioprine was stopped abruptly because of suspected liver toxicity, her INR had increased from 1.8 to 14, and she had bruising and mild epistaxis.[9] A further case has been reported where a patient required a warfarin dose increase from 37.5 mg weekly to 112 mg weekly when azathioprine 150 mg daily was started in order to maintain an INR of 2.5.[10] In two other cases, significant warfarin dose increases were needed in patients given azathioprine.[11]

(b) Mercaptopurine

A man well stabilised on **warfarin** had a marked reduction in his anticoagulant response on two occasions while taking mercaptopurine 100 mg to 150 mg daily: the anticoagulant response returned when mercaptopurine was stopped. He had previously had no changes in anticoagulant response when receiving 6-week courses of single drugs including **busulfan**, **cyclophosphamide**, **cytarabine**, **hydroxycarbamide**, **mitobronitol**, **demecolcine** and **melphalan**.[12] A woman needed a marked increase in her dosage of **acenocoumarol**, from 21 mg weekly to 70 mg weekly, when she was given mercaptopurine 100 mg daily.[13] Another patient had a drop in INR from 3 to 1.1 two weeks after starting mercaptopurine and methotrexate. His **warfarin** requirements varied up to about threefold over three cycles of this chemotherapy, increasing during the mercaptopurine cycle and decreasing when in between cycles of treatment.[14]

Mechanism

Not well understood. From early studies in *rats*, it was concluded that mercaptopurine possibly increases the synthesis or activation of prothrombin, and that it does not alter the half-life, volume of distribution or clearance of warfarin.[15] The authors of one case report noted lower plasma warfarin levels during the use of azathioprine in one patient.[4] Azathioprine is metabolised to mercaptopurine, and would therefore be expected to interact similarly.

Importance and management

Although the evidence is limited, it seems that mercaptopurine and azathioprine may markedly decrease the anticoagulant response to coumarins, and that the anticoagulant doses may need to be significantly increased to achieve adequate anticoagulation. It would therefore be prudent to closely monitor concurrent use.

Note that, from a disease perspective, when treating venous thromboembolic disease in patients with cancer, warfarin is generally inferior (higher risk of major bleeds and recurrent thrombosis) to low-molecular-weight heparins.

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Coumarins + Azoles; Econazole

A case report describes a raised INR and bleeding in a patient taking warfarin, when he used econazole cream.

Clinical evidence, mechanism, importance and management

A 79-year-old man, taking long-term warfarin, was given econazole cream for a fungal groin infection. Within one week of starting to apply the cream, he noticed bruising, including a large area on his hip, resulting from a trivial injury, and prolonged bleeding from a small cut.[1] His INR was found to have increased from 2.2 to 12. He was also taking glucosamine with chondroitin, which seems unlikely to have been responsible as this was not a new medication.

Econazole is structurally similar to miconazole, an inhibitor of the cytochrome P450 isoenzymes CYP2C9 and CYP3A4, which have major and minor roles, respectively, in warfarin metabolism. It seems likely that sufficient econazole was absorbed through the infected skin in the groin (which is thin, and in this particular case, macerated due to the fungal infection) to inhibit warfarin metabolism, leading to raised levels, and the increase in INR seen.

Econazole normally has very low systemic availability after topical application, and therefore the manufacturer notes that clinically relevant interactions are rare;[2,3] however, they do advise monitoring patients taking warfarin or acenocoumarol. In general, an interaction seems unlikely (this case appears to be the only one reported), but it would seem prudent to consider monitoring any patient receiving a coumarin if they need to use large amounts of econazole, especially on broken or damaged skin.

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Coumarins + Azoles; Fluconazole

Fluconazole causes a dose-related reduction in the metabolism of warfarin, and increases its anticoagulant effect. Cases of minor to major bleeding have been reported. There is one similar case report with acenocoumarol and fluconazole.

Clinical evidence

(a) Acenocoumarol

A patient stabilised on acenocoumarol suffered an intracranial haemorrhage (prothrombin time 170 seconds) 5 days after starting to take fluconazole 200 mg daily for the management of relapsed prosthetic valve candidal endocarditis.[1]

(b) Warfarin

1. Multiple-dose fluconazole. In a well-designed study in healthy subjects, fluconazole was given at three dose levels (100 mg, 200 mg and 400 mg daily) for 14 days with a single dose of warfarin given both before fluconazole and on day 7 at each fluconazole dose level. In this study, fluconazole markedly potentiated the anticoagulant effect of warfarin in a dose-related manner. The duration of anticoagulant effect was 4 to 7 days for the single dose of warfarin alone, 5 to 9 days with fluconazole 100 mg daily, 6 to 11 days with fluconazole 200 mg daily, and 8 to 15 days with fluconazole 400 mg daily. Fluconazole increased the levels of both *R*- and *S*-warfarin. With fluconazole 100 mg, 200 mg and 400 mg, the AUC of *R*-warfarin was increased by 28%, 63%, and 70%, respectively, and that of *S*-warfarin by 35%, 86%, and 100%, respectively.[2] Two other studies in healthy subjects have found broadly similar results.[3-5]

The clinical importance of this interaction was shown in an earlier study, which found that when fluconazole 100 mg daily was given to 7 patients stabilised on warfarin, the prothrombin time increased from 15.8 seconds on day one, to 18.9 seconds on day 5, and 21.9 seconds on day 8. The fluconazole was stopped early in 3 of the patients due to high prothrombin times, but none exceeded an increase of more than 9.7 seconds, and no bleeding occurred.[6]

At least 6 reports have described increased prothrombin times or INRs in patients stabilised on warfarin who took fluconazole in doses of 50 to 400 mg daily.[7-13] Several patients had haemorrhagic effects (gastrointestinal bleeding, melaena, ocular haemorrhage, spinal epidural haematoma).[7,9,11-13]

2. Single-dose fluconazole. Six women taking stable doses of warfarin with an INR between 2 and 3 were given a single 150-mg dose of fluconazole, and their prothrombin time measured on days 2, 5 and 8. The prothrombin time increased by 11% on day 2, 34% on day 5, and 2% on day 8, although none of these differences was statistically significant. However, three of the women had an increase in the INR to above 4 or had bleeding.[14]

Mechanism

In vitro studies using human liver microsomes clearly demonstrate that fluconazole inhibits the metabolism (7-hydroxylation) of *S*-warfarin by the cytochrome P450 isoenzyme CYP2C9 and the metabolism of *R*-warfarin by CYP3A4, and possibly other isoenzymes involved in the metabolism of warfarin.[15] *In vivo*, this results in the accumulation of warfarin and in an increase in its effects, possibly leading to bleeding.[5]

Importance and management

An established and clinically important interaction. If fluconazole is given to patients taking warfarin or acenocoumarol the prothrombin times should be very well monitored and the anticoagulant dose reduced as necessary. On the basis of pharmacokinetic studies it has been predicted that the warfarin dose may need to be reduced by about 20% when using fluconazole 50 mg daily, ranging to a reduction of about 70% when using fluconazole 600 mg daily. These larger reductions should be gradual over 5 days or so.[16] However, remember that individual variations between patients can be considerable. Most of the available data relate to multiple-dose fluconazole, with just one small study with a single-dose of fluconazole 150 mg. Although the effect in this study was not as great as that for multiple-dose fluconazole, it suggests that careful monitoring of prothrombin times is still required.[14]

Of the other azole antifungals, ketoconazole (see 'Coumarins + Azoles; Ketoconazole', p.438) and itraconazole (see 'Coumarins + Azoles; Itraconazole', below), appear less likely to interact.

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Coumarins + Azoles; Itraconazole

An isolated report describes a very marked increase in the anticoagulant effects of warfarin, accompanied by bruising and bleeding, in a patient given itraconazole. One case suggests that itraconazole may increase the risk of over-anticoagulation with acenocoumarol or phenprocoumon.

Clinical evidence

A woman stabilised on **warfarin** 5 mg daily and also taking ipratropium bromide, salbutamol, budesonide, quinine sulfate and omeprazole, was given itraconazole 200 mg twice daily for oral candidiasis caused by the inhaled steroid. Within 4 days she developed generalised bleeding and recurrent nosebleeds. Her INR had risen to more than 8. The **warfarin** and itraconazole were stopped, but the next day she had to be admitted to hospital for intractable bleeding and increased bruising, for which she was treated with fresh frozen plasma. Two days later, when the bleeding had stopped and her INR had returned to 2.4, she was restarted on **warfarin** and later restabilised on her original dose.[1]

In one cohort study in patients taking **acenocoumarol** or **phenprocoumon**, itraconazole significantly increased the risk of over-anticoagulation (INR greater than 6: relative risk of 13.9, range 1.7 to 115). However, the authors say this figure should be interpreted cautiously since it was based on just one case.[2]

Mechanism

Itraconazole is a known potent inhibitor of the cytochrome P450 isoenzyme CYP3A4, but this isoenzyme is involved only in the metabolism of the less potent *R*-warfarin, and therefore inhibition would not be expected to have a marked effect on 'warfarin metabolism', (p.405). However, there appear to be no pharmacological studies to confirm this. Omeprazole (see 'Coumarins + Proton pump inhibitors', p.499) may also have had some minor part to play in the case described.[1]

Importance and management

A minor to modest pharmacokinetic interaction would be predicted between itraconazole and the coumarins, but as yet there appear to be no studies to confirm this. The case report and cohort study suggest that this

interaction might be clinically important in some individuals. Therefore, it would be prudent to increase monitoring of anticoagulant control when any patient on a coumarin is given itraconazole. Further study is needed.

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Coumarins + Azoles; Ketoconazole

Limited evidence suggests that the anticoagulant effect of warfarin is unchanged by ketoconazole. However, there are three isolated cases of an increase in the anticoagulant effects of warfarin with ketoconazole. Topical ketoconazole does not appear to interact with acenocoumarol or phenprocoumon.

Clinical evidence

(a) Systemic ketoconazole

Two healthy subjects had no changes in their anticoagulant response to **warfarin** when they were given ketoconazole 200 mg daily over a 3 week period.[1,2] However, an elderly woman, stabilised on **warfarin** for 3 years, complained of spontaneous bruising 3 weeks after starting a course of ketoconazole 200 mg twice daily. Her British Comparative Ratio was found to have risen from 1.9 to 5.4. Her liver function was normal. She was restabilised on her previous **warfarin** dose 3 weeks after the ketoconazole was withdrawn.[3] In 1984, the CSM in the UK had one report of an 84-year-old man taking **warfarin** whose British Comparative Ratio rose to 4.8 when he was given ketoconazole, and fell to 1.4 when it was withdrawn.[3] In 1986, the manufacturers of ketoconazole had one other report of an elderly man taking **warfarin** whose prothrombin time rose from a range of 34 to 39 seconds to over 60 seconds when he was given ketoconazole 400 mg daily.[4]

(b) Topical ketoconazole

In one cohort study in patients taking **acenocoumarol** or **phenprocoumon**, topical ketoconazole did not significantly increase the relative risk of over-anticoagulation (INR greater than 6; relative risk 1.1, range 0.3 to 4.3). However, this figure should be interpreted cautiously as it was based on just two patients.[5]

Mechanism

In a study in *rats*,[6] ketoconazole potentiated the anticoagulant effect of acenocoumarol, but at much higher doses than miconazole (which is known to interact, see 'Coumarins and related drugs + Azoles; Miconazole', p.438. It is now known that ketoconazole is an inhibitor of the cytochrome P450 isoenzyme CYP3A4, but this isoenzyme has only a minor role in the 'metabolism of warfarin' (p.405), specifically the less active *R*-isomer.

Importance and management

Information about this interaction seems to be limited to the reports cited. Its general importance and incidence is therefore uncertain, but it is probably quite small. However, it would seem prudent to bear the possibility of an interaction in mind should any unexplained increase in the coumarin anticoagulant effects occur in a patient given both drugs.

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Coumarins and related drugs + Azoles; Miconazole

The anticoagulant effects of acenocoumarol, phenprocoumon, and warfarin can be markedly increased if miconazole is given orally as an oral (buccal) gel, and bleeding can occur. Oral miconazole has also been reported to interact with ethyl biscoumacetate, fluindione, phenindione and tioclomarol in a few reports. The interaction has also rarely been seen in some women using intravaginal miconazole, and in those using a miconazole cream on the skin.

Clinical evidence

(a) Oral gel

In one early report, a patient with a prosthetic heart valve and stabilised on **warfarin** developed blood blisters and bruised easily 12 days after starting miconazole gel 250 g four times a day for a presumed fungal mouth infection. Her prothrombin time ratio had risen from less than 3 to about 16. She was subsequently restabilised in the absence of miconazole on her former dose of **warfarin**.[1]

Numerous other cases of this interaction with **warfarin** have been reported, and, where stated, often involved the use of 5 mL (125 mg) of the gel four times daily for oral candidiasis.[2-14] However, cases have occurred with lower doses; one case of an increase in INR to 11.4 with frank haematuria and spontaneous bruising was reported in a woman who had used 30 g of non-prescription miconazole (*Daktarin*) over 8 days (estimated daily dose of 75 mg),[7] and three other cases have occurred with non-prescription miconazole.[13-15] In another case, the interaction occurred with use of the miconazole gel locally around the corners of the lips for angular cheilitis.[11]

In 1996, the New Zealand Centre for Adverse Reactions Monitoring reported 5 patients taking **warfarin** whose INRs rose from normal values to between 7.5 and 18 within 7 to 15 days of starting to use miconazole oral gel.[5] In 2002, the Australian Adverse Drug Reactions Advisory Committee (ADRAC) stated that they had received 18 reports of this interaction. In the 17 cases for which it was documented, the INR was above 7.5. Eight of the cases had bleeding complications, 9 required vitamin K, and 5 required fresh frozen plasma.[16]

A few similar cases have also been reported for **acenocoumarol**[17-19] with miconazole oral gel. In addition, in one cohort study in patients taking **acenocoumarol** or **phenprocoumon**, use of oral miconazole (form and doses not stated) markedly increased the risk of over-anticoagulation (INR greater than 6: adjusted relative risk 36.6; range 12.4 to 108). When analysed separately, the adjusted relative risk was higher for **acenocoumarol** than **phenprocoumon** (35.1 versus 16.5).[20]

A case has also been reported with the indanedione, **fluindione**.[21]

(b) Skin creams

An 80-year-old man stabilised on **warfarin** with an INR of 2.2 to 3.1 was found to have an INR of 21.4 at a routine check 2 weeks after starting to use miconazole cream for a fungal infection in his groin. He showed no evidence of bruising or bleeding.[22] In 2001, Health Canada reported that they had on record a case of an 80-year-old man taking **warfarin** and using topical miconazole who had a cerebral vascular accident, although this case was complicated by multiple medical conditions and medications.[23] In 2002, the Australian Adverse Drug Reactions Advisory Committee stated that they had received one report of an interaction involving topical miconazole cream.[16]

In one cohort study in patients taking **acenocoumarol** or **phenprocoumon**, the use of topical miconazole was associated with a small increased risk of over-anticoagulation (INR greater than 6: adjusted relative risk 1.4) but this was not statistically significant. Note that this was markedly less than the increased risk seen with oral miconazole (relative risk 36.6).[20]

(c) Tablets

In a study in 6 healthy subjects, miconazole 125 mg daily for 18 days (in the form of *tablets*) caused a very marked fivefold increase in the prothrombin time response to a single dose of **warfarin** given on day 3. In addition, there was a threefold increase in the AUC of warfarin, with *S*-warfarin most affected (fourfold), and *R*-warfarin increased 1.7 fold.[24] In one early case report with warfarin, one patient with a prosthetic heart valve and stabilised on **warfarin** was found to have a

prothrombin time ratio of 23.4 within 10 days of starting miconazole tablets 250 mg four times a day for a suspected fungal diarrhoea. He developed two haematomas soon after both drugs were withdrawn, and was subsequently restabilised, in the absence of miconazole, on his former dose of **warfarin**.[1]

The Centres de Pharmacovigilance Hospitalière in Bordeaux have on record 5 cases where miconazole (oral doses of 500 mg daily, where stated; form not mentioned) was responsible for a marked increase in prothrombin times and/or bleeding (haematomas, haematuria, gastrointestinal bleeding) in patients taking the coumarins **acenocoumarol** (2 cases), **ethyl biscoumacetate** (1 case) and **tioclomarol** (1 case) and the indanedione **phenindione** (1 case).[25] Other cases and reports of this interaction involving **acenocoumarol** have been described elsewhere.[26-28]

(d) Vaginal dose forms

In 1999, the Netherlands Pharmacovigilance Foundation LAREB reported 2 elderly women patients taking **acenocoumarol** whose INRs rose sharply and rapidly when they were given miconazole pessaries 400 mg daily for 3 days.[29] Another report describes the development of bruising and an INR of almost 10 in a 55-year-old woman taking **warfarin** on the third day of using 200-mg miconazole pessaries. For a subsequent course of intravaginal miconazole 100 mg daily for 7 days, the dose of warfarin was decreased by 28%, and her INR was 3.27.[30] Yet another report describes haemorrhage of the kidney in a 52-year old woman taking **warfarin** after she used vaginal miconazole for 12 days.[23] In one cohort study in patients taking **acenocoumarol** or **phenprocoumon**, use of vaginal miconazole was associated with a small increased risk of over-anticoagulation (INR greater than 6: adjusted relative risk 4.3) but this was not statistically significant. Note that this was markedly less than the increased risk seen with oral miconazole (relative risk 36.6).[20]

Mechanism

There is evidence that miconazole is a very potent inhibitor of the metabolism of *S*-warfarin by the cytochrome P450 isoenzyme CYP2C9, and that it also inhibits the metabolism of *R*-warfarin to a lesser extent.[24] Even low oral doses of miconazole (125 mg daily) markedly inhibit warfarin metabolism, so it is not surprising that prescription doses of miconazole oral gel (480 to 960 mg daily) interact, as this is swallowed after retaining in the mouth. Very unusually, the low absorption of miconazole from the vagina and even exceptionally through the skin, can result in increased anticoagulant effects. Acenocoumarol would be expected to be similarly affected.

Importance and management

The interaction of **miconazole oral gel** and **miconazole tablets** with the coumarins is a very well established and potentially serious interaction. Most of the reports are about warfarin or acenocoumarol, but many other coumarins and indanediones, have been implicated. In some cases the bleeding has taken 7 to 15 days to develop,[1,3,25] whereas others have bled within only 3 days.[27,30] Raised INRs have been seen even sooner. Given the marked nature of the interaction, usual prescription doses of miconazole oral gel (5 to 10 mL (120 to 240 mg) four times daily) should generally be avoided in patients taking any oral anticoagulant. Should concurrent use be necessary, prothrombin times should be closely monitored and suitable dose reductions made. The interaction has also been seen with non-prescription miconazole (one 30 g tube given over 8 days, or about 75 mg daily), which is not surprising in the context of the pharmacokinetic study, and suggests that patients taking coumarins and indanediones should also avoid using non-prescription miconazole. Nevertheless, the UK patient information leaflet for non-prescription *Daktarin* oral gel just advises patients taking oral anticoagulants to talk to their doctor or pharmacist, and does not advise avoiding the product.[31] Nystatin and amphotericin are possible alternative antifungals to miconazole for mouth infections.

An interaction with **intravaginal miconazole** would not normally be expected because its systemic absorption is usually very low (less than 2%) in healthy women of child-bearing age.[32] However, the reports cited above show that significant absorption could apparently occur in a few patients with particular conditions (possibly in postmenopausal women with inflamed vaginal tissue), which allows an interaction to occur. Appropriate monitoring is therefore needed even with this route of administration in potentially at-risk women.

Topical (cutaneous) miconazole would also not be expected to interact, but the few reports cited shows that some caution might be warranted.

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Coumarins + Azoles; Voriconazole

In one pharmacodynamic study, voriconazole approximately doubled the prothrombin time in response to warfarin.

Clinical evidence, mechanism, importance and management

In a study, when 16 healthy subjects were given voriconazole 300 mg twice daily for 12 days, with a single 30-mg dose of **warfarin** on day 7, the maximal increase in prothrombin time was about doubled.[1] The increase in prothrombin time was still present 6 days after the **warfarin** dose, at which point the prothrombin time had returned to values seen with **warfarin** alone. Two subjects were withdrawn from the study because of an increased prothrombin time.[1]

Voriconazole is a known inhibitor of the cytochrome P450 isoenzymes CYP2C9 and CYP3A4, by which the coumarins are metabolised. If voriconazole is added to treatment with any coumarin the prothrombin times

should be very well monitored and the anticoagulant dose reduced as necessary.

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Coumarins + Barbiturates

The effects of the coumarins are substantially reduced by the barbiturates. Primidone is metabolised to phenobarbital and is expected to interact similarly.

Clinical evidence

(a) Phenobarbital

A study in 16 patients stabilised on **warfarin** found that when they were also given phenobarbital 2 mg/kg their average daily **warfarin** requirements rose over a 4-week period by 25% (from 5.7 to 7.1 mg daily).[1] In another study in patients stabilised on **warfarin**, phenobarbital 100 mg at night for 4 weeks reduced the mean prothrombin time by 13%.[2] In a prospective cohort study in children, the use of phenobarbital or carbamazepine was associated with a higher dose of **warfarin** to maintain the target INR (0.24 mg/kg versus 0.15 mg/kg).[3]

Other studies have found that phenobarbital causes a 29% or 46% reduction in the half-life of **warfarin**,[4,5] and that the reduction was similar for both *R*- and *S*-warfarin.[6] A retrospective analysis in patients taking **warfarin** revealed that the use of phenobarbital was associated with more erratic anticoagulation control, and that discontinuation of phenobarbital in a patient taking **warfarin** resulted in severe hypoprothrombinaemia and haematuria 2 weeks later.[7]

A reduced anticoagulant response has also been described in studies with phenobarbital and **dicoumarol**,[8-10] and 2 cases have been reported with phenobarbital and **ethyl biscoumacetate**.[11] One retrospective study[12] found that the concurrent use of enzyme inducers (including phenobarbital and **primidone**) significantly influenced the total weekly **warfarin** dose; further analysis found that an average additional amount of **warfarin** required in patients taking these drugs was 17.2 mg weekly.

In contrast, there is one isolated report of a woman stabilised on **warfarin** who developed haematuria 3 days after starting to take phenobarbital 60 mg four times daily.[13]

(b) Other barbiturates

An investigation in 12 patients taking either **warfarin** or **phenprocoumon** found that **secbutabarbital sodium**, 15 mg four times daily for the first week and 30 mg four times daily for the next 2 weeks, increased their anticoagulant requirements by 35 to 60%, reaching a maximum after 4 to 5 weeks.[14]

This interaction has also been described in pharmacological studies between:

- **acenocoumarol** and **pentobarbital**,[15] or **heptabarb**;[16]
- **dicoumarol** and **aprobarbitone**,[17] **heptabarb**,[16,18] or **vinbarbital**;[17]
- **ethyl biscoumacetate** and **heptabarb**;[16]
- **warfarin** and **amobarbital**,[19-21] **heptabarb**,[22] **secobarbital**,[2,19-21,23-25] or **secbutobarbital**.[14]

Cases have been described in patients taking **ethyl biscoumacetate** who were taking **amobarbital**, **heptabarb**, or **secobarbital**.[11] Cases have also been described of apparent resistance to coumarins in patients taking barbiturates,[17,26] and of bleeding in patients who were stabilised on a coumarin and a barbiturate when they stopped taking the barbiturate.[17,26,27]

Mechanism

Pharmacokinetic studies in man and *animals*[4,5,20-22,24] clearly show that the barbiturates are potent liver enzyme inducers, which increase the metabolism and clearance of the coumarins. The effect is similar on both *R*- and *S*-warfarin.[6,25] Barbiturates may also reduce the absorption of dicoumarol from the gut.[18]

Importance and management

The interactions between the coumarins and barbiturates are clinically important and very well documented. The reduced anticoagulant effects expose the patient to the risk of thrombus formation if the dose is not increased appropriately. A very large number of coumarin and barbiturate pairs have been found to interact and the others may be expected to behave similarly. The reduction in the anticoagulant effects begins within one week, sometimes within 2 to 4 days, reaching a maximum after about 3 weeks, and it may still be evident up to 6 weeks after stopping the barbiturate.[14] Patients' responses can vary considerably. Stable anticoagulant control can be re-established[28] in the presence of the barbiturate by increasing the anticoagulant dose by about 30 to 60%.[1,7,10,14] Care must be taken not to withdraw the barbiturate without also reducing the anticoagulant dose, otherwise over-anticoagulation will occur. Alternative non-interacting drugs, such as the benzodiazepines (see 'Coumarins + Benzodiazepines and related drugs', p.441), are now considered more appropriate sedatives than the barbiturates.

Primidone is metabolised to phenobarbital and is therefore expected to have a similar effect to phenobarbital. This is suggested by the findings of the retrospective study, and therefore, it would be prudent to be alert for reduced anticoagulant effects if primidone is given concurrently with a coumarin.

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Coumarins + Benfluorex

Benfluorex does not alter the anticoagulant effects of phenprocoumon.

Clinical evidence, mechanism, importance and management

No significant changes occurred in the prothrombin times of 22 patients stabilised on **phenprocoumon** when they were given benfluorex 150 mg

three times daily for 9 weeks, when compared with equivalent periods before and after taking benfluorex.[1]

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Coumarins and related drugs + Benzbromarone or Benziodarone

The anticoagulant effects of warfarin are increased by benzbromarone and bleeding has been seen. Similarly, the anticoagulant effects of acenocoumarol, ethyl biscoumacetate, diphenadione and warfarin are increased by benziodarone. Clorindione, dicoumarol and phenindione were not affected by benziodarone in one study. Phenprocoumon was not affected by benziodarone in one study, but was in another.

Clinical evidence

(a) Benzbromarone

The observation that 2 patients bled (haematuria, gastrointestinal bleeding) when given **warfarin** and benzbromarone, prompted a more detailed study in 7 other patients who were stabilised on both drugs. The thrombotest values of these 7 averaged 24.7% while taking both **warfarin** and benzbromarone (average dosage 57.1 mg daily), but when the benzbromarone was stopped for a week they rose to 47.3%. On restarting the benzbromarone the thrombotest values decreased to 30.3% (indicating an enhanced anticoagulant effect). The Factor II activity paralleled the thrombotest values. The total plasma **warfarin** levels were reduced during the period that benzbromarone was stopped.[1] Another later study found that the **warfarin** requirements of 13 patients given benzbromarone 50 mg daily were 36% lower than in 18 other patients given **warfarin** alone (3.9 versus 2.5 mg daily). The oral clearance of *S*-warfarin was 54% lower in the benzbromarone recipients, but the clearance of *R*-warfarin did not differ between the groups.[2] These two studies confirm observations in other patients with prosthetic valve replacements who had haemorrhagic tendencies when given both drugs.[1]

Early information about benzbromarone noted that no increase in the anticoagulant effects of the coumarins **acenocoumarol** and **ethyl biscoumacetate** or the indanedione **phenindione** had been seen in a few patients also given benzbromarone.[3]

(b) Benziodarone

Benziodarone 200 mg three times daily for 2 days then 100 mg three times daily thereafter was given to 90 patients taking various anticoagulants. To maintain constant prothrombin-proconvertin percentages the coumarin anticoagulant doses were reduced as follows: **ethyl biscoumacetate** 17% (9 patients), **acenocoumarol** 25% (7) and **warfarin** 46% (15). No changes in dose were needed in patients taking **dicoumarol** (9) or **phenprocoumon** (8). For the indanedione anticoagulants, a dose reduction of 42% was required in 8 patients taking **diphenadione**, but no changes were needed in those taking **clorindione** (5 patients) or **phenindione** (10 patients).[4] A parallel study in healthy subjects also found that benziodarone 300 mg or 600 mg daily increased the effects of a single dose of **warfarin**.[4]

In another study, benziodarone 300 to 600 mg daily increased the anticoagulant effects of **phenprocoumon** in just 9 out of 29 patients.[5] Plasma levels of **ethyl biscoumacetate** after a single intravenous dose were increased by pre-treatment with benziodarone 600 mg daily for 6 days.[5]

Mechanism

Benzbromarone selectively inhibits the metabolism of *S*-warfarin by the cytochrome P450 isoenzyme CYP2C9 so that its effects are increased. The metabolism of the *R*-warfarin remains unchanged.[2] Acenocoumarol and phenprocoumon are also known to be metabolised by CYP2C9, and would therefore be expected to interact similarly. Benziodarone is another benzofuran derivative with a similar structure to benzbromarone, and therefore probably interacts by a similar mechanism.

Importance and management

The interaction between warfarin and benzbromarone or benziodarone is established and clinically important. If benzbromarone is given to a patient taking warfarin, monitor prothrombin times and be alert for the need to reduce the dosage by about one-third to prevent over-anticoagulation. Information about other coumarins is limited, but what is known about the mechanism of action suggests that acenocoumarol and phenprocoumon would also be predicted to interact, and this has been shown for benziodarone and acenocoumarol or phenprocoumon, in a few patients. The limited evidence suggesting an interaction with some indanediones also suggests that some caution is appropriate with these drugs as well.

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Coumarins + Benzethonium chloride

A rise in INR occurred in a couple who took a grapefruit seed extract product containing considerable amounts of the preservative benzethonium chloride for three days, and one of them developed a minor haematoma.

Clinical evidence

A couple, both well stabilised on warfarin, took some drops of a grapefruit seed extract product (*Estratto di Semillas di Pompelmo*, Lakshmi, Italy) for 3 days. No more was taken, but after a further 3 days the woman developed a minor subcutaneous haematoma, and her INR was found to be 7.9. The man was found to have an INR of 5.1, with no evidence of bleeding.[1]

Mechanism

The product used was stated to contain grapefruit seed extract, glycerol and water. However, chemical analysis of this product revealed that it also contained considerable amounts (77 mg/mL) of the preservative, benzethonium chloride, and did not contain any significant amount of natural substances from grapefruit seeds. The constituents of two other commercial grapefruit seed products were similar on analysis (*Citroseed* and *Citricidal*).

Further, *in vitro* analysis found that benzethonium chloride, and the three products, were potent inhibitors of the cytochrome P450 isoenzyme CYP2C9, suggesting that they could inhibit the metabolism of warfarin.

Importance and management

Data presented in this report, and other papers (one of which is cited as an example[2]), suggests that the primary constituent of many grapefruit seed extract products appears to be the preservative benzethonium chloride. The evidence from the two cases, backed by *in vitro* data, suggests that this has the potential to interact with warfarin. On this basis, it would probably be prudent for patients taking warfarin to avoid grapefruit seed extract products, or for concurrent use to be monitored closely. Some caution might also be appropriate with other pharmaceutical preparations containing benzethonium chloride.

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Coumarins + Benzodiazepines and related drugs

A large number of combinations of coumarins and benzodiazepines have been studied, without finding any evidence of an adverse interaction. An interaction between any coumarin and a benzodiazepine is therefore unlikely, but there are three unex-

plained and unconfirmed cases of increased or decreased anticoagulant responses, which were attributed to an interaction.

Clinical evidence

A. Benzodiazepines

(a) Chlordiazepoxide

In a placebo-controlled study in 7 patients stabilised on **warfarin**, chlordiazepoxide 10 mg three times daily for 2 weeks had no effect on anticoagulant control.[1] Other studies in healthy subjects[2,3] and patients[4] have similarly found that chlordiazepoxide does not alter the anticoagulant effect or the half-life of **warfarin**. Similarly, chlordiazepoxide 10 mg three times daily for 10 days had no effect on the half-life of a single intravenous dose of **ethyl biscoumacetate** in healthy subjects.[5] However, one patient stabilised on warfarin had a small 18% fall in mean plasma **warfarin** levels with a corresponding change in the anticoagulant response when given chlordiazepoxide 15 mg daily.[6]

(b) Diazepam

In 4 patients stabilised on **warfarin**, diazepam 5 mg three times daily for 30 days had no effect on anticoagulant control (thrombotest). In one of the patients, the half-life of **warfarin** was measured, and this was not changed by diazepam.[4] Similarly, diazepam 5 mg daily did not alter the anticoagulant response or the half-life of a single dose of **warfarin** in healthy subjects.[3]

However, there are two discordant reports. A patient stabilised on **dicoumarol** developed multiple ecchymoses and a prothrombin time of 53 seconds within 2 weeks of starting to take **diazepam** 5 mg four times daily.[7] The New Zealand Committee on Adverse Drug Reactions has received one report of an increased anticoagulant effect in a patient taking **warfarin** with **diazepam**.[8] It is by no means certain that these responses were due to an interaction.

(c) Flurazepam

In healthy subjects, flurazepam 30 mg at bedtime for 28 days had no effect on the half-life of a single dose of **warfarin** given on days 14 and 28, but there was a slight statistically significant reduction in prothrombin time. In a further placebo-controlled study in 12 patients stabilised on **warfarin**, flurazepam 30 mg at night for 28 days had no effect on prothrombin time or plasma warfarin concentrations.[9]

(d) Midazolam

In a pharmacokinetic study in 12 healthy subjects, **warfarin** and midazolam were given together as probe substrates for the cytochrome P450 isoenzymes CYP2C9 and CYP3A4, respectively. The *S*-warfarin AUC and midazolam plasma clearance were not altered by concurrent use.[10]

(e) Nitrazepam

In two reports by the same researchers, nitrazepam 10 mg at night for 30 days had no effect on steady-state **warfarin** levels or anticoagulant control in a few patients stabilised on **warfarin**.[4,6] In a placebo-controlled study in 22 patients stabilised on **phenprocoumon**, nitrazepam 5 mg at night for 2 weeks had no effect on thrombotest times.[11]

(f) Oxazepam

Oxazepam 10 mg in the morning and 10 to 20 mg in the evening for 3 weeks had no effect on anticoagulant response in 21 patients stabilised on **phenprocoumon**.[12]

B. Non-benzodiazepine hypnotics

(a) Eszopiclone

In a study in healthy subjects, eszopiclone 3 mg daily for 5 days had no effect on the AUC of *S*- or *R*-warfarin after a single 25-mg dose of **warfarin** and there was no change in the INR.[13]

(b) Zaleplon

In a study in healthy subjects, zaleplon 20 mg daily for 12 days had no effect on the AUC of *S*- or *R*-warfarin after a single 25-mg dose of **warfarin**. There was a minor 17% increase in the maximum serum levels of *S*-warfarin. However, zaleplon did not alter the prothrombin time response to **warfarin**.[14,15]

(c) Zolpidem

The prothrombin times of 8 healthy subjects given **warfarin** were unaffected by zolpidem 20 mg daily for 4 days.[16]

Mechanism

The three discordant reports describing an interaction are not understood. Enzyme induction is a possible explanation in one case with chlordiazepoxide,[6] because increases in the urinary excretion of 6-beta-hydroxycortisol (a marker of enzyme induction) have been described during chlordiazepoxide use.[4,6]

Importance and management

The weight of evidence and common experience shows that the benzodiazepines do not interact with the coumarins. Not all of the coumarins and benzodiazepines have been examined, but none of the possible pairs would be expected to interact. Similarly, based on pharmacodynamic studies, no interaction would be anticipated with the newer non-benzodiazepine hypnotics eszopiclone, zaleplon or zolpidem. As eszopiclone is metabolised to **zopiclone**, an interaction between zopiclone and warfarin would also not be expected, although there is no published data to confirm this.

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Coumarins and related drugs + Beta blockers

The effects of the coumarins are not normally altered by any beta blocker. However, propranolol has caused small increases in warfarin levels in a couple of studies, and an isolated case described an increased INR in a patient taking warfarin and propranolol.

Clinical evidence

(a) Acenocoumarol

In a study in 4 patients stabilised on acenocoumarol there was no difference in anticoagulation tests when **atenolol** 100 mg daily, **metoprolol** 100 mg twice daily, or placebo, was given for 3 weeks.[1]

(b) Phenindione

In one early clinical study, haemorrhagic tendencies without any changes in Quick value or any other impairment of coagulation were described in three patients stabilised on phenindione within 6 weeks of starting **propranolol**.[2]

(c) Phenprocoumon

In healthy subjects, a single dose of **atenolol** 100 mg or **metoprolol** 100 mg did not affect the AUC of a single dose of phenprocoumon, although phenprocoumon levels were slightly higher at 4 and 6 hours after the **metoprolol** dose. Nevertheless, neither beta blocker altered the prothrombin time response.[3]

In healthy subjects, **carvedilol** 25 mg daily for 7 days had no effect on

the pharmacokinetics of a single 15-mg dose of phenprocoumon given on day 5 phenprocoumon.[4]

In 12 patients stabilised on phenprocoumon, there was no difference in Quick time between those randomised to receive **pindolol** 5 mg three times daily for 6 weeks and those who received placebo.[5]

(d) Warfarin

In 6 patients stabilised on warfarin, **acebutolol** 300 mg three times daily for 3 days had no effect on prothrombin time response.[6] Similarly, in one patient taking warfarin, neither **atenolol** 100 mg daily nor **metoprolol** 100 mg twice daily for 3 weeks had any effect on prothrombin time.[1] Similarly, in studies in healthy subjects the following beta blockers had no clinically relevant effects on the pharmacokinetics and/or anticoagulant response to warfarin; **atenolol** 100 mg daily,[7] **betaxolol** 20 mg daily,[8] **bisoprolol** 10 mg daily,[9] **esmolol**,[10] **metoprolol** 100 mg twice daily[7] or **nebivolol** 10 mg daily.[11]

In contrast, the minimum steady-state plasma **warfarin** levels of 6 healthy subjects rose by 15% when they took **propranolol** 80 mg twice daily in one study.[12] Similarly, in another study in 6 healthy subjects given **propranolol** 80 mg twice daily for 7 days with a single dose of warfarin on day 4, the AUC of warfarin was increased by about 16% and the in maximum serum level was increased by 23%, but there was no change in the prothrombin time.[7] A patient stabilised on **warfarin** had a rise in his British Corrected Ratio from a low of 1.3 up to 2.5 while taking **propranolol** 80 mg twice daily.[13]

Mechanism

None known.

Importance and management

Overall, the findings of these pharmacological studies in patients and healthy subjects confirm the general clinical experience that the effects of the coumarins are not normally altered by the beta blockers. No special precautions are needed on concurrent use. The only uncertainty is with propranolol, which has caused a small rise in warfarin levels in two studies, and for which there is one case report describing an increased INR with warfarin. Even so, a clinically significant interaction would seem to be extremely rare.

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Coumarins + Bicalutamide, Flutamide or Nilutamide

A few cases have been reported of flutamide possibly increasing the anticoagulant effects of warfarin. Based on limited *in vitro* evidence, it has been predicted that bicalutamide and nilutamide might interact with coumarins.

Clinical evidence and mechanism

(a) Bicalutamide

The manufacturers say that *in vitro* studies show that bicalutamide can displace **warfarin** from its protein binding sites.[1,2] It used to be thought that the displacement of **warfarin** from its protein binding sites by other drugs normally resulted in clinically important interactions, but that is now known to rarely be true (see 'Protein-binding interactions', (p.3)). In 1995, the manufacturers said that they did not know of any reports of an interaction between **warfarin** and bicalutamide, apart from an isolated case of a raised INR in one patient taking **warfarin** with bicalutamide 150 mg, but no causal link with bicalutamide was established.[3] In a clinical study of bicalutamide and finasteride, it was briefly stated that one patient developed a prolonged prothrombin time while also taking **warfarin**.[4] To date, there appear to be no other published cases of an interaction.

(b) Flutamide

In 1990, the manufacturer had 5 cases on record of patients with prostatic cancer receiving **warfarin** whose prothrombin times had increased when they were given flutamide. For example, one patient needed reductions in his **warfarin** dose from 35 mg weekly to 22.5 mg weekly over a 2-month period. Another had a prothrombin time rise from 15 seconds to 37 seconds within 4 days of starting flutamide 750 mg daily.[5] There appears to be no published information about this interaction.

(c) Nilutamide

The manufacturer notes that, *in vitro*, nilutamide has been shown to inhibit cytochrome P450 isoenzymes (specific isoenzymes not stated). Because of this, they suggest that nilutamide might increase the toxicity of drugs with a low therapeutic margin such as the vitamin K antagonists (i.e. **coumarins** and **indanediones**). There appears to be no published information about this interaction.

Importance and management

No interaction is established, and had there been any interaction, it might have been expected to come to light by now. The lack of any published case reports suggests that there is little reason to believe that these non-steroidal anti-androgens specifically interact with warfarin. Despite this, the manufacturers of bicalutamide, flutamide and nilutamide recommend that the prothrombin time be carefully monitored when these drugs are given with coumarins, adjusting the dose when necessary.[2,6,7]

Consider also that, from a disease perspective, when treating venous thromboembolic disease in patients with cancer, warfarin is generally inferior (higher risk of major bleeds and recurrent thrombosis) to low-molecular-weight heparins.[8]

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Coumarins and related drugs + Bile-acid binding resins

The anticoagulant effects of phenprocoumon and warfarin can be reduced by colestyramine. Conversely, an isolated report describes unexpected sensitivity to warfarin in a patient taking colestyramine, which was attributed to a possible reduction in vitamin K absorption with colestyramine. Colestipol does not alter the absorption or effect of phenprocoumon or warfarin, and colesevelam does not alter the pharmacokinetics of warfarin.

Clinical evidence

(a) Colesevelam

In a single-dose study in 24 healthy subjects, colesevelam 4.5 g had no effect on the pharmacokinetics of **warfarin** 10 mg.[1]

(b) Colestipol

In a placebo-controlled, single-dose study in 4 healthy subjects, **phenprocoumon** plasma levels and the prothrombin response were unaffected by colestipol 8 g given at the same time as **phenprocoumon** 12 mg.[2] Similarly, in a study in healthy subjects quoted in a review,[3] the concurrent use of colestipol 10 g did not cause any changes in the absorption of a single 10-mg dose of **warfarin**.

The long-term use of colestipol might have the potential to decrease fat soluble vitamins such as vitamin K, which result in a prolonged prothrombin time,[4] and thereby increase the effect of warfarin. However, the manufacturers report that in a study, the use of colestipol resulted in a prolonged prothrombin time in only one patient.[4]

(c) Colestyramine

1. Phenprocoumon. It was noted that establishing effective anticoagulation was difficult in patients taking phenprocoumon with colestyramine, in spite of doubling the dose of phenprocoumon. This prompted a study in healthy subjects in which it was found that concurrent single doses of phenprocoumon and colestyramine markedly reduced the plasma levels and effect of phenprocoumon.[5] In another study using *intravenous* phenprocoumon, colestyramine reduced the effect of the anticoagulant by this route, presumably by reducing enterohepatic recycling.[6] This fact has been used clinically to enhance the elimination of phenprocoumon after phenprocoumon overdose. In one case, the half-life of phenprocoumon was measured as 6.8 days without colestyramine, and 3.5 days with colestyramine 4 g three times daily.[7]

A patient stabilised on phenprocoumon developed a fatal valve thrombosis after starting colestyramine, despite separation of doses in accordance with the manufacturer's instructions.[8]

2. Warfarin. In a study, 10 subjects were given warfarin alone or with colestyramine, for one-week periods. When warfarin was taken 30 minutes after colestyramine, peak warfarin levels were reduced by 52% and the prolongation in prothrombin times was reduced by 27%, compared with warfarin alone. However, when warfarin was taken 6 hours after colestyramine, peak warfarin levels were reduced by only 16%, and the prolongation in prothrombin times was the same as with warfarin alone.[9]

Comparable results were found in another similar study; simultaneous administration of warfarin and colestyramine reduced the prothrombin time response by 21%, and separation by 3 hours still caused an 11% reduction in the prothrombin time response.[10] Another study using *intravenous* warfarin has shown that colestyramine also reduces the effect of warfarin by this route, presumably by reducing enterohepatic recycling.[11] Note that colestyramine has been used to speed up the elimination of warfarin in cases of over-anticoagulation.[12,13]

Another report describes a patient taking colestyramine 4 g three times daily who was successfully stabilised on warfarin with alternating doses of 5 mg and 7.5 mg daily. The warfarin was given at 8 am, then the colestyramine at 12 noon with lunch, with dinner, and with an evening snack.[14]

In contrast, an isolated report describes a 77-year-old patient taking multiple medications including colestyramine who was found to have a very high prothrombin time of 78.9 seconds and microscopic haematuria 6 weeks after starting warfarin 5 mg daily. Four days after starting the warfarin her prothrombin time was 17.1 seconds, and it had not been checked again.[15] However, as it is not certain that this patient was properly stabilised on warfarin this may simply have been an effect of the warfarin alone.

Mechanism

Colestyramine binds to coumarins in the gut, thereby preventing their absorption.[5,10,16,17] Data with *intravenous* warfarin and phenprocoumon show that they undergo enterohepatic recycling, and that colestyramine can reduce this as well.[6,11] The long-term use of colestyramine also reduces the absorption of fat-soluble vitamins such as vitamin K so that it can have some direct hypoprothrombinaemic effects of its own.[18,19] This may to some extent offset the full effects of its interaction with anticoagulants. Colestipol on the other hand appears not to bind to any great extent at the pH values in the gut,[2] although, in the same way as colestyramine, it might reduce absorption of vitamin K and prolong the prothrombin time.[4] The paradoxical increase in the effects of warfarin in the isolated case cited above was attributed to the effect of colestyramine on vitamin K.[15]

Importance and management

The interaction of colestyramine with phenprocoumon and warfarin is established, and can be clinically important. If concurrent use is thought necessary, prothrombin times should be monitored and the dose of the anticoagulant increased appropriately. Giving the colestyramine 4 to 6 hours after the anticoagulant has been shown to minimise the effects of this interaction,[9,14] and it is a standard recommendation that other drugs should be given one hour before or 4 to 6 hours after colestyramine. However, despite adequate separation of doses, one patient taking phenprocoumon developed fatal valve thrombosis when given colestyramine, leading the authors to suggest that colestyramine should not be used in patients taking oral anticoagulants.[8] Information about other anticoagulants is lacking but as colestyramine interacts with dicoumarol and ethyl biscoumacetate in *animals*[17] it would be prudent to expect all coumarins to interact similarly. Bear in mind that long-term colestyramine can reduce vitamin K absorption and can cause hypoprothrombinaemia. This might result in an increased effect of warfarin, as has been suggested in one unconfirmed case report, but there seems to be no other evidence to suggest that this is clinically relevant.

No special precautions appear to be necessary if warfarin or phenprocoumon and colestipol or colesevelam are given concurrently. But, as with colestyramine, bear in mind that the long-term use of colestipol might reduce vitamin K absorption and cause hypoprothrombinaemia. This might result in an increased effect of warfarin.

There appear to be no reports of an interaction with the **indanediones**, however, should long-term use of a bile-acid binding resin result in reduced vitamin K absorption and subsequent hypoprothrombinaemia, this would be expected to be additive with the anticoagulant effects of these drugs.

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Coumarins + Boldo or Fenugreek

A report describes a woman taking warfarin whose INR rose modestly when she began to take boldo and fenugreek.

Clinical evidence

A woman taking **warfarin** for atrial fibrillation whose INR was normally within the range 2 to 3 had a modest rise in her INR to 3.4, apparently due to the use of 10 drops of boldo after meals and one capsule of fenugreek before meals. A week after stopping these two herbal medicines her INR had fallen to 2.6. When she restarted them, her INR rose to 3.1 after a week, and to 3.4 after 2 weeks. Her INR was later restabilised in her normal range while continuing to take these two herbs by reducing the **war-**

farin dose by 15%.[1] The patient had no undesirable reactions (e.g. bruising or bleeding).

Mechanism

The mechanism of this apparent interaction remains unknown, and it is not known whether both herbs or just one was responsible for what happened. Both boldo and fenugreek have been reported to contain natural coumarins, but it is unclear whether they have any anticoagulant activity. Consider also, 'Coumarins + Herbal medicines; Miscellaneous', p.472.

Importance and management

Evidence is limited to one isolated case. Because of the many other factors influencing anticoagulant control, it is not possible to reliably ascribe a change in INR specifically to a drug interaction in a single case report without other supporting evidence. It may be better to advise patients to discuss the use of any herbal products they wish to try, and to increase monitoring if this is thought advisable. Cases of uneventful use should be reported, as they are as useful as possible cases of adverse effects.

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Coumarins + Broxuridine

A case report describes an increase in the effects of warfarin in a patient taking broxuridine.

Clinical evidence, mechanism, importance and management

A man taking **warfarin** and with grade III anaplastic astrocytoma was given intravenous broxuridine as a radiosensitiser. His prothrombin times were unaffected by the first course of broxuridine 1.4 g daily for 4 days, but became more prolonged with successive courses, and after the fourth course his prothrombin time reached about 45 seconds. This was managed with 10 mg of vitamin K. Warfarin was stopped after a significant increase in his prothrombin time also took place with a fifth cycle of broxuridine 990 mg daily.[1] The clinical relevance of this single case is uncertain.

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Coumarins + Bucolome

Bucolome increases the anticoagulant effects of warfarin by inhibiting its metabolism.

Clinical evidence

A study in Japanese patients stabilised on **warfarin** found that the addition of bucolome 300 mg daily increased the INR of 21 patients by 50% despite a 58% reduction in the **warfarin** dose, when compared with another group of 34 patients taking **warfarin** and not receiving bucolome.[1] In another 7-day study, 25 Japanese patients with heart disease taking **warfarin** and bucolome 300 mg daily were compared with another control group of 30 patients taking **warfarin** alone. It was found that bucolome had no effect on the serum levels of *R*-warfarin but both the serum levels of *S*-warfarin and the prothrombin times rose. These changes were complete within 7 days.[2] In one analysis, the daily dose of **warfarin** was found to be about 40% lower in 78 patients taking bucolome, when compared with 99 patients not taking bucolome, although the thrombotest values were lower in those also taking bucolome (suggesting greater anticoagulation). Bucolome appeared to reduce the between patient variation in intrinsic hepatic clearance of warfarin.[3]

A patient who had been taking **warfarin** with bucolome for 18 days developed gross haematuria. He was found to have an intraluminal ureteral haematoma and an excessively prolonged prothrombin time, and was treated with intravenous vitamin K.[4]

Mechanism

In vitro studies show that the bucolome can inhibit the metabolism of the more potent enantiomer *S*-warfarin by the cytochrome P450 isoenzyme CYP2C9, thereby reducing its clearance and increasing its effects.[1]

Importance and management

Information appears to be limited to the reports cited here but the interaction would seem to be established and clinically important. Monitor the INR closely. A reduced warfarin dose (the study[2] cited above suggests a 30 to 60% reduction) is likely to be needed if both drugs are used concurrently to avoid excessive anticoagulation and possible bleeding. Note that bucolome is sometimes used with warfarin to enhance its therapeutic effect.[3] Based on the mechanism of action, **acenocoumarol** and **phenprocoumon** would be anticipated to be similarly affected.

1. Takahashi H, Kashima T, Kimura S, Murata N, Takaba T, Iwade K, Abe T, Tainaka H, Yasumori T, Echizen H. Pharmacokinetic interaction between warfarin and a uricosuric agent, bucolome: application of in vitro approaches to predicting in vivo reduction of (S)-warfarin clearance. *Drug Metab Dispos* (1999) 27, 1179–86.
2. Matsumoto K, Ishida S, Ueno K, Hashimoto H, Takada M, Tanaka K, Kamakura S, Miyatake K, Shibakawa M. The stereoselective effects of bucolome on the pharmacokinetics and pharmacodynamics of racemic warfarin. *J Clin Pharmacol* (2001) 41, 459–64.
3. Osawa M, Hada N, Matsumoto K, Hasegawa T, Kobayashi D, Morimoto Y, Yamaguchi M, Kanamoto I, Nakagawa T, Sugibayashi K. Usefulness of coadministration of bucolome in warfarin therapy: pharmacokinetic and pharmacodynamic analysis using outpatient prescriptions. *Int J Pharm* (2005) 293, 43–9.
4. Murosaki N, Senoh H, Takemoto M. Intraluminal ureteral hematoma complicating anticoagulant therapy [In Japanese]. *Nippon Hinyokika Gakkai Zasshi* (2005) 96, 564–7.

Coumarins + Buflomedil

Buflomedil does not alter the anticoagulant effect of acenocoumarol.

Clinical evidence, mechanism, importance and management

In a randomised study in patients with severe or recurrent venous thrombosis, there was no difference in dose of **acenocoumarol** necessary to reach an INR of 2.5 to 3.5 between 100 patients taking **acenocoumarol** with buflomedil 600 mg daily and 100 patients taking **acenocoumarol** alone. No patients had severe bleeding, and 3 to 4% of patients in both groups had moderate bleeding (haematomas, haematuria).[1] This suggests that no **acenocoumarol** dose adjustments are likely to be needed when it is used with buflomedil.

1. Moriau M, Lavenne-Pardonge E, Crasborn L, von Frenckell R, Col-Debeys C. The treatment of severe or recurrent deep venous thrombosis. Beneficial effect of the co-administration of antiplatelet agents with or without rheological effects, and anticoagulants. *Thromb Res* (1995) 78, 469–82.

Coumarins and related drugs + Calcium-channel blockers

Amlodipine and felodipine do not affect the anticoagulant effects of warfarin. Diltiazem, and possibly verapamil, may cause a minor decrease in warfarin metabolism, but the anticoagulant effect of warfarin is unlikely to be affected. Verapamil does not appear to alter the anticoagulant effects of phenindione.

Clinical evidence

(a) Dihydropyridine calcium-channel blockers

The manufacturers say that **amlodipine** did not significantly alter the effect of **warfarin** on prothrombin times in healthy subjects.[1,2]

In healthy subjects given **warfarin** until steady state, **felodipine** 10 mg daily for 14 days did not alter the dose of **warfarin** required to maintain a stable INR, or affect the pharmacokinetics of *S*- or *R*-warfarin.[3] Because **felodipine** does not interact with **warfarin** it has been used as a control drug in retrospective cohort studies assessing **warfarin** drug interactions.[4,5]

(b) Diltiazem

In a study, 11 healthy men were given racemic **warfarin**, and 8 were given *R*-warfarin, both as a single 1.5-mg/kg intravenous dose. Another 10 subjects were given *S*-warfarin as a single 0.75-mg/kg intravenous dose. After taking diltiazem 120 mg three times daily (for 4 days before and 9 days after the dose of **warfarin**) the clearance of *R*-warfarin was decreased by about 20% but the more potent *S*-warfarin remained unaffected. The total anticoagulant response remained unchanged.[6] Similarly, in another study in 20 healthy subjects, diltiazem 30 mg three times daily for one week caused no clinically relevant changes in the anticoagulant effects of a single dose of **warfarin**. There was a small 13% decrease in **warfarin** clear-

ance and an 8% increase in its AUC in the presence of diltiazem, but these changes were not statistically significant.[7]

However, one report describes a patient stabilised on **warfarin** with an INR in the range of 2.5 to 3 who was found to have an INR of 4.2 two weeks after starting diltiazem 180 mg daily.[8]

(c) Verapamil

In a small study in 20 patients to investigate the effectiveness of verapamil 80 mg three times daily for 2 weeks for angina, 10 of these patients were also taking **phenindione** during the study. Although not specifically studied, the authors of this study reported that there was no significant change in the sensitivity of these 10 patients to **phenindione** during the use of verapamil.[9]

Mechanism

Diltiazem is a known inhibitor of the cytochrome P450 isoenzyme CYP3A4. However, this isoenzyme has only a minor role in the 'metabolism of warfarin', (p.405), specifically in the metabolism of the less active *R*-isomer of warfarin. Consequently, only minor increases in the levels of warfarin have been seen in pharmacokinetic studies, which would generally not be expected to be clinically relevant. Verapamil is also an inhibitor of CYP3A4, but the dihydropyridine calcium-channel blockers are not.

Importance and management

No special precautions would seem to be necessary during the concurrent use of warfarin and dihydropyridine calcium-channel blockers. Although the minor pharmacokinetic interaction between diltiazem and warfarin would appear to be established, in the studies cited this did not change anticoagulant control, and is therefore unlikely to be of clinical importance. Verapamil would be expected to cause a similar, minor pharmacokinetic interaction to diltiazem, which would be unlikely to result in clinically significant effects, although the only available data to confirm this appears to be the small study reported above. The absence of adverse reports about these very widely used drugs suggests that concurrent use is normally uneventful.

1. Istin (Amlodipine besilate). Pfizer Ltd. UK Summary of product characteristics, July 2007.
2. Norvasc (Amlodipine besylate). Pfizer Inc. US Prescribing information, August 2006.
3. Grind M, Murphy M, Warrington S, Åberg J. Method for studying drug-warfarin interactions. *Clin Pharmacol Ther* (1993) 54, 381–7.
4. McCall KL, Anderson HG, Jones AD. Determination of the lack of a drug interaction between azithromycin and warfarin. *Pharmacotherapy* (2004) 24, 188–94.
5. McCall KL, Scott JC, Anderson HG. Retrospective evaluation of a possible interaction between warfarin and levofloxacin. *Pharmacotherapy* (2005) 25, 67–73.
6. Abernethy DR, Kaminsky LS, Dickinson TH. Selective inhibition of warfarin metabolism by diltiazem in humans. *J Pharmacol Exp Ther* (1991) 257, 411–15.
7. Stoysich AM, Lucas BD, Mohiuddin SM, Hilleman DE. Further elucidation of pharmacokinetic interaction between diltiazem and warfarin. *Int J Clin Pharmacol Ther* (1996) 34, 56–60.
8. Böttiger Y. Interagerar cardizem och waran? Lakartidningen (2008) 105, 373.
9. Phear DN. Verapamil in angina: a double-blind trial. *BMJ* (1968) 2, 740–1.

Coumarins + Carbamazepine or Oxcarbazepine

The anticoagulant effects of warfarin can be markedly reduced by carbamazepine. Two case reports suggest phenprocoumon is similarly affected, and one case has been described with acenocoumarol. Oxcarbazepine appears not to interact significantly with warfarin.

Clinical evidence

(a) Carbamazepine

1. Acenocoumarol. A man taking stable doses of acenocoumarol and carbamazepine 200 mg daily started coughing up blood about 4 weeks after the carbamazepine was stopped, and he was found to be over-anticoagulated. The acenocoumarol was stopped for 48 hours and he was given vitamin K.[1]

2. Phenprocoumon. A man in his mid-twenties developed multiple thrombotic episodes due to hereditary resistance to activated protein C. Because of cerebral embolic strokes he developed epileptic seizures and was given carbamazepine 400 mg daily, followed 6 days later by phenprocoumon. It was found that relatively large doses of phenprocoumon (8 mg daily) had to be given without achieving adequate anticoagulation (Quick value 50 to 60%; target 10 to 20%) until the carbamazepine was withdrawn, whereupon the phenprocoumon dose could be reduced to 1.5 mg daily with a Quick value of 30 to 40%.[2] Similarly, another patient stabilised on phenprocoumon was found to have a markedly reduced anticoagulant effect (a dramatic increase in his Quick value) 21 days after he started taking carbamazepine 400 mg daily. The values returned to normal when the carbamazepine was stopped.[3]

3. Warfarin. In one study, 2 patients taking warfarin with carbamazepine (200 mg daily for the first week, 400 mg daily for the second and 600 mg for the third) had a fall of about 50% in their serum warfarin levels, and sharp rises in their prothrombin-proconvertin percentages.[4] The half-life of a single intravenous dose of warfarin in three other patients fell by about 11%, 53%, and 60%, respectively, when they were similarly treated.[4] In another analysis, warfarin dose requirements were 2.3-fold higher in 5 patients stabilised on warfarin and carbamazepine than in 54 patients taking warfarin without any interacting drugs (median 9 mg daily versus 3.86 mg daily). The 5 patients taking carbamazepine had higher clearances of both *R*- and *S*-warfarin, and had about 11-fold higher plasma levels of the 10-hydroxymetabolite of warfarin.[5] In a prospective cohort study in children, the use of phenobarbital or carbamazepine was associated with a higher dose of warfarin to maintain the target INR (0.24 mg/kg versus 0.15 mg/kg).[6] A retrospective study[7] similarly found that the concurrent use of enzyme inducers (including carbamazepine) significantly influenced the total weekly warfarin dose; further analysis found that an average additional amount of warfarin required in patients taking these drugs was 17.2 mg weekly.

An interaction between warfarin and carbamazepine has been described in 5 case reports.[8-12] One of them describes a patient stabilised on warfarin and carbamazepine who developed widespread dermal ecchymoses and a prothrombin time of 70 seconds, one week after stopping carbamazepine. She was restabilised on approximately half the dose of warfarin in the absence of carbamazepine.[11]

(b) Oxcarbazepine

In a study in 7 healthy subjects given **warfarin** until steady-state, oxcarbazepine 450 mg twice daily for one week slightly increased the mean Quick values from 36.6% to only 38.1%, which was not statistically significant.[13]

Mechanism

Carbamazepine is a known enzyme inducer, and increases the metabolism of warfarin. Acenocoumarol and phenprocoumon would be similarly affected. Oxcarbazepine has less enzyme-inducing activity than carbamazepine, and, in the study described,[13] this was not sufficient to significantly alter the effects of warfarin.

Importance and management

The interaction between warfarin and carbamazepine is moderately well documented, established and clinically important, although the incidence is uncertain. Monitor the anticoagulant response if carbamazepine is added to established treatment with warfarin and anticipate the need to double the dose. Similarly, anticipate the need to decrease the warfarin dose if carbamazepine is stopped. Oxcarbazepine appears to be a relatively non-interacting alternative.

Information about an interaction between phenprocoumon or acenocoumarol and carbamazepine seems to be limited to the three reports cited. Nevertheless it would be prudent to monitor concurrent use in any patient, being alert for the need to increase the coumarin dose.

1. Rivière I, Barjhoux C, Mallaret M. Hémoptysie sous acénocoumarol: rôle de L'arrêt d'un inducteur enzymatique (carbamazépine). *Therapie* (1994) 49, 142–3.
2. Böttcher T, Buchmann J, Zettl U-K, Benecke R. Carbamazepine-phenprocoumon interaction. *Eur Neurol* (1997) 38, 132–3.
3. Schlienger R, Kurmann M, Drewe J, Müller-Spahn F, Seifritz E. Inhibition of phenprocoumon anticoagulation by carbamazepine. *Eur Neuropsychopharmacol* (2000) 10, 219–21.
4. Hansen JM, Siersbæk-Nielsen K, Skovsted L. Carbamazepine-induced acceleration of diphenylhydantoin and warfarin metabolism in man. *Clin Pharmacol Ther* (1971) 12, 539–43.
5. Herman D, Locatelli I, Grabnar I, Peternel P, Stegnar M, Lainščak M, Mrhar A, Breskvar K, Dolžan V. The influence of co-treatment with carbamazepine, amiodarone and statins on warfarin metabolism and maintenance dose. *Eur J Clin Pharmacol* (2006) 62, 291–6.
6. Streif W, Marzinotto AV, Massicotte P, Chan AKC, Julian JA, Mitchell L. Analysis of warfarin therapy in pediatric patients: a prospective cohort study of 319 patients. *Blood* (1999) 94, 3007–14.
7. Whitley HP, Fermo JD, Chumney ECG, Brzezinski WA. Effect of patient-specific factors on weekly warfarin dose. *Ther Clin Risk Manag* (2007) 3, 499–504.
8. Ross JRY, Beeley L. Interaction between carbamazepine and warfarin. *BMJ* (1980) 1, 1415–16.
9. Kendall AG, Boivin M. Warfarin-carbamazepine interaction. *Ann Intern Med* (1981) 94, 280.
10. Massey EW. Effect of carbamazepine on Coumadin metabolism. *Ann Neurol* (1983) 13, 691–2.
11. Denbow CE, Fraser HS. Clinically significant hemorrhage due to warfarin-carbamazepine interaction. *South Med J* (1990) 83, 981.

12. Parrish RH, Pazdur DE, O'Donnell PJ. Effect of carbamazepine initiation and discontinuation on antithrombotic control in a patient receiving warfarin: case report and review of the literature. *Pharmacotherapy* (2006) 26, 1650–3.
13. Krämer G, Tettenborn B, Klosterkov Jensen P, Menge GP, Stoll KD. Oxcarbazepine does not affect the anticoagulant activity of warfarin. *Epilepsia* (1992) 33, 1145–8.

Coumarins + Carbon tetrachloride

A single case report describes an increase in the anticoagulant effects of dicoumarol in a patient who accidentally drank some cleaning liquid containing carbon tetrachloride.

Clinical evidence, mechanism, importance and management

A patient, well stabilised on **dicoumarol**, accidentally drank a small amount of cleaning liquid later estimated to contain just 0.1 mL of carbon tetrachloride. The next day his prothrombin time had risen to 41 seconds. This value was about the same after another day even though the **dicoumarol** had been withdrawn, and marked hypoprothrombinaemia persisted for another 5 days.[1]

The probable reason for this reaction is that carbon tetrachloride is very toxic to the liver, the changed anticoagulant response being a manifestation of this. Carbon tetrachloride, once used as an anthelmintic in man, is no longer used in human medicine, but is still employed as an industrial solvent and degreasing agent. On theoretical grounds it would seem possible for anticoagulated patients exposed to substantial amounts of the vapour to experience this interaction, but this has not been reported.

1. Luton EF. Carbon tetrachloride exposure during anticoagulant therapy. Dangerous enhancement of hypoprothrombinemic effect. *JAMA* (1965) 194, 1386–7.

Coumarins + Chamomile

A single case report describes a woman stabilised on warfarin who developed a marked increase in her INR with bleeding complications five days after she started using two chamomile products.

Clinical evidence

A 70-year-old woman stabilised on **warfarin** with an INR of 3.6 started drinking 4 to 5 cups of chamomile tea (an infusion of *Matricaria chamomilla*) daily for chest congestion, and using a chamomile-based skin lotion 4 to 5 times daily for foot oedema. About 5 days later she developed ecchymoses and was found to have an INR of 7.9, a retroperitoneal haematoma and other internal haemorrhages.[1]

Mechanism

German chamomile contains the natural coumarin compounds, umbelliferone and heniarin, However, these compounds do not possess the minimum structural requirements (a C-4 hydroxyl substituent and a C-3 non-polar carbon substituent) required for anticoagulant activity. German chamomile essential oil extracts do not appear to significantly affect the cytochrome P450 isoenzyme CYP2C9, the main isoenzyme involved in the metabolism of warfarin, but the effects of chamomile tea do not appear to have been studied.

Importance and management

This appears to be the first report of an interaction between warfarin and German chamomile. There seem to be no reports of German chamomile alone causing anticoagulation, and the natural coumarin constituents of German chamomile do not appear to possess anticoagulant activity, which might suggest that the risk of an additive effect is small. Furthermore, a pharmacokinetic basis for this interaction has not been established. Because of the many other factors influencing anticoagulant control, it is not possible to reliably ascribe a change in INR specifically to a drug interaction in a single case report without other supporting evidence. It may be better to advise patients to discuss the use of any herbal products they wish to try, and to increase monitoring if this is thought advisable. Cases of uneventful use should be reported, as they are as useful as possible cases of adverse effects.

1. Segal R, Pilote L. Warfarin interaction with *Matricaria chamomilla. Can Med Assoc J* (2006) 174, 1281–2.

Coumarins + Chinese angelica (*Angelica sinensis*)

Two case reports describe a very marked increase in the anticoagulant effects of warfarin when Chinese angelica was given.

Clinical evidence

A 46-year-old African-American woman with atrial fibrillation taking **warfarin** had a greater than twofold increase in her prothrombin time and INR after taking Chinese angelica for 4 weeks. The prothrombin time and INR were back to normal 4 weeks after stopping Chinese angelica.[1] In another case, a woman who had been taking **warfarin** for 10 years developed widespread bruising and an INR of 10, a month after starting to take Chinese angelica.[2]

Mechanism

The reasons for this interaction are not fully understood but Chinese angelica is known to contain natural coumarin derivatives, which may possibly have anticoagulant properties: these could be additive with those of warfarin. The data suggest that alteration of warfarin levels is not involved, but other studies suggest that the herb may inhibit the cytochrome P450 isoenzyme CYP2C9, which is the main route of warfarin metabolism.

Importance and management

Clinical evidence for an interaction between Chinese angelica and warfarin appears to be limited to the case reports cited, and an interaction is not fully established. Nevertheless, it would seem prudent to warn patients taking warfarin, and possibly other coumarin anticoagulants, of the potential risks of also taking Chinese angelica. For safety, the use of Chinese angelica should be avoided unless the effects on anticoagulation can be monitored. More study is needed.

1. Page RL, Lawrence JD. Potentiation of warfarin by dong quai. *Pharmacotherapy* (1999) 19, 870–6.
2. Ellis GR, Stephens MR. Untitled report. *BMJ* (1999) 319, 650.

Coumarins and related drugs + Chitosan

An isolated report describes an increase in the INR of an elderly man taking warfarin when he also took chitosan.

Clinical evidence

A case report describes an 83-year-old man, with type 2 diabetes who was receiving **warfarin** (2.5 mg daily for one year, with an INR of between 2 and 3) for atrial fibrillation. At a routine blood test his INR was found to be about 3.7, and, although the dose of **warfarin** was halved, 3 days later his INR was more than 9. On discussion, it was established that he had recently started taking chitosan 1.2 g twice daily. He was advised to stop this supplement and was subsequently restabilised on **warfarin**. About one month later, the patient restarted the chitosan, which again resulted in a raised INR.[1]

Mechanism

Chitosan sulfate has been reported to have anticoagulant activity, but this has not been found with chitosan. The authors therefore suggest that chitosan impaired the absorption of fat soluble vitamins, including vitamin K. Warfarin is a vitamin-K antagonist and a reduction in vitamin K would be expected to enhance its effects.

Importance and management

Evidence is limited to this case, and the mechanism is largely speculative; however an interaction seems probable. The evidence is too slim to forbid patients taking warfarin from also taking chitosan, but it would seem prudent to discuss the possible outcome and advise an increase in the frequency of anticoagulant monitoring; measuring the INR after a few days of concurrent use seems reasonable. There appears to be no evidence regarding other anticoagulants, but if the mechanism is correct, all vitamin K an-

tagonists (coumarins and **indanediones**) would be expected to be similarly affected.

1. Huang S-S, Sung S-H, Chiang C-E. Chitosan potentiation of warfarin effect. *Ann Pharmacother* (2007) 41, 1912–14.

Coumarins + Chlorpromazine

Chlorpromazine probably does not interact significantly with the coumarins.

Clinical evidence, mechanism, importance and management

Although in one early report, chlorpromazine 40 to 100 mg daily was said to have 'slightly sensitised' 2 out of 8 patients to the effects of **acenocoumarol**[1] and in another was reported to increase its anticoagulant effects in *animals*,[2] there appears to be nothing else published to suggest that an interaction occurs. *In vitro* study in human liver microsomes[3] found that chlorpromazine did not inhibit CYP2C9, the cytochrome P450 isoenzyme predominantly involved in the 'metabolism of **warfarin**', (p.405), and other coumarins. No coumarin dose adjustments would therefore be expected to be needed on concurrent use.

1. Johnson R, David A, Chartier Y. Clinical experience with G-23350 (Sintrom). *Can Med Assoc J* (1957) 77, 756–61.
2. Weiner M. Effect of centrally active drugs on the action of coumarin anticoagulants. *Nature* (1966) 212, 1599–1600.
3. Shin J-G, Soukhova N, Flockhart DA. Effect of antipsychotic drugs on human liver cytochrome P-450 (CYP) isoforms in vitro: preferential inhibition of CYP2D6. *Drug Metab Dispos* (1999) 27, 1078–84.

Coumarins and related drugs + Cilostazol

Cilostazol does not appear to have a clinically relevant effect on the pharmacokinetics or pharmacodynamics of warfarin. Nevertheless, as with other antiplatelet drugs, concurrent use might increase the bleeding risk.

Clinical evidence, mechanism, importance and management

In a well-controlled study in 15 healthy subjects, cilostazol 100 mg twice daily for 13 days did not alter the pharmacokinetics of a single 25-mg dose of warfarin given on day 7. Also, prothrombin times, aPTT and Ivy bleeding time were unaffected.[1]

This suggests that no specific interaction is likely during concurrent use. Nevertheless, because cilostazol is an antiplatelet drug, the manufacturer advises caution with the concurrent use of anticoagulants, with more frequent monitoring to reduce the possibility of bleeding.[2] Consider also, 'Coumarins and related drugs + Aspirin or other Salicylates', p.434.

1. Millakaarjun S, Bramer SL. Effect of cilostazol on the pharmacokinetics and pharmacodynamics of warfarin. *Clin Pharmacokinet* (1999) 37 (Suppl 2), 79–86.
2. Pletal (Cilostazol). Otsuka Pharmaceuticals (UK) Ltd. UK Summary of product characteristics, November 2008.

Coumarins + Cinacalcet

Cinacalcet does not appear to affect the pharmacokinetics or anticoagulant effects of warfarin.

Clinical evidence, mechanism, importance and management

In a placebo-controlled study, 21 healthy subjects were given cinacalcet 30 mg twice daily for 15 doses, with a single 25-mg dose of warfarin on day 5. Cinacalcet did not affect the pharmacokinetics of warfarin or its effects on prothrombin time.[1] This study suggests that the dose of warfarin is unlikely to need adjusting in patients given cinacalcet.

1. Padhi D, Sullivan JT. Cinacalcet does not affect the pharmacokinetics or pharmacodynamics of warfarin. *Drugs R D* (2007) 8, 79–87.

Coumarins and related drugs + Clopidogrel

Clopidogrel does not appear to have a clinically relevant effect on the pharmacokinetics or pharmacodynamics of warfarin. Nevertheless, the concurrent use of clopidogrel, either with warfarin or when given with warfarin and aspirin, increases the bleeding risk.

Clinical evidence

(a) Pharmacokinetics

In a well-controlled study involving 43 patients who had been taking **warfarin** for at least 2 months, the addition of clopidogrel 75 mg daily for 8 days had no effect on plasma **warfarin** levels or INRs. No bleeding occurred with clopidogrel and no serious adverse events were reported.[1]

(b) Triple therapy

Dual antiplatelet therapy (usually low-dose aspirin with clopidogrel) is increasingly used in acute coronary syndromes in situations where the benefits have been shown to outweigh the small increased risk of bleeding with the combination (see 'Antiplatelet drugs + Aspirin', p.814). Some of these patients also require anticoagulants for additional indications, for example, for atrial fibrillation or mechanical valves. However, there are limited clinical study data on the benefits and risks of anticoagulants given with dual antiplatelet therapy (triple therapy).

In a 2008 review of 12 studies (mostly retrospective cohort studies),[2] the increased risk of bleeding events for triple therapy versus dual therapy was three- to sixfold in 8 of the studies, with 4 of the studies reporting no increased risk of major bleeding events. In one of these studies, patients who had been taking **warfarin** long-term and who underwent stent implantation and were subsequently discharged taking aspirin, clopidogrel and **warfarin**, had a higher risk of bleeding compared with those taking dual therapy: the incidence of major bleeding was 6.6% and the incidence of minor bleeding was 14.9% in those taking triple therapy compared with 0% and 3.8% for major and minor bleeding, respectively, in patients taking dual therapy with no **warfarin**.[3] Another of the meta-analysis studies reported an incidence of 9.2% of bleeding in patients who had undergone stent placement and received **warfarin**, aspirin and clopidogrel.[4] In an observational cohort study of elderly survivors of acute myocardial infarction, the rate of bleeding was higher in patients receiving **warfarin** with aspirin (0.08 per patient year), or the triple drug combination of **warfarin** and aspirin with either clopidogrel or ticlopidine (0.09 per patient year), than in patients receiving aspirin alone (0.03 per patient year).[5]

Mechanism

As with other antiplatelet drugs (see 'Coumarins and related drugs + Aspirin or other Salicylates', p.434), concurrent use of clopidogrel and oral anticoagulants might increase the risk or intensity of bleeding.

Importance and management

The concurrent use of warfarin and clopidogrel (with or without aspirin) increases the risk of bleeding. These combinations should therefore be used only when there is a clear indication for using both an anticoagulant and antiplatelet, and the expected benefits are likely to outweigh the increased risks of bleeding. The American College of Cardiology and American Heart Association 2007 joint guidelines for acute coronary syndromes recommend that if warfarin is added to dual antiplatelet therapy, the lowest effective INR (e.g. 2 to 2.5) should be targeted and concurrent use undertaken for the shortest reasonable duration.[6] In addition, a 2008 guideline states that a proton pump inhibitor should be used for gastroprotection,[7] although note that the use of clopidogrel with a proton pump inhibitor is controversial (see 'Clopidogrel + Proton pump inhibitors and other CYP2C19 inhibitors', p.821). The joint American and European 2006 guidelines for atrial fibrillation specifically recommend that, in patients undergoing percutaneous coronary intervention, aspirin may be given temporarily but that the maintenance regimen should then consist of clopidogrel and warfarin (INR 2 to 3) without aspirin. Although there are no adequate studies, the consensus of the authors was that the addition of aspirin to oral anticoagulation rather than clopidogrel contributes more risks than benefits,[8] although this has been questioned.[9]

Note that, in the UK, the manufacturers of clopidogrel actually state that the concurrent use of warfarin is not recommended,[10] whereas the US manufacturers just recommend caution.[11]

The manufacturers of clopidogrel note that *in vitro* it has been reported to inhibit the cytochrome P450 isoenzyme CYP2C9.[10,11] They therefore predict that the metabolism of drugs that are substrates of this isoenzyme, such as warfarin[11], may be affected. However, no relevant increase in warfarin levels was found in the study[1] reported above, and the UK manufac-

turer notes that no clinically relevant interaction was reported in patients taking phenytoin or tolbutamide during the CAPRIE study. Also, no significant interaction occurs between clopidogrel and fluvastatin (see 'Clopidogrel + Statins', p.823), another substrate of CYP2C9. Therefore a pharmacokinetic interaction between clopidogrel and warfarin seems unlikely.

1. Lidell C, Svedberg L-E, Lindell P, Bandh S, Job B, Wallentin L. Clopidogrel and warfarin: absence of interaction in patients receiving long-term anticoagulant therapy for non-valvular atrial fibrillation. *Thromb Haemost* (2003) 89, 842–6.
2. Hermosillo AJ, Spinler SA. Aspirin, clopidogrel, and warfarin: is the combination appropriate and effective or inappropriate and too dangerous? Ann Pharmacother (2008) 42, 790–805.
3. Khurram Z, Chou E, Minutello R, Bergman G, Parikh M, Naidu S, Wong SC, Hong MK. Combination therapy with aspirin, clopidogrel and warfarin following coronary stenting is associated with a significant risk of bleeding. *J Invasive Cardiol* (2006) 18, 162–4.
4. Orford JL, Fasseas P, Melby S, Burger K, Steinhubl SR, Holmes DR, Berger PB. Safety and efficacy of aspirin, clopidogrel, and warfarin after coronary stent placement in patients with an indication for anticoagulation. *Am Heart J* (2004) 147, 463–7.
5. Buresly K, Eisenberg MJ, Zhang X, Pilote L. Bleeding complications associated with combinations of aspirin, thienopyridine derivatives, and warfarin in elderly patients following acute myocardial infarction. *Arch Intern Med* (2005) 165, 784–9.
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Coumarins + Cloral hydrate and related drugs

The anticoagulant effects of warfarin are increased in the first few days of cloral hydrate use, but this is normally of little or no clinical importance. Cloral betaine and triclofos may be expected to behave similarly.

Clinical evidence

In a retrospective study in patients just starting **warfarin**, the same loading doses of **warfarin** were given to 32 patients taking **cloral hydrate** daily and 67 patient who did not receive cloral hydrate. The **warfarin** requirements of the **cloral** group during the first 4 days fell by about one-third, but rose again to control requirements by the fifth day.[1]

In a study in 8 subjects, the concurrent use of **warfarin** (loading dose 25 mg then 5 mg daily for 5 days) and **cloral hydrate** 1 g each night resulted in potentiation of the effect of **warfarin**, when compared with placebo (increase in prothrombin time of about 3 to 4 seconds). However, in a longer term study, the addition of **cloral hydrate** 500 mg at night for 4 weeks to subjects stabilised on **warfarin** did not alter the average prothrombin time before, during, and after the use of **cloral** (18.9 seconds, 19.3 seconds, and 19.2 seconds, respectively).[2,3] Similar results have been described in other studies in patients taking **warfarin** and **cloral hydrate**[4-8] or **triclofos**.[9] **Cloral betaine** appears to behave similarly.[10] An isolated and by no means fully explained case of fatal hypoprothrombinaemia occurred in a patient taking **dicoumarol** who was given **cloral hydrate** for 10 days, later replaced by secobarbital.[11] Another patient taking **dicoumarol** had a reduction in prothrombin times when given **cloral hydrate**.[11]

Mechanism

Cloral hydrate is mainly metabolised to trichloroacetic acid, which then successfully competes with warfarin for its binding sites on plasma proteins.[6] As a result, free and active molecules of warfarin are displaced into the plasma water and the effects of the warfarin are increased. However, this effect is only short-lived because the warfarin molecules become exposed to metabolism by the liver, so the warfarin level is reduced.

Importance and management

The interaction between warfarin and cloral hydrate is well documented and well understood, but normally of little or no clinical importance. There is very good evidence that concurrent use need not be avoided.[1-8] However, it may be prudent to keep an eye on the anticoagulant response during the first 4 to 5 days, just to make sure it does not become excessive. It is not certain whether other anticoagulants behave in the same way because the evidence is sparse, indirect and inconclusive,[11,12] but what is known suggests that the coumarins probably do. Triclofos and cloral betaine appear to behave like cloral hydrate. Dichloralphenazone on the other hand interacts quite differently (see 'Coumarins + Dichloralphenazone', p.453).

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Coumarins + Coenzyme Q_{10} (Ubidecarenone)

Ubidecarenone did not alter the INR or required warfarin dose in a controlled study in patients stabilised on warfarin. However, two reports describe reduced anticoagulant effects of warfarin in four patients taking ubidecarenone. A transient increase in INR has been reported in one patient taking ubidecarenone and warfarin. A 4-month prospective, longitudinal study describes an increased risk of self-reported bleeding events in patients taking coenzyme Q_{10} with warfarin.

Clinical evidence

In a randomised, crossover study in 21 patients stabilised on **warfarin**, coenzyme Q_{10} 100 mg daily (*Bio-Quinone*) for 4 weeks did not alter the INR or the required dose of **warfarin**, when compared with placebo.[1] Similarly, 2 patients taking coenzyme Q_{10} to treat alopecia caused by **warfarin** treatment did not have any notable changes in INR, except that one had a transient INR *increase* when coenzyme Q_{10} was started.[2]

In a 4-month prospective, longitudinal study of 78 patients taking **warfarin** and a herbal product or dietary supplement, there was a statistically significant *increased* risk of self-reported bleeding events in 14 patients taking **warfarin** and coenzyme Q_{10} (57 bleeding events, none major, in a total of 181 weeks of concurrent use for an odds ratio of 3.7).[3] There were 4 elevated INRs (specific values not given) for 55 weeks of concurrent use, but this was not a statistically significant increase in risk. Note that the coenzyme Q_{10} products used were not mentioned and some patients were taking more than one potentially interacting supplement. The authors acknowledge that their finding might be due to chance and not a true interaction.

In contrast, another report describes 3 patients taking **warfarin** who had a reduction in their INR while taking coenzyme Q_{10}. In two of these patients, INR reductions from about 2.5 to 1.4 occurred when they took coenzyme Q_{10} 30 mg daily for 2 weeks. The INRs rapidly returned to normal when the coenzyme Q_{10} was stopped.[4] In two other cases, patients appeared to have a reduced response to **warfarin** while taking coenzyme Q_{10}, and responded normally when it was stopped.[5,6]

Mechanism

Not known. Coenzyme Q_{10} may have some vitamin K-like activity, which would explain the decrease in INR. In a study in *rats*, coenzyme Q_{10} reduced the anticoagulant effect of warfarin and increased the clearance of both enantiomers of warfarin.[7] Explanations for the increase in bleeding or INRs are unknown.

Importance and management

The well-controlled study suggests that coenzyme Q_{10} does not interact with warfarin, and that no warfarin dose adjustment would be expected to be necessary in patients who take this substance. However, the contrasting findings of a *decrease* in warfarin effect in the case reports, and an *increase* in bleeding events in the epidemiological study, introduce a note of caution. Moreover, the authors of the controlled study do recommend close monitoring of the INR if a patient decides to use coenzyme Q_{10}, because the underlying health problem resulting in them choosing to take this substance may alter their response to warfarin.[1] Until more is known it would seem prudent to increase the frequency of INR monitoring in patients taking warfarin if coenzyme Q_{10} is started.

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Coumarins and related drugs + Colchicine

Five cases of a possible marked increase in the effect of fluindione caused by colchicine have been reported.

Clinical evidence, mechanism, importance and management

The national pharmacovigilance system in France has reported 5 cases where colchicine appeared to increase the anticoagulant effect of the indanedione **fluindione**. All 5 patients were stabilised on **fluindione** and were given short-term colchicine 1 to 6 mg daily for an acute attack of gout. All 5 patients had markedly raised INRs (6.5 to in excess of 18), but only one had clinical bleeding (haemorrhoidal bleeding).[1] The authors[1] consider that colchicine may have been a factor in a case of raised INR with **warfarin**,[2] which was attributed solely to fluvoxamine (consider also 'Coumarins and related drugs + SSRIs', p.504).

The mechanism of this interaction is unknown, although the authors rule out protein binding or P-glycoprotein alterations. They suggest that it may occur because colchicine decreases the expression of various cytochrome P450 isoenzymes, so decreasing the metabolism of **fluindione**.[1]

This appears to be the only evidence of an interaction of coumarins or indanediones with colchicine, and is insufficient to justify increased monitoring in all patients.

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Coumarins + COMT inhibitors

Entacapone slightly increases *R*-warfarin levels and causes a slight increase in INR. Tolcapone is not expected to alter the pharmacokinetics of *S*-warfarin.

Clinical evidence

In a double-blind, crossover study in 12 healthy subjects given individualised **warfarin** doses to achieve an INR of between 1.4 and 1.8, **entacapone** 200 mg four times daily slightly increased the INR by 13%. The AUC of *R*-warfarin was increased by 18%, with no change in the AUC of the more potent *S*-warfarin.[1]

Mechanism

Not known. Based on *in vitro* data, both entacapone and tolcapone were thought to potentially interfere with the metabolism of drugs by the cytochrome P450 isoenzyme CYP2C9, such as *S*-warfarin.[2-4] However, the above study found that entacapone does not alter *S*-warfarin pharmacokinetics, and tolcapone is also not expected to interact by this mechanism because it does not interact with tolbutamide, another CYP2C9 substrate. Consider also 'Sulfonylureas; Tolbutamide + Tolcapone', p.589.

Importance and management

The minor pharmacokinetic interaction between entacapone and warfarin would appear to be established, but its clinical relevance is uncertain. Changes of this magnitude would not generally be expected to be clinically relevant, and there do not appear to be any published case reports of problems. Nevertheless, it is possible that some patients might show a greater effect, and the manufacturer in the UK recommends that the INR be monitored when entacapone is started in patients taking warfarin.[2]

Similarly, although the manufacturers do not predict a pharmacokinetic interaction between **tolcapone** and warfarin, they still recommend monitoring because of the limited clinical information on the combination.[3,4]

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Coumarins and related drugs + Corticosteroids or Corticotropin

The general picture is that high doses of corticosteroids and corticotrophin significantly increase the INR in patients taking coumarins or fluindione: this has resulted in bleeding in some patients. However, one study found that prednisone opposes the effect of dicoumarol, and case reports describe a reduction in the effects of ethyl biscoumacetate in patients given corticotrophin or cortisone.

Clinical evidence

(a) Corticotropin

Ten out of 14 patients receiving long-term treatment with either **dicoumarol** or **phenindione** had a small but definite increase in their anticoagulant responses when they were given intramuscular or intravenous corticotropin for 4 to 9 days.[1] A patient stable on **ethyl biscoumacetate** developed frank melaena and microscopic haematuria within 3 days of starting treatment with intravenous corticotropin 10 mg twice daily.[2]

In contrast, a decrease in the anticoagulant effects of **ethyl biscoumacetate** was described in one patient given corticotropin and one patient given **cortisone**.[3]

(b) Dexamethasone

The INR and plasma anticoagulant levels were studied in 9 patients stabilised on anticoagulants (8 taking **fluindione** and one taking **warfarin**) during a total of 10 cycles of dexamethasone (40 mg/day for 4 days every 28 days) alone (4 patients) or with melphalan (5 patients). The INR increased in all patients from a mean of 2.75 at baseline to 5.22 within 3 to 6 days of starting dexamethasone. No major bleeding occurred, although 2 cases of minor bleeding were reported. Oral anticoagulants were temporarily withheld during 8 out of 10 cycles, and oral vitamin K 1 mg was taken by 2 patients during 2 cycles. An increase in the plasma levels of fluindione of about 37% was noted (4 patients monitored), and the only patient taking warfarin had an increase in warfarin plasma levels (of about 28%), although neither of these results was statistically significant.[4]

(c) Methylprednisolone

A sharp increase in the INR of a patient with antiphospholipid syndrome occurred after methylprednisolone was added to treatment with an unnamed oral anticoagulant.[5,6] This prompted a controlled study in 10 patients stabilised on anticoagulants (8 taking **fluindione** and 2 taking **acenocoumarol**) and 5 patients not taking an anticoagulant. It was found that

pulse high-dose intravenous methylprednisolone (500 mg or 1 g) increased the mean INR of those patients taking an anticoagulant from a baseline of 2.75 to 8.04, but had no effect on the prothrombin time in those taking methylprednisolone alone.[5,6] Two patients stabilised on **warfarin** are also reported to have had significant prolongations in their prothrombin times when given high-dose methylprednisolone (960 mg or 1 g, followed by **dexamethasone** 60 mg three times daily for 3 days in one case) for the treatment of multiple sclerosis.[7]

Moreover, in a retrospective study, short-term oral corticosteroid use (methylprednisolone or prednisone) was associated with an increase in INR in patients taking **warfarin**, see under *Prednisone*, below.

(d) Prednisone

An early study in 24 patients anticoagulated for several days with **dicoumarol** found that 2 hours after receiving prednisone 10 mg their silicone coagulation time had decreased from 28 minutes to 24 minutes, and 2 hours later was down to 22 minutes, suggesting that prednisone opposes the effect of dicoumarol.[8]

In contrast, in a retrospective analysis of 24 patients stabilised on **warfarin**, short-term oral corticosteroid use (prednisone in 12 patients and **methylprednisolone** in 12 patients for between 5 and 30 days, doses not specified) increased the INR on 29 of 32 occasions, decreased it on 2 occasions, and did not change it on one occasion. The mean INR increased from 2.33 to 3.57 (measured at a mean of 6.7 days after starting the corticosteroid). Warfarin dose adjustments (reduction and/or withheld dose) were required on 16 occasions. On 5 occasions the INR was elevated to greater than 5 (three times with prednisone and twice with **methylprednisolone**).[9] Similarly, in a study of in children with acute leukaemia receiving high-dose prednisone 60 mg/m^2 daily with low-dose **warfarin** for the prevention of central line-associated thrombosis, the warfarin requirement while they were taking the steroid was about half that required during periods without it (0.057 mg/kg versus 0.12 mg/kg daily).[10] Moreover, there is case report of a man taking **warfarin** and prednisone whose INR fluctuations appeared to correlate with when he stopped (subtherapeutic) or re-started (supratherapeutic) prednisone.[11]

(e) Unspecified corticosteroids

An analysis of a cohort of children receiving **warfarin** found that there was no difference in the dose of **warfarin** required to achieve and maintain the target INR between **warfarin** courses if corticosteroids were given (38 courses) and courses where corticosteroids were not given (314 courses). However, courses with corticosteroids were associated with a higher percentage of INR measurements greater than the target (21% versus 14%).[12]

Mechanism

Not understood. Corticotropin, cortisone and prednisone can increase the coagulability of the blood in the absence of anticoagulants, and might therefore antagonise their effects.[13,14] Conversely, it has been suggested that methylprednisolone and prednisone might inhibit the metabolism of anticoagulants increasing their effects.[6] However, note that, if anything, corticosteroids, particularly dexamethasone, are usually considered to be inducers of cytochrome P450 isoenzymes.

Importance and management

The interaction of low to moderate doses of corticosteroids with coumarins is by no means established. There are a few reports from the 1950s and 60s, with very little appearing to have been published until more recently. Nevertheless, in two of the more recent retrospective analyses, the use of corticosteroids appeared to be associated with a higher incidence of INRs over the target range or lower warfarin requirements. The most constructive thing that can be said is that if corticotropin (corticotrophin, ACTH) or any low-dose corticosteroid is given to patients taking anticoagulants, be aware that a modest change in coagulation requirements might occur.

Although the evidence is limited, marked INR increases have been reported with high-dose dexamethasone, prednisone or methylprednisolone, and INRs should be closely monitored (daily has been recommended[6]) if these or other high-dose corticosteroids are added to established treatment with any coumarin or indanedione oral anticoagulant. Also note that corticosteroids are associated with a weak increase in peptic ulceration and gastrointestinal bleeding, and the risk of this could theoretically be increased if over-anticoagulation occurs.

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Coumarins + Cranberry juice

A number of case reports suggest that cranberry juice can increase the INR of patients taking warfarin, and one patient has died as a result of this interaction. Other patients have developed unstable INRs, or, in one isolated case, a *reduced* INR. However, in four controlled studies, cranberry juice did not alter the anticoagulant effect of warfarin, or had only very minor effects on the INR. Neither cranberry juice nor the extract altered warfarin pharmacokinetics.

Clinical evidence

(a) Case reports

In September 2003, the MHRA/CSM in the UK noted that they had received 5 reports suggesting an interaction between **warfarin** and cranberry juice since 1999 (3 cases of INR increases, one case of unstable INR and one case of a decrease in INR).[1] By October 2004, the MHRA/CSM reported that they had now received 12 reports of a suspected interaction, including 5 additional cases of bleeding episodes and two additional cases of unstable INRs in patients drinking cranberry juice while taking warfarin.[2] The most serious case involved a man taking **warfarin** whose INR markedly increased (INR greater than 50) 6 weeks after starting to drink cranberry juice. He died from gastrointestinal and pericardial haemorrhages.[1,3] Further details of this case included that he had recently been taking cefalexin (not known to interact) for a chest infection, and had been eating virtually nothing for at least 2 weeks,[3] a fact that would have contributed to the increase in anticoagulation.

In a further published case report, a patient stabilised on **warfarin** was found to have INRs of 10 to 12 during the surgical procedure, although he had no previous record of an INR greater than 4. Vitamin K was given, and heparin was substituted for warfarin. When warfarin was restarted postoperatively, the INR quickly rose to 8 and then to 11 with haematuria, and postoperative bleeding. The patient was drinking almost 2 litres of cranberry juice daily, because of recurrent urinary tract infections, and was advised to stop drinking this. Three days later the INR had stabilised at 3 with no further intervention.[4] Another case of fluctuating INR (between 1 and 10) in a patient taking **warfarin** has been attributed to cranberry juice.[5]

In the US, a case of major bleeding and a high INR has been reported in a man taking **warfarin**, which occurred shortly after cranberry juice 710 mL daily was started.[6] Another case, describes an increase in the INR

of a patient receiving **warfarin**, from below 3 to 6.45, without bleeding, after the patient drank about 2 litres of cranberry/apple juice over the last week. Of note, the patient was subsequently re-stabilised on a lower dose of warfarin and may have taken an extra dose of warfarin in the week before the raised INR was measured.[7]

(b) Controlled studies

In one controlled crossover study, 7 male patients with atrial fibrillation who were taking stable doses of **warfarin** drank 250 mL of cranberry juice or placebo [daily] for a week without any significant change in their INR from baseline values.[8] The same finding was reported in another very similar study in patients taking **warfarin**.[9] However, note that the daily volume of cranberry juice in these studies was lower than the daily volume in the couple of case reports where cranberry juice intake is known. Nevertheless, in another controlled study in 10 healthy subjects, a higher volume of cranberry juice (200 mL three times daily) for 10 days did not alter the effect of a single 10-mg dose of **warfarin** (given on day 5) on the maximum thromboplastin time or AUC of the thromboplastin time.[10] In addition, cranberry juice had no effect on warfarin pharmacokinetics, except that there was a slight non-significant 7% *decrease* in the AUC of *S*-warfarin.

In yet another study in 12 healthy subjects, cranberry juice concentrate 2 capsules three times daily for 21 days (equivalent to 57 g of fruit daily) had no effect on the maximum INR after a single 25-mg dose of **warfarin** given on day 15 (2.8 versus 2.6). However, the AUC of the INR was slightly increased by 28%, which was statistically significant, but the clinical relevance of this measure is uncertain. The cranberry concentrate had no effect on platelet aggregation, and had no effect on the pharmacokinetics of either *R*- or *S*-warfarin.[11]

Mechanism

Not known. It was originally suggested that one or more of the constituents of cranberry juice might inhibit the metabolism of warfarin by the cytochrome P450 isoenzyme CYP2C9, thereby reducing its clearance from the body and increasing its effects.[1] However, four studies have shown that cranberry juice or cranberry extracts do not alter the pharmacokinetics of warfarin, and cranberry juice had no effect on flurbiprofen pharmacokinetics, a drug used as a surrogate index of CYP2C9 activity.[12] An interaction might therefore be via a pharmacodynamic mechanism. For example, the salicylate constituent of commercial cranberry juice might cause hypoprothrombinaemia.[13]

Importance and management

An interaction is not established. Controlled studies have not found a pharmacokinetic interaction, and only one of four studies found any evidence for an increase in warfarin effect. Moreover, the clinical relevance of the finding of this study of a 0.2 increase in INR and 28% increase in AUC of the INR is likely to be slight at most, and does not fit with the sometimes marked increase in INR seen in some case reports. This might be explained if the interaction is dose dependent (in one of the cases where cranberry intake was mentioned a quantity of 2 litres daily was being consumed), or if it is product dependent (i.e. due to a constituent present in the cranberry juice that is not standardised for and varies widely). However, it could also be that there is no specific interaction, and that the case reports just represent idiosyncratic reactions in which other unknown factors (e.g. altered diet) were more important.

In 2004, on the basis of the then available case reports and lack of controlled studies, the CSM/MHRA in the UK advised that patients taking warfarin should avoid drinking cranberry juice unless the health benefits are considered to outweigh any risks. They recommended increased INR monitoring for any patient taking warfarin and who has a regular intake of cranberry juice.[2] They also advised similar precautions with other cranberry products (such as capsules or concentrates).[2] These might still be prudent precautions, although the controlled studies now available do provide some reassurance that, in otherwise healthy individuals, moderate doses of cranberry juice are unlikely to have an important impact on anticoagulation control.

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Coumarins + *Curbicin*

The INR of one patient taking warfarin modestly increased after he took *Curbicin* (saw palmetto, cucurbita, and vitamin E). This product has also been associated with an increased INR in a patient not taking anticoagulants. Excessive bleeding during surgery has been reported in another patient who had been taking saw palmetto.

Clinical evidence

A 61-year-old man taking **warfarin** and simvastatin, with a stable INR of around 2.4, had an increase in his INR to 3.4 within 6 days of starting to take 5 tablets of *Curbicin* daily. Within a week of stopping the *Curbicin*, his INR had fallen to its previous value. Another elderly man who was not taking any anticoagulants and was taking 3 tablets of *Curbicin* daily was found to have an INR of 2.1 (normal 0.9 to 1.2). His INR decreased (1.3 to 1.4) when he was given vitamin K, but did not normalise until a week after the *Curbicin* was stopped. *Curbicin* is a herbal remedy used for micturition problems, and contains extracts from the fruit of *Serenoa repens* (**saw palmetto**) and the seed of *Cucurbita pepo*.[1]

In addition, saw palmetto has been attributed to excessive bleeding in a 53-year-old man undergoing a surgical procedure to remove a brain tumour. An estimated 2 litres of blood was lost during surgery and bleeding time did not return to normal for 5 days. The patient denied taking NSAIDs pre-operatively but admitted to taking saw palmetto for benign prostatic hypertrophy.[2]

Mechanism

The authors of the first report suggest that what happened was possibly due to the presence of vitamin E in the *Curbicin* preparation (each tablet contains 10 mg), but vitamin E does not normally affect INRs. Experimental evidence suggests that saw palmetto may inhibit the cytochrome P450 isoenzyme CYP2C9, which is an important route of warfarin metabolism.

Importance and management

Evidence appears to be limited to case reports and an experimental study of unknown clinical relevance. Because of the many other factors influencing anticoagulant control, it is not possible to reliably ascribe a change in INR specifically to a drug interaction in a single case report without other supporting evidence. It may be better to advise patients to discuss the use of any herbal products they wish to try, and to increase monitoring if this is thought advisable. Cases of uneventful use should be reported, as they are as useful as possible cases of adverse effects.

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Coumarins + Danazol or Gestrinone

Increased anticoagulant effects and bleeding have been seen in a few patients taking warfarin with danazol. A case describes similar effects in a patient taking warfarin and gestrinone.

Clinical evidence

(a) Danazol

A 40-year-old woman stabilised on **warfarin** 6 mg daily with a prothrombin ratio of 2.3 presented after vomiting blood. She was found to have a prothrombin ratio of 14, and required fresh frozen plasma and 2 litres of blood. Three weeks previously she had been prescribed danazol 200 mg twice daily.[1] Four other similar cases of this interaction with danazol have been reported.[2-4] In two of the cases the patients were subsequently stabilised on **warfarin** and danazol, but with 50 to 70% lower **warfarin** doses.[3,4]

(b) Gestrinone

A bulletin includes a brief mention of an increased INR with vaginal bleeding and multiple bruising in a woman taking **warfarin** and gestrinone.[5]

Mechanism

The reason for this interaction is unknown, but both danazol and gestrinone have androgenic properties, and anabolic steroids (see 'Coumarins and related drugs + Anabolic steroids or Androgens', p.412), are known to increase the effects of warfarin.

Importance and management

Although data are limited, the interaction with danazol would appear to be established, and close monitoring of the INR is advisable if danazol is added to established treatment with a coumarin. Some suggest that the initial dose of the anticoagulant should be halved when danazol is started.[2] However, others note that this may not be appropriate in patients at high thrombogenic risk, such as those with mechanical valves. In these patients, they recommend a cautious reduction in dose with weekly monitoring of the INR until it becomes stable (several weeks).[4] Gestrinone might be expected to interact similarly, and some caution is therefore appropriate.

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Coumarins and related drugs + Danshen (*Salvia miltiorrhiza*)

Three case reports indicate that danshen may increase the effects of warfarin, resulting in bleeding.

Clinical evidence

A woman taking **warfarin**, furosemide and digoxin, who began to take danshen on alternate days, was hospitalised a month later with anaemia and bleeding (prothrombin time greater than 60 seconds, INR greater than 5.62). The anaemia was attributed to occult gastrointestinal bleeding and the over-anticoagulation to an interaction with the danshen. She was later restabilised on warfarin in the absence of the danshen with an INR of 2.5, and within 4 months her haemoglobin levels were normal.[1]

A man taking **warfarin**, digoxin, captopril and furosemide with an INR of about 3, developed chest pain and breathlessness about 2 weeks after starting to take danshen. He was found to have a massive pleural effusion, and an INR of more than 8.4. He was later discharged on his usual dose of warfarin with an INR stable at 3, in the absence of the danshen.[2]

Over-anticoagulation was investigated in Chinese patients admitted to a medical unit during a 9-month period in 1994/1995. An interaction with **warfarin** was reported in a patient using a medicated oil product that contained methyl salicylate 15%, and an analgesic balm that contained danshen, methyl salicylate 50% and diclofenac.[3]

Mechanism

Danshen has antiplatelet actions, which may be additive with the anticoagulant effect of warfarin. The mechanism for the increase in warfarin levels is unknown, because the studies suggest that the usual extracts of danshen do not inhibit the cytochrome P450 isoenzyme CYP2C9, the main route of warfarin metabolism.

Importance and management

Evidence appears to be limited to three case studies, which alone would be insufficient to establish an interaction. Further, one of these cases included the use of methyl salicylate, which has been shown to interact with warfarin. The pharmacokinetic effects of the usual extracts of danshen seem to suggest that an interaction resulting in raised warfarin levels is unlikely in most patients. However, because danshen may have antiplatelet effects, an interaction between warfarin and danshen, resulting in increased bleeding, is possible. Clinically the use of an antiplatelet drug with an anticoagulant should generally be avoided in the absence of a specific indication. It may therefore be prudent to advise against concurrent use. However, if concurrent use is felt desirable it would seem sensible to warn patients to be alert for any signs of bruising or bleeding, and report these immediately, should they occur.

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Coumarins + Darifenacin or Solifenacin

Solifenacin does not appear to alter the pharmacokinetics or anticoagulant response to warfarin. Darifenacin does not alter the prothrombin time in response to warfarin.

Clinical evidence, mechanism, importance and management

(a) Darifenacin

The manufacturer notes that steady state darifenacin 30 mg daily did not alter the prothrombin time after a single 30-mg dose of **warfarin**.[1] Therefore, no **warfarin** dose adjustment or additional monitoring would be expected to be needed on concurrent use.

(b) Solifenacin

In a placebo-controlled, crossover study in healthy subjects, solifenacin 10 mg daily for 10 days had no effect on the pharmacokinetics of *S*- or *R*-warfarin after a single 25-mg dose of **warfarin** was given on day 10. In addition, solifenacin did not alter the prothrombin time.[2] This study suggests that no pharmacokinetic or pharmacodynamic interaction occurs, and that no **warfarin** dose adjustment would be expected to be needed on concurrent use.

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2. Smulders RA, Kuipers ME, Krauwinkel WJJ. Multiple doses of the antimuscarinic agent solifenacin do not affect the pharmacodynamics or pharmacokinetics of warfarin or the steady-state pharmacokinetics of digoxin in healthy subjects. *Br J Clin Pharmacol* (2006) 62, 210–17.

Coumarins + Dichloralphenazone

The anticoagulant effects of warfarin are reduced by dichloralphenazone.

Clinical evidence

Five patients stabilised taking **warfarin** long-term and given dichloralphenazone 1.3 g each night for 30 days had a reduction of about 50% (range 20 to 69%) in plasma **warfarin** levels and a fall in the anticoagulant response during the last 14 days of concurrent use. Another patient given dichloralphenazone 1.3 g nightly for one month had a 70% fall in plasma **warfarin** levels and a thrombotest percentage rise from 9% to 55% (indicating a reduced anticoagulant effect). These values returned to normal when the hypnotic was withdrawn.[1,2]

Mechanism

The phenazone component of dichloralphenazone is a potent liver enzyme inducer (see 'Coumarins + NSAIDs; Phenazone (Antipyrine)', p.488), which increases the metabolism and clearance of the warfarin, thereby reducing its effects.[1,2] The effects of the cloral hydrate component (see

'Coumarins + Cloral hydrate and related drugs', p.449) appear to be minimal.

Importance and management

Information is limited, but the interaction between warfarin and dichloralphenazone appears to be established and clinically important, probably affecting most patients. The dose of warfarin will need to be increased to accommodate this interaction. If the effect of warfarin has been reduced by using dichloralphenazone, it may take up to a month for it to restabilise. There does not appear to be any information about other anticoagulants, but other coumarins would be expected to be similarly affected. The benzodiazepines (see 'Coumarins + Benzodiazepines and related drugs', p.441) are generally preferred hypnotics, and do not interact.

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Coumarins and related drugs + Dipyridamole

The concurrent use of dipyridamole and a coumarin does not alter the prothrombin time, but it might cause an increased risk of serious bleeding. There is some evidence that the risk of bleeding may be lower, without a reduction in efficacy, if the INR is maintained within a lower range.

Clinical evidence

(a) Prosthetic heart valves

In a short-term study in 6 patients stabilised on **warfarin**, the addition of dipyridamole 75 mg three times daily did not alter prothrombin time ratios measured 8 times over 17 days.[1]

A meta-analysis of 6 randomised, controlled studies of the combined use of an oral anticoagulant [presumably a coumarin or indanedione] and dipyridamole compared with an oral anticoagulant alone, found no increased risk of *any* bleeding events when dipyridamole was given (odds ratio 1.001).[2] In contrast, in a later meta-analysis of the same studies, the risk of *major* bleeding with the addition of dipyridamole was increased (odds ratio 2.22). In addition to the difference in classification of bleeding events, the authors of the second analysis stated that they had used published data from two studies, which showed a slightly higher bleeding risk, whereas the earlier meta-analysis had used unpublished data from these studies, showing a lower bleeding risk.[3]

In one randomised study, the risk of excessive bleeding was 4% in patients taking **warfarin** and dipyridamole 400 mg daily, compared with 14% in patients taking **warfarin** and aspirin 500 mg daily. When compared with a non-randomised control group taking **warfarin** alone, the risk of excessive bleeding was not increased by dipyridamole (4% with both drugs versus 5% with **warfarin** alone).[4]

In another randomised study, the risk of bleeding was lower (1% versus 3.7%) in patients receiving dipyridamole 225 mg daily with **phenindione** at a target INR of 2 to 2.5 than in patients receiving **phenindione** alone with a target INR of 2.5 to 3.5, and the combination was more effective.[5] Similarly, the risk of bleeding was lower with a lower target INR of 2 to 3 than with a target INR of 3 to 4.5 (3.9% versus 20.8%) in patients taking **acenocoumarol**, aspirin 330 mg twice daily and dipyridamole 75 mg twice daily.[6]

(b) Other conditions

In a randomised study in patients with severe or recurrent venous thrombosis, there was no difference in dose of **acenocoumarol** necessary to reach an INR of 2.5 to 3.5 between 100 patients taking **acenocoumarol** with dipyridamole 400 mg daily and 100 patients taking **acenocoumarol** alone. None of the patients had severe bleeding, and 3 to 4% of patients in both groups had moderate bleeding (haematomas, haematuria).[7]

Thirty patients with glomerulonephritis stabilised on either **warfarin** (28 patients) or **phenindione** (2 patients) with a prothrombin activity of between 20 to 30% of control had no significant changes in prothrombin times when they were given dipyridamole in doses increased from 100 mg daily up to a maximum of 400 mg daily over about a month. Twelve to 19 days after starting dipyridamole, 3 patients with normal renal function developed mild bleeding (epistaxis, bruising, haematuria), which resolved when either drug was withdrawn or the dose reduced.[8]

In a retrospective, cohort study in patients taking oral anticoagulants with or without antiplatelet drugs, including dipyridamole, the concurrent use of an antiplatelet drug was found to significantly increase the risk of bleeding compared with an oral anticoagulant alone: 4.2% of patients receiving an anticoagulant and an antiplatelet drug had a bleeding event compared with 2% of the patients taking an oral anticoagulant alone. No additional beneficial reduction in the risk of thromboembolism was found.[9]

Mechanism

Dipyridamole reduces platelet adhesiveness or aggregation, which prolongs bleeding time. This may increase the risk or severity of bleeding if over-anticoagulation occurs.

Importance and management

There is clearly some uncertainty regarding the increased risk of bleeding with the combination of warfarin and dipyridamole, with one analysis finding no increased risk,[2] and a second finding about a doubling of risk of serious bleeding.[3] The authors of the second analysis consider that their results represent a more conservative estimate of bleeding risk.[3] There is some evidence that maintaining anticoagulant control at the lower end of the therapeutic range minimises possible bleeding complications and it would therefore seem prudent to consider this wherever possible.

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Coumarins + Disopyramide

In two small uncontrolled studies, the anticoagulant effects of warfarin were slightly reduced by disopyramide. In contrast, there is an isolated report of a patient who needed his warfarin dose to be doubled after *stopping* disopyramide.

Clinical evidence

In a preliminary report of a study in 10 patients with recent atrial fibrillation taking **warfarin** and with a British Corrected Ratio of 2 to 3, disopyramide (dose not stated) increased the clearance of **warfarin** by 21%.[1] Similarly, another study found that 2 out of 3 patients needed a slight **warfarin** dose increase of about 10% after cardioversion and after starting disopyramide 200 mg three times daily for atrial fibrillation.[2]

In contrast, another report describes a patient who, following a myocardial infarction, was given **warfarin** 3 mg daily and disopyramide 100 mg every 6 hours with digoxin, furosemide and potassium supplements. When the disopyramide was withdrawn his **warfarin** requirements doubled over a 9-day period.[3,4]

Mechanism

Unknown. One idea is that when the disopyramide controls fibrillation, changes occur in cardiac output and in the flow of blood through the liver, which might have an effect on the synthesis of the blood clotting factors.[2,5] But the discordant response in the isolated case remains unexplained.

Importance and management

The interaction between disopyramide and warfarin is very poorly documented and not established. Limited data suggest only a minor interaction occurs (a slight reduction in anticoagulant effect), but an isolated case suggests a greater and opposite effect. Bear the possibility of an interaction in mind in the case of an unexpected response to warfarin in a patient starting or stopping disopyramide.

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Coumarins + Disulfiram

The anticoagulant effects of warfarin were increased by disulfiram in two studies, and two cases showing this effect have also been reported.

Clinical evidence

In one study in 7 healthy subjects, **warfarin** (adjusted to maintain a prothrombin activity of 40%) was given alone for 21 days, then given with disulfiram 500 mg daily for 21 days. The plasma **warfarin** levels of 5 of the 7 subjects rose by an average of 20% and their prothrombin activity fell from about 34% to 24% of normal (suggesting an increased anticoagulant effect); one of the subjects had little change, and the other had the opposite effect.[1] Other experiments with single doses of **warfarin** confirm these results.[1] However, a further study found that, although disulfiram potentiated the effect of *S*-warfarin, it did not change the plasma levels of either *R*- or *S*-warfarin.[2]

An alcoholic patient stabilised on **warfarin** had an increase in his prothrombin time associated with gross haematuria when disulfiram 250 mg daily was given. Two subsequent attempts to introduce disulfiram 250 mg on alternate days also had a similar effect. He was eventually stabilised on a 43% lower daily dose of warfarin and disulfiram 250 mg daily.[3] Another case of increased prothrombin time and the need for a reduced warfarin dose has been reported.[4]

Mechanism

Not fully understood. The suggestion[1] that disulfiram inhibits the liver enzymes concerned with the metabolism of warfarin has not been confirmed by later studies.[2] It has instead been suggested[2] that disulfiram may chelate with the metal ions necessary for the production of active thrombin from prothrombin, thereby augmenting the actions of warfarin.

Importance and management

An interaction appears to be established, although direct information about patients is very limited. What is known suggests that most individuals will demonstrate this interaction. If concurrent use is thought appropriate, the effects of warfarin should be monitored and suitable dose adjustments made when adding or withdrawing disulfiram. Care should be taken when starting warfarin in patients already taking disulfiram, and consideration should be given to using a smaller loading dose.

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2. O'Reilly RA. Dynamic interaction between disulfiram and separated enantiomorphs of racemic warfarin. *Clin Pharmacol Ther* (1981) 29, 332–6.
3. Rothstein E. Warfarin effect enhanced by disulfiram. *JAMA* (1968) 206, 1574–5.
4. Rothstein E. Warfarin effect enhanced by disulfiram (Antabuse). *JAMA* (1972) 221, 1052–3.

Coumarins and related drugs + Ditazole

Ditazole does not alter the anticoagulant effects of acenocoumarol. Nevertheless, as with other antiplatelet drugs, concurrent use might increase bleeding risk.

Clinical evidence, mechanism, importance and management

Fifty patients with artificial heart valves taking **acenocoumarol** had no changes in their prothrombin times while taking ditazole 800 mg daily.[1] Nevertheless, as with other antiplatelet drugs, such as aspirin (see 'Coumarins and related drugs + Aspirin or other Salicylates', p.434), concurrent use with oral anticoagulants might increase the risk or intensity of bleeding. Some caution is therefore appropriate on concurrent use.

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Coumarins + Diuretics

The loop diuretics, bumetanide, furosemide and torasemide, the potassium-sparing diuretic spironolactone, and the thiazides, chlortalidone and chlorothiazide, have all been found either not to interact or to cause only a small reduction in the effects of the coumarin anticoagulants. The exception is tienilic acid, which has a pharmacokinetic interaction with warfarin and increases its effects, and possibly etacrynic acid, which on rare occasions has caused a marked increase in the effects of warfarin.

Clinical evidence

A. Loop diuretics

(a) Bumetanide

In 10 healthy subjects, bumetanide 1 mg daily for 14 days did not alter the anticoagulant effect of a single-dose of **warfarin** given on day 8, and did not alter serum **warfarin** levels.[1] This confirms findings of a previous study in 5 healthy subjects given single-dose **warfarin** after bumetanide 2 mg daily for 5 days.[2]

(b) Etacrynic acid

A case report describes a marked increase in the anticoagulant effects of **warfarin** in a woman with hypoalbuminaemia on two occasions when she was given etacrynic acid 150 mg to 300 mg daily.[3] In a preliminary report of a cohort study, it was stated that a therapeutically significant interaction between **warfarin** and etacrynic acid was documented, but no details are given.[4]

(c) Furosemide

In 6 healthy subjects, plasma levels, half-lives and prothrombin times were not altered when a single 50-mg dose of **warfarin** was given after furosemide 80 mg daily for 5 days.[2] However, a 28% decrease in the INR of one patient taking **warfarin** was seen when furosemide was taken on a regular basis. This was attributed to volume depletion caused by the diuretic, although interpretation of this case is complicated by the patient's admission of previous non-compliance and abuse of alcohol and cocaine.[5] In a pharmacokinetic study in 17 healthy subjects, furosemide 40 mg twice daily had no effect on the pharmacokinetics of a single 0.22-mg/kg dose of **phenprocoumon**.[6] In another study in 22 patients with congestive heart failure stabilised on **phenprocoumon**, furosemide 40 mg daily for 8 days did not alter the anticoagulant effects or required dose of **phenprocoumon**.[7]

(d) Tienilic acid (Ticrynafen)

In 6 healthy subjects, tienilic acid 250 mg daily for about 14 days caused a mean 265% increase in the anticoagulant effect of a single dose of **warfarin** given on day 4. Analysis showed the interaction was stereoselective, with the AUC of *S*-warfarin increased by 192%, with the AUC for *R*-warfarin increased by only 8%.[8] Two patients taking **ethyl biscoumacetate** began to bleed spontaneously (haematuria, ecchymoses of the legs and gastrointestinal bleeding) when they started to take tienilic acid 250 mg daily. The thrombotest percentage of one of them was found to have fallen by 10%.[9] Increased anticoagulant effects and/or bleeding, which began within a few days, have been described in a number of other case reports in patients given tienilic acid while taking **ethyl biscoumacetate**,[10,11] **acenocoumarol**[12] or **warfarin**.[10,13]

(e) Torasemide

In a study in 24 patients with congestive heart failure stabilised on **phenprocoumon**, torasemide 20 mg daily for 8 days did not alter the anticoagulant effects or required dose of **phenprocoumon**.[7]

B. Potassium-sparing diuretics

In a study in 9 healthy subjects, **spironolactone** 50 mg four times daily for about 16 days reduced the prothrombin time response to a single dose of warfarin given on day 8 by 24%, when compared with **warfarin** alone. Plasma **warfarin** levels remained unchanged.[14]

C. Thiazides

(a) Chlortalidone

Six healthy subjects given a single 1.5-mg/kg dose of **warfarin** had reduced hypoprothrombinaemia (prothrombin activity reduced from 77 to 58 units) when they were also given chlortalidone 100 mg daily for 7 days with the **warfarin** given on the first day, although the plasma **warfarin** levels remained unaltered.[15] Similarly, reduced anticoagulant effects have been described when chlortalidone was given with **phenprocoumon**, but no significant effects were seen when chlortalidone was given with **acenocoumarol**.[16]

(b) Chlorothiazide

A study in 8 healthy subjects given single 40 to 60-mg doses of **warfarin** before and after chlorothiazide 1 g daily for 21 days found that the mean half-life of the anticoagulant was increased from 39 hours to 44 hours, but the prothrombin time was only decreased by 0.3 seconds.[17]

Mechanism

It has been suggested that the diuresis induced by chlortalidone, furosemide and spironolactone reduces plasma water, which leads to a concentration of the blood clotting factors.[5,14,15] Etacrynic acid can displace warfarin from its plasma protein binding sites,[18] and it was originally thought that other diuretics also interacted by drug displacement.[9,19,20] Only 3% of total plasma warfarin is in the free active form, thus a small displacement could result in marked enhancement of activity,[3] but it is almost certain that this, on its own, does not explain the interaction described.[4] Tienilic acid (ticrynafen), a loop diuretic which is structurally related to etacrynic acid, reduces the metabolism of *S*-warfarin (but not *R*-warfarin) thereby prolonging its stay in the body and increasing its effects.[8] It is possible that etacrynic acid interacts via a similar mechanism.

Importance and management

The documentation relating to diuretics in general (other than tienilic acid) is limited and seems to be confined to the reports cited here, most of which are single-dose pharmacological studies. The evidence suggests that these diuretics either do not interact at all with the coumarins, or interact only to an extent which is of little clinical relevance. This seems to be supported by the lack of case reports of problems with these combinations, and is in general agreement with common experience. No special precautions normally seem to be necessary, except possibly with etacrynic acid where it might be prudent to monitor the outcome particularly in those with hypoalbuminaemia or renal impairment.

The interaction between the coumarins and tienilic acid is established and of clinical importance, but the incidence is uncertain. Concurrent use should be avoided. If that is not possible, prothrombin times should be closely monitored and the anticoagulant dose reduced as necessary. Note that tienilic acid has been withdrawn in many countries because of its hepatotoxicity.

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Coumarins + Dofetilide

Dofetilide did not alter the anticoagulant effect of warfarin in one study.

Clinical evidence, mechanism, importance and management

In a placebo-controlled study in 14 healthy subjects, dofetilide 750 micrograms twice daily for 8 days had no effect on the prothrombin time in response to a single 40-mg dose of **warfarin** given on day 5.[1] No dose adjustment of **warfarin** would be anticipated to be needed on concurrent use.

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Coumarins + Endothelin receptor antagonists

Bosentan appears to cause a modest reduction in warfarin levels, which may result in an increase in warfarin requirements in some patients. Sitaxentan inhibits the metabolism of warfarin and a lower dose of warfarin is likely to be needed. Ambrisentan did not have any clinically relevant effect on warfarin pharmacokinetics or pharmacodynamics in one study.

Clinical evidence

(a) Ambrisentan

In a study in 22 healthy subjects, ambrisentan 10 mg daily for 8 days had no clinically relevant effect on the pharmacokinetics or pharmacodynamics of a single 25-mg dose of **warfarin** given on day 8. There was a minor 5% increase in AUC of *R*-warfarin, and a minor 8% and 10% decrease in maximum levels of *R*- and *S*-warfarin, respectively. The maximum prothrombin time was decreased by about 14%.[1] The manufacturer notes that, in healthy subjects, ambrisentan did not alter the weekly **warfarin** dose, prothrombin time or INR. The pharmacokinetics of ambrisentan are also not affected by warfarin.[2]

(b) Bosentan

In a well-controlled study, 12 healthy subjects were given bosentan 500 mg twice daily or placebo for 10 days, with a single 26-mg dose of **warfarin** on day 6. Bosentan reduced the AUC of *R*-warfarin by 38% and reduced the AUC of *S*-warfarin by 29%. A significant decrease in the anticoagulant effects of **warfarin** was also noted, with a 23% reduction in prothrombin time occurring with bosentan.[3]

Two case reports highlight the clinical significance of this interaction. A 35-year-old woman taking **warfarin** with a stable INR of 2 to 3 over three months started taking bosentan 62.5 mg twice daily. After 10 days her INR was 1.7, and remained at this level over the next 4 weeks, despite an increase in her weekly **warfarin** dose from 27.5 mg to 40 mg. The bosentan dose was then increased to the maintenance dose of 125 mg twice daily, and two further weekly increases in **warfarin** dose were made. The INR was then high (3.2 to 4.1) for 3 weeks, before she was finally stabilised on **warfarin** 45 mg each week.[4] In a second case, the INR decreased to 1.5 on starting bosentan, necessitating an increase in **warfarin** dose from 30 mg weekly to 40 mg weekly. However, when the bosentan dose was later decreased from 250 mg daily to 125 mg daily, the INR increased to 4.6, and the warfarin dose was reduced to 35 mg weekly.[5]

The manufacturer of bosentan notes that, in clinical experience, the use

of bosentan with **warfarin** did not result in clinically relevant changes in the INR or **warfarin** dose. There was no difference in the frequency of **warfarin** dose changes (due to INR changes or adverse effects) between bosentan or placebo recipients.[6] However, in the STRIDE-2 study where 52 patients with pulmonary arterial hypertension took bosentan at usual prescribed doses, daily warfarin dose requirements were 5.1 mg daily, compared with 3.7 mg in 51 patients given placebo. The average number of patients with an INR greater than 3.5 during this study was 20% lower than in the placebo group.[7]

(c) Sitaxentan

Sitaxentan increases the exposure to *S*-warfarin 2.4-fold: patients receiving warfarin tend to require lower doses of warfarin to achieve therapeutic INR values in the presence of sitaxentan.[8] In the STRIDE-2 study in patients with pulmonary arterial hypertension, the average warfarin dose after 18 weeks of the concurrent use of sitaxentan 50 mg or 100 mg daily was 2.8 mg daily and 2.1 mg daily, respectively, compared with 3.7 mg in a placebo group. However, the number of patients taking sitaxentan with an INR of more than 3.5 was similar to the placebo group. Note that in this study an initial warfarin dose reduction of 80% was used in patients randomised to sitaxentan or placebo.[7]

Mechanism

Bosentan induces both the cytochrome P450 isoenzymes CYP3A4 and CYP2C9, which are involved in the metabolism of *R*-warfarin and *S*-warfarin, respectively.[3] In contrast. sitaxentan has been reported to *inhibit* these isoenzymes.[8] Therefore, the use of bosentan increases the metabolism of warfarin, leading to reduced anticoagulant effects, whereas sitaxentan decreases the metabolism of warfarin, resulting in increased anticoagulant effects. Ambrisentan appears to have little effect on warfarin metabolism.

Importance and management

Both the studies and the case reports suggest that a clinically significant reduction in the effects of warfarin may occur in some patients taking **bosentan**, although exactly how frequently this may occur is unclear. The UK manufacturer of bosentan states that the INR should be closely monitored in any patient taking warfarin when bosentan is started or stopped, or if the dose is altered,[6] and given the higher dose requirements reported in the STRIDE-2 study, this seems a prudent precaution. Other coumarins should be similarly monitored.

Sitaxentan increases warfarin levels, and a dose reduction of warfarin appears likely to be needed patients taking both drugs. The manufacturer of sitaxentan also predicts that acenocoumarol, phenprocoumon, and fluindione (and therefore presumably other indanediones) will interact similarly. They advise that if patients taking sitaxentan are started on one of these anticoagulants, they should be started on the lowest possible dose of anticoagulant and small dose increases (0.5 mg daily has been suggested[9]) should be made in order to reach the target INR. The Australian manufacturer recommends initiating warfarin at a dose of 0.5 mg daily in patients taking sitaxentan, and then adjusting according to the INR.[9] If sitaxentan is started in a patient already taking an anticoagulant, the dose of the anticoagulant should be reduced; the Australian manufacturer recommends a warfarin dose reduction of 80%.[9] The INR should be closely monitored in all patients taking both drugs.[8,9]

Available evidence suggests that no clinically significant interaction occurs between warfarin and **ambrisentan**, therefore no special precautions are necessary with concurrent use.

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Coumarins + Etanercept

Etanercept did not alter the pharmacodynamics or pharmacokinetics of a single dose of warfarin in one study.

Clinical evidence, mechanism, importance and management

In a study in 12 healthy subjects, subcutaneous etanercept 25 mg twice weekly for 7 doses did not alter the pharmacodynamics (INR) of a single dose of **warfarin** given with the last dose of etanercept. In addition, there was no change in the AUC of *R*- and *S*-warfarin.[1]

This study suggests that no **warfarin** dose adjustments would be expected to be needed if etanercept is used in patients taking **warfarin**.

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Coumarins + Ethchlorvynol

The anticoagulant effects of dicoumarol and warfarin are reduced by ethchlorvynol.

Clinical evidence

Six patients who had recently started taking **dicoumarol** had a rise in their Quick index from 38% to 55% (indicating a reduction in anticoagulant effect) while taking ethchlorvynol 1 g daily over an 18-day period. Another patient stabilised on **dicoumarol** became over-anticoagulated and developed haematuria on two occasions when ethchlorvynol was withdrawn for periods of 6 days and 4 days.[1] A marked reduction in the anticoagulant effects of **warfarin** occurred in another patient given ethchlorvynol.[2]

Mechanism

Uncertain. The idea that ethchlorvynol increases the metabolism of the anticoagulants by the liver has not been confirmed by studies in *dogs* and *rats*.[3]

Importance and management

Information is very sparse and limited to dicoumarol and warfarin, but the interaction seems to be established. Be alert for other coumarins to behave similarly. Anticipate the need to alter the anticoagulant dose if ethchlorvynol is started or stopped. The benzodiazepines may be a useful non-interacting alternative to ethchlorvynol, see 'Coumarins + Benzodiazepines and related drugs', p.441.

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Coumarins and related drugs + Ezetimibe

No clinically significant interaction occurred between ezetimibe and warfarin in one study. However, there have been post-marketing reports of raised INRs in patients taking warfarin or fluindione after they were also given ezetimibe.

Clinical evidence, mechanism, importance and management

In a two-way, crossover study, 12 healthy subjects were given ezetimibe 10 mg or placebo daily for 11 days, with a single 25-mg dose of **warfarin** on day 7. The pharmacokinetics and pharmacodynamics (prothrombin time) of **warfarin** were not significantly altered by ezetimibe. In addition, the pharmacokinetics of ezetimibe were similar to those previously seen with the drug alone.[1]

However, the UK manufacturers of ezetimibe state that there have been post-marketing reports of raised INRs in patients taking **warfarin** or **fluindione** after they were also given ezetimibe. They therefore advise that the INR should be monitored if ezetimibe is given with any coumarin or **fluindione**[2] (this is probably a prudent precaution for any **indanedione**), and the US manufacturer states the same for **warfarin**.[3] Neverthe-

less, there do not appear to be any published case reports, or other evidence, which suggests that any interaction is not established, and probably rare.

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3. Zetia (Ezetimibe). Merck/Schering-Plough Pharmaceuticals. US Prescribing information, July 2009.

Coumarins + Felbamate

An isolated case report describes a marked increase in the effect of warfarin, which was attributed to starting felbamate, although stopping carbamazepine and phenobarbital could have been the cause.

Clinical evidence, mechanism, importance and management

A 62-year-old man with a seizure disorder who was receiving **warfarin** had his antiepileptic treatment with carbamazepine, phenobarbital and sodium valproate discontinued and replaced by felbamate 2.4 g daily and later 3.2 g daily. Within 14 days his INR had risen from his usual range of 2.5 to 3.5 up to 7.8. After stopping and later restarting **warfarin** his INR rose within about 14 days to 18.2. He was eventually restabilised on about half his former **warfarin** dose. The authors of the report suggest that the withdrawal of the carbamazepine and phenobarbital was an unlikely reason for this reaction because no increases in **warfarin** dose had been needed when they were started.[1] Suspicion therefore fell on the felbamate, but it is clearly difficult to be sure that the withdrawal of the enzyme-inducing antiepileptics did not have some part to play. A letter commenting on this report[2] favours the idea that what occurred was in fact due to the withdrawal of the carbamazepine (see 'Coumarins + Carbamazepine or Oxcarbazepine', p.446), and phenobarbital (see 'Coumarins + Barbiturates', p.440).

The general importance of this interaction (if such it is) is uncertain, and this appears to be the only case. Bear it in mind in the event of an unexpected response to **warfarin**.

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Coumarins and related drugs + Fibrates

Bezafibrate, clofibrate, ciprofibrate and fenofibrate increase the effects of the coumarins, and clofibrate also interacts with phenindione. These interactions have been fatal in a few cases. Gemfibrozil did not interact with warfarin in a controlled study, although two cases of an interaction have been reported.

Clinical evidence

(a) Bezafibrate

In a study in patients with hyperlipidaemia, stabilised on **phenprocoumon**, it was necessary to reduce the anticoagulant dose by about 20% when bezafibrate 450 mg daily was given to 10 patients for 4 weeks, and by 33% when bezafibrate 600 mg daily was given to 5 patients.[1] In another study in 22 patients taking bezafibrate 400 mg daily, the dose of **acenocoumarol** had to be reduced by 20% to maintain a constant INR.[2]

A patient (with hypoalbuminaemia due to nephrotic syndrome and chronic renal failure) stabilised on **acenocoumarol** developed severe haematemesis with an INR of 25.9, two weeks after starting to take bezafibrate 800 mg daily.[3] A woman stabilised on **warfarin** and bezafibrate 400 mg daily had an increase in her INR to 5.29 after being given an incorrect double dose of bezafibrate for a few days, and a man had a reduced response to **warfarin** (INR 1.5) when he stopped taking bezafibrate for one week.[4]

(b) Ciprofibrate

In a well-controlled study, 12 young healthy men were given a single 25-mg dose of **warfarin** on day 21 of a 26-day course of ciprofibrate 100 mg daily. The ciprofibrate increased the anticoagulant response to **warfarin** by 50% and caused a 28% decrease in the apparent intrinsic clearance of *S*-warfarin, which is the more active enantiomer.[5]

(c) Clofibrate

1. Coumarins. In a study including 11 patients stabilised on **warfarin**, clofibrate with androsterone (*Atromid*), given for 5 to 7 months, reduced the weekly **warfarin** dose requirement in all patients by a mean of 32%, with variability between patients.[6,7] This interaction has been confirmed in a number of other similar studies in patients stabilised on **warfarin** and given clofibrate,[8,9] or clofibrate with androsterone,[10] with only 2 of 10 patients affected in one study[8] but all 13 patients affected in another study.[10] One fatal case of haemorrhage has been reported in a man stabilised on **warfarin** who was given clofibrate 500 mg four times daily for one week.[11]

The interaction has been studied in 4 healthy subjects given the enantiomers of **warfarin** separately. In this study, clofibrate increased the effect of *S*-warfarin without altering its clearance, whereas there was no alteration of the effect of *R*-warfarin and an increase in its clearance.[12] In another study in 10 healthy subjects, clofibrate 500 mg four times daily for 18 days increased the anticoagulant effect of a single dose of **dicoumarol** given on day 14 without altering the half-life or plasma **dicoumarol** levels.[13]

2. Indanediones. Ten out of 15 patients stabilised on **phenindione** needed a 33% reduction in **phenindione** dose and 5 of them bled (haematuria or haematoma) when they were given clofibrate, or clofibrate with androsterone (*Atromid*).[7] In another series, of 13 patients stabilised on **phenindione** and given clofibrate with androsterone (*Atromid*) there were 5 cases of haemorrhagic episodes, two of which were not associated with a prolonged prothrombin time, and one of which was fatal.[14,15] In yet another study, clofibrate with androsterone appeared to be less effective in reducing serum cholesterol in patients taking **phenindione** than in 12 other patients taking clofibrate alone.[16]

(d) Fenofibrate

In an early clinical study of fenofibrate, 2 patients stabilised on **acenocoumarol** needed a 30% reduction in their dose to maintain the same prothrombin time when they were given long-term fenofibrate 200 mg in the morning and 100 mg in the evening.[17] In other similar studies, reductions in the dose of unnamed **coumarins** of 12% (range 0 to 21%)[18] or about one-third[19] were needed when fenofibrate was given. One patient developed haematuria.[20]

A number of case reports of this interaction have subsequently been published, as follows:

- A patient taking **warfarin** had a rise in his INR to 8.5 (from a previous range of 2 to 2.5) within one week of starting to take fenofibrate 200 mg daily. His INR later restabilised when the **warfarin** dose was reduced by 27%.
- A patient taking **warfarin** had a marked INR rise from a range of 2.8 to 3.5 up to 5.6 within 10 days of starting to take fenofibrate (dose not stated).[21]
- A patient taking **warfarin** bled, and was found to have an INR of 18 when his gemfibrozil was replaced by fenofibrate.[22]
- In 2 cases, 30 to 40% reductions in the **warfarin** dose were required when fenofibrate was given.[23]

(e) Gemfibrozil

In a well-controlled study, gemfibrozil 600 mg twice daily for 8 days did not alter the anticoagulant effect of a single dose of **warfarin** given on day 3. In addition, gemfibrozil unexpectedly slightly decreased the AUC of both *R*- and *S*-warfarin (by 6% and 11%, respectively).[24] In contrast, a brief report describes bleeding ('menstrual cycle prolonged and lots of blood clots') and much higher prothrombin times (values not given) 2 weeks after a woman stabilised on **warfarin** started to take gemfibrozil 1.2 g daily in divided doses. Halving the **warfarin** dose resolved the problem.[25] Another patient stabilised on **warfarin** developed severe hypoprothrombinaemia (INR 43) and bleeding (melaena, bruising) 4 weeks after starting to take gemfibrozil 1.2 g daily.[26]

Mechanism

Uncertain. Clofibrate can displace warfarin from its plasma protein binding sites,[5,27-29] but this does not adequately explain the interaction. Another suggestion is that the fibrates have an additive pharmacodynamic effect with these anticoagulants.[1,12] Altered metabolism may also account for the

interaction with ciprofibrate, because it decreased the clearance of *S*-warfarin.[5] However, this did not occur with clofibrate[12,13] or gemfibrozil.[24]

Importance and management

The interactions of clofibrate with dicoumarol, warfarin and phenindione are established, clinically important and potentially serious. Severe bleeding (fatal in some instances) has been seen. The incidence of the interaction is reported to be between 20% and 100%, but it would be prudent to assume that all patients will be affected. Coumarin dose reductions of one-third to one-half may be needed to avoid the risk of bleeding. Monitor the INR and adjust the dose accordingly. Information about other coumarins and indanediones is lacking but it would be prudent to assume that they will interact with clofibrate in a similar way.

Bezafibrate, ciprofibrate and fenofibrate have interacted similarly with coumarins. Therefore, the same precautions suggested for clofibrate should be followed if any of these fibrates are given with any oral anticoagulant.

Gemfibrozil did not interact with warfarin in a pharmacological study, but 2 cases of an increased effect of warfarin have been reported, so it might be prudent to apply the same precautions.

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Coumarins + Fish oils

The concurrent use of fish oils does not appear to alter warfarin efficacy, nor the incidence of bleeding episodes. However, there are a couple of reports of an increased INR in patients taking warfarin and fish oils, and one of a life-threatening bleed without an increase in INR in a patient taking high-dose fish oils with aspirin and warfarin.

Clinical evidence

In one early study, 40 patients took 4 g of a fish oil preparation daily for 4 weeks, and 18 of these patients were taking **warfarin**. In the group as a whole (40 patients), the bleeding time was significantly prolonged from 240 seconds to 270 seconds. In the subset of patients taking **warfarin** who had stable anticoagulant control in the preceding 3 months (15 patients), the thrombotest was shortened from 114 seconds to 90 seconds, although no changes in **warfarin** dose were made. One patient taking **warfarin** had a minor nosebleed.[1] In a large randomised study of the effect of fish oils or placebo, taken with either aspirin or **warfarin** over 9 months, there was no difference in the frequency of bleeding episodes between 132 patients taking **warfarin** and fish oil 4 g daily and 154 patients taking **warfarin** alone (17 versus 14, respectively).[2] In yet another small controlled study in 6 patients, the use of fish oil 3 g or 6 g daily for 4 weeks did not alter the INR in patients receiving stable **warfarin** therapy.[3]

Two cases of a possible interaction with a rise in INR have been reported. In one, a woman had INRs in the range of 2 to 3 for five months while taking **warfarin** 1.5 mg and 1 mg on alternate days. During this time, she started taking 1 g of a fish oil preparation daily with no change in her INR. Her **warfarin** was then increased to 1.5 mg daily, with stable INRs for about 5 months. A routine INR was then found to be 4.3 (raised from 2.8 one month earlier). One week previously, she had started to take fish oil 2 g daily (double the previous dose). The dose of **warfarin** was reduced to 1.5 mg and 1 mg on alternate days, and she was asked to reduce the fish oil back to 1 g daily. Eight days later her INR was 1.6, and the **warfarin** was increased back to 1.5 mg daily.[4] In another case, a rise in INR from between 2 and 3 up to 6, without bleeding complications, occurred 2 weeks after a patient started taking fish oil 2 g daily and trazodone 50 mg daily.[5]

In yet another report, a subdural haematoma developed after a minor fall in an elderly patient stabilised on **warfarin** and low-dose aspirin who had been taking omega-3 fatty acids 6 g daily for a year. His INR was only very slightly elevated at the time (3.2 compared with 2.8 previously).[6] Note that use of low-dose aspirin with **warfarin** increases the risk of bleeding, see 'Coumarins and related drugs + Aspirin or other Salicylates', p.434.

Mechanism

Fish oils contain omega-3 fatty acids particularly **eicosapentaenoic acid** and **docosahexaenoic acid**. These are considered to have some antiplatelet activity, and may prolong the bleeding time. In addition, they might reduce levels of some coagulation factors. They might therefore increase the risk of bleeding when used with warfarin, similarly to antiplatelet doses of aspirin (see 'Coumarins and related drugs + Aspirin or other Salicylates', p.434), but this would not be expected to alter the INR.

Importance and management

An interaction between warfarin and fish oils is not established. One large study found no increase in bleeding episodes in over 150 patients taking warfarin and fish oils, suggesting that most patients do not develop an interaction. Nevertheless, a much larger study would be needed to quantify any excess risk in the order of that seen with antiplatelet doses of aspirin. Based on the possible moderate increase in bleeding times with high-dose fish oils, the manufacturers of one product, *Omacor* (omega-3-acid ethyl esters), say that although there have been no reports of haemorrhage with concurrent use, patients receiving anticoagulants should be monitored, and the dose of anticoagulant adjusted as necessary.[7] However, monitoring the INR would not pick up a pharmacodynamic interaction.

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Coumarins + Fluorouracil and related prodrugs

Fluorouracil markedly increases the anticoagulant effects of warfarin, and cases of serious bleeding have been reported. The fluorouracil prodrugs capecitabine and tegafur appear to interact similarly.

Clinical evidence

(a) Capecitabine

In an open study, 4 patients with breast or colorectal cancer received a single 20-mg dose of **warfarin** 8 days before starting oral capecitabine (3 cycles of capecitabine 1250 mg/m^2 twice daily for 14 days, then 7 days rest), then again on day 12 of the third cycle of capecitabine. Capecitabine increased the AUC of *S*-warfarin by 57%, and increased its elimination half-life by 51%, without any significant changes to *R*-warfarin. The maximum INR was increased by 90% and the AUC of the INR increased 2.8-fold. Three of the patients required vitamin K. Because of the clear, statistically significant findings in these 4 patients, the study was terminated early.[1]

Various cases of this interaction have been reported.[2-6] In one of these reports, 2 patients starting **warfarin** developed gastrointestinal bleeding with an INR of greater than 10, after 2 cycles of capecitabine.[2] In another case, a patient who had been taking long-term **warfarin** required a gradual 85% reduction in the warfarin dose to 0.78 mg daily over 3 cycles of capecitabine and **irinotecan**, and required an increase to 4 mg daily over the 3 weeks after stopping chemotherapy.[4] Another patient required a 50% reduction in the **warfarin** dose while taking capecitabine. In addition, in a retrospective analysis of 21 patients who received **warfarin** with capecitabine, 6 patients required a warfarin dose reduction, and there were 4 episodes of major bleeding.[7] Conversely, in another analysis, there was not that much difference in rates of bleeding events and elevated INRs between patients receiving warfarin with capecitabine and those receiving warfarin alone, although the authors concluded that this might just reflect appropriate management of the interaction.[8]

The manufacturers of **capecitabine** also report that this interaction has occurred with other coumarins including **phenprocoumon**,[9,10] and that some cases have been fatal.[10]

(b) Fluorouracil and fluorouracil-based regimens

In an early clinical study, 25 patients with colon cancer were given bolus fluorouracil 15 to 20 mg/kg weekly and **warfarin** daily, titrated to maintain the prothrombin time in the 20 to 30% range, and modified weekly as necessary. Three patients developed blood loss from the gut, which was controlled by giving a transfusion (type unnamed) and stopping the **warfarin**. This study did not report the required dose of warfarin, or how often it needed adjusting in these patients.[11]

Various case reports have described clinically important over-anticoagulation with the concurrent use of dose-adjusted **warfarin** (for treatment of deep vein thrombosis, or in patients with prosthetic heart valves) and fluorouracil, either alone,[12,13] with folinic acid (leucovorin),[14-17] or levamisole.[15,18,19] In one well-described case, an elderly man taking **warfarin** long-term was found to have an INR of almost 40 (usual INR 3) four weeks after he started taking fluorouracil (450 mg/m^2 daily for 5 days then once weekly) and **levamisole** (50 mg every 8 hours for 3 days every other week). He required a two-thirds reduction in his **warfarin** dose. Later, when the chemotherapy was withheld for 5 weeks his INR became subtherapeutic, and then increased again when the chemotherapy was restarted.[18] In another retrospective case series, 4 patients taking **warfarin** long-term (target INR 2 to 3) required an 18 to 74% reduction in their **warfarin** dose during the use of fluorouracil and **folinic acid** or **levamisole**. The maximum INR in 3 of these patients was 3.66 to 8.15, and the other patient had a maximum INR of 23.7 and a retroperitoneal bleed.[15]

Other cases of over-anticoagulation have been reported with **warfarin** and fluorouracil-based regimens including CMF (**cyclophosphamide**, **methotrexate** and fluorouracil),[15,20,21] CMF plus **vincristine** and prednisone,[22] fluorouracil, **cisplatin** and **etoposide**,[23] and fluorouracil, **cisplatin** and **mitomycin**.[13]

A case has also been reported with the use of fixed-dose **warfarin** (1 mg daily) for prophylaxis of venous catheter-associated thrombosis in a patient receiving fluorouracil with **vinblastine**.[24] Similarly, in a large retrospective analysis of fixed dose **warfarin**, 31 of 95 patients given regimens based on continuous infusions of **fluorouracil** had INR elevations above 1.5, and, of these, 18 had an INR of 3 to 4.9 and seven had an INR of more than 5. Epistaxis and haematuria occurred in 8 of the patients. The regimens used were fluorouracil plus **folinic acid**; folinic acid, fluorouracil and **oxaliplatin** (FOLFOX); and folinic acid, fluorouracil and **irinotecan** (FOLFIRI).[25] In a further analysis of the use of fixed dose **warfarin** with the FOLFOX regimen, 25 of 50 patients had an INR greater than 1.5 (range 1.55 to 9.4). Two of these developed haematuria, and one had a nosebleed.[26]

(c) Tegafur

Increased INRs and bleeding (haemoptysis) were seen in a patient taking **warfarin** when *Orzel* (uracil with tegafur in a 4:1 molar ratio) was given, and a 63% reduction in the warfarin dose was needed.[27] The manufacturers of *Uftoral* (tegafur with uracil) also say that marked elevations in prothrombin times and INRs have been reported in patients taking **warfarin** when *Uftoral* was added.[28]

Mechanism

Uncertain. However, in a pharmacokinetic study in *rats*, fluorouracil significantly reduced the total clearance of *S*-warfarin by inhibiting its metabolism.[29] In addition, in a small clinical study, fluorouracil inhibited the metabolism of losartan, used as a probe substrate for the cytochrome P450 isoenzyme CYP2C9 (see 'Angiotensin II receptor antagonists; Losartan + Fluorouracil', p.44).[30] This suggests that fluorouracil possibly inhibits warfarin metabolism via CYP2C9 resulting in increased anticoagulant effects. Fluorouracil prodrugs such as capecitabine and tegafur would be expected to interact by the same mechanism.

Importance and management

Fairly well-documented and established interactions of clinical importance. Prothrombin times should be more frequently monitored in patients taking warfarin and other **coumarins** and requiring fluorouracil, capecitabine, tegafur or other fluorouracil pro-drugs, anticipating the need to reduce the warfarin dose. Note that, from a disease perspective, when treating venous thromboembolic disease in patients with cancer, warfarin is generally inferior (higher risk of major bleeds and recurrent thrombosis) to low-molecular-weight heparins.[31]

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Coumarins + Flupirtine

Flupirtine does not appear to interact with phenprocoumon.

Clinical evidence, mechanism, importance and management

Twelve healthy subjects had no significant changes in their plasma levels of **phenprocoumon** 1.5 mg daily when they were given flupirtine 100 mg three times daily for 14 days. The prothrombin times were also not significantly changed.[1] Therefore, **phenprocoumon** dose adjustments would not be expected to be needed if these drugs are given concurrently.

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Coumarins + Fondaparinux

Warfarin does not alter the pharmacokinetics of fondaparinux, and fondaparinux does not alter the effect of warfarin on prothrombin time.

Clinical evidence, mechanism, importance and management

In a placebo-controlled study, 12 healthy subjects were given subcutaneous fondaparinux 4 mg daily for 5 days, with warfarin 15 mg given on day 4 and 10 mg on day 5. Warfarin had no effect on fondaparinux pharmacokinetics. In addition, the effect of warfarin on prothrombin time was not altered by fondaparinux.[1]

Fondaparinux is an anticoagulant that is an indirect inhibitor of activated factor Xa, and it is sometimes used as a 'bridge' to oral anticoagulation. The findings of this study show that the prothrombin time (INR) can still be used to monitor the effect of coumarin anticoagulants during the switch from fondaparinux to oral anticoagulants.

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Coumarins + Food

The rate of absorption of dicoumarol can be increased by food. Three patients had modest increases in warfarin requirements after starting high-protein, low-carbohydrate diets.

Clinical evidence and mechanism

(a) Dicoumarol

A study in 10 healthy subjects found that the peak serum concentrations of a single 250-mg dose of dicoumarol, were increased on average by 85% by food. Two subjects had increases of 242% and 206%, respectively.[1] Food might cause prolonged retention of dicoumarol in the upper part of the gut, leading to increased tablet dissolution and increased absorption.

(b) Warfarin

One report describes two patients who had well-documented decreases in INR values with modest increases in warfarin requirements (22% and 30%) after switching to high-protein, low-carbohydrate diets (the *Atkins* diet and the *South Beach* diet). On stopping these diets, both patients were eventually restabilised on their original warfarin doses.[2] Another similar case of a 16% increase in warfarin requirement has been reported.[3]

The mechanism for these cases is unknown, but suggested reasons include an increase in albumin with increased protein intake (leading to increased warfarin binding), an induction of cytochrome P450 isoenzymes with increased protein intake (increasing warfarin clearance), or increased intake of dietary vitamin-K, or a combination of these mechanisms.[4]

Importance and management

None of these interactions are very well documented, and their clinical relevance is unclear. Nevertheless, any big changes in diet have the potential to alter the effects of warfarin on the INR, and it would therefore be prudent to increase monitoring in patients wishing to start a diet. Note that vitamin K in food commonly interacts with warfarin, and these interactions are discussed in 'Coumarins and related drugs + Food; Vitamin K_1-rich', p.464.

Other food substances are discussed in their own monographs. Consider also:

- 'Coumarins + Cranberry juice', p.451,
- 'Coumarins and related drugs + Food; Enteral and parenteral nutrition', see below,
- 'Coumarins + Grapefruit juice', p.469,
- 'Coumarins + Food; Ice cream', p.463,
- 'Coumarins + Food; Mango fruit', p.463,
- 'Coumarins + Quinine', p.501, for tonic water,
- 'Coumarins + Food; Soya bean products', p.463,
- 'Coumarins + Sucrose polyesters', p.510, for additives in potato crisps.

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Coumarins and related drugs + Food; Enteral and parenteral nutrition

A number of early case reports described warfarin resistance in patients taking enteral feeds that contained high levels of added vitamin K_1. However, products with a lower vitamin K_1 content have also been reported to interact. Lipid emulsions containing soya oil might contain sufficient natural vitamin K_1 to alter warfarin requirements. Parenteral multivitamin preparations may also contain vitamin K_1.

Clinical evidence

A. Enteral feeds

Case reports from the early 1980s described patients stabilised on **warfarin** who had reversal of the anticoagulant effect when they started taking the liquid dietary supplements *Ensure*,[1,2] or *Osmolite*.[3] Other patients who were resistant to **warfarin** were found to be taking *Ensure*[4] or *Ensure Plus*.[5,6] At this time, these products contained high levels of vitamin K_1 (240 to 380 micrograms per 240 or 250 mL, an amount equivalent to approximately 1 mg of vitamin K_1 for every 1 000 calories). Two of the patients were successfully anticoagulated with **warfarin** when their enteral nutrition was switched to *Compleat B* (vitamin K_1 16.6 micrograms/250 mL)[6] or *Meritene* (trace of vitamin K_1).[4] In response to these reports, *Ensure*, *Ensure-Plus*, and *Osmolite* were reformulated to reduce the vitamin K_1 content to 50 micrograms in 240 mL (140 micrograms per 1000 calories).[4] However, further case reports for *Ensure Plus*[7] and *Osmolite*[8] suggested that this lower level of vitamin K may still be sufficient to cause an interaction. The vitamin K_1 content of these products was reduced further to 36 to 37 micrograms per 1000 calories,[9] but even then one further case of increased **warfarin** requirement was reported with *Ensure*.[10] In another case, a patient taking *Osmolite* and intermittent *Ensure Plus* (total mean vitamin K_1 dose

81 micrograms daily) only achieved satisfactory anticoagulation with **warfarin** when the *Osmolite* was stopped, which reduced the vitamin K_1 intake to 36 micrograms daily.[11] Another patient given *Osmolite* (vitamin K_1 68.4 micrograms daily), only achieved satisfactory anticoagulation with **warfarin** when the dose was given separately from the *Osmolite*.[12]

In another case, *Isocal* 3550 mL daily (equivalent to 460 micrograms of vitamin K_1) caused an increase in **warfarin** requirement from 8 mg daily to 13 mg daily.[13] A further patient had a decrease in anticoagulant response requiring an increase in **warfarin** dose when she started a weight-reducing diet consisting solely of *Nutrilite 330* (vitamin K content unknown).[14] Another patient required twice the dose of **acenocoumarol** during a period of enteral feeding (vitamin K_1 200 micrograms daily).[15]

Isocal and *Sustacal* have also been implicated in cases of **warfarin** resistance in a further report, which attributed the mechanism to binding of the **warfarin** to protein in the enteral feed.[16] This suggested mechanism appears to be supported by a study in 6 patients that found a small increase in INR of 0.74 when continuous enteral feeding was withheld for one hour before and after warfarin administration, although the mean daily dose of **warfarin** did not significantly differ. However, note that there was also a small difference in vitamin K intake of 25 micrograms daily less during the period of separation of administration.[17]

In a prospective cohort study in 319 children, the use of enteral nutrition (mostly vitamin K supplemented formula, and some vitamin K supplemented tube feeds) was associated with a higher dose of **warfarin** to achieve a target INR (0.28 versus 0.16 mg/kg) and similarly a higher dose of **warfarin** was needed to maintain the INR (0.26 versus 0.11 mg/kg).[18]

B. Parenteral nutrition

(a) Intravenous lipids

Warfarin resistance was seen in a patient who was given a constant intravenous infusion of **soya oil emulsion** (*Intralipid*). In this case intravenous **warfarin** up to 15 mg daily only slightly prolonged the prothrombin time.[19] In another patient, an emulsified infusion of **propofol** containing 10% **soya oil** antagonised the effect of **warfarin**; anticoagulation was not achieved until the **propofol** was discontinued despite an increase in the **warfarin** dose to 30 mg daily. The dose of propofol given was estimated to provide about 154 to 231 micrograms of vitamin K_1 daily. The same effect was later see when the patient was given parenteral nutrition supplemented with 20% *Liposyn II*, which also contains **soya oil**, and was estimated to provide 53 micrograms of vitamin K_1 daily.[20]

(b) Multivitamins

The FDA in the US now requires that multivitamin products for inclusion in total parenteral nutrition contain 150 micrograms of vitamin K_1. The aim of this is to provide a daily physiological amount of the vitamin, rather than the previous practice of giving a large single weekly dose. Previously, patients taking anticoagulants were not given this single large weekly dose, therefore it is anticipated that with the new multivitamin preparation, **warfarin** doses for anticoagulation may be higher than previously needed. What effect this level of vitamin K_1 will have on the fixed-dose **warfarin** used for prophylaxis of catheter-associated thrombosis is not known.[21] In the UK, *Vitlipid N* contains vitamin K_1 (phytomenadione) 15 micrograms/mL for adults and 20 micrograms/mL for children under 11 years.

Mechanism

The coumarin and **indanedione** anticoagulants are vitamin K antagonists, and consequently giving vitamin K_1 reduces their effects. The dose at which this might become clinically important is not firmly established, but in one controlled study 150 micrograms of vitamin K_1 daily produced a clinically relevant effect in 25% of subjects (see 'Vitamin K_1-containing dietary supplements', (p.520)). There is also some evidence that a physicochemical interaction (possibly binding to protein) may occur between warfarin and enteral foods in the gut.[12,16] See also 'Coumarins + Food', p.461, for mention that high-protein diets appear to increase warfarin requirements.

Lipid emulsions given as part of parenteral nutrition often contain soya oil, which has a moderate level of vitamin K (see 'Table 12.3', (below)). These preparations may also have direct coagulation effects.[20] Parenteral nutrition may also be supplemented with vitamin K.

Table 12.3 Foods with a moderate to high content of Vitamin K_1 (phytomenadione)

Foods	*Vitamin K_1 content (micrograms/100 g)*
Vegetables	
Asparagus	51 to 80
Beet greens	484
Broccoli	101 to 156
Brussels sprouts	122 to 289
Cabbage	50 to 98
Collards (non-heading cabbage)	440 to 623
Endive	231
Kale	817 to 882
Kelp seaweed	66
Lettuce (iceberg to green leaf)	24 to 174
Parsley (fresh or dried)	360 to 1640
Spinach	270 to 575
Spring onions	207
Turnip greens	367 to 519
Fats and oils	
Soya oil	25 to 145
Rapeseed oil	112 to 150
Olive oil	30 to 60
Margarines	40 to 110
Fruit and nuts	
Avocado	14 to 20
Cashew nuts	19 to 64
Kiwi fruit	25 to 40
Pine nuts	33 to 74
Prunes, dried	1.4 to 68

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Importance and management

Established interactions of clinical importance. Be aware that enteral feeds might contain sufficient vitamin K to alter coagulation status, so starting or stopping these feeds might affect dose requirements of vitamin K

antagonists such as warfarin. It is also possible that there is a local interaction in the gut, as in one case separating the administration of the warfarin and an enteral feed by 3 hours or more was effective,[12] and in another study withholding the enteral feed for one hour before and after warfarin administration slightly reduced the effect of any interaction.[17] Patients should be advised not to add or substitute dietary supplements such as *Ensure* without increased monitoring of their coagulation status. A consistent dose administration time is recommended, such as during the usual break in the feeding regimen, to minimise any possible interaction.[22]

Fat emulsions used for parenteral use containing soya oil may themselves contain sufficient vitamin K_1 for daily needs. Parenteral multivitamin preparations may also contain important levels of vitamin K_1. It would be advisable to keep the vitamin K_1 intake constant in any patient requiring long-term supplemental or total parenteral nutrition and warfarin. If the amount of lipid and/or multivitamins is altered, anticipate a change in warfarin requirement.

Although there is only a single case, bear in mind that propofol may interact because it is formulated with soya oil, which contains vitamin K_1.

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Coumarins + Food; Ice cream

Two isolated reports describe antagonism of the effects of warfarin by ice cream.

Clinical evidence, mechanism and importance and management

A woman taking **warfarin** 22.5 mg daily did not have the expected prolongation of her prothrombin time. It was then discovered that she took the **warfarin** in the evening and she always ate ice cream before going to bed. When the **warfarin** was taken in the mornings, the prothrombin time increased.[1] Another patient's **warfarin** requirements almost doubled when she started to eat very large quantities of ice cream (one litre each evening). She took the **warfarin** at 6 pm and ate the ice cream at about 10 pm.[2] The effect was not seen when she ate normal amounts of ice cream (3 or 4 normal size portions weekly).

The reason for these isolated cases is unknown. Vitamin K in food commonly interacts with warfarin (see 'Coumarins and related drugs + Food; Vitamin K_1-rich', p.464), but ice cream does not contain important amounts of this vitamin. Given the rarity of reports, it would appear very unlikely that eating ice cream as part of a normal diet will have any effect on INR. However, be aware that any big changes in diet have the potential to alter the INR in response to **warfarin**. Consider also 'Coumarins + Food', p.461.

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Coumarins + Food; Mango fruit

A daily intake of one to six mangoes was considered the reason for a moderate increase in the anticoagulant effects of warfarin in one report. None of the patients in whom this interaction was seen showed any evidence of bleeding.

Clinical evidence, mechanism, importance and management

In 13 patients taking **warfarin**, eating mango fruit appeared to increase their INRs by an average of 38% (from 2.79 to 3.85), but no bleeding occurred. No other explanation for the increased INRs could be identified. The patients were reported to have eaten one to 6 mangoes daily for 2 days to one month before attending the anticoagulant clinic. When mango was identified as a possible cause for their increased INRs, the patients were told to stop eating mango, whereupon their mean INR fell within 2 weeks, by almost 18%. When two of the patients whose mean INRs had originally risen by 13% were later rechallenged with mango (rather less than before), their mean INR rose by 9%.[1]

The reason for this apparent interaction is not known, but the authors of the report speculate about the possible role of vitamin A (reported to be 8061 units in an average sized mango of 130 g, without seed). In practical terms this increase in INR would not seem to represent a serious problem, although note that one patient's INR rose to 5.1 (a 54% increase).

There appear to be no other reports in the literature of an interaction between mango and **warfarin**, nor of interactions between mango and any other oral anticoagulant. More study of this interaction is needed, but at the present time there is insufficient reason to suggest that patients taking **warfarin** should avoid mango fruit.

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Coumarins + Food; Soya bean products

Natto, a Japanese food made from fermented soya bean, can markedly reduce the effects of warfarin and acenocoumarol, because of the high levels of vitamin K_2 substance produced in the fermentation process. In one study, soya bean protein also modestly reduced the effects of warfarin, and a similar case has been reported with soy milk. Two cases of 'warfarin resistance' have been seen in patients given intravenous soya oil emulsions.

Clinical evidence

(a) Fermented soya bean products (natto)

In a controlled study in 12 healthy subjects stabilised on **acenocoumarol**, a single meal containing 100 g of natto decreased the mean INR from 2.1 to 1.5 after 24 hours, and the INR had still not returned to the original level after 7 days (INR 1.75 one week later). The effect was considered clinically important in 6 of the 12 subjects.[1] Similarly, in an earlier retrospective study in 10 patients taking **warfarin**, eating natto caused the thrombotest values to rise from a range of 12 to 29% up to a range of 33 to 100%. The extent of the rise appeared to be related to the amount of natto eaten. The thrombotest values fell again when the natto was stopped. A healthy subject taking **warfarin**, with a thrombotest value of 40%, ate 100 g of natto. Five hours later the thrombotest value was unchanged, but 24 hours later it was 86%, and after 48 hours it was 90% (suggesting that the anticoagulant effect was decreased).[2]

(b) Soya milk

In a 70-year-old man stabilised on **warfarin** 3 mg daily, consumption of soya milk 480 mL daily (240 mL of both *Sun Soy* and *8th Continent* mixed together) decreased the INR from 2.5 to 1.6 after about 4 weeks.[3] One week after stopping the soya milk, his INR was 1.9, and 4 weeks after it was 2.5.

(c) Soya oil

Soya oil is an important source of dietary vitamin K, see 'Table 12.3', (p.462). For two cases of 'warfarin resistance' with intravenous soya oil emulsions, see 'Coumarins and related drugs + Food; Enteral and parenteral nutrition', p.461.

(d) Soya protein

In a study in 10 patients with hypercholesterolaemia who were stabilised on **warfarin**, substitution of all animal protein for textured **soya protein** for 4 weeks caused a marked reduction (Quick value approximately doubled) in the anticoagulant effects of warfarin by the second week.[4]

Mechanism

Soya beans are a moderate source of vitamin K_1 (19 micrograms per 100 g),[5] and soya oil and products derived from it are an important dietary source of vitamin K. However, the soy milk brand taken in the case report did not contain vitamin K,[3] and another reference source lists soya milk as containing just 7.5 micrograms vitamin K per 250 mL,[5] which would not be expected to cause an interaction. Why this product decreased the effect of warfarin is therefore open to speculation.

The vitamin K content of textured soya protein is unknown. Note that **soy sauce** made from soya and wheat is reported to contain no vitamin K, and soft **tofu** made from the curds by coagulating soya milk contains only low levels (2 micrograms per 100 g).[5]

In contrast, fermented soya bean products such as natto contain very high levels of a particular vitamin K_2 substance (MK-7)[6], because of the fermentation process with *Bacillus natto*. In addition, the bacteria might continue to act in the gut to increase the synthesis and subsequent absorption of vitamin K_2.[2] Although the role of vitamin K_2 in anticoagulation is less well established than vitamin K_1, it appears that this also opposes the actions of coumarins and indanediones, which are vitamin K antagonists.

Importance and management

The interaction between warfarin and fermented soya bean products is established, marked, and is likely to be clinically relevant in all patients. Patients taking coumarin and probably **indanedione** anticoagulants should probably be advised to avoid natto, unless they want to consume a regular, constant amount.

Although information is limited, it appears that soya protein might also modestly reduce the effect of warfarin. In particular, complete substitution of animal protein for soya protein appears to reduce the effect of warfarin. A single report suggests that soy milk may also interact. Case reports suggest that soya milk and soya oil may also interact, and therefore some caution would be prudent with these products. On the basis of known vitamin K-content, **whole soya beans** could potentially reduce the effect of warfarin, whereas **soy sauce** should not.[5] Note that patients taking coumarins and **indanediones** are advised to have their INR checked if they markedly change their diet. This would seem particularly important if they decide to change their intake of soya-related products.

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Coumarins and related drugs + Food; Vitamin K_1-rich

Unintentional and unwanted antagonism of warfarin has occurred in patients who ate exceptionally large amounts of some green vegetables, which can contain significant amounts of vitamin K_1. Isolated cases have also been reported with avocado, green tea (very large quantities), liver, and seaweed sushi. Foods containing significant amounts of vitamin K_2 substances such as fermented soya beans might also interact.

Clinical evidence and mechanism

The coumarin and indanedione oral anticoagulants are vitamin K antagonists, which inhibit the enzyme vitamin K epoxide reductase so reducing the synthesis of vitamin K-dependent blood clotting factors by the liver. If the intake of dietary vitamin K_1 increases, the synthesis of the blood clotting factors begins to return to normal. As a result the prothrombin time also begins to fall to its normal value. Naturally occurring vitamin K_1 (phytomenadione) is found only in plants.

A. Individual foodstuffs

(a) Avocado

Two women taking **warfarin** had a reduction in their INRs (from 2.5 to 1.7 and from 2.7 to 1.6, respectively) when they started to eat avocado 100 g daily, or 200 g of avocado on two consecutive days. Their INRs climbed again when the avocado was stopped.[1] Avocado contains a small to moderate amount of vitamin K_1, see 'Table 12.3', (p.462), so might occasionally reduce the efficacy of **warfarin** if eaten in these quantities.

(b) Green tea

A patient taking **warfarin** had a reduction in his INR from a range of 3.2 to 3.79 down to 1.37, which was attributed to the ingestion of very large quantities of green tea (about 2 to 4 litres each day for a week). This interaction was attributed to the vitamin-K content of the tea.[2] However, although dried tea, including green tea, is very high in vitamin-K_1, the brewed liquid made from the tea contains negligible amounts of vitamin K_1 (which is a fat-soluble vitamin),[1,3] and is therefore not considered to contribute any vitamin K_1 to the diet.[3] The reason for this interaction is therefore unclear, unless the patient was eating some of the brewed tea leaves. A pharmacokinetic interaction also appears unlikely, because, although black tea inhibited the cytochrome P450 isoenzyme CYP2C9 *in vitro*, brewed tea had no effect on the CYP2C9 substrate flurbiprofen in healthy subjects.[4] CYP2C9 is important in the metabolism of the more potent *S*-warfarin. For discussion of a case where a patient had an increase in INR after stopping taking a herbal preparation of which green tea leaves were one of 25 ingredients, see 'Coumarins + Vitamin K_1-rich herbal medicines', p.521.

(c) Green vegetables

In a formal study in patients stabilised on **warfarin**, one day of a high intake of vitamin K_1-rich vegetables (**brussels sprouts** 400 g, **broccoli** 400 g, **lettuce** 750 g, or **spinach** 300 g, estimated to contain 1 mg of vitamin K_1 daily) decreased anticoagulant effects: the thrombotest values rose above the normal range of 10 to 25% in 2 of 5 patients in 2 to 3 days. Two days of a high intake of the same vegetable caused values above the therapeutic range in 3 of 7 patients, and 7 days intake did the same in 9 of 13 patients.[5] In another similar study, intake of **spinach** 250 g or **broccoli** 250 g daily for 7 days increased the mean thrombotest values to above the therapeutic limit of 15%, and the effect was similar to that of a supplement containing phytomenadione 250 micrograms daily. A reduction in the anticoagulant effect of **warfarin** was also seen in one healthy subject who ate about 450 g **spinach** daily.[6,7]

In a pharmacokinetic study in healthy subjects, a daily intake of 400 g of **brussels sprouts** for 2 weeks slightly decreased the AUC of **warfarin** by 16% and increased its metabolic clearance by 27%.[8] This is probably because **brussels sprouts** induce the cytochrome P450 isoenzyme CYP1A2, which has a role in the 'metabolism of warfarin', (p.405).

A few cases of this interaction (often described as warfarin resistance) have been reported in patients taking **dicoumarol**,[9] or **warfarin**[10-13] when consuming large amounts of green vegetables (about 300 to 700 g daily),[11,12] such as **spinach**,[9,14] **broccoli**,[11,12] or a weight-loss diet consisting of **lettuce**, **turnip greens**, and **broccoli**.[13] The dietary vitamin K was esti-

mated to be 1.3 g daily in one case,[10] and 6 g daily in another.[13] In two cases, patients suffered a serious thromboembolic event.[12,13] For discussion of a case where a patient had an increase in INR after stopping a herbal preparation, of which spinach, broccoli and cabbage were 3 of 25 ingredients, see 'Coumarins + Vitamin K_1-rich herbal medicines', p.521.

Conversely, a single intake of **spinach** 250 g or **broccoli** 250 g had no effect on thrombotest values over 7 days.[14] Similarly, in another study in healthy subjects stabilised on **acenocoumarol**, a single meal containing either **spinach** 400 g or **broccoli** 400 g with corn oil caused just 0.27 and 0.41 reductions in the mean INR, an effect that was not considered clinically relevant. These reductions were equivalent to that seen with about 200 micrograms of vitamin K_1.[15]

(d) Liver

A patient taking **acenocoumarol** had a soft tissue bleed, and was found to have a very low thrombotest value of about 3%. She had always consumed about 142 g daily of green vegetables, but about 4 months previously had been advised to stop eating liver (750 g weekly) as part of a low-fat diet.[16] In another case, a man taking **warfarin** 5 mg daily had diffuse bruising and an INR of 5.6 two weeks after he was advised to stop eating pork **liver**[12] (1 kg per week). He was eventually restabilised on just 1.5 mg of warfarin daily. Early studies found that liver contained high levels of vitamin K, but more recent studies using more specific detection techniques have shown that liver generally contains very low levels of vitamin K_1 (4 and 7 micrograms in 100 g).[17] However, liver may contain vitamin K_2 substances in sufficient levels to be of possible nutritional relevance.[17,18] The precise role of vitamin K_2 substances in anticoagulation control is less clear, but natto, which is a rich source of these, clearly reduces the effects of coumarins. See 'Coumarins + Food; Soya bean products', p.463.

(e) Seaweed

A patient taking **warfarin** had, on two occasions, reduced INRs of 1.6 and 1.8 (usual range 2 to 3) within 24 hours of eating sushi with **seaweed** (***asakusa-nori***). It was estimated that she had consumed only about 45 micrograms of vitamin K_1, which would not usually interact. However, if her vitamin K stores were low, this amount could have accounted for a large percentage of her vitamin K intake or stores, and might therefore have interacted.[19] Note that **kelp** is a moderate source of vitamin K, see 'Table 12.3', (p.462).

(f) Other foodstuffs

In an early report, a Japanese man recently stabilised on **warfarin** developed bleeding episodes on two occasions shortly after resuming his usual diet of Japanese food (specific foods not mentioned), suggesting increased warfarin effects. However, ingestion of three similar Japanese meals in a 24-hour period had no effect on the prothrombin time in 6 Caucasian patients taking **warfarin**.[20]

B. Overall dietary vitamin K intake

(a) Correlation with INR

Some evidence suggests that the average dietary vitamin K_1 intake is correlated with the efficacy of **warfarin**. In one study, patients consuming a diet containing more than 250 micrograms daily of vitamin K_1 had a lower INR five days after starting **warfarin** than patients consuming less dietary vitamin K_1 (median INR 1.9 versus 3). Also, the high-vitamin K_1 group needed a higher maintenance **warfarin** dose (5.7 mg daily versus 3.5 mg daily).[21] In another study, multiple regression analysis indicated that, in patients taking warfarin, the INR was altered by 1, by a weekly change in the intake of vitamin K of 714 micrograms.[22] Similarly, for each increase in daily dietary vitamin K_1 intake of 100 micrograms, the INR decreased by just 0.2 in another study.[23]

In a randomised, crossover study in patients taking **warfarin** or **phenprocoumon**, increasing the dietary intake of vitamin K_1 by 500% relative to the baseline value (from 118 to 591 micrograms daily) for 4 days only modestly decreased the INR from 3.1 to 2.8 on day 4. Decreasing the dietary intake of vitamin K_1 by 80% (from 118 to 26 micrograms daily) for 4 days increased the INR from just 2.6 to 3.3 on day 7.[24]

(b) Stability of anticoagulant control

There is some evidence that patients with a very low dietary vitamin K_1 intake are more sensitive to alterations in vitamin K_1 intake, and have less stable anticoagulant control. For example, in one study, patients with unstable control of anticoagulation were found to have a much lower dietary intake of vitamin K_1, when compared with another group of patients with stable anticoagulant control (29 micrograms daily versus 76 micrograms daily).[25] In another study in 10 patients with poorly controlled anticoagulation taking **acenocoumarol**, a diet with a low, controlled vitamin K_1 content of 20 to 40 micrograms daily increased the percentage of INR values within the therapeutic range, when compared with a control group of 10 patients not subjected to any dietary restrictions.[26] Supplementation of the diet with small doses of vitamin K_1 has had a similar effect, see 'Coumarins + Vitamin K_1-containing dietary supplements', p.520.

Importance and management

A very well established, well documented and clinically important drug-food interaction, expected to occur with every coumarin or indanedione anticoagulant because they have a common mode of action. The evidence suggests that, in patients with normal vitamin K_1 status, in general, clinically relevant changes in coagulation status require large continued changes in intake of vitamin K_1 from foods. However, there is some evidence to suggest that patients with low dietary vitamin K_1 intake may be sensitive to smaller changes in dietary vitamin K_1. This suggests that patients taking anticoagulants should be advised to eat a normal balanced diet, maintaining a relatively consistent amount of vitamin-K_1 rich foods. They should be told to avoid making major changes to their diet, including starting a weight-loss diet, without increased monitoring of their INR. It is estimated that a normal Western diet contains 300 to 500 micrograms of vitamin K_1 daily. The minimum daily requirement is about 1 micrograms/kg and, in the US, an adequate intake has been determined to be 120 micrograms for adult men and 90 micrograms daily for adult women. 'Table 12.3', (p.462), gives the vitamin K_1 content of some vitamin-K_1 rich foods; however, it is important to note that these are not the bioavailable contents, which may be much lower for green vegetables, particularly if they are eaten in the absence of fat.[18,27] Nevertheless, green leafy vegetables usually contribute 40 to 50% of the total intake, followed by certain vegetable oils and margarines made from these oils.[28] Also, processed foods can have moderate to high vitamin K_1 levels if they contain fats with high vitamin K_1 levels. Note that some foods that have a low vitamin K_1 content can contribute significantly to total intake because of how often they are eaten. Cooking and freezing do not alter the vitamin K_1 content, but vitamin K_1 in oils is degraded by exposure to light.[29] In the US, a chart has been devised to help patients and researchers determine the daily intake of vitamin K_1.[30]

For the effect of multivitamins containing vitamin K_1, see 'Coumarins + Vitamin K_1-containing dietary supplements', p.520, and for the effect of supplements in enteral and parenteral feeds, see 'Coumarins and related drugs + Food; Enteral and parenteral nutrition', p.461.

There is growing evidence that vitamin K_2 substances (menaquinones) may also be important, and in one analysis rich dietary sources of these included goose liver paste, hard and soft cheeses, egg yolk,[18] and natto, the effect of which is already established, see 'Coumarins + Food; Soya bean products', p.463.

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Coumarins and related drugs + Garlic

An isolated report described increases in the anticoagulant effects of warfarin in two patients taking garlic supplements. Another report described a decrease in anticoagulant effects of fluindione in a patient taking garlic tablets. Garlic supplements alone have also rarely been associated with bleeding. However, in one study, aged garlic extract did not increase the INR or risk of bleeding in patients taking warfarin.

Clinical evidence

(a) Fluindione

In an 82-year-old man stabilised on fluindione 5 mg (dosage frequency not stated) for chronic atrial fibrillation, the INR dropped to below its usual range (2 to 3) when garlic tablets 600 mg daily were taken, and remained below 2 for 12 consecutive days despite an increase in fluindione dose to 10 mg. The INR returned to normal, with an associated reduction in fluindione dose, when the garlic tablets were stopped. He was also taking enalapril 20 mg, furosemide 40 mg and pravastatin 20 mg (dose frequency not stated).[1]

(b) Warfarin

The INR of a patient stabilised on warfarin more than doubled and haematuria occurred 8 weeks after the patient started to take three *Höfels garlic pearles* daily. The situation resolved when the garlic was stopped. The INR rose on a later occasion while the patient was taking two *Kwai* garlic tablets daily. The INR of another patient was also more than doubled by six *Kwai* garlic tablets daily.[2,3]

In contrast, in a placebo-controlled study in 48 patients stabilised on warfarin, there was no change in INR or evidence of increased bleeding in those receiving 5 mL of aged garlic extract (*Kyolic*) twice daily for 12 weeks.[4] Similarly, in a preliminary report of the use of alternative and complementary medicines in 156 patients taking warfarin, there was no apparent increased risk of bleeding or raised INRs in 57 patients taking potentially interacting complementary medicines (garlic in 10%), compared with 84 who did not.[5]

Mechanism

Garlic has been associated with decreased platelet aggregation, which has on at least two documented occasions led to spontaneous bleeding in the absence of an anticoagulant.[6,7] These effects might therefore increase the risk of bleeding with anticoagulants, see also 'Coumarins + Herbal medicines; Miscellaneous', p.472.

Importance and management

Information about an adverse interaction between warfarin and garlic seems to be limited to two cases from one author. Similarly, the data regarding indanediones is sparse, with just one case reported. Bearing in mind the wide-spread use of garlic and garlic products, and the limited information from the review,[5] and study with aged garlic extract,[4] it seems most unlikely that garlic usually has any generally important interaction with these anticoagulants. Nevertheless, bear the possibility in mind in the event of an unexpected response to treatment.

In addition, garlic may have some antiplatelet effects, and although there appear to be no clinical reports of an adverse interaction between garlic and antiplatelet drugs, it may be prudent to consider the potential for an increase in the severity of bleeding if garlic is given with anticoagulants.

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Coumarins + Gefitinib

An isolated report describes an increase in the effects of warfarin when gefitinib was given.

Clinical evidence, mechanism, importance and management

A woman stabilised on **warfarin** required a gradual decrease in the dose from 4 mg to 2.5 mg daily after starting gefitinib 250 mg/m^2 daily for lung cancer. In contrast, a second patient did not have an increase in the effect of **warfarin** while taking gefitinib.[1] The US manufacturer of gefitinib notes that raised INRs and bleeding have been reported in patients taking **warfarin** and gefitinib; however, there appears to be no specific pharmacokinetic explanation for this interaction as gefitinib did not inhibit the cytochrome P450 isoenzymes CYP2C9 or CYP3A4 *in vitro*.[2] Note that factors related to illness such as decreased appetite can alter **warfarin** requirements. Nevertheless, given that there have been several reports of an interaction, it would be prudent to increase monitoring of **warfarin** effects in patients requiring gefitinib.

Note that, from a disease perspective, when treating venous thromboembolic disease in patients with cancer, **warfarin** is generally inferior (higher risk of major bleeds and recurrent thrombosis) to low-molecular-weight heparins.

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Coumarins + Ginger

Evidence from pharmacological studies suggests that ginger does not increase the anticoagulant effect of warfarin, neither does it alter coagulation or platelet aggregation on its own. However, two case reports describe markedly raised INRs with phenprocoumon and warfarin, which were associated with eating dried ginger and drinking ginger tea. A prospective, longitudinal study also reports of an increased risk of self-reported bleeding events in patients taking warfarin and ginger.

Clinical evidence

In a randomised, crossover study in 12 healthy subjects, 3 ginger capsules taken three times daily for 2 weeks did not affect either the pharmacokinetics or pharmacodynamics (INR) of a single 25-mg dose of **warfarin** taken on day 7. The brand of ginger used was *Blackmores Travel Calm Ginger*, each capsule containing an extract equivalent to 400 mg of ginger rhizome powder. Moreover, ginger alone did not affect the INR or platelet aggregation.[1]

However, a case report describes a rise in INR to greater than 10, with epistaxis, in a woman stabilised on **phenprocoumon** several weeks after she started to eat ginger regularly in the form of pieces of dried ginger and

tea from ginger powder. She was eventually restabilised on the original dose of **phenprocoumon**, and was advised to stop taking ginger.[2] Another very similar case has been described in a woman taking **warfarin**.[3]

Moreover, in a prospective, longitudinal study of patients taking **warfarin** and a herbal product or dietary supplement, there was a statistically significant increased risk of self-reported bleeding events in patients taking **warfarin** and ginger (7 bleeds in 25 weeks, none of which were major: odds ratio 3.2).[4] No elevated INRs were reported for the combination. Note that the number of patients taking ginger was not reported, except to say it was less than 5% of 171; so it was less than 8 patients. Also, the ginger products used were not mentioned and some patients were taking more than one potentially interacting supplement.

Mechanism

Ginger (*Zingiber officinale*) has sometimes been listed as a herb that interacts with warfarin[5,6] on the basis that *in vitro* it inhibits platelet aggregation. However, this antiplatelet effect has generally not been demonstrated in controlled clinical studies (three of which have been reviewed[7]). Consider also 'Coumarins + Herbal medicines; Miscellaneous', p.472.

Importance and management

Evidence from a controlled study suggests that ginger does not increase the anticoagulant effect of warfarin. Despite it being cited as a herb that inhibits platelet aggregation, there is limited evidence that it increases bleeding when given alone or with warfarin, and there are just two case reports of markedly raised INRs with phenprocoumon and warfarin, which were associated with ginger root and ginger tea. Because of the many other factors influencing anticoagulant control, it is not possible to reliably ascribe a change in INR specifically to a drug interaction in a single case report without other supporting evidence. It may be better to advise patients to discuss the use of any herbal products they wish to try, and to increase monitoring if this is thought advisable. Cases of uneventful use should be reported, as they are as useful as possible cases of adverse effects.

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Coumarins + Ginkgo (*Ginkgo biloba*)

Evidence from pharmacological studies in patients and healthy subjects suggests that ginkgo extracts do not interact with warfarin. However, an isolated report describes intracerebral haemorrhage associated with the use of ginkgo and warfarin, and there are a few reports of bleeding associated with the use of ginkgo alone.

Clinical evidence

In a randomised, crossover study in 21 patients stabilised on **warfarin**, ginkgo extract 100 mg daily (*Bio-Biloba*) for 4 weeks did not alter the INR or the required dose of **warfarin**, when compared with placebo.[1] Similarly, in another study in healthy subjects,[2] *Tavonin* (containing standardised dry extract EGb 761 of ginkgo equivalent to 2 g of leaf) 2 tablets three times daily for 2 weeks did not affect either the pharmacokinetics or pharmacodynamics (INR) of a single dose of **warfarin** given on day 7. Moreover, a retrospective review of 21 clinical cases involving the concurrent use of ginkgo and **warfarin** also found no evidence of altered INRs.[3]

Conversely, a report describes an intracerebral haemorrhage in an elderly woman within 2 months of her starting to take ginkgo. Her prothrombin time was found to be 16.9 seconds and her partial thromboplastin time was 35.5 seconds. She had been taking **warfarin** uneventfully for 5 years.[4] The author of the report speculated that ginkgo may have contributed towards the haemorrhage.

Mechanism

Uncertain. Isolated cases of bleeding have been reported with ginkgo alone (which have been the subject of a review[5]). In pharmacological studies, ginkgo extract alone did not alter coagulation parameters or platelet aggregation.[2,3] However, in *animal* studies it was found that the AUC of warfarin was decreased by 23% during EGb 761 administration, and the prothrombin time was also reduced by EGb 761, which would suggest that ginkgo should *reduce* the effects of warfarin.[3] In healthy subjects, ginkgo extract had no effect on diclofenac or tolbutamide, which were used as marker substrates for the cytochrome P450 isoenzyme CYP2C9, suggesting that it will not alter the metabolism of *S*-warfarin.[6]

Importance and management

There is good evidence from pharmacological studies in patients and healthy subjects that ginkgo extract would not be expected to interact with warfarin. However, there is one case report of over-anticoagulation, and a few reports of bleeding with ginkgo alone. This is insufficient evidence to justify telling patients taking warfarin to avoid ginkgo, but they should be told to monitor for early signs of bruising or bleeding and seek informed professional advice if any bleeding problems arise.

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Coumarins + Ginseng

One pharmacological study found that *Panax quinquefolius* (American ginseng) modestly decreased the effect of warfarin, whereas another study found that *Panax ginseng* (Asian ginseng) did not alter the effect of warfarin. Two case reports describe decreased warfarin effects, one with thrombosis, attributed to the use of ginseng (probably *Panax ginseng*).

Clinical evidence

In a placebo-controlled study, 20 healthy subjects were given **warfarin** 5 mg daily for 3 days alone then again on days 15 to 17 of a 3-week course of *Panax quinquefolius* (American ginseng) 1 g twice daily. In the 12 subjects given ginseng, the peak INR was modesty reduced by 0.16, compared with a non-significant reduction of 0.02 in the 8 subjects given placebo. There was also a modest reduction in the AUC of **warfarin**. In this study, *Panax quinquefolius* root was ground and capsulated.[1]

Evidence from two earlier case reports supports a reduction in warfarin effect. A man taking **warfarin** long-term, and also diltiazem, glyceryl trinitrate and salsalate, had a fall in his INR from 3.1 to 1.5 within 2 weeks of starting to take ginseng capsules (*Ginsana*) three times daily. This preparation contains 100 mg of standardised concentrated ginseng [probably *Panax ginseng* (Asian ginseng)] in each capsule. Within 2 weeks of stopping the ginseng his INR had risen again to 3.3.[2] Another patient taking **warfarin** was found to have thrombosis of a prosthetic aortic valve, with a subtherapeutic INR of 1.4. Three months before this episode his INR had become persistently subtherapeutic, requiring a progressive increment in his **warfarin** dose. It was suggested that this might have been because he had begun using a ginseng product (not identified).[3]

In contrast, in a randomised, crossover study in 12 healthy subjects, ginseng capsules 1 g three times daily for 2 weeks did not affect either the pharmacokinetics or pharmacodynamics (INR) of a single 25-mg dose of **warfarin** taken on day 7. The brand of ginseng used was *Golden Glow*, each capsule containing an extract equivalent to 0.5 g of *Panax ginseng* (Asian ginseng) root.[4]

Mechanism

It is unclear why ginseng might reduce the efficacy of warfarin, particularly as no pharmacokinetic interaction occurs. *In vitro* experiments have found that *Panax ginseng* contains antiplatelet components that inhibit platelet aggregation and thromboxane formation,[5] although antiplatelet activity was not demonstrated in a study in healthy subjects.[6] If an antiplatelet effect were confirmed, this might suggest the possibility of an *increased* risk of bleeding with the combination of ginseng and warfarin. There are a few reports of vaginal bleeding in women using ginseng preparations (unspecified) in the absence of an anticoagulant,[7–9] but these are probably due to a possible hormonal effect of ginseng.

Importance and management

The available evidence suggests that ginseng might *decrease* the effect of warfarin. It is possible that the effect is greater with, or specific to, *Panax quinquefolius* (American ginseng), because this interacted in one study whereas *Panax ginseng* (Asian ginseng) did not. Although the ginseng dose was higher in the *Panax ginseng* study, the treatment duration was not as long, which may have obscured an effect. Moreover, the two case reports of decreased warfarin effects attributed to the use of ginseng were probably *Panax ginseng*.

Until further information becomes available it would seem prudent to be alert for decreased effects of warfarin and related drugs in patients using ginseng, particularly *Panax quinquefolius*. However, the possibility of an increased risk of bleeding due to the antiplatelet component of Panax ginseng cannot entirely be ruled out, although the clinical study suggests that this is unlikely.

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Coumarins + Glucagon

In one early analysis, the anticoagulant effects of warfarin were markedly increased by very large doses of glucagon (total dose exceeding 50 mg over 2 days), but not by doses of less than 30 mg over one to 2 days.

Clinical evidence

In an analysis of 24 patients taking **warfarin** who were given glucagon for inadequate cardiac contractility, no potentiation of the action of **warfarin** was noted in 11 patients given a total of less than 30 mg of glucagon over one to 2 days. However, 8 out of 9 patients had a marked increase in anticoagulant effects (prothrombin times of 30 to 50 seconds or more) when they were given higher doses of glucagon (62 to 362 mg over 3 to 8 days). Three of them bled. The interaction was not able to be assessed in 4 patients.[1]

Mechanism

Unknown. Changes in the production of blood clotting factors and an increase in the affinity of warfarin for its site of action have been proposed.[1] A study in *guinea pigs* using **acenocoumarol** suggested that changes in warfarin metabolism or its absorption from the gut are *not* responsible.[2]

Importance and management

Direct information is limited to the report cited,[1] which relates to doses far in excess of those used clinically for hypoglycaemia (1 mg) or in the management of beta blocker overdose (2 to 10 mg then 50 micrograms/kg per hour). As such, its findings are probably of no general relevance. Its authors recommend that if glucagon 25 mg per day or more is given for two or more days, the dose of warfarin should be reduced in anticipation of the interaction, and prothrombin time closely monitored.[1]

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Coumarins + Glucosamine ± Chondroitin

A few reports suggest that glucosamine with or without chondroitin may increase the INR in patients taking warfarin. In contrast, one case of a decreased INR has been reported when glucosamine was given with acenocoumarol.

Clinical evidence

The first indication of a possible interaction between **warfarin** and glucosamine was in 2001, when the Canadian Adverse Drug Reaction Monitoring Program briefly reported that an increase in INR had been noted when glucosamine was given to patients taking **warfarin**, and that INR values decreased when glucosamine was stopped.[1] In 2004, a full case report was published. In this case, a 69-year-old man stabilised on **warfarin** 47.5 mg weekly had an increase in his INR from 2.58 to 4.52 four weeks after starting to take 6 capsules of *Cosamin DS* (glucosamine hydrochloride 500 mg, sodium chondroitin sulfate 400 mg, manganese ascorbate per capsule) daily. His **warfarin** dose was reduced to 40 mg weekly, and his INR returned to the target range of 2 to 3 (INR 2.15) with continued *Cosamin DS* therapy.[2] A comment on this report noted that this is twice the usual dose of glucosamine.[3] Since then, one other similar case of a modest rise in INR has been published. A man taking **warfarin** and glucosamine hydrochloride 500 mg with chondroitin sulfate 400 mg twice daily had a gradual increase in his INR (from 2.3 to 4.7 over 5 weeks) when he trebled the dose of the glucosamine supplement.[4]

Analysis of regulatory authority data has revealed other unpublished reports. In 2006 the CHM in the UK reported that they had received 7 reports of an increase in INR in patients taking **warfarin** after they started taking glucosamine supplements.[5] In 2007, a search of the FDA database identified 20 possible cases,[4] and a search of the WHO database identified 22 possible case reports of an increase in **warfarin** effect with glucosamine, which originated from Australia, Canada, Denmark, Sweden, the UK and USA.[6] In two of the WHO cases, chondroitin was used, but the other cases were with glucosamine alone. Of 15 reports giving details of time to onset, the increased INR was noted within 3 days (in a 99-year-old) and up to 6 months; most commonly the interaction took several weeks to manifest.[6]

In contrast, a 71-year-old man stabilised on **acenocoumarol** 15 mg weekly had a *decrease* in his INR to 1.6 after taking glucosamine sulfate (*Xicil*) 1.5 g daily for 10 days. The glucosamine was stopped and the INR reached 2.1. When the glucosamine was restarted, with an increase in **acenocoumarol** dose to 17 mg weekly, the INR only reached 1.9. The glucosamine was eventually stopped.[7] Similarly, the WHO database contained one report of a decreased effect of warfarin with glucosamine.[6] The Australian Adverse Drug Reactions Advisory Committee have also identified 12 cases of alterations in INR in patients taking **warfarin**. Nine of these cases are included in the WHO report.[8]

There do not appear to have been any controlled studies of the effects of glucosamine supplements on the pharmacodynamics or pharmacokinetics of oral anticoagulants.

Mechanism

Unknown.

Importance and management

Glucosamine is a widely used supplement, particularly in the middle-aged and elderly, who are also the group most likely to be using warfarin or similar anticoagulants. Despite this, there are just three published reports of a possible interaction, two describing moderate rises in INR and one a decrease. Even taking into account the possible cases reported to regulatory authorities, the interaction would seem to be quite rare. Nevertheless, the cases described suggest it would be prudent to monitor the INR more closely if glucosamine is started or stopped. Also, if a patient shows an

unexpected change in INR, bear in mind the possibility of self-medication with supplements such as glucosamine.

Note that in 2006 the CHM in the UK recommend that patients taking warfarin do not take glucosamine,[5] but the subsequent 2007 UK-approved labelling for the prescription-only glucosamine product *Alateris* recommends close monitoring when a patient taking a coumarin anticoagulant starts or stops glucosamine.[9]

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Coumarins + Glutethimide

The anticoagulant effects of warfarin and ethyl biscoumacetate can be decreased by glutethimide.

Clinical evidence

Ten subjects stabilised on **warfarin**, with average prothrombin times of 18.8 seconds, had a mean reduction of 2.7 seconds in their prothrombin times after they took glutethimide 500 mg at bedtime for 4 weeks.[1,2] Other studies have shown that up to 1 g of glutethimide daily for one to 3 weeks reduced the half-life of single-dose **warfarin** by between one-third to one-half.[3,4] Conversely, an unexplained report describes a paradoxical increase in prothrombin times and severe bruising in a patient stabilised on **warfarin** who took 3.5 g of glutethimide over a 5-day period.[5]

Glutethimide 500 or 750 mg daily for 10 days has been found to reduce the half-life of single-dose **ethyl biscoumacetate** by about one-third,[6,7] whereas in contrast, an early study in 25 patients taking **ethyl biscoumacetate** found no evidence of an interaction.[8]

Mechanism

Glutethimide is a liver enzyme inducer, which increases the metabolism and clearance of the anticoagulants from the body, thereby reducing their effects.[1-4,6,7] There is no obvious explanation for the reports finding no interaction or increased effects.

Importance and management

The interaction of glutethimide with warfarin is established, while the interaction with ethyl biscoumacetate is uncertain. Information about both interactions is limited and there seems to be nothing documented about any other anticoagulant. However, it would be prudent to monitor the effect of adding glutethimide to patients taking any coumarin, being alert for the need to increase the anticoagulant dose. Other interactions due to enzyme induction can take several weeks to develop fully and persist after withdrawal, so good monitoring and dose adjustment should continue until anticoagulant stability is confirmed. The benzodiazepines may be a useful non-interacting alternative, see 'Coumarins + Benzodiazepines and related drugs', p.441.

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Coumarins + Grapefruit juice

Grapefruit juice may cause a modest rise in the INR some patients taking warfarin and one case report describes a marked rise in INR, which was attributed to grapefruit juice. However, other studies have suggested that grapefruit juice does not interact with warfarin or acenocoumarol.

Clinical evidence

(a) Acenocoumarol

In the preliminary report of a single-dose, placebo-controlled study in 12 healthy subjects, 150 mL of grapefruit juice did not alter the maximum INR of a 10-mg dose of acenocoumarol, and the AUCs of *S*- and *R*-acenocoumarol were not altered.[1,2]

(b) Warfarin

In a study in 9 patients stabilised on warfarin, consumption of grapefruit juice 240 mL three times daily for one week had no effect on the INR or prothrombin times.[3] Similarly, in the preliminary report of a two-way crossover study in 24 patients stabilised on warfarin, the frequency of the **warfarin** dosage adjustments needed by the group as a whole, when taking 250 mL grapefruit juice daily for 4 weeks was the same as when taking a placebo (orange juice). However, 4 individuals had a clinically significant, progressive and sustained 12 to 25% decrease in the warfarin dose to INR ratio when taking grapefruit juice, but not orange juice.[4] A 64-year-old man stabilised on warfarin was found to have an INR of 6.29 on routine testing 10 days after starting to drink about 1.5 litres of grapefruit juice daily. However, when the author took warfarin to achieve an INR of 2 to 3 and then drank 1.5 litres of grapefruit juice daily there was no clinically relevant change in his INR.[5]

Mechanism

It was suggested that the patients who showed some evidence of an interaction between grapefruit juice and warfarin may possibly have had an increased susceptibility to the inhibitory effects of grapefruit juice on the activity of the cytochrome P450 isoenzyme CYP3A4 in the gut.[4] Note that CYP3A4 has a minor role in the metabolism of *R*-warfarin, which is a much less potent anticoagulant than *S*-warfarin.

Importance and management

Information is limited. One study with warfarin suggests that some patients might require a slight reduction in dose if they regularly consume grapefruit juice, but further study is needed. Current evidence suggests that routine testing should be sufficient to detect any interaction.

For discussion of the interaction of warfarin with grapefruit seed extract, thought to be due to the preservative benzethonium chloride, see 'benzethonium chloride', (p.441).

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Coumarins + Griseofulvin

The anticoagulant effects of warfarin may be reduced by griseofulvin in some patients.

Clinical evidence

The anticoagulant effects of **warfarin** were modestly and markedly reduced in 2 patients, respectively, stabilised on **warfarin** when they were given griseofulvin 1 g daily in divided doses. Griseofulvin 1 g daily had

no effect on the prothrombin time in one healthy subject given **warfarin**, whereas 2 g daily caused a marked reduction in the prothrombin time. Another healthy subject had no interaction, even when the griseofulvin dose was raised to 4 g daily for 2 weeks.[1]

In another study there was no change in the mean prothrombin time in 10 patients stabilised on **warfarin** when they were given griseofulvin 1 g daily in divided doses for 2 weeks. Four of the patients had an equivocal average reduction in prothrombin time of 4.2 seconds.[2] One case report describes decreased anticoagulant effects in a man stabilised on **warfarin** when he took griseofulvin 250 mg twice daily, which took 12 weeks to develop fully.[3] He eventually needed a 41% increase in his daily dose of **warfarin**. Another report very briefly mentions a case of a coagulation defect in a patient taking **warfarin** and griseofulvin.[4]

Mechanism

Not understood. It has been suggested that the griseofulvin acts as a liver enzyme inducer, which increases the metabolism of the warfarin, thereby reducing its effects.[1,3]

Importance and management

The interaction between warfarin and griseofulvin is poorly documented and not well established. However, it possibly results in a clinically significant interaction in some patients. Because of the uncertainty, and the known enzyme-inducing effects of griseofulvin, the prothrombin times of all patients taking warfarin who are given griseofulvin should be monitored, and suitable warfarin dose increases made as necessary.

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Coumarins and related drugs + H_2-receptor antagonists

The anticoagulant effects of warfarin can be increased by cimetidine. Acenocoumarol interacts similarly, but phenprocoumon appears not to be affected. In one patient the effects of phenindione were modestly increased by cimetidine. Famotidine, nizatidine, ranitidine and roxatidine normally do not appear to interact with the coumarins, although isolated cases of bleeding have been reported.

Clinical evidence

(a) Cimetidine

A brief report in 1978, published as a letter by the manufacturers of cimetidine, stated that preliminary details of a study in healthy subjects indicated that cimetidine 1 g daily could cause a prothrombin time rise of about 20% in patients stabilised on **warfarin**. At that time, they were aware of 17 cases worldwide, most of moderate rises in prothrombin times.[1]

A number of studies[2,3] and case reports[4-8] have confirmed this interaction with **warfarin**. In the studies, plasma **warfarin** levels were reported to rise by 25% and 80%, and prothrombin times were increased by 18% and 20% by cimetidine 1.2 g daily. In the case reports, severe bleeding (haematuria, internal haemorrhages) and very prolonged prothrombin times have been seen in a few patients given cimetidine 900 mg or 1.2 g daily.[4,6-8]

In another study, 7 out of 14 patients stabilised on **warfarin** had a greater than 30 second increase in their prothrombin time, whereas the other 7 had no prolongation or only a minor prolongation in their prothrombin time when they were given cimetidine 1.2 g daily for 10 days.[9] A study in 27 patients found that, although the AUC of **warfarin** was increased by 21 to 39% and its clearance fell by 22 to 28%, prothrombin times only increased by 2 to 2.6 seconds by cimetidine 800 mg or 1.2 g daily.[10] A pharmacokinetic study in 6 healthy subjects found that cimetidine did not affect *S*-warfarin but increased the trough plasma levels of *R*-warfarin by 28%, with minimal effect on prothrombin times.[11] Other pharmacokinetic studies have confirmed that the interaction affects only *R*-warfarin.[12-15] In one analysis of the concurrent use of **warfarin** and an H_2-receptor antagonist in hospitalised patients, there was no difference in the intensity of prothrombin time monitoring, and no difference in bleeding rates between 35 patients receiving cimetidine, 38 patients receiving ranitidine, or 36 patients receiving famotidine. Two patients in the cimetidine group had a bleed after they had taken both drugs for one or two days but neither had abnormally high prothrombin times.[16]

In three studies, the AUC of single-dose **acenocoumarol** was increased by cimetidine, and the prothrombin time prolonged,[17-19] with the effect greatest for *R*-acenocoumarol.[19] However, another study found no interaction.[20] Data from one patient taking **acenocoumarol** and one taking **phenindione** showed that cimetidine increased their anticoagulant effects.[2] In one study in patients stabilised on **phenprocoumon**, cimetidine 400 mg twice daily did not alter the pharmacokinetics of **phenprocoumon** or its anticoagulant effect.[21]

(b) Famotidine

In a study in 8 healthy subjects taking doses of **warfarin** titrated to prolong the prothrombin time by 2 to 5 seconds (mean dose 4 mg daily), famotidine 40 mg daily for 7 days did not affect prothrombin times, thrombotest coagulation times or steady-state plasma **warfarin** levels.[22] No changes in prothrombin times were seen in 3 patients stabilised on **acenocoumarol** or **fluindione** when they were given famotidine.[23] However, in another report 2 patients taking **warfarin** are said to have had prolonged prothrombin times and bled when they took famotidine.[24]

(c) Nizatidine

In 7 healthy subjects taking **warfarin**, nizatidine 300 mg daily for 2 weeks had no significant effect on the prothrombin times, kaolin-cephalin clotting times, the activity of factors II, VII, XI and X, or on steady-state serum **warfarin** levels.[25] A lack of a pharmacokinetic interaction was also reported in the preliminary results of another study.[26] An isolated case of gastrointestinal bleeding, associated with markedly prolonged prothrombin times, occurred after a 78-year-old took six doses of nizatidine 300 mg.[24]

(d) Ranitidine

In a study in 5 healthy subjects, ranitidine 200 mg twice daily for 2 weeks had no effect on **warfarin** concentrations or prothrombin times.[27] In another study in 11 healthy subjects, ranitidine 150 mg twice daily for 3 days had no effect on the pharmacodynamics or pharmacokinetics of a single dose of **warfarin**.[3] The same finding was reported in another similar study.[15] In contrast, in a fourth study in 5 subjects, ranitidine 150 mg twice daily for a week reduced the clearance of a single dose of **warfarin** by almost 30%, but the half-life was not significantly changed and prothrombin times were not measured.[28] Ranitidine 750 mg daily given to 2 subjects reduced the **warfarin** clearance by more than 50%.[28] In an isolated case, a patient stabilised on ranitidine 150 mg twice daily and **warfarin** vomited blood one week after her ranitidine dose was doubled to 300 mg twice daily. Her prothrombin time had risen from 17.6 seconds to 36.7 seconds. She was subsequently restabilised on ranitidine 150 mg twice daily and the original dose of **warfarin** with a prothrombin time between 19 and 20 seconds.[29]

In one study in 10 patients stabilised on **phenprocoumon**, ranitidine 150 mg twice daily for 14 days had no effect on anticoagulation or on phenprocoumon plasma levels.[30]

(e) Roxatidine

In a study in 12 healthy subjects, roxatidine 150 mg daily for 4 days had no effect on the steady-state pharmacokinetics of **warfarin** or the prothrombin ratio.[31]

Mechanism

Cimetidine binds with the cytochrome P450 isoenzymes and inhibits oxidative metabolism in the liver. Although cimetidine is considered to be a general inhibitor, it exhibits a degree of specificity for certain isoenzymes such as CYP1A2 and CYP2C19. These isoenzymes are principally involved in the metabolism of *R*-warfarin and not *S*-warfarin (see 'metabolism of the coumarins', (p.405), for more detail). Thus, the interaction between warfarin and cimetidine has been found to be stereoselective (i.e. cimetidine interacts with the *R*-isomer but not with the *S*-isomer).[11-14] As *R*-warfarin is the less active isomer, and the pharmacokinetic interaction is not marked, the interaction is generally modest. The other H_2-receptor antagonists normally do not act as enzyme inhibitors.

Importance and management

The interaction between warfarin and cimetidine is well documented, well established and potentially clinically important. Its effects are generally modest, but rarely, patients have shown a marked interaction. Because of this unpredictability, and to avoid bleeding, the response should be closely monitored in every patient when cimetidine is first added, being alert for the need to reduce the warfarin dose. The onset of the interaction appears rapid and its effects have been seen within days,[4,7] and even as early as 24 hours.[9] The effect of low non-prescription doses of cimetidine on warfarin do not appear to have been studied. Acenocoumarol is reported to interact similarly, and there is one case of phenindione being affected. Expect other coumarins and indanediones to behave in the same way, with the possible exception of phenprocoumon, which was not affected in one study.

Famotidine, nizatidine, ranitidine and roxatidine normally appear not to interact with the coumarins although note that, in rare cases, increases in prothrombin times and bleeding have been seen.

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Coumarins + Heparin

Heparin may prolong the prothrombin time, and increase the risk of bleeding with warfarin.

Clinical evidence, mechanism, importance and management

Heparin may prolong the one-stage prothrombin time.[1] The US manufacturer notes that, if a valid prothrombin time is to be obtained in a patient starting **warfarin** or other coumarins, a period of a least 5 hours after the last intravenous heparin dose or 24 hours after the last subcutaneous dose should be left before measuring the prothrombin time.[2] Note that it is usual clinical practice to start heparin and a coumarin at the same time to ensure the patient is anticoagulated until warfarin reaches steady-state, and to discontinue the heparin when the INR is stable.

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Coumarins and related drugs + Heparinoids

Some of the normal tests of anticoagulation (prothrombin time, thrombotest) are unreliable for a few hours after giving intravenous danaparoid to patients taking coumarins. Oral pentosan polysulfate sodium did not alter the pharmacokinetics or pharmacodynamics of warfarin in healthy subjects, but note that this heparinoid is associated with rectal bleeding. An isolated case report describes bleeding in a patient taking acenocoumarol after a heparinoid-impregnated bandage was applied.
In general, the use of heparinoids with coumarins or indanediones would be expected to increase the risk of bleeding.

Clinical evidence, mechanism, importance and management

(a) Intravenous danaparoid

A study in 6 healthy subjects taking **acenocoumarol** (steady-state thrombotest values of 10 to 15%), found that a single intravenous bolus injection of 3250 anti-Xa units of danaparoid prolonged the prothrombin time and thrombotest for up to one hour and 5 hours, respectively, which was more than would have been expected by the simple addition of the effects of both drugs. However, no significant differences were seen in bleeding time, and danaparoid did not alter **acenocoumarol** pharmacokinetics.[1] The authors concluded that when monitoring the anticoagulant effects of **acenocoumarol**, the prothrombin time and the thrombotest may therefore be unreliable for at least one hour and 5 hours, respectively, after intravenous danaparoid has been given. This advice would apply equally to other coumarins and other drugs monitored using these tests, such as the indanediones.

(b) Pentosan polysulfate sodium

In a placebo-controlled, crossover study in 24 healthy subjects stabilised on **warfarin**, oral pentosan polysulfate sodium 100 mg every 8 hours for 7 days did not alter the anticoagulant effect of **warfarin** or the pharmacokinetics of *R*- or *S*-warfarin.[2] The authors consider it appears that, unlike intravenous administration, oral pentosan polysulfate sodium has no anticoagulant activity. However, the manufacturer notes that rectal haemorrhage was reported as an adverse effect in 6.3% of patients receiving pentosan polysulfate sodium at a dose of 300 mg daily.[3] On the basis of the pharmacological study, the authors considered that it seems unnecessary to make changes in the warfarin dose or the oral pentosan polysulfate sodium dose when the two drugs are used together. However, they do recommend careful monitoring on starting concurrent use.[2] Logic would suggest that, if bleeding occurs, this could be more severe in anticoagulated patients. The patient information provided by the manufacturer states that concurrent use of pentosan polysulfate and warfarin should be avoided until they have spoken with their doctor.[3] See also *Topical heparinoid*, below.

(c) Topical heparinoid

A man who was well stabilised on **acenocoumarol** and also taking metoprolol, dipyridamole and isosorbide dinitrate began to bleed within about 3 days of starting to use a medicated bandage on an inflamed lesion on his

hand, probably caused by a mosquito bite. His prothrombin percentage was found to have fallen to less than 10%. The bandage was impregnated with a semi-synthetic heparinoid compound based on **xylane acid polysulfate** [possibly **pentosan polysulfate**].[4] It would appear that enough of the heparinoid had been absorbed through his skin to increase his anticoagulation to the point where he began to bleed. This case is unusual but it illustrates the need to keep a close watch on patients who are given several drugs that can potentially cause bleeding.

1. Stiekema JCJ, de Boer A, Danhof M, Kroon C, Broekmans AW, van Dinther TG, Voerman J, Breimer DD. Interaction of the combined medication with the new low-molecular-weight heparinoid Lomoparan® (Org 10172) and acenocoumarol. *Haemostasis* (1990) 20,136–46.
2. Modi NB, Kell S, Simon M, Vargas R. Pharmacokinetics and pharmacodynamics of warfarin when coadministered with pentosan polysulfate sodium. *J Clin Pharmacol* (2005) 45, 919–26.
3. Elmiron (Pentosan polysulfate sodium). Ortho-McNeil Pharmaceutical, Inc. US Prescribing information, December 2008.
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Coumarins + Herbal medicines; Miscellaneous

Many of the interactions of herbal medicines (health foods, dietary supplements) with warfarin in the published literature are solely hypothetical based on the postulated pharmacological effects of known chemical constituents of the plants. These mechanisms are discussed further below. Where specific clinical data on a herbal medicine interaction with warfarin are available, this is covered in a separate monograph.
All patients should be encouraged to report their use of herbal medicines and food supplements and cases of uneventful concurrent use should be published as well as cases of possible interactions to increase the clinical information available.

Clinical evidence and mechanism

(a) Antiplatelet effects

Antiplatelet doses of aspirin (see 'Coumarins and related drugs + Aspirin or other Salicylates', p.434), do not alter the anticoagulant efficacy of warfarin (INR); however, these doses of aspirin by themselves increase the risk of gastrointestinal bleeding, and the risk of this is higher in patients taking warfarin. On this basis, many herbs with antiplatelet activity *in vitro* are suggested to interact with warfarin. To establish the increased risk with antiplatelet doses of aspirin with warfarin, very large studies were needed because the absolute risks are small (about 1 in 100 in one study). Studies of this size are very unlikely to be conducted with herbal medicines. One way might be to compare the *in vivo* antiplatelet activity of the herbal product with that of aspirin 75 mg, and then to extrapolate to the likely increased risk of bleeding.

(b) Coumarin constituents

There is a misconception that if a plant contains natural coumarins it will have anticoagulant properties. More than 3 400 coumarins occur naturally throughout at least 160 plant families. Of these, just 13 have been tested for antithrombotic or anticoagulant activity, and only about half (7) were found to be active.[1] There are no established interactions between warfarin and herbal medicines that have been attributed to the coumarin content of the herb. Even in the classic case of hemorrhagic death of livestock that led to the discovery of dicoumarol, it was the action of the mould on the coumarin in the sweet clover that led to the production of the anticoagulant, so consumption of a spoiled product would seem to be necessary for this interaction to occur. This suggests that the occurrence of coumarins in dietary supplements or herbal medicines should not trigger immediate concern.[1]

(c) Vitamin K content

Vitamin K is found in highest levels in green leafy vegetables, which, if ingested in sufficient quantities, can markedly reduce the effects of warfarin and related drugs (see 'Coumarins and related drugs + Food; Vitamin K_1-rich', p.464). It would therefore not be surprising if many herbal medicines derived from dark green leaves contain vitamin K. However, whether enough of these herbs could be taken to cause an interaction seems less likely than with foods. Nevertheless, two case reports of altered coagulation status attributed to the vitamin K content of herbal preparations have been reported, see 'Coumarins + Vitamin K_1-rich herbal medicines', p.521.

Importance and management

There are many reviews of the effect of various herbal medicines on warfarin. Most of these include interactions based on theoretical data, based on the knowledge that a plant has been shown to contain antiplatelet substances or coumarins. The problem with these lists is that a suggested interaction might never be clinically relevant if, for example, the coumarins present are found not to be anticoagulants, or the substances are found in such small quantities and the herb cannot be ingested in sufficient amounts to cause an interaction. With natural substances, there is also the problem of chemical variations between batches of product if they are not standardised. Moreover, even isolated reports of an interaction between a herbal medicine and warfarin cannot definitively establish that such an interaction exists (see also 'anticoagulant interactions', (p.405)).

Because of the potential for interactions, some consider that patients taking warfarin would be well advised to avoid all herbal medications. However, this approach may not be practical: there are many papers showing that patients taking warfarin do use a number of herbal medicines and dietary supplements (19.2% in a UK survey;[2] 26% in a Hong Kong survey[3]). If patients have been told to avoid all herbal products, they may be less likely to admit to their use, and become less cautious in the future if they discover that the use of one product is uneventful. It may be better to advise patients to discuss the use of any products they wish to try, and to increase monitoring if this is thought necessary. Cases of uneventful use should be reported, as they are as useful as possible cases of adverse use.

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3. Wong RSM, Cheng G, Chan TYK. Use of herbal medicines by patients receiving warfarin. *Drug Safety* (2003) 26, 585–8.

Coumarins + Herbicides

An isolated report describes a marked increase in the anticoagulant effects of acenocoumarol, with bleeding, caused by the use of a herbicide containing thiocarbamates.

Clinical evidence, mechanism, importance and management

A 55-year-old patient with mitral and aortic prostheses, stabilised on **acenocoumarol** 2 mg daily and with an INR of 3.6 to 4.2 was hospitalised because of severe and uncontrollable gum bleeding. He responded when given a transfusion of fresh plasma. The cause of the marked increase in the anticoagulant effects of the **acenocoumarol** was eventually identified as almost certainly being due to the use of a herbicide (*SATURN-S*) containing **thiobencarb** and **molinate** (two thiocarbamates), which the patient was using to spray his rice crop. The **thiobencarb** can be absorbed through the skin and the **molinate** by inhalation. Just how these two compounds interact with **acenocoumarol** is not known but the authors of the report suggest that these herbicides may possibly have inhibited the metabolism of the anticoagulant, thereby increasing its effects. The patient was later restabilised on his former dose of **acenocoumarol**.[1]

This seems to be the first and only report of this interaction but it highlights one of the possible risks of using chemical sprays that have never been formally tested for their potential to interact with drugs. A similar problem has been seen with insecticides, see 'Coumarins + Insecticides', p.473.

1. Fernández MA, Aznar J. Potenciación del efecto anticoagulante del acenocumarol por un herbicida. *Rev Iberoamer Tromb Hemostasia* (1988) 1, 40–1.

Coumarins + Hormonal contraceptives or HRT

Acenocoumarol dose requirements appear to be about 20% lower during the use of a combined hormonal contraceptive. An isolated report describes a marked increase in the INR of a woman taking warfarin when she was given emergency contraception with levonorgestrel. In contrast, the anticoagulant effects of dicoumarol and phenprocoumon were slightly decreased by oral contraceptives. Ethinylestradiol with norgestimate did not appear to have much effect on the clearance of warfarin.
There is conflicting data on whether or not the use of HRT (oral

or topical) affects warfarin or phenindione dosing. In one case, the acenocoumarol dose was increased by 75% when oral conjugated oestrogens were changed to transdermal estradiol.

Clinical evidence

A. Hormonal contraceptives

(a) Acenocoumarol

The anticoagulant requirements of 12 patients taking acenocoumarol were about 20% lower while they were taking a combined hormonal contraceptive (average 19 months) than when they were not taking a contraceptive (average 12 months). Even then, they were anticoagulated to a higher degree while taking the contraceptive (prothrombin ratio of 1.67 compared with 1.5) than with the anticoagulant alone. The contraceptives used were *Neogynona*, *Microgynon*, *Eugynon* (**ethinylestradiol** with **levonorgestrel**) or *Topasel* (intramuscular **estradiol enantate** with **algestone**).[1]

(b) Dicoumarol

A study in 4 healthy subjects given single 150- or 200-mg doses of dicoumarol on day 17 of a 20-day course of *Enovid* (**noretynodrel** and **mestranol**) found that the anticoagulant effects were decreased in 3 of the 4 subjects, although the dicoumarol half-life remained unaltered.[2]

(c) Phenprocoumon

In a controlled study in 14 healthy women, the clearance of a single 0.22 mg/kg dose of phenprocoumon was increased by 20% in the 7 subjects taking oral combined hormonal contraceptives, compared with the 7 control subjects not taking hormonal contraceptives.[3]

(d) Warfarin

In a pharmacokinetic study, a single dose of warfarin 10 mg (given with vitamin K 10 mg to prevent anticoagulant effects) was given to 10 women before and while they were taking an oral combined hormonal contraceptive (**ethinylestradiol** 35 micrograms with **norgestimate** 180 micrograms to 250 micrograms for 3 weeks). The mean clearance of *S*-warfarin was not significantly changed, although there was wide variability with 5 subjects having an increase in clearance, 3 having a decrease, and 2 having little change.[4]

A 39-year-old woman with familial type 1 antithrombin deficiency and a history of extensive deep vein thrombosis and pulmonary embolism, taking warfarin, was given **levonorgestrel** for emergency contraception. Within 3 days her INR had risen from 2.1 to 8.1. No bleeding occurred. Her INR returned to normal after stopping the warfarin for 2 days.[5]

B. HRT

In a retrospective analysis, 18 women were identified who had started HRT while taking **warfarin** (16 patients) or **phenindione** (2 patients). A wide variety of HRT preparations were being used, including topical and oral preparations, oestrogens with or without progestogens, and progestogens alone. Half of the women taking **warfarin** had no change in their warfarin dose requirement after starting HRT. Five required a less than 10% increase or decrease in average **warfarin** dose, and 3 required a 13%, 22%, and 28% increase in their average **warfarin** dose, the latter two of these being the only 2 women taking oestrogen-only oral HRT. Of the 2 women taking **phenindione**, one needed no change in dose, and the other a 4.6% increase in dose.[6]

In one case, a postmenopausal 53-year-old woman needed an increase in her daily dose of **acenocoumarol** from 2 to 3.5 mg when her HRT was changed from **oral conjugated oestrogens** 0.625 mg daily to **transdermal estradiol** 50 micrograms daily. When the oral HRT was restarted, her **acenocoumarol** requirements returned to their former levels.[7]

Mechanism

Not understood. The oral contraceptives are known to be associated with a small increased risk of venous thromboembolism in otherwise healthy women, and are therefore contraindicated in women who have had thrombosis. HRT also increases the risk of venous thromboembolism. Oestrogens can apparently increase the metabolism (glucuronidation) of phenprocoumon.[3] The authors of the report about levonorgestrel suggest that it might have displaced the warfarin from its binding sites thereby increasing its activity,[5] although this mechanism is now generally discounted.

Ethinylestradiol with norgestimate did not appear to have an important effect on the activity of the cytochrome P450 isoenzyme CYP2C9, as assessed by the clearance of *S*-warfarin.[4]

Importance and management

Direct information seems to be limited to these reports. Combined hormonal contraceptives (both oral and patch) are normally contraindicated in those with thromboembolic disorders but if they must be used, be alert for any changes in the anticoagulant response if a hormonal contraceptive is started or stopped. The report about the apparent interaction between warfarin and postcoital levonorgestrel seems to be isolated and therefore its general importance is unknown. Note that intrauterine levonorgestrel has been used for menorrhagia in women taking warfarin.[8]

There is very limited published information available on the concurrent use of warfarin and HRT. The retrospective study suggests that usually HRT causes no or only minor changes in warfarin or phenindione requirements.

Note that, because of the increased risk of developing venous thromboembolism with HRT, the use of HRT in women already taking an anticoagulant requires careful consideration of the risks and benefits.

1. de Teresa E, Vera A, Ortigosa J, Alonso Pulpon L, Puente Arus A, de Artaza M. Interaction between anticoagulants and contraceptives: an unsuspected finding. *BMJ* (1979) 2, 1260–1.
2. Schrogie JJ, Solomon HM, Zieve PD. Effect of oral contraceptives on vitamin K-dependent clotting activity. *Clin Pharmacol Ther* (1967) 8, 670–5.
3. Mönig H, Baese C, Heidemann HT, Ohnhaus EE, Schulte HM. Effect of oral contraceptive steroids on the pharmacokinetics of phenprocoumon. *Br J Clin Pharmacol* (1990) 30, 115–18.
4. Shelepova T, Nafziger AN, Victory J, Kashuba AD, Rowland E, Zhang Y, Sellers E, Kearns G, Leeder JS, Gaedigk A, Bertino JS. Effect of a triphasic oral contraceptive on drug-metabolizing enzyme activity as measured by the validated Cooperstown 5+1 cocktail. *J Clin Pharmacol* (2005) 45, 1413–21.
5. Ellison J, Thomson AJ, Greer IA, Walker ID. Apparent interaction between warfarin and levonorgestrel used for emergency contraception. *BMJ* (2000) 321, 1382.
6. McLintock LA, Dykes A, Tait RC, Walker ID. Interaction between hormone replacement therapy preparations and oral anticoagulant therapy. *Br J Obstet Gynaecol* (2003) 110, 777–9.
7. Cotton F, Sorlin P, Corvilain B, Fockedey J-M, Capel P. Interference with oral anticoagulant treatment by oestrogen - influence of oestrogen administration route. *Thromb Haemost* (1999) 81, 471–2.
8. Pisoni CN, Cuadrado MJ, Khamashta MA, Hunt BJ. Treatment of menorrhagia associated with oral anticoagulation: efficacy and safety of the levonorgestrel releasing intrauterine device (Mirena coil). *Lupus* (2006) 15, 877–80.

Coumarins + Insecticides

A patient had a marked increase in his response to acenocoumarol when exposed to insecticides containing ivermectin and methidathion. Another patient was resistant to the effects of warfarin after very heavy exposure to a toxaphene and lindane-containing insecticide.

Clinical evidence

(a) Acenocoumarol

A farmer in Spain, normally well stabilised on acenocoumarol and amiodarone, had marked rises in his INR, from 3.5 up to 7.9, requiring a reduction in his anticoagulant dose (from 12 to 8 mg weekly), which occurred during the summer months. No bleeding occurred. It was then discovered that he was using insecticides containing **ivermectin** and an organophosphate **methidathion** on his trees without any protective clothing.[1]

(b) Warfarin

A rancher in the US, who was taking warfarin, had a very marked reduction in his anticoagulant response after dusting his sheep with an insecticide containing 5% **toxaphene** (**camphechlor**) and 1% **lindane** (**gamma-benzene hexachloride**). Over a 2-year period he had periods of considerable warfarin resistance, which were linked to the use of this insecticide. Normally warfarin 7.5 mg daily maintained his prothrombin time in the therapeutic range, but after exposure to the insecticide even 15 mg daily failed to have any effect.[2] The dusting was done by putting the insecticide in a sack and hitting the sheep with it in an enclosed barn.[2]

Mechanism

The interaction between acenocoumarol and ivermectin with methidathion is not understood. When used on its own, ivermectin used for onchocerciasis normally has no effect on prothrombin times,[3,4] but two unexplained cases of prolonged prothrombin times associated with the development of haematomas have been reported.[5] Methidathion is an organophosphate. Lindane and other chlorinated hydrocarbon insecticides

are known liver enzyme inducers,[6] which increase the metabolism and clearance of the warfarin, thereby reducing or even abolishing its effects.

Importance and management

Information about these interactions appears to be limited to these isolated case reports. Neither interaction is well established or of general clinical importance. The chlorinated hydrocarbon insecticides have been withdrawn from general use in most countries so that the possibility of an interaction with any anticoagulant is now very small. No other cases of an interaction between an anticoagulant and ivermectin, whether used as an insecticide or for the treatment of onchocerciasis, appear to have been reported.

As a general rule, farm workers and others should use proper protection (gloves, masks, protective clothing) if they are exposed to substantial amounts of any insecticide, because these can be both directly toxic and can also apparently interact with some prescribed drugs, including the anticoagulants, even if only very rarely.

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2. Jeffery WH, Ahlin TA, Goren C, Hardy WR. Loss of warfarin effect after occupational insecticide exposure. *JAMA* (1976) 236, 2881–2.
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6. Kolmodin B, Azarnoff DL, Sjöqvist F. Effect of environmental factors on drug metabolism: Decreased plasma half-life of antipyrine in workers exposed to chlorinated hydrocarbon insecticides. *Clin Pharmacol Ther* (1969) 10, 638–42.

Coumarins + Interferons

Two isolated reports indicate that the effects of acenocoumarol and warfarin may be increased by interferons. Conversely, there is evidence that suggests that peginterferon alfa-2b might modestly increase the metabolism of warfarin and other coumarins.

Clinical evidence

The manufacturer of **peginterferon alfa-2b** notes that, in a pharmacokinetic probe study in patients with chronic hepatitis C, **peginterferon alfa-2b** increased the activity of cytochrome P450 isoenzyme CYP2C8/9 by 28%, as assessed by tolbutamide pharmacokinetics.[1,2] This suggests that this interferon might increase the metabolism of *S*-warfarin, the more potent isomer, and therefore decrease the effects of **warfarin**. However, in a similar study in healthy subjects, **peginterferon alfa-2a** had no effect on tolbutamide pharmacokinetics.[3]

However, a woman stabilised on long-term **warfarin** 2.5 to 3.5 mg daily had a prothrombin time rise from 16.7 seconds to 20.4 seconds after receiving 6 million units of **interferon-alfa** daily for 10 days, then three times a week, for chronic hepatitis C. Her serum **warfarin** levels rose from about 0.8 micrograms/mL to 5.2 micrograms/mL. She responded to a reduction in the **warfarin** dose to 2 mg daily. The authors of the report also say that they have seen 4 other patients taking **warfarin** who needed a dose reduction when given interferon, two of them while taking **interferon beta** and the other two while taking **interferon alfa-2b**.[4]

Similarly, a woman taking **acenocoumarol** 1 mg and 2 mg on alternate days had gingival bleeding and a thrombotest change from 35% to 19% (indicating an increased anticoagulant effect) within 6 weeks of starting treatment with 3 million units of **interferon-alpha 2b** three times weekly for chronic hepatitis C. Her thrombotest percentages stabilised between 25 and 40% when the **acenocoumarol** dose was reduced to 1 mg daily. A later reduction in the interferon dose caused a decrease in the anticoagulant effects of **acenocoumarol**.[5]

Mechanism

Not understood. The authors of both reports suggest that interferon reduces the metabolism of the anticoagulants by the liver, thereby reducing their clearance and increasing their effects.[4,5] Some early *in vitro* studies did show that interferons might inhibit some drug metabolising enzymes.[6] Conversely, data for peginterferon alfa-2b suggest that it might modestly increase the metabolism of warfarin by the cytochrome P450 isoenzyme CYP2C9, which would reduce its anticoagulant effects. The manufacturer suggests that this might be because of the improvement in liver function seen when peginterferon is used in chronic hepatitis,[2] rather than any direct effect of peginterferon. However, the effect was not seen for all cytochrome P450 isoenzymes, and the opposite was seen in the two case reports described when other interferons were used for chronic hepatitis.

Importance and management

These two reports seem to be the only ones to describe an increased effect of the coumarins with an interferon, so the interaction is by no means established. Conversely, the data for peginterferon alfa-2b suggest that there might be a modest increase in activity of CYP2C9. Whether this is sufficient to cause a relevant decrease in the effect of warfarin remains to be seen. Nevertheless, the manufacturer advises caution with warfarin.[1,2] It would seem prudent to consider increased monitoring if any of these interferons is given to patients taking coumarins. For a case of decreased warfarin effects in a patient given interferon alfa-2b and ribavirin, see 'Coumarins + Ribavirin', p.502.

1. PegIntron (Peginterferon alfa-2b). Schering Corp. US Prescribing information, August 2009.
2. ViraferonPeg (Peginterferon alfa-2b). Schering-Plough Ltd. UK Summary of product characteristics, November 2009.
3. Pegasys (Peginterferon alfa-2a). Roche Products Ltd. UK Summary of product characteristics, October 2009.
4. Adachi Y, Yokoyama Y, Nanno T, Yamamoto T. Potentation of warfarin by interferon. *BMJ* (1995) 311, 292.
5. Serratrice J, Durand J-M, Morange S. Interferon-alpha 2b interaction with acenocoumarol. *Am J Hematol* (1998) 57, 89–92.
6. Okuno H, Kitao Y, Takasu M, Kano H, Kunieda K, Seki T, Shiozaki Y, Sameshima Y. Depression of drug metabolizing activity in the human liver by interferon-α. *Eur J Clin Pharmacol* (1990) 39, 365–7.

Coumarins + Ispaghula (Psyllium)

Ispaghula (psyllium) did not affect either the absorption or the anticoagulant effects of warfarin in one study. A cohort study also found no evidence of an interaction in patients taking acenocoumarol or phenprocoumon and ispaghula.

Clinical evidence, mechanism, importance and management

In a study in 6 healthy subjects, ispaghula (given as a 14-g dose of colloid (*Metamucil*) in a small amount of water with a single 40-mg dose of **warfarin**, and three further doses of ispaghula every 2 hours thereafter) did not affect either the absorption or the anticoagulant effects of the **warfarin**.[1] Similarly, in a population-based cohort study in patients taking **acenocoumarol** or **phenprocoumon**, there was no increased risk of over-anticoagulation (INR greater than 6) associated with the use of ispaghula (psyllium seeds), although the number of people treated was small.[2] No alteration of the anticoagulant response would therefore be expected on concurrent use.

1. Robinson DS, Benjamin DM, McCormack JJ. Interaction of warfarin and nonsystemic gastrointestinal drugs. *Clin Pharmacol Ther* (1971) 12, 491–5.
2. Visser LE, Penning-van Beest FJA, Wilson JHP, Vulto AG, Kasbergen AAH, De Smet PAGM, Hofman A, Stricker BHC. Overanticoagulation associated with combined use of lactulose and acenocoumarol or phenprocoumon. *Br J Clin Pharmacol* (2003) 57, 522–4.

Coumarins + Lanthanum

Lanthanum does not appear to alter the pharmacokinetics of a single dose of warfarin.

Clinical evidence, mechanism, importance and management

In a pharmacokinetic study in healthy subjects, lanthanum carbonate (3 doses of 1 g the day before **warfarin**, then 1 g thirty minutes before **warfarin**) had no effect on the pharmacokinetics of a single dose of **warfarin**.[1]

Lanthanum carbonate is a phosphate-binding drug, and does not appear to alter **warfarin** absorption. This suggests that no **warfarin** dose adjustments would be expected to be needed on concurrent use. However, note that the pharmacodynamics of **warfarin** (e.g. the effects on INR) were not assessed in this study.

1. Fiddler G. Fosrenol (lanthanum carbonate) does not affect the pharmacokinetics of concomitant treatment with warfarin. *J Am Soc Nephrol* (2002) 13, 749A–750A.

Coumarins + Lasofoxifene

In a study, lasofoxifene caused a minor decrease in the prothrombin time in response to warfarin without changing warfarin pharmacokinetics.

Clinical evidence, mechanism, importance and management

In 12 healthy postmenopausal women, lasofoxifene 4 mg on day one then 500 micrograms daily for 13 days had no effect on the pharmacokinetics of *R*- or *S*-warfarin when a single 20-mg dose of **warfarin** was given on day 8. However, the maximum prothrombin time was decreased by 16%, with a similar decrease in the maximum INR, which was reduced from 1.9 to 1.6.[1]

Because this slight decrease in **warfarin** effects has been seen with raloxifene (see 'Coumarins + Raloxifene', p.502), the authors suggested that it might be because oestrogenic compounds increase plasma concentrations of vitamin K-dependent clotting factors.[1]

The authors suggest that the small decrease in **warfarin** effect with lasofoxifene may not be clinically relevant. Nevertheless, they say that until more data are available on longer-term concurrent use, it is recommended that prothrombin times should be monitored (presumably with any coumarin) when starting or stopping lasofoxifene.[1] This seems a sensible precaution.

1. Quellet D, Bramson C, Carvajal-Gonzalez S, Roman D, Randinitis E, Remmers A, Gardner MJ. Effects of lasofoxifene on the pharmacokinetics and pharmacodynamics of single-dose warfarin. *Br J Clin Pharmacol* (2006) 61, 741–5.

Coumarins + Laxatives

In one cohort study, the long-term use of lactulose appeared to be associated with an increased risk of over-anticoagulation. Limited evidence suggested no interaction occurred with liquid paraffin or colocynth.

Clinical evidence

In a population-based cohort study in patients taking **acenocoumarol** or **phenprocoumon**, lactulose significantly increased the risk of over-anticoagulation (INR greater than 6) with a relative risk of 3.4 (range 2.2 to 5.3). When analysed by duration of use, less than 27 days use of **lactulose** actually decreased the risk of over-anticoagulation, whereas longer use was associated with an increased risk. In this study, neither **liquid paraffin** nor **colocynth** preparations were associated with an increased risk of over-anticoagulation, but the numbers of patients taking these drugs was small.[1]

Mechanism

In theory, drugs that shorten gastrointestinal transit time such as laxatives and liquid paraffin (mineral oil) might be expected to decrease the absorption of both vitamin K and the coumarins or indanediones. Decreasing the absorption of vitamin K would be expected to increase the effect of these anticoagulants, which could be offset by the decrease in absorption of the anticoagulant. In the case of short-term lactulose use, it was suggested that decreasing the colonic pH might have increased the absorption of vitamin K, thereby reducing the effect of the coumarin. On longer term use, it was postulated that lactulose might reduce faecal flora that produce vitamin K, so increasing the risk of over-anticoagulation.[1] Liquid paraffin might also be expected to impair the absorption of vitamin K.

Importance and management

The cohort study cited appears to be the first and only evidence of a possible interaction with laxatives, and it suggests that the long-term use of lactulose may increase the effect of coumarins. This finding requires confirmation in a controlled pharmacological study. Until further data are available, it may be prudent to consider the possibility of an interaction in any patient taking lactulose long-term. Limited evidence suggests that no interaction occurs with liquid paraffin or colocynth but this needs confirmation. Clinical evidence for an interaction with other laxatives is lacking, despite the theoretical considerations.

1. Visser LE, Penning-van Beest FJA, Wilson JHP, Vulto AG, Kasbergen AAH, De Smet PAGM, Hofman A, Stricker BHC. Overanticoagulation associated with combined use of lactulose and acenocoumarol or phenprocoumon. *Br J Clin Pharmacol* (2003) 57, 522–4.

Coumarins + Leflunomide

There are a few reports of increased INRs, some with bleeding complications, in patients taking warfarin with leflunomide.

Clinical evidence, mechanism, importance and management

A short report describes a patient taking **warfarin** whose INR rose from 2.5 to over 6, resulting in a hospital admission, shortly after she started taking leflunomide (3 days of 100 mg daily).[1]

Another report describes a patient taking **warfarin** who developed haematuria after taking leflunomide 100 mg daily for 2 days. His INR was found to have risen from 3.4 to over 11, and **warfarin** was discontinued. The haematuria spontaneously resolved, but as the INR remained elevated for the next 2 days he was given 1 mg of vitamin K, which brought his INR down to 1.9. He was later stabilised on **warfarin** 1 mg daily with a leflunomide maintenance dose of 20 mg daily.[2] The authors of this report stated that at that time (2002) the CSM in the UK had received over 300 reports of leflunomide raising the INRs of patients taking **warfarin**;[2] however, this was an error, and the report should have read that of 300 reports of raised INRs with **warfarin** and another drug, *four* reports related to leflunomide.[3] An additional case describes a patient who required a 22% decrease in her weekly **warfarin** dose after starting leflunomide.[4]

The manufacturers of leflunomide note that *in vitro*, the active metabolite of leflunomide inhibits the cytochrome P450 isoenzyme CYP2C9. They therefore advise caution if leflunomide is given with drugs metabolised by CYP2C9, of which they give **warfarin** and **phenprocoumon** as examples.[5] On the basis of the cases seen, it would seem prudent to monitor the INR of any patient taking a coumarin who starts taking leflunomide.

1. Mason JP. Warfarin and leflunomide. *Pharm J* (2000) 265, 267.
2. Lim V, Pande I. Leflunomide can potentiate the anticoagulant effect of warfarin. *BMJ* (2002) 325, 1333. Erratum *ibid.* (2003) 326, 432.
3. Anonymous. Corrections and clarifications: drug points. *BMJ* (2003) 326, 432.
4. Chonlahan J, Halloran MA, Hammonds A. Leflunomide and warfarin interaction: case report and review of the literature. *Pharmacotherapy* (2006) 26, 868–71.
5. Arava (Leflunomide). Sanofi-Aventis. UK Summary of product characteristics, September 2009.

Coumarins + Leukotriene antagonists

Zafirlukast increases the anticoagulant effects of warfarin and bleeding has been seen. Pranlukast is predicted to interact similarly. In contrast, montelukast did not alter the pharmacokinetics or anticoagulant effects of single-dose warfarin.

Clinical evidence

(a) Montelukast

In a placebo-controlled, randomised study, 12 healthy subjects were given oral montelukast 10 mg daily for 12 days and a single 30-mg dose of **warfarin** on day 7. It was found that the pharmacokinetics of the **warfarin** were virtually unchanged by the montelukast, and prothrombin times and INRs were not significantly altered.[1]

(b) Zafirlukast

In a placebo-controlled study, 16 healthy subjects taking zafirlukast 80 mg twice daily for 10 days were given a single 25-mg dose of **warfarin** on day 5. The mean AUC of *S*-warfarin was increased by 63% and the half-life by 36%, but the pharmacokinetics of *R*-warfarin were not significantly changed. The mean prothrombin time increased by 35%.[2]

An 85-year-old woman taking **warfarin**, salbutamol (albuterol), diltiazem, digoxin, furosemide and potassium was admitted to hospital with various cardiac-related problems and bleeding (epistaxis, melaena, multiple bruising), which was attributed to the use of zafirlukast 20 mg twice daily. Her INR had risen from 1.1 (measured 6 months previously) to 4.5. The report does not say how long she had been taking the both drugs together.[3]

Mechanism

The reason for the interaction is thought to be that the zafirlukast inhibits the cytochrome P450 isoenzyme CYP2C9, which metabolises *S*-warfarin.[2,4] *In vitro* studies suggest that **pranlukast** has a similar effect.[5]

Importance and management

Information appears to be limited to these reports but the interaction with zafirlukast would seem to be established. If zafirlukast is given to patients stabilised on warfarin, monitor prothrombin times well and be alert for the need to reduce the warfarin dose to avoid over-anticoagulation. Other coumarins might be expected to be affected similarly. Pranlukast is also predicted to interact with the coumarins, as it is also an inhibitor of CYP2C9. In contrast, montelukast does not appear to interact with warfarin, and no warfarin dose adjustments are predicted to be needed on concurrent use.

1. Van Hecken A, Depre M, Verbesselt R, Wynants K, De Lepeleire I, Arnoudt J, Wong PH, Freeman A, Holland S, Gertz B, De Schepper PJ. Effect of montelukast on the pharmacokinetics and pharmacodynamics of warfarin in healthy subjects. *J Clin Pharmacol* (1999) 39, 495–500.
2. Suttle AB, Vargo DL, Wilkinson LA, Birmingham BK, Lasseter K. Effect of zafirlukast on the pharmacokinetics of R- and S-warfarin in healthy men. *Clin Pharmacol Ther* (1997) 61, 186.
3. Morkunas A, Graeme K. Zafirlukast-warfarin drug interaction with gastrointestinal bleeding. *J Toxicol Clin Toxicol* (1997) 35, 501.
4. Accolate (Zafirlukast). AstraZeneca UK Ltd. UK Summary of product characteristics, May 2008.
5. Liu KH, Lee YM, Shon JH, Kim MJ, Lee SS, Yoon YR, Cha IJ, Shin JG. Potential of pranlukast and zafirlukast in the inhibition of human liver cytochrome P450 enzymes. *Xenobiotica* (2004) 34, 429–38.

Coumarins + Levetiracetam

In a controlled study, levetiracetam did not alter the pharmacokinetics or pharmacodynamics of warfarin.

Clinical evidence, mechanism, importance and management

In a randomised, double-blind, placebo-controlled study in 42 healthy subjects stabilised on **warfarin**, levetiracetam 1 g twice daily for 7 days had no significant effect on the pharmacokinetics of *R*- or *S*-warfarin and the INRs were not significantly altered.[1] No **warfarin** dose adjustments would therefore be expected to be needed on concurrent use.

1. Ragueneau-Majlessi I, Levy RH, Meyerhoff C. Lack of effect of repeated administration of levetiracetam on the pharmacodynamic and pharmacokinetic profiles of warfarin. *Epilepsy Res* (2001) 47, 55–63.

Coumarins + Levocarnitine

Two isolated reports describe a marked increase in the anticoagulant effects of acenocoumarol in patients taking levocarnitine, one of which was associated with melaena.

Clinical evidence, mechanism, importance and management

A woman who had taken **acenocoumarol** for 17 years because of aortic and mitral prosthetic valves, was admitted to hospital with melaena within 5 days of starting to take levocarnitine 1 g daily, which she was prescribed for congestive heart failure. Her INR had risen from 2.1 to 7. Endoscopy and colonoscopy revealed diffuse bleeding from superficial erosions in the gut. She was discharged 10 days later with the same dose of **acenocoumarol** and an INR of 2.1 without the levocarnitine.[1] A similar case has been described in a man stabilised on **acenocoumarol** (INR 1.99 to 2.94) who had a rise in INR to 4.65 despite a dose correction. The increases in INR occurred when he was using levocarnitine 1 g daily for 10 weeks in the form of a drink (*Maximize*) promoted for bodybuilding and fitness training. When this product was discontinued, the INR returned to the therapeutic range.[2]

The reason for this apparent interaction is not known. These seem to the only recorded cases of an interaction between a coumarin and levocarnitine, but it may be prudent to bear this interaction in mind if levocarnitine is taken with acenocoumarol, or possibly any coumarin, being alert for an increased response.

1. Martinez E, Domingo P, Roca-Cusachs A. Potentiation of acenocoumarol action by L-carnitine. *J Intern Med* (1993) 233, 94.
2. Bachmann HU, Hoffmann A. Interaction of food supplement L-carnitine with oral anticoagulant acenocoumarol. *Swiss Med Wkly* (2004) 134, 385.

Coumarins + Levosimendan

Levosimendan does not alter the effects of warfarin. There is no pharmacokinetic interaction between levosimendan and warfarin.

Clinical evidence, mechanism, importance and management

In an open, randomised, crossover study, 10 healthy subjects were given a single 25-mg oral dose of **warfarin** both before and on day 4 of a 9-day course of oral levosimendan 500 micrograms four times daily. No clinically relevant changes in the anticoagulant effects of the **warfarin** were seen, and levosimendan alone had no effect on blood coagulation. In addition, there was no important pharmacokinetic interaction between **warfarin** and levosimendan. No interactions would therefore be expected if both drugs are used concurrently.[1]

1. Antila S, Jarvinen A, Honkanen T, Lehtonen L. Pharmacokinetic and pharmacodynamic interactions between the new calcium sensitiser levosimendan and warfarin. *Eur J Clin Pharmacol* (2000) 56, 705–10.

Coumarins + Lycium (*Lycium barbarum*)

A case report suggests that lycium may enhance the effects of warfarin.

Clinical evidence

A 61-year-old Chinese woman stabilised on **warfarin** (INRs normally 2 to 3) had an unexpected rise in her INR to 4.1, which was identified during a routine monthly check. No bleeding was seen. She was also taking atenolol, benazepril, digoxin and fluvastatin. It was found that 4 days before visiting the clinic she had started to take one glass (about 170 mL) 3 or 4 times daily of a Chinese herbal tea made from the fruits of lycium to treat blurred vision caused by a sore eye. When the herbal treatment was stopped, her INRs rapidly returned to normal.

Mechanism

Warfarin is metabolised by a number of isoenzymes, the most important being the cytochrome P450 isoenzyme CYP2C9. Inhibition of this isoenzyme may therefore lead to increased warfarin levels and effects. The authors also carried out an *in vitro* study and concluded that although lycium is a weak inhibitor of CYP2C9, this is insufficient to cause an interaction. However, they note that other mechanisms cannot be ruled out.[1]

Importance and management

Although the authors suggest avoiding the concurrent use of lycium and warfarin,[1] because of the many other factors influencing anticoagulant control, it is not possible to reliably ascribe a change in INR specifically to a drug interaction in a single case report without other supporting evidence. It may be better to advise patients to discuss the use of any herbal products they wish to try, and to increase monitoring if this is thought advisable. Cases of uneventful use should be reported, as they are as useful as possible cases of adverse effects. It should be noted that lycium berries are also used as an ingredient in Chinese foods.

1. Lam AY, Elmer GW, Mohutsky M. Possible interaction between warfarin and *Lycium barbarum*. *Ann Pharmacother* (2001) 35, 1199–1201.

Coumarins + MAOIs or RIMAs

Although some *animal* data show that the non-selective MAOIs increase the effects of some oral anticoagulants, there appears to be no clinical evidence of an interaction. Moclobemide did not interact with phenprocoumon in a pharmacological study, and appears unlikely to interact with warfarin.

Clinical evidence, mechanism, importance and management

(a) MAOIs

A number of studies in *animals*[1-4] have shown that some of the non-selective MAOIs can increase the effects of some oral anticoagulants. However, there appear to be no clinical studies or case reports of this interaction, and therefore no special precautions seem to be necessary.

(b) Moclobemide

A study in healthy subjects found that moclobemide 200 mg three times daily for 7 days did not alter the anticoagulant effects of steady-state **phenprocoumon**.[5] No **phenprocoumon** dose adjustments would be expected to be needed on concurrent use.

There appears to be just one review that mentions the possible interaction of moclobemide with **warfarin**.[6] This review reports that (in 1996), the manufacturer had on file six possible cases of anticoagulation problems in patients taking **warfarin** and moclobemide. On the basis that moclobemide is an inhibitor of the cytochrome P450 isoenzyme CYP2C19 and possibly also CYP1A2, the reviewers considered that moclobemide could theoretically increase the levels of *S*-warfarin, and so stated that an interaction with **warfarin** was likely. However, CYP2C19 and CYP1A2 are just two of a number of isoenzymes involved in metabolism of just *R*-warfarin, which is the less pharmacologically active isomer of **warfarin**. Other CYP2C19 inhibitors, such as omeprazole (see 'Coumarins + Proton pump inhibitors', p.499), and ticlopidine (see 'Coumarins + Ticlopidine', p.514), usually have no clinically relevant effect on **warfarin** levels. This, and the absence of published reports of problems, suggests that moclobemide is unlikely to interact with **warfarin**. There appears to be no evidence about other coumarins, but there seems to be no reason to suspect that they may interact.

1. Fumarola D, De Rinaldis P. Ricerche sperimentali sugli inibitori della mono-aminossidasi. Influenza della nialamide sulla attività degli anticoagulanti indiretti. *Haematologica* (1964) 49, 1248–66.
2. Reber K, Studer A. Beeinflussung der Wirkung einiger indirekter Antikoagulantien durch Monoaminoxydase-Hemmer. *Thromb Diath Haemorrh* (1965) 14, 83–7.
3. de Nicola P, Fumarola D, de Rinaldis P. Beeinflussung der gerinnungshemmenden Wirkung der indirekten Antikoagulantien durch die MAO-Inhibitoren. *Thromb Diath Haemorrh* (1964) 12 (Suppl), 125–7.
4. Hrdina P, Rusnáková M, Kovalčík V. Changes of hypoprothrombinaemic activity of indirect anticoagulants after MAO inhibitors and reserpine. *Biochem Pharmacol* (1953) 12 (Suppl), 241.
5. Amrein R, Güntert TW, Dingemanse J, Lorscheid T, Stabl M, Schmid-Burgk W. Interactions of moclobemide with concomitantly administered medication: evidence from pharmacological and clinical studies. *Psychopharmacology (Berl)* (1992) 106, S24–S31.
6. Duncan D, Sayal K, McConnell H, Taylor D. Antidepressant interactions with warfarin. *Int Clin Psychopharmacol* (1998) 13, 87–94.

Coumarins + Medroxyprogesterone or Megestrol

High-dose medroxyprogesterone acetate and megestrol prolonged the half-life of single-dose warfarin in one small study in patients with advanced breast cancer.

Clinical evidence, mechanism, importance and management

In a study in patients with advanced breast cancer, a single 0.3-mg/kg dose of **warfarin** was given to 2 patients before and after oral medroxyprogesterone acetate 500 mg twice daily for 5 weeks and to 2 patients before and after megestrol 160 mg daily for 5 weeks. The half-life of **warfarin** was increased by 71% and the clearance decreased by 35%.[1] Although the evidence is limited, what is known suggests that it would be prudent to monitor prothrombin times in patients taking **warfarin** who are given high-dose medroxyprogesterone acetate or megestrol, being alert for any increased warfarin effects.

1. Lundgren S, Kvinnsland S, Utaaker E, Bakke O, Ueland PM. Effect of oral high-dose progestins on the disposition of antipyrine, digitoxin, and warfarin in patients with advanced breast cancer. *Cancer Chemother Pharmacol* (1986) 18, 270–5.

Coumarins + Mefloquine

The effects of warfarin and an unnamed coumarin were increased in two patients who took mefloquine.

Clinical evidence, mechanism, importance and management

A 66-year-old man taking **warfarin** and various other drugs presented to an emergency department unwell with a distended abdomen while travelling in Kenya. His prothrombin time was grossly prolonged and the distension was found to be due to bleeding. One week before travel he had started mefloquine 250 mg weekly without a check of his prothrombin time. He was given subcutaneous enoxaparin instead of **warfarin** while continuing the mefloquine. Another patient taking a coumarin and oral antidiabetics presented with hypoglycaemia and a large haematoma of the right leg after taking 3 doses of mefloquine 250 mg weekly. His INR was 6.4.[1]

The author considered that mefloquine may have caused the increased anticoagulation in these two cases, and suggested that mefloquine should be started several weeks before travel to allow for monitoring of any changes in anticoagulant effects.[1] The manufacturers of mefloquine also recommend that, before departure, travellers also taking anticoagulants should be checked for any alteration in anticoagulant effect.[2] This is probably prudent, although patients should be advised that many other factors associated with travel, such as altered diet, could contribute to a change in anticoagulant control.

1. Loefler I. Mefloquine and anticoagulant interaction. *J Travel Med* (2003) 10, 194–5.
2. Lariam (Mefloquine hydrochloride). Roche Products Ltd. UK Summary of product characteristics, August 2009.

Coumarins + Melatonin

Case reports suggest that melatonin may raise or lower the INR in response to warfarin.

Clinical evidence

Six case reports of a suspected interaction between melatonin and **warfarin** have been documented by the WHO Uppsala Monitoring Centre, and have been briefly summarised in a review of melatonin.[1] In three cases, the prothrombin time was increased, with bleeding events in two (nosebleed, eye haemorrhage, bruising) occurring up to 8 days after starting to take melatonin. The other three cases reports describe a prothrombin time decrease.[1]

Mechanism

Unknown. Melatonin did not inhibit the cytochrome P450 isoenzyme CYP2C9 *in vitro*,[2] and would not therefore be expected to alter warfarin metabolism by this mechanism.

Importance and management

These appear to be the only reports in the literature of a possible interaction between melatonin and warfarin. They are difficult to interpret, because they include both increased and decreased warfarin effects, and it is possible that they are just idiosyncratic cases. Because of these cases, a study designed to exclude a pharmacokinetic and/or pharmacodynamic interaction would be useful. Until more is known, bear these cases in mind in the event of an unexpected change in coagulation status in patients also taking melatonin supplements.

1. Herxheimer A, Petrie KKJ. Melatonin for the prevention and treatment of jet lag. Available in the Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2009.
2. Yeleswaram K, Vachharajani N, Santone K. Involvement of cytochrome P-450 isozymes in melatonin metabolism and clinical implications. *J Pineal Res* (1999) 26, 190–1.

Coumarins + Melilot (*Melilotus officinalis*)

The INR of a patient taking acenocoumarol was increased after she used a melilot-containing topical cream, and a woman who had been drinking large quantities of a herbal tea containing melilot developed a prolonged prothrombin time.

Clinical evidence

A 66-year-old taking **acenocoumarol**, levothyroxine and prazepam had an increase in her INR after massaging a proprietary topical cream (*Cyclo 3*) containing melilot and butcher's broom on her legs three times daily. On the first occasion her INR rose from about 2 to 5.8 after 7 days of use,

and on a later occasion it rose to 4.6 after 10 days of use.[1] In another report, a woman with unexplained abnormal menstrual bleeding was found to have a prothrombin time of 53 seconds, and laboratory tests showed that her blood clotting factors were abnormally low. When given parenteral vitamin K her prothrombin time rapidly returned to normal (suggesting that she was taking a vitamin K antagonist of some kind). She strongly denied taking any anticoagulant drugs, but it was eventually discovered that she had been drinking large quantities of a herbal tea containing among other ingredients tonka beans, melilot and sweet woodruff, all of which might contain natural coumarins.[2]

Mechanism

Unknown. Melilot is known to contain natural coumarins, which can be turned into dicoumarol by moulds, see 'Coumarins + Herbal medicines; Miscellaneous', p.472.

Importance and management

Evidence appears to be limited to these isolated cases, which are not established. Many factors influence anticoagulant control, and therefore it is not possible to reliably ascribe a change in INR specifically to a drug interaction in a single case report without other supporting evidence. It may be better to advise patients to discuss the use of any herbal products they wish to try, and to increase monitoring if this is thought advisable. Cases of uneventful use should be reported, as they are as useful as possible cases of adverse effects.

1. Chiffoleau A, Huguenin H, Veyrac G, Argaiz V, Dupe D, Kayser M, Bourin M, Jolliet P. Interaction entre mélilot et acénocoumarol ? (mélilot-*ruscus aculeatus*). *Therapie* (2001) 56, 321–7.
2. Hogan RP. Hemorrhagic diathesis caused by drinking an herbal tea. *JAMA* (1983) 249, 2679–80.

Coumarins + Menthol

A man had a reduction in the effects of warfarin, which were attributed to the use of menthol cough lozenges during a flu-like illness.

Clinical evidence, mechanism, importance and management

A 57-year-old man taking **warfarin** 49 mg weekly with an INR in the range of 2.3 to 2.7 for the previous 3 weeks was found to have an INR of 1.45. He had been unwell with a flu-like illness over the past week, for which he had been taking about 6 *Halls* menthol cough lozenges (cough drops) per day for 4 days. He said he had not changed his diet or missed any warfarin doses. The **warfarin** dose was increased to 53 mg weekly for a week with an INR rise to 2.2, then the **warfarin** dose was decreased to 52 mg weekly with an INR of 3.06, so the previous dose of 49 mg weekly was resumed with an INR of 2.92.[1] Whether this case represents an interaction with the menthol lozenges is uncertain. Further study is needed.

1. Kassebaum PJ, Shaw DL, Tomich DJ. Possible warfarin interaction with menthol cough drops. *Ann Pharmacother* (2005) 39, 365–7.

Coumarins + Meprobamate

The anticoagulant effects of warfarin are not altered to a clinically relevant extent by meprobamate.

Clinical evidence, mechanism, importance and management

In a study, 9 patients stabilised on **warfarin** were given meprobamate 400 mg four times daily for 2 weeks. Three patients had a small increase in their prothrombin time, five had a small decrease and one patients remained unaffected: all the changes were considered to fall within the range of variations normally seen in clinical practice.[1] Moreover, in a later placebo-controlled study in 17 patients taking **warfarin**, the 8 patients who were also given meprobamate 2.4 g daily for 4 weeks had only a small clinically unimportant reduction in their prothrombin time.[2] Similar results were found in another study.[3] No **warfarin** dose adjustments would therefore seem to be needed if meprobamate is added to established treatment with **warfarin**.

1. Udall JA. Warfarin therapy not influenced by meprobamate. A controlled study in nine men. *Curr Ther Res* (1970) 12, 724–8.
2. Gould L, Michael A, Fisch S, Gomprecht RF. Prothrombin levels maintained with meprobamate and warfarin. A controlled study. *JAMA* (1972) 220, 1460–2.
3. deCarolis PP, Gelfand ML. Effect of tranquilizers on prothrombin time response to coumarin. *J Clin Pharmacol* (1975) 15, 557.

Coumarins + Methaqualone

Methaqualone may cause a very small and clinically unimportant reduction in the anticoagulant effects of warfarin.

Clinical evidence, mechanism, importance and management

The average prothrombin time of 10 patients stabilised on **warfarin** was 20.9 seconds before, 20.4 seconds during, and 19.6 seconds after taking methaqualone 300 mg at bedtime for 4 weeks.[1] The plasma **warfarin** levels of another patient were unaffected by methaqualone, although there was some evidence that enzyme induction had occurred.[2] Methaqualone has some enzyme-inducing effects so that any small changes in prothrombin times reflect a limited increase in the metabolism and clearance of **warfarin**, but these appear to be too small to be of clinical significance.[2,3] No special precautions seem to be necessary.

1. Udall JA. Clinical implications of warfarin interactions with five sedatives. *Am J Cardiol* (1975) 35, 67–71.
2. Whitfield JB, Moss DW, Neale G, Orme M, Breckenridge A. Changes in plasma γ-glutamyl transpeptidase activity associated with alterations in drug metabolism in man. *BMJ* (1973) 1, 316–18.
3. Nayak RK, Smyth RD, Chamberlain AP, Polk A, DeLong AF, Herczeg T, Chemburkar PB, Joslin RS, Reavey-Cantwell NH. Methaqualone pharmacokinetics after single- and multiple-dose administration in man. *J Pharmacokinet Biopharm* (1974) 2, 107–21.

Coumarins + Methylphenidate

Methylphenidate appears not to interact with ethyl biscoumacetate.

Clinical evidence, mechanism, importance and management

In one study in 4 healthy subjects, the half-life of a single dose of **ethyl biscoumacetate** was approximately doubled after they took methylphenidate 20 mg daily for 3 to 5 days.[1] However, a later double-blind, placebo-controlled study did not find an interaction: the half-life of **ethyl biscoumacetate** was not altered by methylphenidate 20 mg daily for 4 days in 4 healthy subjects, and was not different to that seen in 4 subjects given placebo.[2] The first authors suggested that methylphenidate inhibits the metabolism of **ethyl biscoumacetate**, but this seems unlikely given the findings of the second study.

Although the findings of these two studies are at odds with each other, the better-controlled study and the lack of reports of problems in the literature suggest that an interaction is unlikely. There does not seem to be any information about other coumarins. Nevertheless, the manufacturers recommend caution and suggest that patients taking coumarins should have their INR monitored if methylphenidate is started or stopped.[3,4] This seems over-cautious.

1. Garrettson LK, Perel JM, Dayton PG. Methylphenidate interaction with both anticonvulsants and ethyl biscoumacetate. *JAMA* (1969) 207, 2053–6.
2. Hague DE, Smith ME, Ryan JR, McMahon FG. The effect of methylphenidate and prolintane on the metabolism of ethyl biscoumacetate. *Clin Pharmacol Ther* (1971) 12, 259–62.
3. Ritalin (Methylphenidate hydrochloride). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, June 2007.
4. Ritalin (Methylphenidate hydrochloride). Novartis. US Prescribing information, April 2009.

Coumarins + Metoclopramide

Metoclopramide caused a minor decrease in the AUC of phenprocoumon, without altering its anticoagulant effects. There is one case report of an interaction between phenprocoumon and metoclopramide.

Clinical evidence, mechanism, importance and management

An elderly women taking **phenprocoumon** and metoclopramide developed a renal bleed and a low Quick time shortly after stopping metoclopramide.[1] This prompted a study in 12 healthy subjects, in which metoclopramide 30 mg daily for 10 days slightly reduced the AUC of a single dose of **phenprocoumon** given on day 4 by 16%, but no significant

changes were seen in the anticoagulant effects.[2] The study findings suggests that no **phenprocoumon** dose adjustment would be expected to be necessary if these two drugs are given together. There seems to be no published information about a possible interaction with any other coumarins, and given the widespread use of both metoclopramide and **warfarin**, an interaction appears to be unlikely.

1. Bruhn HD, Kirch W, Ohnhaus EE. Arzneimittelinteraktionen. Metoclopramid-phenprocoumon. *Dtsch Med Wochenschr* (1987) 112, 742.
2. Wesermeyer D, Mönig H, Gaska T, Masuch S, Seiler KU, Huss H, Bruhn HD. Der Einfluß von Cisaprid und Metoclopramid auf die Bioverfügbarkeit von Phenprocoumon. *Hamostaseologie* (1991) 11, 95–102.

Coumarins + Metrifonate

Metrifonate did not interact with single-dose warfarin in one study.

Clinical evidence, mechanism, importance and management

A double-blind, placebo-controlled, crossover study in 14 healthy subjects found that metrifonate 50 mg daily for 8 days did not change the pharmacokinetics and pharmacodynamics of a single 25-mg dose of **warfarin** given on day 4. Plasma **warfarin** levels and prothrombin times remained unchanged.[1] This suggests that no **warfarin** dose adjustments are likely to be needed if these two drugs are used concurrently.

1. Heinig R, Kitchin N, Rolan P. Disposition of a single dose of warfarin in healthy individuals after pretreatment with metrifonate. *Clin Drug Invest* (1999) 18, 151–9.

Coumarins + Misoprostol

An isolated report describes a reduction in the anticoagulant effects of acenocoumarol, which was attributed to the use of misoprostol.

Clinical evidence, mechanism, importance and management

A 39-year-old woman taking **acenocoumarol**, celiprolol, triamterene, cyclothiazide, pravastatin and diosmin had a rise in her prothrombin levels from 0.3 to 1 within 8 days of starting to take diclofenac and misoprostol 400 micrograms daily. A day after these two drugs had been withdrawn her prothrombin level had fallen to 0.67, and after another 3 days to 0.32.[1] The reasons for this reaction are not known, but suspicion falls on the misoprostol because diclofenac, if and when it interacts with coumarins, increases rather than reduces their effects (see 'Coumarins + NSAIDs; Diclofenac', p.483). However, just why misoprostol should cause these changes is not clear.

This is an isolated case, complicated by the presence of a number of other drugs, which suggests that it is unlikely to be of general importance. More study is needed.

1. Martin MP, Jonville-Bera AP, Bera F, Caillard X, Autret E. Interaction entre le misoprostol et l'acénocoumarol. *Presse Med* (1995) 24, 195.

Coumarins + Modafinil

Modafinil does not alter the pharmacokinetics or effect of single-dose warfarin.

Clinical evidence, mechanism, importance and management

In a placebo-controlled study, when 14 healthy subjects taking modafinil 200 to 400 mg daily long-term were given a single 5-mg dose of warfarin, there were no changes in the pharmacokinetics of *R*- and *S*-warfarin. In addition, there was no change in clotting time.[1]

This study was conducted because, *in vitro*, modafinil was shown to be an inhibitor of the cytochrome P450 isoenzyme CYP2C9, and warfarin is an accepted probe substrate of this isoenzyme. It is well recognised that *in vitro* findings do not always predict what will happen *in vivo*, and the findings of the study show that modafinil is not a clinically relevant inhibitor of CYP2C9. Nevertheless, on the basis that this was a single-dose study, the authors suggest some caution.[1] The manufacturers recommend that prothrombin times should be monitored more frequently[2] particularly during the first 2 months of concurrent use and after changes in modafinil dose.[3] This is a cautious interpretation, and a pharmacokinetic interaction seems unlikely.

1. Robertson P, Hellriegel ET, Arora S, Nelson M. Effect of modafinil at steady state on the single-dose pharmacokinetic profile of warfarin in healthy volunteers. *J Clin Pharmacol* (2002) 42, 205–14.
2. Provigil (Modafinil). Cephalon, Inc. US Prescribing information, March 2008.
3. Provigil (Modafinil). Cephalon (UK) Ltd. UK Summary of product characteristics, November 2009.

Coumarins + Moracizine

Moracizine did not alter the pharmacodynamics of single-dose warfarin, and had no clinically relevant effect on warfarin pharmacokinetics. However, an isolated report describes bleeding in a patient taking warfarin with moracizine.

Clinical evidence

In a study in 12 healthy subjects, moracizine 250 mg every 8 hours for 21 days caused little or no change in the pharmacokinetics of a single 25 mg dose of **warfarin** given on day 14. There was only a slight decrease in the **warfarin** elimination half-life, from 37.6 hours to 34.2 hours, and no change in prothrombin times.[1,2] The manufacturer also noted that clinical experience in 34 patients suggests that no significant changes in **warfarin** dose requirements are needed after moracizine is started.[1]

However, in one case report the prothrombin time of a woman taking **warfarin**, digoxin, captopril and prednisone rose from a range of 15 to 20 seconds up to 41 seconds within 4 days of starting moracizine 300 mg three times daily. She bled (haematemesis, haematuria), but responded rapidly to withdrawal of the **warfarin** and moracizine, and phytomenadione.[3]

Mechanism

Not understood.

Importance and management

Information appears to be limited to these reports. The study and early clinical experience suggest that no interaction occurs. The case of an increased effect seems to be an isolated report, and therefore unlikely to be of general importance.

1. Siddoway LA, Schwartz SL, Barbey JT, Woosley RL. Clinical pharmacokinetics of moricizine. *Am J Cardiol* (1990) 65, 21D–25D.
2. Benedek IH, King S-YP, Powell RJ, Agra AM, Schary WL, Pieniaszek HJ. Effect of moricizine on the pharmacokinetics and pharmacodynamics of warfarin in healthy volunteers. *J Clin Pharmacol* (1992) 32, 558–63.
3. Serpa MD, Cossolias J, McGreevy MJ. Moricizine-warfarin: a possible interaction. *Ann Pharmacother* (1992) 26, 127.

Coumarins + Nefazodone or Trazodone

A handful of case reports describe a moderate reduction in the anticoagulant effects of warfarin caused by trazodone, and another case report describes a rise in INR. In one study, nefazodone slightly decreased the level of *S*-warfarin and did not alter the prothrombin ratio.

Clinical evidence

(a) Nefazodone

In one study, 17 healthy subjects given **warfarin** to achieve a prothrombin ratio of 1.2 to 1.5 for 14 days were then given nefazodone 200 mg or placebo every 12 hours for a further 7 days. The only pharmacokinetic changes were a 12% decrease in the AUC and maximum serum levels of *S*-warfarin. No changes occurred in the prothrombin ratios.[1]

(b) Trazodone

In an early case series, a patient stabilised on **warfarin** was given trazodone 75 mg daily for 8 days without any significant changes in the prothrombin time. Similarly, the same dose of trazodone had no obvious effect on the prothrombin time of a patient who had recently started taking **phenprocoumon** or another patient who had recently started taking **ethyl biscoumacetate**.[2]

However, in another report, a woman needed a small increase in her

warfarin dose, from 6.4 mg daily to 7.5 mg daily, when she was given trazodone 300 mg daily, in order to maintain her prothrombin time at 20 seconds. Her **warfarin** requirements fell when the trazodone was later withdrawn.[3] A retrospective review from June 1998 to June 1999 identified 75 patients taking both trazodone and **warfarin**. Of the patients who had started trazodone during this period (number not stated), at least 3 had a probable interaction. One had a decrease in INR from 2.79 to 1.07 six days after starting trazodone, and needed a 25% increase in the dose of **warfarin**. Another patient had an increase in INR when he ran out of trazodone, and a decrease in INR on restarting the trazodone. A third required a 39% increase in **warfarin** dose after starting trazodone.[4] Conversely, there is a report of a rise in INR from between 2 and 3 up to 6, without bleeding complications, that occurred in a patient 2 weeks after trazodone 50 mg daily and fish oil 2 g daily were started.[5] The manufacturer in the US notes that there have been reports of both increased and decreased prothrombin times in patients taking warfarin with trazodone.[6]

Mechanism

Unknown.

Importance and management

The limited evidence available suggests that some patients might require a moderate increase in warfarin dose when starting trazodone, and, conversely, there is one possible case of an increase in INR. Therefore, it might be prudent to monitor the INR in all patients taking warfarin if trazodone is started or stopped, adjusting the warfarin dose if necessary. The clinical relevance of the 12% decrease in *S*-warfarin levels see with nefazodone is likely to be minor. The authors of the study concluded that no change in warfarin dose is likely to be required on concurrent use.[1]

1. Salazar DE, Dockens RC, Milbrath RL, Raymond RH, Fulmor IE, Chaikin PC, Uderman HD. Pharmacokinetic and pharmacodynamic evaluation of warfarin and nefazodone coadministration in healthy subjects. *J Clin Pharmacol* (1995) 35, 730–8.
2. Cozzolino G, Pazzaglia I, De Gaetano V, Macri M. Clinical investigation on the possible interaction between anti-coagulants and a new psychotropic drug (Trazodone). *Clin Eur* (1972) 11, 593–607.
3. Hardy J-L, Sirois A. Reduction of prothrombin and partial thromboplastin times with trazodone. *Can Med Assoc J* (1986) 135, 1372.
4. Small NL, Giamonna KA. Interaction between warfarin and trazodone. *Ann Pharmacother* (2000) 34, 734–6.
5. Jalili M, Dehpour AR. Extremely prolonged INR associated with warfarin in combination with both trazodone and omega-3 fatty acids. *Arch Med Res* (2007) 38, 901–4.
6. Desyrel (Trazodone hydrochloride). Bristol-Myers Squibb Company. US Prescribing information, February 2009.

Coumarins + NNRTIs

Two reports suggest that warfarin requirements are markedly increased by nevirapine. There is one case report of an unusually low warfarin dose requirement in a patient taking an efavirenz-based regimen. The effect of other NNRTIs is unclear.

Clinical evidence

(a) Efavirenz

A woman receiving efavirenz, didanosine and lamivudine was started on **warfarin** for a deep vein thrombosis. After 12 days she was discharged with an INR between 2 and 3 on a mean daily dose of warfarin of 5 mg. About one week later her INR was 2.7, but then 3 days later she had blood in the urine and an INR of 7. She was eventually stabilised on a much lower mean dose of warfarin of 1.25 mg daily.[1]

(b) Etravirine

In a study, 12 healthy subjects were given a single 10-mg dose of **warfarin** on day one and day 14 of a 14-day course of etravirine 200 mg twice daily. Etravirine increased the ratio of the AUC of *S*-warfarin to 7-hydroxy-*S*-warfarin by 63%.[2]

(c) Nevirapine

A man taking **warfarin** 2.5 mg daily (INR 2.1 to 2.4) needed a doubled **warfarin** dose when his treatment with zidovudine and didanosine was replaced by stavudine, lamivudine and nevirapine. A few days later, when his treatment was again changed to stavudine, lamivudine and saquinavir, his original **warfarin** dose was found to be adequate. Another patient was resistant to doses of **warfarin** of up to 17 mg daily while taking zidovudine, lamivudine and nevirapine, but he responded to **warfarin** 5 mg daily when the nevirapine was withdrawn. The warfarin dose had to be raised to 12 mg daily when nevirapine was restarted. Yet another patient showed resistance to **warfarin** while taking nevirapine.[3] Similarly, in another report, a patient taking lamivudine 150 mg twice daily, zidovudine 300 mg twice daily and nevirapine 200 mg twice daily required a high **warfarin** dose of 20 mg daily to maintain a therapeutic INR. When his antiretroviral regimen was changed to nelfinavir, didanosine and tenofovir, a reduction in his warfarin dose to 12.5 mg daily was required.[4] Note that nelfinavir may also interact with warfarin, see 'Coumarins + Protease inhibitors', p.498.

Mechanism

The finding of markedly increased warfarin requirements with nevirapine was not predicted from *in vitro* studies,[5] in which nevirapine did not inhibit the cytochrome P450 isoenzyme CYP2C9, by which the more potent *S*-warfarin is metabolised, and had mixed (induced and inhibited) effects on CYP3A4, which partly metabolises *R*-warfarin. Although induction of CYP3A4 might reduce *R*-warfarin levels, the clinical effect of this would be expected to be modest.

In vitro efavirenz inhibits CYP2C9 and induces CYP3A4,[6] and its effects on the clinical pharmacokinetics of warfarin are unknown. In the case described, it was suggested that efavirenz inhibited warfarin metabolism,[1] but it is unclear why this became suddenly apparent 3 weeks after starting concurrent use.

Importance and management

Information on **nevirapine** seems to be limited to these four cases, but it would be prudent to monitor prothrombin times and INRs in any patient if warfarin and nevirapine are used concurrently, being alert for the need to increase the warfarin dose (possibly twofold). Information about other coumarins seems to be lacking, but if the suggested mechanism is correct, all coumarins would be expected to interact to some extent.

Increased monitoring on the concurrent use of **efavirenz** and warfarin would also seem advisable, the only case available appearing to suggest a decreased warfarin requirement. Until more is known, it would seem prudent to monitor all coumarins.

Etravirine has weak effects on both CYP3A4 and CYP2C9, the isoenzymes involved in the metabolism of warfarin and may therefore have some modest effects on warfarin metabolism. Until the clinical relevance of this is known it may be prudent to be alert for increased warfarin effects.

Delavirdine inhibits CYP3A4, but the effect of this alone on warfarin levels is probably modest. Nevertheless, the US manufacturer of delavirdine advises monitoring the INR of patients also given warfarin.[7]

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Coumarins and related drugs + NSAIDs

The concurrent use of NSAIDs and coumarin anticoagulants increases the risk of gastrointestinal haemorrhage and, to a lesser extent, non-gastrointestinal bleeds. Care is needed with the combination. Some individual NSAIDs also alter the pharmacokinetics and/or pharmacodynamics of warfarin, and these effects are covered in specific monographs.

Clinical evidence

(a) Bleeding

In a retrospective cohort study of patients hospitalised for peptic ulcer disease, the current use of both oral anticoagulants and NSAIDs was associated with a marked increase in the risk of haemorrhagic peptic ulcer

disease of 12.7 (95% confidence interval 6.3 to 25.7). This was much higher than the risk associated with NSAIDs alone or oral anticoagulants alone (both about a fourfold increased risk). In this study, about 10% of the hospitalisations for haemorrhagic peptic ulcer disease in patients taking anticoagulants were attributed to the concurrent use of NSAIDs. The oral anticoagulants used were the coumarins **warfarin**, **phenprocoumon** and **acenocoumarol**, and the indanediones **phenindione** and **anisindione**. The NSAIDs used were nonacetylated salicylates, **ibuprofen**, **indometacin**, **sulindac**, **naproxen**, **fenoprofen**, **piroxicam**, **tolmetin**, and **meclofenamate**.[1]

In a case-control study, patients taking **warfarin** who were admitted to hospital with upper gastrointestinal haemorrhage were significantly more likely to be taking non-selective NSAIDs (odds ratio 1.9). A similar increased risk was seen with the coxibs **celecoxib** and **rofecoxib**.[2] Consider also, 'Coumarins and related drugs + NSAIDs; Coxibs', p.482. Similarly, in a large population-based, retrospective case control-study using records from the UK General Practice Research Database from 2000 to 2005, the use of **warfarin** with NSAIDs was associated with a increased risk of gastrointestinal bleeding when compared with either drug alone (rate ratio of 4.79 for concurrent use compared with 1.94 for warfarin and 1.78 for NSAIDs). The most commonly used NSAIDs were **diclofenac**, **ibuprofen**, and **naproxen**, and the full list of NSAIDs considered was **aclofenac** (sic), **dexketoprofen**, **diclofenac**, **diflunisal**, **etodolac**, **fenoprofen**, **ibuprofen**, **indomethacin**, **ketoprofen**, **ketorolac**, **mefenamic acid**, **meloxicam**, **nabumetone**, **naproxen**, **piroxicam**, **sulindac**, **tenoxicam** and **tiaprofenic acid**. A very similar increased risk (rate ratio 4.62) was seen with the coxibs, **celecoxib** and **rofecoxib**.[3]

In yet another case-control study, the use of NSAIDs with the coumarins **acenocoumarol** or **phenprocoumon** was associated with an increased risk of hospitalisation for gastrointestinal bleeding (odds ratio 4.6) and, to a lesser extent, non-gastrointestinal bleeding (odds ratio 1.7).[4] Similarly, in a questionnaire-based study, 12.2% of patients taking **acenocoumarol** or **phenprocoumon** who had a bleeding complication were found to have used an NSAID in the previous month compared with only 2.5% of coumarin users who did not have a bleed (an increased relative risk of bleeding of 5.8).[5]

In contrast, in a large analysis of claims data, use of NSAIDs (unnamed) with **warfarin** was, unexpectedly, not associated with an increased risk of haemorrhage.[6]

(b) Pharmacokinetic interactions

Phenylbutazone and related drugs (see 'Coumarins and related drugs + NSAIDs; Phenylbutazone and related drugs', p.488) are well known to inhibit the metabolism of **warfarin** by the cytochrome P450 isoenzyme CYP2C9. Few other NSAIDs are known CYP2C9 inhibitors; however; many are CYP2C9 substrates. In one cohort study in patients taking **acenocoumarol** or **phenprocoumon**, the use of NSAIDs that are known substrates of CYP2C9 (**celecoxib**, **diclofenac**, **flurbiprofen**, **ibuprofen**, **indometacin**, **ketoprofen**, **meloxicam**, **naproxen** and **piroxicam**) slightly increased the risk of over-anticoagulation (INR greater than 6) in patients with wild-type CYP2C9 (relative risk of 1.69). However, the risk was greater in patients with variant CYP2C9 (relative risk 2.28), and particularly high in those with *3 variant alleles (relative risk 10.8).[7] In another smaller retrospective cohort study, starting the CYP2C9 substrates **diclofenac**, **naproxen**, or **ibuprofen** increased the INR above the therapeutic range in 52 of 112 patients taking **acenocoumarol**. However, in this study CYP2C9 genotype did not influence the interaction between **acenocoumarol** and **diclofenac**, **naproxen**, and **ibuprofen**.[8] For more general information about the genetic variations in cytochrome P450 isoenzymes, see 'Genetic factors in drug metabolism', (p.4).

(c) Other effects

In a prospective study, the concurrent use of musculoskeletal drugs (said to be mainly NSAIDs, with none specified) was associated with an apparent risk of INR instability (odds ratio 1.68) in 125 hospitalised patients starting **acenocoumarol**.[9] Instability was defined as not having two consecutive INRs within the range of 2 to 3. However, most of the patients defined as unstable had INRs below the therapeutic range, and it was suggested that this may have just reflected conservative dosing of the anticoagulant in patients already taking NSAIDs because of the possible interaction. This would result in these patients taking longer to reach the therapeutic range, and is not therefore an interaction as such.

Mechanism

NSAIDs, to a greater or lesser extent irritate the stomach lining, which can result in gastrointestinal bleeding, which will be more severe in anticoagulated patients. Many also have antiplatelet activity, which can prolong bleeding times, and contribute to the increased bleeding risk.

Some NSAIDs are inhibitors of the cytochrome P450 isoenzyme CYP2C9, and inhibit the metabolism of warfarin by this isoenzyme. There is also possibly a pharmacokinetic interaction with NSAIDs that are substrates for CYP2C9. People with variant CYP2C9 (about 5 to 11% of Caucasians) have a lower metabolising capacity for warfarin, and require much lower maintenance doses. It is possible that use of an NSAID that is a CYP2C9 substrate may result in reduced warfarin metabolism, although this requires confirmation in controlled studies.

Importance and management

The available data indicate that the risk of bleeding is increased if NSAIDs are used in patients taking coumarin or **indanedione** anticoagulants. For this reason, it would be prudent to avoid the unnecessary concurrent use of NSAIDs when simple analgesics are adequate. When concurrent use is necessary, extra caution may be appropriate. It would be advisable to avoid NSAIDs with higher risks of inducing gastrointestinal bleeds, and possibly also to consider prophylactic mucosal protection. Note that patients at higher risk of NSAID-induced gastrointestinal bleeding and those prone to warfarin-related bleeding are likely to be at increased risk. Further study is required to ascertain whether people with CYP2C9 poor metabolising capacity are at increased risk of an interaction when given NSAIDs that are CYP2C9 substrates.

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Coumarins + NSAIDs; Benzydamine

Oral benzydamine did not alter the anticoagulant effects of phenprocoumon. Topical formulations of benzydamine (mouthwash and spray) would not be expected to interact.

Clinical evidence, mechanism, importance and management

In 10 patients stabilised on **phenprocoumon**, the anticoagulant response was not significantly changed by benzydamine 50 mg three times daily for 2 weeks, although there was some evidence of an increase in blood levels of the anticoagulant.[1] This suggests that no **phenprocoumon** dose adjustments are likely to be needed on concurrent use. Note that benzydamine tends to be used as a topical mouthwash or spray. Neither of these topical formulations would be expected to interact.

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Coumarins + NSAIDs; Clonixin

Clonixin lysine did not appear to alter the anticoagulant effects of phenprocoumon in a pharmacological study. However, note that

all NSAIDs increase the risk of bleeding, and an increased risk is seen when they are combined with anticoagulants.

Clinical evidence, mechanism, importance and management

In a randomised, crossover study in 12 healthy men, the pharmacokinetics and the anticoagulant activity of a single 18-mg dose of **phenprocoumon** were unchanged by clonixin lysine 125 mg five times daily, given for 3 days before and for 13 days after the **phenprocoumon**.[1]

On the basis of this study, no adjustment in coumarin dose would be expected to be needed when clonixin is used. However, care is still needed with every NSAID, because, to a greater or lesser extent, they irritate the stomach lining, which can result in gastrointestinal bleeding, which will be more severe in anticoagulated patients. Consider also, 'Coumarins and related drugs + NSAIDs', p.480.

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Coumarins and related drugs + NSAIDs; Coxibs

Etoricoxib, lumiracoxib and rofecoxib cause a slight increase in the INR in response to warfarin, whereas celecoxib and parecoxib have no effect. However, raised INRs accompanied by bleeding, particularly in the elderly, have been attributed to the use of warfarin and celecoxib or rofecoxib. In addition, the use of celecoxib or rofecoxib is associated with an increased risk of hospitalisation for upper gastrointestinal haemorrhage, which was of a similar magnitude to that seen with non-selective NSAIDs.

Clinical evidence

(a) Celecoxib

In a placebo-controlled study, **warfarin** 2 to 5 mg daily was given to 24 healthy subjects to maintain a stable prothrombin time of 1.2 to 1.7 times their pretreatment values for at least 3 consecutive days. They were then given placebo or celecoxib 200 mg twice daily for a week. It was found that the steady-state pharmacokinetics of both *S*- and *R*-warfarin and the prothrombin times were unchanged by the presence of the celecoxib.[1]

Similarly, in a crossover study in 15 osteoarthritic patients stabilised on **warfarin**, celecoxib 200 mg daily for 5 weeks did not alter the mean INR when compared with codeine (see 'Coumarins + Opioids; Codeine', p.490). One patient had an INR of 4.9 when taking celecoxib.[2] However, in 16 patients stabilised on **warfarin** and given celecoxib 200 mg daily for 3 weeks, the INR increased by 13%, 6% and 5% at week one, 2 and 3, respectively, the change at week one being statistically significant.[3] Furthermore, in another analysis of 28 patients taking **warfarin** who were prescribed either celecoxib or rofecoxib, 13 had increases in their INR, of which 7 (5 taking celecoxib) had no other explanation for the INR increase other than the use of the coxib. The average increase in INR in these 7 patients was 1.5, and one patient had bruising and epistaxis and required treatment with phytomenadione.[4]

Case reports of an interaction have also been published.[5-10] In one report, an 88-year-old woman stabilised on **warfarin** had a rise in her INR from 3.1 to 5.8 when celecoxib 200 mg daily was substituted for diclofenac. After several **warfarin** dose adjustments she was later restabilised on a 25% lower **warfarin** dose.[5] There is a similar case report of a 77-year old patient who required a 10% decrease in her **warfarin** dose to maintain her target INR when celecoxib 100 mg twice daily was also given.[8] In another case, the patient was shown to have a variant of CYP2C9, with lower metabolising capacity, which was thought to explain the interaction,[10] see also *Mechanism*, below. The manufacturers also noted that bleeding events have been reported with this combination, predominantly in the elderly, which led to a change in the product labelling.[11] A 2001 report from the Australian Adverse Drug Reactions Advisory Committee noted they had received 21 reports of increases in the INR in patients taking **warfarin** with celecoxib since the introduction of celecoxib in October 1999. Six of these cases reported bleeding complications. In addition, they had 11 cases of bleeding in patients taking the combination, with no reference to INR, or with an unchanged INR in one case.[12] A review of adverse effects of coxibs mentioned 2 patients taking **warfarin** who had increases in their INR while taking celecoxib.[13]

Moreover, in a case-control study, patients taking **warfarin** and admitted to hospital with upper gastrointestinal haemorrhage were significantly more likely to be also taking celecoxib (odds ratio 1.7). A similar increased risk was seen with rofecoxib and non-selective NSAIDs[14] (see 'Coumarins and related drugs + NSAIDs', p.480). The same findings were reported in another study for celecoxib and rofecoxib considered together.[15] In a retrospective analysis, the relative risk of all bleeding complications was slightly increased (1.34) in 123 patients taking celecoxib with **warfarin** when compared with 1022 control patients taking **warfarin** alone.[16]

(b) Etoricoxib

In a controlled study in 14 healthy subjects stabilised on **warfarin**, etoricoxib 120 mg daily for 21 days increased the INR by about 13%. There was no change in the pharmacokinetics of *S*-warfarin, and the AUC of *R*-warfarin showed a minor 10% increase.[17]

(c) Lumiracoxib

The manufacturer noted that in healthy subjects stabilised on **warfarin**, lumiracoxib 400 mg daily increased the INR by about 15%.[18] Lumiracoxib has been withdrawn from a number of countries because of reports of liver toxicity.

(d) Parecoxib

In a randomised study in healthy subjects given **warfarin**, the use of intravenous parecoxib 10 mg twice daily for 7 days had no significant effects on prothrombin times when compared with placebo. Parecoxib did not affect the pharmacokinetics of *S*- or *R*-warfarin.[19]

(e) Rofecoxib

In a study in 12 healthy subjects,[20] rofecoxib 50 mg daily for 12 days increased the maximum INR after a single 30-mg dose of **warfarin** given on day 7 by about 14%. In a steady-state study, 15 healthy subjects were given **warfarin** 5 mg daily to produce a stable prothrombin time of 1.4 to 1.7 for at least 3 consecutive days. They were then additionally given rofecoxib 25 mg or placebo daily for 3 weeks. It was found that the 24-hour average INR was increased by 9% by rofecoxib. Rofecoxib had no effect on the pharmacokinetics of the more potent *S*-warfarin enantiomer, but the AUC of *R*-warfarin was increased by about 40% in both the single dose and steady-state studies.[20] Moreover, in 16 patients stabilised on **warfarin** and given rofecoxib 25 mg daily for 3 weeks, the INR increased by 5%, 9%, and 5% at week one, 2, and 3, respectively, the change at week 2 being statistically significant.[3]

In one case report, an increase in INR was seen in two elderly patients taking **warfarin** and rofecoxib. The INRs were raised, in one case from less than 3 to 4.1 within a month of starting rofecoxib 12.5 mg daily, and in the other case from 3.2 to 4.6 within 2 days of starting rofecoxib. The INRs decreased when the **warfarin** dose was reduced.[4] In another case, this time in a patient taking **acenocoumarol**, the INR rose from the range of 2 to 3 up to over 8 two weeks after starting rofecoxib 50 mg daily.[21] A further possible case with **acenocoumarol** has been reported.[22] A 2002 report from the Australian Adverse Drug Reactions Advisory Committee noted that they had received 8 reports of increases in the INR of patients taking **warfarin** with rofecoxib since the introduction of rofecoxib in late 2000. Two of these cases reported bleeding complications. A further patient died of a cerebral haemorrhage, although the INR was stable.[23] A review of the adverse effects of coxibs included 5 patients taking **warfarin** who had increases in their INR while taking rofecoxib and **warfarin**.[13] Moreover, in a case-control study, patients taking **warfarin** and admitted to hospital with an upper gastrointestinal haemorrhage were significantly more likely to be also taking rofecoxib (odds ratio 2.4).[14] The same findings were reported in another study for celecoxib and rofecoxib considered together.[15] Note that rofecoxib has generally been withdrawn because of adverse cardiovascular effects.

Mechanism

Non-selective NSAIDs (see 'Coumarins and related drugs + NSAIDs', p.480), inhibit platelet aggregation and cause gastrointestinal toxicity, which can result in bleeding, the risk of which is increased in patients taking anticoagulants. Although coxibs are generally considered to be associated with a lower risk of gastrointestinal haemorrhage than non-selective NSAIDs, the only available comparative epidemiological studies found a similar increased risk of bleeding when coxibs were given with warfarin.

There is also possibly a pharmacokinetic interaction. Both warfarin and celecoxib are substrates of the cytochrome P450 isoenzyme CYP2C9, and it is possible that people with variants of CYP2C9 with lower metabolising

capacity may develop an interaction if given the combination. See 'Coumarins and related drugs + NSAIDs', p.480, for further discussion on this, and for more general information, see 'Genetic factors in drug metabolism', (p.4).

Rofecoxib possibly inhibits the metabolism of the less active *R*-warfarin by inhibition of CYP1A2,[20] and the active *R*-acenocoumarol by the same isoenzyme and CYP2C19.[21] It is unclear how etoricoxib increased R-warfarin levels as it has no known inhibitory effects on cytochrome P450, and the minor rise in warfarin levels is unlikely to completely account for the modest increase in INR.[17]

Importance and management

The interaction of the coumarins with these coxibs leading to raised INRs can be clinically significant, but is apparently rare. For example, of the 4 million prescriptions for celecoxib dispensed over the 18-month period from December 1998, about 1% were estimated to be for patients who would have been taking warfarin,[11] and only a handful of cases of an interaction had been reported. However, the manufacturers recommend that anticoagulant activity should be monitored in patients taking warfarin, other coumarins, or indanediones, particularly in the first few days after initiating or changing the dose of a coxib. Others recommend increased monitoring for 3 weeks.[3] Moreover, remember that all NSAIDS, including coxibs, can irritate the gastrointestinal tract and cause bleeding, the risk of which is increased with anticoagulants. Consider also, 'Coumarins and related drugs + NSAIDs', p.480.

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Coumarins + NSAIDs; Diclofenac

Diclofenac does not appear to alter the anticoagulant effect of acenocoumarol, phenprocoumon or warfarin. However, isolated cases of raised INRs have been reported. Note that all NSAIDs increase the risk of bleeding, and an increased risk is seen when they are given with anticoagulants.

Clinical evidence

In a crossover study in 29 patients stabilised on **acenocoumarol**, diclofenac 25 mg four times daily for one week did not alter the anticoagulant effect (prothrombin value) of **acenocoumarol**, when compared with placebo.[1] Other studies similarly confirm that diclofenac does not alter the anticoagulant effect of either **phenprocoumon**[2] or **warfarin**.[3]

However, a patient taking **acenocoumarol** developed a pulmonary haemorrhage associated with a very prolonged prothrombin time within 10 days of starting to take diclofenac.[4] Another report mentions a Chinese patient taking **warfarin** who developed an INR of 4 within 4 days of using a 1% diclofenac topical gel for joint pain.[5]

In a retrospective cohort study of patients taking **acenocoumarol** or **phenprocoumon**, diclofenac was associated with a 2.6-fold increased risk of hospitalisation for bleeding.[6] For a discussion of other studies, including one assessing the effect of CYP2C9 substrates such as diclofenac, on the risk of bleeding when used with **warfarin**, see 'Coumarins and related drugs + NSAIDs', p.480.

There is a report of the rare adverse effect, coumarin necrosis, occurring in an elderly man taking **acenocoumarol**, in which acute renal impairment aggravated by diclofenac was considered a contributory factor.[7]

Mechanism

See 'Coumarins and related drugs + NSAIDs', p.480.

Importance and management

On the basis of the pharmacological studies, no adjustment in coumarin dose would be anticipated to be needed when diclofenac is used. The isolated cases of raised INRs are unexplained. However, care is still needed with every NSAID because, to a greater or lesser extent, they irritate the stomach lining, which can result in gastrointestinal bleeding, which will be more severe in anticoagulated patients. For more information about this and potential CYP2C9-mediated interactions, see 'Coumarins and related drugs + NSAIDs', p.480.

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Coumarins + NSAIDs; Diflunisal

There is limited evidence to suggest that diflunisal might increase the anticoagulant effects of acenocoumarol and possibly warfarin, but apparently not phenprocoumon. All NSAIDs increase the risk of bleeding, and should be used with care in patients taking oral anticoagulants.

Clinical evidence

The total plasma **warfarin** levels of 5 healthy subjects fell by about one-third (from 741 to 533 nanograms/mL) when they were given diflunisal 500 mg twice daily for 2 weeks. Also, unbound **warfarin** increased from 1.02% to 1.34%, but the anticoagulant response was unaffected. When the diflunisal was withdrawn the anticoagulant response was reduced.[1]

A brief report states that 3 out of 6 subjects taking **acenocoumarol** had significant increases in prothrombin times, but no interaction was seen in 2 subjects taking **phenprocoumon**, when they were given diflunisal 750 mg daily.[2]

Mechanism

Uncertain. Diflunisal can displace warfarin from its plasma protein binding sites, but this on its own is almost certainly not the full explanation.[1] The fall in anticoagulant response when diflunisal was stopped is possibly

linked to a difference in the rates that total and unbound plasma warfarin returned to their original levels.[1]

Importance and management

This interaction is neither well defined nor well documented and its importance is uncertain. However, the reports cited suggest that an increased anticoagulant effect should be looked for if diflunisal is added to established treatment with any anticoagulant. A decreased effect might be expected if diflunisal is withdrawn. Note that care is needed with every NSAID because, to a greater or lesser extent, they irritate the stomach lining, which can result in gastrointestinal bleeding, which will be more severe in anticoagulated patients. Consider also 'Coumarins and related drugs + NSAIDs', p.480.

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Coumarins + NSAIDs; Dipyrone (Metamizole sodium)

One report claims that dipyrone does not interact with phenprocoumon or ethyl biscoumacetate, whereas another describes a rapid but transient increase in the effects of ethyl biscoumacetate with dipyrone. All NSAIDs increase the risk of bleeding, and an increased risk is seen when they are given with anticoagulants.

Clinical evidence, mechanism, importance and management

A single 1-g dose of dipyrone did not alter the steady-state anticoagulant effects of either **phenprocoumon** (5 subjects) or **ethyl biscoumacetate** (6 subjects).[1] Conversely, another report describes a short-lived but rapid increase (within 4 hours) in the effects of **ethyl biscoumacetate** caused by single 1-g dose metamizole sodium.[2] The reasons are not understood. However, care is still needed with every NSAID because, to a greater or lesser extent, they irritate the stomach lining, which can result in gastrointestinal bleeding, which will be more severe in anticoagulated patients. Consider also 'Coumarins and related drugs + NSAIDs', p.480.

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Coumarins + NSAIDs; Etodolac

In a pharmacological study, etodolac did not interact significantly with warfarin. Note that all NSAIDs increase the risk of bleeding, and an increased risk is seen when they are combined with anticoagulants.

Clinical evidence, mechanism, importance and management

In a three-period, crossover study, each period lasting 2.5 days, 18 healthy subjects were given **warfarin** 20 mg on day one, 10 mg on days 2 and 3 and etodolac 200 mg every 12 hours. Although the median peak serum levels of the **warfarin** fell by 19% and the median total clearance rose by 13% in the presence of etodolac, the prothrombin time response remained unchanged.[1,2] On the basis of this study, no adjustment in coumarin dose would be expected to be needed when etodolac is used. However, care is still needed with every NSAID, because, to a greater or lesser extent, they irritate the stomach lining, which can result in gastrointestinal bleeding, which will be more severe in anticoagulated patients. Consider also 'Coumarins and related drugs + NSAIDs', p.480.

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Coumarins and related drugs + NSAIDs; Fenamates

The anticoagulant effects of acenocoumarol, phenprocoumon and warfarin may be increased by floctafenine, glafenine, meclofenamic acid, and mefenamic acid. Tolfenamic acid is expected to interact similarly. However, limited evidence from one small study found glafenine did not alter the response to acenocoumarol, or ethyl biscoumacetate. Note also that all NSAIDs increase the risk of bleeding, and an increased risk is seen when they are given with anticoagulants.

Clinical evidence

(a) Floctafenine

In a double-blind study in 20 patients stabilised on **acenocoumarol** or **phenprocoumon** and given either floctafenine 200 mg or placebo four times daily for 3 weeks, floctafenine prolonged their thrombotest times by an average of about one-third, even though the anticoagulant dose of some of the patients was reduced.[1]

(b) Glafenine

In a double-blind study in 20 patients stabilised on **phenprocoumon** and given either glafenine 200 mg or placebo three times daily it was noted that within a week of starting glafenine there was a significant increase in thrombotest times.[2] In another report, 5 out of 7 patients needed a **phenprocoumon** dose reduction while taking glafenine.[3] Conversely, in another study, 10 patients taking **acenocoumarol**, **ethyl biscoumacetate** or '**indanedione**' had no changes in their anticoagulant response when given glafenine 800 mg daily over a 4-week period.[4]

(c) Meclofenamic acid

After taking sodium meclofenamate 200 to 300 mg daily for 7 days, the average dose of **warfarin** required by 7 patients fell from 6.5 to 4.25 mg daily, and by the end of 4 weeks it was 5.5 mg (a 16% reduction with a 0 to 25% range).[5]

(d) Mefenamic acid

After taking mefenamic acid 500 mg four times daily for a week, the mean prothrombin concentrations of 12 healthy subjects stabilised on **warfarin** fell by about 3.5%. Microscopic haematuria was seen in 3 of them, but no overt haemorrhage occurred. Their prothrombin concentrations were 15 to 25% of normal, well within the accepted anticoagulant range.[6]

Mechanism

Uncertain. Mefenamic acid can displace warfarin from its plasma protein binding sites,[7-9] and *in vitro* studies have shown that therapeutic concentrations (equivalent to 4 g daily) can increase the unbound and active warfarin concentrations by 140 to 340%,[7,8] but this interaction mechanism alone is only likely to have a transient effect. See also 'Coumarins and related drugs + NSAIDs', p.480.

Importance and management

The pharmacological studies cited suggest that all the fenamates can cause a small to modest increase in the effects of the coumarins. If both drugs are given, increase monitoring and anticipate the need for a small reduction in the coumarin dose. Although there are no data regarding concurrent use with the fenamate **tolfenamic acid**, the manufacturer similarly recommends close monitoring of coagulation.[10] Also note that, all NSAIDs, to a greater or lesser extent irritate the stomach lining, which can result in gastrointestinal bleeding, which will be more severe in anticoagulated patients. Consider also 'Coumarins and related drugs + NSAIDs', p.480.

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Coumarins + NSAIDs; Ibuprofen and related drugs

Ibuprofen, indoprofen, ketoprofen, naproxen and oxaprozin do not appear to alter the anticoagulant effect of coumarins. However, isolated cases of raised INRs have been described with ibuprofen and ketoprofen, and an increased risk of bleeding has been reported with naproxen. A slight increase in anticoagulant effect has been seen with fenbufen, flurbiprofen and tiaprofenic acid. Note also that all NSAIDs increase the risk of bleeding, and an increased risk is seen when they are given with anticoagulants.

Clinical evidence

(a) Fenbufen

In a study in 10 healthy subjects who were stabilised on **warfarin** and then given either fenbufen 400 mg twice daily or placebo for one week, the prothrombin times were increased by 1.9 seconds within 2 days in the fenbufen recipients, and the serum **warfarin** levels fell by 14%.[1]

(b) Flurbiprofen

In a study in 19 patients stable taking **phenprocoumon** and given flurbiprofen 50 mg three times daily for 2 weeks, a small but significant fall in the Quick value occurred (from 25.05% to 20.68%). Two patients bled (haematuria, epistaxis, haemorrhoidal bleeding) and the prothrombin times of 3 patients fell below the therapeutic range.[2] A case report describes 2 patients taking **acenocoumarol** who had a rise in thrombotest times and bled (haematuria, melaena, haematomas) within 2 to 3 days of starting to take flurbiprofen 150 to 300 mg daily.[3]

(c) Ibuprofen

Ibuprofen 600 mg to 2.4 g daily for 7 to 14 days did not alter the effects of coumarins in studies in patients stabilised on **phenprocoumon**;[4-6] healthy subjects[7,8] or patients[8] stabilised on **warfarin**; or patients stabilised on **dicoumarol**.[9] In one study in 20 patients taking **warfarin**, ibuprofen 600 mg three times daily for one week had no effect on prothrombin time; however, it did prolong bleeding time (4 cases above the therapeutic range) and microscopic haematuria and haematoma were seen.[10] Note that, this finding is probably more of a function of the effect of ibuprofen than an interaction *per se*,[11] although it does explain why the combination of an anticoagulant and an NSAID has an increased risk of haemorrhage.

An isolated case report describes subclinical bleeding with a raised INR in a 74-year-old woman with multiple medical problems taking **warfarin** when she was given ibuprofen.[12]

In a retrospective cohort study of patients taking **acenocoumarol** or **phenprocoumon**, ibuprofen was associated with a 2.2-fold increased risk of hospitalisation for bleeding. The study specifically looked at potentially interacting drugs taken by at least 50 patients, and there were at least 5 cases of bleeding with ibuprofen.[13] A case report describes a woman taking **warfarin**, with an INR of 2.1 on admission, who had a fatal gastrointestinal bleed after taking ibuprofen (dose unknown) for foot pain in the previous week.[14] For other studies, including one assessing the effect of CYP2C9 substrates, such as ibuprofen, on the risk of bleeding with warfarin, see 'Coumarins and related drugs + NSAIDs', p.480.

(d) Indoprofen

In a placebo-controlled study in 18 patients stabilised on **warfarin** and given indoprofen 600 mg daily for 7 days, found no changes occurred in any of the blood coagulation measurements made.[15]

(e) Ketoprofen

In a study in 15 healthy subjects stabilised on **warfarin**, ketoprofen 100 mg twice daily for 7 days had no effect on prothrombin times or coagulation cascade parameters, and there was no evidence of bleeding.[16] This contrasts with an isolated case of bleeding in a patient taking **warfarin** (prothrombin time increased from 18 seconds to 41 seconds) one week after starting ketoprofen 25 mg three times daily.[17]

(f) Naproxen

In a study in 10 healthy subjects, naproxen 375 mg twice daily for 17 days did not alter the pharmacokinetics of a single dose of **warfarin** given on day 10, or alter its anticoagulant effects.[18] Similar results were found in a study of **warfarin** at steady state.[19] A further study in patients taking **phenprocoumon** found that naproxen 250 mg twice daily transiently increased the anticoagulant effects and caused an unimportant change in primary bleeding time.[20]

In a retrospective cohort study of patients taking **acenocoumarol** or **phenprocoumon**, naproxen was associated with a 6.5-fold increased risk of hospitalisation for bleeding. The study specifically looked at potentially interacting drugs taken by at least 50 patients, and there were at least 9 cases of bleeding for naproxen.[13] For other studies, including one assessing the effect of CYP2C9 substrates, such as naproxen, on the risk of bleeding with warfarin, see 'Coumarins and related drugs + NSAIDs', p.480.

(g) Oxaprozin

In a study in 10 healthy subjects stabilised on **warfarin** for an average of 15 days, oxaprozin 1.2 g daily for 7 days did not significantly alter prothrombin times.[21]

(h) Tiaprofenic acid

In a study in 6 healthy subjects, the anticoagulant effects and the pharmacokinetic profile of **phenprocoumon** remained unchanged when they took tiaprofenic acid daily for 2 days.[22] This study is also published elsewhere.[23] No significant interaction occurred in 9 patients stabilised on **acenocoumarol** and given tiaprofenic acid 200 mg three times daily for 2 weeks, but in 4 patients a 'rebound' rise in prothrombin percentages occurred following the withdrawal of the NSAID.[24] However, an elderly man taking **acenocoumarol** had severe epistaxis and bruising 4 to 6 weeks after starting to take tiaprofenic acid 300 mg twice daily. His prothrombin time had risen to 129 seconds.[25]

Mechanism

When given alone, ibuprofen and related drugs can prolong bleeding times because of their antiplatelet effects.[11] They may also cause gastrointestinal toxicity. Because of these effects, the risk of bleeding is increased in patients taking anticoagulants by the concurrent use of NSAIDs. Most of the propionic acid derivatives can displace the anticoagulants from plasma protein binding sites to some extent, but this mechanism on its own is rarely, if ever, responsible for clinically important drug interactions.

Importance and management

It is well established that ibuprofen does not alter the anticoagulant effect of warfarin or other coumarins, (although isolated and unexplained cases of bleeding or raised INRs have occurred, but only very rarely). On the basis of these studies, no adjustment in coumarin dose would be anticipated to be needed when ibuprofen is used. Pharmacological studies also show no interaction for related propionic acid derivatives including indoprofen, ketoprofen, naproxen and oxaprozin, although the documentation is more limited. A slight increase in anticoagulant effects has been seen with fenbufen, flurbiprofen, and possibly tiaprofenic acid, although this is probably of limited clinical relevance. However, note that care is still needed with every NSAID, because, to a greater or lesser extent, they irritate the stomach lining, which can result in gastrointestinal bleeding, which will be more severe in anticoagulated patients. For more information about this, and potential CYP2C9-mediated interactions, see 'Coumarins and related drugs + NSAIDs', p.480.

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Coumarins + NSAIDs; Indometacin and related drugs

The anticoagulant effects of acenocoumarol, phenprocoumon and warfarin are not affected by indometacin, and the anticoagulant effects of phenprocoumon are not affected by acemetacin. However, isolated cases of raised INRs and bleeding complications have been reported. Also, note that, like all NSAIDs, indometacin increases the risk of bleeding, the risk of which is further increased in patients taking anticoagulants.

Clinical evidence

(a) Acemetacin

In a placebo-controlled study in 20 patients stabilised on **phenprocoumon**, acemetacin 60 mg three times daily for 3 weeks did not alter the thromboplastin value.[1]

(b) Indometacin

In a placebo-controlled, double-blind study in 8 healthy subjects, indometacin 100 mg daily for 5 days had no effect on the anticoagulant effects of steady-state **warfarin**.[2] Similarly, when 19 healthy subjects took either indometacin 25 mg four times daily or placebo for 11 days, the anticoagulant effects and the half-life of single doses of **warfarin** were not affected.[2]

Other studies in healthy subjects and patients anticoagulated with **acenocoumarol**[3] or **phenprocoumon**[4-6] similarly found that the anticoagulant effects were not changed by indometacin.

However, isolated cases of possible interactions in patients taking **warfarin** have been reported.[7-9] One patient had a rise in INR from 2 to 5.3,[8] and another had a rise from 2.75 to 3.42, then to 3.6 despite a reduction in **warfarin** dose.[9] However, there are other possible interpretations of this case.[10] In another report a patient taking indometacin appeared to have an enhanced response to **warfarin**, which subsequently improved when ibuprofen was substituted for indometacin.[7] The preliminary report of an analysis of possible drug interactions with **warfarin** stated that indometacin was found to have a clinically relevant effect on the anticoagulant action of warfarin.[11] One patient taking **warfarin** and indometacin died from acute peptic ulceration.[12] In another report, a patient who was very sensitive to **acenocoumarol** was found to have melaena and an INR of greater than 10 one week after starting indometacin and tetrazepam. He was found to have low levels of the cytochrome P450 isoenzyme CYP2C9 (poor metaboliser phenotype of CYP2C9 variant *3).[13]

For studies, including one assessing the effect of CYP2C9 substrates, such as indometacin, on the risk of bleeding with warfarin, see 'Coumarins and related drugs + NSAIDs', p.480.

Mechanism

None. Indometacin reduces platelet aggregation and thereby prolongs bleeding when it occurs. Acemetacin would act similarly since it is a glycolic acid ester of indometacin and indometacin is the major metabolite.

Importance and management

In pharmacological studies it is well established that indometacin does not normally alter the anticoagulant effects acenocoumarol, phenprocoumon or warfarin. No coumarin dose adjustments would therefore expected to be needed during concurrent use. However, caution is still appropriate, because indometacin, like other NSAIDs, can cause gastrointestinal irritation, ulceration and bleeding, which will be more severe in anticoagulated patients. For more information about this and potential CYP2C9-mediated interactions, see 'Coumarins and related drugs + NSAIDs', p.480.

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Coumarins and related drugs + NSAIDs; Ketorolac

Ketorolac does not alter the pharmacokinetics of, or prothrombin time response to, warfarin. However, ketorolac has been associated with serious gastrointestinal bleeding.

Clinical evidence, mechanism, importance and management

In a placebo-controlled, crossover study[1] in 10 healthy subjects, ketorolac 10 mg four times daily for 12 days caused no major changes in the pharmacokinetics of *R*- or *S*-warfarin, nor in the prothrombin time after a single 25-mg dose of **warfarin** given on day 6. This suggests that ketorolac is normally unlikely to affect the anticoagulant response of patients taking **warfarin** long-term, and that no warfarin dose adjustments would be expected to be necessary on concurrent use. However, in 1993 the CSM in the UK reported on an analysis of adverse reactions associated with ketorolac: they had received 5 reports of postoperative haemorrhage and four reports of gastrointestinal haemorrhage (one fatal) in patients taking ketorolac.[2] As result of this analysis, the use of ketorolac with anticoagulants was contraindicated in the UK.[2,3] In the US, the manufacturers stated that patients taking anticoagulants have an increased risk of bleeding complications if they are also given ketorolac, and therefore they should be used together extremely cautiously. They noted that, in particular, there is an increased risk of intramuscular haematoma from intramuscular ketorolac in patients taking anticoagulants.[4] This advice is prudent, because it is now established that use of any NSAID increases the risk of gastrointestinal bleeding when used with anticoagulants, see 'Coumarins and related drugs + NSAIDs', p.480, and it would therefore be wise to avoid the concurrent use of NSAIDs that have a higher risk of gastrointestinal toxicity such as ketorolac.

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Coumarins + NSAIDs; Nabumetone

Nabumetone does not appear to alter the anticoagulant effects of acenocoumarol or warfarin. However, an isolated report describes a raised INR and haemarthrosis in one patient taking warfarin, which was attributed to an interaction with nabumetone. Note that all NSAIDs increase the risk of bleeding, and an increased risk is seen when they are given with anticoagulants.

Clinical evidence, mechanism, importance and management

In a study in 12 healthy subjects, nabumetone 2 g daily for 2 weeks did not significantly alter the anticoagulant effects of steady-state **warfarin**.[1] Similarly, nabumetone 1 to 2 g daily for 6 weeks had no effect on the INR in 58 patients stabilised on **warfarin**.[2] Another clinical study in osteoarthritis patients also found that there was no difference in the proportion of patients with no INR change and no change in **acenocoumarol** dose in 27 patients given nabumetone 1 to 2 g daily for 4 weeks and 29 patients given placebo.[3] Moreover, nabumetone does not appear to affect bleeding time, platelet aggregation or prothrombin times in the absence of an anticoagulant.[4] However, an isolated and unexplained report describes an increase in INR from 2 to 3.7 and haemarthrosis in a patient taking **warfarin** a week after nabumetone 750 mg twice daily was added.[5]

On the basis of the above studies, no coumarin dose adjustment would be expected to be needed with nabumetone. However, care is still needed with every NSAID because, to a greater or lesser extent, they irritate the stomach lining, which can result in gastrointestinal bleeding, which will be more severe in anticoagulated patients. Consider also 'Coumarins and related drugs + NSAIDs', p.480.

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Coumarins + NSAIDs; Nimesulide

In pharmacological studies, nimesulide did not alter the effects of acenocoumarol or warfarin. Note that all NSAIDs increase the risk of bleeding, and an increased risk is seen when they are given with anticoagulants.

Clinical evidence, mechanism, importance and management

In a pilot study in 6 patients stabilised on **acenocoumarol**, a single 100-mg dose of nimesulide did not affect the clotting mechanisms, although the platelet aggregating response to adenosine diphosphate, adrenaline (epinephrine) and collagen was reduced for 2 to 4 hours.[1] Ten patients stabilised on **warfarin** 5 mg daily had no significant changes in their prothrombin times, partial thromboplastin time or bleeding times when they were given nimesulide 100 mg twice daily for a week.[2] However, a few patients had some increase in anticoagulant activity.[1]

These studies suggest that no coumarin dose adjustments are expected to be needed when nimesulide is used. However, care is still needed with every NSAID because, to a greater or lesser extent, they irritate the stomach lining, which can result in gastrointestinal bleeding, which will be more severe in anticoagulated patients. Consider also 'Coumarins and related drugs + NSAIDs', p.480.

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Coumarins + NSAIDs; Oxicam derivatives

Piroxicam increases plasma levels of *R*-acenocoumarol, and a few cases of raised INRs and bleeding have been reported when it was given with acenocoumarol or warfarin. In pharmacological studies, lornoxicam modestly increased the anticoagulant effects of warfarin, and possibly decreased the effect of phenprocoumon, but it did not interact with acenocoumarol. Studies have indicated that meloxicam does not interact with warfarin, and that tenoxicam does not interact with warfarin or phenprocoumon. Note that all NSAIDs increase the risk of bleeding, and an increased risk is seen when they are given with anticoagulants.

Clinical evidence

(a) Lornoxicam

In an open, crossover study in 6 healthy subjects, lornoxicam 8 mg twice daily for 7 days had no effect on the pharmacokinetics or the anticoagulant activity of a single 10-mg dose of **acenocoumarol** given on day 4.[1]

In an open, crossover study in 6 healthy subjects, lornoxicam 8 mg twice daily for 21 days increased the bioavailabilities of *S*- and *R*-phenprocoumon by 14% and 6%, respectively, and decreased their clearances by 15% and 6%, respectively, after a single 9-mg dose of **phenprocoumon** given on day 4. Despite the minor pharmacokinetic changes, statistically significant reductions in the activities of factors II and VII were seen.[2]

Lornoxicam 4 mg twice daily was given to 12 healthy subjects for 5 days, and then **warfarin** was added until a stable prothrombin time, averaging about 23.6 seconds, was achieved. The period to achieve this varied from 9 to 24 days, depending on the subject. The **warfarin** was then continued and the lornoxicam withdrawn, whereupon the mean prothrombin time fell to 19.5 seconds, the INR fell from 1.48 to 1.23 and the serum **warfarin** levels fell by 25%.[3]

(b) Meloxicam

In a group of 13 healthy subjects stabilised with INRs of 1.2 to 1.8, meloxicam 15 mg daily for 7 days did not significantly affect the pharmacokinetics of **warfarin** or INR values[4].

(c) Piroxicam

1. Acenocoumarol. In a single-dose study in healthy subjects, when piroxicam 40 mg was given with acenocoumarol 4 mg the AUC of the less active *R*-isomer was increased by 47% and its maximum plasma level was increased by 28%.[5]

In patients stabilised on acenocoumarol, piroxicam 20 mg daily for 2 weeks increased the effects of acenocoumarol in 4 out of 11 patients: the effect was considered mild in 3 patients, and significant in the fourth, although no specific values were given.[6] A further patient taking acenocoumarol developed gastrointestinal bleeding 3 days after starting to take piroxicam 20 mg daily. His INR rose from 2.2 to 6.5.[7]

2. Warfarin. A man stabilised on warfarin had a fall in his prothrombin time from a range of 1.7 to 1.9 times his control value to 1.3 when he stopped taking piroxicam 20 mg daily. The prothrombin times rose and fell when he re-started and then stopped the piroxicam.[8] Another patient taking warfarin had an increase in her prothrombin time (from a range of 16.5 to 18.1 seconds, up to 24.9 seconds) when piroxicam 20 mg daily was started, and a decrease when it was then stopped.[9] The INR of two Chinese patients rose to 4.5 and 4.2 after they were given piroxicam 20 mg daily and 0.5% topical piroxicam gel. One of them had bruises over the legs within 3 days.[10]

A woman who spread **warfarin** rat poison with her bare hands developed intracerebral bleeding, possibly exacerbated by piroxicam, which she took occasionally.[11]

(d) Tenoxicam

In single-dose and steady-state studies in a total of 16 healthy subjects, tenoxicam 20 mg daily for 14 days had no significant effect on the anticoagulant effects of **warfarin** or on bleeding times.[12] This report also men-

tions case studies in a small number of patients and healthy subjects, which similarly found that tenoxicam had no significant effect on the anticoagulant effects of **phenprocoumon**.[12]

Mechanism

Piroxicam inhibits the metabolism of *R*-acenocoumarol, but its effect on the metabolism of warfarin is unknown. Lornoxicam inhibited the metabolism of warfarin, but not acenocoumarol, *in vitro*.[13] In addition NSAIDs have antiplatelet effects, which can prolong bleeding if it occurs. They may also cause gastrointestinal toxicity. Because of these effects, in patients taking anticoagulants, the risk of bleeding is increased by NSAIDs.

Importance and management

The interaction of piroxicam with acenocoumarol would appear to be established, and case reports suggest that warfarin might be similarly affected. The UK manufacturer of piroxicam[14] contraindicates the concurrent use of anticoagulants, such as warfarin. This seems overly cautious; nevertheless, if piroxicam is given with a coumarin, it would be prudent to monitor the outcome well and anticipate the need to reduce the anticoagulant dose. Lornoxicam appears to have a similar effect with warfarin, although no cases of an interaction have been reported. Meloxicam and tenoxicam appear not to interact. However, care is still needed with every NSAID because, to a greater or lesser extent, they irritate the stomach lining, which can result in gastrointestinal bleeding, which will be more severe in anticoagulated patients. Consider also 'Coumarins and related drugs + NSAIDs', p.480.

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Coumarins + NSAIDs; Phenazone (Antipyrine)

The anticoagulant effects of warfarin are reduced by phenazone.

Clinical evidence

The plasma **warfarin** concentrations were halved (from 2.93 to 1.41 micrograms/mL) and the anticoagulant effects reduced accordingly after 5 patients took phenazone 600 mg daily for 50 days.[1] The thrombotest percentage of one patient rose from 5% to 50%. In an associated study it was found that phenazone 600 mg daily for 30 days caused a reduction in the **warfarin** half-life from 47 hours to 27 hours and from 69 hours to 39 hours, respectively, in 2 patients.[1,2]

Mechanism

Phenazone is an enzyme inducer, which increases the metabolism and clearance of warfarin, thereby reducing its effects.[1,2]

Importance and management

An established interaction. The effects of concurrent use should be monitored and the dose of warfarin increased appropriately. However, note that phenazone is little used clinically, and an alternative NSAID that does not alter the metabolism of coumarins would be more appropriate (see 'Coumarins and related drugs + NSAIDs', p.480). Other coumarins might be expected to be similarly affected.

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Coumarins and related drugs + NSAIDs; Phenylbutazone and related drugs

The anticoagulant effects of warfarin are markedly increased by azapropazone, oxyphenbutazone and phenylbutazone. Feprazone appears to interact similarly.
Bleeding has also been seen in patients taking phenindione or phenprocoumon when given phenylbutazone, but successful concurrent use has been achieved with both phenprocoumon and acenocoumarol. Note also that all NSAIDs increase the risk of bleeding, and an increased risk is seen when they are given with anticoagulants.

Clinical evidence

(a) Azapropazone

A woman taking digoxin, furosemide, spironolactone, allopurinol, and **warfarin** (prothrombin ratio 2.8) developed haematemesis within 4 days of starting to take azapropazone 300 mg four times a day. Her prothrombin ratio was found to have risen to 15.7. Subsequent gastroscopic examination revealed a benign ulcer, the presumed site of the bleeding.[1]

Several other patients are reported to have developed this interaction. Bruising or bleeding (melaena, epistaxis, haematuria) and prolonged prothrombin times have occurred within a few days of starting azapropazone.[2-4] Two patients died.[3,4]

(b) Feprazone

Five patients stabilised on **warfarin** had a mean prothrombin time rise from 29 seconds to 38 seconds after taking feprazone 200 mg twice daily for 5 days, despite a 40% reduction in the **warfarin** dose (from 5 to 3 mg daily). Four days after feprazone was stopped, their prothrombin times were almost back to usual. The interaction with feprazone was less marked than that with phenylbutazone.[5]

(c) Oxyphenbutazone

A man stabilised on **warfarin** developed gross haematuria within 9 days of starting to take oxyphenbutazone 400 mg daily. His prothrombin time had increased to 68 seconds.[6] Two similar cases have been described elsewhere.[7,8] A clinical study has found that oxyphenbutazone slows the clearance of **dicoumarol**.[9]

(d) Phenylbutazone

In a study in 3 subjects and one patient, phenylbutazone 200 mg three times daily and twice daily, respectively, given for 11 to 19 days before and 11 days after a single dose of **warfarin**, markedly increased the prothrombin time, but *decreased* the half-life of **warfarin**, and the **warfarin** AUC.[10] In another study that gave the enantiomers of **warfarin** separately, it was found that phenylbutazone inhibited the clearance of *S*-warfarin, but increased the clearance of *R*-warfarin.[11] This was confirmed in other studies, where the AUC of *R*-warfarin was decreased by 41% and the AUC of *S*-warfarin increased by 18%.[12]

A number of other studies have found markedly increased prothrombin times in patients[5,13] or healthy subjects[14] taking **warfarin** and given phenylbutazone. Moreover, there are a number of case reports demonstrating the clinical importance of this interaction.[10,15-19] In one, a man stabilised on **warfarin** following mitral valve replacement was later given phenylbutazone for back pain by his general practitioner. On admission to hospital a week later he had epistaxis, and his face, legs and arms had begun to swell. He had extensive bruising of the jaw, elbow and calves, some evidence of gastrointestinal bleeding, and a prothrombin time of 89 seconds.

Two similar cases have also been reported.[18] A similar interaction occurs between phenylbutazone and **phenprocoumon**. In one study in healthy subjects, phenylbutazone 300 mg daily for 14 days doubled the prothrombin time response to a single dose of phenprocoumon given on day 4, while decreasing the phenprocoumon AUC by 31%.[20] Cases of a clinically important interaction have also been reported for **phenprocoumon**.[21] In one early report, the required dose of **acenocoumarol** was 25% lower in patients taking phenylbutazone.[22] A single unconfirmed report describes this interaction in two patients taking **phenindione**.[23]

Mechanism

Phenylbutazone very effectively displaces the coumarins and indanediones from their plasma protein binding sites, thereby increasing the concentrations of free and active anticoagulant (an effect easily demonstrated *in vitro*[10,24-28]). By itself, the importance of this mechanism is usually small, since any displaced drug is then available to be cleared, so any effect is usually transient (see 'Protein-binding interactions', (p.3)). However, phenylbutazone also inhibits the metabolism of *S*-warfarin (the more potent of the two warfarin enantiomers) so its effects are increased and prolonged.[11,12,29] In studies, the unbound clearance of *S*-warfarin was decreased about three- to fourfold.[29,30] In contrast, the unbound clearance of *R*-warfarin is not altered, so the total clearance of *R*-warfarin is increased due to displacement.[29] Thus, overall, it appears that phenylbutazone decreases total plasma warfarin levels, while increasing its effect. Azapropazone[31-33] and oxyphenbutazone (the major metabolite of phenylbutazone) probably act similarly.

Importance and management

The pharmacokinetic interaction between warfarin and azapropazone or phenylbutazone is very well established and clinically important. Serious bleeding can result and concurrent use should be avoided. Feprazone and oxyphenbutazone appear to interact similarly. Much less is known about phenindione with phenylbutazone, but they probably interact similarly.[23] Direct evidence of a serious interaction with phenprocoumon seems to be limited to two reports, and there is some evidence (from one paper published in 1957) that successful and apparently uneventful concurrent use is possible, presumably because in the case cited the response and the anticoagulant doses were carefully controlled.[34] However, the practicalities of such close monitoring outside of a study are unclear. One study found that 25% less acenocoumarol was needed in patients given phenylbutazone.[22] Remember too that phenylbutazone and related drugs affect platelet aggregation and can cause gastrointestinal bleeding, and the risk of this is increased in patients taking an anticoagulant. It would seem advisable to use an alternative NSAID that interacts to a lesser extent, such as ibuprofen or naproxen, although it should be noted that no NSAID is entirely free from interactions with anticoagulants. Consider also 'Coumarins and related drugs + NSAIDs', p.480.

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Coumarins + NSAIDs; Sulindac

Sulindac does not usually appear to significantly alter the anticoagulant effect of warfarin or phenprocoumon; however, isolated cases of a modest to marked increase in the anticoagulant effects of warfarin have been reported. Note that all NSAIDs increase the risk of bleeding, and an increased risk is seen when they are given with anticoagulants.

Clinical evidence

In a study in healthy subjects stabilised on **warfarin**, sulindac 200 mg twice daily for 7 days did not significantly alter the prothrombin time, when compared with placebo, although the prothrombin time was slightly higher in the sulindac group.[1] Similarly, in 20 patients stabilised on **phenprocoumon**, sulindac 200 to 400 mg daily for 4 weeks did not alter measures of coagulation or bleeding time.[2]

However, a patient stabilised on **warfarin**, ferrous sulfate, phenobarbital and sulfasalazine had a marked increase in his prothrombin time ratio from about 3.2 to 10 after taking sulindac 100 mg twice daily for 5 days.[3-5] There are 5 similar cases of this interaction on record.[1,5-8] One of the patients had a gastrointestinal bleed after taking only three 100-mg doses of sulindac, although this patient was also taking flurbiprofen.[5] Another patient was stabilised on about a 40% lower dose of **warfarin** with continuation of the sulindac.[6] Another patient had a potassium-losing renal tubular defect, which was thought to contribute to the interaction.[1] In one of these cases, the patient, who was also taking a corticosteroid, developed a retropharyngeal haematoma.[8]

Mechanism

Not understood. In one patient, renal impairment may have caused sulindac accumulation, which in turn may have affected warfarin pharmacokinetics.[1] See also 'Coumarins and related drugs + NSAIDs', p.480.

Importance and management

The pharmacological studies cited suggest that usually no coumarin dose adjustment would be needed in patients given sulindac. However, the isolated cases of an interaction suggest that, rarely, some patients may be affected. Also note that all NSAIDs can irritate the gastric mucosa, affect platelet activity and cause gastrointestinal bleeding, which will be more severe in anticoagulated patients. Consider also 'Coumarins and related drugs + NSAIDs', p.480.

1. Loftin JP, Vesell ES. Interaction between sulindac and warfarin: different results in normal subjects and in an unusual patient with a potassium-losing renal tubular defect. *J Clin Pharmacol* (1979) 19, 733–42.
2. Schenk H, Klein G, Haralambus J, Goebel R. Coumarintherapie unter dem antirheumaticum sulindac. *Z Rheumatol* (1980) 39, 102–8.

3. Beeley L. *Bulletin of the West Midlands Centre for Adverse Drug Reaction Reporting* (1978) No. 6.
4. Beeley L, Baker S. Personal communication, 1978.
5. Ross JRY, Beeley L. Sulindac, prothrombin time, and anticoagulants. *Lancet* (1979) ii, 1075.
6. Carter SA. Potential effect of sulindac on response of prothrombin-time to oral anticoagulants. *Lancet* (1979) ii, 698–9.
7. McQueen EG. New Zealand Committee on Adverse Drug Reactions. 17th Annual Report 1982. *N Z Med J* (1983) 96, 95–9.
8. Thatcher J, George D. Retropharyngeal hematoma as a new cause of acute upper airway obstruction in rheumatoid arthritis. *J Rheumatol* (1987) 14, 1172–3.

Coumarins + NSAIDs; Tolmetin

In pharmacological studies, tolmetin did not alter the anticoagulant effect of the coumarins; however, isolated cases of raised INRs have been described. Note that all NSAIDs increase the risk of bleeding, and an increased risk is seen when they are given with anticoagulants.

Clinical evidence

In a placebo-controlled study, no changes in prothrombin times occurred in 15 healthy subjects stabilised on **warfarin** when they took tolmetin 400 mg three times daily for 14 days.[1] Similarly, no changes in prothrombin times occurred in 15 patients taking **phenprocoumon** when they were given tolmetin 200 mg four times daily for 10 days.[2] Bleeding times were reported to be slightly prolonged, though not to a clinically relevant extent.[2] Bleeding times were not significantly altered in healthy subjects given **acenocoumarol** and tolmetin 400 mg twice daily, or patients taking **acenocoumarol** and tolmetin.[3] However, there is a single published case report of a diabetic patient stabilised on **warfarin**, insulin, digoxin, theophylline, ferrous sulfate, furosemide and sodium polystyrene sulfonate who had a nosebleed after taking three 400-mg doses of tolmetin. His prothrombin time had risen from a range of 15 to 22 seconds up to 70 seconds.[4] The manufacturers of tolmetin and the FDA in the US also have 10 other cases on record involving tolmetin and warfarin,[4,5] received over a 10-year period.[5]

Mechanism

See 'Coumarins and related drugs + NSAIDs', p.480.

Importance and management

The pharmacological studies cited suggest that usually no coumarin dose adjustment would be needed in patients given tolmetin. The isolated cases of an interaction are unexplained. However, care is needed with every NSAID because, to a greater or lesser extent, they irritate the stomach lining, which can result in gastrointestinal bleeding, which will be more severe in anticoagulated patients. Consider also 'Coumarins and related drugs + NSAIDs', p.480.

1. Whitsett TL, Barry JP, Czerwinski AW, Hall WH, Hampton JW. Tolmetin and warfarin: a clinical investigation to determine if interaction exists. In 'Tolmetin, A New Non-steroidal Anti-Inflammatory Agent.' Ward JR (ed). Proceedings of a Symposium, Washington DC, April 1975, Excerpta Medica, Amsterdam, New York, p. 160–7.
2. Rüst O, Biland L, Thilo D, Nyman D, Duckert F. Prüfung des Antirheumatikums Tolmetin auf Interaktionen mit oralen Antikoagulantien. *Schweiz Med Wochenschr* (1975) 105, 752–3.
3. Malbach E. Über die Beeinflussung der Blutungszeit durch Tolectin. *Schweiz Rundsch Med Prax* (1978) 67, 161–3.
4. Koren JF, Cochran DL, Janes RL. Tolmetin-warfarin interaction. *Am J Med* (1987) 82, 1278–9.
5. Santopolo AC. Tolmetin-warfarin interaction. *Am J Med* (1987) 82, 1279–80.

Coumarins + Olanzapine

A single dose of olanzapine did not alter the pharmacokinetics or anticoagulant effect of a single dose of warfarin.

Clinical evidence, mechanism, importance and management

In a three-way, randomised, crossover study, 15 healthy subjects were given olanzapine 10 mg, **warfarin** 20 mg or both drugs together as single doses. No significant changes were seen in the pharmacokinetics of either drug, and the adverse effects of the olanzapine and the anticoagulant effects of the **warfarin** were unchanged.[1] Similarly, a 71-year-old woman stabilised on **warfarin** 15 mg/week with an INR of 2.6 had no significant change in her INR after taking olanzapine 20 mg daily for 6 weeks (INR 2.6 when taking 15 mg/week and 2 while taking 12.5 mg/week).[2] This evidence suggests that no **warfarin** dose adjustments are expected to be needed on concurrent use with olanzapine.

1. Maya JF, Callaghan JT, Bergstrom RF, Cerimele BJ, Kassahun K, Nyhart EH, Brater DC. Olanzapine and warfarin drug interaction. *Clin Pharmacol Ther* (1997) 61, 182.
2. Rogers T, de Leon J, Atcher D. Possible interaction between warfarin and quetiapine. *J Clin Psychopharmacol* (1999) 19, 382–3.

Coumarins + Opioids; Codeine

Codeine does not alter the anticoagulant effect of warfarin.

Clinical evidence, mechanism, importance and management

In a crossover study in 15 patients stabilised on **warfarin** and with osteoarthritis pain, codeine phosphate 7 to 15 mg three or four times daily for 5 weeks did not alter the mean INR when compared with celecoxib[1] (see 'Coumarins and related drugs + NSAIDs; Coxibs', p.482).

Codeine was used as a control analgesic in this study because it does not interact with **warfarin**, although this appears to be based on the absence of any evidence of an interaction, and the fact that it is unlikely to alter **warfarin** metabolism, rather than any direct evidence. Nevertheless, the lack of an interaction in this study suggests that codeine is not expected to alter **warfarin** dosing requirements.

1. Dentali F, Douketis JD, Woods K, Thabane L, Foster G, Holbrook A, Crowther M. Does celecoxib potentiate the anticoagulant effect of warfarin? A randomized, double-blind, controlled trial. *Ann Pharmacother* (2006) 40, 1241–7.

Coumarins + Opioids; Dextropropoxyphene (Propoxyphene)

In one study, dextropropoxyphene did not alter the prothrombin time in patients taking unspecified coumarins. There are isolated cases of patients taking warfarin who have had a marked increase in their prothrombin time and/or bleeding when given co-proxamol (dextropropoxyphene with paracetamol (acetaminophen)).

Clinical evidence

(a) Dextropropoxyphene with Paracetamol (Acetaminophen)

A man taking **warfarin** developed marked haematuria within 6 days of starting to take two tablets of co-proxamol three times daily. Thirteen days previously his **warfarin** dose had been increased from 6 mg to 7 mg daily (thrombotest 16%), and then 9 days previously it had been reduced back to 6 mg daily (thrombotest 5%). His plasma **warfarin** levels had risen by one-third (from 1.8 to 2.4 micrograms/mL) despite the reduction in **warfarin** dose.[1] A woman, stable for 6 weeks on **warfarin**, developed gross haematuria 11 hours after starting co-proxamol. She had taken 6 tablets of co-proxamol over a 6-hour period. Her prothrombin time increased from about 30 to 40 seconds up to 130 seconds.[1]

This interaction has been reported in several other patients taking **warfarin**.[2-5] The prothrombin time of one of them rose from 28 to 44 seconds up to 80 seconds within 3 days of substituting paracetamol with two tablets of co-proxamol four times daily.[3] Another developed a prothrombin time of more than 50 seconds after taking 30 tablets of *Darvocet-N 100* (dextropropoxyphene 100 mg, paracetamol 650 mg) and possibly an unknown amount of ibuprofen over a 3-day period.[4]

(b) Dextropropoxyphene

A double-blind study in 23 patients anticoagulated with un-named coumarins and given dextropropoxyphene 450 mg daily for 15 days or ibuprofen did not find any change in prothrombin times with either drug.[6]

Mechanism

Not understood. The effect dextropropoxyphene has on the metabolism of the warfarin enantiomers does not appear to have been studied. Dextropropoxyphene does not interact with other cytochrome P450 isoenzyme CYP2C9 substrates such as tolbutamide (see 'Antidiabetics + Dextropropoxyphene (Propoxyphene)', p.552), although it does interact with the CYP3A4 substrate carbamazepine (see 'Carbamazepine or Oxcarbazepine + Dextropropoxyphene (Propoxyphene)', p.603). There is also the possibility that the paracetamol component had some part to play (see also

'Coumarins and related drugs + Paracetamol (Acetaminophen)', p.492). Alternatively, these cases may just represent idiosyncratic reactions.

Importance and management

Information about this interaction is very sparse and seems to be limited to the reports cited. The cases cited could just be idiosyncratic reactions. Bear them in mind in the event of an unexpected response to treatment.

1. Orme M, Breckenridge A, Cook P. Warfarin and Distalgesic interaction. *BMJ* (1976) i, 200.
2. Jones RV. Warfarin and Distalgesic interaction. *BMJ* (1976) i, 460.
3. Smith R, Prudden D, Hawkes C. Propoxyphene and warfarin interaction. *Drug Intell Clin Pharm* (1984) 18, 822.
4. Justice JL, Kline SS. Analgesics and warfarin. A case that brings up questions and cautions. *Postgrad Med* (1988) 83, 217-8, 220.
5. Pilszek FH, Moloney D, Sewell JR. Case report: increased anticoagulant effect of warfarin in patient taking a small dose of co-proxamol. Personal communication, 1994.
6. Franchimont P, Heynen G. Comparative study of ibuprofen and dextropropoxyphene in scapulo-humeral periarthritis following myocardial infarction. 13th International Congress of Rheumatol, Kyoto, Japan. 30th Sept–6th Oct 1973.

Coumarins + Opioids; Hydrocodone

In an isolated report, the anticoagulant effects of warfarin were increased by hydrocodone in one patient and in one healthy subject.

Clinical evidence, mechanism, importance and management

A patient, stabilised on **warfarin** (and also taking digoxin, propranolol, clofibrate and spironolactone) had a rise in his prothrombin time of about 2 to 3 times his control value when he began to take *Tussionex* (hydrocodone with phenyltoloxamine) for a chronic cough. When the cough syrup was discontinued, his prothrombin time fell again. In a subsequent study in one healthy subject the equivalent dose of hydrocodone increased the elimination half-life of **warfarin** from 30 hours to 42 hours.[1] The reason for this interaction is not known, and this early report appears to be the only information available. Any interaction is not therefore established.

1. Azarnoff DL. Drug interactions: the potential for adverse effects. *Drug Inf J* (1972) 6, 19–25.

Coumarins + Opioids; Meptazinol

The anticoagulant effects of warfarin were not altered by meptazinol in one study.

Clinical evidence, mechanism, importance and management

Meptazinol 200 mg four times daily for 7 days had no significant effect on the prothrombin indexes of 6 elderly patients stabilised on **warfarin**, nor on the required **warfarin** dose.[1] No **warfarin** dose adjustments would be expected to be needed on concurrent use.

1. Ryd-Kjellen E, Alm A. Effect of meptazinol on chronic anticoagulant therapy. *Hum Toxicol* (1986) 5, 101–2.

Coumarins and related drugs + Opioids; Tramadol

In one study tramadol did not change the mean INR in response to phenprocoumon, although two patients had INR increases. Isolated cases of an increase in anticoagulant effects of warfarin, acenocoumarol, phenprocoumon and fluindione have been reported in patients given tramadol. One retrospective cohort study also found an increased risk of bleeding when acenocoumarol or phenprocoumon was given with tramadol.

Clinical evidence

In a double-blind, placebo-controlled, crossover study the mean INR of 19 patients anticoagulated with **phenprocoumon** was unchanged when they were given tramadol 50 mg three times daily for one week.[1,2] Although the mean difference was not changed, one patient had an INR rise from 4 to 7.3, and another had an INR rise from just under 5 to 6, while taking tramadol, but not while taking placebo.

A brief report describes 5 elderly patients (aged 71 to 84 years), anticoagulated with **warfarin** or **phenprocoumon** and taking a range of other drugs, who had clinically important rises in INRs (up to threefold) shortly after starting to take tramadol. One of the patients had gastrointestinal bleeding. Three of the patients were able to continue the tramadol with a reduced anticoagulant dose.[3]

In another report, a 61-year old woman with a mitral valve replacement stabilised on **warfarin** developed ecchymoses about 2 weeks after starting tramadol 50 mg every 6 hours. Her prothrombin time was found to have risen to 39.6 seconds and her INR was 10.6. These values returned to normal when the tramadol was withdrawn and **warfarin** was temporarily stopped.[4] Other cases have been reported with **warfarin**[5,6] and **phenprocoumon**.[7] In 2004, the Australian Adverse Drug Reactions Advisory Committee said they had received 11 reports of increases in INR or a haemorrhagic event in patients taking **warfarin** and given tramadol. Two patients died of haemorrhagic stroke. They note that this number of cases suggests that the interaction is an uncommon event.[8] Up until March 2003, the Swedish Adverse Drug Reactions Advisory Committee had received reports of 17 cases of a suspected interaction between tramadol and **warfarin** resulting in increases in the INR (to 3.4 to 8.5) and bleeding complications in 35% of patients. One patient who continued tramadol needed the **warfarin** dose to be almost halved.[9] The French regulatory authority has received 2 possible cases with **warfarin** and with the indanedione, **fluindione**, and one possible case with **acenocoumarol**; they note however, that other factors could have contributed to the cases reported.[10] The New Zealand regulatory authority has also commented on 4 possible cases with **warfarin**, two of which they considered were likely due to an interaction.[11]

In a retrospective cohort study of patients taking **acenocoumarol** or **phenprocoumon**, tramadol was associated with a threefold increased risk of hospitalisation for bleeding. The study specifically looked at potentially interacting drugs taken by at least 50 patients and with at least 5 cases of bleeding.[12]

Mechanism

Unknown. It has been suggested that the interaction might be related to a variation in a cytochrome P450 isoenzyme genotype. Seven of 10 patients from the 17 suspected cases of interaction in Sweden had defective CYP2D6 alleles. The authors suggested that as this isoenzyme metabolises tramadol, these patients might have changes in tramadol metabolism that could increase the risk of an interaction with warfarin by CYP3A4. However, CYP3A4 only has a role in the 'metabolism of *R*-warfarin', (p.405), and inhibition of CYP3A4 usually results in no more than a modest increase in INR. Moreover, defective CYP2D6 alleles have a population prevalence of 42.2%, so if this were the mechanism, many more cases would be expected. Because of the rarity of reports, it could just be that it is not really an interaction, and that there were unknown confounding factors in the suspected cases. Possible confounding factors include age, renal impairment, dehydration, under-nourishment, and other medications.[10]

Importance and management

An interaction between tramadol and coumarins or indanediones is not established. One pharmacological study did not show a clear interaction for phenprocoumon and tramadol, although data from 2 patients suggested the possibility. Moreover, isolated cases of an interaction with warfarin, acenocoumarol, phenprocoumon and fluindione have been published or reported to regulatory authorities, but the incidence seems to be low. Because of the uncertainty, it would be prudent to consider monitoring prothrombin times in any patient taking coumarins or indanediones when tramadol is first added, being aware that a small proportion of patients may need a reduction in the anticoagulant dose. Consider using an alternative, non-interacting opioid such as codeine, if appropriate. Further study is needed.

1. Boeijinga JK, van Meegen E, van den Ende R, Schook CE, Cohen AF. Lack of interaction between tramadol and coumarins. *J Clin Pharmacol* (1998) 38, 966–70.
2. Boeijinga JK, van Meegen E, van den Ende R, Schook CE, Cohen AF. Is there interaction between tramadol and phenprocoumon? *Lancet* (1997) 350, 1552.
3. Jensen K. Interaktion mellem tramadol og orale antikoagulantia. *Ugeskr Laeger* (1997) 159, 785–6.
4. Sabbe JR, Sims PJ, Sims MH. Tramadol-warfarin interaction. *Pharmacotherapy* (1998) 18, 871–3.
5. Scher ML, Huntington NH, Vitillo JA. Potential interaction between tramadol and warfarin. *Ann Pharmacother* (1997) 31, 646–7.
6. Dumo PA, Kielbasa LA. Successful anticoagulation and continuation of tramadol therapy in the setting of a tramadol-warfarin interaction. *Pharmacotherapy* (2006) 26, 1654–7.
7. Madsen H, Rasmussen JM, Brøsen K. Interaction between tramadol and phenprocoumon. *Lancet* (1997) 350, 637.
8. ADRAC. Tramadol-warfarin interaction. *Aust Adverse Drug React Bull* (2004) 23, 16.

9. Hedenmalm K, Lindh JD, Säwe J, Rane A. Increased liability of tramadol-warfarin interaction in individuals with mutations in the cytochrome P_{450} 2D6 gene. *Eur J Clin Pharmacol* (2004) 60, 369–72.
10. Chiffoleau A, Veyrac G, Dudouet D, Miremont G, Merle L, David-Laroche M, Bourin M, Jolliet P. Tramadol et anticoagulants oraux: interaction ou facteurs confondants? *Therapie* (2003) 58, 471–4.
11. Savage R. Evidence for tramadol-warfarin interaction. *Prescriber Update* (2006) 27, 23–4.
12. Penning-van Beest F, Erkens J, Petersen K-U, Koelz HR, Herings R. Main comedications associated with bleeding during anticoagulant therapy with coumarins. *Eur J Clin Pharmacol* (2005) 61, 439–44.

Coumarins and related drugs + Orlistat

Orlistat had no effect on the pharmacodynamics or pharmacokinetics of single-dose warfarin in a study in healthy subjects. However, orlistat reduces fat absorption, and might therefore reduce vitamin K absorption. There is a published report of a patient taking warfarin who developed a modest increase in INR after taking orlistat. Similar cases have been reported to regulatory authorities.

Clinical evidence

In a placebo-controlled, randomised, crossover study, 12 healthy subjects were given orlistat 120 mg three times daily for 16 days, with a single 30 mg dose of **warfarin** on day 11. The pharmacokinetics and pharmacodynamics of the **warfarin** were not altered by the orlistat, and markers of vitamin K nutritional status were not affected.[1] However, regarding this study, the manufacturers US prescribing information states that vitamin K levels did tend to decline in subjects taking orlistat.[2] It is also noted that increased INRs and changes in the anticoagulant response have been reported in patients taking orlistat and anticoagulants.[2] In addition, in 2001 the Canadian regulatory authorities reported that unexpected increases in INR were noted after orlistat was given to patients taking either **warfarin** or **acenocoumarol**. These were managed by dose adjustments of the coumarin or discontinuing orlistat.[3]

In a published report, a 66-year-old man stabilised on **warfarin** for 2.5 years who started taking orlistat 120 mg three times daily for weight reduction had a modest increase in his INR, from less than 3, to 4.7 within 18 days. **Warfarin** was withheld and he was later restabilised on approximately two-thirds of the previous dose while continuing the orlistat.[4]

Mechanism

Orlistat may reduce the absorption of fat soluble vitamins including vitamin K,[4,5] and a change to a lower fat diet associated with the use of orlistat may also contribute to changes in the balance between vitamin K and **warfarin**.[4]

Importance and management

The manufacturers say that patients stabilised on anticoagulants [coumarins and **indanediones**] and given orlistat should be closely monitored for changes in coagulation parameters.[2,5] Given the reports of changes in INRs, and the fact that changes in dietary vitamin K (see 'Coumarins and related drugs + Food; Vitamin K_1-rich', p.464), are known to affect warfarin efficacy, this seems prudent in patients taking any coumarin or indanedione.

1. Zhi J, Melia AT, Guerciolini R, Koss-Twardy SG, Passe SM, Rakhit A, Sadowski JA. The effect of orlistat on the pharmacokinetics and pharmacodynamics of warfarin in healthy volunteers. *J Clin Pharmacol* (1996) 36, 659–666.
2. Xenical (Orlistat). Roche Pharmaceuticals. US Prescribing information, July 2008.
3. Canadian Adverse Drug Reaction Monitoring Program. Communiqué. Orlistat (Xenical) interaction with coumarin derivatives: increased INR. *Can Adverse Drug React News* (2001) 11 (Jul), 7.
4. MacWalter RS, Fraser HW, Armstrong KM. Orlistat enhances warfarin effect. *Ann Pharmacother* (2003) 37, 510–12.
5. Xenical (Orlistat). Roche Products Ltd. UK Summary of product characteristics, March 2009.

Coumarins + Oseltamivir

No pharmacokinetic interaction occurs between oseltamivir and warfarin. However isolated cases of raised INRs have been reported.

Clinical evidence, mechanism, importance and management

In a study, 20 patients taking warfarin, with stable prothrombin times for at least 2 weeks before the study, were given oseltamivir 75 mg twice daily for 4.5 days. Oseltamivir did not affect the pharmacokinetics of warfarin and had no clinically significant effect on the INR, when compared with a control group not taking oseltamivir. No increase in bleeding events occurred.[1]

Both the MHRA in the UK and Health Canada have received reports of an increase in clotting time when patients taking warfarin were given oseltamivir.[2,3] Between January 1999 and November 2005, Health Canada received 19 reports (11 submitted by the same source) of an increase in the INR in patients taking warfarin and given oseltamivir. However, in 3 of these cases the warfarin dose had been increased after starting oseltamivir, and in 2 cases the patients were taking other drugs known to interact with warfarin. Three cases of a *decrease* in the INR were also reported. On this basis, a causative relationship could not be established.[3] Anticoagulant control can be affected by influenza and its associated symptoms (such as fever and decreased appetite), and in 2009 the MHRA in the UK stated that there is no strong evidence to suggest that a drug interaction exists between oseltamivir and warfarin.[2] Oseltamivir is not known to have a significant effect on cytochrome P450 (by which warfarin is predominantly metabolised), and the data above support the lack of a likely pharmacokinetic interaction. It is difficult to establish whether the cases reported represent a drug interaction or an effect related to the patients underlying infection. Nevertheless, it would seem unlikely that such an interaction exists. However, until further data is available to confirm a lack of an interaction, it would be prudent to bear the case reports in mind if a patient taking warfarin develops an unexpected alteration in bleeding times after starting oseltamivir.

1. Davies, B. Oseltamivir does not interfere with the effect of warfarin on blood coagulation. Intersci Conf Antimicrob Agents Chemother (2009) 49, A1-596.
2. Medicines and Healthcare Products Regulatory Agency. UK Suspected Adverse Drug Reaction (ADR) Analysis: influenza antivirals – oseltamivir (Tamiflu) and zanamivir (Relenza), November 2009. Available at: http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con062634.pdf (accessed 29/01/10).
3. Health Canada. Oseltamivir (Tamiflu) and warfarin: suspected increase in INR. *Can Adverse React News* (2006) 16, 1–2.

Coumarins + Oxolamine

Oxolamine markedly increases the effect of warfarin.

Clinical evidence, mechanism, importance and management

In a retrospective study, 11 patients were identified who had been receiving stable doses of **warfarin** and were then given oxolamine in doses of 100 to 600 mg daily for 3 to 10 days. Of six patients who did not have their **warfarin** dose adjusted, the INR increased by 70 to 190% from a range of 1.51 to 2.82 up to a range of 3.24 to 6.45. One patient had a **warfarin** dose reduction of 14%, with an INR increase from 2.29 to 9.11. Four patients had their **warfarin** dose reduced by 30 to 36%, but one of these still had an INR increase from 2.14 to 4.01. Two of the 11 patients developed a haematoma.[1] In a further prospective study, 6 patients receiving stable doses of **warfarin** were given oxolamine 300 to 600 mg daily for 4 to 7 days, and the **warfarin** dose was reduced by 50% on starting oxolamine. Three patients had no change in INR, one had a 24% increase and two had a 6% and 17% decrease.[1]

The mechanism of this interaction is unknown. Although published information is limited to this study, an interaction seems to be established. If any patient taking **warfarin** requires oxolamine, anticipate the need to roughly halve the **warfarin** dose.

1. Min KA, Zhu X, Oh JM, Shin WG. Effect of oxolamine on anticoagulant effect of warfarin. *Am J Health-Syst Pharm* (2006) 63, 153–6.

Coumarins and related drugs + Paracetamol (Acetaminophen)

An equal number of randomised studies have found a modest increase in the anticoagulant effect of coumarins as have reported no effect. Other cohort studies found no evidence of a change in anticoagulant effect. One retrospective cohort study reported that concurrent use tends to increase the incidence of upper gastroin-

testinal bleeding. There are isolated case reports of an increase in anticoagulant effects in patients taking warfarin, acenocoumarol or fluindione with paracetamol.

Clinical evidence

Over 10 published studies have investigated whether or not paracetamol alters the effect of the coumarins, with equal numbers finding no effect as finding an increased effect, see 'Table 12.4', (p.494). All the randomised, controlled studies finding an interaction have demonstrated a minor to modest effect (e.g. average increase in INR of 1.2 in one well-controlled study[1,2]). The only study to show a much greater effect (an increased odds ratio of an INR above 6 ranging from 3.5 to 10 for different doses of paracetamol alone or combined with an opioid) was a retrospective case-control study,[3,4] which has the limitations of being non-randomised with all the attendant problems of controlling for possible confounding variables.[5-7] Excluding this study, there appears to be no obvious explanation for the disparate findings between the studies finding an interaction and those not, either by study group, coumarin used, or dose of paracetamol.

There are only 5 published case reports of a possible interaction between paracetamol without opioids and a coumarin (**warfarin** or **acenocoumarol**), and two case reports of a possible interaction with the indanedione, **fluindione**, which are summarised in 'Table 12.4', (p.494). In addition, there are two reports of a possible interaction with paracetamol combined with codeine or dihydrocodeine listed in 'Table 12.4', (p.494), and 7 others with paracetamol combined with 'dextropropoxyphene (propoxyphene)', (p.490). Note that this incidence is very rare, given the widespread use of paracetamol, and the fact that it is generally considered safe for use with warfarin.

Moreover, in response to one case-control study[3] other clinicians running outpatient anticoagulant clinics have contended that they have not seen an interaction with paracetamol in their experience.[6,7]

Mechanism

Not understood. It is possible that paracetamol or one of its metabolites inhibits the enzymes in the vitamin K cycle, and so has additive effects with anticoagulants.[2,8]

A pharmacokinetic interaction has been proposed, but this seems unlikely. Paracetamol does not inhibit the cytochrome P450 isoenzyme CYP2C9, which is the major isoenzyme involved in the metabolism of *S*-warfarin.[9] Paracetamol is mainly metabolised by glucuronidation and sulfation,[10,11] but CYP1A2, CYP3A4 and CYP2E1 metabolise up to 15% of paracetamol under normal conditions.[10] *R*-warfarin is mainly metabolised by CYP3A4 and CYP1A2.[10,11] It has been suggested that in conditions such as ageing, hypoxia or hypertension, the isoenzymes play a more important part in paracetamol metabolism. Consequently paracetamol may then theoretically compete with the metabolism of *R*-warfarin to a sufficient degree to provoke an interaction.[11] However, as the *S*-warfarin enantiomer has significantly greater anticoagulant activity than the *R*-warfarin enantiomer, interactions with *R*-warfarin are considered by some to be of questionable significance.[7] Moreover, this explanation might explain rare case reports, but not the slight increases in INR seen in some studies in otherwise healthy subjects and patients.

Yet another idea is that it is the indications for paracetamol use such as pain or fever that cause the interaction, rather than paracetamol *per se*,[12] but this does not explain why an interaction has been found in otherwise healthy patients or subjects given paracetamol in controlled studies.

Importance and management

Despite the number of studies, an interaction between paracetamol and the coumarins is not firmly established, and the importance of the findings remain controversial. Some consider that the dose of paracetamol and its duration of use should be minimised in patients taking coumarins.[10,13] However, in randomised controlled studies, even maximum daily doses of paracetamol (4 g daily) for 2 weeks, had, at most, a modest effect, see 'Table 12.4', (p.494). A dose-related effect has been suggested in a case-controlled study,[3] but a more recent randomised controlled study did not find a dose-response (i.e. there was a slight change in INR of 0.5 with both 1.5 g daily and 3 g daily).[12] Further evidence is therefore required on the possible dose-response effect, and whether there is any value in minimising the dose. Moreover, on the basis of the studies suggesting an interaction, many have advocated increased monitoring in patients starting regular paracetamol. However, others consider that an increase in monitoring is unnecessary, or that increased monitoring during paracetamol use is not necessary unless the underlying illness (e.g. fever) requires increased monitoring. On the basis of the available data, it is not possible to firmly recommend increased monitoring, or dismiss its advisability. Further study is clearly needed.

Paracetamol is still considered to be safer than aspirin (see 'Coumarins and related drugs + Aspirin or other Salicylates', p.434) or NSAIDs (see 'Coumarins and related drugs + NSAIDs', p.480) as an analgesic in the presence of an anticoagulant because it does not affect platelets or cause gastric bleeding.

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2. Mahé I, Bertrand N, Drouet L, Bal Dit Sollier C, Simoneau G, Mazoyer E, Caulin C, Bergmann J-F. Interaction between paracetamol and warfarin in patients: a double-blind, placebo-controlled, randomized study. *Haematologica* (2006) 91, 1621–7.
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5. Gray CD. Acetaminophen and risk factors for excess anticoagulation with warfarin. *JAMA* (1998) 280, 695.
6. Amato MG, Bussey H, Farnett L, Lyons R. Acetaminophen and risk factors for excess anticoagulation with warfarin. *JAMA* (1998) 280, 695–6.
7. Riser J, Gilroy C, Hudson P, McCay L, Willis TA. Acetaminophen and risk factors for excess anticoagulation with warfarin. *JAMA* (1998) 280, 696.
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10. Shek KLA, Chan L-N, Nutescu E. Warfarin-acetaminophen drug interaction revisited. *Pharmacotherapy* (1999) 19, 1153–8.
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13. Bell WR. Acetaminophen and warfarin: an undesirable synergy. *JAMA* (1998) 279, 702–3.

Coumarins + Pentoxifylline

Some studies have found that pentoxifylline does not alter the anticoagulant effects of phenprocoumon or acenocoumarol; however, one study suggests that there might be an increased risk of serious bleeding if pentoxifylline is given with acenocoumarol. Pentoxifylline alone has rarely been associated with bleeding.

Clinical evidence

The anticoagulant effects of **phenprocoumon** were not altered by pentoxifylline 400 mg four times daily for 27 days in 10 patients stabilised on **phenprocoumon**. Two patients had a slight increase in platelet aggregation.[1]

In a randomised study in patients with recurrent venous thrombosis, there was no difference in the dose of **acenocoumarol** necessary to reach an INR of 2.5 to 3.5 between 100 patients taking **acenocoumarol** with pentoxifylline 1.2 g daily and 100 patients taking **acenocoumarol** alone. No patients had severe bleeding, and 3% to 4% of patients in both groups had moderate bleeding (haematomas, haematuria).[2] However, in another placebo-controlled study of either pentoxifylline 400 mg three times daily, **acenocoumarol** (adjusted to maintain an INR of 2 to 4.5), or both drugs together, three major haemorrhagic problems (2 fatal cerebral, one gastrointestinal) occurred in the 36 patients taking both drugs. In the 36 patients taking **acenocoumarol** alone, one case of cerebral haemorrhage (resulting in hemiplegia) and another of haematuria with epistaxis occurred. This difference was not statistically significant, but the authors considered that the risk of bleeding was probably increased by the combination.[3] In this study, 69% of patients had an INR within desired range, and 7% had an INR above 4.5.

Mechanism

Pentoxifylline alone has rarely been associated with bleeding,[4] which could potentially be more severe in patients taking anticoagulants. Nevertheless, the manufacturers say that a causal relationship between pentoxifylline and bleeding has not been established.[5,6]

Table 12.4 Summary of the evidence for and against an interaction between paracetamol (acetaminophen) and coumarins or indanediones

Study type (year)	*Group*	*Coumarin*	*Paracetamol*	*Outcome*	*Refs*
Studies showing no interaction					
Randomised, crossover (1999)	20 healthy subjects	Warfarin, single-dose	1 g four times daily for one day, and 22 days	No change in warfarin pharmacokinetics or anticoagulant effect with either 1 day or 22 days	1
Clinical (1970)	10 patients	Stable warfarin	3.25 g daily for 2 weeks	No change in average prothrombin time	2
Randomised, placebo-controlled (1969)	20 patients	Phenprocoumon (19 patients) Warfarin (1 patient)	Two doses of 650 mg four hours apart	No change in average prothrombin time over 3 days	3
Randomised, placebo-controlled (2003)	31 patients	Phenprocoumon	Placebo (10 patients), 500 mg three times daily (11 patients), or 1 g three times daily (10 patients) for 2 weeks	Mean rise in INR of 0.46 at day 8 for both doses, which was not considered clinically relevant	4
Cohort (2002)	54 patients taking paracetamol and 180 others not taking paracetamol	Phenprocoumon	2 to 2.5 g per day for 3 days preceding INR determination	No change in anticoagulant effect	5
Cohort (recently started) (2002)	54 patients and 20 controls not given paracetamol	Acenocoumarol or phenprocoumon	Mean of 2.1 g daily	No difference in changes in INR between groups	6
Studies showing an interaction					
Randomised, placebo-controlled, crossover (1968)	50 patients	Stable warfarin, dicoumarol, anisindione,* phenprocoumon	650 mg four times daily for 2 weeks	Average increase in prothrombin time of 3.6 seconds	7
Randomised, placebo-controlled (1982, 1983)	20 patients	Stable acenocoumarol (8 patients) or phenprocoumon (12 patients)	500 mg four times daily for 3 weeks (10 patients); placebo (10 patients)	Average increase in thrombotest value of about 20 seconds (14% increase), which necessitated a reduction in coumarin dose in 5 patients	8, 9
Randomised, placebo-controlled, crossover (1984)	15 healthy subjects	Stable warfarin	4 g daily for 2 weeks	7 of 15 subjects had a prothrombin ratio rise of more than 20% while taking paracetamol compared with 1 of 15 taking placebo	10
Randomised, placebo-controlled, crossover (2005, 2006)	19 patients	Stable warfarin	4 g daily for 2 weeks	INR increased by a mean of 1.20 to a mean maximum of 3.45 in patients taking paracetamol, but did not change with placebo	11, 12
Case-control (1998)	93 cases with INR greater than 6 and 196 controls (INR 1.7 to 3.3)	Warfarin	325 mg each week to greater than 1.3 g daily	52 cases (56%) and 70 controls (36%) reported using paracetamol in the preceding week.† The increased risk (3.5 to 10-fold) was related to paracetamol dose	13
Cohort (2001)	4204 patients	Warfarin and/or Phenprocoumon		Standardised incidence ratio of hospitalisation for upper GI bleeding was higher with combined use of paracetamol (4.4) than oral anticoagulants alone (2.8)	14
Cohort (2007)	171 patients	Warfarin		Statistically significant increased risk of self-reported bleeding events (142 bleeds in 697 weeks, none of which were serious, for an odds ratio of 1.41)	15
Case reports of an interaction: paracetamol					
Case report (1999)	72-year-old	Acenocoumarol	1 to 2 g daily long-term	13 days after stopping paracetamol, the INR decreased from a range of 2.5 to 3 down to 1.62. INR gradually increased on restarting paracetamol	16
Case report (2004)	77-year-old	Acenocoumarol	2 to 2.5 g daily for a few weeks	INR 5.4 then 9.1 one week later. Patient restabilised on same acenocoumarol dose and asked not to take more paracetamol than 2 g daily for more than 3 days	17

Continued

Table 12.4 Summary of the evidence for and against an interaction between paracetamol (acetaminophen) and coumarins or indanediones (continued)

Study type (year)	*Group*	*Coumarin*	*Paracetamol*	*Outcome*	*Refs*
Case report (2005)	72-year-old	Fluindione	4 g daily for 10 days for knee pain	INR of 8 with skin haematomas and gingival bleeding. Two weeks previously the INR had been 2.3	18
Case report (2006)	46-year-old	Fluindione	2 to 3 g daily for 10 days for phlebitis-related pain	INR of 4.46 decreased to 2.68 within 1 day of stopping paracetamol	19
Case report (2002)	62-year-old	Warfarin	4 to 5 g (duration not stated)	INR of 7.5, with retroperitoneal haematoma. One month previously the INR had been 2.5	20
Case report (2003)	74-year-old	Warfarin	a. 1 g twice daily for 3 days b. 1 g four times daily for 3 days	a. INR of 3.4 then 4 b. INR increased from 2.3 to 6.4	21
Case report (2004)	76-year-old	Warfarin	Patient recently taking more paracetamol for a flare of arthritis	INR increase from 2.1 to 7, with haematuria and gingival bleeding	22
Paracetamol in combination with opioids‡					
Case report (1991)	66-year-old	Warfarin	Paracetamol/codeine; about 1.6 g daily of paracetamol over 10 days	Increase in prothrombin time from range of 15 to 19 up to 96 seconds. Haematuria and gingival bleeding	23
Case report (1997)	63-year-old	Warfarin	a. Paracetamol/dihydrocodeine 500 mg/10 mg, four daily for 7 days b. Paracetamol/codeine 500 mg/30 mg, three daily for 8 days	a. Increase in INR to 9.6 then 12, with gingival bleeding b. Increase in INR to 8.5	24

*Note that this is an indanedione
†Including 11 cases and 6 controls who reported taking a preparation of paracetamol in combination with an opioid, mostly codeine and oxycodone
‡There are also cases reported with dextropropoxyphene/paracetamol.

1. Kwan D, Bartle WR, Walker SE. The effects of acetaminophen on pharmacokinetics and pharmacodynamics of warfarin. *J Clin Pharmacol* (1999) 39, 68–75.
2. Udall JA. Drug interference with warfarin therapy. *Clin Med* (1970) 77, 20–5.
3. Antlitz AM, Awalt LF. A double blind study of acetaminophen used in conjunction with oral anticoagulant therapy. *Curr Ther Res* (1969) 11, 360–1.
4. Gadisseur APA, van der Meer FJM, Rosendaal FR. Sustained intake of paracetamol (acetaminophen) during oral anticoagulant therapy with coumarins does not cause clinically important INR changes: a randomized double-blind clinical trial. *J Thromb Haemost* (2003) 1, 714–17.
5. Fattinger K, Frisullo R, Masche U, Braunschweig S, Meier PJ, Roos M. No clinically relevant drug interaction between paracetamol and phenprocoumon based on a pharmacoepidemiological cohort study in medical inpatients. *Eur J Clin Pharmacol* (2002) 57, 863–7.
6. van den Bemt PMLA, Geven LM, Kuitert NA, Risselada A, Brouwers JRBJ. The potential interaction between oral anticoagulants and acetaminophen in everyday practice. *Pharm World Sci* (2002) 24, 201–4.
7. Antlitz AM, Mead JA ,Tolentino MA. Potentiation of oral anticoagulant therapy by acetaminophen. *Curr Ther Res* (1968) 10, 501–7.
8. Boeijinga J, Boerstra EE, Ris P, Breimer DD, Jeletich-Bastiaanse A. Interaction between paracetamol and coumarin anticoagulants. *Lancet* (1982) 1, 506.
9. Boeijinga JK, Boerstra EE, Ris P, Breimer DD, Jeletich-Bastiaanse A. De invloed van paracetamol op antistollingsbehandeling met coumarinederivaten. *Pharm Weekbl* (1983) 118, 209–12.
10. Rubin RN, Mentzer RL, Budzynski AZ. Potentiation of anticoagulant effect of warfarin by acetaminophen (TylenolR). *Clin Res* (1984) 32, 698A.
11. Mahé I, Bertrand N, Drouet L, Simoneau G, Mazoyer E, Bal dit Sollier C, Caulin C, Bergmann JF. Paracetamol: a haemorrhagic risk factor in patients on warfarin. *Br J Clin Pharmacol* (2005) 59, 371–4.
12. Mahé I, Bertrand N, Drouet L, Bal Dit Sollier C, Simoneau G, Mazoyer E, Caulin C, Bergmann J-F. Interaction between paracetamol and warfarin in patients: a double-blind, placebo-controlled, randomized study. *Haematologica* (2006) 91, 1621–7.
13. Hylek EM, Heiman H, Skates SJ, Sheehan MA, Singer DE. Acetaminophen and other risk factors for excessive warfarin anticoagulation. *JAMA* (1998) 279, 657–62.
14. Johnsen SP, Sorensen HT, Mellemkjoer L, Blot WJ, Nielsen GL, McLaughlin JK, Olsen JH. Hospitalisation for upper gastrointestinal bleeding associated with the use of oral anticoagulants. *Thromb Haemost* (2001) 86, 563–8.
15. Shalansky S, Lynd L, Richardson K, Ingaszewski A, Kerr C. Risk of warfarin-related bleeding events and supratherapeutic international normalized ratios associated with complementary and alternative medicine: a longitudinal analysis. *Pharmacotherapy* (2007) 27, 1237–47.
16. Bagheri H, Bernhard NB, Montastruc JL. Potentiation of acenocoumarol anticoagulant effect by acetaminophen. *Ann Pharmacother* (1999) 33, 506.
17. Thijssen HH, Soute BA, Vervoort LM, Claessens JG. Paracetamol (acetaminophen) warfarin interaction: NAPQI, the toxic metabolite of paracetamol, is an inhibitor of enzymes in the vitamin K cycle. *Thromb Haemost* (2004) 92, 797–802.
18. Ornetti P, Ciappuccini R, Tavernier C, Maillefert JF. Interaction between paracetamol and oral anticoagulants. *Rheumatology* (Oxford) (2005) 44, 1584–5.
19. Wilouin F, Baune B, Lidove O, Papo T, Farinott R. Interaction entre le paracétamol et la fluindione: à propos d'un cas. *Thérapie* (2006) 61, 75–7. Correction. *ibid.*, (268).
20. Andrews FJ. Retroperitoneal haematoma after paracetamol increased anticoagulation. *Emerg Med J* (2002) 19. 84–5.
21. Gebauer MG, Nyfort-Hansen K, Henschke PJ, Gallus AS. Warfarin and acetaminophen interaction. *Pharmacotherapy* (2003) 23, 109–112.
22. Lesho EP, Saullo L, Udvari-Nagy S. A 76-year-old woman with erratic anticoagulation. *Cleve Clin J Med* (2004) 71, 651–56.
23. Bartle WR, Blakely JA. Potentiation of warfarin anticoagulation by acetaminophen. *JAMA* (1991) 265, 1260.
24. Fitzmaurice DA, Murray JA. Potentiation of anticoagulant effect of warfarin. *Postgrad Med J* (1997) 73, 439–40.

Importance and management

Information is limited, and an interaction is not established. In the US, the manufacturer recommends that patients taking **warfarin** should have more frequent monitoring of coagulation parameters when given pentoxifylline,[6] and this might be a prudent precaution with this and any other coumarin.

1. Ingerslev J, Mouritzen C, Stenbjerg S. Pentoxifylline does not interfere with stable coumarin anticoagulant therapy: a clinical study. *Pharmatherapeutica* (1986) 4, 595–600.
2. Moriau M, Lavenne-Pardonge E, Crasborn L, von Frenckell R, Col-Debeys C. The treatment of severe or recurrent deep venous thrombosis. Beneficial effect of the co-administration of antiplatelet agents with or without rheological effects, and anticoagulants.*Thromb Res* (1995) 78, 469–82.
3. Dettori AG, Pini M, Moratti A, Paolicelli M, Basevi P, Qintavalla R, Manotti C, Di Lecce C and The APIC Study Group. Acenocoumarol and pentoxifylline in intermittent claudication. A controlled clinical study. *Angiology* (1989) 40, 237–48.
4. Oren R, Yishar U, Lysy J, Livshitz T, Ligumsky M. Pentoxifylline-induced gastrointestinal bleeding. *DICP Ann Pharmacother* (1991) 25, 315–16.
5. Trental 400 (Pentoxifylline). Sanofi-Aventis. UK Summary of product characteristics, October 2006.
6. Trental (Pentoxifylline). Sanofi-Aventis US LLC. US Prescribing information, October 2007.

Coumarins + Phosphodiesterase type-5 inhibitors

In pharmacological studies, sildenafil did not interact with warfarin or acenocoumarol. However, in pulmonary hypertension, there is some evidence of an increased risk of bleeding with concurrent use, and nosebleeds were a common adverse effect of sildenafil alone. Two possible cases of raised INRs have been reported in patients taking acenocoumarol or warfarin and sildenafil. Studies suggest that tadalafil and vardenafil do not interact with warfarin.

Clinical evidence

(a) Sildenafil

The manufacturer of sildenafil notes that no significant interaction occurred when sildenafil 50 mg was given with **warfarin** 40 mg,[1-4] or when sildenafil 100 mg was given with **acenocoumarol**.[3] However, in studies in pulmonary hypertension, nosebleeds were a common adverse effect (9%), and the concurrent use of vitamin K antagonists and sildenafil resulted in a greater incidence of reports of bleeding (primarily nosebleeds; 9% compared with 2%) than placebo.[4]

A 68-year-old man taking **acenocoumarol** and enalapril had an increase in his INR from 3.05 to 7.7 without bleeding complications after taking sildenafil. The patient continued to take sildenafil once a week, and the daily dose of **acenocoumarol** was split into two, with a return to stable therapeutic INR values. Another patient taking **warfarin**, ranitidine and pravastatin had a rise in INR on three occasions after taking sildenafil once a week, omitting the dose of ranitidine when he took the sildenafil. On one of these occasions, he had bleeding gums. This rise in INR no longer occurred when he started taking the ranitidine with the sildenafil.[5]

(b) Tadalafil

A double-blind, randomised, crossover study in which a single dose of **warfarin** was given on day 7 of 12 consecutive days of treatment with either tadalafil 10 mg or placebo found that tadalafil did not affect the AUCs of either *S*-warfarin and *R*-warfarin, and prothrombin times were unchanged.[6]

(c) Vardenafil

The manufacturers note that no pharmacokinetic interaction was observed when vardenafil was given with **warfarin**,[7,8] and the prothrombin time was unchanged.[8]

Mechanism

An interaction as a result of altered coumarin metabolism is unlikely with any of these phosphodiesterase type-5 inhibitors. The two cases of interactions with sildenafil are unexplained. It is not obvious why dividing the acenocoumarol dose, or using ranitidine, would have reversed an interaction.

Sildenafil alone appears to commonly cause nosebleeds in patients with pulmonary hypertension. The reason for this is unknown, but studies with human platelets indicate that sildenafil potentiates the antiaggregatory effect of sodium nitroprusside *in vitro*.[1-4]

Importance and management

There is no established pharmacokinetic or pharmacodynamic interaction between the phosphodiesterase type-5 inhibitors and warfarin, and no warfarin dose adjustment would therefore be expected to be needed on concurrent use. However, in pulmonary hypertension, sildenafil appears to increase the risk of nosebleeds, and this may be greater in patients taking coumarins. Similarly, the two possible cases with acenocoumarol and warfarin, although not conclusive, do introduce a note of caution.

1. Viagra (Sildenafil citrate). Pfizer Ltd. UK Summary of product characteristics, January 2009.
2. Viagra (Sildenafil citrate). Pfizer Inc. US Prescribing information, August 2008.
3. Revatio (Sildenafil citrate). Pfizer Ltd. UK Summary of product characteristics, July 2009.
4. Revatio (Sildenafil citrate). Pfizer Inc. US Prescribing information, November 2009.
5. Fernández MA, Romá E. International normalized ratio increase in patients taking oral anticoagulant therapy and using sildenafil (Viagra®). *Haematologica* (2003) 88, ELT34.
6. Eli Lilly and Company. Personal communication, March 2003.
7. Levitra (Vardenafil hydrochloride trihydrate). Bayer plc. UK Summary of product characteristics, June 2009.
8. Levitra (Vardenafil hydrochloride). Bayer Pharmaceuticals Corporation. US Prescribing information, December 2008.

Coumarins + Picotamide

Picotamide did not alter the anticoagulant effects of warfarin. Nevertheless, as with other antiplatelet drugs, concurrent use might increase the bleeding risk.

Clinical evidence, mechanism, importance and management

Picotamide 300 mg three times daily for 10 days did not alter the anticoagulant effects of established **warfarin** therapy in 10 patients with aortic or mitral valve prostheses.[1] No **warfarin** dose adjustments would therefore be expected to be needed on concurrent use. Nevertheless, as with other antiplatelet drugs, such as aspirin (see 'Coumarins and related drugs + Aspirin or other Salicylates', p.434), the concurrent use of oral anticoagulants might increase the risk or intensity of bleeding. Some caution is therefore appropriate on concurrent use.

1. Parise P, Gresele P, Viola E, Ruina A, Migliacci R, Nenci GG. La picotamide non interferisce con l'attività anticoagulante del warfarin in pazienti portatori di protesi valvolari cardiache. *Clin Ter* (1990) 135, 479–82.

Coumarins + Piracetam

Piracetam does not appear to affect the dose of acenocoumarol required to produce a given INR. A single case report describes a woman stabilised on warfarin who began to bleed within one month of starting to take piracetam.

Clinical evidence, mechanism, importance and management

In a randomised study in patients with severe or recurrent venous thrombosis, there was no difference in the dose of **acenocoumarol** necessary to reach an INR of 2.5 to 3.5 between 100 patients taking **acenocoumarol** with high-dose piracetam 9.6 g daily and 100 patients taking **acenocoumarol** alone. No patients had severe bleeding, and 3 to 4% of patients in both groups had moderate bleeding (haematomas, haematuria). The addition of piracetam decreased platelet aggregation, levels of fibrinogen, and blood viscosity.[1]

A woman taking **warfarin**, insulin, levothyroxine and digoxin complained of menorrhagia at a routine follow up. Investigations revealed that her British Corrected Ratio had risen to 4.1 (from a range of 2.3 to 2.8), and that one month previously she had started to take low-dose piracetam 200 mg three times daily. Within 2 days of withdrawing both the **warfarin** and piracetam her British Corrected Ratio had fallen to 2.07, and the original dose of warfarin was restarted.[2]

Piracetam alone is known to decrease platelet aggregation,[1] and might therefore be expected to increase the risk of bleeding with anticoagulants, similar to other drugs with antiplatelet activity such as aspirin (see 'Coumarins and related drugs + Aspirin or other Salicylates', p.434). The early

case appears to be the only report of a possible interaction, but some caution might be prudent on concurrent use.

1. Moriau M, Lavenne-Pardonge E, Crasborn L, von Frenckell R, Col-Debeys C. The treatment of severe or recurrent deep venous thrombosis. Beneficial effect of the co-administration of antiplatelet agents with or without rheological effects, and anticoagulants.*Thromb Res* (1995) 78, 469–82.
2. Pan HYM, Ng RP. The effect of Nootropil in a patient on warfarin. *Eur J Clin Pharmacol* (1983) 24, 711.

Coumarins + Pirmenol

The anticoagulant effects of warfarin are not altered by pirmenol.

Clinical evidence, mechanism, importance and management

The prothrombin time response to a single 25-mg dose of **warfarin** was slightly reduced (reductions ranged from 0.2 to 1.3 seconds) in most of the 12 healthy subjects who had taken pirmenol 150 mg twice daily for 14 days, with warfarin taken on day 8.[1] This suggested that some changes in the dose of **warfarin** might be required in practice, but a later placebo-controlled study found that the prothrombin times of 10 patients stabilised on **warfarin** were not significantly changed when they were given oral pirmenol 150 mg twice daily for 14 days.[2] No **warfarin** dose adjustments would therefore be expected to be required on concurrent use.

1. Janiczek N, Bockbrader HN, Lebsack ME, Sedman AJ, Chang T. Effect of pirmenol (CI-845) on prothrombin (PT) time following concomitant administration of pirmenol and warfarin to healthy volunteers. *Pharm Res* (1988) 5, S-155.
2. Stringer KA, Switzer DF, Abadier R, Lebsack ME, Sedman A, Chrymko M. The effect of pirmenol administration on the anti-coagulant activity of warfarin. *J Clin Pharmacol* (1991) 31, 607–10.

Coumarins + Probenecid

In healthy subjects, probenecid increased the clearance of single-dose phenprocoumon without altering its anticoagulant effect. The anticoagulant effects of multiple-dose phenprocoumon might be expected to be decreased by probenecid, but this requires confirmation.

Clinical evidence, mechanism, importance and management

In 9 healthy subjects probenecid 500 mg four times daily for 7 days reduced the AUC of a single 0.22-mg/kg dose of **phenprocoumon** given on day one by 47% and reduced the elimination half-life by about one-third. Nevertheless, the reduction in prothrombin time by **phenprocoumon** was not altered by probenecid.[1]

The reasons for this interaction are not understood, but one possibility is that, while probenecid inhibits the glucuronidation of **phenprocoumon** (its normal route of metabolism), it may also increase the formation of hydroxylated metabolites so that its overall loss is increased.[1]

Although the anticoagulant effect of single-dose **phenprocoumon** was not altered in this study, its findings suggests that, in the presence of probenecid, the dose of phenprocoumon might need to be increased, but this awaits formal clinical confirmation in a multiple-dose study. Nevertheless, bear the possibility in mind. Nothing further seems to have been published on this potential interaction and there seems to be nothing documented about other coumarins.

1. Mönig H, Böhm M, Ohnhaus EE, Kirch W. The effects of frusemide and probenecid on the pharmacokinetics of phenprocoumon. *Eur J Clin Pharmacol* (1990) 39, 261–5.

Coumarins + Proguanil

An isolated report describes bleeding in a patient stabilised on warfarin after she took proguanil for about five weeks.

Clinical evidence, mechanism, importance and management

A woman stabilised on **warfarin** developed haematuria, bruising and abdominal and flank discomfort about 5 weeks after starting to take proguanil 200 mg daily. Her prothrombin ratio was found to be 8.6. Within 12 hours of being given fresh frozen plasma and vitamin K her prothrombin ratio had fallen to 2.3. During the 5 weeks she had travelled from Britain to Thailand, Bali, Australia and then New Zealand, and her prothrombin ratio had not been checked during this time. The mechanism of this potential interaction is unknown.[1] Its general importance is uncertain, as factors related to travel (such as a changing diet and changing dose times in different time zones) may have had a part to play in this interaction.

1. Armstrong G, Beg MF, Scahill S. Warfarin potentiated by proguanil. *BMJ* (1991) 303, 789.

Coumarins + Prolintane

The anticoagulant effects of ethyl biscoumacetate are not affected by prolintane.

Clinical evidence, mechanism, importance and management

The response to a single 20-mg/kg dose of **ethyl biscoumacetate** was studied in 4 healthy subjects given prolintane 20 mg daily for 4 days. Assessments were made before prolintane, on day one of prolintane, and 8 days after prolintane was stopped. The mean half-life of the anticoagulant and prothrombin times remained unchanged.[1] No **ethyl biscoumacetate** dose adjustments would appear to be required on concurrent use.

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Coumarins and related drugs + Propafenone

The anticoagulant effects of warfarin, and possibly fluindione and phenprocoumon, are increased by propafenone.

Clinical evidence

The mean steady-state plasma levels of 8 healthy subjects taking **warfarin** 5 mg daily rose by 38% after they took propafenone 225 mg three times daily for a week. Five of the 8 had a distinct prothrombin time increase. The average rise in prothrombin time of the whole group was about 7 seconds, which was considered to be clinically significant.[1] Two case reports describe marked increases in the anticoagulant effects of **fluindione** and **phenprocoumon** in 2 patients taking propafenone.[2,3]

Mechanism

Propafenone may reduce the metabolism of these anticoagulants, thereby increasing their effects. From *in vitro* data, it was concluded that propafenone would affect only *R*-warfarin, whereas both *R*- and *S*-acenocoumarol were affected.[4]

Importance and management

Information seems to be limited to these reports but they suggest that anticoagulant control should be well monitored if propafenone is given to patients taking warfarin, and probably also phenprocoumon and the indanedione fluindione. The anticoagulant dose should be reduced where necessary. It would be prudent to apply the same precautions with any other coumarin or indanedione.

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Coumarins and related drugs + Prostaglandins

The concurrent use of high-dose, intravenous epoprostenol and warfarin may increase the risk of pulmonary haemorrhage. Treprostinil does not appear to alter the pharmacokinetics or the anticoagulant effects of warfarin, and also did not appear to increase the risk of bleeding when used with warfarin in clinical studies. Beraprost did not alter the pharmacokinetics of fluindione. Inhaled iloprost did not appear to increase the incidence of

bleeding in clinical studies in patients using anticoagulants. Because these prostaglandins inhibit platelet aggregation, some caution is appropriate on the concurrent use of anticoagulants.

Clinical evidence

(a) Beraprost

In a controlled study in 12 healthy subjects, oral beraprost sodium 40 micrograms three times daily for 3 days did not alter the pharmacokinetics of a single 20-mg dose of **fluindione** given on day 3. This dose of fluindione had only a marginal effect on the INR, and this effect was not altered by beraprost.[1]

(b) Epoprostenol

In a small retrospective review of 31 patients with primary pulmonary hypertension receiving **warfarin** and continuous intravenous epoprostenol, 9 patients were identified who experienced 11 bleeding episodes (9 cases of pulmonary haemorrhage, 2 of nasal bleeding). Of the 9 cases of pulmonary haemorrhage, 8 were identified clinically by persistent haemoptysis, and 2 cases were associated with severe respiratory distress. Of the 7 patients with an INR available at the time of the first bleeding episode, 6 had an INR under 2 and one had an INR of 3.1. The dose of epoprostenol in patients with bleeds ranged from 28.1 to 164 nanograms/kg per minute, and no patient receiving less than 28 nanograms/kg per minute had a bleed. There was no significant difference in survival in patients with a bleeding episode and those without.[2] In contrast, the manufacturer states that, in clinical studies, there was no evidence of increased bleeding in patients taking anticoagulants and receiving infusions of epoprostenol.[3]

(c) Iloprost

The manufacturer of iloprost notes that there was no difference in the incidence of bleeding between patients receiving inhaled iloprost and those given placebo in clinical studies in which a high proportion of patients were taking anticoagulants (unnamed). However, they note that bleeding events (mostly haematomas) were common.[4]

(d) Treprostinil

In a crossover study in 15 healthy subjects, continuous subcutaneous treprostinil 5 then 10 nanograms/kg every minute for 9 days did not alter the pharmacodynamics (INR) of a single 25-mg oral dose of **warfarin** given on day 3. In addition, there was no change in the pharmacokinetics of *R*- and *S*-warfarin.[5] In the discussion of this study, the authors mention an unpublished retrospective review of data from placebo-controlled clinical studies in patients with pulmonary artery hypertension. From this there was no evidence to suggest that the concurrent use of **warfarin** and treprostinil (155 patients) was associated with increased bleeding or coagulation-related events, when compared with warfarin and placebo (156 patients).[5]

Mechanism

Epoprostenol (prostacyclin) and its analogues beraprost, iloprost and treprostinil are vasodilators that also inhibit platelet aggregation. As such, it is anticipated that they might increase the potential for bleeding when given with anticoagulants.

Importance and management

Anticoagulants such as warfarin are commonly used in patients with pulmonary artery hypertension, a condition for which the prostaglandins beraprost, epoprostenol, iloprost and treprostinil are indicated, so the combination is likely to be used frequently. Because these prostaglandins are potent inhibitors of platelet aggregation, they might increase the risk of bleeding with anticoagulants (including coumarins and **indanediones**), although the manufacturers say that there was no evidence of increased bleeding in clinical studies using epoprostenol,[3] iloprost[4] or treprostinil.[5] Nevertheless, limited evidence from the small survey in Japanese patients given epoprostenol suggests that this may be the case with high-dose epoprostenol. In this study, the authors commented that they no longer use anticoagulants in patients receiving high-dose epoprostenol.[2] However, the manufacturer states that in clinical studies of epoprostenol almost all patients with pulmonary hypertension were receiving oral anticoagulants, and, unless contraindicated, they recommend concurrent oral anticoagulation in those patients with either primary pulmonary hypertension or pulmonary hypertension secondary to scleroderma to reduce the risk of thromboembolism.[3] Some caution would be appropriate if any of these prostaglandins is given with a coumarin or **indanedione**.

Some prostaglandins, such as epoprostenol, may also be used for other indications, such as maintaining renal dialysis catheter patency or for treating peripheral ischaemia: similar caution should be used if these patients are taking anticoagulants.[6]

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4. Ventavis (Iloprost). Bayer plc. UK Summary of product characteristics, November 2009.
5. Wade M, Hunt TL, Lai AA. Effect of continuous subcutaneous treprostinil therapy on the pharmacodynamics and pharmacokinetics of warfarin. *J Cardiovasc Pharmacol* (2003) 41, 908–15.
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Coumarins + Protease inhibitors

In pharmacokinetic studies, ritonavir slightly raised *S*-warfarin levels and modestly decreased *R*-warfarin levels, while ritonavir-boosted lopinavir decreased *R*- and *S*-warfarin levels. A number of case reports of an interaction with protease inhibitors have been reported, most of which show a decrease in warfarin or acenocoumarol effects, although a couple show an increase in warfarin effects.

Clinical evidence

(a) Acenocoumarol

A 46-year-old HIV-positive man with mitraortic valve replacements stabilised on acenocoumarol (INR 2.5 to 3.5) for 5 years and taking zidovudine and didanosine for 17 months was found to have a dramatic decrease in his INR when his drug regimen was changed to stavudine, lamivudine and **ritonavir** 600 mg twice daily. Increasing the acenocoumarol dose over 5 days from an average of 24 mg to over 70 mg failed to increase the INR to target levels. The INR returned to previous levels within 4 days of stopping **ritonavir**, and the acenocoumarol dose could be reduced to 3 mg daily. The patient was subsequently given **nelfinavir** and a similar, though less dramatic interaction occurred: while taking **nelfinavir** an INR of 2.5 was achieved with a 210% increase in the acenocoumarol dose.[1]

(b) Warfarin

1. Indinavir. A 50-year-old HIV-positive man, stabilised on warfarin (prothrombin complex activity (PCA) range of 20 to 35%), started taking indinavir 800 mg every 8 hours, but it had to be withdrawn after 12 days because of a generalised skin rash. It was then found that the indinavir had caused a moderate reduction in his level of anticoagulation: 10 and 25 days after indinavir was stopped his PCA was 53% and 43%, respectively. The warfarin dose was increased to 6.25 and 7.5 mg on alternate days for one week, during which time a PCA of 34% was achieved, and he was then subsequently given warfarin 6.25 mg daily.[2] This patient subsequently needed an increase in warfarin dose when given *ritonavir*, see below. Another patient had a modest rise in INR to 4.5 when his dose of ritonavir was reduced from 600 mg twice daily to 200 mg twice daily and indinavir 800 mg twice daily added. This case suggests that any effect of high dose ritonavir was more marked than that of ritonavir-boosted indinavir.[3]

2. Lopinavir. In a pharmacokinetic study in healthy subjects,[4] ritonavir-boosted lopinavir 100/400 mg twice daily for 10 days modestly decreased the AUCs of *R*- and *S*-warfarin by 37% and 29%, respectively, after a single 10-mg dose of warfarin and vitamin K were given on day 7. The effect of this reduction on the anticoagulant activity of warfarin was not assessed, since vitamin K was given to inhibit the pharmacological effect of warfarin without affecting its pharmacokinetics.

However, there are a couple of case reports suggesting a marked reduction in warfarin effects with ritonavir-boosted lopinavir. In one case, a man taking warfarin required a progressive daily dose increase from between 3.75 to 5 mg up to 10 mg after restarting an antiretroviral regimen including lopinavir with ritonavir. When the protease inhibitors were later stopped, the warfarin dose needed to be reduced again.[5] Another case has

been described where a man was eventually stabilised on warfarin 13 mg daily while taking ritonavir-boosted lopinavir, which was over twice his original dose of 5.5 mg daily.[6] Yet another describes a man who required a 40% warfarin dose increase from 12.5 to 17.5 mg daily when switched from nelfinavir to ritonavir-boosted lopinavir.[7]

3. Nelfinavir. A man taking abacavir, tenofovir and nelfinavir needed an increase in his warfarin dose from 45 mg weekly to 70 mg weekly to achieve a therapeutic INR.[7] Of the other drugs he was taking, ribavirin has been reported to increase warfarin requirements (see 'Coumarins + Ribavirin', p.502). Another patient required a high warfarin dose of 12.5 mg daily while taking a nelfinavir-containing regimen,[7] but this was less than that required while he was taking ritonavir-boosted lopinavir (17.5 mg daily) or nevirapine (20 mg daily). Consider also 'Coumarins + NNRTIs', p.480.

4. Ritonavir. The manufacturer reports that, in 12 healthy subjects given ritonavir 400 mg every 12 hours for 12 days, there was a 9% increase (not statistically significant) in the AUC of *S*-warfarin while the AUC of *R*-warfarin was decreased by 33%, after a single 5-mg dose of warfarin.[8] The effect of these changes on prothrombin time was not mentioned, but potentially could result in an increased warfarin effect due to the more potent *S*-warfarin, or a decreased effect due to the *R*-warfarin. Both of these outcomes have been reported in individual cases. An increase in warfarin effect was seen in a man taking warfarin 10 mg daily (INRs 2.4 to 3) when his treatment for HIV was changed from efavirenz and abacavir to ritonavir, nelfinavir and *Combivir* (zidovudine with lamivudine). Within 5 days his INR had risen to 10.4, without any sign of bleeding. It proved difficult to achieve acceptable and steady INRs both while in hospital and after discharge, but eventually it was discovered that the patient could not tolerate liquid ritonavir because of nausea and vomiting, so that he had sometimes skipped or lowered the ritonavir dose or even refused to take it. On the occasions where no ritonavir or low-dose ritonavir was taken, the INRs had been low, whereas when he took the full dose of ritonavir the INRs were high.[9]

In contrast, the INR of a 27-year-old HIV-positive woman taking warfarin fell when she was given ritonavir, clarithromycin and zidovudine. It was necessary almost to double the warfarin dose to maintain satisfactory INRs. Three months later when the ritonavir was withdrawn, her INR more than tripled within a week. Her final warfarin maintenance dose was half of that needed before the ritonavir was started, and a quarter of the dose needed just before she stopped the ritonavir. This case was complicated by the use or withdrawal of a number of other drugs (co-trimoxazole, rifabutin, an oral hormonal contraceptive, megestrol), which can also interact with warfarin.[10] Similarly, in another patient taking warfarin 6.25 mg daily with a prothrombin activity complex (PCA) of about 34%, a decrease in warfarin effects (PCA increase to 62%) was noted 20 days after starting ritonavir (escalating doses up to 600 mg every 12 hours). The warfarin dose was then increased to 8.75 mg daily and 24 days later a satisfactory PCA of 33% was achieved.[2] This patient had previously had a decrease in warfarin effects while taking *indinavir*, see above. A patient stabilised on warfarin was found to have a subtherapeutic INR of 1 and required a 62% increase in warfarin dose when his protease inhibitor was switched from saquinavir to ritonavir 600 mg twice daily. Another patient taking ritonavir and saquinavir needed a very high warfarin dose to achieve a therapeutic INR.[3]

5. Saquinavir. A 73-year-old man who was HIV-positive and who had been taking warfarin, co-trimoxazole, nizatidine, stavudine and lamivudine for 7 months started taking saquinavir 600 mg three times daily. His INR, which had been stable at around 2 for five months, rose to about 2.5 after 4 weeks, and to about 4.2 after 8 weeks, which the author of the report attributed to an interaction with the saquinavir. The situation was solved by reducing the warfarin dose by 20%.[11]

Mechanism

Protease inhibitors are well known to alter the metabolism of many drugs by inhibition, but sometimes by induction of cytochrome P450 isoenzymes, see 'Table 21.2', (p.914), so it is not surprising that they have altered warfarin effects, although the precise mechanism is unclear. The findings of the two pharmacokinetic studies suggest that, with warfarin, induction predominates, and that the anticoagulant effects are likely to be decreased. However, the modest reductions in levels seen do not explain the sometimes marked reduction in anticoagulant effects.

Importance and management

Pharmacokinetic studies have suggested that ritonavir and ritonavir-boosted lopinavir can modestly reduce warfarin levels. Clinical information on an interaction between coumarins and protease inhibitors is limited to the case reports cited, most of which show a, sometimes very marked, decrease in warfarin or acenocoumarol effects (with indinavir, ritonavir-boosted lopinavir, nelfinavir, ritonavir or ritonavir-boosted saquinavir), although a couple show an increase in warfarin effects (nelfinavir with ritonavir, or saquinavir). These cases show it would be prudent to monitor the prothrombin times and INRs of any patient if any HIV-protease inhibitor is added, being alert for the need to modify the coumarin dose.

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Coumarins + Proton pump inhibitors

Omeprazole causes a minor increase in *R*-warfarin levels, no effect on *S*-warfarin, with, at most, a minor increase in anticoagulant effect. Conversely, lansoprazole, pantoprazole and rabeprazole do not alter warfarin pharmacokinetics or its anticoagulant effect. Omeprazole does not appear to alter the effects of acenocoumarol, and pantoprazole does not appear to alter the effects of phenprocoumon. Nevertheless, a few isolated reports describe increased anticoagulant effects when proton pump inhibitors were given with coumarins.

Clinical evidence

(a) Esomeprazole

Esomeprazole is the *S*-isomer of omeprazole, and would be expected to behave similarly to omeprazole, see *Omeprazole*, below. The manufacturers say that esomeprazole 40 mg daily did not cause any clinically relevant effects on anticoagulant times in patients stabilised on **warfarin**, but a few isolated cases of raised INRs have been reported post-marketing.[1,2]

(b) Lansoprazole

A study in 24 healthy subjects stabilised on **warfarin** found that lansoprazole 60 mg daily for 9 days had no effect on the pharmacokinetics of either *S*- or *R*-warfarin, and did not alter the effect of **warfarin** on prothrombin times.[3] However, in 1998 the manufacturers of lansoprazole had on record two reports of possible interactions. An elderly patient taking **warfarin** developed an INR of 7 when lansoprazole was added. Despite a **warfarin** dose adjustment he had a gastrointestinal haemorrhage, a myocardial infarction and died after 3 weeks. Another man taking **warfarin** (as well as amiodarone, furosemide and lisinopril) became confused, had hallucinations and developed an increased INR (value not known) when given lansoprazole. The lansoprazole was stopped after 4 days, and he then recovered. However, it is uncertain whether this was an interaction or whether he had taken an incorrect **warfarin** dose because of his confusion.[4]

(c) Omeprazole

1. Acenocoumarol. In a placebo-controlled study in 8 healthy subjects, omeprazole 40 mg daily for 3 days had no effect on the pharmacokinetics of *R*- or *S*-acenocoumarol when a single 10-mg dose of acenocoumarol was given on day 2. In addition, omeprazole did not alter the anticoagulant effects of acenocoumarol.[5] Similarly, there was no evidence of an interac-

tion in a retrospective study of 118 patients given acenocoumarol with omeprazole and 299 patients taking acenocoumarol without omeprazole (matched for age and sex).[6] Furthermore, in a retrospective cohort study of patients taking acenocoumarol, omeprazole was not associated with an increased risk of hospitalisation for bleeding.[7] However, an isolated case report describes a 78-year-old woman who had been taking acenocoumarol for 60 days and who developed gross haematuria within 5 days of starting omeprazole 20 mg daily. Her INR had risen from a range of 2.5 to 3 up to 5.7, and when the omeprazole was stopped, her INR fell.[8]

2. Warfarin. In 21 healthy subjects who had been stabilised on warfarin, omeprazole 20 mg daily for 2 weeks caused a small but statistically significant decrease in the mean thrombotest percentage, from 21.1% to 18.7%. *S*-warfarin serum levels remained unchanged, but a small 12% rise in *R*-warfarin levels was seen.[9] In a further study, no changes in coagulation times or thrombotest values occurred in 28 patients anticoagulated with warfarin and given omeprazole 20 mg daily for 3 weeks. *S*-warfarin levels were unchanged, while a 9.5% increase in *R*-warfarin levels occurred.[10] A study in 7 patients who were CYP2C19 poor metabolisers and 10 patients who were CYP2C19 extensive metabolisers (that is, those lacking or deficient in this isoenzyme and those with normal levels of this isoenzyme, respectively) specifically looked at the effect of different CYP2C19 genotypes on the metabolism of warfarin, and also the influence of omeprazole on this interaction. The AUC of *R*-warfarin (from a single 10-mg dose of racemic warfarin) was found to be 24% higher in poor metabolisers than in extensive metabolisers. Omeprazole 20 mg daily taken for 11 days increased the AUC of *R*-warfarin (taken on day 7) in the extensive metabolisers to a level comparable with that in the poor metabolisers. Omeprazole had no effect on *S*-warfarin, and no effect on anticoagulant activity in any subject.[11] However, a man stabilised on warfarin 5 mg daily developed widespread bruising and haematuria 2 weeks after starting to take omeprazole 20 mg daily. His prothrombin time was found to have risen to 48 seconds. He was later restabilised on omeprazole 20 mg daily with the warfarin dose reduced to 2 mg daily.[12]

3. Phenprocoumon. In a retrospective cohort study of patients taking phenprocoumon, omeprazole was not associated with an increased risk of hospitalisation for bleeding.[7]

(d) Pantoprazole

1. Phenprocoumon. The prothrombin time ratio in 16 healthy subjects taking individualised maintenance phenprocoumon doses was not changed when they were given pantoprazole 40 mg daily for 5 days, nor was there any change in the pharmacokinetics of *R*- and *S*-phenprocoumon.[13] However, there is a report of 2 possible cases of an interaction.[14] One patient who was given phenprocoumon (loading dose 12 mg on day one, 9 mg on day 2, 3 mg on day 3, and further as required) and omeprazole 20 mg daily concurrently, had an INR of 3.28 by the fourth day. The phenprocoumon was withheld, but the INR remained high for 9 days, when the omeprazole was stopped. Four days later the INR was 1.5 and phenprocoumon was restarted at 16.5 mg/week, and stabilised at 9 to 10.5 mg/week. She subsequently had a similar loading dose without problems, in the absence of omeprazole, after phenprocoumon had been stopped for 3 weeks before surgery.[14] Another patient stabilised on phenprocoumon 18 mg/week required a slight reduction in dose to 16.5 mg/week after starting omeprazole 20 mg daily.[14]

2. Warfarin. In 26 healthy subjects, pantoprazole 40 mg daily for 8 days caused no change in the response to a single 25-mg dose of warfarin given on day 2. The pharmacokinetics of *R*- and *S*-warfarin were unaltered, and no changes in the pharmacodynamics of the warfarin (prothrombin time, factor VII) were seen.[15] However, the manufacturer notes that there have been reports of increased INR and prothrombin time in patients taking pantoprazole and warfarin.[16]

(e) Rabeprazole

In a placebo-controlled study, a single 0.75-mg/kg dose of **warfarin** was given to 21 patients before and after rabeprazole 20 mg daily for 7 days. No significant changes in prothrombin times or in the pharmacokinetics of *R*- or *S*-warfarin were seen.[17] However, the manufacturer notes that there have been reports of increased INR and prothrombin time in patients receiving rabeprazole and **warfarin**.[18]

Mechanism

Studies have shown that omeprazole partially inhibits the metabolism of *R*-warfarin, but not *S*-warfarin,[19,20] which in line with the findings in the pharmacokinetic studies above. It also partially inhibits the metabolism of acenocoumarol.[19] However, these small changes would generally not be expected to be clinically relevant. It has been suggested that the interaction might occur only in patients who are poor metabolisers of the cytochrome P450 isoenzyme CYP2C19 (seen in about 5% of Caucasians), who have five to tenfold higher levels of omeprazole than extensive metabolisers.[5] Conversely, in the one study addressing this the effect of CYP2C19 genotype was not clinically relevant.[11] Other proton pump inhibitors are generally considered to have less potential for pharmacokinetic interactions than omeprazole, but even with these, isolated cases of anticoagulant interactions have been reported.

Importance and management

The very minor pharmacokinetic interaction between omeprazole and warfarin, resulting in a less than 15% rise in *R*-warfarin levels (the less active isomer), is established, but probably of limited clinical relevance. This is borne out by the fact there is only one published case report of an interaction. No pharmacokinetic or pharmacodynamic interaction occurred between warfarin and lansoprazole, pantoprazole or rabeprazole in clinical studies. However, isolated cases of raised INRs have been reported for all the proton pump inhibitors (esomeprazole, lansoprazole, pantoprazole, omeprazole and rabeprazole) with acenocoumarol (one published), phenprocoumon (2 published), and warfarin. It is possible that the isolated cases of interactions with proton pump inhibitors just represent idiosyncratic effects attributable to other factors, and not to any interaction. Nevertheless, when prescribing proton pump inhibitors to patients taking coumarins it would seem prudent to bear in mind that rarely bleeding can occur. Note that the US prescribing information for every proton pump inhibitors states that patients taking a proton pump inhibitor and warfarin may need to be monitored for increases in INR and prothrombin time. The advice in UK varies from recommending monitoring with warfarin and omeprazole[21] or esomeprazole,[1] recommending monitoring with coumarins and pantoprazole,[22] to no advice with lansoprazole[23] or rabeprazole.[24]

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19. Hermans JJ, Thijssen HH. Human liver microsomal metabolism of the enantiomers of warfarin and acenocoumarol: P450 isozyme diversity determines the differences in their pharmacokinetics. *Br J Pharmacol* (1993) 111, 482–90.
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21. Losec Capsules (Omeprazole). AstraZeneca UK Ltd. UK Summary of product characteristics, February 2008.
22. Protium Tablets (Pantoprazole sodium sesquihydrate). Nycomed UK Ltd. UK Summary of product characteristics, January 2008.
23. Zoton FasTab (Lansoprazole). Wyeth Pharmaceuticals. UK Summary of product characteristics, August 2007.
24. Pariet (Rabeprazole sodium). Eisai Ltd. UK Summary of product characteristics, May 2009.

Coumarins + Quetiapine

A case report describes a woman taking warfarin who developed a raised INR when quetiapine was started.

Clinical evidence, mechanism, importance and management

A 71-year old woman receiving long-term treatment with **warfarin**, phenytoin, olanzapine and benztropine had her **warfarin** dose slightly reduced (from 20 to 19.5 mg weekly) because her INR was raised (from 1. to 2.6). Eight days later her treatment with olanzapine was changed to quetiapine 200 mg daily, and after 5 days her INR was 2.7. Two weeks later she was found to have an INR of 9.2. The quetiapine was stopped and she was given two doses of vitamin K by injection. The only clinical symptoms seen were a small amount of bleeding from the injection site and a bruise on her hand. She was eventually later restabilised taking phenytoin, olanzapine and **warfarin** 21 mg weekly with an INR of 1.6.

The reasons for this apparent interaction are not known, but the authors suggest that the quetiapine may have inhibited the metabolism of the **warfarin** (possibly by competitive inhibition of the cytochrome P450 isoenzymes CYP3A4 and CYP2C9), thereby increasing its effects. They also suggest that the phenytoin may have had some part to play.[1] This is only an isolated case and as such an interaction is not confirmed, but bear it in mind in the case of an unexpected response to concurrent use.

1. Rogers T, de Leon J, Atcher D. Possible interaction between warfarin and quetiapine. *J Clin Psychopharmacol* (1999) 19, 382–3.

Coumarins + Quilinggao

A single case report describes a man who had a marked increase in his INR with bleeding complications, nine days after he switched the brand of quilinggao he was using.

Clinical evidence

A 61-year-old man stabilised on **warfarin** with an INR in the range of 1.6 to 2.8 was found to have an INR greater than 6 and skin bruising, and complained of gum bleeding and epistaxis in the previous 3 days. For the past 3 years he had taken quilinggao, apparently without problems. However, 9 days previously he had started taking a different brand of quilinggao. He was eventually stabilised on the previous dose of **warfarin** with an INR of 2.5, but after discharge started taking a third brand of quilinggao, and 3 days later had an INR of 5.2.[1]

Mechanism

Quilinggao is a Chinese herbal product made from a mixture of herbs. The first brand did not contain any herbs suspected to have anticoagulant effects except one with possible antiplatelet activity, but the second brand contained Chinese peony (*Paeoniae rubra*), *Poncirus trifoliata* and a couple of other herbs known to contain substances with anticoagulant or antiplatelet effects *in vitro*, but see also 'Coumarins + Herbal medicines; Miscellaneous', p.472.

Importance and management

This appears to be the only case of a possible interaction, and as such the interaction is not established. Quilinggao did not affect anticoagulant control in this patient for a number of years, and then did after switching brands. Bear the possibility of an interaction in mind.

1. Wong ALN, Chan TYK. Interaction between warfarin and the herbal product *quilinggao*. *Ann Pharmacother* (2003) 37, 836–8.

Coumarins + Quinidine

Quinidine does not appear to alter the anticoagulant effect of warfarin; however, isolated reports of increased warfarin effects and bleeding, and also decreased dicoumarol and warfarin effects have been reported. Quinidine does not alter the half-life of phenprocoumon.

Clinical evidence

In a controlled study, 10 patients receiving long-term treatment with **warfarin** 2.5 to 12.5 mg daily had no significant alteration in their prothrombin times when they were given quinidine 200 mg four times daily for 2 weeks.[1,2] Similarly, in a retrospective analysis of 8 patients stabilised on **warfarin**, there was no change in anticoagulant control associated with starting or stopping quinidine (600 mg to 1.2 g daily as sulfate or 660 mg daily as gluconate).[3] In the preliminary report of another study in 5 healthy subjects, quinidine 100 mg daily, started 7 days after a single 12-mg dose of **phenprocoumon**, did not change the elimination half-life of **phenprocoumon**.[4]

In contrast, another report described 3 patients stabilised on **warfarin**, with Quick values within the range of 15 to 25%, who began to bleed within 7 to 10 days of starting to take quinidine 800 mg to 1.2 g daily. Their Quick values were found to have fallen to 6 to 8%. Bleeding ceased when the warfarin was withdrawn.[5] There is one other case report of haemorrhage associated with the concurrent use of **warfarin** and quinidine,[6] and in an analysis of haemorrhage in patients taking anticoagulants, it was reported that quinidine seemed partly responsible for some cases.[7]

In a further report, 4 patients taking **warfarin** or **dicoumarol** needed dose *increases* of 8 to 24% to maintain adequate anticoagulation after DC conversion for atrial fibrillation and starting quinidine 400 mg three times daily.[8]

Mechanism

Uncertain. The cases of increased warfarin effects were attributed to quinidine possibly having a direct hypoprothrombinaemic effect of its own.[5] The cases of a slight decrease in anticoagulant effect were attributed to changes in haemodynamic factors as a result of cardioversion.[8]

Importance and management

In one study and one retrospective analysis, quinidine had no effect on the anticoagulant control with warfarin in patients. Therefore, no interaction would normally be anticipated. However, a few isolated cases of increased anticoagulant effect with bleeding have been reported. Nevertheless, the literature is limited, and based almost solely on evidence from more than 40 years ago. The lack of reports of any further interactions in this time suggests that a clinically relevant interaction is unlikely. Limited evidence suggests that quinidine does not alter phenprocoumon pharmacokinetics.

1. Udall JA. Quinidine and hypoprothrombinemia. *Ann Intern Med* (1968) 69, 403–4.
2. Udall JA. Drug interference with warfarin therapy. *Clin Med* (1970) 77, 20–5.
3. Jones FL. More on quinidine-induced hypoprothrombinaemia. *Ann Intern Med* (1968) 69, 1074.
4. Iven H, Lerche L, Kaschube M. Influence of quinine and quinidine on the pharmacokinetics of phenprocoumon in rat and man. *Eur J Pharmacol* (1990) 183, 662.
5. Koch-Weser J. Quinidine-induced hypoprothrombinemic hemorrhage in patients on chronic warfarin therapy. *Ann Intern Med* (1968) 68, 511–17.
6. Gazzaniga AB, Stewart DR. Possible quinidine-induced hemorrhage in a patient on warfarin sodium. *N Engl J Med* (1969) 280, 711–12.
7. Beaumont JL, Tarrit A. Les accidents hémorrhagiques survenus au cours de 1500 traitements anticoagulants. *Sang* (1955) 26, 680–94.
8. Sylvén C, Anderson P. Evidence that disopyramide does not interact with warfarin. *BMJ* (1983) 286, 1181.

Coumarins + Quinine

Isolated reports describe increased anticoagulant effects in two women taking warfarin and a man taking phenprocoumon, which were attributed to the quinine content of tonic water. Limited evidence suggests that quinine does not alter the half-life of phenprocoumon.

Clinical evidence

In the preliminary report of a study in 5 healthy subjects, quinine 100 mg daily started 7 days after a single 12-mg dose of **phenprocoumon** did not change the elimination half-life of **phenprocoumon** in the following 7 days.[1]

However, a patient taking long-term **phenprocoumon** repeatedly developed extensive haematuria within 24 hours of drinking one litre of Indian tonic water containing 30 mg of quinine.[1]

A woman stabilised on **warfarin** needed a dose reduction from 6 mg to 4 mg daily when she started to drink up to 1.5 litres of tonic water containing quinine each day. Her **warfarin** requirements rose again when the ton-

ic water was stopped. Another woman needed a **warfarin** dose reduction from 4 mg to 2 mg daily when she started to drink over 2 litres of tonic water daily. These patients were probably taking about 80 to 180 mg of quinine daily.[2]

Mechanism

Not understood. Two studies[3,4] using the Page method (Russell viper venom)[5] to measure prothrombin times showed that marked increases of up to 12 seconds could occur when 330-mg doses of quinine were given in the absence of an anticoagulant, but other studies[4,6] using the Quick method found that the prothrombin times were only prolonged by up to 2.1 seconds. The changes in prothrombin times could be completely reversed by vitamin K (menadiol sodium diphosphate),[3,4] which suggests that quinine, like the **indanediones** and coumarins, is a competitive inhibitor of vitamin K.

Importance and management

The interaction between quinine and the coumarins is not established. The lack of reports relating to the therapeutic use of quinine suggest that no interaction of clinical importance occurs, and because the only reports relate to tonic water, it cannot be excluded that some other ingredient is responsible for the effect seen in these patients. Also, they may just represent idiosyncratic reactions. Nevertheless, because some isolated cases appear to suggest that very exceptionally decreased anticoagulant requirements and even bleeding can occur when large quantities of tonic water are ingested the possibility of a rare interaction cannot entirely be dismissed.

1. Iven H, Lerche L, Kaschube M. Influence of quinine and quinidine on the pharmacokinetics of phenprocoumon in rat and man. *Eur J Pharmacol* (1990) 183, 662.
2. Clark DJ. Clinical curio: warfarin and tonic water. *BMJ* (1983) 286, 1258.
3. Pirk LA, Engelberg R. Hypoprothrombinemic action of quinine sulfate. *JAMA* (1945) 128, 1093–5.
4. Pirk LA, Engelberg R. Hypoprothrombinemic action of quinine sulfate. *Am J Med Sci* (1947) 213, 593–7.
5. Page RC, de Beer EJ, Orr ML. Prothrombin studies using Russell viper venom. II. Relation of clotting time to prothrombin concentration in human plasma. *J Lab Clin Med* (1941) 27, 197–201.
6. Quick AJ. Effect of synthetic vitamin K and quinine sulfate on the prothrombin level. *J Lab Clin Med* (1946) 31, 79–84.

Coumarins + Raloxifene

Raloxifene may cause a minor increase in warfarin levels. However, a 10% decrease in prothrombin time may also occur. Other coumarins would be expected to be similarly affected.

Clinical evidence, mechanism, importance and management

In a study in 15 healthy postmenopausal women, raloxifene 120 mg daily for 15 days had minor effects on the pharmacokinetics and pharmacodynamics of a single 20-mg dose of **warfarin** given on day 11. The clearance of both *R*- and *S*-warfarin was slightly decreased (by 7% and 14%, respectively), with similar increases in AUC. Conversely, a 10% reduction in the maximum prothrombin time was reported.[1] As has been suggested for lasofoxifene (see 'Coumarins + Lasofoxifene', p.475), this might be because oestrogenic compounds increase plasma concentrations of vitamin K-dependent clotting factors, so antagonising the effect of **warfarin**.

The manufacturers recommend that because modest decreases in prothrombin times have been seen, which may develop over several weeks, prothrombin times should be monitored.[2,3] In the UK, they extend this recommendation to cover the use of other coumarins.[2]

1. Miller JW, Skerjanec A, Knadler MP, Ghosh A, Allerheiligen SRB. Divergent effects of raloxifene HCl on the pharmacokinetics and pharmacodynamics of warfarin. *Pharm Res* (2001) 18, 1024–8.
2. Evista (Raloxifene hydrochloride). Daiichi Sankyo UK Ltd. UK Summary of product characteristics, August 2003.
3. Evista (Raloxifene hydrochloride). Eli Lilly and Company. US Prescribing information, October 2008.

Coumarins + Retinoids

Two isolated case reports describe reduced warfarin effects in one patient given etretinate, and in one patient given isotretinoin. Acitretin did not significantly alter the anticoagulant effects of phenprocoumon in healthy subjects.

Clinical evidence

(a) Phenprocoumon

Acitretin 50 mg daily for 10 days slightly increased the Quick test of 10 healthy subjects stabilised on phenprocoumon, from 22% to 24%, and the corresponding INR value decreased from 2.91 to 2.71. However, these changes were not considered to be clinically significant.[1]

(b) Warfarin

1. Etretinate. A man with T-cell lymphoma who had recently been given chemotherapy (cyclophosphamide, doxorubicin, vincristine and prednisolone) was anticoagulated with warfarin after developing a pulmonary embolism. About three weeks later, he started etretinate 40 mg daily and it was found necessary to increase his warfarin dose from 7 to 10 mg daily. His liver function tests were normal.[2] This patient had also recently started taking 'co-proxamol', (p.490), 'tolbutamide', (p.430), and 'cimetidine', (p.470), but all of these have been reported to only rarely *increase* the effect of warfarin.

2. Isotretinoin. A 61-year-old man stabilised on warfarin 2.5 mg daily for 2 to 3 years had a decrease in his INR to below 2.5 after starting oral cefpodoxime proxetil 200 mg twice daily and oral isotretinoin 30 mg daily for inflammatory lesions of the face. He required an increase in warfarin dose to 3.75 mg daily. The cefpodoxime was stopped after 10 days without a further change in his warfarin requirement. However, when the isotretinoin was discontinued after 40 days, the INR progressively increased and the warfarin dose was eventually reduced to the pre-isotretinoin dose of 2.5 mg daily.[3]

Mechanism

Not understood. It has been suggested that etretinate or isotretinoin may increase the rate of metabolism of warfarin.[2,3]

Importance and management

Information appears to be limited to these reports. The clinical relevance of the two case reports of a modest increase in warfarin requirements on starting etretinate or isotretinoin is uncertain. No definite conclusions can be drawn from these isolated cases. The study with acitretin suggests that no phenprocoumon dose adjustments are expected to be needed on starting acitretin.

1. Hartmann D, Mosberg H, Weber W. Lack of effect of acitretin on the hypoprothrombinemic action of phenprocoumon in healthy volunteers. *Dermatologica* (1989) 178, 33–6.
2. Ostlere LS, Langtry JAA, Jones S, Staughton RCD. Reduced therapeutic effect of warfarin caused by etretinate. *Br J Dermatol* (1991) 124, 505–10.
3. Fiallo P. Reduced therapeutic activity of warfarin during treatment with oral isotretinoin. *Br J Dermatol* (2004) 150, 164.

Coumarins + Ribavirin

Ribavirin appears to decrease the anticoagulant effects of warfarin.

Clinical evidence

A 61-year-old patient who had been taking **warfarin** for a number of years with an INR in the range of 1.8 to 2.7 required a progressive 40% increase in his **warfarin** dose (from 45 to 62.5 mg weekly) over the month after starting oral ribavirin 600 mg twice daily and subcutaneous interferon alfa-2b for active hepatitis C infection. During the following 11 months, the **warfarin** dose was stabilised at 57.5 mg weekly. Three weeks after discontinuation of the ribavirin and interferon, his INR had increased from 2.2 to 3.4 requiring a reduction in his **warfarin** dose to 47.5 mg weekly. One year later, when the patient was rechallenged with ribavirin alone (1 g daily for 4 weeks), his INR decreased from 2.6 to 1.8 and he required a weekly **warfarin** dose of 52.5 mg.[1]

For mention of another patient requiring a high **warfarin** dose (70 mg weekly), which was attributed to nelfinavir, but who was also receiving ribavirin, see 'Coumarins + Protease inhibitors', p.498.

Mechanism

Unknown. The few cases with interferon (see 'Coumarins + Interferons', p.474) have suggested that interferon may *increase* the effect of warfarin. In this case, ribavirin seems to have decreased the effect of warfarin, and

overridden any effect of interferon. However, ribavirin is not known to be an inhibitor or inducer of any cytochrome P450 isoenzyme.

Importance and management

This is the only case of this interaction, so it is not established, although the evidence on rechallenge with ribavirin alone lends weight to the effects potentially being due to an interaction. The authors recommended increased monitoring of anticoagulant effects in patients taking warfarin requiring ribavirin. Until more is known, this may be prudent.

1. Schulman S. Inhibition of warfarin activity by ribavirin. *Ann Pharmacother* (2002) 36, 72–4.

Coumarins + Ropinirole

A man stabilised on warfarin had an increase in his INR, necessitating a 25% decrease in his warfarin dose, while taking ropinirole.

Clinical evidence, mechanism, importance and management

A frail 63-year-old man taking levodopa with carbidopa daily and **warfarin** 4 mg daily with a stable INR ranging from 1.8 to 2.6 over the past 14 months was evaluated for possible progression of Parkinson's disease. He was then given ropinirole 250 micrograms three times daily with a 25% reduction in the dose of levodopa with carbidopa, and 9 days later his INR was noted to have increased to 4.6, but there were no apparent signs of bleeding. **Warfarin** was withheld for 4 days, and then restarted at 2 mg daily, and increased to 3 mg daily 19 days later when his INR was 1.2. After one month the ropinirole was discontinued because of adverse gastrointestinal effects, and 2 months later his INR was 1.4 necessitating an increase in the **warfarin** dose to the original dose of 4 mg daily.[1] The mechanism of this probable interaction is unknown, and it appears to be the first evidence of such an interaction. No definite conclusions can be drawn from this isolated case.

1. Bair JD, Oppelt TF. Warfarin and ropinirole interaction. *Ann Pharmacother* (2001) 35, 1202–4.

Coumarins + Royal jelly

An isolated report describes a patient taking warfarin, who developed a raised INR with haematuria one week after starting a royal jelly supplement.

Clinical evidence, mechanism, importance and management

An 87-year-old man stabilised on warfarin (INR 1.9 to 2.4) and a variety of other drugs presented with haematuria and was found to have an INR of 6.88. He reported starting to take a supplement containing just royal jelly one week earlier. The name of the supplement and the dose taken were not given in the report.[1]

Royal jelly is a substance secreted by worker honeybees (*Apis mellifera*) to feed their larvae. It is essentially a nutrient substance, and why it might interact with warfarin is unknown. This appears to be an isolated case, and its general relevance is therefore uncertain.

1. Lee NJ, Fermo JD. Warfarin and royal jelly interaction. *Pharmacotherapy* (2006) 26, 583–6.

Coumarins + Salicylates; Topical

Cases of increased warfarin effects have been reported with topical methyl salicylate or trolamine salicylate.

Clinical evidence

Methyl salicylate, in the form of gels, oil, or ointment applied to the skin, has been found to increase the effects of **warfarin**. Bleeding and bruising and/or raised INRs have been seen with both high[1-4] and low doses[5] of topical **methyl salicylate**. One report[6] described the possible additive effects of **methyl salicylate oil** (*Kwan Loong Medicated Oil*) and a decoction of *Danshen* (the root of *Salvia miltiorrhiza*) on the response to **warfarin** (see also 'Coumarins and related drugs + Danshen (*Salvia miltiorrhiza*)', p.453). A raised prothrombin time has also been reported with topical **trolamine salicylate**.[3]

Mechanism

Methyl and trolamine salicylates possibly interact like high-dose aspirin (see 'Coumarins and related drugs + Aspirin or other Salicylates', p.434), if they are absorbed through the skin. In one case report, the blood level of salicylate suggested significant percutaneous absorption.[1] However, in a study in healthy subjects, systemic absorption of salicylate was low after a single application of *Deep Heat* (local absorption was comparatively high).[7]

Importance and management

Although the evidence is limited, it appears that topical methyl salicylate and trolamine salicylate might be sufficiently absorbed in some circumstances for them to increase the effect of warfarin. Bear the potential for an interaction in mind should a patient have an otherwise unexplained rise in their INR or experience bleeding.

1. Chow WH, Cheung KL, Ling HM, See T. Potentiation of warfarin anticoagulation by topical methylsalicylate ointment. *J R Soc Med* (1989) 82, 501–2.
2. Yip ASB, Chow WH, Tai YT, Cheung KL. Adverse effect of topical methylsalicylate ointment on warfarin anticoagulation: an unrecognized potential hazard. *Postgrad Med J* (1990) 66, 367–9.
3. Littleton F. Warfarin and topical salicylates. *JAMA* (1990) 263, 2888.
4. Chan TY. Drug interactions as a cause of overanticoagulation and bleedings in Chinese patients receiving warfarin. *Int J Clin Pharmacol Ther* (1998) 36, 403–5.
5. Joss JD, LeBlond RF. Potentiation of warfarin anticoagulation associated with topical methyl salicylate. *Ann Pharmacother* (2000) 34, 729–33.
6. Tam LS, Chan TYK, Leung WK, Critchley JAJH. Warfarin interactions with Chinese traditional medicines: danshen and methyl salicylate medicated oil. *Aust N Z J Med* (1995) 25, 258.
7. Collins AJ, Notarianni LJ, Ring EFJ, Seed MP. Some observations on the pharmacology of 'deep-heat', a topical rubifacient. *Ann Rheum Dis* (1984) 43, 411–15.

Coumarins + Sevelamer

Sevelamer does not alter the pharmacokinetics of warfarin.

Clinical evidence, mechanism, importance and management

In a study in healthy subjects, the pharmacokinetics of a single 30-mg oral dose of **warfarin** were not statistically changed by sevelamer 2.4 g (equivalent to 6 capsules). Five more doses of sevelamer were given with meals over 2 days to check whether it had any effect on the enterohepatic circulation of **warfarin**. No effect was seen.[1] Thus it appears that sevelamer does not bind to **warfarin** within the gut to reduce its absorption. No warfarin dose adjustment would be expected to be required on concurrent use.

1. Burke SK, Amin NS, Incerti C, Plone MA, Watson N. Sevelamer hydrochloride (Renagel®), a nonabsorbed phosphate-binding polymer, does not interfere with digoxin or warfarin pharmacokinetics. *J Clin Pharmacol* (2001) 41, 193–8.

Coumarins + SNRIs

A case report describes a markedly raised INR in a patient taking warfarin when duloxetine was also given, and another case report describes a decrease in INR with acenocoumarol when duloxetine was given. Unpublished cases of bleeding and raised prothrombin times have been reported with venlafaxine and warfarin. Note that SNRIs alone have, rarely, been associated with bleeding, and there is the theoretical possibility that the risk might be increased when used with warfarin and related drugs.

Clinical evidence

(a) Duloxetine

A woman taking **warfarin** with a stable INR (mean 2.2 over the previous year) developed petechiae and purpura 55 days after starting duloxetine 30 mg daily, and was found to have an INR of 5. **Warfarin** was stopped on day 58, but the INR continued to rise to greater than 19 on day 85, and she was given vitamin K. On day 94 the duloxetine was stopped. **Warfarin** was restarted on day 110 and by day 140 the INR was 2.2 with the **warfarin** dose stabilised at the original level.[1] Conversely, another patient taking **acenocoumarol** had a decrease in INR from about 2.6 to 1.5 after

taking a single 60-mg dose of duloxetine, the effect of which persisted for 3 weeks.[2]

(b) Venlafaxine

The possible interactions of **warfarin** or other anticoagulants with venlafaxine do not appear to have been studied, but, as of May 2000, the manufacturers had on record 6 case reports of increased prothrombin times, raised INRs and bleeding (haematuria, gastrointestinal bleeding, melaena, haemarthrosis) in patients taking **warfarin** with venlafaxine.[3]

Mechanism

Just why these adverse interactions should have occurred is not understood, especially as no pharmacokinetic interaction is thought likely. Serotonin release by platelets plays an important role in haemostasis, and, as with all drugs that inhibit serotonin reuptake (see 'Coumarins and related drugs + SSRIs', below), SNRIs such as duloxetine, **milnacipran** and venlafaxine may uncommonly cause ecchymosis, mucosal bleeding and, rarely, prolonged bleeding time and haemorrhage. This theoretically might result in an increased risk of bleeding when used with warfarin and related drugs, but would not explain increased INRs. In a large case-control study, venlafaxine alone was associated with an increased risk of gastrointestinal haemorrhage (rate ratio 1.85), but the study was insufficiently powered to detect whether combined use with warfarin increased this.[4] Note that there was no interaction effect between SSRIs and warfarin for gastrointestinal bleeds in this study.

Importance and management

The interaction between the SNRIs and the coumarins is not established, and the general relevance of the unpublished cases with venlafaxine and the case with duloxetine is uncertain. If one subscribes to the view that increased monitoring is necessary when any drug is started or stopped in a patient on warfarin or related drugs, then it would be prudent to monitor prothrombin times with venlafaxine, duloxetine and milnacipran. Bear in mind the possibility of increased bleeding risk in the absence of alterations in INR when any SNRI is used with warfarin. More study is needed.

1. Glueck CJ, Khalil Q, Winiarska M, Wang P. Interaction of duloxetine and warfarin causing severe elevation of international normalized ratio. *JAMA* (2006) 295, 1517–18.
2. Monastero R, Camarda R, Camarda C. Potential drug-drug interaction between duloxetine and acenocoumarol in a patient with Alzheimer's disease. *Clin Ther* (2007) 29, 2706–9.
3. Wyeth Laboratories. Personal communication, May 2000.
4. Opatrny L, Delaney JA, Suissa S. Gastro-intestinal haemorrhage risks of selective serotonin receptor antagonist therapy: a new look. Br J Clin Pharmacol (2008) 66, 76–81.

Coumarins + Sodium edetate

A man had a reduction in the effects of warfarin, which was attributed to intravenous chelation therapy that included sodium edetate.

Clinical evidence, mechanism, importance and management

A 64-year-old man who had been taking **warfarin** for 3 weeks, with a gradually increasing dose to 25 mg weekly, had an INR decrease from 2.6 to 1.6 the day after he received intravenous chelation therapy with sodium edetate. He was given a single 10-mg dose of **warfarin** that day, then continued on his 25 mg weekly dose, with an INR in the range of 2.3 to 2.8. The chelation therapy also contained high-dose vitamin C along with various other vitamins and electrolytes.[1] Whether this case represents an interaction with the chelation therapy is uncertain. Further study is needed.

1. Grebe HB, Gregory PJ. Inhibition of warfarin anticoagulation associated with chelation therapy. *Pharmacotherapy* (2002) 22, 1067–69.

Coumarins and related drugs + SSRIs

In a study, fluvoxamine increased warfarin plasma levels, and raised INRs have been seen in several cases of the concurrent use of these drugs. In another study with warfarin and paroxetine, the majority of patients experienced no interaction, but a few had minor bleeding events. Other studies suggest that citalopram and sertraline do not significantly alter the pharmacokinetics or effects of warfarin. However, isolated reports describe bleeding in patients taking SSRIs and coumarins or fluindione. In addition, SSRIs alone have, rarely, been associated with bleeding, and there is some evidence that the risk of bleeding might be increased when they are used with coumarins.

Clinical evidence

(a) Citalopram

In a study in 12 healthy subjects given a single 25-mg oral dose of **warfarin** either alone or on day 15 of a 21-day course of citalopram 40 mg daily, the pharmacokinetics of both *R*- and *S*-warfarin remained unchanged in the presence of the citalopram, but the maximum prothrombin time was increased by 6.4% (1.6 seconds). This was considered to be clinically irrelevant.[1] Nevertheless, a 63-year-old patient who had just started **acenocoumarol** 18 mg weekly developed spontaneous gingival haemorrhage 10 days after also starting citalopram 20 mg daily for depression. Her INR had increased from a value of 1.8 to greater than 15. She was treated with 2 units of blood and citalopram was withdrawn. Her INR decreased to 1.95 within 5 days and she was able to continue on **acenocoumarol** 18 mg weekly.[2]

(b) Escitalopram

Escitalopram is the *S*-isomer of citalopram, and as such would not be expected to have a pharmacokinetic interaction with **warfarin**, see *Citalopram*, above.

(c) Fluoxetine

In a study in 3 healthy subjects, the half-life of a single 20-mg dose of **warfarin** was not altered by either a single 30-mg dose of fluoxetine given 3 hours before the **warfarin**, or by fluoxetine 30 mg daily for a week with the **warfarin** dose given 3 hours after the last dose of fluoxetine. In addition, fluoxetine had no effect on the warfarin-induced prolongation of prothrombin time.[3] In another study, 6 patients stabilised on **warfarin** had no significant changes in their prothrombin times or INRs while taking fluoxetine 20 mg daily for 21 days. The maximum change was a decrease in prothrombin time of 3.5% (15%) in one patient.[4]

However, there are few reports of increases in INR in patients taking **warfarin** with fluoxetine. In one report, the INR of a man stabilised on **warfarin**, amiodarone, furosemide, digoxin, ciprofloxacin and levothyroxine rose sharply from a range of 1.8 to 2.3 up to 14.9 within 5 days of starting fluoxetine 30 mg daily.[5] The INR of another man with metastatic carcinoma taking **warfarin**, dexamethasone, bisacodyl and lactulose rose from a range of 2.5 to 3.5 up to 15.5 within 2 weeks of starting fluoxetine 20 mg daily. He showed microscopic haematuria but no bleeding.[5] Other reports describe an abdominal haematoma,[5] cerebral haemorrhage,[6] severe bruising[7] and increases in INRs[8] in patients taking fluoxetine and **warfarin**. In 1993, the CSM in the UK was also said to have 4 other similar cases on record.[8] In the preliminary report of one retrospective review of patients' records, all of 8 evaluable cases of concurrent use of fluoxetine and **warfarin** had an abnormally prolonged prothrombin time.[9]

In a case-control study in patients stabilised on **warfarin**, the increase in risk of hospitalisation for an upper gastrointestinal bleed after starting either fluvoxamine or fluoxetine was marginally higher than for other SSRIs (relative risk 1.2 versus 1.1), but neither risk was statistically significant.[10] Note that fluvoxamine and fluoxetine were not considered separately, and the number taking each one was not stated.

(d) Fluvoxamine

In a study in healthy subjects, fluvoxamine 50 mg three times daily for 12 days increased steady-state plasma **warfarin** levels by about 65% and increased prothrombin times by 28%.[11,12] A worldwide literature search by the manufacturers of fluvoxamine identified only 11 reported interactions between **warfarin** and fluvoxamine by 1995, all with clinical signs that included prolonged prothrombin times.[13] An 80-year-old woman who had recently started taking **warfarin**, digoxin and 'colchicine', (p.450), had an increase in her INR from 1.8 to about 10 within a week of starting to take fluvoxamine 25 mg daily. Both the **warfarin** and fluvoxamine were stopped, but her INR only stabilised on the original dose of **warfarin** after the colchicine was withdrawn.[14] Another report describes a 79-year-old woman admitted to hospital because of suicidal thoughts. She was taking **warfarin** (INR 1.6 to 1.8) and citalopram 10 mg at night and other medications including paracetamol with dextropropoxyphene. On the third day in hospital the citalopram dose was increased to 30 mg at bedtime and after 2 days it was discontinued and fluvoxamine 50 mg daily was started to treat depression and possibly obsessive thoughts. Within 4 days the patient's INR had increased to 3.7. Fluvoxamine was replaced

with venlafaxine and **warfarin** was omitted for one day. The INR gradually decreased to the normal range over about 7 days.[15]

A further isolated report describes a woman stabilised on **fluindione** whose INR rose to 7.13 (from a normal value of about 2.5) within 13 days of starting to take fluvoxamine 100 mg daily. She had received fluoxetine, dosulepin and lorazepam for 15 days before fluvoxamine was started.[16]

In a case-control study in patients stabilised on **warfarin**, the increase in risk of hospitalisation for an upper gastrointestinal bleed after starting either fluvoxamine or fluoxetine was marginally higher than for other SSRIs (relative risk 1.2 versus 1.1), but neither risk was statistically significant.[10] Note that fluoxetine and fluvoxamine were not considered separately, and the number taking each one was not stated.

(e) Paroxetine

Paroxetine 30 mg daily, given to healthy subjects with **warfarin** 5 mg daily, did not significantly increase mean prothrombin times, but mild, clinically significant bleeding was seen in 5 out of 27 subjects given the combination. Two withdrew from the study because of increased prothrombin times, and another because of haematuria. The pharmacokinetics of **warfarin** and paroxetine remained unchanged by concurrent use.[17] In a brief retrospective review, 4 patients taking **warfarin** were said to have had an increase in INR by an average of 3 points (increases of nearly 100% in some cases) associated with the use of paroxetine and sertraline.[18]

A single case report[19] describes severe bleeding (abdominal haematoma) in a patient taking **acenocoumarol** and paroxetine when given phenytoin, but it is by no means clear whether the paroxetine had any part to play in what happened (see 'Phenytoin + Coumarins and related drugs', p.634).

(f) Sertraline

In a placebo-controlled study in healthy subjects, sertraline, in increasing doses up to 200 mg daily for 22 days, increased the prothrombin time AUC in response to a single 0.75-mg/kg dose of **warfarin** by 8%. This was statistically significant, but regarded as too small to be clinically relevant.[20]

In a brief retrospective review, 4 patients taking **warfarin** were said to have had an increase in INR by an average of 3 points (increases of nearly 100% in some cases) associated with the use of paroxetine and sertraline.[18]

(g) Unspecified SSRIs

In a large case-control study using data from the Netherlands, the concurrent use of coumarins (**acenocoumarol** and **phenprocoumon**) and SSRIs increased the risk of hospitalisation for non-gastrointestinal bleeding (odds ratio 1.7). However, the risk of hospitalisation for gastrointestinal bleeding was not increased (odds ratio 0.8).[21] Another case-control study using data from the UK General Practice Research Database, also found no increased risk of gastrointestinal haemorrhage with the concurrent use of **warfarin** and SSRIs compared with warfarin or an SSRIs given alone (rate ratio 0.81).[22,23] In yet another analysis, **warfarin** alone was associated with an increased risk of haemorrhagic stroke (odds ratio 3) whereas SSRIs alone were not (odds ratio 0.8). The concurrent use of SSRIs and **warfarin** did not increase the risk compared with warfarin alone (odds ratios 4.7 versus 3).[24]

Mechanism

Pharmacokinetic interactions. Fluvoxamine is a moderate inhibitor of the cytochrome P450 isoenzyme CYP2C9, by which *S*-warfarin is metabolised, and is also a potent inhibitor of CYP1A2 and CYP2C19, by which the less active *R*-warfarin is partially metabolised. Consequently, fluvoxamine would be expected to increase warfarin effects. *In vitro*, fluoxetine, paroxetine, sertraline, and citalopram had little or no inhibitory effect on CYP2C9 mediated *S*-warfarin hydroxylation.[25] In addition, these SSRIs do not inhibit CYP1A2 or CYP2C19, therefore they would not be anticipated to increase warfarin levels.

Pharmacodynamic interactions. Serotonin release by platelets plays an important role in haemostasis, and epidemiological studies and case reports suggest that SSRIs alone are rarely associated with bleeding events.[21,26] Evidence to date suggests that the risk of gastrointestinal bleeding is not significantly further increased if SSRIs are given with anticoagulants,[10,22] but that the risk of non-gastrointestinal bleeding might be increased.[21]

Importance and management

A pharmacokinetic interaction between fluvoxamine and warfarin that leads to increased anticoagulant effects is established. Therefore, the response should be monitored when fluvoxamine is first added, being alert for the need to decrease the anticoagulant dose.

None of the other SSRIs studied (citalopram, fluoxetine, paroxetine) have been shown to alter the pharmacokinetics of warfarin. Neither fluoxetine nor paroxetine increased the prothrombin time, but citalopram and sertraline caused a less than 10% increase in prothrombin time, and a few patients taking paroxetine with warfarin had bleeds. However, in general, these effects would not be expected to be clinically relevant. Nevertheless, because SSRIs alone can rarely cause bleeding, some predict that this may result in additive effects with coumarins and indanediones, and recommend caution with all SSRIs. This excess risk was not apparent for gastrointestinal bleeding, but might be relevant for bleeds from other sites.[21] Note that there are case reports of interactions with warfarin for many of the SSRIs (citalopram, fluoxetine, paroxetine, sertraline); bear these in mind should bleeding occur in a patient taking both drugs.

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Coumarins + St John's wort (*Hypericum perforatum*)

St John's wort can cause a moderate reduction in the anticoagulant effects of phenprocoumon and warfarin.

Clinical evidence

(a) Phenprocoumon

In a randomised, placebo-controlled crossover study in 10 healthy men,[1] St John's wort extract (*LI 160*, *Lichtwer Pharma*) 900 mg daily for 11 days reduced the AUC of a single 12-mg dose of phenprocoumon by a modest 17%. There is also a case report of a 75-year-old woman taking

phenprocoumon who had a reduced anticoagulant response (a rise in the Quick value) 2 months after starting to take St John's wort.[2]

(b) Warfarin

In a randomised, crossover study in 12 healthy subjects, one tablet of St John's wort three times daily for 3 weeks modestly decreased the AUC of both *R*- and *S*-warfarin by about 25% after a single 25-mg dose of warfarin taken on day 14. In this study, the brand of St John's wort used was *Bioglan* tablets, each tablet containing an extract equivalent to 1 g of *Hypericum perforatum* flowering herb top containing 825 micrograms of hypericin and 12.5 mg of hyperforin.[3]

Over the 1998 to 1999 period, the Swedish Medical Products Agency received 7 case reports of patients stabilised on warfarin who had decreased INRs when St John's wort was added. Their INRs fell from the normal therapeutic range of about 2 to 4 to about 1.5. Two patients needed warfarin dosage increases of 6.6% and 15%, respectively, when St John's wort was added. The INRs of 4 of the patients returned to their former values when the St John's wort was stopped.[4]

A retrospective study[5] similarly found that the concurrent use of enzyme inducers (including St John's wort) significantly influenced the total weekly warfarin dose; further analysis found that an average additional amount of warfarin required in patients taking these drugs was 17.2 mg weekly.

Mechanism

Uncertain, but it is suggested that the St John's wort increases the metabolism and clearance of the anticoagulants[1,3,4] possibly by induction of the cytochrome P450 isoenzyme CYP3A4 and possibly also CYP2C9 as both *R*- and *S*-warfarin were affected.[3] However, note that St John's wort is not usually considered to be a CYP2C9 inducer.

Importance and management

Information seems to be limited to these reports, but a modest pharmacokinetic interaction is established, which might be clinically important in some patients. It would be prudent to monitor the INRs of patients taking phenprocoumon, warfarin or any other coumarin if they start taking St John's wort, being alert for the need to slightly raise the anticoagulant dose. However, note that the advice of the CSM in the UK is that St John's wort should not be used with warfarin. They note that the degree of induction of warfarin metabolism is likely to vary because levels of active ingredients may vary between St John's wort preparations. If a patient is already taking the combination, they advise checking the INR, stopping the St John's wort and then monitoring the INR closely and adjusting the anticoagulant dose as necessary.[6]

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Coumarins and related drugs + Statins

Studies and case reports have suggested that fluvastatin can increase warfarin levels and/or effects. Rosuvastatin can increase the anticoagulant effects of warfarin but does not alter warfarin levels. Other studies with atorvastatin, lovastatin, pravastatin, and simvastatin suggest that they do not usually significantly alter the effects of warfarin, although isolated cases of bleeding have been seen when these statins were given with coumarins and fluindione.

Clinical evidence

Pharmacological studies of the effect of statins on **warfarin** are summarised in 'Table 12.5', (p.507). These show that **rosuvastatin** increases **warfarin** effects without altering **warfarin** pharmacokinetics, and that **fluvastatin**, at high clinical doses, modestly increases **warfarin** levels. Conversely, **atorvastatin**, **pravastatin**, **lovastatin** and **simvastatin** appear to have little effect on the anticoagulant effects of **warfarin**. Nevertheless, isolated case reports of interactions with coumarins have been reported for all statins and these are summarised in 'Table 12.6', (p.508).

Moreover, in one analysis of 42 patients taking warfarin and starting **fluvastatin** 20 mg daily,[1] three patients had a moderate rise in INR (further details given in 'Table 12.6', (p.508)), 5 patients had possible elevations in INR, 17 patients had no change, and data were not available for 17.

An early report, from the first 7 months after **lovastatin** became available in the US, notes that the manufacturers had received 10 spontaneous reports of bleeding and/or increased prothrombin times in patients taking **warfarin** with lovastatin.[2,3] In an analysis of factors that might be useful to construct a warfarin-dosing algorithm, **warfarin** maintenance doses were found to be 12% lower in patients taking **simvastatin**.[4] In another similar analysis, there was a trend towards a lower **warfarin** dose with lower 10-hydroxywarfarin (a metabolite of ***R*-warfarin**) levels in 17 patients taking simvastatin or lovastatin.[5]

In the preliminary analysis of a large, retrospective, case-control study in patients taking warfarin, the use of statins in patients who were receiving **warfarin** did not decrease the risk for bleeding (odds ratio 0.91).[6]

Coumarins are not expected to alter statin pharmacokinetics or effects. However, an isolated report[7] describes rhabdomyolysis with acute renal failure in an 82-year-old man taking **simvastatin** 20 mg daily within 7 days of starting **warfarin** 5 mg daily; his INR was raised to 4.3.

Mechanism

Fluvastatin is a modest inhibitor of the cytochrome P450 isoenzyme CYP2C9, by which the more potent *S*-warfarin is metabolised. Evidence from an interaction study with the CYP2C9 substrate diclofenac suggests that this interaction is most likely with higher and sustained fluvastatin levels,[8] which might explain why, with warfarin, it was demonstrated in healthy subjects with the maximum recommended daily dose of 80 mg daily, but not the more commonly encountered clinical dose of 40 mg daily, and why it has not been seen in all patients.

Lovastatin and simvastatin appear less likely to interact via CYP2C9,[9] although it is possible they might interact via other isoenzymes. In one analysis, patients taking these statins had lower levels of 10-hydroxywarfarin, a metabolite of *R*-warfarin, but clearance of *R*-warfarin was not reduced.[5] It may be that because warfarin has multiple routes of metabolism that other isoenzymes can 'pick up' warfarin metabolism if competition for metabolism occurs. Interactions may therefore only occur if other confounding factors are present. Alternatively, the cases seen may just represent idiosyncratic reactions.

Rosuvastatin clearly shows a dose related increase in warfarin effects, but this was not due to an increase in *R*- or *S*-warfarin levels, and the mechanism for this effect is unknown.[10]

Bear in mind that patients starting a statin might also alter their dietary fat consumption. Vegetable fats are a good source of vitamin K (see 'Table 12.3', (p.462)), and a marked reduction in consumption of foods rich in these could increase the sensitivity to warfarin.

Importance and management

Data are limited, which is surprising given the widespread use of statins and warfarin, and are sometimes contradictory, all of which complicates making firm recommendations. Some evidence suggests that a modest pharmacokinetic interaction occurs between **fluvastatin** and warfarin at high doses, and this would explain the case reports of an interaction with this statin. The clinical evidence suggests that only some patients develop an important interaction (3 of 25 evaluable patients in one analysis). In the UK, the manufacturer states that concurrent use of fluvastatin and warfarin may commonly cause significant increases in prothrombin time.[11] Clearly, with **fluvastatin**, increased monitoring is required when starting or stopping the statin, or changing the dose. Similar advice also applies to **rosuvastatin**, which has the best pharmacological data on concurrent use in patients, clearly showing that clinically important increases in INR can occur. In contrast to fluvastatin, this interaction does not appear to have a pharmacokinetic basis.

Data for **simvastatin** appear to be limited to retrospective analyses. In general these show that simvastatin can cause a minor increase in warfarin effects. This would appear to be supported by the fact that there is only one full published report of an interaction in a patient taking warfarin and one for acenocoumarol. Some consider that any interaction is of limited clini-

Table 12.5 Summary of pharmacological studies of the effect of statins on warfarin

Study type	*Group*	*Warfarin*	*Statin dose*	*Findings*		*Refs*
				Pharmacokinetics	Anticoagulant effects	
Atorvastatin						
Prospective	12 patients	Stable therapy	80 mg daily for 14 days	NR	Prothrombin time decreased from 18.6 to 17 seconds on days 3 to 5, but was not changed on other days	1
Fluvastatin						
Placebo-controlled	Healthy subjects	Single 30-mg dose	40 mg daily for 8 days	No change in racemic warfarin levels	No change in prothrombin complex activity	2
Crossover	18 healthy subjects	Single 10-mg dose	40 mg twice daily for 18 days	Increase in AUC of *S*-warfarin of 42% in smokers and 26% in non-smokers	NR	3
Lovastatin						
NR	Patients	Stable therapy	NR	NR	No change in prothrombin time	4
Crossover, placebo-controlled	8 patients	Stable therapy	40 mg daily for 7 days	NR	INR increased from 2.6 to 3 (17%) by day 7	5
Pravastatin						
Prospective	Healthy subjects	5 mg daily	20 mg twice daily	17% increase in warfarin AUC*	No change in prothrombin time on concurrent use for 6 days	6
Crossover, placebo-controlled	8 patients	Stable therapy	20 mg daily for 7 days	NR	No change in INR over the 7 days	5
NR	Elderly healthy subjects	Stable therapy	40 mg	NR	No change in prothrombin time	7
Rosuvastatin						
Placebo-controlled, crossover	18 healthy subjects	Single 25-mg dose	40 mg daily for 10 days	No change in pharmacokinetics of *S*- or *R*-warfarin	INR AUC increased by 10%, and maximum INR increased by 19%	8
Prospective	7 patients	Stable therapy	10 mg daily for up to 14 days then 80 mg daily for up to 14 days	NR	With 10 mg daily, 2 patients had INR increases of 1.5 and 3.7 to values greater than 4. With 80 mg daily, 4 of 5 patients had increases of 1.5 to 2.6 to values greater than 4	8
Placebo-controlled, crossover	12 healthy subjects	5 mg daily for 14 days	40 mg daily for 7 days	NR	No change in steady-state warfarin pharmacodynamics	9
Simvastatin						
Retrospective analysis of a placebo-controlled study	23 patients	NR	20 mg or 40 mg daily	NR	INR increased from a mean of 2.6 to 3.4 in the simvastatin group without changes in warfarin dose, compared with a decrease from 2.6 to 2.4 in the placebo group	10
NR	Healthy subjects	NR	20 mg or 40 mg daily	NR	INR increased from a mean of 1.7 to 1.8	11, 12
Retrospective cohort	46 patients	Stable with no change	Switch from pravastatin to simvastatin	NR	Mean INR increased from 2.42 to 2.74. Eleven patients had a warfarin dose adjustment after the INR change, 7 a decrease and 4 an increase	13
Retrospective	29 patients	Stable therapy	NR	NR	Warfarin dose decreased from a mean of 4.2 mg daily before to 3.8 mg daily after, while INR increased from a mean of 2.5 to 3.15	14
Historical control group taking warfarin alone	56 patients 56 controls	Stable therapy	20 mg daily (35 patients) or 40 mg daily (21 patients)	Median clearance of *S*-warfarin was 18%, and *R*-warfarin 23%, lower in patients than controls	Mean dose of warfarin was 3.3 mg daily in patients and 4 mg in controls	15

NR = not reported.

Continued

Table 12.5 Summary of pharmacological studies of the effect of statins on warfarin (continued)

*Atributed to warfarin being nearer steady state by the combined phase of this longitudinal study, in which there was no washout between phases, and sequence of phases was pravastatin alone for 3.5 days, warfarin alone for 6 days, and then both drugs for 6 days.

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Table 12.6 Summary of the case reports of statins interacting with coumarins

Year of study	*Patient*	*Coumarin*	*Statin dose (duration before event)*	*INR or PT* before*	*INR or PT after*	*Bleeding complications*	*Longer-term management*	*Refs*
Fluvastatin								
1996	68-year-old	Warfarin	20 mg daily (6 weeks)	3	4.8	None	Warfarin dose decreased by 14%	1
			40 mg daily (2 months)	2.9	3.81	None	Warfarin dose decreased by 12.5%	
	61-year-old	Warfarin	20 mg daily (4 weeks**)	2.29	3.54	None	Warfarin dose decreased by 10%	
	71-year-old	Warfarin	20 mg daily (3 weeks**)	2.92	4.45	None	Warfarin dose decreased by 14%	
1997	68-year-old	Warfarin	20 mg daily (2 weeks)	2.11 to 2.99	4.17	None	Warfarin dose decreased by 18%, then increased back again on withdrawal of fluvastatin	2
	83-year-old	Warfarin	20 mg daily (1 week)	1.84 to 2.73	3.47	None	Warfarin dose decreased by 36%, then increased back again on withdrawal of fluvastatin	
	51-year-old	Warfarin	20 mg daily (1 week)	1.95 to 3.4	4.2	Minor rectal bleeding	Warfarin dose decreased by 13%	
2004	67-year-old	Warfarin	80 mg daily (5 weeks†)	2 to 3	6.6	None	Fluvastatin switched back to atorvastatin, and warfarin restablised at a 14% lower dose	3
Lovastatin								
1990	48-year-old	Warfarin	20 mg daily (3 weeks)	PT 18 to 24 seconds	PT 48 seconds	Minor rectal bleeding	Warfarin dose decreased by 60%	4
	58-year-old	Warfarin	20 mg daily (10 days)	PT 19 to 22 seconds	PT 42 seconds	Epistaxis and haematuria	Warfarin dose decreased by 60%	
1992	85-year-old	Warfarin	20 mg daily (2 weeks)	PT 15 to 17 seconds	PT 24 seconds	None	Lovastatin discontinued	5
1995	78-year-old	Warfarin	40 mg daily (2 months)	1.9 to 3.1	12.3	Gross haematuria, haematoma	Lovastatin discontinued	6

Continued

Table 12.6 Summary of the case reports of statins interacting with coumarins (continued)

Year of study	*Patient*	*Coumarin*	*Statin dose (duration before event)*	*INR or PT* before*	*INR or PT after*	*Bleeding complications*	*Longer-term management*	*Refs*
Pravastatin								
1996	64-year-old	Fluindione‡	10 mg daily (5 days)	2.5 to 3.5	10.2	Haematuria	Not reported	7
Rosuvastatin								
2004	74-year-old	Warfarin	Not reported (4 weeks)	2	8	Bruising, haematuria	Not reported	8
2005	36-year-old	Acenocoumarol	10 mg daily (about 45 days)	2 to 3	5.8	Haematoma	Rosuvastatin discontinued	9
2005	56-year-old	Warfarin	20 mg daily (about 8 weeks)	Stable before and twice during	5.9	None	Rosuvastatin discontinued and atorvastatin started	10
Simvastatin								
1996	70-year-old	Acenocoumarol	20 mg daily (3 weeks)	2 to 3.5	9	Not reported	Simvastatin discontinued	11
2007	82-year-old	Warfarin	10 mg daily (4 weeks†)	2.6	>8	Cerebral haemorrhage	Fatal	12

*Prothrombin time
**Switched from lovastatin
†Switched from atorvastatin
‡Note that this is an indanedione

1. Trilli LE, Kelley CL, Aspinall SL, Kroner BA. Potential interaction between warfarin and fluvastatin. *Ann Pharmacother* (1996) 30, 1399–1402.
2. Kline SS, Harrell CC. Potential warfarin-fluvastatin interaction. *Ann Pharmacother* (1997) 31, 790.
3. Andrus MR. Oral anticoagulant drug interactions with statins: case report of fluvastatin and review of the literature. *Pharmacotherapy* (2004) 24, 285–90.
4. Ahmad S. Lovastatin. Warfarin interaction. *Arch Intern Med* (1990) 150, 2407.
5. Hoffman HS. The interaction of lovastatin and warfarin. *Conn Med* (1992) 56, 107.
6. Iliadis EA, Konwinski MF. Lovastatin during warfarin therapy resulting in bleeding. *PA Medicine* (1995) 98, 31.
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8. Barry M. Rosuvastatin–warfarin drug interaction. *Lancet* (2004) 363, 328.
9. Mondillo S, Ballo P, Galderisi M. Rosuvastatin–acenocoumarol interaction. *Clin Ther* (2005) 27, 782–4.
10. Finsterer J, Stöllberger C. Myalgia, hyper-CK-aemia, and hypocoagulability in a patient under rosuvastatin and warfarin. *Eur J Neurol* (2005) 12, 660.
11. Grau E, Perella M, Pastor E. Simvastatin-oral anticoagulant interaction. *Lancet* (1996) 347, 405–6.
12. Westergren T, Johansson P, Molden E. Probable warfarin–simvastatin interaction. *Ann Pharmacother* (2007) 41, 1292–5.

cal importance, and that statin therapy may be switched to simvastatin without any additional monitoring over and above that usually practised for warfarin.[12] However, others,[13,14] including the manufacturers[15,16] recommend increased monitoring when starting or stopping the statin, or changing the dose, and this may be prudent. There are even less data for **lovastatin**, an analogue of simvastatin, but it appears to interact similarly to simvastatin, and the manufacturer also recommends increased monitoring.[17] There appear to be no data on the effect of lovastatin on the pharmacokinetics of coumarins, and only one poor quality study suggesting a minor reduction in warfarin clearance with simvastatin.

In one pharmacological study, **atorvastatin** did not interact with warfarin, and no cases of an interaction have been published. This suggests that with this statin, no increased monitoring is necessary. In the US, the manufacturer does not give any advice on monitoring,[18] but in the UK, the manufacturer recommends close monitoring,[19] which seems over-cautious.

Limited data for **pravastatin** also suggest that no interaction occurs with warfarin, there being just one isolated case report with the indanedione fluindione. No increased monitoring would appear to be necessary on concurrent use.

1. Trilli LE, Kelley CL, Aspinall SL, Kroner BA. Potential interaction between warfarin and fluvastatin. *Ann Pharmacother* (1996) 30, 1399–1402.
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3. Tobert JA. Efficacy and long-term adverse effect pattern of lovastatin. *Am J Cardiol* (1988) 62, 28J–34J.
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7. Mogyorósi A, Bradley B, Showalter A, Schubert ML. Rhabdomyolysis and acute renal failure due to combination therapy with simvastatin and warfarin. *J Intern Med* (1999) 246, 599–602.
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14. Westergren T, Johansson P, Molden E. Probable warfarin–simvastatin interaction. *Ann Pharmacother* (2007) 41, 1292–5.
15. Zocor (Simvastatin). Merck Sharp & Dohme Ltd. UK Summary of product characteristics, October 2009.
16. Zocor (Simvastatin). Merck & Co., Inc. US Prescribing information, June 2008.
17. Mevacor (Lovastatin). Merck & Co., Inc. US Prescribing information, September 2008.
18. Lipitor (Atorvastatin calcium). Pfizer Inc. US Prescribing information, June 2009.
19. Lipitor (Atorvastatin calcium trihydrate). Pfizer Ltd. UK Summary of product characteristics, December 2009.

Coumarins + Sucralfate

The simultaneous administration of warfarin and sucralfate did not alter the anticoagulant effect of warfarin in studies in patients on stable therapy. However, case reports describe a marked reduction in the effects of warfarin in four patients taking sucralfate.

Clinical evidence

In an open, crossover study in 8 elderly patients taking **warfarin**, their anticoagulant response (thromboplastin time) and plasma **warfarin** levels remained unchanged while taking sucralfate 1 g three times a day over a 2-week period.[1] Similarly, in a preliminary report of another study, sucralfate 1 g four times daily for 2 weeks had no effect on prothrombin time or plasma **warfarin** levels in 5 patients on stable **warfarin** therapy.[2] In both these studies, the daily **warfarin** dose was taken simultaneously with one of the sucralfate doses.[1,2]

However, there are four case reports of reduced **warfarin** effects with sucralfate. In one of these, a man taking several drugs (digoxin, furosemide, chlorpropamide, potassium chloride) had serum **warfarin** levels that were about two-thirds lower when he was given sucralfate (dose not stated). When the sucralfate was withdrawn, his serum **warfarin** levels rose to their former levels accompanied by a prolongation of prothrombin times.[3] Another patient taking sucralfate had subtherapeutic prothrombin times on starting **warfarin**, despite **warfarin** doses of up to 17.5 mg daily. When the sucralfate was stopped his prothrombin time rose to 1.5 times the control, even though the **warfarin** dose was reduced to 10 mg daily.[4] One other patient appeared to have reduced responses to **warfarin** while taking sucralfate, despite separation of administration.[5] However, another patient taking **warfarin** and sucralfate had a reduced response to **warfarin** only when it was taken simultaneously with sucralfate, but not when administration was separated.[6]

Mechanism

Unknown. It is suggested that the sucralfate may possibly adsorb the warfarin so that its bioavailability is reduced.[4]

Importance and management

The documentation regarding an interaction between warfarin and sucralfate appears to be limited to the reports cited. Any interaction would therefore seem to be uncommon. Concurrent use need not be avoided, but bear this interaction in mind if a patient has a reduced anticoagulant response to warfarin. Note that, although separating dosing has been suggested as a strategy for avoiding this interaction, one of the cases occurred despite this.

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3. Mungall D, Talbert RL, Phillips C, Jaffe D, Ludden TM. Sucralfate and warfarin. *Ann Intern Med* (1983) 98, 557.
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5. Rey AM, Gums JG. Altered absorption of digoxin, sustained-release quinidine, and warfarin with sucralfate absorption. *DICP Ann Pharmacother* (1991) 25, 745–6.
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Coumarins + Sucrose polyesters

Short-term, moderate consumption of potato crisps containing sucrose polyesters (*Olestra, Olean*), which include vitamin K_1, did not alter the INR in response to warfarin.

Clinical evidence

In a randomised, double-blind, placebo-controlled study in 36 patients stabilised on **warfarin**, sucrose polyester 12 g daily (as *Pringles Original Flavor Fat Free Potato Crisps with Olean* 42 g) for one week did not significantly alter the anticoagulant effects of **warfarin** (mean INR increase of 0.02, versus 0.17 for placebo). After one week, greater than expected numbers of patients from both the placebo and sucrose polyester groups had INRs outside the therapeutic range of 2 to 3 (3 sucrose polyester recipients and 3 placebo recipients had an INR above 3 (max 4.1) and 2 in the sucrose polyester group and one in the placebo group had an INR less than 2). Two of each group also withdrew because of diarrhoea: their INRs were therapeutic. Only 22 patients entered the second week of the study, and there was no important effect on INR in these patients after the second week.[1]

Mechanism

Sucrose polyesters are non-absorbable, non-calorific fat replacements. It has been concluded that sucrose polyesters are unlikely to reduce the absorption of oral drugs in general; however, they are known to reduce the absorption of some fat-soluble vitamins, and therefore might lower vitamin K stores.[2] Because of this, snacks containing *Olestra* are supplemented with vitamin K_1 at a level of 8 micrograms per gram of *Olestra*.[3] It is possible that this supplementation could be insufficient to offset the vitamin K-lowering effect and therefore increase patient sensitivity to warfarin, or it could be too much and result in an antagonism of warfarin.

Importance and management

No evidence was found in the above study to suggest that short-term moderate consumption of a snack containing sucrose polyesters (12 g daily, including 96 micrograms of vitamin K daily) altered the anticoagulant effect of warfarin. In 1996, the FDA in the US considered that the changes in dietary vitamin K intake attributable to eating vitamin-K compensated *Olestra* would likely be within the normal range of dietary variation.[3] However, an intake similar to this of a vitamin K_1 supplement has altered coagulation status in some subjects (see 'Coumarins + Vitamin K_1-containing dietary supplements', p.520), and pure vitamin K_1 is much more bioavailable than that from plant sources (see 'Coumarins and related drugs + Food; Vitamin K_1-rich', p.464). Some consider that the snacks may have an impact on serum vitamin K levels.[4] Given these concerns, further study is probably needed.

1. Beckey NP, Korman LB, Parra D. Effect of the moderate consumption of olestra in patients receiving long-term warfarin therapy. *Pharmacotherapy* (1999) 19, 1075–9.
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4. Harrell CC, Kline SS. Vitamin K–supplemented snacks containing olestra: implication for patients taking warfarin. *JAMA* (1999), 282, 1133–4.

Coumarins + Sulfinpyrazone

The anticoagulant effects of warfarin are markedly increased by sulfinpyrazone, and there are case reports of moderate to serious bleeding on concurrent use. Acenocoumarol is modestly affected. Phenprocoumon does not appear to be significantly affected. The antiplatelet effects of sulfinpyrazone might increase the risk of bleeding with coumarins.

Clinical evidence

(a) Acenocoumarol

In a placebo-controlled, crossover study in 22 patients taking acenocoumarol, sulfinpyrazone 800 mg daily for 2 weeks led to a drop in the mean prothrombin time requiring a reduction in the anticoagulant dose by an average of 20%. Four patients withdrew because of bleeding episodes, 3 patients while taking sulfinpyrazone and one while taking placebo.[1]

(b) Phenprocoumon

In a study in 6 healthy subjects, sulfinpyrazone 400 mg daily for 17 days had little effect on phenprocoumon levels after a single 0.6-mg/kg dose of phenprocoumon given on day 4. The AUC of prothrombin time increased in 4 subjects and decreased in 2, resulting in an overall non-significant mean increase of 16%.[2] Similar findings were reported in another study of similar design.[3]

(c) Warfarin

In a double-blind, placebo-controlled study in 11 patients stabilised on warfarin, sulfinpyrazone 200 mg four times daily for 6 to 12 months reduced the average warfarin dose requirement by 44% from 7.3 to 4.1 mg week, compared with no change in the placebo group. There were four episodes of bleeding (haematoma, epistaxis and bleeding gums) in 3 patients

receiving sulfinpyrazone and one in the placebo group. The authors noted it was difficult to regulate anticoagulant control in the patients taking sulfinpyrazone.[4,5] Similarly, in another study, the prothrombin ratios of 5 patients taking warfarin rose rapidly over 2 to 3 days after sulfinpyrazone 200 mg every 6 hours was added. The average warfarin requirements fell by 46% and 2 patients needed vitamin K to combat the excessive hypoprothrombinaemia. When the sulfinpyrazone was withdrawn, the warfarin requirements returned to their former levels within one to 2 weeks.[6]

A number of case reports have described increased effects of warfarin in patients starting sulfinpyrazone,[7-12] or an exaggerated anticoagulant response in patients taking sulfinpyrazone and then starting warfarin.[13] Moderate to severe bleeding occurred in some instances.[8,10,11] An increased anticoagulant effect of warfarin in the first 15 days after starting sulfinpyrazone, followed by an unexplained progressive increased warfarin dose requirement has been described in one report.[14] However, this may have had other explanations, as a constant potentiation of warfarin is usually seen on long-term sulfinpyrazone use.[5]

In subsequent studies in healthy subjects, sulfinpyrazone 200 mg twice daily for 10 days was shown to augment the effect of warfarin (99% or 83% increase in the AUC of the prothrombin time) by inhibiting the clearance of *S*-warfarin (by 51% or 40%) when a single dose of warfarin was given on day 4. In contrast, sulfinpyrazone did not alter the effect of *R*-warfarin, and actually increased its clearance by 30% or 42%.[15,16]

Mechanism

Sulfinpyrazone inhibits the metabolism of the more potent *S*-isomer of warfarin, probably because its sulfide metabolite inhibits the cytochrome P450 isoenzyme CYP2C9.[17] It probably interacts by a similar mechanism with acenocoumarol. It could be speculated that sulfinpyrazone induces the metabolism of *R*-warfarin via CYP1A2, as it modestly induces the metabolism of theophylline (see 'Theophylline + Sulfinpyrazone', p.1459). Some early *in vitro* evidence[18] suggested that plasma protein binding displacement might explain this interaction, but a study in healthy subjects found that sulfinpyrazone did not alter the free fraction of either *R*- or *S*-warfarin.[19] Sulfinpyrazone also has antiplatelet effects, so might be expected to increase the risk or severity of bleeding should over-anticoagulation occur.

Importance and management

The increased effect of warfarin with sulfinpyrazone is a well established interaction of clinical importance. If sulfinpyrazone is added, the prothrombin time should be well monitored and suitable anticoagulant dose reductions made. Halving the dose of warfarin[4,6,20] has proven to be adequate in patients taking sulfinpyrazone 600 to 800 mg daily. The interaction with acenocoumarol[1] is less marked, and a 20% dose reduction appears adequate in patients taking sulfinpyrazone 600 to 800 mg daily. Phenprocoumon is reported not to have a pharmacokinetic interaction with sulfinpyrazone. Bear in mind that the antiplatelet effects of sulfinpyrazone might increase the risk of bleeding with coumarins.

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13. Bailey RR, Reddy J. Potentiation of warfarin action by sulphinpyrazone. *Lancet* (1980) i, 254.
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16. Toon S, Low LK, Gibaldi M, Trager WF, O'Reilly RA, Motley CH, Goulart DA. The warfarin-sulfinpyrazone interaction: stereochemical considerations. *Clin Pharmacol Ther* (1986) 39, 15–24.
17. He M, Kunze KL, Trager WF. Inhibition of (*S*)-warfarin metabolism by sulfinpyrazone and its metabolites. *Drug Metab Dispos* (1995) 23, 659–63.
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19. O'Reilly RA, Goulart DA. Comparative interaction of sulfinpyrazone and phenylbutazone with racemic warfarin: alteration *in vivo* of free fraction of plasma albumin. *J Pharmacol Exp Ther* (1981) 219, 691–4.
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Coumarins + Tamoxifen or Toremifene

Tamoxifen may increase the effects of warfarin and cases of serious bleeding, in one case fatal, have been reported. A case report describes a similar effect with acenocoumarol. It has been suggested that a similar interaction may occur with toremifene and the coumarins.

Clinical evidence

A woman who had been taking **warfarin** for 11 years after a heart valve replacement (prothrombin time of 23 to 34 seconds taking **warfarin** 27 to 28.5 mg weekly), was given tamoxifen 10 mg twice daily after mastectomy for early breast cancer. Three days later her prothrombin time was 39 seconds, and 3 weeks later it was 75.6 seconds, although this was attributed to a 5-day course of co-trimoxazole, and so the warfarin dose was unchanged. Six weeks later she developed haematemesis, abdominal pain and haematuria, and her prothrombin time was found to be 206 seconds. She was restabilised on a little over half the **warfarin** dose (17.5 mg weekly) while continuing to take tamoxifen.[1] One case report describes a significantly raised INR and rectal bleeding in a patient who had been taking tamoxifen 20 mg daily long-term and had recently started taking warfarin. The patient had an initial increase in the INR to about 10, which stabilised when omeprazole was stopped and the patient was discharged with an INR of 2.3. However, 7 days later, the patient was readmitted with an INR of 10.8 and rectal bleeding.[2] In another case, a 43-year-old woman was given **warfarin** for a deep vein thrombosis. Seven weeks later tamoxifen 40 mg daily was started, and her prothrombin time increased from 19 seconds to 38 seconds. A warfarin dose reduction from 5 to 1 mg daily was eventually needed to keep her prothrombin time within the range of 20 to 25 seconds. A subsequent retrospective study of the records of women with breast cancer who had been admitted to hospital for serious thromboembolism from 1981 to 1986 revealed 5 other patients taking tamoxifen when **warfarin** was started, and 13 patients not taking tamoxifen. Of the 5 patients taking tamoxifen, 2 had shown marked increases in prothrombin times, and bleeding, shortly after receiving loading doses of **warfarin** (three daily doses of 10 mg, 10 mg and 5 mg). The other 3 patients needed daily **warfarin** doses of 2 mg, 2 mg and 3 mg, respectively, which were about one-third of those taken by the 13 other patients not taking tamoxifen (mean 6.25 mg).[3] In another retrospective analysis of hospital admissions from 1980 to 1988, 22 patients were identified who had been given tamoxifen with **warfarin**. Of these, 17 had no problems, but 2 developed grossly elevated British Comparative Ratios and 3 developed serious bleeding.[4]

A 53-year-old woman who had been taking **acenocoumarol** for 2 years after a heart valve replacement died after a massive brain haemorrhage about 3 weeks after starting to take tamoxifen 20 mg daily for a benign breast condition.[5]

Mechanism

The mechanism for this interaction is unclear. However, one study has reported that tamoxifen may inhibit the metabolism of losartan by the cytochrome P450 isoenzyme CYP2C9, see 'Angiotensin II receptor antagonists; Losartan + Tamoxifen', p.44. CYP2C9 is the isoenzyme involved in the metabolism of the more potent isomer *S*-warfarin, and therefore concurrent use may lead to increased warfarin levels and effects.

Importance and management

Evidence is limited to the above reports, but it appears that a clinically important interaction between **tamoxifen** and warfarin can occur, which apparently affects some but not all patients. Monitor the effects closely if tamoxifen is given to patients taking warfarin or acenocoumarol, and reduce the anticoagulant dose as necessary; the reports indicate a reduction of between one-half to two-thirds for warfarin. Consider also that, from a disease perspective, when treating venous thromboembolic disease in pa-

tients with cancer, warfarin is generally inferior (higher risk of major bleeds and recurrent thrombosis) to low-molecular-weight heparins.[6]

Because of the data with tamoxifen, the UK manufacturer[7] of **toremifene** recommends avoiding the concurrent use of coumarins, whereas the US manufacturer recommends careful monitoring of prothrombin time.[8] However, there appear to be no published reports of any interaction between toremifene and warfarin.

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Coumarins + Tegaserod

Tegaserod does not appear to alter the pharmacokinetics or pharmacodynamics of warfarin.

Clinical evidence, mechanism, importance and management

In a study in healthy subjects, tegaserod 6 mg twice daily for 7 days did not alter the pharmacokinetics of either *S*- or *R*-warfarin when a single 30 mg dose of **warfarin** was given on day 4. Similarly, tegaserod did not alter the prothrombin time response to warfarin. No warfarin dose adjustments are therefore recommended when tegaserod is given with **warfarin**.[1] Note that tegaserod has been associated with an excess risk of rare serious cardiovascular ischaemic events,[2] and it should generally not be used in patients with cardiac disease.

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Coumarins + Terbinafine

Terbinafine does not affect the pharmacokinetics or anticoagulant effects of warfarin. However, there is one isolated case of markedly reduced anticoagulation, and one case of markedly increased anticoagulation when terbinafine was given with warfarin. No increased risk of over-anticoagulation appears to occur when acenocoumarol or phenprocoumon are given with oral or topical terbinafine.

Clinical evidence

In a randomised, placebo-controlled, study in 16 healthy subjects, terbinafine 250 mg daily for 14 days did not alter the pharmacokinetics or anticoagulant effects of a single 30-mg oral dose of **warfarin** given on day 8.[1] In a post-marketing surveillance study of terbinafine, 26 patients were identified who were also taking **warfarin** and there was no evidence to suggest an interaction occurred in these patients.[2,3] In one cohort study in patients taking **acenocoumarol** or **phenprocoumon**, the concurrent use of oral terbinafine (49 patients) or cutaneous terbinafine (29 patients) was not associated with an increased risk of over-anticoagulation (INR greater than 6).[4]

However, an isolated report describes a 68-year-old woman taking long-term **warfarin** whose INR fell from 2.1 to 1.1 within one month of starting a 3-month course of terbinafine 250 mg daily for tinea unguium. It was necessary to raise her **warfarin** dose from 5.5 mg daily to a range of 7.5 mg to 8 mg daily while taking the terbinafine, and to reduce it stepwise to 5.5 mg over the 4 weeks after the terbinafine was stopped.[5] In contrast, another isolated case report describes an elderly woman stabilised on **warfarin** and cimetidine who developed gastrointestinal bleeding about one month after starting to take terbinafine 250 mg daily. Her INR had increased from 3.1 (about 4 weeks previously) to 11 on admission to hospital.[6]

Mechanism

The isolated cases are not understood, and have been questioned.[7] They may simply represent idiosyncratic reactions.

Importance and management

The available evidence suggests that no interaction usually occurs between the coumarins and terbinafine, and no coumarin dose adjustment is therefore predicted to be needed during concurrent use. The two isolated cases of opposite effects are rarities, and unexplained. There is insufficient evidence to recommend monitoring all patients; however, bear the isolated case reports in mind in the event of an unexpected response.

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5. Warwick JA, Corrall RJ. Serious interaction between warfarin and oral terbinafine. *BMJ* (1998) 316, 440.
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Coumarins + Tetracyclic and related antidepressants

Mirtazapine may cause a slight increase in INR in subjects given warfarin. Maprotiline does not appear to alter the anticoagulant effect of acenocoumarol. Mianserin does not appear alter the anticoagulant effect of phenprocoumon, however, two isolated cases of an increased effect of warfarin and a decreased effect of acenocoumarol have been reported in patients taking mianserin.

Clinical evidence

(a) Maprotiline

In a study in 20 patients stabilised on **acenocoumarol**, the anticoagulant effects of **acenocoumarol** were not affected by maprotiline 50 mg three times daily for 2 weeks.[1]

(b) Mianserin

In a randomised, double-blind study in 60 patients taking **phenprocoumon** for 5 weeks, there was no difference in anticoagulant control and **phenprocoumon** dose between placebo recipients and those receiving mianserin, either up to 30 mg daily or up to 60 mg daily, for 20 days.[2]

A single case report describes a man stabilised on **warfarin** whose British standard ratio rose from 1.8 to 4.6 (prothrombin time rise from 20 to 25 seconds) after taking mianserin 10 mg daily for 7 days.[3] However, another patient taking **warfarin** received mianserin in varying doses of up to 120 mg daily for 22 weeks without any change in prothrombin ratio.[4] A further patient stabilised on **acenocoumarol** and amiodarone needed an *increase* in his **acenocoumarol** dose after starting mianserin, and a decrease when this drug was stopped.[5]

(c) Mirtazapine

In a study in healthy subjects stabilised on individual doses of **warfarin**,[6] mirtazapine 15 mg for 2 days then 30 mg daily for 5 days increased the mean INR from 1.6 to 1.8. This small increase was not considered clinically relevant by the authors of the study or by one of the UK manufacturers.[6,7] However, the manufacturer does state that a more pronounced effect cannot be excluded at higher doses of mirtazapine.[7]

Mechanism

Not understood. The cases with mianserin might just represent idiosyncratic reactions.

Importance and management

Maprotiline does not interact with acenocoumarol and mianserin does not interact with phenprocoumon. The isolated cases of an increase in warfarin effects and a decrease in acenocoumarol effects with mianserin are unexplained, and probably of little general relevance.

One UK manufacturer of mirtazapine very cautiously advises that the prothrombin time should be controlled if mirtazapine is given with warfarin.[7] However, there do not appear to be any reports of problems with this combination.

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Coumarins and related drugs + Thyroid and Antithyroid compounds

Hypothyroidism decreases, and hyperthyroidism increases, the metabolism of the clotting factors. Correction of these disease states therefore alters anticoagulant requirements. Bleeding has been seen in patients given thyroid hormones without an adjustment of their warfarin dose, and increased coumarin requirements have been seen in patients given thiamazole or carbimazole.

Clinical evidence

(a) Hypothyroidism and Thyroid compounds

In a study in 7 patients with myxoedema (hypothyroidism), the response to a single dose of **warfarin** was increased after 3 months of treatment with **liothyronine** (when euthyroid), when compared with before treatment, without a change in plasma warfarin levels.[1]

Various case reports describe similar effects.[2-5] In one report, brief mention is made of one patient who had an increased response to **warfarin** after an increase in the dose of thyroid replacement therapy, and of another patient taking long-term **warfarin** who had a bleeding episode when thyroid replacement therapy was started.[2] Another patient taking **warfarin** developed oral mucosal bleeding with an INR of greater than 11 when her hypothyroidism was over-corrected with **levothyroxine**, although she had no clinical signs of hyperthyroidism.[3] In another case, a subdural haematoma occurred in a child stabilised on **warfarin** when **levothyroxine** was started, and her dose of **warfarin** was eventually reduced from 7.5 mg daily to 5 mg daily.[4]

A patient with myxoedema required a gradual reduction in his dose of **phenindione** from 200 mg daily to 75 mg daily as his thyroid status was corrected by **liothyronine**.[5] A similar patient required a reduction in the dose of **acenocoumarol**, from 16 mg daily to 5 mg daily, when hypothyroidism was corrected with **liothyronine**.[5]

(b) Hyperthyroidism and Antithyroid compounds

In 5 patients with hyperthyroidism, the response to a single dose of **warfarin** was decreased (prothrombin ratio 1.35 versus 1.75) after treatment with **iodine-131** (when euthyroid), when compared with before treatment. Three of the 5 patients required a small increase in their warfarin dose of between 0.5 mg and 1 mg. There was no significant difference in the plasma half-life of **warfarin**.[6] Another similar study also reported a decreased sensitivity to **warfarin** after correction of hyperthyroidism, but found that the plasma half-life and levels of **warfarin** were higher after treatment.[7]

Various case reports describe alterations in anticoagulant effects.[3,8-12] In one, a hyperthyroid patient taking **warfarin** had a marked increase in his prothrombin times on two occasions when his treatment with **thiamazole** (**methimazole**) was stopped and he became hyperthyroid again.[8] Another similar case has been described where the required dose of **warfarin** increased from 35 mg weekly to 65 mg weekly as the patients hyperthyroid state was corrected with **thiamazole** 30 mg daily. However, the patient then became hypothyroid and required up to 85 mg of **warfarin** weekly. When the **thiamazole** dose was withheld for 5 days and then reduced to 5 mg daily, the patient rapidly developed a raised INR of 7 without bleeding complications.[9] In another report, a patient required just 0.5 mg of **warfarin** daily while hyperthyroid.[3] Another case of possible enhanced response to **warfarin** in a hyperthyroid patient has been reported.[10,11] A woman taking **acenocoumarol**, required a dose reduction as she became hyperthyroid and the dose of **acenocoumarol** was increased again when she was treated with **carbimazole**.[12]

Mechanism

In hypothyroid patients the catabolism (destruction) of the blood clotting factors (II, VII, IX and X) is low and this tends to cancel, to some extent, the effects of the anticoagulants, which reduce blood clotting factor synthesis. Conversely, in hyperthyroid patients in whom the catabolism is increased, the net result is an increase in the effects of the anticoagulants.[13] In studies in healthy subjects, **dextrothyroxine** (which has weak thyroid activity compared with levothyroxine) potentiated the anticoagulant effect of **dicoumarol**[14] and warfarin[15] without altering the half-life and plasma levels of the anticoagulants, and without altering vitamin K-dependent clotting activity.[14] Because of this, it was suggested that the thyroid hormones might increase the affinity of the anticoagulants for its receptor sites.[14,15]

Importance and management

A well documented and clinically important interaction occurs if oral anticoagulants and thyroid hormones are taken concurrently.

Hypothyroid patients taking an anticoagulant who are subsequently treated with thyroid hormones as replacement therapy will need a downward adjustment of the anticoagulant dose as treatment proceeds if excessive hypoprothrombinaemia and bleeding are to be avoided. Conversely, as the thyroid status of hyperthyroid patients returns to normal with the use of antithyroid drugs (e.g. carbimazole, thiamazole, **propylthiouracil**) an increase in the anticoagulant requirements would be expected. As this is more of a drug-disease interaction rather than a direct drug-drug interaction, it is therefore likely to occur with any coumarin or indanedione given with any drug that affects thyroid function. Close anticoagulant monitoring and dose adjustment are required, particularly while thyroid hormone levels are being stabilised. Note that, in one case the authors commented that the magnitude and clinical complexity of the interaction between the drugs and disease state was unexpected.[9]

Note that propylthiouracil in the absence of an anticoagulant has very occasionally been reported to cause hypoprothrombinaemia and bleeding.[16,17]

Some drugs can alter thyroid status as an unwanted effect, and this will also alter the response to the oral anticoagulants. For example, amiodarone (see 'Coumarins and related drugs + Amiodarone', p.411), can cause thyrotoxicosis, which decreases warfarin requirements. Also, the use of **dextrothyroxine** for hypercholesterolaemia decreased the required dose of warfarin[18,19] and dicoumarol,[20] presumably because it has weak thyroid activity.

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Coumarins + Tiabendazole

An isolated case report describes a marked increase in the anticoagulant effects of acenocoumarol in a patient given tiabendazole.

Clinical evidence, mechanism, importance and management

An increase in the anticoagulant effects of **acenocoumarol** occurred in a patient with nephrotic syndrome undergoing dialysis, who was given tiabendazole 8 g daily for 2 days, on two occasions about 7 weeks apart.[1] On both occasions, his INR rose from 2.9 to more than 5 without any clinical consequence. The reasons for this effect are not understood, nor is the general importance of this interaction known. There seem to be no other reports.

1. Henri P, Mosquet B, Hurault de Ligny B, Lacotte J, Cardinau E, Moulin M, Ryckelinck JP. Imputation d'une hypocoagulabilité à l'interaction tiabendazole-acénocoumarol. *Therapie* (1993) 48, 500–501.

Coumarins and related drugs + Tibolone

Tibolone may increase the INR in some patients taking warfarin or phenindione.

Clinical evidence

In a well-controlled study in 16 postmenopausal women taking **warfarin**, the use of tibolone 2 mg daily for 21 days increased the mean INR by just 0.4. No clinically significant adverse effects occurred on concurrent use.[1] In a retrospective analysis, five women were identified who had started tibolone while taking **warfarin** or **phenindione**. All of the 5 patients had an increase in INR to a range of 4.6 to 9.5 after starting tibolone, and required reductions in their anticoagulant dose (range of 12 to 53% reductions in **warfarin** dose, and 56% for **phenindione**). One further patient who discontinued tibolone while taking **warfarin** required an increase in her **warfarin** dose from 6 to 7.5 mg daily.[2]

Mechanism

Not understood. Tibolone alone increases fibrinolytic activity without altering the prothrombin time,[3] and might therefore be expected to increase the risk of bleeding with anticoagulants. However, this would not result in raised INRs, and it was suggested that the effect on the INR might be because of the androgenic effect of tibolone causing a reduction in factor VIIa.[2]

Importance and management

There is very limited published information available on the concurrent use of warfarin and tibolone. The study suggests tibolone causes minor increases in INR; however, the retrospective analysis reported more clinically significant increases in the INR, and reduced warfarin and phenindione requirements of up to about 50%. Because of this, increased INR monitoring is advised when starting tibolone in patients stabilised on warfarin, other coumarins, or indanediones.

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Coumarins + Ticlopidine

The anticoagulant effects of acenocoumarol may be modestly reduced by ticlopidine. However, the anticoagulant effects of warfarin are unchanged by ticlopidine. As with other antiplatelet drugs, concurrent use with coumarins might possibly increase bleeding risk. Cholestatic hepatitis has been reported in some patients given warfarin and ticlopidine.

Clinical evidence

(a) Acenocoumarol

A retrospective study of 36 patients with heart valve prostheses found that when they took ticlopidine 250 mg daily, 29 of them needed a mean 13% increase in their acenocoumarol dose from 15.5 to 17.5 mg weekly, accompanied by a small INR rise from 3.05 to 3.13. One patient needed a dose increase from 14 to 22 mg weekly. INR changes were detectable with a week of starting the ticlopidine.[1]

(b) Warfarin

Ticlopidine 250 mg twice daily for 2 weeks, given to 9 men taking warfarin long-term, increased the mean *R*-warfarin levels by 26% but did not change *S*-warfarin levels or their INRs.[2] *R*-warfarin is the much less active of the two enantiomers. In a Japanese study, 4 out of 132 patients (3%) given both warfarin and ticlopidine after cardiovascular surgery developed cholestatic hepatitis.[3]

Mechanism

It seems possible that ticlopidine inhibits the metabolism of *R*-warfarin, but the interaction with acenocoumarol is not understood. Ticlopidine alone can cause raised liver enzymes and cholestatic hepatitis,[4] and whether these cases with warfarin represent an interaction is unclear.

Importance and management

Information seems to be limited to the reports cited. A small to moderate increase in the acenocoumarol dose may be needed if ticlopidine is added, but none seems to be necessary with warfarin. However, as with other antiplatelet drugs, such as aspirin (see 'Coumarins and related drugs + Aspirin or other Salicylates', p.434), an increased risk of bleeding (a combination of anticoagulant and platelet anti-aggregant activity) might be anticipated on concurrent use. The manufacturer states that the long-term safety of concurrent use of ticlopidine with oral anticoagulants has not been established, and they recommend that if a patient is switched from an anticoagulant to ticlopidine, the anticoagulant should be discontinued before ticlopidine is given.[4] For discussion of the combined use of anticoagulants and dual antiplatelet therapy (aspirin plus a thienopyridine derivative such as ticlopidine), see under 'Coumarins and related drugs + Clopidogrel', p.448.

Whether the incidence of cholestatic hepatitis is higher with the concurrent use of warfarin and ticlopidine than with ticlopidine alone is unclear.

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Coumarins + Tobacco

Smoking appears to cause a small increase in the clearance of warfarin and a minor reduction in warfarin levels, and two cases have been reported of patients who required warfarin dose reductions on stopping smoking.

One patient who stopped chewing tobacco had an increase in INR.

Clinical evidence

(a) Chewing tobacco

In a patient using smokeless tobacco (chewing tobacco) for greater than 85% of waking hours, the INR was found to have increased from 1.1 to 2.3 six days after discontinuation of tobacco use. This patient had usually had an INR of 1.1 to 1.9 since restarting warfarin 4 months earlier, despite gradually increasing the warfarin dose from 10 mg daily to 25 mg daily alternating with 30 mg daily. However, during this time, he did have two INR spikes of 2.5 and 4.2, which were attributed to dietary changes,[1] but see *Mechanism*, below.

(b) Smoking tobacco

In a controlled study in 9 healthy subjects who normally smoked at least one pack of cigarettes daily (size unknown) and who were given **warfarin** to steady-state, smoking abstention for about 6 weeks increased the average steady-state **warfarin** levels by 13%, decreased **warfarin** clearance by 13% and increased the **warfarin** half-life by 23%, but no changes in the prothrombin time occurred.[2] A population pharmacokinetic analysis similarly found that smoking appeared to increase **warfarin** clearance by 10%.[3]

An 80-year-old man taking **warfarin** had a steady rise in his INR (from a range of 2 to 2.8 up to 3.7) over a 3-month period when he gave up smoking. No bleeding occurred. His dose of **warfarin** was reduced by 14%, and the INR stabilised at 2.3 to 2.8 over the next 9 months.[4] Similarly, another patient required a 23% reduction in **warfarin** dose after stopping smoking following recovery from bacterial meningitis.[5]

In a retrospective study of factors relating to **warfarin** dose, smoking status appeared to be a factor in **warfarin** dose requirements.[6] In contrast, in one retrospective study of patients who had undergone cardiac valve replacement, there was no statistically significant difference between the **warfarin** dose requirements of 117 non-smokers, 23 light smokers (20 or less cigarettes daily) or 34 heavy smokers (greater than 20 cigarettes daily).[7] The same finding had earlier been briefly reported by the Boston Collaborative Drug Surveillance Program.[8] Note that smoking status had no effect on the AUC of *S*-warfarin in one study.[9]

Mechanism

Some of the components of tobacco smoke act as cytochrome P450 isoenzyme inducers, which might cause a small increase in the metabolism of warfarin. When smoking stops and the enzymes are no longer stimulated, the metabolism of warfarin falls slightly and its effects are correspondingly slightly increased. Tobacco smoke is known to induce CYP1A2, which has a partial role in the metabolism of the less active *R*-warfarin enantiomer. The metabolism of *S*-warfarin is primarily by CYP2C9, and this does not appear to be affected by smoking.[9]

The possible case of an interaction with smokeless tobacco was attributed to the very high vitamin K content of tobacco resulting in relative warfarin resistance (consider also 'Coumarins and related drugs + Vitamin K substances', p.520). However, there were two previous INR spikes in this patient, which were attributed to dietary changes,[1] an explanation that seems unlikely if there was a high background vitamin K intake from the tobacco. The reasons for the effects in this case are therefore unclear.

Importance and management

The overall picture seems to be that smoking (or giving up smoking) only has a slight to moderate effect on the response to warfarin, and only the occasional patient will need a small dose alteration. This should easily be detected in the course of routine INR checks. Note that tobacco smoking increases cardiovascular disease risk, and patients requiring anticoagulants should be encouraged and helped to stop smoking.

The isolated case with smokeless tobacco is unclear, further study is needed.

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Coumarins + Tolterodine

In healthy subjects, tolterodine did not alter the pharmacokinetics or pharmacodynamics of warfarin, but isolated cases of raised INRs have been reported when patients taking warfarin also took tolterodine.

Clinical evidence, mechanism, importance and management

In a placebo-controlled study in healthy subjects, tolterodine 2 mg twice daily for 7 days did not affect the pharmacokinetics of *R*- or *S*-warfarin after a single 25-mg dose of **warfarin** given on day 4, nor were the pharmacokinetics of tolterodine altered by **warfarin**. In addition, the prothrombin time and factor VII activity were not altered by tolterodine.[1]

However, a report describes 2 patients on stable **warfarin** doses who had elevated INRs shortly after tolterodine 2 mg daily was started and stopped: one patients had an INR of 6.1 one day after stopping tolterodine, which had been taken for 13 days, and the other patient had an INR of 7.4 two days after stopping tolterodine, which had been taken for 8 days. In both cases no bleeding occurred and **warfarin** was withheld for three doses and successfully reinstated at the original dose.[2] Another case report describes a patient who required a 15% reduction in her **warfarin** dose while taking tolterodine 4 mg daily. Her maximum INR had been 3.9. However, she had undergone several warfarin dose increases over the previous 2 months and her INR had been fluctuating.[3]

The controlled study suggests that no **warfarin** dose adjustment would be expected to be necessary when tolterodine is added to **warfarin**. However, the 3 cases introduce a note of caution. Although additional monitoring would seem over-cautious on the basis of these cases, bear them in mind in the case of an unexpected response to warfarin.

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2. Colucci VJ, Rivey MP. Tolterodine-warfarin drug interaction. *Ann Pharmacother* (1999) 33, 1173–6.
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Coumarins + Trastuzumab

An isolated report describes an increase in the effects of warfarin in two women taking trastuzumab.

Clinical evidence, mechanism, importance and management

Two women stabilised on **warfarin** developed nosebleeds after 10 and 8 doses of trastuzumab (one dose given each week), and were found to have INRs of 6 and 5.8, respectively.[1] However, the manufacturer notes that, in an analysis of clinical study data, the rate of bleeding events was similar for patients receiving or not receiving trastuzumab, with or without anticoagulants.[2] There is no known mechanism for an interaction. Note that factors related to illness such as decreased appetite can alter **warfarin** requirements. The general relevance of these two cases is uncertain, but bear them in mind in the event of an unexpected response to treatment.

Note that, from a disease perspective, when treating venous thromboembolic disease in patients with cancer, **warfarin** is generally inferior (higher risk of major bleeds and recurrent thrombosis) to low-molecular-weight heparins.

1. Nissenblatt MJ, Karp GI. Bleeding risk with trastuzumab (Herceptin) treatment. *JAMA* (1999) 282, 2299–2300.
2. Stewart SJ. Bleeding risk with trastuzumab (Herceptin) treatment. In reply. *JAMA* (1999) 282, 2300–1.

Coumarins + Tricyclic antidepressants

Amitriptyline and nortriptyline do not appear to alter the half-life of warfarin, and probably do not alter that of dicoumarol. Limit-

ed evidence suggests that the use of tricyclics might be associated with greater variability in prothrombin times. An isolated case of the potentiation of warfarin by lofepramine has been reported.

Clinical evidence

(a) Dicoumarol

A study in 6 healthy subjects given **nortriptyline** 200 micrograms/kg three times daily for 8 days reported that it increased the mean half-life of dicoumarol from 35 hours to 106 hours. In a parallel group, the same dose of **nortriptyline** also increased the half-life of antipyrine.[1] However, in later identical studies by the same research group, **nortriptyline** decreased the half-life of antipyrine in one study, and had no effect in another.[2] The authors were unable to explain these disparate findings with antipyrine,[2] and they cast doubt on the results seen with dicoumarol. In a later study by another group, both **amitriptyline** 75 mg daily and **nortriptyline** 40 mg daily had no consistent effect on the half-life of a single dose of dicoumarol, although there was some evidence of increased dicoumarol plasma levels (about 24% with nortriptyline and 6% with **amitriptyline**).[3]

(b) Phenprocoumon

In a retrospective analysis of 7 patients taking phenprocoumon and **amitriptyline**, found unpredictable fluctuations in prothrombin times (said to be massive, both increases and decreases seen); these were absent in a control group of 7 other patients not taking **amitriptyline**. Note that the **amitriptyline** dose was not stable. Anticoagulant control improved on stopping the **amitriptyline** in 5 of the patients.[4] The same authors reported another similar case in a patient taking phenprocoumon and **amitriptyline**.[5]

(c) Warfarin

In a study in 12 healthy subjects,[3] **amitriptyline** 75 mg daily or **nortriptyline** 40 mg daily for 13 days did not affected the plasma half-life of a single dose of warfarin given on day 9. However, in the preliminary report of an analysis of 500 patients taking warfarin, a statistically significant difference in the warfarin dose index (prothrombin time prolongation/cumulative warfarin dose) before, during and after therapy was detected for a number of unexpected drugs including **amitriptyline**. However, no further details were given.[6] In another analysis of the stability of anticoagulant control in 277 patients, the use of tricyclics (**imipramine**, **amitriptyline**, **nortriptyline**) in 16 patients was associated with an increased need for anticoagulant dose modifications (average 3.56 over 6 months). Most of the patients were taking warfarin.[7]

Mechanism

Not understood. One suggestion is that the tricyclic antidepressants inhibit the metabolism of the anticoagulant (seen in *animals* with nortriptyline or amitriptyline and warfarin,[8] but not with **desipramine** and **acenocoumarol**[9]). However, the tricyclics are not established inhibitors of the metabolism of any drug so this seems unlikely. Another idea is that the tricyclics slow gastrointestinal motility because of their antimuscarinic effects, thereby increasing the time available for the dissolution and absorption of dicoumarol.[3]

Importance and management

Information about interactions between the coumarins and tricyclic antidepressants is limited, patchy and inconclusive. It appears that amitriptyline and nortriptyline do not alter the half-life of warfarin, and probably do not affect that of dicoumarol either. A greater fluctuation in anticoagulant control was noted in two analyses, one with warfarin and one with phenprocoumon. However, these were uncontrolled studies, and the findings need confirming in a randomised study. Moreover, there do not appear to be any published case reports of an interaction between tricyclics and warfarin. Thus, there is insufficient evidence to recommend any special precautions in patients taking coumarins and requiring tricyclics. However, consider the possibility of an interaction if the INR is difficult to stabilise.

1. Vesell ES, Passananti GT, Greene FE. Impairment of drug metabolism in man by allopurinol and nortriptyline. *N Engl J Med* (1970) 283, 1484–8.
2. Vesell ES, Passananti GT, Aurori KC. Anomalous results of studies on drug interaction in man. *Pharmacology* (1975) 13, 101–111.
3. Pond SM, Graham GG, Birkett DJ, Wade DN. Effects of tricyclic antidepressants on drug metabolism. *Clin Pharmacol Ther* (1975) 18, 191–9.
4. Hampel H, Berger C, Kuss H-J, Müller-Spahn F. Unstable anticoagulation in the course of amitriptyline treatment. *Pharmacopsychiatry* (1996) 29, 33–7.
5. Hampel H, Berger C, Müller-Spahn F. Modified anticoagulant potency in an amitriptyline-treated patient? *Acta Haematol (Basel)* (1996) 96, 178–80.
6. Koch-Weser J. Hemorrhagic reactions and drug interactions in 500 warfarin-treated patients. *Clin Pharmacol Ther* (1973) 14, 139.
7. Williams JRB, Griffin JP, Parkins A. Effect of concomitantly administered drugs on the control of long term anticoagulant therapy. *Q J Med* (1976) 45, 63.
8. Loomis CW, Racz WJ. Drug interactions of amitriptyline and nortriptyline with warfarin in the rat. *Res Commun Chem Pathol Pharmacol* (1980) 30, 41–58.
9. Weiner M. Effect of centrally active drugs on the action of coumarin anticoagulants. *Nature* (1966) 212, 1599–1600.

Coumarins and related drugs + Vaccines; Influenza

The concurrent use of warfarin and influenza vaccination is usually safe and uneventful, but there are reports of bleeding in a handful of patients (life threatening in one case) attributed to an interaction. Acenocoumarol also does not normally interact with influenza vaccination.

Clinical evidence

(a) Effect on anticoagulant control

Seventeen studies on the effects of influenza vaccine on the anticoagulant effect of coumarins have been published, and these are summarised in 'Table 12.7', (p.517). Most of these are non-controlled studies in small to moderate numbers of patients, and the majority did not demonstrate a significant change in prothrombin time or INR in patients taking coumarins, including the only randomised placebo-controlled study, and one very large retrospective cohort study. Some studies found a slight change in anticoagulant effect (both slight increases and slight reductions), but they are probably of limited clinical relevance. However, in one large case-control study, a clear increase in INR from 2.64 to 3.85 was seen in about half of the 90 patients involved in the study, and 2 of these patients had bleeding episodes. The reasons for the clear difference between this study and the many others are not known.

There are also various brief case reports of a possible interaction. In one review paper, there is a very brief report of a patient receiving **warfarin** who had serious bleeding, which was almost fatal, after receiving a 'flu shot'. No further details are given.[1] An elderly man receiving **warfarin** developed bleeding (haematemesis and melaena) within 10 days of being given an influenza vaccination. His prothrombin time was found to be 36 seconds.[2]

(b) Route of injection of vaccine

In a randomised study in 26 patients stabilised on **warfarin**, there was no difference in injection site adverse events between intramuscular or subcutaneous injection of a standard trivalent influenza vaccine, and no patient had bruising or swelling. In addition, both routes of administration produced similar levels of antibody titres.[3] In another study that specifically assessed the local reactions to intramuscular influenza vaccination, there were no detectable local complications after intramuscular injection, including no change in arm circumference.[4]

Mechanism

Not understood. In a placebo-controlled study in healthy subjects, influenza vaccination did not alter the half-life of either *R*- or *S*-warfarin.[2] It has therefore been suggested that when an interaction occurs the synthesis of the blood clotting factors is altered.[2]

Importance and management

A well-investigated interaction, but with some contradictory data. The weight of evidence suggests that influenza vaccination in those taking warfarin is normally safe and uneventful; nevertheless, it would be prudent to be on the alert because very occasionally and unpredictably bleeding may occur. Acenocoumarol appears not to be affected. Limited evidence suggests that intramuscular administration of the vaccine is not associated with increased local complications, but also that subcutaneous administration is effective. Because of the theoretical risk of local muscle haematoma, it may be preferable to give influenza vaccines by deep subcutaneous injection in patients taking coumarins and related anticoagulants.

Table 12.7 Summary of the evidence for and against an interaction between influenza vaccine and coumarins

Study type (year)	*Group*	*Coumarin*	*Influenza vaccine*	*Route*	*Notes*	*Refs*
Studies showing no interaction						
Prospective (1983)	33 patients and 15 controls	Warfarin	Not stated	Not stated	No evidence of an interaction (one vaccinated patient had haematuria 27 days later, and one control patient had epistaxis)	1
Prospective series (1984)	21 patients	Stable warfarin	Trivalent type A and B, Wyeth	Not stated	No change in average prothrombin time at 0, 3, 7, 10 and 14 days after vaccination	2
Randomised, placebo-controlled (1984)	25 patients vaccinated and 25 placebo	Stable warfarin	Trivalent type A and B (*Fluvirin*)	Deep subcutaneous	No change in mean ratio of prothrombin times at 0, 2, 7 and 21 days after vaccination	3
Prospective (1984)	4 healthy subjects	Low-dose warfarin	*Influvac*	Intramuscular	No change in average prothrombin time at 7, 11, 14, 16, 21 and 28 days after vaccination, and no change in warfarin levels	4
Prospective series (1985)	7 patients	Stable warfarin	Trivalent type A and B, Wyeth	Not stated	No change in prothrombin time at 4, 6, 10, 14 and 21 days after vaccination	5
Prospective series (1986)	26 patients	Stable warfarin	Trivalent (subvirion) type A and B (*Fluogen*)	Intramuscular	No change in mean INR at day 14 after vaccination	6
Prospective series (1986)	7 patients and 9 controls	Stable warfarin	Trivalent type A and B, Wyeth	Not stated	No change in prothrombin time at 1, 3 and 5 weeks after vaccination, or compared with controls	7
Prospective series (1990)	9 patients	Stable warfarin	Trivalent, split virion, A and B (*MFV-Ject*)	Not stated	No significant change in INR at 3, 6, 8, 10, 13, 22 and 30 days after vaccination (mean decrease of 4.8%)	8
Prospective series (1993)	43 patients	Stable acenocoumarol	Trivalent type A and B	Subcutaneous	No change in mean INR at 7, 15 and 30 days after vaccination. INR values increased in 3 patients and decreased in 6 patients requiring modification in acenocoumarol dose	9
Prospective series (1995)	41 patients	Stable warfarin	Not stated	Intramuscular	No significant change in prothrombin time at 3, 7 and 14 days after vaccination, and no local complications	10
Prospective series (2007)	78 patients	Stable warfarin	Not stated	Not stated	No apparent effect on INR within 10 days of vaccination	11
Retrospective cohort (2007)	4923 patients	Stable warfarin	Trivalent inactivated	Not stated	No change in mean INR in the 14 or 28 days after vaccination	12
Studies showing an increase in effect						
Prospective series (1984)	8 patients	Stable warfarin	Trivalent type A and B	Not stated	All patients had an increase in prothrombin time to at least the upper limit of their range for the previous year (40% from baseline)*	13
Prospective series (1986)	10 patients	Stable warfarin	Trivalent (subvirion) type A and B (*Fluogen*)	Intramuscular	Slight maximal 7.6% increase in mean INR at day 14 after vaccination	6
Case-control (2003)	90 patients and 45 controls	Stable warfarin (98%) Acenocoumarol (2%)	*Inflexel V, Isiflu V, Fluad*, or *Agrippal*	Intramuscular	49 out of 90 patients had a clear increase in INR from a mean of 2.64 to 3.85, and 2 of these had bleeding episodes. In the remaining patients and controls there was no change in INR	14
Studies showing a decrease in effect						
Prospective series (1988)	24 patients	Stable warfarin	Trivalent type A and B	Not stated	A slight 8.3% decrease in prothrombin time occurred in the first 2 weeks after vaccination.	15
Prospective series (2002)	73 patients and 72 controls	Stable warfarin	Not stated	Subcutaneous	Overall, there was no change in anticoagulation, but the 34 vaccinated patients aged 70 or more had a slight reduction in INR in month after vaccination (mean 2.8 versus 2.99)	16

*Other researchers[5] state that their analysis of these data failed to show a statistical difference after vaccination.

1. Patriarca PA, Kendal AP, Stricof RL, Weber JA, Meissner MK, Dateno B. Influenza vaccination and warfarin or theophylline toxicity in nursing-home residents. *N Engl J Med* (1983) 308, 1601–2.
2. Lipsky BA, Pecoraro RE, Roben NJ, de Blaquiere P, Delaney CJ. Influenza vaccination and warfarin anticoagulation. *Ann Intern Med* (1984) 100, 835–7.
3. Farrow PR, Nicholson KG. Lack of effect of influenza and pneumococcal vaccines on anticoagulation by warfarin. *J Infect* (1984) 9, 157–60.
4. Scott AK, Cannon J, Breckenridge AM. Lack of effect of influenza vaccination on warfarin in healthy volunteers. *Br J Clin Pharmacol* (1984) 19, 144P–145P.

Continued

Table 12.7 Summary of the evidence for and against an interaction between influenza vaccine and coumarins (continued)

5. Gomolin IH, Chapron DJ, Luhan PA. Lack of effect of influenza vaccine on theophylline levels and warfarin anticoagulation in the elderly. *J Am Geriatr Soc* (1985) 33, 269–72.
6. Weibert RT, Lorentz SM, Norcross WA, Klauber MR, Jagger PI. Effect of influenza vaccine in patients receiving long-term warfarin therapy. *Clin Pharm* (1986) 5, 499–503.
7. Gomolin IH. Lack of effect of influenza vaccine on warfarin anticoagulation in the elderly. *Can Med Assoc J* (1986) 135, 39–41.
8. Arnold WSG, Mehta MK, Roberts JS. Influenza vaccine and anticoagulation control in patients receiving warfarin. *Br J Clin Pract* (1990) 44, 136–9.
9. Souto JC, Oliver A, Montserrat I, Mateo J, Sureda A, Fontcuberta J. Lack of effect of influenza vaccine on anticoagulation by acenocoumarol. *Ann Pharmacother* (1993) 27, 365–8.
10. Raj G, Kumar R, McKinney WP. Safety of intramuscular influenza immunization among patients receiving long-term warfarin anticoagulation therapy. *Arch Intern Med* (1995) 155, 1529–31.
11. MacCallum P, Madhani M, Mt-Isa S, Ashby D. Lack of effect of influenza immunisation on anticoagulant control in patients on long-term warfarin. *Pharmacoepidemiol Drug Saf* (2007) 16, 786–9.
12. Jackson ML, Nelson JC, Chen RT, Davis RL, Jackson LA; for the Vaccine Safety Datalink investigators. Vaccines and changes in coagulation parameters in adults on chronic warfarin therapy: a cohort study. *Pharmacoepidemiol Drug Saf* (2007) 16, 790–6.
13. Kramer P, Tsuru M, Cook CE, McClain CJ, Holtzman JL. Effect of influenza vaccine on warfarin anticoagulation. *Clin Pharmacol Ther* (1984) 35, 416–18.
14. Paliani U, Filippucci E, Gresele P. Significant potentiation of anticoagulation by flu-vaccine during the season 2001-2002. *Haematologica* (2003) 88, 599–600.
15. Bussey HI, Saklad JJ. Effect of influenza vaccine on chronic warfarin therapy. *Drug Intell Clin Pharm* (1988) 22, 198–201.
16. Poli D, Chiarugi L, Capanni M, Antonucci E, Abbate R, Gensini GF, Prisco D. Need of more frequent international normalized ratio monitoring in elderly patients on long-term anticoagulant therapy after influenza vaccination. *Blood Coag Fibrinol* (2002) 13, 297–300.

Pneumococcal, tetanus and hepatitis A vaccines do not appear to alter anticoagulant status, see 'Coumarins + Vaccines; Miscellaneous', below.

1. Sumner HW, Holtzman JL, McClain CJ. Drug-induced liver disease. *Geriatrics* (1981) 36, 83–96.
2. Kramer P, Tsuru M, Cook CE, McClain CJ, Holtzman JL. Effect of influenza vaccine on warfarin anticoagulation. *Clin Pharmacol Ther* (1984) 35, 416–18.
3. Delafuente JC, Davis JA, Meuleman JR, Jones RA. Influenza vaccination and warfarin anticoagulation: a comparison of subcutaneous and intramuscular routes of administration in elderly men. *Pharmacotherapy* (1998) 18, 631–6.
4. Raj G, Kumar R, McKinney WP. Safety of intramuscular influenza immunization among patients receiving long-term warfarin anticoagulation therapy. *Arch Intern Med* (1995) 155, 1529–31.

Coumarins + Vaccines; Miscellaneous

Pneumococcal, tetanus with diphtheria toxoid, and hepatitis A vaccines do not appear to alter the response to warfarin.

Clinical evidence, mechanism, importance and management

In a large, retrospective, cohort study in patients stabilised on warfarin, there was no clinically relevant change in INR found between mean values in the 14 days or 28 days after vaccination with a 23-valent **pneumococcal polysaccharide** vaccine (1207 patients), **tetanus** plus **diphtheria toxoid** vaccine (1024 patients), or **hepatitis A** vaccine (121 patients) compared with mean values at other times. The change in mean INR was 0.01 to 0.03.[1] Similarly, in an earlier placebo-controlled study, a 14-valent **pneumococcal vaccine** (*Pneumovax*) did not have any effect on anticoagulant control at 2, 7 and 21 days after vaccination.[2] These studies suggest that no alteration in coagulation status would be anticipated after use of these vaccines.

For discussion of the numerous studies with influenza vaccine, see 'Coumarins and related drugs + Vaccines; Influenza', p.516.

1. Jackson ML, Nelson JC, Chen RT, Davis RL, Jackson LA; for the Vaccine Safety Datalink investigators. Vaccines and changes in coagulation parameters in adults on chronic warfarin therapy: a cohort study. *Pharmacoepidemiol Drug Safety* (2007) 16, 790–6.
2. Farrow PR, Nicholson KG. Lack of effect of influenza and pneumococcal vaccines on anticoagulation by warfarin. *J Infect* (1984) 9, 157–60.

Coumarins + Valproate

An isolated case describes a patient who had an increase in her INR the day after starting valproic acid, but was eventually restabilised on the original dose of warfarin while still taking the valproic acid. Valproic acid did not alter the anticoagulant effects of phenprocoumon in one patient. Note that valproate alone can cause altered bleeding time, bruising, haematoma, epistaxis, haemorrhage, and thrombocytopenia.

Clinical evidence

A woman was given **warfarin** for a deep vein thrombosis, and was stabilised on 5 mg alternating with 2.5 mg daily with an INR of between 1.8 and 2.6. Valproic acid 250 mg twice daily and fluphenazine 5 mg daily were then added. The morning after her first dose of valproic acid, the INR increased to 3.9, and **warfarin** dose was decreased to 2.5 mg daily. Four days later the valproic acid dose was doubled, and numerous **warfarin** dose adjustments were needed to keep the INR therapeutic. However, 3 weeks after starting the valproic acid she was discharged on the same **warfarin** dose as before the valproic acid was started.[1] In one patient taking **phenprocoumon**, valproic acid 500 mg to 1 g daily did not alter the prothrombin time ratio.[2]

Mechanism

There is *in vitro* evidence that the serum binding of warfarin is decreased by sodium valproate so that free warfarin levels rise,[1,3,4] by 32% according to one study.[1] The increase in free warfarin levels is transient until a new equilibrium is reached, but theoretically could result in a transient increase in INR, as is seen with cloral hydrate (see 'Coumarins + Cloral hydrate and related drugs', p.449).

Valproate inhibits the second stage of platelet aggregation, and a reversible prolongation of bleeding times and thrombocytopenia has been reported, usually with high doses, which can result in spontaneous bruising and bleeding.

Importance and management

Evidence for an interaction is limited. There seem to be no other reports of problems associated with the concurrent use of valproate and warfarin, nor any other direct evidence that an interaction of clinical importance normally occurs. It may be that any interaction occurs only transiently when valproate is added, and the situation rapidly restabilises without any real need to adjust the warfarin dose. Nevertheless, the manufacturers of sodium valproate and divalproex recommend closely monitoring the prothrombin time because of the possibility of warfarin protein binding displacement.[5-8] Note that valproate alone can cause thrombocytopenia and spontaneous bruising or bleeding, and if these effects occur, the manufacturers recommend withdrawing valproate pending investigations.[5-8] A reduction of the valproate dose or permanent withdrawal of valproate may be required.[6]

1. Guthrie SK, Stoysich AM, Bader G, Hilleman DE. Hypothesized interaction between valproic acid and warfarin. *J Clin Psychopharmacol* (1995) 15, 138–9.
2. Schlienger R, Kurmann M, Drewe J, Müller-Spahn F, Seifritz E. Inhibition of phenprocoumon anticoagulation by carbamazepine. *Eur Neuropsychopharmacol* (2000) 10, 219–21.
3. Urien S, Albengres E, Tillement J-P. Serum protein binding of valproic acid in healthy subjects and in patients with liver disease. *Int J Clin Pharmacol Ther Toxicol* (1981) 19, 319–25.
4. Panjehshahin MR, Bowmer CJ, Yates MS. Effect of valproic acid, its unsaturated metabolites and some structurally related fatty acids on the binding of warfarin and dansylsarcosine to human albumin. *Biochem Pharmacol* (1991) 41, 1227–33.
5. Epilim (Sodium valproate). Sanofi-Aventis. UK Summary of product characteristics, November 2008.
6. Depakote (Divalproex sodium). Abbott Laboratories. US Prescribing information, October 2006.

7. Depakote (Valproate semisodium). Sanofi-Aventis. UK Summary of product characteristics, November 2009.
8. Depakene (Valproic acid). Abbott Laboratories. US Prescribing information, January 2007.

Coumarins + Varenicline

Varenicline does not appear to alter the pharmacokinetics or anticoagulant effect of warfarin.

Clinical evidence, mechanism, importance and management

In a controlled study in 24 smokers, varenicline 1 mg twice daily for 13 days had no effect on the pharmacokinetics of a single 25-mg dose of warfarin given on day 8. There was no difference in warfarin pharmacodynamics (INR time curve).[1] The lack of pharmacokinetic interaction is consistent with *in vitro* findings.[1] No warfarin dose adjustments would be expected to be needed in patients taking varenicline. Nevertheless, bear in mind that smoking cessation (for which varenicline is used as an aid) can sometimes cause a minor to modest decrease in warfarin requirements, see 'Coumarins + Tobacco', p.514.

1. Burstein AH, Clark DJ, O'Gorman M, Willavize SA, Brayman TG, Grover GS, Walsky RL, Obach RS, Faessel HM. Lack of pharmacokinetic and pharmacodynamic interactions between a smoking cessation therapy, varenicline, and warfarin: an in vivo and in vitro study. *J Clin Pharmacol* (2007) 47, 1421–9.

Coumarins and related drugs + Viloxazine

A single report describes three cases where viloxazine possibly increased the anticoagulant effects of acenocoumarol and fluindione.

Clinical evidence

An 82-year-old woman with angina, hypertension and atrial fibrillation, who was taking **acenocoumarol**, molsidomine and flunitrazepam, had a rise in her INR from 3.3 to 7.9 when she started to take viloxazine (dose not stated) for depression. Five days after stopping the viloxazine her INR had fallen to 2.6. This report also briefly describes two other cases where viloxazine possibly caused an increase in the anticoagulant effects of **acenocoumarol** and **fluindione**.[1]

Mechanism

Not understood. The authors of the report suggest that viloxazine possibly inhibits cytochrome P450 within the liver, resulting in a reduction in the metabolism of the anticoagulants.[1]

Importance and management

Information seems to be limited to this report so that its general importance is uncertain. Be alert for the need to reduce the dose of acenocoumarol and fluindione if viloxazine is added to established anticoagulant treatment. Take the same precautions with any of the other coumarin or indanedione anticoagulants, but so far there seems to be no direct evidence that they interact.

1. Chiffoleau A, Delavaud P, Spreux A, Fialip J, Kergueris MF, Chichmanian RM, Lavarenne J, Bourin M, Larousse C. Existe-t-il une interaction métabolique entre la viloxazine et les antivitamines K? *Therapie* (1993) 48, 492–3.

Coumarins + Vinpocetine

In healthy subjects, the anticoagulant effect and the AUC of warfarin was slightly reduced by vinpocetine.

Clinical evidence, mechanism, importance and management

In a study in 18 healthy subjects taking vinpocetine 10 mg three times daily for 19 days, the anticoagulant effects and pharmacokinetics of a single 25-mg dose of **warfarin** were compared when given before vinpocetine was started, and on day 15.[1] A small 15% reduction in the mean prothrombin time occurred, and also an 8% reduction in the AUC of **warfarin**. The clinical relevance of these changes is unclear; however, they are slight, and a clinically relevant interaction would not be expected.

1. Hitzenberger G, Sommer W, Grandt R. Influence of vinpocetine on warfarin-induced inhibition of coagulation. *Int J Clin Pharmacol Ther Toxicol* (1990) 28, 323–8.

Coumarins + Vitamin E substances

The anticoagulant effects of warfarin are usually unchanged by small to large doses of vitamin E, although one isolated case of bleeding has been attributed to concurrent use. The effects of dicoumarol may be slightly increased by vitamin E.

Clinical evidence

(a) Dicoumarol

A study in 3 healthy subjects found that 42 units of vitamin E daily for one month increased the response to a single dose of dicoumarol after 36 hours (decrease in prothrombin activity from 52% to 33%).[1]

(b) Warfarin

In a double-blind, placebo-controlled study in 25 patients stabilised on warfarin, moderate to large daily doses of vitamin E (800 or 1200 units) for one month caused no clinically relevant changes in prothrombin times and INRs.[2] Similarly, in another study in 12 patients taking warfarin, the anticoagulant effects of warfarin were unchanged by smaller daily doses of 100 or 400 units of vitamin E given for 4 weeks.[3]

However, in one case, a patient taking warfarin (and multiple other drugs) developed ecchymoses and haematuria, which was attributed to him taking 1 200 units of vitamin E daily over a 2-month period. His prothrombin time was found to be 36 seconds. A later study in this patient found that 800 units of vitamin E daily for 6 weeks reduced his blood clotting factor levels, increased the prothrombin time from about 21 seconds to 29 seconds, and caused ecchymoses.[4] In addition, a modest rise in the INR of one patients with *Curbicin* was considered to be possible due to the presence of vitamin E in the *Curbicin* preparation (each tablet contains 10 mg).[5] For further information, see 'Coumarins + *Curbicin*', p.452.

Moreover, in a population cohort study, the concurrent use of vitamin E and warfarin was associated with an increased risk of mortality (adjusted hazard ratio 3.7). The hazard ratio for warfarin alone was 1.6 and for vitamin E alone was 0.91. The findings of this observational data require confirmation.[6]

Mechanism

Not understood. The suggested explanation is that vitamin E interferes with the activity of vitamin K in producing the blood clotting factors,[4,7] and increases in the dietary requirements of vitamin K.[8,9]

Importance and management

Information is limited but the evidence suggests that most patients taking warfarin are unlikely to have changes in coagulation status if given even quite large daily doses (up to 1 200 units) of vitamin E. Nevertheless, the isolated case cited here suggests that occasionally and unpredictably the warfarin effects can be changed. It has been recommended that prothrombin times should be monitored when vitamin E is first given (within one to 2 weeks has been recommended).[2] The same precautions could be applied to dicoumarol as well. However, as only one case of bleeding has been reported this does seem somewhat over-cautious. However, the finding of higher mortality in the observation cohort introduces some caution about the value of vitamin E supplements in patients taking warfarin. This requires further study. Information about other oral anticoagulants is lacking.

1. Schrogie JJ. Coagulopathy and fat-soluble vitamins. *JAMA* (1975) 232, 19.
2. Kim JM, White RH. Effect of vitamin E on the anticoagulant response to warfarin. *Am J Cardiol* (1996) 77, 545–6.
3. Corrigan JJ, Ulfers LL. Effect of vitamin E on prothrombin levels in warfarin-induced vitamin K deficiency. *Am J Clin Nutr* (1981) 34, 1701–5.
4. Corrigan JJ, Marcus FI. Coagulopathy associated with vitamin E ingestion. *JAMA* (1974) 230, 1300–1.
5. Yue, Q-Y, Jansson K. Herbal drug Curbicin and anticoagulant effect with and without warfarin: possibly related to the vitamin E component. *J Am Geriatr Soc* (2001) 49, 838.
6. Hayden KM, Welsh-Bohmer KA, Wengreen HJ, Zandi PP, Lyketsos CG, Breitner JCS, for the Cache County Investigators. Risk of mortality with vitamin E supplements: the Cache County study. *Am J Med* (2007) 120, 180–4.
7. Booth SL, Golly I, Sacheck JM, Roubenoff R, Dallal GE, Hamada K, Blumberg JB. Effect of vitamin E supplementation on vitamin K status in adults with normal coagulation status. *Am J Clin Nutr* (2004) 80, 143–8.

8. Anon. Vitamin K, vitamin E and the coumarin drugs. *Nutr Rev* (1982) 40, 180–2.
9. Anon. Megavitamin E supplementation and vitamin K-dependent carboxylation. *Nutr Rev* (1983) 41, 268–70.

Coumarins and related drugs + Vitamin K substances

The effects of the coumarin and indanedione anticoagulants can be reduced or abolished by vitamin K_1 (phytomenadione). Unintentional and unwanted antagonism can occur in patients unknowingly taking vitamin K_1. There is also a case of antagonism of acenocoumarol in a patient using a proprietary chilblain product containing the vitamin K_4 substance acetomenaphthone.

Clinical evidence

A woman taking **acenocoumarol** had a fall in her British Corrected Ratio to 1.2 (normal range 1.8 to 3) within 2 days of starting to take a non-prescription chilblain preparation (*Gon*) containing **acetomenaphthone** 10 mg per tablet. She took a total of 50 mg of vitamin K_4 over 48 hours.[1]

Mechanism

The coumarin and indanedione oral anticoagulants are vitamin K antagonists, and probably inhibit the enzyme vitamin K epoxide reductase so reducing the synthesis of vitamin K-dependent blood clotting factors by the liver. If the intake of vitamin K_1 increases, the competition swings in favour of the vitamin and the synthesis of the blood clotting factors begins to return to normal. As a result the prothrombin time also begins to fall to its normal value. The role of other vitamin K substances, such as K_4 and K_2, in coagulation is less clear.

Importance and management

The interaction with vitamin K_1 is very well established and clinically important, and is expected to occur with every coumarin and indanedione oral anticoagulant because they have a common mode of action as vitamin K antagonists. Vitamin K treatment is used as an effective antidote for excessive oral anticoagulation. The drug intake and diet of any patient who shows warfarin resistance should be investigated for the possibility of this interaction. It can be accommodated either by increasing the anticoagulant dose, or by reducing the intake of vitamin K_1. For more information on specific situations, see 'Coumarins + Vitamin K_1-containing dietary supplements', below, 'Coumarins and related drugs + Food; Enteral and parenteral nutrition', p.461, and 'Coumarins and related drugs + Food; Vitamin K_1-rich', p.464.

However, the role of other vitamin K substances in coagulation is less clear. The case report with acetomenaphthone, a vitamin K_4 substance suggests that this can also antagonise the effect of vitamin K antagonists. It may be prudent for patients to avoid preparations containing this substance. Similarly, the antagonism of coumarins by fermented soya beans has been attributed to the vitamin K_2 content (see 'Coumarins + Food; Soya bean products', p.463).

1. Heald GE, Poller L. Anticoagulants and treatment for chilblains. *BMJ* (1974) 1, 455.

Coumarins + Vitamin K_1-containing dietary supplements

In patients with normal vitamin K status, multivitamin supplements containing small amounts of vitamin K_1 (phytomenadione) will generally have no clinically important effect on the INR or anticoagulant requirements. Larger doses of vitamin K are likely to require a dose adjustment in a proportion of patients. Conversely, in patients with poor vitamin K status, even low vitamin K doses may have an important effect.

Clinical evidence

In a controlled study in healthy subjects stabilised on individual doses of **acenocoumarol**, the dose of vitamin K_1 tablets required to cause a statistically significant reduction in INR was 150 micrograms daily (INR 1.59 versus 2.04). Each dose of vitamin K_1 was taken daily for a week, and in successive weeks the dose was increased in increments of 50 micrograms from 50 to 300 micrograms daily, then 500 micrograms daily for the final week. The authors noted that their usual clinical criteria requiring an adjustment in **acenocoumarol** dose would have been met in 3 of the 12 subjects at a dose of vitamin K_1 of 150 micrograms daily.[1]

However, in another study in 9 patients stabilised on **warfarin** with low vitamin K levels the median INR dropped by 0.51 requiring a **warfarin** dose increase of 5.3% after they took just one multivitamin tablet containing vitamin K_1 25 micrograms daily for 4 weeks. Conversely, in a control group with normal plasma vitamin K levels, the same multivitamin did not change the INR or warfarin requirement.[2] In a well-controlled study in patients with unstable control of anticoagulation, vitamin K_1 150 micrograms daily increased the **warfarin** requirement by 16% from a mean of 3.8 mg daily to 4.4 mg daily, but also improved stability of control.[3]

In another study in patients taking **phenprocoumon**, supplementation with vitamin K_1 50 micrograms daily for 3 weeks had little effect on the INR, and required just a 3% increase in **phenprocoumon** dose. A higher dose of vitamin K_1 of 100 micrograms daily resulted in a mean dose increase of 9%. On stopping the supplements, a mean 7% decrease in dose was needed. However, there was wide variation between patients.[4]

A patient who required **warfarin** 15 to 17.5 mg daily to maintain an INR of about 3 was found to be taking vitamin K (dose not stated) as part of a vitamin supplement. When he stopped taking the vitamin K, his **warfarin** dose requirement decreased to between 10.5 and 12.5 mg daily.[5] In another report, a woman required an increase in her **warfarin** dose from 45 mg to 60 mg weekly when she started taking a daily multivitamin containing vitamin K_1 25 micrograms (*Centrum Plus*). Two weeks after stopping the multivitamin, she had haematuria and flank pain and was found to have a haematoma of the kidney and an INR of 13.2. A second patient had an acute occlusion of an aorto-bifemoral graft, requiring emergency surgery, 4 weeks after starting *Centrum Plus*. His INR had fallen from a mean of 2.48 to 1.1. A third patient had a fall in INR from a mean of 2.54 to 1.65 after taking *Centrum Plus* for 2 weeks. It was suggested that all three patients had low levels of vitamin K.[6]

Mechanism

Vitamin K_1 reduces the effect of vitamin K-antagonists (coumarins and **indanediones**). The dose of vitamin K_1 at which this becomes clinically important appears to depend on the vitamin K status of the individual.

Importance and management

The data from the controlled studies suggest that taking multivitamin supplements containing 10 to 50 micrograms of vitamin K_1 is probably acceptable in most patients taking coumarins or indanediones, and is likely to require no change or only small changes to the anticoagulant dose. However, in patients with poor vitamin K status, even these low levels of vitamin K may be sufficient to antagonise the effect of the anticoagulant. Note that a review of selected US supplements found that they contained 10 to 80 micrograms of vitamin K_1. Therefore, patients should be advised to *not* take a multivitamin preparation containing vitamin K_1 (phytomenadione) without increased monitoring when starting or stopping treatment. Because of this, and because of the increasing recognition of the importance of vitamin K in bone health, some consider that patients taking anticoagulants should be advised to consume sufficient vitamin K to meet the recommended adequate intakes.[7] Consider also *Importance and management* under 'Coumarins and related drugs + Food; Vitamin K_1-rich', p.464. Others have even suggested that a low and steady vitamin K supplement may reduce the risk of excessive anticoagulation without altering efficacy.[3,8]

1. Schurgers LJ, Shearer MJ, Hamulyák K, Stöcklin E, Vermeer C. Effect of vitamin K intake on the stability of oral anticoagulant treatment: dose-response relationships in healthy subjects. *Blood* (2004) 104, 2682–9.
2. Kurnik D, Loebstein R, Rabinovitz H, Austerweil N, Halkin H, Almog S. Over-the-counter vitamin K_1-containing multivitamin supplements disrupt warfarin anticoagulation in vitamin K_1-depleted patients. A prospective, controlled trial. *Thromb Haemost* (2004) 92, 1018–24.
3. Sconce E, Avery P, Wynne H, Kamali F. Vitamin K supplementation can improve stability of anticoagulation for patients with unexplained variability in response to warfarin. *Blood* (2007) 109, 2419–23.
4. Rombouts EK, Rosendaal FR, van der Meer FJM. The effect of vitamin K supplementation on anticoagulant treatment. *J Thromb Haemost* (2006) 4, 691–2.
5. Eliason BC, Larson W. Acetaminophen and risk factors for excess anticoagulation with warfarin. *JAMA* (1998) 280, 696–7.
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7. Johnson MA. Influence of vitamin K on anticoagulant therapy depends on vitamin K status and the source and chemical forms of vitamin K. Nutr Rev 2003; 63, 91–7
8. Oldenburg J. Vitamin K intake and stability of oral anticoagulant treatment. *Thromb Haemost* (2005) 93, 799–800.

Coumarins + Vitamin K_1-rich herbal medicines

A man had a modest rise in his INR after stopping taking a herbal nutritional supplement (*Nature's Life Greens*), which contained a number of plants known to be high in vitamin K_1. Another patient had a subtherapeutic INR after starting to drink a plant extract juice (called *Noni Juice*).

Clinical evidence, mechanism, importance and management

(a) Nature's Life Greens

A 72-year-old man stabilised on **warfarin** was found to have an INR of 4.43 at a routine clinic visit, which was increased from 3.07 six weeks previously. The patient had stopped taking a herbal product *Nature's Life Greens* that month because he did not have enough money to buy it. He had been taking it for the past 7 years as a vitamin supplement because he had previously been instructed to limit his intake of green leafy vegetables. He was eventually restabilised on **warfarin** and the same nutritional product.

The product label listed 25 vegetables without stating the amounts or concentrations,[1] but at least 5 of the listed ingredients are known to contain high levels of vitamin K_1 including **parsley**, **green tea leaves**, **spinach**, **broccoli**, and **cabbage** (see also 'Coumarins and related drugs + Food; Vitamin K_1-rich', p.464). It is therefore likely it contained sufficient vitamin K to antagonise the effect of the **warfarin** so that when it was stopped the warfarin requirements fell, and without an appropriate adjustment in dose, this resulted in an increased INR.

This case reinforces the view that all patients taking **warfarin** should seek advice when they want to stop or start any herbal medicine or nutritional supplement.

(b) Plant extracts juices

A 41-year-old woman stabilised on **warfarin** was found to have an INR of 1.6 at a routine clinic visit. The only possible cause identified was that the patient had begun to drink one to two small glasses daily of *Noni Juice 4 Everything*. This was identified as a brown liquid that contains extracts and derivates from more than 115 components. The authors noted that many of the listed plants contained vitamin K and that vitamin K was listed as a separate component, indicating that the juice might have been fortified with vitamin K. The patient was given heparin and then discharged on her previous dose of **warfarin**, and advised to stop taking this brand of juice.[2]

The authors concluded that this case reinforces the view that all patients taking **warfarin** should seek advice when they want to stop or start any herbal medicine or nutritional supplement.

1. Bransgrove LL. Interaction between warfarin and a vitamin K-containing nutritional supplement: a case report. *J Herb Pharmacother* (2001) 1, 85–89.
2. Carr ME, Klotz J, Bergeron M. Coumadin resistance and the vitamin supplement "Noni". *Am J Hematol* (2004) 77, 103–4.

Coumarins + Zileuton

Zileuton slightly increases the anticoagulant effects of warfarin and slightly increases *R*-warfarin levels.

Clinical evidence

In a placebo-controlled study, zileuton 600 mg every 6 hours for 6 days or placebo was given to healthy subjects who had been stabilised on racemic **warfarin** to achieve prothrombin times of 14 to 18 seconds for one week. The zileuton had no effect on the pharmacokinetics of *S*-warfarin, but the *R*-warfarin AUC rose by 22%, and its clearance fell by 15%. The mean prothrombin times increased by 2.3 seconds (morning) and 2 seconds (evening) in the zileuton group. The corresponding increases in the placebo group were 0.7 and 0.2 seconds, respectively.[1]

Mechanism

It seems likely that zileuton inhibits the metabolism of *R*-warfarin, probably by the cytochrome P450 isoenzyme CYP1A2.[2]

Importance and management

Information seems to be limited to this study, but the pharmacokinetic interaction appears to be established. The clinical significance of a 2 second rise in prothrombin times is unclear, but it seems likely to be small. The lack of any published reports of problems with the combination would tend to support this.

1. Awni WM, Hussein Z, Granneman GR, Patterson KJ, Dube LM, Cavanaugh JH. Pharmacodynamic and stereoselective pharmacokinetic interactions between zileuton and warfarin in humans. *Clin Pharmacokinet* (1995) 29 (Suppl 2), 67–76.
2. Lu P, Schrag ML, Slaughter DE, Raab CE, Shou M, Rodrigues AD. Mechanism-based inhibition of human liver microsomal cytochrome P450 1A2 by zileuton, a 5-lipoxygenase inhibitor. *Drug Metab Dispos* (2003) 31, 1352–60.

Drotrecogin alfa + Other drugs that affect coagulation

The concurrent use of drotrecogin alfa and prophylactic doses of heparin causes a slight increased risk of non-serious bleeding. The manufacturers of drotrecogin alfa caution its use in patients taking or who have recently received therapeutic doses of heparin, hirudins, oral anticoagulants, antiplatelet drugs, NSAIDs, prostacyclins, and thrombolytics.

Clinical evidence, mechanism, importance and management

(a) Heparins

Heparins are frequently used for prophylaxis of venous thromboembolic events in patients with severe sepsis. Because drotrecogin alfa increases the risk of bleeding, there has been concern that its use with heparin would further increase bleeding risk. Nevertheless, in phase III studies of drotrecogin alfa, two-thirds of patients received prophylactic doses of heparin or low-molecular-weight heparin with no observed increase in the risk of serious bleeding events reported.[1,2] Moreover, in a more recent study in patients treated with drotrecogin and randomised to receive prophylactic heparins or placebo, no increased risk of serious bleeding or adverse effects was found.[3] Except for a slight increase in any bleeding event in the first 6 days (10.8% heparin, 8.1% placebo), there was no difference in serious bleeding events, central nervous system bleeding events, or fatal bleeds on concurrent use. The US manufacturer notes that, in this study, the clearance and steady-state level of drotrecogin alfa (24 micrograms/kg per hour for 96 hours) was not affected by prophylactic **enoxaparin** 40 mg every 24 hours, or **unfractionated sodium heparin** 5000 units every 12 hours (although this was not evaluated when heparin 5000 units was given every 8 hours).[4] It therefore appears that low-dose heparin may be given for the prophylaxis of venous thromboembolic events concurrently with drotrecogin alfa. No dose adjustments are required.[1]

There appear to be little data on using drotrecogin alfa with therapeutic doses of heparin. The US manufacturer states that the increased risk of bleeding should be carefully considered when deciding to use drotrecogin alfa with therapeutic doses of heparin for treating an active thromboembolic event.[4] In the UK, the manufacturers specifically contraindicate use with heparin at doses of 15 units/kg per hour or more.[1]

(b) Other drugs affecting coagulation

Because of the possible increased risk of bleeding, the manufacturers state that the risks of giving drotrecogin alfa should be weighed against the benefits in patients who have received **thrombolytics** within 3 days, **oral anticoagulants** within 7 days, or **aspirin** (US information specifies greater than 650 mg daily) or other **antiplatelet drugs** within 7 days.[1,4] Caution should be used when prescribing these drugs and other drugs that affect haemostasis, such as the **hirudins**, **prostacyclins** such as **iloprost**, and other drugs that adversely affect platelet function such as **NSAIDs**, in patients given drotrecogin alfa.[1]

1. Xigris (Drotrecogin alfa). Eli Lilly and Company Ltd. UK Summary of product characteristics, December 2008.
2. Meshaka P. Question de l'agence européenne du médicament (EMEA): interaction drotrécogine alfa (activée) et héparine à dose prophylactique. *Ann Fr Anesth Reanim* (2003) 22, 23–7.

3. Levi M, Levy M, Williams MD, Douglas I, Artigas A, Antonelli M, Wyncoll D, Janes J, Booth FV, Wang D, Sundin DP, Macias WL for the Xigris and Prophylactic HepaRin Evaluation in Severe Sepsis (XPRESS) Study Group. Prophylactic heparin in patients with severe sepsis treated with drotrecogin alfa (activated). *Am J Respir Crit Care Med* (2007) 176, 483–90.
4. Xigris (Drotrecogin alfa). Eli Lilly and Company. US Prescribing information, October 2008.

Fondaparinux + Antiplatelet drugs or NSAIDs

Neither aspirin nor piroxicam appear to alter the pharmacokinetics of fondaparinux, and no significant change in bleeding time has been reported with concurrent use. However, concurrent use may be expected to increase the risk of bleeding.

Clinical evidence

In a study in 16 healthy subjects, a single 975-mg dose of **aspirin** given on day 4 of an 8-day course of subcutaneous fondaparinux 10 mg daily had no effect on fondaparinux pharmacokinetics. The increase in bleeding time with fondaparinux and **aspirin** was greater than with **aspirin** alone, but this was not statistically significant. **Aspirin** had no effect on the small prolongation of aPTT seen with fondaparinux.[1]

In another study, **piroxicam** 20 mg daily for 10 days was given to 12 healthy subjects with fondaparinux 10 mg daily starting on day 7. Both drugs were also given alone. **Piroxicam** had no effect on fondaparinux pharmacokinetics, and had no effect on the small prolongation of aPTT seen with fondaparinux. There was no difference in bleeding time between the treatments.[1]

Mechanism

Fondaparinux commonly causes bleeding as a consequence of its action.[2] As antiplatelet drugs and NSAIDs also increase the risk of bleeding, the risk and severity of bleeding is likely to be increased with the combination.

Importance and management

The pharmacological studies described show that the pharmacokinetics of fondaparinux are not changed by aspirin and piroxicam, and that there is only a minor increase in bleeding time. Nevertheless, the manufacturers of fondaparinux say that antiplatelet drugs (**aspirin**, **dipyridamole**, **sulfinpyrazone**, **ticlopidine** or **clopidogrel**) and NSAIDs should be used with caution because of the possible increased risk of haemorrhage. They recommend that if concurrent use is essential, close monitoring is necessary.[2,3] This is considered particularly important in patients undergoing peridural or spinal anaesthesia or spinal puncture, in whom antiplatelet drugs, NSAIDs and fondaparinux are possible risk factors for epidural or spinal haematoma resulting in prolonged or permanent paralysis.[2,3]

1. Ollier C, Faaij RA, Santoni A, Duvauchelle T, van Haard PMM, Schoemaker RC, Cohen AF, de Greef R, Burggraaf J. Absence of interaction of fondaparinux sodium with aspirin and piroxicam in healthy male volunteers. *Clin Pharmacokinet* (2002) 41 (Suppl 2), 31–37.
2. Arixtra (Fondaparinux sodium). GlaxoSmithKline UK. UK Summary of product characteristics, March 2009.
3. Arixtra (Fondaparinux sodium). GlaxoSmithKline. US Prescribing information, October 2009.

Fondaparinux + Miscellaneous

In the UK, the manufacturer of fondaparinux recommends avoiding other drugs that may enhance the risk of haemorrhage. They specifically name, desirudin, fibrinolytics, glycoprotein IIb/IIIa-receptor antagonists, heparin, heparinoids and low-molecular-weight heparins.[1] Similarly, in the US, the manufacturer states that drugs that may enhance the risk of haemorrhage should be discontinued before starting fondaparinux. They say that if concurrent use is essential, close monitoring may be appropriate.[2] See also 'Coumarins + Fondaparinux', p.461, and 'Fondaparinux + Antiplatelet drugs or NSAIDs', above.

1. Arixtra (Fondaparinux sodium). GlaxoSmithKline UK. UK Summary of product characteristics, March 2009.
2. Arixtra (Fondaparinux sodium). GlaxoSmithKline. US Prescribing information, October 2009.

Heparin and LMWHs + Antiplatelet drugs; Aspirin

The concurrent use of aspirin with heparin or low-molecular-weight heparins slightly increases the risk of haemorrhage. Concurrent use may be a contributing factor to the very rare complication of epidural or spinal haematoma occurring after epidural anaesthesia.

Clinical evidence

(a) Heparin

Eight out of 12 patients with hip fractures developed serious bleeding when they were given heparin 5 000 units subcutaneously every 12 hours and aspirin 600 mg twice daily as perioperative prophylaxis for deep vein thrombosis. Haematomas of the hip and thigh occurred in 3 patients, bleeding through the wound in 4, and uterine bleeding in the other patient.[1] In a large, randomised, placebo-controlled study, aspirin 500 mg three times daily, subcutaneous heparin 5000 units twice daily, or the combination were compared for prophylaxis of deep vein thrombosis in 1 210 patients undergoing surgery. Haemorrhage severe enough to discontinue the prophylaxis occurred in significantly more patients in the combination group (11 of 402 patients versus 3 of 404 patients in the heparin and aspirin alone groups). In addition, minor haemorrhage occurred more frequently in the combination group (89 patients) compared with aspirin alone (41 patients) or heparin alone (30 patients).[2] In another randomised study in patients with acute unstable angina, the combination of aspirin 325 mg twice daily and an intravenous infusion of heparin 1 000 units/hour resulted in slightly greater incidence of serious bleeding than either drug alone (3.3% for concurrent use versus 1.7% for either drug alone).[3]

In an epidemiological study of hospitalised patients receiving heparin, the incidence of bleeding was almost 2.4 times higher in 302 patients also receiving aspirin than in 2354 patients not given aspirin (doses not stated). Surgical patients were excluded from this analysis, as were patients with a discharge diagnosis of cancer or haematological disease.[4]

(b) LMWHs

In a crossover study in 9 healthy subjects, the bleeding time was prolonged by the use of aspirin 300 mg daily and subcutaneous **reviparin** 6 300 units daily, when compared with either drug alone (9.6 minutes versus 5.5 minutes and 5 minutes, respectively). However, the affect of aspirin on platelet aggregation and the effect of **reviparin** on aPTT were not altered by concurrent use.[5] However, in a clinical study in patients undergoing surgery for total hip or knee replacement, there was no difference in risk of bleeding or other bleeding-related parameters (total blood loss, need for transfusion, mean change in haemoglobin levels) between patients receiving **enoxaparin** and aspirin (51 patients) and those receiving **enoxaparin** and no aspirin (394 patients). Aspirin use was low-dose (up to 500 mg daily).[6] In addition, in an analysis of risk factors for bleeding in patients receiving **enoxaparin** for treating acute coronary syndrome, the use of aspirin was not associated with an increased risk of any bleeding.[7]

During a 5-year period in one hospital, 3 elderly patients had presented with sudden severe abdominal pain after coughing, which was found to be due to a rectus muscle sheath haematoma. These patients had been receiving subcutaneous **enoxaparin** 40 mg daily for an average of 6 days with aspirin 100 mg daily.[8] Other cases of retroperitoneal haematoma have been reported with **enoxaparin** in which aspirin may have been one of various contributing factors.[9-12] Similarly, the use of aspirin may have been one of a number of contributing factors in a case of spinal epidural haematoma occurring with **enoxaparin**.[13]

Mechanism

Aspirin inhibits platelet aggregation and prolongs bleeding times, and increases the risk of upper gastrointestinal haemorrhage, even at doses of 300 mg daily and less.[14] This risk is likely to be higher in patients also taking anticoagulants. See also 'Coumarins and related drugs + Aspirin or other Salicylates', p.434.

Importance and management

The concurrent use of heparin or LMWHs with aspirin is indicated in specific situations such as the prophylaxis of ischaemic complications of

unstable angina.[15] However, unless specifically indicated, it may be prudent to avoid the concurrent use of aspirin with these drugs, because of the likely increased risk of bleeding. If they are used together, some caution and consideration of increased monitoring would seem appropriate.

Heparin and some LMWHs have rarely caused epidural or spinal haematomas resulting in long-term or permanent paralysis when used for thromboprophylaxis in procedures involving spinal/epidural anaesthesia or spinal puncture. The risk of this may be increased if they are used concurrently with other drugs affecting haemostasis such as aspirin, and extreme caution is needed if concurrent use is considered appropriate in these situations.

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7. Macie C, Forbes L, Foster GA, Douketis JD. Dosing practices and risk factors for bleeding in patients receiving enoxaparin for the treatment of an acute coronary syndrome. *Chest* (2004) 125, 1616–21.
8. Macías-Robles MD, Peliz MG, Gonzalez-Ordonez AJ. Prophylaxis with enoxaparin can produce a giant abdominal wall haematoma when associated with low doses of aspirin among elderly patients suffering cough attacks. *Blood Coagul Fibrinolysis* (2005) 16, 217–19.
9. Melde SL. Enoxaparin-induced retroperitoneal hematoma. *Ann Pharmacother* (2003) 37, 822–4.
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12. Ernits M, Mohan PS, Fares LG, Hardy H. A retroperitoneal bleed induced by enoxaparin therapy. *Am Surg* (2005) 71, 430–3.
13. Chan L, Bailin MT. Spinal epidural hematoma following central neuraxial blockade and subcutaneous enoxaparin: a case report. *J Clin Anesth* (2004) 16, 382–5.
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Heparin and LMWHs + Antiplatelet drugs; Miscellaneous

The dose of heparin does not need adjusting when clopidogrel is also given. The antiplatelet effects of clopidogrel are not altered by heparin. Nevertheless, the concurrent use of heparin or low-molecular-weight heparins with antiplatelet drugs, such as clopidogrel, prasugrel, and ticlopidine, may increase the risk of bleeding.

Clinical evidence

(a) Clopidogrel

In a placebo-controlled study in 12 healthy subjects, the dose of heparin given over 4 days did not need modification when clopidogrel 75 mg daily was also given, and the inhibitory effects of clopidogrel on platelet aggregation were unchanged by concurrent use.[1] Moreover, the manufacturers of clopidogrel note that in various large clinical studies in patients with acute coronary syndrome or myocardial infarction, most patients received heparin or LMWHs without an obvious difference in the rate of bleeding or the incidence of major bleeding.[2,3] Nevertheless, in an analysis of risk factors for bleeding in 208 patients receiving **enoxaparin** for acute coronary syndrome, the use of clopidogrel was associated with an increased risk of any bleeding (odds ratio 2.49).[4]

In one case the use of **enoxaparin** with clopidogrel was considered to be a contributing factor in a case of spinal epidural haematoma occurring after spinal anaesthesia.[5] Another similar case occurred in a patient taking clopidogrel and given **dalteparin**,[6] and serious retroperitoneal bleeding occurred in a patient with acute coronary syndrome receiving **enoxaparin**, clopidogrel and aspirin.[7]

(b) Prasugrel

The manufacturer reports that heparin, given as a single intravenous bolus of 100 units/kg, had no significant effect on the antiplatelet effect of prasugrel. They also report that no clinically significant interaction was reported with the use of prasugrel and LMWHs in phase III clinical studies. However, they advise that concurrent use may possibly increase the risk of bleeding.[8]

(c) Ticlopidine

The manufacturer of ticlopidine notes that it has been used concurrently with heparin for about 12 hours in studies of cardiac stenting, but that longer-term safety has not been established.[9]

Mechanism

Antiplatelet drugs increase the risk of bleeding, and the risk is likely to be increased further in patients who are anticoagulated with heparin or LMWHs.

Importance and management

The concurrent use of heparin or LMWHs with antiplatelet drugs such as clopidogrel is indicated in specific conditions such as acute coronary syndrome. However, unless specifically indicated, the concurrent use of heparin or LMWHs with antiplatelet drugs should probably be avoided because of the likely increase in haemorrhagic risk. If they are used together, the manufacturers of the LMWHs (**bemiparin**, dalteparin, enoxaparin, **tinzaparin**) recommend caution or careful clinical and laboratory monitoring.

Heparin and some LMWHs have rarely caused epidural or spinal haematomas resulting in long-term or permanent paralysis when used for thromboprophylaxis in procedures involving spinal/epidural anaesthesia or spinal puncture. The risk of this may be increased if they are used concurrently with other drugs affecting haemostasis such as antiplatelet drugs, and extreme caution is needed if concurrent use is considered appropriate in these situations.

Consider also 'Heparin and LMWHs + Antiplatelet drugs; Aspirin', p.522, and 'Glycoprotein IIb/IIIa antagonists + Miscellaneous', p.826.

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2. Plavix Film-coated Tablets (Clopidogrel hydrogen sulphate). Bristol-Myers Squibb Pharmaceuticals Ltd. UK Summary of product characteristics, August 2009.
3. Plavix (Clopidogrel bisulfate). Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership. US Prescribing information, October 2009.
4. Macie C, Forbes L, Foster GA, Douketis JD. Dosing practices and risk factors for bleeding in patients receiving enoxaparin for the treatment of an acute coronary syndrome. *Chest* (2004) 125, 1616–21.
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8. Efient (Prasugrel hydrochloride). Eli Lilly and Company Ltd. UK Summary of product characteristics, September 2009.
9. Ticlid (Ticlopidine hydrochloride). Roche Laboratories Inc. US Prescribing information, March 2001.

Heparin + Aprotinin

The activated clotting time (ACT) may not be a reliable method to monitor heparin when aprotinin is used concurrently. This is because aprotinin increases the ACT monitored by some methods, without actually increasing anticoagulation.

Clinical evidence, mechanism, importance and management

Aprotinin prolongs the activated clotting time (ACT) as measured by a celite surface activation method, although the kaolin ACT is much less affected.[1] Therefore, if the ACT is used to monitor the effectiveness of heparin anticoagulation during cardiopulmonary bypass incorporating aprotinin, this may lead to an overestimation of the degree of anticoagulation. This may result in patients not receiving additional necessary heparin during extended extracorporeal circulation, or receiving excess protamine to reverse the effects of heparin at the end of the procedure. The UK manufacturer of aprotinin noted that it is not necessary to adjust the usual reg-

imen of heparin and protamine used in cardiopulmonary bypass procedures when aprotinin is also used.[2] The US manufacturer provided additional detailed information on appropriate methods to monitor heparin anticoagulation in the presence of aprotinin.[1] Note that aprotinin has generally been withdrawn because of a possible increased risk of death when it is used in cardiac surgery.

1. Trasylol (Aprotinin). Bayer HealthCare. US Prescribing information, December 2003.
2. Trasylol (Aprotinin). Bayer plc. UK Summary of product characteristics, September 2006.

Heparin + Dextrans

The concurrent use of heparin and dextrans can further prolong clotting time and increase the risk of bleeding.

Clinical evidence, mechanism, importance and management

A study in 9 patients with peripheral vascular disease given 500 mL of dextran found that the mean clotting time one hour after an infusion of 10 000 units of heparin was increased from 36 minutes to 69 minutes. Dextran alone had no effect, but the mean clotting time after 5000 units of heparin with dextran was almost the same as after 10 000 units of heparin alone.[1,2] This study would seem to support two other reports[3,4] of an increase in the incidence of bleeding in those given both heparin and dextran 70. Uneventful concurrent use[5,6] has been described with dextran 40.

Note that these findings are probably of little clinical significance if these drugs are given for their anticoagulant effects; however, increased anticoagulation may be undesirable if dextrans are used as volume expanders in patients already receiving heparin. In this situation some caution is warranted.

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Heparin + LMWHs; Enoxaparin

There is some evidence that patients receiving enoxaparin preoperatively require more heparin during surgery.

Clinical evidence, mechanism, importance and management

In a clinical study, 30 patients with unstable coronary disease treated preoperatively with enoxaparin needed more heparin to maintain an activated clotting time above 480 seconds during surgery than 31 stable control patients not treated with enoxaparin. In addition, the enoxaparin recipients had higher heparin levels and lower antithrombin values compared with control patients. All patients were taking low-dose aspirin until the day before surgery, and received tranexamic acid as a bolus dose before cardiopulmonary bypass.[1]

The reasons for these differences are unclear, and their clinical relevance is uncertain. Further study is needed.

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Heparin + Miscellaneous

Changes in the protein binding of diazepam, propranolol, quinidine and verapamil caused by heparin do not appear to be of clinical importance.

Clinical evidence, mechanism, importance and management

A number of studies have found that heparin reduces the plasma protein binding of several drugs including **diazepam**,[1,2] **propranolol**,[1] **quinidine**[3] and **verapamil**[4] in man and in *animals*. For example, 3 patients taking oral **propranolol** and 5 patients given intramuscular **diazepam** 10 mg were given 3000 units of heparin just before cardiac catheterisation. Five minutes after the heparin was given, the free fraction of **diazepam** was found to have risen fourfold (from 1.8 to 7.9%) while the free **diazepam** levels had similarly risen (from 2 to 8.4 nanograms/mL). The free fraction of the **propranolol** rose from 7.4% to 12.5% and the free levels rose from 1.7 nanograms/mL to 2.7 nanograms/mL.[1]

It was suggested that these changes occur because heparin displaces these drugs from their binding sites on the plasma albumin and that these changes in protein binding might possibly have some clinical consequences. For example, there could, theoretically, be sudden increases in sedation or respiratory depression because of the rapid increase in the active (free) fraction of **diazepam**.

However, these changes are unlikely to be of clinical importance (see 'Protein-binding interactions', (p.3)). One study even suggested that the heparin-induced protein binding changes are an artefact of the study methods used,[5] and this would seem to be supported by an experimental study, which found that heparin did not have any effect on the beta-blockade caused by **propranolol**.[6] Moreover, there seem to be no other reports confirming that these interactions are of real clinical importance. No special precautions would seem to be necessary.

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Heparin + Nitrates

The effects of heparin were reduced by an infusion of glyceryl trinitrate in some studies, but other studies have not confirmed this interaction. No interaction has been seen with heparin and isosorbide dinitrate or molsidomine.

Clinical evidence

(a) Glyceryl trinitrate (Nitroglycerin)

An interaction between heparin and glyceryl trinitrate was originally reported[1] in 1985. A lower aPTT value was found in patients receiving both intravenous glyceryl trinitrate and heparin, when compared with control patients receiving heparin alone. In a further study in healthy subjects, the same effect was seen with the propylene glycol diluent alone, so the interaction was attributed to the diluent.[1] However, in another study, the same interaction was noted in 2 patients receiving a glyceryl trinitrate preparation without propylene glycol. In this study, while receiving intravenous glyceryl trinitrate, 7 patients with coronary artery disease needed an increased dose of intravenous heparin to achieve satisfactory aPTT ratios of 1.5 to 2.5 on eight occasions. When the glyceryl trinitrate was stopped, in 6 out of 8 occasions there was a marked increase in aPTT values to 3.5. One patient had transient haematuria.[2]

Four other studies have also found a reduction in the effects of heparin in the presence of intravenous glyceryl trinitrate.[3-6] In one of these, the prothrombin time of 27 patients given heparin was more than halved (from 130 to about 60 seconds) when they were given intravenous glyceryl trinitrate 2 to 5 mg/hour. The prothrombin time rose again when the glyceryl trinitrate was stopped.[3] In one study, there was some evidence that the effect might occur only at higher doses of intravenous glyceryl trinitrate (above 350 micrograms/minute),[5] whereas in another, an effect was seen at low doses of 25 to 50 micrograms/minute.[6]

In contrast to the above studies, a total of 12 other studies have found no changes in aPTT in patients[7-16] or healthy subjects[17,18] given intravenous glyceryl trinitrate with heparin. In the randomised, placebo-controlled studies in healthy subjects, a 60-minute infusion of glyceryl trinitrate 5 mg had no effect on the aPTT or prothrombin time following a 5000 unit intravenous injection of heparin,[17] and a 100 micrograms/minute infusion of glyceryl trinitrate did not alter the anticoagulant effect of a 40 units/kg bolus of intravenous heparin in 7 healthy subjects.[18] Two randomised, pla-

cebo-controlled studies in patients have also not found any effect of intravenous glyceryl trinitrate on a heparin infusion titrated to a given effect,[12] or on an intravenous heparin bolus dose.[14] In the first of these studies, the glyceryl trinitrate preparation contained propylene glycol.[12]

(b) Isosorbide dinitrate

In a randomised, placebo-controlled study in 12 patients receiving a stable infusion of heparin, the use of isosorbide dinitrate 4.8 ± 0.8 mg/hour for 24 hours did not alter the AUC of the prothrombin time, when compared with placebo, nor was there any change in prothrombin time in the 5 hours after stopping the nitrate.[12] Similarly, other studies have not found any important change in anticoagulation when intravenous isosorbide dinitrate is given with heparin.[8,14,16]

(c) Molsidomine

In a study in 15 patients given intravenous heparin then intravenous molsidomine 2 mg/hour, molsidomine had no effect on the prothrombin time.[19]

Mechanism

Not understood. One study suggests that what occurs is related to a glyceryl trinitrate-induced antithrombin III abnormality, and is apparent at doses above 350 micrograms/minute.[5] One study found that heparin levels were lowered,[6] whereas another reported unchanged heparin levels.[3]

Importance and management

The discord between these reports for glyceryl trinitrate infusion is not understood. However, the best controlled studies in the largest number of patients have not found any evidence of an interaction. On balance therefore, it appears that a clinically relevant interaction is generally unlikely to be seen. Moreover, given that heparin is routinely monitored, it is likely that if any interaction occurs, it will be rapidly detected and compensated for. No special precautions would appear to be needed if heparin is given with molsidomine or isosorbide dinitrate.

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13. Berk SI, Grunwald A, Pal S, Bodenheimer MM. Effect of intravenous nitroglycerin on heparin dosage requirements in coronary artery disease. *Am J Cardiol* (1993) 72, 393–6.
14. Muikku O. Isosorbide dinitrate does not interfere with heparin anticoagulation: a placebo-controlled comparison with nitroglycerin in patients scheduled for coronary artery surgery. *Acta Anaesthesiol Scand* (1994) 38, 583–6.
15. Williams H, Langlosi PF, Kelly JL. The effect of simultaneous intravenous administration of nitroglycerin and heparin on partial thromboplastin time. *Mil Med* (1995) 160, 449–52.
16. Koh KK, Park GS, Song JH, Moon TH, In HH, Kim JJ, Lee HJ, Cho SK, Kim SS. Interaction of intravenous heparin and organic nitrates in acute ischemic syndromes. *Am J Cardiol* (1995) 76, 706–9.
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19. Wiemer M, Pizzulli L, Reichert H, Lüderitz B. Gibt es eine Wechselwirkung zwischen Heparin und Moldisomin?. *Med Klin* (1994) 89, 45–6.

Heparin and LMWHs + NSAIDs

Some evidence suggests that the bleeding risk is increased when enoxaparin is used with NSAIDs, whereas other evidence suggests no increased bleeding risk with these drugs. The bleeding time was prolonged when ketorolac was given with dalteparin, but not when it was given with heparin. Parecoxib does not alter the effect of heparin on aPTT. Cases of spinal haematomas after epidural anaesthesia have been reported with the concurrent use of heparin or low-molecular-weight heparins and NSAIDs.

Clinical evidence

(a) Heparin

In a crossover, placebo-controlled study in healthy subjects, there was no evidence of an interaction between **ketorolac** and heparin in terms of prolongation of skin bleeding time, platelet aggregation, anti-factor Xa activity, or kaolin-cephalin clotting time. In this study, two doses of oral **ketorolac** were given (the previous evening, and in the morning), then two 10-mg intramuscular doses of ketorolac were given at 10 am and 2 pm, with simultaneous doses of subcutaneous heparin 5000 units.[1] Similarly, in an open-label, crossover study in 18 healthy subjects, giving heparin on day 5 of the use of intravenous **parecoxib** 40 mg twice daily for 6 days produced no clinically or statistically significant differences in coagulation parameters (prothrombin time, aPTT and platelet counts), when compared with heparin alone (bolus dose of heparin 4000 units then a 36-hour infusion of 10 to 14 units/kg). The use of these drugs together was well tolerated. However, prolongation of bleeding time was not assessed.[2]

Use of heparin and **ibuprofen** were considered to be contributing factors in a case of spinal haematoma occurring after epidural anaesthesia.[3]

(b) Low-molecular-weight heparins

In a placebo-controlled, crossover study in healthy subjects, giving **ketorolac** with **dalteparin** resulted in prolongation of the skin bleeding time, when compared with ketorolac alone (13.95 minutes versus 10.55 minutes). **Dalteparin** alone had no effect on the bleeding time when compared with placebo. In this study, two doses of oral **ketorolac** 30 mg were given the day before, and one dose an hour after a single 5000-unit subcutaneous dose of **dalteparin**. The combination did not have any greater effect on platelet aggregation, anti-factor Xa activity, or aPTT time than the individual drugs alone.[4] In an analysis of risk factors for bleeding in patients receiving **enoxaparin** for acute coronary syndrome, the use of NSAIDs was associated with an increased risk of any bleeding (odds ratio 3.44), but not major bleeding.[5] However, a study in hip replacement patients given subcutaneous **enoxaparin** 40 mg daily found that there were no significant differences in intra-operative blood loss, post-operative drainage, transfusion requirements, bruising, wound oozing, and leg swelling between 34 patients given intramuscular **ketorolac** 30 mg on induction of anaesthesia then daily for 4 days postoperatively and 26 patients given unnamed opioids. Patients in this study had any previous NSAID medication stopped 4 weeks before admission, and were not taking aspirin.[6] Similarly, in a large study in patients undergoing surgery for total hip or knee replacement, there was no difference in risk of bleeding or other bleeding-related parameters (total blood loss, need for transfusion, mean change in haemoglobin levels) between patients receiving **enoxaparin** and NSAIDs (830 patients) and those receiving **enoxaparin** and no NSAIDs (394 patients). NSAIDs permitted in this study were said to be short-acting (with a half-life up to 20 hours), but none were specifically named.[7]

The use of **enoxaparin**, **ketorolac**, and aspirin were considered to be contributing factors in a case of spinal haematoma occurring after lumbar puncture, which resulted in paraplegia.[8] Another case has also been briefly described.[9] In an analysis of reports from the FDA in the US, 16 of 43 patients who developed spinal or epidural haematoma after receiving **enoxaparin** had received concurrent drugs known to prolong bleeding, such as **ketorolac** or other NSAIDs.[10]

Mechanism

NSAIDs, to a greater or lesser extent, irritate the stomach lining. This can result in gastrointestinal bleeding, which will be more severe in anticoagulated patients. Many NSAIDs also have antiplatelet activity, which can prolong bleeding times. There are studies showing that use of NSAIDs

increases the risk of perioperative bleeding (one is cited as an example[11]), and theoretically this might be greater in those also receiving heparins.

Importance and management

An interaction between NSAIDs and heparins (including low-molecular-weight heparins) is established. The CSM in the UK and the UK manufacturers say that ketorolac is contraindicated with anticoagulants, including low-dose **heparin**.[12,13] Conversely, the US manufacturers of ketorolac advise that physicians should carefully weigh the benefits against the risks and use concurrent heparin only extremely cautiously.[14]

If NSAIDs and LMWHs are used together, the manufacturers of the LMWHs (**bemiparin**, **dalteparin**, **enoxaparin**, **tinzaparin**) recommend caution or careful clinical and laboratory monitoring.

Heparin and some LMWHs have rarely caused epidural or spinal haematomas resulting in long-term or permanent paralysis when used for thromboprophylaxis in procedures involving spinal/epidural anaesthesia or spinal puncture. The risk of this may be increased if they are used concurrently with other drugs affecting haemostasis such as ketorolac or other NSAIDs, and extreme caution is needed if concurrent use is considered appropriate in these situations.

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11. Slappendel R, Weber EWG, Benraad B, Dirksen R, Bugter MLT. Does ibuprofen increase perioperative blood loss during hip arthroplasty? *Eur J Anaesthesiol* (2002) 19, 829–31.
12. Committee on Safety of Medicines/Medicines Control Agency. Ketorolac: new restrictions on dose and duration of treatment. *Current Problems* (1993) 19, 5–6.
13. Toradol (Ketorolac trometamol). Roche Products Ltd. UK Summary of product characteristics, July 2009.
14. Toradol (Ketorolac tromethamine). Roche Pharmaceuticals. US Prescribing information, September 2002.

Heparin + Probenecid

An isolated case report from the 1950s suggests that the effects of heparin may be possibly increased by probenecid, and bleeding may occur.

Clinical evidence, mechanism, importance and management

In 1950 (but not reported until 1975) a woman with subacute bacterial endocarditis was given probenecid orally and penicillin by intravenous drip, which was kept open with minimal doses of heparin. After about 20 000 units of heparin had been given over a 3-week period, increasing epistaxis developed and the clotting time was found to be 24 minutes (reference range 5 to 6 minutes). This was controlled with protamine.[1] However, no reports of this interaction appear to have been made subsequently. This interaction seems unlikely to be of general significance.

1. Sanchez G. Enhancement of heparin effect by probenecid. *N Engl J Med* (1975) 292, 48.

Heparin and LMWHs + SSRIs

Severe bleeding was attributed to the use of tinzaparin in an elderly woman with renal impairment taking fluoxetine.

Clinical evidence, mechanism, importance and management

A 78-year-old woman taking **fluoxetine** was started on once-daily subcutaneous injections of weight-adjusted **tinzaparin** for a deep vein thrombosis. Five days later she suffered a massive intraperitoneal and parietal haematoma. Poor renal function in this patient could have led to accumulation of the low-molecular-weight heparin, but **fluoxetine** was also considered a contributing factor because SSRIs have antiplatelet effects and can contribute to bleeding.[1] Consider also 'Coumarins and related drugs + SSRIs', p.504. The general relevance of this isolated case is unclear.

1. de Maistre E, Allart C, Lecompte T, Bollaert P-E. Severe bleeding associated with use of low molecular weight heparin and selective serotonin reuptake inhibitors. *Am J Med* (2002) 113, 530–2.

Heparin and LMWHs + Tobacco

There is some evidence that heparin and dalteparin might be slightly less effective in smokers. However, smoking status is probably not important in predicting the dose of heparin and LMWHs.

Clinical evidence, mechanism, importance and management

In a study of the factors affecting the sensitivity of individuals to heparin, the heparin half-life in smokers was 0.62 hours compared with 0.97 hours in non-smokers. The dose requirements of the smokers were slightly increased (18.8 units/hour compared with 16 units/hour; both per lean body-weight). However, when lean body-weight was taken into account, smoking status was no longer related to heparin clearance.[1] In a retrospective analysis of weight-based heparin dosing, smoking was predictive of a subtherapeutic aPTT response, which is consistent with the idea that heparin has a shorter half-life in smokers.[2]

In a sub-study of dalteparin for unstable coronary artery disease, high-dose weight-adjusted dalteparin was associated with lower anti-factor Xa levels and a lower risk of bleeding in smokers. This suggests that dalteparin was slightly less effective in smokers.[3]

The limited data provide some evidence that heparin and LMWHs might be slightly less effective in smokers. Nevertheless, smoking status is not usually a factor used in calculating the dose of heparins. Note that as unfractionated heparin is usually dose adjusted according to bleeding times, any minor interaction should be accounted for in this adjustment.

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Heparinoids; Danaparoid + Antiplatelet drugs or NSAIDs

No haemostatic interaction was noted between danaparoid and aspirin in healthy subjects. However, caution is recommended on concurrent use because of the possibility of increased bleeding risk.

Clinical evidence

In a randomised, crossover study in healthy subjects, there were no important alterations in coagulation tests and plasma anti-Xa activity when danaparoid (3250 anti-Xa units intravenous bolus followed by 750 units subcutaneously twice daily for 8 days) was given with **aspirin** 500 mg, 14 hours and 2 hours before the intravenous danaparoid. Similarly, danaparoid did not alter the effects of **aspirin** on platelet function, but the prolongation in bleeding time tended to be longer after the combination.[1]

Mechanism

The manufacturer notes that, in general, combination with antithrombotics that act by other mechanisms, such as aspirin, would be additive.[2]

Importance and management

Any effects in the study with aspirin where not considered to be clinically relevant.[1,2] The manufacturers note that danaparoid may be used with drugs that interfere with platelet function, such as aspirin and NSAIDs, but considers that caution remains necessary.[2,3] This is considered particularly important in patients undergoing peridural or spinal anaesthesia or spinal puncture, in whom the use of NSAIDs, and probably also danaparoid, are risk factors for epidural or spinal haematoma resulting in prolonged or permanent paralysis.[2,3]

1. de Boer A, Danhof M, Cohen AF, Magnani HN, Breimer DD. Interaction study between Org 10172, a low molecular weight heparinoid, and acetylsalicylic acid in healthy male volunteers. *Thromb Haemost* (1991) 66, 202–7.
2. Orgaran (Danaparoid sodium). Organon Canada Ltd. Canadian product monograph, June 2001.
3. Orgaran (Danaparoid sodium). Organon Laboratories Ltd. UK Summary of product characteristics, July 2003.

Heparinoids; Danaparoid + Diuretics

Chlortalidone had no clinically relevant effect on the anti-Xa activity of danaparoid in healthy subjects, but it caused an increase in the volume of distribution of antithrombin activity of uncertain relevance. Nevertheless, in clinical use danaparoid is frequently used with a number of other drugs including diuretics, and there is no evidence of an interaction.

Clinical evidence, mechanism, importance and management

In a randomised, crossover study in healthy subjects, a slight decrease in clearance (7%) and volume of distribution (19%) of the anti-Xa activity of danaparoid (3250 anti-Xa units intravenous bolus) occurred when it was given about 12 hours after a single 100-mg dose of chlortalidone. Conversely, the apparent volume of distribution of antithrombin activity was increased by 80%. However, chlortalidone did not change the effect of danaparoid on clotting tests, except for a 4% increase in prothrombin time, which was thought to be a spurious finding.[1] The reasons for these changes are uncertain.

The minor changes in anti-Xa activity are unlikely to be clinically relevant.[1,2] However, the authors considered that relevance of the change in antithrombin activity was uncertain.[1] Nevertheless, the manufacturer notes that, in clinical use, danaparoid has frequently been used with a variety of drugs, including diuretics, and that there is no evidence of any direct interaction with danaparoid.[2]

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2. Orgaran (Danaparoid). Organon Canada Ltd. Canadian Prescribing information, June 2001.

Heparinoids; Danaparoid + Penicillins

Cloxacillin and ticarcillin caused an increase in elimination half-life of anti-Xa activity of danaparoid in one study. Ticarcillin had no effect on haemostasis, but cloxacillin appeared to have some pro-coagulant effects, which were not likely to be due to an interaction with danaparoid.

Clinical evidence

(a) Cloxacillin

In a randomised, crossover study in 6 healthy subjects, there was a 74% increase in the elimination half-life of the plasma anti-Xa activity of danaparoid (3250 anti-Xa units intravenous bolus) when it was given with oral cloxacillin 500 mg four times daily for 3 days beginning 24 hours before the danaparoid. Unexpectedly, there were slight decreased effects on thrombin time and bleeding time, and increased effects on aPTT with the combination, effects that were attributed to cloxacillin alone.[1]

(b) Ticarcillin

In a randomised, crossover study in 12 healthy subjects, there was a 56% increase in the elimination half-life of the plasma anti-Xa activity of danaparoid (3250 anti-Xa units intravenous bolus) when it was given with intravenous ticarcillin 4 g four times daily for 2 days beginning immediately before the danaparoid. There were no changes in haemostatic parameters when ticarcillin was given with danaparoid.[1]

Mechanism

Uncertain, but penicillins might compete with danaparoid for renal tubular secretion.[1]

Importance and management

The pharmacokinetic changes seen in the studies with cloxacillin and ticarcillin were not considered clinically relevant.[1,2] In addition, the haemostatic changes seen in the study with cloxacillin were unlikely to be due to an interaction.[1] The manufacturer notes that in clinical use danaparoid has frequently been used with a variety of drugs, including antibacterials, and that there is no evidence of any direct interaction with danaparoid.[2]

1. de Boer A, Stiekema JCJ, Danhof M, van Dinther TG, Boeijinga JK, Cohen AF, Breimer DD. Studies of interaction of a low-molecular-weight heparinoid (Org 10172), with cloxacillin and ticarcillin in healthy male volunteers. *Antimicrob Agents Chemother* (1991) 35, 2110–15.
2. Orgaran (Danaparoid). Organon Canada Ltd. Canadian product monograph, June 2001.

Indanediones + Haloperidol

A single case report describes a marked reduction in the anticoagulant effects of phenindione in a patient given haloperidol.

Clinical evidence, mechanism, importance and management

A man stabilised on **phenindione** 50 mg daily was given haloperidol by injection (5 mg every 8 hours for 24 hours) followed by 3 mg twice daily by mouth. Adequate anticoagulation was not achieved even when the **phenindione** dose was increased to 150 mg daily. When the haloperidol dose was halved, the necessary dose of anticoagulant was reduced to 100 mg daily, and only when the haloperidol was withdrawn was it possible to achieve adequate anticoagulation with the original dose.[1] The reasons for this effect are not understood. This appears to be the only report of an interaction, and its general importance is therefore limited. Bear it in mind in the event of an unexpected response to treatment.

1. Oakley DP, Lautch H. Haloperidol and anticoagulant treatment. *Lancet* (1963) ii, 1231.

Indanediones + Oxaceprol

An isolated report describes a marked reduction in the response to fluindione in a patient given oxaceprol.

Clinical evidence, mechanism, importance and management

A 77-year-old woman with hypertension and atrial fibrillation, taking propafenone, furosemide, enalapril and **fluindione** 15 mg daily, started taking oxaceprol 300 mg daily. Within 2 days her Quick Time had risen from 26% to 57% and by the end of the week to 65%. When the oxaceprol was withdrawn, her Quick value returned to its previous range of 23 to 30%.[1] The mechanism for this effect is not understood. The general importance of this interaction is unclear, but bear it in mind when prescribing oxaceprol and **fluindione**. Be alert for the need to modify the anticoagulant dose.

1. Bannwarth B, Tréchot P, Mathieu J, Froment J, Netter P. Interaction oxacéprol-fluindione. *Therapie* (1990) 45, 162–3.

Rivaroxaban + Antiplatelet drugs or NSAIDs

Neither aspirin nor naproxen alter the pharmacokinetics of rivaroxaban, or cause a clinically relevant change in the anticoagulant effects of rivaroxaban. However, the bleeding time during concurrent use may be slightly prolonged. Note that all NSAIDs and antiplatelets increase the risk of bleeding, and concurrent use with rivaroxaban may possibly increase this risk.

Clinical evidence

(a) Aspirin

In a controlled study in 13 healthy subjects, aspirin 500 mg on day one then 100 mg on day 2 had no effect on the pharmacokinetics of a single 15-mg dose of oral rivaroxaban given at the same time as aspirin on day 2. Concurrent use slightly increased the bleeding time (by 2.28 minutes) compared with aspirin alone. Rivaroxaban did not alter the effect of aspirin on platelet aggregation and aspirin did not alter the effects of rivaroxaban on clotting parameters (inhibition of factor Xa activity, prolongation of prothrombin time, aPTT and HepTest).[1]

(b) Clopidogrel

The manufacturer of rivaroxaban reports that no pharmacokinetic interaction occurred in patients given rivaroxaban with clopidogrel 300 mg as a single dose followed by 75 mg daily. However, an increase in bleeding times was reported in some patients.[2]

(c) NSAIDs

In a controlled study in 11 healthy subjects, **naproxen** 500 mg daily on two consecutive days was given with a single 15-mg dose of oral rivaroxaban on the second day. Concurrent use increased bleeding time by a mean of 3.43 minutes compared with naproxen alone, and one subject had a greater increase. **Naproxen** slightly increased the rivaroxaban AUC (by 10%), but this was not statistically significant. Naproxen did not have any clinically relevant effect on the pharmacodynamics of rivaroxaban (prolongation of aPTT, prothrombin time and HepTest and inhibition of factor Xa activity).[3]

Mechanism

Rivaroxaban (a inhibitor of activated factor X) alone does not increase the bleeding time, but it appears to increase this effect with aspirin and NSAIDs. There is the possibility that some patients might be at increased risk of bleeding on concurrent use.

Importance and management

The pharmacological studies described show that the pharmacokinetics of rivaroxaban are not changed by aspirin and naproxen, and that, in general, there is only a minor increase in bleeding time. Nevertheless, it would be prudent to use NSAIDs and antiplatelet drugs, such as aspirin and clopidogrel, with caution because of the possible increased risk of haemorrhage.[2] Additional care should also be taken in those patients given combination antiplatelet therapies. Note that aspirin and naproxen do not affect the clotting parameters used to monitor the effect of rivaroxaban.

1. Kubitza D, Becka M, Mueck W, Zuehlsdorf M. Safety, tolerability, pharmacodynamics, and pharmacokinetics of rivaroxaban—an oral, direct factor Xa inhibitor—are not affected by aspirin. *J Clin Pharmacol* (2006) 46, 981–90.
2. Xarelto (Rivaroxaban). Bayer plc. UK Summary of product characteristics, May 2009.
3. Kubitza D, Becka M, Mueck W, Zuehlsdorf M. Rivaroxaban (BAY 59-7939) – an oral, direct Factor Xa inhibitor – has no clinically relevant interaction with naproxen. *Br J Clin Pharmacol* (2007) 63, 469–76.

Rivaroxaban + Miscellaneous

Ketoconazole and ritonavir can increase rivaroxaban levels and increase the risk of bleeding: other azoles may interact similarly, although fluconazole is likely to interact to a lesser extent. Clarithromycin and erythromycin may cause a small increase in rivaroxaban levels. Rifampicin (rifampin) a potent CYP3A4 inducer) reduces the levels of rivaroxaban: other potent CYP3A4 inducers are predicted to interact similarly. Food moderately increases the oral absorption of rivaroxaban, but antacids and ranitidine have no effect. Atorvastatin, digoxin and midazolam do not interact with rivaroxaban.

Clinical evidence, mechanism, importance and management

(a) Anticoagulants

Enoxaparin does not affect the pharmacokinetics of rivaroxaban; however, the concurrent use of single doses of rivaroxaban 10-mg and enoxaparin 40-mg had an additive effect on anti-factor Xa levels, with no additional effects on either prothrombin time or the aPTT. The manufacturers advise caution in patients taking other drugs that affect coagulation such as anticoagulants (not specified) due to the increased risk of additive bleeding effects.[1]

(b) CYP3A4 inducers

The manufacturer reports that **rifampicin** reduces the AUC of rivaroxaban by about 50%, with an associated reduction in its anticoagulant effects. Therefore they recommend caution with concurrent use of other strong inducers of CYP3A4 such as **carbamazepine**, **phenobarbital**, **phenytoin**, and **St John's wort**. If possible, it would be prudent to consider using an alternative drug; however, if this is not possible, consider monitoring the prothrombin time to ensure the anticoagulant effect of rivaroxaban is maintained.[1]

(c) CYP3A4 and P-glycoprotein inhibitors

In a clinical study, **ketoconazole** 400 mg daily increased the maximum levels and AUC of rivaroxaban by 70% and 2.6-fold, respectively. Similarly, **ritonavir** 600 mg twice daily increased the maximum levels and AUC of rivaroxaban by 60% and 2.5-fold, respectively. In both cases the pharmacodynamic effects of rivaroxaban were increased, which may increase the risk of bleeding.[1]

Rivaroxaban is metabolised by the cytochrome P450 isoenzyme CYP3A4 and is also a substrate for P-glycoprotein. Ritonavir and ketoconazole are considered to be potent inhibitors of both CYP3A4 and P-glycoprotein, and therefore concurrent use increases rivaroxaban levels. The manufacturers therefore recommend against the concurrent use of rivaroxaban with ketoconazole or ritonavir. They also suggest that other azole antifungals (they name **itraconazole**, **posaconazole** and **voriconazole**) may interact similarly.[1] **Fluconazole** is predicted to have less effect on rivaroxaban levels than the other azoles, and therefore the manufacturers recommend caution on concurrent use. It would therefore seem prudent to monitor the prothrombin time more frequently if **fluconazole** is given. Other less potent inhibitors of CYP3A4 and P-glycoprotein have less effect on rivaroxaban levels. **Clarithromycin** 500 mg twice daily increased the maximum levels and AUC of rivaroxaban by 40% and 50%, respectively; and **erythromycin** 500 mg three times daily increased the maximum levels and AUC of rivaroxaban by 30%.[1] These changes were not considered to be clinically relevant.

(d) Drugs that affect gastric pH

In a controlled study in fasted healthy subjects, simultaneous administration of a single 10-mL dose of an **aluminium/magnesium hydroxide** antacid (*Maalox*) had no effect on the pharmacokinetics or pharmacodynamics of a single 30-mg dose of oral rivaroxaban.[2] Similarly, in a study in 12 healthy subjects, pretreatment with **ranitidine** 150 mg twice daily for 3 days did not alter the pharmacokinetics or pharmacodynamics of single dose rivaroxaban.[2] These studies show that alteration of the gastric pH does not affect rivaroxaban absorption. On the basis of these studies, no interaction would be anticipated with antacids or ranitidine in clinical use.

(e) Food

In controlled studies in healthy subjects, the absorption of rivaroxaban was moderately increased and delayed when it was given within 30 minutes of a high-fat, high-calorie meal, when compared with the fasted state, as reflected by an increase in the AUC of 28% and an increase in time to maximum level from 2.75 hours to 4 hours. Elimination was not altered. The increase in inhibition of factor Xa activity mirrored the increase in absorption (26% increase). Further study did not find any difference between the effect of a high-carbohydrate meal and a high-fat meal.[2] In clinical studies in elective surgery, rivaroxaban has been given within one to 2 hours of food before surgery, and in the fasting state in the postoperative period. The authors of this report studies speculate that the moderately smaller peak levels of rivaroxaban in the fasted state may be somewhat beneficial for wound haemostasis in the postoperative period.[2] The manufacturers state that rivaroxaban may be taken with or without food.[1]

(f) Other drugs

The manufacturers note that rivaroxaban has no significant pharmacokinetic or pharmacodynamic interaction with midazolam, digoxin or atorvastatin. No dose adjustments are therefore necessary if these drugs are given together. This also suggests that rivaroxaban has no clinically rele-

vant effect on drugs that are substrates of P-glycoprotein or the cytochrome P450 isoenzyme CYP3A4.[1]

1. Xarelto (Rivaroxaban). Bayer plc. UK Summary of product characteristics, May 2009.
2. Kubitza D, Becka M, Zuehlsdorf M, Mueck W. Effect of food, an antacid, and the H_2 antagonist ranitidine on the absorption of BAY 59-7939 (rivaroxaban), an oral, direct factor Xa inhibitor, in healthy subjects. *J Clin Pharmacol* (2006) 46, 549–58.

Thrombin inhibitors + Antiplatelet drugs

Low-dose aspirin does not appear to alter the pharmacokinetics or pharmacodynamic effects of argatroban. Neither abciximab nor eptifibatide appear to alter argatroban pharmacokinetics. The concurrent use of aspirin and high-dose dabigatran slightly increased the risk of major haemorrhage. There is no pharmacodynamic interaction between bivalirudin and aspirin, ticlopidine, clopidogrel, abciximab, eptifibatide or tirofiban.

Clinical evidence, mechanism, importance and management

A. Synthetic thrombin inhibitors

(a) Argatroban

In a study in healthy subjects, pretreatment with oral **aspirin** 162.5 mg, given 26 and 2 hours before argatroban 1 microgram/kg per minute over 4 hours, caused no changes in the pharmacokinetics or pharmacodynamic effects of the argatroban.[1]

In a large clinical study of the concurrent use of argatroban and a glycoprotein IIb/IIIa-receptor antagonist (**abciximab** or **eptifibatide**) in patients undergoing percutaneous coronary intervention, using a population model assessment, the pharmacokinetics of argatroban were similar to those previously seen in healthy subjects. This suggests that neither **abciximab** nor **eptifibatide** alter argatroban pharmacokinetics.[2] Nevertheless, the manufacturer warns that the use of argatroban with **antiplatelet drugs** may increase the risk of bleeding.[3]

(b) Dabigatran

In a study in patients with atrial fibrillation given dabigatran 50 to 300 mg twice daily alone or with **aspirin** 81 mg or 325 mg daily, the risk of major haemorrhage was higher with concurrent use of **aspirin** and dabigatran 300 mg twice daily (4 of 64 patients) than with dabigatran 300 mg twice daily alone (0 of 105 patients). Three major haemorrhages occurred at the 325 mg **aspirin** dose and one at the 81 mg dose, and **aspirin** was subsequently stopped in all patients receiving the 300 mg twice daily dose of dabigatran. With the lower doses of dabigatran, the total number of bleeding events tended to be higher in the groups also receiving **aspirin** (about 22% versus 15% for the 150 mg twice daily dabigatran dose, and 9.5% versus 3.4% for the 50 mg twice daily dose).[4] Note that this is not a licensed indication for dabigatran, and the 600 mg daily dose is much higher than that recommended in elective orthopaedic surgery.

A study in patients undergoing total hip replacements and randomised to receive either dabigatran 150 mg or 220 mg daily or enoxaparin allowed patients to continue to take low-dose **aspirin** (less than 160 mg daily) during the study. The full paper gave no specific data on the distribution of **aspirin** use between the groups or specifically if **aspirin** use contributed to the risk of bleeding;[5] however, some data were given in a subsequent letter.[6] The authors stated that there was no significant difference in efficacy or safety outcomes among patients receiving low-dose **aspirin** and those not taking **aspirin**, although the proportion of patients taking **aspirin** with dabigatran was small, at about 4 to 5%.[6]

The manufacturer states that drugs that may enhance the risk of haemorrhage should not be given concurrently or should be given with caution with dabigatran. They specifically recommend avoiding the use of the antiplatelet drugs **clopidogrel**, **ticlopidine**, **glycoprotein IIb/IIIa inhibitors**, and **sulfinpyrazone**, and say that if concurrent use is essential, patients should be closely monitored for signs and symptoms of bleeding.[7] Although not specifically mentioned, it would be prudent to similarly monitor the concurrent use of antiplatelet doses of **aspirin**.

B. Hirudins

(a) Bivalirudin

The UK manufacturer says that no pharmacodynamic interactions were detected when bivalirudin was used with platelet inhibitors, including **aspirin**, **ticlopidine**, **clopidogrel**, **abciximab**, **eptifibatide**, and **tirofiban**.[8] The US manufacturer states that bivalirudin is intended for use with **aspirin** 300 to 325 mg daily, and has been studied only in patients receiving **aspirin**.[9] Both manufacturers state that bivalirudin may be used with a glycoprotein IIb/IIIa-receptor antagonist[8,9] (e.g. **abciximab**, **eptifibatide**, **tirofiban**). Nevertheless, the US manufacturer states that in clinical studies, the concurrent use of bivalirudin with these inhibitors was associated with increased risks of major bleeding events compared to patients not receiving them.[9] The UK manufacturer recommends regular monitoring of haemostasis when bivalirudin is used with platelet inhibitors.[8]

(b) Lepirudin

The manufacturers of lepirudin say that no formal interaction studies have been done but they reasonably warn about the increased risks of bleeding if antiplatelet drugs such as **clopidogrel**, **ticlopidine**, **abciximab**, **eptifibatide** or **tirofiban** are used concurrently.[10,11]

1. Clarke RJ, Mayo G, FitzGerald GA, Fitzgerald DJ. Combined administration of aspirin and a specific thrombin inhibitor in man. *Circulation* (1991) 83, 1510–8.
2. Cox DS, Kleiman NS, Boyle DA, Aluri J, Parchman G, Holdbrook F, Fossler MJ. Pharmacokinetics and pharmacodynamics of argatroban in combination with a platelet glycoprotein IIB/IIIA receptor antagonist in patients undergoing percutaneous coronary intervention. *J Clin Pharmacol* (2004) 44, 981–90.
3. Argatroban. GlaxoSmithKline. US Prescribing information, March 2009.
4. Ezekowitz MD, Reilly PA, Nehmiz G, Simmers TA, Nagarakanti R, Parcham-Azad K, Pedersen KE, Lionetti DA, Stangier J, Wallentin L. Dabigatran with or without concomitant aspirin compared with warfarin alone in patients with nonvalvular atrial fibrillation (PETRO study). *Am J Cardiol* (2007) 100, 1419–26.
5. Eriksson BI, Dahl OE, Rosencher N, Kurth AA, van Dijk CN, Frostick SP, Prins MH, Hettiarachchi R, Hantel S, Schnee J, Büller HR, for the RE-NOVATE study group. Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial. *Lancet* (2007) 370, 949–56.
6. Eriksson BI, Hantel. Dabigatran versus enoxaparin after total hip replacement. Authors' reply. *Lancet* (2007) 370, 2003.
7. Pradaxa (Dabigatran etexilate). Boehringer Ingelheim Ltd. UK Summary of product characteristics, October 2009.
8. Angiox (Bivalirudin). The Medicines Company. UK Summary of product characteristics, November 2009.
9. Angiomax (Bivalirudin). The Medicines Company. US Prescribing information, December 2005.
10. Refludan (Lepirudin). Celgene Ltd. UK Summary of product characteristics, March 2007.
11. Refludan (Lepirudin). Bayer HealthCare Pharmaceuticals Inc. US Prescribing information, December 2006.

Thrombin inhibitors + Other drugs that affect coagulation

The use of argatroban with warfarin and related oral anticoagulants has an effect on the measurement of the INR, and the manufacturer provides equations to adjust for this. Argatroban does not alter warfarin pharmacokinetics. The manufacturers warn of the increased bleeding risks if argatroban, bivalirudin, dabigatran, or lepirudin are used with other anticoagulants.

Clinical evidence, mechanism, importance and management

A. Synthetic thrombin inhibitors

(a) Argatroban

In a study in 12 healthy subjects, argatroban 1.25 micrograms/kg per minute was given for 100 hours, with a single 7.5-mg dose of **warfarin** given at hour 4. Neither drug affected the pharmacokinetics of the other. The single dose of **warfarin** in this study did not add to the anticoagulant effect of argatroban.[1] However, a previous study found that the INR and prothrombin time were increased when **warfarin** (7.5 mg on day one, then 3 to 6 mg for 9 days) was used with argatroban (1 to 4 micrograms/kg per minute for 5 hours daily for 11 days), but without any additional effect on vitamin K-dependent factor Xa activity.[2] A similar finding was reported in a study using **acenocoumarol** or **phenprocoumon** and argatroban.[3]

This means that the INR reading needs to be corrected before it can be used as a clinical indicator of coagulation status when **warfarin** or other vitamin K antagonists (i.e. any coumarin or **indanedione**) are used with argatroban. The manufacturer provides detailed information on how this should be done while switching from argatroban to **warfarin**.[4]

Argatroban is currently licensed for use in patients with or at risk of heparin-induced thrombocytopenia, and the manufacturer states that if **heparin** is to be switched to argatroban, sufficient time for the effect of heparin on the aPTT to decrease should be allowed before starting argatroban. They recommend that all parenteral anticoagulants should be discontinued before starting argatroban.[4]

(b) Dabigatran

The manufacturer states that drugs that may enhance the risk of haemorrhage should not be given concurrently or should be given with caution to patients receiving dabigatran. They specifically recommend avoiding the concurrent use of dabigatran and vitamin K antagonist anticoagulants[5] (i.e. **coumarins** and **indanediones**). They also advise against the use of parenteral anticoagulants such as **heparin**, heparin derivatives, **low-molecular-weight heparins**, **dextrans**, **desirudin** and **fondaparinux**, although they note that **heparin** can be given at doses necessary to maintain a patent central venous or arterial catheter. They recommend waiting 24 hours after the last dose of dabigatran before starting parenteral anticoagulants. They also state that, as there are no data available on switching patients from a parenteral anticoagulant to dabigatran, dabigatran should not be started before the next scheduled dose of the parenteral anticoagulant would have been due.[5]

B. Hirudins

(a) Bivalirudin

In the US, the manufacturers state that the concurrent use of bivalirudin with **heparin** or **warfarin** was associated with increased risks of major bleeding events, when compared with patients not receiving these drugs concurrently.[6] In the UK, the manufacturers state that bivalirudin can be started 30 minutes after stopping intravenous **heparin**, but 8 hours should be left after stopping a **low-molecular-weight heparin** given subcutaneously.[7] They recommend regular monitoring of haemostasis when bivalirudin is used with other anticoagulants.[7]

(b) Lepirudin

The manufacturers of lepirudin say that no formal interaction studies have been done but they reasonably warn about the increased risks of bleeding if vitamin K antagonists (i.e. **coumarins** and **indanediones**) are used concurrently.[8,9] Their recommendation for changing from lepirudin to an oral anticoagulant is to reduce the lepirudin dose gradually to reach an aPTT ratio just above 1.5 before beginning the oral anticoagulant, which should be started at the intended maintenance dose without a loading dose. They suggest that parenteral anticoagulation should be continued for 4 to 5 days, and then stopped when the INR stabilises within the target range.[8,9]

1. Brown PM, Hursting MJ. Lack of pharmacokinetic interactions between argatroban and warfarin. *Am J Health-Syst Pharm* (2002) 59, 2078–83.
2. Sheth SB, DiCicco RA, Hursting MJ, Montague T, Jorkasky DK. Interpreting the international normalized ratio (INR) in individuals receiving argatroban and warfarin. *Thromb Haemost* (2001) 85, 435–40. Correction. ibid. 86, 727.
3. Harder S, Graff J, Klinkhardt U, von Hentig N, Walenga JM, Watanabe H, Osakabe M, Breddin HK. Transition from argatroban to oral anticoagulation with phenprocoumon or acenocoumarol: effects on prothrombin time, activated partial thromboplastin time, and Ecarin clotting time. *Thromb Haemost* (2004) 91, 1137–45.
4. Argatroban. GlaxoSmithKline. US Prescribing information, March 2009.
5. Pradaxa (Dabigatran etexilate). Boehringer Ingelheim Ltd. UK Summary of product characteristics, October 2009.
6. Angiomax (Bivalirudin). The Medicines Company. US Prescribing information, December 2005.
7. Angiox (Bivalirudin). The Medicines Company. UK Summary of product characteristics, November 2009.
8. Refludan (Lepirudin). Celgene Ltd. UK Summary of product characteristics, March 2007.
9. Refludan (Lepirudin). Bayer HealthCare Pharmaceuticals Inc. US Prescribing information, December 2006.

Thrombin inhibitors + Thrombolytics

The risks of bleeding are expected to be increased if argatroban, bivalirudin, dabigatran or lepirudin are used with thrombolytics.

Clinical evidence, mechanism, importance and management

A. Synthetic thrombin inhibitors

(a) Argatroban

The manufacturer of argatroban notes that, in patients with acute myocardial infarction receiving both argatroban and a thrombolytic (**streptokinase** or **alteplase**), the incidence of intracranial bleeding was 1% (8 out of 810 patients).[1] They therefore state that the safety and effectiveness of argatroban with thrombolytics has not been established, and that concurrent use may increase the risk of bleeding.[1]

(b) Dabigatran

The manufacturer of dabigatran advises against the use of thrombolytics (e.g. **streptokinase**, **alteplase**) because of the potential increased risk of haemorrhage.[2]

B. Hirudins

(a) Bivalirudin

The US manufacturer of bivalirudin states that the concurrent use of thrombolytics was associated with increased risks of major bleeding events.[3]

(b) Lepirudin

The manufacturers of lepirudin say that no formal interaction studies have been undertaken but they reasonably warn that the concurrent use of lepirudin and thrombolytics (they name **alteplase** and **streptokinase**) may increase the risk of bleeding complications and considerably enhance the effect of lepirudin on the aPTT.[4,5] The UK manufacturers advise a dose reduction of lepirudin with concurrent use; however, they state that the optimal dose for concurrent use with a thrombolytic is not known.[4]

1. Argatroban. GlaxoSmithKline. US Prescribing information, March 2009.
2. Pradaxa (Dabigatran etexilate). Boehringer Ingelheim Ltd. UK Summary of product characteristics, October 2009.
3. Angiomax (Bivalirudin). The Medicines Company. US Prescribing information, December 2005.
4. Refludan (Lepirudin). Celgene Ltd. UK Summary of product characteristics, March 2007.
5. Refludan (Lepirudin). Bayer HealthCare Pharmaceuticals Inc. US Prescribing information, December 2006.

Thrombin inhibitors; Argatroban + Erythromycin

Erythromycin has no effect on the pharmacokinetics or anticoagulant activity of argatroban.

Clinical evidence, mechanism, importance and management

In 10 healthy subjects, erythromycin 500 mg four times daily was given for 7 days with a 5-hour intravenous infusion of argatroban 1 microgram/kg per minute on day 6. Erythromycin had no effect on the pharmacokinetics of argatroban, and had no effect on the argatroban-induced prolongation of the aPTT.[1] No special precautions are likely to be required on the concurrent use of argatroban and erythromycin.

1. Tran JQ, Di Cicco RA, Sheth SB, Tucci M, Peng L, Jorkasky DK, Hursting MJ, Benincosa LJ. Assessment of the potential pharmacokinetic and pharmacodynamic interactions between erythromycin and argatroban. *J Clin Pharmacol* (1999) 39, 513–19.

Thrombin inhibitors; Argatroban + Lidocaine

No pharmacokinetic interaction occurs between argatroban and lidocaine, and lidocaine does not appear to alter the anticoagulant effects of argatroban.

Clinical evidence, mechanism, importance and management

In a study in 12 healthy subjects, lidocaine 2 mg/kg per hour was infused for 16 hours (after a loading dose of 1.5 mg/kg over 10 minutes) alone, then with intravenous argatroban 1.5 micrograms/kg per minute for 16 hours. Concurrent use did not affect the pharmacokinetics of either drug, and lidocaine did not alter the effect of argatroban on aPTT.[1] No special precautions appear likely to be necessary on concurrent use of lidocaine and argatroban.

1. Inglis AML, Sheth SB, Hursting MJ, Tenero DM, Graham AM, DiCicco RA. Investigation of the interaction between argatroban and acetaminophen, lidocaine, or digoxin. *Am J Health-Syst Pharm* (2002) 59, 1257–66.

Thrombin inhibitors; Argatroban + Paracetamol (Acetaminophen)

No pharmacokinetic interaction occurs between argatroban and paracetamol, and paracetamol does not alter the anticoagulant effects of argatroban.

Clinical evidence, mechanism, importance and management

In 11 healthy subjects, paracetamol 1 g every 6 hours for 5 doses had no effect on the pharmacokinetics of a 19-hour infusion of argatroban 1.5 micrograms/kg per minute, started with the second dose of paraceta-

mol. In addition, argatroban had no effect on paracetamol pharmacokinetics. Paracetamol did not alter the effect of argatroban on the aPTT.[1] No special precautions appear necessary on the concurrent use of paracetamol and argatroban.

1. Inglis AML, Sheth SB, Hursting MJ, Tenero DM, Graham AM, DiCicco RA. Investigation of the interaction between argatroban and acetaminophen, lidocaine, or digoxin. *Am J Health-Syst Pharm* (2002) 59, 1257–66.

Thrombin inhibitors; Dabigatran + Amiodarone and other drugs that affect P-glycoprotein

Amiodarone increases the levels of dabigatran. Verapamil, clarithromycin and quinidine are predicted to have a similar effect. Rifampicin and St John's wort are predicted to decrease the efficacy of dabigatran.

Clinical evidence

The manufacturer briefly notes that in an interaction study, amiodarone increased the AUC and maximum concentration of dabigatran by 60% and 50%, respectively. Dabigatran did not affect the pharmacokinetics of amiodarone and of its active metabolite.[1]

Mechanism

Dabigatran etexilate, the prodrug for the active dabigatran, is a substrate for P-glycoprotein and it is thought that the interaction may be due to inhibition of P-glycoprotein by amiodarone; however, the mechanism has not been clarified.[1]

Importance and management

Evidence for an interaction between dabigatran and amiodarone is limited. The manufacturer recommends that the dose of dabigatran should be reduced to 150 mg daily in patients who are also taking amiodarone, and this seems a prudent precaution. Note that amiodarone has a long half-life and therefore the potential for an interaction with dabigatran may still exist for weeks after stopping amiodarone.[1]

On the basis of the predicted mechanism for this interaction, the manufacturer recommends caution when dabigatran is given with other drugs that are potent inhibitors of P-glycoprotein. They specifically contraindicate the concurrent use of **quinidine** and caution use with **verapamil** and **clarithromycin**[1] (for a list of other P-glycoprotein inhibitors, see 'Table 1.6', (p.8)). The dose of dabigatran should be reduced to 150 mg daily with concurrent use of verapamil, and a further dose reduction to 75 mg daily should also be considered in those patients with moderate renal impairment.[1]

Close monitoring for signs of bleeding or anaemia is required on concurrent use, and dabigatran should be discontinued if severe bleeding occurs. Conversely, the manufacturer of dabigatran recommends caution when it is given with drugs that are potent inducers of P-glycoprotein, such as **rifampicin** (**rifampin**) and **St John's wort**.[1] Note that dabigatran is used without routine coagulation monitoring, but it can be monitored with aPTT and ecarin clotting time (ECT).[2,3] ECT is the more sensitive and accurate measure, but is not widely available. Study of the pharmacokinetic interaction of these drugs with dabigatran would be helpful in assessing the relevance of any interaction.

1. Pradaxa (Dabigatran etexilate). Boehringer Ingelheim Ltd. UK Summary of product characteristics, October 2009.
2. Liesenfeld K-H, Schäfer HG, Trocóniz IF, Tillmann C, Eriksson BI, Stangier J. Effects of the direct thrombin inhibitor dabigatran on ex vivo coagulation time in orthopaedic surgery patients: a population model analysis. *Br J Clin Pharmacol* (2006) 62, 527–37.
3. Stangier J, Rathgen K, Stähle H, Gansser D, Roth W. The pharmacokinetics, pharmacodynamics and tolerability of dabigatran etexilate, a new oral direct thrombin inhibitor, in healthy male subjects. *Br J Clin Pharmacol* (2007) 64, 292–303.

Thrombin inhibitors; Dabigatran + Miscellaneous

No significant pharmacokinetic interaction occurs between dabigatran and atorvastatin, diclofenac, or digoxin. However, concurrent use with NSAIDs might increase the risk of haemorrhage, and should be well monitored. Ranitidine has no effect on the absorption of dabigatran. Pantoprazole modestly reduces the bioavailability of dabigatran but does not reduce its therapeutic efficacy.

Clinical evidence, mechanism, importance and management

(a) Atorvastatin

In a study in 22 healthy subjects, atorvastatin 80 mg daily for 4 days slightly reduced the overall exposure to dabigatran 150 g twice daily taken for 4 days by a minor 16%.[1] Atorvastatin is a substrate of the cytochrome P450 isoenzyme CYP3A4, and the results of this study suggest that dabigatran does not significantly affect CYP3A4. These findings confirmed *in vitro* interaction studies, which found that dabigatran does not inhibit or induce CYP3A4. Therefore no special precautions are necessary on the concurrent use of atorvastatin and dabigatran.

(b) Digoxin

In a study in 24 healthy subjects, there was no evidence of a pharmacokinetic interaction between dabigatran and digoxin.[2] Digoxin is a substrate of P-glycoprotein, and the findings of this study suggest that dabigatran does not alter P-glycoprotein. No special precautions are therefore needed on the concurrent use of dabigatran and digoxin.

(c) Food

In a study in 18 healthy subjects, although food delayed the time to the peak plasma concentration of dabigatran by around 2 hours, it had no effect on the overall bioavailability (AUC) of dabigatran when compared with fasting conditions.[3] Therefore, the manufacturer states that it may be taken with or without food.[2]

(d) NSAIDs

No pharmacokinetic interaction occurred between dabigatran and **diclofenac** in a study in healthy subjects.[2] Diclofenac is a substrate of the cytochrome P450 isoenzyme CYP2C9, and the findings confirmed *in vitro* interaction studies, which found that dabigatran does not inhibit or induce CYP2C9. Nevertheless, drugs such as the NSAIDs may increase the risk of haemorrhage, and should be used cautiously with dabigatran. The manufacturers advise that patients taking NSAIDs with dabigatran should be closely monitored for signs of bleeding, particularly with NSAIDs that have a half-life of greater than 12 hours.[2] Caution would seem appropriate.

(e) Proton pump inhibitors

In a study in 18 healthy subjects, pre-treatment with **pantoprazole** 40 mg twice daily for 2 days reduced the AUC and maximum concentration of a single 150-mg dose of dabigatran by around 22% and 33%, respectively. However, high intersubject variability in these parameters was reported, which the authors suggested may have been due to the interindividual efficacy of pantoprazole.[3] Similarly, in another study in 35 healthy elderly subjects, **pantoprazole** 40 mg twice daily for 10 days, started 2 days before dabigatran 150 mg twice daily for 7 days, reduced the overall bioavailability of dabigatran by around 20 to 24%. However these decreases in bioavailability did not result in a significant reduction in the anticoagulant effect of dabigatran, as measured by the aPTT and ecarin clotting time (ECT). The pharmacokinetic interaction was slightly greater (29% reduction in bioavailability) when the 4 subjects who did not respond to pantoprazole were excluded, along with the one subject with hypoacidity.[4] This suggests that the effect of pantoprazole on dabigatran absorption might be due to reduced gastric acidity, but see also *Ranitidine*, below.

The effect of pantoprazole on dabigatran pharmacokinetics is modest, and probably unlikely to be clinically relevant. The manufacturer notes that the concurrent use of pantoprazole and other proton pump inhibitors with dabigatran in clinical studies did not result in a reduction in its efficacy and no effects on bleeding were seen.[2] Therefore no dabigatran dose alteration appears to be necessary if dabigatran is given with pantoprazole, and probably also other proton pump inhibitors.

(f) Ranitidine

The manufacturer of dabigatran briefly states that ranitidine had no clinically relevant effect on the extent of absorption of dabigatran.[2] No special precautions are therefore needed on the concurrent use of dabigatran and ranitidine.

1. Stangier J, Rathgen K, Stähle H, Reseski K, Körnicke T, Roth W. Coadministration of dabigatran etexilate and atorvastatin: assessment of potential impact on pharmacokinetics and pharmacodynamics. Am J Cardiovasc Drugs (2009) 9, 59–68.
2. Pradaxa (Dabigatran etexilate). Boehringer Ingelheim Ltd. UK Summary of product characteristics, October 2009.

3. Stangier J, Eriksson BI, Dahl OE, Ahnfelt L, Nehmiz G, Stähle H, Rathgen K, Svärd R. Pharmacokinetic profile of the oral direct thrombin inhibitor dabigatran etexilate in healthy volunteers and patients undergoing total hip replacement. *J Clin Pharmacol* (2005) 45, 555–63.
4. Stangier J, Stähle H, Rathgen K, Fuhr R. Pharmacokinetics and pharmacodynamics of the direct oral thrombin inhibitor dabigatran in healthy elderly subjects. Clin Pharmacokinet (2008) 47, 47–59.

Thrombin inhibitors; Ximelagatran + Miscellaneous

Aspirin did not alter the pharmacokinetics of melagatran, the active metabolite of ximelagatran, or its effects on the aPTT, but the combination had additive effects on bleeding time. Erythromycin and azithromycin increase the AUC of melagatran, the active metabolite of ximelagatran, and cause a small additional effect on coagulation parameters. The concurrent use of amiodarone and ximelagatran caused a slight increase in the AUC of melagatran and a slight decrease in the AUC of amiodarone.
No pharmacokinetic interaction occurs between ximelagatran and atorvastatin or digoxin, and concurrent use does not change coagulation status. No pharmacokinetic interaction appears to occur between ximelagatran and diazepam, diclofenac or nifedipine. This suggests that ximelagatran has no clinically relevant effect on drugs that are substrates for the cytochrome P450 isoenzymes CYP2C9, CYP2C19, and CYP3A4.

Clinical evidence, mechanism, importance and management

(a) Amiodarone

In a placebo-controlled study in 26 healthy subjects, ximelagatran 36 mg was given every 12 hours for 8 days with a single 600-mg dose of amiodarone on day 4. Concurrent use resulted in a slight 21% increase in the AUC of melagatran (the active metabolite of ximelagatran), and a slight 15% decrease in the AUC of amiodarone. Amiodarone did not alter the effect of melagatran on aPTT.[1] The mechanism of this interaction is unknown. The pharmacokinetic changes seen were not considered to be clinically relevant.

(b) Antibacterials

In 16 healthy subjects, **erythromycin** 500 mg three times daily was given for 5 days with a single 36-mg oral dose of ximelagatran given before erythromycin, and on day 5. Erythromycin increased the AUC of melagatran (the active metabolite of ximelagatran) by 82%, and the maximum plasma level by 76%. This resulted in a small increase in peak aPTT from 41 seconds to 44 seconds.[2] In another study, healthy subjects were given a single 36-mg dose of ximelagatran on day 1 and 5 of a 5-day course of azithromycin (500 mg on day 1 followed by 250 mg on days 2 to 5). **Azithromycin** increased the AUC of melagatran by 60% and caused a minor 15% increase in the peak aPTT. **Cefuroxime** (250 mg twice daily for 9 doses) also caused a minor increase in the AUC of melagatran of 23%, without affecting the aPTT, and **amoxicillin**, **ciprofloxacin** and **doxycycline** did not interact.[3]

Ximelagatran is not metabolised by cytochrome P450 isoenzymes, so the known inhibitory effect of erythromycin on CYP3A4 is not thought to be the mechanism for this interaction. The mechanism may involve inhibition of transport proteins, possibly P-glycoprotein.[2,3]

Based on the findings of a pharmacokinetic interaction with a small pharmacodynamic effect it would certainly be prudent to be cautious if ximelagatran is used in patients taking azithromycin or erythromycin, although note that the pharmacodynamic effect was small and the combination of erythromycin and ximelagatran was well tolerated.[2]

(c) Aspirin

In young healthy subjects, aspirin 450 mg the day before, and 150 mg just before melagatran had no effect on the pharmacokinetics of intravenous melagatran 4.12 mg. In addition, aspirin did not alter the increases seen in aPTT or activated clotting time seen with melagatran. Both aspirin and melagatran increased bleeding time, and the increase with the combination was additive.[4]

(d) Atorvastatin

In 15 healthy subjects, ximelagatran 36 mg twice daily was given for 5 days with a single 40-mg dose of atorvastatin on day 4. There was no change in the pharmacokinetics of either drug or their active metabolites. Atorvastatin did not alter the effect of melagatran on aPTT.[5] No special precautions are expected to be needed if ximelagatran is used in patients taking atorvastatin.

(e) Diazepam

In 24 healthy subjects, ximelagatran 24 mg twice daily was given for 8 days with a single 100-microgram/kg intravenous dose of diazepam on day 3. There was no change in the pharmacokinetics of either drug or of *N*-desmethyl-diazepam.[6]

Metabolism of diazepam to *N*-desmethyl-diazepam occurs via the cytochrome P450 isoenzyme CYP2C19, and *in vitro* studies had shown that melagatran was a weak inhibitor of this isoenzyme.[6] However, the lack of a pharmacokinetic interaction with diazepam suggests that no clinically relevant interaction occurs, and is also unlikely with other CYP2C19 substrates[6] by this mechanism (for a list see 'Table 1.3', (p.6)).

(f) Diclofenac

In a single-dose study in 24 healthy subjects, simultaneous administration of ximelagatran 24 mg and enteric-coated diclofenac 50 mg caused no change in the pharmacokinetics of either drug. In this study, there was also no additional effect of the combination on activated partial thromboplastin time or capillary bleeding time, suggesting that no pharmacodynamic interaction occurs.[6]

Diclofenac is a substrate for the cytochrome P450 isoenzyme CYP2C9, and *in vitro* study has shown that ximelagatran and melagatran are weak inhibitors of this isoenzyme.[6] However, the lack of a pharmacokinetic interaction with diclofenac suggests that no clinically relevant interaction occurs, and is also unlikely with other CYP2C9 substrates[6] by this mechanism (for a list see 'Table 1.3', (p.6)).

(g) Digoxin

In a double-blind, crossover study, 16 healthy subjects were given oral ximelagatran 36 mg twice daily or placebo for 8 days and a single 500-microgram oral dose of digoxin on day 4. Ximelagatran had no effects on the pharmacokinetics of digoxin. Similarly, digoxin had no effects on the pharmacokinetics of melagatran (the active metabolite) when ximelagatran was given orally. The anticoagulant effect of melagatran (measured as aPTT prolongation) was not altered by digoxin.[7]

(h) Nifedipine

In a single-dose study in 34 healthy subjects, giving ximelagatran 24 mg four hours after slow-release nifedipine 60 mg caused no change in the pharmacokinetics of either drug.[6]

Nifedipine is a substrate for the cytochrome P450 isoenzyme CYP3A4, and *in vitro* studies had shown that ximelagatran metabolites might be weak inhibitors of this isoenzyme.[6] However, the lack of a pharmacokinetic interaction with nifedipine suggests that no clinically relevant interaction occurs, and is also unlikely with other CYP3A4 substrates[6] by this mechanism (for a list see 'Table 1.4', (p.6)).

1. Teng R, Sarich TC, Eriksson UG, Hamer JE, Gillette S, Schützer K-M, Carlson GF, Knowey PR. A pharmacokinetic study of the combined administration of amiodarone and ximelagatran, an oral direct thrombin inhibitor. *J Clin Pharmacol* (2004) 44, 1063–71.
2. Eriksson UG, Dorani H, Karlsson J, Fritsch H, Hoffmann K-J, Olsson L, Sarich TC, Wall U, Schützer K-M. Influence of erythromycin on the pharmacokinetics of ximelagatran may involve inhibition of P-glycoprotein-mediated excretion. *Drug Metab Dispos* (2006) 34, 775–82.
3. Dorani H, Schützer K-M, Sarich TC, Wall U, Logren U, Ohlsson L, Eriksson UG. Pharmacokinetics and pharmacodynamics of the oral direct thrombin inhibitor ximelagatran co-administered with different classes of antibiotics in healthy volunteers. *Eur J Clin Pharmacol* (2007) 63, 571–81.
4. Fager G, Cullberg M, Eriksson-Lepkowska M, Frison L, Eriksson UG. Pharmacokinetics and pharmacodynamics of melagatran, the active form of the oral direct thrombin inhibitor ximelagatran, are not influenced by acetylsalicylic acid. *Eur J Clin Pharmacol* (2003) 59, 283–9.
5. Sarich TC, Schützer K-M, Dorani H, Wall U, Kalies I, Ohlsson L, Eriksson UG. No pharmacokinetic or pharmacodynamic interaction between atorvastatin and the oral direct thrombin inhibitor ximelagatran. *J Clin Pharmacol* (2004) 44, 928–34.
6. Bredberg E, Andersson TB, Frison L, Thuresson A, Johansson S, Eriksson-Lepkowska M, Larsson M, Eriksson UG. Ximelagatran, an oral direct thrombin inhibitor, has a low potential for cytochrome P450-mediated drug-drug interactions. *Clin Pharmacokinet* (2003) 42, 765–77.
7. Sarich TC, Schützer K-M, Wollbratt M, Wall U, Kessler E, Eriksson UG. No pharmacokinetic or pharmacodynamic interaction between digoxin and the oral direct thrombin inhibitor ximelagatran in healthy volunteers. *J Clin Pharmacol* (2004) 44, 935–41.

13

Antidiabetics

The antidiabetics are used to control diabetes mellitus, a disease in which there is total or partial failure of the beta-cells within the pancreas to secrete enough insulin, one of the hormones concerned with the handling of glucose. There are two main types of diabetes: one develops early in life and occurs when the ability of the pancreas suddenly, and often almost totally, fails to produce insulin. This type is called type 1, juvenile, or insulin-dependent diabetes (IDDM), and requires insulin replacement therapy. The other form is type 2, maturity-onset, or non-insulin dependent diabetes mellitus (NIDDM), which is most often seen in those over 40 years old. This occurs when the pancreas gradually loses the ability to produce insulin over a period of months or years and/or resistance to the action of insulin develops. It is often associated with being overweight and can sometimes be satisfactorily controlled simply by losing weight and adhering to an appropriate diet. This may then be augmented with oral antidiabetic drugs, and eventually insulin. A classification of the antidiabetics is given in 'Table 13.1', (p.534).

Modes of action of the antidiabetics

A. Parenteral antidiabetics

(a) Amylin analogues

Pramlintide is a synthetic analogue of amylin, a pancreatic hormone involved in glucose homoeostasis. It slows the rate of gastric emptying and reduces appetite. It is given subcutaneously immediately before meals, and is used in patients already receiving insulin.

(b) Incretin mimetics

Exenatide and liraglutide are incretin mimetics that act as a glucagon-like peptide-1 (GLP-1) receptor agonist. This increases insulin secretion when glucose levels are high. These drugs are given subcutaneously, as an adjunct, in patients with type 2 diabetes who are already receiving metformin, a sulfonylurea, or both.

(c) Insulin

Insulin extracted from the pancreatic tissue of pigs and cattle is so similar to human insulin that it can be used as a replacement. However, human insulin, manufactured by genetically engineered microorganisms, is more commonly used. Insulin is usually given by injection in order to bypass the enzymes of the gut, which would digest and destroy it like any other protein. The onset and duration of action of insulin may be prolonged by complexing with zinc or protamine. Various insulin analogues have been developed, which have specific pharmacokinetic profiles. Insulin aspart, glulisine and lispro have a faster onset and shorter duration of action than soluble insulin. Insulin glargine and detemir both have a prolonged duration of action.

An inhaled form of insulin for use in adult patients with diabetes mellitus was launched and subsequently discontinued (*Exubera*), but others are still in development.

B. Oral antidiabetics

(a) Aldose reductase inhibitors

Epalrestat inhibits the enzyme aldose reductase, which converts glucose to sorbitol. The accumulation of sorbitol may play a role in some diabetic complications.

(b) Alpha-glucosidase inhibitors

Acarbose, miglitol and voglibose act against alpha glucosidases and specifically against sucrase in the gut to delay the digestion and absorption of monosaccharides from starch and sucrose.

(c) Biguanides

The mode of action of the biguanides, such as metformin, is obscure, but they do not stimulate the pancreas like the sulfonylureas to release insulin, but appear to facilitate the uptake and utilisation of glucose by the cells in some way. Their use is restricted to type 2 diabetes because they are not effective unless insulin is present.

(d) Dipeptidylpeptidase-4 inhibitors

Saxagliptin, sitagliptin and vildagliptin increase the level of incretin hormones, and so augment insulin secretion, and are principally used in type 2 diabetes in combination with metformin and/or a sulfonylurea.

(e) Meglitinides

The meglitinides (e.g. nateglinide and repaglinide) increase endogenous insulin secretion, and so are used in type 2 diabetes.

(f) Sulfonylureas

The sulfonylurea and other sulfonamide-related compounds such as chlorpropamide and tolbutamide were the first synthetic compounds used in medicine as antidiabetics. Among their actions they stimulate the remaining beta-cells of the pancreas to grow and secrete insulin which, with a restricted diet, controls blood glucose levels and permits normal metabolism to occur. Clearly they can only be effective in those diabetics whose pancreas still has the capacity to produce some insulin, so their use is confined to type 2 diabetes.

(g) Thiazolidinediones

The thiazolidinediones (e.g. rosiglitazone) appear to decrease insulin resistance through activation of gamma-PPAR (peroxisome proliferator-activated receptor). They are used in type 2 diabetes.

(h) Other oral antidiabetics

Outside orthodox Western medicine, there are herbal preparations which are used to treat diabetes and which can be given by mouth. Blueberries were traditionally used by the Alpine peasants, and bitter gourd or karela (*Momordica charantia*) is an established part of herbal treatment in the Indian subcontinent and elsewhere. Traditional Chinese medicine also has herbal medicines for diabetes. As yet it is not known how these herbal medicines act and their efficacy awaits formal clinical evaluation.

Interactions

The commonest interactions with antidiabetic drugs are those that result in a rise or fall in blood glucose levels, thereby disturbing the control of diabetes. These are detailed in this section. Other interactions where the antidiabetic drug is the affecting drug are described elsewhere.

Table 13.1 Drugs used in the management of diabetes

Group		*Drugs*
Parenteral antidiabetics		
Amylin analogues		Pramlintide
Incretin mimetics (Glucagon like peptide-1 receptor agonists)		Exenatide
Insulins	Short-acting	Soluble insulin
	Intermediate- and long-acting	Insulin zinc suspension, Isophane insulin, Protamine zinc insulin
	Short-acting analogues	Insulin aspart, Insulin glulisine, Insulin lispro
	Intermediate to long-acting analogues	Insulin aspart protamine, Insulin detemir, Insulin glargine, Insulin lispro protamine
Oral antidiabetics		
Aldose reductase inhibitors		Epalrestat
Alpha glucosidase inhibitors		Acarbose, Miglitol, Voglibose
Biguanides		Buformin, Metformin, Phenformin
Meglitinides		Nateglinide, Repaglinide
Dipeptidyl peptidase-4 inhibitors		Alogliptin, Linagliptin, Saxagliptin, Sitagliptin, Vildagliptin
Sulphonylureas		Acetohexamide, Carbutamide, Chlorpropamide, Glibenclamide (Glyburide), Glibornuride, Gliclazide, Glimepiride, Glipizide, Gliquidone, Glisentide, Glisolamide, Glisoxepide, Glycyclamide, Tolazamide, Tolbutamide
Thiazolidinediones		Pioglitazone, Rosiglitazone
Other drugs		Guar gum

Acarbose + Miscellaneous

Neomycin may increase the efficacy and the gastrointestinal adverse effects of acarbose. Paralytic ileus has been reported in a Japanese patient given acarbose and promethazine. A study in *animals* suggested that acarbose alone or with alcohol may increase the hepatotoxicity of paracetamol (acetaminophen).

Clinical evidence, mechanism, importance and management

(a) Antimuscarinics

A 69-year-old man with a partial gastrectomy and type 2 diabetes, receiving insulin 24 units and acarbose 300 mg daily, was admitted to hospital with diabetic gangrene. After developing cold symptoms he was given *PL granules* (salicylamide, paracetamol, caffeine, and **promethazine** methylene disalicylate). The next day he experienced sudden abdominal pain, nausea and vomiting, which was diagnosed as paralytic ileus. He was given intravenous fluids and piperacillin. Oral intake and acarbose were withheld and the ileus resolved after 2 days. The authors note that there are several reports of ileus developing in Japanese patients within 3 months of treatment with alpha-glucosidase inhibitors such as acarbose. The risk seems to be increased with increasing age, a history of abdominal surgery, and a Japanese diet (high in carbohydrates and fibre) rather than Western diet. However, in this case the patient had been taking acarbose for 15 months without problem and it is possible that the antimuscarinic effects of **promethazine** may have contributed to the development of ileus.[1] The general clinical relevance of this case is uncertain. However, the authors consider that patients at risk should be monitored if they are given alpha-glucosidase inhibitors, especially if the dose is increased or if antimuscarinics are also given.[1]

(b) Neomycin

Neomycin alone can reduce postprandial blood glucose levels and may enhance the reduction in postprandial glucose levels associated with acarbose.[2] In 7 healthy subjects, neomycin 1 g three times daily increased the unpleasant gastrointestinal adverse effects (flatulence, cramps and diarrhoea) of acarbose 200 mg three times daily.[3] The manufacturers suggest that if these adverse effects are severe, a temporary reduction in the dose of acarbose may be needed.[4]

(c) Paracetamol

Studies in *rats* have found that acarbose alone or in combination with alcohol may potentiate the hepatotoxicity of paracetamol. Both acarbose and alcohol induced the cytochrome P450 isoenzyme CYP2E1, by which paracetamol is metabolised to its hepatotoxic metabolite.[5] These findings require confirmation in humans, because *animal* data are not always reproduced in humans.

1. Oba K, Kudo R, Yano M, Watanabe K, Ajiro Y, Okazaki K, Susuki T, Nakano H, Metori S. Ileus after administration of cold remedy in an elderly diabetic patient treated with acarbose. *J Nippon Med Sch* (2001) 68, 61–4.
2. Bayer, Personal Communication, June 1993.
3. Lembcke B, Caspary WF, Fölsch UR, Creutzfeldt W. Influence of neomycin on postprandial metabolic changes and side effects of an α-glucosidehydrolase inhibitor (BAY g 5421). I. Effects on intestinal hydrogen gas production and flatulence. In Frontiers of Hormone Research, vol 7. The Entero-Insular Axis. Satellite Symposium to Xth IDF-Meeting, September 7–8, Göttingen 1979, p 294–5.
4. Glucobay 50 (Acarbose). Bayer plc. UK Summary of product characteristics, April 2009.
5. Wang P-Y, Kaneko T, Wang Y, Sato A. Acarbose alone or in combination with ethanol potentiates the hepatotoxicity of carbon tetrachloride and acetaminophen in rats. *Hepatology* (1999) 29, 161–5.

Alpha-glucosidase inhibitors + Antacids

Antacids appear not to interact with acarbose or miglitol.

Clinical evidence, mechanism, importance and management

(a) Acarbose

In 24 healthy subjects given a 75-g dose of sucrose, a placebo-controlled study found that 10 mL of *Maalox 70* (**aluminium**/**magnesium hydroxide**) had no effect on the blood glucose- and insulin-lowering effects of acarbose 100 mg. It was concluded that no special precautions are needed if this or similar antacids are used with acarbose.[1]

(b) Miglitol

The manufacturer notes that an antacid (not specified) did not alter the pharmacokinetics of miglitol in healthy subjects.[2] No miglitol dose adjustment would be expected to be necessary on concurrent use.

1. Höpfner M, Durani B, Spengler M, Fölsch UR. Effect of acarbose and simultaneous antacid therapy on blood glucose. *Arzneimittelforschung* (1997) 47, 1108–1111.
2. Glyset (Miglitol). Pharmacia & Upjohn Company. US Prescribing information, September 2009.

Alpha-glucosidase inhibitors + Charcoal or Digestive enzymes

The manufacturers of acarbose[1,2] and miglitol[3] reasonably suggest that intestinal adsorbents (e.g. charcoal) or digestive enzyme preparations containing carbohydrate splitting enzymes (such as amylase, pancreatin) should be avoided because, theoretically, they would be expected to reduce the effects of these alpha glucosidase inhibitors.

1. Glucobay 50 (Acarbose). Bayer plc. UK Summary of product characteristics, April 2009.
2. Precose (Acarbose). Bayer Pharmaceuticals Corporation. US Prescribing information, August 2008.
3. Glyset (Miglitol). Pharmacia & Upjohn Company. US Prescribing information, September 2009.

Alpha-glucosidase inhibitors + Other antidiabetics

Some minor decreases in the plasma levels of glibenclamide (glyburide), metformin, and rosiglitazone have been seen with acarbose or miglitol. Voglibose had no effect on glibenclamide pharmacokinetics. Alpha-glucosidase inhibitors cause a moderate additional blood glucose-lowering effect when used with other antidiabetics, and a possible increased risk of hypoglycaemia should be borne in mind with insulin and sulfonylureas. In patients taking alpha-glucosidase inhibitors, treatment of hypoglycaemia should be with a monosaccharide such as glucose (dextrose) or glucagon, not a disaccharide such as sucrose. The manufacturer of pramlintide recommends that it should not be used in patients taking alpha-glucosidase inhibitors.

Clinical evidence

(a) Glibenclamide (Glyburide)

Voglibose had no effect on the pharmacokinetics of glibenclamide in a double-blind crossover study in 12 healthy male subjects. In this study, subjects were given either **voglibose** 5 mg or a placebo three times daily for 8 days and a single 1.75-mg dose of glibenclamide on the morning of day 8, taken at the same time as the first dose of the **voglibose** or placebo.[1] Similarly, the manufacturers of **acarbose** note that it had no effect on the absorption or disposition of glibenclamide in diabetic patients.[2] However, in a randomised, placebo-controlled study in 28 patients with type 2 diabetes mellitus, **miglitol** reduced the maximum plasma glibenclamide levels and AUC by 16% and 19%, respectively. The patients were given glibenclamide 2.5 mg twice daily with either **miglitol** 100 mg three times daily or placebo for 2 days. Nevertheless, the average blood glucose levels were reduced more by the drug combination than by the glibenclamide alone: over 5 hours there was a 15% greater reduction, and over 10 hours a 9% greater reduction.[3] There was no increased incidence of hypoglycaemia when **miglitol** was used with sulfonylureas in clinical studies.[4]

(b) Metformin

A study in 6 healthy subjects found that **acarbose** 50 to 100 mg three times daily reduced the maximum serum levels and the AUC_{0-9} of metformin 1 g by about 35%, but the 24-hour urinary excretion was unchanged.[5] Another study in 19 diabetic patients given **acarbose** 50 or 100 mg three times daily and metformin 500 mg twice daily, also found that **acarbose** lowered metformin levels (AUC reduced by 12 to 13%, maximum plasma levels reduced by 17 to 20%). Nevertheless, the drug combination reduced the postprandial glucose concentration at 3 hours by 15% more than metformin alone.[6] There was no increased incidence of

hypoglycaemia when **acarbose** was used with metformin.[2]

The manufacturer notes that, in a study in healthy subjects, **miglitol** 100 mg three times daily for 7 days reduced the AUC and maximum level of a single 1-g dose of metformin by 12% and 13%, respectively, although this difference was not statistically significant.[4]

(c) Pramlintide

The manufacturer of pramlintide suggests that it should not be used in patients taking drugs that slow the intestinal absorption of nutrients, such as the alpha-glucosidase inhibitors.[7] This is because pramlintide slows gastric emptying (see also 'Pramlintide + Miscellaneous', p.585). Clinical study is needed to see if there is any important effect if the drugs are used together.

(d) Rosiglitazone

A study in 16 healthy subjects found that **acarbose** 100 mg three times daily for a week slightly reduced the absorption of a single 8-mg oral dose of rosiglitazone (AUC reduced by 12%), but this was not considered to be clinically relevant.[8]

Mechanism

The reason for the minor pharmacokinetic changes is uncertain.

Importance and management

The pharmacokinetic changes seen are minor and unlikely to be clinically relevant. The manufacturers say that while alpha-glucosidase inhibitors such as acarbose and miglitol do not cause hypoglycaemia when given alone, they may increase the blood glucose-lowering effects of insulin and the sulfonylureas, for which reason it may be necessary to reduce their doses. Monitor the outcome when acarbose, miglitol, or voglibose is first given. Any hypoglycaemic episodes should be treated with glucose (dextrose), not sucrose, because alpha-glucosidase inhibitors delay the digestion and absorption of disaccharides such as sucrose, but do not affect monosaccharides.[2,4,9] Patients taking alpha-glucosidase inhibitors should not be given pramlintide until the combination has been studied clinically.

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Antidiabetics + ACE inhibitors

The concurrent use of ACE inhibitors and antidiabetics normally appears to be uneventful but hypoglycaemia, marked in some instances, has occurred in a small number of diabetic patients taking insulin or sulfonylureas with captopril, enalapril, lisinopril or perindopril. This has been attributed, but not proved, to be due to an interaction. The United Kingdom Prospective Diabetes Study Group (UKPDS) found no difference in the incidence of hypoglycaemia between patients taking atenolol and those taking captopril. No pharmacokinetic interaction has been found to occur between spirapril and glibenclamide. Subcutaneous exenatide has no important effect on the pharmacokinetics of lisinopril, and does not alter its efficacy.

Clinical evidence

(a) Hypoglycaemia

Numerous case reports, small case-control studies, and a pharmacological study in healthy subjects suggest that ACE inhibitors increase the risk of hypoglycaemia when used with insulin or oral antidiabetics (mainly sulfonylureas where specified), and these are summarised in 'Table 13.2', (p.537). Conversely several larger case-control studies and two randomised controlled studies have not found a significantly increased risk of hypoglycaemia with ACE inhibitors in patients with diabetes, and these are also summarised in Table 13.2. It is worth highlighting that one of these, the United Kingdom Prospective Diabetes Study Group (UKPDS), found that the number of patients experiencing hypoglycaemic attacks did not differ between patients receiving atenolol 50 to 100 mg daily or **captopril** 25 to 50 mg twice daily for hypertension.[1] For more information about the use of beta blockers with antidiabetics, see 'Antidiabetics + Beta blockers', p.547.

(b) Pancytopenia

There is an isolated case of pancytopenia (possibly drug related) that occurred in a 72-year old man taking enalapril, an alpha blocker and a calcium antagonist (glomerular filtration rate 60 mL/minute), shortly after he started to take **glipizide** 5 mg twice daily for diabetes.[2]

(c) Pharmacokinetics

A brief report states that **spirapril** does not have a pharmacokinetic interaction with **glibenclamide**.[3]

The manufacturer of **exenatide** notes that, in a study in hypertensive patients, exenatide 10 micrograms twice daily did not alter the steady-state AUC or maximum level of **lisinopril** 5 to 20 mg daily, but it did delay the time to maximum level by 2 hours. **Exenatide** did not alter the blood-pressure lowering effect of **lisinopril**.[4,5]

Mechanism

The hypoglycaemia is not understood. An increase in glucose utilisation and increased insulin sensitivity have been suggested.[6,7] Other possibilities (e.g. altered renal function) are discussed in a series of letters in *The Lancet*.[8-13] There is also an isolated report of persistent severe hypoglycaemia in a non-diabetic patient associated with both **captopril** and **ramipril**.[14] Conversely, high natural ACE activity has been associated with a higher risk of severe hypoglycaemia in type 1 diabetics receiving insulin and not taking ACE inhibitors, leading to the hypothesis that ACE inhibitors might reduce the risk of hypoglycaemia in these individuals.[15]

Blood dyscrasias are a rare adverse effect of ACE inhibitors used alone, and have also occurred with glipizide alone. Whether concurrent use could increase this risk is uncertain.

Importance and management

This interaction is not well established and not understood, and it remains the subject of considerable study and debate. However, some cases of severe hypoglycaemia have undoubtedly occurred in diabetic patients managed with insulin or sulfonylureas as a result of the use of ACE inhibitors. Nevertheless, some authors consider the risk of severe hypoglycaemia in diabetic patients taking ACE inhibitors to be very low and negligible compared with the benefits of this class of drugs in diabetes.[16] Moreover, a number of guidelines on the treatment of hypertension in diabetes recommend that all patients with diabetes and hypertension should be given an ACE inhibitor.[17,18] To be on the safe side, it might be prudent to warn all patients receiving insulin or sulfonylureas who are just starting any ACE inhibitor (although only captopril, enalapril, lisinopril and perindopril have been implicated) that excessive hypoglycaemia has been seen very rarely and unpredictably. The problem has been resolved in some patients by reducing the sulfonylurea dose by 50 to 75%.[19,20]

Subcutaneous exenatide has no important pharmacokinetic interaction with lisinopril, and pharmacokinetic interactions with other ACE inhibitors would not be expected.

A false positive urine ketone test can also occur with captopril when using the alkaline-nitroprusside test (*Ketodiastix*), which may affect the monitoring of diabetic control.[21]

The isolated case of pancytopenia is probably of limited general relevance.

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Table 13.2 Interactions between antidiabetics and ACE inhibitors

Patients	*ACE inhibitor*	*Antidiabetic*	*Notes*	*Refs*
Evidence for hypoglycaemia				
1 case	Captopril 50 mg/day	Glibenclamide (glyburide) 10.5 mg/day Metformin 1.7 g/day	Blood glucose 2.2 mmol/L 24 hours after the addition of captopril.	1
1 case	Captopril	Glibenclamide 10.5 mg/day Metformin 1.7 g/day	Blood glucose of 2.9 mmol/L 48 hours after starting captopril. Antidiabetic drugs stopped.	1
3 cases	Captopril	Glibenclamide	Hypoglycaemia reported to a Spanish Regional Pharmacosurveillance centre.	2
1 case	Captopril 12.5 mg/day	Glibenclamide 2.5 mg/day	Hypoglycaemia 7 hours after first dose, blood glucose 2.1 mmol/L, glibenclamide stopped.	3
1 case	Captopril	Unspecified oral antidiabetic	Hypoglycaemia, oral antidiabetic withdrawn.	4
5 cases	Captopril	Unspecified sulfonylureas	Hypoglycaemia reported to Centres Regionaux de Pharmacovigilance in France.	5
3 cases case control study	Captopril	Unspecified oral antidiabetics	Risk of hypoglycaemia increased 3.1-fold.	6
9 cases case control study	Captopril	Insulin	Risk of hypoglycaemia increased 3.7-fold.	6
4 cases	Captopril	Insulin	Hypoglycaemia reported to a Spanish Regional Pharmacosurveillance centre.	2
3 cases	Captopril	Insulin	Unexplained hypoglycaemia.	4
1 case	Enalapril 5 mg/day	Glibenclamide 5 mg/day	Hypoglycaemia, blood glucose 2.3 mmol/L. Dose of glibenclamide reduced to 2.5 mg/day.	3
2 cases	Enalapril 5 mg/day	Glibenclamide 5 mg/day	Hypoglycaemic attacks, glibenclamide reduced to 1.25 mg/day.	7
9 healthy subjects (double-blind, crossover study)	Enalapril 5 mg/day, then 10 mg/day	Glibenclamide 3.5 mg single dose	Hypoglycaemic effects of glibenclamide temporarily enhanced between 2 and 4 hours after enalapril was taken.	8
4 cases	Enalapril	Glibenclamide	Hypoglycaemia reported to a Spanish Regional Pharmacosurveillance centre.	2
1 case	Enalapril	Gliclazide 80 mg/day	Hypoglycaemia when enalapril dose increased from 5 to 10 mg/day.	9
4 cases	Enalapril	Unspecified sulfonylureas	Hypoglycaemia reported to Centres Regionaux de Pharmacovigilance in France.	5
1 case	Enalapril	Unspecified sulfonylurea	Recurrent hypoglycaemia, sulfonylurea withdrawn.	10
10 cases case control study	Enalapril	Unspecified sulfonylurea Insulin	2.4-fold increase in the risk of hypoglycaemia with sulfonylureas. However, no increased risk was seen in insulin users. In addition when all ACE inhibitors were considered together, no significant increase in risk was seen.	11
2 cases case control study	Enalapril	Unspecified oral antidiabetics	Non-significant 5.4-fold increase in the risk of hypoglycaemia.	6
3 cases case control study	Enalapril	Insulin	Non-significant 1.7-fold increase in the risk of hypoglycaemia.	6
1 case	Enalapril	Insulin	Reduced insulin requirements.	10
11 cases	Enalapril	Insulin	Hypoglycaemia reported to a Spanish Regional Pharmacosurveillance centre.	2
1 case	Lisinopril	Glibenclamide and metformin	Hypoglycaemia reported to a Spanish Regional Pharmacosurveillance centre.	2
1 case	Lisinopril 10 mg/day	Gliclazide	Hypoglycaemia resolved on stopping gliclazide.	9
1 case	Perindopril	Glibenclamide	Hypoglycaemia reported to a Spanish Regional Pharmacosurveillance centre.	2

Continued

Table 13.2 Interactions between antidiabetics and ACE inhibitors (continued)

Patients	*ACE inhibitor*	*Antidiabetic*	*Notes*	*Refs*
1 case	Ramipril 2.5 mg/day	Glibenclamide 5 mg/day Metformin 1.7 g/day	Patient also on naproxen, renal function deteriorated causing hypoglycaemia due to accumulation of oral antidiabetics.	12
7 cases case control study	Unspecified ACE inhibitor	Insulin or oral antidiabetics	3.2-fold increase in the risk of hypoglycaemia leading to hospitalisation.	13
Evidence of no interaction				
8 cases	Captopril 37.5 mg/day	Insulin	No change to daily insulin requirements. No evidence of symptomatic hypoglycaemia.	14
38 cases	Captopril 50 to 100 mg/day or Enalapril 20 to 40 mg/day	Insulin or oral antidiabetics	Antidiabetic treatment unaltered, no evidence of unusual or unexplained hypoglycaemia.	15
18 cases double blind controlled study	Enalapril 20 to 40 mg/day	Insulin	No change to daily insulin requirements. No evidence of unexplained hypoglycaemia.	15
428 patients randomised controlled study	Lisinopril 10 to 20 mg/day or placebo	Insulin	No difference in the number of hypoglycaemic episodes between lisinopril and placebo recipients.	16
22 cases case control study	Captopril or Enalapril	Insulin or oral antidiabetics	Data from Centres Regionaux de Pharmacovigilance in France used. No increased risk of hypoglycaemia detected.	17
598 cases of hypoglycaemia in a retrospective study	Captopril or Enalapril or other classes of antihypertensive	Insulin or oral antidiabetics	No statistically significant increase or decrease in the risk of serious hypoglycaemia among users of ACE inhibitors or any other class of antihypertensives compared with non users of antihypertensives.	18
758 patients randomised controlled study	Captopril 50 to 100 mg/day or atenolol	Insulin or oral antidiabetics or diet alone	The proportion of patients with hypoglycaemic attacks did not differ between the captopril and atenolol groups.	19
336 reports case control study	Captopril or Enalapril	Antidiabetics	Data from the French pharmacovigilance database used. No increased risk of hypoglycaemia detected when confounding by indication considered.	20

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Antidiabetics + Alcohol

Diabetic patients managed with insulin, oral antidiabetics or diet alone need not abstain from alcohol, but they should drink only in moderation and accompanied by food. Epidemiological evidence suggests that heart disease may be less common in diabetic patients who drink in moderation. However, alcohol makes the signs of hypoglycaemia less clear and delayed hypoglycaemia can occur. The CNS depressant effects of alcohol in conjunction with hypoglycaemia can make driving or the operation of dangerous machinery much more hazardous. A flushing reaction is common in patients taking chlorpropamide who drink alcohol, but is less common with other sulfonylureas. Limited evidence suggests that alcoholic patients may require above-average doses of tolbutamide.

Clinical evidence

(a) Antidiabetics, general

1. Effect on glucose levels. The blood glucose levels of diabetics may be reduced, remain unchanged, or be increased by alcohol, depending on the amount drunk at one time, if it is drunk with food or not, and if use is chronic and excessive.[1] In one early study, 2 out of 7 diabetic patients receiving **insulin** became severely hypoglycaemic after drinking the equivalent of about 3 measures of spirits.[2] In a hospital study over a 3-year period, five type 1 diabetics were hospitalised with severe hypoglycaemia after binge-drinking. Two of them died without recovery from the initial coma and the other 3 suffered permanent damage to the nervous system.[3] In another study it was found that alcohol was involved in about 4% of hypoglycaemic episodes requiring hospitalisation.[4] In contrast to these alcohol-induced hypoglycaemic episodes, it was found in two other studies[5,6] that pure alcohol and dry wine had little effect on blood glucose levels. In a recent review of six studies, it was concluded that consumption of a moderate amount of alcohol does not acutely impair glycaemic control in diabetic patients, and may in fact result in a small decrease in plasma glucose concentrations.[7] However, another study found that 46 patients with type 2 diabetes and a mean age of 67 years who were regular chronic alcohol users (mean 45 g/day) had a reversible deterioration in metabolic control (higher fasting and postprandial glucose levels and higher HbA_{1c} levels), when compared with 35 non-alcohol users.[8] Another study reported similar findings.[9]

2. Effect on diabetic complications. A review of 4 epidemiological studies concluded that heart disease is less common in people with diabetes who drink moderate amounts of alcohol than in those who do not.[7]

(b) Biguanides

A controlled study in 5 ketosis-resistant patients with type 2 diabetes taking **phenformin** 50 to 100 mg daily found that the equivalent of about 85 mL (3 oz) of whiskey markedly raised their blood lactate and lactate-pyruvate levels. Two of them had blood-lactate levels of more than 50 mg%, and one of these patients had previously experienced nausea, weakness and malaise while taking **phenformin** and alcohol.[10] The ingestion of alcohol is described in other reports as having preceded the onset of **phenformin**-induced lactic-acidosis.[11-13] Some patients have complained that alcohol tastes metallic.

(c) Rosiglitazone

An 8-week study in type 2 diabetics taking rosiglitazone 8 mg daily or a placebo found that 0.6 g/kg of alcohol taken with a meal did not have a clinically relevant effect on plasma glucose levels and no episodes of hypoglycaemia were seen.[14]

(d) Sulfonylureas

About one-third of patients taking **chlorpropamide** who drink alcohol, even in quite small amounts, experience a warm, tingling or burning sensation of the face, and sometimes the neck and arms as well. It may also involve the conjunctivae. This can begin within 5 to 20 minutes of drinking, reaching a peak within 30 to 40 minutes, and may persist for one to 2 hours. Very occasionally headache occurs, and light-headedness, palpitations, wheezing and breathlessness have also been experienced.[15,16]

This disulfiram-like flushing reaction has been described in numerous reports (far too many to list here) involving large numbers of patients taking **chlorpropamide**. These reports have been extensively reviewed.[15,17-19] A similar reaction can occur, but much less frequently, with other sulfonylureas including **carbutamide**,[20] **glibenclamide** (**glyburide**),[16,21] **gliclazide**,[22] **glipizide**,[16] **tolazamide**,[23] and **tolbutamide**.[24,25] In one crossover study, evident flushing phenomenon after an oral ethanol-loading test was seen in 6 of 10 patients taking **chlorpropamide**, 3 of 10 taking **tolbutamide**, 2 of 10 taking **glibenclamide**, one of 10 taking **glibornuride** and none of 10 taking **glipizide**.[26]

A study found that the mean half-life of **tolbutamide** in alcoholics was about one-third lower than in control subjects.[27] Alcohol is also reported to prolong but not increase the blood glucose-lowering effects of **glipizide**.[28] Another study in 10 elderly patients (age range 60 to 75 years) with type 2 diabetes taking **glibenclamide** 20 mg daily found that intravenous infusion of ethanol (equivalent to one to 2 units of alcoholic drinks) significantly decreased the nadir plasma glucose level during a fast.[29]

Mechanism

The exacerbation of hypoglycaemia by alcohol is not fully understood. However, it is known that if hypoglycaemia occurs when liver glycogen stores are low, the liver turns to the formation of new glucose from amino acids (gluconeogenesis). This gluconeogenesis is inhibited by the presence of alcohol so that the fall in blood glucose levels may not be prevented and a full-scale hypoglycaemic episode can result.

The chlorpropamide-alcohol flush reaction, although extensively studied, is by no means fully understood. It seems to be related to the disulfiram-alcohol reaction, and is accompanied by a rise in blood-acetaldehyde levels (see also 'Alcohol + Disulfiram', p.66). It also appears to be genetically determined[16] and may involve both prostaglandins and endogenous opioids.[30] The decreased half-life of tolbutamide in alcoholics is probably due to the inducing effects of alcohol on liver microsomal enzymes.[27,31,32]

The reasons for the raised blood lactate levels seen during the concurrent use of phenformin and alcohol are not clear, but one suggestion is that it may possibly be related to the competitive demands for isoenzymes by the reactions that convert alcohol to acetaldehyde, and lactate to pyruvate.[10] A study in healthy subjects found that moderate alcohol consumption both improves insulin action, without affecting non-insulin mediated glucose uptake, and decreases lactate clearance. The increase in blood lactate with alcohol is therefore mainly due to inhibition of clearance. Alcohol did not appear to significantly affect beta-cell function.[33]

Importance and management

The documentation of the interactions between antidiabetic drugs and alcohol is surprisingly patchy (with the exception of chlorpropamide and alcohol) but they are of recognised clinical importance.

General comments

The following contains the main recommendations of Diabetes UK (formerly The British Diabetic Association) based on a review of what is currently known:[34,35] most diabetics need not avoid alcohol totally, but they are advised not to exceed 2 drinks (for women) or 3 drinks (for men) daily. A drink (or unit) is defined in 'Table 3.1', (p.47). The intake of drinks with high-carbohydrate content (sweet sherries, sweet wines, most liqueurs, and low alcohol wines) should be limited. Diabetics should not drink on

an empty stomach and they should know that the warning signs of hypoglycaemia may possibly be obscured by the effects of the alcohol. Driving or handling dangerous machinery should be avoided because the CNS depressant effects of alcohol plus hypoglycaemia can be particularly hazardous. Warn patients of the risks of hypoglycaemia occurring several hours after drinking. Those with peripheral neuropathy should be told that alcohol may aggravate the condition and they should not have more than one drink daily. Provided drinking is restricted as suggested, and drinks containing a lot of carbohydrate are avoided, there is no need to include the drink in the dietary allowance. However, diabetics on a weight-reducing diet should try to limit intake to the occasional drink and should include it in their daily calorie allowance.

The advice of the American Diabetes Association is similar: if individuals choose to drink alcohol, daily intake should be limited to one drink (for women) or 2 drinks (for men). [This equates to about 1.75 units for women and 3.5 units for men]. To reduce the risk of hypoglycaemia in individuals using insulin or oral insulin secretagogues, alcohol should be consumed with food.[1]

There is some evidence that heart disease in patients with diabetes may be less common in patients who consume moderate amounts of alcohol, but this is currently not sufficient to recommend that patients who do not drink alcohol should begin to drink in moderation.[7]

Specific comments about oral antidiabetics

The **chlorpropamide**-alcohol interaction (flushing reaction) is very well documented, but of minimal importance. It is a nuisance and possibly socially embarrassing but normally requires no treatment. Patients should be warned. The incidence is said to lie between 13 and 33%[36,37] although one study claims that it may be as low as 4%.[38] As it can be provoked by quite small amounts of alcohol (half a glass of sherry or wine) it is virtually impossible for sensitive patients to avoid it if they drink. Most manufacturers issue warnings about the possibility of this reaction with other sulfonylureas, but it is very rarely seen and can therefore almost always be avoided by replacing chlorpropamide with another sulfonylurea.

Alcoholic subjects may need above-average doses of tolbutamide. **Metformin** does not carry the same risk of lactic acidosis seen with phenformin and it is suggested in a paper[34] prepared for and approved by The British Diabetic Association [now Diabetes UK] that one or two drinks a day are unlikely to be harmful in patients taking **metformin**. However, the drug should not be given to alcoholic patients because of the possibility of liver damage.

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Antidiabetics + Allopurinol

Allopurinol adversely affected glycaemic control in a patient with type 2 diabetes receiving insulin. Marked hypoglycaemia and coma occurred in one patient taking gliclazide and allopurinol. Allopurinol causes an increase in the half-life of chlorpropamide, and a minor decrease in the half-life of tolbutamide.

Clinical evidence

A. Insulin

A case report describes improved glycaemic control in a type 2 diabetic patient after allopurinol was stopped. Despite restricted food intake and an increasing dose of insulin, his glycaemic control was poor (fasting blood glucose 14.8 mmol/L) when he took allopurinol 100 mg twice daily. However, within a few days of stopping the allopurinol, an unexpected improvement in glycaemic control was observed (fasting blood glucose reduced to less than 11 mmol/L). He was later rechallenged with allopurinol, which resulted in reduced glucose tolerance, but increased insulin response, suggesting increased insulin resistance. Hyperuricaemia was later controlled with **probenecid**, which did not adversely affect glycaemic control.[1]

B. Sulfonylureas

(a) Chlorpropamide

A brief report describes 6 patients taking chlorpropamide with allopurinol. The half-life of chlorpropamide in one patient with gout and normal renal function exceeded 200 hours (normally 36 hours) after allopurinol had been taken for 10 days, and in 2 other patients the half-life of chlorpropamide was extended to 44 hours and 55 hours. The other 3 patients were given allopurinol for only one or 2 days and the half-life of chlorpropamide remained unaltered.[2]

(b) Gliclazide

Severe hypoglycaemia (1.6 mmol/L) and coma occurred in a patient with renal impairment taking gliclazide and allopurinol.[3] Hypoglycaemia has been seen in another patient taking both drugs, but an interaction is less clear, as enalapril and ranitidine, which may also (rarely) interact were also involved.[3]

(c) Tolbutamide

In 10 healthy subjects, allopurinol 2.5 mg/kg twice daily for 15 days reduced the half-life of intravenous tolbutamide by 25% (from 360 to 267 minutes).[4,5]

Mechanism

Not understood. In the case of chlorpropamide it has been suggested that the interaction possibly involves some competition for renal tubular mechanisms.[2]

Importance and management

Information regarding interactions between the sulfonylureas and allopurinol is very limited. Only gliclazide has been implicated in severe hypoglycaemia with allopurinol and there seem to be no reports of either grossly enhanced hypoglycaemia with chlorpropamide and allopurinol, or a reduced effect with tolbutamide and allopurinol. More study is needed to find out whether any of these interactions has general clinical importance, but it seems unlikely.

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Antidiabetics + Anabolic steroids or Androgens

Nandrolone, methandienone, testosterone and stanozolol can enhance the blood glucose-lowering effects of insulin, and testosterone may also improve glycaemic control in those taking oral antidiabetics.

Clinical evidence

(a) Insulin

In a study in 54 diabetic patients taking **nandrolone phenylpropionate** 25 mg weekly or **nandrolone decanoate** 50 mg given every 3 weeks by intramuscular injection, it was found necessary to reduce the **insulin** dose by an average of 36% (reduction of 4 to 56 units) in about one-third of the patients.[1] In another placebo-controlled study in hypogonadal men with type 2 diabetes, of 10 patients using **insulin**, 5 reduced their daily insulin dose (by a mean of 7 units) while receiving intramuscular **testosterone esters** (*Sustanon*) once every 2 weeks for 3 months.[2]

Other reports similarly describe an enhanced reduction in blood glucose levels in diabetics receiving **insulin** and **nandrolone**,[3,4] **methandienone**,[5] **testosterone propionate**[6] or **stanozolol**.[7] No changes were seen when **ethylestrenol** was used.[1,3]

(b) Oral antidiabetics

In a placebo-controlled study in hypogonadal men with type 2 diabetes, intramuscular **testosterone esters** (*Sustanon*) once every 2 weeks for 3 months reduced fasting glucose by a mean of 1.6 mmol/L and HbA_{1c} by 0.37% (from over 7.4% to about 7.1%) in the 14 who were taking oral antidiabetics (11 patients) or diet alone (3 patients). The oral antidiabetics being taken were **metformin** alone or with **gliclazide** and/or **rosiglitazone**.[2]

Mechanism

Uncertain. Some evidence suggests that androgens improve insulin sensitivity, although androgens are often considered to impair glucose tolerance. A reduction in blood glucose levels has been seen in healthy subjects given testosterone propionate.[8]

Importance and management

The interactions between the anabolic steroids or androgens and antidiabetics are established but the total picture is incomplete because not all of the anabolic steroids appear to have been studied and they may not necessarily behave identically. A fall in the dose requirements of insulin (of an average of one-third[1]) may be expected in many patients with the steroids cited. Some improvement in glycaemic control may also occur in patients receiving oral antidiabetics. Given these results, and the fact that, conversely, anabolic steroids have also been shown to *impair* glucose tolerance it would seem prudent to closely monitor the concurrent use of any antidiabetic drug.

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Antidiabetics + Angiotensin II receptor antagonists

Glibenclamide (glyburide) causes a small reduction in valsartan levels. No clinically relevant pharmacokinetic interaction occurs between glibenclamide and candesartan or telmisartan, or between tolbutamide and irbesartan. Eprosartan does not alter the efficacy of glibenclamide. There is some experimental evidence that suggests that losartan and eprosartan may possibly reduce awareness of hypoglycaemic symptoms, but no increased risk was seen in a large epidemiological study.

Clinical evidence

(a) Hypoglycaemia

A study in 16 healthy subjects found that a single 600-microgram dose of **eprosartan** did not significantly affect adrenaline (epinephrine) release in response to **insulin**-induced hypoglycaemia, but the eprosartan tended to blunt some of the haemodynamic responses to hypoglycaemia.[1] Theoretically, therefore, hypoglycaemic symptoms could be reduced in some diabetic patients. Three patients with type 1 diabetes spontaneously reported reduced awareness of hypoglycaemic symptoms (tremor, palpitations, nervousness) after **losartan** was started. A placebo-controlled study in 16 healthy subjects given **losartan** 50 mg daily for 8 days confirmed an attenuation of the symptomatic and hormonal responses to hypoglycaemia.[2] However, in contrast, an early similar study found no such effect.[3]

The French pharmacovigilance database was examined for an association between angiotensin II receptor antagonists and reported hypoglycaemia. Although an association was found (odds ratio 2) this was confounded by an association between use of angiotensin II receptor antagonists and antidiabetic drugs. When looking specifically at patients taking antidiabetic drugs, there was no association between angiotensin II receptor antagonist use and hypoglycaemia, and in fact, a reduced risk of reporting hypoglycaemia (odds ratio 0.4). Angiotensin II receptor antagonists used in order of frequency included **losartan**, **irbesartan**, **valsartan**, **candesartan**, **telmisartan** and **eprosartan**.[4]

(b) Pharmacokinetic studies

1. Candesartan. **Glibenclamide (glyburide)** 3.5 mg daily did not significantly affect the pharmacokinetics of candesartan 16 mg daily, both given for 7 days, although the maximum plasma concentration of candesartan was slightly increased by 12%. The pharmacokinetics of glibenclamide were not altered by the candesartan.[5]

2. Eprosartan. Fifteen patients with type 2 diabetes stable taking **glibenclamide (glyburide)** 3.75 to 10 mg daily for at least 30 days had no changes in their 24-hour plasma glucose concentrations when eprosartan 200 mg twice daily was added, for a further 7 days. It was concluded that there is no clinically relevant interaction between these two drugs.[6]

3. Irbesartan. A study in 18 healthy subjects given irbesartan 300 mg daily and **tolbutamide** 1 g daily, either alone or in combination, found that no clinically important pharmacokinetic interactions occurred.[7]

4. Valsartan. In a randomised, crossover study, 12 healthy subjects were given single oral doses of valsartan 160 mg and **glibenclamide (glyburide)** 1.75 mg, alone and together.[8] Glibenclamide appeared to decrease the valsartan AUC by 16%, but the plasma concentrations of valsartan

showed wide variations between subjects. The pharmacokinetics of glibenclamide were not affected.[8] The changes in valsartan pharmacokinetics seen with glibenclamide appear to have little or no clinical relevance.

Mechanism

It has been suggested that blocking angiotensin II will block the adrenaline (epinephrine) response to insulin-induced hypoglycaemia, and thereby reduce awareness of hypoglycaemia. However, early studies found that angiotensin II receptor antagonists of the AT1 subtype such as losartan were not able to do this on their own, and AT2 subtype blockers were needed as well.[3,9]

Importance and management

No special precautions would appear to be needed if candesartan, eprosartan, telmisartan or valsartan are given with glibenclamide (glyburide), or if irbesartan is given with tolbutamide. However, there is some experimental evidence that suggests that symptoms of hypoglycaemia might be reduced by losartan and possibly other angiotensin II receptor antagonists, although one epidemiological study provided some reassurance that this may not be clinically important. Bear the possibility in mind. Further clinical study is needed, but note that this is similar to the possible effect of ACE inhibitors, see 'Antidiabetics + ACE inhibitors', p.536.

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Antidiabetics + Antimalarials

Hydroxychloroquine may reduce insulin requirements by about 25%, and two cases of hypoglycaemia have been reported. It has also improved glycaemic control in patients taking glibenclamide (glyburide). Similarly, hypoglycaemia has occurred in a patient taking chloroquine and insulin. Reduced glucose levels or hypoglycaemia have been reported with mefloquine, quinidine, quinine, and sulfadoxine with pyrimethamine. Note that falciparum malaria *per se* can result in severe hypoglycaemia, and quinine in particular may contribute to this.

Clinical evidence

(a) Effect on diabetic control

1. Chloroquine. A case report describes a patient with type 1 diabetes who had developed insulin resistance and was maintained on intravenous **insulin**, who showed a dramatic return of sensitivity to subcutaneous **insulin**, heralded by a series of hypoglycaemic attacks, within 15 days of starting to take chloroquine phosphate 200 mg every 8 hours.[1] Similarly, chloroquine phosphate (150 mg of chloroquine base) four times daily improved glucose tolerance in 5 out of 6 patients with type 2 diabetes controlled by diet, but had little effect in healthy subjects.[2]

2. Hydroxychloroquine. The effect of hydroxychloroquine on diabetic control with **insulin** or **glibenclamide** (**glyburide**) was investigated in a randomised, double-blind, placebo-controlled study in 38 patients with poorly controlled type 2 diabetes. The addition of hydroxychloroquine 200 mg three times daily to **insulin** caused a significant improvement in the glycaemic profile and the daily **insulin** dose had to be reduced by about 25%. Patients taking **glibenclamide** with hydroxychloroquine also had a significant improvement in their plasma glucose levels. One patient receiving **insulin** and hydroxychloroquine had severe hypoglycaemia after 2 months of concurrent use, and it was necessary to drastically reduce the daily dose of **insulin**.[3] In another similar study, 135 patients with poorly controlled type 2 diabetes taking **glibenclamide** 10 mg twice daily were randomised to receive placebo or hydroxychloroquine 300 mg daily, increased up to a maximum of 300 mg twice daily. Fewer patients discontinued hydroxychloroquine than placebo because of a lack of effect on improving blood glucose control (54% versus 82%). In addition, hydroxychloroquine reduced HbA_{1c} by 0.96% more than placebo.[4]

A case report describes a 77-year old man receiving a stable dose of **insulin** of 16 units twice daily who was diagnosed with rheumatoid arthritis. He was started on prednisolone 5 mg daily and hydroxychloroquine 400 mg daily, with an increase in insulin dose of 4 units daily in anticipation of prednisolone-induced impairment of glucose control. However he continued to have nightly hypoglycaemic episodes, and, one week later he had a hypoglycaemic attack requiring intravenous dextrose. His insulin dose was reduced back to the original dose, and over 6 weeks was gradually reduced to 10 units twice daily with good glycaemic control.[5]

3. Quinine. A study in 12 patients (age 51 to 79 years) with type 2 diabetes taking **gliclazide**, and 10 similar, non-diabetic subjects, found that a single 600-mg dose of **quinine sulphate** at night reduced serum glucose levels in both groups, without affecting serum insulin concentrations.[6] **Quinine** has been responsible for hypoglycaemia in non-diabetic patients, one of whom was taking **quinine sulphate** 325 mg four times daily for leg muscle cramps.[7] Two other non-diabetic patients, one with congestive heart failure and the other with terminal cancer, similarly developed hypoglycaemia when given **quinine** for leg cramps.[8,9]

(b) Treatment of malaria

Hypoglycaemia is a complication of falciparum malaria, which occurs mainly in severe life-threatening disease,[10,11] in pregnant women[10] or children,[12,13] and in patients who are given **quinine** or **quinidine**.[11,13-16] The reasons are not fully understood but renal impairment and poor nutrition may be contributing factors. In severe malaria, hypoglycaemia may increase as the patient's glucose production becomes insufficient for the host/parasite demand because in this situation glucose utilisation can be increased by 50%.[17]

Additionally, **quinine** reduces plasma glucose by stimulating the release of large amounts of **insulin** from the pancreas,[18] possibly associated with an increase in the sensitivity to **insulin** as the malaria improves,[19] although other factors may also be involved. A study in 32 patients with malaria found that their pre-treatment capillary glucose was below normal in 12.5% of cases. One hour after intravenous **quinine** was given, glucose levels in all patients fell by an average of 11.4% and after 6 hours a further fall of 20.5% was found in 75% of patients (with an increase at 6 hours in the remaining 25% of patients).[16] **Quinidine** has been shown to have a similar effect.[20] Whether these changes can also occur in patients with **quinine**- or **quinidine**-treated malaria and diabetes, despite their pancreatic beta cell impairment, seems not to have been studied, although one isolated report argues against significant **quinine**-mediated mechanisms. Profound and persistent hypoglycaemia was seen in a diabetic patient (type 2 diabetes) with severe falciparum malaria treated with **quinine**, but the hypoglycaemia evolved before the use of **quinine** and resolved as the parasitaemia was successfully eradicated, despite continuation of the **quinine**. Subsequently, as she had discontinued antidiabetic medication (chlorpropamide) before hospital admission, hyperglycaemia developed (blood glucose ranging from 7.5 to 16 mmol/L) despite continuing to take **quinine**.[21] Any interpretation of disturbances in the control of the diabetes should take into account the severity of the malaria and the possible effects of these drugs.

An isolated report describes life-threatening hypoglycaemia in a 3-year-old boy, with uncomplicated malaria, 90 minutes after he took **sulfadoxine** with **pyrimethamine** (*Fansidar*).[22] **Artemisinin derivatives** such as **artemether** may be associated with fewer episodes of hypoglycaemia than **quinine** in children with severe malaria.[13]

Mefloquine has been reported to reduce plasma glucose levels in healthy subjects.[23]

Mechanism

Both quinine and quinidine have been shown in experimental studies to stimulate insulin release, whereas this was not shown for chloroquine, mefloquine, amodiaquine and halofantrine.[20] A later study in patients with diabetes found that chloroquine both inhibits insulin degradation and increases insulin secretion.[24]

Importance and management

Not well established, but it appears that hydroxychloroquine can cause a modest reduction in blood glucose, which is additive with antidiabetic

treatment such as insulin and glibenclamide (glyburide). Bear this in mind if hydroxychloroquine is required in a patient with diabetes. Chloroquine appears to act similarly. Mefloquine and quinine have also been reported to reduce blood glucose. Some evidence is complicated by the malaria indication, as malaria can also cause hypoglycaemia.

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Antidiabetics + Antineoplastics

Asparaginase sometimes induces temporary diabetes mellitus. It seems possible that some diabetic patients will need changes in the dose of their antidiabetic drugs. There is also evidence that the control of diabetes can be severely disturbed in patients given cyclophosphamide. Capecitabine may cause hyperglycaemia and therefore could aggravate diabetes.

Clinical evidence and mechanism

(a) Asparaginase (Colaspase)

Three patients with acute lymphocytic leukaemia developed diabetes after receiving asparaginase with or without corticosteroids. In two of them this occurred 2 and 4 days after a single dose of asparaginase, and in another patient it occurred 2 days after the fourth dose. Plasma insulin was undetectable. A normal insulin response returned in one patient after 23 days, whereas the other 2 patients continued to have a suboptimal response 2 weeks, and 9 months afterwards.[1] In another study in 39 patients, 3 adults and 2 children developed hyperglycaemia and glycosuria after treatment with asparaginase. This responded to insulin, and blood glucose levels returned to normal in about 2 weeks.[2] In a retrospective analysis, it was found that about 10% of 421 children with leukaemia given asparaginase and prednisone developed hyperglycaemia, which resolved in all patients. A family history of diabetes and obesity were found to be risk factors.[3] Other cases of this effect have been described,[4-6] including one patient who, unusually, developed persistent hyperglycaemia and required long-term treatment with oral antidiabetics.[5] The reasons for this reaction are not understood but suggestions include inhibition of insulin synthesis,[7] direct damage to the islets of Langerhans,[1] and reduced insulin binding.[7] Hyperglycaemia can be caused by corticosteroids (see 'Antidiabetics + Corticosteroids', p.551) and their concurrent use with asparaginase is probably a contributing factor.

(b) Capecitabine

There appear to be no reports of adverse interactions between antidiabetics and capecitabine, but the manufacturer notes that the control of diabetes mellitus may be affected by capecitabine, for which reason they advise caution.[8]

(c) Cyclophosphamide

Acute hypoglycaemia has been described in 2 diabetic patients receiving **insulin** and **carbutamide** who were also given cyclophosphamide.[9] Three cases of diabetes, apparently induced by the use of cyclophosphamide, have also been reported.[10] The reasons for this reaction are not understood.

Importance and management

Strictly speaking probably none of these reactions is a drug interaction, but they serve to underline the importance of monitoring the diabetic control of patients receiving asparaginase, capecitabine or cyclophosphamide.

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Antidiabetics + Antipsychotics

Chlorpromazine may raise blood glucose levels, particularly in daily doses of 100 mg or more, and other classical antipsychotics appear to act similarly. The atypical antipsychotics, clozapine, olanzapine and risperidone are also associated with an increased risk of glucose intolerance. One epidemiological study found classical antipsychotics (haloperidol, pipamperone, levomepromazine, and zuclopenthixol) to be associated with an increased risk of needing insulin. Another epidemiological study found that patients with diabetes were particularly at risk of hospitalisation for hyperglycaemia during their first month of treatment with both classical and atypical antipsychotics.

Clinical evidence

(a) Classical antipsychotics

Early in the use of classical antipsychotics it was shown that they were associated with new-onset diabetes and impaired glucose control. For example, one long-term study was undertaken over the period 1955 to 1966 in a large number of women treated for a year or longer with **chlorpromazine** 100 mg daily or more, or corresponding doses of **perphenazine**, **thioridazine**, **trifluoperazine**. This found that about 25% developed hyperglycaemia accompanied by glycosuria, compared with less than 9% in a control group who were not taking phenothiazines. Of those given a phenothiazine, about a quarter had complete remission of the symptoms when the drug was withdrawn or the dosage reduced.[1]

There are other reports of this response to **chlorpromazine**.[2-11] However, in contrast one study in 850 patients suggests that **chlorpromazine** has no effect on blood glucose levels. Five patients developed diabetes, but this was believed to be due to factors other than the use of **chlorpromazine**.[12] **Chlorpromazine** 50 to 70 mg daily does not affect blood glucose levels significantly.[11] Further, a more recent analysis (discussed further under *Atypical antipsychotics*, below) did not find an increased risk of glucose intolerance with **chlorpromazine** or **haloperidol**, and notes that the number of reports of glucose intolerance with these drugs has remained small.[13]

Very much less appears to have been published about the effect of these antipsychotics on the control of existing diabetes. The large study above that found no effect of **chlorpromazine** on blood glucose levels included 22 diabetic patients, who also had no significant changes in their blood glucose levels.[12] Nevertheless, in a large cohort study in 2585 patients with type 2 diabetes who had been taking oral antidiabetics for at least 2 years, the use of antipsychotics was associated with a twofold increased risk of needing **insulin** at 2 years after diagnosis when compared with non-users of antipsychotics (18.4% versus 9.3%). In addition, more patients taking antipsychotics were switched to insulin alone rather than receiving oral antidiabetics with insulin. However, no difference in rates of initiation of insulin was found for later years after the diagnosis of diabetes (3, 4 or 5 years). The antipsychotics most frequently being used were **haloperidol**, **pipamperone**, **levomepromazine**, and **zuclopenthixol**. Too few patients were receiving an atypical antipsychotic for these results to be analysed separately.[14] Moreover, in a case-control study of older patients with diabetes hospitalised for hyperglycaemia, the concurrent use of a classical antipsychotic (not named) was associated with an increased risk of hyperglycaemia. This occurred irrespective of diabetes treatment. With **insulin** use the adjusted rate ratio was 1.27, with **oral antidiabetics** alone was 1.31, and with diet alone was 3.43. The risk appeared to be greater during initial use, with the adjusted rate ratio 8 to 15 times higher. Furthermore, of those patients who had taken an antipsychotic for up to one month, almost 70% of the episodes of hyperglycaemia occurred within the first 14 days of treatment.[15]

(b) Atypical antipsychotics

There are lots of data on the increased risk of new-onset diabetes with atypical antipsychotic drugs, and this is not cited here. There is some evidence that the risk of new-onset diabetes may be higher with atypical antipsychotics than classical antipsychotics. For example, an analysis of reports of glucose intolerance in the adverse reaction database of the WHO Collaborating Centre for International Drug Monitoring found that **clozapine**, **olanzapine** and **risperidone** were associated with an increased risk of glucose intolerance, whereas the classical antipsychotics chlorpromazine and haloperidol were not. It is uncertain whether this is a dose-related effect. Additional risk factors with these antipsychotics were an underlying diabetic condition, weight increase, male gender, or the concurrent use of valproic acid, SSRIs or buspirone.[13] However, a recent meta-analysis of all the available evidence found that the atypical antipsychotics were associated with only a tentative small increased risk of diabetes when compared with classical antipsychotics (relative risk 1.32).[16]

Very much less appears to have been published about the effect of any antipsychotics on control of existing diabetes. In a case-control study of older patients with diabetes hospitalised for hyperglycaemia, current atypical antipsychotic treatment (**olanzapine**, **quetiapine** or **risperidone**), was associated with an increased risk of hyperglycaemia, particularly during the first month of treatment. The adjusted relative risk of developing hyperglycaemia in patients taking an atypical antipsychotic and managed with insulin, oral hypoglycaemic drugs. or diet alone was 1.4, 1.37, and 2.37, respectively.[15]

Mechanism

Although some studies found that drugs such as chlorpromazine and haloperidol were not associated with glucose intolerance,[11,13] it seems that chlorpromazine can inhibit the release of insulin, and possibly cause adrenaline release from the adrenals, both of which could result in a rise in blood glucose levels. This may be a dose-related effect.[11] Further, chlorpromazine may cause aggregation and inactivation of insulin by reduction of disulfide bonds.[17] Clozapine may induce insulin resistance and a compensatory increase in insulin secretion. Patients may develop diabetes if this compensatory increase is not achieved. Alternatively or additionally, weight gain is a common adverse effect of antipsychotics, and may contribute to worsening of metabolic control.[13,14] Schizophrenia itself may be associated with an increased risk of hyperglycaemia.

Importance and management

A long-established reaction first recognised in the early 1950s. The incidence of hyperglycaemia with chlorpromazine in doses of 100 mg or more is about 25%. Increases in the dosage requirements of the antidiabetic should be anticipated during concurrent use.[1] Smaller chlorpromazine doses, of 50 to 70 mg daily do not appear to cause hyperglycaemia. Other classical and atypical antipsychotics appear to act similarly. In patients with diabetes, one study found evidence of an association between antipsychotic drug use and worsening of metabolic control and another found an increased risk of hospitalisation for hyperglycaemia, especially in the first month of use of the antipsychotic. It would seem prudent to increase monitoring for glycaemic control, particularly when starting or stopping any classical or atypical antipsychotic in a patient with diabetes.

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Antidiabetics + Azoles; Fluconazole

Fluconazole does not appear to affect the diabetic control of most patients taking sulfonylureas, but isolated reports describe hypoglycaemic coma in one patient taking glipizide and hypoglycaemia and aggressive behaviour in a patient taking gliclazide. There is some evidence that the blood glucose-lowering effects of both glipizide and glibenclamide (glyburide) may be modestly increased by fluconazole. Fluconazole may cause increases in plasma levels of glimepiride (marked) and nateglinide (modest).

Clinical evidence

(a) Chlorpropamide

After 18 healthy subjects took fluconazole 100 mg daily for 7 days, the AUC of single 250-mg doses of chlorpropamide was increased by 28% but the maximum plasma levels and blood glucose levels were unchanged. There was no evidence of hypoglycaemia.[1]

(b) Glibenclamide (Glyburide)

After 20 healthy subjects took fluconazole 100 mg daily for 7 days, the AUC of a single 5-mg dose of glibenclamide was increased by 44% and its maximum plasma levels rose by 19%. The change in blood glucose levels was not statistically significant but the number of subjects who had symptoms of hypoglycaemia increased.[2] In another study, a group of 14 postmenopausal women with diabetes and vulvovaginal candidiasis, taking either gliclazide or glibenclamide, were given fluconazole 50 mg daily for 14 days. None of the patients in this study developed symptoms

of hypoglycaemia and their HbA_{1c} and fructosamine concentrations were unchanged. No pharmacokinetic data were reported.[3]

(c) Gliclazide

A group of 14 postmenopausal diabetic women with vulvovaginal candidiasis taking either gliclazide or glibenclamide were given fluconazole 50 mg daily for 14 days. None of the patients developed symptoms of hypoglycaemia and their HbA_{1c} and fructosamine concentrations were unchanged. No pharmacokinetic data were reported.[3] However, a 56-year-old HIV-positive patient (antiretroviral treatment refused) and type 2 diabetes who had been taking gliclazide for 2 years was given fluconazole 50 mg daily for 2 weeks for oral candidiasis, and prophylactic co-trimoxazole (sulfamethoxazole 400 mg and trimethoprim 80 mg daily). One week after the re-introduction of fluconazole at a higher dose of 200 mg daily he was hospitalised because of weakness and aggressive behaviour. His blood glucose level was 2.2 mmol/L and gliclazide was stopped. He experienced brief loss of consciousness 2 days later while driving his car, but his condition then improved and neurological symptoms did not recur during 3 months of follow-up without gliclazide treatment.[4] For the possible contribution of sulfamethoxazole to this interaction, see *Mechanism*, below.

(d) Glimepiride

A double-blind study in 12 healthy subjects found that fluconazole 400 mg on day one then 200 mg daily for a further 3 days increased the AUC and peak plasma level of a single 500-microgram dose of glimepiride about 2.5-fold and 1.5-fold, respectively. Fluconazole increased the mean elimination half-life of glimepiride from 2 hours to 3.3 hours.[5]

(e) Glipizide

After 13 healthy subjects took fluconazole 100 mg daily for 7 days, the AUC of a single 2.5-mg dose of glipizide was increased by 49% and its maximum serum levels rose by 17%. Although blood glucose levels were lowered the change was not statistically significant. However, the number of subjects who had symptoms suggestive of hypoglycaemia increased.[6]

A diabetic patient taking glipizide 2.5 mg three times daily went into a hypoglycaemic coma within 4 days of starting to take fluconazole 200 mg daily. Her blood glucose levels had fallen to less than about 0.05 mmol/L. She rapidly recovered when given glucose.[7]

(f) Nateglinide

In a randomised, double-blind, crossover study, 10 healthy subjects were given a single 30-mg dose of nateglinide on day 4 of a course of fluconazole (given as 400 mg on day one, then 200 mg daily). Fluconazole raised the AUC of nateglinide by 48% (range 20 to 73%) and increased the nateglinide half-life from 1.6 hours to 1.9 hours. Despite these pharmacokinetic changes fluconazole did not potentiate the blood glucose lowering effects of nateglinide.[8] It was predicted that this interaction may occur with **miconazole** (which inhibits the same isoenzymes as fluconazole), but this needs confirmation.

(g) Tolbutamide

After 13 healthy subjects took a single 150-mg dose of fluconazole, and then 6 doses of fluconazole 100 mg daily, the AUC of a single 500-mg dose of tolbutamide was increased by about 50%, and its peak plasma levels were raised. The half-life of the tolbutamide was increased about 40%. Blood glucose levels remained unaltered and none of the subjects showed any evidence of hypoglycaemia.[9,10] However, the authors caution against extrapolating this finding to diabetic patients taking tolbutamide regularly.[9,10]

Mechanism

Fluconazole is an inhibitor of the cytochrome P450 isoenzyme CYP2C9, by which many of the sulfonylureas are metabolised. Inhibition of this isoenzyme leads to an accumulation of the sulfonylurea and therefore an increase in its effects. The hypoglycaemia in the patient taking gliclazide and fluconazole may have been enhanced by sulfamethoxazole, which also inhibits CYP2C9 (see also 'Antidiabetics + Sulfonamides', p.574).[4] The moderate pharmacokinetic changes seen when fluconazole is given with nateglinide are also thought to be mediated by CYP2C9.

Importance and management

The almost total absence of adverse reports implies that fluconazole does not usually markedly disturb the control of diabetes in patients taking sulfonylureas. For fluconazole the increased plasma levels of glipizide and glimepiride, and the single case of severe hypoglycaemia, as well as the hypoglycaemic symptoms shown by those taking glibenclamide (glyburide) or gliclazide suggest that patients taking these sulfonylureas in particular should be warned to be alert for any evidence of hypoglycaemia. However, there seems to be no reason for avoiding concurrent use. Note that in the study of fluconazole with nateglinide a sub-therapeutic dose was given to healthy subjects, so in clinical practice a greater blood glucose-lowering effect may possibly occur.

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Antidiabetics + Azoles; Itraconazole or Ketoconazole

Itraconazole also appears not to affect diabetic control in most patients, but there are reports of hypoglycaemia or hyperglycaemia associated with its use in patients taking a variety of antidiabetics. Itraconazole causes modest increases in repaglinide and nateglinide levels, but has no effect on pioglitazone pharmacokinetics. Ketoconazole increases the blood glucose-lowering effects of tolbutamide in healthy subjects and possibly increases the AUC of rosiglitazone and pioglitazone.

Clinical evidence

(a) Itraconazole

Post-marketing surveillance over 10 years indicated that in most patients itraconazole given with either **insulin** or **oral antidiabetics** did not affect diabetic control. However, there were 15 reports suggesting hyperglycaemia and 9 reports suggesting hypoglycaemia when itraconazole was given to patients taking antidiabetics.[1] In clinical studies only one of 189 patients with diabetes experienced aggravated diabetes when given itraconazole.[1] The patient in question was also receiving ciclosporin for a kidney transplant.

In a study in 12 healthy subjects, itraconazole 200 mg then 100 mg twice daily for 4 days did not alter the pharmacokinetics of a single 15-mg dose of **pioglitazone**.[2]

In healthy subjects, itraconazole 200 mg then 100 mg twice daily for 3 days increased the AUC of a single 250-microgram dose of **repaglinide** by 40%. No change was noted in blood glucose levels, when compared with **repaglinide** alone.[3] However, itraconazole enhanced the pharmacokinetic interaction between gemfibrozil and **repaglinide**; itraconazole with gemfibrozil increased the AUC of **repaglinide** nearly 20-fold and considerably enhanced the blood glucose-lowering effect of **repaglinide**. In a similar study in healthy subjects, itraconazole with gemfibrozil increased the AUC of a single 30-mg dose of **nateglinide** by 47%, without causing any significant change in blood glucose response to **nateglinide**.[4]

(b) Ketoconazole

After an overnight fast and breakfast the next morning, 7 healthy subjects were given a single 500-mg dose of **tolbutamide** before and after taking ketoconazole 200 mg daily for a week. Ketoconazole increased the elimination half-life of **tolbutamide** more than threefold (from 3.7 to 12.3 hours) and increased its AUC by 77%. Ketoconazole increased the blood glucose-lowering effects of **tolbutamide** by about 10 to 15%, and 5 of the subjects experienced mild hypoglycaemic symptoms (weakness, sweating and a reeling sensation) at about 2 hours after the dose.[5]

In healthy subjects, ketoconazole 200 mg daily for 5 days increased the AUC and maximum plasma levels of a single 2-mg dose of **repaglinide** by 15% and 8%, respectively.[6]

In 10 healthy Korean subjects, ketoconazole 200 mg twice daily for 5 days increased the AUC of a single 8-mg dose of **rosiglitazone** by 47%.[7]

The US manufacturer refers to a 7-day study in which ketoconazole 200 mg twice daily modestly increased the AUC of **pioglitazone** by 34%.[8]

Mechanism

The modest changes in repaglinide pharmacokinetics with ketoconazole and itraconazole may be because repaglinide is metabolised by both of the cytochrome P450 isoenzymes CYP2C8 and CYP3A4, and one pathway may have the capacity to compensate if the other is inhibited.[9] Similarly, itraconazole modestly affects nateglinide metabolism by CYP3A4.[4]

Although it has been suggested that ketoconazole may inhibit the metabolism of rosiglitazone by CYP2C8 and CYP2C9, ketoconazole is normally only considered to be a significant inhibitor of CYP3A4.

Importance and management

Itraconazole does not usually disturb the control of diabetes, although there are rare reports of hyperglycaemia or hypoglycaemia associated with its use. The effect of itraconazole on repaglinide could potentially be important, especially if a drug that inhibits CYP2C8 such as gemfibrozil is also given, so increased monitoring of blood glucose levels is advisable. Similarly, itraconazole may interact with nateglinide to a modest extent. Itraconazole is unlikely to interact with pioglitazone.

Information about ketoconazole and sulfonylureas appears to be limited to one study in healthy subjects. The reaction in diabetics is uncertain, but if ketoconazole is added to tolbutamide, patients should be warned to be alert for any evidence of increased hypoglycaemia. It may become necessary to reduce the tolbutamide dose. Ketoconazole increases the AUC of rosiglitazone and pioglitazone, and more frequent blood glucose monitoring is recommended in the presence of this azole. The pharmacokinetic changes with ketoconazole and repaglinide are minor, and unlikely to be of any clinical relevance.

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Antidiabetics + Azoles; Miscellaneous

Hypoglycaemia has been seen in few diabetic patients taking tolbutamide, glibenclamide or gliclazide when they were given miconazole tablets. Posaconazole slightly enhanced the blood glucose-lowering effects of glipizide in healthy subjects, but did not affect the metabolism of a single dose of tolbutamide. Voriconazole is predicted to increase the levels of the sulfonylureas. Clotrimazole used intravaginally appears not to interact with gliclazide or glibenclamide.

Clinical evidence

(a) Clotrimazole

A group of 15 postmenopausal diabetic women with vulvovaginal candidiasis taking either **gliclazide** or **glibenclamide** (**glyburide**) were treated with intravaginal clotrimazole 100 mg daily for 14 days. None of the patients developed symptoms of hypoglycaemia and their HbA_{1c} and fructosamine concentrations were unchanged. No pharmacokinetic data were reported.[1]

(b) Miconazole

A diabetic patient taking **tolbutamide** was hospitalised with severe hypoglycaemia about 10 days after starting to take miconazole tablets.[2] In 1983 the French Commission Nationale de Pharmacovigilance reported 6 cases of hypoglycaemia in diabetic patients taking sulfonylureas (5 with **gliclazide** and one with **glibenclamide** (**glyburide**)), which occurred within 2 to 6 days of miconazole being started.[2] The same organisation reported a further 8 cases in the 1985 to 1990 period.[3] Three other cases of hypoglycaemia (two with **gliclazide** and one with **glibenclamide**) are reported elsewhere, in patients given miconazole up to 750 mg daily.[4] Miconazole has been predicted to interact with **nateglinide**, see 'Antidiabetics + Azoles; Fluconazole', p.544.

(c) Posaconazole

A study in 12 healthy subjects found that posaconazole 400 mg twice daily for 10 days had no significant effects on the steady-state pharmacokinetics of **glipizide** 10 mg daily, but there was a small significant decrease in blood glucose levels following concurrent use. **Glipizide** did not affect the pharmacokinetics of posaconazole.[5] In another study, posaconazole 200 mg daily for 10 days had no effect on **tolbutamide** metabolism.[6]

(d) Voriconazole

The manufacturers of voriconazole predict that it will raise the levels of the sulfonylureas.[7,8]

Mechanism

Miconazole and voriconazole are inhibitors of the cytochrome P450 isoenzyme CYP2C9, by which many of the sulfonylureas are metabolised. Inhibition of this isoenzyme would therefore be expected to lead to an accumulation of the sulfonylurea and therefore an increase in its effects, as seen with miconazole tablets. Clotrimazole is probably not absorbed in sufficient quantities to cause an interaction.

Importance and management

The interaction between miconazole tablets and the sulfonylureas is established and clinically important, but of uncertain incidence. Concurrent use need not be avoided but it should be monitored and the dose of the sulfonylurea reduced if necessary. Although there are no specific data, a large proportion of miconazole oral gel (both prescription and non-prescription doses) may be swallowed and therefore adequate systemic absorption may occur to produce an interaction. It is therefore possible that oral miconazole gel might interact similarly. Intravaginal miconazole and miconazole topical creams are probably unlikely to interact, because absorption by these routes is minimal.

Posaconazole slightly enhanced the blood glucose-lowering effects of glipizide in healthy subjects, but the clinical relevance of this is not known. Posaconazole does not appear to affect tolbutamide metabolism.

The manufacturers of voriconazole advise increased blood-glucose monitoring in patients taking sulfonylureas,[7,8] and until more is known this seems prudent.

Information about intravaginal clotrimazole is very sparse, but it appears not to interact with gliclazide or glibenclamide, and probably not with any of the other oral antidiabetics, not least because its absorption from the vagina is very small.

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Antidiabetics + Benzodiazepines

No adverse interaction normally occurs between antidiabetics and benzodiazepines, but an isolated case of hyperglycaemia has been seen in an insulin-treated patient with type 2 diabetes associated with the use of chlordiazepoxide. The effects of lorazepam were found to be increased in patients given beef/pork insulin rather than human insulin. Pioglitazone caused a minor decrease in the AUC of midazolam, which is probably not clinically relevant.

Clinical evidence, mechanism, importance and management

(a) Insulin

A woman with long-standing type 2 diabetes, which was stabilised with 45 units of isophane insulin suspension daily, had a rise in her mean fasting blood glucose from about 12 mmol/L to 21 mmol/L during a 3-week period while taking **chlordiazepoxide** 40 mg daily.[1] A preliminary report in 8 healthy type 1 diabetics given **lorazepam** 2 mg suggested that while they were taking human insulin they were more alert and less sedated than when taking beef/pork insulin.[2]

There seems to be nothing in the literature to suggest that a clinically important adverse interaction normally takes place between insulin and the benzodiazepines. No special precautions would appear to be necessary.

(b) Oral antidiabetics

Four patients with type 2 diabetes, two diet-controlled and two taking **tolbutamide**, had no changes in blood glucose levels while taking **chlordiazepoxide**.[1] In another study **diazepam** did not change the half-life of **chlorpropamide**.[3]

The manufacturer notes that **pioglitazone** 45 mg daily for 15 days reduced the AUC and maximum level of a single dose of **midazolam** syrup by 26% in healthy subjects.[4] This is possibly because **pioglitazone** is a weak inducer of the cytochrome P450 isoenzyme CYP3A4,[4] by which **midazolam** is metabolised. The clinical relevance of this small decrease in **midazolam** levels has not been assessed, but it is likely to be minor.

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3. Petitpierre B, Perrin L, Rudhardt M, Herrera A, Fabre J. Behaviour of chlorpropamide in renal insufficiency and under the effect of associated drug therapy. *Int J Clin Pharmacol* (1972) 6, 120–4.
4. Actos (Pioglitazone hydrochloride). Takeda Pharmaceutical Company Ltd. US Prescribing information, August 2008.

Antidiabetics + Beta blockers

In diabetics using insulin, the normal recovery reaction (blood sugar rise) if hypoglycaemia occurs may be impaired to some extent by propranolol, but serious and severe hypoglycaemia seems rare. Cardioselective beta blockers seem less likely to interact.
The blood glucose-lowering effects of the sulfonylureas may possibly be reduced by the beta blockers. Whether insulin or oral antidiabetic drugs are given, patients should be made aware that some of the familiar warning signs of hypoglycaemia (tachycardia, tremor) may not occur, although sweating may be increased. Hypoglycaemia in patients taking beta blockers has been noted to result in significant increases in blood pressure and possibly bradycardia in some studies. Miglitol has been found to reduce the bioavailability of propranolol by 40%.

Clinical evidence

(a) Insulin

1. Hypoglycaemia. Although **propranolol** has occasionally been associated with spontaneous episodes of hypoglycaemia in non-diabetics,[1] and a number of studies in diabetic patients[2] and healthy subjects[3-6] have found that **propranolol** impairs the normal blood sugar rebound if blood sugar levels fall, there appear to be few reports of severe hypoglycaemia or coma in diabetics receiving insulin and **propranolol**. Marked hypoglycaemia and/or coma occurred in 5 diabetic patients receiving insulin as a result of the use of **propranolol**,[1,7,8] **pindolol**,[8] or **timolol** eye drops.[9] Other contributory factors (fasting, haemodialysis, etc.) probably had some part to play.[8] **Metoprolol** interacts like **propranolol** but to a lesser extent,[3,5,10] whereas **acebutolol**,[2,5] **alprenolol**,[11] **atenolol**,[2,12,13] **oxprenolol**,[10] **penbutolol**,[6] and **pindolol**[14] have been found to interact minimally or not at all. The situation with **pindolol** is therefore not clear. **Carvedilol** has been associated with the onset of diabetes mellitus in one patient.[15] **Propranolol** (a peripheral vasoconstrictor) has also been found to reduce the rate of absorption of subcutaneous insulin by almost 50%, but the importance of this is uncertain.[16] However, a large case-control study found no statistically significant increase or decrease in the risk of a serious hypoglycaemic episode in patients over 65 years of age receiving insulin and taking either cardioselective beta blockers (**atenolol** and **metoprolol**) or non-cardioselective beta blockers (**propranolol** and **nadolol**) when compared with patients taking no antihypertensive drugs. Overall, of the different antihypertensive drug classes, the risk of hypoglycaemia was lowest with cardioselective beta blockers and highest with non-cardioselective beta blockers, although none of the changes were statistically significant when controlled for demographic factors and markers of comorbidity.[17] Similarly, in two other case-control studies, there was no increase in the risk of hypoglycaemia in patients with diabetes receiving insulin and also taking a beta blocker.[18,19]

2. Hypertension. Marked increases in blood pressure and bradycardia may develop if hypoglycaemia occurs in diabetic patients receiving **insulin** and a beta blocker.[20] In one study in diabetic patients, insulin-induced hypoglycaemia resulted in blood pressure rises of 38.8/14.3 mmHg in those taking **propranolol** 80 mg twice daily, 27.9/0 mmHg in those taking **atenolol** 100 mg daily and in those taking placebo the systolic blood pressure rose by 15.2 mmHg whereas the diastolic blood pressure fell by 9.9 mmHg.[21] In another study, **insulin**-induced hypoglycaemia resulted in blood pressure rises of 27/14 mmHg in those taking **alprenolol** 200 to 800 mg daily, but no rise occurred in those taking **metoprolol** 100 to 400 mg daily.[22] A report describes a blood pressure rise to 258/144 mmHg in a patient having a hypoglycaemic episode within 2 days of starting **propranolol**.[7] Another patient taking **metoprolol** 50 mg twice daily experienced a rise in blood pressure from 190/96 mmHg to 230/112 mmHg during a hypoglycaemic episode.[20]

(b) Oral antidiabetics

1. Effects on blood glucose. The sulfonylurea-induced insulin release from the pancreas can be inhibited by beta blockers so that the blood glucose-lowering effects are opposed to some extent.

- **Acebutolol** appears to inhibit the effects of **glibenclamide** (**glyburide**),[23] but has no effect on **tolbutamide**.[24] Also, two isolated cases of hypoglycaemia have been seen with acebutolol, in one patient taking **gliclazide** and one patient taking **chlorpropamide**.[25]
- **Betaxolol** had no effect on the response to **glibenclamide** or **metformin** in one study.[26]
- **Metoprolol** did not affect the insulin-response to **tolbutamide** in one study.[27]
- **Propranolol** inhibits the effects of **glibenclamide**,[23] and **chlorpropamide**[28] and reduced the insulin-response to **tolbutamide** in one study,[29] but not in another.[27] Also, an isolated report describes hyperosmolar non-ketotic coma in a patient taking **tolbutamide** and propranolol.[30]

It is worth noting that the United Kingdom Prospective Diabetes Study Group (UKPDS) used **atenolol** 50 to 100 mg daily or captopril 25 to 50 mg twice daily for hypertension in diabetic patients taking a range of antidiabetic drugs. Those given **atenolol** had a slightly greater increase in HbA_{1c} levels, and gained slightly more weight (3.4 kg for the **atenolol** group compared with 1.6 kg for the captopril group over 9 years). However, both drugs were equally effective in reducing the risk of predefined clinical end points (e.g. diabetic complications, death related to diabetes, heart failure). The number of patients experiencing hypoglycaemic attacks did not differ between the two antihypertensives.[31] This would suggest that beta blockers are generally useful in the treatment of diabetic patients. Another large case-control study found no statistically significant increase or decrease in the risk of a serious hypoglycaemic episode in elderly patients taking sulfonylureas with either cardioselective beta blockers (**atenolol** and **metoprolol**) or non-cardioselective beta blockers (**propranolol** and **nadolol**) when compared with patients taking no antihypertensive drugs.[17]

2. Pharmacokinetic studies. **Acarbose** 300 mg daily for one week had no effect on the pharmacokinetics or pharmacodynamics of a single 80-mg dose of **propranolol** in healthy subjects.[32] Conversely, the manufacturer of **miglitol** notes that it reduced the bioavailability of **propranolol** by a modest 40%.[33]

No pharmacokinetic interaction was seen in a study in healthy subjects given a single 1.75-mg dose of **glibenclamide** (**glyburide**) with **carvedilol** 25 mg daily for 6 days.[34]

For a theoretical pharmacokinetic interaction between tolbutamide and propranolol, see 'Beta blockers; Propranolol + Miscellaneous', p.1023.

Mechanism

One of the normal physiological responses to a fall in blood sugar levels is the mobilisation of glucose from the liver under the stimulation of adrenaline from the adrenals. This sugar mobilisation is blocked by non-cardioselective beta blockers (such as propranolol) so that recovery from hypoglycaemia is delayed and may even proceed into a full-scale episode in a hypoglycaemia-prone diabetic. Normally the adrenaline would also increase the heart rate, but with the beta-receptors in the heart already blocked this fails to occur. A rise in blood pressure occurs because the stimulant effects of adrenaline on the beta-2 receptors (vasodilation) are blocked leaving the alpha (vasoconstriction) effects unopposed.

Non-selective beta blockers can also block beta-2 receptors in the pancreas concerned with insulin-release, so that the effects of the sulfonylureas may be blocked.

Importance and management

Extremely well-studied interactions. Concurrent use can be uneventful but there are some risks. Diabetics receiving insulin may have a prolonged or delayed recovery response to hypoglycaemia while taking a beta blocker, but very severe hypoglycaemia and/or coma is rare. If hypoglycaemia occurs it may be accompanied by a sharp rise in blood pressure. The risk is greatest with propranolol and possibly other non-cardioselective blockers and least with the cardioselective blockers. The cardioselectivity of a number of beta blockers is given in 'Table 22.1', (p.995). Monitor the effects of concurrent use well, avoid the non-cardioselective beta blockers where possible, and check for any evidence that the insulin dose needs some adjustment. Warn all patients that some of the normal premonitory signs of a hypoglycaemic attack may not appear, in particular tachycardia and tremors, whereas the hunger, irritability and nausea signs may be unaffected and sweating may even be increased.

Diabetics taking oral sulfonylureas rarely seem to have serious hypoglycaemic episodes caused by beta blockers, and any reductions in the blood glucose-lowering effects of the sulfonylureas normally appear to be of little clinical importance. The cardioselective beta blockers are probably safer than those that are non-selective. Nevertheless, always monitor concurrent use to confirm that diabetic control is well maintained, adjusting the dose of antidiabetic as necessary, and warn all patients (as above) that some of the premonitory signs of hypoglycaemia may not occur.

One experimental study indicated that no interaction occurred between betaxolol and **metformin**,[26] but direct information about other beta blockers seems to be lacking.

There is also a hint from one report that the peripheral vasoconstrictive effects of non-cardioselective beta blockers and the poor peripheral circulation in diabetics could be additive,[7] which is another possible reason for avoiding this type of beta blocker in diabetic patients.

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13. Waal-Manning HJ. Atenolol and three nonselective β-blockers in hypertension. *Clin Pharmacol Ther* (1979) 25, 8–18.
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33. Glyset (Miglitol). Pharmacia & Upjohn Company. US Prescribing information, September 2009.
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Antidiabetics + Bile-acid binding resins

A report suggests that the hypocholesterolaemic effect of colestipol is unaffected in insulin-treated diabetics but it may be reduced in patients taking phenformin and sulfonylureas. Colestyramine may enhance the effect of acarbose, and insulin levels may rebound if both drugs are stopped at the same time. The absorption of glipizide may be reduced by about 30% if it is taken at the same time as colestyramine, but tolbutamide does not appear to be affected. Colesevelam may reduce the absorption of glibenclamide if it is taken at the same time. The absorption of pioglitazone and repaglinide are not significantly affected by colesevelam.

Clinical evidence

(a) Colesevelam

1. Glibenclamide. Colesevelam 3.75 g reduced the AUC and maximum concentration of glibenclamide 3 mg by 32% and 47%, respectively, when taken at the same time. When glibenclamide was taken one hour before colesevelam, the AUC and maximum concentration were still slightly reduced, by 20% and 15%, respectively. When glibenclamide was taken 4 hours before colesevelam, the reduction was minimal.[1,2]

2. Repaglinide. Colesevelam 3.75 g caused a minor 19% reduction in the maximum concentration of repaglinide 2 mg when taken at the same time, and a 7% reduction in the AUC of repaglinide. No clinically relevant interaction was seen when repaglinide was taken one hour after colesevelam.[1,2]

3. Other antidiabetics. The manufacturers state that colesevelam does not alter the bioavailability of **pioglitazone**, but no study details are given.[1,2] The US manufacturers of colesevelam state that **metformin** did not bind with colesevelam during *in vitro* testing, so they consider a clinical interaction unlikely.[1]

(b) Colestipol

The concurrent use of **phenformin** and a sulfonylurea (**chlorpropamide**, **tolbutamide** or **tolazamide**) inhibited the normal hypocholesterolaemic effects of the colestipol in 12 diabetic patients with elevated serum cholesterol levels. No such antagonism was seen in 2 patients with type 2 diabetes receiving **insulin**. The control of diabetes was not affected by the colestipol.[3]

(c) Colestyramine

1. Acarbose. Colestyramine 12 g daily for 6 days, given to 8 healthy subjects taking acarbose 100 mg three times daily, improved the reduction in postprandial insulin levels.[4] The mean serum insulin levels fell by 23% while taking both drugs, but showed a rebound 31% increase above baseline when both drugs were stopped.[4]

2. Glipizide. In 6 healthy subjects, colestyramine 8 g in 150 mL of water reduced the absorption of a single 5-mg dose of glipizide by a mean of 29%. One subject had a 41% reduction in glipizide levels. Peak serum levels were reduced by 33%. The AUC_{0-10} was used to measure absorption.[5]

3. Tolbutamide. A single-dose study indicated that colestyramine 8 g, given 2 minutes before, and 6 and 12 hours after a 500-mg dose of tolbutamide, did not reduce the amount of tolbutamide absorbed, although the rate of absorption may have changed.[6]

Mechanism

Colestyramine, colestipol, and colesevelam are bile-acid binding resins, intended to bind to bile acids within the gut, but they can also bind with some acidic drugs thereby reducing the amount available for absorption.

Importance and management

Information about glipizide is limited to a single-dose study so that the clinical importance of the reduction in glipizide levels with colestyramine is unknown, but it would seem prudent to monitor the effects of concurrent use in patients. It has been suggested[5] that the glipizide should be taken one to 2 hours before the colestyramine to minimise admixture in the gut, but this may only be partially effective because it is believed that glipizide undergoes some entero-hepatic circulation (i.e. after absorption it is excreted in the bile and reabsorbed). The effect of colestyramine on other sulfonylureas is uncertain, with the exception of tolbutamide, which is reported not to interact. The clinical importance of the effects of colestyramine on acarbose in diabetics is uncertain, although the manufacturers note that some enhancement of the effects of acarbose may occur, and they suggest care if both drugs are stopped at the same time because of the possible rebound phenomenon with respect to insulin levels.[7]

The study with colestipol suggests that it may not be suitable for lowering the blood cholesterol levels of diabetics taking chlorpropamide, tolbutamide, tolazamide or phenformin, but more study is needed to confirm these findings. Phenformin has been withdrawn from many countries because of severe, often fatal, lactic acidosis.

Colesevelam appears to reduce the absorption of glibenclamide and this may have a modest clinically significant effect. Therefore the manufacturers recommend that glibenclamide should be taken at least 4 hours before colesevelam.[1] As colesevelam does not appear to interact to a clinically relevant extent with repaglinide or pioglitazone, there would appear to be no reason to separate administration.

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2. Cholestagel (Colesevelam hydrochloride). Genzyme Therapeutics. UK Summary of product characteristics, March 2009.
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7. Glucobay 50 (Acarbose). Bayer plc. UK Summary of product characteristics, April 2009.

Antidiabetics + Calcium-channel blockers

Calcium-channel blockers are known to have effects on insulin secretion and glucose regulation, but significant disturbances in the control of diabetes caused by these drugs appear to be rare. A report describes a patient whose diabetes worsened, requiring an increase in the dose of insulin, when diltiazem was given, and a similar case has occurred in a patient taking nifedipine. Deterioration in glucose tolerance has also occurred during nifedipine use. Hypoglycaemia occurred in a patient taking gliclazide and nicardipine. No clinically important changes in nifedipine pharmacokinetics have been seen with acarbose, miglitol, pioglitazone or rosiglitazone; in glibenclamide pharmacokinetics with nimodipine or verapamil; in glipizide, metformin or repaglinide pharmacokinetics with nifedipine; or between tolbutamide and diltiazem.

Clinical evidence

A. Dihydropyridines

(a) Effect on glucose tolerance

A study in 20 patients with type 2 diabetes (5 taking **metformin** and 15 diet-controlled) found that both **nifedipine** 10 mg every 8 hours and **nicardipine** 30 mg every 8 hours for 4 weeks did not affect either glucose tolerance tests or the control of the diabetes, but both systolic and diastolic blood pressures were reduced by 4 to 7 mmHg.[1] No important changes in glucose metabolism occurred in 6 patients with type 2 diabetes taking **glibenclamide** (**glyburide**) when they were given **nifedipine** 20 to 60 mg daily for 12 to 25 weeks.[2] Similarly, other studies have found no important changes in glucose tolerance or the control of diabetes in patients taking **chlorpropamide**,[3] **glibenclamide**,[4] **gliclazide**,[5] **glipizide**[3,6] or unspecified antidiabetics[7,8] while also taking **nifedipine**,[3,5-7] **nimodipine**[4] or **nitrendipine**.[8] No change in **insulin** dose was needed in one patient taking **nicardipine**[9] and in 4 patients taking **nitrendipine**.[8] However, there are reports of a deterioration in glucose tolerance during the use of **nifedipine** in a total of 12 subjects with impaired glucose tolerance.[10,11] A further case report describes a 30% increase in the **insulin** requirements of a diabetic man after he took **nifedipine** 60 mg daily.[12] An isolated case of hypoglycaemia has been described in a patient taking **gliclazide** when **nicardipine** was given.[13] However, a large case-control study found no statistically significant increase or decrease in the risk of a serious hypoglycaemic episode in patients over 65 years of age taking insulin or sulfonylureas, who were also taking calcium-channel blockers (**nifedipine** and **verapamil** were the most frequently used), when compared with patients not taking antihypertensive drugs.[14]

(b) Pharmacokinetic studies

1. Alpha-glucosidase inhibitors. The manufacturers of **acarbose** state that in a pilot study of a possible interaction with **nifedipine**, no significant or reproducible changes were seen in plasma **nifedipine** profiles.[15,16] Similarly, the manufacturers of **miglitol** note that it had no effect on the pharmacokinetics and pharmacodynamics of **nifedipine**.[17]

2. Insulin. One study found that **nifedipine** 10 mg increased the rate of absorption of subcutaneous insulin by about 50%.[18]

3. Metformin. One US manufacturer of nifedipine noted that in a single-dose study in healthy subjects, nifedipine very slightly increased the AUC of metformin by 9%, and increased its maximum level by 20%.[19]

4. Pioglitazone or Rosiglitazone. Rosiglitazone 8 mg daily for 2 weeks was found to have no clinically relevant effect on the pharmacokinetics of **nifedipine** in 28 healthy subjects.[20] The manufacturer notes that pioglitazone 45 mg daily for 7 days given with **nifedipine** extended-release 30 mg daily for 4 days resulted in a small change in **nifedipine** pharmacokinetics (12% decrease in AUC).[21]

5. Repaglinide. A three-period, crossover study in healthy subjects found that **nifedipine** 10 mg daily decreased the maximum plasma level of repaglinide 2 mg three times daily by 3% and increased the bioavailability of repaglinide by 11%, but this was not statistically significant. There was a higher incidence of adverse effects during concurrent use.[22]

6. Sulfonylureas. A study in 6 patients type 2 diabetes found that a single 20-mg dose of **nifedipine** had no effect on the pharmacokinetics of **glipizide** 5 to 30 mg daily.[6] Similarly, **nimodipine** caused no change in the pharmacokinetics of **glibenclamide** in 11 patients.[4]

B. Diltiazem

A patient with type 1 diabetes developed worsening and intractable hyperglycaemia (mean serum glucose levels above 13 mmol/L) when given diltiazem 90 mg every 6 hours. Her **insulin** requirements dropped when the diltiazem was withdrawn. When she started taking diltiazem 30 mg every 6 hours her blood glucose levels were still high, but she needed less **insulin** than when taking the higher diltiazem dose.[23]

A study in 12 healthy subjects found that diltiazem 60 mg three times daily had no effect on the secretion of **insulin** or glucagon, or on plasma glucose levels.[24] Similarly, diltiazem 120 mg three times daily for 3 days had no effect on **insulin** and glucose levels during an oral glucose tolerance test in 10 patients taking **gliclazide**.[5]

A study in 8 healthy subjects found that a single 500-mg dose of **tolbutamide** had no effect on the serum levels of a single 60-mg dose of diltiazem. There was a minor increase of about 10% in the AUC_{0-24} and maximum serum levels of **tolbutamide** in the presence of diltiazem but the blood glucose-lowering effects of **tolbutamide** were not significantly changed.[25]

C. Verapamil

A study in 23 patients with type 2 diabetes, 7 of whom were taking **glibenclamide** (**glyburide**), found that verapamil improved the response to an oral glucose tolerance test but did not increase the blood glucose-lowering effects of the **glibenclamide**.[26] Two studies in type 2 diabetics found that verapamil improved the response to glucose tolerance tests,[27,28] but in one of the studies, no alterations in the blood glucose-lowering effects of **glibenclamide** were found.[27] A study in healthy subjects found that verapamil modestly raised the **glibenclamide** AUC by 26% but plasma glucose levels were unchanged.[29] A large case-control study found no statistically significant increase or decrease in the risk of a serious hypoglycaemic episode in patients over 65 years of age taking insulin or sulfonylureas, who were also taking calcium-channel blockers (**nifedipine** and **verapamil** were the most frequently used), when compared with patients not taking antihypertensive drugs.[14]

Mechanism

The changes that occur are not fully understood. Suggestions include: inhibition of insulin secretion by the calcium-channel blockers and inhibition of glucagon secretion by glucose; changes in glucose uptake by the liver and other cells; blood glucose rises following catecholamine release after vasodilation, and changes in glucose metabolism. In contrast, one study in non-diabetics suggested that long-acting nifedipine could improve insulin sensitivity.[30]

Importance and management

Very extensively studied, but many of the reports describe single-dose studies or multiple-dose studies in healthy subjects (only a few are cited here), which do not give a clear picture of what may be expected in diabetic patients. Those studies that have concentrated on diabetic patients indicate that the control of the diabetes is not usually adversely affected by calcium-channel blockers, although isolated cases with diltiazem, nicardipine and nifedipine have been reported.[12,13,23] Similarly, there appear to be no important pharmacokinetic interactions with any of the combinations studied. Therefore, in general, no particular precautions normally seem necessary. However, if an otherwise unexplained worsening of diabetic control occurs it may be prudent to consider the use of a calcium-channel blocker as a possible cause.

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Antidiabetics + Cibenzoline (Cifenline)

Hypoglycaemia has been seen in patients taking cibenzoline alone, and in one case with gliclazide.

Clinical evidence, mechanism, importance and management

Cibenzoline occasionally and unpredictably causes hypoglycaemia, which may be severe. Marked hypoglycaemia was seen in a 67-year-old non-diabetic patient when cibenzoline was given.[1] A further case report describes hypoglycaemia in an 84-year-old, in whom age, renal impairment and/or malnutrition acted as facilitating factors.[2] The authors of this report noted that hypoglycaemia has been reported in another 20 cases, where the dose was not corrected for age and renal function.[2] A more recent report describes an elderly patient with type 2 diabetes controlled by diet who developed hypoglycaemia and associated dementia-like symptoms while taking low-dose cibenzoline.[3] Hypoglycaemia also occurred in a 61-year-old patient with renal impairment taking **gliclazide** and cibenzoline.[4] In a study of reports of hypoglycaemia in the French pharmacovigilance database, cibenzoline was used as a positive control, and a very strong association between cibenzoline and hypoglycaemia was noted, both in reports including antidiabetic drugs (odds ratio 5) and in reports not including antidiabetic drugs (odds ratio 174). The odds ratio of hypoglycaemia compared with all reports for the study as a whole was 107 (78 to 148).[5]

The reasons for this effect are not understood. However, in a controlled study in patients with abnormal glucose tolerance and ventricular arrhythmias, cibenzoline exerted a hypoglycaemic effect by facilitating insulin secretion.[6]

This appears to be a drug-disease rather than a drug-drug interaction and diabetic patients do not seem to be more at risk than non-diabetics, but good monitoring is advisable if cibenzoline is given, particularly if risk factors such as increased age, renal impairment, malnutrition and high cibenzoline dose are present..

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Antidiabetics + Clonidine

Some evidence suggests that clonidine may possibly suppress the signs and symptoms of hypoglycaemia in diabetic patients. Marked hyperglycaemia occurred in a child using insulin when clonidine was given. However, the effect of clonidine on carbohydrate metabolism appears to be variable, as other reports have described both increases and decreases in blood glucose levels. Clonidine premedication may decrease or increase the hyperglycaemic response to surgery.

Clinical evidence

(a) Non-diabetics

Studies in healthy subjects and patients with hypertension found that their normal response to hypoglycaemia (tachycardia, palpitations, perspiration) caused by a 0.1 unit/kg dose of **insulin** was markedly reduced when they were taking clonidine 450 to 900 micrograms daily.[1,2] A study in healthy subjects and non-diabetic patients found that clonidine raises blood glucose levels, apparently by reducing **insulin** secretion,[3] whereas, in contrast, hypoglycaemia was associated with clonidine testing for growth hormone deficiency in 4 children.[4] Furthermore, in yet another study, clonidine 100 or 200 micrograms twice daily had no effect on fasting glucose levels or oral glucose tolerance testing.[5]

(b) Diabetic patients

A 9-year-old girl with type 1 diabetes stabilised with **insulin** 4 units daily, developed substantial hyperglycaemia and needed up to 56 units of **insulin** daily when she began to take clonidine 50 micrograms daily for Tourette's syndrome. When the clonidine was stopped, she had numerous hypoglycaemic episodes, and within a few days it was possible to reduce her daily dose of **insulin** to 6 units.[6] A patient with type 2 diabetes and hypertension experienced elevated blood glucose levels and decreased **insulin** secretion when clonidine was given.[7] However, a study in 10 diabetic patients with hypertension found that although clonidine impaired the response to an acute glucose challenge, it did not significantly affect diabetic control over a 10-week period.[8] Similarly, in 20 patients with type 2 diabetes and hypertension, clonidine 75 to 300 micrograms daily for 3 months had no effect on glucose control. The antidiabetic therapy (sulfonylureas (11 patients), metformin (2 patients), a combination (3 patients), or diet alone (4 patients)) was kept constant.[9]

In contrast, a placebo-controlled, crossover study in 20 patients with type 2 diabetes found that transdermal clonidine significantly reduced mean fasting plasma glucose levels by 9%.[10]

(c) Hyperglycaemia during surgery

Forty patients with type 2 diabetes (controlled by diet alone, **sulfonylureas**, **biguanides**, or **insulin**), having eye surgery under general anaesthesia, were given either clonidine 225 to 375 micrograms or flunitrazepam as premedication. In diabetic patients there is an increase in blood glucose during stress because of an increase in catecholamine release. Therefore the patients were also given a continuous infusion of **insulin** to maintain blood glucose at 5.5 to 11.1 mmol/L. Clonidine decreased the **insulin** requirement because of improved blood glucose control due to inhibition of catecholamine release.[11] Contrasting results were found in a study in 16 non-diabetic women undergoing abdominal hysterectomy. Eight were given intravenous clonidine 1 microgram/kg and 8 control patients were given saline. Intraoperative plasma glucose levels were higher in the clonidine group and these patients also had lower insulin levels.[12]

Mechanism

The suggested reason for a reduced response to hypoglycaemia is that clonidine depresses the output of the catecholamines (adrenaline (epinephrine), noradrenaline (norepinephrine)), which are secreted in an effort to raise blood glucose levels, and which are also responsible for these signs.[2] It seems possible that clonidine will similarly suppress the signs and symptoms of hypoglycaemia that can occur in diabetics, but there seem to be no reports confirming this.

Importance and management

The effect of clonidine on carbohydrate metabolism in diabetic patients appears to be variable and the general importance of these interactions is uncertain. In diabetic patients there is an increase in blood glucose levels during stress because of an increase in catecholamine release. The influence of clonidine on the surgical stress response appears to vary depending on the dose of clonidine and the type of surgery.[12] Thus, clonidine at about 4 micrograms/kg may attenuate the hyperglycaemic response to neurosurgical and non-abdominal procedures, but low-dose clonidine accentuates the hyperglycaemic response to lower abdominal surgery, which results from a decrease in plasma insulin.[11,12]

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Antidiabetics + Corticosteroids

The blood glucose-lowering effects of the antidiabetics are opposed by corticosteroids with glucocorticoid (hyperglycaemic) activity and significant hyperglycaemia has been seen with systemic corticosteroids. A report also describes deterioration in diabetic control with *inhaled* high-dose fluticasone, then high-dose budesonide, in a patient taking glibenclamide and metformin. High doses of high-potency corticosteroid creams may also, rarely, cause hyperglycaemia.

Clinical evidence, mechanism, importance and management

(a) Local corticosteroids

1. Inhaled. A 67-year-old man with diabetes taking **glibenclamide** 5 mg daily and **metformin** 1.7 g daily had a deterioration in diabetic control (glycosuria and an increase in HbA_{1c}) 3 weeks after starting inhaled **fluticasone** 2 mg daily, by metered dose inhaler with a spacer device, for asthma. The **fluticasone** dose was gradually decreased to 500 micrograms daily after about 3 months, with an improvement in diabetic control. Subsequently, the **fluticasone** dose was increased from 500 micrograms to 1 mg, and within a week he again developed glycosuria.[1] This same patient was later given inhaled high-dose **budesonide** 2 mg daily and he again developed glycosuria and increased HbA_{1c} levels, which improved as the dose was gradually decreased to 800 micrograms daily.[2] The adverse effects of *systemic* corticosteroids on glucose tolerance are well known. Although only one case appears to have been reported, it suggests that high-dose inhaled corticosteroids may have a similar effect. It may be prudent to increase monitoring of diabetic control in patients requiring high-dose corticosteroids and consider reducing the dose of the inhaled corticosteroid if possible, or adjusting the dose of the antidiabetic medication as necessary.

2. Topical. Two patients with an abnormal response to the glucose tolerance test, but without overt signs of diabetes mellitus, developed postprandial hyperglycaemia and one developed glycosuria when they used topical corticosteroids for severe psoriasis. These patients were given 15 g of **halcinonide** 0.1% or **betamethasone** 0.1% cream, applied every 12 hours for 15 days under occlusive dressings.[3] These cases appear to be rare, and were associated with high doses of potent or very potent corticosteroids,

used under occlusive dressings, which increases systemic absorption. No additional special precautions would generally appear to be necessary in diabetics using moderate amounts of topical corticosteroids.

(b) Systemic corticosteroids

Systemic corticosteroids with glucocorticoid activity can raise blood glucose levels and induce diabetes.[4] This can oppose the blood glucose-lowering effects of the antidiabetics used in the treatment of diabetes mellitus. For example, a disturbance of the control of diabetes is very briefly described in a patient given **insulin** and **hydrocortisone**.[5] A study in 5 patients with type 2 diabetes taking **chlorpropamide** found that a single 200-mg dose of **cortisone** modified their glucose tolerance. The blood glucose levels of 4 of them rose (3 showed an initial fall), whereas in a previous test with **chlorpropamide** alone the blood glucose levels of 4 of them had fallen.[6] This almost certainly reflects a direct antagonism between the pharmacological effects of the two drugs. Another glucocorticoid, **prednisone**, had no significant effect on the metabolism or clearance of **tolbutamide** in healthy subjects.[7]

There are very few studies of this interaction, probably because the hyperglycaemic activity of the **corticosteroids** has been known for such a long time that the outcome of concurrent use is self-evident. A case-control study found that in patients taking glucocorticoids, the relative risk for development of hyperglycaemia requiring treatment was 2.23, when compared with controls. The risk increased with an increasing daily dose of **hydrocortisone**: doses of 1 to 39 mg were associated with a 1.77-fold increase in risk, doses of 40 to 79 mg were associated with a 3.02-fold increase in risk, doses of 80 to 119 mg were associated with a 5.82-fold increase in risk, and doses of greater than 120 mg were associated with a 10.34-fold increase in risk.[8] Similarly, another study, in healthy subjects, found dose-related decreases in glucose tolerance and higher serum insulin levels associated with single intravenous doses of **hydrocortisone** and **methylprednisolone,** but these changes were more marked with **methylprednisolone** than **hydrocortisone**.[9] **Dexamethasone** has also been shown to cause a deterioration in glucose tolerance with an incidence of about 35% in non-diabetic, first-degree relatives of patients with type 2 diabetes, primarily due to reduced insulin secretory capacity.[10]

The effects of systemic corticosteroids in diabetics should be closely monitored and the dose of the antidiabetic raised as necessary. Antidiabetics are sometimes needed in non-diabetic patients taking **corticosteroids** to reduce blood glucose levels.

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Antidiabetics + Danazol

Danazol causes insulin resistance. Therefore, on theoretical grounds, danazol would be expected to oppose the effects of antidiabetics.

Clinical evidence, mechanism, importance and management

Danazol can disturb glucose metabolism. A study in 14 non-diabetic subjects found that 3 months of treatment with danazol 600 mg daily caused a mild but definite deterioration in glucose tolerance, associated with high insulin levels. Insulin resistance was also seen in 5 subjects taking danazol when they were given intravenous **tolbutamide**.[1] Similarly, another study in 9 non-diabetic women found that danazol 600 mg daily raised insulin levels in response to glucose or intravenous **tolbutamide**.[2] A further study in 9 non-diabetic women also found that danazol caused a mild deterioration in glucose tolerance and a marked increase in the insulin response to glucose loading.[3] Other studies have found that danazol causes marked resistance to both insulin[4-6] and glucagon,[5,6] which could be due to receptor down-regulation resulting from hypersecretion of insulin and glucagon.[5,6]

There is also a report of danazol-associated type 1 diabetes in a patient with endometriosis who took danazol 400 mg twice daily for 8 weeks. The diabetes resolved on withdrawal of danazol, but the development of hyperglycaemia about 5 months later suggested a predisposition to diabetes.[7] However, it has been suggested that the patient probably had type 2 diabetes precipitated by danazol-induced insulin resistance, which would possibly have responded to dietary restriction. Danazol-associated hyperglucagonaemia may have exacerbated the symptoms.[8,9]

For these reasons the manufacturer of danazol advises caution if danazol is given to diabetic patients.[10] Danazol would be expected to oppose the actions of antidiabetics to some extent, but there do not appear to be any studies assessing the clinical relevance of this.

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Antidiabetics + Dextropropoxyphene (Propoxyphene)

Dextropropoxyphene does not appear to affect the pharmacokinetics of tolbutamide. Hypoglycaemia was seen in a patient taking an unnamed sulfonylurea with co-proxamol, and has also been reported in non-diabetic patients given dextropropoxyphene alone.

Clinical evidence, mechanism, importance and management

After 6 healthy subjects took dextropropoxyphene 65 mg every 8 hours for 4 days, the clearance of a 500-mg intravenous dose of **tolbutamide** was not affected.[1] There is an isolated case of hypoglycaemia in a patient taking an unnamed **sulfonylurea** with **co-proxamol** (dextropropoxyphene with paracetamol (acetaminophen)).[2] There are also several reports of hypoglycaemia in non-diabetic patients taking dextropropoxyphene alone,[3-7] sometimes associated with renal failure,[3,4] advanced age,[5] or with high doses or in overdose.[6] The general importance of these isolated reports is uncertain, and there would normally seem to be little reason for avoiding the concurrent use of antidiabetics and dextropropoxyphene, or for taking particular precautions.

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Antidiabetics + Disopyramide

Disopyramide occasionally causes hypoglycaemia, which may be severe. Isolated reports describe severe hypoglycaemia when dis-

opyramide was given to diabetic patients taking gliclazide, or metformin and/or insulin.

Clinical evidence, mechanism, importance and management

Disopyramide occasionally and unpredictably causes hypoglycaemia, which may be severe.[1-7] The reasons for this effect are not fully understood, but *in vitro* studies suggest that disopyramide and its main metabolite may enhance insulin release from the pancreas.[8] A case report describes severe hypoglycaemia in an 82-year-old woman with diabetes who was taking **gliclazide**, which occurred 6 months after she started taking disopyramide 300 mg daily.[9] A further case of hypoglycaemia associated with disopyramide occurred in a 70-year-old woman who had been taking **metformin** 500 mg twice daily and **insulin** 62 units daily. Within 3 months of starting disopyramide 250 mg twice daily her **insulin** dose was reduced to 24 units daily, she stopped taking **metformin** and was eating 'substantial snacks' to avoid hypoglycaemia.[10] The **insulin** requirements of another patient with type 2 diabetes were markedly reduced when disopyramide was started.[11]

The manufacturers note that patients at particular risk for hypoglycaemia are the elderly, the malnourished, and diabetics, and that impaired renal function and impaired cardiac function may be predisposing factors.[12,13] They advise close monitoring of blood glucose levels[12,13] and withdrawal of disopyramide if problems arise.[12] This is not simply a problem for diabetics, but certainly within the context of diabetes the blood glucose-lowering effects of disopyramide may possibly cause particular difficulties. Although not strictly an interaction, the concurrent use of disopyramide and antidiabetics should be well monitored because of the potential for severe hypoglycaemia, as the cases show.

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13. Norpace (Disopyramide). Pfizer Inc. US Prescribing information, September 2006.

Antidiabetics + Disulfiram

Disulfiram appears not to affect the control of diabetes mellitus. Disulfiram does not affect the pharmacokinetics of tolbutamide.

Clinical evidence, mechanism, importance and management

The manufacturers of disulfiram say that caution should be exercised if it is used in diabetics,[1] but a reviewer[2] who had given disulfiram to over 20 000 alcoholics said that he had prescribed disulfiram for several hundred patients with diabetes mellitus over 20 years without any apparent adverse effects and therefore any theoretical interaction is rarely, if ever, applicable to clinical practice. It would be reasonable to assume that many of these patients were also taking **insulin** or one of the older oral antidiabetics. There do not appear to be any reported cases in the literature of adverse interactions between disulfiram and any of the antidiabetics. In a study in 5 healthy subjects, disulfiram (400 mg three times daily for one day, then once daily for one day, then 200 mg daily for 2 days) had no significant effect on the half-life or clearance of intravenous **tolbutamide** 500 mg.[3] The conclusion to be drawn from all of this is that any reaction is very rare (if it ever occurs), and no special precautions would normally appear to be necessary.

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Antidiabetics + Diuretics; Loop

The control of diabetes is not usually disturbed to a clinically relevant extent by etacrynic acid, furosemide, or torasemide. However, there are a few reports suggesting that etacrynic acid and furosemide can, rarely, raise blood glucose levels.

Clinical evidence

(a) Etacrynic acid

A double-blind study in 24 hypertensive patients, one-third of whom were diabetics, found that etacrynic acid 200 mg daily for 6 weeks impaired their glucose tolerance and raised the blood glucose levels of the diabetic patients to the same extent as hydrochlorothiazide 200 mg daily in diabetic patients and non-diabetics .[1] However, in other studies no change in carbohydrate metabolism or glucose tolerance was seen in 6 diabetic patients given etacrynic acid 150 mg daily for a week,[2] or in 10 patients described as pre-diabetic given etacrynic acid 50 mg for a week.[3]

(b) Furosemide

Although furosemide can elevate blood glucose levels,[4] worsen glucose tolerance[5] and occasionally cause glycosuria or even acute diabetes in individual patients,[6,7] the general picture is that the control of diabetes is not usually affected by furosemide.[8] No change in glucose tolerance was seen in 10 patients described as pre-diabetic when they were given furosemide 40 mg daily for a week.[3] No clinically relevant changes in the control of diabetes were seen in a 3-month study of 29 patients with type 2 diabetes taking furosemide 40 mg daily and an average of 7 mg of **glibenclamide** (**glyburide**) daily.[9]

(c) Torasemide

A three-month study in 32 patients with congestive heart failure and type 2 diabetes mellitus taking **glibenclamide** found that torasemide 5 mg daily caused a small but clinically insignificant fall in blood glucose levels.[9]

Mechanism

Uncertain.

Importance and management

Information is limited. Some impairment of glucose tolerance may possibly occur, but there seems to be a lack of evidence in the literature to show that any loop diuretic has much effect on the control of diabetes in most patients.

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Antidiabetics + Diuretics; Thiazide and related

By raising blood glucose levels, the thiazide and related diuretics can reduce the effects of the antidiabetics and impair the control

of diabetes. However, this effect appears to be dose related, and is less frequent at the low doses now more commonly used for hypertension. Hyponatraemia has rarely been reported when chlorpropamide was given with a thiazide and potassium-sparing diuretic. An isolated report describes severe hypoglycaemia in a patient taking glibenclamide (glyburide) shortly after metolazone was started. Voglibose had no important effect on the pharmacokinetics of hydrochlorothiazide, and hydrochlorothiazide did not appear to alter metformin pharmacokinetics.

Clinical evidence

(a) Effects on glucose control

Chlorothiazide, the first of the thiazide diuretics, was found within a year of its introduction in 1958 to have hyperglycaemic effects.[1] Since then a very large number of reports have described hyperglycaemia, the precipitation of diabetes in pre-diabetics, and the disturbance of blood sugar control in diabetics taking thiazides. One example from many:

A long-term study in 53 patients with type 2 diabetes found that **chlorothiazide** 500 mg or 1 g daily or **trichlormethiazide** 4 or 8 mg daily caused a mean rise in blood glucose levels from about 6.7 mmol/L to 7.8 mmol/L. Only 7 patients needed a change in their treatment: 4 required more of their oral antidiabetic, 2 an increase in **insulin** dose, and one was transferred from **tolbutamide** to **insulin**. The oral antidiabetics used included **tolbutamide**, **chlorpropamide**, **acetohexamide** and **phenformin**.[2]

A rise in blood glucose levels has been observed with **bendroflumethiazide**,[3,4] **benzthiazide**,[5] **hydrochlorothiazide** 100 to 300 mg daily,[3] and **chlortalidone** 50 to 100 mg daily.[6] A study in hypertensive patients found that **chlortalidone** 50 mg daily increased glucose and insulin levels, but **hydrochlorothiazide** 50 mg daily alone or as part of a potassium and/or magnesium-sparing regimen did not.[7]

More recent data suggest that the effects of thiazides on blood glucose may be dose related. In a double-blind randomised study comparing the effects of 1.25 or 5 mg of **bendroflumethiazide** on blood glucose, the lower dose had no effects on insulin action, whereas when the higher dose was given, there was evidence of impaired glucose tolerance.[8] A review of the literature on **hydrochlorothiazide** similarly reports that low doses (6.25 to 12.5 mg) lack significant effects on blood glucose levels.[9]

A man with type 2 diabetes, stabile taking **glibenclamide** (**glyburide**) 10 mg daily and hospitalised for congestive heart failure, became clinically hypoglycaemic (blood glucose levels unmeasurable by *Labstix*) within 40 hours of starting **metolazone** 5 mg daily. He was treated with intravenous glucose. Although both **glibenclamide** and **metolazone** were stopped, he had 4 further hypoglycaemic episodes over the next 30 hours.[10] The reasons are not understood. *In vitro* studies did not find any evidence that **metolazone** displaces **glibenclamide** from its protein binding sites, which might possibly have provided some explanation for what happened.[10]

The hypoglycaemic responses of 10 healthy subjects were studied following an intravenous infusion of **tolbutamide** 3 mg/kg, given 3 days before and one hour after the last dose of oral **cicletanine** 100 mg daily for a week.[11] No clinically relevant changes were seen. Note that, studies in *animals* and in non-diabetic hypertensive patients found that, at therapeutic doses, **cicletanine** did not affect glycoregulation.[12] The conclusion to be drawn is that **cicletanine** is unlikely to affect the control of diabetes in patients, but this needs confirmation from longer-term clinical studies.

(b) Hyponatraemia

A hospital report describes 8 cases of low serum sodium concentrations observed over a 5-year period in patients taking **chlorpropamide** and **hydrochlorothiazide** 50 mg with amiloride 5 mg.[13]

(c) Pharmacokinetics

A study in 12 healthy subjects given a single 25-mg dose of **hydrochlorothiazide** before and after taking **voglibose** 5 mg three times daily for 11 days found that the **hydrochlorothiazide** plasma levels were slightly increased by the **voglibose** (AUC increased 8%, maximum plasma levels increased 15%) but these changes were considered to be clinically irrelevant. The combination was well tolerated and adverse events were unchanged.[14]

In a study in 6 patients with diabetes taking **metformin**, adding **hydrochlorothiazide** for 2 weeks (4 patients) or stopping **hydrochlorothiazide** for 2 weeks (2 patients) had no effect on metformin AUC or clearance. This study was undertaken because of an earlier indication in 2 of these patients that hydrochlorothiazide might have increased metformin levels, but this was not confirmed.[15]

Mechanism

Not understood. One study suggested that the hyperglycaemia is due to the inhibition of insulin release by the pancreas.[16] Another suggestion is that the peripheral action of insulin is affected in some way.[5,17] There is also evidence that the effects may be related in part to potassium depletion.[18] The hyponatraemia appears to be due to the additive sodium-losing effects of chlorpropamide, the thiazide and amiloride. Obese patients may be more sensitive to the effects of hydrochlorothiazide on insulin metabolism.[7]

Importance and management

The reduction in the blood glucose-lowering effects of the antidiabetics with thiazides is extremely well documented (not all references are given here) but of only moderate practical importance, particularly as much of the data relates to higher doses of thiazides than those now used clinically for hypertension. Low doses of thiazides have a lesser effect on plasma glucose, and 2009 guidelines on the treatment of hypertension in diabetes recommend the use of thiazides as add-on therapy if ACE inhibitors or angiotensin II receptor antagonists alone are not effective.[19] If higher doses are used, increased monitoring of diabetic control would seem prudent. There is evidence that the full effects may take many months to develop in some patients.[4] Most patients respond to a modest increase in the dose of their antidiabetics. This interaction may be expected to occur with all thiazides and possibly related diuretics, such as clopamide and metolazone. Hyponatraemia is a rare but recognised adverse effect of the thiazides and no additional precautions would therefore seem necessary.

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Antidiabetics + Fenfluramine

Fenfluramine has inherent blood glucose-lowering activity that can add to, or in some instances replace, the effects of conventional antidiabetic drugs.

Clinical evidence, mechanism, importance and management

A study of the substitution of fenfluramine (initially 40 mg daily, increased to 120 mg daily) for a biguanide found that diabetes was equally

well controlled by either drug in 4 of 6 patients.[1] The blood glucose-lowering effects of fenfluramine have also been described elsewhere.[2,3] It seems that fenfluramine increases the uptake of glucose into skeletal muscle, thereby lowering blood glucose levels.[3,4]

This is a well established and, on the whole, an advantageous rather than an adverse reaction, but it would be prudent to check on the extent of the response if fenfluramine is added or withdrawn from the treatment being received by diabetics. However, note that fenfluramine was generally withdrawn in 1997 because its use was found to be associated with a high incidence of abnormal echocardiograms indicating abnormal functioning of heart valves.

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Antidiabetics + Fibrates

A number of reports describe hypoglycaemia and/or an enhancement of the effects of antidiabetic drugs (mostly insulin and sulfonylureas) in patients given fibrates. The combination of gemfibrozil and repaglinide should be avoided, because a marked pharmacokinetic interaction can result in serious hypoglycaemia. Gemfibrozil also causes large increases in the AUCs of pioglitazone and rosiglitazone. Only a modest pharmacokinetic interaction occurs between gemfibrozil and nateglinide. The antidiuretic effects of clofibrate in the treatment of diabetes insipidus are opposed by glibenclamide (glyburide). There are cases of paradoxical reductions in HDL-cholesterol with the combination of fibrates and thiazolidinediones.

Clinical evidence

A. Bezafibrate

(a) Repaglinide

In a study in healthy subjects bezafibrate 400 mg daily for 5 days had no effect on the pharmacokinetics of a single 250-microgram dose of repaglinide, and did not alter the blood glucose-lowering effect of repaglinide.[1]

(b) Sulfonylureas and Biguanides

Three elderly patients with type 2 diabetes and mild renal impairment taking **glibenclamide** (**glyburide**) developed hypoglycaemia when they were given bezafibrate: one of them needed a 60% dose reduction, another was given **tolbutamide** instead, and the third was able to stop both **glibenclamide** and **buformin**.[2] During the period 1985 to 1990, the French Centres Régionaux de Pharmacovigilance recorded 7 cases of hypoglycaemia, which developed in patients taking unnamed sulfonylureas when they were given fibrates (one case with bezafibrate).[3]

B. Ciprofibrate

During the period 1985 to 1990, the French Centres Régionaux de Pharmacovigilance recorded 7 cases of hypoglycaemia, which developed in patients taking unnamed **sulfonylureas** when they were given fibrates (3 cases with ciprofibrate).[3]

C. Clofibrate

(a) Hypoglycaemia

Over a 5-day period while taking clofibrate 2 g daily, the control of diabetes was improved in 6 out of 13 patients with type 2 diabetes taking various unnamed sulfonylureas. Hypoglycaemia (blood glucose levels of about 1.7 to 2.2 mmol/L) was seen in 4 patients.[4] Other studies confirm that some, but not all, patients have a fall in blood glucose levels while taking clofibrate and the control of the diabetes can improve.[5-12] In one study[13] the half-life of **chlorpropamide** ranged from 40 to 62 hours in 5 subjects taking clofibrate compared with a mean of about 36 hours in control subjects.

(b) Reduced antidiuretic effects

Clofibrate 2 g daily reduced the volume of urine excreted by 2 patients with pituitary diabetes insipidus, but when **glibenclamide** was also given the volume increased once again. Without treatment they excreted 5.8 litres and 6.5 litres of urine daily, and this reduced to only 2.4 litres and 1.7 litres, respectively, while taking clofibrate, whereas with **glibenclamide** and clofibrate they excreted 3.6 litres and 3.7 litres daily, respectively.[14]

D. Fenofibrate

(a) Pioglitazone or Rosiglitazone

There are reports of paradoxical reductions in HDL-cholesterol levels in a few patients taking a fibrate (bezafibrate, fenofibrate) with a thiazolidinedione, and a few are cited as examples.[15-19] In one analysis, this was more likely with the combination than either fibrates or rosiglitazone alone.[18]

(b) Repaglinide

In a study in healthy subjects, fenofibrate 200 mg daily for 5 days had no effect on the pharmacokinetics of a single 250-microgram dose of repaglinide, and did not alter the glucose-lowering effect of repaglinide.[1]

(c) Sulfonylureas

During the period 1985 to 1990, the French Centres Régionaux de Pharmacovigilance recorded 7 cases of hypoglycaemia, which developed in patients taking unnamed sulfonylureas when they were given fibrates (3 cases with fenofibrate).[3]

E. Gemfibrozil

(a) Nateglinide or Repaglinide

In a randomised, crossover study, 12 healthy subjects were given gemfibrozil 600 mg twice daily for 5 doses, with a 250-microgram dose of repaglinide one hour after the final gemfibrozil dose. Gemfibrozil raised the AUC of repaglinide eightfold and increased the plasma levels nearly 29-fold.[20] The interaction was still marked even when the dose of repaglinide was taken 12 hours after the final dose of gemfibrozil (fivefold increase in AUC).[21] Itraconazole (which may interact, see 'Antidiabetics + Azoles; Itraconazole or Ketoconazole', p.545) given with gemfibrozil and repaglinide further increased these effects. The blood glucose-lowering effects of repaglinide were considerably enhanced and prolonged, both by gemfibrozil alone and in combination with itraconazole.[20] In 2003, the European Agency for the Evaluation of Medicinal Products had received five reports of serious hypoglycaemic episodes with gemfibrozil and repaglinide.[22]

In contrast, in a very similar study by the same research group, the concurrent use of gemfibrozil and itraconazole caused only a modest 47% increase in the AUC of a single 30-mg dose of nateglinide, and did not significantly alter the blood glucose response to nateglinide in healthy subjects.[23]

(b) Pioglitazone or Rosiglitazone

In a study in healthy subjects, gemfibrozil 600 mg twice daily for 4 days increased the mean AUC of a single 4-mg dose of rosiglitazone 2.3-fold, the peak plasma level by 20% and the 24-hour plasma level almost ten-fold.[24] In the same way, gemfibrozil increased the mean AUC of a single dose of pioglitazone 3.2-fold without altering its maximum level, but raised the 48-hour plasma level approximately 15-fold.[25] A similar increase in the AUC of pioglitazone was reported in another study.[26] In these studies, the effects of these pharmacokinetic changes on the pharmacodynamics of rosiglitazone or pioglitazone were not assessed.[24-26]

(c) Sulfonylureas or Insulin

Fasting blood glucose levels decreased in 10 patients with diabetes, and increased in 4 of 14 patients with diabetes receiving insulin, **acetohexamide**, **chlorpropamide** or **glipizide** who were given gemfibrozil (800 mg daily initially, reduced later to 400 to 600 mg daily).[27] Another study found that of 20 patients, 9 required a slight increase in the dose of insulin or sulfonylurea (**glibenclamide** or **chlorpropamide**), and one a decreased dose, when they were given gemfibrozil 800 mg to 1.6 g daily.[28] A single report describes hypoglycaemia, which occurred in a diabetic taking **glibenclamide** when they were given gemfibrozil 1.2 g daily. The **glibenclamide** dose was reduced from 5 to 1.25 mg daily with satisfactory diabetic control. When the gemfibrozil was later stopped and restarted, the dose of the **glibenclamide** had to be increased and then reduced.[29] A placebo-controlled study in 10 healthy subjects found that gemfibrozil 600 mg twice daily for 5 doses increased the AUC of a single 500-microgram dose of **glimepiride** by 23%, but there were no significant changes in serum insulin or blood glucose.[30]

Mechanism

The suggested reasons for the alteration in diabetic control with fibrates include the displacement of the sulfonylureas from their plasma protein binding sites,[7] alterations in their renal excretion,[13] and a decrease in insulin resistance.[6,31] Clofibrate has also been shown to have a blood glucose-lowering action of its own, which improves the glucose tolerance of diabetics.[12]

It is thought that gemfibrozil inhibits the metabolism of repaglinide by the cytochrome P450 isoenzyme CYP2C8, and that inhibition of CYP3A4 (its other main route of metabolism) by itraconazole further blocks repaglinide metabolism.[20] The organic anion transporting polypeptide 1B1 (OATP1B1) appears to have a limited role in the interaction of gemfibrozil with repaglinide.[32] Gemfibrozil also inhibits the CYP2C8-mediated metabolism of rosiglitazone and pioglitazone.[24,25] In addition, gemfibrozil may inhibit CYP2C9-mediated metabolism of glimepiride and other sulfonylureas such as glipizide, glibenclamide or **gliclazide**,[30] and also nateglinide.[23] It seems possible that any or all of these mechanisms might contribute towards enhanced hypoglycaemia.

Usually, fibrates, and also thiazolidinediones, increase HDL-cholesterol, but both thiazolidinediones and fibrates alone have caused paradoxical reductions in HDL-cholesterol. The reason for this is unknown.

Importance and management

The interaction between the sulfonylureas and clofibrate is established and well documented. The incidence is uncertain, but what is known suggests that between about one-third and one-half of patients may be affected. Alteration in diabetic control, most usually hypoglycaemia, has been seen in diabetics taking sulfonylureas with bezafibrate, ciprofibrate, fenofibrate, and gemfibrozil. There would seem to be no good reason for avoiding the concurrent use of sulfonylureas and fibrates, but be aware that the dose of the antidiabetic may need adjustment. Patients should be warned that excessive hypoglycaemia occurs occasionally and unpredictably.

Note that on the basis of the study,[20] and following five reports of serious hypoglycaemic episodes with gemfibrozil and repaglinide, the European Agency for the Evaluation of Medicinal Products decided to contraindicate concurrent use.[22]

Marked increases in the AUC of rosiglitazone and pioglitazone have been seen with gemfibrozil, but the clinical relevance of these has not been assessed. Until further experience is gained, caution is warranted. Only modest increases in plasma levels of nateglinide have been seen with gemfibrozil, but the manufacturer recommends caution if nateglinide is given with gemfibrozil.[33]

The general relevance of the cases of paradoxical reductions in HDL-cholesterol in patients taking a fibrate with rosiglitazone or pioglitazone is unclear, but bear them in mind in the event of an unexpected response to treatment.

Information about reduced diuretic effects is limited. It would seem prudent to avoid the concurrent use of drugs with actions that are antagonistic.

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Antidiabetics + Glucosamine ± Chondroitin

In a controlled study, glucosamine supplements with chondroitin had no effect on glycaemic control in patients taking oral antidiabetic drugs but one report notes that unexpected increases in blood glucose levels have occurred.

Clinical evidence, mechanism, importance and management

In 2000, the Canadian Adverse Drug Reaction Monitoring Programme (CADRMP) briefly reported that unexpected increases in blood glucose levels had occurred in diabetic patients taking glucosamine sulfate, or glucosamine with chondroitin.[1] However, in a well controlled study, *Cosamin DS* (glucosamine hydrochloride 1.5 g daily plus chondroitin sulfate sodium 1.2 g) daily for 90 days had no effect on the control of diabetes (HbA_{1c}) in 22 patients with type 2 diabetes, 18 of whom were receiving oral antidiabetics (specific drugs not named) and 4 who were diet controlled.[2]

Endogenous glucosamine has a role in glucose metabolism, and may increase insulin resistance. In one case, glucosamine also reduced hypoglycaemic episodes in a patient with metastatic insulinoma.[3]

The interaction is not established, and the results of the controlled study suggest that glucosamine supplements are unlikely to affect the control of diabetes. However, it has been suggested that the results may not be applicable to patients with later stages of diabetes[4] (i.e. those with type 2 diabetes who require, or are expected to require, insulin). Therefore, it may be prudent to increase monitoring of blood glucose in these patients if glucosamine supplements are taken. Also, if glucose control unexpectedly deteriorates, bear in mind the possibility of self-medication with supplements such as glucosamine.

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Antidiabetics + Guanethidine and related drugs

Limited evidence suggests that guanethidine has blood glucose-lowering activity, which may possibly add to the effects of conventional antidiabetics. One case report suggests soluble insulin may exaggerate the hypotensive effects of debrisoquine.

Clinical evidence

(a) Debrisoquine

An man with type 1 diabetes taking debrisoquine 20 mg twice daily developed severe postural hypotension within an hour of receiving 28 units of a short-acting **insulin** (soluble insulin) and 20 units of **isophane insulin**. He became dizzy and was found to have a standing blood pressure of 97/72 mmHg. The postural fall in systolic pressure was 65 mmHg. He had no evidence of hypoglycaemia and no hypotension when using 48 units of **isophane insulin** without the soluble insulin.[1] **Insulin** can cause hypotension but this is only seen in those with an impaired reflex control of blood pressure.[1]

(b) Guanethidine

A diabetic needed an **insulin** dose increase from 70 to 94 units daily when guanethidine was withdrawn.[2] A later study in 3 patients with type 2 diabetes found that guanethidine 50 to 90 mg daily caused a significant improvement in their glucose tolerance.[3] Two other reports also suggest that guanethidine has blood glucose-lowering effects.[4,5]

Mechanism

It has been suggested that the interaction between insulin and guanethidine occurs because guanethidine can impair the homoeostatic mechanism concerned with raising blood glucose levels, by affecting the release of catecholamines. The balance of the system thus impaired tends to be tipped in favour of a reduced blood glucose level, resulting in a reduced requirement for the antidiabetic. The interaction between debrisoquine and insulin is not understood.

Importance and management

Information about both of these interactions is very limited, and their general importance is uncertain. Increase the frequency of blood glucose monitoring if guanethidine or related drugs are started or stopped. Also check patients given debrisoquine (no longer generally available) and insulin, particularly if they are taking vasodilators, to ensure that excessive hypotension does not develop.

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Antidiabetics + Guar gum or Glucomannan

Guar gum appeared not to affect the absorption of glipizide or glibenclamide (glyburide) to a clinically relevant extent. Although guar gum modestly reduced the absorption of metformin, it enhanced its postprandial hypoglycaemic effect. Glucomannan appeared to reduce the initial absorption of glibenclamide, but also enhanced its hypoglycaemic effect.

Clinical evidence, mechanism, importance and management

(a) Glucomannan

Glucomannan 3.9 g reduced the plasma levels of a single 2.5-mg dose of **glibenclamide** (**glyburide**) in 9 healthy subjects. Four samples taken over 30 to 150 minutes found that the plasma levels of **glibenclamide** were reduced by about 50%.[1] Despite this, plasma glucose levels were lower with the combination than with **glibenclamide** alone. Because plasma samples were not taken beyond 150 minutes, it is unclear what effect glucomannan has on the extent of **glibenclamide** absorption. The clinical relevance of these changes is unclear, but they seem unlikely to be important.

(b) Guar gum

In one study in 10 healthy subjects guar gum was found to have no effect on the AUC or maximum serum levels of a single 2.5-mg dose of **glipizide**. In this study **glipizide** was given alone, or 30 minutes before breakfast, and this treatment was compared with guar gum granules (4.75 g guar gum) given either with the breakfast or with the **glipizide**.[2]

In one comparative study, guar gum was found to reduce the AUC of **glibenclamide** from one formulation (*Semi-Euglucon*) by about 30%, but not another formulation (*Semi-Euglucon-N*),[3] possibly because the latter preparation is more rapidly and completely absorbed. Similarly, in a crossover study in 9 patients with type 2 diabetes, guar gum granules 5 g three times daily with meals did not significantly affect the AUC or maximum serum level of **glibenclamide** 3.5 mg twice daily from *Semi-Euglucon-N*. In addition, the combination slightly reduced fasting blood glucose when compared with baseline values.[4]

In a single-dose study, guar gum 10 g reduced the absorption rate of **metformin** 1.7 g and reduced the AUC by 39% in healthy subjects, but the total reduction in postprandial blood glucose levels was increased.[5]

It seems doubtful if any of these modest pharmacokinetic interactions has much, if any, clinical relevance because guar gum can improve the metabolic control and decrease serum lipids in patients with type 2 diabetes.[4]

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Antidiabetics + H_2-receptor antagonists

On the whole cimetidine and ranitidine do not appear to significantly alter diabetic control with sulfonylureas, although cases of adverse effects have been seen when glibenclamide (glyburide) was given with ranitidine, and when gliclazide or glipizide were given with cimetidine.

Cimetidine appears to reduce the clearance of metformin, and may have contributed to a case of metformin-associated lactic acidosis. Cimetidine does not appear to alter repaglinide pharmacokinetics, and ranitidine does not appear to alter pioglitazone or rosiglitazone pharmacokinetics. Acarbose did not alter ranitidine pharmacokinetics in one study, but miglitol decreased the AUC of ranitidine by 60%.

Clinical evidence

A. Alpha-glucosidase inhibitors

The manufacturer of **acarbose** notes that it had no effect on the pharmacokinetics or pharmacodynamics of **ranitidine** in healthy subjects.[1] The manufacturer of **miglitol** notes that it reduced the bioavailability of **ranitidine** by 60%.[2]

B. Biguanides

Cimetidine 800 mg daily was found to reduce the renal clearance of **metformin** in 7 healthy subjects by 27% and increase the AUC by 50%.[3] A 59-year-old woman with type 2 diabetes taking long-term **metformin** 500 mg three times daily developed severe metabolic acidosis with cardiovascular collapse and acute renal failure. Three months previously she had started orlistat 120 mg three times daily, which caused chronic diarrhoea. During the 4 days before hospital admission, she was prescribed **cimetidine** 400 mg twice daily for her abdominal pain. The **metformin**-associated lactic acidosis was considered to have been precipitated by the orlistat and **cimetidine**.[4]

C. Sulfonylureas

(a) Chlorpropamide

Cimetidine had no effect on the pharmacokinetics of chlorpropamide in healthy subjects,[5] and in another study the blood glucose-lowering effects of chlorpropamide remained unaltered when **cimetidine** was given.[6]

(b) Glibenclamide (Glyburide)

A study in healthy subjects reported that the blood glucose-lowering effects of glibenclamide were slightly reduced by **cimetidine** and **ranitidine**. This occurred despite the fact that **cimetidine** increased the AUC of glibenclamide by 37% and ranitidine had no significant pharmacokinetic effect on glibenclamide.[7] Marked hypoglycaemia was seen in a patient taking glibenclamide 5 mg daily when **ranitidine** 150 mg twice daily was also taken.[8] Conversely, a study in healthy subjects found that the blood glucose-lowering effects of glibenclamide remained unaltered by **cimetidine**.[6]

(c) Gliclazide

An elderly patients with type 2 diabetes taking gliclazide 160 mg daily developed very low blood glucose levels (1 mmol/L) after starting to take **cimetidine** 800 mg daily.[9]

(d) Glimepiride

In a study in healthy subjects no relevant interactions, either pharmacokinetic or pharmacodynamic, were seen when glimepiride was given with either **cimetidine** or **ranitidine**.[10]

(e) Glipizide

Six patients with type 2 diabetes were given **cimetidine** 400 mg one hour before taking a dose of glipizide (average dose 5.8 mg) and then 3 hours later they were given a standard meal with **cimetidine** 200 mg. The expected rise in blood glucose levels after the meal was reduced by 40% and in two of the patients plasma glucose levels fell to less than 3 mmol/L. Cimetidine increased the glipizide AUC by 23%.[11,12] However, a study in healthy subjects found that the hypoglycaemic activity of glipizide remained unaltered by **cimetidine**.[6] Two studies in type 2 diabetics found that **ranitidine** 150 mg increased the AUC of glipizide by 29% and 34%,[12,13] and reduced the expected rise in blood sugar levels after a meal by 22%.[12] However, another study by the same research group reported that **ranitidine** 300 mg had no significant effects on either the pharmacokinetics or the effects of glipizide, except that the absorption was delayed.[14]

(f) Tolbutamide

The pharmacokinetics of tolbutamide 250 mg daily for 4 days were not significantly changed in 7 healthy subjects when **cimetidine** 800 mg daily was added for a further 4 days.[15] Other studies also found no pharmacokinetic interaction between tolbutamide and **cimetidine**,[16,17] or between tolbutamide and **ranitidine**,[17] and the hypoglycaemic activity of tolbutamide remained unaltered by **cimetidine**.[6] In contrast, in another study in healthy subjects, the AUC of tolbutamide was found to be slightly increased by 20% and the elimination half-life decreased by 17% by **cimetidine** 1.2 g daily, but plasma glucose levels were not significantly changed. **Ranitidine** 300 mg had no effect.[18] A later study found effectively the same results.[19]

(g) Unnamed sulfonylureas

A report briefly describes hypoglycaemia when 2 patients taking unnamed sulfonylureas were given **cimetidine**.[20]

D. Other oral antidiabetics

(a) Pioglitazone

A study in healthy subjects found that when pioglitazone 45 mg daily was given with **ranitidine** 150 mg twice daily the pharmacokinetics of both drugs were not significantly affected.[21]

(b) Repaglinide

An open-label, crossover study in 14 healthy subjects found that **cimetidine** 400 mg twice daily had no effect on the pharmacokinetics of repaglinide 2 mg three times daily.[22]

(c) Rosiglitazone

A crossover study in 12 healthy subjects found that pre-treatment with **ranitidine** 150 mg twice daily for 4 days had no effect on the pharmacokinetics of either a single 4-mg oral dose or a single 2-mg intravenous dose of rosiglitazone.[23]

Mechanism

Where an interaction occurs[18] it may be because the cimetidine inhibits the metabolism of the sulfonylurea by the liver, thereby increasing its effects. Cimetidine appears to inhibit the excretion of metformin by the kidneys,[3] and this may have contributed to the case of metformin-associated lactic acidosis described.[4]

Importance and management

The many studies cited here show that cimetidine generally causes no important changes in the pharmacokinetics or pharmacodynamics of the sulfonylureas (chlorpropamide, glimepiride and tolbutamide). Similarly, ranitidine did not interact with glimepiride or tolbutamide. Only a few isolated cases of hypoglycaemia have been reported with ranitidine or cimetidine and sulfonylureas (glibenclamide (glyburide), gliclazide and unnamed), and only one research group has found a possible increase in the blood glucose-lowering effect of glipizide with cimetidine and ranitidine.

It has been suggested that the dose of metformin may need to be reduced if cimetidine is used, bearing in mind the possibility of lactic acidosis if levels become too high,[3] and there is one case where cimetidine may have contributed to lactic acidosis.

The only other possible interaction of significance appears to be that between miglitol and ranitidine, although the clinical relevance of this has not been assessed.

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Antidiabetics + Hormonal contraceptives

Some women may require small increases or decreases in their dose of antidiabetic drug while taking hormonal contraceptives, but it is unusual for the control of diabetes to be seriously disturbed. Irrespective of diabetic control, hormonal contraceptives should be used with caution in patients with diabetes because of the increased risk of arterial disease. Exenatide, pioglitazone, rosiglitazone and repaglinide do not appear to have a clinically significant effect on the pharmacokinetics of contraceptive steroids, and a hormonal contraceptive containing ethinylestradiol and levonorgestrel does not appear to have an important effect on the pharmacokinetics of repaglinide.

Clinical evidence

There are numerous reports of the effect of contraceptive steroids on glucose tolerance in non-diabetics. More recent reports from studies using low-dose oral hormonal contraceptives, support the suggestion that changes in glucose metabolism are minimal.[1,2] Problems with glucose metabolism seem very unlikely when the dose of oestrogen is less than 50 micrograms.[3] The progestogen in the hormonal contraceptive may also be important.[3-6] Progestogens with androgenic properties, such as **norgestrel**, **levonorgestrel** and to a lesser extent **norethisterone** (**norethindrone**), may affect carbohydrate metabolism. **Etynodiol** (**etynodrel**), which has weak androgenic activity, was found to cause smaller reductions in glucose tolerance, and **noretynodrel** was found to have no effect.[3-5] Studies of healthy, non-diabetic women using oral hormonal contraceptives containing **ethinylestradiol** 20 to 40 micrograms with third generation progestogens (**gestodene**, **desogestrel** or **norgestimate**) found no effect on carbohydrate metabolism in women using monophasic oral hormonal contraceptives, but impaired glucose tolerance developed in 10% of the women taking triphasic oral hormonal contraceptives. It was considered that the clinical consequences of impaired glucose tolerance and reduced **insulin** sensitivity induced by hormonal contraceptives are probably confined to risk groups e.g. women with ovarian hyperandrogenism, obesity, previous gestational diabetes mellitus, perimenopausal women, or women with a family history of diabetes.[7]

A study in 11 **insulin**-dependent diabetics, free of vascular complications, taking low-dose oral hormonal contraceptives (**ethinylestradiol** 30 micrograms with **gestodene** 75 micrograms) found that although the plasma levels of most haemostatic variables were comparable to those of non-diabetics using the same contraceptive preparation, the rate of fibrin formation was increased and the fibrinolytic response attenuated. This implies that women with diabetes can have a higher sensitivity to the thrombogenic effects of hormonal contraceptives.[7]

1. Exenatide. The manufacturers state that when an oral combined hormonal contraceptive (**ethinylestradiol** 30 micrograms with **levonorgestrel** 150 micrograms) was given one hour before exenatide 10 micrograms twice daily the AUC and maximum levels of the contraceptive steroids were unaffected. Giving the contraceptive 30 minutes after exenatide delayed the time to maximum level by 2 to 4 hours and reduced the maximum levels of **ethinylestradiol** and **levonorgestrel** by up to about 40%, but without any effect on AUC.[8] This is not clinically relevant.

2. Insulin. In one study in 179 diabetic women, 34% needed an increase and 7% needed a decrease in their insulin dose when they were given an oral hormonal contraceptive.[9] There are also a few scattered reports of individual diabetics who experienced a marked disturbance of their diabetic control when given an oral hormonal contraceptive, some of which were low dose.[10-13]

However, in a study of 38 patients with type 1 diabetes it was found that progestogen-only and oral combined hormonal contraceptives had little effect on the control of diabetes,[14] and another report[15] about women taking *Orthonovin* (**norethisterone** with **mestranol**) stated that no insulin dose changes were necessary. Similarly, no change in glycaemic control was found in 22 women with well-regulated type 1 diabetes who took a monophasic combination of **ethinylestradiol** and **gestodene** for one year.[7]

3. Pioglitazone. In a study in 35 healthy women given pioglitazone 45 mg daily with either an oral combined hormonal contraceptive (**ethinylestradiol** 35 micrograms with **norethisterone** 1 mg) or placebo for 21 days, pioglitazone slightly reduced the AUC of ethinylestradiol by 11%, but had no effect on the AUC of norethisterone.[16] Similar results were reported in another study.[17] This is unlikely to be clinically relevant.

4. Repaglinide. A crossover study in healthy subjects found that an oral combined hormonal contraceptive (**ethinylestradiol** 30 micrograms with **levonorgestrel** 150 micrograms) slightly increased the maximum plasma level of repaglinide 2 mg three times daily by 17%, although the bioavailability of repaglinide was not altered.[18] Repaglinide did not significantly alter the bioavailability of **ethinylestradiol** or **levonorgestrel**.[18]

5. Rosiglitazone. Rosiglitazone 8 mg daily, given for the first 2 weeks of two cycles in 32 women taking an oral combined hormonal contraceptive (**ethinylestradiol** 35 micrograms with **norethisterone** 35 micrograms), was found to have no effect on the pharmacokinetics of either contraceptive steroid.[19]

6. Sitagliptin. Sitagliptin did not appear to alter the pharmacokinetics of **norethisterone** or **ethinylestradiol** given as part of an oral hormonal contraceptive.[20]

Mechanism

The reasons for changes in glucose metabolism are not understood. Many mechanisms have been considered including changes in cortisol secretion, alterations in tissue glucose utilisation, production of excessive amounts of growth hormone, and alterations in liver function.[21] The effect of exenatide on contraceptive levels is thought to occur because exenatide delays gastric emptying.[8]

Importance and management

The interactions between hormonal contraceptives and antidiabetic drugs are moderately well documented. Concurrent use need not be avoided, but some patients may need a small adjustment in their dose of antidiabetic (increases or decreases). However, it seems likely that routine blood glucose monitoring will identify any problems. Serious disturbances of diabetic control seem extremely rare. Bear in mind that the lowest-strength oral combined hormonal contraceptive preparations (20 micrograms of oestrogen) are recommended for patients with risk factors for circulatory disease (such as diabetics), so the potential for interference with their diabetic control will be minimised if this recommendation is followed. The choice of progestogen may also be important, with levonorgestrel having the most detrimental effect.

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Antidiabetics + Isoniazid

Some reports suggest that isoniazid causes an increase in blood glucose levels in diabetics, whereas another suggests it causes a decrease.

Clinical evidence

A study in 6 diabetics taking **insulin** found that isoniazid 300 to 400 mg daily increased their fasting blood glucose levels by 40% (from an average

of about 14.2 mmol/L to 19.8 mmol/L), and their glucose tolerance curves rose and returned to normal levels more slowly. After 6 days of treatment the average rise was only 20%. Two other patients needed an increased dose of **insulin** while taking isoniazid 200 mg daily, but this was reduced again when the isoniazid was withdrawn.[1]

Another report describes glycosuria and the development of frank diabetes in 3 out of 50 patients given isoniazid 300 mg daily,[2] and hyperglycaemia has been seen in cases of isoniazid poisoning.[3]

In contrast, another study found that isoniazid had a hypoglycaemic effect in 6 out of 8 diabetics.[4] A 500-mg dose of isoniazid caused an 18% (range 5 to 34%) reduction in blood glucose levels after 4 hours; 3 g of **tolbutamide** caused a 28% (19 to 43%) reduction, and together they caused a 35% (17 to 57%) reduction. However, one patient had a 10% increase in blood glucose levels after taking isoniazid, a 41% decrease after **tolbutamide**, and a 30% decrease after taking both drugs. The diabetic control of another patient was not affected by either drug.[4]

Mechanism

Not understood.

Importance and management

The major documentation for these reactions dates back to the 1950s, since when the literature has been virtually (and perhaps significantly) silent. The outcome of concurrent use is therefore somewhat uncertain. Nevertheless, given the effects of isoniazid alone on blood glucose, it would be prudent for diabetics given isoniazid to be monitored for changes in the control of the diabetes. Appropriate dose adjustments of the antidiabetic should be made where necessary.

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Antidiabetics + Karela (*Momordica charantia*)

The blood glucose-lowering effects of chlorpropamide and other antidiabetics can be increased by karela.

Clinical evidence

A report of a patient whose diabetes was poorly controlled on diet and **chlorpropamide**, but much better controlled when she ate curry containing karela, provides evidence that the blood glucose-lowering effects of karela and conventional oral antidiabetics can be additive.[1] Other small, non-controlled studies have subsequently shown that karela produces a significant improvement in glucose tolerance in patients with type 2 diabetes, both when they are taking **chlorpropamide**,[2] **tolbutamide**,[2] **glibenclamide**,[2,3] **glymidine**[2] or **metformin**,[3] and when they are not taking antidiabetics.[4-6] In these studies, karela was given orally as a juice from the fruit,[2,4] dried powdered fruit,[5,6] fried fruits,[2] aqueous extract,[6] or solvent extract from the fruit.[3]

However, in a small randomised placebo-controlled study in 40 patients with type 2 diabetes given karela capsules (*Charantia*) taken three times daily after meals for 3 months, both karela and placebo had no statistically significant effect on HbA_{1c} (there was a very slight *increase* of 0.28% and 0.5%, respectively) and there was no change in mean fasting blood glucose (slight decrease with karela and increase with placebo). In this study, karela was taken in addition to standard **oral antidiabetics** (types not stated) and patients included both those newly diagnosed and those with established diabetes, with HbA_{1c} levels of 7 to 9%.[7]

A case report describes hypoglycaemic coma and seizures in two young non-diabetic children after they were given bitter melon (karela) tea.[8]

Mechanism

Karela (also known as bitter melon, bitter gourd, balsam pear, cundeamor) is the fruit of *Momordica charantia* which is indigenous to Asia and South America. The blood glucose-lowering effects of karela may be due to its content of polypeptide P, a blood glucose-lowering peptide,[9] also known as vegetable insulin (v-insulin).[10] This substance is effective when given subcutaneously,[10] but its oral activity is uncertain.[11] Other blood glucose-lowering compounds isolated from karela include charantin (sterol glucoside mixture in the fruit) and vicine a pyrimidine nucleoside found in the seeds). Karela fruit may have both insulin-like effects and stimulate insulin secretion.[11]

Importance and management

Karela is available in the UK and elsewhere, and is used to flavour foods such as curries, and also used as a herbal medicine for the treatment of diabetes mellitus. Its blood glucose-lowering activity appears to be established, although the best-controlled study so far found its effects to be minimal. Health professionals should therefore be aware that patients may possibly be using karela as well as more orthodox drugs to control their diabetes. Irregular consumption of karela as part of the diet could possibly contribute to unexplained fluctuations in diabetic control.

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Antidiabetics + Ketotifen

The concurrent use of sulfonylureas or biguanides and ketotifen appears to be well tolerated, but a fall in the number of platelets has been seen in one study in patients taking biguanides with oral ketotifen.

Clinical evidence, mechanism, importance and management

A study in 30 hospitalised diabetics (10 diet controlled, 10 taking unnamed **sulfonylureas**, 10 taking unnamed **biguanides**) found that the concurrent use of oral ketotifen 4 mg daily for 14 days was generally well tolerated. However, those taking **biguanides** had a significant decrease in platelet counts and 3 had a marked fall on day 14 to slightly below 100×10^9/L, which returned to normal after a few days.[1] This finding underlies the precaution issued by the UK manufacturers of oral ketotifen,[2] that the concurrent use of oral antidiabetics and ketotifen should be avoided until this effect is explained. However, no other studies appear to have confirmed the fall in platelet count so that its importance remains uncertain.[3]

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Antidiabetics + Lithium

An isolated report describes a diabetic patient receiving insulin who developed hyperglycaemia when his lithium levels were high, but not when the lithium dose was reduced. Conversely, in another isolated case of a patient with type 2 diabetes, glucose control improved when lithium was started. Lithium use has been associated with raised blood glucose levels and the development of diabetes mellitus, but the association is unclear and there is little or

no evidence that its use normally causes significant changes in diabetic control.

Clinical evidence

One patient with mania and diabetes developed hyperglycaemia, in the presence of a constant **insulin** dose, when his serum lithium levels were high (about 1.4 mmol/L), but reducing the lithium level to 1.1 mmol/L led to a lowering of the fasting blood glucose.[1] In contrast, a patient with type 2 diabetes managed with diet and insulin, had a reduction in blood glucose on starting lithium. Insulin was stopped, and at a on-year follow up she was said to have normal blood glucose levels without dietary restrictions or insulin.[2]

However, in a study in 6 patients with type 2 diabetes controlled by diet alone, lithium, taken for one week, did not alter the metabolic response to a standard 50 g carbohydrate breakfast.[3]

Mechanism

Uncertain. A study in 10 psychiatric patients found that lithium carbonate for 2 weeks raised their blood glucose levels and impaired their glucose tolerance.[4] There are also a few case reports of hyperglycaemia, impaired glucose tolerance and diabetes mellitus in patients taking lithium.[5-7] However, a long-term investigation over a period of 6 years, involving 460 patients, found that the mean blood glucose levels remained the same before and after the use of lithium. One patient did develop diabetic ketoacidosis after 4 years of uneventful lithium use, but the authors concluded that the long-term use of lithium did not increase the risk of developing diabetes mellitus.[8] Conversely, there is an isolated case of a patient who developed temporary diabetes requiring insulin after the *withdrawal* of lithium.[9] Note that the incidence of diabetes tends to be higher in patients with manic depression than in the general population.[10]

Importance and management

There are only a couple of reports of disturbed diabetic control in patients taking lithium. Bear the possibility of an interaction in mind if glycaemic control changes when lithium is started in a patient with diabetes.

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Antidiabetics + Macrolides

An isolated report describes severe liver damage with prolonged cholestasis in a patient taking chlorpropamide and erythromycin. Isolated cases of hypoglycaemia have been described in patients taking glibenclamide (glyburide) or glipizide with clarithromycin or erythromycin, and, in a pharmacokinetic study, clarithromycin modestly increased glibenclamide levels. A study in healthy subjects found that hypoglycaemia may occur if tolbutamide and clarithromycin are given concurrently. Pharmacokinetic studies suggest that clarithromycin and telithromycin may enhance the effects of repaglinide, and a case report describes severe hypoglycaemia in a patient taking repaglinide with clarithromycin.

Clinical evidence, mechanism, importance and management

(a) Effects on the liver

A man with type 2 diabetes taking **chlorpropamide** was given **erythromycin ethylsuccinate** 1 g daily for 3 weeks for a respiratory infection. Two weeks later he complained of increasing fatigue and fever. A short episode of pruriginous skin rash was followed by the appearance of dark urine, jaundice and hepatomegaly. The picture over the next 2 years was that of profound cholestasis, complicated by steatorrhoea and marked hyperlipidaemia with disappearance of interlobular bile ducts. He died of ischaemic cardiomyopathy.[1] The reasons for this serious reaction are not understood, but the authors point out that liver damage occurs in a very small number of patients given sulfonylureas, such as **chlorpropamide**, and also with **erythromycin**. They suggest that there may have been an interaction between the two drugs. This case is also complicated by a history of long-term use of phenformin, which is known to be hepatotoxic.[1] No general conclusions can be drawn from this unusual case.

(b) Hypoglycaemia

1. Repaglinide. **Clarithromycin** 250 mg twice daily given to healthy subjects increased the AUC and maximum plasma concentrations of a single 250-microgram dose of repaglinide, given on day 5, by 40% and 67%, respectively. There was a similar corresponding rise in circulating insulin levels.[2] In another similar study, **telithromycin** 800 mg daily for 3 days increased the AUC of a single 250-microgram dose of repaglinide, given on day 3, by 77%. In addition, it increased the blood glucose lowering effect of repaglinide.[3]

An 80-year-old man with diabetes taking repaglinide 500 micrograms three times daily had a hypoglycaemic episode requiring intravenous glucose within 48 hours of starting **clarithromycin** 500 mg twice daily, and another similar episode 2 days later. Repaglinide was stopped.[4]

Clarithromycin and **telithromycin** may inhibit the metabolism of repaglinide by inhibition of cytochrome P450 isoenzyme CYP3A4. The effect of the concurrent use of these drugs should therefore be monitored. Other macrolides that inhibit CYP3A4 (such as erythromycin) would be expected to interact in a similar manner.

2. Sulfonylureas. Two isolated cases of severe hypoglycaemia occurred in elderly, type 2 diabetic patients, with renal impairment, given **glibenclamide** (**glyburide**) or **glipizide** and **clarithromycin**.[5] A further case of hypoglycaemia occurred when an elderly diabetic patient with normal renal function, taking **glibenclamide** 5 mg daily, also took **clarithromycin** 1 g daily as part of an *Helicobacter pylori* eradication regimen.[6] However, in a later pharmacokinetic study, **clarithromycin** had only modest effects on **glibenclamide** levels. In this study, the AUC of **glibenclamide** was increased by 35% when a single 875-microgram dose of **glibenclamide** was given after **clarithromycin** 250 mg twice daily for 2 days.[7] It is possible that **clarithromycin** causes this effect by inhibiting P-glycoprotein.[7]

A case of hypoglycaemia was reported in a patient taking **glibenclamide** and **erythromycin**.[8] However, an earlier single-dose study in 12 patients with type 2 diabetes found that **erythromycin** had little effect on **glibenclamide** pharmacokinetics or on its blood glucose-lowering effects.[9] Nevertheless, a placebo-controlled study involving 34 patients with type 2 diabetes (most of whom were taking **glibenclamide** or **glipizide**) found that oral **erythromycin** 400 mg three times daily for a week reduced fructosamine and fasting blood glucose concentrations and increased insulin secretion. Glycaemic control was also improved in a similar study using oral **erythromycin** 200 mg three times daily for 4 weeks.[10] A later study by the same research group found greater improvements in glucose control in patients with type 2 diabetes taking **glibenclamide** when given **erythromycin** 400 mg daily before sleep.[11] Further studies have shown that **erythromycin** increases gastric motility, which results in better control of blood glucose in patients with type 2 diabetes.[12,13]

A single-dose study in 9 healthy subjects found that **clarithromycin** 250 mg increased the rate of absorption of **tolbutamide** 500 mg by about 20% and increased its bioavailability by 26%. Hypoglycaemia, reported as uneasiness and giddiness, occurred on taking the combination.[14]

The general importance of these cases is uncertain, but some caution may be warranted on concurrent use,[5] and the dose of the sulfonylurea may need to be reduced.

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Antidiabetics + MAOIs or RIMAs

The blood glucose-lowering effects of insulin and the oral antidiabetics can be increased by MAOIs. This may improve the control of blood glucose levels in most diabetics, but in a few it may cause undesirable hypoglycaemia. Moclobemide appears not to interact.

Clinical evidence

(a) Moclobemide

A study in healthy subjects given **glibenclamide** 2.5 mg daily found that moclobemide 200 mg three times daily for a week had no effect on glucose or insulin concentrations after oral glucose tolerance tests.[1] In clinical studies, 8 diabetics taking **glibenclamide** (**glyburide**), **gliclazide**, **metformin** or **chlorpropamide** were given moclobemide, and there was no effect on blood glucose levels or any other evidence of an interaction.[1]

(b) Non-selective MAOIs

A diabetic patient receiving **insulin** experienced postural syncope and hypoglycaemia, which required a reduction in **insulin** dose, when **mebanazine** was also taken.[2] Other reports in diabetics indicate that **mebanazine** increases the blood glucose-lowering effects of **insulin**, **tolbutamide** and **chlorpropamide,** and improves diabetic control.[3-6]

Mechanism

Not fully understood. Mebanazine,[4] iproniazid,[7] isocarboxazid,[8] phenelzine,[4] and tranylcypromine[9] have all been shown to reduce blood glucose levels in the absence of conventional antidiabetics, possibly due to some direct action on the pancreas, which causes the release of insulin.[9] It would seem that this can be additive with the effects of the conventional hypoglycaemics.

Importance and management

The interaction of the non-selective MAOIs and antidiabetics is an established interaction of only moderate clinical importance. It can benefit the control of diabetes in many patients, but some individuals may need a reduction in the dose of their antidiabetic to avoid excessive hypoglycaemia. The effects of concurrent use should be monitored. This interaction would seem possible with any combination of an antidiabetic and a non-selective MAOI.

No clinically important interaction seems to occur between antidiabetics and moclobemide.

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Antidiabetics + Nicotinic acid (Niacin)

Nicotinic acid causes a deterioration in glucose tolerance, which may be dose-related.

Clinical evidence

It is well recognised that nicotinic acid can cause a deterioration in blood glucose tolerance. For example, in a small randomised crossover study, immediate-release nicotinic acid 1.5 g three times daily caused a 16% increase in mean plasma glucose levels and a 21% increase in HbA_{1c} levels in 13 patients with type 2 diabetes.[1] In a retrospective study of patients taking controlled-release nicotinic acid (average dose about 1.5 g daily), nicotinic acid was discontinued in 106 out of 160 patients who were diabetics; of these, 43 patients (about 40%) had the nicotinic acid discontinued because of poor glycaemic control. Furthermore, 14 patients required the addition of oral antidiabetic drugs to control their diabetes.[2]

In contrast, in another placebo-controlled study including 125 patients with diabetes, immediate-release nicotinic acid 3 g daily (or the maximum tolerated dose) only modestly increased plasma glucose levels in patients with diabetes. Moreover, there were no significant differences in antidiabetic medication in diabetic patients taking nicotinic acid versus placebo, although insulin use was increased by 13% in the nicotinic acid group, when compared with 4% in the placebo group.[3] In a placebo-controlled study in patients with type 2 diabetes taking controlled-release nicotinic acid 1 g daily or 1.5 g daily, HbA_{1c} marginally increased by 0.29% in the group receiving 1.5 g daily. There was an initial rise in fasting blood glucose levels between weeks 4 and 8, but this had returned to baseline by week 16. This was probably because some adjustment was made in antidiabetic medication; 29% of patients taking nicotinic acid 1.5 g required an increase in antidiabetic medication compared with 16% taking placebo (difference not significant). Only one patient (2%) taking nicotinic acid 1 g and 3 patients (6%) taking nicotinic acid 1.5 g discontinued treatment because of inadequate glucose control.[4] However, it has been noted that patients enrolled in both these studies had good glycaemic control, and that the findings may not be applicable to those with poor glycaemic control.[5]

Mechanism

Nicotinic acid reduces glucose tolerance, possibly by causing or aggravating insulin resistance.

Importance and management

It is well known that nicotinic acid can cause a deterioration in glycaemic control in patients with diabetes, but the incidence and clinical relevance of this finding is more controversial. The beneficial lipid-modifying effects of nicotinic acid directly improve the main lipid disorders seen in diabetes, which are considered an important contributing factor to the high incidence of cardiovascular disease seen in diabetic patients. The question then is, do the lipid-regulating benefits of nicotinic acid outweigh its adverse effects on glucose homoeostasis? Some consider that they do, especially if low doses of nicotinic acid (2 g or less) are used, and recommend the use of nicotinic acid in diabetic patients in some situations.[6,7] Whenever nicotinic acid is used, diabetic control should be closely monitored, recognising that adjustment of antidiabetic medication may be needed.

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Antidiabetics + NSAIDs

No adverse interaction normally occurs between most NSAIDs and antidiabetic drugs. However, there are isolated cases of hypoglycaemia in patients given fenclofenac with chlorpropamide and metformin; ibuprofen with glibenclamide; indometacin with chlorpropamide; and naproxen with glibenclamide and metformin. Rofecoxib and celecoxib may have been a precipitating factor in cases of acute renal failure and metformin-associated lactic acidosis. The risk of fluid retention with pioglitazone or rosiglitazone is increased by the NSAIDs.

Clinical evidence

A. Metformin

A 58-year-old woman with longstanding type 2 diabetes taking metformin 500 mg twice daily developed serious acute renal failure and lactic acidosis one month after starting **rofecoxib**. She made a full recovery. **Rofecoxib** could have precipitated acute renal failure, which would lead to the accumulation of metformin, and metformin-associated lactic acidosis.[1] Another similar case has been reported in a 61-year-old woman taking metformin and given **rofecoxib**.[2] Similarly, renal failure and metformin-associated lactic acidosis occurred in a 50-year-old woman taking metformin 2 months after starting **celecoxib**. In this case, hydrochlorothiazide and candesartan were thought to have contributed to the renal failure.[3] For a case of hypoglycaemia attributed to ramipril and **naproxen**-induced renal failure in a patient taking metformin and glibenclamide, see *Glibenclamide (Glyburide)*, below.

B. Nateglinide

In a randomised crossover study, 18 healthy subjects were given modified-release **diclofenac** 75 mg on the same day as two 120-mg doses of nateglinide, given 4 hours apart. The pharmacokinetics of both drugs were unaltered by concurrent use.[4]

C. Pioglitazone or Rosiglitazone

In a single-dose study in healthy subjects, there was no change in the pharmacokinetics of a single 8-mg dose of rosiglitazone when it was given with a single 400-mg dose of **ibuprofen**.[5]

The manufacturers say that pioglitazone and rosiglitazone can cause fluid retention, which may exacerbate or precipitate heart failure, particularly in those with limited cardiac reserve.[6,7] Because NSAIDs can also cause fluid retention, the manufacturers issue a warning that concurrent use may possibly increase the risk of oedema.[7]

D. Sulfonylureas

(a) Chlorpropamide

Ibuprofen 1.2 g daily for 4 weeks had no significant effect on the blood glucose levels of 10 patients with type 2 diabetes taking chlorpropamide 62.5 to 375 mg daily.[8]

A woman whose type 2 diabetes was well controlled with chlorpropamide 500 mg daily and metformin 1.7 g daily, developed hypoglycaemia within 2 days of changing her NSAIDs from **flurbiprofen** 150 mg daily and **indometacin** 150 mg daily to **fenclofenac** 1.2 g daily. The antidiabetic drugs were withdrawn the next day, but later in the evening she went into a hypoglycaemic coma. The reason for this is not understood, but it was attributed to a protein binding interaction between chlorpropamide and **fenclofenac**.[9]

(b) Glibenclamide (Glyburide)

1. Acemetacin. No changes in the control of diabetes were seen in 20 patients with type 2 diabetes taking glibenclamide when they were given acemetacin 60 mg three times daily.[10]

2. Bromfenac. The blood glucose levels of 12 diabetic patients taking glibenclamide 10 mg daily were unchanged by bromfenac 50 mg three times daily for 3 days, and the pharmacokinetics of glibenclamide were also unaltered.[11]

3. Diclofenac. The blood glucose levels of 12 diabetic patients with rheumatic diseases taking glibenclamide were unchanged by diclofenac 150 mg daily for 4 days.[12]

4. Diflunisal. An isolated case of hypoglycaemia has been reported in a patient taking glibenclamide with diflunisal.[13]

5. Etodolac. Etodolac does not appear to affect the pharmacokinetics of glibenclamide.[14]

6. Ibuprofen. A study in 16 healthy subjects found that ibuprofen did not affect the pharmacokinetics of glibenclamide. However, ibuprofen with glibenclamide caused a greater blood glucose-lowering effect than glibenclamide alone, but the clinical significance of this was uncertain.[15] A 72-year-old man with longstanding type 2 diabetes, well-controlled with glibenclamide 2.5 mg daily took a single 150-mg dose of ibuprofen, and 30 minutes later experienced severe nausea, sweating and palpitations, which were immediately relieved by taking sugar. The symptoms occurred again the next morning after a second dose of ibuprofen and after a further dose in the afternoon he became unconscious and was given intravenous glucose. Ibuprofen was withdrawn and there were no further episodes of hypoglycaemia. It was also noted that hypoglycaemia had not occurred when he had previously taken aspirin, paracetamol or diclofenac.[16]

7. Lornoxicam. In 15 healthy subjects, lornoxicam 4 mg twice daily for 6 days had no effect on the pharmacokinetics of a single 5-mg dose of glibenclamide. The pharmacokinetics of lornoxicam also remained unchanged. However, concurrent use significantly increased plasma insulin levels (AUC increased by 47%) and lowered serum glucose levels (by 8%), but this is probably not clinically important.[17]

8. Naproxen. A case of severe hypoglycaemia in a diabetic patient was attributed to the accumulation of glibenclamide and **metformin** due to deterioration in renal function caused by the concurrent use of ramipril and naproxen.[18]

9. Nimesulide. Although a preliminary report suggested that nimesulide slightly increased the effects of glibenclamide,[19] a later study using various [unnamed] sulfonylureas did not find that it affected fasting blood glucose levels or the glucose tolerance of diabetic patients.[19]

10. Parecoxib. Valdecoxib, the active metabolite of parecoxib, does not appear to affect either the pharmacokinetics of glibenclamide or its effects on insulin or blood glucose levels.[20]

11. Piroxicam. Healthy subjects and type 2 diabetic patients had an increased hypoglycaemic response to glibenclamide (blood glucose levels reduced by 13 to 15%) when they were given piroxicam 10 mg.[21]

12. Tenoxicam. Tenoxicam 20 mg daily was found not to affect the glycoregulation of 8 healthy subjects given glibenclamide 2.5 mg daily.[22]

13. Tolmetin. No changes were seen in the blood glucose levels of 40 diabetic patients taking glibenclamide when they were given either tolmetin 1.2 g or placebo daily for 5 days.[23]

(c) Glibornuride

A study in healthy subjects found that **tenoxicam** 20 mg daily did not affect the pharmacokinetics of glibornuride or its effect on plasma insulin and blood glucose levels.[24]

(d) Glipizide

In a study in 6 healthy subjects, **indobufen** 200 mg twice daily for 5 days caused a 25% rise in the AUC of a single 5-mg dose of glipizide and a non-significant reduction in their blood glucose levels.[25] No important changes in blood glucose levels occurred in 24 patients with type 2 diabetes taking tolbutamide or glipizide when they took **indoprofen** 600 mg daily for 5 days.[26] A study found that although **indoprofen** (200 mg on day one, then 600 mg daily on days 3 to 8) lowered the plasma levels of a single 5 mg dose of glipizide, the blood glucose levels remained unaffected.[27]

(e) Tolbutamide

A report briefly states that no changes in blood tolbutamide levels or in fasting blood glucose levels were seen in diabetic patients given **diflunisal** 375 mg twice daily.[28] In a study in 12 patients with type 2 diabetes, **sulindac** 400 mg daily did not affect the half-life, plasma levels, time-to-peak levels or AUC of tolbutamide. An unimportant reduction in fasting blood glucose levels was seen.[29] **Naproxen** 375 mg every 12 hours for 3 days had no effect on the pharmacokinetics or pharmacological effects of tolbutamide in 10 patients with type 2 diabetes.[30] The pharmacokinetics of a single 500-mg dose of tolbutamide were unaffected in 7 healthy subjects

after they took **tenoxicam** 20 mg daily for 14 days, and blood glucose concentrations were not altered.[31] No important changes in blood glucose levels occurred in 24 patients with type 2 diabetes taking tolbutamide or glipizide when they were given **indoprofen** 600 mg daily for 5 days.[26] In other patients taking tolbutamide it was found that **ibuprofen** lowered fasting blood glucose levels, but not below the lower limits of normal.[32]

Mechanism, importance and management

The reports briefly cited here indicate that no adverse or clinically relevant interaction normally occurs between the oral antidiabetics and the NSAIDs named. The general silence in the literature would seem to confirm this. Caution is appropriate with pioglitazone or rosiglitazone and NSAIDs, and patients should be monitored for signs of heart failure. Note that the NSAIDs, including coxibs, can cause renal failure, which can precipitate metformin-associated lactic acidosis. In addition, a reduction in the renal clearance of antidiabetic drugs can result in hypoglycaemia. Adverse interactions can certainly occur between antidiabetics and azapropazone, phenylbutazone, oxyphenbutazone and the salicylates, see 'Antidiabetics + NSAIDs; Phenylbutazone and related drugs', below and 'Antidiabetics + Salicylates', p.569.

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Antidiabetics + NSAIDs; Phenylbutazone and related drugs

The blood glucose-lowering effects of acetohexamide, carbutamide, chlorpropamide, glibenclamide (glyburide), glymidine and tolbutamide can be increased by phenylbutazone. Severe hypoglycaemia has occurred in a few patients. Similarly, azapropazone can increase the effects of tolbutamide and cause severe hypoglycaemia. Oxyphenbutazone may be expected to behave similarly. Dipyrone and mofebutazone did not interact with glibenclamide.

Clinical evidence

(a) Azapropazone

A woman whose diabetes was well controlled for 3 years with **tolbutamide** 500 mg twice daily, became confused and semi-comatose 4 days after starting to take azapropazone 900 mg daily. She complained of having felt agitated since starting the azapropazone, so it was withdrawn on suspicion of causing hypoglycaemia. Later that evening she became semi-comatose and was found to have a plasma glucose level of 2 mmol/L.[1] A subsequent study in 3 healthy subjects found that azapropazone 900 mg daily increased the plasma half-life of **tolbutamide** 500 mg threefold (from 7.7 to 25.2 hours) and reduced its clearance accordingly.[1] Acute hypoglycaemia occurred in another patient taking **tolbutamide** 500 mg three times daily, 5.5 hours after a single 600-mg dose of azapropazone was taken.[2]

(b) Dipyrone (Metamizole)

One randomised, placebo-controlled, crossover study in 12 diabetic patients taking **glibenclamide** suggested that metamizole 1 g daily for 2 days did not interact with **glibenclamide**: no relevant alteration in blood glucose levels was found.[3]

(c) Mofebutazone

Mofebutazone 900 mg daily has not been found to cause any clinically important changes in blood glucose levels in patients taking **glibenclamide**.[4]

(d) Oxyphenbutazone

Oxyphenbutazone has been found to alter[5] or raise **glymidine** levels[6] and **tolbutamide** levels.[7,8]

(e) Phenylbutazone

A man with type 2 diabetes taking **tolbutamide** experienced an acute hypoglycaemic episode 4 days after starting phenylbutazone 200 mg three times daily, although there was no change in his diet or in the dose of **tolbutamide**. He was able to control the hypoglycaemia by eating a large bar of chocolate.[9]

There are numerous other case reports and studies of this interaction involving phenylbutazone with **acetohexamide**,[10] **carbutamide**,[11] **chlorpropamide**,[12-14] **glibenclamide** (**glyburide**),[15] **glymidine**,[16] and **tolbutamide**,[13,17-23] some of which describe acute hypoglycaemic episodes.[10,12,13,18,20] Several of these interactions have been fatal.[13,23] There is a report suggesting that the interaction between **glibornuride** and phenylbutazone may not be clinically important.[24] In contrast to these reports, a single study describes a paradoxical *rise* in blood glucose levels in 3 African patients taking **tolbutamide** and phenylbutazone.[25] In addition to these reports there is some evidence that **tolbutamide** increases the metabolism of phenylbutazone by 42%,[22] but the extent to which this affects its therapeutic effects is uncertain.

Mechanism

Not fully resolved. Some evidence suggests that phenylbutazone can inhibit the renal excretion of glibenclamide (glyburide),[15] tolbutamide,[19] and the active metabolite of acetohexamide[10] so that they are retained in the body longer and their blood glucose-lowering effects are increased and prolonged. It has also been shown that phenylbutazone can inhibit the metabolism of the sulfonylureas[7,22] as well as causing their displacement from protein binding sites.[26] Azapropazone also possibly inhibits the metabolism of tolbutamide,[1] as well as maybe causing displacement from plasma protein binding sites.[2]

Importance and management

The interactions between the antidiabetics and phenylbutazone are well documented and potentially clinically important. Blood glucose levels may be lowered, but the number of reports of acute hypoglycaemic episodes seems to be small. Concurrent use should therefore be well monitored. A reduction in the dose of the sulfonylurea may be necessary if excessive hypoglycaemia is to be avoided. Not all sulfonylureas have been shown to interact (glibornuride probably does not do so) but it would be prudent to assume that they all interact until there is good evidence to suggest otherwise. Oxyphenbutazone may be expected to interact like phenylbutazone (it is a metabolite of phenylbutazone) but, unexpectedly, possibly not mofebutazone, although more study would be needed to confirm this.

The information regarding an interaction between azapropazone and the sulfonylureas seems to be limited to the cases and small study involving tolbutamide. Nevertheless, the manufacturers of azapropazone state that the concurrent use of sulfonylureas is not recommended.[27]

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Antidiabetics + Orlistat

Orlistat improved glycaemic control, which resulted in the need to reduce the dose of glibenclamide (glyburide) or glipizide in almost half the patients in one study. In other studies, orlistat also reduced the dose requirement for metformin and for insulin. Orlistat does not appear to alter the pharmacokinetics of glibenclamide or metformin. Orlistat and cimetidine may have contributed to a case of metformin-associated lactic acidosis. The manufacturers recommend avoiding the concurrent use of acarbose and orlistat because of the lack of interaction studies.

Clinical evidence

(a) Acarbose

The UK manufacturer of orlistat says that in the absence of pharmacokinetic studies its concurrent use with acarbose should be avoided.[1]

(b) Insulin

In a randomised, placebo-controlled, double-blind study in patients with type 2 diabetes receiving insulin with or without metformin or a sulfonylurea, orlistat 120 mg three times daily for one year, and a reduced-calorie diet improved glycaemic control and allowed a greater reduction in insulin dose (mean reduction of 8.1 units daily versus 1.6 units daily for placebo). Hypoglycaemic episodes occurred in about 17% of orlistat recipients and about 10% of placebo recipients: three orlistat recipients and one placebo recipient required medical intervention due to hypoglycaemia.[2]

(c) Metformin

In a randomised study, 21 healthy subjects were given metformin 500 mg daily for 6 days, with or without orlistat 120 mg three times daily. Orlistat had no effect on the pharmacokinetics of metformin, and concurrent use was well-tolerated.[3] In a randomised, placebo-controlled, study in patients with type 2 diabetes taking metformin with or without a sulfonylurea (mainly glibenclamide (glyburide) or glipizide), orlistat 120 mg three times daily for one year improved glycaemic control and allowed a small reduction in the dose of metformin (mean daily reduction of 16 mg versus a mean increase of 49 mg for placebo). Twice as many patients in the orlistat group either reduced or discontinued one or more of their antidiabetics (17% versus 8% with placebo). Hypoglycaemic episodes (mild to moderate and not requiring treatment) occurred in 10% of orlistat recipients and 4% of placebo recipients.[4] Similarly, improvement in glycaemic control and a reduced requirement for oral antidiabetics was reported in another study.[5]

A 59-year-old woman with type 2 diabetes taking long-term metformin 500 mg three times daily, developed severe metabolic acidosis with cardiovascular collapse and acute renal failure. Three months previously she had started orlistat 120 mg three times daily, which caused abdominal pain and chronic diarrhoea. During the 4 days before hospital admission, she was prescribed cimetidine 400 mg twice daily for her abdominal pain. The metformin-associated lactic acidosis[6] was considered to have been precipitated by the orlistat and cimetidine.

(d) Sulfonylureas

A placebo-controlled study in 12 healthy subjects found that orlistat 80 mg three times daily for a little over 4 days had no effect on the pharmacokinetics of a single 5-mg oral dose of **glibenclamide** (**glyburide**) and the blood glucose lowering effects remained unchanged.[7] A later one-year, randomised, placebo-controlled, study in obese patients with type 2 diabetes, in which 139 patients took orlistat, found that orlistat reduced fasting blood glucose and HbA_{1c} levels. In addition, 43% of patients taking orlistat 120 mg three times daily were able to decrease their sulfonylurea dose (**glibenclamide** or **glipizide**), and 11.7% of them were able to discontinue the sulfonylurea. The average dose decrease was 23% compared with 9% in the placebo group.[8]

Mechanism

The benefits of orlistat are likely to be as a result of the beneficial effects of weight reduction on glycaemic control, although in some studies the reduction in HbA_{1c} was not entirely dependent on the magnitude of weight loss.[2]

Importance and management

The benefits of orlistat on glycaemic control in overweight or obese patients with diabetes are established. Antidiabetic treatment should be more closely monitored in patients taking orlistat, and the dose adjusted as necessary.

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Antidiabetics + Pentoxifylline

The UK manufacturer notes that, rarely, high-dose *injections* of pentoxifylline have intensified the blood glucose-lowering effects of insulin and oral antidiabetic drugs. This effect has not been seen with oral pentoxifylline.[1] For example, in one study oral pentoxifylline 600 mg daily for 9 months did not affect HbA_{1c} levels in type 2 diabetic patients.[2] It may therefore be prudent to be alert for alterations in diabetic control in patients given intravenous pentoxifylline, but no particular precautions seem necessary with oral pentoxifylline.

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Antidiabetics + Quinolones

A number of reports describe severe hypoglycaemia in diabetic patients treated with gatifloxacin and various antidiabetics including insulin, metformin, pioglitazone, repaglinide, rosiglitazone, some sulfonylureas, or voglibose. In contrast, other reports describe hyperglycaemia when diabetics taking metformin and/or glipizide were given gatifloxacin. Retrospective reviews have revealed the high incidence of adverse events associated with gatifloxacin involving abnormal glucose homoeostasis, including both hypoglycaemia and hyperglycaemia, which was 4.3 to 16.7-fold higher than with other quinolones. Interaction studies have shown that gatifloxacin may cause hypoglycaemia and hyperglycaemia, and systemic formulations of this fluoroquinolone have been withdrawn in many countries.
Studies using ciprofloxacin and levofloxacin with glibenclamide suggest plasma glucose levels are not usually affected to a clinically relevant extent. However, isolated reports describe hypoglycaemia in diabetic patients taking glibenclamide, when ciprofloxacin, levofloxacin, or norfloxacin was given, and deaths associated with abnormal glucose homoeostasis have been reported in patients taking ciprofloxacin or levofloxacin.

Clinical evidence

A search of the FDA database for adverse drug events associated with **gatifloxacin**, **ciprofloxacin**, **levofloxacin**, and **moxifloxacin** between November 1997 and September 2003 found 10 025 unique adverse events, including 568 involving glucose homoeostasis abnormalities, of which 25 were fatal. **Gatifloxacin** use was associated with 453 (80%) of the adverse events involving glucose homoeostasis, and 17 of these were fatal compared with 3, 5, and 0 fatalities with **ciprofloxacin**, **levofloxacin**, and **moxifloxacin**, respectively. Of all the adverse events associated with **gatifloxacin**, 24% involved glucose homoeostasis, compared with **ciprofloxacin** (1.3%), **levofloxacin** (1.6%) and **moxifloxacin** (1.3%). The risk of adverse events involving glucose homoeostasis was higher in older patients, in patients taking medications for diabetes (almost 70% of those taking **gatifloxacin** were also using **insulin** or **oral antidiabetics**) and in patients with renal dysfunction whose dosage had not been appropriately adjusted.[1]

In another analysis, large case-control studies were conducted in a cohort of elderly patients from Ontario, Canada, who had received broad-spectrum antibacterials and been treated in hospital for either hypoglycaemia or hyperglycaemia within 30 days of receiving the antibacterial. **Gatifloxacin** was associated with a marked 4.3-fold risk of hypoglycaemia, as compared to macrolide antibacterials, and **levofloxacin** was associated with a slight 1.5-fold increased risk, whereas there was no increased risk with **moxifloxacin** or **ciprofloxacin**. Similarly, **gatifloxacin** was associated with a very marked 16.7-fold increased risk of hyperglycaemia when compared with macrolides, whereas no other quinolones were associated with an increased risk. The risk for hypoglycaemia or hyperglycaemia with **gatifloxacin** was not significantly different between those patients receiving treatment for diabetes and those not. Overall, 1.1% of courses of **gatifloxacin** were associated with hospital visits for dysglycaemia compared with 0.3% for **ciprofloxacin**, 0.3% for **levofloxacin,** 0.2% for **moxifloxacin** and 0.1% for macrolides.[2]

(a) Ciprofloxacin

A study in 12 patients with type 2 diabetes mellitus taking **glibenclamide** (**glyburide**) 10 mg in the morning, plus in some instances 5 mg in the evening, found that ciprofloxacin 1 g daily for a week caused rises in maximum serum **glibenclamide** levels of 20 to 30%, and a rise in the AUC of 25 to 36%. However, none of these changes were statistically significant, and, more importantly, blood glucose levels were not altered.[3] In another study in 9 healthy subjects, a single 200-mg intravenous dose of ciprofloxacin had no effect on the pharmacokinetics of a single 1.25-mg oral dose of **glibenclamide** given 20 minutes later.[4] Ciprofloxacin was not associated with an increased risk of hospital treatment for hypo or hyperglycaemia in the Canadian study, above.

Nevertheless, an elderly patient who had been taking **glibenclamide** 5 mg daily for over 2 years was found to be confused, with slurred speech and diaphoresis within a week of starting ciprofloxacin 250 mg twice daily for acute cystitis, and was found to have a serum **glibenclamide** level several times greater than that normally seen.[5] She needed treatment with intravenous glucose to correct the hypoglycaemia. Two further similar cases have been reported, in which hypoglycaemia developed after the first or second dose of ciprofloxacin, for either a wound infection[6] or a urinary tract infection,[7] although the association of this latter case with ciprofloxacin has been questioned.[8]

In a single-dose study in healthy subjects, there was no change in the pharmacokinetics of **rosiglitazone** 8 mg when given with ciprofloxacin 500 mg.[9]

(b) Gatifloxacin

In a study in patients with type 2 diabetes controlled by diet and exercise, gatifloxacin 400 mg daily for 10 days had no significant effect on glucose tolerance or most aspects of glucose homoeostasis, but did cause a brief increase in serum insulin levels.[10] In contrast, the US manufacturer of gatifloxacin noted that in another study in patents with type 2 diabetes taking **metformin** with or without **glibenclamide**, oral gatifloxacin 400 mg daily for 14 days was associated with initial hypoglycaemia followed by hyperglycaemia.[11]

Moreover, there is a report of 3 cases of hypoglycaemia in elderly type 2 diabetic patients given gatifloxacin. In one of these cases a patient taking **glibenclamide** 5 mg daily and **pioglitazone** 30 mg daily experienced severe, persistent hypoglycaemia within an hour of the first dose of oral gatifloxacin 200 mg. It resolved on withdrawal of all three drugs and she had no further episodes of hypoglycaemia when **glibenclamide** and **pioglitazone** were restarted.[12] Another case describes a patient taking **glimepiride** 2 mg before breakfast and 1 mg before dinner who developed severe hypoglycaemia 12 hours after the first dose of intravenous gatifloxacin 400 mg. Both drugs were discontinued and **glimepiride** was later restarted without further hypoglycaemia.[12] In the remaining case, a patient taking **repaglinide** 500 micrograms every 8 hours was given oral gatifloxacin 400 mg daily for a urinary-tract infection. **Repaglinide** was discontinued 6 hours after the first dose of gatifloxacin because of the patient's lack of appetite. Two hours after the second dose of gatifloxacin, he developed severe hypoglycaemia and also experienced a tonic-clonic seizure. Gatifloxacin was discontinued but hypoglycaemia persisted for 32 hours. **Repaglinide** was restarted 4 days later without further hypoglycaemia.[12] Other case reports have described severe hypoglycaemia when gatifloxacin was given to patients with diabetes taking **insulin** with **repaglinide** and **voglibose**,[13] **glibenclamide**,[14-16] **glibenclamide** with **metformin**,[17] **glibenclamide** with **rosiglitazone**,[16] or **glipizide**.[14]

In contrast, an 82-year-old woman taking **metformin** and **glipizide** who was discharged from hospital taking gatifloxacin 200 mg daily developed

severe *hyperglycaemia* within 48 hours. Her serum glucose rapidly reduced with low-dose intravenous **insulin**, but increased again the following day after she took oral gatifloxacin while receiving subcutaneous **insulin**.[14] A similar case was described in an 80-year-old man taking glipizide and gatifloxacin.[18] Hyperglycaemia has also been noted in 2 non-diabetic patients within 48 to 72 hours of starting gatifloxacin.[13,14]

Analysis of adverse events in large numbers of patients in the US and in Canada have confirmed that gatifloxacin is associated with a markedly increased risk of hypo and hyperglycaemia, see above.

(c) Levofloxacin

A study in 24 healthy subjects found that oral levofloxacin had no effect on the pharmacokinetics of a single oral dose of **glibenclamide** nor its effect on plasma glucose levels.[19] No recurrence of hypoglycaemia occurred in a patient taking **gliclazide** and oral levofloxacin who had a severe hypoglycaemic episode while receiving **glibenclamide** and gatifloxacin.[15] However, a fatal case of hypoglycaemia related to intravenous levofloxacin use occurred in an elderly patient with diabetes who was taking **glibenclamide**.[20] Similarly, hypoglycaemia developed in a malnourished 58-year-old man taking oral levofloxacin 750 mg once every 2 days and **glipizide**.[21] Levofloxacin was associated with a slight 1.5-fold increased risk of hospital treatment for hypoglycaemia, but no increased risk of hyperglycaemia, in the Canadian study, above.

(d) Moxifloxacin

The manufacturer notes that the concurrent use of moxifloxacin and **glibenclamide** resulted in an approximate 21% decrease in the peak plasma level of **glibenclamide** in diabetic subjects, but this did not alter blood glucose and endogenous insulin.[22] A pooled analysis from clinical and postmarketing studies suggested that moxifloxacin had no clinically relevant effect on blood glucose homoeostasis, even in patients with diabetes mellitus.[23] Moxifloxacin was not associated with an increased risk of hospital treatment for hypo or hyperglycaemia in the Canadian study, above.

(e) Norfloxacin

The manufacturer notes that the concurrent use of norfloxacin with **glibenclamide** has resulted in severe hypoglycaemia.[24]

(f) Ofloxacin

The manufacturer of ofloxacin states that it may cause a slight increase in the serum concentration of glibenclamide: they advise that this is based on unpublished case reports of an interaction and the possibility that the interaction is due to a class effect of the quinolones.[25,26]

Mechanism

Uncertain. However, it has also been postulated that quinolones may increase insulin secretion,[7,20] similar to 'quinine', (p.542). Gatifloxacin appears to increase insulin release initially, but then it appears to decrease insulin productivity or increase insulin disintegration.[27] Of the quinolones, the severe effects of gatifloxacin on glucose homoeostasis appear to be unique, with levofloxacin and ciprofloxacin having very much less effect.[2,12]

The authors of one report suggest that the ciprofloxacin may have inhibited the metabolism of the glibenclamide, thereby raising its serum levels.[5] This may possibly be exaggerated in elderly patients whose liver function may be reduced. Ciprofloxacin appears not to affect hepatic uptake of glibenclamide via OATP2B1.[4]

Importance and management

Gatifloxacin has been much more frequently associated with disturbances of blood glucose than other fluoroquinolones. The US manufacturer noted that when systemic gatifloxacin was to be used in diabetic patients, blood glucose should be closely monitored. Signs and symptoms of *hypo*glycaemia should be monitored, especially in the first 3 days of therapy, and signs and symptoms of *hyper*glycaemia should be monitored, especially with continued treatment beyond 3 days.[11] However, later they contraindicated its use in patients with diabetes,[28] and then withdrew the product.[29] These concerns do not apply to the topical eye drop product.

Isolated cases of hypoglycaemia in patients with diabetes have also been reported for ciprofloxacin, levofloxacin and norfloxacin. The general clinical relevance of these cases is uncertain but probably minor. However, it may be prudent to consider increasing the frequency of blood glucose monitoring in the elderly, who appear more at risk.

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Antidiabetics + Rifamycins

Rifampicin (rifampin) reduces the serum levels and blood glucose lowering effects of tolbutamide, gliclazide, chlorpropamide (single case) and glibenclamide (glyburide), and to a lesser extent glimepiride, glipizide and glymidine. Conversely, a single intravenous dose of rifampicin given with glibenclamide markedly increased its levels and effect.

Rifampicin reduces the effects of repaglinide, and possibly also nateglinide. Rifampicin also reduces the AUCs of pioglitazone and rosiglitazone. An isolated report describes an increased insulin requirement in a patient with type 1 diabetes taking rifampicin.

Clinical evidence

(a) Insulin

A case report describes a 54-year-old woman with type 1 diabetes whose insulin requirements increased from 36 units daily to 48 units daily when she took **rifampicin**. Immediately on discontinuing her antimycobacterials, she developed frequent hypoglycaemic attacks, which persisted until her insulin dose was reduced back to 36 units daily.[1]

(b) Nateglinide

In a randomised, crossover study, 10 healthy subjects were given a single 60-mg dose of nateglinide the day after a 5-day course of **rifampicin** 600 mg daily. **Rifampicin** reduced the AUC_{0-7} of nateglinide by 24%

(range 5 to 53%) and decreased the nateglinide half-life from 1.6 hours to 1.3 hours. Overall **rifampicin** did not significantly decrease the blood glucose-lowering effects of nateglinide.[2] However, because of the high degree of intersubject variation, the authors suggest that the blood glucose-lowering effects of nateglinide may be reduced in some subjects.[2]

(c) Pioglitazone

A randomised study in 10 healthy subjects found that **rifampicin** 600 mg daily for 6 days decreased the AUC of a single 30-mg dose of pioglitazone by 54%. In addition, **rifampicin** decreased the AUC and shortened the half-life of the active metabolites of pioglitazone by about 50% and 35%, respectively.[3]

(d) Repaglinide

In a study in healthy subjects, a single 4-mg dose of repaglinide was given one hour after the final dose of **rifampicin** 600 mg daily for 7 days. **Rifampicin** decreased the AUC and the mean maximum plasma concentration of repaglinide by 31% and 26%, respectively, but the blood glucose-lowering effect of repaglinide was not affected.[4] In another study,[5] pre-treatment with **rifampicin** 600 mg daily for 5 days decreased the AUC and maximum level of a single 500-microgram dose of repaglinide given on day 6 by 57% and 41%, respectively. In this study, **rifampicin** reduced the blood glucose-lowering effect of repaglinide by 35%. A third study investigated the effect of **rifampicin** 600 mg daily for 7 days on a single 4-mg dose of repaglinide given at the same time as the last **rifampicin** dose on day 7, or 24 hours later. When **rifampicin** was given simultaneously, the median AUC of repaglinide was reduced by almost 50%, but when the repaglinide was given 24 hours after the last **rifampicin** dose, the median AUC was reduced by 80%. The size of the effect of **rifampicin** on repaglinide may therefore depend on the administration schedule.[6]

(e) Rosiglitazone

In a study in healthy subjects, **rifampicin** 600 mg daily for 5 days reduced the AUC of a single 4-mg dose of rosiglitazone by 54% and reduced the maximum plasma level by 28%. **Rifampicin** increased the formation of the metabolite, *N*-desmethylrosiglitazone.[7] Very similar findings were reported in a study in healthy Korean subjects.[8]

(f) Sulfonylureas

1. Chlorpropamide. A single case report describes a man with type 2 diabetes who needed an increase in his dose of chlorpropamide from 250 to 400 mg daily when he was given **rifampicin** 600 mg daily. His serum chlorpropamide levels rose dramatically 12 months later when the **rifampicin** was withdrawn.[9]

2. Glibenclamide (Glyburide). A study in 29 patients with type 2 diabetes taking glibenclamide, found that when they were also given **rifampicin** 450 or 600 mg daily for 10 days, their blood glucose levels, both fasting and after meals, were raised. Glibenclamide dose changes were needed in 15 out of 17 patients in whom the diabetes became uncontrolled. Their blood glucose levels normalised 6 days after stopping the **rifampicin**.[10] Another patient with type 2 diabetes taking glibenclamide had a deterioration in diabetic control over the 8 months after she started **rifampicin**, which required an increase in glibenclamide dose and the addition of insulin. On stopping **rifampicin**, she had a marked rise in trough serum glibenclamide levels, from 40 nanograms/mL to 200 nanograms/mL, but no appreciable change in blood glucose concentrations.[11]

A study in 10 healthy subjects found that **rifampicin** 600 mg daily for 5 days decreased the AUC and peak plasma level of a single 1.75-mg dose of glibenclamide given on day 6 by 39% and 22%, respectively. The elimination half-life was shortened from 2 hours to 1.7 hours. The maximum reduction in blood glucose level was decreased by 36% by **rifampicin**.[12] Similarly, one week of **rifampicin** markedly reduced the AUC of a single 1.25-mg dose of glibenclamide given 2 days later by 65%. However, in contrast, a single 600-mg intravenous dose of **rifampicin** given over 30 minutes immediately before a single 1.25-mg dose of glibenclamide, caused about a twofold marked *increase* in the AUC of glibenclamide, leading to a greater reduction in blood glucose and hypoglycaemia in one subject. When a single intravenous dose of rifampicin was given on day 7 after 6 days of oral rifampicin, there was a 28% reduction in the AUC of glibenclamide given on the same day, which was less than the 65% reduction seen 2 days later.[13]

3. Gliclazide. A 65-year-old patient with type 2 diabetes taking gliclazide 80 mg daily for 2 years without problem was given **rifampicin** 450 mg daily, isoniazid, ethambutol and clarithromycin for an atypical mycobacteriosis. Fasting blood glucose levels became elevated requiring an increase in the dose of gliclazide to 120 mg daily then 160 mg daily. The plasma level of gliclazide on day 75 was 1.4 micrograms/mL, 2 hours after an 80-mg dose. When **rifampicin** was discontinued the gliclazide level increased to 4.7 micrograms/mL and the dose was reduced back to 80 mg daily.[14] A study in 9 healthy subjects found that pre-treatment with **rifampicin** 600 mg for 6 days decreased the AUC of a single 80-mg dose of gliclazide given on day 7 by 70%. The mean elimination half-life of gliclazide was reduced from 9.5 hours to 3.3 hours and the gliclazide oral clearance was increased by about fourfold. The blood glucose-lowering effects of gliclazide were significantly reduced by **rifampicin**.[15]

4. Glimepiride. A placebo-controlled study in 10 healthy subjects found that **rifampicin** 600 mg daily for 5 days decreased the AUC of a single 1-mg dose of glimepiride given on day 6 by 34%. **Rifampicin** reduced the elimination half-life of glimepiride by 25%. However, no significant differences in blood glucose were found between the **rifampicin** and placebo regimens.[16]

5. Glipizide. A placebo-controlled study in 10 healthy subjects found that **rifampicin** 600 mg daily for 5 days decreased the AUC of a single 2.5-mg dose of glipizide given on day 6 by 22%. The elimination half-life was shortened from 3 hours to 1.9 hours by **rifampicin**. However, no significant differences in blood glucose concentrations were found.[12]

6. Glymidine. In one study the half-life of glymidine was reduced by about one-third by the concurrent use of **rifampicin**.[17]

7. Tolbutamide. After treatment for 4 weeks with **rifampicin** the half-life of tolbutamide in 9 diabetic patients with tuberculosis was reduced by 43%, and the serum concentrations measured at 6 hours were halved, when compared with other patients not taking **rifampicin**.[18] Similar results have been found in other studies in patients with cirrhosis or cholestasis,[19] in healthy subjects[20] and in other patients.[21]

Mechanism

Rifampicin is a potent inducer of the liver enzymes concerned with the metabolism of tolbutamide (the cytochrome P450 isoenzyme CYP2C9), which hastens its clearance from the body, thereby reducing its effects.[18-20] The interaction between rifampicin and glibenclamide (glyburide), gliclazide, glimepiride, glipizide, and nateglinide is probably also due to induction of CYP2C9.[2,12,14,15] However, rifampicin is also an inhibitor of hepatic organic anion-transporting polypeptide 1B1 (OATP1B1), and acute administration of a single intravenous dose of rifampicin with glibenclamide inhibited glibenclamide uptake into the liver, and therefore reduced its metabolism.[13]

The interaction of rifampicin with repaglinide, rosiglitazone and pioglitazone is probably due to induction of CYP2C8,[7-9] although in the case of rosiglitazone, CYP2C9 may also play some part.[7,8] The case report with insulin is unexplained, although there is a case of a patient who developed diabetes requiring insulin treatment while receiving rifampicin and ethambutol, which resolved when the antimycobacterials were stopped.[22] It is possible that rifampicin or tuberculosis *per se* might cause hyperglycaemia.[22]

Importance and management

Information is limited, but the interactions of tolbutamide, glibenclamide (glyburide) and gliclazide with rifampicin (rifampin) appear to be established. Patients taking these sulfonylureas may need an increase in the dose while taking rifampicin. This also seems possibly true for chlorpropamide, but the documentation for this interaction is even more limited. The effect of rifampicin on the blood glucose-lowering effects of glimepiride, glipizide or glymidine may be of only limited clinical significance, but it should be noted that these were single-dose studies and it is possible that some effect may occur with multiple dosing. Caution is warranted. Conversely, bear in mind that the first intravenous dose of rifampicin may increase the effect of oral glibenclamide given at a similar time. Whether this occurs with the first oral dose of rifampicin remains to be determined.

Although the information regarding **nateglinide** and **repaglinide** is limited, a significant interaction is possible, especially with repaglinide, and so an increase in blood glucose monitoring would be prudent. Similarly, the reduction in the AUCs of **pioglitazone** and **rosiglitazone** also indicates that diabetic control should be closely monitored if rifampicin is started or stopped.

The isolated case of increased **insulin** requirement suggests that ri-

fampicin may possibly affect the glycaemic control of patients with type 1 diabetes, but this needs further investigation.

There does not seem to be any information regarding the other rifamycins, **rifabutin** (a weak enzyme inducer) and **rifapentine** (a moderate enzyme inducer). However, the manufacturers and the CSM in the UK warn that rifabutin may possibly reduce the effects of a number of drugs, including oral antidiabetics.[23,24]

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Antidiabetics + Salicylates

Aspirin and other salicylates can lower blood glucose levels, but small analgesic doses do not normally have an adverse effect on patients taking antidiabetics. Larger doses of salicylates may have a more significant effect.

Clinical evidence

(a) Chlorpropamide

In 5 healthy subjects the blood glucose-lowering effects of chlorpropamide and **sodium salicylate** were found to be additive. A further study in 6 healthy subjects found that chlorpropamide 100 mg given with **sodium salicylate** 1.5 g lowered blood glucose levels by the same amount as either chlorpropamide 200 mg or **sodium salicylate** 3 g alone.[1]

The blood glucose levels of a patient taking chlorpropamide 500 mg daily were lowered about two-thirds by **aspirin** in doses sufficient to give serum salicylate levels of about 1.9 mmol/L.[2]

(b) Glibenclamide (Glyburide)

In a study, 16 healthy subjects took a single 5-mg dose of glibenclamide both before and on the fourth day of taking **aspirin** 975 mg four times daily for 4 days. It was found that the **aspirin** reduced the AUC_{0-4} of the glibenclamide by 68% and reduced its mean peak serum levels by 35%. The effects of these changes on glucose tolerance tests and insulin responses were difficult to interpret, but there was no clear evidence that any clinically relevant changes occurred.[3]

(c) Insulin

Twelve children with type 1 diabetes receiving insulin had a reduction in their blood glucose levels (from about 10.4 to 8.8 mmol/L) averaging 15% when they were given **aspirin** (patients under 27.2 kg given 1.2 g daily, patients over 27.2 kg given 2.4 g daily) for a week. No significant changes in insulin doses were necessary.[4]

Eight patients receiving 12 to 48 units of insulin zinc suspension daily required no insulin when, for 2 to 3 weeks, they took **aspirin** in doses of 3.5 to 7.5 g daily, which were large enough to give maximum therapeutic serum salicylate levels of about 2.5 to 3.3 mmol/L. Six other patients were able to reduce their insulin requirements by about 20 to 65%.[5]

Mechanism

It has been known for over 100 years that aspirin and salicylates have blood glucose-lowering properties and in relatively large doses can be used on their own in the treatment of diabetes.[6-10] The simplest explanation for this interaction with antidiabetics is that the blood glucose lowering effects are additive,[1] but there is some evidence that other mechanisms may come into play.[10] In addition aspirin can raise serum chlorpropamide levels, possibly by interfering with renal tubular excretion, and therefore the effects of chlorpropamide are enhanced.[2]

Importance and management

The interaction between the sulfonylureas or insulin and the salicylates is established but of limited importance. Considering the extremely wide use of aspirin it might reasonably be expected that any generally serious interaction would have come to light by now. The data available, coupled with the common experience of diabetic patients,[11] is that excessive and unwanted hypoglycaemia is very unlikely with small to moderate analgesic doses of salicylates. Some downward adjustment of the dose of the antidiabetic may be appropriate if large doses of salicylates are used. Information about other antidiabetics and salicylates appears to be lacking, but they are expected to behave similarly.

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Antidiabetics + Somatostatin analogues

Octreotide decreases insulin resistance so that the dose of insulin used by type 1 diabetics can be reduced. Fatal diabetic ketoacidosis occurred in one patient when octreotide was withdrawn. Octreotide appears to have little effect in those with intact insulin reserves (type 2 diabetes), and it may actually reduce insulin secretion and impair glucose tolerance in non-diabetic patients. In addition, octreotide has been reported to reduce sulfonylurea-induced hypoglycaemia. Lanreotide may also affect glucose levels in diabetic patients.

Clinical evidence

Changes in glucose tolerance may occur in patients with acromegaly who are given somatostatin analogues. In a prospective study, in 24 acromegalic patients given long-acting **octreotide** or **lanreotide,** insulin resistance

was reduced, but insulin secretion was impaired resulting in deterioration of glucose homoeostasis in non-diabetic patients. Of 16 patients with normal glucose tolerance before receiving **octreotide**, 4 developed impaired glucose tolerance, and of 7 patients with impaired glucose tolerance, 4 improved, one remained stable and 2 deteriorated to diabetes mellitus; the status of one diabetic patient remained the same.[1] In another study in patients with acromegaly given **octreotide**, impaired glucose tolerance or frank diabetes developed in about half of the 55 patients who initially had normal glucose tolerance, but glucose tolerance improved in 3 of the 11 patients who were diabetic.[2] Similar results were reported in a further study, although **octreotide** appeared to be more detrimental to glucose metabolism than **lanreotide**.[3]

(a) Insulin

1. Type 1 diabetes. When 7 patients with type 1 diabetes with poor metabolic control were given **octreotide** 50 micrograms subcutaneously three times daily (at 8, 15 and 23 hours) or by continuous subcutaneous infusion (62.5 or 112.5 micrograms over 24 hours), their blood glucose levels were about 50% lower than when they were given insulin alone. The effects of **octreotide** on blood glucose levels were virtually the same regardless of route of administration or dose.[4] Another study in 6 patients with type 1 diabetes also found that **octreotide** 50 micrograms subcutaneously before meals reduced their daily insulin requirements by about 50%,[5] and other studies confirm that **octreotide** behaves in this way.[6,7] An isolated report describes clinical and biochemical improvement with **lanreotide** 30 mg intramuscularly every 10 days, in a diabetic acromegalic man whose glucose levels were poorly controlled with insulin. However, he experienced hypoglycaemia when the **lanreotide** was replaced with intramuscular **octreotide** 20 mg (depot preparation) and he had to reduce his insulin dose by 30 to 50% for the first week after each **octreotide** injection.[8] Another report describes deterioration in glucose tolerance leading to death from diabetic ketoacidosis when **octreotide** was stopped in a patient with acromegaly and insulin-resistant diabetes mellitus.[9]

2. Type 2 diabetes. Eight obese type 2 diabetic patients whose diabetes was not controlled with oral antidiabetics and who needed insulin, had no significant increases in blood glucose levels following a meal when they were given subcutaneous **octreotide** 25 micrograms.[10] **Octreotide** reduced insulin requirements in 6 patients with type 2 diabetes and chronic renal failure, but did not significantly affect the glycaemic profile of similar diabetic patients with normal renal function. This effect was thought to be due to a greater reduction in glucagon levels, which are elevated in renal failure.[11]

(b) Oral antidiabetics

Octreotide does not appear to have a clinically relevant beneficial or harmful effect on the blood glucose-lowering effects of oral antidiabetics such as **glibenclamide** (**glyburide**) in patients with type 2 diabetes, although some metabolic changes can occur including suppression of postprandial serum insulin levels.[12,13] A retrospective study of 9 patients with hypoglycaemia occurring as a result of a sulfonylurea overdose (with **glibenclamide** or **glipizide**) found that there was a dramatic and significant reduction in the number of episodes of hypoglycaemia after **octreotide** was given (29 episodes before, versus 2 episodes after, **octreotide**).[14]

Mechanism

Octreotide is an analogue of the natural hormone somatostatin, and similarly has blood glucose-lowering effects because it inhibits the actions of glucagon and growth hormone (which raise blood glucose levels), and because it also delays the absorption of carbohydrate from the gut. However, somatostatin is also diabetogenic, because it suppresses insulin release. In type 1 diabetes, because there is no endogenous insulin, the blood glucose-lowering effects predominate. In non-diabetics and type 2 diabetics, the actions may cancel out, or there may be poorer glycaemic control. Octreotide is thought to cause less suppression of insulin release than somatostatin, but this may still be important in those with insulin-secreting reserves.

Lanreotide, like somatostatin and its analogues, may produce a transient inhibition of the secretion of insulin and glucagon,[15] but lanreotide may have less affinity for receptors found in the pancreas and so possibly produces a different response to that of octreotide.[1,8]

Sulfonylureas lower blood glucose levels primarily by facilitating preformed insulin release from pancreatic beta cells, and octreotide may oppose this by directly inhibiting insulin secretion from the pancreas.[14]

Importance and management

The interaction between insulin and octreotide in patients with type 1 diabetes is established, and hypoglycaemia has been reported. If both drugs are used, anticipate the need to reduce the insulin dose. The studies cited above[4,5] suggest that a reduction of about 50% is possible.

The manufacturers of octreotide state that in patients with type 2 diabetes with intact insulin reserves, octreotide may result in prandial *increases* in glycaemia,[16] but two clinical studies in patients with type 2 diabetes given glibenclamide (glyburide) did not show any deterioration (or benefit) in glycaemia.[12,13] However, octreotide has been reported to reduce sulfonylurea-induced hypoglycaemia. Octreotide may affect insulin secretion, and therefore glucose tolerance, and so it would certainly be prudent to monitor the effects of giving octreotide with any of the oral antidiabetics.

The manufacturer of lanreotide also recommends that blood glucose levels should be checked in diabetic patients to determine whether antidiabetic treatment needs to be adjusted,[15] which seems prudent.

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Antidiabetics + SSRIs

In various clinical studies in patients with diabetes, SSRIs have generally caused minor improvements in glycaemic control. However, isolated cases of severe hypoglycaemia, hyperglycaemia and hypoglycaemia unawareness have been reported.
Fluvoxamine slightly reduces the clearance of tolbutamide and increases the maximum plasma levels of glimepiride, and slightly increased the AUC of rosiglitazone. Fluoxetine did not alter the pharmacokinetics of tolbutamide, and sertraline did not significantly affect the pharmacokinetics of glibenclamide (glyburide) or tolbutamide.

Clinical evidence

One research group from the Netherlands have conducted a number of analyses to look at the association between antidepressants and dysglycaemia.[1-3] In one analysis of cases of patients hospitalised for hypoglycaemia, use of antidepressants (including SSRIs) was not associated with an increased risk. The authors suggested that there was a trend for an increased risk with SSRIs when compared with antidepressants not affecting serotonin uptake,[1] but there were too few cases to reasonably assess

this. Conversely, in an analysis of spontaneous reports in the WHO adverse drug reaction database, use of antidepressants was associated with a small increased risk of both hyperglycaemia (odds ratio 1.5) and hypoglycaemia (odds ratio 1.8). SSRIs had a slightly greater risk of hypoglycaemia than hyperglycaemia (odds ratio 2 versus 1.4), which was not statistically significant.[2] In a further longitudinal study in 133 patients using **insulin** for at least 12 months before starting an antidepressant, and for at least 6 months with an antidepressant, the dose of insulin used did not change after starting the antidepressant. When analysed by type, the 85 SSRI users (individual SSRIs not named) had a small 13% decrease in dose of **insulin** while taking the antidepressant.[3]

(a) Citalopram

In a small uncontrolled study in 14 patients with diabetes (type 1 or 2 managed with **insulin** and/or **oral antidiabetics**) given citalopram (10 mg daily increased to 20 mg daily if needed for 16 weeks), there was a non-statistically significant modest improvement in measures of glycaemic control (HbA_{1c} decreased by 0.36%).[4] The fact that this study was small and not placebo-controlled limits its findings, but it does provide some indication that major effects of citalopram on glucose control are possibly uncommon.

(b) Fluoxetine

In a drug interaction study in healthy subjects, single, or multiple doses of fluoxetine 30 mg daily for 8 days, did not affect the pharmacokinetics or the blood glucose-lowering effects of a single 1-g dose of **tolbutamide**.[5]

Various placebo-controlled clinical studies in patients with type 1 or 2 diabetes receiving insulin and/or oral antidiabetics have shown that fluoxetine can cause weight loss, reduce fasting plasma glucose levels and improve glycaemic control (modest decrease in HbA_{1c} levels),[6-8] which in some cases were statistically greater than with placebo. In one study in patients receiving **insulin**, a decrease in the daily **insulin** dose was required over the 24 weeks (44% reduction in dose compared with 20% for placebo).[9]

An **insulin**-dependent diabetic experienced symptoms of hypoglycaemia (nausea, tremor, sweating, anxiety, lightheadedness) after starting to take fluoxetine 20 mg each night. The symptoms disappeared when the fluoxetine was stopped and reappeared when it was restarted. However, blood glucose levels were found to be normal (9 to 11 mmol/L), so it is likely that the effects were purely adverse effects of fluoxetine that were mistaken for symptoms of hypoglycaemia.[10] A further case report describes a patient who experienced symptoms of hypoglycaemia and whose blood glucose levels fell on several occasions (lowest result, 2.36 mmol/L) while taking **glibenclamide** (**glyburide**) 20 mg daily and fluoxetine 20 mg daily.[11] In contrast, another patient with type 1 diabetes experienced a loss of hypoglycaemic awareness while taking fluoxetine 40 mg daily. Approximately one month after fluoxetine was started, he reported an increased incidence of hypoglycaemia, but these episodes were not accompanied by typical adrenergic symptoms (which he had previously experienced). After 3 grand mal seizures which occurred with blood glucose readings ranging from 1.9 to 2.2 mmol/L, the dose of fluoxetine was gradually decreased. Hypoglycaemic unawareness resolved when the fluoxetine dose was reduced to 10 mg every second day. Within weeks of discontinuing fluoxetine, blood glucose levels had risen considerably and hypoglycaemia did not recur.[12] These authors reported two very similar cases with **paroxetine** and **sertraline**.[13] However, in a placebo-controlled study in 18 patients with type 1 diabetes, fluoxetine 20 mg daily titrated to 80 mg daily over 6 weeks actually had no effect on hypoglycaemic symptoms experienced during induced hypoglycaemia (clamp study). Moreover, fluoxetine markedly increased the physiological counter-regulatory responses (e.g. adrenaline (epinephrine) release) to induced hypoglycaemia.[14]

The manufacturers of fluoxetine say that hypoglycaemia has occurred in diabetic patients when they took fluoxetine alone, and hyperglycaemia has developed following discontinuation.[15,16]

(c) Fluvoxamine

Hyperglycaemia occurred in a 60-year-old woman with type 2 diabetes managed with **insulin**, 5 days after fluvoxamine was started. Blood glucose levels, which had approximately doubled, decreased when the fluvoxamine was stopped, but increased and then decreased again when the fluvoxamine was restarted and then stopped.[17]

A study in 14 healthy subjects given fluvoxamine 75 or 150 mg daily for 5 days, with a single 500-mg dose of **tolbutamide** on the third day, found that the clearance of **tolbutamide** was modestly reduced by 19% by the 75 mg dose and by 33% by the 150 mg dose of fluvoxamine. The clearance of its metabolites (4-hydroxytolbutamide and carboxytolbutamide) was also significantly decreased.[18]

A randomised, crossover study in 12 healthy subjects given fluvoxamine 100 mg or placebo daily for 4 days, with a single 500-microgram dose of **glimepiride** on the fourth day, found the AUC of **glimepiride** was not significantly affected by fluvoxamine. Peak plasma levels of **glimepiride** were increased by 43% and the elimination half-life was prolonged from 2 hours to 2.3 hours, but there was no significant change in the effects of **glimepiride** on blood glucose concentrations.[19]

In a study in healthy subjects, fluvoxamine 50 mg daily for 4 days slightly increased the AUC of **rosiglitazone** by 21% when a single 4-mg dose was given on day 4. There was no change in pharmacokinetics of the *N*-desmethyl metabolite.[20]

(d) Paroxetine

In a small placebo-controlled study in 15 patients with type 2 diabetes given paroxetine 20 mg daily, there was a non-statistically significant modest improvement in measures of glycaemic control. HbA_{1c} decreased by 0.44% compared with 0.07% in the placebo group.[21] This study provides some indication that major effects of paroxetine on glucose control are possibly uncommon.

For mention of a case of reduced hypoglycaemic awareness in a type 1 diabetic given paroxetine, see *Fluoxetine*, above.

(e) Sertraline

After taking sertraline 200 mg daily for 22 days the clearance of a single intravenous dose of **tolbutamide** was decreased by 16% in 25 healthy subjects.[22] In another study in 11 healthy subjects, the pharmacokinetics of a single 5-mg dose of **glibenclamide** (**glyburide**) were found to be unaffected by sertraline, taken in increasing doses up to 200 mg daily over 15 days. Blood glucose levels were also unchanged.[23] However, there is a report of a patient with schizoaffective disorder and type 2 diabetes who developed hypoglycaemia during treatment with sertraline, risperidone and **glibenclamide**.[24] For mention of a case of reduced hypoglycaemic awareness in a type 1 diabetic given sertraline, see *Fluoxetine*, above. In contrast, another report describes a patient with diet-controlled, type 2 diabetes, whose glucose levels increased after initiation of sertraline treatment.[25]

Mechanism

Fluvoxamine probably decreases the clearance of tolbutamide by inhibition of its metabolism by the cytochrome P450 isoenzyme CYP2C9. This mechanism may also partly explain the increase in plasma levels of glimepiride. However, as the glimepiride AUC was not increased and the half-life was only slightly increased, the increase in plasma levels may also be due to an increased rate of glimepiride absorption caused by the SSRI.[18,19] Fluvoxamine may have a weak inhibitory effect on CYP2C8, by which rosiglitazone is metabolised.[20] The effects of other SSRIs may also be associated with enzyme inhibition.[24] However, these pharmacokinetic effects seem minor.

The SSRIs themselves appear to be associated with some effects on glucose homeostasis. For example, in one pharmacodynamic study, fluoxetine improved insulin sensitivity in type 2 diabetics managed with diet alone.[26]

Importance and management

Fluoxetine, fluvoxamine and sertraline do not appear to cause any clinically relevant pharmacokinetic interactions with sulfonylureas, neither does fluvoxamine with rosiglitazone. However, note that all SSRIs may affect diabetic control, usually causing a minor improvement, although isolated cases of marked effects have been reported. The dose requirements of insulin or oral antidiabetics, may therefore change. It may therefore be prudent to consider increasing the frequency of blood glucose monitoring if an SSRI is started or stopped.

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Antidiabetics + St John's wort (*Hypericum perforatum*)

St John's wort modestly decreases the AUC of rosiglitazone. Pioglitazone and repaglinide are similarly metabolised and may therefore be expected to interact similarly. St John's wort also modestly decreased the AUC of gliclazide, but, in contrast, it did not affect the metabolism of tolbutamide.

Clinical evidence

(a) Gliclazide

In a study in 21 healthy subjects, a 300-mg dose of a St John's wort preparation with a high hyperforin content (*LI 160, Lichtwer Pharma*) was given 3 times daily for 15 days. On the last day of treatment, a single 80-mg dose of gliclazide was given, followed 30 minutes later by glucose 75 g. St John's wort reduced the maximum levels and AUC of gliclazide by 22% and 35%, respectively. The clearance was increased by 47%. No statistically significant changes were found in the AUC_{0-4} or blood levels of glucose or insulin.[1]

(b) Rosiglitazone

A preliminary report of a pharmacokinetic study[2] states that St John's wort 900 mg daily decreased the AUC of a single dose of rosiglitazone by 26% and increased its clearance by 35%.

(c) Tolbutamide

In a study using tolbutamide as a probe drug for CYP2C9 activity, St John's wort 900 mg daily had no effect on the metabolism of a single dose of tolbutamide either after one day or after 2 weeks of use. The St John's wort product used was from *Sundown Herbals* and provided about 33 mg of hyperforin daily.[3] Similarly, in another study, a St John's wort preparation with low hyperforin content (*Esbericum*) at a dose of 240 mg daily (which provided about 3.5 mg of hyperforin daily) had no effect on tolbutamide metabolism.[4]

Mechanism

Gliclazide is a substrate of the cytochrome P450 isoenzyme CYP2C9 and the authors suggest that St John's wort induces this isoenzyme, thereby increasing the metabolism of gliclazide and reducing its levels. The magnitude of this effect was not influenced by CYP2C9 genotype.[1] However, the fact that **tolbutamide**, another CYP2C9 substrate, was unaffected by St John's wort suggests that other factors may be involved.

Rosiglitazone is known to be metabolised principally by the cytochrome P450 isoenzyme CYP2C8, and it was therefore concluded that St John's wort induces this isoenzyme. The magnitude of the effect of St John's wort was not influenced by CYP2C8 genotype.[2]

Importance and management

The clinical relevance of the modest reduction in rosiglitazone levels has not been assessed, but it would seem unlikely to be important. However, the authors state that St John's wort use should be monitored when patients are given CYP2C8 substrates. **Pioglitazone** and **repaglinide** are also substrates of CYP2C8, and would therefore be expected to be similarly affected, although possibly not to a clinically relevant extent. A large decrease in pioglitazone levels would not be expected on the basis that rifampicin, a more potent enzyme inducer than St John's wort, only caused a 54% reduction in the AUC of pioglitazone. However, the UK manufacturer[5] recommends caution when prescribing pioglitazone with drugs that induce CYP2C8. All three drugs are also substrates for CYP3A4, of which St John's wort is an established inducer. Further study is needed.

The small reduction in the levels of gliclazide does not appear to be clinically important as its blood-glucose-lowering effects were unaffected. No special precautions appear to be necessary if tolbutamide and St John's wort are used together.

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Antidiabetics + Statins

No clinically relevant adverse interactions appear to have been reported between the statins and the sulfonylureas, but in one pharmacokinetic study, fluvastatin increased the AUC of glibenclamide (glyburide) in diabetic patients. Simvastatin had no clinically relevant effect on the pharmacokinetics of repaglinide, and fluvastatin did not affect nateglinide. Most studies have shown no pharmacokinetic interaction or increased incidence of adverse effects when pioglitazone or rosiglitazone were used with atorvastatin or simvastatin, but one study suggested a possible excess of hepatic adverse events in patients taking atorvastatin with these drugs. Subcutaneous exenatide modestly decreased the AUC of lovastatin, but no clear pattern of altered efficacy of statins was noted in exenatide clinical studies.

Clinical evidence

A. Exenatide

In a study in healthy subjects, subcutaneous exenatide 10 micrograms twice daily for 3 days decreased the AUC of a single 40-mg dose of **lovastatin** given on day 2 by 40%, and decreased its maximum level by 28% and increased the median time to maximum level by 4 hours.[1] In an analysis of three phase III clinical studies of exenatide in patients with type 2 diabetes, the use of exenatide for 30 weeks in the subset of 348 patients already taking

statins (51% **atorvastatin**, 31% **simvastatin**, 11% **pravastatin**, 5% **lovastatin**, 3% **fluvastatin**) was not associated with consistent changes in lipid profiles or statin doses when compared with placebo.[1]

B. Meglitinides

In the preliminary report of a study in healthy subjects, **fluvastatin** 30 mg daily for 8 days caused a minor 18% increase in the AUC of a single 120-mg dose of **nateglinide**, with no change in glucose levels.[2]

In a three-period, crossover, study in 12 healthy subjects, the concurrent use of **simvastatin** 20 mg daily and **repaglinide** 2 mg three times daily for 5 days increased the AUC of repaglinide by just 8%, and increased its maximum level by 26%, although there was high variability in these findings. There was a higher incidence of adverse events (headache was most common, then hypoglycaemia) during concurrent use compared with either drug alone (45 with the combination, 23 with **repaglinide** and 13 with **simvastatin**). However, these adverse events were mild or moderate, and were considered to be due to the additive effects of both drugs.[3] In another study in healthy subjects, atorvastatin 40 mg daily for 3 doses had little effect on the pharmacokinetics of a single 250-microgram dose repaglinide given one hour after the final dose of atorvastatin. The only statistically significant changes (minor 18% increase in AUC, and 41% increase in maximum level) were in the subset of subjects with a genetically reduced ability to metabolise repaglinide by the organic anion transporting polypeptide 1B1 (OATP1B1).[4]

C. Sulfonylureas

(a) Chlorpropamide

A study in 7 patients with type 2 diabetes and hypercholesterolaemia, taking chlorpropamide 125 to 750 mg daily, found that **lovastatin** 20 mg twice daily for 6 weeks reduced low-density lipoprotein cholesterol by 28%, total cholesterol by 24% and apolipoprotein B by 24%. The chlorpropamide plasma levels were unchanged, and the diabetic control remained unaltered.[5]

(b) Glibenclamide (Glyburide)

Groups of 16 healthy subjects taking **fluvastatin** 40 mg or **simvastatin** 20 mg daily were given a single 3.5-mg oral dose of glibenclamide on days one, 8 and 15. The maximum plasma concentration and the AUC of glibenclamide were increased by about 20% by the statins. The blood glucose-lowering effects of glibenclamide remained virtually unchanged by both **fluvastatin** and **simvastatin** in these subjects, and also when **fluvastatin** was tested in a group of 32 patients with type 2 diabetes.[6] Nevertheless, the manufacturers of **fluvastatin** report a study in which a higher dose of **fluvastatin**, of 40 mg twice daily for 14 days, was given to 32 patients with diabetes stable taking glibenclamide 5 to 20 mg daily. **Fluvastatin** increased the AUC of glibenclamide by 70%, increased the maximum serum levels by 60% and increased the elimination half-life from about 8.5 hours to 19 hours, although there were no significant changes in glucose levels.[7,8]

(c) Tolbutamide

A single 1-g dose of oral tolbutamide was given to two groups of 16 healthy subjects taking **fluvastatin** 40 mg or **simvastatin** 20 mg. The pharmacokinetics of the tolbutamide were affected only to a very minor extent, and the blood glucose-lowering effects of the tolbutamide were unchanged.[6]

D. Thiazolidinediones

One review suggested that patients receiving thiazolidinediones (95% taking **troglitazone**) were more likely to develop hepatotoxicity if taking **atorvastatin** than when taking **simvastatin**.[9] However, **troglitazone** has now been withdrawn due to its hepatotoxic effects. The same authors subsequently conducted a similar study. They analysed the adverse event reporting database of the FDA in the US for reactions affecting muscle, liver, pancreas, or bone marrow where **simvastatin** or **atorvastatin** were implicated. They then looked for events where antidiabetic drugs also featured. Of the 3767 events identified for **atorvastatin**, 40 also involved rosiglitazone and 20 also involved pioglitazone. Of the 3651 events identified for **simvastatin**, 10 also involved rosiglitazone and 9 also involved pioglitazone. About half of these events involving pioglitazone or rosiglitazone resulted in hospitalisation or death. Although the data did not allow for an assessment of whether this rate was greater than that expected, the authors say that if **simvastatin** is used as the control, the data suggest that the number of cases of adverse events with **atorvastatin** and a thiazolidinedione are greater than would be expected by chance alone.[10]

However, in a study in healthy subjects, **pioglitazone** 45 mg daily did not significantly affect the pharmacokinetics of **simvastatin** 80 mg daily and concurrent use was well tolerated.[11] Similarly, there was no pharmacokinetic interaction between **pioglitazone** 45 mg daily and **atorvastatin** 80 mg daily.[12] Moreover, clinical use of **rosiglitazone** with **atorvastatin** in patients with type 2 diabetes for 16 weeks was well tolerated,[13] as was the clinical use of **rosiglitazone** or **pioglitazone** with **simvastatin**.[14]

Mechanism

The changes in the pharmacokinetics of glibenclamide (glyburide) caused by fluvastatin and simvastatin are not understood. The interaction between atorvastatin or simvastatin and the thiazolidinediones is thought to involve the cytochrome P450 isoenzyme CYP3A4, although this is as yet unconfirmed.

Importance and management

There is little evidence to suggest that special precautions appear to be needed by diabetic patients taking any of the pairs of sulfonylureas and statins cited here (chlorpropamide with lovastatin; or glibenclamide or tolbutamide with fluvastatin or simvastatin). Nevertheless, one study found a fairly marked increase in exposure to glibenclamide with fluvastatin, and the UK manufacturers of fluvastatin say that there is a potential for serious hypoglycaemia and therefore advise that the use of glibenclamide should be avoided wherever possible.[7] However, the US manufacturers just advise close monitoring, which should continue if the fluvastatin dose is increased to 40 mg twice daily.[8]

Most studies have shown no pharmacokinetic interaction or increased incidence of adverse effects when pioglitazone or rosiglitazone were used with atorvastatin or simvastatin. The clinical relevance of the apparent increased incidence of adverse muscle and liver effects with the use of pioglitazone or rosiglitazone together with atorvastatin is unclear. Further study is needed.

The clinical relevance of the modest decrease in lovastatin levels with exenatide is also unclear, but experience in clinical studies suggests that it is unlikely to be significant.

Note that a number of the large-scale studies of the use of lipid-regulating drugs in primary or secondary prevention of cardiovascular events included patients with diabetes. A review of these subgroups concluded that statins were the drug of choice for lipid-lowering therapy in patients with type 2 diabetes and known coronary artery disease or other cardiovascular risk factors. There was no evidence to recommend one statin over another.[15]

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Antidiabetics + Sucralfate

Sucralfate appears not to affect the pharmacokinetics of chlorpropamide or rosiglitazone.

Clinical evidence, mechanism, importance and management

(a) Chlorpropamide

A two-way, crossover study in 12 healthy subjects found that sucralfate 1 g four times daily, given one hour before meals, had no significant effect on the pharmacokinetics of a single 250-mg dose of chlorpropamide.[1] No additional precautions would therefore seem to be necessary on concurrent use.

(b) Rosiglitazone

A single-dose study found that sucralfate 2 g taken 45 minutes before rosiglitazone 8 mg had no significant effect on the pharmacokinetics of rosiglitazone. No special precautions are needed during concurrent use.[2]

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Antidiabetics + Sugar-containing pharmaceuticals

Some pharmaceutical preparations may contain sufficient amounts of sugar to affect the control of diabetes.

Clinical evidence, mechanism, importance and management

Pharmaceuticals, especially liquid formulations, may contain sugar in significant amounts. The extent to which the use of preparations like these will affect the control of diabetes clearly depends upon the amounts taken, but the problem is by no means merely theoretical. One report describes the loss of diabetic control (glycosuria) in a woman with type 1 diabetes receiving insulin when given psyllium effervescent powder (*Metamucil* instant-mix), which contains sugar.[1]

The range of other sugar-containing preparations is far too extensive to be listed here. Because of concerns over sugar-containing medicines and dental caries, in children in particular, the number of sugar-free preparations has grown considerably over recent years. In the UK the BNF and MIMS provide guidance as to which preparations are sugar-free. Diabetics should be warned about sugar-containing medicines, and given guidance about the terminology used in labelling. Sweetening agents of note to diabetics include: **invert sugar** (dextrose and fructose), **invert syrup** (67% w/w invert sugar), **syrup BP** (66% w/w sucrose), **glucose liquid** (dextrose content 10 to 20%), **glucose syrup** (33.3% liquid glucose in syrup) and **honey** (70 to 80% glucose and fructose).[2]

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Antidiabetics + Sulfinpyrazone

Sulfinpyrazone has no effect on the insulin requirements of diabetics, nor does it affect the control of diabetes in patients taking glibenclamide (glyburide). Increased blood glucose-lowering effects might occur if sulfinpyrazone is given with tolbutamide, but as yet there appear to be no case reports of this interaction. Sulfinpyrazone modestly increased the AUC of nateglinide in one study.

Clinical evidence

(a) Insulin

A double-blind study in 41 adult patients with diabetes found that sulfinpyrazone 600 to 800 mg daily had no clinically significant effects on insulin requirements over a 12-month period.[1]

(b) Nateglinide

In a crossover study in healthy subjects, sulfinpyrazone 200 mg twice daily for 7 days increased the mean AUC of a single 120-mg dose of nateglinide by 28%, but did not change the mean maximum plasma level.[2]

(c) Sulfonylureas

A study in 19 patients with type 2 diabetes taking **glibenclamide** found that sulfinpyrazone 800 mg daily did not affect diabetic control.[3]

A detailed study of the pharmacokinetics of **tolbutamide** in 6 healthy subjects found that sulfinpyrazone 200 mg every 6 hours for a week, almost doubled the half-life of a 500-mg intravenous dose of **tolbutamide**, from 7.3 hours to 13.2 hours, and reduced the plasma clearance by 40%.[4]

Mechanism

Sulfinpyrazone is an inhibitor of the cytochrome P450 isoenzyme CYP2C9, by which tolbutamide and some other sulfonylureas, and nateglinide are metabolised.

Importance and management

Information about an interaction between tolbutamide and sulfinpyrazone appears to be limited to the report cited. So far there appear to be no reports of adverse interactions in patients, but what is known suggests that increased blood glucose-lowering effects, and possibly hypoglycaemia could occur if the dose of tolbutamide is not reduced. Such an interaction has been described with phenylbutazone, which has a close structural similarity to sulfinpyrazone (see 'Antidiabetics + NSAIDs; Phenylbutazone and related drugs', p.564). Patients should be warned if sulfinpyrazone is added to established treatment with tolbutamide. It is also possible that other sulfonylureas metabolised similarly to tolbutamide may be affected in the same way.

The modest increase in nateglinide exposure when given with sulfinpyrazone has not been assessed in diabetics, but it seems unlikely to be clinically relevant. There seems to be nothing documented about any other clinically important interactions between antidiabetics and sulfinpyrazone.

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Antidiabetics + Sulfonamides

The blood glucose-lowering effects of some of the sulfonylureas are increased by some, but not all, sulfonamides, due to inhibition of their metabolism. Occasionally and unpredictably acute hypoglycaemia has occurred in individual patients taking various combinations of sulfonamides and sulfonylureas. There appear to be no reports of a serious adverse interaction between insulin and the sulfonamides. Co-trimoxazole alone may rarely cause hypoglycaemia.

Clinical evidence

'Table 13.3', (p.575) summarises the information on the interactions between sulfonylureas and sulfonamides. For a report of the concurrent use of co-trimoxazole and fluconazole causing hypoglycaemia with gliclazide, see 'Antidiabetics + Azoles; Fluconazole', p.544.

Mechanism

The sulfonamides may inhibit the metabolism of the sulfonylureas so that they accumulate in the body. In this way their serum levels and

Table 13.3 Interactions between antidiabetics and sulfonamides

Drugs	*Information documented*	*Refs*
Chlorpropamide		
+ sulfafurazole (sulfisoxazole)	1 case of acute hypoglycaemia	1
+ sulfadimidine	1 case of acute hypoglycaemia	2
+ co-trimoxazole	2 cases of acute hypoglycaemia	3, 4
Glibenclamide		
+ co-trimoxazole	In a large review of glibenclamide-associated hypoglycaemia 6 of 57 patients were also taking co-trimoxazole	5
	1 case of hypoglycaemia	6
	No pharmacokinetic interaction in 8 patients	7
Glibornuride		
+ sulfaphenazole	Half-life increased by 34% in 4 subjects (2 diabetic, 2 healthy)	8
Gliclazide		
+ co-trimoxazole	4 cases of acute hypoglycaemia	6
Glipizide		
+ co-trimoxazole	1 case of acute hypoglycaemia	9
	No pharmacokinetic interaction, or change in blood glucose-lowering effects in 8 healthy subjects	10
Insulin		
+ co-trimoxazole	No overall changes in blood glucose or insulin concentrations in 8 patients	11
Tolbutamide		
+ co-trimoxazole	Clearance of intravenous tolbutamide reduced by 25%, half-life increased by 30% in 7 healthy subjects	12
+ sulfafurazole (sulfisoxazole)	3 cases of severe hypoglycaemia	13, 14
	No pharmacokinetic interaction	15, 16
+ sulfamethizole	Half-life of tolbutamide increased 60%. Metabolic clearance reduced by about 40%	17
+ sulfaphenazole	Two cases of severe hypoglycaemia	16
	Half-life of tolbutamide increased three to sixfold	15, 16, 18, 19, 20
+ sulfadiazine	Half-life of tolbutamide increased by about 57%	18
+ sulfadimethoxine	No pharmacokinetic interaction	15, 16
+ sulfamethoxazole	Clearance reduced 14%, half-life increased 20% after intravenous use	12
	Half-life increased by about 65%	15
+ sulfamethoxypyridazine	No pharmacokinetic interaction	16
Unnamed sulfonylurea		
+ co-trimoxazole	1 case of acute hypoglycaemia	11

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Continued

Table 13.3 Interactions between antidiabetics and sulfonamides (continued)

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blood glucose-lowering effects are enhanced.[1-4] Greater understanding of metabolic mechanisms has led to the realisation that some sulfonamides are inhibitors of the cytochrome P450 isoenzyme CYP2C9 by which many of the sulfonylureas are metabolised. Tolbutamide, in particular, is now recognised as an important substrate of CYP2C9.[5,6] Of the sulfonamides, *in vitro* data suggest that sulfaphenazole is a potent inhibitor of CYP2C9, with sulfadiazine, sulfamethizole, sulfafurazole (sulfisoxazole) and sulfamethoxazole being moderate to minor inhibitors, and sulfapyridine, sulfadimethoxine and sulfamonomethoxine having little inhibitory activity.[6] CYP2C9 shows genetic polymorphism, therefore any interaction might only be clinically relevant in a subgroup of the population. There is also some evidence that the sulfonamides can displace the sulfonylureas from their protein binding sites.[4]

Where some of the cases of hypoglycaemia cannot be predicted on pharmacokinetic grounds, it is worth noting that hypoglycaemia induced by co-trimoxazole, in the absence of a conventional antidiabetic,[7-11] and sometimes associated with renal failure,[9] high dose of sulfonamide,[7,11] advanced age,[8,10] or malnutrition,[7] has been described. Note that trimethoprim alone may cause interactions by inhibiting CYP2C8 and CYP2C9, see 'Antidiabetics + Trimethoprim', p.579.

Importance and management

Information is very patchy and incomplete. Most sulfonamides seem to have caused marked problems (acute hypoglycaemia) in only a few patients and serious interactions are uncommon. When a sulfonamide is first added to established treatment with a sulfonylurea, warn the patient that increased blood glucose-lowering effects, sometimes excessive, are a possibility, but that problems appear to be uncommon or rare. Nevertheless, the cautious approach would be to increase the frequency of blood glucose monitoring. In one study, co-trimoxazole did not appear to cause any significant changes in blood glucose or insulin concentrations in patients receiving **insulin**.[12] However, note that co-trimoxazole alone may rarely cause hypoglycaemia (see *Mechanism*, above). For the interactions of trimethoprim alone, see 'Antidiabetics + Trimethoprim', p.579.

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Antidiabetics + Terbinafine

Terbinafine is reported not to interact with tolbutamide, and did not affect glucose control in a study in patients receiving insulin or oral antidiabetics.

Clinical evidence

A large-scale post-marketing survey did not find any interaction in patients taking terbinafine with **tolbutamide** (number unknown).[1] In a subgroup of this survey no additional risk was noted in 154 patients taking antidiabetics with terbinafine.[2] In a clinical study in 89 patients with diabetes and toenail fungal infections, oral terbinafine 250 mg daily for 12 weeks had no effect on blood glucose levels in 83% of patients. Eleven (12.4%) of the patients had an elevated blood glucose level at baseline, which was normal at the end of the study, and 4 patients had a normal baseline blood glucose, which became elevated at the end of the study. No episodes of hypoglycaemia were reported. Patients in this study were receiving **insulin** or **oral antidiabetics** (not specified).[3]

Mechanism

On the basis of studies with human liver microsomes, terbinafine is unlikely to alter the metabolism of tolbutamide.[4]

Importance and management

Terbinafine does not appear to interact with tolbutamide or affect glucose control in patients receiving insulin or oral antidiabetics. No special precautions are required on concurrent use.

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Antidiabetics + Tetracyclines

A few early reports indicated that the blood glucose-lowering effects of insulin and the sulfonylureas may sometimes be increased by oxytetracycline. There is also a case of hypoglycaemia involving insulin and doxycycline. Phenformin-induced lactic acidosis may be precipitated by tetracyclines.

Clinical evidence

(a) Insulin

A diabetic with poorly controlled blood glucose levels needed a marked reduction in his insulin dose, from 208 to 64 units daily, in order to control the hypoglycaemia that developed when **oxytetracycline** 250 mg four times daily was given. This reaction was also seen when the patient was

given a second course of antibacterials, and in another patient.[1] A report briefly lists a case of hypoglycaemia when a patient receiving insulin was given **doxycycline**,[2] and another case describes doxycycline-induced hypoglycaemia in an elderly diabetic patient managed by diet alone.[3]

(b) Phenformin

There are at least 6 cases on record of lactic-acidosis in patients taking phenformin that were apparently precipitated by the concurrent use of **tetracycline**.[4-7]

(c) Sulfonylureas

Marked hypoglycaemia occurred in an elderly patient taking **tolbutamide** when **oxytetracycline** was given,[8] and another study in diabetic patients similarly found that **oxytetracycline** could reduce blood glucose levels.[9] The half-life of **glymidine** has been found to be prolonged from 4.6 hours to 7.6 hours by **doxycycline**,[10] whereas a brief comment in another report suggests that **demeclocycline** and **doxycycline** may not affect **chlorpropamide** disposition.[11]

Mechanism

Not understood. Several mechanisms have been suggested including a prolongation of the half-life of insulin and interference with adrenaline-induced glycaemia.[3]

Importance and management

Information about the interactions between the sulfonylureas or insulin and the tetracyclines is very limited indeed, and clinically important interactions appear to be very uncommon. Concurrent use need not be avoided, but be aware of this interaction in case of an unexpected response to treatment.

Phenformin was withdrawn in some countries because it was associated with a high incidence of lactic acidosis; where available, concurrent use with tetracyclines should be avoided. However, there is nothing to suggest that there is an increased risk if tetracyclines are given with **metformin**.

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Antidiabetics + Thioctic acid

Thioctic acid is reported not to interact with acarbose, metformin or glibenclamide (glyburide).

Clinical evidence, mechanism, importance and management

A study in 24 healthy subjects given tablets containing thioctic acid 200 mg and **metformin** 500 mg found that the pharmacokinetics of the **metformin** were unchanged by the presence of the thioctic acid, and the authors of the report say that there was also no pharmacodynamic interaction.[1] The report gives very few details. A further study in 24 healthy subjects found that a single 600-mg dose of thioctic acid given with **glibenclamide** (**glyburide**) 3.5 mg did not result in any clinically relevant pharmacokinetic interaction, and thioctic acid did not alter the effect of **glibenclamide** on glucose or insulin levels.[2] Similarly, there was no evidence of a change in thioctic acid pharmacokinetics or pharmacodynamics when it was given to healthy subjects with **acarbose**.[2]

No special precautions seem to be required if thioctic acid is given to patients taking **acarbose**, **metformin** or **glibenclamide**.

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Antidiabetics + Tibolone

Tibolone may slightly impair glucose tolerance and therefore possibly reduce the effects of the antidiabetics.

Clinical evidence, mechanism, importance and management

One woman developed diabetes 14 weeks after starting tibolone 2.5 mg daily. However, she had a high normal fasting blood glucose level before starting tibolone, and the diabetes did not resolve on withdrawing the drug.[1] In 1994, the manufacturers of tibolone noted that on their adverse drug event database they had only 3 cases of diabetes occurring during the use of tibolone, and 3 cases of aggravation of diabetes during its use, which they considered a very low number in relation to the extent of tibolone use.[2]

A metabolic study in 10 women with type 2 diabetes stabilised with diet and oral antidiabetics, and given tibolone 2.5 mg daily found there were no changes in glycaemic control, as measured by HbA_{1c} levels.[3] Conversely, a longer 12-month study in 14 women with type 2 diabetes given tibolone found a slight deterioration in glycaemic control (as measured by serum fructosamine),[4] and an early study found that tibolone caused a slight decrease in glucose tolerance in non-diabetic patients.[5]

The manufacturers of tibolone say that patients with diabetes should be closely supervised.[6] It would therefore seem prudent to increase the frequency of blood glucose monitoring if tibolone is started or stopped.

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Antidiabetics + Tobacco or Nicotine

Diabetics who smoke tobacco may need more subcutaneous insulin than non-smokers. Smoking and, to a lesser extent, nicotine patches, may increase insulin resistance, and stopping smoking can improve glycaemic control in both type 1 and type 2 diabetics. However, the effects of smoking on diabetes appear to be complex, as some studies have reported that smoking does not affect insulin sensitivity or glycaemic control. Preliminary evidence shows that smoking increases the absorption of inhaled insulin.

Clinical evidence, mechanism, importance and management

A study in 163 patients with type 1 diabetes found that, on average, the 114 who smoked needed 15 to 20% more subcutaneous **insulin** than the non-smokers, and up to 30% more **insulin** if they smoked heavily.[1] Possible mechanisms include decreased absorption of **insulin** from the subcutaneous tissue because of peripheral vasoconstriction,[2] and a significant rise (40 to 100%) in the levels of the hormones that oppose the actions of **insulin**.[3,4]

Serum **insulin** levels during the first 6 hours after inhaled **insulin** were 58% higher in smokers than in non-smokers, and peak **insulin** levels were about threefold higher. Minor hypoglycaemia requiring a glucose infusion occurred in 12 smokers but in only one non-smoker. The increased absorption was possibly due to cigarette smoke increasing the permeability of the alveolar-capillary barrier.[5] It should be noted that the first marked inhaled insulin (*Exubera*, now withdrawn) was contraindicated in patients who smoked, or had smoked within the past 6 months.[6]

In a double-blind, crossover study in 12 smokers with type 2 diabetes, stabilised with diet alone or with **oral antidiabetics**, the effect of smoking one cigarette every hour for 6 hours was compared with transdermal nicotine (30 cm^2 patch) or a placebo patch. Cigarette smoking and the nicotine patch did not affect endogenous insulin secretion, when compared with placebo, but smoking impaired peripheral insulin action, and resulted in lower rates of glucose utilisation and greater hepatic glucose production. The nicotine patch similarly impaired insulin action, but this was much less pronounced than after cigarette smoking, possibly due to the lower plasma levels of nicotine attained with the patch.[7]

In another study, glycaemic control (as measured by HbA_{1c}) was modestly improved in 7 subjects with type 1 diabetes and 27 subjects with type 2 diabetes, one year after they had stopped smoking. This improved control was considered clinically significant.[8] In a study in patients with type 2 diabetes stabilised with diet alone or diet and **sulfonylureas** with or without **metformin**; insulin resistance was higher in the 28 smokers than the 12 non-smokers.[9] Further studies have reported that smoking in diabetics is associated with poor glycaemic control,[10] microalbuminuria,[10] and impaired insulin clearance.[11] However, other studies have suggested that smoking does not affect **insulin** requirement in type 1 diabetics[12] or have a significant effect on glycaemic control in type 1 or type 2 diabetics.[3,12,13] There are numerous other studies on the relationship between smoking and diabetes or insulin resistance in non-diabetics, and only a few are cited here as examples. Some studies have indicated that smoking could increase the risk of type 2 diabetes (relative risk of 2.6) and that tobacco use is associated with a low insulin response.[14] However, other studies suggest that a causal relationship between smoking and insulin resistance is unlikely,[15,16] although in one of the studies[16] exposure to environmental tobacco smoke was associated with lower insulin sensitivity.

Glycaemic control is not the only factor of importance with smoking in diabetics. Cigarette smoking may also accelerate progression of atherosclerosis, increase blood pressure, and increase macrovascular complications.[7,16,17] Diabetics who smoke should be given all the help they need to stop smoking.[10,17]

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Antidiabetics + Tricyclic and related antidepressants

Interactions between antidiabetics and tricyclic or tetracyclic antidepressants appear to be rare, but isolated cases of hypoglycaemia have been reported.

Clinical evidence

(a) Retrospective evidence

One research group from the Netherlands have conducted a number of analyses to look at the association between antidepressants and dysglycaemia.[1-3] In one analysis of cases of patients hospitalised for hypoglycaemia, the use of antidepressants (including tricyclics and related drugs) was not associated with an increased risk. The authors suggested that there was a trend for an increased risk with amitriptyline, doxepin and imipramine, as a group, when compared with maprotiline, nortriptyline, mianserin and mirtazapine, as a group,[1] but there were too few cases to reasonably assess this. Conversely, in an analysis of spontaneous reports in the WHO adverse drug reaction database, the use of antidepressants was associated with a small increased risk of both hyperglycaemia (odds ratio 1.5) and hypoglycaemia (odds ratio 1.8). Tricyclics and related drugs had a slightly greater risk of hyperglycaemia than hypoglycaemia, but this was not statistically significant.[2] In a further longitudinal study in 133 patients using **insulin** for at least 12 months before starting an antidepressant, and for at least 6 months with an antidepressant, the dose of insulin used did not change after starting the antidepressant. When analysed by antidepressant type, no change in insulin requirement was seen with tricyclic antidepressants.[3]

(b) Prospective studies

A study in 4 patients suggested that **amitriptyline** 75 mg daily for 9 days did not affect the half-life of a single 500-mg dose of **tolbutamide**.[4] Although there is some evidence of a change in glucose metabolism during treatment with **mianserin**,[5-7] the alteration did not affect the control of diabetes in a study in 10 patients and there appear to be no reports of adverse effects caused by concurrent use.[6]

(c) Case reports

In contrast to the above data, there are four case reports describing hypoglycaemic interactions:

- A patient taking **tolazamide** became hypoglycaemic 11 days after starting to take **doxepin** 250 mg daily. The patient was eventually stabilised on a daily dose of **tolazamide** that was only 10% of that used before the **doxepin** was given.[8]
- A patient taking **chlorpropamide** (initially 25 mg increased to 75 mg daily) developed marked hypoglycaemia 3 days after starting **nortriptyline** 125 mg daily. The **chlorpropamide** was stopped.[8]
- A patient receiving **insulin** developed violent and agitated behaviour (but no adrenergic symptoms) and hypoglycaemia when she started to take **amitriptyline** 25 mg at bedtime.[9]
- An elderly diabetic woman taking **glibenclamide** (**glyburide**) and **phenformin** developed hypoglycaemia when given **maprotiline**. She was restabilised on half the dose of **glibenclamide** and **phenformin**.[10]

Mechanism

The reason for the cases of hypoglycaemia is unknown. Depression *per se*, may alter factors (e.g. weight gain or weight loss) that influence glucose homeostasis.

Importance and management

Apart from the isolated cases there seems to be very little evidence that the tricyclic or tetracyclic antidepressants can cause hypoglycaemia in patients with diabetes. Bearing in mind the length of time these groups of drugs have been available, the risk of a clinically important interaction would seem to be very small. Therefore no particular precautions seem warranted on concurrent use

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Antidiabetics + Trimethoprim

Trimethoprim increases the AUC of repaglinide and might be expected to increase its effects in some patients. The effect of trimethoprim on the AUC of pioglitazone and rosiglitazone is somewhat more modest and probably less likely to be clinically relevant. Trimethoprim does not appear to significantly affect the pharmacokinetics of intravenous tolbutamide.

Clinical evidence

(a) Pioglitazone

In a study in 16 healthy subjects, trimethoprim 160 mg twice daily for 6 days increased the AUC of a single 15-mg dose of pioglitazone given on day 3 by 42%, without any relevant change in the peak plasma level. The formation of various pioglitazone metabolites was slightly reduced.[1]

(b) Repaglinide

In a study in 9 healthy subjects, trimethoprim 160 mg twice daily for 3 days increased the AUC and the maximum plasma level of a single 250-microgram dose of repaglinide by 61% and 41%, respectively. However, the blood glucose-lowering effect of this small dose of repaglinide was unchanged.[2]

(c) Rosiglitazone

In a study in 10 healthy subjects, trimethoprim 160 mg twice daily for 4 days increased the AUC of a single 4-mg dose of rosiglitazone given on day 3 by 37%. The half-life of rosiglitazone was increased by 26% but the peak plasma level was only slightly affected (14% increase).[3] Similarly, in another study, trimethoprim 200 mg twice daily for 5 days increased the AUC of a single 8-mg dose of rosiglitazone by 31% and increased its half-life by 27%.[4]

(d) Tolbutamide

In a study in 7 healthy subjects, trimethoprim 150 mg twice daily for 7 days prolonged the elimination half-life of a single intravenous 500-mg dose of tolbutamide by 19%.[5]

Mechanism

Data suggest that trimethoprim inhibits the metabolism of repaglinide, pioglitazone and rosiglitazone by the cytochrome P450 isoenzyme CYP2C8. Tolbutamide is metabolised by CYP2C9, and it is thought possible that trimethoprim may have a slight inhibitory effect on this isoenzyme, although there is very little information about this.[6]

Importance and management

The clinical relevance of the pharmacokinetic changes has not been assessed. However, the fairly marked changes seen with repaglinide suggest that some patients might experience an increase in the effects of this drug when trimethoprim is also given. The UK manufacturers of repaglinide[7] suggest that the concurrent use of trimethoprim should be avoided as the effect of larger doses of both drugs is unknown. The US manufacturers suggest caution, and advise that repaglinide dose adjustments may be necessary.[8] If trimethoprim is required in a patient taking repaglinide, it would seem prudent to increase the frequency of blood glucose monitoring.

The more modest increase in the AUC of pioglitazone and rosiglitazone seen with trimethoprim is less likely to be clinically important, but, until more experience is gained, some caution is warranted. No interaction would be expected between trimethoprim and tolbutamide, although note that co-trimoxazole has rarely caused hypoglycaemia, both alone and when given with various sulfonylureas, see 'Antidiabetics + Sulfonamides', p.574.

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7. Prandin (Repaglinide). Daiichi Sankyo UK Ltd. UK Summary of product characteristics, December 2008.
8. Prandin (Repaglinide). Novo Nordisk Inc. US Prescribing information, June 2006.

Antidiabetics + Tyrosine kinase inhibitors

An improvement in diabetic control with a reduction in dose of insulin or oral antidiabetics has been seen in a few reports of diabetics given imatinib for chronic myelogenous leukaemia, but one report found no benefit. In one case, an increased insulin dose was required with imatinib and then subsequently also with nilotinib, but a reduced insulin requirement then occurred with dasatinib.

Clinical evidence

Use of **imatinib** 400 or 600 mg daily for the treatment of chronic myelogenous leukaemia (CML) was associated with improved glycaemic control in 6 of 7 diabetic patients who had a clinical response to the drug. This allowed a reduction in **insulin** dose in 2 patients and a reduction in the dose of the **oral antidiabetic** in 4 patients.[1] The same research group described a further case, in a woman with type 2 diabetes managed with insulin, who had a sequential reduction in fasting blood glucose and HbA_{1c} over 18 weeks after starting **imatinib** 400 mg daily.[2] Another case report describes a 70-year-old woman with type 2 diabetes who needed a reduction in her **insulin** dose when she was given imatinib for CML. Later, while still taking imatinib, she was able to stop the **insulin** completely.[3] However, in a retrospective review of patients who had received **imatinib**, of 7 patients who had pre-existing type 2 diabetes, and 2 who developed diabetes during therapy, no effect of **imatinib** on glycaemic control was noted.[4]

In yet another case report, the use of **imatinib** was associated with an increased insulin dose, and, the use of **nilotinib** (which proved ineffective for CML) for 3 months was also associated with a further increased insulin requirement. In contrast, the subsequent use of **dasatinib** resulted in two episodes of hypoglycaemia, and a reduced insulin requirement.[5]

Mechanism

It was thought that imatinib and dasatinib may have a direct effect on glycaemic control,[1,3,5] rather than an indirect effect by improving the leukaemia.[1] Nilotinib is reported to cause hyperglycaemia,[5,6] so it is perhaps not surprising that this drug caused an increased insulin requirement.

Importance and management

These preliminary findings suggest that diabetic patients should be well monitored in those given tyrosine kinase inhibitors such as dasatinib, imatinib and nilotinib, because of the possibility of altered glucose metabolism. Further study is needed.

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Dipeptidylpeptidase-4 inhibitors + Calcium-channel blockers

Diltiazem markedly increased the AUC of saxagliptin and modestly reduced that of its active metabolite (which is about half as potent as saxagliptin) in one study. Verapamil is expected to interact similarly. No clinically relevant pharmacokinetic interaction has been detected between vildagliptin and amlodipine.

Clinical evidence

(a) Amlodipine

In a crossover study in 19 healthy subjects, there were no clinically relevant changes in the pharmacokinetics of **vildagliptin** or amlodipine when **vildagliptin** 100 mg daily was given with amlodipine 5 mg daily for 10 days, when compared with either drug alone.[1]

(b) Diltiazem

In a study in 12 healthy subjects, modified-release diltiazem 360 mg daily for 8 days increased the maximum level and AUC of **saxagliptin** by 63% and 2.1-fold, respectively, when a single 10-mg dose of saxagliptin was given on day 8. In addition, there was a 36% reduction in the AUC of the active metabolite of **saxagliptin** (which is about half as potent as saxagliptin). **Saxagliptin** did not alter the AUC of diltiazem.[2]

Mechanism

Diltiazem is a modest inhibitor of the cytochrome P450 isoenzyme CYP3A4 by which saxagliptin is metabolised to its principal metabolite (which is about half as active as the parent compound).

Importance and management

The pharmacokinetic interaction between diltiazem and **saxagliptin** is established, but its clinical relevance has not yet been assessed. **Verapamil**, also an inhibitor of CYP3A4, is predicted to interact similarly.[3] Nevertheless, the US manufacturer does *not* recommend any saxagliptin dose reduction in the presence of diltiazem or verapamil.[3]

There is no clinically relevant pharmacokinetic interaction between **vildagliptin** and amlodipine.

1. He Y-L, Ligueros-Saylan M, Sunkara G, Sabo R, Zhao C, Wang Y, Campestrini J, Pommier F, Dole K, Marion A, Dole WP, Howard D. Vildagliptin, a novel dipeptidyl peptidase IV inhibitor, has no pharmacokinetic interactions with the antihypertensive agents amlodipine, valsartan, and ramipril in healthy subjects. J Clin Pharmacol (2008) 48, 85–95.
2. Girgis S, Patel CG, Li L, Gooding L, Frevert EU, Whigan D, Boulton DW. Effect of diltiazem on the pharmacokinetics of saxagliptin in healthy subjects. 36th Annual Meeting of the American College of Clinical Pharmacology, San Francisco, California, 2007.
3. Onglyza (Saxagliptin). Bristol-Myers Squibb. US Prescribing information, July 2009.

Dipeptidylpeptidase-4 inhibitors + Ketoconazole and other CYP3A4 inhibitors

Ketoconazole, a CYP3A4 inhibitor, markedly raises the levels of saxagliptin and markedly reduces the levels of the active metabolite (which is about half as potent as saxagliptin). Other inhibitors of CYP3A4 would be expected to interact similarly. Sitagliptin and vildagliptin would not be expected to interact to a clinically relevant extent with CYP3A4 inhibitors.

Clinical evidence

In studies in healthy subjects, ketoconazole 200 mg every 12 hours until steady-state increased the AUC of a single 100-mg dose of **saxagliptin** (high-dose) 2.5-fold and increased the AUC of a single 20-mg dose of **saxagliptin** 3.7-fold. In addition, there was a marked 90% reduction in the AUC of the active metabolite of **saxagliptin** (which is about half as potent as saxagliptin). **Saxagliptin** 100 mg caused a minor 13% decrease in the AUC of ketoconazole.[1,2]

Mechanism

Ketoconazole is a potent inhibitor of the cytochrome P450 isoenzyme CYP3A4 by which saxagliptin is metabolised to its principal metabolite (which is about half as active as the parent compound). Metabolism by CYP3A4 is a minor route for **sitagliptin** (up to 16% of a dose),[3,4] and **vildagliptin** is not metabolised by P450 isoenzymes.[5]

Importance and management

It appears that ketoconazole markedly increases **saxagliptin** levels, but any effect of this should be partially offset by a marked reduction in active metabolite levels. The clinical relevance of this interaction with clinical use of the lower daily doses of saxagliptin recommended (5 mg daily) is not known. Nevertheless, the US manufacturer recommends that the saxagliptin dose be limited to 2.5 mg daily when used with ketoconazole and other similar potent inhibitors of CYP3A4, and they specifically name **atazanavir**, **clarithromycin**, **indinavir**, **itraconazole**, **nefazodone**, **nelfinavir**, **ritonavir**, **saquinavir** and **telithromycin**.[1] No dose adjustment is recommended for moderate inhibitors of CYP3A4, and they specifically name **amprenavir**, **aprepitant** [and therefore its prodrug, **fosaprepitant**], diltiazem and verapamil (see 'Dipeptidylpeptidase-4 inhibitors + Calcium-channel blockers', p.580), **erythromycin**, **fluconazole**, **fosamprenavir**, and **grapefruit juice**.[1] Conversely, the UK manufacturer does not give any advice about the use of CYP3A4 inhibitors.[6] Further study is needed to establish the clinical relevance of these interactions.

Sitagliptin and **vildagliptin** would not be expected to be affected by ketoconazole by inhibition of CYP3A4. However, the UK manufacturer of sitagliptin does not rule out the possibility of an interaction with potent CYP3A4 inhibitors (they name **clarithromycin**, **itraconazole**, **ketoconazole**, **ritonavir**) in patients with severe renal impairment or end-stage renal disease, in whom metabolism may play a more important role in elimination. However, they also state that, because of limited clinical experience, sitagliptin should not be used in patients with more than mild impairment of renal function.[4] The US manufacturer recommends sitagliptin dose reductions by degree of renal impairment, and this is likely to compensate for any theoretical interaction with potent CYP3A4 inhibitors.[3]

1. Onglyza (Saxagliptin). Bristol-Myers Squibb. US Prescribing information, July 2009.
2. Patel CG, Boulton DW, Brenner E, Royzman K, Li L. Effect of ketoconazole on the pharmacokinetics of saxagliptin in healthy subjects. 36th Annual Meeting of the American College of Clinical Pharmacology, San Francisco, California, 2007.
3. Januvia (Sitagliptin phosphate). Merck & Co., Inc. US Prescribing information, March 2009.
4. Januvia (Sitagliptin phosphate monohydrate). Merck Sharp & Dohme Ltd. UK Summary of product characteristics, November 2009.
5. Galvus (Vildagliptin). Novartis Pharmaceuticals Ltd. UK Summary of product characteristics, August 2009.
6. Onglyza (Saxagliptin). AstraZeneca UK Ltd. UK Summary of product characteristics, October 2009.

Dipeptidylpeptidase-4 inhibitors + Metformin

No clinically relevant pharmacokinetic interactions have been detected between linagliptin, saxagliptin, sitagliptin or vildagliptin and metformin.

Clinical evidence and mechanism

(a) Linagliptin

In a study in healthy subjects, the concurrent use of linagliptin 10 mg daily and metformin 850 mg three times daily had no effect on the pharmacokinetics of metformin. In addition, there was no change in pharmacokinetics of linagliptin, except for a minor 20% increase in its AUC.[1]

(b) Saxagliptin

In a single-dose study in 16 healthy subjects, there was no change in the pharmacokinetics of metformin 1 g when it was given with saxagliptin 100 mg. In addition, there was no change in the AUC of saxagliptin and just a minor 21% decrease in the maximum saxagliptin level.[2]

(c) Sitagliptin

In a study in 13 patients with type 2 diabetes, there were no changes in the pharmacokinetics of sitagliptin or metformin when sitagliptin 50 mg twice daily was given with metformin 1 g twice daily for 7 days, when compared with either drug alone.[3]

(d) Vildagliptin

In a study in 17 patients with type 2 diabetes, when vildagliptin 100 mg daily was given with metformin 1 g daily, there was a slight 15% increase in AUC of metformin, but no change in AUC of vildagliptin.[4] This small change in metformin levels is unlikely to be clinically relevant.

Importance and management

These combinations of drugs are being used in the management of diabetes for their additive blood glucose lowering effects, and the studies show that there are no pharmacokinetic interactions that will complicate such use.

1. Graefe-Mody EU, Padula S, Ring A, Withopf B, Dugi KA. Evaluation of the potential for steady-state pharmacokinetic and pharmacodynamic interactions between the DPP-4 inhibitor linagliptin and metformin in healthy subjects. Curr Med Res Opin (2009) 25, 1963–72.
2. Patel CG, Komoroski BJ, Brenner E, Li L, Boulton DW. No meaningful pharmacokinetic drug-drug interaction between saxagliptin and metformin in healthy subjects. 36th Annual Meeting of the American College of Clinical Pharmacology, San Francisco, California, 2007.
3. Herman GA, Bergman A, Yi B, Kipnes M; Sitagliptin Study 012 Group. Tolerability and pharmacokinetics of metformin and the dipeptidyl peptidase-4 inhibitor sitagliptin when co-administered in patients with type 2 diabetes. *Curr Med Res Opin* (2006) 22, 1939–47.
4. He Y-L, Sabo R, Picard F, Wang Y, Herron J, Ligueros-Saylan M, Dole WP. Study of the pharmacokinetic interaction of vildagliptin and metformin in patients with type 2 diabetes. Curr Med Res Opin (2009) 25, 1265–72.

Dipeptidylpeptidase-4 inhibitors + Rifampicin (Rifampin) and other CYP3A4 inducers

Rifampicin, a potent CYP3A4 inducer, markedly reduces the levels of saxagliptin and did not alter the levels of the active metabolite (which is about half as potent as saxagliptin). Other potent inducers of CYP3A4 might be expected to interact similarly. Sitagliptin and vildagliptin would not be expected to interact with CYP3A4 inducers.

Clinical evidence

In a study in healthy subjects, rifampicin 600 mg daily until steady-state reduced the AUC of a single 5-mg dose of **saxagliptin** by 76%. There was no change in the AUC of the active metabolite of **saxagliptin** (which is about half as potent as saxagliptin). However, the US manufacturer notes that there was no change in the dipeptidylpeptidase-4 inhibitory activity of **saxagliptin** over 24 hours when given with rifampicin.[1]

Mechanism

Rifampicin is a potent inducer of the cytochrome P450 isoenzyme CYP3A4 by which saxagliptin is metabolised to its principal metabolite (which is about half as active as the parent compound).[1] Metabolism by CYP3A4 is a minor route for **sitagliptin** (up to 16% of a dose),[2,3] and **vildagliptin** is not metabolised by cytochrome P450 isoenzymes.[4]

Importance and management

It appears that rifampicin markedly reduces saxagliptin exposure, and there is no increase in exposure to the active metabolite to offset this. The clinical relevance of this has not been assessed, but the US manufacturer considers that no dose adjustment of saxagliptin is needed because dipeptidylpeptidase-4 inhibitory activity was not altered.[1] Nevertheless, until more is known, it cannot be ruled out that rifampicin might reduce the blood glucose lowering effect of saxagliptin, and the UK manufacturer recommends caution with the use of potent inducers of CYP3A4, and they specifically name **carbamazepine**, **dexamethasone**, **phenobarbital**, **phenytoin** and **rifampicin**.[5] Some caution would therefore seem prudent with **primidone**, which is metabolised to phenobarbital, and **fosphenytoin**, a prodrug of phenytoin. Further study is needed to establish the clinical relevance of these interactions.

Sitagliptin and vildagliptin would not be expected to be affected by rifampicin by induction of CYP3A4.

1. Onglyza (Saxagliptin). Bristol-Myers Squibb. US Prescribing information, July 2009.
2. Januvia (Sitagliptin phosphate). Merck & Co., Inc. US Prescribing information, March 2009.
3. Januvia (Sitagliptin phosphate monohydrate). Merck Sharp & Dohme Ltd. UK Summary of product characteristics, November 2009.
4. Galvus (Vildagliptin). Novartis Pharmaceuticals Ltd. UK Summary of product characteristics, August 2009.
5. Onglyza (Saxagliptin). AstraZeneca UK Ltd. UK Summary of product characteristics, October 2009.

Dipeptidylpeptidase-4 inhibitors + Sulfonylureas

No clinically relevant pharmacokinetic interactions have been detected between alogliptin, saxagliptin, sitagliptin or vildagliptin and glibenclamide (glyburide). The risk of hypoglycaemia may be increased by the concurrent use of a dipeptidylpeptidase-4 inhibitor and a sulfonylurea.

Clinical evidence

(a) Alogliptin

In a study in 24 healthy subjects, there was no change in the pharmacokinetics of **glibenclamide** (glyburide) when a single 5-mg dose was given before and on the last day of alogliptin 25 mg daily for 7 days, except for a minor 15% increase in the glibenclamide maximum level.[1]

(b) Saxagliptin

In a single-dose study in 30 healthy subjects, there was no change in the AUC of **glibenclamide** or saxagliptin when both drugs were given together, and a minor 16% increase in the maximum glibenclamide level and an 8% increase in the maximum saxagliptin level.[2]

In a large placebo-controlled study where saxagliptin 2.5 mg or 5 mg was given to patients with type 2 diabetes taking **glibenclamide**, there was a slightly increased incidence of reports of hypoglycaemia in patients taking saxagliptin (13.3% and 14.6% for the two doses, respectively) when compared with placebo (10.1%).[3]

(c) Sitagliptin

In a study in 8 healthy subjects,[4] sitagliptin 200 mg daily for 6 days had no effect on the AUC of a single 1.25-mg dose of **glibenclamide** given on day 5.

In a large placebo-controlled study where sitagliptin 100 mg was given to patients with type 2 diabetes taking **glimepiride**, there was an increased incidence of hypoglycaemia in patients taking sitagliptin (12.2%) when compared with placebo (1.8%).[5]

(d) Vildagliptin

In a study in 17 patients with type 2 diabetes, there were no clinically relevant changes in the pharmacokinetics of vildagliptin or **glibenclamide** when vildagliptin 100 mg twice daily was given with glibenclamide 10 mg daily, when compared with either drug alone. As expected, the combination had greater glucose lowering effects than either drug alone.[6]

In clinical studies, the incidence of hypoglycaemia when vildagliptin 50 mg daily was added to **glimepiride** was 1.2%, compared with 0.6% for placebo added to **glimepiride**.[7]

Mechanism

Sulfonylureas increase the risk of hypoglycaemia because they increase the secretion of insulin. Dipeptidylpeptidase-4 inhibitors may increase this risk because they slow the inactivation of incretin hormones, which also increases the release of insulin.

Importance and management

Sulfonylureas and dipeptidylpeptidase-4 inhibitors are being used concurrently in the management of diabetes for their additive blood glucose lowering effects, and the studies show that there are no pharmacokinetic interactions that will complicate this use. Bear in mind that the risk of hypoglycaemia may be greater with the combination of a dipeptidylpeptidase-4 inhibitor and a sulfonylurea. Because of this, when starting the dipeptidylpeptidase-4 inhibitor in a patient already taking a sulfonylurea, consideration should be given to lowering the dose of the sulfonylurea.

1. Karim A, Laurent A, Munsaka M, Wann E, Fleck P, Mekki Q. Coadministration of pioglitazone or glyburide and alogliptin: pharmacokinetic drug interaction assessment in healthy participants. J Clin Pharmacol (2009) 49, 1210–19.
2. Patel CG, Komoroski BJ, Li L, Boulton DW. No meaningful pharmacokinetic drug-drug interaction between saxagliptin and glyburide in healthy subjects. 36th Annual Meeting of the American College of Clinical Pharmacology, San Francisco, California, 2007.
3. Chacra AR, Tan GH, Apanovitch A, Ravichandran S, List J, Chen R; CV181-040 Investigators. Saxagliptin added to a submaximal dose of sulphonylurea improves glycaemic control compared with uptitration of sulphonylurea in patients with type 2 diabetes: a randomised controlled trial. Int J Clin Pract (2009) 63, 1395–1406.
4. Mistry GC, Bergman AJ, Zheng W, Hreniuk D, Zinny MA, Gottesdiener KM, Wagner JA, Herman GA, Ruddy M. Sitagliptin, an dipeptidyl peptidase-4 inhibitor, does not alter the pharmacokinetics of the sulphonylurea, glyburide, in healthy subjects. Br J Clin Pharmacol (2008) 66, 36–42.

5. Januvia (Sitagliptin phosphate). Merck & Co., Inc. US Prescribing information, March 2009.
6. Serra D, He Y-L, Bullock J, Riviere G-J, Balez S, Schwartz S, Wang Y, Ligueros-Saylan M, Jarugula V, Dole WP. Evaluation of pharmacokinetic and pharmacodynamic interaction between the dipeptidyl peptidase IV inhibitor vildagliptin, glyburide and pioglitazone in patients with Type 2 diabetes. Int J Clin Pharmacol Ther (2008) 46, 349–64..
7. Galvus (Vildagliptin). Novartis Pharmaceuticals Ltd. UK Summary of product characteristics, August 2009.

Dipeptidylpeptidase-4 inhibitors + Thiazolidinediones

No clinically relevant pharmacokinetic interactions have been seen between sitagliptin and rosiglitazone, or between alogliptin, saxagliptin or vildagliptin with pioglitazone. There may be an increased risk of peripheral oedema if saxagliptin is used with a thiazolidinedione.

Clinical evidence and mechanism

(a) Alogliptin

In a crossover study in 27 healthy subjects, the concurrent use of alogliptin 25 mg daily and **pioglitazone** 45 mg daily for 12 days slightly increased the AUC of alogliptin by 10% and caused no changes in the pharmacokinetics of pioglitazone or its active metabolites.[1] In a phase III clinical study, there was no difference in incidence of peripheral oedema when alogliptin was used with pioglitazone. However, cardiac disorders of any cause (e.g. atrial fibrillation, heart failure, myocardial infarction, angina, tachycardia, palpitations) occurred more frequently in those receiving alogliptin than placebo (alogliptin 25 mg 6.5%, alogliptin 12.5 mg 3%, placebo 1%). One possible explanation for this was that the groups were not equally matched for pre-existing cardiac disorders [it should be possible to retrospectively analyse the data to see if this was so]. The authors considered the cardiac events unlikely to be attributable to a drug interaction.[2] However, further study is needed to establish any cardiovascular adverse effect and its relationship to the concurrent use of these drugs.

(b) Saxagliptin

In a study in 28 healthy subjects, when saxagliptin 10 mg daily and pioglitazone 45 mg daily were given together for 5 days, there was no change in the pharmacokinetics of saxagliptin and just a minor 14% increase in the maximum level of **pioglitazone** (no change in AUC), when compared with either drug alone.[3] In a placebo-controlled clinical study where saxagliptin 2.5 mg daily or 5 mg daily was added to the established use of **pioglitazone** or **rosiglitazone** in patients with type 2 diabetes, there was a higher incidence of peripheral oedema in those given saxagliptin 5 mg than those given saxagliptin 2.5 mg or placebo (8.1%, 3.1% and 4.3%, respectively).[3]

(c) Sitagliptin

In a study in healthy subjects,[4] sitagliptin 200 mg daily for 5 days had no effect on the AUC of a single 4-mg dose of **rosiglitazone** given on day 5.

(d) Vildagliptin

In a study in 15 patients with type 2 diabetes, there were no clinically relevant changes in the pharmacokinetics of vildagliptin or **pioglitazone** when vildagliptin 100 mg twice daily was given with pioglitazone 45 mg daily compared with either drug alone. As expected, the combination had greater glucose lowering effects than either drug alone.[5]

Importance and management

Dipeptidylpeptidase-4 inhibitors and thiazolidinediones may be used in the management of diabetes for their additive blood glucose lowering effects, and the studies show that there are no pharmacokinetic interactions that will complicate such use. Bear in mind the possibility of an increased risk of peripheral oedema if saxagliptin is added to thiazolidinedione therapy.

1. Karim A, Laurent A, Munsaka M, Wann E, Fleck P, Mekki Q. Coadministration of pioglitazone or glyburide and alogliptin: pharmacokinetic drug interaction assessment in healthy participants. J Clin Pharmacol (2009) 49, 1210–19.
2. Pratley RE, Reusch JE-B, Fleck PR, Wilson CA, Mekki Q; Alogliptin Study 009 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor alogliptin added to pioglitazone in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled study. Curr Med Res Opin (2009) 25, 2361–71.
3. Onglyza (Saxagliptin). Bristol-Myers Squibb. US Prescribing information, July 2009.
4. Mistry GC, Bergman AJ, Luo W-L, Cilissen C, Haazen W, Davies MJ, Gottesdiener KM, Wagner JA, Herman GA. Multiple-dose administration of sitagliptin, a dipeptidyl peptidase-4 inhibitor, does not alter the single-dose pharmacokinetics of rosiglitazone in healthy subjects. *J Clin Pharmacol* (2007) 47, 159–64.
5. Serra D, He Y-L, Bullock J, Riviere G-J, Balez S, Schwartz S, Wang Y, Ligueros-Saylan M, Jarugula V, Dole WP. Evaluation of pharmacokinetic and pharmacodynamic interaction between the dipeptidyl peptidase IV inhibitor vildagliptin, glyburide and pioglitazone in patients with Type 2 diabetes. Int J Clin Pharmacol Ther (2008) 46, 349–64..

Dipeptidylpeptidase-4 inhibitors; Saxagliptin + Drugs that affect gastric pH

The pharmacokinetics of saxagliptin are not altered by antacids, famotidine or omeprazole.

Clinical evidence, mechanism, importance and management

(a) Antacids

In a study in 15 healthy subjects, the AUC of saxagliptin was unchanged when a single 10-mg dose of saxagliptin was given at the same time as 30 mL of an antacid containing **aluminium/magnesium hydroxide** with simeticone.[1] The saxagliptin maximum level was slightly decreased (by 26%), but this is not expected to be clinically relevant. No saxagliptin dose adjustment is likely to be needed if antacids are also given.

(b) Famotidine

In a study in 15 healthy subjects, the AUC of saxagliptin was unchanged when a single 10-mg dose of saxagliptin was given 3 hours after a single 40-mg dose of famotidine .[1] No saxagliptin dose adjustment is likely to be needed if famotidine is also given.

(c) Omeprazole

In a study in 15 healthy subjects, there was no change in the pharmacokinetics of saxagliptin when a single 10-mg dose of saxagliptin was given on day 5 of omeprazole 40 mg daily for 5 days.[1] No saxagliptin dose adjustment is likely to be needed if omeprazole is also given.

1. Boulton DW, Adams D, Li L, Patel CG, Komoroski BJ, Whigan D, Frevert EU, Goyal A, Kornhauser DM. 36th Annual Meeting of the American College of Clinical Pharmacology, San Francisco, California, 2007.

Dipeptidylpeptidase-4 inhibitors; Sitagliptin + Ciclosporin

Single-dose ciclosporin slightly increased the absorption of sitagliptin, although this was not considered clinically relevant.

Clinical evidence, mechanism, importance and management

A crossover study in 8 healthy subjects found that when a single 100-mg dose of sitagliptin was given with a single 600-mg dose of ciclosporin there was a 68% increase in the maximum plasma levels of sitagliptin, with a slight increase in overall exposure to sitagliptin (AUC increased by 28%). There was no change in renal clearance of sitagliptin.[1]

It is likely that ciclosporin enhances the absorption of sitagliptin by inhibiting P-glycoprotein. However, these changes were considered unlikely to be clinically meaningful, because of the apparent wide therapeutic index of sitagliptin.[1] However, note that one of the rare adverse effects of ciclosporin is hyperglycaemia.

1. Krishna R, Bergman A, Larson P, Cote J, Lasseter K, Dilzer S, Wang A, Zeng W, Chen L, Wagner J, Herman G. Effect of a single cyclosporine dose on the single-dose pharmacokinetics of sitagliptin (MK-0431), a dipeptidyl peptidase-4 inhibitor, in healthy male subjects. *J Clin Pharmacol* (2007) 47, 165–74.

Dipeptidylpeptidase-4 inhibitors; Vildagliptin + ACE inhibitors or Angiotensin II receptor antagonists

No clinically relevant pharmacokinetic interactions have been detected between vildagliptin and ramipril or valsartan.

Clinical evidence, mechanism, importance and management

In a crossover study in 18 healthy subjects, there were no clinically relevant changes in the pharmacokinetics of **vildagliptin**, **ramipril** or its active metabolite ramiprilat when **vildagliptin** 100 mg daily was given with **ramipril** 5 mg daily for 7 days, when compared with either drug alone.[1]

In another similar study in 28 healthy subjects, there were no clinically relevant changes in the pharmacokinetics of **vildagliptin** when **vildagliptin** 100 mg daily was given with **valsartan** 320 mg daily for 7 days, whereas **vildagliptin** modestly increased the AUC of **valsartan** by 24%.[1]

These studies provide evidence that there is no clinically relevant pharmacokinetic interaction between **vildagliptin** and **ramipril** or **valsartan**. On this basis, no pharmacokinetic interaction would be anticipated with **vildagliptin** and any ACE inhibitor or angiotensin II receptor antagonist.

For the conflicting data on the possible increased risk of hypoglycaemia when some antidiabetics are used with ACE inhibitors, see 'Antidiabetics + ACE inhibitors', p.536.

1. He Y-L, Ligueros-Saylan M, Sunkara G, Sabo R, Zhao C, Wang Y, Campestrini J, Pommier F, Dole K, Marion A, Dole WP, Howard D. Vildagliptin, a novel dipeptidyl peptidase IV inhibitor, has no pharmacokinetic interactions with the antihypertensive agents amlodipine, valsartan, and ramipril in healthy subjects. J Clin Pharmacol (2008) 48, 85–95.

Exenatide + Miscellaneous

The rate of paracetamol (acetaminophen) absorption is reduced by exenatide, even when the paracetamol is given up to four hours after the exenatide. The manufacturer therefore recommends that exenatide be used with caution with drugs that require rapid gastrointestinal absorption or drugs that require a threshold level for efficacy (such as some antibacterials).

Clinical evidence

In a single-dose, placebo-controlled study using oral **paracetamol** (**acetaminophen**) elixir as a marker of gastric emptying, subcutaneous exenatide 10 micrograms, given before breakfast, reduced the maximum plasma levels of **paracetamol** by 56% and delayed the time to maximum level from 0.6 hours to 4.2 hours when the paracetamol was given one hour after the exenatide. The overall extent of absorption was slightly reduced (23% reduction in AUC), This effect was seen when **paracetamol** was given at the same time as exenatide, or 2, and 4 hours after exenatide although the extent of the interaction was smaller. It was not seen when **paracetamol** was given one hour *before* exenatide.[1]

Mechanism

Exenatide markedly slows gastric emptying, and has the potential to delay the absorption of other drugs.

Importance and management

Because exenatide delays gastric emptying and may reduce the rate of absorption of orally administered drugs, the manufacturers recommend that exenatide should be used with caution in patients receiving oral drugs that require rapid gastrointestinal absorption. They do not give any specific examples.[2,3] However, where a rapid effect of an oral drug is required, for example, an analgesic for acute pain or fever, it may be prudent to give the drug at least one hour before exenatide, or delay exenatide until more than 2 hours after the drug.

The manufacturers also suggest that exenatide should be used with caution in patients receiving oral drugs that are dependent on threshold concentrations for efficacy. They give **antibacterials** as an example (but no drugs are specifically named), and recommend that they should be taken at least one hour before exenatide.[2,3] Whether this is clinically necessary remains to be shown.

In addition, for drugs that are formulated as gastric-resistant formulations, or that are sensitive to degradation by gastric acid, the UK manufacturer recommends that they are taken one hour before exenatide or at least 4 hours afterwards.[3]

1. Blase E, Taylor K, Gao H, Wintle M, Fineman M. Pharmacokinetics of an oral drug (acetaminophen) administered at various times in relation to subcutaneous injection of exenatide (exendin-4) in healthy subjects. *J Clin Pharmacol* (2005) 45, 570–7.
2. Byetta (Exenatide). Amylin Pharmaceuticals, Inc. US Prescribing information, October 2009.
3. Byetta (Exenatide). Eli Lilly and Company Ltd. UK Summary of product characteristics, March 2009.

Insulin + Naltrexone

The insulin requirements of a patient rose by about 30% when naltrexone was given.

Clinical evidence, mechanism, importance and management

A patient with type 1 diabetes was given naltrexone in an experimental study of the treatment of anorexia nervosa. During two periods of 5 days while taking the naltrexone (dose not stated), the blood glucose levels of the patient remained unchanged but the insulin dose requirements rose from 52.8 and 61.4 units daily to 71.4 and 76 units daily (a rise of about 30%). The reason is not known but the authors of this report point out that this apparent interaction must have been due to the actions of insulin rather than on its release because this patient had no endogenous insulin.[1]

The general clinical importance of this interaction is not known but it would be prudent to be alert for any evidence of increased insulin requirements if naltrexone is used in any patient.

1. Marrazzi MA, Jacober S, Luby ED. A naltrexone-induced increase in insulin requirement. *J Clin Psychopharmacol* (1994) 14, 363–5.

Liraglutide + Miscellaneous

Liraglutide had no clinically relevant effects on the pharmacokinetics of atorvastatin, an oral combined hormonal contraceptive, digoxin, griseofulvin, lisinopril or paracetamol (acetaminophen). Although theoretically unlikely, the manufacturer does not rule out an interaction with warfarin

Clinical evidence, mechanism, importance and management

(a) Atorvastatin

In a pharmacokinetic study, liraglutide modestly decreased the maximum level of a single 40-mg dose of atorvastatin by 38% and its median time to maximum level was delayed from one to 3 hours, but there was no change the overall exposure (AUC).[1]

This study shows that liraglutide modestly delays the rate, but not extent, of atorvastatin absorption; a finding that is not likely to have clinically relevant adverse effects. Therefore, no adjustment of the atorvastatin dose is likely to be needed in patients also given liraglutide.

(b) Combined hormonal contraceptives

After administration of a single dose of an oral combined hormonal contraceptive (ethinylestradiol with levonorgestrel), liraglutide had no effect on overall exposure (AUC) of the contraceptive steroids. There was a slight decrease in the maximum level of ethinylestradiol and levonorgestrel, by 12% and 13%, respectively, and the time to maximum level was slightly delayed by 1.5 hours.[1] No clinically relevant pharmacokinetic interaction is therefore anticipated when oral hormonal contraceptives are given with liraglutide.

(c) Digoxin

Liraglutide slightly reduced the AUC of a single 1-mg dose of digoxin by 16% and decreased its maximum level by 31%, with a slight delay in time to maximum level of 30 minutes.[1] These pharmacokinetic changes are unlikely to be clinically relevant, and no adjustment of digoxin dose is expected to be needed in patients also given liraglutide.

(d) Griseofulvin

In a pharmacokinetic study, liraglutide modestly increased the maximum level of a single 500-mg dose of griseofulvin by 37% without any change in median time to maximum level or in the overall exposure (AUC).[1] Therefore, no adjustment of the griseofulvin dose is likely to be needed in patients also given liraglutide.

(e) Insulin

The manufacturer of liraglutide states that the concurrent use of insulin is not recommended because it has not been evaluated.[1]

(f) Lisinopril

Liraglutide slightly reduced the AUC of a single 20-mg dose of lisinopril by 15% and decreased the maximum level by 27%, with a delay in time to maximum level from 6 hours to 8 hours.[1] These pharmacokinetic changes are unlikely to be clinically relevant, and no adjustment of the lisinopril dose is expected to be needed in patients also given liraglutide.

(g) Paracetamol (Acetaminophen)

When paracetamol was given as a single 1-g dose, liraglutide did not change the overall exposure (AUC), and only slightly decreased the rate of absorption (maximum level decreased by 31% and median time to maximum level delayed by up to 15 minutes).[1]

Paracetamol is often used to assess gastric emptying rate, and these findings suggest that liraglutide actually has little effect on gastric emptying. This is confirmed from the pharmacokinetic studies with other drugs mentioned here, where no examples of clinically relevant delays in absorption have been found. Nevertheless, the manufacturer states that the small delay of gastric emptying with liraglutide may influence absorption of oral medicinal products given concurrently. Note that they also say that severe diarrhoea has been reported in a few patients given liraglutide, and that diarrhoea may affect the absorption of oral medicinal products given concurrently.[1]

(h) Warfarin

On the basis of other studies discussed here, liraglutide would not be expected to alter the absorption of warfarin. In addition, liraglutide does not affect cytochrome P450, by which warfarin is principally metabolised. No interaction would therefore be anticipated. However, the manufacturer says that a clinically relevant interaction with active substances with narrow therapeutic index such as warfarin cannot be excluded. They therefore recommend that more frequent monitoring of the INR is recommended if patients taking warfarin are given liraglutide. As there is little clinical experience with liraglutide this may be prudent.

1. Victoza (Liraglutide). Novo Nordisk Ltd. UK Summary of product characteristics, June 2009.

Metformin + Aliskiren

The concurrent use of metformin and aliskiren modestly reduced aliskiren levels and slightly reduced metformin levels in one study.

Clinical evidence, mechanism, importance and management

In a study in 19 healthy subjects, giving aliskiren 300 mg daily with metformin 1 g daily for 4 days reduced the AUC of aliskiren by 27% and reduced the AUC of metformin by 12%, when compared with either drug given alone.[1] The reason for these minor changes is unclear; however, they are not considered to be clinically relevant.

1. Vaidyanathan S, Maboudian M, Warren V, Yeh C-M, Dieterich HA, Howard D, Dole WP. A study of the pharmacokinetic interactions of the direct renin inhibitor aliskiren with metformin, pioglitazone and fenofibrate in healthy subjects. Curr Med Res Opin (2008) 24, 2313–26.

Metformin + Cefalexin

Cefalexin modestly increased metformin levels in a single-dose study.

Clinical evidence, mechanism, importance and management

In a placebo-controlled study in 12 healthy subjects, cefalexin 500 mg increased the AUC and maximum serum levels of a single 500-mg dose of metformin by 24% and 34%, respectively. Cefalexin reduced the renal clearance of metformin by 14% by inhibiting metformin tubular secretion via the organic cation system.[1] The clinical relevance of these small changes is uncertain, but they could possibly be greater with longer-term use. The authors recommend that patients receiving metformin with cefalexin should have metformin levels monitored or an alternative antibacterial to cefalexin should be considered.[1] However, based on the available evidence this seems somewhat overcautious.

1. Jayasagar G, Krishna Kumar M, Chandrasekhar K, Madhusudan Rao C, Madhusudan Rao Y. Effect of cephalexin on the pharmacokinetics of metformin in healthy human volunteers. *Drug Metabol Drug Interact* (2002) 19, 41–8.

Metformin + Eslicarbazepine

Eslicarbazepine did not alter the pharmacokinetics of metformin in one study.

Clinical evidence, mechanism, importance and management

In a study[1] in 19 healthy subjects, eslicarbazepine 1.2 g daily for 6 days had no effect on the pharmacokinetics of a single 850-mg dose of metformin given on day 5. This study provides evidence that no pharmacokinetic interaction would be expected on the concurrent use of these drugs and therefore no metformin dose adjustment would be expected to be necessary if eslicarbazepine is also given.

1. Rocha JF, Vaz-da-Silva M, Almeida L, Falcão A, Nunes T, Santos AT, Martins F, Fontes-Ribeiro C, Macedo T, Soares-da-Silva P. Effect of eslicarbazepine acetate on the pharmacokinetics of metformin in healthy subjects. Int J Clin Pharmacol Ther (2009) 47, 255–61.

Metformin + Ginkgo (*Ginkgo biloba*)

Ginkgo did not appear to alter the pharmacokinetics of metformin, and appeared to have a slight beneficial effect on glycaemic control.

Clinical evidence, mechanism, importance and management

In a small crossover study that included 10 patients with type 2 diabetes taking metformin, ginkgo (EGb 761) 120 mg daily for 3 months slightly improved HbA_{1c} when compared with placebo (HbA_{1c} 7.2% versus 7.7%). The pharmacokinetics of metformin were assessed on one day at the end of the study, when the usual daily dose of metformin was taken with the daily dose of ginkgo. Ginkgo did not appear to have any effects on metformin pharmacokinetics.[1] In a further 10 healthy subjects, ginkgo 120 mg daily had no effect on the pharmacokinetics of a single 500-mg dose of metformin, except for a reduction in the time to reach the maximum plasma level.[1]

This study indicates that ginkgo is unlikely to alter the pharmacokinetics of metformin. In addition, it provides some limited evidence that it may have a slight beneficial effect on glycaemic control, although this requires confirmation in a larger study.

1. Kudolo GB, Wang W, Javors M, Blodgett J. The effect of the ingestion of Ginkgo biloba extract (EGb 761) on the pharmacokinetics of metformin in non-diabetic and type 2 diabetic subjects--a double blind placebo-controlled, crossover study. *Clin Nutr* (2006) 25, 606–16.

Metformin + Iodinated contrast media

Parenteral administration of iodinated contrast media may cause renal failure, which could result in lactic acidosis in patients taking metformin.

Clinical evidence, mechanism, importance and management

Parenteral administration of iodinated contrast media to patients taking metformin may result in lactic acidosis. However, the problem is reported to occur only if the contrast media causes renal failure and metformin use is continued. This is because metformin is mainly excreted by the kidneys and in renal failure toxic levels may accumulate,[1] which may result in lactic acidosis. A literature search identified 18 cases of lactic acidosis after the use of contrast media in patients taking metformin.[2] Of these 18 cases, 14 or 15 were associated with pre-existing renal impairment and 2 cases with other contraindications to metformin (sepsis and cirrhosis). The remaining case was in an elderly woman with neurological disease. Note that diabetes-related renal impairment *per se* is an important risk factor for contrast-media associated renal failure.[3,4]

The manufacturers of metformin say that it should be stopped before, or at the time of giving the contrast media and not restarted until 48 hours lat-

er, and then only after renal function has been re-checked and found to be normal.[5,6] Guidelines issued by the European Society of Urogenital Radiology,[7] suggest that there is no need to stop metformin before giving the contrast media in patients with normal renal function. In patients with an estimated glomerular filtration rate of 30 to 60 mL/minute, or a raised serum creatinine level, then metformin should be withheld for 48 hours before and after the contrast media, and only restarted if creatine levels are unchanged.[7] Metformin and/or contrast media are not usually recommended in patients with an estimated glomerular filtration rate of less than 30 mL/minute. In emergency cases where renal function is abnormal or unknown, alternative imaging should be used, if possible. If this is not possible, then the risks and benefits of using contrast media should be weighed carefully. If concurrent use is necessary, the metformin should be stopped, and special care taken with intravenous hydration and monitoring of renal function and lactic acidosis.[7] The American College of Radiologist make similar recommendations, but additionally mention risk factors for lactic acidosis with metformin (e.g. liver impairment, alcohol abuse, myocardial ischaemia, sepsis), and recommend additional caution if these factors are also present.[8] For example, patients with normal renal function and multiple risk factors should withhold from taking metformin for 48 hours after the administration of iodinated contrast media, and consideration should be given to measuring the serum creatinine before re-starting metformin.[8]

Although these guidelines minimise the risk, some patients may still develop an adverse reaction. For example, an analysis of 97 patients taking metformin who were given intravenous contrast media, 4 developed contrast media-associated nephropathy (all 4 had baseline normal renal function). These patients could have been at increased risk of metformin-associated lactic acidosis had the metformin not been stopped and withheld.[9] Furthermore, a fatal case of metformin-induced lactic acid occurred in a 47-year-old man with normal renal function who was admitted as an emergency for aneurysmal subarachnoid haemorrhage and who underwent two contrast procedures (CT scan and angiography) with ionic contrast iohexol.[10]

1. Rasuli P, Hammond DI. Metformin and contrast media: where is the conflict? *Can Assoc Radiol J* (1998) 49, 161–6.
2. McCartney MM, Gilbert FJ, Murchison LE, Pearson D, McHardy K, Murray AD. Metformin and contrast media – a dangerous combination? *Clin Radiol* (1999) 54, 29–33.
3. Morcos SK, Thomsen HS. European Society of Urogenital Radiology guidelines on administering contrast media. *Abdom Imaging* (2003) 28, 187–190.
4. Thomsen HS, Morcos SK. Contrast media and the kidney: European Society of Urogenital Radiology (ESUR) guidelines. *Br J Radiol* (2003) 76, 513–8.
5. Glucophage (Metformin hydrochloride). Merck Pharmaceuticals. UK Summary of product characteristics, November 2008.
6. Glucophage (Metformin hydrochloride). Bristol-Myers Squibb Co. US Prescribing information, January 2009.
7. European Society of Urogenital Radiology. ESUR guidelines on contrast media version 7.0, August 2008. Available at: http://www.esur.org/Contrast-media.46.0.html?&cHash=5f43d7bc0a&directory=&picid=0&totalCount=32 accessed (29/01/10).
8. American College of Radiology. Manual on contrast media, version 6, 2008. Available at www.acr.org/contrast-manual (accessed 29/01/10).
9. Parra D, Legreid AM, Beckey NP, Reyes S. Metformin monitoring and change in serum creatinine levels in patients undergoing radiologic procedures involving administration of intravenous contrast media. *Pharmacotherapy* (2004) 24, 987–93. Erratum ibid., 1489.
10. Jain V, Sharma D, Prabhakar H, Dash HH. Metformin-associated lactic acidosis following contrast media-induced nephrotoxicity. Eur J Anaesthesiol. (2008) 25, 166–7.

Pramlintide + Miscellaneous

Pramlintide modestly slows gastric emptying, and therefore it has been recommended that it should not be used with other drugs that alter gastrointestinal motility.

Clinical evidence, mechanism, importance and management

In a single-dose study using oral **paracetamol** (**acetaminophen**) elixir as a marker of gastric emptying, subcutaneous pramlintide, given immediately before breakfast, increased the time to maximum plasma **paracetamol** levels by up to 72 minutes and reduced the maximum **paracetamol** level by about 29%, without altering the overall extent of absorption, when compared with placebo. This effect was seen when **paracetamol** was given at the same time as pramlintide, or for up to 2 hours after pramlintide. It was not seen when **paracetamol** was given one to 2 hours before pramlintide.[1]

This study demonstrates that pramlintide modestly slows gastric emptying, and has the potential to delay the absorption of other drugs.

The manufacturer notes that if a rapid onset of action is required (for example when giving an oral **analgesic**), the drug should be given at least one hour before or 2 hours after pramlintide.[2] Furthermore, because of this delay in gastric emptying, the manufacturer recommends that pramlintide should not be used in patients taking other drugs that alter gastrointestinal motility. They specifically name **antimuscarinics** such as **atropine**,[2] which delay gastric emptying. Note that pramlintide could, theoretically, oppose the effects of **metoclopramide**, which increases gastric emptying.

1. Kellmeyer TA, Kesty NC, Wang Y, Frias JP, Fineman MS. Pharmacokinetics of an oral drug (acetaminophen) administered at various times relative to subcutaneous injection of pramlintide in subjects with type 2 diabetes. *J Clin Pharmacol* (2007) 47, 798–805.
2. Symlin (Pramlintide acetate). Amylin Pharmaceuticals, Inc. US Prescribing information, July 2008.

Repaglinide + Enzyme inducers

Phenytoin, barbiturates and carbamazepine might reduce repaglinide levels and efficacy.

Clinical evidence, mechanism, importance and management

The plasma levels and effects of repaglinide are known to be reduced by rifampicin (see 'Antidiabetics + Rifamycins', p.567), probably principally via induction of the cytochrome P450 isoenzyme CYP2C8 and also CYP3A4. The manufacturers state that they cannot exclude the possibility that other enzyme inducers may interact similarly, and they also name mention **phenytoin**,[1] **carbamazepine**,[1,2] and **phenobarbital**.[1,2] Bear the possibility of reduced repaglinide efficacy in mind if any of these enzyme inducing drugs is used. Note that **fosphenytoin** is a prodrug of phenytoin, and **primidone** is metabolised to phenobarbital, and therefore some caution also seems warranted with these drugs.

For a list of CYP2C8 inducers, see 'Table 1.3, (p.6) and for CYP3A4 inducers, see 'Table 1.4', (p.6). For mention that high doses of phenytoin have rarely caused hyperglycaemia, see 'Phenytoin + Antidiabetics', p.627.

1. Prandin (Repaglinide). Daiichi Sankyo UK Ltd. UK Summary of product characteristics, December 2008.
2. Prandin (Repaglinide). Novo Nordisk Inc. US Prescribing information, June 2006.

Repaglinide + Grapefruit juice

Grapefruit juice caused a small increase in repaglinide levels in one study.

Clinical evidence, mechanism, importance and management

In a study in 36 healthy subjects, drinking 300 mL of grapefruit juice with a single dose of repaglinide increased the AUC of repaglinide by 13% without any effect on blood glucose levels. The effect was more noticeable with a low 250 microgram dose of repaglinide than with the therapeutic dose of 2 mg.[1] The small increase in AUC of repaglinide in this study is most likely due to inhibition of intestinal CYP3A4 by grapefruit juice constituents; however, and increase of this size is not clinically relevant.

1. Bidstrup TB, Damkier P, Olsen AK, Ekblom M, Karlsson A, Brøsen K. The impact of CYP2C8 polymorphism and grapefruit juice on the pharmacokinetics of repaglinide. *Br J Clin Pharmacol* (2006) 61, 49–57.

Repaglinide + Montelukast

Montelukast did not alter the pharmacokinetics of repaglinide.

Clinical evidence, mechanism, importance and management

In a controlled study[1] in healthy subjects, montelukast 10 mg daily for 3 days had no effect on the AUC of a single 250-microgram dose of repaglinide given on day 3.

In vitro, montelukast inhibited the cytochrome P450 isoenzyme CYP2C8, by which repaglinide is principally metabolised. This study provides conclusive evidence that this interaction does not occur *in vivo*. No repaglinide dose adjustment is therefore expected to be necessary if montelukast is also given.

1. Kajosaari LI, Niemi M, Backman JT, Neuvonen PJ. Telithromycin, but not montelukast, increases the plasma concentrations and effects of the cytochrome P450 3A4 and 2C8 substrate repaglinide. *Clin Pharmacol Ther* (2006) 79, 231–42.

Sulfonylureas + Antacids

The rate of absorption of some sulfonylureas is increased by some antacids, but there appear to be no reports of adverse responses in diabetic patients as a result of any of these interactions.

Clinical evidence

(a) Chlorpropamide

Magnesium hydroxide 850 mg increased the rate of absorption of chlorpropamide 250 mg in healthy subjects, but the insulin and glucose responses were unaffected.[1]

(b) Glibenclamide (Glyburide)

A single-dose study in healthy subjects found that **magnesium hydroxide** 850 mg had little effect on the rate or extent of absorption of a micronised glibenclamide preparation (*Semi-Euglucon*), but it caused a threefold increase in the peak plasma concentration and the bioavailability of a non-micronised preparation (*Gilemid*).[2] *Maalox* (**aluminium**/**magnesium hydroxide**) increased the AUC of glibenclamide (given as *Daonil*) by one-third, and increased its maximum serum level by 50%.[3]

Sodium bicarbonate 1 to 3 g very markedly increased the early bioavailability of non-micronised glibenclamide in healthy subjects, but its activity remained unaltered.[4]

(c) Glipizide

Sodium bicarbonate 3 g significantly increased the absorption of glipizide 5 mg and enhanced its effects to some extent, but the total absorption was unaltered.[5] The 30 minute, 1-hour, and 2-hour AUCs, were increased sixfold, fourfold and twofold, respectively, and the time to reach the peak serum level fell from 2.5 hours to one hour. **Aluminium hydroxide** 1 g did not appear to affect the absorption of glipizide 5 mg.[5] **Magnesium hydroxide** 850 mg considerably increased the rate of absorption of glipizide 5 mg: the 30-minute and one-hour AUCs being increased by 180% and 69%, respectively.[6]

(d) Tolbutamide

In healthy subjects **magnesium hydroxide** 850 mg increased the 1-hour and 2-hour AUCs of a single 500-mg dose of tolbutamide 5-fold and 2.5-fold, respectively. The total AUC was unaffected. The maximum insulin response was increased fourfold and occurred about an hour earlier, and the glucose responses were also larger, and occurred earlier.[1]

Mechanism

Uncertain. The small increase in gastric pH caused by these antacids possibly increases the solubility of these sulfonylureas and therefore increases their absorption.[7]

Importance and management

Although some interactions between antacids and sulfonylureas certainly occur in healthy subjects, their clinical importance in patients with diabetes is uncertain. No reports of adverse reactions appear to have been published, but note that patients taking glipizide with sodium bicarbonate or magnesium hydroxide, or tolbutamide with magnesium hydroxide may experience transient hypoglycaemia. Generally no action seems necessary, but if a problem does occur, separating the doses as much as possible would probably minimise any effects. Giving glibenclamide 30 minutes to one hour before the antacid has been suggested as a strategy to minimise any interaction.[3]

1. Kivistö KT, Neuvonen PJ. Effect of magnesium hydroxide on the absorption and efficacy of tolbutamide and chlorpropamide. *Eur J Clin Pharmacol* (1992) 42, 675–80.
2. Neuvonen PJ, Kivistö KT. The effects of magnesium hydroxide on the absorption and efficacy of two glibenclamide preparations. *Br J Clin Pharmacol* (1991) 32, 215–20.
3. Zuccaro P, Pacifici R, Pichini S, Avico U, Federzoni G, Pini LA, Sternieri E. Influence of antacids on the bioavailability of glibenclamide. *Drugs Exp Clin Res* (1989) 15, 165–9.
4. Kivistö KT, Lehto P, Neuvonen PJ. The effects of different doses of sodium bicarbonate on the absorption and activity of non-micronized glibenclamide. *Int J Clin Pharmacol Ther Toxicol* (1993) 31, 236–40.
5. Kivistö KT, Neuvonen PJ. Differential effects of sodium bicarbonate and aluminium hydroxide on the absorption and activity of glipizide. *Eur J Clin Pharmacol* (1991) 40, 383–6.
6. Kivistö KT, Neuvonen PJ. Enhancement of absorption and effect of glipizide by magnesium hydroxide. *Clin Pharmacol Ther* (1991) 49, 39–43.
7. Lehto P, Laine K, Kivistö K, Neuvonen PJ. The effect of pH on the *in vitro* dissolution of sulfonylurea preparations — a mechanism for the antacid-sulfonylurea interaction? *Therapie* (1995) 50 (Suppl), 413.

Sulfonylureas + Bosentan

There appears to be an increased risk of liver toxicity if bosentan is given with glibenclamide. Glibenclamide (glyburide) modestly reduces the plasma levels of bosentan, and bosentan reduces the plasma levels of glibenclamide. Bosentan is predicted to reduce the plasma levels, and possibly effect, of other similarly metabolised antidiabetics, which would include many other sulfonylureas.

Clinical evidence and mechanism

In clinical studies, bosentan was noted to be associated with dose-related asymptomatic elevations in liver enzymes in some patients, and these elevations were higher in patients also receiving **glibenclamide** (**glyburide**).[1] Study in *rats* suggested that the concurrent use of bosentan and **glibenclamide** caused increases in serum bile salt levels that were greater than with either drug alone.[1] In addition, *in vitro* study showed that bosentan inhibits the bile salt export pump,[1] which is also inhibited by **glibenclamide**.

Because of the possibility that there may be a pharmacokinetic component to the interaction, the pharmacokinetics of both bosentan and **glibenclamide** were determined in a crossover study in 12 healthy subjects. However, **glibenclamide** actually reduced the maximum plasma levels and AUC of bosentan by 24% and 29%, respectively, while bosentan reduced the maximum plasma levels and AUC of **glibenclamide** by 22% and 40%, respectively. Two subjects had asymptomatic elevated liver enzyme levels while taking bosentan with **glibenclamide**.[2] Bosentan is an inducer of the cytochrome P450 isoenzymes CYP2C9 and CYP3A4,[3] both of which may be responsible for **glibenclamide** metabolism, and this may explain the reduced **glibenclamide** levels seen.

Importance and management

Based on the limited evidence available about the increased risk of liver toxicity, the manufacturer of bosentan recommends that bosentan should not be used with glibenclamide. They suggest that an alternative antidiabetic drug should be used.[3,4] This seems a sensible precaution. However, note that a decrease of 40% in the AUC of glibenclamide may possibly decrease its blood glucose-lowering effects to a clinically relevant extent,[2-4] and although there are no data, bosentan would be expected to reduce the plasma concentrations of other oral antidiabetics that are predominantly metabolised by CYP2C9 or CYP3A, which includes many other **sulfonylureas**. The possibility of worsened glucose control in patients using these drugs should be considered.[3]

1. Fattinger K, Funk C, Pantze M, Weber C, Reichen J, Stieger B, Meier PJ. The endothelin antagonist bosentan inhibits the canalicular bile salt export pump: a potential mechanism for hepatic adverse reactions. *Clin Pharmacol Ther* (2001) 69, 223–31.
2. van Giersbergen PLM, Treiber A, Clozel M, Bodin F, Dingemanse J. In vivo and in vitro studies exploring the pharmacokinetic interaction between bosentan, a dual endothelin receptor antagonist, and glyburide. *Clin Pharmacol Ther* (2002) 71, 253–62.
3. Tracleer (Bosentan). Actelion Pharmaceuticals US, Inc. US Prescribing information, August 2009.
4. Tracleer (Bosentan monohydrate). Actelion Pharmaceuticals UK Ltd. UK Summary of product characteristics, July 2009.

Sulfonylureas + Chloramphenicol

The blood glucose-lowering effects of tolbutamide and chlorpropamide can be increased by chloramphenicol and acute hypoglycaemia can occur.

Clinical evidence

A man taking chloramphenicol 2 g daily started taking **tolbutamide** 2 g daily. Three days later he had a typical hypoglycaemic collapse and was found to have serum **tolbutamide** levels three- to fourfold higher than expected.[1]

Studies in diabetics have found that chloramphenicol 2 g daily can increase the serum level and half-life of **tolbutamide** two- to threefold.[1,2] Blood glucose levels were reduced by about 25 to 30%.[2,3] Hypoglycaemia, acute in one case, developed in two other patients taking **tolbutamide** with chloramphenicol.[4,5] In another study chloramphenicol 1 to 2 g daily caused an average twofold increase in the half-life of **chlorpropamide**.[6]

Mechanism

Chloramphenicol inhibits the liver enzymes concerned with the metabolism of tolbutamide, and probably chlorpropamide as well, leading to their accumulation in the body. This is reflected in prolonged half-lives, reduced blood glucose levels and occasionally acute hypoglycaemia.[1-4,6]

Importance and management

The interaction between tolbutamide and chloramphenicol is well established and of clinical importance. The incidence is uncertain, but increased blood glucose-lowering effects should be expected if both drugs are given. The interaction between chlorpropamide and chloramphenicol is less well documented. Nevertheless, monitor concurrent use carefully and reduce the dose of the sulfonylurea as necessary. Some patients may show a particularly exaggerated response. The manufacturers of other sulfonylureas often list chloramphenicol as an interacting drug, based on its interactions with tolbutamide and chlorpropamide, but direct information of an interaction does not appear to be available. No interaction would be expected with chloramphenicol eye drops, because the systemic absorption is likely to be small.

1. Christensen LK, Skovsted L. Inhibition of drug metabolism by chloramphenicol. *Lancet* (1969) ii, 1397–9.
2. Brunová E, Slabochová Z, Platilová H, Pavlík F, Grafnetterová J, Dvoráček K. Interaction of tolbutamide and chloramphenicol in diabetic patients. *Int J Clin Pharmacol Biopharm* (1977) 15, 7–12.
3. Brunová E, Slabochová Z, Platilová H. Influencing the effect of Dirastan (tolbutamide). Simultaneous administration of chloramphenicol in patients with diabetes and bacterial urinary tract inflammation. *Cas Lek Cesk* (1974) 113, 72–5.
4. Ziegelasch H-J. Extreme hypoglykämie unter kombinierter behandlung mit tolbutamid, n-1-butylbiguanidhydrochlorid und chloramphenikol. *Z Gesamte Inn Med* (1972) 27, 63–6.
5. Soeldner JS, Steinke J. Hypoglycemia in tolbutamide-treated diabetes. *JAMA* (1965) 193, 398–9.
6. Petitpierre B, Perrin L, Rudhardt M, Herrera A, Fabre J. Behaviour of chlorpropamide in renal insufficiency and under the effect of associated drug therapy. *Int J Clin Pharmacol* (1972) 6, 120–4.

Sulfonylureas + Grapefruit juice

Grapefruit juice did not alter the pharmacokinetics of glibenclamide in one study.

Clinical evidence, mechanism, importance and management

In a study in healthy subjects, grapefruit juice 200 mL three times daily for 2 days and then simultaneously with a single 875-microgram dose of **glibenclamide** had no effect on the pharmacokinetics of **glibenclamide**.[1]

No pharmacokinetic interaction would therefore be expected on clinical use, either with glibenclamide, or other sulfonylureas that are similarly metabolised.

1. Lilja JJ, Niemi M, Fredrikson H, Neuvonen PJ. Effects of clarithromycin and grapefruit juice on the pharmacokinetics of glibenclamide. *Br J Clin Pharmacol* (2007) 63, 732–40.

Sulfonylureas + Probenecid

The clearance of chlorpropamide is reduced by probenecid. Tolbutamide appears not to interact with probenecid.

Clinical evidence, mechanism, importance and management

A study in 6 patients given single oral doses of **chlorpropamide** found that probenecid 1 to 2 g daily increased the **chlorpropamide** half-life from about 36 hours to 50 hours.[1] It seems that the probenecid reduces the renal excretion of **chlorpropamide**. Another report in healthy subjects suggested that the half-life of **tolbutamide** was also prolonged by probenecid,[2] but this was not confirmed by a further controlled study.[3]

Information is very limited but it may possibly be necessary to reduce the dose of **chlorpropamide** in the presence of probenecid. It seems unlikely that a clinically important interaction will occur with **tolbutamide**. Information about other sulfonylureas appears to be lacking.

1. Petitpierre B, Perrin L, Rudhardt M, Herrera A, Fabre J. Behaviour of chlorpropamide in renal insufficiency and under the effect of associated drug therapy. *Int J Clin Pharmacol* (1972) 6, 120–4.
2. Stowers JM, Mahler RF, Hunter RB. Pharmacology and mode of action of the sulphonylureas in man. *Lancet* (1958) i, 278–83.
3. Brook R, Schrogie JJ, Solomon HM. Failure of probenecid to inhibit the rate of metabolism of tolbutamide in man. *Clin Pharmacol Ther* (1968) 9, 314–17.

Sulfonylureas; Chlorpropamide + Nevirapine

In a single-dose study, nevirapine did not alter the levels or blood glucose-lowering effects of chlorpropamide.

Clinical evidence, mechanism, importance and management

In a single-dose study in 6 fasting subjects, simultaneous administration of **nevirapine** 200 mg with **chlorpropamide** 250 mg had no effect on the AUC of chlorpropamide, when compared with chlorpropamide alone, and no effect on plasma glucose levels.[1]

This study provides some evidence that nevirapine might not alter the levels or effect of chlorpropamide, but it needs confirming in a study with longer-term nevirapine use, as the enzyme-inducing effects of nevirapine would not be maximal with a simultaneous single dose.

1. Bakare-Odunola MT, Enemali I, Garba M, Obodozie OO, Mustapha KB. The influence of lamivudine, stavudine and nevirapine on the pharmacokinetics of chlorpropamide in human subjects. Eur J Drug Metab Pharmacokinet (2008) 33, 165–71.

Sulfonylureas; Chlorpropamide + NRTIs

In a single-dose study, lamivudine and stavudine reduced the levels of chlorpropamide and thereby reduced its effects on blood glucose levels.

Clinical evidence, mechanism, importance and management

In a single-dose study in 6 fasting subjects, the simultaneous administration of **lamivudine** 150 mg with **chlorpropamide** 250 mg reduced the AUC of chlorpropamide by 42% when compared with chlorpropamide alone. A similar 41% reduction in the AUC of chlorpropamide was seen when **stavudine** 40 mg was given simultaneously. With both NRTIs, the plasma glucose levels were higher than with chlorpropamide alone.[1]

The finding of this study is surprising as NRTIs are not known to decrease the absorption or induce the metabolism of any other drugs. Further study is needed to confirm these findings, especially with multiple doses. Until such time, bear the possibility of an interaction in mind if chlorpropamide efficacy is poor in patients taking these NRTIs.

1. Bakare-Odunola MT, Enemali I, Garba M, Obodozie OO, Mustapha KB. The influence of lamivudine, stavudine and nevirapine on the pharmacokinetics of chlorpropamide in human subjects. Eur J Drug Metab Pharmacokinet (2008) 33, 165–71.

Sulfonylureas; Chlorpropamide + Urinary acidifiers or alkalinisers

On theoretical grounds the response to chlorpropamide may be decreased if the urine is made alkaline, and increased if urine is acidified.

Clinical evidence, mechanism, importance and management

A study in 6 healthy subjects given a 250-mg oral dose of chlorpropamide found that when the urine was made alkaline (pH 7.1 to 8.2) with **sodium bicarbonate**, the half-life of the chlorpropamide was reduced from 50 hours to 13 hours, and the 72-hour clearance was increased fourfold. In contrast, when the urine was acidified (pH 5.5 to 4.7) with **ammonium chloride**, the chlorpropamide half-life was increased from 50 hours to 69 hours and the 72-hour urinary clearance was decreased to 5%, and non-renal (i.e. metabolic) clearance predominated.[1] Another study found that the renal clearance of chlorpropamide was almost 100 times greater at pH 7 than at pH 5.[2] The reason for this effect is that changes in urinary pH affect the ionisation of chlorpropamide, and this affects the ability of the kidney to reabsorb it from the kidney filtrate (see more details under 'Drug excretion interactions', (p.7)). Thus, urinary pH determines the relative contribution of renal and metabolic clearance.

There appear to be no reports of adverse interactions between chlorpropamide and drugs that can alter urinary pH, but prescribers should be

aware of the possibilities: a reduced response if the pH is raised significantly and renal clearance predominates (e.g. with **sodium bicarbonate**, **acetazolamide**, some **antacids**); an increased response if the pH is made more acid than usual and metabolic clearance predominates (e.g. with **ammonium chloride**). Perhaps more importantly, the effects of drugs that alter the hepatic clearance of chlorpropamide are likely to be more significant when its renal clearance is low (i.e. when the urine is acid).[2]

1. Neuvonen PJ, Kärkkäinen S. Effects of charcoal, sodium bicarbonate, and ammonium chloride on chlorpropamide kinetics. *Clin Pharmacol Ther* (1983) 33, 386–93.
2. Neuvonen PJ, Kärkkäinen S, Lehtovaara R. Pharmacokinetics of chlorpropamide in epileptic patients: effects of enzyme induction and urine pH on chlorpropamide elimination. *Eur J Clin Pharmacol* (1987) 32, 297–301.

Sulfonylureas; Glibenclamide (Glyburide) + Pantoprazole

The concurrent use of glibenclamide (glyburide) and pantoprazole does not affect the pharmacokinetics of either drug, and pantoprazole does not alter the glucose-lowering effect of glibenclamide.

Clinical evidence, mechanism, importance and management

Pantoprazole 40 mg daily or placebo, were given to 20 healthy subjects for 5 days. On day 5 the subjects were also given 3.5 mg of a micronised preparation of glibenclamide. The pharmacokinetics of the glibenclamide and the pharmacodynamic profiles of glucose and insulin serum concentrations were not significantly altered, and the pharmacokinetics of pantoprazole were not affected. It was concluded that dose changes of the micronised preparation of glibenclamide are not needed during treatment with pantoprazole.[1]

1. Walter-Sack IE, Bliesath H, Stötzer F, Huber R, Steinijans VW, Ding R, Mascher H, Wurst W. Lack of pharmacokinetic and pharmacodynamic interaction between pantoprazole and glibenclamide in humans. *Clin Drug Invest* (1998) 15, 253–60.

Sulfonylureas; Glibenclamide (Glyburide) + Vinpocetine

Vinpocetine does not alter the pharmacokinetics or efficacy of glibenclamide.

Clinical evidence, mechanism, importance and management

A study in 18 elderly patients, with type 2 diabetes and symptoms of dementia, who were taking glibenclamide (glyburide), found that 4 days of treatment with vinpocetine 10 mg three times daily did not affect either the pharmacokinetics of the glibenclamide or the control of blood glucose levels.[1] There would seem to be no reason for avoiding concurrent use.

1. Grandt R, Braun W, Schulz H-U, Lührmann B, Frercks H-J. Glibenclamide steady-state plasma levels during concomitant vinpocetine administration in type II diabetic patients. *Arzneimittelforschung* (1989) 39, 1451–4.

Sulfonylureas; Glipizide + Heparin

An isolated report describes hypoglycaemia in a diabetic patient taking glipizide. The effects were attributed to the concurrent use of heparin.

Clinical evidence, mechanism, importance and management

A diabetic, taking glipizide 5 mg daily for 6 months, with fair control of the diabetes was hospitalised for the treatment of a foot ulcer. Over a period of 4 days he experienced recurring episodes of hypoglycaemia after taking a routine 5-mg dose of glipizide. It was suggested that this might possibly have been due to an interaction with subcutaneous heparin calcium 5000 units every 12 hours which, it is suggested, might have displaced the glipizide from its protein binding sites.[1] No other information seems to be available. The general importance of this report is unknown, but seems likely to be small.

1. McKillop G, Fallon M, Slater SD. Possible interaction between heparin and a sulphonylurea a cause of prolonged hypoglycaemia? *BMJ* (1986) 293, 1073.

Sulfonylureas; Tolbutamide + Aprepitant

Aprepitant slightly reduces tolbutamide levels.

Clinical evidence, mechanism, importance and management

In a study in 12 healthy subjects, aprepitant (125 mg on day one, then 80 mg daily on days 2 and 3) decreased the AUC of a single 500-mg dose of tolbutamide by 23%, 28% and 15%, when given on days 4, 8, and 15, respectively, when compared with 12 subjects not given aprepitant.[1] Even less effect was seen in another study where a single 40-mg oral dose of aprepitant given on day one decreased the AUC of tolbutamide by 8% on day 2, by 16% on day 4, by 15% on day 8, and by 10% on day 15.[2]

Aprepitant is a mild inducer of the cytochrome P450 isoenzyme CYP2C9 by which tolbutamide is metabolised. It therefore slightly increases tolbutamide metabolism, which leads to a reduction in tolbutamide levels. The clinical relevance of these small changes has not been assessed, but is unlikely to be important. Nevertheless, the manufacturer recommends caution when tolbutamide is used with aprepitant (at the higher doses for chemotherapy induced nausea and vomiting).[2,3] No clinically relevant interaction is expected with the low single-dose of aprepitant used for post-operative nausea and vomiting.[2] Note that **fosaprepitant** is a prodrug of aprepitant, and it may therefore be expected to interact similarly.

1. Shadle CR, Lee Y, Majumdar AK, Petty KJ, Gargano C, Bradstreet TE, Evans JK, Blum RA. Evaluation of potential inductive effects of aprepitant on cytochrome P450 3A4 and 2C9 activity. *J Clin Pharmacol* (2004) 44, 215–23.
2. Emend (Aprepitant). Merck & Co., Inc. US Prescribing information, July 2009.
3. Emend (Aprepitant). Merck Sharp & Dohme Ltd. UK Summary of product characteristics, July 2009.

Sulfonylureas; Tolbutamide + Echinacea

Echinacea does not have a clinically relevant effect on the pharmacokinetics of tolbutamide.

Clinical evidence

In a pharmacokinetic study, 12 healthy subjects were given *Echinacea purpurea* root 400 mg four times daily for 8 days with a single 500-mg dose of tolbutamide on day 6. The AUC of tolbutamide was increased by 14%, and the time to maximum levels was increased from 4 to 6 hours.[1] The oral clearance was decreased by a mean of 11%, although 2 subjects had a 25% or greater reduction.

Mechanism, importance and management

This one study suggests that echinacea does not significantly affect the pharmacokinetics of tolbutamide, and therefore no tolbutamide dose adjustments appear necessary if echinacea is also taken.

1. Gorski JC, Huang S-M, Pinto A, Hamman MA, Hilligoss JK, Zaheer NA, Desai M, Miller M, Hall SD. The effect of echinacea (*Echinacea purpurea* root) on cytochrome P450 activity in vivo. *Clin Pharmacol Ther* (2004) 75, 89–100.

Sulfonylureas; Tolbutamide + Methysergide

A preliminary study indicated that methysergide may enhance the effects of tolbutamide.

Clinical evidence, mechanism, importance and management

In 8 patients with type 2 diabetes, pretreatment with methysergide 2 mg every 6 hours for 2 days increased the amount of insulin secreted in response to a 1-g intravenous dose of **tolbutamide** by almost 40%.[1] Whether in practice the addition or withdrawal of methysergide adversely affects

the control of diabetes is uncertain, but the possibility should be borne in mind.

1. Baldridge JA, Quickel KE, Feldman JM and Lebovitz HE. Potentiation of tolbutamide-mediated insulin release in adult onset diabetics by methysergide maleate. *Diabetes* (1974) 23, 21–4.

Sulfonylureas; Tolbutamide + Tolcapone

Tolcapone did not alter tolbutamide pharmacokinetics in a single-dose study.

Clinical evidence, mechanism, importance and management

In a single-dose study in 12 healthy subjects, tolcapone 200 mg had no effect on the pharmacokinetics of tolbutamide 500 mg, and did not alter the glucose-lowering effect of tolbutamide.[1] This study was conducted because *in vitro* evidence had shown that tolcapone inhibits the cytochrome P450 isoenzyme CYP2C9, by which tolbutamide is metabolised. However, the findings in healthy subjects suggest that no clinically relevant changes in pharmacokinetics of tolbutamide are likely.

1. Jorga KM, Fotteler B, Gasser R, Banken L, Birnboeck H. Lack of interaction between tolcapone and tolbutamide in healthy volunteers. *J Clin Pharmacol* (2000) 40, 544–51.

Thiazolidinediones + Insulin

Pioglitazone and rosiglitazone may cause fluid retention and peripheral oedema, which can worsen or cause heart failure. There is evidence that the incidence of these effects is higher with the concurrent use of insulin. In addition, there may be an increased risk of myocardial ischaemia when rosiglitazone is used with insulin. The incidence of hypoglycaemia may also be increased, and the required dose of insulin reduced.

Clinical evidence

(a) Pioglitazone

In one 16-week, randomised, placebo-controlled study,[1] pioglitazone 15 or 30 mg with insulin was compared with insulin alone in 566 patients with long-standing diabetes. Oedema was reported in 15.3% of the patients receiving pioglitazone with insulin (12.6% and 17.6% with pioglitazone 15 mg and 30 mg, respectively) compared with 7% when insulin was given alone. Four of the 379 patients given pioglitazone and insulin developed congestive heart failure compared with none of the 187 patients given insulin alone; all 4 had a history of cardiovascular disease. Analysis of this study did not identify specific factors that predict this possible increased risk of congestive heart failure in patients taking insulin.[2] In an analysis of 8 randomised controlled studies of giving pioglitazone to patients already receiving insulin, concurrent use was associated with a tendency for more hypoglycaemic episodes (relative risk 1.27), a greater increase in weight (about 3 kg), a reduction in required insulin dose (about 12 units/day), and a more frequent incidence of peripheral oedema.[3]

One case report describes a 57-year-old obese man with type 2 diabetes, no history of heart failure and excellent exercise tolerance, who was given insulin and pioglitazone 30 mg daily. Over the first 4 weeks after starting pioglitazone he developed significant weight gain and subsequently developed heart failure and pulmonary oedema.[4]

(b) Rosiglitazone

A randomised, double-blind, placebo-controlled study in patients with poorly-controlled type 2 diabetes receiving insulin twice daily found that the addition of rosiglitazone 2 or 4 mg twice daily for 26 weeks improved the control of their blood glucose levels and they needed less insulin.[5] Mean total daily insulin reductions were 12% for the 4 mg dose, 5.6% for the 2 mg dose, and 0.6% for placebo. Symptoms consistent with hypoglycaemia also occurred more frequently with the combination; 67% with the 4 mg rosiglitazone dose, 53% with the 2 mg dose, and 38% with placebo. The incidence of oedema was about threefold higher in those patients given insulin and rosiglitazone; 16.2% with the 4 mg dose, and 13.1% with the 2 mg dose, compared with 4.7% in those given placebo. Congestive heart failure occurred in 4 of 209 patients receiving the combination compared with one of 104 receiving placebo. However, 2 of the patients receiving rosiglitazone had a history of coronary heart disease.[5] Other cases of peripheral oedema and congestive heart failure have been reported.[6-8]

From results of 5 placebo-controlled clinical studies, the manufacturer has reported an incidence of heart failure of 1.1% with insulin monotherapy and 2.4% when combined with rosiglitazone (about a twofold increase).[9,10]

In addition, subsequent analyses of clinical study data have suggested an increased risk of myocardial ischaemia when rosiglitazone is used with insulin, leading to a possible increased risk of myocardial infarction. The US manufacturer reports an incidence of myocardial ischaemic events of 2.8% for rosiglitazone with insulin compared with 1.4% for placebo with insulin, which is about a twofold increase (odds ratio of 2.1).[10]

Mechanism

Pioglitazone or rosiglitazone alone can exacerbate or precipitate heart failure because they can cause fluid retention and weight gain.[2,9-11] The incidence appears to be greatly increased in patients who are also receiving insulin. An estimated 2 to 5% of patients receiving thiazolidinedione monotherapy and 5 to 15% receiving concurrent insulin experience peripheral oedema.[12] Fluid retention and tissue oedema appear to be part of a vascular 'leak' syndrome but, additionally, thiazolidinediones may potentiate the renal effects of insulin on sodium and water retention. It is conceivable that increased fluid retention caused by thiazolidinediones may alter the already precarious volume status in patients with underlying cardiac or renal impairment thus leading to congestive heart failure.[12] However, congestive heart failure has been estimated to occur in as many as 12% of patients who have type 2 diabetes[12] and whether the incidence of heart failure in patients given thiazolidinediones and insulin is simply a reflection of other factors that increase the risk in these patients, or due to some specific interaction with insulin, remains to be established.

Importance and management

The fact that rosiglitazone and pioglitazone can cause weight gain and peripheral oedema, and that the incidence of this is greater in patients who are also using insulin is well established. However, the relevance of this appears to be controversial. In addition, the relationship of rosiglitazone to myocardial ischaemia is also uncertain. Nevertheless, as a result of a review, in October 2007 the European Medicines Agency concluded that the combination of rosiglitazone and insulin should only be used in exceptional cases and under close supervision, and this recommendation was not considered necessary for pioglitazone.[13] Similarly, in the US, pioglitazone[2] is licensed for use with insulin, and the use of rosiglitazone with insulin is not recommended.[10] If oedema occurs in a patient taking a thiazolidinedione it has been recommended that the possible causes be assessed, and that if symptoms and signs suggest congestive heart failure, a dose change and temporary or permanent discontinuance of the thiazolidinedione should be considered.[14]

Concurrent use of insulin and a thiazolidinedione increases the incidence of hypoglycaemia. It has been noted that in patients receiving insulin, the insulin dose may need to be reduced by 10 to 25% if pioglitazone 15 or 30 mg daily is given.[2]

1. Rosenstock J, Einhorn D, Hershon K, Glazer NB, Yu S; Pioglitazone 014 Study Group. Efficacy and safety of pioglitazone in type 2 diabetes: a randomised, placebo-controlled study in patients receiving stable insulin therapy. *Int J Clin Pract* (2002) 56, 251–7.
2. Actos (Pioglitazone hydrochloride). Takeda Pharmaceutical Company Ltd. US Prescribing information, August 2008.
3. Clar C, Royle P, Waugh N. Adding pioglitazone to insulin containing regimens in type 2 diabetes: systematic review and meta-analysis. PLoS One (2009) 4, e6112.
4. Cheng AYY, Fantus IG. Thiazolidinedione-induced congestive heart failure. *Ann Pharmacother* (2004) 38, 817–20.
5. Raskin P, Rendell M, Riddle MC, Dole JF, Freed MI, Rosenstock J; Rosiglitazone Clinical Trials Study Group. A randomized trial of rosiglitazone therapy in patients with inadequately controlled insulin-treated type 2 diabetes. *Diabetes Care* (2001) 24, 1226–32.
6. Buch HN, Baskar V, Barton DM, Kamalakannan D, Akarca C, Singh BM. Combination of insulin and thiazolidinedione therapy in massively obese patients with type 2 diabetes. *Diabet Med* (2002) 19, 572–4.
7. Singh N. Rosiglitazone and heart failure: long-term vigilance. *J Cardiovasc Pharmacol Ther* (2004) 9, 21–5.
8. Bell DSH. Unilateral edema due to a thiazolidinedione. *Diabetes Care* (2003) 26, 2700.
9. Avandia (Rosiglitazone maleate). GlaxoSmithKline UK. UK Summary of product characteristics, May 2009.
10. Avandia (Rosiglitazone maleate). GlaxoSmithKline. US Prescribing information, February 2009.
11. Actos (Pioglitazone hydrochloride). Takeda UK Ltd. UK Summary of product characteristics, February 2009.
12. Scheen AJ. Combined thiazolidinedione-insulin therapy. Should we be concerned about safety? *Drug Safety* (2004) 27, 841–56.

13. European Medicines Agency. Press release. European Medicines Agency confirms positive benefit-risk balance for rosiglitazone and pioglitazone. London, 18 October 2007. Available at: http://www.emea.europa.eu/pdfs/human/press/pr/48427707en.pdf (accessed 29/01/10).
14. Nesto RW, Bell D, Bonow RO, Fonseca V, Grundy SM, Horton ES, Le Winter M, Porte D, Semenkovich CF, Smith S, Young LH, Kahn R. Thiazolidinedione use, fluid retention, and congestive heart failure: a consensus statement from the American Heart Association and American Diabetes Association. *Circulation* (2003) 108, 2941–8.

Thiazolidinediones + Leukotriene antagonists

Montelukast and zafirlukast do not alter the pharmacokinetics of pioglitazone, and montelukast does not alter the pharmacokinetics of rosiglitazone.

Clinical evidence

In a controlled study in healthy subjects, both **montelukast** 10 mg daily for 6 days and **zafirlukast** 20 mg twice daily for 6 days did not affect either the AUC of a single 15-mg dose of **pioglitazone** given on day 3, or the metabolites of pioglitazone.[1] Similarly, montelukast 10 mg daily for 6 days had no effect on the AUC of a single 4-mg dose of **rosiglitazone** 4 mg given on day 5. In addition, there was no change in the AUC ratio of the *N*-desmethyl metabolite to **rosiglitazone**.[2]

Mechanism

In vitro, the leukotriene antagonists inhibited the metabolism of pioglitazone and rosiglitazone by the cytochrome P450 isoenzyme CYP2C8.[3,4] However, the clinical studies provide conclusive evidence that this interaction does not occur *in vivo*, and this emphasises the fact that positive *in vitro* findings will not always directly translate to the clinical situation.

Importance and management

No pharmacokinetic interaction is expected if montelukast or zafirlukast are used with pioglitazone or rosiglitazone, and therefore dose adjustments of these antidiabetics are not expected to be necessary on concurrent use.

1. Jaakkola T, Backman JT, Neuvonen M, Niemi M, Neuvonen PJ. Montelukast and zafirlukast do not affect the pharmacokinetics of the CYP2C8 substrate pioglitazone. *Eur J Clin Pharmacol* (2006) 62, 503–9.
2. Kim K-A, Park P-W, Kim KR, Park J-Y. Effect of multiple doses of montelukast on the pharmacokinetics of rosiglitazone, a CYP2C8 substrate, in humans. *Br J Clin Pharmacol* (2007) 63, 339–45.
3. Walsky RL, Obach RS, Gaman EA, Gleeson J-PR, Proctor WR. Selective inhibition of human cytochrome P4502C8 by montelukast. *Drug Metab Dispos* (2005) 33, 413–18.
4. Jaakkola T, Laitila J, Neuvonen PJ, Backman JT. Pioglitazone is metabolised by CYP2C8 and CYP3A4 *in vitro*: potential for interactions with CYP2C8 inhibitors. *Basic Clin Pharmacol Toxicol* (2006) 99, 44–51.

Thiazolidinediones + Metformin

The pharmacokinetics of metformin are not altered by pioglitazone or rosiglitazone, and metformin does not alter the pharmacokinetics of rosiglitazone.

Clinical evidence, mechanism, importance and management

In healthy subjects, **pioglitazone** 45 mg daily for 7 days did not alter the pharmacokinetics of a single 1-g dose of metformin.[1,2]

The steady-state pharmacokinetics of metformin 500 mg twice daily and **rosiglitazone** 2 mg twice daily were not affected when they were given to healthy subjects for 4 days.[3]

The combination of a thiazolidinedione and metformin is used in the management of diabetes for additive blood glucose lowering effects, and the studies show that there are no pharmacokinetic interactions that will complicate their use. Because neither metformin nor thiazolidinediones increase the secretion of insulin, the risk of hypoglycaemia is not raised by the combination.

1. Actos (Pioglitazone hydrochloride). Takeda Pharmaceutical Company Ltd. US Prescribing information, August 2008.
2. Kortboyer JM, Eckland DJA. Pioglitazone has low potential for drug interactions. *Diabetologia* (1999) 42 (Suppl 1), A228.
3. Di Cicco RA, Allen A, Carr A, Fowles S, Jorkasky DK, Freed MI. Rosiglitazone does not alter the pharmacokinetics of metformin. *J Clin Pharmacol* (2000) 40, 1280–5.

Thiazolidinediones + Nitrates

There may be an increased risk of myocardial ischaemia when rosiglitazone is used with nitrates.

Clinical evidence, mechanism, importance and management

Meta-analysis of clinical studies[1,2] suggest that treatment with **rosiglitazone** is associated with an increased risk for myocardial ischaemic events, such as angina or myocardial infarction, especially in patients taking nitrates or insulin (consider also 'Thiazolidinediones + Insulin', p.589). In patients taking nitrates, the odds ratio of myocardial ischaemic events was 2.9 for **rosiglitazone** recipients, when compared with controls, while for patients not taking nitrates, the odds ratio was 1.3 for **rosiglitazone** recipients, when compared with controls. This increased risk represents a difference of 12 myocardial ischaemic events per 100 patient-years. Most of the nitrate users had established coronary heart disease. Among patients with known coronary heart disease who were not taking a nitrate, an increased risk of myocardial ischaemic events for **rosiglitazone** versus controls was not demonstrated.[1]

Definitive conclusions regarding this risk await completion of an adequately-designed cardiovascular outcome study. Until such time, in the US, the use of **rosiglitazone** with nitrates is not recommended.[1] This advice is not specifically stated by the UK manufacturer, who state that, as a precaution, rosiglitazone should not be used in patients with myocardial ischaemia, particularly if this is symptomatic (which is the main indication for nitrates).[2] Pioglitazone has not been associated with similar risks of myocardial ischaemia, see 'Thiazolidinediones + Insulin', p.589.

1. Avandia (Rosiglitazone maleate). GlaxoSmithKline. US Prescribing information, February 2009.
2. Avandia (Rosiglitazone maleate). GlaxoSmithKline UK. UK Summary of product characteristics, May 2009.

Thiazolidinediones + Sulfonylureas

Pioglitazone does not alter glipizide pharmacokinetics. Rosiglitazone does not have an important effect on glibenclamide (glyburide) pharmacokinetics, and does not alter glimepiride pharmacokinetics. The use of thiazolidinediones with sulfonylureas increases the risk of hypoglycaemia, and sulfonylurea dose reductions might be required. The concurrent use of rosiglitazone and sulfonylureas may be associated with a greater risk of fluid retention, particularly with higher rosiglitazone doses.

Clinical evidence

(a) Pioglitazone

In healthy subjects, pioglitazone 45 mg daily for 7 days did not alter the steady-state pharmacokinetics of **glipizide** 5 mg daily.[1,2] The manufacturer notes that hypoglycaemia is more common when pioglitazone is given with a sulfonylurea.[1,3]

(b) Rosiglitazone

Rosiglitazone 2 mg twice daily for 7 days did not alter the mean steady-state 24-hour plasma glucose levels in diabetic patients taking **glibenclamide** (**glyburide**) 3.75 to 10 mg daily. However, rosiglitazone 8 mg daily for 8 days caused a decrease of about 30% in the AUC of **glibenclamide** in healthy Caucasian subjects, and a slight increase in the AUC of **glibenclamide** in Japanese subjects.[4] These changes are not considered clinically relevant.[4,5] No pharmacokinetic interaction appears to occur between **glimepiride** and rosiglitazone.[4]

The manufacturer notes that hypoglycaemia is more common when rosiglitazone is given with a sulfonylurea.[4,5] Furthermore, the combined use of rosiglitazone and a sulfonylurea leads to an increase in weight, which is greater than with rosiglitazone alone or concurrent use with metformin.[4] In addition, in clinical studies, the incidence of oedema was greater with rosiglitazone and sulfonylureas than with rosiglitazone and metformin,[4,5] and an increased incidence of heart failure has been seen when rosiglitazone was given with a sulfonylurea (either as dual or triple therapy), and appeared higher with rosiglitazone 8 mg daily compared with 4 mg daily.[5]

Mechanism

Thiazolidinediones increase insulin sensitivity, and therefore cause an increased incidence of hypoglycaemia when used with sulfonylureas.

Importance and management

No dose changes as a result of pharmacokinetic interactions appear to be needed if these sulfonylureas are used with the thiazolidinediones. However, if hypoglycaemia occurs, consider reducing the sulfonylurea dose.[1,3-5] The UK manufacturer advises that when rosiglitazone is used with a sulfonylurea, the dose of rosiglitazone should be increased to 8 mg daily only with caution, assessing the risk of fluid retention.[5] Note that, in the UK, the concurrent use of a pioglitazone or rosiglitazone with a sulfonylurea is a second-line option only where metformin cannot be given with the sulfonylurea.[3,5]

1. Actos (Pioglitazone hydrochloride). Takeda Pharmaceutical Company Ltd. US Prescribing information, August 2008.
2. Kortboyer JM, Eckland DJA. Pioglitazone has low potential for drug interactions. *Diabetologia* (1999) 42 (Suppl 1), A228.
3. Actos (Pioglitazone hydrochloride). Takeda UK Ltd. UK Summary of product characteristics, February 2009.
4. Avandia (Rosiglitazone maleate). GlaxoSmithKline. US Prescribing information, February 2009.
5. Avandia (Rosiglitazone maleate). GlaxoSmithKline UK. UK Summary of product characteristics, May 2009.

Thiazolidinediones; Pioglitazone + Aliskiren

There was no pharmacokinetic interaction between pioglitazone and aliskiren in one study.

Clinical evidence, mechanism, importance and management

In a study in 29 healthy subjects, the concurrent use of aliskiren 300 mg daily with pioglitazone 45 mg daily for 7 days had no effect on the AUC of aliskiren and very slightly reduced the AUC of pioglitazone by 6%, when compared with either drug given alone. There was no change in AUC of pioglitazone metabolites.[1] No dose adjustment of either drug would therefore be expected to be needed if aliskiren is given with pioglitazone.

1. Vaidyanathan S, Maboudian M, Warren V, Yeh C-M, Dieterich HA, Howard D, Dole WP. A study of the pharmacokinetic interactions of the direct renin inhibitor aliskiren with metformin, pioglitazone and fenofibrate in healthy subjects. Curr Med Res Opin (2008) 24, 2313–26.

Thiazolidinediones; Pioglitazone + Fexofenadine

A study in healthy subjects indicated that the pharmacokinetics of pioglitazone 45 mg daily are not significantly affected by fexofenadine 60 mg twice daily, and that pioglitazone does not affect the pharmacokinetics of fexofenadine.[1]

1. Robert M. Pharmacokinetics of coadministration of pioglitazone with fexofenadine. *Diabetes* (2001) 50 (Suppl 2), A443.

Thiazolidinediones; Rosiglitazone + NNRTIs

Rosiglitazone appears to have no effect on the pharmacokinetics of efavirenz, but limited evidence suggests it may decrease nevirapine levels.

Clinical evidence, mechanism, importance and management

In a study which included 10 patients taking **efavirenz** 600 mg daily and four taking **nevirapine** 200 mg twice daily (both given with NRTIs), **rosiglitazone** 4 mg daily for 28 days had no effect on the AUC, minimum levels or maximum levels of **efavirenz**. However, the AUC, minimum level and maximum level of **nevirapine** appeared to decrease, with the 44% decrease in maximum level reaching statistical significance.[1] A mechanism for this effect is not clear, as **rosiglitazone** is not known to be an enzyme inducer.

Because of the small number of patients taking **nevirapine**, the findings of this study require confirmation. Until more is known, it may be prudent to increase monitoring of antiretroviral efficacy and/or drug levels when **rosiglitazone** is used with **nevirapine**. **Rosiglitazone** appears not to alter the pharmacokinetics of **efavirenz**.

1. Oette M, Kurowski M, Feldt T, Kroidl A, Sagir A, Vogt C, Wettstein M, Häussinger D. Impact of rosiglitazone treatment on the bioavailability of antiretroviral compounds in HIV-positive patients. *J Antimicrob Chemother* (2005) 56, 416–19.

Thiazolidinediones; Rosiglitazone + Protease inhibitors

Atazanavir alone modestly increased the AUC of rosiglitazone, but ritonavir-boosted atazanavir slightly decreased it. Rosiglitazone appears to have no effect on the pharmacokinetics of lopinavir taken as lopinavir. Protease inhibitors themselves may rarely cause hyperglycaemia and have been associated with an exacerbation of diabetes.

Clinical evidence

(a) Atazanavir

The US manufacturer notes that atazanavir 400 mg daily for 6 days modestly increased the AUC of a single 4-mg dose of **rosiglitazone** given on day 7 by 35%. Conversely, ritonavir-boosted atazanavir 100/300 mg daily caused a minor 17% decrease in rosiglitazone AUC.[1]

(b) Lopinavir

In a study that included 4 patients taking ritonavir-boosted lopinavir 100/400 mg twice daily with NRTIs, **rosiglitazone** 4 mg daily for 28 days had no effect on the AUC, minimum levels and maximum levels of lopinavir.[2]

Mechanism

Atazanavir alone is a weak inhibitor of the cytochrome P450 isoenzyme CYP2C8, by which rosiglitazone and pioglitazone are principally metabolised. The finding that rosiglitazone appears not to affect lopinavir pharmacokinetics is not unexpected as rosiglitazone does not affect CYP3A4.

Importance and management

The modest changes in rosiglitazone pharmacokinetics seen with atazanavir alone and ritonavir-boosted atazanavir are probably unlikely to be clinically relevant. The manufacturer cautions the use of atazanavir monotherapy in patients taking drugs that are CYP2C8 substrates with a narrow therapeutic window, and they specifically name the antidiabetic **repaglinide**.[1] Note that repaglinide is also partially metabolised by CYP3A4, therefore all protease inhibitors might be expected to increase its levels. Until further information is available with this antidiabetic, some caution may be appropriate.

Rosiglitazone appears not to affect lopinavir pharmacokinetics. The effect of ritonavir-boosted lopinavir on rosiglitazone pharmacokinetics does not appear to have been studied, but it might be expected to interact like ritonavir-boosted atazanavir causing a minor decrease in the AUC of rosiglitazone AUC. Therefore, it appears that a clinically relevant pharmacokinetic interaction is unlikely.

Bear in mind that new onset diabetes mellitus, hyperglycaemia or exacerbation of existing diabetes mellitus has been reported in patients receiving protease inhibitors.

1. Reyataz (Atazanavir sulfate). Bristol-Myers Squibb. US Prescribing information, November 2009.
2. Oette M, Kurowski M, Feldt T, Kroidl A, Sagir A, Vogt C, Wettstein M, Häussinger D. Impact of rosiglitazone treatment on the bioavailability of antiretroviral compounds in HIV-positive patients. *J Antimicrob Chemother* (2005) 56, 416–19.

14

Antiepileptics

The antiepileptic drugs find their major application in the treatment of various kinds of epilepsy, although some of them are also used for other conditions, such as pain management.

Drug interactions

The drugs used as antiepileptics are a disparate group, and their interactions need to be considered individually. Carbamazepine and phenytoin have established ranges of therapeutic plasma levels and these are typically fairly narrow. Modest changes in their plasma levels may therefore be clinically important.

(a) Carbamazepine or Oxcarbazepine

Carbamazepine is extensively metabolised by the cytochrome P450 isoenzyme CYP3A4 to the active metabolite, carbamazepine-10,11-epoxide, which is then further metabolised. The concurrent use of carbamazepine and CYP3A4 inhibitors or inducers may therefore lead to toxicity or reduced efficacy. However, importantly, carbamazepine induces CYP3A4 and also induces its own metabolism (autoinduction). Because of this, it is important that drug interaction studies are multiple dose and carried out at steady state. Autoinduction also means that moderate inducers of CYP3A4 may have less of an effect on steady-state carbamazepine levels than expected.

Oxcarbazepine is a derivative of carbamazepine, but it has less effect on CYP3A4. Both carbamazepine and oxcarbazepine can act as inhibitors of CYP2C19, see 'Phenytoin + Carbamazepine', p.632.

(b) Phenobarbital

Phenobarbital is an inducer of a wide range of cytochrome P450 isoenzymes, and may increase the metabolism of a variety of drugs. It may, itself, also be affected by some enzyme inducers or inhibitors, although these interactions are less established.

(c) Phenytoin

Phenytoin is extensively metabolised by hydroxylation, principally by CYP2C9, although CYP2C19 also plays a role. These isoenzymes show 'genetic polymorphism', (p.4), and CYP2C19 may assume a greater role in individuals who have are CYP2C9 poor metabolisers (that is, patients lacking this isoenzyme). The concurrent use of inhibitors of CYP2C9, and sometimes also CYP2C19, can lead to phenytoin toxicity. In addition, phenytoin metabolism is saturable (it shows non-linear pharmacokinetics), and therefore small changes in either the metabolism or the dose of phenytoin can result in marked changes in its plasma levels. Moreover, phenytoin is highly protein bound, and drugs that alter its protein binding may alter its levels. Although protein binding interactions are usually not clinically relevant (unless metabolism is also inhibited, see 'Phenytoin + Valproate', p.646), they can be important in interpreting drug levels.

(d) Valproate

Valproate is a generic name that is applied in this section to cover valproic acid and its salts and esters. Valproate undergoes glucuronidation and β-oxidation, and possibly also some metabolism by CYP2C isoenzymes. It can therefore undergo drug interactions by a variety of mechanisms. It acts as an inhibitor of glucuronidation and so may affect other drugs that undergo glucuronidation. Valproate also has non-linear pharmacokinetics due to saturation of plasma protein binding, and so may interact with drugs that alter its protein binding. However, note that, although protein binding interactions are usually not clinically relevant unless metabolism is also inhibited, they can be important in interpreting drug levels.

(e) Other antiepileptics

Of the newer antiepileptics, both felbamate and topiramate are weak inducers of CYP3A4. They may also inhibit CYP2C19. They are also partially metabolised by the cytochrome P450 isoenzyme system, so may have their metabolism altered by other drugs such as the enzyme-inducing antiepileptics.

Gabapentin, lamotrigine, levetiracetam, tiagabine, vigabatrin, and zonisamide do not appear to act as inhibitors or inducers of cytochrome P450 isoenzymes, and so appear to cause less drug interactions than the older antiepileptics. Moreover, gabapentin, levetiracetam, and vigabatrin do not appear to be metabolised by the cytochrome P450 system, so appear to be little affected by drug interactions that result from this mechanism. Tiagabine and zonisamide are metabolised by the cytochrome P450 system, so may have their metabolism altered by other drugs such as the enzyme-inducing antiepileptics. Lamotrigine is metabolised by glucuronidation, and may be affected by inhibitors (e.g. valproate) or inducers (e.g. carbamazepine, phenytoin) of this process. Lamotrigine may also act as an inducer of glucuronidation, and may therefore affect the pharmacokinetics of valproate.

Rufinamide undergoes hydrolysis by carboxylesterases. It is not significantly metabolised by cytochrome P450 isoenzymes, but its plasma concentrations are slightly reduced by other antiepileptics such as phenytoin, phenobarbital and primidone. It does act as a modest inducer of CYP3A4, although clinically significant interactions by this mechanism are uncommon.

Stiripentol is metabolised by a number of isoenzymes but interactions as a result of this effect have yet to be established. Stiripentol inhibits CYP3A4, and may inhibit CYP1A2 and CYP2C19, but the clinical relevance of its effects on these latter two isoenzymes have not been established.

Antiepileptics; Enzyme-inducing + Acetazolamide

Severe osteomalacia and rickets have been seen in a few patients taking phenytoin, phenobarbital, or primidone with acetazolamide. A marked reduction in serum primidone levels with a loss in seizure control, rises in serum carbamazepine levels with toxicity, and rises in phenytoin levels have also been described in a very small number of patients given acetazolamide.

Clinical evidence

(a) Osteomalacia

Severe osteomalacia developed in 2 women taking **phenytoin** or **primidone** and **phenobarbital** when they were given acetazolamide 750 mg daily, despite a normal intake of calcium. When acetazolamide was withdrawn, the hyperchloraemic acidosis that had been seen in both patients abated and their high urinary excretion of calcium fell by 50%.[1,2]

Similar cases have been described in 3 children, who developed rickets after taking acetazolamide, **phenytoin** and **primidone**, with **phenobarbital** and/or metharbital.[3]

(b) Reduced serum primidone levels

A patient taking primidone had an increase in seizure-frequency and a virtual absence of primidone (or its metabolite, phenobarbital) in the serum while taking acetazolamide 250 mg daily. Primidone levels rose when the acetazolamide was withdrawn, probably due to improved absorption. A subsequent study in 2 other patients found that acetazolamide had a small effect on primidone absorption in one patient, and no effect in the other.[4]

(c) Increased serum carbamazepine levels

A 9-year-old girl and two teenage boys, all of them taking the highest doses of carbamazepine tolerable without adverse effects, developed signs of toxicity after taking acetazolamide 250 to 750 mg daily. Their serum carbamazepine levels were found to have increased by about 25 to 50%. In one instance toxicity appeared within 48 hours.[5]

The seizure control of 54 children with grand mal and temporal lobe epilepsy was improved when acetazolamide 10 mg/kg daily was given with carbamazepine. Serum carbamazepine levels rose by 1 to 6 mg/L in 60% of the 33 patients sampled. Adverse effects developed in 10 children, and in 8 children this was within 1 to 10 days of starting the acetazolamide. The adverse effects responded to a reduction in the carbamazepine dose.[6]

(d) Increased serum phenytoin levels

When acetazolamide was given with phenytoin to 6 children, 5 of them had an increase in their phenytoin level (range 20 to 132%, representing an increase of 3 to 12.5 mg/L), and one had a slight decrease (20% or 3 mg/L) [values estimated from figure].[7]

Mechanism

Uncertain. Mild osteomalacia induced by antiepileptics is a recognised phenomenon[8] (see also 'Vitamin D substances + Antiepileptics; Enzyme-inducing', p.1410). It seems that this is exaggerated by acetazolamide, which increases urinary calcium excretion, possibly by causing systemic acidosis, which results from the reduced absorption of bicarbonate by the kidney. The changes in the antiepileptic levels are not understood.

Importance and management

The documentation of all of these interactions is very limited, and their incidence is uncertain. Concurrent use should be monitored for the possible development of osteomalacia or altered antiepileptic levels (reduced primidone efficacy, and increased carbamazepine or phenytoin adverse effects) and steps taken to accommodate them. Withdraw the acetazolamide if necessary, or adjust the dose of the antiepileptic appropriately. In the case of the children with rickets[3] the acetazolamide was withdrawn and high doses of vitamin D was given. It seems possible that other carbonic anhydrase inhibitors may behave like acetazolamide.

1. Mallette LE. Anticonvulsants, acetazolamide and osteomalacia. *N Engl J Med* (1975) 293, 668.
2. Mallette LE. Acetazolamide-accelerated anticonvulsant osteomalacia. *Arch Intern Med* (1977) 137, 1013–17.
3. Matsuda I, Takekoshi Y, Shida N, Fujieda K, Nagai B, Arashima S, Anakura M, Oka Y. Renal tubular acidosis and skeletal demineralization in patients on long-term anticonvulsant therapy. *J Pediatr* (1975) 87, 202–5.
4. Syversen GB, Morgan JP, Weintraub M, Myers GJ. Acetazolamide-induced interference with primidone absorption. *Arch Neurol* (1977) 34, 80–4.
5. McBride MC. Serum carbamazepine levels are increased by acetazolamide. *Ann Neurol* (1984) 16, 393.
6. Forsythe WI, Owens JR, Toothill C. Effectiveness of acetazolamide in the treatment of carbamazepine-resistant epilepsy in children. *Dev Med Child Neurol* (1981) 23, 761–9.
7. Norell E, Lilienbeg G, Gamstorp I. Systematic determination of the serum phenytoin level as an aid in the management of children with epilepsy. *Eur Neurol* (1975) 13, 232–44.
8. Anast CS. Anticonvulsant drugs and calcium metabolism. *N Engl J Med* (1975) 292, 587–8.

Antiepileptics + Aciclovir

Isolated reports describe a marked reduction in phenytoin and valproate levels in two children given aciclovir. Seizure frequency increased.

Clinical evidence, mechanism, importance and management

A 7-year-old boy with epilepsy taking **phenytoin**, **valproate** and nitrazepam was given oral aciclovir 1 g daily for 6 days. After 4 days his trough plasma **phenytoin** levels had fallen from 17 micrograms/mL to 5 micrograms/mL, and his trough **valproate** levels similarly fell, from 32 micrograms/mL to 22 micrograms/mL. When the aciclovir was stopped the plasma levels of both antiepileptics rose over a period of 3 to 6 days. During the period when the antiepileptic levels were restabilising, the seizure frequency markedly increased and his EEG worsened.

The reason for this apparent interaction is not known, but the authors of the report suggest that aciclovir may possibly have reduced the absorption of these antiepileptics, in some way not understood.[1] Reduced **phenytoin** and **valproate** levels during treatment with aciclovir have been reported in another child.[2]

These cases appear to be the only reports of an interaction between aciclovir and valproate or phenytoin, and their general clinical importance is not known. More study is needed to establish an interaction.

1. Parmeggiani A, Riva R, Posar A, Rossi PG. Possible interaction between acyclovir and antiepileptic treatment. *Ther Drug Monit* (1995) 17, 312–15.
2. Iglesias Iglesias A-A, Ortega García MP, Guevara Serrano J. Disminución de la concentración sérica de antiepilépticos durante el tratamiento con aciclovir. *Med Clin (Barc)* (2005) 124, 355–6.

Antiepileptics + Antineoplastics; Cytotoxic

Carbamazepine, phenytoin and valproate serum levels can be reduced by several antineoplastic drug regimens and seizures can occur if the antiepileptic doses are not raised appropriately. In contrast, phenytoin toxicity has occurred when fluorouracil and fluorouracil prodrugs, such as capecitabine, doxifluridine and tegafur, were given. The effects of many antineoplastics are reduced or changed by enzyme-inducing antiepileptics. Increased haematological toxicity may occur if valproate is given with fotemustine and cisplatin.

Clinical evidence

(a) Antiepileptic levels reduced

There are a number of reports (mainly case reports) that implicate a variety of types of chemotherapy in reducing the levels of **carbamazepine**, **phenytoin**, and **valproate**. See 'Table 14.1', (p.594) for details.

(b) Phenytoin levels raised

A patient with epilepsy taking phenytoin developed phenytoin toxicity when given **fluorouracil** to treat colon cancer.[1] Three patients with malignant brain tumours developed acute phenytoin toxicity associated with raised serum phenytoin levels when they were given *UFT* (**uracil** and **tegafur**, a prodrug of **fluorouracil**).[2] Another case of phenytoin toxicity has been reported with *UFT*.[3] Phenytoin toxicity was also seen in a woman treated with combination therapy that included the fluorouracil prodrug **doxifluridine**.[4] Similarly, phenytoin toxicity has occurred in a patient given **capecitabine** (another prodrug of fluorouracil).[5] Although in one report,[2] no interaction occurred in one of the patients when the *UFT* was replaced by **fluorouracil**, cases of phenytoin toxicity have been reported in 3 patients receiving **fluorouracil** with folinic acid.[5,6]

Table 14.1 Reduced antiepileptic levels during antineoplastic therapy

Antiepileptic	*Antineoplastic*	*Malignancy*	*Outcome*	*Refs*
Phenytoin	Cisplatin Carmustine	Brain tumours	A retrospective study reviewed the effects of 3 or more cycles of 72 hours of carmustine and cisplatin chemotherapy in 19 patients who did not vomit. A phenytoin dose increase was required in three-quarters of patients, which was, on average, 40% of the original dose (range 20 to 100%). The effect on phenytoin levels persisted after the chemotherapy had finished, with levels returning to normal 2 to 3 weeks later.	1
Phenytoin	Cisplatin Vinblastine Bleomycin	Metastatic germ cell tumour	Estimated phenytoin level 15 micrograms/mL, but level only reached 2 micrograms/mL. Patient fitted.	2
Phenytoin Primidone	Cisplatin Vinblastine Bleomycin	Metastatic embryonal cell cancer	Phenytoin 800 mg daily gave a level of 15 micrograms/mL whilst receiving chemotherapy. After chemotherapy the same dose produced a toxic level of 42.8 micrograms/mL. Phenobarbital levels unaffected.	3
Phenytoin Phenobarbital	Vinblastine Carmustine Methotrexate	Lung cancer with brain metastases	Phenytoin levels fell from 9.4 micrograms/mL to 5.6 micrograms/mL 24 hours after vinblastine. Patient fitted. Phenytoin levels returned to normal 2 weeks after chemotherapy. Phenobarbital levels unaffected.	4
Phenytoin Carbamazepine Sodium valproate	Doxorubicin Cisplatin Cyclophosphamide Altretamine	Papillary adenocarcinoma of the ovaries	Seizures occurred 2 to 3 days after starting chemotherapy. All drug levels dropped to one-third or lower. Doses increased to compensate, which led to phenytoin toxicity when the chemotherapy finished.	5
Phenytoin	Carboplatin	Small cell lung cancer with brain metastases	Phenytoin level dropped from 9.7 micrograms/mL to 4.6 micrograms/mL 10 days into chemotherapy, resulting in seizures. Phenytoin dose had to be increased by 35% to achieve a level of 10.7 micrograms/mL.	6
Phenytoin	Dacarbazine Carmustine Cisplatin Tamoxifen	Malignant melanoma with brain metastases	Phenytoin level of only 2.5 micrograms/mL despite a loading 1-g dose and a daily dose of 500 mg phenytoin.	7
Phenytoin followed by Carbamazepine	Vincristine Cytarabine Hydroxycarbamide Daunorubicin Methotrexate Tioguanine Cyclophosphamide Carmustine	Stage IV T-cell lymphoma	Phenytoin failed to reach therapeutic levels and so was substituted with carbamazepine. Chemotherapy caused carbamazepine levels to drop below therapeutic levels resulting in seizures. Increasing the dose from 30 mg/kg to 50 mg/kg per day prevented subtherapeutic levels.	8
Phenytoin	Methotrexate Mercaptopurine Vincristine	Acute lymphoblastic leukaemia	Phenytoin levels dropped from 19.8 micrograms/mL on the day before chemotherapy to 3.6 micrograms/mL on the 6th day of chemotherapy.	9
Phenytoin	Cisplatin Carmustine Etoposide	CNS tumours	Dose of phenytoin had to be increased by 50 to 300% in 10 patients to maintain phenytoin levels in the therapeutic range.	10
Sodium valproate	Methotrexate (high dose)	Acute lymphoblastic leukaemia	A child had a seizure a few hours after methotrexate. Serum valproate levels reduced by 75%. The valproate dose was increased by 50% and clonazepam added.	11
Sodium valproate	Methotrexate Cytarabine Nimustine (by CSF perfusion)	Glioblastoma	CSF valproic acid levels reduced by 70% during the perfusion, but returned to normal levels within 7 hours.	12
Sodium valproate Phenytoin	Cisplatin Etoposide Bleomycin	Testicular cancer	Serum valproate levels reduced by 50% after the first cycle and generalised tonic-clonic seizures occurred. There was no effect on phenytoin levels.	13

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Continued

Table 14.1 Reduced antiepileptic levels during antineoplastic therapy (continued)

9. Jarosinski PF, Moscow JA, Alexander MS, Lesko LJ, Balis FM, Poplack DG. Altered phenytoin clearance during intensive treatment for acute lymphoblastic leukemia. *J Pediatr* (1988) 112, 996-9.
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11. Schrøder H, Østergaard JR. Interference of high-dose methotrexate in the metabolism of valproate? *Pediatr Hematol Oncol* (1994) 11, 445-9.
12. Morikawa N, Mori T, Abe T, Kawashima H, Takeyama M, Hori S. Pharmacokinetics of cytosine arabinoside, methotrexate, nimustine and valproic acid in cerebrospinal fluid during cerebrospinal fluid perfusion chemotherapy. *Biol Pharm Bull* (2000) 23, 784-7.
13. Ikeda H, Murakami T, Takano M, Usui T, Kihira K. Pharmacokinetic interaction on valproic acid and recurrence of epileptic seizures during chemotherapy in an epileptic patient. *Br J Clin Pharmacol* (2005) 59, 593-7.

(c) Antineoplastic effects reduced or altered

A number of antiepileptic drugs affect the levels of various antineoplastics. These are discussed elsewhere. See:

- 'Anthracyclines; Doxorubicin + Barbiturates', p.700,
- 'Busulfan + Phenytoin', p.710,
- 'Cyclophosphamide or Ifosfamide + Barbiturates', p.714,
- 'Cyclophosphamide or Ifosfamide + Phenytoin', p.718,
- 'Etoposide + Antiepileptics; Enzyme-inducing', p.724,
- 'Imatinib + CYP3A4 inducers', p.735,
- 'Irinotecan + Antiepileptics', p.736,
- 'Methotrexate + Antiepileptics; Enzyme-inducing', p.748,
- 'Procarbazine + Antiepileptics; Enzyme-inducing', p.762,
- 'Streptozocin + Phenytoin', p.765,
- 'Taxanes; Paclitaxel + CYP3A4 inducers', p.770,
- 'Teniposide + Antiepileptics; Enzyme-inducing', p.772,
- 'Topotecan + Phenytoin', p.777,
- 'Toremifene + Antiepileptics; Enzyme-inducing', p.778.

(d) Miscellaneous

One report found that **valproate** increased haematological toxicity in patients taking **fotemustine** and **cisplatin**.[7]

Mechanism

Not fully understood, but a suggested reason for the fall in serum antiepileptic levels is that these antineoplastics damage the intestinal wall, which reduces the absorption of the antiepileptic. Other mechanisms may also have some part to play. The raised serum phenytoin levels possibly occur because the liver metabolism of phenytoin is reduced by these antineoplastics. Changes in plasma protein binding may also have been involved.

Importance and management

Information is scattered and incomplete. However, it appears that altered antiepileptic levels can occur, possibly leading to loss of efficacy or toxicity. Where possible, it may be prudent to avoid the concurrent use of enzyme-inducing antiepileptics and antineoplastics. If this is not possible, serum antiepileptic levels should be closely monitored during treatment with any of these antineoplastics, making dose adjustments as necessary. Advice on the management of altered antineoplastic levels with antiepileptics is discussed in the individual monographs.

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Antiepileptics; Enzyme-inducing + Calcium carbimide or Disulfiram

Phenytoin levels are markedly and rapidly increased by disulfiram. Phenytoin toxicity can develop. There is evidence that phenobarbital and carbamazepine levels are not affected by disulfiram, and that phenytoin levels are not affected by calcium carbimide.

Clinical evidence

(a) Calcium carbimide

A study in 4 patients found that calcium carbimide 50 mg daily for a week followed by 100 mg daily for 2 weeks had no effect on serum **phenytoin** levels.[1]

(b) Disulfiram

The serum **phenytoin** levels of 4 patients rose by 100 to 500% over a 9 day period when they were given disulfiram 400 mg daily. **Phenytoin** levels were still rising even 3 to 4 days after the disulfiram was withdrawn, and had still not returned to normal after 14 days. Two patients developed signs of mild **phenytoin** toxicity.[2] In a follow-up study in two of the patients, one developed ataxia and both had a rise in serum **phenytoin** levels, of 25% and 50%, respectively, during 5 days of disulfiram treatment.[1] In 10 healthy subjects disulfiram increased the half-life of **phenytoin** from 11 hours to 19 hours.[3] There are also other case reports describing this interaction.[4-8]

Phenobarbital levels (from **primidone** in 3 patients and **phenobarbital** in one patient) fluctuated by about 10% (which is unlikely to be clinically significant) when disulfiram was given for 9 days.[1,2]

A case report suggested that **carbamazepine** did not interact with disulfiram,[6] and this has been confirmed in a study of 5 epileptic, non-alcoholic patients.[9]

Mechanism

Disulfiram inhibits the liver enzymes concerned with the metabolism of phenytoin (possibly the cytochrome P450 isoenzyme CYP2C9) thereby reducing its metabolism and resulting in a rise in its serum levels, to toxic concentrations in some instances. One study concluded that the inhibition was non-competitive.[7]

Importance and management

The interaction between phenytoin and disulfiram is established, moderately well documented, clinically important and potentially serious. It seems to occur in most patients and develops rapidly. Recovery may take 2 to 3 weeks after the disulfiram is withdrawn. It has been suggested that the dose of phenytoin could be reduced to accommodate the interaction, but it may be difficult to maintain the balance required. Monitor for phenytoin adverse effects (e.g. blurred vision, nystagmus, ataxia or drowsiness) and monitor phenytoin levels if both drugs are given.[1]

Carbamazepine and phenobarbital do not appear to interact with disulfiram, and calcium carbimide does not appear to interact with phenytoin.

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2. Olesen OV. Disulfiramum (Antabuse®) as inhibitor of phenytoin metabolism. *Acta Pharmacol Toxicol (Copenh)* (1966) 24, 317–22.
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9. Krag B, Dam M, Angelo H, Christensen JM. Influence of disulfiram on the serum concentration of carbamazepine in patients with epilepsy. *Acta Neurol Scand* (1981) 63, 395–8.

Antiepileptics + Chinese herbal medicines

A study in patients with epilepsy found that Saiko-ka-ryukotsu-borei-to (TJ-12) enhanced the antiepileptic effects of carbamazepine. Paeoniae radix does not appear to affect the pharmacokinetics of valproic acid.

Clinical evidence

(a) Carbamazepine

A study in patients with epilepsy found the antiepileptic effects of carbamazepine were enhanced by concurrent **Saiko-ka-ryukotsu-borei-to** (**TJ-12**);[1] patients experienced fewer seizures and had improved neurological symptoms.[2]

(b) Valproate

In 6 healthy subjects, the pharmacokinetics of a single 200-mg dose of valproic acid were unaffected by 1.2 g of a powder extract of **Paeoniae radix** taken daily for 7 days.[3]

Mechanism

Not fully understood. As a pharmacokinetic interaction has not been found between Saiko-ka-ryukotsu-borei-to and carbamazepine, the enhanced effects found in the patients with epilepsy may therefore have been due to a pharmacodynamic interaction.[2] Paeoniae radix (the dried root of *Paeonia lactiflora*[3]) is reported to reduce the rate of gastric emptying;[3] however, this does not appear to affect valproate absorption.

Importance and management

Evidence is limited, but there appears to be no evidence of an adverse effect when using Paeoniae radix with valproate, or Saiko-ka-ryukotsu-borei-to with carbamazepine. More study is needed to confirm all these findings. Note that adulteration of Chinese medicines with various antiepileptics may lead to unexpected toxicity.[4]

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3. Chen LC, Chou MH, Lin MF, Yang LL. Lack of pharmacokinetic interaction between valproic acid and a traditional Chinese medicine, Paeoniae Radix, in healthy volunteers. *J Clin Pharm Ther* (2000) 25, 453–9.
4. Lau KK, Lai CK, Chan AYM. Phenytoin poisoning after using Chinese proprietary medicines. *Hum Exp Toxicol* (2000) 19, 385–6.

Antiepileptics + Folinates

If folate supplements are given to treat folate deficiency, which can be caused by the use of antiepileptics (phenytoin, phenobarbital, primidone and possibly carbamazepine and pheneturide), the serum antiepileptic levels may fall, leading to decreased seizure control in some patients.

Clinical evidence

A study in 50 folate-deficient patients with epilepsy (taking **phenytoin**, **phenobarbital** and **primidone** in various combinations) found that after one month of treatment with folic acid 5 mg daily, the plasma **phenytoin** levels of one group of 10 patients had fallen from 20 micrograms/mL to 10 micrograms/mL. In another group of patients taking folic acid 15 mg daily, the levels of **phenytoin** fell from 14 micrograms/mL to 11 micrograms/mL. Only one patient (in the 5-mg folic acid group) had a marked increase in seizure frequency and severity. No alterations were seen in **phenobarbital** levels.[1]

Another long-term study in 26 patients with folic acid deficiency (serum folate less than 5 nanograms/mL) and taking two or more drugs (**phenytoin**, **phenobarbital**, **primidone**), found that the mental state of 22 patients (as shown by increased alertness, concentration, sociability etc.) improved to a variable degree when they were given folic acid 5 mg three times daily. However, the frequency and severity of seizures in 13 patients (50%) increased to such an extent that the folic acid had to be withdrawn from 9 of them.[2]

Similar results, both of increased seizure activity and decreased serum folate levels, have been described in other studies and reports in patients taking **phenytoin**, **phenobarbital**, **primidone** and **pheneturide**.[3-7]

Another report describes a lack of **phenytoin** efficacy in a patient receiving *UFT* (tegafur and uracil) with **folinic acid**, which was attributed to the effect of the **folinic acid** on **phenytoin** levels.[8]

Mechanism

Patients taking antiepileptics may have subnormal serum folic acid levels. Frequencies of 27 to 76% have been reported for phenobarbital, primidone, and phenytoin, alone or in various combinations.[9] There is conflicting information regarding **carbamazepine**[10-13] and **valproate**[10,11,13] causing reduced folic acid levels. **Zonisamide** has not been shown to reduce serum folate levels.[10] One possible explanation is that a reduction in folate occurs with enzyme-inducing antiepileptics, which make excessive demands on folate for the synthesis of the enzymes concerned with drug metabolism, but does not occur with valproate and zonisamide, which are not enzyme inducers. Ultimately the metabolism of the enzyme-inducing antiepileptics becomes limited by the lack of folate, and patients may also develop a reduction in their general mental health[2] and even frank megaloblastic anaemia.[9,14] If folic acid is then given to treat this deficiency, the metabolism of the antiepileptic increases,[15] resulting in a reduction in serum antiepileptic levels, which in some instances may become so low that seizure control is partially or totally lost.

Importance and management

A very well documented and clinically important interaction, which has been the subject of review.[16] Reductions in serum phenytoin levels of 16 to 50% have been described in patients taking 5 to 15 mg folic acid daily for 2 to 4 weeks.[1,3,17] One report suggests that folate doses as low as 1 mg daily may affect phenytoin levels and that even smaller doses may be advisable.[6]

If folic acid supplements are given to folate-deficient patients with epilepsy taking phenytoin, phenobarbital, primidone, and possibly pheneturide, their serum antiepileptic levels should be well monitored so that suitable dose increases can be made. Less information is available about primidone and phenobarbital, but similar precautions would seem prudent. An interaction with carbamazepine is not established, but as some evidence suggests that it may interact similarly some caution is warranted.

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Antiepileptics + Ginkgo (*Ginkgo biloba*)

Case reports describe seizures in three patients taking valproate, or valproate and phenytoin, when ginkgo was also taken.

Clinical evidence

A 55-year-old man taking **valproate** and **phenytoin** for a seizure disorder that developed following coronary artery bypass surgery, suffered a fatal breakthrough seizure while swimming a year later. Analysis of his medical history showed that he had unexplained subtherapeutic serum levels of **valproate** and **phenytoin** on three occasions over the previous year. It was later found that the patient had also been taking numerous vitamins, supplements and herbal medicines without the knowledge of his physician, of which a ginkgo extract was stated to be the most common ingredient.[1] The only other herbal medicines named in the report were ginseng and saw palmetto.

In another case, a 78-year-old man, whose epileptic seizures had been well controlled by **valproate** 1.2 g daily for 7 years, suffered a cluster of seizures after taking a ginkgo extract 120 mg daily for 2 weeks for the management of mild cognitive impairment. The ginkgo was stopped and the patient was reportedly seizure-free 8 months later. All other medications taken by the patient remained unchanged.[2]

An 84-year-old epileptic woman with severe dementia taking **valproate** 1.2 g daily had been seizure-free for 2 years. After taking a ginkgo extract 120 mg daily for 12 days prescribed by her psychiatrist, she suffered a cluster of seizures, which were treated with intravenous diazepam in the emergency department. The ginkgo extract was stopped on admission and the patient remained free of seizures 4 months later. All other medications taken by the patient were unchanged.[2]

Mechanism

Unknown. Ginkgo *seeds* (nuts) contain the neurotoxin 4-*O*-methoxypyridoxine (ginkgotoxin), which indirectly inhibits the activity of glutamate decarboxylase, which in turn results in seizure induction by lowering the levels of γ-amino-butyric acid (GABA). A large quantity of ginkgo nuts (about 70 to 80) alone have been reported to be the cause of seizures in a healthy 36-year-old woman.[3] However, leaf extracts would not generally be expected to contain sufficient levels of this neurotoxin to be a problem.

Another possible mechanism is induction of the cytochrome P450 isoenzyme CYP2C19 by ginkgo. Phenytoin is a substrate of CYP2C19 and therefore, in theory, ginkgo may increase the metabolism of phenytoin and thereby reduce its levels. Ginkgo has been seen to induce CYP2C19 in clinical studies. See 'Proton pump inhibitors + Ginkgo (*Ginkgo biloba*)', p.1159.

Importance and management

Evidence for an interaction between ginkgo and valproate and phenytoin appears to be limited to case reports. The only case that measured serum levels of these antiepileptics is complicated by the use of numerous other supplements. An interaction is therefore by no means established. Nevertheless, it may be prudent to consider the possibility of reduced effects if a patients taking phenytoin and/or valproate wishes to also take ginkgo.

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Antiepileptics + Mefloquine

A woman whose epilepsy was controlled with valproic acid developed convulsions when she took mefloquine.

Clinical evidence, mechanism, importance and management

An isolated report describes a 20-year-old woman, with a 7-year history of epilepsy (bilateral myoclonus and generalised tonic-clonic seizures) controlled with **valproic acid** 1.3 g daily, who developed tonic-clonic seizures 8 hours after taking the second of 3 prophylactic doses of mefloquine 250 mg.[1] It is not clear whether this resulted from a drug-drug or a drug-disease interaction. The manufacturer of mefloquine advises its avoidance in those with a history of convulsions as it may increase the risk of convulsions. In these patients mefloquine should be used only for curative treatment if compelling reasons exist.[2]

1. Besser R, Krämer G. Verdacht auf anfallfördernde Wirkung von Mefloquin (Lariam®). *Nervenarzt* (1991) 62, 760–1.
2. Lariam (Mefloquine hydrochloride). Roche Products Ltd. UK Summary of product characteristics, August 2009.

Antiepileptics + Melatonin

Carbamazepine levels are not affected by melatonin. Melatonin levels are predicted to be reduced by carbamazepine.

Clinical evidence, mechanism, importance and management

In a placebo-controlled study on the effects of melatonin on antioxidant enzymes, melatonin 6 to 9 mg/kg daily for 14 days was given to children with epilepsy taking carbamazepine. The serum levels of carbamazepine and its metabolite carbamazepine-10,11-epoxide were not affected by melatonin. Melatonin appeared to antagonise the accumulation of reactive oxygen species (which can be damaging to cells in the body) caused by carbamazepine.[1]

One manufacturer predicts that carbamazepine may increase the metabolism of melatonin (by induction of the cytochrome P450 isoenzyme CYP1A2), thereby decreasing its levels.[2] However, note that carbamazepine is not a particularly potent inducer of this isoenzyme. Furthermore, when 22 children with epilepsy were given either **carbamazepine** or **valproate**, with a single 6- or 9-mg dose of melatonin, the serum levels of melatonin increased from 1.5 picograms/mL to 165 picograms/mL (range: 50 to 350 picograms/mL) in the **carbamazepine** group and from 1.3 picograms/mL to 78 picograms/mL (range 13 to 260 picograms/mL) in the **valproate** group. Although median levels of melatonin in the **carbamazepine** group were about twice those in the **valproate** group, the difference was not statistically significant because of the wide range of results.[3]

It appears that dose adjustments are unlikely to be needed on the concurrent use of melatonin and carbamazepine.

1. Gupta M, Gupta YK, Agarwal S, Aneja S, Kalaivani M, Kohli K. Effects of add-on melatonin administration on antioxidant enzymes in children with epilepsy taking carbamazepine monotherapy: a randomized, double-blind, placebo-controlled trial. *Epilepsia* (2004) 45, 1636–9.
2. Circadin (Melatonin). Lundbeck Ltd. UK Summary of product characteristics, March 2009.
3. Gupta M, Kohli K, Gupta YK. Modulation of serum concentrations of melatonin by carbamazepine and valproate. *Indian J Physiol Pharmacol* (2006) 50, 79–82.

Antiepileptics; Enzyme-inducing + Quinine

Preliminary evidence suggests that the effects of carbamazepine and phenobarbital may be increased by quinine, possibly leading to toxicity. An isolated report suggests that phenytoin may reduce the levels of quinine but the levels of phenytoin do not appear to be affected by quinine.

Clinical evidence, mechanism, importance and management

Single doses of **carbamazepine** 200 mg, **phenobarbital** 120 mg or **phenytoin** 200 mg were given to 3 groups of 6 healthy subjects, with and without a single 600-mg dose of quinine sulfate. The AUC of **carbamazepine** and **phenobarbital** were increased by 104% and 57%, respectively, and the peak plasma levels were increased by 81% and 53%, respectively. **Phenytoin** was not significantly affected. The reasons for these effects are not known but the authors suggest that quinine inhibits the metabolism of **carbamazepine** and **phenobarbital** (but not **phenytoin**) by the liver, so that their levels become raised.[1]

In an earlier study in 2 healthy subjects, **phenobarbital** 125 mg daily for 4 days caused only a small reduction in the plasma half-life of quinine.[2]

Information seems to be limited to these studies. The importance of the interactions with **carbamazepine** and **phenobarbital** await assessment in a clinically realistic situation (i.e. in patients taking multiple doses) but in the meantime it would seem prudent to monitor for adverse effects of **carbamazepine** (e.g. nausea, vomiting, ataxia, drowsiness) or **phenobarbital** (e.g. hypotension, irritability, sedation) if quinine is also taken.

An isolated report describes a 22-month-old girl taking **phenytoin**, **sodium valproate** and **topiramate** for epilepsy was given quinine sulfate

(initially intravenously, then orally) followed by a single dose of sulfadoxine with pyrimethamine for malaria. Her malaria film became negative after 4 days of the 7-day quinine course. About one month later she was found to have recrudescent falciparum malaria, and so she was given quinine sulfate and then atovaquone with proguanil. Although it is possible that quinine resistance may have occurred, the authors also considered that enzyme induction by **phenytoin** may have led to suboptimal quinine levels.[3]

Although quinine does not appear to affect **phenytoin** levels, the isolated case report suggests that levels of quinine may be reduced in the presence of **phenytoin**. Until more is known it would seem prudent to monitor concurrent use carefully.

1. Amabeoku GJ, Chikuni O, Akino C, Mutetwa S. Pharmacokinetic interaction of single doses of quinine and carbamazepine, phenobarbitone and phenytoin in healthy volunteers. *East Afr Med J* (1993) 70, 90–3.
2. Saggers VH, Hariratnajothi N, McLean AEM. The effect of diet and phenobarbitone on quinine metabolism in the rat and in man. *Biochem Pharmacol* (1970) 19, 499–503.
3. Fabre C, Criddle J, Nolder D, Klein JL. Recrudescence of imported falciparum malaria after quinine therapy: potential drug interaction with phenytoin. *Trans R Soc Trop Med Hyg* (2005) 99, 871–3.

Antiepileptics + Quinolones

Studies suggest that ciprofloxacin, clinafloxacin, and enoxacin do not usually have a clinically significant effect on phenytoin levels. However, case reports describe both a rise and a fall in phenytoin levels in patients given ciprofloxacin.

Clinical evidence

(a) Ciprofloxacin

In a study in 4 healthy subjects there was no difference in the pharmacokinetics of **phenytoin** 200 mg daily when it was given with ciprofloxacin 500 mg twice daily. However, one of the 4 subjects experienced a 30% decrease in the **phenytoin** maximum serum levels when ciprofloxacin was added.[1] Four case reports describe falls of 50% or more in **phenytoin** serum levels when ciprofloxacin was added, accompanied by seizures in 3 instances.[2-5] Another report describes unexpectedly low **phenytoin** levels (measured after a loading dose) in a woman taking ciprofloxacin.[6]

Conversely, **phenytoin** levels rose in an elderly woman, possibly as a result of the ciprofloxacin she was taking.[7] In another study in 7 patients taking **phenytoin**, ciprofloxacin 500 mg twice daily for 10 days caused no significant change in **phenytoin** levels, although there was a tendency for an increase (mean 24% rise).[8]

In one report, blood levels of **phenytoin** and **valproic acid** were not affected by ciprofloxacin although a seizure occurred on the fourth day of concurrent use.[9] Other cases describe seizures in patients taking **phenytoin** when given ciprofloxacin, but with little or no information on **phenytoin** levels.[10]

(b) Clinafloxacin

In a study, **phenytoin** 300 mg daily was given to healthy subjects for 10 days, then clinafloxacin 400 mg twice daily was added for a further 2 weeks. The maximum serum **phenytoin** levels rose by 18% (from 6.74 to 7.95 mg/L), the AUC rose by 20% and the clearance fell by 17%.[11]

(c) Enoxacin

In a study in healthy subjects, enoxacin did not appear to alter **phenytoin** serum levels, nor were multiple-dose serum enoxacin levels significantly altered by **phenytoin**.[12]

Mechanism

Fluoroquinolones alone rarely cause convulsions both in patients with and without a history of seizures. The mechanism for the effect of ciprofloxacin on phenytoin levels is unknown, and is unlikely to be due to effects on hepatic metabolism or oral absorption.[13,14] However, ciprofloxacin decreased phenytoin levels in an *animal* study, and a suggested reason for this was increased urinary excretion.[15]

Importance and management

The known potential for quinolones to induce seizures suggests that these antibacterials should either be avoided in patients with epilepsy, or only used when the benefits of treatment outweigh the potential risks of seizures. Some of the reactions seem to be drug-disease interactions rather than drug-drug interactions, the usual outcome being that the control of epilepsy is worsened. However, it appears that ciprofloxacin may also alter (usually decrease) phenytoin levels, and if this combination is used it would be prudent to consider monitoring phenytoin levels. Enoxacin appears not to alter phenytoin levels.

1. Job ML, Arn SK, Strom JG, Jacobs NF, D'Souza MJ. Effect of ciprofloxacin on the pharmacokinetics of multiple-dose phenytoin serum concentrations. *Ther Drug Monit* (1994) 16, 427–31.
2. Dillard ML, Fink RM, Parkerson R. Ciprofloxacin-phenytoin interaction. *Ann Pharmacother* (1992) 26, 263.
3. Pollak PT, Slayter KL. Hazards of doubling phenytoin dose in the face of an unrecognized interaction with ciprofloxacin. *Ann Pharmacother* (1997) 31, 61–4.
4. Brouwers PJ, DeBoer LE, Guchelaar H-J. Ciprofloxacin-phenytoin interaction. *Ann Pharmacother* (1997) 31, 498.
5. Otero M-J, Morán D, Valverde M-P. Interaction between phenytoin and ciprofloxacin. *Ann Pharmacother* (1999) 33, 251–2.
6. McLeod R, Trinkle R. Comment: unexpectedly low phenytoin concentration in a patient receiving ciprofloxacin. *Ann Pharmacother* (1998) 32, 1110–11.
7. Hull RL. Possible phenytoin-ciprofloxacin interaction. *Ann Pharmacother* (1993) 27, 1283.
8. Schroeder D, Frye J, Alldredge B, Messing R, Flaherty J. Effect of ciprofloxacin on serum phenytoin concentrations in epileptic patients. *Pharmacotherapy* (1991) 11, 275.
9. Slavich IL, Gleffe R, Haas EJ. Grand mal epileptic seizures during ciprofloxacin therapy. *JAMA* (1989) 261, 558–9.
10. Anon. Risk of seizures from concomitant use of ciprofloxacin and phenytoin in patients with epilepsy. *Can Med Assoc J* (1998) 158, 104–5.
11. Randinitis EJ, Koup JR, Bron NJ, Hounslow NJ, Rausch G, Abel R, Vassos AB, Sedman AJ. Drug interaction studies with clinafloxacin and probenecid, cimetidine, phenytoin and warfarin. *Drugs* (1999) 58 (Suppl 2), 254–5.
12. Thomas D, Humphrey G, Kinkel A, Sedman A, Rowland M, Toon S, Aarons L, Hopkins K. A study to evaluate the potential pharmacokinetic interaction between oral enoxacin (ENX) and oral phenytoin (PHE). *Pharm Res* (1986) 3 (Suppl), 99S.
13. Pollak PT, Slayter KL. Comment: ciprofloxacin-phenytoin interaction. *Ann Pharmacother* (1997) 31, 1549–50.
14. Brouwers PJ, de Boer LE, Guchelaar H-J. Comment: ciprofloxacin-phenytoin interaction. *Ann Pharmacother* (1997) 31, 1550.
15. al-Humayyd MS. Ciprofloxacin decreases plasma phenytoin concentrations in the rat. *Eur J Drug Metab Pharmacokinet* (1997) 22, 35–9.

Antiepileptics + St John's wort (*Hypericum perforatum*)

St John's wort modestly increased the clearance of single-dose carbamazepine in one study, but had no effect on multiple-dose carbamazepine pharmacokinetics in another study. Carbamazepine does not appear to significantly affect the pharmacokinetics of hypericin or pseudohypericin (constituents of St John's wort). St John's wort increases the clearance of mephenytoin, and is predicted to reduce the blood levels of phenytoin and phenobarbital, but this awaits clinical confirmation.

Clinical evidence

In a multiple-dose study in 8 healthy subjects, St John's wort had no effect on the pharmacokinetics of **carbamazepine** or its active metabolite, carbamazepine-10,11-epoxide. In this study, subjects took **carbamazepine** 200 mg increased to 400 mg daily alone for 20 days, then with St John's wort 300 mg (standardised to 0.3% hypericin) three times daily for a further 14 days.[1] In contrast, the AUC of a single 400-mg dose of **carbamazepine** was reduced by 21% after St John's wort 300 mg was given three times daily for 14 days, and the AUC of the 10,11-epoxide metabolite was increased by 26%.[2]

A double-blind, placebo-controlled study in healthy subjects found that, apart from a modest 29% decrease in the AUC of pseudohypericin, **carbamazepine** did not significantly affect the pharmacokinetics of either hypericin or pseudohypericin, which are both constituents of St John's wort.[3]

In another placebo-controlled study in 6 extensive metabolisers of CYP2C19 (that is, those with normal levels of this isoenzyme), St John's wort 300 mg three times daily for 14 days increased the clearance of a single oral dose of **mephenytoin** 100 mg given on day 15, by about 3-fold. There were no significant effects when **mephenytoin** was given to 6 poor metabolisers of CYP2C19 (that is, those lacking this isoenzyme). Each St John's wort tablet contained 0.3% hypericin and 4% hyperforin.[4]

Mechanism

St John's wort is a known inducer of the cytochrome P450 isoenzyme CYP3A4, and the results with single-dose carbamazepine are as predicted. However, carbamazepine is also an inducer of CYP3A4, which induces its own metabolism (autoinduction). It is suggested that St John's wort is not sufficiently potent an inducer to further induce carbamazepine metabolism

when autoinduction has occurred,[1] and therefore a small interaction is seen with single doses but no interaction is seen with multiple doses. However, the lack of effect seen in some of these studies may also be due to the different preparations used, and therefore differing levels of hyperforin.

Mephenytoin is a substrate of CYP2C19 and St John's wort appears to induce this isoenzyme.

Importance and management

The available evidence suggests that a clinically significant interaction between carbamazepine and St John's wort is unlikely. Before the publication of the above reports, the CSM in the UK had advised that patients taking a number of drugs including the antiepileptics carbamazepine, **phenytoin** and **phenobarbital** should not take St John's wort.[5] This advice was based on predicted pharmacokinetic interactions. In the light of the above studies, this advice may no longer apply to carbamazepine, although further study is needed. As the pharmacokinetic effects reported were modest, it may not be necessary for patients taking carbamazepine to avoid St John's wort; however, concurrent use should probably still be monitored to ensure adequate carbamazepine levels and efficacy.

Until more is known, it would probably be prudent to avoid the concurrent use of St John's wort in patients taking mephenytoin, **phenytoin** and **phenobarbital** (and therefore **primidone**), especially as **phenytoin** is also a substrate of CYP2C19, which St John's wort also appears to induce.

1. Burstein AH, Horton RL, Dunn T, Alfaro RM, Piscitelli SC, Theodore W. Lack of effect of St John's wort on carbamazepine pharmacokinetics in healthy volunteers. *Clin Pharmacol Ther* (2000) 68, 605–12.
2. Burstein AH, Piscitelli SC, Alfaro RM, Theodore W. Effect of St John's wort on carbamazepine single-dose pharmacokinetics. *Epilepsia* (2001) 42 (Suppl 7), 253.
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4. Wang L-S, Zhu B, El-Aty AMA, Zhou G, Li Z, Wu J, Chen G-L, Liu J, Tang ZR, An W, Li Q, Wang D, Zhou H-H. The influence of St. John's wort on CYP2C19 activity with respect to genotype. *J Clin Pharmacol* (2004) 44, 577–81.
5. Committee on the Safety of Medicines (UK). Message from Professor A Breckenridge (Chairman of CSM) and Fact Sheet for Health Care Professionals, 29th February 2000.

Antiepileptics + Terbinafine

A report describes the development of fatal toxic epidermal necrolysis shortly after a patient taking phenobarbital and carbamazepine started taking terbinafine. Another report describes elevated carbamazepine levels with symptoms of toxicity when a patient taking carbamazepine also took terbinafine.

Clinical evidence

A report describes a 26-year-old woman with cerebral palsy who had been taking **phenobarbital** 15 mg with **carbamazepine** 400 mg daily for 12 years to control epilepsy, and who developed fatal toxic epidermal necrolysis 2 weeks after starting oral terbinafine 250 mg daily for tinea corporis. The reasons are not understood, but the authors point out that all three drugs can cause adverse skin reactions (erythema multiforme) and suggest that some synergism may have occurred.[1] It is uncertain whether this was a true interaction or a terbinafine adverse effect.

A further report describes a 50-year-old man taking **carbamazepine** who developed symptoms of **carbamazepine** toxicity including gait ataxia, dizziness and falls and raised carbamazepine levels about 3 days after starting to take terbinafine 250 mg daily. These symptoms resolved on stopping the terbinafine, but recurred when treatment was restarted. It was suggested that terbinafine may have inhibited the metabolism of **carbamazepine**. A **carbamazepine** level of 17.2 micrograms/mL was recorded, which had only fallen to 2 micrograms/mL 10 days after stopping all treatment.[2]

Mechanism

The mechanism of this interaction is unclear, as terbinafine is thought to only affect the cytochrome P450 isoenzyme CYP2D6, which is not a major route of carbamazepine metabolism.

An antiepileptic drug hypersensitivity syndrome characterised by fever, skin rash (which may rarely be severe) and internal organ involvement (agranulocytosis, hepatitis, nephritis, and myositis) may occur 2 to 8 weeks after starting treatment with carbamazepine or phenytoin. As the patient in the first case report had been taking these drugs for several years, they are unlikely to be the cause, but this syndrome may also occur with other drugs including terbinafine.[3]

Importance and management

These appear to be isolated cases, and their general significance is unknown. If a patient taking terbinafine and carbamazepine experiences otherwise unexplained signs of carbamazepine toxicity (e.g. nausea, vomiting, ataxia and drowsiness) it may be prudent to suspect an interaction. Take carbamazepine levels and adjust the dose accordingly.

1. White SI, Bowen-Jones D. Toxic epidermal necrolysis induced by terbinafine in a patient on long-term anti-epileptics. *Br J Dermatol* (1996) 134, 188–9.
2. Baath NS, Hong J, Sattar SP. Possible carbamazepine toxicity with terbinafine. *Can J Clin Pharmacol* (2006) 13, e228–e231.
3. Schlienger RG, Shear NH. Antiepileptic drug hypersensitivity syndrome. *Epilepsia* (1998) 39 (Suppl 7), S3–S7.

Antiepileptics; Enzyme-inducing + Tobacco

Smoking tobacco appears to have no important effect on the serum levels of phenytoin, phenobarbital or carbamazepine.

Clinical evidence, mechanism, importance and management

A comparative study in 88 patients with epilepsy, taking **phenobarbital**, **phenytoin** and **carbamazepine** alone or in combination, found that although tobacco smoking had a tendency to lower the steady-state serum levels of these drugs, a statistically significant effect on the concentration-dose ratios was only found in the patients taking **phenobarbital**.[1] However, in another study in healthy subjects, there was no difference in the pharmacokinetics of a single 60-mg dose of **phenobarbital** in smokers and non-smokers.[2] In practical terms smoking appears to have only a negligible effect on the serum levels of these antiepileptic drugs and patients with epilepsy who smoke are unlikely to need higher doses than non-smokers.

1. Benetello P, Furlanut M, Pasqui L, Carmillo L, Perlotto N, Testa G. Absence of effect of cigarette smoking on serum concentrations of some anticonvulsants in epileptic patients. *Clin Pharmacokinet* (1987) 12, 302–4.
2. Mirfazaelian A, Jahanzad F, Tabatabaei-far M, Farsam H, Mahmoudian M. Effect of smoking on single dose pharmacokinetics of phenobarbital. *Biopharm Drug Dispos* (2001) 22, 403–6.

Antiepileptics; Enzyme-inducing + Vitamin B substances

High daily doses of pyridoxine can reduce phenytoin and phenobarbital levels in some patients. Some evidence suggests that high doses of nicotinamide reduce the conversion of primidone to phenobarbital, and increase carbamazepine levels.

Clinical evidence

(a) Nicotinamide

Nicotinamide 41 to 178 mg/kg daily increased the levels of **primidone** and decreased the levels of **primidone**-derived phenobarbital in 3 children. Although two of the children had refractory seizures, seizure frequency decreased while they were taking nicotinamide. Two of the children taking **carbamazepine** had increases in their **carbamazepine** levels.[1]

(b) Pyridoxine

Pyridoxine 200 mg daily for 4 weeks reduced the **phenobarbital** serum levels of 5 patients with epilepsy by about 50%. Reductions in serum **phenytoin** levels of about 35% (range 17 to 70%) were also seen when patients were given pyridoxine 80 to 400 mg daily for 2 to 4 weeks. However, no interaction occurred in a number of other patients taking these drugs.[2]

Mechanism

It is suggested that the pyridoxine increases and nicotinamide decreases the activity of the liver enzymes concerned with the metabolism of these antiepileptics.[1,2]

Importance and management

Information seems to be limited, but what is known suggests that the concurrent use of carbamazepine, phenytoin, phenobarbital or primidone should be monitored if large doses of pyridoxine or nicotinamide are used, being alert for the need to modify the antiepileptic dose. It seems unlikely that small doses (as in multivitamin preparations) will interact to any great extent.

1. Bourgeois BF, Dodson WE, Ferrendelli JA. Interactions between primidone, carbamazepine, and nicotinamide. *Neurology* (1982) 32, 1122–26.
2. Hansson O, Sillanpaa M. Pyridoxine and serum concentration of phenytoin and phenobarbitone. *Lancet* (1976) i, 256.

Carbamazepine + Allopurinol

There is some evidence to suggest that high-dose allopurinol (15 mg/kg or 600 mg daily) can gradually raise serum carbamazepine levels by about one-third. It appears that allopurinol 300 mg daily has no effect on carbamazepine levels.

Clinical evidence

In a 6-month study, 7 patients with epilepsy taking antiepileptics including carbamazepine, were also given allopurinol 100 mg three times daily for 3 months then 200 mg three times daily for 3 months. The mean trough steady-state serum carbamazepine levels of 6 of the patients rose by 30% or more and the carbamazepine clearance fell by 32% during the second 3-month period. A reduction in the carbamazepine dose was needed in 3 patients because of the symptoms that developed.[1] Similarly, in 11 patients taking antiepileptics including carbamazepine, allopurinol 10 mg/kg increased to 15 mg/kg daily for 12 weeks increased carbamazepine levels by 29%.[2] Conversely, in another study, allopurinol (150 mg daily in those less than 20 kg, and 300 mg daily for other patients) for 4 months had no effect on carbamazepine levels in 53 patients taking antiepileptics including carbamazepine.[3]

Mechanism

Uncertain. A possible explanation is that allopurinol can act as a liver enzyme inhibitor, which reduces the metabolism and clearance of carbamazepine.

Importance and management

Information is limited to these studies, but be alert for the need to reduce the dose of carbamazepine if high doses of allopurinol are used long-term. This interaction apparently takes several weeks or even months to develop fully. From one study, it appears that no interaction occurs between carbamazepine and low-dose allopurinol (such as that used for gout).

1. Mikati M, Erba G, Skouteli H, Gadia C. Pharmacokinetic study of allopurinol in resistant epilepsy: evidence for significant drug interactions. *Neurology* (1990) 40 (Suppl 1), 138.
2. Coppola G, Pascotto A. Double-blind, placebo-controlled, cross-over trial of allopurinol as add-on therapy in childhood refractory epilepsy. *Brain Dev* (1996) 18, 50–2.
3. Zagnoni PG, Bianchi A, Zolo P, Canger R, Cornaggia C, D'Alessandro P, DeMarco P, Pisani F, Gianelli M, Verzé L, Viani F, Zaccara G. Allopurinol as add-on therapy in refractory epilepsy: a double-blind placebo-controlled randomized study. *Epilepsia* (1994) 35, 107–12.

Carbamazepine + Amiodarone

Amiodarone does not appear to affect the pharmacokinetics of carbamazepine.

Clinical evidence, mechanism, importance and management

A single 400-mg dose of carbamazepine was given to 9 patients with cardiac disease (premature ventricular contractions, supraventricular tachycardia, sinus arrhythmia) before and after they took amiodarone 200 mg twice daily for a month. The pharmacokinetics of carbamazepine were found to be unchanged by amiodarone. This suggests that no clinically important interaction occurs, but it needs confirmation in patients who are given both drugs long term. Furthermore, the authors postulate that a higher amiodarone dose may inhibit the metabolism of the carbamazepine by the liver,[1] this also needs confirmation.

1. Leite SAO, Leite PJM, Rocha GA, Routledge PA, Bittencourt PRM. Carbamazepine kinetics in cardiac patients before and during amiodarone. *Arq Neuropsiquiatr* (1994) 52, 210–15.

Carbamazepine + Aspirin or NSAIDs

Carbamazepine levels are unaffected by aspirin or tolfenamic acid.

Clinical evidence, mechanism, importance and management

The carbamazepine levels of 10 patients were unaffected when they took aspirin 1.5 g daily for 3 days.[1] Similarly, the carbamazepine levels of 11 patients were not significantly affected by tolfenamic acid 300 mg, given for 3 days. It would appear that no carbamazepine dose adjustments are necessary in patients also given aspirin or tolfenamic acid.

1. Neuvonen PJ, Lehtovaara R, Bardy A, Elomaa E. Antipyretic analgesics in patients on antiepileptic drug therapy. *Eur J Clin Pharmacol* (1979) 15, 263–8.

Carbamazepine + Azoles

Ketoconazole causes a small to moderate rise in serum carbamazepine levels. Case reports describe a marked rise in carbamazepine levels in patients taking fluconazole; sometimes accompanied by toxicity. Adverse effects were seen in another patient when carbamazepine was given with miconazole. Carbamazepine may markedly reduce the levels of itraconazole, and is predicted to lower the levels of posaconazole and voriconazole.

Clinical evidence

(a) Fluconazole

A 33-year-old man whose seizures were stabilised by carbamazepine became extremely lethargic after taking fluconazole 150 mg daily for 3 days. His carbamazepine level was found to have risen from 11.1 micrograms/mL to 24.5 micrograms/mL. Symptoms resolved when both drugs were stopped, and carbamazepine was later re-introduced without problem.[1] Another patient, treated with carbamazepine, lamotrigine and barbexaclone for many years, developed blurred vision and dizziness when she took fluconazole 150 mg with her morning dose of antiepileptics. The symptoms worsened over 11 days of fluconazole treatment during which she complained of severe diplopia, oscillopsia, nausea, vomiting and gait instability and levels of carbamazepine were found to have more than doubled. Twenty-four hours after fluconazole withdrawal, carbamazepine levels returned to normal and the symptoms resolved. Lamotrigine and **barbexaclone** levels were not significantly affected by concurrent fluconazole.[2] Another well-documented case report describes a threefold increase in carbamazepine levels (without any signs of toxicity) 10 days after fluconazole 400 mg daily was started.[3]

(b) Itraconazole

A patient taking itraconazole 200 mg daily was noted to have low itraconazole levels (0.15 mg/L) about 14 days after starting carbamazepine 400 mg daily; about 2 months later itraconazole was undetectable. About 3 weeks after stopping carbamazepine, the itraconazole levels had reached the reference range (0.36 mg/L).[4]

For mention of 2 patients taking carbamazepine with phenytoin, who had undetectable or very low itraconazole levels, and who relapsed or did not respond to itraconazole, see 'Phenytoin + Azoles', p.630.

(c) Ketoconazole

A study in 8 patients with epilepsy taking carbamazepine found that oral ketoconazole 200 mg daily for 10 days increased their serum carbamazepine levels by 29% (from 5.6 micrograms/mL to 7.2 micrograms/mL) without affecting carbamazepine-10,11-epoxide levels. When the ketoconazole was stopped the serum carbamazepine levels returned to their former levels.[5]

(d) Miconazole

A patient receiving long-term treatment with carbamazepine 400 mg daily developed malaise, myoclonia and tremor within 3 days of being given oral miconazole 1.125 g. The same reaction occurred on each subsequent occasion that miconazole was given. These toxic effects disappeared when miconazole was withdrawn.[6]

Mechanism

Carbamazepine levels are thought to rise because azole antifungals inhibit the cytochrome P450 isoenzyme CYP3A4, which is concerned with the metabolism of carbamazepine. Different azoles affect CYP3A4 to varying degrees, see 'azole antifungals', (p.233). Carbamazepine is an enzyme inducer, and appears to decrease the levels of azole antifungals by increasing their metabolism.

Importance and management

Evidence for these interactions is limited and in some cases the effects are only modest. Nevertheless, it would seem prudent to monitor the outcome of adding azole antifungals to established carbamazepine treatment, being alert for any evidence of increased carbamazepine adverse effects (e.g. nausea, vomiting, ataxia and drowsiness).

Note also that carbamazepine may reduce the levels of azole antifungals: a marked reduction in itraconazole levels has been reported, and one manufacturer of itraconazole consequently says that the concurrent use of carbamazepine is not recommended.[7] Based on the interaction with 'phenytoin', (p.630), which results in reduced **posaconazole** levels, the manufacturer of posaconazole suggests that concurrent use of carbamazepine should be avoided, unless the benefits outweigh the risks.[8] If both drugs are given it would seem sensible to consider increasing the posaconazole dose, and increase monitoring of carbamazepine levels. Similarly, the manufacturers of **voriconazole** contraindicate the concurrent use of carbamazepine.[9,10]

1. Nair DR, Morris HH. Potential fluconazole-induced carbamazepine toxicity. *Ann Pharmacother* (1999) 33, 790–2.
2. Ulivelli M, Rubegni P, Nuti D, Bartalini S, Giannini F, Rossi S. Clinical evidence of fluconazole-induced carbamazepine toxicity. *J Neurol* (2004) 251, 622–3.
3. Finch CK, Green CA, Self TH. Fluconazole-carbamazepine interaction. *South Med J* (2002) 95, 1099–1100.
4. Bonay M, Jonville-Bera AP, Diot P, Lemarie E, Lavandier M, Autret E. Possible interaction between phenobarbital, carbamazepine and itraconazole. *Drug Safety* (1993) 9, 309–11.
5. Spina E, Arena D, Scordo MG, Fazio A, Pisani F, Perucca E. Elevation of plasma carbamazepine concentrations by ketoconazole in patients with epilepsy. *Ther Drug Monit* (1997) 19, 535–8.
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Carbamazepine + Bile-acid binding resins

In a study in 6 healthy subjects, colestyramine 8 g did not affect the absorption of carbamazepine 400 mg, whereas colestipol 10 g reduced it by 10%. Both colestyramine and colestipol were given as a single dose 5 minutes after the carbamazepine.[1] This small reduction is unlikely to be clinically important.

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Carbamazepine or Oxcarbazepine + Calcium-channel blockers

Both diltiazem and verapamil can increase carbamazepine levels causing toxicity. A single case report describes neurological toxicity in a patient taking phenytoin and carbamazepine with isradipine. Limited evidence suggests that amlodipine and nifedipine do not affect carbamazepine levels.

The plasma levels of felodipine, nifedipine, nilvadipine, and nimodipine are reduced by carbamazepine. Felodipine levels are slightly reduced by oxcarbazepine.

Clinical evidence

(a) Diltiazem

An patient with epilepsy taking carbamazepine 400 mg in the morning and 600 mg in the evening developed symptoms of toxicity (dizziness, nausea, ataxia and diplopia) within 2 days of starting to take diltiazem 60 mg three times daily. His serum carbamazepine levels had risen by about 40% to 21 micrograms/mL, but fell again when the diltiazem was stopped. No interaction occurred when the diltiazem was replaced by **nifedipine** 20 mg three times daily.[1] Other case reports describe carbamazepine toxicity and a rise in serum levels of up to fourfold in a total of 11 patients given diltiazem.[2-7] One patient required a 62% reduction in the carbamazepine dose.[2] Another patient had a marked fall in serum carbamazepine levels of 54% when diltiazem was *stopped*.[8]

For a further case report involving diltiazem, see *Nifedipine*, below.

(b) Felodipine

After taking felodipine 10 mg daily for 4 days, 10 patients with epilepsy (including 4 taking carbamazepine alone and 3 taking carbamazepine with phenytoin) had markedly reduced plasma felodipine levels (peak levels of 1.6 nanomol/L compared with 8.9 nanomol/L in 12 control subjects). The felodipine bioavailability was reduced to 6.6%.[9] A study in 8 subjects found that the AUC of felodipine was reduced by only 28% by oxcarbazepine 600 to 900 mg daily for a week.[10]

(c) Isradipine

A man taking carbamazepine and phenytoin developed neurological toxicity while taking isradipine, which was attributed to an interaction between the phenytoin and isradipine.[11] However, although carbamazepine levels remained within normal limits, a commentator suggested that an interaction between carbamazepine and isradipine was plausible.[12]

(d) Nifedipine

In 12 patients with epilepsy, nifedipine 20 mg twice daily for 2 weeks did not affect the steady-state carbamazepine levels.[13] Similarly, a retrospective study of 5 patients suggested that nifedipine does not usually raise carbamazepine levels or cause toxicity.[4] However, a man had a marked rise in serum carbamazepine levels when nifedipine was replaced by **diltiazem**. When **diltiazem** was replaced by **amlodipine**, his carbamazepine levels returned to normal, suggesting that neither nifedipine nor **amlodipine** interact with carbamazepine.[14] Another patient had no change in carbamazepine levels when also given nifedipine.[1]

A study in 12 patients with epilepsy receiving long-term treatment with carbamazepine found that the AUC of concurrent nifedipine 20 mg was only 22% of the values seen in 12 healthy subjects not taking carbamazepine.[13]

(e) Nilvadipine

A 59-year-old man taking nilvadipine 8 mg daily for hypertension and haloperidol for psychotic symptoms was given carbamazepine because haloperidol alone did not control symptoms of mania. The carbamazepine dose was gradually increased from 100 mg to 600 mg daily. Although the manic symptoms were improved, his blood pressure rose to 230/140 mmHg after 3 days of treatment with carbamazepine 600 mg daily. Blood pressure was temporarily controlled by **nifedipine** 10 mg sublingually. Retrospective analyses found that plasma levels of nilvadipine were reduced during the use of carbamazepine 100 and 300 mg daily and undetectable when the carbamazepine dose was increased to 600 mg daily. Plasma levels of nilvadipine rose after carbamazepine was discontinued and blood pressure returned to normal after about 2 weeks.[15]

(f) Nimodipine

A study in 8 patients with epilepsy receiving long-term treatment (including 2 taking carbamazepine with phenobarbital, one taking carbamazepine with clobazam, and one taking carbamazepine with phenytoin) found that the AUC of a single 60-mg oral dose of nimodipine was only about 15% of that achieved in a group of healthy subjects,[16] suggesting that carbamazepine lowers nimodipine exposure.

(g) Verapamil

Carbamazepine toxicity developed in 6 patients with epilepsy within 36 to 96 hours of them starting to take verapamil 120 mg three times daily. The symptoms disappeared when the verapamil was withdrawn. Total carbamazepine plasma levels had risen by 46% (a 33% rise in free plasma carbamazepine levels). Rechallenge of two of the patients, who only experienced mild toxicity with a lower dose of verapamil 120 mg twice a day, caused a similar rise in serum verapamil levels, again with mild toxicity. This report also describes another patient who had elevated serum carbamazepine levels while also taking verapamil.[17] Carbamazepine toxicity is described in 3 other patients, again caused by verapamil.[18,19] The verapamil was successfully replaced by **nifedipine** in one patient.[18]

In a study, 10 healthy subjects were given oxcarbazepine 450 mg twice

daily and then also verapamil 120 mg twice daily for 5 days. The AUC of the monohydroxy derivative of the oxcarbazepine (the active metabolite) fell by about 20% but oxcarbazepine levels were unaltered.[20]

Mechanism

It would appear that diltiazem and verapamil inhibit the metabolism of carbamazepine by the cytochrome P450 isoenzyme CYP3A4, thereby reducing its loss from the body and increasing serum levels. In contrast, carbamazepine is an enzyme inducer, which increases the metabolism of the calcium-channel blockers by the liver, resulting in a very rapid loss from the body.

Importance and management

Information about the effects of calcium-channel blockers on carbamazepine is limited, but what is known indicates that if carbamazepine is given with verapamil or diltiazem, the carbamazepine dose may possibly need to be reduced to avoid toxicity. A 50% reduction in the dose of carbamazepine has been suggested if diltiazem is to be used.[5] Nifedipine and amlodipine normally appear to be non-interacting alternatives. Oxcarbazepine appears to be a non-interacting alternative for carbamazepine.

Carbamazepine has been shown to lower the levels of a number of calcium-channel blockers. Given that the majority are metabolised by CYP3A4 (see 'calcium-channel blockers', (p.1025)) most calcium-channel blockers would be expected to interact similarly. If a calcium-channel blocker is given to a patient taking carbamazepine expect to need to use a larger dose. If carbamazepine is added to existing treatment with a calcium-channel blocker monitor the blood pressure and expect to need to increase the dose. Note that the manufacturer of nimodipine[21] contraindicates its use with carbamazepine. Oxcarbazepine interacts to a lesser extent than carbamazepine and it may therefore be a suitable alternative in some patients.

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Carbamazepine + Danazol

Serum carbamazepine levels can be doubled by danazol and carbamazepine toxicity may occur.

Clinical evidence

The serum carbamazepine levels of 6 patients with epilepsy approximately doubled within 7 to 30 days of taking danazol 400 to 600 mg daily. Acute carbamazepine toxicity (dizziness, drowsiness, blurred vision, ataxia, nausea) was experienced by 5 out of the 6 patients.[1]

Other reports similarly describe rises in serum carbamazepine levels of 50 to 100% (with toxicity seen in some instances) when danazol was given.[2-4]

Mechanism

Danazol inhibits the metabolism (by the epoxide-trans-diol pathway) of carbamazepine by the liver, thereby reducing its loss from the body.[2,5] During the use of danazol the clearance of carbamazepine has been found to be reduced by 60%.[2]

Importance and management

An established and clinically important interaction. If concurrent use is necessary carbamazepine serum levels should be monitored and the dose reduced as necessary.

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Carbamazepine + Dantrolene and Oxybutynin

Carbamazepine toxicity has been reported in a patient given oxybutynin and dantrolene.

Clinical evidence, mechanism, importance and management

A woman with incomplete tetraplegia who had taken carbamazepine 1 g daily for neuropathic pain for 2 years was given dantrolene in a gradually increasing dose and oxybutynin 5 mg twice daily. Two weeks after starting oxybutynin and while receiving dantrolene 125 mg daily, she experienced dizziness and vomiting, drowsiness, confusion, slurred speech, and nystagmus, and was found to have a raised carbamazepine level of 16 micrograms/mL. All drugs were stopped and the plasma carbamazepine level fell to 8.3 micrograms/mL (reference range 4 to 12 micrograms/mL). Because of pain, urinary frequency and spasticity, daily doses of carbamazepine 600 mg, oxybutynin 10 mg and dantrolene 100 mg were restarted, which resulted in a carbamazepine level of 9.2 micrograms/mL. The dantrolene dose was increased to 125 mg daily because of continuing spasticity, but after one day, symptoms of carbamazepine toxicity occurred and the carbamazepine plasma level was 29 micrograms/mL. Carbamazepine and oxybutynin were discontinued and the dantrolene dose was reduced to 25 mg. In order to relieve the patient's symptoms of pain and spasticity, carbamazepine 400 mg daily and dantrolene 25 mg daily were given (carbamazepine levels of 8.4 micrograms/mL at 7 days). The addition of oxybutynin 5 mg daily was associated with an increase in the carbamazepine level to 32 micrograms/mL and symptoms of toxicity. Carbamazepine was replaced by valproate 600 mg daily, which appeared to be beneficial and without an interaction with dantrolene or oxybutynin.[1]

Oxybutynin was being taken on each occasion when carbamazepine levels increased and therefore it was suggested that oxybutynin inhibited the metabolism of carbamazepine by the cytochrome P450 isoenzyme CYP3A4. Dantrolene was also being taken and the second episode of carbamazepine toxicity occurred after the dantrolene dose was increased. The exact mechanism of dantrolene metabolism is not known but it may decrease the activity of cytochrome P450 isoenzymes in a dose-dependent manner. However, there appears to be little evidence to suggest that these two drugs generally inhibit the metabolism of other drugs, and therefore the mechanism, and an interaction, is not established. The authors recommend careful monitoring and, if necessary, dose adjustments if carbamazepine is given with dantrolene and/or oxybutynin.[1]

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Carbamazepine + Dextromethorphan

Dextromethorphan appears not to affect the serum levels of carbamazepine.

Clinical evidence, mechanism, importance and management

A double-blind, crossover study in 5 patients with severe complex partial seizures found that dextromethorphan 120 mg daily in liquid form (*Delsym*) over 3 months had no effect on their serum carbamazepine levels. There was a non-significant alteration in the complex partial seizure and tonic-clonic seizure frequency.[1] No carbamazepine dose adjustment therefore appears necessary if dextromethorphan is also taken.

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Carbamazepine or Oxcarbazepine + Dextropropoxyphene (Propoxyphene)

Carbamazepine levels can be raised by dextropropoxyphene. Oxcarbazepine appears not to interact with dextropropoxyphene.

Clinical evidence

(a) Carbamazepine

The observation of toxicity (headache, dizziness, ataxia, nausea, tiredness) in patients taking both carbamazepine and dextropropoxyphene prompted further study. Five patients taking carbamazepine who were given dextropropoxyphene 65 mg three times daily had a mean rise in their serum carbamazepine levels of 65%, and 3 patients developed signs of carbamazepine toxicity. Carbamazepine levels were not taken in a further 2 patients because they withdrew from the study after 2 days of treatment due to adverse effects.[1,2] In a further study a 66% rise in carbamazepine levels was seen after 6 days of treatment with dextropropoxyphene.[3]

Carbamazepine toxicity due to this interaction has been reported elsewhere,[4-7] and rises in trough serum carbamazepine levels of 69% to 600% have been described.[8] A study in the elderly compared groups of patients taking either carbamazepine or dextropropoxyphene alone, with patients taking both drugs (21 subjects). The carbamazepine dose was about one-third lower in those taking both drugs, yet the mean serum carbamazepine levels were still 25% higher than in the patients not taking dextropropoxyphene. The prevalence of adverse effects was also higher in patients taking both drugs.[9]

(b) Oxcarbazepine

In a study in 7 patients with epilepsy or trigeminal neuralgia, dextropropoxyphene 65 mg three times daily for 7 days did not affect the steady-state levels of the active metabolite of oxcarbazepine.[10]

Mechanism

Uncertain. It is suggested that dextropropoxyphene inhibits the metabolism of carbamazepine by the liver, leading to its accumulation in the body.[1,2]

Importance and management

The interaction between carbamazepine and dextropropoxyphene is very well established and clinically important. If concurrent use is necessary reduce the dose of carbamazepine appropriately to prevent the development of toxicity. In many cases it may be simpler to use a non-interacting analgesic, although the occasional single dose of dextropropoxyphene probably does not matter. No special precautions seem necessary with oxcarbazepine.

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Carbamazepine or Oxcarbazepine + Diuretics

Hyponatraemia has been reported in patients taking carbamazepine with furosemide, hydrochlorothiazide, or hydrochlorothiazide and paroxetine. Hyponatraemia occurred in another patient taking oxcarbazepine and furosemide.

Clinical evidence, mechanism, importance and management

Two patients with epilepsy taking carbamazepine developed symptomatic hyponatraemia while also taking **hydrochlorothiazide** or **furosemide**.[1] Another case has been described when a patient taking carbamazepine also took **hydrochlorothiazide** and paroxetine.[2] A further case describes a patient taking **hydrochlorothiazide** who developed hyponatraemia within 2 weeks of starting to take carbamazepine 200 mg twice daily. Carbamazepine was continued but **hydrochlorothiazide** was stopped and sodium levels returned to normal within one week indicating that in this patient each drug appeared to be well tolerated alone.[3]

Another report describes a patient with a 20-year history of complex partial seizures treated with oxcarbazepine 1800 mg daily (30 mg/kg daily) who developed confusion, auditory and visual hallucinations and delirium about one month after starting to take **furosemide** 25 mg daily for hypertension. Sodium levels were found to have decreased from 138 mmol/L to 115 mmol/L with concurrent **furosemide** and an EEG showed abnormal activity compared to baseline values before she started **furosemide**. Oxcarbazepine and **furosemide** were stopped and valproic acid and amlodipine started, and within 20 days the neurological symptoms had stopped, the EEG normalised to baseline, and sodium levels increased to within the reference range.[4]

The reasons for the interaction between carbamazepine or oxcarbazepine and diuretics are uncertain but all these drugs can cause sodium to be lost from the body. This seems to be an uncommon interaction, but be aware that it can occur.

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Carbamazepine + Felbamate

Felbamate modestly reduces serum carbamazepine levels but increases the levels of the active metabolite, carbamazepine-10,11-epoxide. Carbamazepine may reduce felbamate levels.

Clinical evidence

The serum carbamazepine levels of 22 patients, with doses adjusted to keep levels in the range of 4 to 12 micrograms/mL, fell by 25% (range 10 to 42%) when they were given felbamate 3 g daily. The decrease occurred within a week, reaching a plateau after 2 to 4 weeks, and returning to the original levels within 2 to 3 weeks of stopping the felbamate.[1] Other studies in patients with epilepsy have found reductions in carbamazepine levels of between 18 and 31% when felbamate was given.[2-7] Some of these studies also found that the serum levels of the active carbamazepine metabolite carbamazepine-10,11-epoxide rose by 33 to 57%.[1,4,5]

Carbamazepine increases the clearance of felbamate by up to about 50%.[8-10]

Mechanism

Not established. Felbamate does not induce the metabolism of carbamazepine by the cytochrome P450 isoenzyme CYP3A4, but it does appear to alter the interaction of carbamazepine with CYP3A4.[11]

Importance and management

This interaction is established, but its clinical importance is uncertain because the modest fall in serum carbamazepine levels would seem to be offset by the rise in the levels of its metabolite, carbamazepine-10,11-epoxide, which also has antiepileptic activity. However, be alert for any changes in the antiepileptic control and consider monitoring carbamazepine levels, adjusting the dose as necessary. The importance of the increased felbamate clearance is uncertain. More study is needed.

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Carbamazepine + Gemfibrozil

Two patients had a rise in their carbamazepine levels after they took gemfibrozil.

Clinical evidence, mechanism, importance and management

Two patients, stable taking carbamazepine, had rises in their serum carbamazepine levels when they were given gemfibrozil for type IV hyperlipoproteinaemia. One patient had a rise of about 30% (from 8.8 micrograms/mL to 11.4 micrograms/mL) within 4 days of starting to take gemfibrozil 300 mg daily, and the other patient had a rise of 65% (from 8.3 micrograms/mL to 13.7 micrograms/mL) three months after gemfibrozil 300 mg twice daily was started.[1] It was suggested that the clearance of carbamazepine is increased in those with elevated cholesterol and total lipids. Thus, when the condition is treated with gemfibrozil, the clearance becomes more normal, which results in a rise in the serum carbamazepine levels.[2] These appear to be the only reports of an interaction, and their clinical importance is uncertain, but consider the possibility of an interaction if carbamazepine toxicity (nausea, vomiting, ataxia and drowsiness) develops in a patient given gemfibrozil.

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Carbamazepine + Grapefruit juice

Grapefruit juice increases carbamazepine levels. A case of possible carbamazepine toxicity has been seen when a man taking carbamazepine started to eat grapefruit.

Clinical evidence

A 58-year-old man, taking carbamazepine 1 g daily for epilepsy, developed visual disturbances with diplopia, and was found to have a carbamazepine level of 11 micrograms/mL (reference range 4 to 10 micrograms/mL). Previous levels had not exceeded 5.4 micrograms/mL. The patient said that one month previously he had started to eat one whole grapefruit each day. The levels restabilised at 5.1 micrograms/mL after the carbamazepine dose was reduced to 800 mg daily.[1]

A randomised, crossover study in 10 patients with epilepsy taking carbamazepine 200 mg three times daily found that a single 300-mL drink of grapefruit juice increased the plasma levels and AUC of carbamazepine by about 40%.[2]

Mechanism

The cytochrome P450 isoenzyme CYP3A4 is the main enzyme involved in the metabolism of carbamazepine.[3] Components of whole grapefruit and grapefruit juice are known to inhibit CYP3A4, which could lead to a reduction in the metabolism of carbamazepine, and therefore an increase in its levels.[1,2,4]

Importance and management

Although the information is sparse, the interaction has been predicted, demonstrated in a study, and has also occurred in practice. The authors of the study[2] suggest that grapefruit juice should be avoided in patients taking carbamazepine. In the case report,[1] the patient continued to eat grapefruit, and this was successfully managed by a reduction in the carbamazepine dose. However, it should be noted that intake of a set amount of grapefruit would need to be maintained for this approach to have a chance of working, and even then, the natural variability in the constituents of grapefruit may make adequate control difficult. The manufacturers advise carbamazepine dose adjustment and monitoring of carbamazepine levels in patients taking substances that may raise carbamazepine levels, such as grapefruit juice.[3] If monitoring is not practical, or regular intake of grapefruit is not desired, it would seem prudent to avoid grapefruit and grapefruit juice.

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Carbamazepine or Oxcarbazepine + H_2-receptor antagonists

The serum levels of those taking long-term carbamazepine may transiently increase, possibly accompanied by an increase in adverse effects, for the first few days after starting to take cimetidine, but these adverse effects rapidly disappear. Cimetidine does not appear to have this effect on oxcarbazepine levels. Ranitidine appears not to interact with carbamazepine.

Clinical evidence

(a) Carbamazepine

The steady-state carbamazepine levels of 8 healthy subjects taking carbamazepine 300 mg twice daily were increased by 17% within 2 days of them starting to take **cimetidine** 400 mg three times daily. Adverse effects occurred in 6 subjects, but after 7 days of treatment the carbamazepine levels had fallen again and the adverse effects disappeared.[1]

Conversely, the steady-state carbamazepine levels of 7 epileptic patients receiving long-term treatment remained unaltered when they were given **cimetidine** 1 g daily for a week.[2] Another study also found a lack of an interaction in 11 patients with epilepsy.[3] However, an 89-year-old woman taking carbamazepine 600 mg daily developed symptoms of carbamazepine toxicity within 2 days of starting to take **cimetidine** 400 mg daily, and had a rise in serum carbamazepine levels, which fell when the **cimetidine** was withdrawn.[4] The effects of **cimetidine** may be additive with those of isoniazid, see 'Carbamazepine + Isoniazid or Rifampicin (Rifampin)', p.605.

The results of these studies in patients and subjects taking carbamazepine long-term differ from single-dose studies and short-term stud-

ies in healthy subjects. For example, a 20% fall in clearance[5] and a 26% increase in the AUC[6] have been reported, which would indicate that there may be some potential for a clinically significant interaction (see 'Mechanism' below).

In 8 healthy subjects **ranitidine** 300 mg daily did not affect the pharmacokinetics of a single 600-mg dose of carbamazepine.[7]

(b) Oxcarbazepine

In 8 healthy subjects, **cimetidine** 400 mg twice daily for 7 days did not affect the pharmacokinetics of a single 600-mg oral dose of oxcarbazepine.[8]

Mechanism

Not fully understood. It is thought that cimetidine can inhibit the activity of the liver enzymes concerned with the metabolism of carbamazepine (such as the cytochrome P450 isoenzyme CYP3A4), resulting in its reduced clearance from the body. The auto-inducing effects of carbamazepine oppose this, although one study suggests the autoinducing effects of carbamazepine are blocked by cimetidine.[9] However, autoinduction would possibly explain why the single-dose and short-term studies in healthy subjects suggest that a clinically important interaction could occur, but in practice the combination causes few problems in patients receiving long-term carbamazepine.

Importance and management

The interaction between carbamazepine and cimetidine is established but of minimal importance. Patients receiving long-term treatment with carbamazepine should be warned that for the first few days after starting to take cimetidine they may possibly experience some increase in carbamazepine adverse effects (nausea, headache, dizziness, fatigue, drowsiness, ataxia, an inability to concentrate, a bitter taste). However, because the serum levels are only transiently increased, these effects should subside and disappear by the end of a week. Ranitidine appears to be a non-interacting alternative to cimetidine.

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Carbamazepine + Influenza vaccines

Influenza vaccination appears to raise carbamazepine levels. In one case this resulted in carbamazepine toxicity.

Clinical evidence, mechanism, importance and management

The serum carbamazepine levels of 20 children rose by 47% from 6.17 micrograms/mL to 9.04 micrograms/mL 14 days after they were given 0.5 mL of influenza vaccine USP, types A and B, whole virus (Squibb). Levels remained elevated on day 28.[1] A teenager taking carbamazepine 400 mg in the morning and 600 mg at night with gabapentin 600 mg three times daily developed signs of carbamazepine toxicity (unsteady, lethargic, slurred speech) 13 days after she was given an influenza vaccination (*Fluzone*, Aventis Pasteur). Her serum carbamazepine level was 27.5 micrograms/mL (previous levels 8.2 to 12.4 micrograms/mL), and she required ventilation for 19 hours. A urine drug screen was positive for tricyclic antidepressants and cocaine, but it was eventually concluded that these were likely to represent false-positive results.[2]

It has been suggested that the vaccine inhibits the liver enzymes concerned with the metabolism of carbamazepine, and therefore raises its levels. The moderate increase in serum carbamazepine levels seen in the first study is unlikely to have much clinical relevance as the vaccine is usually given as a single dose and therefore levels will decline over time. However, the case report of markedly increased carbamazepine levels introduces a note of caution.

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Carbamazepine + Isoniazid or Rifampicin (Rifampin)

Carbamazepine levels are markedly and very rapidly increased by isoniazid and toxicity can occur. Rifampicin has been reported both to augment and negate this interaction. There is evidence to suggest that carbamazepine may potentiate isoniazid hepatotoxicity.

Clinical evidence

Disorientation, listlessness, aggression, lethargy and, in one case, extreme drowsiness developed in 10 out of 13 patients taking carbamazepine when they were given isoniazid 200 mg daily. Serum carbamazepine levels were measured in 3 of the patients and they were found to have risen above the reference range (initial level not stated).[1]

Carbamazepine toxicity, associated with marked rises in serum carbamazepine levels, has been described in other reports.[2-5] Some of the patients were also taking sodium valproate, which does not seem to be implicated in the interaction, and in one case cimetidine (see also 'Carbamazepine or Oxcarbazepine + H_2-receptor antagonists', p.604) was thought to have potentiated the interaction.[5]

One report describes carbamazepine toxicity in a patient given isoniazid, but only when rifampicin was present as well. Usually the enzyme-inducing effects of rifampicin would be expected to counteract any enzyme inhibition by isoniazid, so this report is somewhat inexplicable.[6] Conversely, a case report describes reduced carbamazepine levels in a woman given rifampicin and isoniazid, which resulted in reduced carbamazepine efficacy (symptoms of hypomania).[7]

Isoniazid-induced fulminant liver failure occurred in a 16-year-old girl taking carbamazepine and clonazepam, within 5 days of starting isoniazid, rifampicin and pyrazinamide. She recovered with supportive measures and later tolerated the antiepileptics with concurrent rifampicin and pyrazinamide.[8] Isoniazid hepatotoxicity has also occurred in a 74-year-old woman[9] and a 10-year-old boy[10] taking carbamazepine, shortly after treatment with isoniazid, rifampicin, and ethambutol, with or without pyrazinamide, was started.

Mechanism

Unknown. It has been suggested that isoniazid inhibits the activity of the cytochrome P450 isoenzyme CYP3A4, which is concerned with the metabolism of carbamazepine, causing it to accumulate in the body;[11] however, isoniazid does not usually cause clinically relevant interactions by this mechanism. Rifampicin is a potent enzyme inducer, and would be expected to negate the effects of isoniazid, and to induce the metabolism of carbamazepine. This is supported by one report, but not another.

Importance and management

The documentation is limited, but a clinically important and potentially serious interaction is established between isoniazid and carbamazepine. Toxicity can develop quickly (within 1 to 5 days) and also seems to disappear quickly if the isoniazid is withdrawn. Concurrent use should not be undertaken unless the effects can be closely monitored and suitable downward dose adjustments made (a carbamazepine dose reduction of between one-half and two-thirds was effective in 3 patients[1]). It seems probable that slow metabolisers of isoniazid may develop this interaction more quickly and to a greater extent than fast metabolisers.[2]

The effect of concurrent rifampicin on the interaction between isoniazid and carbamazepine is unclear. One report showed negation of the interaction, whereas another showed potential augmentation.

Limited evidence suggests that carbamazepine may potentiate isoniazid

hepatotoxicity; routine isoniazid monitoring should be adequate to detect any interaction.

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Carbamazepine + Lamotrigine

Most studies have found that lamotrigine has no effect on the pharmacokinetics of carbamazepine or its metabolite, carbamazepine-10,11-epoxide. However, some studies have found that lamotrigine raises the serum levels of carbamazepine-10,11-epoxide. Carbamazepine reduces lamotrigine levels. Symptoms of toxicity have been seen irrespective of changes in levels.

Clinical evidence

(a) Effects on carbamazepine

In 3 patients with epilepsy, the addition of lamotrigine increased the serum levels of carbamazepine-10,11-epoxide, the active metabolite of carbamazepine, but carbamazepine levels remained unchanged. One of the patients had carbamazepine-10,11-epoxide serum levels of 2 to 2.2 micrograms/mL while taking carbamazepine 1.1 g daily. The levels rose to 4.7 to 8.7 micrograms/mL when lamotrigine was added. Symptoms of toxicity occurred in 2 patients (dizziness, double vision, sleepiness, nausea).[1]

In another study in 9 patients, the addition of lamotrigine 200 mg increased the mean serum carbamazepine-10,11-epoxide levels by 45%. Toxicity was seen in 4 patients (dizziness, nausea, diplopia).[2] The addition of lamotrigine resulted in cerebellar toxicity (nausea, vertigo, nystagmus, ataxia) in 8 out of 9 patients taking subtoxic and just-tolerated doses of carbamazepine when lamotrigine was added. Analysis showed that in all 8 cases at least one of the levels of carbamazepine, carbamazepine-10,11-epoxide or lamotrigine had become unusually high.[3]

In contrast other studies have found that the concurrent use of lamotrigine and carbamazepine does not result in any clinically significant pharmacokinetic changes. Lamotrigine caused no changes in carbamazepine levels[4-8] or carbamazepine-10,11-epoxide levels in several studies[6,7,9] However, in one study 9 of 47 subjects developed diplopia or dizziness, predominantly in those whose carbamazepine levels were already high before the lamotrigine was added.[6] In another study in 14 children, lamotrigine had no effect on mean carbamazepine levels, and actually decreased mean carbamazepine-10,11-epoxide levels by 23%. Two children developed diplopia, which was unrelated to drug levels, but responded to a reduction in the lamotrigine dose in one, and a reduction in the carbamazepine dose in the other.[10]

(b) Effects on lamotrigine

In a retrospective study, the lamotrigine serum concentration to dose ratio was much lower in patients also taking carbamazepine than in those taking lamotrigine monotherapy (0.38 versus 0.84).[11] Other studies have reported similar findings.[12-14] In one of these studies, mean increases in lamotrigine levels of about 60% occurred in patients taking lamotrigine with carbamazepine when the carbamazepine was withdrawn.[14] Similarly, a case report describes a rapid increase in lamotrigine levels when carbamazepine was withdrawn.[15] A review of patients taking antiepileptics found that carbamazepine increased the clearance of lamotrigine by 30 to 50%.[16]

Mechanism

One suggestion to account for the toxic symptoms seen in some patients is that an interaction occurs at the site of action (a pharmacodynamic interaction) rather than because lamotrigine increases the carbamazepine-10,11-epoxide serum levels.[3,6] Carbamazepine may induce the glucuronidation of lamotrigine.

Importance and management

Overall lamotrigine does not appear to significantly alter carbamazepine levels. However, toxicity has occurred, and therefore patients should be well monitored if lamotrigine is added, and the carbamazepine dose reduced if CNS adverse effects occur. In one case, reducing the dose of lamotrigine was effective.

Carbamazepine induces the metabolism of lamotrigine, and the recommended starting dose and long-term maintenance dose of lamotrigine in patients already taking carbamazepine is twice that of patients taking lamotrigine monotherapy.[17,18] However, if patients are also taking valproate in addition to carbamazepine, the lamotrigine dose should be reduced.[17,18] See 'Lamotrigine + Valproate', p.620.

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Carbamazepine + Loxapine

An increase in the serum levels of the epoxide metabolite of carbamazepine has been reported in patients given loxapine.

Clinical evidence, mechanism, importance and management

One patient taking loxapine 500 mg daily developed toxicity (ataxia, nausea, anxiety) when given carbamazepine 600 mg daily, even though the serum carbamazepine level was low to normal.[1] In another case, neurotoxicity (ataxia, lethargy, visual disturbances) developed in a man given carbamazepine and loxapine.[2] In both cases, the toxicity appeared to be due to elevated carbamazepine-10,11-epoxide levels (the metabolite of carbamazepine).[1,2] The problem resolved when the carbamazepine doses were reduced. The reasons for these effects are not understood, and evidence appears to be limited to the two cases cited. The general significance of these reports is therefore unclear. Consider the possibility of an interac-

tion if a patient taking carbamazepine and loxapine develops neurotoxic adverse effects.

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Carbamazepine + Macrolides

Carbamazepine levels are markedly and rapidly increased by clarithromycin, erythromycin or troleandomycin, and toxicity can often develop within 1 to 5 days. Telithromycin is predicted to interact similarly. Studies suggest that azithromycin, flurithromycin, josamycin, midecamycin, and roxithromycin have no interaction, or no clinically significant interaction, with carbamazepine, but note that a case of carbamazepine toxicity has been reported in a patient given roxithromycin.

Clinical evidence

(a) Azithromycin

In a study in healthy subjects, azithromycin 500 mg daily for 3 days had no effect on the pharmacokinetics of carbamazepine 200 mg twice daily or its active metabolite, carbamazepine-10,11-epoxide.[1]

(b) Clarithromycin

A pharmacokinetic study[2] in healthy subjects found that clarithromycin 500 mg every 12 hours for 5 days increased the AUC of a single 400-mg dose of carbamazepine by 26%. A retrospective study of 5 patients with epilepsy found that when they were given clarithromycin (dose not stated) their serum carbamazepine levels rose by 20 to 50% within 3 to 5 days, despite 30 to 40% reductions in the carbamazepine dose in 4 of them. Carbamazepine levels in the toxic range were seen in 3 of them, and their carbamazepine doses were then even further reduced.[3] A number of case reports have described carbamazepine toxicity following the addition of clarithromycin in adults,[4-7] and children.[7-9] Two other patients with epilepsy had marked rises in serum carbamazepine levels when they were given clarithromycin 500 mg three times daily and omeprazole.[10] It is not clear whether the omeprazole also had some part to play.[11,12] See also 'Carbamazepine + Proton pump inhibitors', p.610. One case report describes a patient taking carbamazepine 200 mg twice daily who developed hyponatraemia 4 days after the addition of clarithromycin 500 mg twice daily: the hyponatraemia resolved when the clarithromycin was stopped.[13]

(c) Erythromycin

An 8-year-old girl taking phenobarbital 50 mg and carbamazepine 800 mg daily was given 500 mg, then later 1 g of erythromycin daily. Within 2 days she began to experience balancing difficulties and ataxia, which were eventually attributed to carbamazepine toxicity. Her serum carbamazepine levels were found to have risen from a little below 10 micrograms/mL to over 25 micrograms/mL (reference range 2 to 10 micrograms/mL). The levels rapidly returned to normal after carbamazepine was withheld for 24 hours and the erythromycin stopped.[14]

A study in 7 healthy subjects confirmed that erythromycin can cause significant increases in carbamazepine levels,[15] and a study in 8 healthy subjects found that the clearance of carbamazepine is reduced by an average of 20% (range 5 to 41%) by erythromycin 1 g daily for 5 days.[16] Another study, in healthy subjects given erythromycin 500 mg three times daily for 10 days, found that the clearance of a single dose of carbamazepine was reduced by about 20% and the maximum serum levels of carbamazepine-10,11-epoxide were reduced by about 40% by erythromycin.[17]

Marked rises in serum carbamazepine levels (up to fivefold in some cases) and/or toxicity (including cases of hepatorenal failure and AV block as well as more typical signs of carbamazepine toxicity) have been described in over 30 cases involving both children and adults. Symptoms commonly began within 24 to 72 hours of starting erythromycin, although in some cases it was as early as 8 hours. In most cases toxicity resolved within 3 to 5 days of stopping the erythromycin.[8,18-36]

(d) Flurithromycin

In a study in healthy subjects, flurithromycin 500 mg three times daily for a week increased the AUC of a single 400-mg dose of carbamazepine by about 20% and moderately reduced the production of carbamazepine-10,11-epoxide.[37]

(e) Josamycin

In studies in healthy subjects and in patients, josamycin 1 g twice daily for a week reduced the clearance of carbamazepine by about 20%.[38-40]

(f) Midecamycin acetate

A single-dose study in 14 subjects found that after taking midecamycin acetate 800 mg twice daily for 8 days the AUC of a single 200-mg dose of carbamazepine was increased by 15%, and the AUC of its active metabolite, carbamazepine-10,11-epoxide, was reduced by 26%.[41] Another study in patients taking carbamazepine found that the addition of midecamycin acetate 600 mg twice daily caused a small increase in the trough serum levels of carbamazepine, and only a 12% increase in its AUC.[42]

(g) Roxithromycin

In a study in healthy subjects, roxithromycin 150 mg twice daily for 8 days did not affect the pharmacokinetics of a single 200-mg dose of carbamazepine.[43] However, an isolated report describes carbamazepine toxicity (levels increased to 21.7 mg/L) in a patient taking carbamazepine and atorvastatin the day after she started to take roxithromycin 150 mg twice daily. Roxithromycin and atorvastatin were stopped and the carbamazepine level fell to 12.5 mg/L within a day. The increased carbamazepine levels were attributed to the concurrent use of roxithromycin.[44]

(h) Troleandomycin

In 8 patients with epilepsy, symptoms of carbamazepine toxicity (dizziness, nausea, vomiting, excessive drowsiness) developed within 24 hours of them also starting to take troleandomycin. The 2 patients available for examination had a sharp rise in serum carbamazepine levels, from about 5 micrograms/mL to 28 micrograms/mL over 3 days, and a rapid fall following withdrawal of the troleandomycin.[45,46]

Another report by the same authors describes a total of 17 similar cases of carbamazepine toxicity caused by troleandomycin.[18] Some of the patients had three or fourfold increases in serum carbamazepine levels. Another case has been described elsewhere.[14] In most instances the serum carbamazepine levels returned to normal within about 3 to 5 days of withdrawing the macrolide.[18]

Mechanism

It seems probable that clarithromycin, erythromycin and troleandomycin, and to a lesser extent some of the other macrolides, slow the rate of metabolism of the carbamazepine by the cytochrome P450 isoenzyme CYP3A4 so that the antiepileptic accumulates within the body.[47,48] Telithromycin is predicted to interact similarly.[49] It was suggested that the carbamazepine toxicity seen with roxithromycin may have been mediated by P-glycoprotein inhibition, which occurred as a result of an interaction between roxithromycin and atorvastatin; however, roxithromycin is a modest CYP3A4 inhibitor, and so it seems possible that it may have interacted by this mechanism.

Importance and management

The interaction between carbamazepine and troleandomycin is established, clinically important and potentially serious. The incidence is high. The rapidity of its development (within 24 hours in some cases) and the extent of the rise in serum carbamazepine levels suggest that it would be difficult to control carbamazepine levels by reducing the dose. Concurrent use should probably be avoided.

The interaction between carbamazepine and erythromycin is also very well documented, well established and of clinical importance. Concurrent use should be avoided unless the effects can be very closely monitored by measurement of serum carbamazepine levels and suitable dose reductions made. Toxic symptoms (ataxia, vertigo, drowsiness, lethargy, confusion, diplopia) can develop within 24 hours, but serum carbamazepine levels can return to normal within 8 to 12 hours of withdrawing the antibacterial.[38] Similar precautions would seem prudent if **telithromycin** is given with carbamazepine. However, the manufacturer of telithromycin advises avoidance of the combination, and suggests that telithromycin should not be used within 2 weeks of stopping carbamazepine. They also suggest that the levels of the antibacterial may be reduced.[49]

The interaction between carbamazepine and clarithromycin is also established, clinically important and potentially serious. It has been recommended that the carbamazepine dose should be reduced by 30 to 50% during treatment with clarithromycin, with monitoring within 3 to 5 days,

and patients should be told to tell their doctor of any symptoms of toxicity (dizziness, diplopia, ataxia, mental confusion).

Analysis of the interactions between the macrolides and carbamazepine has shown that patients requiring high doses of carbamazepine to reach therapeutic levels are likely to have a greater rise in their carbamazepine levels.[50] The extent of the interactions is also correlated with the macrolide dose.[50]

Josamycin, flurithromycin, midecamycin acetate and roxithromycin appear to be safer alternatives to either clarithromycin, erythromycin, telithromycin or troleandomycin. Nevertheless a small or moderate reduction in the dose of carbamazepine may be needed, with subsequent good monitoring. Pharmacokinetic data suggest that azithromycin does not interact.

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Carbamazepine or Oxcarbazepine + MAOIs

Phenelzine, moclobemide and tranylcypromine appear not to interact adversely with carbamazepine, although both carbamazepine and oxcarbazepine are predicted to interact with the MAOIs.

Clinical evidence, mechanism, importance and management

There appear to be no reports of adverse reactions during the concurrent use of MAOIs and carbamazepine or oxcarbazepine. However, the manufacturers of carbamazepine[1] and oxcarbazepine[2] suggest that an interaction is possible because of the close structural similarity between carbamazepine and the tricyclic antidepressants (and therefore the theoretical risk of an adverse interaction). The UK manufacturer of carbamazepine[1] does not recommend concurrent use and suggests that MAOIs should be discontinued at least 2 weeks before carbamazepine is started. Several reports describe the successful use of carbamazepine and MAOIs, namely **tranylcypromine**,[3-5] **phenelzine**,[5,6] and **moclobemide**.[7] Bearing in mind that the MAOIs and the tricyclics can be given together under certain well controlled conditions (see 'MAOIs or RIMAs + Tricyclic and related antidepressants', p.1391), the warning about the risks may possibly prove to be over-cautious.

Note that, rarely, the MAOIs have been seen to cause convulsions and they should therefore be used cautiously in patients with epilepsy.

1. Tegretol (Carbamazepine). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, November 2009.
2. Trileptal (Oxcarbazepine). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, March 2009.
3. Lydiard RB, White D, Harvey B, Taylor A. Lack of pharmacokinetic interaction between tranylcypromine and carbamazepine. *J Clin Psychopharmacol* (1987) 7, 360.
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Carbamazepine + Metronidazole

Increased serum carbamazepine levels and toxicity have been seen in a patient given metronidazole.

Clinical evidence, mechanism, importance and management

A woman taking carbamazepine 1 g daily started taking co-trimoxazole twice daily and metronidazole 250 mg three times daily for diverticulitis. After 2 days the co-trimoxazole was stopped, she was changed to intravenous metronidazole 500 mg three times daily, and cefazolin 500 mg every 8 hours. After 2 days she complained of diplopia, dizziness and nausea, and her serum carbamazepine levels were found to have risen from 9 micrograms/mL to 14.3 micrograms/mL. A month later (presumably

after the metronidazole had been withdrawn) her serum carbamazepine levels had fallen to 7.1 micrograms/mL. The reasons for this reaction are not understood.[1]

This appears to be the only report of an interaction between carbamazepine and metronidazole, so its general importance is uncertain.

1. Patterson BD. Possible interaction between metronidazole and carbamazepine. *Ann Pharmacother* (1994) 28, 1303–4.

Carbamazepine + Nefazodone

Five patients developed elevated serum carbamazepine levels and toxicity when nefazodone was given. A study in healthy subjects using lower carbamazepine doses found only modest increases in carbamazepine levels, and no evidence of toxicity when nefazodone was given. Carbamazepine markedly reduces nefazodone levels.

Clinical evidence

A patient taking carbamazepine 1 g daily developed evidence of toxicity (light-headedness, ataxia) within 15 days of starting to take nefazodone (initially 100 mg twice daily increasing to 150 mg twice daily after a week). Her serum carbamazepine levels had risen from below 8.3 micrograms/mL up to 10.8 micrograms/mL. It was found necessary to reduce the carbamazepine dose to 600 mg daily to eliminate these adverse effects and to achieve a serum level of 7.4 micrograms/mL.[1] In 4 other patients taking carbamazepine 800 mg or 1 g daily the addition of nefazodone caused up to threefold rises in carbamazepine levels. The carbamazepine dose was reduced by 25 to 60%.[1,2] In a study in 12 healthy subjects, no evidence of toxicity was seen when carbamazepine 200 mg twice daily was given with nefazodone 200 mg twice daily for 5 days. However, the exposure to carbamazepine was slightly increased (23% increase in AUC) and the exposure to nefazodone markedly decreased (93% decrease in AUC). The authors suggest that there may be a greater effect with higher doses of carbamazepine.[3]

Mechanism

Both drugs are metabolised by the cytochrome P450 isoenzyme CYP3A4. Nefazodone is known to inhibit CYP3A4, whereas carbamazepine is a potent inducer of CYP3A4. Hence concurrent use reduces carbamazepine metabolism, leading to raised levels, and increases nefazodone metabolism, leading to lowered levels.

Importance and management

Information is limited, but it would seem prudent to monitor for signs of carbamazepine toxicity if nefazodone is added to established treatment, especially with doses of carbamazepine above 800 mg. The nefazodone dose may need to be increased in the presence of carbamazepine, so be alert for a reduced effect. Nefazodone has largely been withdrawn, but the US manufacturer of nefazodone did contraindicate its concurrent use with carbamazepine.[4]

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2. Roth L, Bertschy G. Nefazodone may inhibit the metabolism of carbamazepine: three case reports. *Eur Psychiatry* (2001) 16, 320–1.
3. Laroudie C, Salazar DE, Cosson J-P, Cheuvart B, Istin B, Girault J, Ingrand I, Decourt J-P. Carbamazepine-nefazodone interaction in healthy subjects. *J Clin Psychopharmacol* (2000) 20, 46–53.
4. Nefazodone hydrochloride. Watson Laboratories Inc. US Prescribing information, June 2004.

Carbamazepine + Phenobarbital

Carbamazepine levels are reduced to some extent by phenobarbital, whereas the levels of its active metabolite carbamazepine-10,11-epoxide are raised. In children, phenobarbital clearance is decreased by carbamazepine.

Clinical evidence

A comparative study found that, on average, patients taking both carbamazepine and phenobarbital (44 patients) had carbamazepine serum levels that were 18% lower than those taking carbamazepine alone (43 patients).[1] Similar results were found in other studies in both adult and paediatric patients taking both drugs.[2-5] Levels of the active metabolite, carbamazepine-10,11-epoxide, were increased.[3-6] However, one study found that, after a single dose of carbamazepine, the clearance of carbamazepine-10,11-epoxide was higher and its plasma half-life shorter in patients with epilepsy taking phenobarbital, when compared with healthy subjects not taking phenobarbital.[7]

In a prospective study, the clearance of phenobarbital in 222 patients receiving monotherapy was compared with that in 63 patients who were also taking carbamazepine. The clearance of carbamazepine was found to be decreased by phenobarbital. Further, the effects of carbamazepine on phenobarbital clearance were maximal in young children (about 54%) and minimal in adults.[8]

Mechanism

Phenobarbital and carbamazepine are both known enzyme inducers, and may therefore increase each others metabolism. Phenobarbital may also induce the metabolism of carbamazepine-10,11-epoxide.[7]

Importance and management

An established interaction. It would be prudent to monitor phenobarbital levels in children also given carbamazepine, as changes in clearance may affect dose requirements. The small fall in serum carbamazepine levels probably has little practical importance, especially as the metabolite carbamazepine-10,11-epoxide also has antiepileptic activity. Consider also 'Carbamazepine + Primidone', below.

1. Christiansen J, Dam M. Influence of phenobarbital and diphenylhydantoin on plasma carbamazepine levels in patients with epilepsy. *Acta Neurol Scand* (1973) 49, 543–6.
2. Cereghino JJ, Brock JT, Van Meter JC, Penry JK, Smith LD, White BG. The efficacy of carbamazepine combinations in epilepsy. *Clin Pharmacol Ther* (1975) 18, 733–41.
3. Rane A, Höjer B, Wilson JT. Kinetics of carbamazepine and its 10,11-epoxide metabolite in children. *Clin Pharmacol Ther* (1976) 19, 276–83.
4. Rambeck B, May T, Juergens U. Serum concentrations of carbamazepine and its epoxide and diol metabolites in epileptic patients: the influence of dose and comedication. *Ther Drug Monit* (1987) 9, 298–303.
5. Liu H, Delgado MR. Interactions of phenobarbital and phenytoin with carbamazepine and its metabolites' concentrations, concentration ratios, and level/dose ratios in epileptic children. *Epilepsia* (1995) 36, 249–54.
6. Dam M, Jensen A, Christiansen J. Plasma level and effect of carbamazepine in grand mal and psychomotor epilepsy. *Acta Neurol Scand* (1975) 75 (Suppl 51), 33–8.
7. Spina E, Martines C, Fazio A, Trio R, Pisani F, Tomson T. Effect of phenobarbital on the pharmacokinetics of carbamazepine-10,11-epoxide, an active metabolite of carbamazepine. *Ther Drug Monit* (1991) 13, 109–12.
8. Yukawa E, To H, Ohdo S, Higuchi S, Aoyama T. Detection of a drug-drug interaction on population-based phenobarbitone clearance using nonlinear mixed-effects modelling. *Eur J Clin Pharmacol* (1998) 54, 69–74.

Carbamazepine + Primidone

A single case report suggests that primidone can reduce the effects of carbamazepine. Other evidence suggests that carbamazepine may reduce primidone serum levels and increase primidone-derived phenobarbital levels.

Clinical evidence

A 15-year-old boy had complex partial seizures that were not controlled despite treatment with primidone 12 mg/kg daily and carbamazepine 10 mg/kg daily, both in three divided doses. Even when the carbamazepine dose was increased to 20 mg/kg daily and then 30 mg/kg daily his serum carbamazepine levels only reached 4.8 micrograms/mL, and his seizures continued. When the primidone was gradually withdrawn his serum carbamazepine levels increased to 12 micrograms/mL and his seizures completely disappeared.[1]

An analysis of the serum levels of antiepileptic drugs in children found that the serum levels of primidone tended to be lower in those also taking carbamazepine, but no details were given.[2] Another study found that the levels of phenobarbital derived from primidone were 42 micrograms/mL in patients taking primidone, carbamazepine and phenytoin, 24.7 micrograms/mL in patients taking phenytoin and primidone, and just 9.9 micrograms/mL in patients taking primidone alone.[3] A further study found that primidone levels were lower in patients also taking carbamazepine, but there were no significant changes in primidone-derived phenobarbital levels. Carbamazepine-10,11-epoxide levels were increased by primidone.[4] In a retrospective study, the plasma level to dose ratio for primidone was lower in patients also taking carbamazepine than

in those taking primidone alone, and the primidone-derived phenobarbital levels were higher.[5]

Mechanism

When primidone was stopped in the single case cited, the clearance of carbamazepine decreased by about 60%.[1] This is consistent with the known enzyme-inducing effects of primidone (converted in the body to phenobarbital), which can increase the metabolism of other drugs by the liver. There is some evidence to suggest that carbamazepine may increase the metabolism of primidone to phenobarbital.

Importance and management

Direct information seems to be limited to these reports. It may be prudent to monitor combined treatment, and adjust the antiepileptic doses if necessary. Consider also 'Carbamazepine + Phenobarbital', p.609.

1. Benetello P, Furlanut M. Primidone-carbamazepine interaction: clinical consequences. *Int J Clin Pharmacol Res* (1987) 7, 165–8.
2. Windorfer A, Sauer W. Drug interactions during anticonvulsant therapy in childhood: diphenylhydantoin, primidone, phenobarbitone, clonazepam, nitrazepam, carbamazepin and dipropylacetate. *Neuropadiatrie* (1977) 8, 29–41.
3. Callaghan N, Feeley M, Duggan F, O'Callaghan M, Seldrup J. The effect of anticonvulsant drugs which induce liver microsomal enzymes on derived and ingested phenobarbitone levels. *Acta Neurol Scand* (1977) 56, 1–6.
4. Callaghan N, Duggan B, O'Hare J, O'Driscoll D. Serum levels of phenobarbitone and phenylethylmalonamide with primidone used as a single drug and in combination with carbamazepine or phenytoin. In Johannessen SI et al. Antiepileptic Therapy: Advances in Drug Monitoring. New York: Raven Press; 1980, 307–13.
5. Battino D, Avanzini G, Bossi L, Croci D, Cusi C, Gomeni C, Moise A. Plasma levels of primidone and its metabolite phenobarbital: effect of age and associated therapy. *Ther Drug Monit* (1983) 5, 73–9.

Carbamazepine + Probenecid

Probenecid appears to increase the metabolism of carbamazepine to carbamazepine-10,11-epoxide.

Clinical evidence, mechanism, importance and management

In a placebo-controlled study, 10 healthy subjects were given probenecid 500 mg twice daily for 10 days with a single 200-mg dose of carbamazepine on day 6. The AUC of carbamazepine was decreased by about 19% and the AUC of carbamazepine-10,11-epoxide was increased by about 33%. Probenecid tended to decrease the formation of conjugated forms of both carbamazepine and its epoxide metabolite but this was not statistically significant. Probenecid increased the oral clearance of carbamazepine by 26%.

The increased metabolism of carbamazepine to carbamazepine-10,11-epoxide was thought to be due to induction of cytochrome P450 isoenzymes CYP3A4 and CYP2C8 by probenecid.[1] The clinical significance of the increase in levels of the active metabolite, carbamazepine-10,11-epoxide is unclear. This was a single-dose study, and it is known that following multiple doses, carbamazepine also induces its own metabolism by CYP3A4. The effect of carbamazepine on this isoenzyme would be expected to be much greater than any effect of probenecid, which does not usually cause clinically relevant interactions by this mechanism.

1. Kim K-A, Oh SO, Park P-W, Park J-Y. Effect of probenecid on the pharmacokinetics of carbamazepine in healthy subjects. *Eur J Clin Pharmacol* (2005) 61, 275–80.

Carbamazepine + Proton pump inhibitors

Omeprazole markedly raises the levels of a single dose of carbamazepine, but has no significant effect on the levels of carbamazepine taken long-term. Some anecdotal reports suggest that carbamazepine levels may possibly be reduced by lansoprazole. Pantoprazole did not affect the pharmacokinetics of carbamazepine in one study.

Clinical evidence

(a) Lansoprazole

In 2001 the manufacturers of lansoprazole had on record 5 undetailed case reports of apparent interactions between lansoprazole and carbamazepine. One of them describes the development of carbamazepine toxicity when lansoprazole was added, but there is some doubt about this case because it is thought that the patient may have started to take higher doses of carbamazepine.

The other 4 cases are consistent, in that carbamazepine levels fell shortly after lansoprazole was added and/or the control of seizures suddenly worsened. One patient had a fall in carbamazepine serum levels from 11.5 mg/mL to 7.7 mg/L. The carbamazepine levels of another patient returned to normal when the lansoprazole was stopped.[1]

(b) Omeprazole

In a study in 7 patients, omeprazole 20 mg daily for 14 days was found to increase the AUC of a single 400-mg dose of carbamazepine by 75%. The clearance of carbamazepine was reduced by 40% and its elimination half-life was more than doubled (from 17.2 to 37.3 hours).[2] In a study in 10 healthy subjects, omeprazole 20 mg twice daily for 14 days increased the AUC, peak plasma level and elimination half-life of a single 400-mg dose of sustained-release carbamazepine (*Mazetol*) by about 90%, 31%, and 57%, respectively.[3] However, a retrospective study of the records of 10 patients who had been taking omeprazole 20 mg daily with long-term carbamazepine (rather than a single dose) found a non-significant reduction in carbamazepine serum levels.[4]

(c) Pantoprazole

In healthy subjects, pantoprazole 40 mg daily for 5 days had no effect on the AUC of carbamazepine or its metabolite, carbamazepine-10,11-epoxide, after a single 400-mg dose of carbamazepine.[5]

Mechanism

Omeprazole may inhibit the oxidative metabolism of single doses of carbamazepine. However, when carbamazepine is taken continuously it induces its own metabolism by the cytochrome P450 isoenzyme CYP3A4, thereby possibly opposing the effects of this interaction.[4]

Importance and management

It seems that in practice no clinically relevant interaction is likely to occur between omeprazole and carbamazepine. For lansoprazole, information seems to be limited to this handful of reports from which no broad general conclusions can be drawn. Pantoprazole appears not to affect the pharmacokinetics of carbamazepine.

1. Wyeth (UK). Personal communication, September 2001.
2. Naidu MUR, Shoba J, Dixit VK, Kumar A, Kumar TR, Sekhar KR, Sekhar EC. Effect of multiple dose omeprazole on the pharmacokinetics of carbamazepine. *Drug Invest* (1994) 7, 8–12.
3. Dixit RK, Chawla AB, Kumar N, Garg SK. Effect of omeprazole on the pharmacokinetics of sustained-release carbamazepine in healthy male volunteers. *Methods Find Exp Clin Pharmacol* (2001) 23, 37–9.
4. Böttiger Y, Bertilsson L. No effect on plasma carbamazepine concentration with concomitant omeprazole treatment. *Drug Invest* (1995) 9, 180–1.
5. Huber R, Bliesath H, Hartmann M, Steinijans VW, Koch H, Mascher H, Wurst W. Pantoprazole does not interact with the pharmacokinetics of carbamazepine. *Int J Clin Pharmacol Ther* (1998) 36, 521–4.

Carbamazepine + Retinoids

An isolated report describes a patient who did not respond to etretinate until the carbamazepine she was taking was withdrawn. A study in one patient found that isotretinoin modestly reduced the plasma levels of both carbamazepine and its active metabolite.

Clinical evidence, mechanism, importance and management

(a) Etretinate

A girl taking carbamazepine and valproate and with pityriasis rubra pilaris did not respond to etretinate for a period of 2 months and had none of its characteristic mucocutaneous adverse effects. When the carbamazepine was withdrawn and the valproate dose increased, she had a good response to etretinate within 6 weeks. It was suggested that carbamazepine may have reduced the bioavailability or increased the metabolism of etretinate.[1] Note that etretinate is extensively metabolised to acitretin, and that acitretin use is now preferred to etretinate. This appears to be an isolated case, and its general relevance to the use of etretinate or acitretin is unknown.

(b) Isotretinoin

The AUC of carbamazepine in a patient with epilepsy taking carbamazepine 600 mg daily was reduced by 11% when isotretinoin

500 micrograms/kg daily was taken, and by 24% when isotretinoin 1 mg/kg daily was taken. The AUC of carbamazepine-10,11-epoxide (the active metabolite of carbamazepine) was reduced by 21% and 44% by the small and large doses of isotretinoin, respectively. The patient had no adverse effects.[2] Although the author of the report suggests that monitoring may be necessary in patients given both drugs, changes of this magnitude, especially those seen with the lower dose of isotretinoin, are not usually clinically significant.

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2. Marsden JR. Effect of isotretinoin on carbamazepine pharmacokinetics. *Br J Dermatol* (1988) 119, 403–4.

Carbamazepine + SSRIs

Some, but not all, reports indicate that carbamazepine levels can be increased by fluoxetine and fluvoxamine. Toxicity may develop. Citalopram, paroxetine and sertraline do not normally affect carbamazepine, but there is an isolated case of raised carbamazepine levels with sertraline.
Citalopram, paroxetine and sertraline levels may be reduced by carbamazepine. The use of carbamazepine with an SSRI has, rarely, led to effects such as hyponatraemia, serotonin syndrome, and parkinsonism.

Clinical evidence

(a) Citalopram

In a study in 12 healthy subjects, citalopram 40 mg daily for 2 weeks did not affect the pharmacokinetics of carbamazepine 400 mg daily.[1] An approximate 30% decrease in citalopram levels occurred in 6 patients taking citalopram 40 to 60 mg daily when they were given carbamazepine 200 to 400 mg daily for 4 weeks. Despite this decrease, the combination was considered clinically useful.[2] Similarly, two patients with epilepsy, major depression, and panic disorder had increased citalopram levels (one had an improved antidepressant response, but the other patient experienced tremor and increased anxiety) when their treatment with carbamazepine was replaced by oxcarbazepine.[3]

(b) Fluoxetine

Two patients developed carbamazepine toxicity (diplopia, blurred vision, tremor, vertigo, nausea, tinnitus etc.) within 7 and 10 days of starting to take fluoxetine 20 mg daily. Their serum carbamazepine levels were found to have risen by about 33% and 60%, respectively. The problem was resolved in one of them by reducing the carbamazepine dose from 1 g to 800 mg daily, and in the other by stopping fluoxetine.[4] The effects seen in these cases are supported by a study in 6 healthy patients, where adding fluoxetine 20 mg daily to steady-state carbamazepine caused a rise in the AUC of carbamazepine and carbamazepine-10,11-epoxide (its active metabolite) of about 25 to 50%.[5]

In contrast, in 8 patients with epilepsy taking stable doses of carbamazepine, fluoxetine 20 mg daily for 3 weeks was found to have no effect on the serum levels of carbamazepine or carbamazepine-10,11-epoxide.[6]

Aside from these pharmacokinetic changes two cases of parkinsonism developed within 3 and 9 days of adding fluoxetine to carbamazepine treatment. In both cases carbamazepine levels were unaffected.[7] A case of serotonin syndrome (shivering, agitation, myoclonic-like leg contractions, diaphoresis, etc.) has also been seen in a woman taking carbamazepine 200 mg daily and fluoxetine 20 mg daily.[8]

(c) Fluvoxamine

Increased serum levels and signs of carbamazepine toxicity (nausea, vomiting) were seen in 3 patients taking long-term carbamazepine when they were given fluvoxamine. The carbamazepine level almost doubled in one of them within 10 days of starting fluvoxamine 50 to 100 mg daily. The interaction was accommodated by reducing the carbamazepine dose by 200 mg daily in all three (from 1 g to 800 mg in one of them, and from 800 to 600 mg daily in the other two).[9,10] An approximate doubling of carbamazepine levels has also been seen in other patients given fluvoxamine.[11-14]

In contrast, in 7 patients with epilepsy taking stable doses of carbamazepine, fluvoxamine 100 mg daily for 3 weeks was found to have no effect on the serum levels of carbamazepine or carbamazepine-10,11-epoxide.[6] Furthermore, a literature search[15] by the manufacturers of fluvoxamine only identified 8 cases of an interaction between fluvoxamine and carbamazepine up until 1995.

(d) Paroxetine

In patients with epilepsy, paroxetine 30 mg daily for 16 days did not affect the plasma levels or therapeutic effects of carbamazepine. Steady-state paroxetine plasma levels were lower in those taking carbamazepine (27 nanograms/mL) than in those taking sodium valproate (73 nanograms/mL).[16]

An elderly patient taking carbamazepine 200 mg daily then 400 mg daily for neuropathic pain associated with herpes zoster infection was given paroxetine 20 mg daily to treat depression. He developed vertigo, bradycardia and syncope and his plasma sodium was found to be low (120 mmol/L). Sodium levels returned to normal (135 mmol/L) over several weeks after carbamazepine was withdrawn.[17]

(e) Sertraline

A placebo-controlled study in 13 healthy subjects (7 taking sertraline, 6 taking placebo) found that sertraline 200 mg daily for 17 days had no effect on the pharmacokinetics of carbamazepine 200 mg twice daily or on its metabolite, carbamazepine-10,11-epoxide. In addition, sertraline did not potentiate the cognitive effects of carbamazepine.[18]

However, an isolated report describes a woman who had taken carbamazepine 600 mg and flecainide 100 mg daily for 2 years, who had a rise in her trough serum carbamazepine levels from 4.7 micrograms/mL to 8.5 micrograms/mL within 4 weeks of starting sertraline 100 mg daily. After 3 months of treatment, carbamazepine levels were 11.9 micrograms/mL. At the same time she developed pancytopenia (interpreted as a toxic bone marrow reaction to the increased carbamazepine levels), which improved when both carbamazepine and sertraline were stopped.[19]

An isolated report describes a woman with a schizoaffective disorder, successfully treated for 3 years with haloperidol and carbamazepine, who was given sertraline 50 mg daily for depression. When she failed to respond, the sertraline dose was progressively increased to 300 mg daily but her sertraline plasma levels remained low (about 17 to 25% of those predicted). Another patient taking carbamazepine similarly failed to respond to the addition of sertraline and had low sertraline levels.[20] In an analysis of plasma sertraline levels, the concentration to daily-dose ratio of sertraline was significantly lower in patients who had taken sertraline with carbamazepine compared with those who had taken sertraline without carbamazepine,[21] suggesting that carbamazepine lowered sertraline levels.

Mechanism

The evidence suggests that fluoxetine and fluvoxamine inhibit the metabolism of carbamazepine by the liver (presumably by inhibiting the cytochrome P450 isoenzyme CYP3A4) so that its loss from the body is reduced, leading to a rise in its serum levels.[5,12] However, fluoxetine usually only has weak effects on this isoenzyme.

Citalopram, sertraline and possibly paroxetine serum levels may be reduced because carbamazepine induces their metabolism by CYP3A4, which results in lower levels of these SSRIs. Oxcarbazepine appears not to interact. Carbamazepine and paroxetine may cause hyponatraemia so the reduced sodium levels in these two cases could be due to the combined adverse effects of these drugs.[17,22]

Importance and management

Information for fluoxetine and fluvoxamine appears to be limited to these reports. Not all patients appear to be affected, but because it is not possible to identify which patients are at risk, it would seem prudent to be alert for an increase in carbamazepine serum levels and toxicity (e.g. nausea, vomiting, ataxia and drowsiness) if fluoxetine or fluvoxamine is added. If toxicity is suspected, monitor carbamazepine levels and reduce the dose as necessary. The manufacturers of fluoxetine suggest that carbamazepine should be started at or adjusted towards the lower end of the dose range in those taking fluoxetine. They additionally suggest caution if fluoxetine has been taken during the previous 5 weeks.[23]

There would seem to be no particular need to monitor carbamazepine levels in patients taking citalopram, paroxetine, or sertraline. However, be aware that the SSRIs may be less effective in the presence of carbamazepine. Consider increasing the dose if necessary.

Note that SSRIs may increase seizure frequency and should therefore be

used with caution in patients with epilepsy, and avoided in those with unstable epilepsy.

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23. Prozac (Fluoxetine hydrochloride). Eli Lilly and Company Ltd. UK Summary of product characteristics, February 2009.

Carbamazepine + Terfenadine

Carbamazepine toxicity, attributed to the use of terfenadine, has been described in one case report.

Clinical evidence, mechanism, importance and management

A 18-year-old woman taking carbamazepine after treatment for brain metastases, developed confusion, disorientation, visual hallucinations, nausea and ataxia shortly after starting to take terfenadine 60 mg twice daily for rhinitis. The symptoms were interpreted as carbamazepine toxicity. However, her total carbamazepine serum level of 8.9 mg/L was within the reference range. An interaction due to protein binding displacement was suspected and measurement of free carbamazepine revealed levels of 6 mg/L, almost three times the upper limit of normal. All the symptoms disappeared when the terfenadine was stopped. The authors speculate that the terfenadine had displaced the carbamazepine from its plasma protein binding sites, thereby increasing the levels of free and active carbamazepine.[1] The report is very brief and does not say whether any other drugs were being taken concurrently, so that this interaction is not established.

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Carbamazepine + Ticlopidine

One case report suggests that ticlopidine may have increased carbamazepine levels, with associated toxicity.

Clinical evidence, mechanism, importance and management

A 67-year-old man taking carbamazepine 600 mg twice daily developed symptoms of carbamazepine toxicity (drowsiness, dizziness, ataxia) within a week of starting to take ticlopidine 250 mg twice daily. His carbamazepine level one week after starting the ticlopidine was 17.7 [micrograms/mL], but it had been only 10.1 [micrograms/mL] five weeks earlier. The carbamazepine dose was reduced to 500 mg twice daily, which resolved the symptoms, and resulted in a carbamazepine level of 12.5 [micrograms/mL] one week later. After stopping the ticlopidine, carbamazepine levels fell to 9.9 [micrograms/mL]. It was suggested that ticlopidine may interfere with carbamazepine metabolism.[1] However, carbamazepine is principally metabolised by the cytochrome P450 isoenzyme CYP3A4, and ticlopidine is not usually considered an inhibitor of this isoenzyme. This appears to be the only report of an interaction between carbamazepine and ticlopidine, and its general relevance is uncertain.

1. Brown RIG, Cooper TG. Ticlopidine-carbamazepine interaction in a coronary stent patient. *Can J Cardiol* (1997) 13, 853–4.

Carbamazepine + Trazodone

A single case report describes a moderate rise in carbamazepine levels in a patient given trazodone. Carbamazepine may moderately decrease trazodone levels.

Clinical evidence, mechanism, importance and management

A 53-year-old man who had been taking carbamazepine 700 mg daily for 7 months (serum levels 7.2 mg/L and 7.9 mg/L) started taking trazodone 100 mg daily. Two months later his serum carbamazepine levels were 10 mg/L and the concentration-to-dose ratio had increased by about 26%, but no signs or symptoms of carbamazepine toxicity were seen. The reasons for this interaction are not known but the authors suggest that it might occur because trazodone inhibits the cytochrome P450 isoenzyme CYP3A4, resulting in a reduction in the metabolism of carbamazepine.[1]

This seems to be the first and only report of raised carbamazepine levels with trazodone, and its general importance is unknown. The rise was only moderate and in this case was clinically irrelevant, but a carbamazepine serum rise of 26% might possibly be of importance in those patients with serum levels already near the top end of the therapeutic range. Therefore if carbamazepine adverse effects (e.g. nausea, vomiting, ataxia, drowsiness) develop in a patient taking trazodone, consider an interaction as a possible cause.

In 6 patients taking trazodone 150 or 300 mg daily, the addition of carbamazepine 400 mg daily for 4 weeks decreased the plasma levels of trazodone by 24%, and decreased the levels of the active metabolite of trazodone by 40%.[2] However, the combination was considered clinically useful in three of the cases.[2,3] In another study, when carbamazepine 400 mg daily was given with trazodone 100 to 300 mg daily, the plasma levels of trazodone and its active metabolite were reduced by 76% and 60%, respectively.[4,5] The FDA in the US and the manufacturers of trazodone recommend that patients should be closely monitored and trazodone doses increased if necessary when both drugs are given.[4-7]

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4. Desyrel (Trazodone hydrochloride). Bristol-Myers Squibb Company. US Prescribing information, February 2009.
5. Trazodone hydrochloride. Watson Laboratories Inc. US Prescribing information, August 2007.
6. Molipaxin Tablets (Trazodone hydrochloride). Sanofi-Aventis. UK Summary of product characteristics, March 2008.
7. Lewis-Hall FC. Bristol-Myers Squibb Company. Letter to healthcare professionals, April 2004.

Carbamazepine + Valnoctamide

Carbamazepine toxicity may develop if valnoctamide is also taken.

Clinical evidence

A study in 6 patients with epilepsy taking carbamazepine 800 to 1200 mg daily found that valnoctamide 200 mg three times daily for 7 days caused a 1.5- to 6.5-fold increase in the serum levels of carbamazepine-10,11-epoxide (an active metabolite of carbamazepine). Clinical signs of carbamazepine toxicity (drowsiness, ataxia, nystagmus) were seen in 4 patients. Two patients were also taking phenobarbital or phenytoin, and the serum levels of these drugs were unaffected by valnoctamide.[1] A further study in 6 healthy subjects found that valnoctamide 600 mg daily for 8 days increased the half-life of carbamazepine-10,11-epoxide, after a single 100-mg dose of carbamazepine, threefold (from 6.7 to 19.7 hours) and decreased its oral clearance fourfold.[2]

Mechanism

Valnoctamide inhibits the enzyme epoxide hydrolase, which is concerned with the metabolism and elimination of carbamazepine and its active epoxide metabolite.[1,2]

Importance and management

Information is limited but the interaction between carbamazepine and valnoctamide appears to be established. Patients taking carbamazepine who also take valnoctamide could rapidly develop carbamazepine toxicity because the metabolism of its major metabolite, carbamazepine-10,11-epoxide, is inhibited. This interaction is very similar to the interaction that occurs between carbamazepine and valpromide (an isomer of valnoctamide), see 'Carbamazepine + Valproate', below. Concurrent valnoctamide should be avoided unless the carbamazepine dose can be reduced appropriately.

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Carbamazepine + Valproate

Carbamazepine levels are usually only slightly affected by sodium valproate, valproic acid or valpromide but a moderate to marked rise in the levels of its active metabolite, carbamazepine-10,11-epoxide, may occur.
Carbamazepine may reduce the serum levels of valproate by 60% or more. Concurrent use may possibly increase the incidence of sodium valproate-induced hepatotoxicity.

Clinical evidence

(a) Carbamazepine and carbamazepine-10,11-epoxide levels

1. Sodium valproate or Valproic acid. A study in 7 adult patients with epilepsy who had been taking carbamazepine 8.3 to 13.3 mg/kg for more than 2 months found that their steady-state serum carbamazepine levels fell by an average of 24% (range 3 to 59%) over a 6-day period when they were given sodium valproate 1 g twice daily. The carbamazepine levels were reduced in 6 of the patients and remained unchanged in one. The levels of the active metabolite of carbamazepine, carbamazepine-10,11-epoxide, increased by a mean of 38%, with small decreases or no change in 4 patients and 24 to 150% increases in the remaining 3 patients.[1,2]
Other reports state that falls,[3,4] no changes[3,5-7] and even a slight rise[4] in carbamazepine levels have been seen in some patients also taking sodium valproate or valproic acid. The serum levels of carbamazepine-10,11-epoxide are reported to be increased by about 50 to 100%.[6,8-10] This active metabolite may cause the development of marked adverse effects such as blurred vision, dizziness, vomiting, tiredness and even nystagmus.[6-8,11] Acute psychosis, tentatively attributed to elevated epoxide levels, occurred when carbamazepine was given to a patient taking sodium valproate.[12]

2. Valpromide. Symptoms of carbamazepine toxicity, without increases in carbamazepine levels, developed in 5 out of 7 patients with epilepsy taking carbamazepine when concurrent treatment with sodium valproate was replaced by valpromide. The toxicity appeared to be connected with a fourfold increase in the serum levels of the active metabolite of carbamazepine, carbamazepine-10,11-epoxide, which rose to 8.5 micrograms/mL.[13]
In another study in 6 patients with epilepsy the serum levels of carbamazepine-10,11-epoxide rose by 330% (range 110 to 864%) within a week of starting valpromide, and two of the patients developed confusion, dizziness and vomiting. The symptoms disappeared and serum carbamazepine-10,11-epoxide levels fell when the valpromide dose was reduced by one-third.[6]
A study in healthy subjects given a single 100-mg oral dose of carbamazepine-10,11-epoxide confirmed that valpromide 300 mg twice daily for 8 days reduced carbamazepine-10,11-epoxide clearance by 73%, and increased peak levels by 62%.[14]

(b) Valproate levels

A pharmacokinetic study in 6 healthy subjects found that carbamazepine, 200 mg daily, over a 17-day period, increased the valproic acid clearance by 30%.[15]

Other reports have described reductions in serum valproate levels of 34 to 38% when carbamazepine was added,[16-18] and rises of 50 to 65% when the carbamazepine was withdrawn.[19,20] The rise appears to reach a plateau after about 4 weeks.[20] A pharmacokinetic model has been devised to estimate valproate clearance when given with carbamazepine.[21]

(c) Other effects

Evidence from epidemiological studies suggests that the risk of fatal hepatotoxicity is higher when valproate is given with other antiepileptics than when it is given alone, especially in infants.[22,23] A single case report describes hepatocellular and cholestatic jaundice and a reversible Parkinsonian syndrome in a woman taking sodium valproate and carbamazepine, which reversed when the carbamazepine was withdrawn. Levels of both drugs did not exceed the therapeutic range at any stage. The Parkinsonian syndrome was attributed to a drug interaction, whereas the hepatotoxicity was considered most likely to be due to the carbamazepine, although the valproate may have contributed.[24]

Mechanism

The evidence suggests that carbamazepine increases the metabolism of valproate, so that it is cleared from the body more quickly. Carbamazepine may also possibly increase the formation of a minor but hepatotoxic metabolite of valproic acid (2-propyl-4-pentenoic acid or 4-ene-VPA).[25,26]

The latter stages of carbamazepine metabolism appear to be inhibited by both valproate and its amide derivative, valpromide.[27] The levels of the metabolite carbamazepine-10,11-epoxide increase during concurrent use, probably by inhibition of its metabolism to carbamazepine-10,11-trans-diol,[28-30] by epoxide hydrolase. Valpromide was found to be about 100 times more potent an inhibitor of this enzyme than valproic acid *in vitro*[31] and caused a threefold higher rise in epoxide levels than valproate in one study.[6] The carbamazepine-10,11-epoxide metabolite has anticonvulsant activity, but it may also cause toxicity if its serum levels become excessive.[6,32]

It has also been suggested that valproate is not a selective inhibitor of epoxide hydrolase but that it inhibits all the steps of the epoxide-diol pathway.[33] The trans-diol metabolite is then further converted by glucuronidation, and it seems that this step is also inhibited.[30]

Importance and management

Moderately well documented interactions, which are established. A minor to modest fall in carbamazepine levels may occur, but there may be a moderate to marked rise in the active epoxide metabolite. Therefore, be alert for signs of toxicity, which may indicate high levels of carbamazepine-10,11-epoxide and a need to reduce the carbamazepine dose.

Be alert for falls in the serum levels of valproate if carbamazepine is added, and rises if carbamazepine is withdrawn. Sodium valproate has been associated with serious hepatotoxicity, especially in children aged less than 3 years, and this has been more common in those receiving other antiepileptics. Sodium valproate monotherapy is to be preferred in this group.

There is also some debate about whether the combination of valproate (especially valpromide) and carbamazepine should be avoided, not only because of the risk of toxicity but also because inhibition of epoxide hydrolase may be undesirable.[13] This enzyme is possibly important for the

detoxification of a number of teratogenic, mutagenic and carcinogenic epoxides.[6,13] More study is needed.

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Carbamazepine + Venlafaxine

The concurrent use of venlafaxine and carbamazepine led to hyponatraemia in one patient.

Clinical evidence, mechanism, importance and management

A case report describes a woman who was taking carbamazepine 800 mg at breakfast, and 400 mg at lunch and dinner, lamotrigine 100 mg twice daily and phenobarbital 100 mg twice daily who developed hyponatraemia following the addition of venlafaxine 150 mg daily and mirtazapine. Her sodium level fell from 142.5 mmol/L at the time when venlafaxine was added, to 124.8 mmol/L 2 years later, at which point she experienced syncope. The authors attribute this to the syndrome of inappropriate secretion of antidiuretic hormone caused by the combination of carbamazepine, lamotrigine and venlafaxine.[1] However, of these drugs, carbamazepine and venlafaxine are associated with this effect, whereas lamotrigine is not. Therefore an interaction between venlafaxine and carbamazepine seems a likely cause of the hyponatraemia. The clinical relevance of this isolated case is unclear.

Note that venlafaxine may cause seizures and should therefore be used with caution in patients with epilepsy.

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Carbamazepine + Vigabatrin

Vigabatrin does not normally alter carbamazepine levels, although one study has found a modest increase, and one a modest decrease, in carbamazepine levels when vigabatrin was given.

Clinical evidence

In an early clinical study in 12 patients, vigabatrin 2 to 3 g daily did not change the serum levels of carbamazepine.[1] Similarly, other studies found that carbamazepine levels were not significantly altered by the addition of vigabatrin.[2,3] However, in one study, in which 59 patients taking carbamazepine received vigabatrin, 34 patients had an increase in carbamazepine levels, 3 had no change, and 22 had a decrease in carbamazepine levels, resulting in a mean overall increase of 6%, which was not significant.[4] Similarly, in another study 46 out of 66 patients had an increase in carbamazepine level of at least 10% (mean increase about 24%), and in 24 of these patients the carbamazepine level exceeded the reference range.[5] In this study, the increase in carbamazepine level was greater the lower the initial carbamazepine level.[5] In contrast, one study in 15 patients reported a mean 18% *decrease* in carbamazepine levels when vigabatrin was added.[6]

Mechanism

Not understood.

Importance and management

The studies seem to suggest that any change in carbamazepine levels with vigabatrin is of borderline clinical significance and therefore the majority of patients will not be affected. Any change is likely to be more important in patients at the top of the therapeutic carbamazepine range. It would therefore seem prudent to be alert for any increase in carbamazepine adverse effects (such as nausea and vomiting, ataxia, and drowsiness) and consider taking carbamazepine levels and reducing the carbamazepine dose if these develop.

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Carbamazepine or Oxcarbazepine + Viloxazine

Viloxazine can cause a marked rise in carbamazepine levels and toxicity has been seen. Viloxazine does not appear to alter oxcarbazepine levels.

Clinical evidence

(a) Carbamazepine

The serum carbamazepine levels of 7 patients rose by 50% (from 8.1 micrograms/mL to 12.1 micrograms/mL) after they took viloxazine 100 mg three times daily for 3 weeks.[1] Signs of mild toxicity (dizziness, ataxia, fatigue, drowsiness) developed in 5 of the 7 patients. These symptoms disappeared and the serum carbamazepine levels fell when viloxazine was withdrawn.[1] Another report found a 2.5-fold increase in serum carbamazepine levels in one patient that occurred within 2 weeks of starting viloxazine 300 mg daily.[2] Another report found an average 55% rise in plasma carbamazepine levels and toxicity in 4 of 7 patients also taking viloxazine.[3] Yet another patient developed choreoathetosis and increased serum carbamazepine levels, which were attributed to the use of viloxazine.[4]

In one study, the pharmacokinetics of a single dose of viloxazine were reported to be unaffected by carbamazepine,[5] but in the case report cited above, which was at steady-state, the viloxazine levels were found to be reduced by carbamazepine.[2]

(b) Oxcarbazepine

In 6 patients with simple or partial seizures the steady-state serum levels of oxcarbazepine (average dose 1.5 g daily) were unaffected by the addition of viloxazine 100 mg twice daily for 10 days. No adverse effects were seen.[6]

Mechanism

Uncertain. What is known suggests that viloxazine inhibits the metabolism of carbamazepine, thereby reducing its clearance and raising its serum levels.

Importance and management

Information seems to be limited to the reports cited. If concurrent use is undertaken, serum carbamazepine levels should be monitored closely and suitable dose reductions made as necessary to avoid possible toxicity. No dose adjustment seems to be necessary with oxcarbazepine.

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3. Pisani F, Fazio A, Oteri G, Perucca E, Russo M, Trio R, Pisani B, Di Perri R. Carbamazepine-viloxazine interaction in patients with epilepsy. *J Neurol Neurosurg Psychiatry* (1986) 49, 1142–5.
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5. Pisani F, Fazio A, Spina E, Artesi C, Pisani B, Russo M, Trio R, Perucca E. Pharmacokinetics of the antidepressant drug viloxazine in normal subjects and in epileptic patients receiving chronic anticonvulsant treatment. *Psychopharmacology (Berl)* (1986) 90, 295–8.
6. Pisani F, Fazio A, Oteri G, Artesi C, Xiao B, Perucca E, Di Perri R. Effects of the antidepressant drug viloxazine on oxcarbazepine and its hydroxylated metabolites in patients with epilepsy. *Acta Neurol Scand* (1994) 90, 130–2.

Ethosuximide + Isoniazid

A single report describes a patient who developed psychotic behaviour and signs of ethosuximide toxicity when isoniazid was also given.

Clinical evidence, mechanism, importance and management

An patient with epilepsy, who had been stable taking ethosuximide and sodium valproate for 2 years, developed persistent hiccuping, nausea, vomiting, anorexia and insomnia within a week of starting to take isoniazid 300 mg daily. Psychotic behaviour gradually developed over the next 5 weeks and so the isoniazid was stopped. The appearance of these symptoms appeared to be related to the sharp rise in serum ethosuximide levels (from about 50 micrograms/mL up to 198 micrograms/mL).[1] It is suggested that the isoniazid may have inhibited the metabolism of the ethosuximide, leading to accumulation and toxicity. The general importance of this case is uncertain. More study is needed to establish an interaction.

1. van Wieringen A, Vrijlandt CM. Ethosuximide intoxication caused by interaction with isoniazid. *Neurology* (1983) 33, 1227–8.

Ethosuximide + Other antiepileptics

Minor to modest falls in ethosuximide levels may occur if carbamazepine, primidone or phenytoin are also given, whereas methylphenobarbital or valproate may cause a rise in ethosuximide levels. Lamotrigine appears not to affect ethosuximide levels.
Ethosuximide is reported to have caused phenytoin toxicity in a few cases, and it appears that ethosuximide can reduce valproate levels.

Clinical evidence

(a) Barbiturates

In a retrospective analysis, the level-to-dose ratio of ethosuximide was 33% lower in 29 patients with epilepsy taking ethosuximide and **primidone** than in 39 patients taking ethosuximide alone,[1] suggesting that primidone reduces ethosuximide levels.

Similarly, in a study that compared the pharmacokinetics of a single dose of ethosuximide in 10 patients with epilepsy taking **phenobarbital**, phenytoin and/or carbamazepine with 12 healthy controls, the epileptic group had markedly shorter (about halved) ethosuximide half-lives.[2] Conversely, another report stated that ethosuximide levels tended to rise (amount not stated) when **methylphenobarbital** was given (the opposite effect to that which would be expected), but ethosuximide did not appear to be affected by **phenobarbital** or **primidone**.[3] Phenobarbital levels (derived from **primidone**) do not appear to be affected by ethosuximide.[4]

(b) Carbamazepine

A study in 6 healthy subjects taking ethosuximide 500 mg daily found that the mean plasma levels of ethosuximide were reduced by 17% (from 32 mg/mL to 27 mg/mL) by carbamazepine 200 mg daily for 18 days. One individual had a 35% reduction in ethosuximide levels.[5] Another study, which compared 10 patients with epilepsy taking enzyme-inducing antiepileptic drugs, including 4 taking carbamazepine, with 12 healthy controls found that the epileptic group had markedly shorter (about halved) ethosuximide half-lives.[2]

In contrast, the concurrent use of carbamazepine did not affect the correlation between ethosuximide dose and levels in another study.[3]

(c) Lamotrigine

Five children taking ethosuximide and various other antiepileptics had no change in their plasma ethosuximide levels when lamotrigine was also given.[6]

(d) Phenytoin

A study compared the pharmacokinetics of a single dose of ethosuximide in 10 patients with epilepsy taking phenobarbital, phenytoin and/or carbamazepine with 12 healthy controls. The epileptic group had markedly shorter (about halved) ethosuximide half-lives.[2] In contrast, the concurrent use of phenytoin did not affect the correlation between ethosuximide levels and dose in another study.[3]

Three cases have occurred in which ethosuximide appeared to have been responsible for increasing phenytoin levels,[7-9] leading to the development of phenytoin toxicity in 2 patients.[8,9]

(e) Valproate

Four out of 5 patients taking ethosuximide (average dose 27 mg/kg) had an increase in their serum levels of about 50% (from 73 micrograms/mL to 112 micrograms/mL), within 3 weeks of starting to take valproic acid (adjusted to the maximum tolerated dose). Sedation occurred and ethosuximide dose reductions were necessary.[10] In a single-dose study in 6 healthy subjects, the use of sodium valproate for 9 days was reported to have increased the ethosuximide half-life and reduced its clearance by 15%.[11] However, other studies have described no changes[12,13] or even lower serum ethosuximide levels (level to dose ratio reduced by 36%) when valproate was given.[1]

One study in 13 children found that ethosuximide can lower valproate serum levels. In the presence of ethosuximide the valproate levels were lower than with valproate alone (87 micrograms/mL versus 120 micrograms/mL). After stopping ethosuximide the valproate levels rose by about 40%.[14]

Mechanism

The most probable explanation for the fall in ethosuximide levels is that carbamazepine and the other enzyme-inducing antiepileptics increase the metabolism and clearance of ethosuximide, which is known to be metabolised by the cytochrome P450 subfamily CYP3A.[2]

Importance and management

The concurrent use of antiepileptics is common and often advantageous. Information on these interactions is sparse and even contradictory and their clinical importance is uncertain. Nevertheless, good monitoring would clearly be appropriate if these drugs are used with ethosuximide to monitor for potential toxicity and to ensure adequate seizure control.

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5. Warren JW, Benmaman JD, Wannamaker BB, Levy RH. Kinetics of a carbamazepine-ethosuximide interaction. *Clin Pharmacol Ther* (1980) 28, 646–51.
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7. Lander CM, Eadie MJ, Tyrer JH. Interactions between anticonvulsants. *Proc Aust Assoc Neurol* (1975) 12, 111–16.
8. Dawson GW, Brown HW, Clark BG. Serum phenytoin after ethosuximide. *Ann Neurol* (1978) 4, 583–4.
9. Frantzen E, Hansen JM, Hansen OE, Kristensen M. Phenytoin (Dilantin) intoxication. *Acta Neurol Scand* (1967) 43, 440–6.
10. Mattson RH, Cramer JA. Valproic acid and ethosuximide interaction. *Ann Neurol* (1980) 7, 583–4.
11. Pisani F, Narbone MC, Trunfio C, Fazio A, La Rosa G, Oteri G, Di Perri R. Valproic acid-ethosuximide interaction: a pharmacokinetic study. *Epilepsia* (1984) 25, 229–33.
12. Fowler GW. Effect of dipropylacetate on serum levels of anticonvulsants in children. *Proc West Pharmacol Soc* (1978) 21, 37–40.
13. Bauer LA, Harris C, Wilensky AJ, Raisys VA, Levy RH. Ethosuximide kinetics: possible interaction with valproic acid. *Clin Pharmacol Ther* (1982) 31, 741–5.
14. Sälke-Kellermann RA, May T, Boenigk HE. Influence of ethosuximide on valproic acid serum concentrations. *Epilepsy Res* (1997) 26, 345–349.

Felbamate + Antacids

In one study, an aluminium/magnesium hydroxide-containing antacid had no effect on the absorption of felbamate.

Clinical evidence, mechanism, importance and management

Felbamate 2.4 g daily was given to 9 women with epilepsy for 2 weeks. For a third week the felbamate was taken with an antacid containing **aluminium/magnesium hydroxide** (*Maalox Plus*). No significant changes in the plasma levels or AUC of felbamate were seen.[1] No felbamate dose adjustments would seem to be needed if it is taken with this or any other similar antacid.

1. Sachdeo RC, Narang-Sachdeo SK, Howard JR, Dix RK, Shumaker RC, Perhach JL, Rosenberg A. Effect of antacid on the absorption of felbamate in subjects with epilepsy. *Epilepsia* (1993) 34 (Suppl 6), 79–80.

Felbamate + Erythromycin

Erythromycin does not alter the pharmacokinetics of felbamate.

Clinical evidence, mechanism, importance and management

In a randomised, crossover study, 12 patients with epilepsy were given felbamate 3 g or 3.6 g daily, either alone or with erythromycin 333 mg every 8 hours for 10 days. The pharmacokinetics of felbamate were unchanged by erythromycin.[1] There would therefore seem no need to adjust the dose of felbamate if erythromycin is given.

1. Sachdeo RJ, Narang-Sachdeo SK, Montgomery PA, Shumaker RC, Perhach JL, Lyness WH, Rosenberg A. Evaluation of the potential interaction between felbamate and erythromycin in patients with epilepsy. *J Clin Pharmacol* (1998) 38, 184–90.

Felbamate + Gabapentin

There is some evidence that the half-life of felbamate may be prolonged by gabapentin.

Clinical evidence, mechanism, importance and management

In a retrospective examination of clinical data from patients taking felbamate, its half-life was found to be 24 hours in 40 patients taking felbamate alone, whereas in 18 other patients also taking gabapentin (including 7 taking a third drug), the half-life of felbamate was extended to 32.7 hours.[1] The practical clinical importance of this effect is uncertain. More study is needed.

1. Hussein G, Troupin AS, Montouris G. Gabapentin interaction with felbamate. *Neurology* (1996) 47, 1106.

Fosphenytoin + Miscellaneous

Fosphenytoin is a prodrug of phenytoin, which is rapidly and completely hydrolysed to phenytoin in the body. It is predicted to interact with other drugs in the same way as phenytoin.[1,2] No drugs are known to interfere with the conversion of fosphenytoin to phenytoin.[2]

1. Fierro LS, Savulich DH, Benezra DA. Safety of fosphenytoin sodium. *Am J Health-Syst Pharm* (1996) 53, 2707–12.
2. Pro-Epanutin (Fosphenytoin sodium). Pfizer Ltd. UK Summary of product characteristics, December 2008.

Gabapentin + Antacids

Aluminium/magnesium hydroxide slightly reduces the absorption of gabapentin.

Clinical evidence, mechanism, importance and management

An **aluminium/magnesium hydroxide** antacid (*Maalox TC*) reduced the bioavailability of gabapentin 400 mg by about 20% when given either at the same time or 2 hours after gabapentin. When the antacid was given 2 hours before gabapentin, the bioavailability was reduced by about 10%.[1] These small changes are unlikely to be of clinical importance. Nevertheless, the manufacturers of gabapentin recommend that it is taken at least 2 hours after **aluminium/magnesium-containing antacids**.[2,3]

1. Busch JA, Radulovic LL, Bockbrader HN, Underwood BA, Sedman AJ, Chang T. Effect of Maalox TC® on single-dose pharmacokinetics of gabapentin capsules in healthy subjects. *Pharm Res* (1992) 9 (10 Suppl), S-315.
2. Neurontin (Gabapentin). Pfizer Ltd. UK Summary of product characteristics, December 2008.
3. Neurontin (Gabapentin). Pfizer Inc. US Prescribing information, April 2009.

Gabapentin + Cimetidine

A brief report notes that cimetidine decreased the renal clearance of gabapentin by 12%, which was not expected to be clinically important. No study details were given.[1]

1. Busch JA, Bockbrader HN, Randinitis EJ, Chang T, Welling PG, Reece PA, Underwood B, Sedman AJ, Vollmer KO, Türck D. Lack of clinically significant drug interactions with Neurontin (Gabapentin). 20th International Epilepsy Congress. Oslo, Norway, July 1993. Abstract 013958.

Gabapentin + Food

Food, including protein and enteral feeds, does not have a clinically important effect on the absorption of gabapentin.

Clinical evidence, mechanism, importance and management

A high-protein meal (80 g of total protein) increased the maximum serum levels of a single 800-mg dose of gabapentin by 36% in healthy subjects. The AUC was increased by 11%, which was not statistically significant.

These findings were the opposite of those expected, because L-amino acids compete for gabapentin intestinal transport *in vitro*.[1] Another study also reported no significant differences in the pharmacokinetics of gabapentin when a single 400- or 800-mg dose was given after a high protein meal rather than in the fasting state.[2]

In another single-dose study, the absorption of gabapentin from capsules did not differ when given intact or opened and mixed with either apple sauce or orange juice, but tended to be higher (AUC increased by 26%) when opened and mixed with a protein-containing vehicle (chocolate pudding).[3] Similarly, no change in absorption was found when gabapentin syrup was mixed with tap water, grape juice, or an **enteral feed** (*Sustacal*), but a modest 31% increase in the AUC was seen when the gabapentin was mixed with **chocolate milk**.[4]

These small changes are unlikely to be of clinical importance, so it does not matter when gabapentin is taken in relation to food.

1. Gidal BE, Maly MM, Budde J, Lensmeyer GL, Pitterle ME, Jones JC. Effect of a high-protein meal on gabapentin pharmacokinetics. *Epilepsy Res* (1996) 23, 71–6.
2. Benetello P, Furlanut M, Fortunato M, Baraldo M, Pea F, Tognon A, Testa G. Oral gabapentin disposition in patients with epilepsy after a high-protein meal. *Epilepsia* (1997) 38, 1140–2.
3. Gidal BE, Maly MM, Kowalski JW, Rutecki PA, Pitterle ME, Cook DE. Gabapentin absorption: effect of mixing with foods of varying macronutrient composition. *Ann Pharmacother* (1998) 32, 405–9.
4. Parnell J, Sheth R, Limdi N, Gidal BE. Oral absorption of gabapentin syrup is not impaired by concomitant administration with various beverages or enteral nutrition supplement. *Epilepsia* (2001) 42 (Suppl 7), 91.

Gabapentin + Other antiepileptics

Gabapentin does not normally affect the pharmacokinetics of carbamazepine, phenytoin, phenobarbital or valproate. However, isolated reports describe increased phenytoin levels and toxicity in two patients given gabapentin.

Clinical evidence, mechanism, importance and management

The pharmacokinetics of both **phenytoin** and gabapentin remained unchanged in 8 patients with epilepsy who were given gabapentin 400 mg three times daily for 8 days, in addition to **phenytoin**, which they had been taking for at least 2 months.[1] Other studies confirm that the steady-state pharmacokinetics of **phenytoin** are unaffected by gabapentin, and that the pharmacokinetics of gabapentin are similarly unaffected by **phenytoin**.[2,3] These reports contrast with an isolated report of a patient taking **phenytoin**, **carbamazepine** and **clobazam** whose serum **phenytoin** levels increased three to fourfold, with symptoms of toxicity, on two occasions when gabapentin 300 to 600 mg daily was given. **Carbamazepine** serum levels remained unchanged. The author suggests that this differing reaction may be because the patient was taking more than one antiepileptic, unlike previous studies where only single drugs had been used.[4] However, another case of **phenytoin** toxicity possibly attributable to gabapentin has been described in a patient who was not taking any other antiepileptics.[5]

Gabapentin does not affect **phenobarbital** levels, nor is it affected by **phenobarbital**.[2,3,6] Other studies confirm that the steady-state pharmacokinetics of **carbamazepine** and **valproate** are unaffected by gabapentin, and that the pharmacokinetics of gabapentin are similarly unaffected by these antiepileptics.[2,3,7]

It would seem therefore that no dose adjustments are normally needed if gabapentin is added to treatment with most of these antiepileptics. However, if gabapentin is added to **phenytoin** it may be wise to bear the possibility of raised **phenytoin** levels in mind. Be alert for phenytoin adverse effects (e.g. blurred vision, nystagmus, ataxia or drowsiness).

For mention that gabapentin may prolong the half-life of felbamate, see 'Felbamate + Gabapentin', p.616.

For mention of the lack of interaction between levetiracetam and gabapentin, see 'Levetiracetam + Other antiepileptics', p.621.

1. Anhut H, Leppik I, Schmidt B, Thomann P. Drug interaction study of the new anticonvulsant gabapentin with phenytoin in epileptic patients. *Naunyn Schmiedebergs Arch Pharmacol* (1988) 337 (Suppl), R127.
2. Brockbrader HN, Radulovic LL, Loewen G, Chang T, Welling PG, Reece PA, Underwood B, Sedman AJ. Lack of drug-drug interactions between Neurontin (gabapentin) and other antiepileptic drugs. 20th International Epilepsy Congress, Oslo, Norway. July 1993 (Abstract).
3. Richens A. Clinical pharmacokinetics of gabapentin. In: Chadwick D, ed. New Trends in Epilepsy Management: The Role of Gabapentin. International Congress and Symposium Series No 198, Royal Society of Medicine Services, London, NY 1993, 41–6.
4. Tyndel F. Interaction of gabapentin with other antiepileptics. *Lancet* (1994) 343, 1363–4.
5. Sánchez-Romero A, Durán-Quintana JA, García-Delgado R, Margariot-Rangel C, Proveda-Andrés JL. Posible interacción gabapentina-fenitoína. *Rev Neurol* (2002) 34, 952–3.
6. Hooper WD, Kavanagh MC, Herkes GK, Eadie MJ. Lack of a pharmacokinetic interaction between phenobarbitone and gabapentin. *Br J Clin Pharmacol* (1991) 31, 171–4.
7. Radulovic LL, Wilder BJ, Leppik IE, Bockbrader HN, Chang T, Posvar EL, Sedman AJ, Uthman BM, Erdman GR. Lack of interaction of gabapentin with carbamazepine or valproate. *Epilepsia* (1994) 35, 155–61.

Gabapentin + Probenecid

A brief report notes that probenecid had no effect on the renal clearance of gabapentin. No study details were given.[1]

1. Busch JA, Bockbrader HN, Randinitis EJ, Chang T, Welling PG, Reece PA, Underwood B, Sedman AJ, Vollmer KO, Türck D. Lack of clinically significant drug interactions with Neurontin (Gabapentin). 20th International Epilepsy Congress. Oslo, Norway, July 1993. Abstract 013958.

Lacosamide + Miscellaneous

No clinically relevant pharmacokinetic interactions occur between lacosamide and digoxin, metformin or omeprazole. Food does not affect the pharmacokinetics of lacosamide. Potent enzyme inducers such as rifampicin (rifampin) are predicted to reduce the levels of lacosamide. Caution is required if class I antiarrhythmics are given with lacosamide because of the possibility of enhanced PR prolongation.

Clinical evidence, mechanism, importance and management

(a) Antiarrhythmics

Dose-dependent prolongation of the PR interval may occur with lacosamide.[1,2] The UK manufacturer advises that lacosamide should be used with caution in patients taking class I antiarrhythmics (see 'Table 9.1', (p.273)) or other drugs that prolong the PR interval. See also 'Lacosamide + Other antiepileptics', p.618.

(b) Enzyme inducers

The UK manufacturer notes that potent enzyme inducers (presumably CYP3A4 inducers as they name **rifampicin** (**rifampin**) and **St John's wort**) may moderately reduce the exposure to lacosamide and advises caution when starting or ending treatment with these drugs in patients taking lacosamide.[1] For a list of CYP3A4 inducers, see 'Table 1.4', (p.6).

(c) Food

In a study, 24 healthy subjects were given a single 300-mg dose of lacosamide in the fasted state or after a high-fat meal. Food did not affect lacosamide pharmacokinetics,[3] and it may therefore be taken without regard to food.[1,2]

(d) Omeprazole

Omeprazole 40 mg daily increased the AUC of lacosamide by 19%.[1] The US manufacturer notes that plasma levels of the (inactive[1]) *O*-desmethyl metabolite of lacosamide were decreased by about 60% in the presence of omeprazole,[2] possibly due to inhibition of lacosamide metabolism by cytochrome P450 isoenzyme CYP2C19.[1] These changes would not be expected to be clinically relevant. Lacosamide 600 mg daily did not affect the pharmacokinetics of a single 40-mg dose of omeprazole,[1,2] although the US manufacturer states that *in vitro* data suggest that lacosamide has the potential to inhibit CYP2C19.[2] However, one *in vitro* study suggests the interaction only occurs at levels 30-fold higher than therapeutic lacosamide plasma levels.[4]

(e) Other drugs

In studies in healthy subjects there were no pharmacokinetic interactions between lacosamide and digoxin or metformin.[1,2,5]

1. Vimpat (Lacosamide). UCB Pharma Ltd. UK Summary of product characteristics, July 2009.
2. Vimpat (Lacosamide). UCB, Inc. US Prescribing information, January 2009.
3. Horstmann R, Bonn R, Cawello W, Doty P, Rudd D. Basic clinical investigations of the new antiepileptic drug SPM 927. *Epilepsia* (2002) 43 (Suppl. 7) 188.
4. Beyreuther BK, Freitag J, Heers C, Krebsfänger N, Scharfenecker U, Stöhr T. Lacosamide: a review of preclinical properties. *CNS Drug Rev* (2007) 13, 21–42.
5. Thomas D, Scharfenecker U, Schiltmeyer B, Doty P, Cawella W, Horstmann R. Low potential for drug-drug-interaction of lacosamide. American Epilepsy Association, Epilepsia 2006, Abstract 2.235. Available at: http://www.aesnet.org/go/publications/aes-abstracts/abstract-search/?mode=display&st=lacosamide&sy=all&sb=All&startrow=31&id=6674 (accessed 29/01/10).

Lacosamide + Other antiepileptics

No significant pharmacokinetic interaction appears to occur between lacosamide and carbamazepine, lamotrigine, oxcarbazepine, or valproate. Lacosamide does not affect plasma levels of phenytoin or phenobarbital, clonazepam, gabapentin, levetiracetam, topiramate and zonisamide. However, limited evidence suggests that the enzyme-inducing antiepileptics may reduce lacosamide exposure.

Clinical evidence, mechanism, importance and management

(a) Carbamazepine or Oxcarbazepine

In a study in 19 healthy subjects given lacosamide 200 mg twice daily, modified-release carbamazepine 200 mg twice daily had no clinically significant effect on the pharmacokinetics of lacosamide.[1] In a further study in 18 healthy subjects given modified-release carbamazepine 200 mg twice daily with lacosamide 200 mg twice daily, there were no significant changes in the pharmacokinetics of carbamazepine.[1] In studies in patients with uncontrolled partial seizures taking one or two antiepileptic drugs, the addition of lacosamide 100 mg to 600 mg daily did not affect the plasma levels of carbamazepine and its 10,11-epoxide metabolite or oxcarbazepine.[2,3] In placebo-controlled clinical studies in patients with partial-onset seizures, the plasma levels of carbamazepine and carbamazepine-10,11-epoxide or the active metabolite of oxcarbazepine, monohydroxyoxcarbazepine, were unaffected by the concurrent use lacosamide.[4] The manufacturers of lacosamide note that, in a population pharmacokinetic analysis, the concurrent use of lacosamide with other antiepileptic drugs known to be enzyme inducers (carbamazepine, phenytoin, phenobarbital) decreased the exposure of lacosamide by 15 to 25%.[4,5] This finding is expected to be of limited clinical relevance, and it would appear that, in general, no dose adjustment of either carbamazepine or lacosamide is likely to be needed on concurrent use. However, the manufacturers advise caution if lacosamide is given with drugs known to be associated with PR prolongation, and they name carbamazepine.[4,5] However, the UK manufacturer states that a subgroup analysis of clinical study results did not find an increase in PR prolongation in patients given lacosamide and carbamazepine.[5]

(b) Lamotrigine

In studies in patients with uncontrolled partial seizures taking one or two antiepileptic drugs, the addition of lacosamide in doses of 100 mg to 600 mg daily did not affect plasma levels of lamotrigine.[2,3] The manufacturers advise caution if lacosamide is given with drugs known to be associated with PR prolongation, and they name lamotrigine.[4,5] However, the UK manufacturer of lacosamide states that subgroup analysis of clinical study results did not find an increase in PR prolongation in patients given lacosamide and lamotrigine.[5]

(c) Phenobarbital or Phenytoin

In studies in patients with uncontrolled partial seizures taking one or two antiepileptic drugs, the addition of lacosamide in doses of 100 mg to 600 mg daily did not affect the plasma levels of phenytoin.[2,3] In clinical studies, lacosamide did not affect the plasma levels of phenobarbital.[4] The manufacturer of lacosamide notes that, in a population pharmacokinetic analysis in patients with partial-onset seizures, the concurrent use of lacosamide with other antiepileptic drugs known to be enzyme inducers (carbamazepine, phenytoin, phenobarbital) decreased the exposure of lacosamide by 15 to 25%.[4,5] However, this would be expected to be of little clinical relevance, and no dose adjustments would be expected to be needed if lacosamide is given with phenytoin or phenobarbital.

(d) Pregabalin

The manufacturers of lacosamide advise caution if lacosamide is given with drugs known to be associated with PR prolongation: they name pregabalin.[4,5]

(e) Valproate

Phase I studies in healthy subjects have found no pharmacokinetic interaction between lacosamide and valproate.[6] In studies in patients with uncontrolled partial seizures taking one or two antiepileptic drugs, the addition of lacosamide in doses of 100 mg to 600 mg daily did not affect the plasma levels of valproate.[2,3] Further, in clinical studies, the concurrent use of lacosamide did not affect the plasma levels of valproate.[4] No dose adjustment of lacosamide or valproate appears to be necessary on concurrent use.

(f) Other antiepileptics

In studies in patients with uncontrolled partial seizures taking one or two antiepileptic drugs, the addition of lacosamide in doses of 100 mg to 600 mg daily did not affect the plasma levels of **gabapentin**, **levetiracetam**, **topiramate**, or **zonisamide**.[2,3] In clinical studies, the concurrent use of lacosamide did not affect the steady-state levels of **clonazepam**.[4]

1. Cawello W, Nickel B, Eggert-Formella A. No pharmacokinetic interaction between lacosamide and carbamazepine in healthy volunteers. J Clin Pharmacol (2009) Oct 19.
2. Jatuzis D, Biton V, Ben-Menachem E, Abou-Khalil B, Doty P, Rudd GD. Evaluation of the effect of oral lacosamide on concomitant AED plasma concentrations in patients with partial seizures. *Epilepsia* (2005) 46 (Suppl 8), 170.
3. Fountain NB, Horstmann R, Cawello W, Doty P, Rudd GD. Absence of effect of adjunctive SPM927 on concomitant AED plasma concentrations in subjects with partial seizures. *Epilepsia* (2003) 44 (Suppl 9), 96.
4. Vimpat (Lacosamide). UCB, Inc. US Prescribing information, January 2009.
5. Vimpat (Lacosamide). UCB Pharma Ltd. UK Summary of product characteristics, July 2009.
6. Horstmann R, Bonn R, Cawello W, Doty P, Rudd D. SPM 927 does not interact with valproic acid and carbamazepine. *Epilepsia* (2003) 44 (Suppl 9), 97.

Lamotrigine + Antimycobacterials

Rifampicin markedly increased the clearance of lamotrigine in a pharmacokinetic study. A case report described a similar finding, and also included some limited evidence suggesting that isoniazid may inhibit lamotrigine metabolism.

Clinical evidence

In a pharmacokinetic study in 10 healthy subjects, **rifampicin** (**rifampin**) 600 mg daily for 5 days increased the clearance of a single 25-mg dose of lamotrigine by 97% and decreased its AUC by 44%. The amount of lamotrigine glucuronide recovered in the urine was increased by 36%.[1] Similarly, a case report describes a 56-year-old woman taking lamotrigine 150 mg daily who had unexpectedly low serum lamotrigine levels of 1.3 mg/L after starting **rifampicin**, **isoniazid** and pyrazinamide. The lamotrigine dose was therefore increased to 250 mg daily. After rifampicin and pyrazinamide were stopped, isoniazid continued and ethambutol started, the lamotrigine serum levels rose to 12.4 mg/L but no toxicity was seen.[2] It is unclear whether there is any relationship between lamotrigine plasma levels and toxicity.[3]

Mechanism

Rifampicin (rifampin) increases the loss of lamotrigine from the body, probably by inducing glucuronidation via glucuronyltransferases.[1] It was suggested that isoniazid may have inhibited lamotrigine metabolism.[2]

Importance and management

Information appears to be limited to these reports, but the interaction between lamotrigine and rifampicin (rifampin) would appear to be established. Be aware that rifampicin could reduce the efficacy of lamotrigine, and that increased lamotrigine doses are likely to be required.

The case report also raises the possibility of an interaction between lamotrigine and isoniazid. If isoniazid is added to or withdrawn from lamotrigine treatment, be alert for the need to adjust the lamotrigine dosage.

1. Ebert U, Thong NQ, Oertel R, Kirch W. Effects of rifampicin and cimetidine on pharmacokinetics and pharmacodynamics of lamotrigine in healthy subjects. *Eur J Clin Pharmacol* (2000) 56, 299–304.
2. Armijo JA, Sánchez B, Peralta FG, Cuadrado A, Leno C. Lamotrigine interaction with rifampicin and isoniazid. A case report. *Methods Find Exp Clin Pharmacol* (1996) 18 (Suppl C), 59.
3. Chong E, Dupuis LL. Therapeutic drug monitoring of lamotrigine. *Ann Pharmacother* (2002) 36, 917–20.

Lamotrigine + Cimetidine

In a study in 10 healthy subjects, cimetidine 400 mg twice daily for 5 days had no effect on the pharmacokinetics of a single 25-mg

dose of lamotrigine. No lamotrigine dose adjustment appears to be needed during concurrent use.[1]

1. Ebert U, Thong NQ, Oertel R, Kirch W. Effects of rifampicin and cimetidine on pharmacokinetics and pharmacodynamics of lamotrigine in healthy subjects. *Eur J Clin Pharmacol* (2000) 56, 299–304.

Lamotrigine + Felbamate

Felbamate does not appear to affect the pharmacokinetics of lamotrigine.

Clinical evidence, mechanism, importance and management

In 21 healthy subjects, felbamate 1.2 g twice daily had minimal effects on the pharmacokinetics of lamotrigine 100 mg twice daily, when both drugs given together for 10 days. The AUC of lamotrigine was increased by 14%, which was not considered to be clinically relevant.[1] Similarly, there was no difference in lamotrigine pharmacokinetics in 6 patients receiving lamotrigine and felbamate and 5 patients taking lamotrigine alone.[2] Therefore the dose of lamotrigine does not need to be adjusted if felbamate is given.

1. Colucci R, Glue P, Holt B, Banfield C, Reidenberg P, Meehan JW, Pai S, Nomeir A, Lim J, Lin C-C, Affrime MB. Effect of felbamate on the pharmacokinetics of lamotrigine. *J Clin Pharmacol* (1996) 36, 634–8.
2. Gidal BE, Kanner A, Maly M, Rutecki P, Lensmeyer GL. Lamotrigine pharmacokinetics in patients receiving felbamate. *Epilepsy Res* (1997) 27, 1–5.

Lamotrigine + Fluconazole

An isolated case suggests that fluconazole does not affect lamotrigine levels.

Clinical evidence, mechanism, importance and management

A patient who had been taking carbamazepine, lamotrigine and barbexaclone for many years, was given fluconazole 150 mg with her morning dose of antiepileptics. Although she developed symptoms of carbamazepine toxicity and raised carbamazepine levels, her lamotrigine levels were not significantly affected by the concurrent use fluconazole.[1]

1. Ulivelli M, Rubegni P, Nuti D, Bartalini S, Giannini F, Rossi S. Clinical evidence of fluconazole-induced carbamazepine toxicity. *J Neurol* (2004) 251, 622–3.

Lamotrigine + Orlistat

Orlistat may reduce the absorption of lamotrigine.

Clinical evidence, mechanism, importance and management

An patient with epilepsy taking lamotrigine 200 mg daily had an increase in seizure frequency from one each month to more than one each week after starting orlistat 120 mg three times daily. It was suggested that orlistat, which is known to affect the absorption of lipophilic drugs, may have reduced the absorption of lamotrigine which is considered to be highly lipophilic.[1]

This appears to be the only report of an interaction between orlistat and lamotrigine, and therefore its clinical relevance is unclear.

1. Bigham S, McGuigan C, MacDonald BK. Reduced absorption of lipophilic anti-epileptic medications when used concomitantly with the anti-obesity drug orlistat. *Epilepsia* (2006) 47, 2207.

Lamotrigine + Phenobarbital or Primidone

Phenobarbital has been associated with reduced lamotrigine levels. Lamotrigine does not appear to affect phenobarbital and primidone levels.

Clinical evidence, mechanism, importance and management

In a retrospective study, the lamotrigine serum concentration-to-dose ratio was lower in patients also taking phenobarbital than in those taking lamotrigine alone (0.52 versus 0.99),[1] suggesting that phenobarbital lowers lamotrigine levels. Similar findings have been reported in another study.[2] No changes in the serum levels of phenobarbital or primidone were seen in a study in 12 patients also given lamotrigine 75 to 400 mg daily.[3]

Phenobarbital induces the metabolism of lamotrigine, and the recommended starting dose and long-term maintenance dose of lamotrigine in patients already taking phenobarbital or primidone is twice that of patients receiving lamotrigine monotherapy.[4,5] However, note that if patients are also taking valproate in addition to phenobarbital, the lamotrigine dose should be reduced, see ‘Lamotrigine + Valproate’, p.620. The lamotrigine dose may need to be reduced if phenobarbital is withdrawn.

1. May TW, Rambeck B, Jürgens U. Serum concentrations of lamotrigine in epileptic patients: the influence of dose and comedication. *Ther Drug Monit* (1996) 18, 523–31.
2. Armijo JA, Bravo J, Cuadrado A, Herranz JL. Lamotrigine serum concentration-to-dose ratio: influence of age and concomitant antiepileptic drugs and dosage implications. *Ther Drug Monit* (1999) 21, 182–190.
3. Jawad S, Richens A, Goodwin G, Yuen WC. Controlled trial of lamotrigine (Lamictal) for refractory partial seizures. *Epilepsia* (1989) 30, 356–63.
4. Lamictal (Lamotrigine). GlaxoSmithKline UK. UK Summary of product characteristics, October 2009.
5. Lamictal (Lamotrigine). GlaxoSmithKline. US Prescribing information, September 2009.

Lamotrigine + Phenytoin

Phenytoin has been associated with reduced lamotrigine serum levels. Lamotrigine has no effect on phenytoin levels.

Clinical evidence, mechanism, importance and management

In a retrospective study, the lamotrigine serum concentration-to-dose ratio was much lower in patients also taking phenytoin than in those taking lamotrigine alone (0.32 versus 0.98),[1] suggesting that phenytoin lowers lamotrigine levels. Other studies in patients taking lamotrigine with phenytoin have reported similar findings.[2,3] In another study, the mean lamotrigine levels were approximately doubled when phenytoin was withdrawn.[4]

One study suggests that the serum level of phenytoin is unchanged in patients taking lamotrigine 75 to 400 mg daily.[5]

Phenytoin is a known hepatic enzyme inducer, which increases lamotrigine metabolism. The recommended starting dose and long-term maintenance dose of lamotrigine in patients already taking phenytoin is twice that of patients receiving lamotrigine monotherapy.[6,7] The lamotrigine dose may need to be reduced if phenytoin is withdrawn.

However, note that if patients are also taking valproate in addition to phenytoin, the lamotrigine dose should be reduced, see ‘Lamotrigine + Valproate’, p.620.

1. May TW, Rambeck B, Jürgens U. Serum concentrations of lamotrigine in epileptic patients: the influence of dose and comedication. *Ther Drug Monit* (1996) 18, 523–31.
2. Armijo JA, Bravo J, Cuadrado A, Herranz JL. Lamotrigine serum concentration-to-dose ratio: influence of age and concomitant antiepileptic drugs and dosage implications. *Ther Drug Monit* (1999) 21, 182–190.
3. Böttiger Y, Svensson J-O, Ståhle L. Lamotrigine drug interactions in a TDM material. *Ther Drug Monit* (1999) 21, 171–4.
4. Anderson GD, Gidal BE, Messenheimer J, Gilliam FG. Time course of lamotrigine de-induction: impact of step-wise withdrawal of carbamazepine or phenytoin. *Epilepsy Res* (2002) 49, 211–17.
5. Jawad S, Richens A, Goodwin G, Yuen WC. Controlled trial of lamotrigine (Lamictal) for refractory partial seizures. *Epilepsia* (1989) 30, 356–63.
6. Lamictal (Lamotrigine). GlaxoSmithKline UK. UK Summary of product characteristics, October 2009.
7. Lamictal (Lamotrigine). GlaxoSmithKline. US Prescribing information, September 2009.

Lamotrigine + Sertraline

A report describes two cases in which sertraline appeared to increase lamotrigine levels and cause toxicity.

Clinical evidence, mechanism, importance and management

A patient’s lamotrigine levels were found to have doubled, and symptoms of toxicity were noted (confusion, cognitive impairment), 6 weeks after sertraline 25 mg daily was started.[1] The lamotrigine dose was halved, and the sertraline dose titrated to 50 mg daily. Symptoms of toxicity resolved, but the lamotrigine levels were still 24% higher than before sertraline was started. Another patient taking sertraline and lamotrigine had signs of lamotrigine toxicity. The sertraline dose was reduced by 33%, which resulted in a halving of the lamotrigine level even though the lamotrigine dose was increased by 33%.

The authors suggest that sertraline may competitively inhibit the glucuronidation of lamotrigine. Evidence so far appears limited to this report of 2 cases. In view of the increased risk of rash with increased lamotrigine levels, until more is known, it may be prudent to monitor the outcome of concurrent use.

1. Kaufman KR, Gerner R. Lamotrigine toxicity secondary to sertraline. *Seizure* (1998) 7, 163–5.

Lamotrigine + Topiramate

Although one study suggested that topiramate reduces lamotrigine levels, in general a clinically relevant interaction would not be expected. Lamotrigine has no effect on topiramate levels.

Clinical evidence, mechanism, importance and management

In the preliminary report of one study, it was found that serum lamotrigine levels of 4 of 7 patients who were stable taking lamotrigine 350 to 800 mg daily decreased by 40 to 50% when they were given topiramate, titrated to 800 mg daily.[1] In contrast, other authors reported that the addition of topiramate 75 to 800 mg daily had little effect on the steady-state serum levels of lamotrigine 100 to 950 mg daily in 24 patients. The mean lamotrigine level before topiramate was 10.4 mg/L and during topiramate was 9.7 mg/L. Only 2 of the patients had reductions of greater than 30% (40% and 43%).[2] A further study by the same research group confirmed the lack of effect of topiramate on lamotrigine pharmacokinetics.[3] The authors of the second study[2] note that there is some evidence that peak-to-trough variations of as much as 30 to 40% can occur during the use of lamotrigine, and therefore timing of blood sampling might be a factor in the findings of the first study.[1]

In one study in 13 patients lamotrigine had no effect on topiramate pharmacokinetics. The oral clearance of topiramate 400 mg daily was 2.6 L/hour when given alone, and 2.7 L/hour when given with lamotrigine, and the AUC and plasma levels of topiramate were also similar.[3]

The balance of the evidence suggests that there is no important pharmacokinetic interaction between topiramate and lamotrigine. No special precautions appear to be necessary during concurrent use.

1. Wnuk W, Volanski A, Foletti G. Topiramate decreases lamotrigine concentrations. *Ther Drug Monit* (1999) 21, 449.
2. Berry DJ, Besag FMC, Pool F, Natarajan J, Doose D. Lack of an effect of topiramate on lamotrigine serum concentrations. *Epilepsia* (2002) 43, 818–23.
3. Doose DR, Brodie MJ, Wilson EA, Chadwick D, Oxbury J, Berry DJ, Schwabe S, Bialer M. Topiramate and lamotrigine pharmacokinetics during repetitive monotherapy and combination therapy in epilepsy patients. *Epilepsia* (2003) 44, 917–22.

Lamotrigine + Valproate

The serum levels of lamotrigine can be markedly increased by valproate. Concurrent use has been associated with skin rashes, tremor and other toxic reactions. Lamotrigine has been found to cause small increases, decreases or no changes in valproate levels.

Clinical evidence

(a) Effects on lamotrigine levels

In 6 healthy subjects sodium valproate 200 mg every 8 hours reduced the clearance of lamotrigine by 20% and increased its AUC by 30%.[1] In another study in 18 healthy subjects taking valproate 500 mg twice daily, the clearance of lamotrigine 50, 100 or 150 mg daily was also markedly reduced and its half-life increased.[2] In a retrospective study, the lamotrigine serum concentration-to-dose ratio was markedly higher in patients also taking valproate than in those taking lamotrigine monotherapy (3.57 versus 0.98), suggesting that valproate increases lamotrigine levels. In patients also taking phenytoin, the effects of valproate on lamotrigine were offset (0.99 versus 0.98). However, the effects of valproate on lamotrigine were not completely offset by either carbamazepine or phenobarbital (1.67 or 1.8, respectively versus 0.98).[3] Other studies have reported broadly similar findings.[4-6] Three studies have found that the effect of valproate on lamotrigine was independent of the valproate dose or serum level (that is, it is maximal within the usual therapeutic dose range of valproate).[6-8] Another study has shown that the inhibition of lamotrigine clearance by valproate begins at very low valproate doses (less than 125 mg daily), and is maximal at doses of about 500 mg daily.[9] A study in women found that valproate appears to reduce the induction of lamotrigine metabolism associated with pregnancy or the use of oral contraceptives thus resulting in higher lamotrigine plasma levels.[10] Consider also 'Combined hormonal contraceptives + Lamotrigine', p.1183.

(b) Effects on valproate levels

In one study, 18 healthy subjects taking valproate 500 mg twice daily were also given lamotrigine 50, 100 or 150 mg daily. The lamotrigine caused a 25% decrease in valproate serum levels and a 25% increase in valproate oral clearance.[2] A study in 11 children taking valproate and other antiepileptics noted that no clinically important changes in valproate serum levels occurred when lamotrigine was added.[11] A retrospective analysis found that lamotrigine was associated with only a 7% reduction in valproate levels, which would not be expected to be clinically significant.[12]

(c) Toxic reactions

1. Rash. A patient who had taken valproate for 3 years and whose seizures were not adequately controlled by 600 mg daily was also given lamotrigine 25 mg every other day for 2 weeks, then 25 mg daily. In the fourth week of treatment he mistakenly took lamotrigine 200 mg instead of 25 mg and within hours he developed fever, oral lesions and then skin lesions, diagnosed as the Stevens-Johnson syndrome. Lamotrigine was withdrawn, the valproate dose was increased to 750 mg daily and he was treated with prednisolone, fluids, cephalosporins and proton pump inhibitors and after one month he had no active skin or mucosal lesions. It was suggested that an interaction between lamotrigine and valproate may have contributed to the development of Stevens-Johnson syndrome.[13] The authors of another report suggest that the development of Stevens-Johnson syndrome in a patient whose daily lamotrigine dose was increased gradually from 25 mg to 150 mg daily occurred as a result of the concurrent use of valproic acid. The patient was also taking trifluoperazine and zuclopenthixol.[14]

In a survey of adult patients with epilepsy who had lamotrigine added to their existing treatment, 33 were also taking valproate. Of these, 10 patients (30%) developed a rash, whereas only 6 of the 70 (8%) not taking valproate did so.[15] In another analysis of skin rash in patients taking lamotrigine, 11 of 12 patients with serious rash were also taking sodium valproate, and all but one had a lamotrigine starting dose that is higher than currently recommended.[16] However, in another study in which patients taking valproate were given lower initial doses of lamotrigine, there was no difference in incidence of rash when compared with those taking lamotrigine and other antiepileptics (13% versus 14.2%).[17]

2. Tremor. In 3 patients severe and disabling tremor (sometimes preventing them from feeding themselves) occurred when they were given lamotrigine and sodium valproate. The problem resolved when the doses were reduced.[18] In a study of 13 adult patients, all developed upper limb tremor when given lamotrigine with valproate, which could be minimised by reducing the dose of either or both drugs.[19] Other studies have found similar effects.[7,20,21]

3. Other. Severe multiorgan dysfunction and disseminated intravascular coagulation was seen in 2 children when they took lamotrigine with valproate.[22] Three patients taking lamotrigine developed neurotoxicity (confusion, lethargy) after starting to take valproate (an intravenous bolus dose of valproic acid then oral therapy). Lamotrigine levels had risen 2.9- to 6.9-fold.[20] Confusion, disorientation, visual disturbances and behavioural changes were reported in another patient 4 days after valproate was added to her treatment with lamotrigine. Lamotrigine levels were found to be 22.9 micrograms/mL (reference range 1 to 13 micrograms/mL). She recovered within 2 days of the discontinuation of both drugs.[23]

One study reported that the formation of hepatotoxic metabolites of valproate was unaffected by lamotrigine.[2]

Mechanism

Not fully understood. It is thought that valproate reduces lamotrigine glucuronidation by competitive inhibition, which results in a decreased lamotrigine clearance.[1,2,24,25] Raised lamotrigine levels have been implicated in the development of rash and serious skin reactions including Stevens-Johnson syndrome; concurrent valproate appears to increase the risk.[13,14,17,26] If lamotrigine is given with valproate rather than as lamotrigine monotherapy in pregnancy, there is a possibility that the foetus will be exposed to greater levels of lamotrigine, as valproate may counter the decline in lamotrigine levels that occur in pregnancy.[10]

Increased valproate clearance may be due to enzyme induction. Tremor may be the result of a pharmacodynamic interaction.[7,19]

Importance and management

A well documented interaction. Concurrent use can be therapeutically valuable, but the lamotrigine dose should be reduced by about half when valproate is added to avoid possible toxicity (sedation, tremor, ataxia, fatigue, rash).[2,7-9,17,18,27] In patients already taking valproate, the manufacturer of lamotrigine recommends a lamotrigine starting dose that is half that of lamotrigine monotherapy, irrespective of whether they are also receiving enzyme-inducing antiepileptics, and a very gradual dose-escalation rate.[28] The outcome should be very well monitored. The CSM in the UK has suggested that the concurrent use of sodium valproate is one of the main risk factors for the development of serious skin reactions to lamotrigine, because it prolongs the half-life of lamotrigine.[26] Rashes are potentially serious and should be evaluated promptly.[17,28,29] The reports cited above[18,22] also suggest that sometimes other serious reactions (disabling tremor, multiorgan dysfunction) can occur.

1. Yuen AWC, Land G, Weatherley BC, Peck AW. Sodium valproate acutely inhibits lamotrigine metabolism. *Br J Clin Pharmacol* (1992) 33, 511–13.
2. Anderson GD, Yau MK, Gidal BE, Harris SJ, Levy RH, Lai AA, Wolf KB, Wargin WA, Dren AT. Bidirectional interaction of valproate and lamotrigine in healthy subjects. *Clin Pharmacol Ther* (1996) 60, 145–56.
3. May TW, Rambeck B, Jürgens U. Serum concentrations of lamotrigine in epileptic patients: the influence of dose and comedication. *Ther Drug Monit* (1996) 18, 523–31.
4. Armijo JA, Bravo J, Cuadrado A, Herranz JL. Lamotrigine serum concentration-to-dose ratio: influence of age and concomitant antiepileptic drugs and dosage implications. *Ther Drug Monit* (1999) 21, 182–190.
5. Böttiger Y, Svensson J-O, Ståhle L. Lamotrigine drug interactions in a TDM material. *Ther Drug Monit* (1999) 21, 171–4.
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29. Lamictal (Lamotrigine). GlaxoSmithKline. US Prescribing information, September 2009.

Levetiracetam + Food

The oral absorption of levetiracetam is not significantly affected by food.

Clinical evidence, mechanism, importance and management

In a study, 10 healthy subjects were given a 500-mg tablet of levetiracetam with 120 mL of water or crushed and mixed with either 4 oz (about 113 g) of apple sauce or 120 mL of an enteral nutrition formulation (*Sustacal*). The overall rate and extent of absorption of oral levetiracetam were not significantly affected by crushing and mixing the tablet with either apple sauce or an enteral nutrition preparation, although the peak serum level of levetiracetam may be slightly reduced if it is mixed with enteral nutrition.[1] The clinical relevance of any effect seems likely to be small.

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Levetiracetam + Other antiepileptics

There is some evidence that the enzyme-inducing antiepileptics (carbamazepine, phenobarbital, phenytoin and primidone) may modestly reduce levetiracetam levels. Levetiracetam does not usually alter the levels of these antiepileptics. However, some studies have found modestly raised phenytoin levels, and cases of possible carbamazepine toxicity have also been reported. There appears to be no pharmacokinetic interaction between levetiracetam and gabapentin, lamotrigine, topiramate, or valproate.

Clinical evidence, mechanism, importance and management

(a) Carbamazepine

Evidence from clinical studies suggests that levetiracetam does not affect the serum levels of carbamazepine.[1-3] A study in 187 children treated with antiepileptic drugs either alone or in combination found that levetiracetam did not significantly affect plasma levels of carbamazepine.[4] However, one report describes 4 patients who experienced disabling symptoms compatible with carbamazepine toxicity when levetiracetam was added. The symptoms resolved after a decrease in the carbamazepine dose or withdrawal of the levetiracetam. A pharmacodynamic interaction was suggested, because levels of carbamazepine and its metabolite, carbamazepine-10,11-epoxide, were not affected.[5]

Some evidence suggests that patients taking levetiracetam with enzyme-inducing antiepileptics such as carbamazepine had modestly (24%) lower levetiracetam levels than those also receiving antiepileptics not considered to be enzyme-inducers (gabapentin, lamotrigine, vigabatrin), but this was not considered clinically relevant.[6] Similarly, another retrospective analysis of patient data found that the serum levetiracetam level to dose ratio was modestly lower in patients also receiving carbamazepine than those receiving monotherapy (0.32 versus 0.52),[7] suggesting that carbamazepine moderately lowers levetiracetam levels.

In general, there is no need to modify the dose of either carbamazepine or levetiracetam when used together. However, the report of possible carbamazepine toxicity introduces a note of caution.

(b) Phenytoin

Some evidence suggests that patients taking levetiracetam with enzyme-inducing antiepileptics such as phenytoin had modestly (24%) lower levetiracetam levels than those taking other antiepileptics not considered to be enzyme inducers (gabapentin, lamotrigine, vigabatrin), but this was not considered clinically relevant.[6] A retrospective analysis of patient data found that the serum levetiracetam level-to-dose ratio was lower in patients also receiving phenytoin than those receiving monotherapy (0.32 versus 0.52),[7] suggesting that phenytoin modestly lowers levetiracetam levels.

Evidence from clinical studies suggests that levetiracetam does not affect the serum levels of phenytoin.[1-3] Similarly, in one study, levetiracetam 1.5 g twice daily for 12 weeks had no effect on the steady-state pharmacokinetics of phenytoin in 6 subjects with epilepsy who were taking stable doses of phenytoin.[8] However, in one clinical study the addition of levetiracetam increased phenytoin levels by 27% to 52% in 4 patients. A further patient had a 75% increase in phenytoin levels [estimated from figure] and experienced signs of toxicity (sedation, ataxia) and required a reduction in his phenytoin dose. Another patient with raised phenytoin levels [estimated increase of 47%] had the dose of levetiracetam reduced.[9]

In general therefore, there is no need to modify the dose of either phenytoin or levetiracetam when they are used together. However, the report of raised phenytoin levels suggests that some caution is warranted.

(c) Valproate

In healthy subjects, sodium valproate 500 mg twice daily for 8 days did not affect the pharmacokinetics of a single 1.5-g dose of levetiracetam. In addition, levetiracetam did not affect the pharmacokinetics of valproate.[10] In an analysis of clinical study data, the AUC of levetiracetam in 57 patients also taking valproic acid was slightly (11%) higher than in 28 patients also taking antiepileptics not thought to affect microsomal enzymes (gabapentin, lamotrigine, vigabatrin), but this was not thought to be clinically relevant.[6] In another retrospective analysis of patient data, the serum levetiracetam level-to-dose ratio was the same in patients also receiving valproic acid than those receiving monotherapy (0.53 versus 0.52),[7] suggesting that valproate does not alter levetiracetam levels. Furthermore, evidence from clinical studies suggests that levetiracetam does not affect the serum levels of valproate.[1,3,4] There appears to be no need to adjust the doses of either sodium valproate or levetiracetam if these drugs are used together.

(d) Other antiepileptics

The AUC of levetiracetam tended to be lower in 436 patients also taking enzyme-inducing antiepileptics (carbamazepine, phenobarbital, phenytoin, **primidone**) than in 28 patients also taking antiepileptics not thought to affect microsomal enzymes (**gabapentin**, **lamotrigine**, **vigabatrin**), but the difference was modest (24%).[6] Another retrospective analysis of patient data found that the serum levetiracetam level-to-dose ratio did not differ significantly between patients also taking **lamotrigine** and those taking levetiracetam alone (0.45 versus 0.52), but was modestly lower in those taking **oxcarbazepine** (0.34 versus 0.52).[7] A study in 187 children taking antiepileptic drugs either alone or in combination found that levetiracetam did not significantly affect plasma levels of **lamotrigine** or **topiramate**.[4]

Furthermore, evidence from clinical studies suggests that levetiracetam does not affect the serum levels of **gabapentin**, **lamotrigine**, **phenobarbital**, or **primidone**.[1-3] In general, therefore, no dose adjustments would seem to be needed if levetiracetam is used as add-on therapy with any of these drugs.

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Levetiracetam + Probenecid

Probenecid increases the plasma levels of an inactive metabolite of levetiracetam.

Clinical evidence, mechanism, importance and management

One report suggests that probenecid 500 mg four times daily does not affect the renal excretion of levetiracetam. However, the renal excretion of the primary and pharmacologically inactive metabolite of levetiracetam, ucb L057, was reduced by 61%, and its plasma concentrations increased 2.5-fold,[1] although the manufacturer notes that these levels are still low.[2] The clinical relevance of elevated levels of ucb L057 is not known, therefore some have suggested caution is warranted in patients given both drugs.[1] The effect of levetiracetam on probenecid has not been studied.[2,3]

1. Patsalos PN. Pharmacokinetic profile of levetiracetam: toward ideal characteristics. *Pharmacol Ther* (2000) 85, 77–85.
2. Keppra (Levetiracetam). UCB Pharma Ltd. UK Summary of product characteristics, September 2009.
3. Keppra (Levetiracetam). UCB Inc. US Prescribing information, April 2009.

Mesuximide + Other antiepileptics

Phenobarbital, phenytoin, and possibly felbamate increase the levels of the active metabolite of mesuximide, *N*-desmethylmesuximide. Mesuximide increases the levels of phenobarbital and phenytoin, and decreases the levels of lamotrigine, and to a lesser extent, valproate.

Clinical evidence

(a) Felbamate

Three adolescent patients with epilepsy taking mesuximide developed mild adverse effects within 3 days of starting to take felbamate, which became more serious after one month (decreased appetite, nausea, weight loss, insomnia, dizziness, hiccups, slurred speech). During this time the levels of the active metabolite of mesuximide, *N*-desmethylmesuximide, rose by 26% and 46% in two patients, respectively. The adverse effects disappeared and *N*-desmethylmesuximide levels fell when the mesuximide dose was reduced. Other antiepileptics being taken were carbamazepine, ethotoin and valproate.[1]

(b) Lamotrigine

In 6 patients taking mesuximide, lamotrigine levels were 53% lower (range 36 to 72%), when compared with lamotrigine levels before starting or after stopping mesuximide. In some patients deterioration in seizure control was seen while taking mesuximide, and an improvement in seizure control occurred after mesuximide was stopped.[2] In another study, lamotrigine levels were about 70% lower in 13 patients also taking mesuximide than in 64 patients taking lamotrigine alone, when corrected for dose. Note that in patients also taking valproate, the reduction in lamotrigine levels caused by mesuximide was compensated for by the increase caused by valproate, see also 'Lamotrigine + Valproate', p.620.[3]

(c) Phenobarbital or Primidone

A study in hospitalised patients with petit mal epilepsy found that when mesuximide was given to 8 patients taking phenobarbital and 13 patients taking primidone, the mean serum levels of phenobarbital rose by 38% and 40%, respectively. Dose reductions were needed in 50% and 62% of patients, respectively. It was also found that the concurrent use of phenobarbital increased the serum levels of the active metabolite of mesuximide, *N*-desmethylmesuximide.[4]

(d) Phenytoin

Mesuximide was given to 17 patients taking phenytoin, which resulted in a 78% rise in the phenytoin serum levels requiring dose reductions in about 30% of the patients. It was also found that the concurrent use of phenytoin increased the serum levels of the active metabolite of mesuximide, *N*-desmethylmesuximide.[4]

(e) Valproate

A retrospective analysis of serum valproate levels was carried out in 17 patients who started and/or stopped taking mesuximide and whose concurrent medication remained unaltered. In the 14 patients starting mesuximide, a mean decrease in valproate levels of 32% was seen. In the 8 patients who stopped mesuximide a 30% increase in valproate levels occurred.[5] Note that the related drug, ethosuximide, has also been reported to lower valproate levels, see 'Ethosuximide + Other antiepileptics', p.615.

Mechanism

It has been suggested that phenobarbital, phenytoin and felbamate compete with mesuximide for the same metabolic mechanisms (hydroxylation) in the liver. As a result each one is metabolised more slowly and therefore their levels increase. Mesuximide appears to increase the clearance of valproate and lamotrigine (which principally occurs by glucuronidation).

Importance and management

Information about these interactions is limited. Nevertheless, concurrent use should be monitored. Anticipate the need to reduce the dose of phenytoin, phenobarbital or primidone if mesuximide is given. The dose of lamotrigine may need to be increased if mesuximide is given. There is also some evidence that the dose of valproate may need to be increased.

The activity of mesuximide is thought to be due to its active metabolite, *N*-desmethylmesuximide. Therefore, it has been suggested that levels of this metabolite should also be monitored. Anticipate the need to reduce the dose of mesuximide if felbamate is added. Other antiepileptics such as phenobarbital and phenytoin may also increase levels of *N*-desmethylmesuximide.[4]

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2. Besag FM, Berry DJ, Pool F. Methsuximide lowers lamotrigine blood levels: a pharmacokinetic antiepileptic drug interaction. *Epilepsia* (2000) 41, 624–7.
3. May TW, Rambeck B, Jürgens U. Influence of oxcarbazepine and methsuximide on lamotrigine concentrations in epileptic patients with and without valproic acid comedication: results of a retrospective study. *Ther Drug Monit* (1999) 21, 175–81.
4. Rambeck B. Pharmacological interactions of mesuximide with phenobarbital and phenytoin in hospitalized epileptic patients. *Epilepsia* (1979) 20, 147–56.
5. Besag FMC, Berry DJ, Vasey M. Methsuximide reduces valproic acid serum levels. *Ther Drug Monit* (2001) 23, 694–7.

Oxcarbazepine + Erythromycin

Erythromycin does not appear to affect the pharmacokinetics of oxcarbazepine.

Clinical evidence, mechanism, importance and management

In a study in 8 healthy subjects, the pharmacokinetics of a single 600-mg dose of oxcarbazepine were unaffected by erythromycin 500 mg twice daily for 7 days.[1] Erythromycin appears not to interact with oxcarbazepine, and no oxcarbazepine dose adjustments therefore seem to be necessary during concurrent use.

1. Keränen T, Jolkkonen J, Jensen PK, Menge GP, Andersson P. Absence of interaction between oxcarbazepine and erythromycin. *Acta Neurol Scand* (1992) 86, 120–3.

Oxcarbazepine + Felbamate

Felbamate has no clinically relevant effect on the pharmacokinetics of oxcarbazepine, but concurrent use appears to increase the incidence of adverse effects.

Clinical evidence, mechanism, importance and management

A double-blind, randomised study in 8 healthy subjects found that oxcarbazepine 300 to 600 mg every 12 hours, given with felbamate 600 to 1200 mg every 12 hours for 10 days had no effect on the plasma levels of the major active metabolite of oxcarbazepine (monohydroxyoxcarbazepine). However, the levels of dihydroxyoxcarbazepine (a minor, inactive metabolite) were reduced, and the maximum serum levels of oxcarbazepine were reduced, by about 20%. Although these changes were considered to be clinically irrelevant, the incidence of some adverse effects (dizziness, somnolence, nausea, diplopia) rose during concurrent use.[1] It may be prudent to consider this interaction as a possible cause if oxcarbazepine adverse effects become troublesome in a patient also taking felbamate.

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Oxcarbazepine + Other antiepileptics

Oxcarbazepine does not appear to affect the pharmacokinetics of carbamazepine, phenobarbital or valproate to a clinically relevant extent, but it may modestly reduce lamotrigine levels. High doses of oxcarbazepine increase phenytoin levels.
Phenytoin and phenobarbital can increase the loss of the active metabolite of oxcarbazepine, monohydroxyoxcarbazepine. Lamotrigine but not valproate, may increase levels of monohydroxyoxcarbazepine, although one study found no pharmacokinetic interaction.

Clinical evidence

(a) Effects of replacing carbamazepine with oxcarbazepine on other antiepileptics

A double-blind, crossover comparison of oxcarbazepine and carbamazepine in patients with epilepsy found that when carbamazepine was replaced by oxcarbazepine in 14 patients also taking **valproate**, the serum levels of **valproate** rose by 32%, and in 7 patients also **phenytoin**, the serum levels of **phenytoin** rose by 23%. In 18 patients taking carbamazepine, **valproate** and **phenytoin**, replacement of carbamazepine with oxcarbazepine caused a rise in the serum **valproate** and **phenytoin** levels of 21% and 25%, respectively. The study extended over 12 weeks to establish steady-state levels.[1] Another study in 4 patients with epilepsy (aged 13 to 17 years) found that the level to dose ratio of free **valproate** rose when the patients were switched from carbamazepine to oxcarbazepine, with an increase in valproate adverse effects, which resolved when the valproate dose was decreased.[2]

(b) Effects of oxcarbazepine on other antiepileptics

A study in 35 patients with epilepsy found that when oxcarbazepine 300 mg three times daily was added to treatment with **carbamazepine**, **sodium valproate** or **phenytoin** for 3 weeks there were no clinically relevant changes in the pharmacokinetics of any of these antiepileptics.[3] However, analysis of data from clinical studies found that oxcarbazepine decreased **carbamazepine** levels by about 15 to 22%, increased **phenobarbital** levels by about 14%, and at high doses increased **phenytoin** levels by up to 40%.[4,5]

In another analysis, **lamotrigine** levels were about 34% lower in 14 patients also taking oxcarbazepine than in 64 patients taking **lamotrigine** alone, when corrected for dose. In this study, the effect of oxcarbazepine was less than that of **carbamazepine** (34% versus 47%).[6] Similarly, in another analysis, the addition of oxcarbazepine to **lamotrigine** reduced **lamotrigine** levels by 15 to 75%.[7] However in contrast to these findings, one study in healthy subjects found that oxcarbazepine had no effect on the pharmacokinetics of **lamotrigine**, although adverse effects were reported to be more frequent and severe during concurrent use.[8]

(c) Effects of other antiepileptics on oxcarbazepine

1. Carbamazepine. In a study in patients given oxcarbazepine, the AUC of the metabolite monohydroxyoxcarbazepine was 40% lower in the presence of carbamazepine.[3] Similarly, in a study in children, carbamazepine was found to increase the apparent clearance of monohydroxyoxcarbazepine by 31 to 35%.[9]

2. Lamotrigine. A retrospective analysis found that monohydroxyoxcarbazepine levels to oxcarbazepine dose ratios were higher in 7 patients also taking lamotrigine than in those taking oxcarbazepine alone,[10] suggesting that lamotrigine decreased oxcarbazepine metabolism. However, in contrast to these findings, one study in healthy subjects found that lamotrigine had no effect on the pharmacokinetics of oxcarbazepine or its metabolite, monohydroxyoxcarbazepine, although adverse effects were reported to be more frequent and more severe during concurrent use.[8]

3. Phenobarbital. The AUCs of oxcarbazepine and its active metabolite, monohydroxyoxcarbazepine, were reduced by phenobarbital by 43% and 25%, respectively. There were no other significant effects on the pharmacokinetics of oxcarbazepine.[11] Similarly, in a study in children, phenobarbital was found to increase the apparent clearance of monohydroxyoxcarbazepine by 31 to 35%.[9] Another study found that the serum levels of monohydroxyoxcarbazepine were not affected by phenobarbital but its further conversion to dihydroxyoxcarbazepine was increased.[12] Since the conversion to dihydroxyoxcarbazepine is a minor step in the metabolism of monohydroxyoxcarbazepine, the overall antiepileptic action of oxcarbazepine is unlikely to be altered.

4. Phenytoin. A study found that phenytoin caused a 29% reduction in the AUC of monohydroxyoxcarbazepine.[3] Another study found that the serum levels of monohydroxyoxcarbazepine were not affected by phenytoin but its further conversion to dihydroxyoxcarbazepine was increased.[12] Since the conversion to dihydroxyoxcarbazepine is a minor step in the metabolism of monohydroxyoxcarbazepine, the overall antiepileptic action of oxcarbazepine is unlikely to be altered. Correspondingly, a study found that phenytoin 100 to 375 mg daily increased the clearance of the active metabolite, monohydroxyoxcarbazepine, by almost 40%.[13] Similarly, in a study in children, phenytoin was found to increase the apparent clearance of monohydroxyoxcarbazepine by 31 to 35%.[9]

5. Valproate. In a study in children given oxcarbazepine, valproic acid had no significant effect on the clearance of the monohydroxyoxcarbazepine metabolite of oxcarbazepine.[9]

Mechanism

Unlike carbamazepine, oxcarbazepine appears not to have marked enzyme-inducing properties so that it would not be expected to have as great an effect on the metabolism of other antiepileptics. However, oxcarbazepine does appear to act as an inhibitor of the cytochrome P450 isoenzyme CYP2C19 at high concentrations and therefore may raise phenytoin levels (see 'Phenytoin + Carbamazepine', p.632, for more on this mechanism). Other antiepileptics can increase the metabolism of the active metabolite of oxcarbazepine, monohydroxyoxcarbazepine. The situation with lamotrigine is not clear. In one study lamotrigine appeared to decrease the metabolism of oxcarbazepine but another study found no pharmacokinetic interaction.

Importance and management

Information about the concurrent use of oxcarbazepine and other antiepileptics is limited, but growing. The overall picture seems to be that oxcarbazepine is a less potent enzyme inducer than carbamazepine, and therefore it does not markedly affect the serum levels of other antiepileptics. If oxcarbazepine is substituted for carbamazepine, be aware that the drug levels of some other antiepileptics may rise. High oxcarbazepine doses may increase phenytoin levels, and the manufacturer notes that a decrease in the phenytoin dose may be required.[4] The clinical relevance of the modest reductions in lamotrigine levels is uncertain. For mention of modestly reduced levetiracetam levels in the presence of oxcarbazepine, see 'Levetiracetam + Other antiepileptics', p.621.

Any changes in the pharmacokinetics of oxcarbazepine brought about by other antiepileptics seem to be of minimal clinical relevance. However, the clinical relevance of the increase in the active metabolite monohydroxyoxcarbazepine with lamotrigine requires further study. In addition, there is the theoretical risk that monohydroxyoxcarbazepine levels might rise to toxic levels if carbamazepine or phenytoin were withdrawn.[3] For mention that there may be an increase in adverse effects if oxcarbazepine is used with felbamate, see 'Oxcarbazepine + Felbamate', p.623.

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Paraldehyde + Disulfiram

***Animal* data suggest that disulfiram can increase paraldehyde levels and prolong its effects. There is a theoretical potential for a disulfiram reaction.**

Clinical evidence, mechanism, importance and management

It is thought that paraldehyde is depolymerised in the liver to acetaldehyde, and then oxidised by acetaldehyde dehydrogenase.[1] As disulfiram inhibits this enzyme, concurrent use would be expected to result in the accumulation of acetaldehyde and result in a modified disulfiram reaction.[2] However, studies in *animals* given disulfiram and paraldehyde found increases in the levels of paraldehyde and an increase in its hypnotic effect, with only small increases in acetaldehyde levels and no increase in toxicity.[2,3] In addition, there appear to be no reports of a disulfiram reaction involving paraldehyde in humans. However, three cases of mental confusion have been reported in patients receiving disulfiram and paraldehyde.[4] Note that, patients with liver disease are at greater risk of paraldehyde adverse effects, and the addition of disulfiram results in a further risk. Therefore it may be prudent to avoid concurrent use in this type of patient.

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3. Keplinger ML, Wells JA. The effect of disulfiram on the action and metabolism of paraldehyde. *J Pharmacol Exp Ther* (1957), 119: 19–25.
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Phenobarbital or Primidone + Allopurinol

Allopurinol appears not to alter phenobarbital levels, including those derived from primidone.

Clinical evidence, mechanism, importance and management

In a study of add-on therapy, allopurinol (150 mg daily in those less than 20 kg, and 300 mg daily for other patients) for 4 months, had no effect on the phenobarbital levels in 46 patients taking antiepileptics including phenobarbital.[1] In another similar study, allopurinol 10 mg/kg increased to 15 mg/kg daily for 12 weeks had no effect on serum phenobarbital levels in 11 patients taking primidone or phenobarbital with or without other antiepileptics.[2] Therefore phenobarbital or primidone dose alterations are unlikely to be required if allopurinol is also given.

1. Zagnoni PG, Bianchi A, Zolo P, Canger R, Cornaggia C, D'Alessandro P, DeMarco P, Pisani F, Gianelli M, Verzé L, Viani F, Zaccara G. Allopurinol as add-on therapy in refractory epilepsy: a double-blind placebo-controlled randomized study. *Epilepsia* (1994) 35, 107–12.
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Phenobarbital + Azoles

Limited evidence suggests phenobarbital causes a marked decrease in itraconazole levels, and might decrease ketoconazole levels. Phenobarbital is also predicted to decrease posaconazole levels and markedly decrease voriconazole levels.

Clinical evidence, mechanism, importance and management

Note that primidone is metabolised to phenobarbital, and therefore **primidone** may also be expected to interact similarly with azole antifungals.

(a) Fluconazole

For a report that fluconazole does not significantly affect the levels of **barbexaclone** (a compound of levopropylhexedrine with phenobarbital), see 'Carbamazepine + Azoles', p.600.

(b) Itraconazole

The serum levels of itraconazole 200 mg daily were very low (0.01 to 0.03 mg/L, reference range 0.25 to 2 mg/L) in a patient taking phenobarbital. Two months after stopping the phenobarbital they were higher (0.15 mg/L), but still below the therapeutic range, apparently because carbamazepine had been recently started.[1] For mention of two other patients who had very low itraconazole levels while taking both phenytoin and phenobarbital, see 'Phenytoin + Azoles', p.630. Some manufacturers of itraconazole say that the concurrent use of potent enzyme inducers such as phenobarbital is not recommended.[2]

(c) Ketoconazole

Low ketoconazole levels in a patient with leukaemia receiving various antineoplastics was attributed to the concurrent use of phenytoin and pheno-

barbital.[3] It may be prudent to monitor the efficacy of ketoconazole if phenobarbital is also given.

(d) Posaconazole

Based on the evidence with 'phenytoin', (p.630), the manufacturer of posaconazole predicts that phenobarbital will reduce posaconazole levels, and therefore suggests avoiding the combination unless the benefits outweigh the risks.[4] If concurrent use is necessary monitor for posaconazole efficacy.

(e) Voriconazole

Based on the evidence with 'phenytoin', (p.630), the manufacturer of voriconazole predicts that phenobarbital will reduce voriconazole levels, and therefore contraindicates their concurrent use.[5,6] In the US, the manufacturer extends this contraindication to all long-acting barbiturates.[6]

1. Bonay M, Jonville-Bera AP, Diot P, Lemarie E, Lavandier M, Autret E. Possible interaction between phenobarbital, carbamazepine and itraconazole. *Drug Safety* (1993) 9, 309–11.
2. Sporanox Capsules (Itraconazole). Janssen-Cilag Ltd. UK Summary of product characteristics, October 2009.
3. Stockley RJ, Daneshmend TK, Bredow MT, Warnock DW, Richardson MD, Slade RR. Ketoconazole pharmacokinetics during chronic dosing in adults with haematological malignancy. *Eur J Clin Microbiol* (1986) 5, 513–17.
4. Noxafil (Posaconazole). Schering-Plough Ltd. UK Summary of product characteristics, November 2009.
5. VFEND (Voriconazole). Pfizer Ltd. UK Summary of product characteristics, September 2009.
6. VFEND (Voriconazole). Pfizer Inc. US Prescribing information, December 2009.

Phenobarbital + Dextropropoxyphene (Propoxyphene)

When 4 patients with epilepsy took dextropropoxyphene 65 mg three times a day for a week there was an average 20% rise in their serum phenobarbital levels.[1] This rise is unlikely to be clinically significant in most patients.

1. Hansen BS, Dam M, Brandt J, Hvidberg EF, Angelo H, Christensen JM, Lous P. Influence of dextropropoxyphene on steady state serum levels and protein binding of three anti-epileptic drugs in man. *Acta Neurol Scand* (1980) 61, 357–67.

Phenobarbital or Primidone + Felbamate

Felbamate causes a moderate increase in phenobarbital levels (including those derived from primidone), which has resulted in phenobarbital toxicity.

Clinical evidence

When 24 healthy subjects taking phenobarbital 100 mg daily were also given felbamate 1.2 g twice daily for 10 days, the AUC and the maximum plasma levels of phenobarbital were raised by 22% and 24%, respectively. Concurrent use was said to be safe and well tolerated.[1] A 30% increase in phenobarbital plasma concentrations was seen in another 19 patients taking phenobarbital or primidone (which is metabolised to phenobarbital) when they were given felbamate (average dose 2458 mg daily).[2] A phenobarbital dose reduction of about 30% was needed in another 6 patients when they started to take felbamate.[3]

A man taking sodium valproate and phenobarbital had an almost 50% increase in phenobarbital serum levels over a 5-week period after felbamate 50 mg/kg was added, despite an initial phenobarbital dose reduction from 230 mg to 200 mg daily. He was hospitalised because of increased lethargy, anorexia and ataxia and was eventually discharged taking phenobarbital 150 mg daily.[4]

It has also been noted that felbamate levels are lower in patients taking phenobarbital than in historical control patients not taking phenobarbital.[1] The manufacturer notes that steady-state felbamate levels were 29% lower in patients also given phenobarbital, when compared with levels in newly diagnosed epileptics given felbamate 2.4 g daily.[5] However, in a modelling study, phenobarbital apparently had little or no effect on the pharmacokinetics of felbamate.[6]

Mechanism

Not established. It seems possible that the felbamate may inhibit more than one pathway in the metabolism of phenobarbital, resulting in a reduction in its loss from the body. The cytochrome P450 isoenzyme CYP2C19 may be involved.[1,7]

Importance and management

An established interaction. If felbamate is added to established treatment with phenobarbital or primidone, particularly in patients already taking substantial doses, monitor closely for any evidence of increased adverse effects (drowsiness, lethargy, anorexia, ataxia) and reduce the doses of phenobarbital or primidone if necessary.

1. Reidenberg P, Glue P, Banfield CR, Colucci RD, Meehan JW, Radwanski E, Mojavarian P, Lin C-C, Nezamis J, Guillaume M, Affime MB. Effects of felbamate on the pharmacokinetics of phenobarbital. *Clin Pharmacol Ther* (1995) 58, 279–87.
2. Kerrick JM, Wolff DL, Risinger MW, Graves NM. Increased phenobarbital plasma concentrations after felbamate initiation. *Epilepsia* (1994) 35 (Suppl 8), 96.
3. Sachdeo RC, Padela MF. The effect of felbamate on phenobarbital serum concentrations. *Epilepsia* (1994) 35 (Suppl 8), 94.
4. Gidal BE, Zupanc ML. Potential pharmacokinetic interaction between felbamate and phenobarbital. *Ann Pharmacother* (1994) 28, 455–8.
5. Felbatol (Felbamate). Meda Pharmaceuticals. US Prescribing information, June 2008.
6. Kelley MT, Walson PD, Cox S, Dusci LJ. Population pharmacokinetics of felbamate in children. *Ther Drug Monit* (1997) 19, 29–36.
7. Glue P, Banfield CR, Perhach JL, Mather GG, Racha JK, Levy RH. Pharmacokinetic interactions with felbamate. *Clin Pharmacokinet* (1997) 33, 214–24.

Phenobarbital + Influenza vaccines

Influenza vaccine can cause a moderate rise in the levels of phenobarbital.

Clinical evidence, mechanism, importance and management

The serum levels of phenobarbital rose by about 30% in 11 out of 27 children who were given 0.5 mL of a whole virus influenza vaccine USP, types A and B, (Squibb). Levels remained elevated 28 days after vaccination.[1]

It was suggested that the vaccine inhibits the liver enzymes concerned with the metabolism of phenobarbital, thereby reducing its loss from the body. Information is very limited, but note that, a similar 30% increase in phenobarbital levels with felbamate has eventually required a dose adjustment after long-term concurrent use. However, as influenza vaccines are usually given as a single dose phenobarbital accumulation seems unlikely, and the increase in levels will eventually be self-limiting. Therefore it seems unlikely that this moderate increase in phenobarbital levels will be of clinical significance.

1. Jann MW, Fidone GS. Effect of influenza vaccine on serum anticonvulsant concentrations. *Clin Pharm* (1986) 5, 817–20.

Phenobarbital + Troleandomycin

Troleandomycin caused a modest fall in the phenobarbital levels of one patient.

Clinical evidence, mechanism, importance and management

A patient taking phenobarbital and carbamazepine had a modest reduction in plasma phenobarbital levels from about 40 micrograms/mL to 31 micrograms/mL when given troleandomycin.[1] The general importance of this single report is uncertain, but this 23% fall is probably of limited clinical importance.

1. Dravet C, Mesdjian E, Cenraud B and Roger J. Interaction between carbamazepine and triacetyloleandomycin. *Lancet* (1977) i, 810–11.

Phenobarbital + Valproate

Serum phenobarbital levels can be increased by valproate, which may result in excessive sedation and lethargy. Small reductions in valproate levels have also been reported. Combined use of phenobarbital and valproate may cause an increase in serum liver enzymes.

Clinical evidence

A 6-month study in 11 patients with epilepsy taking phenobarbital 90 to 400 mg daily found that when they were also given valproic acid 11.2 to 42.7 mg/kg daily sedation developed. On average the dose of phenobarbital was reduced to 54% of the original dose with continued good seizure control. Another 2 patients who did not have their phenobarbital dose reduced had an increase in their phenobarbital levels of 12% and 48%, respectively, when valproic acid was added.[1]

Another study found that sodium valproate 1.2 g daily raised serum phenobarbital levels in 20 patients by an average of 27%. Signs of toxicity occurred in 13 patients, but the dose only needed to be reduced in 3 patients.[2] This interaction has been described in numerous other reports, and dose reductions of the phenobarbital were almost always necessary to avoid excessive drowsiness.[3-17] In one study the rise in phenobarbital levels was much greater in children (over 100%) than in adults (about 50%).[18]

A small reduction in sodium valproate levels (of about 25%) has also been reported, but the effect on seizure control was not mentioned.[19] A reduction in valproate levels caused by phenobarbital has also been reported elsewhere.[20]

The incidence of increased liver enzyme activity was found to be higher in 41 patients receiving phenobarbital with valproate than in 40 patients taking valproate alone (ALT 7.3% versus 0%). When phenytoin was also given an even greater incidence of increases (ALT 26.1% and AST 28.3% versus about 20%) occurred. However, the increases were mild and were not considered clinically important.[21]

Mechanism

The evidence indicates that valproate inhibits three steps in the metabolism of phenobarbital by the liver, leading to its accumulation in the body. The inhibited steps are the formation of *p*-hydroxyphenobarbital by the cytochrome P450 isoenzyme CYP2C9,[22] the *N*-glucosidation of phenobarbital[23] and the *O*-glucuronidation of *p*-hydroxyphenobarbital.[23]

Importance and management

An extremely well documented and well established interaction of clinical importance. The incidence seems to be high. The effects of concurrent use should be well monitored and suitable phenobarbital dose reductions made as necessary to avoid toxicity. The dose may need to be reduced by one-third to one-half.[1] The significance of the modest reduction in valproate levels is not clear, especially as valproate levels do not correlate well with efficacy of treatment. Valproate has been associated with serious hepatotoxicity, especially in children aged less than 3 years, and this has been more common in those receiving other antiepileptics. Valproate monotherapy is to be preferred in this group.

1. Wilder BJ, Willmore LJ, Bruni J, Villarreal HJ. Valproic acid: interaction with other anticonvulsant drugs. *Neurology* (1978) 28, 892–6.
2. Richens A, Ahmad S. Controlled trial of sodium valproate in severe epilepsy. *BMJ* (1975) 4, 255–6.
3. Schobben F, van der Kleijn E and Gabreëls FJM. Pharmacokinetics of di-n-propylacetate in epileptic patients. *Eur J Clin Pharmacol* (1975) 8, 97–105.
4. Gram L, Wulff K, Rasmussen KE, Flachs H, Würtz-Jørgensen A, Sommerbeck KW, Løhren V. Valproate sodium: a controlled clinical trial including monitoring of drug levels. *Epilepsia* (1977) 18, 141–8.
5. Jeavons PM, Clark JE. Sodium valproate in treatment of epilepsy. *BMJ* (1974) 2, 584–6.
6. Völzke E, Doose H. Dipropylacetate (Dépakine®, Ergenyl®) in the treatment of epilepsy. *Epilepsia* (1973) 14, 185–93.
7. Millet Y, Sainty JM, Galland MC, Sidoine R, Jouglard J. Problèmes posés par l'association thérapeutique phénobarbital-dipropylacétate de sodium. A propos d'un cas. *Eur J Toxicol Environ Hyg* (1976) 9, 381–3.
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12. Loiseau P, Orgogozo JM, Brachet-Liermain A, Morselli PL. Pharmacokinetic studies on the interaction between phenobarbital and valproic acid. In Adv Epileptol Proc Cong Int League Epilepsy 13th. Edited by Meinardi H and Rowan A. (1977/8) p 261–5.
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16. Kapetanovic IM, Kupferberg HJ, Porter RJ, Theodore W, Schulman E, Penry JK. Mechanism of valproate-phenobarbital interaction in epileptic patients. *Clin Pharmacol Ther* (1981) 29, 480–6.
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18. Fernandez de Gatta MR, Alonso Gonzalez AC, Garcia Sanchez MJ, Dominguez-Gil Hurle A, Santos Borbujo J, Monzon Corral L. Effect of sodium valproate on phenobarbital serum levels in children and adults. *Ther Drug Monit* (1986) 8, 416–20.
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Phenytoin + Allopurinol

A case report describes phenytoin toxicity in a boy given allopurinol. Another study found that allopurinol may raise phenytoin levels but only in some patients.

Clinical evidence, mechanism, importance and management

A 13-year-old boy with Lesch-Nyhan syndrome who was taking phenobarbital, clonazepam, valproic acid and phenytoin 200 mg daily became somnolent within 7 days of starting to take allopurinol 150 mg daily. His serum phenytoin levels were found to have increased from 7.5 micrograms/mL to 20.8 micrograms/mL.[1] In a study, 2 patients had a marked increase in phenytoin levels when they were given allopurinol (150 mg daily in those less than 20 kg, and 300 mg daily for other patients) for 4 months, which in one case led to withdrawal from the study, and in the other to a phenytoin dose reduction. However, 16 other patients had no change in phenytoin levels while taking this dose of allopurinol.[2]

The reason for this reaction is not known. An *animal* study confirmed that 50 mg/kg, but not 20 mg/kg, of allopurinol reduced phenytoin elimination, but was unable to work out the mechanism.[3]

Although information is limited, it appears that allopurinol may raise phenytoin levels in some patients. It would therefore be prudent to monitor for phenytoin toxicity (e.g. blurred vision, nystagmus, ataxia or drowsiness) when allopurinol, particularly in high doses, is added.

1. Yokochi K, Yokochi A, Chiba K, Ishizaki T. Phenytoin-allopurinol interaction: Michaelis-Menten kinetic parameters of phenytoin with and without allopurinol in a child with Lesch-Nyhan syndrome. *Ther Drug Monit* (1982) 4, 353–7.
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Phenytoin + Amiodarone

Serum phenytoin levels can be raised by amiodarone, markedly so in some individuals, and phenytoin toxicity may occur. Amiodarone serum levels are reduced by phenytoin.

Clinical evidence

(a) Phenytoin serum levels increased

Three patients had a marked rise in serum phenytoin levels 10 days to 4 weeks after being given amiodarone 400 mg to 1.2 g daily. One patient developed phenytoin toxicity (ataxia, lethargy, vertigo) within 4 weeks of starting to take amiodarone and had a serum phenytoin level of 40 micrograms/mL, representing a three to fourfold increase. Levels restabilised when the phenytoin dose was withheld and then reduced from 300 to 200 mg daily. The serum phenytoin levels of the other 2 patients were approximately doubled by amiodarone.[1] Other case reports describe 3 patients who had two- to threefold rises in serum phenytoin levels, and toxicity, 2 to 6 weeks after starting amiodarone.[2-4]

A study in healthy subjects found that amiodarone 200 mg daily for 3 weeks increased the AUC of a single 5-mg/kg intravenous dose of phenytoin by 40%.[5] Another pharmacokinetic study found that amiodarone 200 mg daily for 6 weeks raised the AUC and steady-state peak serum

levels of phenytoin by 40% and 33%, respectively. In this study, phenytoin 2 to 4 mg/kg daily was given orally for 14 days before and during the last 2 weeks of amiodarone use.[6]

(b) Amiodarone serum levels reduced

A study in 5 healthy subjects given amiodarone 200 mg daily found that over a 5-week period the serum amiodarone levels gradually increased. When phenytoin 3 to 4 mg/kg daily was added for a period of 2 weeks, the serum amiodarone levels fell to concentrations that were between about 50% and 65% of those predicted.[7]

Mechanism

Uncertain. It seems possible that amiodarone inhibits the liver enzymes concerned with the metabolism of phenytoin, resulting in a rise in its serum levels.[6] It seems unlikely that drug displacement from protein binding sites had a part to play as free and bound levels of phenytoin remained constant.[6]

Phenytoin is an enzyme-inducing drug that possibly increases the metabolism of the amiodarone by the liver.

Importance and management

Information seems to be limited to the reports cited, but both interactions appear to be clinically important. Concurrent use should not be undertaken unless the effects can be well monitored.

Monitor phenytoin levels and for adverse effects (e.g. blurred vision, nystagmus, ataxia or drowsiness) and reduce the phenytoin dose as necessary. A 25 to 30% reduction has been recommended for those taking phenytoin 2 to 4 mg/kg daily, but it should be remembered that small alterations in phenytoin dose may result in a large change in phenytoin levels, as phenytoin kinetics are non-linear.[6,8,9] Note that the phenytoin levels in some individuals were doubled after only 10 days of concurrent use.[1] Amiodarone has a long half-life so that this interaction will persist for weeks after its withdrawal. Continued monitoring is important. Be aware that ataxia due to phenytoin toxicity may be confused with amiodarone-induced ataxia.[1,3]

It is not clear whether or not the amiodarone dose should be increased to accommodate this interaction because the metabolite of amiodarone (*N*-desethylamiodarone) also has important antiarrhythmic effects.[7]

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Phenytoin + Antacids

Some studies have found that antacids can reduce phenytoin levels and this may have been responsible for some loss of seizure control in a few patients. However other studies have not found any interaction and it seems that usually no clinically important interaction occurs.

Clinical evidence

A review briefly mentions that 3 patients taking phenytoin were found to have low serum phenytoin levels of 2 to 4 micrograms/mL when they were given phenytoin at the same time as antacids (unnamed), but when antacid administration was delayed by 2 to 3 hours the serum phenytoin levels rose two to threefold.[1]

Elsewhere, 2 patients with epilepsy are reported to have had inadequate seizure control, which coincided with the ingestion of **aluminium/magnesium hydroxide** antacids for dyspepsia.[2]

In a study in 8 healthy subjects, the AUC of a single dose of phenytoin was reduced by a modest 25% by either **aluminium/magnesium hydroxide** or **calcium carbonate**.[3] A study in 6 healthy subjects given **aluminium** or **magnesium hydroxide** did not find any change in the rate or extent of absorption of a single dose of phenytoin,[2] and a similar study found that **calcium carbonate** also had no effect on the absorption of phenytoin.[4] A controlled study in 6 patients with epilepsy found that a **magnesium trisilicate** and **aluminium hydroxide** antacid (*Gelusil*) caused a slight 12% reduction in steady-state serum phenytoin levels, which would not be expected to be clinically significant. Seizure frequency was not affected.[4] A study in 2 subjects found that the absorption of phenytoin was not altered by a mixture of **aluminium/magnesium hydroxide** and **magnesium trisilicate**, or **calcium carbonate**.[5] In another study in 6 healthy subjects, no statistically significant decrease in absorption was seen when phenytoin was given with an antacid containing **simeticone**, **aluminium hydroxide** and **magnesium oxide** (*Asilone*).[6]

Mechanism

Not understood. One suggestion is that diarrhoea and a general increase in peristalsis caused by some antacids may cause a reduction in phenytoin absorption. Another is that antacids may cause changes in gastric acid secretion, which could affect phenytoin solubility.

Importance and management

This possible interaction is fairly well documented, but the results are conflicting. In practice it appears not to be important in most patients, although some loss of seizure control has been seen to occur in isolated cases. Concurrent use need not be avoided but if there is any hint that phenytoin levels are reduced, separation of the doses by 2 to 3 hours may, as with other interactions caused by antacids, minimise the effects.

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Phenytoin + Antidiabetics

Large and toxic doses of phenytoin have been seen to cause hyperglycaemia, but normal therapeutic doses do not usually affect the control of diabetes. Two isolated cases of phenytoin toxicity have been attributed to the use of tolazamide or tolbutamide. Miglitol does not affect the bioavailability of phenytoin.

Clinical evidence

(a) Effects on phenytoin

In a study, tolbutamide 500 mg two or three times daily was given to 17 patients taking phenytoin 100 to 400 mg daily.[1] The patients had a transient 45% rise in the amount of non-protein-bound phenytoin by day 2, which had disappeared by day 4. The introduction to this report briefly mentions a man given phenytoin and **tolazamide** who developed phenytoin toxicity, which disappeared when **tolazamide** was replaced by **insulin**.[1] A woman previously uneventfully treated with phenytoin and **tolbutamide** developed toxicity on a later occasion when she took **tolbutamide** with twice the previous dose of phenytoin.[2] One study in healthy subjects found that **miglitol** 100 mg three times daily for 5 days did not affect the bioavailability of a single 400-mg dose of phenytoin.[3]

(b) Response to antidiabetics

Phenytoin has been found in a number of reports[4-9] to raise the blood glucose levels of both diabetics and non-diabetics. However, in all but one of these cases the phenytoin dose was large (at least 8 mg/kg) or even in the toxic range (70 to 80 mg/kg). There is little evidence that a hyperglycaemic response to usual doses of phenytoin is normally large enough to interfere with the control of diabetes, either with diet alone or with conventional antidiabetic drugs. In the one case where the interaction occurred with a therapeutic dose of phenytoin (1.2 g in the 24 hours follow-

ing status epilepticus), the situation was complicated by the use of many other drugs and by renal impairment.[5]

Mechanism

Studies in *animals* and man[10-13] suggest that phenytoin-induced hyperglycaemia occurs because the release of insulin from the pancreas is impaired. This implies that no interaction is possible without functional pancreatic tissue. Just why phenytoin appeared to interact with tolazamide and tolbutamide is uncertain, but it is possible that these antidiabetics competitively inhibit phenytoin hydroxylation[14,15] by the cytochrome P450 isoenzyme CYP2C9.[16]

Importance and management

The weight of evidence shows that no interaction of clinical importance normally occurs between phenytoin and the antidiabetic drugs (most of the studies involved sulfonylureas). No special precautions would generally be expected to be necessary.

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Phenytoin + Antimycobacterials

Phenytoin levels are markedly reduced by rifampicin, but can be raised by isoniazid. Patients who are slow acetylators (slow metabolisers) of isoniazid may develop phenytoin toxicity. If rifampicin (rifampin) and isoniazid are given together, serum phenytoin levels may fall in patients who are fast acetylators of isoniazid, but may occasionally rise in those who are slow acetylators. Clofazimine may reduce serum phenytoin levels.

Clinical evidence

(a) Isoniazid

A study in 32 patients given phenytoin 300 mg daily found that within a week of starting to take isoniazid 300 mg daily and **aminosalicylic acid** 15 g daily, 6 of them had phenytoin levels almost 5 micrograms/mL higher than the rest of the group. On the following days, when the phenytoin levels of these 6 patients rose above 20 micrograms/mL, the typical signs of phenytoin toxicity were seen. All 6 patients with raised phenytoin levels had unusually high serum isoniazid levels and were identified as slow acetylators of isoniazid.[1]

Rises in serum phenytoin levels and toxicity induced by the concurrent use of isoniazid has been described in numerous other reports,[2-15] involving large numbers of patients, one of which describes a fatality.[8]

(b) Rifampicin (Rifampin)

A study in 6 patients found that the clearance of intravenous phenytoin 100 mg doubled (from 46.7 to 97.8 mL/minute), when rifampicin 450 mg daily was taken for 2 weeks.[16]

A man taking phenytoin 400 mg daily experienced a seizure 3 days after starting rifampicin 600 mg daily. His phenytoin level was low (5.1 micrograms/mL) so rifampicin was stopped and the phenytoin dose increased to 500 mg daily. His level increased slowly over the next 2 weeks, eventually ranging between 16 and 25 micrograms/mL.[17] Another man taking phenytoin needed a dose reduction from 375 to 325 mg daily to keep his serum phenytoin levels within the therapeutic range when he stopped taking rifampicin.[18] A man with AIDS taking a large number of drugs (rifampicin, clofazimine, ciprofloxacin, ethambutol, clarithromycin, diphenoxylate, bismuth, octreotide, co-trimoxazole, amphotericin, flucytosine, amikacin, zalcitabine) was also given phenytoin to control a right-sided seizure disorder. Despite taking phenytoin 1.6 g daily, and a trial of intravenous treatment, his trough phenytoin plasma levels remained almost undetectable until rifampicin was withdrawn, when they rose to 5 micrograms/mL with the oral dose. When **clofazimine** was withdrawn the levels rose even further to 10 micrograms/mL.[19]

(c) Rifampicin (Rifampin) and Isoniazid

A patient taking phenytoin 300 mg daily developed progressive drowsiness (a sign of phenytoin toxicity) during the first week of taking isoniazid, rifampicin and ethambutol. His serum phenytoin levels rose to 46.1 micrograms/mL. He slowly recovered when the phenytoin was stopped, and he was later stabilised taking phenytoin 200 mg daily. He proved to be a slow acetylator of isoniazid.[20] Another patient taking phenytoin 300 mg daily was also given isoniazid, rifampicin and ethambutol but, in anticipation of the response seen in the previous patient, his phenytoin dose was reduced to 200 mg daily. Within 3 days he developed seizures because his serum phenytoin levels had fallen to only 8 micrograms/mL. He needed to take phenytoin 400 mg daily to keep the serum levels within the therapeutic range. He was a fast acetylator of isoniazid.[20]

The clearance of phenytoin was doubled in 14 patients given rifampicin 450 mg, isoniazid 300 mg and ethambutol 900 mg to 1.2 g daily for 2 weeks. No further changes occurred in the pharmacokinetics of phenytoin after 3 months of antimycobacterial treatment. In this study, the interaction was of a similar magnitude in both the 8 slow acetylators and the 6 fast acetylators.[16]

Mechanism

Rifampicin (a known potent liver enzyme inducer) increases the metabolism and clearance of phenytoin from the body so that a larger dose is needed to maintain adequate serum levels. Isoniazid inhibits the liver microsomal enzymes that metabolise phenytoin, and as a result phenytoin accumulates and its serum levels rise.[21] Only patients who are slow acetylators (slow metabolisers) of isoniazid normally attain blood levels of isoniazid that are sufficiently high to cause extensive inhibition of phenytoin metabolism. Fast acetylators (fast metabolisers) remove the isoniazid too quickly for this to occur. Acetylator status is genetically determined. Thus some individuals will show a rapid rise in phenytoin levels, which eventually reaches toxic concentrations, whereas others will show only a relatively slow and unimportant rise to a plateau within, or only slightly above the therapeutic range.

If isoniazid and rifampicin are given together, the enzyme inhibitory effects of isoniazid may oppose the effects of rifampicin in patients who are slow acetylators of isoniazid, but in patients who are fast acetylators, the isoniazid will be cleared too quickly for it effectively to oppose the rifampicin effects. However, in one study isoniazid did not counter the effects of rifampicin in slow acetylators.[16]

The interaction involving clofazimine is not understood.

Importance and management

Direct information seems to be limited to these reports, but the interactions appear to be of clinical importance. Monitor the serum phenytoin levels and increase the dose appropriately if rifampicin alone is started. Reduce the phenytoin dose if rifampicin is stopped. If both rifampicin and isoniazid are given, the outcome may depend on the isoniazid acetylator status of the patient. Patients who are fast acetylators will probably also need an increased phenytoin dose, whereas patients who are slow acetylators may need a smaller phenytoin dose if toxicity is to be avoided. All patients

should be monitored very closely as, unless acetylator status is known, the outcome is unpredictable.

The interaction with phenytoin and isoniazid alone is well documented, well established, clinically important and potentially serious. About 50% of the population are slow or relatively slow metabolisers of isoniazid,[1] but not all of them develop serum phenytoin levels in the toxic range. The reports indicate that somewhere between 10 and 33% of patients are at risk.[1-4,10] This adverse interaction may take only a few days to develop fully in some patients, but several weeks in others. Therefore concurrent use should be very closely monitored (e.g. for evidence of phenytoin adverse effects, such as blurred vision, nystagmus, ataxia or drowsiness), making suitable dose reductions as necessary. One patient was reported to have had better seizure control with fewer adverse effects while taking both drugs than with phenytoin alone.[22]

Information about clofazimine seems to be limited to one report. Monitor concurrent use, anticipating the need to increase the phenytoin dose.

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Phenytoin + Aspirin or NSAIDs

Phenytoin levels can be markedly increased by azapropazone and toxicity can develop rapidly. It is inadvisable for patients to take these drugs together. Phenytoin levels can also be increased by phenylbutazone, and phenytoin toxicity may occur. It seems likely that oxyphenbutazone will interact similarly.

Phenytoin toxicity has been seen in one patient taking ibuprofen, although no pharmacokinetic interaction was found in a study. Phenytoin toxicity occurred in a patient taking celecoxib. High-dose aspirin can cause protein-binding displacement of phenytoin, but this does not usually seem to be clinically important. No clinically significant interaction occurs between phenytoin and bromfenac, etodolac or tolfenamic acid.

Clinical evidence, mechanism, importance and management

(a) Aspirin

It has been suggested that if a patient has been taking large quantities of aspirin, phenytoin is 'potentiated'.[1] This comment remains unconfirmed, although a study in 10 healthy subjects did find that aspirin 975 mg every 4 hours caused protein binding displacement of phenytoin, resulting in a 16% rise in free salivary phenytoin levels and a 24% decrease in serum levels. However, these changes were considered unlikely to be clinically significant, and aspirin doses of 325 and 650 mg every 4 hours had no appreciable effect on phenytoin.[2] Similar effects on protein binding displacement have been seen in other studies.[3-7] However, although the ratios of free and bound phenytoin may change, there does not appear to be a clinical effect, possibly because the extra free phenytoin is metabolised by the liver.[6] A study in 10 patients with epilepsy taking phenytoin found that when they were also given aspirin 500 mg three times daily for 3 days, no significant changes in serum phenytoin levels or antiepileptic effects occurred.[8] The extremely common use of aspirin, and the almost total silence in the literature about an adverse interaction between phenytoin and aspirin implies that no special precautions are likely to be needed when both drugs are given.

(b) Azapropazone

A patient taking phenytoin developed phenytoin toxicity within 2 weeks of starting azapropazone 600 mg twice daily. Further study in 5 healthy subjects given phenytoin 125 to 250 mg daily found that azapropazone 600 mg twice daily, briefly decreased their mean serum phenytoin levels from 5 micrograms/mL to 3.7 micrograms/mL before they rose steadily over the next 7 days to 10.5 micrograms/mL.[9,10] An extension of this study is described elsewhere.[11] Another report describes phenytoin toxicity in a woman taking phenytoin and primidone when **fenclofenac** was replaced by azapropazone 1.2 g daily.[12]

The most likely explanation is that azapropazone inhibits the liver enzymes concerned with the metabolism of phenytoin, resulting in its accumulation. It also seems possible that azapropazone displaces phenytoin from its plasma protein binding sites so that levels of unbound (and active) phenytoin are increased. Information seems to be limited to the reports cited, but it appears to be a clinically important interaction. The incidence is uncertain, but an interaction occurred in all 5 of the subjects in the study cited.[9,11] The concurrent use of azapropazone and phenytoin has been contraindicated.[13]

(c) Bromfenac

Twelve healthy subjects were given bromfenac 50 mg three times daily for 4 days and then phenytoin 300 to 330 mg for up to 14 days (to achieve stable levels), and then both drugs for 8 days. It was found that the peak phenytoin serum levels and AUC were increased by 9% and 11%, respectively, while the bromfenac peak levels and AUC were reduced by 42%. The suggested reason for the reduction in bromfenac levels is that phenytoin increases its metabolism by the liver.[14] In practical terms these results indicate that there is no need to adjust the dose of phenytoin if bromfenac is added, nor any need to increase the bromfenac dose unless there is any evidence that its efficacy is diminished.

(d) Celecoxib

An elderly woman taking phenytoin 300 mg daily who had also been taking celecoxib for the previous 6 months, developed signs of phenytoin toxicity. She was found to have a phenytoin level of 42 micrograms/mL, and a very slow rate of elimination.[15] It was thought that celecoxib may have competed with phenytoin for elimination by the cytochrome P450 isoenzyme CYP2C9. The general relevance of this isolated report is unclear.

(e) Etodolac

A crossover study in 16 healthy subjects found that etodolac 200 mg every 12 hours for 3 days had no effect on the pharmacokinetics or the pharmacological effects of phenytoin (100 mg twice daily for 2 days and 100 mg on day three).[16] There would seem to be no reason for avoiding the concurrent use of these drugs.

(f) Ibuprofen or Dexibuprofen

Studies in healthy subjects found that the pharmacokinetics of single 300- or 900-mg doses of phenytoin were not significantly altered by ibuprofen 300 or 400 mg every 6 hours.[17,18] However, a report describes a woman stabilised on phenytoin 300 mg daily who developed phenytoin toxicity within a week of starting to take ibuprofen 400 mg four times daily.[19] Her serum phenytoin levels had risen to about 25 micrograms/mL. The phenytoin was stopped for 3 days and the ibuprofen withdrawn, and within 10 days the phenytoin level had dropped to about 17 micrograms/mL. Another report describes a patient stabilised taking phenytoin 300 mg daily (4.3 mg/kg daily) who developed symptoms of phenytoin toxicity 72 hours after starting dexibuprofen 800 mg daily. Phenytoin levels were found to be 30.6 micrograms/mL. Dexibuprofen was withdrawn and phenytoin was stopped for 3 days. Two weeks after

the re-introduction of phenytoin, symptoms of toxicity had resolved and levels had fallen to 17.3 micrograms/mL.[20] The reasons for this interaction are not understood.

Both phenytoin and ibuprofen have been available for many years. Dexibuprofen, the active enantiomer of ibuprofen, has been introduced more recently. These 2 cases, some 25 years apart, appear to be the only reports of an adverse interaction. No special precautions would normally seem to be necessary.

(g) Oxyphenbutazone or Phenylbutazone

Six patients with epilepsy taking phenytoin 200 to 350 mg daily who were then also given phenylbutazone 100 mg three times daily had a mean fall in their phenytoin serum levels from 15 micrograms/mL to 13 micrograms/mL over the first 3 days, after which the levels rose steadily to 19 micrograms/mL over the next 11 days. One patient developed symptoms of toxicity. His levels of free phenytoin more than doubled.[8] Another study found that phenylbutazone increased the steady-state half-life of phenytoin from 13.7 hours to 22 hours.[21]

The predominant effect of phenylbutazone seems to be the inhibition of the enzymes concerned with the metabolism of phenytoin,[21] leading to its accumulation in the body and a rise in its serum levels. The initial transient fall may possibly be related in some way to the displacement by phenylbutazone of phenytoin from its plasma protein binding sites.[22] This is an established interaction, although the documentation is very limited. Monitor the outcome of adding phenylbutazone and reduce the phenytoin dose as necessary. There is no direct evidence that oxyphenbutazone interacts like phenylbutazone, but as it is the main metabolic product of phenylbutazone in the body and has been shown to prolong the half-life of phenytoin in *animals*,[23] it would be expected to interact similarly.

(h) Tolfenamic acid

In a study in 11 patients, tolfenamic acid 300 mg daily for 3 days had no significant effect on the serum levels of phenytoin.[8] No special precautions seem necessary if these drugs are taken concurrently.

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Phenytoin + Atovaquone

In 12 healthy subjects, atovaquone (1 g given twelve hours before and with a single 600-mg dose of phenytoin) did not affect the pharmacokinetics of phenytoin. It was concluded that a clinically important pharmacokinetic interaction is unlikely.[1]

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Phenytoin + Azoles

Phenytoin levels are raised by fluconazole (toxicity seen). Posaconazole, voriconazole and possibly miconazole interact similarly. Itraconazole (and therefore probably ketoconazole) have little effect on phenytoin levels.

Phenytoin decreases itraconazole and possibly ketoconazole levels (treatment failures seen). Posaconazole and voriconazole are similarly affected. Fluconazole levels are not usually affected by phenytoin, although there is one report of reduced efficacy.

Clinical evidence

(a) Fluconazole

In a randomised, placebo-controlled study, 10 subjects taking fluconazole 200 mg daily for 14 days with phenytoin 200 mg daily for the last 3 days were compared with 10 other subjects taking phenytoin alone. Fluconazole caused the phenytoin AUC to rise by 75%, and the trough phenytoin levels to rise by 128%.[1] Two other studies reported similar findings,[2,3] and there are reports describing at least 7 cases of phenytoin toxicity caused by fluconazole.[4-7]

Some studies suggest that phenytoin does not alter fluconazole levels;[1,3] however, a brief report noted that 3 of 9 patients taking fluconazole and phenytoin required an increase in their fluconazole dose or the substitution of another antifungal due to a lack of efficacy. It was suggested that phenytoin may reduce fluconazole levels in some patients.[8]

(b) Itraconazole

In a study in 13 healthy subjects, oral phenytoin 300 mg daily for 15 days reduced the AUC of a single 200-mg dose of itraconazole by more than 90%. The half-life of itraconazole fell from 22.3 hours to 3.8 hours.[9] A parallel study in 15 healthy subjects found that itraconazole 200 mg for 15 days increased the phenytoin AUC by 10%.[9]

Two patients taking phenytoin and two taking phenytoin with carbamazepine either did not respond to treatment with itraconazole 400 mg daily for aspergillosis, coccidioidomycosis or cryptococcosis, or suffered a relapse. All of them had undetectable or substantially reduced serum itraconazole levels compared with other patients taking itraconazole alone.[10] Two other patients also had very low itraconazole serum levels while taking phenytoin and phenobarbital.[11]

(c) Ketoconazole

A study in 9 healthy subjects found that ketoconazole 200 mg twice daily for 6 days did not significantly alter the AUC_{0-48} of a single 250-mg dose of phenytoin.[2]

A man being treated for coccidioidal meningitis with ketoconazole 400 mg daily relapsed when he was given phenytoin 300 mg daily. A pharmacokinetic study found that his peak serum ketoconazole levels and AUC were reduced, when compared with the values seen before the phenytoin was started. Even though the ketoconazole dose was increased to 600 mg, and later 1.2 g, his serum levels remained low compared with other patients taking only 400 or 600 mg of ketoconazole.[12] Coccidioidomycosis progressed in another patient taking phenytoin despite the use of ketoconazole.[10] Low serum ketoconazole levels were seen in one patient taking phenytoin and phenobarbital.[13]

(d) Miconazole

A man with epilepsy, well controlled with phenytoin, developed symptoms of phenytoin toxicity within one day of starting *intravenous* miconazole 500 mg every 8 hours and flucytosine. After one week of concurrent use his serum phenytoin levels had risen by 50% (from 29 micrograms/mL to 43 micrograms/mL). He had some very mild symp-

toms of phenytoin toxicity before the antifungal treatment was started.[14] Another patient developed symptoms of phenytoin toxicity (nystagmus, ataxia) within 5 days of starting to take oral miconazole 500 mg daily. His serum phenytoin level rose to 40.8 micrograms/mL. After discontinuation of the miconazole the same dose of phenytoin resulted in a level of 14.5 micrograms/mL.[15]

(e) Posaconazole

In a study in healthy subjects the concurrent use of posaconazole 200 mg daily and phenytoin 200 mg daily for 10 days decreased the AUC of posaconazole by 50%, when compared with controls. Although there was no statistically significant change in phenytoin pharmacokinetics, some subjects had increases in phenytoin levels, which the authors thought could be clinically relevant.[16]

(f) Voriconazole

Studies in healthy subjects found that phenytoin 300 mg daily decreased the maximum serum levels and AUC of voriconazole by 49% and 69%, respectively. Also, voriconazole 400 mg twice daily increased the maximum serum levels and AUC of phenytoin 300 mg daily by 67% and 81%, respectively.[17] A patient with systemic lupus erythematosus presented with seizures, and multiple brain lesions were found on imaging. She was given phenytoin 400 mg daily for seizure control and oral voriconazole 300 mg twice daily for possible CNS *Aspergillus* infection. After one month, because voriconazole trough levels were low (0.2 micrograms/mL) and clinical improvement had not occurred, the dose of voriconazole was increased to 400 mg twice daily. Nine days later trough levels of voriconazole had increased to 0.68 micrograms/mL, but 6 weeks later the patient developed oral candidiasis. Voriconazole was increased to 400 mg three times daily. At steady-state her serum levels were 4.08 micrograms/mL and the candidiasis improved.[18]

Mechanism

Fluconazole inhibits the cytochrome P450 isoenzymes responsible for phenytoin metabolism (probably CYP2C9).[2] Voriconazole and miconazole probably act similarly, but ketoconazole and itraconazole do not affect this isoenzyme and therefore do not significantly affect phenytoin levels. Phenytoin is an enzyme inducer, and appears to induce the metabolism of these azoles to varying degrees.

Importance and management

The increase in serum phenytoin levels with **fluconazole** is established and clinically important. Toxicity can develop within 2 to 7 days unless the phenytoin dose is reduced. Monitor serum phenytoin levels closely and reduce the dose appropriately. Also be alert for any evidence of reduced fluconazole effects. Evidence for increased phenytoin levels with **miconazole** is limited, even so it would be prudent to monitor serum phenytoin levels. Note that, a large proportion of miconazole oral gel (both prescription and non-prescription doses) may be swallowed and therefore adequate systemic absorption may occur to produce an interaction.

The decrease in **itraconazole** levels with phenytoin is established, clinically important and its incidence appears to be high. Because such a marked fall in itraconazole levels occurs, it is difficult to predict by how much its dose should be increased, and indeed, dose increases may not be effective. The authors of one report advise using another antifungal instead,[9] and this seems prudent. The small rise in serum phenytoin levels caused by itraconazole is unlikely to be clinically important.

Information on the interaction between **ketoconazole** and phenytoin appears to be limited to these reports, but be alert for any signs of a reduced antifungal response. It may be necessary to increase the dose of the ketoconazole, but note that this may not be wholly successful. Ketoconazole probably does not have an important effect on phenytoin levels.

Phenytoin halves **posaconazole** levels, and posaconazole might increase phenytoin levels. The manufacturer of posaconazole suggests that concurrent use should be avoided unless the benefits outweigh the risks.[19] If used together it would seem sensible to consider increasing the posaconazole dose, and increase monitoring of phenytoin adverse effects (e.g. blurred vision, nystagmus, ataxia or drowsiness), taking levels as necessary, and adjusting the phenytoin dose as appropriate.

The interaction between phenytoin and **voriconazole** is established. The UK manufacturers say that concurrent use of voriconazole and phenytoin should be avoided unless the benefits outweigh the risks.[20] If used together, the manufacturers recommend careful monitoring of phenytoin levels and adverse effects, and doubling the dose of oral voriconazole (from 200 to 400 mg twice daily and from 100 mg to 200 mg twice daily in patients less than 40 kg) or increasing the dose of intravenous voriconazole (from 4 to 5 mg/kg twice daily).[20,21] However, note that, in the case report described above,[18] doses of voriconazole 50% greater than those recommended were required to treat breakthrough infection.

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Phenytoin + Bile-acid binding resins

The absorption of phenytoin does not appear to be affected by colestyramine or colestipol.

Clinical evidence, mechanism, importance and management

In a study in 6 healthy subjects, colestyramine 5 g or colestipol 10 g did not have a significant effect on the absorption of a single 500-mg dose of phenytoin. Colestyramine and colestipol were given 2 minutes before and 6 and 12 hours after the phenytoin.[1] Another study in 6 healthy subjects found that colestyramine 4 g four times daily for 5 days had no significant effect on the extent of the absorption of a single 400-mg dose of phenytoin (given on day 3, two minutes after the colestyramine).[2] No special precautions would seem to be necessary if either of these drugs and phenytoin is taken concurrently.

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Phenytoin + Calcium-channel blockers

Diltiazem can increase phenytoin levels. A single case report describes phenytoin toxicity with nifedipine and another case report describes neurological toxicity when a patient taking phenytoin (with carbamazepine) was given isradipine.

The levels of felodipine and nisoldipine are very markedly reduced by phenytoin. Case reports suggest that nimodipine and verapamil levels may be reduced by phenytoin.

Clinical evidence

(a) Diltiazem

Elevated serum phenytoin levels and signs of toxicity developed in 2 out of 14 patients taking phenytoin when they were also given diltiazem.[1] A patient taking phenytoin 250 mg twice daily developed signs of toxicity within 2 weeks of starting to take diltiazem 240 mg every 8 hours.[2]

(b) Felodipine

After taking felodipine 10 mg daily for 4 days, 10 patients with epilepsy (including 2 taking phenytoin alone and 3 taking phenytoin with carbamazepine) had markedly reduced plasma felodipine levels (peak levels of 1.6 nanomol/L compared with 8.9 nanomol/L in 12 control subjects). The felodipine bioavailability was reduced to 6.6%.[3]

(c) Isradipine

A man taking carbamazepine and phenytoin developed neurological toxicity while also taking isradipine, which the authors attributed to a pharmacokinetic or pharmacodynamic interaction between the phenytoin and isradipine.[4] However, a commentator considered that an interaction between carbamazepine and isradipine was more plausible.[5]

(d) Nifedipine

An isolated report describes phenytoin toxicity in a man taking phenytoin, 3 weeks after he started to take nifedipine 30 mg daily. His serum phenytoin level was 30.4 micrograms/mL. The nifedipine was stopped, and over the next 2 weeks his serum phenytoin levels fell to 10.5 micrograms/mL. A further 2 weeks later all the symptoms had resolved.[6] However, a retrospective study of 8 patients suggested that nifedipine does not usually interact with phenytoin.[1]

One of the manufacturers of nifedipine notes that the bioavailability of nifedipine may be reduced by phenytoin.[7]

(e) Nimodipine

A study in 8 patients with epilepsy, one of whom was taking phenytoin with carbamazepine, found that the AUC of a single 60-mg oral dose of nimodipine was only about 15% of that obtained in a group of healthy subjects.[8]

(f) Nisoldipine

Twelve patients with epilepsy receiving long-term phenytoin and 12 healthy subjects were given single 40- or 20-mg doses of nisoldipine. The mean nisoldipine AUCs (normalised for a 20-mg dose) were 1.6 micrograms/L per hour for the patients, and 15.2 micrograms/L per hour for the healthy subjects.[9]

(g) Verapamil

A woman taking phenytoin who was then also given verapamil had persistently subtherapeutic plasma verapamil levels (less than 50 nanograms/mL) despite increases in the verapamil dose from 80 mg twice daily to 160 mg three times daily. When the phenytoin was stopped, her plasma verapamil levels rose to the expected concentrations.[10]

Mechanism

Diltiazem may inhibit the metabolism of phenytoin. In contrast, the antiepileptics are well recognised as enzyme inducers, which can increase the metabolism of the calcium-channel blockers by the liver, resulting in a very rapid loss from the body.

Importance and management

Information about the effects of calcium-channel blockers on phenytoin is limited, but what is known indicates that if diltiazem is given with phenytoin, the dose of phenytoin may possibly need to be reduced to avoid toxicity; however, it should be noted that there are only 3 case reports describing this interaction and not all patients appear to be affected, so any effect appears to be rare. The case report of phenytoin toxicity with nifedipine is isolated, and of unknown importance.

Phenytoin markedly reduces felodipine, verapamil, and possibly nifedipine levels. Although not all calcium-channel blockers have been studied, most would be expected to interact with phenytoin similarly, as they are metabolised by the same isoenzymes (see 'Calcium-channel blockers', (p.1025)). A considerable increase in the dose of any calcium-channel blocker will probably be needed in the presence of phenytoin. In some cases the decreases in levels are so large, that dose increases may not be effective, and alternatives to the calcium-channel blocker may be necessary.

Note that the manufacturers of nimodipine[11] and nisoldipine[12] contraindicate the concurrent use of phenytoin because of the possibility of a large reduction in their levels.

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Phenytoin + Carbamazepine

Some reports describe rises in phenytoin levels, with toxicity, whereas others describe falls in phenytoin levels, when carbamazepine is given. Falls in carbamazepine levels, sometimes with rises in carbamazepine-10,11-epoxide levels, have also been described.

Clinical evidence

(a) Reduced serum phenytoin levels

Carbamazepine 600 mg daily for 4 to 14 days reduced the serum phenytoin levels of 3 out of 7 patients, from 15 to 7 micrograms/mL, from 18 to 12 micrograms/mL and from 16 to 10 micrograms/mL, respectively. Phenytoin serum levels rose again 10 days after carbamazepine was withdrawn.[1]

Reduced serum phenytoin levels in patients given carbamazepine have been described in other reports.[2-5]

(b) Raised serum phenytoin levels

A study in 6 patients with epilepsy taking phenytoin 350 to 600 mg daily found that over a 12-week period the addition of carbamazepine 600 to 800 mg daily increased the phenytoin serum levels by 35%, increased its half-life by 41% and reduced its clearance by 37%. Neurotoxicity increased by 204%, with additional symptoms of toxicity (sedation, ataxia, nystagmus, etc.) developing in 5 of the 6 patients. The phenytoin dose remained unchanged throughout the period of the study.[6]

Other reports have also described increases in serum phenytoin levels,[7-12] which were as large as 81%, and even up to 100% in some cases.[8,10] One study found that carbamazepine increased the free fraction of phenytoin by 39%.[13]

(c) Reduced serum carbamazepine levels

A series of multiple regression analyses on data from a large number of patients [the precise number is not clear from the report] found that phenytoin reduced plasma carbamazepine levels by, on average, 0.9 micrograms/mL for each 2 mg/kg per day of phenytoin.[7]

Reduced serum carbamazepine levels have been described in other studies and reports.[3,11,14-17] Two studies found that phenytoin markedly increased the levels of the active metabolite of carbamazepine, carbamazepine-10,11-epoxide.[18,19]

Mechanism

Not understood. Both carbamazepine and phenytoin are enzyme inducers, and might therefore be expected to increase the metabolism of each other. However, more recently it has been shown that carbamazepine can inhibit the cytochrome P450 isoenzyme CYP2C19, which is one of the enzymes involved in phenytoin metabolism.[20] Carbamazepine might therefore

cause increases in phenytoin levels by this mechanism. Moreover, CYP2C19 shows genetic polymorphism (that is, different patients have different amounts of this isoenzyme), so an interaction by this mechanism would not occur in all patients.

Importance and management

Phenytoin may decrease carbamazepine levels, but carbamazepine has a variable effect on phenytoin levels, with both increases and decreases described. Monitor antiepileptic levels during concurrent use (where possible including the active metabolite of carbamazepine, carbamazepine-10,11-epoxide) so that steps can be taken to avoid the development of toxicity or lack of efficacy. Not all patients appear to have an adverse interaction, and, at present, it does not seem possible to identify those potentially at risk. The risk of carbamazepine-induced water intoxication is reported to be reduced in patients also taking phenytoin.[15]

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Phenytoin + Chloramphenicol

Phenytoin levels can be raised by intravenous chloramphenicol and phenytoin toxicity may occur. Other evidence indicates that phenytoin may increase or decrease chloramphenicol levels in children.

Clinical evidence

(a) Effect on chloramphenicol

A child given a 6-week course of intravenous chloramphenicol 100 mg/kg daily in four divided doses had a reduction in chloramphenicol peak and trough serum levels of 46% and 74%, respectively, within 2 days of starting phenytoin 4 mg/kg daily.[1] In contrast, 6 children (aged 1 month to 12 years) developed raised, toxic chloramphenicol levels while receiving phenytoin.[2]

(b) Effect on phenytoin

A man taking phenytoin 100 mg four times daily developed signs of phenytoin toxicity within a week of starting intravenous chloramphenicol (1 g every 6 hours for 4 doses then 2 g every 6 hours). His serum phenytoin levels had risen by about threefold, from about 7 to 24 micrograms/mL.[3]

This interaction has been described in a number of other reports.[4-12] One study found that intravenous chloramphenicol more than doubled the half-life of phenytoin.[4] The AUC of phenytoin after a single intravenous dose of **fosphenytoin** was 23% higher (not significant) in children also given intravenous chloramphenicol, when compared with those given intravenous cefotaxime. In addition, the phenytoin half-life was significantly prolonged by chloramphenicol (23.7 hours versus 15.5 hours).[13]

Mechanism

It seems probable that chloramphenicol, a known enzyme inhibitor,[14] affects the liver enzymes (possibly cytochrome P450 isoenzyme CYP2C19[15]) concerned with the metabolism of phenytoin thereby reducing its rate of clearance from the body. The changes in the pharmacokinetics of chloramphenicol in children are not understood.

Importance and management

The rise in serum phenytoin levels with intravenous chloramphenicol in adults is well documented and clinically important. A two to fourfold rise can occur within a few days. Concurrent use should be avoided unless the effects can be closely monitored and appropriate phenytoin dose reductions made as necessary. The use of a single prophylactic dose of phenytoin or fosphenytoin may be an exception to this.[13] It seems very doubtful if enough chloramphenicol is absorbed from eye drops or ointments for an interaction to occur.

The general clinical importance of the changes in serum chloramphenicol levels in children is uncertain, but the effects of concurrent use should certainly be monitored. More study is needed.

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14. Dixon RL, Fouts JR. Inhibition of microsomal drug metabolic pathways by chloramphenicol. *Biochem Pharmacol* (1962) 11, 715–20.
15. Park J-Y, Kim K-A, Kim S-L. Chloramphenicol is a potent inhibitor of cytochrome P450 isoforms CYP2C19 and CYP3A4 in human liver microsomes. *Antimicrob Agents Chemother* (2003) 47, 3464–9.

Phenytoin + Chlorphenamine

Phenytoin toxicity was attributed to the concurrent use of chlorphenamine in two patients.

Clinical evidence, mechanism, importance and management

A woman taking phenytoin and phenobarbital developed phenytoin toxicity with serum phenytoin levels of about 65 micrograms/mL about a week after starting to take chlorphenamine 4 mg three times daily. The toxic symptoms disappeared and phenytoin levels fell when chlorphenamine was withdrawn.[1] Another woman taking antiepileptics, including phenytoin, developed slight grimacing of the face and involuntary jaw movements (but no speech slurring, ataxia or nystagmus) within 12 days of starting to take chlorphenamine 12 to 16 mg daily. Her serum phenytoin level had risen to 30 micrograms/mL but it fell when chlorphenamine was withdrawn.[2]

The reason for these reactions is not clear but it has been suggested that

chlorphenamine may have inhibited the metabolism of phenytoin by the liver; however, chlorphenamine is not usually associated with enzyme inhibition. These are isolated cases, and their general relevance is uncertain, but it seems likely to be small.

1. Pugh RNH, Geddes AM, Yeoman WB. Interaction of phenytoin with chlorpheniramine. *Br J Clin Pharmacol* (1975) 2, 173–5.
2. Ahmad S, Laidlaw J, Houghton GW, Richens A. Involuntary movements caused by phenytoin intoxication in epileptic patients. *J Neurol Neurosurg Psychiatry* (1975) 38, 225–31.

Phenytoin + Coumarins and related drugs

Phenytoin levels can be increased by dicoumarol (toxicity seen) and phenprocoumon, but they are usually unchanged by warfarin and phenindione. However, a single case of phenytoin toxicity has been seen with warfarin. Phenytoin would be expected to reduce the anticoagulant effects of coumarin anticoagulants, and this has been seen with dicoumarol and warfarin. However, cases of increased effects of warfarin have been reported, and one study found that the effects of phenprocoumon were generally unaltered. A single case of severe bleeding has been described in a patient taking acenocoumarol and phenytoin.

Clinical evidence

The reports of interactions between phenytoin and various anticoagulants are summarised in 'Table 14.2', (below), and discussed in further detail below.

(a) Acenocoumarol

A 68-year-old woman with a double mitral valve lesion, atrial fibrillation and hypertension, taking digoxin and diuretics, was stabilised taking acenocoumarol 17 mg per week in divided doses and paroxetine. Phenytoin 400 mg daily for 3 days then 300 mg daily was started because of a seizure, and 11 days later she developed ataxia, lethargy and nystagmus (free phenytoin level 12.5 micromol/L). At the same time her INR was found to have risen from a range of 2 to 4, up to 14.5 and a huge retroperitoneal haematoma was discovered. After appropriate treatment she was discharged taking acenocoumarol 13 mg per week in divided doses and half the phenytoin dose.[1]

(b) Dicoumarol

Phenytoin 300 mg daily was given to 6 subjects taking dicoumarol 40 to 160 mg daily for a week. No significant changes in the prothrombin-proconvertin concentration occurred until 3 days after stopping the phenytoin. In the following 5 days it climbed from 20 to 50%, with an accompanying drop in the serum dicoumarol levels.[2] Four other subjects taking dicoumarol 60 mg daily were also given phenytoin 300 mg daily for the first week of treatment, and then 100 mg daily for 5 more weeks. The prothrombin-proconvertin concentration had risen from 20 to 70% after 2 weeks of concurrent use, representing an antagonism of the anticoagulant effect, and only fell to previous levels 5.5 weeks after stopping phenytoin.[2]

A study in 6 subjects taking phenytoin 300 mg daily found that when they were also given dicoumarol (doses adjusted to give prothrombin values of about 30%) their serum phenytoin levels rose on average by almost 10 micrograms/mL (126%) over 7 days.[3] In another study in 3 patients the half-life of phenytoin increased by about fivefold during dicoumarol use.[4]

A patient taking dicoumarol developed phenytoin toxicity within a few days of starting to take phenytoin 300 mg daily (dose based on a weight of 62 kg). Phenytoin was withdrawn, and re-introduced at 200 mg daily, which gave satisfactory phenytoin levels.[5]

(c) Phenindione

A study in 4 patients taking phenytoin 300 mg daily found that phenindione did not affect their serum phenytoin levels.[4]

(d) Phenprocoumon

An investigation in patients taking long-term phenprocoumon found that in the majority of cases phenytoin had no significant effect on either serum phenprocoumon levels or the anticoagulant control, although a few patients had a fall and others a rise in serum anticoagulant levels, with consequent decreased or increased effects.[6]

A study in 4 patients taking phenytoin 300 mg daily found that when they were given phenprocoumon their serum phenytoin levels rose from about 10 micrograms/mL to 14 micrograms/mL over 7 days.[4] The phenytoin half-life increased from 9.9 hours to 14 hours.

(e) Warfarin

The prothrombin time of a patient taking warfarin increased from 21 to 32 seconds over a month when phenytoin 300 mg daily was also given, despite a 22% reduction in the warfarin dose. He was restabilised on the original warfarin dose when phenytoin was withdrawn. Six other reports

Table 14.2 Summary of interactions between phenytoin and anticoagulants

Concurrent treatment with phenytoin and anticoagulant	*Effect on anticoagulant*	*Effect on serum phenytoin levels*
Acenocoumarol	Single case of increase[1]	Uncertain
Dicoumarol	Reduced[2]	Markedly increased[3-5]
Phenindione	Not documented	Usually unchanged[3,4]
Phenprocoumon	Usually unchanged[6]	Increased[4]
Warfarin	Increased[7-12,13] Single case of increase followed by decrease[10]	Usually unchanged[4] Increased in two cases[12,14]

1. Abad-Santos F, Carcas AJ, F-Capitán C, Frias J. Case report. Retroperitoneal haematoma in a patient treated with acenocoumarol, phenytoin and paroxetine. *Clin Lab Haematol* (1995) 17, 195-7.
2. Hansen JM, Siersbæk-Nielsen K, Kristensen M, Skovsted L,Christensen LK. Effect of diphenylhydantoin on the metabolism of dicoumarol in man. *Acta Med Scand* (1971) 189, 15-19.
3. Hansen JM, Kristensen M, Skovsted L, Christensen LK. Dicoumarol-induced diphenylhydantoin intoxication. *Lancet* (1966) ii, 265-6.
4. Skovsted L, Kristensen M, Hansen JM, Siersbæk-Nielsen K. The effect of different oral anticoagulants on diphenylhydantoin (DPH) and tolbutamide metabolism. *Acta Med Scand* (1976) 199, 513-15.
5. Franzten E, Hansen JM, Hansen OE, Kristensen M. Phenytoin (Dilantin®) intoxication. *Acta Neurol Scand* (1967) 43, 440-6.
6. Chrishe HW, Tauchert M, Hilger HH. Effect of phenytoin on the metabolism of phenprocoumon. *Eur J Clin Invest* (1974) 4, 331.
7. Nappi JM. Warfarin and phenytoin interaction. *Ann Intern Med* (1979) 90, 852.
8. Koch-Weser J. Haemorrhagic reactions and drug interactions in 500 warfarin treated patients. *Clin Pharmacol Ther* (1973) 14, 139.
9. Taylor JW, Alexander B, Lyon LW. A comparative evaluation of oral anticoagulant-phenytoin interactions. *Drug Intell Clin Pharm* (1980) 14, 669-73.
10. Levine M, Sheppard I. Biphasic interaction of phenytoin with warfarin. *Clin Pharm* (1984) 3, 200-3.
11. Panegyres PK, Rischbieth RH. Fatal phenytoin warfarin interaction. *Postgrad Med J* (1991) 67, 98.
12. Meisheri YV. Simultaneous phenytoin and warfarin toxicity on chronic concomitant therapy. *J Assoc Physicians India* (1996) 44, 661-2.
13. Hassan Y, Awaisu A, Aziz NA, Ismail O. The compexity of achieving anticoagulation control in the face of warfarin-phenytoin interaction. *Pharm World Sci* (2005) 27, 16-19.
14. Rothermich NO. Diphenylhydantoin intoxication. *Lancet* (1966) ii, 640.

describe this interaction.[7-12] One of them describes a patient who had an increased anticoagulant response to warfarin for the first 6 days after phenytoin was added. The anticoagulant effect then declined to less than the level seen before the addition of phenytoin.[10] Conversely, a population pharmacokinetic analysis reported that the clearance of warfarin was *increased* by 30% in 6 patients taking phenytoin or phenobarbital.[13] However, the findings were not reported separately for the two drugs, and are therefore difficult to interpret (phenobarbital is a known inducer of warfarin clearance, see 'Coumarins + Barbiturates', p.440).

A study in 2 patients taking phenytoin 300 mg daily found that their serum phenytoin levels were unaffected by warfarin given for 7 days, and the half-life of phenytoin in 4 other patients was unaffected.[4] However, a patient taking phenytoin 300 mg daily developed symptoms of toxicity shortly after starting to take warfarin.[14] Another patient developed phenytoin toxicity 6 months after starting to take phenytoin with warfarin.[12]

Mechanism

Multiple, complex and poorly understood. Dicoumarol and phenprocoumon (but not normally warfarin) appear to inhibit the metabolism of phenytoin by the liver, so that its loss from the body is reduced. Phenytoin is an inducer of the cytochrome P450 isoenzyme CYP2C9, which is involved (to varying degrees) in the metabolism of the coumarin anticoagulants. Phenytoin would therefore be expected to decrease the levels and effect of some coumarins, and this has been shown for dicoumarol. However, increased effects of warfarin have been noted, suggesting reduced metabolism of warfarin. Why this occurs is uncertain, but poor CYP2C9 metaboliser phenotype (that is, those patients genetically lacking this isoenzyme) may provide an explanation.[15] Phenytoin possibly also has a diverse depressant effect on the liver, which lowers blood clotting factor production.[16]

Importance and management

None of these interactions has been extensively studied nor are they well established, but what is known suggests that the use of dicoumarol with phenytoin should be avoided or monitored very closely. Similarly, serum phenytoin levels and anticoagulant control should be well monitored if acenocoumarol, phenprocoumon or warfarin is given with phenytoin. Dose adjustments may be needed to accommodate any interactions. Information about other anticoagulants (apart from phenindione, which had no effect on phenytoin levels) appears to be lacking, but it would clearly be prudent to monitor the effects of concurrent use.

1. Abad-Santos F, Carcas AJ, F-Capitán C, Frias J. Case report. Retroperitoneal haematoma in a patient treated with acenocoumarol, phenytoin and paroxetine. *Clin Lab Haematol* (1995) 17, 195–7.
2. Hansen JM, Siersbæk-Nielsen K, Kristensen M, Skovsted L,Christensen LK. Effect of diphenylhydantoin on the metabolism of dicoumarol in man. *Acta Med Scand* (1971) 189, 15–19.
3. Hansen JM, Kristensen M, Skovsted L, Christensen LK. Dicoumarol-induced diphenylhydantoin intoxication. *Lancet* (1966) ii, 265–6.
4. Skovsted L, Kristensen M, Hansen JM, Siersbæk-Nielsen K. The effect of different oral anticoagulants on diphenylhydantoin (DPH) and tolbutamide metabolism. *Acta Med Scand* (1976) 199, 513–15.
5. Franzten E, Hansen JM, Hansen OE, Kristensen M. Phenytoin (Dilantin®) intoxication. *Acta Neurol Scand* (1967) 43, 440–6.
6. Chrishe HW, Tauchert M, Hilger HH. Effect of phenytoin on the metabolism of phenprocoumon. *Eur J Clin Invest* (1974) 4, 331.
7. Nappi JM. Warfarin and phenytoin interaction. *Ann Intern Med* (1979) 90, 852.
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10. Levine M, Sheppard I. Biphasic interaction of phenytoin with warfarin. *Clin Pharm* (1984) 3, 200–3.
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12. Meisheri YV. Simultaneous phenytoin and warfarin toxicity on chronic concomitant therapy. *J Assoc Physicians India* (1996) 44, 661–2.
13. Mungall DR, Ludden TM, Marshall J, Hawkins DW, Talbert RL, Crawford MH. Population pharmacokinetics of racemic warfarin in adult patients. *J Pharmacokinet Biopharm* (1985) 13, 213–27.
14. Rothermich NO. Diphenylhydantoin intoxication. *Lancet* (1966) ii, 640.
15. Rettie AE, Haining RL, Bajpai M, Levy RH. A common genetic basis for idiosyncratic toxicity of warfarin and phenytoin. *Epilepsy Res* (1999) 35, 253–5.
16. Solomon GE, Hilgartner MW, Kutt H. Coagulation defects caused by diphenylhydantoin. *Neurology* (1972) 22, 1165–71.

Phenytoin + Dextromethorphan

Dextromethorphan appears not to affect phenytoin levels.

Clinical evidence, mechanism, importance and management

A double-blind, crossover study in 4 patients with severe complex partial seizures found that dextromethorphan 120 mg daily in liquid form (*Delsym*) over 3 months had no effect on their serum phenytoin levels. There was a non-significant alteration in the complex partial seizure and tonic-clonic seizure frequency.[1] This suggests that the dose of phenytoin does not need to be adjusted in patients also given dextromethorphan.

1. Fisher RS, Cysyk BJ, Lesser RP, Pontecorvo MJ, Ferkany JT, Schwerdt PR, Hart J, Gordon B. Dextromethorphan for treatment of complex partial seizures. *Neurology* (1990) 40, 547–9.

Phenytoin + Dextropropoxyphene (Propoxyphene)

Although no interaction generally appears to occur between phenytoin and dextropropoxyphene, a case report describes phenytoin toxicity in a patient given both drugs.

Clinical evidence, mechanism, importance and management

In a study, 6 patients taking phenytoin were given dextropropoxyphene 65 mg three times daily for 6 to 13 days. Dextropropoxyphene caused only a very small rise in phenytoin levels.[1] In contrast, a review briefly mentions one patient who developed toxic serum phenytoin levels while taking dextropropoxyphene in doses of up to 600 mg daily on an as-required basis.[2]

Concurrent use need not be avoided, but as rises in the serum levels of phenytoin can occur it would be prudent to monitor the outcome, especially if large doses of dextropropoxyphene are being taken. It is probably sufficient to monitor for increased phenytoin adverse effects (blurred vision, nystagmus, ataxia or drowsiness).

1. Hansen BS, Dam M, Brandt J, Hvidberg EF, Angelo H, Christensen JM, Lous P. Influence of dextropropoxyphene on steady state serum levels and protein binding of three anti-epileptic drugs in man. *Acta Neurol Scand* (1980) 61, 357–67.
2. Kutt H. Biochemical and genetic factors regulating Dilantin metabolism in man. *Ann N Y Acad Sci* (1971) 179, 704–22.

Phenytoin + Diazoxide

Three children and one adult had very marked reductions in their phenytoin levels when diazoxide was given, and in one case seizures developed. There is some evidence that the effects of diazoxide may be reduced by phenytoin.

Clinical evidence

A child taking phenytoin 29 mg/kg daily and an adult taking phenytoin 1 g daily were unable to achieve therapeutic phenytoin serum levels while taking diazoxide. When the diazoxide was withdrawn, satisfactory serum phenytoin levels were achieved with doses of only 6.6 mg/kg and 400 mg daily, in the child and the adult, respectively. When diazoxide was restarted experimentally in the adult, the serum phenytoin levels became undetectable after 4 days, and seizures occurred.[1] Two other reports describe this interaction.[2,3]

Limited evidence suggests that the half-life and effects of the diazoxide can be reduced by phenytoin.[2,4]

Mechanism

What is known suggests that diazoxide increases the metabolism and the clearance of phenytoin from the body.[1,2]

Importance and management

Information is limited to these reports, but the interaction would appear to be established. Given the rapid development of seizures in one case, it would seem prudent to avoid concurrent use where possible. If both drugs must be given, monitor the effects of concurrent use, being alert for the need to increase the phenytoin dose. The clinical importance of the reduced diazoxide effects is uncertain.

1. Roe TF, Podosin RL, Blaskovics ME. Drug Interaction: diazoxide and diphenylhydantoin. *J Pediatr* (1975) 87, 480–4.
2. Petro DJ, Vannucci RC, Kulin HE. Diazoxide-diphenylhydantoin interaction. *J Pediatr* (1976) 89, 331–2.

3. Turck D, Largilliere C, Dupuis B, Farriaux JP. Interaction entre le diazoxide et la phénytoïne. *Presse Med* (1986) 15, 31.
4. Pruitt AW, Dayton PG, Patterson JH. Disposition of diazoxide in children. *Clin Pharmacol Ther* (1973) 14, 73–82.

Phenytoin + Dichloralphenazone

There is some evidence that phenytoin levels may be reduced by dichloralphenazone.

Clinical evidence, mechanism, importance and management

In 5 healthy subjects, dichloralphenazone 1.3 g each night for 13 nights doubled the total body clearance of a single intravenous dose of phenytoin.[1] The phenazone component of dichloralphenazone is a known enzyme inducer and the increased clearance of phenytoin is probably due to an enhancement of its metabolism by the liver. There seem to be no additional reports of adverse effects in patients given both drugs, so that the clinical importance of this interaction is uncertain. However, it would seem prudent to be alert for a reduction in serum phenytoin levels if dichloralphenazone is also given.

1. Riddell JG, Salem SAM, McDevitt DG. Interaction between phenytoin and dichloralphenazone. *Br J Clin Pharmacol* (1980) 9, 118P.

Phenytoin + Felbamate

Felbamate causes a moderate increase in phenytoin levels. Felbamate levels are reduced by phenytoin.

Clinical evidence

A pilot study in 4 patients noted that felbamate increased plasma phenytoin levels.[1] Therefore, in a further study in 5 patients, the phenytoin dose was automatically reduced by 20% when felbamate was given. One patient needed a slight increase in phenytoin dose, whereas 2 other patients needed a further reduction in their phenytoin dose.[2] In a later full report of this study, it was noted that phenytoin dose decreases of 10 to 30% were required to maintain stable levels in the presence of felbamate.[3] Another study in patients with epilepsy found that felbamate 1.2 or 1.8 g daily increased the maximum plasma phenytoin levels by 31% and 69%, respectively. Higher felbamate doses necessitated phenytoin dose reductions of 20 to 40%.[4]

Studies in children and adults have found that phenytoin increased the clearance of felbamate by about 40%,[5,6] and decreased maximum felbamate levels by 56 to 60%, when compared with patients taking felbamate alone.[4] Another report suggested that this effect was dose-dependent.[7]

Mechanism

Uncertain but felbamate probably acts as a competitive inhibitor of phenytoin metabolism, thereby reducing its loss from the body and increasing its serum levels,[2,8] whereas phenytoin induces felbamate metabolism, thereby increasing its clearance.[7]

Importance and management

Established interactions. The phenytoin dose may need to be reduced (a 20 to 40% reduction seems to be about right[2,4,8]) if felbamate is added, and increased if felbamate is withdrawn. However, note that, as phenytoin pharmacokinetics are non-linear, any dose adjustments will need to be assessed in individual patients. The importance of the reduced felbamate levels is uncertain, but they are probably less important because felbamate has a wide therapeutic range.[4]

1. Sheridan PH, Ashworth M, Milne K, White BG, Santilli N, Lothman EW, Dreifuss FE, Jacobs MP, Martinez P, Leppik IE. Open pilot study of felbamate (ADD 03055) in partial seizures. *Epilepsia* (1986) 27, 649.
2. Fuerst RH, Graves NM, Leppik IE, Remmel RP, Rosenfeld WE, Sierzant TL. A preliminary report on alteration of carbamazepine and phenytoin metabolism by felbamate. *Drug Intell Clin Pharm* (1986) 20, 465–6.
3. Leppik IE, Dreifuss FE, Pledger GW, Graves NM, Santilli N, Drury I, Tsay JY, Jacobs MP, Bertram E, Cereghino JJ, Cooper G, Sahlroot JT, Sheridan P, Ashworth M, Lee SI, Sierzant TL. Felbamate for partial seizures: results of a controlled clinical trial. *Neurology* (1991) 41, 1785–9.
4. Sachdeo R, Wagner M, Sachdeo S, Schumaker RC, Lyness WH, Rosenberg A, Ward D, Perhach JL. Coadministration of phenytoin and felbamate: evidence of additional phenytoin dose-reduction requirements based on pharmacokinetics and tolerability with increasing doses of felbamate. *Epilepsia* (1999) 40, 1122–8.
5. Kelley MT, Walson PD, Cox S, Dusci LJ. Population pharmacokinetics of felbamate in children. *Ther Drug Monit* (1997) 19, 29–36.
6. Banfield CR, Zhu G-RR, Jen JF, Jensen PK, Schumaker RC, Perhach JL Affrime MB, Glue P. The effect of age on the apparent clearance of felbamate: a retrospective analysis using nonlinear mixed-effects modeling. *Ther Drug Monit* (1996) 18, 19–29.
7. Wagner ML, Graves NM, Marienau K, Holmes GB, Remmel RP, Leppik IE. Discontinuation of phenytoin and carbamazepine in patients receiving felbamate. *Epilepsia* (1991) 32, 398–406.
8. Fuerst RH, Graves NM, Leppik IE, Brundage RC, Holmes GB, Remmel RP. Felbamate increases phenytoin but decreases carbamazepine concentrations. *Epilepsia* (1988) 29, 488–91.

Phenytoin + Food

The absorption of phenytoin can be affected by some foods. A very marked reduction in phenytoin absorption has been described when it was given with enteral feeds (e.g. *Isocal*, *Osmolite*), by nasogastric or jejunostomy tubes.

Clinical evidence

(a) Food by mouth

A study found that serum drug levels were lower than expected when phenytoin was disguised in **vanilla pudding** and given to children. However, when the phenytoin was mixed with **apple sauce**, 3 out of 10 patients developed serum phenytoin levels within the toxic range, and the mean levels were twice those seen when the tablets were mixed with the **vanilla pudding**.[1] The absorption of phenytoin as the acid in a micronised form (*Fenantoin*, ACO, Sweden) was faster and the peak serum levels were on average 40% higher when it was given after a **standardised breakfast**.[2] In a further study to investigate the effects of component parts of the **standardised breakfast**, the same authors found that **fat** had no measurable effect, but **carbohydrate** may enhance, and **protein** reduce, the absorption of phenytoin.[3]

Another study in 5 subjects found that the bioavailability of a single dose of phenytoin was enhanced when it was given immediately after a '**balanced**' **meal**. Administration after a **high-lipid meal** resulted in large inter-patient variability in phenytoin bioavailability.[4] One single-dose study found that, when taken with a **high-protein meal**, the total absorption of phenytoin was not affected, although it was slightly delayed.[5]

A patient with epilepsy had a marked fall in his serum phenytoin levels accompanied by an increased seizure frequency when phenytoin was given at bedtime with 8 oz of a food supplement (***Ensure***).[6] Another patient had reduced phenytoin serum levels when phenytoin was given as an oral suspension with oral ***Fresubin liquid food concentrate***.[7]

However, in contrast, a study in 10 healthy subjects found that when ***Ensure*** or ***Vivonex TEN*** was given every 4 hours for 24 hours, the absorption of a single 400-mg dose of phenytoin was unaffected.[8] Similarly, a single-dose study in healthy subjects found that the bioavailability of phenytoin sodium 400 mg in a capsule formulation (*Dilantin Kapseals*) was not affected by ***Ensure***.[9]

A study in healthy subjects found that phenytoin levels were reduced by enteral feeds, but that it was easier to attain therapeutic levels of phenytoin in those also receiving a **meat-based** formulation (***Compleat Modified***) rather than a **protein hydrolysate** formulation (***Osmolite***).[10]

(b) Food by nasogastric tube

A patient taking phenytoin 300 mg daily who was being fed with ***Fortison*** through a nasogastric tube, following a brain injury sustained in a road traffic accident, had a phenytoin serum level of only 1 mg/L. When phenytoin 420 mg was given diluted in water and separated from the food by 2 hours, a serum level of 6 mg/L was achieved.[11] This report describes a similar reaction in another patient with a cerebral tumour.[11]

A study in 20 patients and 5 healthy subjects found that phenytoin absorption was reduced by about 70% when it was given by nasogastric tube with an **enteral feed** product (***Isocal***) at a rate of 100 to 125 mL/hour.[12] Other reports describe the same interaction in patients given ***Ensure***,[13] ***Isocal***,[14,15] or ***Osmolite***.[13,16-18] However, another study in healthy subjects found that the absolute bioavailability of phenytoin suspension or phenytoin sodium solution given by nasogastric tube was not affected by an enteral feed product (***Isocal***).[19]

(c) Food by jejunostomy tube

A woman with a history of seizures had acceptable serum phenytoin levels when phenytoin was given intravenously, but they fell from 19.1 micrograms/mL to less than 2.5 micrograms/mL when a comparable dose of phenytoin suspension was given in the presence of an **enteral feed** product (***Jevity***), given by jejunostomy tube.[20]

Mechanism

Not fully resolved. Phenytoin can bind to some food substances, which reduces its absorption.[21,22] One study in healthy subjects failed to find any difference in phenytoin bioavailability after fasting or with *Ensure* (given hourly or every 4 hours), suggesting that factors other than direct contact of phenytoin and feed contribute to decreased phenytoin bioavailability.[23] Phenytoin can also become bound to the nasogastric tubing[24] and may also be poorly absorbed if the tubing empties into the duodenum rather than the stomach.[24] Delivery into the jejunum appears to have an even greater detrimental effect on phenytoin absorption, because there is even less time for adequate absorption.[20] Other factors that could contribute to the interaction are gastrointestinal transit time, the nitrogen source in the feed, the calcium content and pH of the feed, the dose form of phenytoin or its dilution before administration.[25]

Importance and management

Phenytoin is often taken orally with food to reduce gastric irritation. This normally appears not to have a marked effect on absorption, but the studies cited above show that some formulations and some foods can interact. If there are problems with the control of seizures or evidence of toxicity, review how and when the patient is taking the phenytoin.

Some studies in healthy subjects failed to find an interaction between phenytoin and enteral feeding.[8,9,19,23] However, many studies in patients have found a clinically important interaction between phenytoin and enteral feeds given orally or by nasogastric tube. The markedly reduced bioavailability associated with the nasogastric route has been successfully managed by giving the phenytoin diluted in water 2 hours after stopping the feed, flushing with 60 mL of water, and waiting another 2 hours before restarting the feed,[11,12] However, one limited study failed to confirm that this method is successful,[13] and some sources suggest waiting 1 hour[26] or 6 hours[14] after the phenytoin dose before restarting the feed. Some increase in the phenytoin dose may also be needed. Monitor concurrent use closely. The same problem can clearly also occur when enteral feeds are given by jejunostomy tube. Approaches on how to minimise any potential interaction have been reported,[25,27] including the development and use of an algorithm.[25] In patients requiring phenytoin and enteral nutrition, the initial use of intravenous phenytoin to establish therapeutic levels has been suggested. It may also be considered if therapeutic levels cannot be maintained without compromising nutritional intake. Stopping continuous feed 1 hour rather than 2 hours before and after phenytoin administration and the use of twice daily phenytoin rather than three times daily administration have also been suggested as methods of maintaining adequate caloric intake as well as phenytoin levels in some patients.[27]

1. Jann MW, Bean J, Fidone G. Interaction of dietary pudding with phenytoin. *Pediatrics* (1986) 78, 952–3.
2. Melander A, Brante G, Johansson Ö, Lindberg T, Wåhlin-Boll E. Influence of food on the absorption of phenytoin in man. *Eur J Clin Pharmacol* (1979) 15, 269–74.
3. Johansson Ö, Wahlin-Boll E, Lindberg T, Melander A. Opposite effects of carbohydrate and protein on phenytoin absorption in man. *Drug Nutr Interact* (1983) 2, 139–44.
4. Sekikawa H, Nakano M, Takada M, Arita T. Influence of dietary components on the bioavailability of phenytoin. *Chem Pharm Bull (Tokyo)* (1980) 28, 2443–9.
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Phenytoin + H_2-receptor antagonists

Phenytoin levels are raised by the use of cimetidine and toxicity has occurred. Limited evidence suggests that low doses of cimetidine may not interact. Very rarely bone marrow depression develops on concurrent use. Famotidine, nizatidine and ranitidine do not normally interact with phenytoin, although, rarely, cases of elevated phenytoin levels have been reported.

Clinical evidence

(a) Cimetidine

The serum phenytoin levels of 9 patients rose by 60% (from 5.7 micrograms/mL to 9.1 micrograms/mL) when they were given cimetidine 200 mg three times daily and 400 mg at night for 3 weeks. The serum phenytoin level returned to its former levels within 2 weeks of stopping the cimetidine.[1]

This interaction has been described in many reports and studies involving patients[2-7] and healthy subjects.[8-11] Phenytoin toxicity has developed in some individuals. The extent of the rise in serum levels is very variable being quoted as 13 to 33% over about 6 days in one report[2] and 22 to 280% over 3 weeks in others.[4,12] There is some evidence that the effect may be dependent on the dose of cimetidine. One study found that the effect of cimetidine 2.4 g daily was greater than that of 1.2 g daily or 400 mg daily; the effect of the lower two doses did not differ from each other.[9] In another study, cimetidine 200 mg twice daily for 2 weeks had no effect on serum phenytoin levels in 9 patients taking stable doses of phenytoin.[13]

Severe and life-threatening agranulocytosis in 2 patients[14,15] and thrombocytopenia in 6 other patients[16-18] has been attributed to the concurrent use of phenytoin and cimetidine. Severe skin reactions have also been reported in 3 patients taking phenytoin, cimetidine, and dexamethasone after resection of brain tumours, which resolved on discontinuing phenytoin.[19]

(b) Famotidine

A study in 10 subjects found that famotidine 40 mg daily for 7 days did not alter the pharmacokinetics of a single dose of phenytoin.[20] However, a single case report describes phenytoin toxicity and an almost doubled serum level (increase from 18 to 33 micrograms/mL) in a patient given famotidine. This was managed by a reduction in the phenytoin dose.[21]

(c) Nizatidine

In a study in 18 healthy subjects, nizatidine 150 mg twice daily for 9 doses had no effects on the pharmacokinetics of a single dose of phenytoin.[22]

(d) Ranitidine

A study in 4 patients found that ranitidine 150 mg twice daily for 2 weeks did not alter phenytoin levels.[4,12] Similarly, a double-blind, crossover study in healthy subjects found that ranitidine 150 mg twice daily for 6 days had no significant effect on steady-state phenytoin levels.[23] However, one patient had a 40% increase in serum phenytoin levels over a month when ranitidine 150 mg twice daily was given,[24] and two others also developed elevated serum phenytoin levels and signs of toxicity,

which were attributed to the use of ranitidine.[25,26] Another patient developed a severe skin reaction when treated with phenytoin, ranitidine and dexamethasone after resection of a brain tumour, which resolved on discontinuing phenytoin.[19]

Mechanism

Cimetidine inhibits the activity of the liver enzymes concerned with the metabolism of phenytoin, thus allowing it to accumulate in the body and, in some instances, to reach toxic concentrations. Famotidine, nizatidine and ranitidine normally do not affect these enzymes. Agranulocytosis and thrombocytopenia are relatively rare manifestations of bone marrow depression caused by both phenytoin and the H_2-receptor antagonists.

Importance and management

The interaction between phenytoin and cimetidine is well documented and clinically important. It is not possible to identify individuals who will show the greatest response, but those with serum levels at the top end of the therapeutic range are most at risk. Do not give cimetidine to patients already taking phenytoin unless the serum levels can be monitored and suitable phenytoin dose reductions made as necessary. The results from one small study suggest that low doses of cimetidine (such as those available without a prescription in the UK) may not interact.[13] As there are only rare cases of an interaction with phenytoin reported for famotidine, nizatidine, and ranitidine, extra monitoring beyond that usually carried out in patients receiving phenytoin does not appear to be warranted but be alert for signs of phenytoin toxicity (e.g. blurred vision, nystagmus, ataxia or drowsiness) when these H_2-receptor antagonists are first added to established treatment with phenytoin.

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Phenytoin + Immunoglobulins

An isolated report describes a patient taking phenytoin who died, probably from hypersensitivity myocarditis, two days after receiving immunoglobulins for Guillain-Barré syndrome.

Clinical evidence, mechanism, importance and management

A man who had been taking phenytoin for 8 years was diagnosed as having Guillain-Barré syndrome for which intravenous immunoglobulin was started at 400 mg/kg daily. On day 2 the patient complained of abdominal pain, aching shoulders and backache. He subsequently developed hypotension and died, despite resuscitation attempts. A post-mortem suggested that he had died from hypersensitivity myocarditis, which the authors of the report suggest might have resulted from the long-term use of phenytoin.[1] This hypersensitivity with phenytoin has been reported before.[2] Because this complication is so serious, the authors of this report suggest that leukocyte counts, in particular eosinophils, should be monitored if immunoglobulins and phenytoin are given concurrently.[1] The general importance of this alleged interaction is not known. However, note that, subsequent to this report, intravenous immunoglobulin has successfully been used to treat a few cases of a hypersensitivity syndrome to phenytoin,[3-5] one including eosinophilia.[3] Furthermore, intravenous immunoglobulin alone has also been associated with causing myocarditis.[6] An interaction is therefore by no means established.

1. Koehler PJ, Koudstaal J. Lethal hypersensitivity myocarditis associated with the use of intravenous gammaglobulin for Guillain-Barré syndrome, in combination with phenytoin. *J Neurol* (1996) 243, 366–7.
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Phenytoin + Influenza vaccines

Influenza vaccination is reported to increase, decrease or to have no effect on phenytoin serum levels. The efficacy of the vaccine remains unchanged.

Clinical evidence

The serum phenytoin levels of 8 children with epilepsy were increased by about 50% (from 9.5 to 15.16 micrograms/mL) 7 days after they were given 0.5 mL of an influenza virus vaccine USP, types A and B, whole virus (Squibb). The phenytoin levels returned to baseline over the following 7 days.[1] Temporary rises in the serum phenytoin levels of 3 patients, apparently caused by influenza vaccination, are briefly described in another report.[2]

In contrast, another study in 16 patients given 0.5 mL of an inactivated whole-virion trivalent influenza vaccine found that 7 and 14 days later their mean serum phenytoin levels were not significantly altered, although 4 of them showed a trend towards raised levels. Subsequently, these 4 patients had serum phenytoin increases ranging from 46 to 170%, which returned to baseline between week 4 and 17 after immunisation.[3]

In yet another study, within 4 days of receiving 0.5 mL of a subvirion, trivalent influenza vaccine, the serum phenytoin levels of 7 patients were reduced by 11 to 14%, which is unlikely to have much clinical significance.[4] A further study[5] measured both free and total phenytoin levels in 8 patients receiving phenytoin. Two days after receiving 0.5 mL of a trivalent influenza vaccine, the total phenytoin level had increased by 10%, and this then returned to baseline levels by day 7. However, the free phenytoin level gradually decreased after vaccination, reaching a maximum decrease of 25% below baseline at day 14.

The efficacy of influenza vaccine is reported to be unchanged by phenytoin.[6]

Mechanism

Where an interaction occurs it is suggested that it may be due to the inhibitory effect of the vaccine on the liver enzymes concerned with the metabolism of the phenytoin, resulting in a reduced clearance from the body.[1]

Importance and management

The outcome of immunisation with influenza vaccine on phenytoin levels is uncertain. Concurrent use need not be avoided but it would be prudent to monitor the effects closely. Be aware that any alteration in levels may take a couple of weeks to develop and usually resolves spontaneously.

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2. Mooradian AD, Hernandez L, Tamai IC, Marshall C. Variability of serum phenytoin concentrations in nursing home patients. *Arch Intern Med* (1989) 149, 890–2.
3. Levine M, Jones MW, Gribble M. Increased serum phenytoin concentration following influenza vaccination. *Clin Pharm* (1984) 3, 505–9.
4. Sawchuk RJ, Rector TS, Fordice JJ, Leppik IE. Case report. Effect of influenza vaccination on plasma phenytoin concentrations. *Ther Drug Monit* (1979) 1, 285–8.
5. Smith CD, Bledsoe MA, Curran R, Green L, Lewis J. Effect of influenza vaccine on serum concentrations of total and free phenytoin. *Clin Pharm* (1988) 7, 828–32.
6. Levine M, Beattie BL, McLean DM, Corman D. Phenytoin therapy and immune response to influenza vaccine. *Clin Pharm* (1985) 4, 191–4.

Phenytoin + Isotretinoin

A study in 7 healthy subjects taking phenytoin 300 mg daily found that the addition of isotretinoin 40 mg twice daily for 11 days had no effect on the steady-state pharmacokinetics of phenytoin.[1] No phenytoin dose adjustments would seem to be needed if these drugs are given concurrently.

1. Oo C, Barsanti F, Zhang R. Lack of effect of isotretinoin on the pharmacokinetics of phenytoin at steady-state. *Pharm Res* (1997) 14 (11 Suppl), S-561.

Phenytoin + Loxapine

A single case report describes decreased serum phenytoin levels in a patient given loxapine.

Clinical evidence, mechanism, importance and management

The serum phenytoin levels of a patient with epilepsy were reduced by loxapine: when loxapine was withdrawn, the phenytoin levels rose markedly.[1] The general importance of this case is uncertain, but bear this interaction in mind, particularly as loxapine can lower the convulsive threshold.

1. Ryan GM, Matthews PA. Phenytoin metabolism stimulated by loxapine. *Drug Intell Clin Pharm* (1977) 11, 428.

Phenytoin + Macrolides

Erythromycin appears not to interact with phenytoin. Limited evidence suggests that clarithromycin may possibly raise phenytoin levels. Phenytoin is predicted to reduce telithromycin levels.

Clinical evidence

(a) Clarithromycin

A retrospective study of serum phenytoin levels in a group of 21 patients with AIDS and a large control group of 557 subjects suggested that the concurrent use of clarithromycin (a total of 22 samples from at least 10 patients) was associated with higher serum phenytoin levels. The concentration-to-dose ratio of the phenytoin was 1.6 without clarithromycin and 3.9 with clarithromycin.[1]

(b) Erythromycin

A single-dose study in 8 healthy subjects found that the mean clearance of phenytoin was unchanged by erythromycin 333 mg every 8 hours for 7 days. However, there were occasional large changes in phenytoin clearance.[2] Similarly, in another study in 8 healthy subjects, erythromycin 250 mg every 6 hours for 7 days had no effect on the pharmacokinetics of a single dose of phenytoin.[3]

Mechanism

Not known, but it could be that clarithromycin inhibits the metabolism of phenytoin by the liver.

Importance and management

This seems to be the first and only evidence that clarithromycin possibly interacts like this. Given that the effect was identified retrospectively any interaction seems unlikely to cause an acute problem. Erythromycin appears not to interact with phenytoin, but nevertheless caution has been recommended,[2] because of the occasional large changes in clearance that were seen.

Other macrolides appear not to have been studied. However, based on an interaction with the known enzyme inducer rifampicin (rifampin) (see 'Macrolides + Rifamycins', p.357), the manufacturers of **telithromycin** predict that its levels will be reduced by phenytoin, possibly making them sub-therapeutic. They advise avoiding telithromycin use during and for up to 2 weeks after phenytoin has been taken.[4]

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4. Ketek (Telithromycin). Sanofi-Aventis. UK Summary of product characteristics, June 2009.

Phenytoin + Methylphenidate

Although two small studies found that methylphenidate did not alter phenytoin levels, case reports describe raised phenytoin levels and phenytoin toxicity in patients also given methylphenidate.

Clinical evidence

A 5-year-old hyperkinetic boy with epilepsy taking phenytoin 8.9 mg/kg and **primidone** 17.7 mg/kg daily, developed ataxia without nystagmus when he was also given methylphenidate 40 mg daily. Serum levels of both of the antiepileptics were found to be toxic and only began to fall when the methylphenidate dose was reduced.[1] A further case also describes phenytoin toxicity in a child given methylphenidate.[2]

Only one other case has been reported, but this patient was later re-challenged with the two drugs and phenytoin toxicity was not seen.[3] Furthermore, this interaction has not been seen in clinical studies and observations in 3 healthy subjects[3] and more than 11 patients[4] taking phenytoin and methylphenidate.

Mechanism

Not fully understood. The suggestion is that methylphenidate acts as an enzyme inhibitor, slowing the metabolism of the phenytoin by the liver and leading to its accumulation in those individuals whose drug metabolising system is virtually saturated by phenytoin.

Importance and management

These appear to be the only reports of a possible interaction between phenytoin and methylphenidate, and an interaction is not established. The concurrent use of both drugs need not be avoided but be alert for any evidence of toxicity, particularly if the phenytoin dose is high. It would seem prudent to monitor for symptoms of phenytoin toxicity (e.g. blurred vision, nystagmus, ataxia or drowsiness) and take levels if necessary.

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2. Ghofrani M. Possible phenytoin-methylphenidate interaction. *Dev Med Child Neurol* (1988) 30, 267–8.
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Phenytoin + Metronidazole

One study found that the half-life of intravenous phenytoin was modestly prolonged by metronidazole, whereas another found

that metronidazole did not affect the pharmacokinetics of oral phenytoin. An anecdotal report describes a few patients who developed toxic phenytoin levels when given metronidazole.

Clinical evidence, mechanism, importance and management

A pharmacokinetic study in 7 healthy subjects found that metronidazole 250 mg three times daily increased the half-life of a single 300-mg intravenous dose of phenytoin by about 40% (from 16 to 23 hours) and reduced its clearance by 15%.[1] In contrast, another study in 5 healthy subjects found that the pharmacokinetics of a single 300-mg oral dose of phenytoin were unaffected by metronidazole 400 mg twice daily for 6 days.[2] An anecdotal report describes several patients (exact number not stated) who developed toxic phenytoin serum levels when given metronidazole.[3] These appear to be the only reports of this potential interaction, and the reason for their discordant findings is not clear. It seems that few patients are likely to experience a clinically significant interaction.

1. Blyden GT, Scavone JM, Greenblatt DJ. Metronidazole impairs clearance of phenytoin but not of alprazolam or lorazepam. *J Clin Pharmacol* (1988) 28, 240–5.
2. Jensen JC, Gugler R. Interaction between metronidazole and drugs eliminated by oxidative metabolism. *Clin Pharmacol Ther* (1985) 37, 407–10.
3. Picard EH. Side effects of metronidazole. *Mayo Clin Proc* (1983) 58, 401.

Phenytoin + Nefazodone

Nefazodone did not affect the pharmacokinetics of phenytoin in healthy subjects.

Clinical evidence, mechanism, importance and management

Nefazodone 200 mg twice daily for 7 days had no effect on the pharmacokinetics of a single 300-mg dose of phenytoin in healthy subjects, and no changes in vital signs, ECGs or other physical measurements were seen. There was no evidence that a clinically significant interaction was likely.[1]

1. Marino MR, Langenbacher KM, Hammett JL, Nichola P, Uderman HD. The effect of nefazodone on the single-dose pharmacokinetics of phenytoin in healthy male subjects. *J Clin Psychopharmacol* (1997) 17, 27–33.

Phenytoin + Nitrofurantoin

An isolated report describes a reduction in phenytoin levels and poor seizure control in a patient given nitrofurantoin.

Clinical evidence, mechanism, importance and management

A man with seizures due to a brain tumour was taking phenytoin 300 mg daily. He had a seizure within one day of starting nitrofurantoin 200 mg daily for a urinary-tract infection and, despite a recent increase in the phenytoin dose to 350 mg, his serum phenytoin levels were found to be modestly reduced (from about 9 to 7.6 micrograms/mL). They continued to fall, and were 6.3 micrograms/mL despite a further increase in the phenytoin dose to 400 mg daily. When the nitrofurantoin was stopped the patient was restabilised on his original dose of phenytoin. The reasons for this effect are not understood but, on the basis of a noted rise in serum gamma glutamyltransferase levels during the use of the nitrofurantoin, the authors speculate that it increased the metabolism of the phenytoin by the liver.[1] The general importance of this interaction is uncertain, but probably small.

1. Heipertz R, Pilz H. Interaction of nitrofurantoin with diphenylhydantoin. *J Neurol* (1978) 218, 297–301.

Phenytoin + Orlistat

Orlistat does not alter the pharmacokinetics of phenytoin.

Clinical evidence, mechanism, importance and management

In a placebo-controlled, randomised study, 12 healthy subjects were given orlistat 120 mg three times daily for 7 days, with a single 300-mg dose of phenytoin on day 4. The pharmacokinetics of phenytoin were unchanged by orlistat,[1] and no phenytoin dose adjustments are therefore thought to be needed if these two drugs are given concurrently.

1. Melia AT, Mulligan TE, Zhi J. The effect of orlistat on the pharmacokinetics of phenytoin in healthy volunteers. *J Clin Pharmacol* (1996) 36, 654–8.

Phenytoin + Penicillins

An isolated case describes a marked reduction in serum phenytoin levels, resulting in seizures, which was attributed to the use of oxacillin.

Clinical evidence, mechanism, importance and management

An woman with epilepsy taking phenytoin 400 mg daily, hospitalised for second degree burns sustained during a generalised seizure, experienced brief clonic seizures and was found to have an marked reduction in her serum phenytoin levels, from 16.3 micrograms/mL to 3.5 micrograms/mL, which was attributed to the concurrent use of oral **oxacillin** 500 mg every 6 hours. The phenytoin dose was increased, but seizures continued and progressed to status epilepticus, and intravenous phenytoin was given. Doses of oral phenytoin of about 600 mg daily were required to maintain minimum therapeutic levels, sometimes with supplementation of small intravenous doses. Just before the **oxacillin** was withdrawn the serum phenytoin level was 22.3 micrograms/mL, but 6 months later it had risen to 39.9 micrograms/mL, and the phenytoin dose was reduced.[1] Other studies have shown that penicillins such as **oxacillin**, **cloxacillin** and **dicloxacillin** can displace phenytoin from plasma protein binding, decreasing total serum levels but increasing the free fraction of phenytoin. If anything, this would be predicted to increase phenytoin toxicity,[2,3] rather than decrease its levels, as seen in the case. This seems to be only report of an adverse interaction between phenytoin and a penicillin. Its general importance is probably small.

1. Fincham RW, Wiley DE, Schottelius DD. Use of phenytoin levels in a case of status epilepticus. *Neurology* (1976) 26, 879–81.
2. Arimori K, Nakano M, Otagiri M, Uekama K. Effects of penicillins on binding of phenytoin to plasma proteins *in vitro* and *in vivo*. *Biopharm Drug Dispos* (1984) 5, 219–27.
3. Dasgupta A, Sperelakis A, Mason A, Dean R. Phenytoin-oxacillin interactions in normal and uremic sera. *Pharmacotherapy* (1997) 17, 375–8.

Phenytoin + Pheneturide

Phenytoin levels can be increased by about 50% by pheneturide.

Clinical evidence, mechanism, importance and management

In 9 patients, the steady-state half-life of phenytoin was prolonged from 32 hours to 47 hours by pheneturide. Mean serum levels were raised by about 50% but fell rapidly over the 2 weeks after pheneturide was withdrawn.[1] This study confirms a previous report of this interaction.[2] However, the reason for this interaction is uncertain, but as the two drugs have a similar structure it is possible that they compete for the same metabolising enzymes in the liver, thereby resulting, at least initially, in a reduction in the metabolism of the phenytoin. If concurrent use is undertaken the outcome should be well monitored. Reduce the phenytoin dose as necessary.

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Phenytoin + Phenobarbital

The concurrent use of phenytoin and phenobarbital is normally advantageous and uneventful. Changes in phenytoin levels (often decreases but sometimes increases) can occur if phenobarbital is added, but seizure control is not usually affected. Phenytoin toxicity following phenobarbital withdrawal has been seen. Increased phenobarbital levels and possibly toxicity may result if phenytoin is given to patients taking phenobarbital.

Clinical evidence

A study in 10 patients with epilepsy taking phenytoin 2.8 to 6.8 mg/kg daily found that while taking phenobarbital 1.1 to 2.5 mg/kg daily their serum phenytoin levels were reduced. Five patients had a mean reduction of about 65% (from 15.7 to 5.7 micrograms/mL). In most cases phenytoin levels rose when phenobarbital was withdrawn. In one patient this was so rapid and steep that he developed ataxia and a cerebellar syndrome with phenytoin levels of up to 60 micrograms/mL, despite a reduction in the phenytoin dose.[1]

This reduction in phenytoin levels by phenobarbital has been described in other reports.[2-7] Some of these reports also described a very transient and small rise[4] or no alteration[4,5] in serum phenytoin levels in individual patients. Three other studies have found that phenobarbital does not alter phenytoin levels.[8-10]

Elevated serum phenobarbital levels occurred in children with epilepsy when they were also given phenytoin. In 5 patients the phenobarbital levels were approximately doubled. In some cases mild ataxia was seen but the relatively high barbiturate levels were well tolerated.[1] A long-term study in 6 adults with epilepsy found that when phenytoin was added to phenobarbital, the level-to-dose ratio of phenobarbital gradually rose by about 60% over one year, and then gradually fell again over the next 2 years.[11] This suggests that initially, phenytoin reduces phenobarbital metabolism.

In a patient taking phenobarbital 100 mg and phenytoin 160 mg daily, the serum levels of phenobarbital increased by about 53% within about 2 days when the dose of phenytoin was increased to 490 mg daily.[12]

Mechanism

Phenobarbital can have a dual effect on phenytoin metabolism: it may cause enzyme induction, which results in a more rapid clearance of the phenytoin from the body, or with large doses it may inhibit metabolism by competing for enzyme systems. The total effect will depend on the balance between the two drugs. The reason for the elevation of serum phenobarbital levels is not fully understood, but the extent of the effect may be dependent on the serum level of phenytoin.[12,13]

Importance and management

Concurrent use can be therapeutically valuable. Changes in dose or the addition or withdrawal of either drug needs to be monitored to ensure that toxicity does not occur, or that seizure control is not worsened. The contradictory reports cited here do not provide a clear picture of what is likely to happen. Consider also 'Primidone + Phenytoin', p.649.

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Phenytoin + Phenothiazines

Phenytoin levels can be raised or lowered by the use of chlorpromazine, prochlorperazine or thioridazine. Phenytoin may reduce levels of the active metabolite of thioridazine.

Clinical evidence

(a) Chlorpromazine

The serum phenytoin levels of a patient taking phenytoin, primidone and sultiame doubled after chlorpromazine 50 mg daily was taken for a month.[1] However, another 4 patients taking chlorpromazine 50 to 100 mg daily showed no interaction.[1] In another report, one out of 3 patients taking phenytoin and phenobarbital had a fall in their serum phenytoin levels when they were also given chlorpromazine.[2] A further very brief report states that in rare instances chlorpromazine has been noted to impair phenytoin metabolism.[3]

In a large study in patients taking phenytoin with various phenothiazines (chlorpromazine, **thioridazine** or **mesoridazine**), phenytoin levels were decreased by 44% when the phenothiazines were started, and decreased by 33% when the phenothiazine dose was increased. A number of patients experienced an increased frequency of seizures. In patients who had these phenothiazines discontinued or the dose *decreased*, the phenytoin levels increased by 55% and 71%, respectively, and toxic levels occurred in some patients.[4]

(b) Prochlorperazine

A single very brief report states that in rare instances prochlorperazine has been noted to impair phenytoin metabolism.[3]

(c) Thioridazine

One out of 6 patients taking phenytoin and phenobarbital had a marked rise in serum phenytoin levels when thioridazine was added, whereas 4 others had a fall in phenytoin levels.[2] Phenytoin toxicity has also been described in 2 patients after about 2 weeks of the concurrent use of thioridazine.[5] A retrospective study in 27 patients taking phenytoin found that when they were given thioridazine their serum phenytoin levels were increased by at least 4 micrograms/mL (4 patients), decreased by at least 4 micrograms/mL (2 patients), or were unchanged (21 patients).[6] Another retrospective study comparing 28 patients taking both phenytoin and thioridazine with patients taking either drug alone found no evidence that thioridazine increased the risk of phenytoin toxicity.[7] A further study found no changes in serum phenytoin or thioridazine levels in patients given both drugs, but the serum levels of mesoridazine (the active metabolite of thioridazine) were reduced, suggesting that higher doses of thioridazine may be necessary to achieve the same effect.[8] See also the study[4] in section (a), which found a decrease in phenytoin levels and an increase in seizure frequency when patients took phenothiazines including thioridazine.

Mechanism

Uncertain. Phenothiazines such as thioridazine are said to be inhibitors of the cytochrome P450 isoenzyme CYP2D6, and as such would not be expected to affect phenytoin metabolism, at least by this mechanism.

Importance and management

A confusing situation as the results are inconsistent. The concurrent use of phenytoin and these phenothiazines need not be avoided, but it would be prudent to watch for any signs of changes in serum phenytoin levels that would affect antiepileptic control. It is also worth remembering that phenothiazines may decrease the seizure threshold. In one study a trend towards increased seizure frequency was noted after phenothiazines were added, or doses increased.[4] Also note that phenytoin may reduce levels of some phenothiazines. Whether all phenothiazines interact similarly is uncertain.

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Phenytoin + Proton pump inhibitors

Studies have found that omeprazole either does not affect phenytoin levels, or may raise phenytoin levels: the differences may be due to the different doses and subjects involved in these studies. A study with esomeprazole suggests it may cause a minor rise in phenytoin levels. Lansoprazole does not normally affect phenytoin levels, but an isolated case report of toxicity is tentatively attributed to an interaction. Pantoprazole and rabeprazole appear not to affect the pharmacokinetics of phenytoin.

Clinical evidence

(a) Esomeprazole

The manufacturer of esomeprazole reports that, in patients with epilepsy, esomeprazole 40 mg increases the trough plasma levels of phenytoin by 13%.[1]

(b) Lansoprazole

In a group of 12 healthy subjects lansoprazole 60 mg daily for 7 days caused only a very small and clinically irrelevant rise (less than 3%) in the AUC of a single intravenous dose of phenytoin.[2,3] In contrast the manufacturer has received an isolated report of the development of blurred vision, diarrhoea, muscle pain, dizziness, abdominal pain, salivary hypersecretion, increased sweating and incoordination in a man taking phenytoin, which occurred within a day of stopping sustained-release propranolol 80 mg and starting lansoprazole.[4] The phenytoin serum levels were not measured but the symptoms might possibly have been due to phenytoin toxicity, although it should be said that if an interaction with lansoprazole was responsible, it developed unusually quickly.

(c) Omeprazole

In 8 patients with epilepsy, omeprazole 20 mg daily for 3 weeks caused no changes in the mean steady-state serum phenytoin levels.[5] Four patients had unchanged levels, 2 had falls and 2 had rises, but none of them was adversely affected by the use of omeprazole.[5]

In 10 healthy subjects, omeprazole 40 mg daily for 7 days increased the AUC of a single 300-mg dose of phenytoin by 25%.[6] In another study the clearance of a 250-mg intravenous dose of phenytoin was reduced by 15% by omeprazole 40 mg given for 7 days.[7] A further study found that 3 doses of omeprazole 40 mg had no effect on the pharmacokinetics of a single dose of phenytoin.[8]

(d) Pantoprazole

A randomised, crossover study in 23 healthy subjects found that pantoprazole 40 mg daily for 7 days did not alter the pharmacokinetics (AUC, maximum serum levels, half-life) of a single 300-mg dose of phenytoin.[9] This study has also been published elsewhere.[10]

(e) Rabeprazole

A preliminary report, which gives no details, states that when rabeprazole was used with phenytoin, no significant changes in the pharmacokinetics of phenytoin were seen.[11]

Mechanism

Not understood. A possible explanation is that if the dose of omeprazole is high enough, it may possibly reduce the metabolism of phenytoin by CYP2C19. Esomeprazole may have similar effects. However, CYP2C19 has only a minor role in phenytoin metabolism,[12] and so the effects are usually small. With lansoprazole, the overall picture is that it does not act as an enzyme inducer or inhibitor[13] (or it is only very weak) so that it would not be expected to interact with phenytoin to a clinically relevant extent (confirmed by the study cited above[2]). The same appears to be true for pantoprazole and rabeprazole.

Importance and management

Information is very limited but it seems that omeprazole 20 mg daily does not affect serum phenytoin levels, whereas 40 mg daily may possibly cause a slight increase, although this is probably of no clinical relevance in most patients. However, multiple dose studies are ideally needed to confirm this. No special precautions would normally seem necessary if lansoprazole or omeprazole is given with phenytoin.

The manufacturers of esomeprazole suggest that the concurrent use of phenytoin should be monitored,[1] although the elevation in levels seen in the study would almost certainly not be clinically significant. No special precautions would seem to be necessary if rabeprazole or pantoprazole and phenytoin are given concurrently.

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Phenytoin + *Shankhapushpi* (*SRC*)

A case report, and an *animal* study, indicate that an antiepileptic Ayurvedic herbal preparation, *Shankhapushpi* (*SRC*), can markedly reduce phenytoin levels, leading to an increased seizure frequency.

Clinical evidence

An man with epilepsy taking **phenobarbital** 120 mg daily and **phenytoin** 500 mg daily developed an increase in seizure frequency when *Shankhapushpi* (*SRC*) three times daily was given. His plasma **phenytoin** levels were found to have fallen from 18.2 micrograms/mL to 9.3 micrograms/mL, whereas his **phenobarbital** levels were little changed. When the *SRC* was stopped the **phenytoin** plasma levels rose to 30.3 micrograms/mL, and toxicity was seen. A reduction in the dose of **phenytoin** to 400 mg daily resulted in levels of 16.2 micrograms/mL. Another possible case of this interaction has also been reported.[1,2]

Subsequent studies in *rats* found that *SRC* reduces the plasma levels of **phenytoin** by about half.[3] These pharmacokinetic effects were only seen after multiple doses, not single doses of **phenytoin**. A pharmacodynamic interaction, resulting in reduced antiepileptic activity was also noted.[1,3,4]

Mechanism

Not understood. There is evidence from *animal* studies that *SRC* may affect the pharmacokinetics of the phenytoin and possibly its pharmacodynamics as well,[1,3] thereby reducing its antiepileptic activity. It is also suggested that one of the ingredients of *SRC* may have some antiepileptic activity.[3]

Importance and management

Information about this interaction appears to be limited to these reports. *Shankhapushpi* (*SRC*) is given because it has some antiepileptic activity (demonstrated in *animal* studies[3,4]), but there is little point in combining it with phenytoin if the outcome is a fall in plasma phenytoin levels, accompanied by an increase in seizure frequency. For this reason concurrent use should be avoided. *SRC* is a syrup prepared from *Convolvulus pluricaulis* leaves, *Nardostachys jatamansi* rhizomes, *Onosma bracteatum* leaves and flowers and the whole plant of *Centella asiatica*, *Nepeta hindostana* and *Nepeta elliptica*.[3] The first two of these plants appear to contain compounds with antiepileptic activity.[5]

It has been suggested that adulteration of traditional medicines with various antiepileptics[6,7] may be an unexpected factor in these interactions.

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Phenytoin + SSRIs

Phenytoin levels can be increased in some patients by fluoxetine and toxicity may occur. There are also isolated reports of phenytoin toxicity in patients taking fluvoxamine. Phenytoin and sertraline do not normally interact, but rarely patients have developed increased phenytoin levels.
Sertraline and possibly paroxetine levels may be reduced by phenytoin.

Clinical evidence

(a) Fluoxetine

A woman taking phenytoin 370 mg, diazepam 4 mg, and clonazepam 6 mg daily was given fluoxetine 20 mg for depression. Five days later her serum phenytoin levels had risen from 18 micrograms/mL to 26.5 micrograms/mL, and a further 9 days later to 30 micrograms/mL, accompanied by signs of toxicity (tremor, headache, abnormal thinking, increased partial seizure activity). Seven days after stopping the phenytoin the serum levels had fallen to 22 micrograms/mL.[1]

Two other patients, taking phenytoin 300 and 400 mg daily, respectively, had marked rises in serum phenytoin levels (from 15 to 35 micrograms/mL and from 11.5 to 47 micrograms/mL), accompanied by signs of phenytoin toxicity, within 5 to 10 days of starting fluoxetine 20 or 40 mg daily. The problem resolved when the fluoxetine was stopped or the phenytoin dose reduced.[2] Another patient only developed this interaction after taking fluoxetine for about 9 months.[3] Another case describes raised phenytoin levels with improved efficacy when fluoxetine was started, and reduced levels and possible loss of efficacy when fluoxetine was stopped.[4]

A review initiated by the FDA in the US and the manufacturers of fluoxetine briefly describes another 23 anecdotal observations of suspected interactions between phenytoin and fluoxetine (most of them incompletely documented). These suggest that a 50% increase in serum phenytoin levels, with accompanying toxicity, can occur within 1 to 42 days (mean onset time of 2 weeks) after starting fluoxetine.[5] Conversely, a retrospective review of 7 patients taking phenytoin and fluoxetine found no cases of an interaction.[6]

(b) Fluvoxamine

About one month after starting to take fluvoxamine 50 mg daily, a woman taking phenytoin 300 mg daily experienced ataxia and was found to have a threefold increase in her phenytoin levels (from 16.6 to 49.1 micrograms/mL). Fluvoxamine was subsequently discontinued, and the phenytoin dose reduced, with gradual recovery.[7] Another report describes phenytoin toxicity (serum levels of 48 micrograms/mL) in an 86-year-old woman after she took fluvoxamine 100 to 200 mg daily for 10 days.[8] However the fluvoxamine was started only 2 days after phenytoin 200 mg twice daily had been started, and the serum phenytoin levels were not checked until the toxicity had actually developed. Both drugs were then stopped and the phenytoin later successfully reinstated without the fluvoxamine. A worldwide analysis of data up to 1995 by the manufacturers of fluvoxamine identified only 2 reported cases of interactions (clinical symptoms only) between phenytoin and fluvoxamine.[9]

(c) Paroxetine

In a group of patients with epilepsy, paroxetine 30 mg daily for 16 days caused no changes in the plasma levels or therapeutic effects of phenytoin. Steady-state paroxetine plasma levels were lower in those also taking phenytoin (16 nanograms/mL) than in those taking valproate (73 nanograms/mL).[10]

The US manufacturer of paroxetine notes that phenytoin 300 mg daily for 14 days decreased the AUC and half-life of a single 30-mg dose of paroxetine by 50% and 35%, respectively. In another study, paroxetine 30 mg daily for 14 days had minimal effects on a single 300-mg dose of phenytoin (AUC reduced by 12%).[11]

(d) Sertraline

A randomised, placebo-controlled study in 30 healthy subjects taking phenytoin 100 mg three times daily, found that sertraline 50 to 200 mg daily did not affect the steady-state trough serum levels of phenytoin, nor was there any evidence that concurrent use impaired cognitive function.[12] However, another report describes 2 elderly patients whose serum phenytoin levels rose when they were given sertraline, but there was no evidence of toxicity. One of them had an almost fourfold rise in serum phenytoin levels whereas the other had a rise of only about one-third.[13]

In an analysis of plasma sertraline levels the concentration to daily dose ratio of sertraline was significantly lower in patients who had taken sertraline with phenytoin compared with those who had taken sertraline without phenytoin,[14] which suggested that phenytoin increases sertraline metabolism

Mechanism

An *in vitro* investigation found that fluoxetine and fluvoxamine inhibited the metabolism of phenytoin by the cytochrome P450 isoenzyme CYP2C9 in human liver tissue.[15] This would presumably lead to a rise in serum phenytoin levels. In this study, sertraline was a weaker inhibitor of CYP2C9, and was considered less likely to interact with phenytoin.[15] A similar study also suggested that the risk of interaction was greatest for fluoxetine, and less likely with sertraline and paroxetine.[16] Sertraline plasma levels may be reduced because of enzyme induction by phenytoin which would increase its metabolism and clearance from the body.[14]

Importance and management

The interaction between phenytoin and fluoxetine appears to be established but its incidence is not known. Because of the unpredictable nature of this interaction, if fluoxetine is added to treatment with phenytoin in any patient, be alert for the need to reduce the phenytoin dose. Ideally the phenytoin serum levels should be monitored. Similarly, to be on the safe side phenytoin levels should be monitored when fluvoxamine is first added to treatment with phenytoin so that any patient affected can be quickly identified. Although an interaction with sertraline appears less likely, be alert for any evidence of an increase in phenytoin adverse effects (e.g. blurred vision, nystagmus, ataxia or drowsiness) if sertraline is given. The clinical relevance of the reduction in paroxetine levels caused by phenytoin is unknown, but it would seem prudent to be alert for a reduction in the effects of paroxetine, and increase its dose as necessary. More study of these interactions is needed.

Note that SSRIs should be avoided in patients with unstable epilepsy, and the use of SSRIs in those with controlled epilepsy should be carefully monitored, because of the potential increased seizure risk.

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Phenytoin + Sucralfate

The absorption of single-dose phenytoin can be modestly reduced by sucralfate, but this effect was not seen in a multiple-dose study.

Clinical evidence

In 8 healthy subjects, sucralfate 1 g was found to reduce the absorption (measured over a 24-hour period) of a single 300-mg dose of phenytoin by 20%.[1] Peak serum phenytoin levels were also reduced, but this was not statistically significant. Another single-dose study found a mean reduction in phenytoin absorption of up to 9.5%.[2] In a study in 6 healthy subjects, sucralfate 1 g four times daily for 7 days had no effect on the steady-state levels of phenytoin 5 to 7 mg/kg daily. The fourth daily dose of sucralfate was taken simultaneously with the daily phenytoin dose at bedtime. After 7 days, all phenytoin levels were within 15% of the baseline values (range, 6% decrease to 15% increase).[3]

Mechanism

Uncertain. Reduced bioavailability has been demonstrated in a single-dose study in *dogs* when the drugs were given simultaneously, and this did not occur if the phenytoin was given 2 hours after the sucralfate.[4]

Importance and management

Information about an interaction between sucralfate and phenytoin is limited. The reduction in phenytoin absorption found in single-dose studies was quite small, and was not seen in a multiple-dose study, suggesting it is unlikely to be clinically relevant.

1. Smart HL, Somerville KW, Williams J, Richens A, Langman MJS. The effects of sucralfate upon phenytoin absorption in man. *Br J Clin Pharmacol* (1985) 20, 238–40.
2. Hall TG, Cuddy PG, Glass CJ, Melethil S. Effect of sucralfate on phenytoin bioavailability. *Drug Intell Clin Pharm* (1986) 20, 607–11.
3. Malli R, Jones WN, Rindone JP, Labadie EL. The effect of sucralfate on the steady-state serum concentrations of phenytoin. *Drug Metabol Drug Interact* (1989) 7, 287–93.
4. Lacz JP, Groschang AG, Giesing DH, Browne RK. The effect of sucralfate on drug absorption in dogs. *Gastroenterology* (1982) 82, 1108.

Phenytoin + Sulfinpyrazone

Phenytoin levels may be markedly increased by sulfinpyrazone.

Clinical evidence

A review of the drug interactions of sulfinpyrazone identified two studies that found interactions with phenytoin.[1] In the first, the serum phenytoin levels of 2 out of 5 patients taking phenytoin 250 to 350 mg daily were doubled (from about 10 micrograms/mL to 20 micrograms/mL) within 11 days of starting to take sulfinpyrazone 800 mg daily. One of the remaining patients had a small increase in phenytoin levels, but the other two had no changes at all. When the sulfinpyrazone was withdrawn, the serum phenytoin concentrations fell to their former levels. The second study was a clinical study in patients with epilepsy, which found that sulfinpyrazone 800 mg daily for a week increased the phenytoin half-life from 10 hours to 16.5 hours and reduced the metabolic clearance by 46% (from 59 mL/minute to 32 mL/minute).

Mechanism

Uncertain. It seems probable that sulfinpyrazone inhibits the metabolism of phenytoin by the liver, thereby allowing it to accumulate in the body and leading to a rise in its serum levels. Displacement of phenytoin from its plasma protein binding sites may also have a small part to play.

Importance and management

Information seems to be limited to these studies. A similar interaction with phenytoin has been reported with phenylbutazone, which has a very close chemical relationship with sulfinpyrazone. Thus, what is known suggests that concurrent use should be monitored and suitable phenytoin dose reductions made if necessary.

1. Pedersen AK, Jacobsen P, Kampmann JP, Hansen JM. Clinical pharmacokinetics and potentially important drug interactions of sulphinpyrazone. *Clin Pharmacokinet* (1982) 7, 42–56.

Phenytoin + Sulfonamides and/or Trimethoprim

Phenytoin levels can be raised by co-trimoxazole, sulfamethizole, sulfamethoxazole, sulfadiazine and trimethoprim. Phenytoin toxicity may develop in some cases. A single case of liver failure has been described in a patient taking phenytoin with co-trimoxazole. Sulfamethoxypyridazine and sulfadimethoxine are reported not to interact with phenytoin.

Clinical evidence

(a) Co-trimoxazole or Trimethoprim

A patient taking phenytoin 400 mg daily developed signs of toxicity (ataxia, nystagmus, loss of balance) within 2 weeks of starting to take co-trimoxazole 960 mg twice daily. His serum levels were found to have risen to about 38 micrograms/mL (reference range 10 to 20 micrograms/mL).[1]

A child who was stable taking phenytoin and sultiame developed phenytoin toxicity within 48 hours of starting co-trimoxazole. Toxicity resolved when the antibacterial was changed to amoxicillin.[2] A clinical study found that co-trimoxazole and trimethoprim can increase the phenytoin half-life by 39% and 51%, respectively, and decrease the mean metabolic clearance of phenytoin by 27% and 30%, respectively.[3] Sulfamethoxazole alone had only a small effect on the half-life of phenytoin, and did not affect its clearance.[3] A case report describes fatal acute hepatic failure in a 60-year-old woman 10 days after she started taking co-trimoxazole and 14 days after she started taking phenytoin.[4] This patient was also given cimetidine, which may raise phenytoin levels (see 'Phenytoin + H_2-receptor antagonists', p.637).

(b) Sulfadiazine

In a study in 8 patients, sulfadiazine 4 g daily for a week increased the half-life of a single intravenous dose of phenytoin by 80%. The mean metabolic clearance of phenytoin decreased by 45%.[3]

(c) Sulfamethizole

The development of phenytoin toxicity in a patient taking sulfamethizole prompted a study of this interaction in 8 patients. After the concurrent use of phenytoin and sulfamethizole 1 g four times daily for 7 days the phenytoin half-life had increased from 11.8 hours to 19.6 hours. Of the 4 patients receiving long-term treatment with phenytoin, 3 had rises in serum phenytoin levels from 22 micrograms/mL to 33 micrograms/mL, from 19 micrograms/mL to 23 micrograms/mL and from 4 micrograms/mL to 7 micrograms/mL, respectively. The phenytoin levels of the fourth patient were not affected.[5,6] Another single-dose study found that the half-life of phenytoin was increased and its mean metabolic clearance reduced by 36% by sulfamethizole.[3]

(d) Other sulfonamides

Pretreatment for one week with **sulfamethoxypyridazine** or **sulfadimethoxine** did not significantly alter the pharmacokinetics of a single dose of phenytoin.[3]

Mechanism

The sulfonamides that interact appear to do so by inhibiting the metabolism of the phenytoin by the liver (possibly by the cytochrome P450 isoenzyme CYP2C9)[7], resulting in its accumulation in the body. This would also seem to be true for trimethoprim. Depletion of glucuronic acid by phenytoin may have increased the hepatotoxicity of co-trimoxazole.[4]

Importance and management

The documentation seems to be limited to the reports cited, but the interaction is established. Co-trimoxazole, sulfamethizole, sulfadiazine and trimethoprim can increase serum phenytoin levels. The interaction probably occurs in most patients, but the small number of adverse reaction reports suggests that the risk of toxicity is small. It is clearly most likely in those with serum phenytoin levels at the top end of the range. If concurrent use is thought appropriate, serum phenytoin levels should be closely monitored and the phenytoin dose reduced if necessary. Alternatively, if appropriate, use a non-interacting antibacterial (in some circumstances 'penicillins', (p.640), or 'macrolides', (p.639), may be appropriate). There seems to be little information about other sulfonamides. Limited data suggests that sulfamethoxypyridazine or sulfadimethoxine may not interact, but until more is known it may be prudent to be alert for this interaction with any of them.

1. Wilcox JB. Phenytoin intoxication and co-trimoxazole. *N Z Med J* (1981) 94, 235–6.
2. Gillman MA, Sandyk R. Phenytoin toxicity and co-trimoxazole. *Ann Intern Med* (1985) 102, 559.
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5. Lumholtz B, Siersbaek-Nielsen K, Skovsted L, Kampmann J, Hansen JM. Sulfamethizole-induced inhibition of diphenylhydantoin, tolbutamide and warfarin metabolism. *Clin Pharmacol Ther* (1975) 17, 731–4.
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7. Giancarlo GM, Venkatakrishnan K, Granda BW, von Moltke LL, Greenblatt DJ. Relative contributions of CYP2C9 and 2C19 to phenytoin 4-hydroxylation in vitro: inhibition by sulfaphenazole, omeprazole, and ticlopidine. *Eur J Clin Pharmacol* (2001) 57, 31–36.

Phenytoin + Sultiame

Serum phenytoin levels can be approximately doubled by sultiame and phenytoin toxicity may occur.

Clinical evidence

The serum phenytoin levels in 6 out of 7 patients with epilepsy approximately doubled within about 5 to 25 days of starting to take sultiame 400 mg daily. All experienced an increase in adverse effects and definite phenytoin toxicity occurred in 2 patients. In most of the patients, phenytoin serum levels fell back to baseline over the 2 months following the withdrawal of sultiame.[1] All of the patients were also taking **phenobarbital** and although greater variations in serum **phenobarbital** levels were seen, they were not considered to be clinically significant.[1]

A number of other reports confirm this interaction,[2-8] some of which describe the development of phenytoin toxicity.

Mechanism

The evidence suggests that sultiame interferes with the metabolism of the phenytoin by the liver, leading to its accumulation in the body.

Importance and management

A reasonably well-documented, established and clinically important interaction. The incidence seems to be high. If sultiame is added to established treatment with phenytoin, increases in serum phenytoin levels of up to 75% or more may be expected.[3,7] Phenytoin serum levels should be closely monitored and appropriate dose reductions made to prevent the development of toxicity. The changes in phenobarbital levels appear to be unimportant.

1. Olesen OV, Jensen ON, Drug-interaction between sulthiame (Ospolot (R)) and phenytoin in the treatment of epilepsy. *Dan Med Bull* (1969) 16, 154–8.
2. Houghton GW, Richens A. Inhibition of phenytoin metabolism by sulthiame. *Br J Pharmacol* (1973) 49, 157P–158P.
3. Houghton GW, Richens A. Inhibition of phenytoin metabolism by sulthiame in epileptic patients. *Br J Clin Pharmacol* (1974) 1, 59–66.
4. Richens A, Houghton GW. Phenytoin intoxication caused by sulthiame. *Lancet* (1973) ii, 1442–3.
5. Houghton GW, Richens A. Inhibition of phenytoin metabolism by other drugs used in epilepsy. *Int J Clin Pharmacol Biopharm* (1975) 12, 210–16.
6. Frantzen E, Hansen JM, Hansen OE, Kristensen M. Phenytoin (Dilantin®) intoxication. *Acta Neurol Scand* (1967) 43, 440–6.
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Phenytoin + Tamoxifen

Some preliminary evidence suggests that high-dose tamoxifen can cause increase phenytoin levels, causing toxicity. Phenytoin may lower tamoxifen levels.

Clinical evidence, mechanism, importance and management

A man who had undergone an operation 10 years previously for a brain tumour and had since remained seizure-free while taking phenytoin 200 mg twice daily began to have breakthrough seizures. It was established that his brain tumour had recurred and so tamoxifen was started as experimental treatment. The dose of tamoxifen was slowly titrated to 200 mg daily over a 6-week period. He continued to receive phenytoin and was also given **carbamazepine** as his seizures were not controlled, but when the maximum dose of tamoxifen (200 mg daily) was reached he began to develop symptoms of phenytoin toxicity with a serum level of 28 micrograms/mL. The toxicity disappeared and the phenytoin levels decreased when the phenytoin dose was reduced. The **carbamazepine** serum levels remained unchanged throughout.[1] The authors of this report say that other patients similarly treated with tamoxifen also developed phenytoin toxicity, which disappeared when the phenytoin dose was reduced by 15 to 20%.

Another study of the pharmacokinetics of high-dose tamoxifen in patients with brain tumours found that the mean tamoxifen levels in 15 patients taking phenytoin were about 60% lower than in patients not taking phenytoin, although this did not reach statistical significance due to high inter-patient variability.[2]

The reasons for these possible interactions are not known, but it could be that tamoxifen and phenytoin both compete for the same metabolising enzymes.

The evidence for this interaction is very slim indeed and it may possibly only occur with high-dose tamoxifen. Consider monitoring phenytoin levels if high-dose tamoxifen is added and monitor the efficacy of the tamoxifen. More study is needed to establish an interaction.

1. Rabinowicz AL, Hinton DR, Dyck P, Couldwell WT. High-dose tamoxifen in treatment of brain tumors: interaction with antiepileptic drugs. *Epilepsia* (1995) 36, 513–15.
2. Ducharme J, Fried K, Shenouda G, Leyland-Jones B, Wainer IW. Tamoxifen metabolic patterns within a glioma patient population treated with high-dose tamoxifen. *Br J Clin Pharmacol* (1997) 43: 189–93.

Phenytoin + Terfenadine

In 12 patients with epilepsy, a one-day and a 2-week course of terfenadine 60 mg twice daily had no effect on the pharmacokinetics of phenytoin.[1] No phenytoin dose adjustments seem likely to be needed if both drugs are used.

1. Coniglio AA, Garnett WR, Pellock JH, Tsidonis O, Hepler CD, Serafin R, Small RE, Driscoll SM, Karnes HT. Effect of acute and chronic terfenadine on free and total serum phenytoin concentrations in epileptic patients. *Epilepsia* (1989) 30, 611–16.

Phenytoin + Ticlopidine

Ticlopidine reduces the metabolism of phenytoin. A number of case reports describe patients who developed phenytoin toxicity when ticlopidine was also taken.

Clinical evidence

A 65-year-old man taking phenytoin 200 mg daily and clobazam developed signs of phenytoin toxicity (vertigo, ataxia, somnolence) within a week of starting ticlopidine 250 mg daily. His serum phenytoin levels had risen from 18 mg/L to 34 mg/L. When the phenytoin dose was reduced to 200 mg daily the toxic symptoms disappeared within a few days and his serum phenytoin levels fell to 18 mg/L. To test whether an interaction had occurred, ticlopidine was stopped, whereupon the serum phenytoin levels fell, within about 3 weeks, to 8 mg/L, during which time the patient experienced his first seizure in 2 years. When ticlopidine was restarted, his serum phenytoin levels rose again, and within a month had reached 19 mg/L.[1] A number of other case reports describe phenytoin toxicity, which occurred within 2 to 6 weeks of starting ticlopidine 250 mg once or twice daily.[2-7] These were usually managed by reducing the phenytoin

dose. One patient then experienced breakthrough seizures after the ticlopidine was stopped without re-adjusting the phenytoin dose.[6] One case in a patient also taking **phenobarbital** reported that no change in **phenobarbital** levels occurred.[4]

A study in 6 patients taking phenytoin found that ticlopidine 250 mg twice daily approximately halved the steady-state phenytoin clearance.[8]

Mechanism

The metabolism of phenytoin to 5-(4-hydroxyphenyl)-5-phenylhydantoin (HPPH) by the cytochrome P450 isoenzyme CYP2C19, and to a lesser extent by CYP2C9, in the liver is inhibited by ticlopidine.[1,3,4,9] Further metabolism of HPPH to dihydroxylated products is mediated mainly by CYP2C19 and this may also be inhibited by ticlopidine.[9]

Importance and management

The interaction is established and clinically important, but its incidence is unknown. It would seem prudent to monitor for phenytoin adverse effects (blurred vision, nystagmus, ataxia or drowsiness) and consider monitoring phenytoin levels in any patient if ticlopidine is added to established treatment, being alert for the need to reduce the phenytoin dose. If ticlopidine is discontinued, the phenytoin dose may need to be increased.

1. Riva R, Cerullo A, Albani F, Baruzzi A. Ticlopidine impairs phenytoin clearance: a case report. *Neurology* (1996) 46, 1172–3.
2. Rindone JP, Bryan G. Phenytoin toxicity associated with ticlopidine administration. *Arch Intern Med* (1996) 156, 1113.
3. Privitera M, Welty TE. Acute phenytoin toxicity followed by seizure breakthrough from a ticlopidine-phenytoin interaction. *Arch Neurol* (1996) 53, 1191–2.
4. Donahue SR, Flockhart DA, Abernethy DR, Ko J-W. Ticlopidine inhibition of phenytoin metabolism mediated by potent inhibition of CYP2C19. *Clin Pharmacol Ther* (1997) 62, 572–7.
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6. Klaassen SL. Ticlopidine-induced phenytoin toxicity. *Ann Pharmacother* (1998) 32, 1295–8.
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8. Donahue S, Flockhart DA, Abernethy DR. Ticlopidine inhibits phenytoin clearance. *Clin Pharmacol Ther* (1999) 66, 563–8.
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Phenytoin + Tizanidine

An isolated report describes a modest increase in serum phenytoin levels in a patient also taking tizanidine.

Clinical evidence, mechanism, importance and management

An isolated report describes a 59-year-old man whose phenytoin levels rose by one-third, from about 19 micrograms/mL to 25.5 micrograms/mL, and who experienced drowsiness within a week of starting to take tizanidine 6 mg daily. The phenytoin was stopped for 3 days and restarted at a reduced dose, but the drowsiness recurred in 3 weeks (phenytoin level 20.5 micrograms/mL). Therefore, the tizanidine was withdrawn.[1] The general importance of this interaction is unclear, but it would seem prudent to remain aware of this interaction in case of otherwise unexplained phenytoin adverse effects.

1. Ueno K, Miyai K, Mitsuzane K. Phenytoin-tizanidine interaction. *DICP Ann Pharmacother* (1991) 25, 1273.

Phenytoin + Trazodone

An isolated case report describes phenytoin toxicity in a patient given trazodone.

Clinical evidence, mechanism, importance and management

A patient taking phenytoin 300 mg daily developed progressive signs of phenytoin toxicity after taking trazodone 500 mg daily for 4 months. His serum phenytoin levels had risen from 17.8 micrograms/mL to 46 micrograms/mL.[1] Therapeutic phenytoin serum levels were restored by reducing the phenytoin dose to 200 mg daily and the trazodone dose to 400 mg daily. The reasons for this apparent interaction are not understood, and this appears to be the only reported case of an interaction. No general conclusions can be drawn.

1. Dorn JM. A case of phenytoin toxicity possibly precipitated by trazodone. *J Clin Psychiatry* (1986) 47, 89–90.

Phenytoin + Tricyclic antidepressants

Evidence from two patients suggests that imipramine can raise serum phenytoin levels, but nortriptyline and amitriptyline appear not to do so. Phenytoin possibly reduces serum desipramine levels.

Clinical evidence

(a) Phenytoin levels

The serum phenytoin levels of 2 patients rose over a 3-month period when they were given **imipramine** 75 mg daily. One patient had an increase in phenytoin levels from about 7.6 micrograms/mL to 15 micrograms/mL and developed mild toxicity (drowsiness and uncoordination). These signs disappeared and the phenytoin serum levels of both patients fell when **imipramine** was withdrawn. One of them was also taking nitrazepam and clonazepam, and the other was also taking sodium valproate and carbamazepine, but both patients were stable on these combinations before the addition of **imipramine**.[1]

Other studies have found that **nortriptyline** 75 mg daily had an insignificant effect on the serum phenytoin levels of 5 patients,[2] and that **amitriptyline** had no effect on the elimination of phenytoin in 3 subjects.[3]

(b) Tricyclic antidepressant levels

A report describes 2 patients who had low serum **desipramine** levels, despite taking standard doses, while they were also taking phenytoin.[4]

Mechanism

One suggestion is that imipramine inhibits the metabolism of phenytoin by the liver, which results in its accumulation in the body. An *in vitro* study[5] has shown that the tricyclics can inhibit the cytochrome P450 isoenzyme CYP2C19, but this isoenzyme usually has only a minor role in phenytoin metabolism (see 'Antiepileptics', (p.592)). The reduced desipramine levels may be a result of enzyme induction by phenytoin.

Importance and management

The documentation is very limited indeed and none of these interactions is adequately established. The results of the *in vitro* study suggest that the interaction may only assume importance in those subjects that are deficient in CYP2C9, the enzyme usually responsible for phenytoin metabolism.[5] The tricyclic antidepressants as a group lower the seizure threshold, which suggests that extra care should be taken if deciding to use them in patients with epilepsy. If concurrent use is undertaken the effects should be very well monitored.

1. Perucca E, Richens A. Interaction between phenytoin and imipramine. *Br J Clin Pharmacol* (1977) 4, 485–6.
2. Houghton GW, Richens A. Inhibition of phenytoin metabolism by other drugs used in epilepsy. *Int J Clin Pharmacol Biopharm* (1975) 12, 210–16.
3. Pond SM, Graham GG, Birkett DJ, Wade DN. Effects of tricyclic antidepressants on drug metabolism. *Clin Pharmacol Ther* (1975) 18, 191–9.
4. Fogel BS, Haltzman S. Desipramine and phenytoin: a potential drug interaction of therapeutic relevance. *J Clin Psychiatry* (1987) 48, 387–8.
5. Shin J-G, Park J-Y, Kim M-J, Shon J-H, Yoon Y-R, Cha I-J, Lee S-S, Oh S-W, Kim S-W, Flockhart DA. Inhibitory effects of tricyclic antidepressants (TCAs) on human cytochrome P450 enzymes in vitro: mechanism of drug interaction between TCAs and phenytoin. *Drug Metab Dispos* (2002) 30, 1102–7.

Phenytoin + Valproate

The concurrent use of phenytoin and valproate is common and usually uneventful. Initially total phenytoin levels may fall but this is offset by a rise in the levels of free (and active) phenytoin, which may very occasionally cause some toxicity. After continued use the total phenytoin levels rise, and there might be sustained increases in free phenytoin levels. There is also some very limited evidence to suggest that concurrent use possibly increases the incidence of valproate hepatotoxicity.

Clinical evidence

(a) Phenytoin levels

A number of reports clearly show that the total serum levels of phenytoin fall during the early concurrent use of valproate, while the concentrations of free phenytoin rise.[1-5] In one report it was noted that within 4 to 7 days the total serum phenytoin levels had fallen from 19.4 micrograms/mL to 14.6 micrograms/mL.[1] A study extending over a year in 8 patients taking phenytoin and valproate found that by the end of 8 weeks the total serum phenytoin levels of 6 of them had fallen by almost as much as 50%, but had returned to their original levels in all but one patient by the end of the year.[6] Similar results were found in another study.[7] However, in a further study, some patients had a sustained increase in the free fraction of phenytoin.[4] Another regression analysis showed that valproate increased the free fraction of phenytoin.[8] The occasional patient may have symptoms of phenytoin toxicity.[9] Delirium and an increased seizure frequency were seen in one patient taking valproic acid with phenytoin.[10]

(b) Valproate levels

Studies have found that valproate levels are reduced by the presence of phenytoin.[11,12] Another study reported that valproate levels were increased by 30 to 200% when phenytoin was discontinued in 12 patients taking both drugs, which allowed dose reductions in 6 patients. In these patients, there was no change in seizure control when phenytoin was stopped.[13]

(c) Hepatotoxicity

Epidemiological studies suggest that the risk of fatal hepatotoxicity is higher when valproate is given as polytherapy with enzyme inducers such as phenytoin than when it is given as monotherapy, especially in infants.[14,15] For mention of raised liver enzymes with concurrent use of valproate, phenobarbital and phenytoin, see 'Phenobarbital + Valproate', p.625.

Mechanism

The initial fall in total serum phenytoin levels appears to result from the displacement of phenytoin from its protein binding sites by valproate,[1-5,10] the extent being subject to the diurnal variation in valproate levels.[16] This allows more of the unbound drug to be exposed to metabolism by the liver and the total phenytoin levels fall. After several weeks the metabolism of phenytoin is inhibited by valproate and phenytoin levels rise.[2,4] This may result in sustained elevation of free (active) phenytoin levels.[17] Phenytoin reduces valproate levels, probably because it increases its metabolism by the liver. Because phenytoin is an enzyme inducer it may also possibly increase the formation of a minor but hepatotoxic metabolite of valproate (2-propyl-4-pentenoic acid or 4-ene-VPA).[18]

Importance and management

An extremely well-documented interaction (only a selection of the references being listed here). Concurrent use is common and usually advantageous, the adverse effects of the interactions between the drugs usually being of only minor practical importance. However, the outcome should still be monitored. A few patients may experience mild toxicity if valproate is started, but most patients taking phenytoin do not need a dose change. During the first few weeks total serum phenytoin levels may fall by 20 to 50%, but usually no increase in the dose is needed, because it is balanced by an increase in the levels of free (active) phenytoin levels. In the following period, the total phenytoin levels may rise again. This may result in a sustained rise in free phenytoin levels.

When monitoring concurrent use it is important to understand fully the implications of changes in 'total' and 'free' or 'unbound' serum phenytoin concentrations. Where monitoring of free phenytoin levels is not available, various nomograms have been designed for predicting unbound phenytoin concentrations during the use of valproate.[17,19] Bear in mind the evidence that the incidence of valproate-induced liver toxicity may be increased when it is given with phenytoin, especially in infants.

1. Mattson RH, Cramer JA, Williamson PD, Novelly RA. Valproic acid in epilepsy: clinical and pharmacological effects. *Ann Neurol* (1978) 3, 20–5.
2. Perucca E, Hebdige S, Frigo GM, Gatti G, Lecchini S, Crema A. Interaction between phenytoin and valproic acid: plasma protein binding and metabolic effects. *Clin Pharmacol Ther* (1980) 28, 779–89.
3. Tsanaclis LM, Allen J, Perucca E, Routledge PA, Richens A. Effect of valproate on free plasma phenytoin concentrations. *Br J Clin Pharmacol* (1984) 18, 17–20.
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5. Friel PN, Leal KW, Wilensky AJ. Valproic acid-phenytoin interaction. *Ther Drug Monit* (1979) 1, 243–8.
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Phenytoin + Vigabatrin

Vigabatrin causes a small to moderate reduction in phenytoin levels.

Clinical evidence

In one early clinical study in 19 patients, the mean plasma phenytoin levels were about 30% lower when they were given vigabatrin 2 to 3 g daily: in 2 patients phenytoin levels fell below the therapeutic range. However, the change in phenytoin levels was not correlated with the change in seizure frequency.[1] Another clinical study found that vigabatrin reduced the mean serum phenytoin levels by 20% in 53 patients; 41 patients had a decrease in phenytoin levels and 12 had an increase. In this study, some of the patients (number not stated) with decreased phenytoin levels had an increase in seizure frequency and required a phenytoin dose increase.[2,3] In another analysis, the decrease in phenytoin levels did not occur until the fifth week of vigabatrin use.[4] Three other studies have shown roughly similar decreases in phenytoin levels when vigabatrin was added.[5-7]

Mechanism

Not understood. Studies in patients found that decreases in phenytoin levels do not appear to be due to reduced metabolism or altered plasma protein binding.[4] Similarly, it is not due to altered bioavailability, as the interaction occurred with intravenous phenytoin.[5]

Importance and management

The interaction between phenytoin and vigabatrin would appear to be established. Vigabatrin causes a modest decrease in phenytoin levels in some patients, which takes a number of weeks to become apparent. A small increase in the dose of phenytoin may possibly be needed in some patients.

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4. Rimmer EM, Richens A. Double-blind study of γ-vinyl GABA in patients with refractory epilepsy. *Lancet* (1984) i, 189–90.

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Phenytoin + Viloxazine

Viloxazine can raise phenytoin levels, and signs of toxicity have developed in some patients. Phenytoin does not appear to affect the pharmacokinetics of viloxazine.

Clinical evidence

The serum phenytoin levels of 10 patients with epilepsy rose by 37% (from 18.8 micrograms/mL to 25.7 micrograms/mL) over the 3 weeks following the addition of viloxazine 150 to 300 mg daily. The increase ranged from 7 to 94%. Signs of toxicity (ataxia, nystagmus) developed in 4 of the patients 12 to 16 days after starting viloxazine. Their serum phenytoin levels had risen to between 32.3 and 41 micrograms/mL. When viloxazine was withdrawn the symptoms disappeared and phenytoin levels fell.[1] The pharmacokinetics of viloxazine were unaffected by phenytoin.[2]

Mechanism

Uncertain. What is known suggests that viloxazine inhibits the metabolism of phenytoin, thereby reducing its clearance and raising its serum levels.

Importance and management

Information seems to be limited to the reports cited. If concurrent use is undertaken, serum phenytoin levels should be monitored closely and suitable dose reductions made as necessary to avoid possible toxicity.

1. Pisani F, Fazio A, Artesi C, Russo M, Trio R, Oteri G, Perucca E, Di Perri R. Elevation of plasma phenytoin by viloxazine in epileptic patients: a clinically significant interaction. *J Neurol Neurosurg Psychiatry* (1992) 55, 126–7.
2. Pisani F, Fazio A, Spina E, Artesi C, Pisani B, Russo M, Trio R, Perucca E. Pharmacokinetics of the antidepressant drug viloxazine in normal subjects and in epileptic patients receiving chronic anticonvulsant treatment. *Psychopharmacology (Berl)* (1986) 90, 295–8.

Phenytoin + Zidovudine

Although one study found that zidovudine did not alter the pharmacokinetics of phenytoin, there is other evidence suggesting that some changes possibly occur, although these may actually be due to HIV infection.

Clinical evidence, mechanism, importance and management

Although there are said to have been 13 cases of a possible interaction between zidovudine and phenytoin, the details are not described in the report.[1] No significant changes in the pharmacokinetics of phenytoin 300 mg daily were seen in 12 asymptomatic HIV-positive patients who were taking zidovudine 200 mg every 4 hours.[1] Another study found that the mean phenytoin dose was higher in HIV-positive patients, when compared with subjects with epilepsy without the virus, while the mean phenytoin levels in the HIV-positive group were lower (i.e. a higher phenytoin dose resulted in lower serum levels in HIV-positive subjects). Zidovudine did not appear to affect the levels.[2,3] The current evidence would suggest that it is HIV infection, rather than zidovudine, that affects phenytoin levels, but more study is needed to confirm this.

1. Sarver P, Lampkin TA, Dukes GE, Messenheimer JA, Kirby MG, Dalton MJ, Hak LJ. Effect of zidovudine on the pharmacokinetic disposition of phenytoin in HIV positive asymptomatic patients. *Pharmacotherapy* (1991) 11, 108–9.
2. Burger DW, Meerhorst PL, Koks CHW, Beijnen JH. Phenytoin (PH) monitoring in HIV (+) individuals: is there an interaction with zidovudine (ZDV)? 9th International Conference on AIDS & 5th World Congress on Sexually Transmitted Diseases, Berlin. June 6–11, 1993. Abstract PO-B31-2214.
3. Burger DM, Meenhorst PL, Mulder JW, Kraaijeveld CL, Koks CHW, Bult A, Beijnen JH. Therapeutic drug monitoring of phenytoin in patients with the acquired immunodeficiency syndrome. *Ther Drug Monit* (1994) 16, 616–20.

Phenytoin + Zileuton

The pharmacokinetics of phenytoin are not affected by zileuton.

Clinical evidence, mechanism, importance and management

A controlled study in 20 healthy subjects found that the pharmacokinetics of a single 300-mg dose of phenytoin were unaltered by zileuton 600 mg every 6 hours for 5 days.[1] An *in vitro* study found that zileuton had little effect on the isoenzymes responsible for the metabolism of phenytoin.[2] These studies suggest that zileuton is unlikely to affect phenytoin levels in clinical use.

1. Samara E, Cavanaugh JH, Mukherjee D, Granneman GR. Lack of pharmacokinetic interaction between zileuton and phenytoin in humans. *Clin Pharmacokinet* (1995) 29 (Suppl 2), 84–91.
2. Lu P, Schrag ML, Slaughter DE, Raab CE, Shou M, Rodrigues AD. Mechanism-based inhibition of human liver microsomal cytochrome P450 1A2 by zileuton, a 5-lipoxygenase inhibitor. *Drug Metab Dispos* (2003) 31, 1352–60.

Piracetam + Other antiepileptics

Piracetam does not appear to alter the levels of sodium valproate or primidone. No interaction has been found between piracetam and carbamazepine, clonazepam, phenobarbital, or phenytoin.

Clinical evidence, mechanism, importance and management

The addition of piracetam (2 to 4 g three times daily, increased to a maximum of 18 to 24 g daily) did not affect plasma levels of **sodium valproate** or **primidone** in patients with myoclonus. The exact number of patients taking these drugs is unclear, as the report just states that 28 patients were taking **clonazepam**, **sodium valproate**, or **primidone**, alone or in combination.[1] Another similar report, briefly noted the same findings.[2] The manufacturer of piracetam notes that no interaction has been found between piracetam and **clonazepam**, **carbamazepine**, **phenytoin**, **phenobarbital** and **sodium valproate**, although this is based on a small number of patients.[3] No dose adjustments appear to be required if piracetam is used with these antiepileptics.

1. Obeso JA, Artieda J, Quinn N, Rothwell JC, Luquin MR, Vaamonde J, Marsden CD. Piracetam in the treatment of different types of myoclonus. *Clin Neuropharmacol* (1988) 11, 529–36.
2. Raychev I. Piracetam (pyramem) in the treatment of cortical myoclonus. 5th European Congress of Epileptology, Madrid 2002. P382.
3. Nootropil (Piracetam). UCB Pharma Ltd. UK Summary of product characteristics, December 2006.

Pregabalin + Miscellaneous

Carbamazepine, oxcarbazepine, and phenytoin may decrease serum levels of pregabalin. Levetiracetam does not affect the pharmacokinetics of pregabalin, and there appears to be no pharmacokinetic interaction between pregabalin and gabapentin, lamotrigine, phenobarbital, topiramate, valproate, alcohol, lorazepam, or oxycodone. However, the impairment of cognitive and gross motor function caused by oxycodone was additive with pregabalin, and pregabalin may potentiate the effects of alcohol and lorazepam.

Clinical evidence, mechanism, importance and management

(a) Alcohol or Lorazepam

The manufacturer notes that there was no clinically relevant pharmacokinetic interaction between pregabalin and lorazepam or alcohol, and that concurrent use caused no clinically important effect on respiration. However, they note that pregabalin may potentiate the effects of lorazepam and alcohol.[1]

(b) Other antiepileptics

Pregabalin 200 mg three times daily for 7 days was added to monotherapy with various antiepileptics in patients with partial epilepsy. Pregabalin did not alter the steady-state levels of **phenytoin**, **carbamazepine** (or its active metabolite, carbamazepine-10,11-epoxide), **valproate** or **lamotrigine**. In addition, the steady-state pharmacokinetics of pregabalin were not different to those seen previously in healthy subjects taking pregabalin

alone, suggesting that these antiepileptics do not alter pregabalin pharmacokinetics.[2] Similarly, population pharmacokinetic analyses of clinical studies found no important changes in the pharmacokinetics of **lamotrigine**, **phenobarbital**, **phenytoin**, **topiramate** or **valproate** when they were given with pregabalin, and the pharmacokinetics of pregabalin were unaffected by these drugs.[3] However, this sort of analysis gives only the broadest impression of whether or not a drug interacts, and another study in patients with epilepsy found that pregabalin levels were 30%, 22%, and 23% lower when it was given with the enzyme-inducing drugs **carbamazepine**, **oxcarbazepine**, and **phenytoin**, respectively. In this study **levetiracetam** had no effect on the serum concentrations of pregabalin.[4] The manufacturer also notes that there is no pharmacokinetic interaction between pregabalin and **gabapentin**.[1]

(c) Oxycodone

The manufacturer notes that there was no clinically relevant pharmacokinetic interaction between pregabalin and oxycodone, and that there was no clinically important effect on respiration. However, pregabalin appeared to cause an additive impairment in cognitive and gross motor function when given with oxycodone.[1] This suggests caution is warranted during combined use.

1. Lyrica (Pregabalin). Pfizer Ltd. UK Summary of product characteristics, August 2009.
2. Brodie MJ, Wilson EA, Wesche DL, Alvey CW, Randinitis EJ, Posvar EL, Hounslow NJ, Bron NJ, Gibson GL, Bockbrader HN. Pregabalin drug interaction studies: lack of effect on the pharmacokinetics of carbamazepine, phenytoin, lamotrigine, and valproate in patients with partial epilepsy. *Epilepsia* (2005) 46, 1407–13.
3. Bockbrader HN, Burger PJ, Corrigan BW, Kugler AR, Knapp LE, Garofalo EA, Lalonde RL. Population pharmacokinetic analyses of commonly prescribed antiepileptic drugs coadministered with pregabalin in adult patients with refractory partial seizures. *Epilepsia* (2001) 42 (Suppl 7), 84.
4. May TW, Rambeck B, Neb R, Jürgens U. Serum concentrations of pregabalin in patients with epilepsy: the influence of dose, age, and comedication. *Ther Drug Monit* (2007) 29, 789–94.

Primidone + Isoniazid

A single case report describes elevated primidone levels and reduced levels of its phenobarbital metabolite when primidone was given with isoniazid.

Clinical evidence, mechanism, importance and management

A patient taking primidone had raised serum primidone levels and reduced serum phenobarbital levels. This was attributed to the concurrent use of isoniazid, which inhibited the metabolism of primidone by the liver. The half-life of primidone rose from 8.7 hours to 14 hours and the steady-state primidone levels rose by 83% in the presence of isoniazid.[1] The importance of this interaction is uncertain, but prescribers should bear this interaction in mind in case of an unexpected response to primidone.

1. Sutton G, Kupferberg HJ. Isoniazid as an inhibitor of primidone metabolism. *Neurology* (1975) 25, 1179–81.

Primidone + Miscellaneous

Primidone is substantially converted to phenobarbital within the body and it is therefore expected to interact with other drugs in the same way as phenobarbital. Some drugs may increase the conversion of primidone to phenobarbital.

Clinical evidence, mechanism, importance and management

Primidone is substantially converted to phenobarbital within the body. For example, a group of patients taking long-term primidone developed serum primidone levels of 9 micrograms/mL and serum phenobarbital levels of 31 micrograms/mL.[1] Primidone would therefore be expected to interact with other drugs in the same way as phenobarbital. Some enzyme-inducing drugs might increase the conversion of primidone to phenobarbital, and this has been demonstrated for 'phenytoin', (below), and 'carbamazepine', (p.609). Some patients have been treated with a combination of phenobarbital and primidone. In this situation higher phenobarbital levels might be expected.

1. Booker HE, Hosokowa K, Burdette RD, Darcey B. A clinical study of serum primidone levels. *Epilepsia* (1970) 11, 395–402.

Primidone + Phenytoin

Primidone-derived serum phenobarbital levels are increased by phenytoin. This is normally an advantageous interaction, but phenobarbital toxicity occasionally occurs.

Clinical evidence

A study in 44 patients with epilepsy taking primidone and phenytoin found that their serum phenobarbital to primidone ratio was high (4.35) when compared with that in 15 other patients who were only taking primidone (1.05).[1] This suggests that in the presence of phenytoin, primidone-derived phenobarbital levels are higher than when primidone is given alone. Similar results are described in other studies.[2-7] A few patients may develop barbiturate toxicity.[8]

An initial marked decrease in phenytoin levels, then an increase to half the initial phenytoin level, was seen in the first few weeks after withdrawing primidone in an infant. Primidone-derived phenobarbital levels before discontinuing the primidone were very high, and were associated with marked sedation.[9]

Mechanism

Phenytoin increases the metabolic conversion of primidone to phenobarbital, while possibly reducing the subsequent metabolism (hydroxylation) of the phenobarbital. The net effect is a rise in phenobarbital levels.[10] Phenobarbital may increase or decrease phenytoin levels, see 'Phenytoin + Phenobarbital', p.640.

Importance and management

Well documented. This is normally an advantageous interaction because phenobarbital is itself an active antiepileptic. However, it should be noted that phenobarbital serum levels could sometimes reach toxic concentrations,[8] even if only a small dose of phenytoin is added. Changes in phenytoin levels may also occur (see 'Phenytoin + Phenobarbital', p.640).

1. Fincham RW, Schottelius DD, Sahs AL. The influence of diphenylhydantoin on primidone metabolism. *Arch Neurol* (1974) 30, 259–62.
2. Fincham RW, Schottelius DD, Sahs AL. The influence of diphenylhydantoin on primidone metabolism. *Trans Am Neurol Assoc* (1973) 98, 197–9.
3. Schmidt D. The effect of phenytoin and ethosuximide on primidone metabolism in patients with epilepsy. *J Neurol* (1975) 209, 115–23.
4. Reynolds EH, Fenton G, Fenwick P, Johnson AL, Laundy M. Interaction of phenytoin and primidone. *BMJ* (1975) 2, 594–5.
5. Callaghan N, Feeley M, Duggan F, O'Callaghan M, Seldrup J. The effect of anticonvulsant drugs which induce liver microsomal enzymes on derived and ingested phenobarbitone levels. *Acta Neurol Scand* (1977) 56, 1–6.
6. Battino D, Avanzini G, Bossi L, Croci D, Cusi C, Gomeni C, Moise A. Plasma levels of primidone and its metabolite phenobarbital: effect of age and associated therapy. *Ther Drug Monit* (1983) 5, 73–9.
7. Garrettson LK, Gomez M. Phenytoin-primidone interaction. *Br J Clin Pharmacol* (1977) 4, 693–5.
8. Galdames D, Ortiz M, Saavedra I, Aguilera L. Interaccion fenitoina-primidona: intoxicacion por fenobarbital, en un adulto tratado con ambas drogas. *Rev Med Chil* (1980) 108, 716–20.
9. Wilson JT, Wilkinson GR. Chronic and severe phenobarbital intoxication in a child treated with primidone and diphenylhydantoin. *J Pediatr* (1973) 83, 484–9.
10. Porro MG, Kupferberg HJ, Porter RJ, Theodore WH, Newmark ME. Phenytoin: an inhibitor and inducer of primidone metabolism in an epileptic patient. *Br J Clin Pharmacol* (1982) 14, 294–7.

Primidone + Valproate

Valproate has been reported to cause increases, decreases, and no change in primidone levels. Primidone-derived phenobarbital levels appear to be increased by valproate.

Clinical evidence

In a number of cases, patients taking primidone required a decrease in the primidone dose after valproate was added.[1-4] In 6 cases this was due to an increase in the primidone-derived phenobarbital level,[1] and in the other cases phenobarbital levels were not measured, but the dose reduction was needed to overcome the sedation that occurred when valproate was added.[2-4] Primidone levels were not measured in any of these cases.[1-4] In two other studies, primidone levels either decreased,[5] or did not change when valproate was added.[6] However, phenobarbital levels, where measured, had increased.[6]

In 7 children the serum levels of primidone 10 to 18 mg/kg daily rose two- to threefold when valproate (dose not stated) was also given. After

1 to 3 months of concurrent use the serum primidone levels fell in 3 of the patients but persisted in one. Follow-up primidone levels were not taken in the other 3 patients, and none of the patients had phenobarbital levels measured.[7]

In contrast, in a further study, neither phenobarbital levels nor primidone levels were significantly altered when valproate was given.[8]

Mechanism

It has been suggested that valproate decreases the conversion of primidone to phenobarbital, and decreases the metabolism of phenobarbital (see also 'Phenobarbital + Valproate', p.625). This would result in increased primidone and phenobarbital levels. However, increased renal clearance of primidone may also occur, resulting in no overall change to primidone levels. Depending on the balance between these various effects a variety of levels may result.[8] The results of one study suggest that the proposed inhibition of primidone metabolism caused by valproate may diminish over the first few months of concurrent use.[7]

Importance and management

There seems to be little consistency about the effect of valproate on primidone levels. However, in the majority of cases phenobarbital levels seem to be raised (see also 'Phenobarbital + Valproate', p.625). It would therefore seem prudent not to act on primidone levels without considering the corresponding phenobarbital levels. Monitor the patient for increased signs of sedation, which may be resolved by a reduction in the primidone dose.

1. Wilder BJ, Willmore LJ, Bruni J, Villarreal HJ. Valproic acid: interaction with other anticonvulsant drugs. *Neurology* (1978) 28, 892–6.
2. Haigh D, Forsythe WI. The treatment of childhood epilepsy with sodium valproate. *Dev Med Child Neurol* (1975) 17, 743–8.
3. Richens A, Ahmad S. Controlled trial of sodium valproate in severe epilepsy. *BMJ* (1975) 4, 255–6.
4. Völzke E, Doose H. Dipropylacetate (Dépakine®, Ergenyl®) in the treatment of epilepsy. *Epilepsia* (1973) 14, 185–93.
5. Varma R, Michos GA, Varma RS, Hoshino AY. Clinical trials of Depakene (valproic acid) coadministered with other anticonvulsants in epileptic patients. *Res Commun Psychol Psychiatr Behav* (1980) 5, 265–73.
6. Yukawa E, Higuchi S, Aoyama T. The effect of concurrent administration of sodium valproate on serum levels of primidone and its metabolite phenobarbital. *J Clin Pharm Ther* (1989) 14, 387–92.
7. Windorfer A, Sauer W, Gädeke R. Elevation of diphenylhydantoin and primidone serum concentration by addition of dipropylacetate, a new anticonvulsant drug. *Acta Paediatr Scand* (1975) 64, 771–2.
8. Bruni J. Valproic acid and plasma levels of primidone and derived phenobarbital. *Can J Neurol Sci* (1981) 8, 91–2.

Progabide + Other antiepileptics

Progabide may raise phenytoin levels and alter the levels of carbamazepine. Clonazepam, phenobarbital and valproate levels are minimally affected by progabide.

Clinical evidence

(a) Phenytoin

Marked increases in serum phenytoin levels have been seen in a few patients also given progabide,[1-4] while smaller changes have been described in some studies,[5,6] and negligible changes in others.[7]

In one study, 17 out of 26 patients with epilepsy needed a reduction in their phenytoin dose to keep the levels within 25% of the serum levels achieved in the absence of progabide. Over half the patients needed a dose reduction within 4 weeks of starting concurrent use. Most of those needing a dose reduction had a maximum increase in the serum level of 40% or more, which was sometimes accompanied by toxicity.[2,8] In a later report of this study, of a total of 32 patients with epilepsy taking carbamazepine with phenytoin and then given progabide, 22 needed a reduction in their phenytoin dose to maintain serum levels within 25% of those achieved in the absence of progabide. In addition, it appeared this effect on phenytoin serum levels continued for a while after progabide was withdrawn.[4]

(b) Other antiepileptics

Information about antiepileptics other than phenytoin is limited, but progabide is reported to minimally reduce,[1,9,10] minimally increase[1] or not to change[2,3,5-7] **carbamazepine** serum levels. An increase of up to 24% in the levels of carbamazepine-10-11-epoxide (the active metabolite of **carbamazepine**) has also been reported.[6,10] **Valproate**[3,5-7] and **clonazepam**[11] serum levels do not seem to be significantly affected by progabide. Progabide appears to cause a small increase in serum **phenobarbital** levels, which is of little clinical importance.[1,5-7]

Mechanism

Uncertain.

Importance and management

Some small to moderate changes in the serum levels of carbamazepine, clonazepam, phenobarbital, and valproate can apparently occur in the presence of progabide, but only the interaction with phenytoin appears to be clinically relevant. Be alert for evidence of phenytoin adverse effects (e.g. blurred vision, nystagmus, ataxia or drowsiness) and consider reducing the dose of phenytoin if progabide is used concurrently.

1. Schmidt D, Utech K. Progabide for refractory partial epilepsy: a controlled add-on trial. *Neurology* (1986) 36, 217–221.
2. Cloyd JC, Brundage RC, Leppik IE, Graves NM, Welty TE. Effect of progabide on serum phenytoin and carbamazepine concentrations: a preliminary report. In: LERS Monograph series, volume 3. Edited by Bartholini G et al. Epilepsy and GABA receptor agonists: basic and therapeutic research. Meeting, Paris, March 1984. Raven Press, New York. (1985) pp 271–8. ISBN: 0881671061
3. Crawford P, Chadwick D. A comparative study of progabide, valproate and placebo as add-on therapy in patients with refractory epilepsy. *J Neurol Neurosurg Psychiatry* (1986) 49, 1251–7.
4. Brundage RC, Cloyd JC, Leppik IE, Graves NM and Welty TE. Effect of progabide on serum phenytoin and carbamazepine concentrations. *Clin Neuropharmacol* (1987) 10, 545–54.
5. Bianchetti G, Thiercelin JF, Thenot JP, Feuerstein J, Lambert D, Rulliere R, Thebault JJ, Morselli PL. Effect of progabide on the pharmacokinetics of various antiepileptic drugs. *Neurology* (1984) 34 (Suppl 1), 213.
6. Bianchetti G, Padovani P, Thénot JP, Thiercelin JF, Morselli PL. Pharmacokinetic interactions of progabide with other antiepileptic drugs. *Epilepsia* (1987) 28, 68–73.
7. Thénot JP, Bianchetti G, Abriol C, Feuerstein J, Lambert D, Thébault JJ, Warrington SJ, Rowland M. Interactions between progabide and antiepileptic drugs. In: LERS Monograph series, volume 3. Edited by Bartholini G et al. Epilepsy and GABA receptor agonists: basic and therapeutic research. Meeting, Paris, March 1984. Raven Press, New York. (1985) pp 259–69. ISBN: 0881671061
8. Brundage RC, Leppik IE, Cloyd JC, Graves NM. Effect of progabide on phenytoin pharmacokinetics. *Epilepsia* (1984) 25, 656–7.
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10. Graves NM, Fuerst RH, Cloyd JC, Brundage RC, Welty TE, Leppik IE. Progabide-induced changes in carbamazepine metabolism. *Epilepsia* (1988) 29, 775–80.
11. Warrington SJ, O'Brien C, Thiercelin JF, Orofiamma B and Morselli PL. Evaluation of pharmacodynamic interaction between progabide and clonazepam in healthy men. In: LERS Monograph series, volume 3. Edited by Bartholini G et al. Epilepsy and GABA receptor agonists: basic and therapeutic research. Meeting, Paris, March 1984. Raven Press, New York. (1985) pp 279–86. ISBN: 0881671061

Remacemide + Other antiepileptics

Remacemide causes modest increases in carbamazepine and phenytoin serum levels. Carbamazepine, phenobarbital and phenytoin moderately reduce remacemide serum levels. Valproate and lamotrigine do not appear to interact with remacemide.

Clinical evidence

(a) Carbamazepine

When a group of 10 patients taking carbamazepine were also given up to 300 mg of remacemide twice daily for 2 weeks the minimum serum levels and the AUC of carbamazepine were increased by 20% and 22%, respectively. None of the patients had symptoms of carbamazepine toxicity.[1] Another study in 11 patients taking carbamazepine found that remacemide caused a similar 20 to 30% increase in the AUC of carbamazepine, again without signs of toxicity. No consistent changes in the AUC of carbamazepine-10,11-epoxide, the main metabolite of carbamazepine, were seen.[2] Another study has reported a slight inhibitory effect of remacemide on carbamazepine metabolism, which is in line with these other findings.[3] One of these studies also reported that the AUC of remacemide was decreased by 40 to 50% and the AUC of its main metabolite by about 70% in the presence of carbamazepine, when compared with healthy subjects (presumably not taking carbamazepine).[2]

However, a further study of the efficacy of remacemide and carbamazepine in combination found that about two-thirds of the 120 patients treated needed 14 to 50% reductions in their carbamazepine dose, to ensure levels remained in the therapeutic range.[4]

(b) Lamotrigine

In a study in healthy subjects there was no clinically relevant pharmacokinetic interaction between remacemide (200 mg daily increased to 200 mg

three times daily) and lamotrigine (200 mg twice daily decreased to 100 mg daily).[5]

(c) Phenobarbital

In a study in healthy subjects, phenobarbital 30 mg daily increased to 90 mg daily increased the clearance of remacemide 200 mg twice daily by 67%, and slightly increased the plasma levels of phenobarbital (by 9%).[6]

(d) Phenytoin

A group of 10 patients taking phenytoin were also given up to 300 mg remacemide twice daily for 2 weeks. On average remacemide did not affect phenytoin pharmacokinetics but 5 patients had an increase in minimum serum levels of 30% or more. None of the patients had symptoms of phenytoin toxicity.[1] In another study 10 patients with epilepsy, who had been taking phenytoin for at least 3 months, were given remacemide 300 mg twice daily for 12 days. Phenytoin maximum plasma levels were increased by 14% and the AUC was raised by 12%. Average concentrations of remacemide and its main metabolite were around only 40% and 30%, respectively, of those achieved in healthy subjects taking remacemide alone, at the same dose.[7] Another study reported a slight inhibitory effect of remacemide on phenytoin metabolism, which is in line with these other findings.[3]

(e) Valproate

A group of 10 patients taking valproate were also given remacemide up to 300 mg twice daily for 14 days. The pharmacokinetics of valproate remained unchanged.[1] Another study in 17 patients confirmed these findings,[8] and an earlier study by the same authors also noted no effect of remacemide on valproate metabolism.[3]

Mechanism

Not fully understood, but *in vitro* studies indicate that remacemide inhibits the cytochrome P450 isoenzyme CYP3A4, which in practice would be expected to result in a reduction in the metabolism of the carbamazepine resulting in an increase in its serum levels. Remacemide appears to inhibit CYP2C9 to a lesser extent, which is reflected in a smaller interaction with phenytoin. Valproate is metabolised by glucuronidation and is therefore unaffected.[1]

Carbamazepine and phenytoin, known enzyme inducers, also seem to increase the metabolism of the remacemide.[7]

Importance and management

Information is limited, but the interactions of remacemide with carbamazepine, phenobarbital and phenytoin appear to be established, but so far only the carbamazepine interaction seems to have been shown to be of clinical importance. Even so, it may be prudent to monitor the effects of concurrent use with phenytoin or phenobarbital. No interaction occurs between remacemide and valproate or lamotrigine.

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2. Leach JP, Blacklaw J, Stewart M, Jamieson V, Jones T, Oxley R, Richens A, Brodie MJ. Mutual pharmacokinetic interactions between remacemide hydrochloride and carbamazepine. *Epilepsia* (1995) 36 (Suppl 3), S163.
3. Leach JP, Blacklaw J, Stewart M, Jamieson V, Oxley R, Richens A, Brodie MJ. Interactions between remacemide and the established antiepileptic drugs. *Epilepsia* (1994) 35 (Suppl 7), 75.
4. Mawer GE, Jamieson V, Lucas SB, Wild JM. Adjustment of carbamazepine dose to offset the effects of the interaction with remacemide hydrochloride in a double-blind, multicentre, add-on drug trial (CR2237) in refractory epilepsy. *Epilepsia* (1999) 40, 190–6.
5. Blakey GE, Lockton JA, Rolan IP. The effect of lamotrigine on the disposition of remacemide hydrochloride. *Epilepsia* (1999) 40 (Suppl 2), 251.
6. Hooper WD, Eadie MJ, Blakey GE, Lockton JA, Manun'Ebo M. Evaluation of a pharmacokinetic interaction between remacemide hydrochloride and phenobarbitone in healthy males. *Br J Clin Pharmacol* (2001) 51, 249–55.
7. Leach JP, Girvan J, Jamieson V, Jones T, Richens A, Brodie MJ. Mutual interaction between remacemide hydrochloride and phenytoin. *Epilepsy Res* (1997) 26, 381–8.
8. Leach JP, Girvan J, Jamieson V, Jones T, Richens A, Brodie MJ. Lack of pharmacokinetic interaction between remacemide hydrochloride and sodium valproate in epileptic patients. *Seizure* (1997) 6, 179–84.

Retigabine + Other antiepileptics

The clearance of retigabine is increased by carbamazepine and phenytoin, but not affected by phenobarbital, topiramate, or valproate. Retigabine does not alter the pharmacokinetics of any of these antiepileptics. There is a modest pharmacokinetic interaction between retigabine and lamotrigine.

Clinical evidence, mechanism, importance and management

(a) Enzyme-inducing antiepileptics

The preliminary report of a study in patients with epilepsy notes that the clearance of retigabine was increased (amount not stated) by **carbamazepine** and **phenytoin**, whereas retigabine did not alter **carbamazepine** or **phenytoin** pharmacokinetics.[1] This is consistent with the known enzyme-inducing properties of **carbamazepine** and **phenytoin**, and the fact that retigabine has not been shown to induce hepatic enzymes. In contrast, in a study in healthy subjects, **phenobarbital** 90 mg daily did not affect the pharmacokinetics of retigabine 200 mg every 8 hours, and the pharmacokinetics of **phenobarbital** were not altered by retigabine.[2] The clinical relevance of the effect of **carbamazepine** and **phenytoin** on retigabine remains to be assessed. No dose adjustments seem to be necessary with **phenobarbital**.

(b) Lamotrigine

In a study in 14 healthy subjects, lamotrigine 25 mg daily for 5 days increased the AUC of a single 200-mg dose of retigabine by 15% and decreased its clearance by 13%.[3] In another 15 subjects, retigabine (200 mg twice daily increased to 300 mg twice daily over 15 days) decreased the AUC of a single 200-mg dose of lamotrigine by 18% and increased its clearance by 22%. It was suggested that lamotrigine competes for renal elimination with retigabine, but the mechanism behind the decreased lamotrigine levels is unknown.[3] These modest changes are unlikely to be clinically important for most patients, but the authors suggest that the effects need to be assessed at the upper recommended dose ranges, and therefore advise caution.

(c) Topiramate

The preliminary report of a study notes that the pharmacokinetics of retigabine and topiramate were not altered by concurrent use in patients with epilepsy.[1] No special dosing precautions are necessary.

(d) Valproate

The preliminary report of a study notes that the pharmacokinetics of retigabine and valproic acid were not altered by concurrent use in patients with epilepsy.[1] No special dosing precautions are necessary.

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2. Ferron GM, Patat A, Parks V, Rolan P, Troy SM. Lack of pharmacokinetic interaction between retigabine and phenobarbitone at steady state in healthy subjects. *Br J Clin Pharmacol* (2003) 56, 39–45.
3. Hermann R, Knebel NG, Niebch G, Richards L, Borlak J, Locher M. Pharmacokinetic interaction between retigabine and lamotrigine in healthy subjects. *Eur J Clin Pharmacol* (2003) 58, 795–802.

Rufinamide + Food

Food increases the rate and extent of absorption of rufinamide.

Clinical evidence, mechanism, importance and management

In a study to investigate the effect of food on the pharmacokinetics of rufinamide, 12 healthy subjects were given a single 600-mg dose of rufinamide after an overnight fast, or with a fat- and protein-rich breakfast. The AUC of rufinamide was increased by 44% by food, when compared with the fasted state, and the maximum plasma level was increased twofold. The time to reach the maximum plasma level was shortened from 8 hours to 6 hours in the group that took rufinamide with food. Headache was reported more frequently in the fed group, but the use of analgesics was not different between the two groups.[1] The manufacturer recommends that rufinamide is taken with food,[2] to maximise absorption.

1. Cardot J-M, Lecaillon J-B, Czendlik C, Godbillon J. The influence of food on the disposition of the antiepileptic rufinamide in healthy volunteers. *Biopharm Drug Dispos* (1998) 19, 259–62.
2. Inovelon (Rufinamide). Eisai Ltd. UK Summary of product characteristics, October 2009.

Rufinamide + Miscellaneous

Rufinamide may increase the clearance of drugs that are substrates of CYP3A4, such as triazolam. Other cytochrome P450 isoenzymes are unlikely to be affected.

Clinical evidence and mechanism

(a) CYP3A4

Rufinamide has been shown to induce the cytochrome P450 isoenzyme CYP3A4 to a moderate degree. A study found that rufinamide 400 mg twice daily for 11 days increased the clearance of **triazolam**, a substrate of CYP3A4, by 55% and reduced its exposure by 36%.[1]

(b) CYP1A2

Rufinamide 400 mg twice daily did not affect the pharmacokinetics of **olanzapine**, a substrate of CYP1A2.[1]

Importance and management

Evidence about CYP3A4 substrates is limited, but is in line with the *in vitro* effects of rufinamide, and the way in which triazolam is known to be metabolised. The manufacturers recommend that any patient taking a drug that is a substrate of CYP3A4 should be monitored for 2 weeks after starting, stopping, or changing the dose of rufinamide, and dose adjustments made as appropriate. Note that the effects of CYP3A4 substrates are likely to be diminished. For a list of known substrates of this isoenzyme, see 'Table 1.4', (p.6).

The manufacturer[1] also advises that similar precautions should be taken when rufinamide is given with drugs with a narrow therapeutic margin, and specifically mentions **warfarin** and **digoxin**. However, warfarin is only metabolised to a limited extent by this isoenzyme, and moderate CYP3A4 inhibitors do not generally interact with warfarin (see 'diltiazem', (p.445), and 'erythromycin', (p.417)), although cases of bleeding may occur. The prediction with digoxin, a P-glycoprotein substrate, appears to be based on the fact that an effect of rufinamide on P-glycoprotein has not been excluded. Further study is needed.

No pharmacokinetic interaction would be expected with substrates of CYP1A2. For a list of known substrates of this isoenzyme, see 'Table 1.2', (p.4).

1. Inovelon (Rufinamide). Eisai Ltd. UK Summary of product characteristics, October 2009.

Rufinamide + Other antiepileptics

The clearance of rufinamide is increased by phenytoin, phenobarbital and primidone. Valproate may raise rufinamide levels in some patients, particularly children. No pharmacokinetic interaction appears to occur between rufinamide and carbamazepine, clobazam, lamotrigine, oxcarbazepine or topiramate. Vigabatrin does not appear to alter the pharmacokinetics of rufinamide, and rufinamide does not alter the trough levels of clonazepam.

Clinical evidence

(a) Carbamazepine or Oxcarbazepine

Preliminary evidence suggests that the pharmacokinetics of rufinamide are not affected by the concurrent use of carbamazepine or oxcarbazepine.[1] Furthermore, rufinamide does not cause a clinically relevant alteration in the trough concentrations of carbamazepine[1,2] or oxcarbazepine.[1]

(b) Clobazam or Clonazepam

Preliminary evidence suggests that the pharmacokinetics of rufinamide are not affected by the concurrent use of clobazam, and rufinamide does not alter the trough concentrations of clobazam or clonazepam.[1]

(c) Lamotrigine

The pharmacokinetics of rufinamide and lamotrigine do not appear to be affected by concurrent use.[2,3]

(d) Phenobarbital, Phenytoin, and Primidone

It has been reported that any combination of phenobarbital, phenytoin, and primidone increased the clearance of rufinamide by about 25%, but that rufinamide had no effect on the trough concentrations of these drugs.[1] However, the manufacturer suggests that the plasma levels of phenytoin may be increased by rufinamide, and that the dose of phenytoin may need to be reduced.[3]

(e) Topiramate

The pharmacokinetics of topiramate and rufinamide do not appear to be affected by concurrent use.[2,3]

(f) Valproate

Valproate has been found to reduce the clearance of rufinamide: one paper reports a modest reduction of 22%.[1] Based on predicted plasma levels, valproate was found to increase rufinamide levels by 55 to 70% in children, 23 to 26% in adolescents, and less than 16% in adults,[4] which suggests that the magnitude of the effects depends upon the age of the patient. Rufinamide has not been found to have any effect on the trough concentrations of valproate.[1]

(g) Vigabatrin

Vigabatrin is reported not to affect the pharmacokinetics of rufinamide.[1]

Mechanism, importance and management

Evidence is limited; however, the interaction between valproate and rufinamide appears to be established. In patients taking valproate, and weighing less than 30 kg, the manufacturer advises starting rufinamide at 200 mg daily, and increasing the dose by no more than 200 mg every 2 days (according to clinical response and efficacy) until a maximum dose of 600 mg daily is achieved.[3] No dose adjustment is recommended for patients weighing more than 30 kg.

It would seem prudent to monitor the plasma levels and clinical effects of rufinamide when it is started or stopped in patients taking phenobarbital, phenytoin, and primidone. Furthermore, monitor for phenytoin adverse effects (e.g. blurred vision, nystagmus, ataxia or drowsiness) and consider taking phenytoin levels if these occur. Note that fosphenytoin is a prodrug of phenytoin, and in the absence of direct evidence it would seem prudent to follow the same precautions described for phenytoin.

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2. Perucca E, Cloyd J, Critchley D, Fuseau E. Rufinamide: Clinical pharmacokinetics and concentration-response relationships in patients with epilepsy. Epilepsia (2008) 49, 1123–41.
3. Inovelon (Rufinamide). Eisai Ltd. UK Summary of product characteristics, October 2009.
4. Eisai Ltd. Personal communication, July 2008.

Stiripentol + Miscellaneous

Stiripentol inhibits the metabolism of caffeine and is therefore expected to inhibit the metabolism of other similarly metabolised drugs (e.g. theophylline).
Stiripentol may inhibit the metabolism of drugs by CYP2C19 (e.g. omeprazole) and CYP3A4 (e.g. ciclosporin, simvastatin, ergot derivatives). Stiripentol has no significant effect on the pharmacokinetics of dextromethorphan and an interaction with other CYP2D6 substrates is not expected. Food may protect stiripentol from degradation by gastric acid.

Clinical evidence, mechanism, importance and management

(a) CYP1A2 substrates

In a study, 12 healthy subjects were given **caffeine** before and after stiripentol (500 mg twice daily on day one, 1 g twice daily on day 2, and 1.5 g twice daily from day 3 to day 13) found that the AUC of a metabolite of caffeine expired in the breath was almost 8-fold lower after treatment with stiripentol.[1] Caffeine can be used as a probe drug to assess the activity of the cytochrome P450 isoenzyme CYP1A2 and this study therefore suggests that stiripentol may inhibit this isoenzyme. The manufacturer of stiripentol therefore does not recommend that **theophylline** (and therefore probably **aminophylline**) or **caffeine** are taken with stiripentol. They extend this warning to foodstuffs containing **caffeine** or **chocolate**, and specifically name **cola** drinks.[2] Clinical evidence regarding an interaction appears to be lacking. If a patient taking stiripentol develops adverse effects such as headache, jitteriness, restlessness, insomnia, consider the inadvertent intake of caffeine as a possible cause. Note that, other drugs that are potent CYP1A2 inhibitors can usually be given with caffeine, if adverse effects are appropriately monitored, see 'Caffeine + SSRIs', p.1422.

(b) CYP2C19 substrates

An *in vitro* study has shown that stiripentol is an inhibitor of the cytochrome P450 isoenzyme CYP2C19.[1] The manufacturer of stiripentol predicts that there may be an increased risk of adverse effects when drugs metabolised by this enzyme are also taken, and that dose adjustment may be required. They specifically name **citalopram** and **omeprazole**, and suggest caution if these drugs are required.[2] For a full list of substrates of this enzyme see 'Table 1.3', (p.6). Note that the clinical relevance of any interaction does not appear to have been established.

(c) CYP2D6 substrates

In vitro studies have found that stiripentol is an inhibitor of the isoenzyme CYP2D6,[1,2] and the manufacturers predict that there may be an increased risk of adverse effects when drugs metabolised by this isoenzyme are also taken, and that dose adjustment may be required. They specifically name **propranolol**, **carvedilol**, **timolol**, **fluoxetine**, **paroxetine**, **sertraline**, **imipramine**, **clomipramine**, **haloperidol**, **codeine**, **dextromethorphan**, and **tramadol**.[2] However, in a study in 12 healthy subjects, stiripentol (500 mg twice daily on day one, 1 g twice daily on day 2, and 1.5 g twice daily from day 3 to 13) did not affect the metabolism of dextromethorphan.[1] Dextromethorphan is used as a probe drug to assess the activity of CYP2D6, and this study therefore suggests that stiripentol does not have a clinically relevant effect on drugs metabolised by this isoenzyme.

(d) CYP3A4 substrates

A study, 12 healthy subjects were given **dextromethorphan** before and after stiripentol (500 mg twice daily on day one, 1 g twice daily on day 2, and 1.5 g twice daily on days 3 to 13). Although dextromethorphan is usually used as a probe drug for the cytochrome P450 isoenzyme CYP2D6, its metabolism by *N*-demethylation can be used as a measure of CYP3A4 activity. This study found that stiripentol does inhibit dextromethorphan N-demethylation, and therefore suggests that stiripentol may inhibit CYP3A4.[1] The manufacturer therefore predicts that there may be an increased risk of adverse effects when drugs metabolised by this isoenzyme are also taken, and that dose adjustment may be required. They specifically name the **protease inhibitors**, **astemizole**, **chlorphenamine**, **calcium-channel blockers**, **atorvastatin**, **simvastatin**, and **oral** [**hormonal**] **contraceptives**, and suggest caution if these drugs are required.

The manufacturer also advises caution if drugs that have a narrow therapeutic index and are metabolised by CYP3A4 are given with stiripentol. They name **tacrolimus**, **ciclosporin** and **sirolimus**.

The manufacturer also suggests that ergotism may occur if **ergot derivatives** are taken with stiripentol, with the possibility of necrosis of the extremities, and recommend that ergot preparations are not taken with stiripentol unless strictly necessary.

It is suggested that there may be an increase in the plasma levels of benzodiazepines that are substrates of this enzyme (they name **alprazolam**, **midazolam** and **triazolam**), resulting in excessive sedation. Caution is recommended when these drugs are used with stiripentol.[2]

For a list of CYP3A4 substrates, see 'Table 1.4', (p.6).

(e) Food

Stiripentol is known to degrade in an acidic environment, and the manufacturer therefore advises that stiripentol is taken with food to avoid exposure to gastric acid. Additionally they advise avoiding milk or dairy products, carbonated drinks, and fruit juice at the same time as stiripentol,[2] but state that they have no evidence of any interaction with milk or dairy products, but have predicted this interaction based on the known ability of dairy products to complex with other drugs.[3]

1. Tran A, Rey E, Pons G, Rousseau M, d'Athis P, Olive G, Mather GG, Bishop FE, Wurden CJ, Labroo R, Trager WF, Kunze KL, Thummel KE, Vincent JC, Gillardin J-M, Lepage F, Levy RH. Influence of stiripentol in cytochrome P450-mediated metabolic pathways in humans: in vitro and in vivo comparison and calculation of in vivo inhibition constants. *Clin Pharmacol Ther* (1997) 62, 490–504.
2. Diacomit (Stiripentol). Biocodex. UK Summary of product characteristics, January 2007.
3. Alan Pharmaceuticals. Personal communication, June 2008.

Stiripentol + Other antiepileptics

Stiripentol causes marked rises in the levels of carbamazepine, clobazam, phenobarbital and phenytoin. Stiripentol causes only a small rise in the levels of valproate. Levetiracetam and topiramate do not appear to interact with stiripentol.

Clinical evidence

(a) Carbamazepine

The clearance of carbamazepine in one subject fell by 39% when stiripentol 1.2 g daily was taken and by 71% when stiripentol 2.4 g daily was taken.[1] Three other studies in adults and children confirmed that stiripentol reduces the clearance of carbamazepine by about 50 to 65%,[2-4] and significantly increases carbamazepine levels.[5] Another study found that the formation of carbamazepine-10,11-epoxide, the active metabolite of carbamazepine, was markedly reduced in children taking carbamazepine with stiripentol.[6]

In 11 patients no adverse effects on motor, perceptual or attention tests were seen when stiripentol was given with other antiepileptic drugs (carbamazepine, **clobazam**, **phenobarbital**, **phenytoin**, and **valproate**) but the doses of carbamazepine, **phenobarbital**, **phenytoin** were reduced before the combination was taken.[7]

(b) Clobazam

In a study, 41 children with myoclonic epilepsy were given valproate and clobazam for one month with stiripentol 50 mg/kg daily or placebo added for a further 2 months. The dose of clobazam was reduced from 0.5 to 0.38 mg/kg daily in those also given stiripentol because of adverse effects. Plasma levels of clobazam and norclobazam were significantly increased, and levels of hydroxynorclobazam significantly decreased, by stiripentol.[8,9]

For a small study suggesting a lack of adverse effects, see under *Carbamazepine*, above.

(c) Phenobarbital

Phenobarbital clearance in 2 subjects fell by about 30 to 40% when they took stiripentol 2.4 g daily.[1] For a further study, see under *Carbamazepine*, above.

(d) Phenytoin

Patients with epilepsy taking two or three antiepileptics (phenytoin, phenobarbital, carbamazepine, clobazam, primidone, nitrazepam) were also given stiripentol, increasing from 600 mg to 2.4 g daily. The 5 patients taking phenytoin had an average 37% reduction in the phenytoin clearance when they took stiripentol 1.2 g daily, and a 78% reduction when they took stiripentol 2.4 g daily. These changes in clearance were reflected in marked rises in the steady-state serum levels of phenytoin: for example the serum phenytoin levels of one patient rose from 14.4 mg/L to 27.4 mg/L over 30 days while he was taking stiripentol, despite a 50% reduction in his phenytoin dose. Phenytoin toxicity was seen in another two subjects.[1] For a further study, see under *Carbamazepine*, above.

(e) Valproate

In a study, 41 children with myoclonic epilepsy were given valproate and clobazam for one month with stiripentol 50 mg/kg daily or placebo for a further 2 months. The dose of valproate did not change from a baseline maximum of 30 mg/kg daily when given with stiripentol.[8,9]

Valproate 1 g daily was given to 8 subjects with or without stiripentol 1.2 g daily. The stiripentol caused a 14% increase in the peak serum levels of valproate.[10] For a small study suggesting a lack of adverse effects, see under *Carbamazepine*, above.

(f) Other antiepileptics

There is no evidence to suggest that a pharmacokinetic interaction will occur between **levetiracetam** or **topiramate** and stiripentol.[11]

Mechanism

Stiripentol inhibits the activity of various cytochrome P450 isoenzymes in the liver, including CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4, some of which are concerned with the metabolism of other antiepileptics. As a result the loss of the antiepileptic from the body is reduced and the serum levels rise accordingly.[3,9,12] In the case of valproate, cytochrome P450 is only involved in minor valproate metabolic pathways and therefore only a small rise in serum levels occurs.[10] However, there is evidence that stiripentol may reduce the formation of a minor but hepatotoxic metabolite of valproate (2-propyl-4-pentenoic acid or 4-ene-VPA).[13]

Importance and management

Established and clinically important interactions. The carbamazepine, clobazam, phenobarbital and phenytoin doses should be reduced to avoid the development of elevated serum levels and possible toxicity during the

concurrent use of stiripentol. One study[3] suggests that the carbamazepine dose should be decreased incrementally over 7 to 10 days, beginning as soon as the stiripentol is started and, regardless of age, the maintenance dose of carbamazepine should aim to give serum levels of 5 to 10 micrograms/mL.

Stiripentol causes only small changes in the serum levels of valproate and dose adjustments are unlikely to be needed with this combination.

No dose adjustment is needed when stiripentol is given with levetiracetam or topiramate.

1. Levy RH, Loiseau P, Guyot M, Blehaut HM, Tor J, Morland TA. Stiripentol kinetics in epilepsy: nonlinearity and interactions. *Clin Pharmacol Ther* (1984) 36, 661–9.
2. Levy RH, Kerr BM, Farwell J, Anderson GD, Martinez-Lage JM, Tor J. Carbamazepine/stiripentol interaction in adult and pediatric patients. *Epilepsia* (1989) 30, 701.
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4. Levy RH, Martinez-Lage JM, Tor J, Blehaut H, Gonzalez I, Bainbridge B. Stiripentol level-dose relationship and interaction with carbamazepine in epileptic patients. *Epilepsia* (1985) 26, 544–5.
5. Tran A, Vauzelle-Kervroedan F, Rey E, Pons G. d'Athis P, Chiron C, Dulac O, Renard F, Olive G. Effect of stiripentol on carbamazepine plasma concentration and metabolism in epileptic children. *Eur J Clin Pharmacol* (1996) 50, 497–500.
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7. Loiseau P, Strube E, Tor J, Levy RH, Dodrill C. Evaluation neuropsychologique et thérapeutique du stiripentol dans l'épilepsie. *Rev Neurol (Paris)* (1988) 144, 165–72.
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9. In vitro and in vivo inhibitory effect of stiripentol on clobazam metabolism. Giraud C, Treluyer J-M, Rey E, Chiron C, Vincent J, Pons G, Tran A. *Drug Metab Dispos* (2006) 34, 608–611.
10. Levy RH, Loiseau P, Guyot M, Acheampong A, Tor J, Rettenmeier AW. Effects of stiripentol on valproate plasma level and metabolism. *Epilepsia* (1987) 28, 605.
11. Diacomit (Stiripentol). Biocodex. UK Summary of product characteristics, January 2007.
12. Mather GG, Bishop FE, Trager WF, Kunze KK, Thummel KE, Shen DD, Roskos LK, Lepage F, Gillardin JM, Levy RH. Mechanisms of stiripentol interactions with carbamazepine and phenytoin. *Epilepsia* (1995) 36 (Suppl 3), S162.
13. Levy RH, Rettenmeier AW, Anderson GD, Wilensky AJ, Friel PN, Baillie TA, Acheampong A, Tor J, Guyot M, Loiseau P. Effects of polytherapy with phenytoin, carbamazepine, and stiripentol on formation of 4-ene-valproate, a hepatotoxic metabolite of valproic acid. *Clin Pharmacol Ther* (1990) 48, 225–35.

Tiagabine + Cocaine

Tiagabine does not affect the cardiovascular effects of cocaine, but may attenuate some of its subjective effects.

Clinical evidence, mechanism, importance and management

In a placebo-controlled study, 7 cocaine-users were given two oral doses of tiagabine 4 mg, ten hours apart. Two hours after the second dose they were given an injection of sodium chloride 0.9%, then two doses of cocaine (0.15 mg/kg, and then, 30 minutes later, 0.3 mg/kg). Tiagabine did not affect the cocaine-induced changes in blood pressure and heart rate, but was reported to attenuate some of the subjective effects (stimulation and craving) of cocaine.[1]

The clinical relevance of this findings is unclear, but is does suggest that concurrent use is unlikely to result in adverse cardiac effects.

1. Sofuoglu M, Poling J, Mitchell E, Kosten TR. Tiagabine affects the subjective responses to cocaine in humans. *Pharmacol Biochem Behav* (2005) 82, 569–73.

Tiagabine + Miscellaneous

The pharmacokinetics of tiagabine were not altered by cimetidine or erythromycin. No clinically relevant pharmacokinetic interactions occur between tiagabine and theophylline or warfarin.

Clinical evidence, mechanism, importance and management

In a study in 12 healthy subjects, **cimetidine** 400 mg twice daily for 5 days increased the steady-state AUC of tiagabine 4 mg twice daily by just 5%.[1,2]

In a study in 14 healthy subjects, **erythromycin** 500 mg twice daily had no clinically relevant effect on the steady-state pharmacokinetics of tiagabine 4 mg twice daily.[3]

Multiple dose studies in healthy subjects have also excluded any clinically relevant pharmacokinetic interactions between tiagabine and **theophylline** or **warfarin** but no further study details were given.[1]

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2. Snel S, Jonkman JHG, van Heiningen PNM, Jansen JA, Mengel HB. Tiagabine: evaluation of risk of interaction with cimetidine in healthy male volunteers. *Epilepsia* (1994) 35 (Suppl 7), 74.
3. Thomsen MS, Groes L, Agersø H, Kruse T. Lack of pharmacokinetic interaction between tiagabine and erythromycin. *J Clin Pharmacol* (1998) 38, 1051–6.

Tiagabine + Other antiepileptics

Tiagabine plasma levels are reduced by enzyme-inducing antiepileptics (carbamazepine, phenytoin, phenobarbital and primidone). Tiagabine may cause a slight reduction in valproate levels, but has no effect on carbamazepine, phenytoin or vigabatrin levels.

Clinical evidence, mechanism, importance and management

In an early clinical study, tiagabine was reported to have no significant effect on the plasma levels of **carbamazepine**, **phenytoin**, **valproate**, and **vigabatrin**.[1] Similarly, in 12 patients with epilepsy, tiagabine (titrated from 8 mg up to a maximum of 48 mg daily over 18 days) did not alter the steady-state pharmacokinetics of **phenytoin** or **carbamazepine**.[2] However, in another similar study, tiagabine reduced the AUC of **valproate** by 10%, but this reduction is not expected to be clinically significant.[3]

A study in patients taking 1 to 3 other enzyme-inducing antiepileptics (**phenobarbital**, **phenytoin**, **carbamazepine**, **primidone**) found that tiagabine half-lives were shorter (3.8 to 4.9 hours) when compared with historical values in healthy subjects taking tiagabine alone (7.1 hours).[4] The manufacturers say that the plasma concentrations of tiagabine may be reduced 1.5- to 3-fold by these enzyme-inducing antiepileptics.[5] Based on this, they recommend that the initial maintenance dose of tiagabine in patients *not* taking enzyme-inducing drugs should be lower (15 to 30 mg daily) than in those taking these drugs (30 to 45 mg daily).[5]

1. Richens A, Chadwick DW, Duncan JS, Dam M, Gram L, Mikkelsen M, Morrow J, Mengel H, Shu V, McKelvy JF, Pierce MW. Adjunctive treatment of partial seizures with tiagabine: a placebo-controlled trial. *Epilepsy Res* (1995) 21, 37–42.
2. Gustavson LE, Cato A, Boellner SW, Cao GX, Qian JX, Guenther HJ, Sommerville KW. Lack of pharmacokinetic drug interactions between tiagabine and carbamazepine or phenytoin. *Am J Ther* (1998) 5, 9–16.
3. Gustavson LE, Sommerville KW, Boellner SW, Witt GF, Guenther HJ, Granneman GR. Lack of a clinically significant pharmacokinetic drug interaction between tiagabine and valproate. *Am J Ther* (1998) 5, 73–79.
4. So EL, Wolff D, Graves NM, Leppik IE, Cascino GD, Pixton GC, Gustavson LE. Pharmacokinetics of tiagabine as add-on therapy in patients taking enzyme-inducing drugs. *Epilepsy Res* (1995) 22, 221–6.
5. Gabitril (Tiagabine). Cephalon (UK) Ltd. UK Summary of product characteristics, June 2009.

Topiramate + Carbamazepine

Topiramate levels may be reduced by carbamazepine. Carbamazepine levels are not affected by topiramate. However, one report suggests that the toxicity seen when topiramate is added to maximum tolerated doses of carbamazepine may respond to a reduction in the carbamazepine dose.

Clinical evidence

(a) Carbamazepine levels

In a study in 12 patients with epilepsy, topiramate titrated up to a maximum of 400 mg twice daily had no effect on the steady-state plasma levels of carbamazepine 300 to 800 mg every 8 hours or on its main metabolite, carbamazepine-10,11-epoxide.[1] An earlier study in patients with epilepsy also reported that topiramate does not affect the pharmacokinetics of carbamazepine.[2] In contrast, another report describes 2 patients taking a maximum tolerated dose of carbamazepine who started treatment with topiramate and subsequently developed symptoms suggestive of carbamazepine toxicity. In both these cases, the symptoms resolved when the carbamazepine dose was reduced, and this enabled continued titration of

the topiramate dose in one patient. A review of the clinical use of these two drugs found another 23 cases that fitted this pattern. Carbamazepine levels were not reported.[3]

(b) Topiramate levels

In a study in 12 patients with epilepsy, the topiramate plasma levels and AUC were found to be about 40% lower in the presence of carbamazepine.[1] A population pharmacokinetic study reported that patients taking carbamazepine had 32% lower morning topiramate level than patients not taking enzyme-inducing antiepileptics.[4] In a study in healthy subjects, carbamazepine 600 mg daily was found to cause a twofold increase in the clearance of a single 200-mg dose of topiramate. The mean half-life of topiramate decreased from 29 hours to 19 hours. There was also a two- to threefold increase in the formation of the 2 major metabolites of topiramate (2,3-diol-topiramate and 10-hydroxy-topiramate), although 41% of topiramate was excreted unchanged in the urine in the presence of carbamazepine.[5] The same group have reported similar results in a study in patients.[6] In contrast, an earlier study reported that carbamazepine did not have a major effect on the pharmacokinetics of topiramate.[2]

Mechanism

Carbamazepine appears to induce the metabolism of topiramate. Although topiramate can weakly induce CYP3A4 this does not usually appear to have a clinically relevant effect on carbamazepine metabolism, unless carbamazepine is already at the maximum tolerated dose. The increase in topiramate clearance by carbamazepine may be partly due to the stimulation of oxidative pathways resulting in the formation of 2,3-diol-topiramate and 10-hydroxy-topiramate.[6]

Importance and management

Carbamazepine possibly results in a moderate reduction in topiramate plasma levels, but this is probably of limited clinical importance. There is some evidence that the toxicity seen when topiramate is added to maximum tolerated doses of carbamazepine may respond to a reduction in the carbamazepine dose.

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2. Wilensky AJ, Ojemann LM, Chemelir T, Margul BL, Doose DR. Topiramate pharmacokinetics in epileptic patients receiving carbamazepine. *Epilepsia* (1989) 30, 645–6.
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4. May TW, Jürges U. Serum concentrations of topiramate in epileptic patients: the influence of dose and comedication. *Epilepsia* (1999) 40 (Suppl 2), 249.
5. Britzi M, Perucca E, Soback S, Levy RH, Fattore C, Crema F, Gatti G, Doose DR, Maryanoff BE, Bialer M. Pharmacokinetic and metabolic investigation of topiramate disposition in healthy subjects in the absence and in the presence of enzyme induction by carbamazepine. *Epilepsia* (2005) 46, 378–84.
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Topiramate + Phenobarbital or Primidone

Topiramate appears not to alter the pharmacokinetics of phenobarbital or primidone. Phenobarbital modestly reduces topiramate levels.

Clinical evidence, mechanism, importance and management

A review of data from double-blind, placebo-controlled studies found that over periods of 8 to 12 weeks the plasma levels of phenobarbital or primidone in patients (number not stated) with partial seizures remained unchanged when they were also given topiramate.[1]

A population pharmacokinetic study reported that patients taking phenobarbital had 31% lower morning topiramate levels than patients not taking enzyme-inducing antiepileptics.[2] Another study that grouped carbamazepine, phenobarbital and phenytoin reported that patients taking one or more of these drugs had a 50% greater topiramate clearance than patients taking lamotrigine or valproate.[3]

Phenobarbital probably induces the metabolism of topiramate thereby reducing its levels. When topiramate is added to existing treatment with phenytoin or phenobarbital its dose should be titrated to effect and therefore any interaction is automatically accounted for. If phenobarbital or primidone are withdrawn or added to established treatment with topiramate, be aware that the dose of topiramate may need adjustment.

1. Doose DR, Walker SA, Pledger G, Lim P, Reife RA. Evaluation of phenobarbital and primidone/phenobarbital (primidone's active metabolite) plasma concentrations during administration of add-on topiramate therapy in five multicenter, double-blind, placebo-controlled trials in outpatients with partial seizures. *Epilepsia* (1995) 36 (Suppl 3), S158.
2. May TW, Jürges U. Serum concentrations of topiramate in epileptic patients: the influence of dose and comedication. *Epilepsia* (1999) 40 (Suppl 2), 249.
3. Contin M, Riva R, Albani F, Avoni P, Baruzzi A. Topiramate therapeutic monitoring in patients with epilepsy: effect of concomitant antiepileptic drugs. *Ther Drug Monit* (2002) 24, 332–7.

Topiramate + Phenytoin

In some patients the plasma levels of phenytoin are slightly raised by topiramate, and topiramate plasma levels may be reduced by phenytoin.

Clinical evidence

Topiramate, titrated to a maximum of 400 mg twice daily, was given to 12 patients with epilepsy taking phenytoin 260 to 600 mg daily. When the maximum tolerated dose of topiramate was reached, the phenytoin dose was then reduced, and in some cases phenytoin was subsequently discontinued. Topiramate clearance was assessed in 2 patients and was found to be increased two- to threefold by phenytoin.[1] Similarly, a population pharmacokinetic study reported that patients taking phenytoin and topiramate had 50% lower morning topiramate levels than patients not taking enzyme-inducing antiepileptics.[2]

In the first study above, 3 of the 12 patients had a decrease in phenytoin clearance and an increase of 25 to 55% in the AUC of phenytoin when taking topiramate: the other 9 had no changes.[1] This slight increase is said not to be clinically significant based on analyses from six add-on studies.[3]

Mechanism

An *in vitro* study using human liver microsomes found that topiramate does not inhibit most hepatic cytochrome P450 isoenzymes, except for CYP2C19 at high concentrations.[1] This isoenzyme plays a minor role in phenytoin metabolism, but it has been suggested this may become important at high doses of topiramate in patients who are CYP2C9 poor metabolisers,[1] (that is, those lacking this isoenzyme). Phenytoin appears to induce the metabolism of topiramate.

Importance and management

The interaction between topiramate and phenytoin appears to be established, and topiramate dose adjustments may be required if phenytoin is added or discontinued. No reduction in the phenytoin dose seems necessary in the majority of patients, but be aware that a few patients may have increased phenytoin levels, particularly at high topiramate doses. Monitor for phenytoin adverse effects (e.g. blurred vision, nystagmus, ataxia or drowsiness), take phenytoin levels if these occur, and adjust the dose of phenytoin accordingly.

1. Sachdeo RC, Sachdeo SK, Levy RH, Streeter AJ, Bishop FE, Kunze KL, Mather GG, Roskos LK, Shen DD, Thummel KE, Trager WF, Curtin CR, Doose DR, Gisclon LG, Bialer M. Topiramate and phenytoin pharmacokinetics during repetitive monotherapy and combination therapy to epileptic patients. *Epilepsia* (2002) 43: 691–6.
2. May TW, Jürges U. Serum concentrations of topiramate in epileptic patients: the influence of dose and comedication. *Epilepsia* (1999) 40 (Suppl, 2), 249.
3. Johannessen SI. Pharmacokinetics and interaction profile of topiramate: review and comparison with other newer antiepileptic drugs. *Epilepsia* (1997) 38 (Suppl 1), S18–S23.

Topiramate + Valproate

Encephalopathy has been reported in patients given topiramate with valproate. Two studies found no clinically relevant pharmacokinetic interaction between topiramate and valproate.

Clinical evidence, mechanism, importance and management

Five patients with severe epilepsy developed stuporous encephalopathy with marked cognitive impairment when taking topiramate with valproate. A further patient experienced this effect when taking topiramate alone.

Four of the patients had hyperammonaemia which resolved when topiramate or valproate was withdrawn. The toxicity was possibly due to a synergistic effect of valproate and topiramate on liver ornithine metabolism resulting in hyperammonaemia. It was also possible that the encephalopathy was due to topiramate toxicity in at-risk patients, such as those with pre-existing chronic encephalopathy.[1]

In a study in 12 patients with epilepsy, the pharmacokinetics of both topiramate, titrated to 400 mg twice daily, and valproate 1 to 4.5 g daily were slightly changed by concurrent use. The topiramate AUC was raised by about 18%, and the valproate AUC was reduced by about 11%, but these changes were not considered to be clinically relevant.[2] However, the proportion of various metabolites of valproate was altered by topiramate: metabolism to 4-ene-valproate (a putative hepatotoxin) and metabolism by oxidation increased, whereas conjugation decreased.[2] Similar changes have been seen with other enzyme-inducing antiepileptics (see *Mechanism* in 'Phenytoin + Valproate', p.646). Another study in patients with epilepsy found that valproate did not have any clinically significant effects on topiramate pharmacokinetics and metabolism.[3]

The pharmacokinetic studies suggest that dose adjustments are not required during concurrent use.[2] However, the report of encephalopathy with topiramate and valproate indicates that, particularly for at-risk patients such as those with pre-existing encephalopathy, careful monitoring is advisable.[1]

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Valproate + Acarbose

An isolated case report describes reduced valproate levels in a patient taking acarbose.

Clinical evidence, mechanism, importance and management

A patient with epilepsy taking sodium valproate for 10 years had a 40% reduction in his normally stable valproate levels, from 67 micrograms/mL to 40.5 micrograms/mL, when acarbose was added. No other drugs were being taken. When the acarbose was stopped and then restarted, the valproate levels rose and then fell once again. The reason for this effect is not understood but the authors of the report suggest that acarbose possibly reduces the absorption of valproate.[1] This is an isolated report and its general importance is unknown, but it would seem prudent to be alert for any evidence of reduced effects if acarbose is given to a patient taking valproate.

1. Serrano JS, Jiménez CM, Serrano MI, Garrido H, Balboa B. May acarbose impair valproate bioavailability? *Methods Find Exp Clin Pharmacol* (1996) 18 (Suppl C), 98.

Valproate + Allopurinol

Allopurinol appears not to alter the levels of valproate.

Clinical evidence, mechanism, importance and management

A study investigating allopurinol in refractory epilepsy found that allopurinol (150 mg daily in those less than 20 kg, and 300 mg daily for other patients), given for 4 months, had no effect on valproate levels in 28 patients taking antiepileptics including valproate.[1] In another similar study, allopurinol 10 mg/kg increased to 15 mg/kg daily for 12 weeks had no effect on serum valproate levels in 6 patients taking antiepileptics including valproate.[2] Therefore valproate dose alterations are unlikely to be required if allopurinol is used.

1. Zagnoni PG, Bianchi A, Zolo P, Canger R, Cornaggia C, D'Alessandro P, DeMarco P, Pisani F, Gianelli M, Verzé L, Viani F, Zaccara G. Allopurinol as add-on therapy in refractory epilepsy: a double-blind placebo-controlled randomized study. *Epilepsia* (1994) 35, 107–12.
2. Coppola G, Pascotto A. Double-blind, placebo-controlled, cross-over trial of allopurinol as add-on therapy in childhood refractory epilepsy. *Brain Dev* (1996) 18, 50–2.

Valproate + Antacids

The absorption of valproate was slightly, but not significantly, increased by an aluminium/magnesium hydroxide suspension, but was not affected by magnesium trisilicate or a calcium carbonate suspension.

Clinical evidence, mechanism, importance and management

In 7 healthy subjects the AUC of a single 500-mg dose of valproic acid, given one hour after breakfast, was increased by 12% (range 3 to 28%) by 62 mL of an **aluminium/magnesium hydroxide** suspension (*Maalox*) given with and 2 hours after valproate. Neither **magnesium trisilicate** suspension (*Trisogel*) nor **calcium carbonate** suspension (*Titralac*) had a significant effect on valproate absorption.[1] No special precautions would seem necessary during concurrent use.

1. May CA, Garnett WR, Small RE, Pellock JM. Effects of three antacids on the bioavailability of valproic acid. *Clin Pharm* (1982) 1, 244–7.

Valproate + Aspirin or NSAIDs

Valproate toxicity developed in several young patients given large and repeated doses of aspirin and in an elderly patient taking low-dose aspirin. Increased levels of free valproate were found in a number of children within hours of them taking aspirin. Conversely, a slightly reduced valproate level was reported in one patient who took ibuprofen. Modestly altered protein binding has been shown when sodium valproate was given with diflunisal or naproxen.

Clinical evidence, mechanism, importance and management

(a) Aspirin

A 17-year-old girl taking valproate 21 mg/kg daily was prescribed aspirin 18 mg/kg daily for lupus arthritis. Within a few days she developed a disabling tremor which disappeared when the aspirin was stopped. Total serum valproate levels were not significantly changed, but the free fraction fell from 24% to 14% when the aspirin was withdrawn. Similar toxic reactions (tremor, nystagmus, drowsiness, ataxia) were seen in 2 children, aged 6 and 4 years, given 12 and 20 mg/kg aspirin every 4 hours while taking valproate.[1] In 5 children with epilepsy taking valproate, free valproate levels increased by 31 to 66% (average 49%) 17 hours after starting aspirin 11.5 to 16.9 mg/kg four times daily.[2]

A 76-year-old man given valproate semisodium 750 mg daily had a total valproate blood level of 13.5 nanograms/mL, which rose to 19.3 nanograms/mL after aspirin 325 mg daily was added. The valproate semisodium dose was increased over a period of 2 months in an attempt to increase levels to the reference range. Two weeks after the dose of valproate semisodium was increased to 2.5 g daily he experienced dizziness and incoordination with difficulty standing and transferring from a bed to a wheelchair and he experienced a fall. It was found that his trough total valproate level was 64 nanograms/mL (reference range 50 to 70 nanograms/mL), but his trough free valproate level was 24.7 nanograms/mL (reference range 4.8 to 17.3 nanograms/mL). Aspirin was discontinued and 5 days later total and free trough valproate levels were 36 nanograms/mL and 3.9 nanograms/mL, respectively. Dizziness and incoordination resolved when the dose of valproate semisodium was reduced to 1.25 g daily..[3]

One case report of fatal hyperammonaemia was speculated to have been induced by valproate, and the authors also considered that concurrent use of aspirin and 'cimetidine', (p.659), may have contributed.[4]

Aspirin displaces valproate from its protein binding sites[2,3,5] and also alters its metabolism by the liver[6] so that the levels of free (and pharmacologically active) valproate rise. This could temporarily increase both the therapeutic and toxic effects of the valproate. However, there is evidence that increased hepatic elimination of valproate counterbalances this effect.

Direct information seems to be limited to the studies and case reports cited. Clinically relevant interactions appear rare, probably because in most cases the effects of aspirin on free valproate levels cancel each other out.

The combination need not necessarily be avoided, but it would seem prudent to be aware of this interaction if valproate and high-dose aspirin are used.

(b) Diflunisal

In 7 healthy subjects, diflunisal 250 mg twice daily for 7 days given with sodium valproate 200 mg twice daily caused a 20% increase in the unbound fraction of valproate. There was a 35% increase in the AUC of one of the oxidation metabolites of valproate, and a small decrease in the AUC of some of the diflunisal glucuronide metabolites. This was due to changes in the renal clearance of these metabolites.[7] Whether any of these modest changes have any clinical relevance remains to be seen, but it appears unlikely.

(c) Ibuprofen

A 15-year-old boy was found to have a subtherapeutic valproate level (43 micrograms/mL) 3 days after starting to take ibuprofen 600 mg every 6 hours for post-fracture analgesia. The ibuprofen was stopped, and after one week the valproate levels were within the therapeutic range (60 micrograms/mL).[8] The general importance of this isolated case is unknown. More study is needed.

(d) Naproxen

A study in 6 healthy subjects found that naproxen 500 mg twice daily moderately decreased the AUC of a single 800-mg dose of sodium valproate by 11%.[9] Similarly, in another study, when naproxen 500 mg twice daily was given with sodium valproate 500 mg twice daily, the AUC of valproate was decreased by 20% and the AUC of naproxen was increased by 7%.[10] It is suggested that naproxen and sodium valproate displace each other from their protein binding sites.[9,10] The clinical relevance of these modest changes is uncertain, but is likely to be small.[9]

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4. Ichikawa H, Amano T, Kawabata K, Kushiro M, Wada J, Nagake Y, Makino H. Fatal hyperammonemia in a patient with systemic lupus erythematosus. *Intern Med* (1998) 37, 700–3.
5. Orr JM, Abbott FS, Farrell K, Ferguson S, Sheppard I, Godolphin W. Interaction between valproic acid and aspirin in epileptic children: serum protein binding and metabolic effects. *Clin Pharmacol Ther* (1982) 31, 642–9.
6. Abbott FS, Kassam J, Orr JM, Farrell K. The effect of aspirin on valproic acid metabolism. *Clin Pharmacol Ther* (1986) 40, 94–100.
7. Addison RS, Parker-Scott SL, Eadie MJ, Hooper WD, Dickinson RG. Steady-state dispositions of valproate and diflunisal alone and coadministration to healthy volunteers. *Eur J Clin Pharmacol* (2000) 56, 715–21.
8. Mankin KP, Scanlon M. Side effect of ibuprofen and valproic acid. *Orthopedics* (1998) 21, 264, 270.
9. Grimaldi R, Lecchini S, Crema F, Perucca E. *In vivo* plasma protein binding interaction between valproic acid and naproxen. *Eur J Drug Metab Pharmacokinet* (1984) 9, 359–63.
10. Addison RS, Parker-Scott SL, Hooper WD, Eadie MJ, Dickinson RG. Effect of naproxen coadministration on valproate disposition. *Biopharm Drug Dispos* (2000) 21, 235–42.

Valproate + Bile-acid binding resins

Colestyramine causes a small reduction in the absorption of valproate. No interaction occurs if administration of the drugs is separated by 3 hours. Colesevelam does not interact with valproate.

Clinical evidence

(a) Colesevelam

In a study in 26 healthy subjects, colesevelam 4.5 g had no effect on the pharmacokinetics of a single 250-mg dose of valproic acid.[1]

(b) Colestyramine

In a study, 6 healthy subjects were given a single 250-mg dose of valproic acid either alone, at the same time as colestyramine 4 g twice daily, or 3 hours before colestyramine. The bioavailability of valproate taken alone and when separated from the colestyramine by 3 hours remained the same. When the valproate was taken at the same time as the colestyramine, the valproate AUC fell by 15% and its maximum serum levels fell by 21%.[2]

Mechanism

Colestyramine is an ion-exchange resin intended to bind with bile acids in the gut, but it can also bind with drugs, leading to a reduction in their absorption. This apparently occurs to a limited extent with valproate.

Importance and management

Direct information about an interaction between colestyramine and valproate appears to be limited to this single study. The fall in the bioavailability is small and probably of very limited clinical importance, but the interaction can apparently be totally avoided by separating administration by 3 hours so that admixture in the gut is minimised. Colesevelam does not appear to interact with valproate.

1. Donovan JM, Stypinski D, Stiles MR, Olson TA, Burke SK. Drug interactions with colesevelam hydrochloride, a novel, potent lipid-lowering agent. *Cardiovasc Drugs Ther* (2000) 14, 681–90.
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Valproate + Carbapenems

Panipenem with betamipron dramatically reduces valproate serum levels. Ertapenem, imipenem and meropenem have similar effects and seizures have occurred when they were given to patients taking valproate. All carbapenems are expected to interact similarly.

Clinical evidence

(a) Ertapenem

A report describes a patient taking valproate semisodium 2 g daily who had recurring tonic-clonic seizures after starting ertapenem. His serum valproic acid levels had decreased from 130 micrograms/mL (measured about 3 months earlier) to 70 micrograms/mL on day 7 of treatment with ertapenem 1 g daily when the seizures occurred. He was given intravenous valproic acid 750 mg and the dose of valproate semisodium was increased to 2.75 g daily. Four days later he presented with recurrent seizures and serum valproic acid levels of 10.7 micrograms/mL. He was given intravenous valproic acid 1 g followed by oral valproate semisodium 100 mg. Ertapenem was discontinued and the next day his serum valproic acid was 55 micrograms/mL. An increase in his valproate semisodium dose followed by a gradual decrease allowed therapeutic levels to be achieved and he had no further seizures.[1]

In another case report, total valproate levels in a patient taking valproic acid solution 1.1 g daily in divided doses (separated from enteral nutrition she was receiving) fell from 72 micrograms/mL to 36.4 micrograms/mL about 4 days after she was also given ertapenem 1 g daily. The valproic acid dose was increased to 1.6 g daily, but 2 days later valproate levels had further decreased to 18.4 micrograms/mL. The dose of valproic acid was further increased to 2 g daily and levels 4 days later had decreased to about 1 microgram/mL. Ertapenem was discontinued and intravenous valproic acid was given as a loading dose of 800 mg then 400 mg every 6 hours. Once valproate levels returned to the therapeutic range she was given valproic acid solution 1.4 g daily.[2]

(b) Imipenem

A report describes a reduction in valproate levels from 80 micrograms/mL to 24 micrograms/mL then 33 micrograms/mL in a patient with epilepsy 4 and 11 days after imipenem was given to treat a *Pseudomonas aeruginosa* infection.[3] In another report, a patient taking valproate 800 mg daily had a 57% reduction in plasma valproate levels during treatment with imipenem 500 mg twice daily for 5 days. A second patient taking valproate 600 mg daily had a reduction in plasma valproate levels of 49% when given imipenem 500 mg twice daily for 7 days.[4] Decreased valproate levels and recurrence of tonic-clonic convulsions occurred in another patient during concurrent treatment with imipenem.[5]

(c) Meropenem

A report describes 2 patients whose valproate levels fell when meropenem and amikacin were given. The first patient had been maintained on intravenous valproate 1.2 to 1.6 g daily with valproate levels of between 50 and 100 micrograms/mL. Two days after the addition of the antibacterials the levels had halved, and after 3 days of subtherapeutic levels, phenytoin was substituted for valproate. The other patient experienced a drop in valproate levels from 44 micrograms/mL to 5 micrograms/mL within 24 hours of being given meropenem, despite being given greater doses of valproic acid.[6] Other reports[3,7-14] describe reductions in valproate levels in several other patients when they were also given meropenem: 4 of them developed seizures.[3,11-13] A retrospective study of an 18-month period identified 39 patients who had been treated with valproate and meropenem. Plasma

valproate levels fell in all patients by an average of 66% (range 34 to 92%) within 24 hours of concurrent use. Clinical assessment of the interaction in 20 of the patients found worsening seizures or epileptic activity on EEG or both in 11 patients (55%).

(d) Panipenem

A report describes 3 cases of Japanese children taking antiepileptic drugs who had marked reductions in valproate serum levels while receiving panipenem with betamipron for serious chest infections.[15] An increased seizure frequency occurred in 2 of the patients. In one case the serum valproate levels fell from 30.1 micrograms/mL to 1.53 micrograms/mL within 4 days of starting panipenem, and rose again when it was stopped. All 3 patients were also taking carbamazepine but its serum levels were unchanged by the antibacterial. In a further 3 cases, 60 to 100% reductions in valproate levels were reported, which occurred within 2 days of starting concurrent treatment: increased seizure frequency occurred in 2 cases.[16]

Mechanism

Unknown, but the speed of the interaction is said to be inconsistent with enzyme induction, and accelerated renal excretion has been suggested.[6] Altered protein binding has been shown in *animal* and *in vitro* studies.[17] Enhanced glucuronidation of valproate, by up-regulation of the catalysing cofactor, is reported to increase hepatic intrinsic clearance and renal excretion of valproate.[18] Decreased hydrolysis of glucuronidated valproate due to inhibition of the hydrolytic enzyme by carbapenems may also be involved.[18,19] It has been suggested that decreased plasma valproate levels may partly be due to an increase in the distribution of valproate into erythrocytes.[4]

Importance and management

Although there are few reports of an interaction between valproate and imipenem or ertapenem, there are now several reports of the interaction between valproate and meropenem or panipenem. Seizures or increased seizure frequency as well as significant decreases in valproate levels have been reported. It would therefore seem prudent to monitor the valproate levels in any patient also given a carbapenem, being alert for the need to increase the valproate dose, or to use another antibacterial, or an alternative to valproate. Carbamazepine[15] and phenytoin[6] did not interact in the above reports.

1. Lunde JL, Nelson RE, Storandt HF. Acute seizures in a patient receiving divalproex sodium after starting ertapenem therapy. *Pharmacotherapy* (2007) 27, 1202–5.
2. Cabanes Mariscal MA, Sánchez López P, Álvarez Herranz P, Chamorro Merino G. Pharmacokinetic interaction between valproic acid and ertapenem. *Farm Hosp* (2006) 30, 313–15.
3. Llinares Tello F, Bosacoma Ros N, Hernández Prats C, Climent Grana E, Selva Otaolaurruchi J, Ordovás Baines JP. Interacción farmacocinética entre ácido valproico y antibióticos carbapenémicos: descripción de tres casos. *Farm Hosp* (2003) 27, 258–63.
4. Omoda K, Murakami T, Yumoto R, Nagai J, Maeda Y, Kiribayashi Y, Takano M. Increased erythrocyte distribution of valproic acid in pharmacokinetic interaction with carbapenem antibiotics in rat and human. *J Pharm Sci* (2005) 94, 1685–93.
5. Perea Falomir M, Roura Poch P, Higueruelo Demasón S, García Gil VJ. Descripción de un caso de interacción farmacocinética entre ácido valproico e imipenem. *Farm Hosp* (2006) 30, 316–17.
6. De Turck BJG, Diltoer MW, Cornelis PJWW, Maes V, Spapen HDM, Camu F, Huyghens LP. Lowering of plasma valproic acid concentrations during concomitant therapy with meropenem and amikacin. *J Antimicrob Chemother* (1998) 42, 563–4.
7. Plasencia AP, Soy D, Nicolas JM. Interacción farmacocinética entre el ácido valproico y el meropenem. *Med Clin (Barc)* (2004) 123, 38–9.
8. Nacarkucuk E, Saglam H, Okan M. Meropenem decreases serum level of valproic acid. *Pediatr Neurol* (2004) 31, 232–4.
9. Clause D, Decleire P-Y, Vanbinst R, Soyer A, Hantson P. Pharmacokinetic interaction between valproic acid and meropenem. *Intensive Care Med* (2005) 31, 1293–4.
10. Sala Piñol F, Padullés Zamora N, Hidalgo Albert E, Clemente Bautista S, Cabañas Poy MJ, Oliveras Arenas M, Balcells Ramírez J. Interacción farmacocinética entre ácido valproico y meropenem. *An Pediatr (Barc)* (2006) 64, 93–5.
11. Coves-Orts FJ, Borrás-Blasco J, Navarro-Ruiz A, Murcia-López A, Palacios-Ortega F. Acute seizures due to a probable interaction between valproic acid and meropenem. *Ann Pharmacother* (2005) 39, 533–7.
12. Santucci M, Parmeggiani A, Riva R. Seizure worsening caused by decreased serum valproate during meropenem therapy. *J Child Neurol* (2005) 20, 456–7.
13. Fudio S, Carcas A, Piñana E, Ortega R. Epileptic seizures caused by low valproic acid levels from an interaction with meropenem. *J Clin Pharm Ther* (2006) 31, 393–6.
14. Spriet I, Meersseman W, De Troy E, Wilmer A, Casteels M, Willems L. Meropenem–valproic acid interaction in patients with cefepime-associated status epilepticus. *Am J Health-Syst Pharm* (2007) 64, 54–8.
15. Nagai K, Shimizu T, Togo A, Takeya M, Yokomizo Y, Sakata Y, Matsuishi T, Kato H. Decrease in serum levels of valproic acid during treatment with a new carbapenem, panipenem/betamipron. *J Antimicrob Chemother* (1997) 39, 295–6.
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17. Hobara N, Hokama N, Ohshiro S, Kameya H, Sakanashi M. Possible mechanisms of low levels of plasma valproate concentration following simultaneous administration of sodium valproate and meropenem. *Biog Amines* (2003) 17, 409–20.
18. Spriet I, Goyens J, Meersseman W, Wilmer A, Willems L, Van Paesschen W. Interaction between valproate and meropenem: a retrospective study. *Ann Pharmacother* (2007) 41, 1130–6.
19. Nakajima Y, Mizobuchi M, Nakamura M, Takagi H, Inagaki H, Kominami G, Koike M, Yamaguchi T. Mechanism of the drug interaction between valproic acid and carbapenem antibiotics in monkeys and rats. *Drug Metab Dispos* (2004) 32, 1383–91.

Valproate + Chlorpromazine

Valproate levels are slightly raised in patients given chlorpromazine, but this appears to be of minimal clinical importance. An isolated report describes severe hepatotoxicity in a patient taking chlorpromazine and valproate.

Clinical evidence, mechanism, importance and management

When 6 patients taking valproate 400 mg daily were given chlorpromazine 100 to 300 mg daily, their steady-state trough valproate serum levels rose by 22%. The half-life increased by 14% and the clearance fell by 14% (possibly due to some reduction in its liver metabolism).[1] However, these changes are modest, and this interaction would normally seem to be of minimal importance. Severe hepatotoxicity occurred in another patient given both drugs,[2] which could have been due to the combined hepatotoxic effects of both drugs.

1. Ishizaki T, Chiba K, Saito M, Kobayashi K, Iizuka R. The effects of neuroleptics (haloperidol and chlorpromazine) on the pharmacokinetics of valproic acid in schizophrenic patients. *J Clin Psychopharmacol* (1984) 4, 254–61.
2. Bach N, Thung SN, Schaffner F, Tobias H. Exaggerated cholestasis and hepatic fibrosis following simultaneous administration of chlorpromazine and sodium valproate. *Dig Dis Sci* (1989) 34, 1303–7.

Valproate + Erythromycin

Two isolated reports describe valproate toxicity in a woman and a child given erythromycin. Another report describes vitamin K deficiency in a child given valproate and erythromycin.

Clinical evidence, mechanism, importance and management

A child taking valproic acid developed a deficiency of prothrombin complex after taking erythromycin 300 mg three times daily. This resolved when the patient was given oral vitamin K. It was suggested that the effect was because the numbers of vitamin-K producing intestinal bacteria were reduced.[1] A woman taking lithium and valproate 3.5 g daily developed fatigue and walking difficulties a day after starting to take erythromycin 250 mg four times daily. Within a week she had also developed slurred speech, confusion, difficulty in concentrating and a worsening gait. Her serum valproate levels had risen from 88 mg/L (measured 2 months before) to 260 mg/L. She recovered within 24 hours of the valproate and erythromycin being withdrawn. Her serum lithium levels remained unchanged.[2] In another case, a child taking sodium valproate had a threefold increase in serum valproate levels after taking erythromycin 150 mg every 8 hours and aspirin 250 mg every 6 hours for 3 days.[3]

These case reports contrast with another study in a 10-year-old boy taking valproic acid 375 mg twice daily who had only very small and clinically unimportant changes in the pharmacokinetics of valproate, consistent with inhibition of cytochrome P450 metabolism, when given erythromycin 250 mg four times daily.[4]

The general relevance of these isolated reports is unclear, but probably small.

1. Cordes I, Buchmann S, Scheffner D. Vitamin K-mangel unter Erythromycin. Beobachtung bei einem mit Valproat behandelten Jungen. *Monatsschr Kinderheilkd* (1990) 138, 85–7.
2. Redington K, Wells C, Petito F. Erythromycin and valproate interaction. *Ann Intern Med* (1992) 116, 877–8.
3. Sanchez-Romero A, Pamirez IO. Interacción ácido valproico-eritromicina. *An Esp Pediatr* (1990) 32, 78–9.
4. Gopaul SV, Farrell K, Rakshi K, Abbott FS. A case study of erythromycin interaction with valproic acid. *Pharm Res* (1996) 13 (9 Suppl), S434.

Valproate + Felbamate

Felbamate can raise valproate serum levels causing toxicity. Valproate may slightly decrease the clearance of felbamate.

Clinical evidence

(a) Effect on sodium valproate

The average steady-state valproate serum levels in 7 patients with epilepsy were raised by 28% (from 66.9 micrograms/mL to 85.4 micrograms/mL) by felbamate 1.2 g daily, and by 54% (from 66.9 micrograms/mL to 103 micrograms/mL) by felbamate 2.4 g daily. In addition, the AUC of valproate was raised by 28% and 54% by felbamate 1.2 g and 2.4 g, respectively. Valproate clearance was correspondingly reduced by felbamate.[1] Similar effects were seen in another study,[2,3] and one of these studies suggested that in children the interaction may be more marked.[3] Many of the patients experienced nausea. Other toxic effects included lethargy, drowsiness, headaches, cognitive disturbances and low platelet counts.[1,2]

(b) Effect on felbamate

The clearance of felbamate was decreased by 21% by valproate in one study,[4] and another study reported a significantly lower felbamate clearance in the presence of valproate.[5] However, a further study noted only a minimal effect of valproate on felbamate clearance.[6]

Mechanism

Uncertain. Altered plasma protein binding of valproate is unlikely to be important.[7] Felbamate may cause inhibition of the oxidative pathway of valproate metabolism.[8]

Importance and management

An established interaction. It may be necessary to reduce the valproate dose to avoid toxicity if felbamate is given. The authors of one report suggest a 30 to 50% reduction. It may also be necessary to reduce the felbamate dose, although the effects appear modest. If both drugs are given monitor the outcome closely, being alert for valproate adverse effects (e.g. nausea, vomiting and dizziness) particularly during the initial stages of treatment.

1. Wagner ML, Graves NM, Leppik IE, Remmel RP, Shumaker RC, Ward DL, Perhach JL. The effect of felbamate on valproic acid disposition. *Clin Pharmacol Ther* (1994) 56, 494–502.
2. Liu H, Delgado MR. Significant drug interaction between valproate and felbamate in epileptic children. *Epilepsia* (1995) 36 (Suppl 3), S160.
3. Delgado MR. Changes in valproic acid concentrations and dose/level ratios by felbamate coadministration in children. *Ann Neurol* (1994) 36, 538.
4. Kelley MT, Walson PD, Cox S, Dusci LJ. Population pharmacokinetics of felbamate in children. *Ther Drug Monit* (1997) 19, 29–36.
5. Wagner ML, Leppik IE, Graves NM, Remme RP, Campbell JI. Felbamate serum concentrations: effect of valproate, carbamazepine, phenytoin and phenobarbital. *Epilepsia* (1990) 31, 642.
6. Banfield CR, Zhu G-RR, Jen JF, Jensen PK, Schumaker RC, Perhach JL Affrime MB, Glue P. The effect of age on the apparent clearance of felbamate: a retrospective analysis using nonlinear mixed-effects modeling. *Ther Drug Monit* (1996) 18, 19–29.
7. Bernus I, Dickinson RG, Hooper WD, Franklin ME, Eadie MJ. Effect of felbamate on the plasma protein binding of valproate. *Clin Drug Invest* (1995) 10, 288–95.
8. Hooper WD, Franklin ME, Glue P, Banfield CR, Radwanski E, McLaughlin DB, McIntyre ME, Dickinson RG, Eadie MJ. Effect of felbamate on valproic acid disposition in healthy volunteers: inhibition of β-oxidation. *Epilepsia* (1996) 37, 91–7.

Valproate + Fluoxetine

Isolated reports describe marked increases or modest decreases in valproate levels in a small number of patients given fluoxetine. Valproate toxicity occurred in one patient.

Clinical evidence

A woman with an atypical bipolar disorder and 'severe mental retardation' taking semisodium valproate (divalproex sodium) 3 g daily had a rise in her serum valproic acid levels from 93.5 mg/L to 152 mg/L within 2 weeks of starting to take fluoxetine 20 mg daily. The valproate dose was reduced to 2.25 g daily and 2 weeks later the serum valproic acid levels had fallen to 113 mg/L. No adverse effects were seen.[1] Another woman taking valproic acid developed elevated serum valproate levels (a rise from 78 mg/L to 126 mg/L) without any accompanying clinical symptoms within one month of starting to take fluoxetine 20 mg daily. Valproate levels fell again when the fluoxetine was stopped.[2] Similarly, a 17-year-old taking valproic acid and felbamate developed drowsiness and difficulty in being roused 2 weeks after starting fluoxetine 20 mg daily. His valproate level had increased to 141 micrograms/mL from a previous range of 100 to 110 micrograms/mL. His valproate dose was reduced by about 15%, and his consciousness improved.[3]

In contrast 2 cases of *reduced* valproate levels have also been reported in patients taking fluoxetine. In the first case, a 67-year-old woman taking valproic acid 2 g daily and fluoxetine 20 mg daily had a serum valproate level of 51.9 mg/L. This increased to 64.9 mg/L 9 days after fluoxetine was discontinued and fell to 32.6 mg/L 6 days after fluoxetine was restarted. In the second case, an 81-year-old woman was taking valproic acid 1 g with fluoxetine 20 mg daily and had serum valproate levels of 41.9 mg/L. The fluoxetine was stopped, and 6 days later valproate serum levels had risen to 56.2 mg/L. After re-introduction of fluoxetine her valproate levels fell to 45.6 mg/L.[4]

Mechanism

Not understood.

Importance and management

These reports are somewhat confusing and inconsistent. The overall picture is that concurrent use need not be avoided, but that the outcome should probably be monitored. Indicators of valproate toxicity include nausea, vomiting, and dizziness. More study is needed to establish an interaction.

1. Sovner R, Davis JM. A potential drug interaction between fluoxetine and valproic acid. *J Clin Psychopharmacol* (1991) 11, 389.
2. Lucena MI, Blanco E, Corrales MA, Berthier ML. Interaction of fluoxetine and valproic acid. *Am J Psychiatry* (1998) 155, 575.
3. Cruz-Flores S, Hayat GR, Mirza W. Valproic toxicity with fluoxetine therapy. Missouri Med 1995 Jun 92 (6) 296–7.
4. Droulers A, Bodak N, Oudjhani M, Lefevre des Noettes V, Bodak A. Decrease of valproic acid concentration in the blood when coprescribed with fluoxetine. *J Clin Psychopharmacol* (1997) 17, 139–40.

Valproate + Food

Food appears not to affect the bioavailability of valproate, although in one study, the rate of absorption was increased.

Clinical evidence, mechanism, importance and management

In a study in 12 healthy subjects, the absorption of a single dose of a sustained-release formulation containing sodium valproate 333 mg and valproic acid 145 mg (*Depakine Chrono*) was increased when it was given with a standard breakfast rather than in the fasting state. However, the extent of absorption, the AUC, the mean residence time and the elimination half-life were not changed.[1] Similarly, in another study in healthy subjects, the bioavailability of a single 300-mg dose of sustained-release sodium valproate (*Orfiril long*) was not affected when it was given with a high-energy, high-fat breakfast.[2] A further study in 12 healthy subjects found that dietary fibre (citrus pectin 14 g) did not affect the rate or extent of absorption of a single 500-mg dose of valproate.[3]

1. Royer-Morrot M-J, Zhiri A, Jacob F, Necciari J, Lascombes F, Royer RJ. Influence of food intake on the pharmacokinetics of a sustained release formulation of sodium valproate. *Biopharm Drug Dispos* (1993) 14, 511–18.
2. Retzow A, Vens-Cappell B, Wangemann M. Influence of food on the pharmacokinetics of a new multiple unit sustained release sodium valproate formulation. *Arzneimittelforschung* (1997) 47, 1347–50.
3. Issy AM, Lanchote VL, de Carvalho D, Silva HC. Lack of kinetic interaction between valproic acid and citrus pectin. *Ther Drug Monit* (1997) 19, 516–20.

Valproate + H_2-receptor antagonists

Aside from one tentative case report, cimetidine and ranitidine do not appear to have a clinically significant interaction with valproate.

Clinical evidence, mechanism, importance and management

In 6 patients, the clearance of a single oral dose of sodium valproate was reduced by 2 to 17% after a 4-week course of **cimetidine**, but was not affected by **ranitidine**.[1] It seems doubtful if the interaction between valproate and **cimetidine** is of clinical importance. However, a case of fatal hyperammonaemia in a patient with systemic lupus erythematosus was

speculated to have been induced by valproate, and the authors also considered that the concurrent use of **cimetidine** and aspirin (see 'Valproate + Aspirin or NSAIDs', p.656) may have contributed.[2] The general importance of this case is unknown.

1. Webster LK, Mihaly GW, Jones DB, Smallwood RA, Phillips JA, Vajda FJ. Effect of cimetidine and ranitidine on carbamazepine and sodium valproate pharmacokinetics. *Eur J Clin Pharmacol* (1984) 27, 341–3.
2. Ichikawa H, Amano T, Kawabata K, Kushiro M, Wada J, Nagake Y, Makino H. Fatal hyperammonemia in a patient with systemic lupus erythematosus. *Intern Med* (1998) 37, 700–3.

Valproate + Isoniazid

An isolated report describes the development of raised serum valproate levels and toxicity in a child given isoniazid while taking valproate. Another report describes raised liver enzymes and drowsiness in a patient taking both drugs.

Clinical evidence, mechanism, importance and management

A 5-year-old girl with left partial seizures, successfully treated with valproate 600 mg daily and clonazepam for 7 months, developed signs of valproate toxicity (drowsiness, asthenia) shortly after starting to take isoniazid 200 mg daily because of a positive tuberculin reaction. Her serum valproate levels were found to have risen to around 121 to 139 mg/L (reference range 50 to 100 mg/L).[1] Over the next few months various changes were made in her treatment, the most significant being a 62% reduction in the dose of valproate, which was needed to maintain satisfactory therapeutic valproate levels. Later when the isoniazid was stopped her valproate levels fell below the reference range and seizures recurred. It was then found necessary to increase the valproate to its former dose. The suggested explanation for this interaction is that isoniazid inhibited the metabolism (oxidation) of valproate by the liver so that it accumulated. The child was found to be a very slow acetylator of isoniazid.[1]

Another child who had been treated with valproate for several years was given isoniazid for the treatment of tuberculosis. At the same time, seizures recurred, and the valproate was stopped and primidone 750 mg daily started. Seven months later seizures persisted, and she was admitted to hospital. Liver enzyme values were normal. She was given valproate 300 mg daily increased to 600 mg daily, and within 2 days she was vomiting and drowsy. After 5 days she had increased liver enzymes and her prothrombin time had fallen, so the valproate was stopped. Valproate levels were 81 micrograms/mL. It was speculated that the CNS effects and hepatic impairment were due to an interaction between valproate and isoniazid.[2]

The general importance of these cases is uncertain, but bear them in mind in the event of an unexpected response to treatment.

1. Jonville AP, Gauchez AS, Autret E, Billard C, Barbier P, Nsabiyumva F, Breteau M. Interaction between isoniazid and valproate: a case of valproate overdosage. *Eur J Clin Pharmacol* (1991) 40, 197–8.
2. Dockweiler U. Isoniazid-induced valproic-acid toxicity, or vice versa. *Lancet* (1987) ii, 152.

Valproate + Methylphenidate

Two children taking valproic acid rapidly developed severe dyskinesias and bruxism (teeth grinding and jaw clenching) after the first and second dose of methylphenidate, respectively. Valproate appears to potentiate the effects of methylphenidate, possibly by a pharmacokinetic mechanism, or because of additive dopaminergic effects. The authors of the report advise clinical observation while the dose of methylphenidate is being established.[1]

1. Gara L, Roberts W. Adverse response to methylphenidate in combination with valproic acid. *J Child Adolesc Psychopharmacol* (2000) 10, 39–43.

Valproate + Propranolol

One patient had a reduction in valproate clearance when propranolol was also given, but 12 other patients had no change in valproate clearance when taking propranolol.

Clinical evidence, mechanism, importance and management

An isolated report describes a 28% reduction in valproate clearance in a patient taking valproate semisodium with propranolol 40 mg, and a 35% reduction in valproate clearance with propranolol 80 mg. However, 12 other patients taking valproate had no changes in the clearance, serum levels or half-life of valproate when they were given propranolol 60 or 120 mg daily for 3 weeks.[1] This interaction would therefore not appear to be of general importance. No special precautions would seem necessary if propranolol is given to patients taking valproate.

1. Nemire RE, Toledo CA, Ramsay RE. A pharmacokinetic study to determine the drug interaction between valproate and propranolol. *Pharmacotherapy* (1996) 16, 1059–62.

Valproate + Theophylline

A study in 6 healthy subjects found that oral aminophylline 200 mg every 6 hours for 3 doses did not affect the pharmacokinetics of a single 400-mg dose of sodium valproate.[1] No dose adjustment of sodium valproate appears to be needed with concurrent use of aminophylline, and therefore theophylline.

1. Kulkarni C, Vaz J, David J, Joseph T. Aminophylline alters pharmacokinetics of carbamazepine but not that of sodium valproate — a single dose pharmacokinetic study in human volunteers. *Indian J Physiol Pharmacol* (1995) 39, 122–6.

Vigabatrin + Clomipramine

An isolated case report describes mania in an patient with epilepsy taking vigabatrin and clomipramine.

Clinical evidence, mechanism, importance and management

An isolated report describes an man with epilepsy, taking carbamazepine and clobazam, who started taking clomipramine 35 mg daily for depression. About one month later, vigabatrin 2 g daily was added to improve seizure control. After about a week, the patient progressively developed signs of mania, which required him to be hospitalised after about 10 weeks. The clomipramine was stopped, the vigabatrin continued (because of its efficacy), and haloperidol started. Within a week the patient's mood had stabilised. The authors of the report attributed the mania to an interaction between the vigabatrin and the clomipramine.[1,2] Note that both clomipramine and vigabatrin can cause psychiatric disorders including mania, and vigabatrin should be used with caution in patients with depression. No general conclusions can be based on this single report.

1. Sastre-Garau P, Thomas P, Beaussart M, Goudemand M. Accès maniaque consécutif à une association vigabatrin-clomipramine. *Encephale* (1993) 19, 351–2.
2. Sastre-Garau P, Thomas P, Beaussart M, Goudemand M. Accès maniaque consécutif à une association vigabatrin-clomipramine. *Encephale* (1994) 20, 363.

Vigabatrin + Felbamate

No clinically relevant pharmacokinetic interactions appear to occur between vigabatrin and felbamate.

Clinical evidence, mechanism, importance and management

In a study in 16 healthy subjects, felbamate 2.4 g daily increased the AUC of vigabatrin 2 g daily by 13%, which is unlikely to be clinically significant. In a second study, in a further 18 healthy subjects, vigabatrin did not affect felbamate pharmacokinetics.[1] It therefore appears that concurrent use can be undertaken without the need to adjust the dose of either drug.

1. Reidenberg P, Glue P, Banfield C, Colucci R, Meehan J, Rey E, Radwanski E, Nomeir A, Lim J, Lin C, Guillaume M, Affrime MB. Pharmacokinetic interaction studies between felbamate and vigabatrin. *Br J Clin Pharmacol* (1995) 40, 157–60.

Vigabatrin + Phenobarbital or Primidone

Vigabatrin causes a small decrease in phenobarbital and primidone levels. There is some evidence that phenobarbital may reduce the efficacy of vigabatrin in infantile spasms.

Clinical evidence

In an early clinical study in 26 patients, vigabatrin 2 to 3 g daily did not change the serum levels of phenobarbital.[1] Similarly, another study found that phenobarbital levels were not significantly altered by vigabatrin.[2] A further study found that vigabatrin caused serum level reductions of 7% with phenobarbital and 11% with primidone.[3,4] Alterations of this size would not be expected to be clinically relevant.

There is some evidence that the efficacy of vigabatrin for infantile seizures may be reduced in those taking phenobarbital. The median time to response after starting vigabatrin was 3 days in 3 infants not taking phenobarbital and 34 days in 6 patients taking phenobarbital. Three patients did not respond to vigabatrin until after phenobarbital was withdrawn.[5]

Mechanism

Not understood.

Importance and management

There appears to be no change in phenobarbital levels with vigabatrin, but some suggestion that vigabatrin may be less effective for infantile spasms in the presence of phenobarbital. Bear this possibility in mind.

1. Tassinari CA, Michelucci R, Ambrosetto G, Salvi F. Double-blind study of vigabatrin in the treatment of drug-resistant epilepsy. *Arch Neurol* (1987) 44, 907–10.
2. Bernardina BD, Fontana E, Vigevano F, Fusco L, Torelli D, Galeone D, Buti D, Cianchetti C, Gnanasakthy A, Iudice A. Efficacy and tolerability of vigabatrin in children with refractory partial seizures: a single-blind dose-increasing study. *Epilepsia* (1995) 36, 687–91.
3. Browne TR, Mattson RH, Penry JK, Smith DB, Treiman DM, Wilder BJ, Ben-Menachem E, Miketta RM, Sherry KM, Szabo GK. A multicentre study of vigabatrin for drug-resistant epilepsy. *Br J Clin Pharmacol* (1989) 95S–100S.
4. Browne TR, Mattson RH, Penry JK, Smith DB, Treiman DM, Wilder BJ, Ben-Menachem E, Napoliello MJ, Sherry KM, Szabo GK. Vigabatrin for refractory complex partial seizures: multicenter single-blind study with long-term follow up. *Neurology* (1987) 37, 184–9.
5. Spence SJ, Nakagawa J, Sankar R, Shields WD. Phenobarbital interferes with the efficacy of vigabatrin in treating infantile spasms in patients with tuberous sclerosis. *Epilepsia* (2000) 41 (Suppl 7), 189.

Vigabatrin + Valproate

No pharmacokinetic interaction appears to occur between vigabatrin and valproate, but one retrospective study found a correlation between valproate levels and vigabatrin levels.

Clinical evidence, mechanism, importance and management

In 11 children, vigabatrin 40 to 80 mg/kg daily did not change the serum levels of sodium valproate.[1] The combined use of vigabatrin and sodium valproate in 16 children with refractory epilepsy was found not to affect the steady-state serum levels of either drug and the combination reduced the frequency of seizures.[2] However, a retrospective analysis of serum samples from 53 patients found that the vigabatrin concentration-to-dose ratio was increased as the valproate trough steady-state levels increased,[3] suggesting that valproate slightly raises vigabatrin levels. Nevertheless, no dose adjustments usually appear to be necessary on concurrent use.

1. Bernardina BD, Fontana E, Vigevano F, Fusco L, Torelli D, Galeone D, Buti D, Cianchetti C, Gnanasakthy A, Iudice A. Efficacy and tolerability of vigabatrin in children with refractory partial seizures: a single-blind dose-increasing study. *Epilepsia* (1995) 36, 687–91.
2. Armijo JA, Arteaga R, Valdizán EM, Herranz JL. Coadministration of vigabatrin and valproate in children with refractory epilepsy. *Clin Neuropharmacol* (1992) 15, 459–69.
3. Armijo JA, Cuadrado A, Bravo J, Arteaga R. Vigabatrin serum concentration to dosage ratio: influence of age and associated antiepileptic drugs. *Ther Drug Monit* (1997) 19, 491–8

Zonisamide + Miscellaneous

Cimetidine does not alter zonisamide pharmacokinetics. Food has no effect on the absorption of zonisamide. A case of reduced zonisamide levels possibly caused by risperidone has been described.
Potent inhibitors of CYP3A4 are predicted to modestly decrease zonisamide clearance.

Clinical evidence, mechanism, importance and management

(a) Cimetidine

In a study in healthy subjects, cimetidine 300 mg four times daily for 13 days did not affect the clearance, half-life, apparent volume of distribution or the amount of drug recovered from the urine after a single 300-mg oral dose of zonisamide. The drugs were well tolerated.[1,2] No special precautions would seem to be needed if both drugs are used.

(b) CYP3A4 inhibitors

In vitro studies have shown that the cytochrome P450 isoenzyme CYP3A4 is the principal isoenzyme involved in the metabolism of zonisamide.[3] Based on *in vitro* data, it is predicted that **ketoconazole**, **ciclosporin**, **miconazole** and **fluconazole** may cause a modest to minor decrease in the clearance of zonisamide. Conversely, **itraconazole** and **triazolam** were not predicted to have an effect.[3] This casts some doubt on these findings as *in vivo*, **ketoconazole** and **itraconazole** usually interact similarly. *In vitro* predictions do not always mirror what happens in clinical use, and therefore further study is needed to establish an effect.

(c) Food

In a study in healthy subjects there was no difference in the pharmacokinetics of a single 300- or 400-mg dose of zonisamide when given in the fasted state or when it was given after breakfast. Zonisamide may be taken without regard to the timing of meals.[4]

(d) Risperidone

A 57-year-old man taking zonisamide was given risperidone 2 mg daily, which was gradually increased to 10 mg daily. About 2 months after starting the risperidone, the zonisamide level had fallen from 23.7 micrograms/mL to 10.7 micrograms/mL. The risperidone was stopped, and the zonisamide level had slightly increased again to 12.4 micrograms/mL about one month later. It was suggested that a metabolic interaction occurred.[5] More study is needed to establish any interaction.

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Zonisamide + Other antiepileptics

Phenobarbital, phenytoin and carbamazepine can cause a small to moderate reduction in the levels of zonisamide, while lamotrigine may increase zonisamide levels. Clonazepam and valproate have little or no effect.
Zonisamide has variable effects (a modest decrease, an increase, or no effect) on carbamazepine serum levels, but has no important effect on lamotrigine, phenobarbital, primidone or valproate levels. Most studies also suggest that zonisamide has no effect on phenytoin levels, but two showed a modest increase. In theory, the combination of zonisamide and topiramate may increase the risk of renal calculi.

Clinical evidence

(a) Carbamazepine

In one study the ratio of plasma level to zonisamide dose was 39% lower in 17 patients taking carbamazepine than in 28 patients taking zonisamide alone, suggesting that carbamazepine modestly reduces zonisamide levels.[1] Similarly, in another study in 12 children with epilepsy taking zonisamide 8.6 to 13.6 mg/kg daily, carbamazepine 12.1 to 18.1 mg/kg daily reduced zonisamide plasma levels by about 35 to 37%.[2] In an early study in 2 groups of patients, one taking carbamazepine and the other phenytoin, it was noted that the zonisamide AUC following a single 400-mg dose was 40% higher in the carbamazepine group than the phenytoin group.[3] However, in the first study, the plasma concentration-to-dose ratio was the same in patients taking carbamazepine as in those taking phenytoin.[1] Therefore the comparative effects of carbamazepine and phenytoin on zonisamide levels are unclear.

In one study, the ratio of carbamazepine-10,11-epoxide (the major active metabolite of carbamazepine) to carbamazepine in the plasma was 50% lower in patients also taking zonisamide, suggesting that zonisamide reduces carbamazepine metabolism. However, the plasma concentration-to-dose ratio of carbamazepine was only 20% higher, which was not signifi-

cant.[1] An early pilot study in 7 patients noted a consistent rise in carbamazepine plasma levels (range 26 to 270%) after zonisamide was started.[4] The opposite effect was seen in a study of 16 paediatric patients in whom zonisamide reduced the ratio of carbamazepine serum levels to dose by up to 22% and increased the relative amount of its major metabolite in the serum by up to 100%, suggesting that zonisamide increases the metabolism of carbamazepine. However, the free fraction of carbamazepine remained unaltered.[5]

Contrasting with these three studies are four others that found no changes in the serum levels of carbamazepine or carbamazepine-10,11-epoxide when zonisamide was used,[2,6-8] although in one of the studies, the renal clearance of carbamazepine-10,11-epoxide was reduced by zonisamide.[8] A further study similarly found no change in the plasma level of carbamazepine in 41 patients also given zonisamide (7.5 micrograms/mL versus 7.4 micrograms/mL).[9]

(b) Clonazepam

In one study the ratio of plasma level to dose ratio of zonisamide did not differ between 8 patients also taking clonazepam and 28 patients taking zonisamide alone, suggesting clonazepam has no effect on zonisamide levels.[1]

(c) Lamotrigine

In 18 patients, zonisamide 100 mg daily increased to 200 mg twice daily did not alter the steady-state pharmacokinetics of lamotrigine.[10,11] Further, the pharmacokinetics of zonisamide were unaffected by lamotrigine.[11] However, in 2 patients who were stable taking zonisamide 600 mg daily or 800 mg daily, the addition of lamotrigine (incremental doses up to 400 mg daily) caused roughly twofold increases in their zonisamide levels, with symptoms of toxicity that were maximal 40 to 60 minutes after taking a zonisamide dose.[12]

(d) Phenobarbital or Primidone

In one study the ratio of plasma level to dose ratio of zonisamide was 29% lower in 11 patients also taking phenobarbital than in 28 patients taking zonisamide alone, suggesting that phenobarbital reduces zonisamide levels.[1] Similarly, another study in healthy subjects found that pretreatment with phenobarbital roughly doubled the clearance of a single dose of zonisamide.[13] A further study found no changes in the serum levels of phenobarbital or primidone in 34 and 13 patients, respectively, who were also given zonisamide.[9]

(e) Phenytoin

In one study the ratio of plasma level to dose ratio of zonisamide was 39% lower in 14 patients also taking phenytoin than in 28 patients taking zonisamide alone, suggesting phenytoin modestly reduces zonisamide levels.[1] In an early study in two groups of patients, one taking carbamazepine and the other phenytoin, it was noted that the zonisamide AUC following a single 400-mg dose was 40% higher in the carbamazepine group than the phenytoin group.[3] However, in the first study, the reduction in zonisamide level-to-dose ratio was the same for phenytoin as for carbamazepine.[1] Therefore the comparative effect of phenytoin and carbamazepine on zonisamide levels is unclear.

Other studies in both adults and children suggest that zonisamide does not affect phenytoin levels.[6,9,14] However, in a population pharmacokinetic analysis, the clearance of phenytoin at a given dose was 14% lower and the serum level 16% higher in 39 patients also taking zonisamide.[15] Similarly, the preliminary results from 9 patients in another study showed that there was a 28% increase in the steady-state AUC of phenytoin when zonisamide 100 mg daily increased to 200 mg twice daily was given,[16] although a later study by the same authors, in 19 patients, found that zonisamide did not affect the pharmacokinetics of phenytoin to a clinically relevant extent.[17]

(f) Topiramate

Zonisamide and topiramate are both weak inhibitors of carbonic anhydrase and either may increase the risk of renal calculi. However, a study in children with epilepsy found that giving either topiramate or zonisamide with a ketogenic diet (high-fat, adequate protein, low-carbohydrate used in difficult to control epilepsy) did not increase the risk of renal calculi that occurred with a ketogenic diet alone.[18] In a retrospective study including 10 patients taking zonisamide and topiramate, there were no reports of renal calculi.[19]

(g) Valproate

In one study the ratio of plasma level to dose of zonisamide was about 20% lower in 24 patients also taking valproate than in 28 taking zonisamide alone, suggesting that valproate has little effect on zonisamide levels.[1] Similarly, another study in 16 patients found that valproate did not affect the pharmacokinetics of zonisamide.[20] Further, the steady-state pharmacokinetics of valproate did not change when zonisamide 100 mg daily increased to 200 mg twice daily was given 16 patients taking valproate.[20,21]

Another study found that zonisamide did not affect the serum levels of sodium valproate in 12 children.[14] A further study similarly found no marked changes in the plasma level of valproic acid in 7 patients also given zonisamide.[9]

Mechanism

Uncertain. It seems possible that phenobarbital, phenytoin and carbamazepine can induce the metabolism of zonisamide thereby reducing its serum levels. The plasma protein binding of zonisamide is unaffected by other antiepileptics (phenobarbital, phenytoin, carbamazepine, valproate).[22]

Importance and management

None of these studies reported any major problems during concurrent use of zonisamide and these other antiepileptic drugs. Zonisamide serum levels are lower with phenobarbital, phenytoin and carbamazepine, and there is the possibility of carbamazepine or phenytoin level changes, so it would be prudent to monitor patients taking any of these combinations.

There appears to be a theoretical risk of a pharmacodynamic interaction between zonisamide and topiramate, but the limited evidence available suggests the interaction is unlikely to be of importance.

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15

Antihistamines

Antihistamines (histamine H_1-antagonists) vary in their interaction profiles by sedative potential, route of metabolism, and cardiotoxicity (QT interval prolongation).

(a) Additive sedative effects

The older antihistamines (e.g. chlorphenamine, diphenhydramine and hydroxyzine) are also referred to as sedating antihistamines or first-generation antihistamines. As the former name suggests they have the potential to cause additive sedative effects with other sedating drugs. This type of interaction is discussed elsewhere, see 'CNS depressants + CNS depressants', p.1553. The sedating antihistamines also tend to have antimuscarinic (also called anticholinergic) adverse effects and so therefore may interact additively with other antimuscarinic-type drugs. This is also discussed elsewhere, see 'Antimuscarinics + Antimuscarinics', p.786.

The newer (non-sedating antihistamines or second-generation antihistamines) have a low potential to cause sedative effects. This appears to be because they are substrates for P-glycoprotein, an efflux transporter found in many organs, which would have the effect of actively ejecting any drug molecules that crossed the blood-brain barrier. Nevertheless, sedation may occur on rare occasions and patients should be advised to be alert to the possibility of drowsiness if they have not taken the drug before. Any drowsiness is likely to become apparent after the first few doses, and would indicate that additive sedative effects with other sedating drugs might be expected. The antihistamines are listed, by sedative potential, in 'Table 15.1', (below).

(b) Metabolism

Some of the sedating antihistamines, such as diphenhydramine, are inhibitors of the cytochrome P450 isoenzyme CYP2D6. None of the non-sedating antihistamines are known to inhibit cytochrome P450 isoenzymes, but some are substrates for CYP3A4 including astemizole, desloratadine, ebastine, loratadine, mizolastine, rupatadine and terfenadine, see 'Table 15.2', (p.664). This has important consequences for the potential cardiotoxicity of astemizole and terfenadine, see below. Loratadine and desloratadine are also substrates for CYP2D6, and mizolastine is also metabolised by glucuronidation. Cetirizine, levocetirizine and fexofenadine are minimally metabolised. Where pharmacokinetic interactions occur with fexofenadine, these appear to be mediated via drug transporters such as P-glycoprotein and/or organic anion transport polypeptide (OATP). For more information about the effects of drug transporters, see 'Drug transporter proteins', (p.8).

(c) QT interval prolongation and cardiac arrhythmias

Important drug interactions occur with the non-sedating antihistamines, astemizole and terfenadine. Raised serum levels of these two antihistamines can block potassium channels, lengthening the QT interval and increasing the risk of potentially fatal cardiac arrhythmias (torsade de pointes). Therefore, dangerous interactions may result when other drugs reduce the metabolism of astemizole or terfenadine, usually by inhibition of the cytochrome P450 isoenzyme CYP3A4. Such drugs include the 'macrolides', (p.671) and the 'azoles', (p.665). Adverse interactions are also predicted when astemizole or terfenadine are used with drugs that prolong the QT interval, see 'Antihistamines + Drugs that prolong the QT interval', p.669. Due to these potentially fatal interactions, astemizole and terfenadine have been withdrawn from many countries. Apart from possibly ebastine, loratadine and mizolastine, where information is inconclusive, none of the other non-sedating antihistamines have been clearly shown to be associated with QT prolongation (see 'Table 15.2', (p.664)). Therefore, even when pharmacokinetic interactions result in increased levels, these are unlikely to be clinically important in terms of cardiotoxicity.

Table 15.1 Systemic antihistamines (classified by sedative potential) and topical antihistamines

Sedative potential	*Antihistamine*
Non-sedating	Acrivastine, Astemizole,* Cetirizine, Desloratadine, Ebastine,* Fexofenadine, Levocetirizine, Loratadine, Mizolastine,* Rupatadine, Terfenadine*
Sedating	Azatadine, Brompheniramine, Buclizine, Chlorphenamine, Cinnarizine, Clemastine, Cyclizine, Cyproheptadine, Dexchlorpheniramine, Flunarizine, Meclozine, Mepyramine, Mequitazine, Pheniramine, Tripelennamine, Triprolidine
Significantly sedating	Alimemazine, Bromazine, Carbinoxamine, Dimenhydrinate, Diphenhydramine, Doxylamine, Hydroxyzine, Promethazine, Trimeprazine
Topical use (mainly)	Antazoline, Azelastine, Emedastine, Epinastine, Levocabastine, Olopatadine

*Important QT prolongation known to occur (astemizole, terfenadine), or may possibly occur (ebastine, mizolastine), see Table 15.2

Table 15.2 Metabolism and cardiac effects of non-sedating antihistamines

Drug	*Drug blocks the HERG† potassium channel in vitro*	*QTc interval prolongation shown in pharmacological studies with drug alone*	*QTc interval prolongation shown in pharmacological studies with CYP3A4 inhibitors*	*Case reports of torsade de pointes with drug alone*	*Case reports of torsade de pointes with CYP3A4 inhibitors*
Metabolised by CYP3A4					
Astemizole	Yes[1]	Yes[2]	Yes. See Azoles	Several[2-8]	Yes. See Azoles or Macrolides
Desloratadine	No	No	No	No	No
Ebastine	Yes[9]	Uncertain	Yes. See Azoles or Macrolides	No	No
Loratadine	Yes, in one study[10]	No	Yes. See Azoles or Nefazodone	Possible case[11-13]	Yes. See Azoles or Macrolides
Mizolastine	Yes[14]	Uncertain	Yes. See Azoles	No	No
Rupatadine	No	No	No	Yes[15]	No
Terfenadine	Yes[10,16]	Yes	Yes. See Azoles, Macrolides or Nefazodone	A few[17,18]	Yes. See Azoles or Macrolides
Not metabolised by CYP3A4					
Cetirizine	No	No	No	Possible case[19]	No
Fexofenadine	No	No	No	Possible case[20,21]	No
Levocetirizine	No	No	No	No	No

†The HERG (human ether-a-go-go related gene) channel is involved in cardiac action potential repolarisation and is known to be blocked by certain drugs. Blocking HERG channels results in prolongation of the QT interval.

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Antihistamines + Azoles

The azole antifungals raise the levels of astemizole and terfenadine, which can result in life-threatening arrhythmias; this has been seen in a number of cases. Mizolastine, ebastine and acrivastine either are, or are predicted to be, similarly affected. The situation with loratadine is unclear as one study found that the concurrent use of ketoconazole caused a small increase in the QT interval.

Ketoconazole raises the levels of desloratadine, emedastine, fexofenadine and rupatadine but no adverse cardiac effects were seen. No interaction occurs between ketoconazole and azelastine, cetirizine, intranasal levocabastine, and none is expected with levocetirizine.

Clinical evidence

The effect of various azole antifungals on the plasma levels of the non-sedating antihistamines, and their cardiac effects from controlled studies are summarised in 'Table 15.3', (p.666). The subsections below include data from case reports and further studies.

(a) Astemizole

A 63-year old woman developed torsade de pointes and was found to have a prolonged QT interval after taking astemizole and **ketoconazole**. These two drugs were withdrawn and she was successfully treated with a temporary pacemaker, magnesium sulphate and lidocaine. She was later discharged with a normal ECG.[1]

(b) Desloratadine

A patient undergoing chemotherapy developed severe pruritus and was given desloratadine and clemastine. Because of pyrexia of unknown origin she was treated with meropenem and then 48 hours later **fluconazole** was added. After about 36 hours severe hepatotoxicity was detected, and apart from the anti-infectives the other drugs were stopped. Liver parameters recovered over the following week. Because the patient had previously received clemastine and **fluconazole** without problems, this case was attributed to a possible interaction between **fluconazole** and desloratadine.[2]

(c) Ebastine

A review of the safety of ebastine cites two studies assessing the potential interaction between ebastine and **ketoconazole**. A single-dose study, found that the combination did not affect the QTc interval, whereas a multiple-dose study found that the QTc interval was prolonged by 18.1 milliseconds by the combination.[3]

(d) Fexofenadine

1. Itraconazole. In a single-dose study, giving itraconazole 200 mg one hour before fexofenadine 180 mg increased the AUC of fexofenadine 2.3-fold, and 3-fold in two groups of subjects with different genotypes for the gene encoding P-glycoprotein. Itraconazole pretreatment increased the effect of fexofenadine on histamine-induced wheal and flare reaction.[4]

2. Ketoconazole. Fexofenadine has no effect on the pharmacokinetics of ketoconazole, but fexofenadine levels are increased by ketoconazole.[5]

(e) Loratadine

In one study the cardiac effects of loratadine were found to be similar to those of ebastine (see above), which caused a small increase in the QTc interval.[6] However, loratadine alone, given at 4 times the recommended dose for 90 days, had no effect on the QTc interval when compared with placebo.[7] See also 'Table 15.2', (p.664), for the potential effects of loratadine on the QT interval.

(f) Rupatadine

A review reports a study in which the systemic exposure to rupatadine 20 mg was increased 10-fold by **ketoconazole** 200 mg daily for 7 days. The pharmacokinetics of **ketoconazole** were unaffected by rupatadine. There were no clinically relevant changes in the QTc interval, vital signs or adverse effects.[8]

(g) Terfenadine

1. Fluconazole. The US manufacturer of fluconazole reports that fluconazole 400 mg or 800 mg daily significantly increased plasma levels of terfenadine (magnitude not stated).[9] In an interaction study, 6 healthy subjects were given fluconazole 200 mg daily with terfenadine 60 mg twice daily for about 6 days. Although fluconazole increased the AUC of terfenadine by 34%, there was no statistically significant prolongation of the QTc interval.[10]

2. Itraconazole. A 26-year-old woman taking terfenadine 60 mg twice daily began to have fainting episodes on the third evening after starting to take itraconazole 100 mg twice daily for vaginitis. When admitted to hospital the next morning her ECG showed a QT interval of 580 milliseconds and her heart rate was 67 bpm. Several episodes of torsade de pointes were recorded, and she fainted during two of them. No arrhythmias were seen 20 hours after the last itraconazole dose, and her QT interval returned to normal after 3 days. She was found to have terfenadine levels of 28 nanograms/mL in the first sample of serum taken (normally less than 5 nanograms/mL) and she still had levels of 12 nanograms/mL about 60 hours after taking the last tablet.[11,12] Two other similar cases have been reported,[13,14] and the FDA has received four well-documented cases of severe cardiac complications due to this interaction.[15]

3. Ketoconazole. A 39-year-old woman taking terfenadine 60 mg twice daily developed a number of episodes of syncope and light-headedness, preceded by palpitations, dyspnoea and diaphoresis, within 2 days of starting to take ketoconazole 200 mg twice daily. ECG monitoring revealed torsade de pointes and a QTc interval of 655 milliseconds. Her terfenadine serum levels were 57 nanograms/mL (levels expected to be 10 nanograms/mL or less). Other drugs being taken were cefaclor (stopped 3 to 4 days before the problems started) and medroxyprogesterone acetate. She had taken terfenadine and cefaclor on two previous occasions in the absence of ketoconazole without problems.[16,17] Other cases of an interaction between terfenadine and ketoconazole have also been reported.[18,19]

4. Oxiconazole. A 25-year-old woman complained of palpitations and chest pain radiating down her left arm, and was also found to be having frequent ventricular premature beats in a pattern of bigeminy. On questioning it turned out that she was taking terfenadine and using topical oxiconazole for ringworm on her arm. Both drugs were stopped and her symptoms disappeared the following week.[20]

Mechanism

Astemizole and terfenadine are known to be metabolised by the cytochrome P450 isoenzyme CYP3A4. The azole antifungals are known inhibitors of this isoenzyme, with ketoconazole having potent effects, and fluconazole in low doses having modest effects. Concurrent use of these antihistamines and the azoles therefore leads to increased antihistamine levels. High serum levels of astemizole and terfenadine (but not its metabolites) block cardiac potassium channels leading to prolongation of the QT interval, which may precipitate the development of torsade de pointes (see 'Table 15.2', (p.664)). The risk of cardiac arrhythmias with other non-sedating antihistamines appears to be non-existent or very much lower (see 'Table 15.2', (p.664)), so any pharmacokinetic interactions do not result in clinically relevant cardiac toxicity. In fact, studies have shown that desloratadine at nine times the recommended dose,[21] fexofenadine in overdose,[5,22] and mizolastine at four times the recommended dose[23] do not affect the QT interval. However, some questions remain about loratadine and ebastine. Additionally, some studies have reported that ketoconazole alone is associated with a small increase in QT interval,[6] and at least one case of torsade de pointes has been reported for ketoconazole alone.[24] Therefore the cardiac effects of ketoconazole may be additive with those of the antihistamines, and this may be important for ebastine and loratadine.

In vitro studies have suggested that rupatadine is mainly metabolised by CYP3A4.[25] Therefore its levels are raised by the azoles. Fexofenadine is not metabolised by CYP3A4, but it is a substrate for P-glycoprotein and OATP,[26] therefore azole antifungals may increase its levels by inhibiting drug transporter proteins.

Importance and management

The interactions of astemizole and terfenadine with the azoles are established and clinically important, although much of the evidence for particular pairs of these antihistamines and the azoles is indirect. The incidence of an interaction is probably low, but because of the potential severity and unpredictability of this interaction, the concurrent use of astemizole and terfenadine is contraindicated with all azole antifungals in all patients. Note that a large proportion of **miconazole** oral gel (both prescription and

Table 15.3 Summary of the effects of azoles on the pharmacokinetics and cardiovascular effects of non-sedating antihistamines

Antihistamine (Oral unless specified)	*Azole (Oral unless specified)*	*Duration of combined use (days)*	*Subjects*	*Cmax increase‡*	*AUC increase*	*Effect on QTc*	*Refs*
Astemizole* 10 mg single dose	Itraconazole 200 mg twice daily	Single dose	12 healthy subjects	No change	82%	No change	1
Azelastine* 4 mg twice daily	Ketoconazole 200 mg twice daily	7	12 healthy subjects	Not determined. In vitro tests suggest no change likely.	Not determined. In vitro tests suggest no change likely.	No change	2
Cetirizine 20 mg daily	Ketoconazole 400 mg daily	10	Healthy subjects	No change	No change	No change	3
Desloratadine 7.5 mg daily	Ketoconazole 200 mg twice daily	10	24 healthy subjects	27%	21%	No change	4
Ebastine 20 mg daily	Ketoconazole 400 mg daily	8	55 healthy subjects	16-fold	42-fold	Mean increase of 5.25 milliseconds when antihistamine added to ketoconazole. Mean increase of 12.21 milliseconds from baseline. QTc did not exceed 500 milliseconds in any subject.†	5
Emedastine 4 mg daily	Ketoconazole 200 mg twice daily	5	12 healthy subjects	37%	34%	No change	6
Fexofenadine 120 mg single dose	Itraconazole 100 mg twice daily	Single dose	8 healthy subjects	93%	173%	Not measured	7
Fexofenadine 60 mg daily	Itraconazole 200 mg daily	Intermittent over 6 days	10 healthy subjects	2-fold	2-fold	Not measured	8
Fexofenadine 60 mg single dose	Ketoconazole 50 mg, 100mg and 200mg	Single dose	11 healthy subjects	80%, 105% and 103% respectively	109%, 153% and 141% respectively	Not measured	9
Fexofenadine 120 mg twice daily	Ketoconazole 400 mg daily	7	24 healthy subjects	135%	164%	No change	10
Levocabastine 200 micrograms twice daily intranasal	Ketoconazole 200 mg single dose	Single dose	37 subjects	No change	No change	No change	11
Loratadine 10 mg daily	Ketoconazole 200 mg twice daily	10	24 healthy subjects	172% loratadine 76% desloratadine	247% loratadine 82% desloratadine	No change	12
Loratadine 20 mg single dose	Ketoconazole 200 mg twice daily	Single dose	12 healthy subjects	144% loratadine 33% desloratadine	184% loratadine 54% desloratadine		13
Loratadine 10 mg daily	Ketoconazole 400 mg daily	8	62 healthy subjects	248% loratadine 82% desloratadine	346% loratadine 94% desloratadine	Mean increase of 3.16 milliseconds when antihistamine added to ketoconazole. Mean increase of 10.68 milliseconds from baseline. QTc did not exceed 500 milliseconds in any subject.†	5
Mizolastine 10 mg single dose	Ketoconazole 100 mg, 200 mg, 400 mg single doses	Single dose	12 healthy subjects		45%, 61% and 95% respectively		14
Mizolastine 10 mg daily	Ketoconazole 200 mg twice daily	5				Mean increase of 7 milliseconds over mizolastine or placebo alone. None exceeded 500 milliseconds	15
Terfenadine* 60 mg twice daily	Fluconazole 200 mg daily	6	6 healthy subjects		No change terfenadine 34% terfenadine acid metabolite	No change	16

Continued

Table 15.3 Summary of the effects of azoles on the pharmacokinetics and cardiovascular effects of non-sedating antihistamines (continued)

Antihistamine (Oral unless specified)	*Azole (Oral unless specified)*	*Duration of combined use (days)*	*Subjects*	*Cmax increase*‡	*AUC increase*	*Effect on QTc*	*Refs*
Terfenadine* 60 mg twice daily	Fluconazole 800 mg daily	7	Note - 6 subjects previously found to have measurable terfenadine levels at steady state		52% terfenadine 5% terfenadine acid metabolite	Increase	17
Terfenadine* 120 mg single dose	Itraconazole 200 mg daily	Single dose	6 healthy subjects	Terfenadine 25%, 115%, 156% in the 3 subjects who had measurable levels before itraconazole	30% terfenadine acid metabolite	Mean increase of 27 milliseconds when compared to terfenadine alone	18
Terfenadine* 120 mg single dose	Ketoconazole 400 mg daily	Single dose	12 healthy subjects	Greater than or equal to 170% terfenadine ↓71% terfenadine acid metabolite		Prolongation by 10 to 20 milliseconds	19,20
Terfenadine* 60 mg twice daily	Ketoconazole 200 mg twice daily	4 to 7	6 healthy subjects	Below 5 to 7 nanograms/mL terfenadine levels increased to 81 nanograms/mL in one subject	57% terfenadine acid metabolite	Mean increase of 74 milliseconds	21

*Cases of torsade de pointes have been reported for this antihistamine

†QTc intervals calculated using the Fridericia cube route formula, rather than the more commonly used Bazett square root formula, which the authors suggest would lead to a 5 to 6 millisecond overestimation

‡Note that terfenadine levels are normally undetectable

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non-prescription doses) may be swallowed and therefore adequate systemic absorption may occur to produce an interaction. A similar effect was seen in one case with topical oxiconazole. Note that, the UK manufacturer of terfenadine extended this contraindication to the concurrent use of topical azoles.[27] However, the US manufacturer of fluconazole contraindicates the concurrent use of terfenadine with daily doses of fluconazole 400 mg or greater, but only advises careful monitoring with fluconazole doses below 400 mg.[9]

The use of azole antifungals with mizolastine is also contraindicated,[28] and the manufacturer of ebastine advises against the concurrent use of ketoconazole and itraconazole.[29] Similarly, the manufacturer of rupatadine[25] advises that it should be used with caution with ketoconazole, and other inhibitors of CYP3A4, which would include all the azoles. Because there are no data on **acrivastine** with ketoconazole, the manufacturer advises caution.[30]

Ketoconazole markedly raises loratadine levels. In one study, this was associated with a small increase in QT interval, but no obvious alteration in adverse event profile. No special precautions appear to have been recommended for the use of loratadine with azoles.

Desloratadine, emedastine and fexofenadine levels are raised by ketoconazole but because this does not result in adverse cardiac effects concurrent use is considered safe. Azelastine, cetirizine (and therefore probably its isomer **levocetirizine**) and levocabastine seem to be free from clinically significant pharmacokinetic interactions, and have no cardiac effects, and so may therefore provide suitable alternatives if a non-sedating antihistamine is needed in a patient taking azole antifungals.

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Antihistamines + Benzodiazepines and related drugs

Benzodiazepines impair psychomotor performance, but astemizole, ebastine, mizolastine and terfenadine (non-sedating antihistamines) do not further impair this. An enhanced sedative effect would be expected if known sedative antihistamines are given with benzodiazepines. Diphenhydramine does not alter the pharmacokinetics of zaleplon, but it did enhance the sedative effects of diazepam in one study.

Clinical evidence

(a) Astemizole

A study in 32 healthy subjects found that a single 10-mg dose of astemizole did not enhance the effects of a single 10-mg dose of **diazepam**.[1]

(b) Diphenhydramine

1. Diazepam. A study in 13 healthy subjects who took diphenhydramine 50 mg twice daily for 5 days, with a single 300-microgram/kg dose of diazepam on day 5 found no additive effects on sedation or the performance of a number of psychomotor tests. The plasma levels of diazepam measured 100 minutes after administration were increased by 39%, but this was not statistically significant. It was suggested that the subjects may have developed tolerance to the sedative effects of the antihistamine.[2]
Oral administration of diazepam 10 mg with diphenhydramine 100 mg impaired psychomotor performance compared with diazepam alone, up to 4 hours after the two drugs had been taken. Subjects noted a significant feeling of drunkenness after taking diazepam and diphenhydramine together which persisted for 4 hours. This feeling persisted for about 2 hours after taking diazepam alone.[3]

2. Zaleplon. A randomised, single-dose study in healthy subjects found that diphenhydramine 50 mg had no significant effect on the pharmacokinetics of a single 10-mg dose of zaleplon, despite the fact diphenhydramine is a moderate inhibitor of the primary metabolic pathway [aldehyde oxidase] of zaleplon.[4]

(c) Ebastine

In 12 healthy subjects ebastine 20 mg daily did not impair the performance of a number of psychomotor tests, although body sway and flicker fusion tests were altered. When ebastine was given with a single 15-mg dose of **diazepam**, it did not further impair performance, when compared with diazepam alone, and did not alter plasma **diazepam** levels.[5]

(d) Mizolastine

Mizolastine appears to lack sedative effects, and does not have a detrimental effect on psychomotor performance.[6] A single 2-mg dose of oral **lorazepam** was found to impair the performance of psychomotor tests in 16 healthy subjects, and caused some sedation and amnesia, but these effects were not changed when the subjects also took mizolastine 10 mg daily for 8 days.[6]

(e) Terfenadine

A study in 20 healthy subjects found that the concurrent use of **diazepam** 10 mg with terfenadine 120 mg had no effect on psychomotor performance.[3]

Mechanism, importance and management

A number of older antihistamines cause sedation, and this would be expected to be increased by some of the benzodiazepines by the simple addition of their CNS depressant effects. Non-sedating antihistamines would not be expected to have this effect (but see also ‘Antihistamines’, (p.663)), and this has been confirmed for astemizole, ebastine, mizolastine and terfenadine.

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Antihistamines + Drugs that prolong the QT interval

Astemizole and terfenadine should generally not be used with other drugs that can also prolong the QT interval. The manufacturer of mizolastine issues the same advice. One early study found that hydroxyzine caused ECG abnormalities in high doses. The authors suggested that its use with other drugs that can cause cardiac abnormalities might increase the likelihood of arrhythmias and sudden death, but there is no published evidence of this. A retrospective review has confirmed that patients taking astemizole or terfenadine with inhibitors of CYP3A4 are exposed to an increased risk of ventricular arrhythmias.

Clinical evidence, mechanism, importance and management

(a) Non-sedating antihistamines

A review of data on the use of five non-sedating antihistamines (**acrivastine**, **astemizole**, **cetirizine**, **loratadine** and **terfenadine**) from the UK General Practice Research Database showed a relative risk of ventricular arrhythmias of 4.2 compared to non-use. It did not identify a higher risk of ventricular arrhythmias following terfenadine use than following use of the other non-sedating antihistamines. The relative risk of developing a ventricular arrhythmia was highest during astemizole use (19). Within the data used for this study there were no cases of ventricular arrhythmias in patients taking terfenadine and CYP3A4 inhibitors.[1] The authors concluded that the absolute risk of ventricular arrhythmias with the use of one of these drugs alone, was quite small. However, in the presence of other drugs that prolong the QT interval, the risk may be larger. The manufacturers of **astemizole**[2] and **terfenadine**[3] contraindicated the concurrent use of any other drugs that can also prolong the QT interval (for a list, see 'Table 9.2', (p.290)). However, the primary risk of QT prolongation and torsade de pointes with **astemizole** and **terfenadine** appears to be from drugs that significantly inhibit their metabolism (e.g. 'azoles', (p.665) and 'macrolides', (p.671)). Clinically relevant QT prolongation has not yet been shown conclusively for any of the other antihistamines (see 'Table 15.2', (p.664)), although the manufacturers of **mizolastine**[4] still contraindicate its use with drugs that prolong the QT interval. Isolated cases have been described with other antihistamines: a case report of torsade de pointes with sotalol and '**terfenadine**', (p.1024) was attributed solely to additive effects of QT prolongation with these drugs; and a small additional QT-prolonging effect has also been shown when **terfenadine** was given with 'sparfloxacin', (p.676). A case report describes a 73-year-old woman taking amiodarone for atrial fibrillation, who was given **loratadine**, and developed syncope and multiple episodes of torsade de pointes.[5] In a review of torsade de pointes in patients taking amiodarone long-term, two elderly female patients taking amiodarone 200 mg daily developed torsade de pointes 2 days and 7 days, respectively, after **loratadine** 10 mg daily was added.[6] Amiodarone may have inhibited the metabolism of **loratadine** by the cytochrome P450 isoenzyme CYP3A4; however, even in high-dose **loratadine** dose not appear to affect the QT interval. The general clinical relevance of these cases is uncertain, but the authors consider that the QT interval should be monitored if **loratadine** is given with other drugs that may potentially prolong the QT interval.[5]

A retrospective review of a cohort of 14 638 patients with urinary incontinence diagnosed between January 1991 and June 1995, identified that there was a significant association between the use of non-sedating antihistamines (**terfenadine** and **astemizole**) with drugs that are inhibitors of cytochrome P450 isoenzyme CYP3A4 and the incidence of ventricular arrhythmias, with an adjusted relative risk of 5.47. This combination was also shown to carry a significant risk of sudden death (relative risk 21.5).[7]

Consider also 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290.

(b) Sedating antihistamines

A study, conducted in 1958, in 25 elderly patients with psychoses, taking high-dose **hydroxyzine** 300 mg daily over a 9-week period, found that ECG changes were mild, except for an alteration in T waves, which were definite in 9 patients. In each case the T waves were lower in altitude, broadened and flattened and sometimes notched. The QT interval was usually prolonged. A repeat of the study in a few patients, at least one given **hydroxyzine** 400 mg, found similar effects, the most pronounced change being a marked attenuation of cardiac repolarisation. On the basis of these observations the authors suggest that other drugs that cause ECG abnormalities such as thioridazine might aggravate and exaggerate these **hydroxyzine**-induced changes and increase the risk of sudden death.[8] However, note that in the decades of use of **hydroxyzine** since this study was conducted there appear to be only a few isolated reports of arrhythmias (tachycardia) associated with its use.[9,10] Note also that some manufacturers do not give any warnings regarding the use of **hydroxyzine** in patients with cardiac disorders, nor are any cardiac adverse effects mentioned, even for overdose.[11,12] However, one manufacturer does suggest that caution is necessary in patients pre-disposed to arrhythmias, or taking drugs that may cause arrhythmias.[13]

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Antihistamines + Food

The pharmacokinetics of cetirizine, desloratadine, loratadine and rupatadine are not affected to a clinically relevant extent by food.

Clinical evidence, mechanism, importance and management

(a) Cetirizine

The manufacturer of cetirizine notes that the extent of absorption of cetirizine is unaffected by food, but the rate of absorption is decreased.[1] This is not expected to be clinically relevant.

(b) Desloratadine

A study in 18 healthy subjects found no difference in the pharmacokinetics of a single 7.5-mg dose of desloratadine taken after a 10-hour fast, or after a high-fat, high-calorie breakfast.[2]

(c) Loratadine

In a study, 24 healthy subjects were given a single 10-mg dose of extended-release loratadine after a 10-hour fast, or with a high-fat, high-calorie breakfast. Food increased the maximum plasma levels of loratadine by 53% and the AUC by 76%. However, this was not considered to be clinically significant, and there was no significant difference in the reporting of adverse effects between the two groups.[3] The UK manufacturer of an immediate-release preparation of loratadine notes that food can slightly delay the absorption of loratadine, but that this has no clinical effect.[4]

(d) Rupatadine

In a crossover study, 24 healthy subjects were given a single 20-mg dose of rupatadine after a high-fat breakfast, or when fasting. When taken with food, the AUC and half-life of rupatadine increased by 26% and 72%, respectively. The time to reach maximum plasma levels increased by 133%, although the maximum plasma levels were not significantly affected. The pharmacokinetics of desloratadine and 3-hydroxydesloratadine, two active metabolites of rupatadine, were not significantly affected by the presence of food. There was no apparent difference in the prevalence or

severity of adverse effects between the two groups.[5] The UK manufacturer states that rupatadine may be taken without regard to food.[6]

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Antihistamines + Grapefruit and other fruit juices

Grapefruit juice raises terfenadine levels, increasing the risk of QT interval prolongation and torsade de pointes. Grapefruit juice does not appear to alter the pharmacokinetics of astemizole and desloratadine. The absorption of fexofenadine is modestly reduced by grapefruit juice, orange juice and apple juice.

Clinical evidence

(a) Astemizole

In a study in 12 healthy subjects the steady-state pharmacokinetics of astemizole 30 mg daily for 4 days, then 10 mg daily for the next 20 days, were unaffected by 200 mL of **grapefruit juice** given every 4 hours.[1]

(b) Desloratadine

The bioavailability of a single 5-mg dose of desloratadine was unaffected by 8 oz (240 mL) of double-strength **grapefruit juice**, which was given three times daily for 2 days before the desloratadine and then 5 minutes before and 2 hours after the dose.[2]

(c) Fexofenadine

A study in 12 healthy subjects found that a single 300-mL dose of normal strength **grapefruit juice** reduced the AUC of a single 120-mg dose of fexofenadine by 42% when they were given simultaneously.[3] An effect was apparent for 300 mL of **grapefruit juice** given up to 10 hours before fexofenadine 120 mg in at least some of the subjects involved in this study.[4] In a study in 23 healthy subjects the AUC of fexofenadine 60 mg was reduced by 30% by 8 oz (about 240 mL) of double-strength **grapefruit juice**, which was given three times daily for 2 days before the fexofenadine and then 5 minutes before and 2 hours after the dose.[2] Similarly, another study found that **grapefruit juice** at normal strength decreased the AUC of a single 120-mg dose of fexofenadine by 67%. Dilute **grapefruit juice** (25%) caused a smaller reduction in the AUC of fexofenadine of 23%. Normal strength **orange juice** and **apple juice** similarly decreased the AUC of fexofenadine by 72% and 77% respectively.[5] In this study, 300 mL of juice was given with the fexofenadine, followed by 150 mL every 30 minutes to a total volume of 1.2 litres.

(d) Rupatadine

The manufacturer of rupatadine notes that the concurrent use of grapefruit juice increases the systemic exposure of rupatadine 3.5-fold.[6]

(e) Terfenadine

Terfenadine 60 mg was given to 6 healthy subjects every 12 hours for 14 days, simultaneously with 240 mL of double-strength **grapefruit juice** every 12 hours for the final 7 days. Terfenadine was only detectable in the plasma when **grapefruit juice** was taken. The mean QTc interval was found to have risen from 420 to 434 milliseconds,[7] which is not of a magnitude usually considered to be clinically significant. The effects were less pronounced in a further 6 subjects who took the **grapefruit juice** 2 hours after the terfenadine.[7] Several other reports confirm these pharmacokinetics findings, although some did not find any changes in the QTc interval.[8-10]

Mechanism

Not fully understood, but it seems likely that some component of grapefruit juice inhibits the metabolism of the terfenadine to its active metabolite (by the cytochrome P450 isoenzyme CYP3A4), so that the parent drug accumulates.[9] Terfenadine, but not its metabolite, causes QTc prolongation. Increased QTc intervals are associated with the development of torsade de pointes and ventricular tachycardia, which is potentially life-threatening.

Fexofenadine is a substrate for P-glycoprotein, and organic anion transporting polypeptide (OATP), and changes in their function may affect fexofenadine uptake. OATP in particular may be inhibited by grapefruit juice, apple juice, and orange juice, so these juices may reduce fexofenadine levels by preventing its absorption.[5]

Importance and management

The interaction between terfenadine and grapefruit juice is established and potentially clinically important. However, the serious cardiac effects may only occur in a small subset of individuals. As of 1996 neither the FDA nor the CSM appeared to have reports of problems in patients that were attributable to the use of antihistamines and grapefruit juice,[8,11] although in 1997 the CSM had one report of a probable interaction with terfenadine.[12] Nevertheless because of the risk of serious cardiotoxicity (however small) it would be prudent for all patients taking terfenadine to avoid grapefruit juice: the UK manufacturer contraindicated concurrent use.[13] The manufacturer of rupatadine advises that grapefruit juice should not be taken simultaneously,[6] and the manufacturer of acrivastine advises caution but notes that there are no data to demonstrate an interaction.[14]

The evidence from healthy subjects suggests that astemizole does not interact with grapefruit juice, but it is possible that individuals predisposed to cardiac conduction disorders are at risk.

Further study is required to determine the clinical relevance, if any, of the reductions in fexofenadine bioavailability in the presence of grapefruit juice, orange juice, and apple juice. Consider this interaction as the cause if fexofenadine seems less effective than expected. Note that the amounts of fruit juice consumed in the study were quite large (1.2 litres). Desloratadine appears to be a safe alternative.

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14. Benadryl Allergy Relief (Acrivastine). McNeil Ltd. UK Summary of product characteristics, March 2008.

Antihistamines + H_2-receptor antagonists

No pharmacokinetic interaction appears to occur when cimetidine is given with cetirizine, desloratadine, ebastine or terfenadine, or when ranitidine is given with terfenadine or chlorphenamine. However, an isolated case report describes torsade de pointes in one patient taking terfenadine with cimetidine. Cimetidine moderately raises hydroxyzine levels and considerably raises loratadine levels. The renal clearance of fexofenadine was reduced by cimetidine in one study.

Clinical evidence

A. Non-sedating antihistamines

(a) Cetirizine

Cetirizine 10 mg was given to 8 patients with chronic urticaria before and after they took **cimetidine** 600 mg every 12 hours for 10 days. The pharmacokinetics of cetirizine were statistically unaltered and its effects remained unchanged.[1]

(b) Desloratadine

In a parallel study in 18 healthy subjects, **cimetidine** 600 mg every 12 hours had little effect on the pharmacokinetics of desloratadine 5 mg daily. The desloratadine AUC was increased by about 20% and its maximum level was increased by about 10%,[2,3] but there was no change in ECG parameters, including the QTc interval.[2]

(c) Ebastine

In a study in 12 healthy subjects, **cimetidine** had no significant effect on the conversion of single 20-mg doses of ebastine to its active metabolite, carebastine, and there was no evidence of sedation or other adverse effects. In this study **cimetidine** was given as 2 g in divided doses the day before the ebastine dose and 400 mg four times daily both on the day of, and the day after, the ebastine dose.[4]

(d) Fexofenadine

In 12 healthy subjects, **cimetidine** 400 mg twice daily for 6 days did not cause any changes in the plasma pharmacokinetics of a single 120-mg dose of fexofenadine. However, the renal clearance of fexofenadine was decreased by 39%.[5]

(e) Loratadine

In a study, 24 healthy subjects were given loratadine 10 mg and **cimetidine** 300 mg every 6 hours, alone and together for 10 days. The AUCs of loratadine and its metabolite were increased by 103% and 6%, respectively, but the safety profile of loratadine (clinical laboratory tests, vital signs and adverse events) was unchanged. Cardiac repolarisation and all other ECG measurements were unaltered, and no sedation or syncope were seen.[6]

(f) Terfenadine

In 12 healthy subjects, **cimetidine** 1.2 g daily for 5 days had no effect on the pharmacokinetics of a single 120-mg dose of terfenadine.[7] Another study in two groups of 6 healthy subjects found that **cimetidine** 600 mg every 12 hours or **ranitidine** 150 mg every 12 hours had no effect on the pharmacokinetics of terfenadine 60 mg every 12 hours. No adverse ECG changes were seen.[8] However, an isolated case report describes a 63-year-old woman who had 8 episodes of syncope (later identified as being due to torsade de pointes) and a convulsion 2 days after starting to take terfenadine 60 mg twice daily and **cimetidine** 400 mg twice daily. She was also taking chlorphenamine and co-proxamol (paracetamol (acetaminophen) and dextropropoxyphene (propoxyphene)).[9]

B. Sedating antihistamines

(a) Chlorphenamine

A study in healthy subjects found that the pharmacokinetics of a single 4-mg dose of chlorphenamine were unaffected by **ranitidine** 75 mg twice daily for 6 days.[10]

(b) Hydroxyzine

In one study, 8 patients with chronic urticaria were given hydroxyzine 25 mg before and after taking **cimetidine** 600 mg every 12 hours for 10 days. The **cimetidine** increased the AUC of hydroxyzine by 33% and also increased its suppression of the wheal and flare response (although this was not statistically significant).[1] A previous study in 7 patients found that **cimetidine** raised serum hydroxyzine levels.[11]

Mechanism

Cimetidine is a non-specific cytochrome P450 isoenzyme inhibitor, but it would seem that in most cases, with the exception of loratadine, these enzyme inhibitory effects do not significantly affect the metabolism of antihistamines. More recent evidence has shown that cimetidine can also affect drug transporter proteins, in particular it may inhibit organic cation transporters. However, it probably does not affect anion transporter proteins since it does not affect the plasma pharmacokinetics of fexofenadine, which is a substrate of these transporters.[5]

Importance and management

There would seem to be no good reason for avoiding the concurrent use of either cetirizine, ebastine, fexofenadine, hydroxyzine, or loratadine with cimetidine, or chlorphenamine with ranitidine, nor would any of the other H_2-receptor antagonists be expected to interact with any of these antihistamines.

The situation with terfenadine and cimetidine is not totally clear because of the isolated case report of toxicity cited here, but currently there is not enough evidence to advise against the concurrent use of these two drugs. The manufacturer of **mizolastine** recommends caution on the concurrent use of cimetidine,[12] with the implication that cimetidine might increase mizolastine levels and prolong the QT interval. This is a cautious approach because a link between mizolastine and cardiac arrhythmias has not been proven.

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Antihistamines + Macrolides

Erythromycin causes terfenadine and astemizole to accumulate in a few individuals, which can prolong the QT interval and lead to life-threatening torsade de pointes arrhythmias. Other macrolides are believed to interact similarly, with the exception of azithromycin and possibly dirithromycin.

Erythromycin markedly raised ebastine levels, which caused a modest prolongation of the QT interval. Erythromycin also raises mizolastine and rupatadine levels, without affecting the QT interval. Acrivastine may interact similarly. The situation with erythromycin and loratadine is unclear as one study found that the combination caused a very slight increase in QT interval.

Both azithromycin and erythromycin raise fexofenadine levels, but this has no effect on the QT interval, or on adverse events. Azelastine, cetirizine, desloratadine, and intranasal levocabastine seem to be free of clinically relevant interactions with macrolides. An isolated case describes torsade de pointes possibly due to the use of spiramycin with mequitazine.

Clinical evidence

The effect of various macrolides on the plasma levels of the non-sedating antihistamines, and their cardiac effects from controlled studies are summarised in 'Table 15.4', (p.672). The subsections below include data from case reports and other studies.

(a) Astemizole

An 87-year-old woman collapsed suddenly in her kitchen 4 days after starting to take astemizole 10 mg daily and **erythromycin** twice daily [dose unknown]. An ECG showed her to be having multiple episodes of torsade de pointes, the longest of which lasted 17 seconds. Her QTc was 720 milliseconds and she was mildly hypokalaemic. She was given a temporary pacemaker and when she was eventually discharged with a normal sinus rhythm, her QTc had fallen to 475 milliseconds.[1] A second case report describes a 30-year-old woman who took

Table 15.4 Summary of the effect of macrolides on the pharmacokinetics and cardiovascular effects of non-sedating antihistamines

Antihistamine	*Macrolide*	*Duration of combined use (days)*	*Subjects*	*Cmax increase*[†]	*AUC increase*	*Effect on QTc*	*Refs*
Astemizole* 30 mg single dose	Dirithromycin 500 mg daily	Single dose of antihistamine	18 healthy subjects	No change	36%	No change	1
Astemizole 200 micrograms/kg daily	Erythromycin 50 mg/kg per day	14	10 patients aged 5 to 12 years			No significant change with Bazett's correction	2
Azelastine* 4 mg twice daily	Erythromycin 500 mg three times daily	7	8 healthy subjects	No change	No change	No change	3
Cetirizine 20 mg daily	Azithromycin 500 mg day 7 and 250 mg daily days 8 to 11	5	14 healthy subjects	No change	No change	No change	4
Cetirizine 20 mg daily	Erythromycin 500 mg three times daily	10	Healthy subjects	No change	No change	No change	3
Cetirizine 10 mg daily in children over 30 kg	Erythromycin 50 mg/kg per day	14	10 patients aged 5 to 12 years	No change	No change	No significant change with Bazett's correction	2
Desloratadine 5 mg daily	Azithromycin 500 mg, then 250 mg daily	5	18 healthy subjects	No change	No change	No change	4
Desloratadine 7.5 mg daily	Erythromycin 500 mg three times daily	10	24 healthy subjects	20%	10%	No change	5
Ebastine 20 mg daily	Erythromycin 2.4 g daily	10	30 healthy subjects	119% Similar changes found for carebastine	164% Similar changes found for carebastine	Mean increase of 19.6 milliseconds	6
Fexofenadine 60 mg twice daily	Azithromycin 500 mg, then 250 mg daily	5	18 healthy subjects	69%	67%	No change	4
Fexofenadine 120 mg twice daily	Erythromycin 500 mg three times daily	7	24 healthy subjects	82%	109%	No change	7
Levocabastine 200 micrograms twice daily intranasal	Erythromycin 333 mg single dose	Single dose of macrolide	38 healthy subjects	No change	No change	No change	8
Loratadine 10 mg daily	Clarithromycin 500 mg twice daily	10	24 healthy subjects	36% loratadine 69% descarbo-ethoxyloratadine	76% loratadine 49% descarbo-ethoxyloratadine	Mean increase of 4 milliseconds. Maximum QTc 439 milliseconds	9
Loratadine 10 mg daily	Erythromcyin 500 mg three times daily	10	24 healthy subjects	53% loratadine 61% descarbo-ethoxyloratadine	40% loratadine 46% descarbo-ethoxyloratadine	No change	10
Loratadine 5 mg daily for children less than 30 kg; 10 mg daily for children greater than or equal to 30 kg	Erythromcyin 50 mg/kg per day	14	10 patients aged 5 to 12 years			No significant change with Bazett's correction	2
Mizolastine 10 mg daily	Erythromycin 1 g twice daily	6	12 healthy subjects	40%	53%	No change	11
Terfenadine* 60 mg twice daily	Azithromycin 500 mg, then 250 mg daily	5	Healthy subjects	Terfenadine undetectable. No change in terfenadine acid metabolite	No change in terfenadine acid metabolite	No change	12, 13

Continued

Table 15.4 Summary of the effect of macrolides on the pharmacokinetics and cardiovascular effects of non-sedating antihistamines (continued)

Antihistamine	*Macrolide*	*Duration of combined use (days)*	*Subjects*	*Cmax increase*[†]	*AUC increase*	*Effect on QTc*	*Refs*
Terfenadine[*] 60 mg twice daily	Clarithromycin 500 mg twice daily	7	6 healthy subjects	4 of 6 subjects with measurable terfenadine levels 110% terfenadine acid metabolite	156% terfenadine acid metabolite	Mean increase of 20 milliseconds	12
Terfenadine[*] 60 mg twice daily	Clarithromycin 500 mg twice daily	5	14 healthy subjects	2 of 14 subjects with measurable terfenadine levels 119% terfenadine acid metabolite	181% terfenadine acid metabolite	Not documented	14
Terfenadine[*] 60 mg twice daily	Dirithromycin 500 mg daily	10	6 healthy subjects	No change in terfenadine acid metabolite	No change in terfenadine acid metabolite	No change	15
Terfenadine[*] 60 mg twice daily	Erythromycin 500 mg three times daily	7	9 subjects	3 of 9 subjects with measurable terfenadine levels 107% terfenadine acid metabolite	170% terfenadine acid metabolite	64 milliseconds in the 3 subjects with measurable terfenadine levels. No significant change in the other 6 subjects	16
Terfenadine[*] 60 mg twice daily	Erythromycin 500 mg three times daily	7	6 healthy subjects	4 of 6 subjects with measurable terfenadine levels 87% terfenadine acid metabolite	109% terfenadine acid metabolite	Mean increase of 34 milliseconds	12
Terfenadine[*] 60 mg twice daily	Erythromycin 333 mg three times daily	7		22% terfenadine acid metabolite	42% terfenadine acid metabolite	Mean increase of 4 to 10 milliseconds with erythromycin alone. No further increase with terfenadine	17, 18
Terfenadine[*] 1 mg/kg twice daily	Erythromycin 50 mg/kg per day	14	10 patients aged 5 to 12 years			No significant change with Bazett's correction	2

[*]Cases of torsade de pointes have been reported for this antihistamine, see Macrolides.
[†]Note that terfenadine levels are normally undetectable.

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Continued

Table 15.4 Summary of the effect of macrolides on the pharmacokinetics and cardiovascular effects of non-sedating antihistamines (continued)

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astemizole 10 mg twice daily with **erythromycin** 250 mg every 6 hours for 3 days and developed syncope, which was shown to be due to torsade de pointes.[2] This patient was known to have congenital long QT syndrome, and had previously experienced syncope when taking astemizole, and therefore in this case an interaction is not established.

(b) Mequitazine

A 21-year-old woman with congenital long QT syndrome had several syncopal attacks, at least one of which was caused by torsade de pointes. This was attributed to the concurrent use of mequitazine and **spiramycin** over a 2-day period. The problem resolved when the drugs were withdrawn.[3]

(c) Rupatadine

1. Azithromycin. In a study, 24 healthy subjects were given rupatadine 10 mg daily for 6 days with azithromycin, 500 mg on day 2 and 250 mg daily thereafter. There were no clinically significant changes in the pharmacokinetics of rupatadine or its metabolites.[4]

2. Erythromycin. The systemic exposure to rupatadine was increased two- to threefold when rupatadine 20 mg was taken with erythromycin 500 mg three times daily for 7 days. There were no clinically relevant changes in the QT interval, vital signs or adverse effects.[5]

(d) Terfenadine

1. Erythromycin. An 18-year-old girl who was taking terfenadine 60 mg twice daily and erythromycin 250 mg every 6 hours, fainted while at school and, when later hospitalised, was seen to have repeated episodes of ventricular tachycardia and ventricular fibrillation requiring resuscitation. Later she was also noted to have torsade de pointes. Her QTc interval was found to be prolonged at 630 milliseconds. The drugs were withdrawn and 9 days later, after a period in intensive care, she was discharged symptom-free with a normal QTc interval.[6] A further case describes a 63-year-old man who had taken terfenadine 240 mg each day and erythromycin 2 g each day for 3 days, and subsequently experienced three syncopal episodes in one day. An ECG showed a prolonged QT interval and torsade de pointes, which resolved after intravenous magnesium sulphate was given.[7] In contrast, a retrospective report found no documented cardiac adverse events in 92 patients who had received erythromycin and terfenadine.[8]

2. Troleandomycin. A woman taking terfenadine 60 mg three times daily developed torsade de pointes and a prolonged QTc interval when troleandomycin 500 mg three times daily was added. She recovered when both were stopped, but again developed a significantly prolonged QTc interval when both were restarted.[9]

Mechanism

Some macrolides (particularly erythromycin and clarithromycin) appear to reduce the metabolism of terfenadine and astemizole by inhibition of the cytochrome P450 isoenzyme CYP3A4.[10,11] High serum levels of astemizole and terfenadine cause a prolongation of the QT interval and may precipitate the development of torsade de pointes, see 'Table 15.2', (p.664). The risk of cardiac arrhythmias with other non-sedating antihistamines appears to be non-existent or very much lower (see 'Table 15.2', (p.664)), so any pharmacokinetic interactions do not result in clinically relevant cardiac toxicity. In fact, studies have shown that fexofenadine in overdose,[12,13] and mizolastine at four times the recommended dose[14] do not affect the QT interval. However, some questions remain about mizolastine and ebastine. Erythromycin may increase the absorption and decrease the biliary secretion of fexofenadine[13] by an effect on drug transporters: this leads to an increase in fexofenadine levels. *In vitro* studies have suggested that rupatadine is mainly metabolised by CYP3A4.[15]

Importance and management

The interactions of **terfenadine** with erythromycin, clarithromycin, and troleandomycin; and **astemizole** with erythromycin are established, clinically important and potentially hazardous. From the reports above it does seem that only a very few individuals develop a clinically important adverse interaction with these macrolides, but identifying them in advance is not often practical or possible. Because of the unpredictability and potential severity of this interaction, the FDA in the US,[8] the CSM in the UK,[16] and the manufacturers of terfenadine[17] and astemizole[18] contraindicated macrolides in anyone taking terfenadine or astemizole. The only exception to this was azithromycin with astemizole.[18] The manufacturer of terfenadine extended this contraindication to the concurrent use of topical macrolides.[17]

The manufacturer of **mizolastine** also contraindicates the concurrent use of the macrolides,[19] although evidence of a clinically significant interaction appears to be lacking. Erythromycin markedly raises **ebastine** levels causing a modest increase in QT interval. The manufacturer of ebastine advises against concurrent use of the macrolides erythromycin, clarithromycin and josamycin.[20] The manufacturer of **rupatadine**[15] advises that it should be used with caution with erythromycin, and other inhibitors of CYP3A4, which would include a number of the macrolides. Because there are no data on **acrivastine** with erythromycin, the manufacturer advises caution.[21] Erythromycin also raises **loratadine** levels, which caused a very slight increase in QTc interval in one study. However, no special precautions appear to have been recommended for the use of loratadine with macrolides; high levels of loratadine are usually considered to be safe.

Fexofenadine levels are raised by both azithromycin and erythromycin but because this does not result in adverse cardiac effects concurrent use is considered safe. **Azelastine**, **cetirizine** (and therefore probably its isomer **levocetirizine**) **desloratadine** and **levocabastine** seem to be free from clinically significant pharmacokinetic interactions, and have no cardiac effects, and so may therefore provide suitable alternatives if a non-sedating antihistamine is needed in a patient taking macrolides.

The isolated case with **mequitazine** is unlikely to be of general importance, as this sedating antihistamine is not usually associated with causing ventricular arrhythmias.

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13. Telfast (Fexofenadine hydrochloride). Sanofi-Aventis. UK Summary of product characteristics, June 2008.

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20. Kestin (Ebastine). Almirall SAS. French prescribing information, August 2003.
21. Benadryl Allergy Relief (Acrivastine). McNeil Ltd. UK Summary of product characteristics, March 2008.

Antihistamines + Nefazodone

Nefazodone inhibits the metabolism of terfenadine and thereby prolongs the QT interval. Astemizole may interact similarly. There is also some evidence that the combination of nefazodone and loratadine increases the QT interval, although to a lesser extent than terfenadine.

Clinical evidence, mechanism, importance and management

(a) Astemizole

The manufacturers of nefazodone and astemizole noted that an *in vitro* study suggests that nefazodone may increase astemizole levels. The UK manufacturer contraindicated concurrent use.[1,2] This seems prudent because raised levels of astemizole with other inhibitors of the cytochrome P450 isoenzyme CYP3A4 such as the macrolides (see 'Antihistamines + Macrolides', p.671), have been rarely associated with life-threatening torsade de pointes.

(b) Loratadine

A randomised, placebo-controlled study in healthy subjects found that when they were given nefazodone 300 mg twice daily with loratadine 20 mg daily, the loratadine AUC was increased by 39%. Similarly, the QTc interval was increased by 21.6 milliseconds by the combination, which was about half the increase seen with terfenadine 60 mg twice daily given with the same dose of nefazodone. Neither nefazodone or loratadine alone prolonged the QTc interval.[3] The findings for loratadine in this study were unexpected, as this antihistamine was considered to have no clinically relevant effect on the QT interval (but see also 'Table 15.2', (p.664)). The use of the Bazett formula to calculate QTc has been questioned,[4] but this is the most commonly used formula, and any overestimation would also apply to terfenadine. This appears to be the only study to have directly compared loratadine with terfenadine, and although it shows that loratadine at twice the recommended dose has half the QT-prolonging effect of terfenadine (at the maximum recommended dose), it nevertheless raises questions about the cardiac safety of loratadine.[4,5] Further study is needed.

(c) Terfenadine

In a randomised, placebo-controlled study, healthy subjects were given nefazodone 300 mg twice daily and terfenadine 60 mg twice daily, alone and in combination. Nefazodone increased the AUC of terfenadine about fivefold, which was associated with a mean increase in the QTc interval of 42.4 milliseconds. This was considered to result in a clinically significant increase in the risk of torsade de pointes.[3] This effect probably occurred because nefazodone inhibits the cytochrome P450 isoenzyme by which terfenadine is metabolised. Both nefazodone and terfenadine have largely been withdrawn from the market, but the combination was commonly contraindicated,[1,6] and it has been suggested that this contraindication explains the lack of clinical reports.[7]

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2. Hismanal (Astemizole). Janssen-Cilag Ltd. UK Summary of product characteristics, June 1998.
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Antihistamines + Protease inhibitors

Nelfinavir markedly increases terfenadine levels, which is expected to increase the risk of QT prolongation and torsade de pointes arrhythmias. Other protease inhibitors are predicted to interact similarly with terfenadine, astemizole and mizolastine. Ritonavir modestly increases cetirizine levels. Ritonavir and ritonavir-boosted lopinavir raise the levels of fexofenadine. Nelfinavir and hydroxyzine have been used together without adverse effects.

Clinical evidence, mechanism, importance and management

(a) Astemizole

Protease inhibitors are inhibitors of the cytochrome P450 isoenzyme CYP3A4, by which astemizole is metabolised. On the basis of the interaction of astemizole with other CYP3A4 inhibitors, such as the 'azoles', (p.665), the concurrent use of astemizole with any protease inhibitor was contraindicated.[1] This seems a sensible precaution.

(b) Cetirizine

In a study in 16 healthy subjects the concurrent use of cetirizine 10 mg daily and **ritonavir** 600 mg twice daily for 4 days (after reaching steady-state **ritonavir** levels), increased the AUC of cetirizine by 42% with a slight 9% increase in maximum plasma levels. It was suggested that **ritonavir** may have decreased the renal excretion of cetirizine. The increase in cetirizine levels was not considered to be clinically relevant. **Ritonavir** pharmacokinetics were minimally affected by cetirizine.[2]

(c) Fexofenadine

In a study, 12 healthy subjects took **ritonavir** in increasing doses up to 400 mg twice daily for 2 weeks, followed by a single 60-mg dose of fexofenadine. The maximum plasma levels of fexofenadine were increased by 60% and its AUC was increased 2.8-fold after the subjects took **ritonavir** 200 mg three times a day for one day, but after steady-state was attained, **ritonavir** increased the AUC of fexofenadine by 40%, and the increase in its plasma levels was not significant.[3] Similarly in a study in 8 healthy subjects the median AUC and maximum plasma levels of fexofenadine were increased 2.7-fold and 2.2-fold, respectively by **ritonavir**.[4] An extension to this study in 16 healthy subjects who took a single 120-mg dose of fexofenadine before, and after taking **ritonavir**-boosted **lopinavir** 100/400 mg daily for 11 days found that the median AUC and maximum plasma level of fexofenadine were increased 3.5-fold and 3-fold, respectively. The pharmacokinetics of fexofenadine were evaluated in 8 of the subjects in this study after a single dose of **ritonavir**-boosted **lopinavir**: the increase in median AUC and maximum plasma level was 4-fold and 3.8-fold, respectively.[4]

However, the marked increases in fexofenadine levels seen in studies with 'erythromycin', (p.671), and 'ketoconazole', (p.665), did not increase the adverse effects of fexofenadine and were not associated with any prolongation of the QT interval. This suggests that a clinically relevant interaction between **ritonavir** or **ritonavir**-boosted **lopinavir** and fexofenadine is unlikely.

(d) Hydroxyzine

A report describes the uneventful use of hydroxyzine in 10 HIV-positive children, who had developed a rash thought to be related to **nelfinavir** use.[5]

(e) Mizolastine

The manufacturers of mizolastine suggest that, because of the effects of ketoconazole and erythromycin, which raise mizolastine levels, the concurrent use of other potent inhibitors of the cytochrome P450 isoenzyme CYP3A4 with mizolastine should be approached with caution.[6] Although not specifically named, this would be expected to include the protease inhibitors.

(f) Terfenadine

Nelfinavir 750 mg every 8 hours for 5 days raised the levels of a single 60-mg dose of terfenadine from less than 5 nanograms/mL to a range of 5 to 15 nanograms/mL. The pharmacokinetics of **nelfinavir** were unaffected.[7] This rise in terfenadine levels is predicted to prolong the QT interval, and to increase the risk of torsade de pointes. On the basis of what is known about interactions with other inhibitors of the cytochrome P450 isoenzyme CYP3A4 such as the 'azoles', (p.665), all protease inhibitors (which inhibit CYP3A4 to a greater or lesser extent) are predicted to raise

terfenadine levels. Although terfenadine has been widely withdrawn from the market, concurrent use with protease inhibitors was contraindicated.[8] Because of the seriousness of this reaction, and the fact that it is not possible to predict which individuals will be affected, this seems a sensible precaution.

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Antihistamines + Quinolones

Studies in healthy subjects found that there was a small additive effect on the QT interval when terfenadine was given with sparfloxacin.

Clinical evidence, mechanism, importance and management

In a single-dose, placebo-controlled study in 8 healthy subjects, **sparfloxacin** 400 mg increased the QT interval by 14 milliseconds, **terfenadine** 60 mg increased the QT interval by 7.5 milliseconds (not statistically significant), and the combination caused an increase of 24.7 milliseconds. The effects of the combination in this study were shown to be purely additive.[1]

Similarly, in a placebo-controlled study 22 patients were given **sparfloxacin** 400 mg on day one and 200 mg on days 2 to 4 with **terfenadine** 60 mg twice daily for 7 doses. The increase in the QT interval when the two drugs were given together was additive, and no pharmacokinetic interaction was found.[2]

As the effects of therapeutic doses of **terfenadine** on the QT interval are minimal, any additional effect with **sparfloxacin** would be small. Nevertheless, because torsade de pointes can cause sudden death, the combination of two drugs with the potential to prolong the QT interval is generally considered to be contraindicated (see 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290). Note that the UK manufacturer of **terfenadine** specifically contraindicated **sparfloxacin**.[3]

If an antihistamine is required in a patient taking **sparfloxacin**, one that has no effect on the QT interval should be used, for example, **cetirizine**, see 'Table 15.2', (p.664). Other quinolones that cause QT prolongation include **gatifloxacin** and **moxifloxacin**, see 'Table 9.2', (p.290), and it would also be prudent to avoid use of antihistamines that prolong the QT interval (e.g. **astemizole** and **terfenadine**) with these quinolones.

1. Akhtar M, Saha N, Roy A, Pillai KK. Effect of sparfloxacin and terfenadine combination on QT-intervals at various RR-intervals. *Indian J Pharmacol* (2002) 34, 264–8.
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Antihistamines + SSRIs

Two isolated reports describe cardiotoxicity, which was attributed to the concurrent use of terfenadine and fluoxetine, although other evidence suggests that an interaction is unlikely. Terfenadine does not appear to interact with paroxetine or sertraline. A case report describes prolonged delirium in a patient who took an overdose of promethazine with fluvoxamine. There does not appear to be a significant interaction between desloratadine and fluoxetine.

Clinical evidence

(a) Desloratadine

In a placebo-controlled study in healthy subjects, the concurrent use of desloratadine 5 mg daily and **fluoxetine** 20 mg daily for 7 days (after attainment of **fluoxetine** steady-state) had no clinically relevant effects on the pharmacokinetics of either drug (changes in maximum levels and AUC were less than 15%). There was no change in ECG parameters including the QTc interval, and the combination did not increase the incidence of adverse effects.[1]

(b) Promethazine

A case report describes a 14-year-old girl taking **fluvoxamine** 150 mg daily who took an overdose of promethazine 1150 mg and cyproheptadine 200 mg. She developed an anticholinergic delirium, which lasted for 6 days. The authors suggest that this effect was prolonged because both promethazine and **fluvoxamine** are inhibitors and metabolites of CYP2D6, and thus the clearance of both drugs may have been impaired. However, other factors such as her small size, and the use of olanzapine to control the delirium may have been contributing factors.[2]

(c) Terfenadine

1. Fluoxetine. A 41-year-old man with no previous history of heart disease awoke one night short of breath, with a sensation of his heart missing beats and beating irregularly. He also experienced orthostatic hypotension on a number of occasions. However, a later ECG showed a normal sinus rhythm. He was taking daily doses of terfenadine 120 mg, fluoxetine 20 mg (started a month previously), ibuprofen 2.4 g, misoprostol 400 micrograms, *Midrin* (paracetamol (acetaminophen), dichloralphenazone, isometheptene mucate) and ranitidine 300 mg. This reaction was attributed to an interaction between fluoxetine and terfenadine. However, a few days after stopping the terfenadine, and 12 days after this episode, his cardiac rhythm as recorded by a 24-hour Holter monitor showed some minor abnormalities (intermittent sinus tachycardia, isolated premature beats), although nothing approaching the previous alarming episode.[3] A woman taking several drugs (topical aciclovir, beclometasone, pseudoephedrine, ibuprofen) had a prolonged QTc interval of 550 milliseconds 2 weeks after starting to take terfenadine and fluoxetine, but she remained asymptomatic. Within a week of stopping terfenadine her QTc interval had returned to normal.[4]

In contrast, 12 healthy subjects who were given a single 60-mg dose of terfenadine before and after taking fluoxetine 60 mg daily for 8 days showed no significant changes in the pharmacokinetics of terfenadine or its acid metabolite.[5]

2. Paroxetine. A two-period crossover study in 11 healthy subjects given terfenadine 60 mg twice daily found that paroxetine 20 mg daily for 8 days had no effect on the AUC of terfenadine or the QTc interval. A small, clinically unimportant reduction in the levels of carboxyterfenadine was seen. It was concluded that there is no clinically relevant interaction between terfenadine and paroxetine.[6]

Mechanism

Not understood. Terfenadine is metabolised by the cytochrome P450 isoenzyme CYP3A4, but fluoxetine usually has only weak effects on this isoenzyme. The case reports suggest that this may be significant in some patients.

Importance and management

The interaction between the SSRIs and terfenadine is not adequately established, and there seems to be no evidence regarding interactions between the SSRIs and astemizole, although it is possible that the contraindication with astemizole contributed to minimal usage of the combination and therefore a lack of reported interactions. In addition to fluoxetine and paroxetine, the manufacturers of terfenadine listed **fluvoxamine** and **citalopram** as drugs that were expected to increase terfenadine serum levels and therefore concurrent use was contraindicated.[7] Although the CSM in the UK initially stated that terfenadine should not be used with **sertraline**, they subsequently reviewed the data and suggested that an interaction is unlikely.[8]

There seems to be no reason to suspect a pharmacokinetic interaction between the SSRIs and other antihistamines, and this has been demonstrated with desloratadine and fluoxetine.

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6. Martin DE, Zussman BD, Everitt DE, Benincosa LJ, Etheredge RC, Jorkasky DK. Paroxetine does not affect the cardiac safety and pharmacokinetics of terfenadine in healthy adult men. *J Clin Psychopharmacol* (1997) 17, 451–9.
7. Histafen (Terfenadine). Approved Prescription Services Ltd. UK Summary of product characteristics, December 1999.
8. Committee on Safety of Medicines/Medicines Control Agency. Sertraline and terfenadine. *Current Problems* (1998) 24, 4.

Antihistamines + Statins

Atorvastatin does not appear to alter the pharmacokinetics of terfenadine. The manufacturers suggest that rupatadine could exacerbate the muscle toxicity caused by the statins.

Clinical evidence, mechanism, importance and management

(a) Rupatadine

The UK manufacturer of rupatadine[1] reports that in clinical studies asymptomatic rises in creatine phosphokinase levels have occurred. As rupatadine is a substrate of the cytochrome P450 isoenzyme CYP3A4, by which some of the statins are also metabolised, the manufacturer advises caution on concurrent use, on the basis that the risk of interactions is unknown. However, it seems unlikely that a pharmacokinetic interaction will result in muscle disorders, because muscle disorders usually develop because of a several fold rise in the levels of the statin, which is unlikely to occur as a result of competition for metabolism by the same isoenzyme. For more information on the metabolism of individual statins, and monitoring for muscle disorders, see under 'Lipid regulating drugs', (p.1313)).

(b) Terfenadine

A group of healthy subjects were given a single 120-mg dose of terfenadine on day 8 of a 10-day course of atorvastatin 80 mg daily. It was found that atorvastatin caused some small to moderate changes in the pharmacokinetics of terfenadine and its metabolite fexofenadine (AUC increased by 35% and decreased by 2%, respectively, maximum serum levels decreased by 8% and decreased by 16%, respectively), none of which reached statistical significance. More importantly there were no changes in the QTc interval, which indicates that atorvastatin does not increase the cardiotoxicity of terfenadine.[2] There would therefore appear to be no reason for avoiding concurrent use.

1. Rupafin (Rupatadine fumarate). GlaxoSmithKline UK. UK Summary of product characteristics, December 2007.
2. Stern RH, Smithers JA, Olson SC. Atorvastatin does not produce a clinically significant effect on the pharmacokinetics of terfenadine. *J Clin Pharmacol* (1998) 38, 753–7.

Antihistamines + Terbinafine

Terbinafine does not interact with astemizole or terfenadine to a clinically relevant extent.

Clinical evidence, mechanism, importance and management

In a large-scale post-marketing survey of 25,884 patients taking terbinafine, over 40% were taking at least one other drug. From amongst this group, an unknown number of patients were taking **astemizole** or **terfenadine**. No adverse interactions were reported.[1] A crossover study in 26 healthy subjects given terbinafine 250 mg daily or placebo, with **terfenadine** 60 mg twice daily for 7 days, found that terbinafine reduced the trough levels of terfenadine acid metabolite by about 20% on the last day of concurrent use. Other **terfenadine** acid metabolite pharmacokinetic parameters were not affected. The AUC, and peak and trough plasma levels of terbinafine were increased by about 16%, 7%, and 22%, respectively, after 7 days of concurrent use. Although the incidence of ECG abnormalities was not significantly higher in any group, a 10% prolongation of the QT interval was found in those receiving **terfenadine** either alone or with terbinafine. However, concurrent use was well-tolerated and it was concluded that terbinafine could safely be given with **terfenadine**.[2]

1. Hall M, Monka C, Krupp P, O'Sullivan D. Safety of oral terbinafine. Results of a postmarketing surveillance study in 25 884 patients. *Arch Dermatol* (1997) 133, 1213–19.
2. Robbins B, Chang C-T, Cramer JA, Garreffa S, Hafkin B, Hunt TL, Meligeni J. Safe coadministration of terbinafine and terfenadine: a placebo-controlled crossover study of pharmacokinetic and pharmacodynamic interactions in healthy volunteers. *Clin Pharmacol Ther* (1996) 59, 275–83.

Antihistamines; Ocular + Miscellaneous

No specific interaction studies have been performed with eye-drop formulations of the antihistamines azelastine, emedastine, epinastine, or olopatadine. However, interactions are not anticipated because very little drug is expected to reach the systemic circulation.

Clinical evidence, mechanism, importance and management

The UK manufacturer of **azelastine** eye drops notes that interaction studies with high oral doses of **azelastine** bear no relevance to the eye drops, as systemic levels are only in the picogram range after administration of eye drops.[1] Similarly, the manufacturer of **epinastine** eye drops notes that no drug interactions are anticipated as systemic **epinastine** levels are extremely low after ocular use. They note that **epinastine** is also excreted mostly unchanged.[2] The manufacturer of **olopatadine** eye drops notes that *in vitro* studies showed that it was not an inhibitor of the common cytochrome P450 isoenzymes.[3] No drug interactions would be anticipated between these, or any other, antihistamine eye drops and systemically administered drugs.

The manufacturer of **emedastine** eye drops notes that an interval of 10 minutes should be allowed after the administration of the eye drops and other ophthalmically administered medicines,[4] which is good practice for any ocular drugs.

1. Optilast Eye Drops (Azelastine). Meda Pharmaceuticals. UK Summary of product characteristics, July 2008.
2. Relestat (Epinastine). Allergan Ltd. UK Summary of product characteristics, October 2007.
3. Opatanol (Olopatadine). Alcon Laboratories (UK) Ltd. UK Summary of product characteristics, August 2007.
4. Emadine (Emedastine). Alcon Laboratories (UK) Ltd. UK Summary of product characteristics, February 2009.

Antihistamines; Astemizole + Quinine

Quinine causes a marked but transient increase in plasma astemizole levels, which potentially increases the risk of cardiac arrhythmias. Three case reports confirm that this is a clinically important interaction.

Clinical evidence

In a study, 12 healthy subjects were given astemizole 30 mg daily for 4 days followed by 10 mg daily for the next 20 days. The steady-state pharmacokinetics of astemizole were then examined after the subjects took quinine 20 mg every 4 hours for 12 hours (a total of 80 mg quinine), and after a single 430-mg dose of quinine. The smaller dose of quinine caused only a slight increase in the maximum plasma astemizole levels and AUC, but the larger single dose of quinine resulted in a transient threefold increase in both the maximum plasma levels and AUC of both astemizole and particularly desmethylastemizole, the metabolite of astemizole.[1]

A patient who had been taking astemizole 10 mg daily for 10 months with fluoxetine, alprazolam, isradipine, and diuretics with potassium had a syncopal episode one hour after taking the first dose of quinine sulphate 260 mg for leg cramp. The ECG showed recurrent episodes of torsade de pointes with a QT interval of greater than 680 milliseconds. The only electrolyte abnormality was slight hypomagnesaemia. Intravenous magnesium was given and the patient's QT interval shortened to 420 milliseconds over 3 days.[2] The manufacturers have on record two other case reports[3] of cardiac arrhythmias possibly attributable to an interaction between astemizole and quinine.

Mechanism

Uncertain. One suggestion is that the interaction is not primarily due to inhibition of the metabolism of astemizole by the quinine, but rather to a

transient quinine-induced displacement of both astemizole and its metabolite from its tissue binding sites.[1] Note that the desmethyl metabolite of astemizole causes QTc prolongation.

Importance and management

Information is very limited, but on the basis of the evidence cited above the manufacturer of astemizole contraindicated the concurrent use of quinine in order to avoid the risk of cardiac arrhythmias.[4] The case report that is cited here confirms that this is a potentially clinically hazardous drug combination.[2]

The larger single 430-mg dose of quinine used in the study approached the dose used for the treatment of malaria, whereas the smaller dose of 80 mg was equivalent to the amount contained in 2 litres of a quinine-containing soft drink.[1] There would therefore appear to be no reason for those taking astemizole to avoid moderate quantities of quinine-containing drinks. For more information about QT prolongation, see 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290.

1. Janssen-Cilag Ltd, Data on file (Study AST-BEL-7 + Amendment) 1995.
2. Martin ES, Rogalski K, Black JN. Quinine may trigger torsades de pointes during astemizole therapy. *Pacing Clin Electrophysiol* (1997) 20, 2024–5.
3. Janssen-Cilag Ltd. Personal Communication, May 1997.
4. Hismanal (Astemizole). Janssen-Cilag Ltd. UK Summary of product characteristics, June 1998.

Antihistamines; Cinnarizine + Phenylpropanolamine

In 12 healthy subjects, phenylpropanolamine 50 mg counteracted the mild sedation caused by cinnarizine 25 or 50 mg, and improved the performance of some skills related to driving.[1]

1. Savolainen K, Mattila MJ, Mattila ME. Actions and interactions of cinnarizine and phenylpropanolamine on human psychomotor performance. *Curr Ther Res* (1992) 52, 160–8.

Antihistamines; Fexofenadine + Antacids or Omeprazole

An aluminium/magnesium hydroxide-containing antacid modestly reduced fexofenadine levels in one study. Fexofenadine does not appear to affect the pharmacokinetics of omeprazole.

Clinical evidence, mechanism, importance and management

(a) Antacids

The manufacturer[1] notes that when a single 120-mg dose of fexofenadine was given within 15 minutes of an **aluminium/magnesium hydroxide** antacid (*Maalox*), the fexofenadine AUC was decreased by 41% and the maximum level was decreased by 43%. Although the effect of these reductions on possible efficacy has not been assessed, the manufacturer recommends that it is advisable to leave 2 hours between the administration of fexofenadine and antacids containing **aluminium** and **magnesium hydroxide**.[2]

(b) Omeprazole

A study in 8 healthy subjects found that fexofenadine 60 mg twice daily for 6 days had no effect on the pharmacokinetics of a single 40-mg dose of omeprazole given on day 6. In addition, there was no significant change in the pharmacokinetics of the metabolites of omeprazole.[3]

1. Allegra (Fexofenadine hydrochloride). Sanofi-Aventis US LLC. US Prescribing Information, July 2007.
2. Telfast (Fexofenadine hydrochloride). Sanofi-Aventis. UK Summary of product characteristics, June 2008.
3. Takahata T, Yasui-Furukori N, Yoshiya G, Uno T, Sugawara K, Tateishi T. Fexofenadine does not affect omeprazole pharmacokinetics: both are putative P-glycoprotein substrates. *Basic Clin Pharmacol Toxicol* (2004) 94, 252–6.

Antihistamines; Fexofenadine + Probenecid

Probenecid reduces the renal clearance of fexofenadine and raises its AUC.

Clinical evidence

In a study, 8 healthy subjects and 8 patients with cystic fibrosis were given two doses of probenecid 1 g, 12 hours apart, with a single 180-mg dose of fexofenadine one hour after the first dose of probenecid. The AUC of fexofenadine was increased by 53% and its renal clearance was reduced by 70% by probenecid.[1] Similarly, a further study in 12 healthy subjects who took a single 120-mg dose of fexofenadine alone, or after probenecid 1 g twice daily for 6 days found the renal clearance of fexofenadine was reduced by 63% and the AUC of fexofenadine was increased by 50% by probenecid. There was marked interindividual variation in the findings.[2]

Mechanism

An *in vitro* study has demonstrated that fexofenadine is a substrate for the human organic anion transporter-3 (OAT3), which probenecid inhibits. Therefore concurrent use results in decreased clearance and an increase in exposure to fexofenadine.[3]

Importance and management

Evidence for an interaction between fexofenadine and probenecid appears to be limited to these two studies, neither of which found that probenecid increased the adverse effects of fexofenadine. Note that much greater increases in the exposure to fexofenadine are not considered harmful (see 'Antihistamines + Azoles', p.665). Therefore this interaction is unlikely to be clinically significant.

1. Liu S, Beringer PM, Hidayat L, Rao AP, Louie S, Burckart GJ, Shapiro B. Probenecid, but not cystic fibrosis, alters the total and renal clearance of fexofenadine. J Clin Pharmacol (2008) 48, 957–65.
2. Yasui-Furukori N, Uno T, Sugawara K, Tateishi T. Different effects of three transporting inhibitors, verapamil, cimetidine, and probenecid, on fexofenadine pharmacokinetics. *Clin Pharmacol Ther* (2005) 77, 17–23.
3. Tahara H, Kusuhara H, Maeda K, Koepsell H, Fuse E, Sugiyama Y. Inhibition of OAT3-mediated renal uptake as a mechanism for drug-drug interaction between fexofenadine and probenecid. *Drug Metab Dispos* (2006) 34, 743–7.

Antihistamines; Fexofenadine + Rifampicin (Rifampin)

Rifampicin increases the oral clearance of fexofenadine.

Clinical evidence, mechanism, importance and management

A single 60-mg dose of fexofenadine was given to 24 healthy subjects 2 days before and on the last day of a 6-day course of rifampicin 600 mg daily. The oral clearance of fexofenadine was increased 1.3- to 5.3-fold, with no effect on renal clearance or half-life. This was thought to be due to the effect of rifampicin on P-glycoprotein, which is involved in the uptake of fexofenadine.[1] The clinical significance of this interaction is unclear, but until more is known it would seem prudent to monitor the efficacy of fexofenadine if it is given in combination with rifampicin.

1. Hamman MA, Bruce MA, Haehner-Daniels BD, Hall SD. The effect of rifampin administration on the disposition of fexofenadine. *Clin Pharmacol Ther* (2001) 69, 114–21.

Antihistamines; Fexofenadine + St John's wort (*Hypericum perforatum*)

Pretreatment with St John's wort (*Hypericum perforatum*) had no clinically relevant effect on the plasma levels of single-dose fexofenadine in one study, but markedly reduced fexofenadine levels in two others.

Clinical evidence

In a study in 12 healthy subjects a single 900-mg dose of St John's wort (*Hypericum perforatum*) increased the maximum plasma level and AUC of a single 60-mg dose of fexofenadine by 45% and 31%, respectively. Conversely, St John's wort 300 mg three times daily for 14 days caused a slight 5 to 10% decrease in the maximum level and AUC of a single 60-mg dose of fexofenadine in the same subjects.[1] In contrast, in another study in healthy subjects, 12 days of pretreatment with St John's wort increased the oral clearance of a single dose of fexofenadine by about 60%.[2] Similarly, a study in 30 healthy subjects found that 10 days of pretreatment with St

John's wort 300 mg 3 times daily, almost doubled the oral clearance of a single 60-mg dose of fexofenadine.[3]

Mechanism

In these studies St John's wort was thought to be interacting via its effects on P-glycoprotein.

Importance and management

The findings from these multiple-dose studies suggest that St John's wort either has no clinically relevant effect on fexofenadine, or that a decrease occurs that is possibly clinically important. It may be prudent to monitor closely for signs of reduced fexofenadine efficacy in a patient taking regular St John's wort, and if this is the case, consider St John's wort as a possible cause. Further study is needed.

1. Wang Z, Hamman MA, Huang S-M, Lesko LJ, Hall SD. Effect of St John's wort on the pharmacokinetics of fexofenadine. *Clin Pharmacol Ther* (2002) 71, 414–20.
2. Dresser GK, Schwarz UI, Wilkinson GR, Kim RB. Coordinate induction of both cytochrome P4503A and MDR1 by St John's wort in healthy subjects. *Clin Pharmacol Ther* (2003) 73, 41–50.
3. Xie R, Tan LH, Polasek EC, Hong C, Teillol-Foo M, Gordi T, Sharma A, Nickens DJ, Arakawa T, Knuth DW, Antal EJ. CYP3A and P-glycoprotein activity induction with St. John's wort in healthy volunteers from 6 ethnic populations. *J Clin Pharmacol* (2005) 45, 352–6.

Antihistamines; Flunarizine + Antiepileptics

Limited evidence suggests that phenytoin and carbamazepine can reduce serum flunarizine levels. Flunarizine does not appear to alter phenytoin or carbamazepine levels.

Clinical evidence, mechanism, importance and management

A study found that flunarizine levels were lower in patients taking multiple antiepileptics than in those taking only one antiepileptic (statistically significant only for flunarizine 10 mg). The antiepileptics taken were **carbamazepine**, **phenytoin**, and **sodium valproate**. Flunarizine did not affect the serum levels of these antiepileptics.[1] In another study, involving 12 patients, four of whom were taking **phenytoin**, four **carbamazepine** and four both **phenytoin** and **carbamazepine**, there was no difference in the pharmacokinetics of a single 30-mg dose of flunarizine or of multiple-dose flunarizine between the three groups. However, the apparent clearance values of flunarizine were several fold greater in these patients than in historical data from healthy subjects. There were no differences identified in the mean steady-state levels of the antiepileptics before and during flunarizine use.[2]

Although not conclusive, these data suggest that enzyme-inducing antiepileptics increase the metabolism of flunarizine and may reduce its steady-state serum level. There would seem to be no reason for avoiding concurrent use, but the outcome should be monitored as an increase in the dose of flunarizine may possibly be required.

1. Binnie CD, de Beukelaar F, Meijer JWA, Meinardi H, Overweg J, Wauquier A, van Wieringen A. Open dose-ranging trial of flunarizine as add-on therapy in epilepsy. *Epilepsia* (1985) 26, 424–8.
2. Kapetanovic IM, Torchin CD, Kupferberg HJ, Treiman DM, Di Giorgio C, Barber K, Norton L, Lau M, Whitley L, Cereghino JJ. Pharmacokinetic profile of flunarizine after single and multiple dosing in epileptic patients receiving comedication. *Epilepsia* (1988) 29, 770–4.

Antihistamines; Meclozine + Metaxalone

A case report describes a patient who experienced auditory hallucinations when he took the maximum doses of both meclozine and metaxalone together. This effect disappeared when the drugs were stopped, but recurred on re-challenge. Note that this is an isolated report, and its clinical significance is unclear.[1]

1. Kuykendall JR, Rhodes RS. Auditory hallucinations elicited by combined meclizine and metaxalone use at bedtime. *Ann Pharmacother* (2004) 38, 1968–9.

Antihistamines; Terfenadine + Paracetamol (Acetaminophen)

An isolated report describes the development of torsade de pointes in an elderly man taking very large doses of paracetamol (acetaminophen) and amitriptyline when he began to take terfenadine.

Clinical evidence, mechanism, importance and management

An 86-year-old man taking **amitriptyline** 25 mg at night, prednisone 3 mg daily and excessive amounts of paracetamol (up to 1 g every 2 hours over a 6-month period) developed breathlessness and bradycardia shortly after starting to take terfenadine 60 mg twice daily. In hospital he became unconscious and was initially pulseless but recovered spontaneously. An ECG showed that he had AV block and a prolonged QT interval, which resulted in runs of self-limiting torsade de pointes.[1] The reasons for this reaction are not known, but a suggested explanation is that overdosage with paracetamol produced large amounts of a metabolite (*N*-acetyl-p-benzoquinoneimine). This metabolite could have inhibited the metabolism of the terfenadine by the cytochrome P450 isoenzyme CYP3A4, thereby resulting in terfenadine accumulation and the development of its cardiotoxic effects.[1] The **amitriptyline** may additionally have had some part to play because it can also (although rarely) cause torsade de pointes.

This is an isolated case and unlikely to be of general importance. There would seem to be little reason on the basis of this report for patients on terfenadine to avoid normal therapeutic doses of paracetamol. There appear to be no other reports of this interaction.

1. Matsis PP, Easthope RN. Torsades de pointes ventricular tachycardia associated with terfenadine and paracetamol self medication. *N Z Med J* (1994) 107, 402–403.

Antihistamines; Terfenadine + Venlafaxine

Venlafaxine does not appear to affect the pharmacokinetics of terfenadine to a clinically relevant extent.

Clinical evidence, mechanism, importance and management

A study in 24 subjects given a single 120-mg oral dose of terfenadine before and after taking venlafaxine 75 mg every 12 hours for 9 days found that the pharmacokinetic profile of terfenadine was unchanged, although its acid metabolite concentrations were slightly decreased by about 25%.[1] This study was undertaken to confirm that venlafaxine lacks inhibitory activity on the cytochrome P450 isoenzyme CYP3A4, but at the same time it also indicates that venlafaxine does not raise the serum levels of terfenadine, which are associated with serious cardiotoxicity. There would therefore seem to be no reason for avoiding concurrent use.

1. Amchin J, Zarycranski W, Taylor K, Albano D, Klockowski PM. Effect of venlafaxine on the pharmacokinetics of terfenadine. *Psychopharmacol Bull* (1998) 34,383–9.

Antihistamines; Terfenadine + Zileuton

In one study zileuton modestly increased terfenadine levels, without altering the QTc interval.

Clinical evidence, mechanism, importance and management

Terfenadine 60 mg every 12 hours for 7 days was given to 15 healthy subjects with either zileuton 600 mg every 6 hours or a placebo. The mean $AUC_{0\text{-}6}$ and the maximum plasma concentrations of terfenadine increased by 35% in the presence of zileuton, but the levels were still very low (less than 5 nanograms/mL). The maximum plasma concentration and AUC of carboxyterfenadine (a terfenadine metabolite) were increased by about 15% by zileuton. ECG measurements showed that the addition of zileuton did not increase the QTc interval nor cause any other significant changes.[1] The authors concluded that the interaction was unlikely to be of clinical significance. However, any drug that inhibits terfenadine metabolism may result in accumulation of terfenadine and prolongation of the QT interval with the risk of life-threatening arrhythmias. Note that the UK manufacturer contraindicated the concurrent use of terfenadine and zileuton.[2]

1. Awni WM, Cavanaugh JH, Leese P, Kasier J, Cao G, Locke CS, Dube LM. The pharmacokinetic and pharmacodynamic interaction between zileuton and terfenadine. *Eur J Clin Pharmacol* (1997) 52, 49–54.
2. Histafen (Terfenadine). Approved Prescription Services Ltd. UK Summary of product characteristics, December 1999.

16

Antimigraine drugs

The drugs dealt with in this section are the ergot derivatives and the triptans (or more properly the serotonin 5-HT_1 agonists), whose main use is in the treatment of migraine. 'Table 16.1', (below) lists some of the drugs commonly used in migraine. Drugs such as propranolol, which are more commonly used in other conditions, are discussed elsewhere in this publication.

(a) Ergot derivatives

The main problem with the use of the ergot derivatives is that of ergotism. Drug interactions may result in additive effects, or cause raised levels of ergot derivatives, which may result in the symptoms of ergot poisoning. This can include severe circulatory problems e.g. the extremities may become numb, cold to the touch, tingle, and muscle pain may result. In extreme cases there may be no palpable pulse. Ultimately gangrene may develop, and amputation may be required. Chest pain can also occur, and in some cases myocardial infarction has been reported. Since dihydroergotamine, ergotamine and methysergide are metabolised in the liver by the isoenzyme CYP3A4, drugs which inhibit this isoenzyme, particularly potent inhibitors, such as some 'protease inhibitors', (p.684), should be avoided due to the risk of precipitating ergotism.

(b) Triptans

Although the triptans would be expected to share a number of pharmacodynamic drug interactions, due to their differing metabolic pathways they will not all necessarily share the same pharmacokinetic interactions. For example, sumatriptan, which is metabolised mainly by monoamine oxidase A, is unlikely to interact with macrolide antibacterials, which are inhibitors of the cytochrome P450 isoenzyme CYP3A4. However, eletriptan, which is mainly metabolised by CYP3A4 does interact (see 'Triptans + Macrolides', p.688). Frovatriptan and zolmitriptan are substrates for CYP1A2, and their metabolism is affected by CYP1A2 inhibitors such as fluvoxamine. However, the picture with zolmitriptan is more complicated, because it is also metabolised by monoamine oxidase A. Naratriptan appears unlikely to undergo significant pharmacokinetic interactions because half the dose is excreted unchanged and the rest is metabolised by a variety of isoenzymes. A summary of the enzymes involved in the metabolic pathways of the triptans can be found in 'Table 16.2', (below).

Early in the development of triptans it was theorised that they might present a high risk of excess serotonergic activity and increase the risk of 'serotonin syndrome', (p.9), especially when used with other drugs with serotonergic actions. Therefore sumatriptan was contraindicated in patients taking drugs such as the SSRIs and lithium. However, with more experience of the triptans it appears that interactions resulting in serotonin syndrome are rare, and so concurrent use with these other serotonergic drugs may now be undertaken, with an appropriate awareness of the potential problems.

Table 16.1 Antimigraine drugs

Group	*Drugs*
Antihistamines	Flunarizine, Pizotifen
Beta blockers	Atenolol, Metoprolol, Nadolol, Propranolol, Timolol
Ergot derivatives	Codergocrine, Ergotamine, Dihydroergocryptine, Dihydroergotamine, Methysergide
Triptans (Serotonin (5-HT_1) agonists)	Almotriptan, Eletriptan, Frovatriptan, Naratriptan, Rizatriptan, Sumatriptan, Zolmitriptan

Table 16.2 Principal enzymes involved in the metabolism of the triptans†

	MAO-A	*CYP1A2*	*CYP2C9*	*CYP2C19*	*CYP2D6*	*CYP3A4*
Almotriptan	Substrate				Substrate (minor)	Substrate
Eletriptan					Substrate (minor)	Substrate
Frovatriptan		Substrate			Substrate (minor)	
Naratriptan		Substrate (minor)	Substrate (minor)	Substrate (minor)	Substrate (minor)	Substrate (minor)
Rizatriptan	Substrate	Substrate (minor)				
Sumatriptan	Substrate					
Zolmitriptan	Substrate	Substrate				Substrate

†Other isoenzymes have been implicated, but not at clinically relevant concentrations of the triptans

Ergot derivatives + Antidepressants

One isolated report describes three cases in which patients developed symptoms indicative of serotonin syndrome when they took dihydroergotamine with amitriptyline, paroxetine and imipramine, or sertraline. Some antidepressants such as fluoxetine, fluvoxamine or nefazodone may increase the levels of the ergot derivatives.

Clinical evidence

A woman taking **imipramine**, **paroxetine** and lithium, who had a 3-week continuous headache, was given 300 micrograms and then 500 micrograms of **dihydroergotamine** intravenously. Within 5 minutes of the 500-microgram dose she developed dysarthria, dilated pupils, diaphoresis, diffuse weakness, and barely responded to commands. She was diffusely hyperreflexic and showed occasional myoclonic jerks. She recovered after 90 minutes.[1]

A woman with a history of migraine headaches responded well to **amitriptyline**, metoclopramide and **dihydroergotamine**. Six weeks after the **amitriptyline** was replaced by **sertraline**, she was again successfully treated for acute migraine with 10 mg of intravenous metoclopramide and 1 mg of intravenous **dihydroergotamine**. However, 2 hours later she developed nausea, emesis, agitation, weakness, diaphoresis, salivation, chills, and fever. All of the symptoms subsided after 24 hours.[1]

A woman with a history of migraines (treated prophylactically with **amitriptyline** and propranolol) was admitted to hospital in status migrainosus. She was given 1 mg of **dihydroergotamine**, 10 mg of prochlorperazine and 10 mg of metoclopramide (all intravenously). Within 20 minutes she became diaphoretic, tachycardic, diffusely hyperreflexic, agitated, confused, and briefly lost consciousness twice. Diazepam 8 mg given intramuscularly calmed her agitation, and all the symptoms resolved after 6 hours. A year later she was given 6 mg of subcutaneous sumatriptan while taking **nortriptyline** daily with no ill effects.[1]

Mechanism

Not understood. All of these patients appeared to have developed symptoms similar to those of 'serotonin syndrome', (p.9), which is thought to be due to hyperstimulation of 5-HT receptors in the brain. Dihydroergotamine is a 5-HT agonist while paroxetine and sertraline are both serotonin (5-HT) reuptake inhibitors, all of which might be expected to increase 5-HT concentrations in the CNS, and thereby increase receptor stimulation.

Importance and management

These appear to be isolated cases and not of general importance, nevertheless they illustrate the potential for the development of serotonin syndrome in patients given multidrug regimens that affect 5-HT receptors. The syndrome is rare and it may (so it has been suggested[1]) sometimes be an idiosyncratic reaction.

Note that some antidepressants e.g. **fluoxetine**, **fluvoxamine** and **nefazodone** can inhibit the cytochrome P450 isoenzyme CYP3A4, which is involved in the metabolism of ergot derivatives. This may result in reduced metabolism and therefore possibly ergot toxicity. The manufacturers of dihydroergotamine[2] and **ergotamine**[3,4] suggest giving these particular antidepressants with caution. Note that **methysergide** is also metabolised by CYP3A4 and therefore may be expected to interact similarly.

The manufacturer of **reboxetine** warns that its concurrent use with ergot derivatives might result in increased blood pressure, although no clinical data are quoted.[5]

1. Mathew NT, Tietjen GE, Lucker C. Serotonin syndrome complicating migraine pharmacotherapy. *Cephalalgia* (1996) 16, 323–7.
2. Migranal (Dihydroergotamine mesylate). Valeant Pharmaceuticals Inc. US Prescribing information, June 2007.
3. Migril (Ergotamine tartrate, cyclizine hydrochloride and caffeine). Wockhardt UK Ltd. UK Summary of product characteristics, March 2008.
4. Ergomar (Ergotamine tartrate). Rosedale Therapeutics. US Prescribing information, August 2007.
5. Edronax (Reboxetine). Pharmacia Ltd. UK Summary of product characteristics, July 2008.

Ergot derivatives + Beta blockers

The use of beta blockers with ergot derivatives in the management of migraine is not uncommon, but concurrent use has, rarely, resulted in severe peripheral vasoconstriction and hypertension.

Clinical evidence

A man with recurrent migraine headaches, reasonably well-controlled over a 6-year period with *Cafergot* suppositories (containing **ergotamine tartrate**), developed progressively painful and purple feet a short while after starting to take **propranolol** 30 mg daily. When he eventually resumed taking the *Cafergot* alone there was no further evidence of peripheral vasoconstriction.[1]

A similar case has been reported elsewhere, although an interaction is inconclusive in this patient, as neither the **ergotamine** nor the **propranolol** were taken alone.[2] Another case occurred in a woman who had been taking **oxprenolol** and **ergotamine tartrate** (dosages unknown) for some considerable time. Arteriography showed severe spasm in a number of arteries, which responded eventually to an intra-arterial infusion of glyceryl trinitrate and heparin.[3] Severe pain in the legs and feet occurred in another man after he took **methysergide** 3 mg and **propranolol** 120 mg daily for 2 weeks. He did not respond to various therapies, and in 6 days it was necessary to amputate both his legs below the knee because of gangrene.[3] A woman taking **propranolol** for migraine prophylaxis became hypertensive (BP 180/120 mmHg) with a crushing substernal pain immediately after being given oxygen, prochlorperazine 5 mg and intravenous **dihydroergotamine** 750 micrograms for an acute migraine headache. She recovered uneventfully. She was later found to be hyperthyroid, which, it was suggested, may have contributed to the interaction.[4]

These reports contrast with another stating that the use of **propranolol** with **ergotamine** was both effective and uneventful in 50 patients.[5]

Mechanism

Uncertain. One suggestion is that additive vasoconstriction occurs.[1,3] Ergot derivatives cause vasoconstriction, and the beta blockers do the same by blocking the normal ($beta_2$-stimulated) sympathetic vasodilatation. Beta blockers also reduce blood flow by reducing cardiac output.

Importance and management

Concurrent use is usually safe and effective, and there are only a handful of reports of adverse interactions. It was suggested that the disease state may have contributed to the interaction in one case,[4] and at least one of the other cases could have been due to the ergotamine alone (i.e. ergotism).[5] However, it would clearly be prudent to be extra alert for any signs of an adverse response, particularly those suggestive of reduced peripheral circulation (coldness, numbness or tingling of the hands and feet).

1. Baumrucker JF. Drug interaction — propranolol and cafergot. *N Engl J Med* (1973) 288, 916–17.
2. Greenberg DJ, Hallett JW. Lower extremity ischemia due to combined drug therapy for migraine. *Postgrad Med* (1982) 72, 103–7.
3. Venter CP, Joubert PH, Buys AC. Severe peripheral ischaemia during concomitant use of beta blockers and ergot alkaloids. *BMJ* (1984) 289, 288–9.
4. Gandy W. Dihydroergotamine interaction with propranolol. *Ann Emerg Med* (1990) 19, 221.
5. Diamond S. Propranolol and ergotamine tartrate (cont.). *N Engl J Med* (1973) 289, 159.

Ergot derivatives + CYP3A4 inducers

CYP3A4 inducers such as nevirapine and rifampicin would be expected to reduce the clinical effect of ergot derivatives. Efavirenz may increase or decrease the levels of ergot derivatives.

Clinical evidence, mechanism, importance and management

Drugs that induce the cytochrome P450 isoenzyme CYP3A4 would be expected to increase the metabolism of ergot alkaloids and decrease their plasma levels. This type of interaction may result in reduced efficacy, but

is unlikely to cause serious adverse effects. The manufacturer of **nevirapine** suggests that, although specific drug interaction studies have not been conducted, there could be a potential drug interaction with ergot alkaloids such as **ergotamine**, and additional clinical monitoring may be warranted when giving these drugs together.[1] It may be prudent to consider an alternative antimigraine treatment, such as one of the triptans not metabolised by CYP3A4, see 'Table 16.2', (p.680).

Note that **rifampicin** has been used as a potent enzyme inducer to reduce **ergotamine** levels in a patient with ergotism, and was said to play a key role in reducing ergotamine levels.[2]

A list of CYP3A4 inducers is given in 'Table 1.4', (p.6).

Efavirenz also induces CYP3A4, and therefore would also be expected to reduce the levels of ergot derivatives. However, the manufacturers[3,4] advise that, due to competition for metabolism by CYP3A4, **efavirenz** may possibly *increase* the levels of ergot derivatives, leading to ergot toxicity. For this reason they contraindicate concurrent use.[3,4] See 'Ergot derivatives + CYP3A4 inhibitors', below. However, there appear to be no published reports of the outcome of this interaction.

1. Viramune (Nevirapine). Boehringer Ingelheim Pharmaceuticals, Inc. US Prescribing information, November 2008.
2. Richardson JD, Sorensen S. Rifampin to treat ritonavir ergotamine drug interaction. *Clin Infect Dis* (1999) 29, 1002.
3. Cafergot Tablets (Ergotamine tartrate and caffeine). Alliance Pharmaceuticals. UK Summary of product characteristics, March 2009.
4. Sustiva Film-coated Tablets (Efavirenz). Bristol-Myers Squibb Pharmaceuticals Ltd. UK Summary of product characteristics, June 2009.

Ergot derivatives + CYP3A4 inhibitors

The azole antifungals are predicted to raise the levels of ergot derivatives, which may lead to ergotism. Other CYP3A4 inhibitors, such as cimetidine, delavirdine, grapefruit juice and quinupristin/dalfopristin are expected to interact similarly, although possibly to a lesser extent.

Clinical evidence, mechanism, importance and management

The ergot alkaloids are mainly metabolised by the cytochrome P450 isoenzyme CYP3A4. The manufacturers of **ergotamine**, **dihydroergotamine** and **methysergide** therefore logically predict that their levels will be raised by CYP3A4 inhibitors, which may lead to ergotism: this has been seen with the 'macrolides', (p.683), and the 'protease inhibitors', (p.684).

Drugs such as the **azole antifungals** would be expected to interact similarly, although there appear to be no studies or case reports describing an interaction. Note that, of the azoles, **ketoconazole** and **itraconazole** are the most potent CYP3A4 inhibitors, and would therefore be expected to interact to the greatest extent; their use, as well as the use of **posaconazole**[1] or **voriconazole**[1,2] is generally contraindicated.[3-6] Other CYP3A4 inhibitors that are contraindicated with ergot derivatives include **delavirdine**[2] and **efavirenz**;[1] however, note that **efavirenz** also typically *induces* CYP3A4 in clinical practice, and may therefore also *reduce* the levels of ergot derivatives, consider 'Ergot derivatives + CYP3A4 inducers', p.681. However, there appear to be no published reports of the outcome of this interaction.

The concurrent use of less potent CYP3A4 inhibitors such as **cimetidine**,[1,2] **clotrimazole**,[3-6] **fluconazole**,[3-6] **grapefruit juice**,[3-6] **quinupristin**/**dalfopristin**[1] and **zileuton**,[4,6] should either be avoided if possible, or used with caution. Not all of the manufacturers mention all combinations, but these are all reasonable predictions, and it would therefore seem appropriate to apply them to all ergot derivatives used in the management of migraine. Therefore if any of these less potent CYP3A4 inhibitors is given with an ergot derivative it would be prudent to be aware that raised levels may occur. Strongly advise patients not to take any further doses and seek medical advice if early symptoms of increased levels, such as a decreased sensitivity to touch or pain, numbness or tingling in the fingers and toes, nausea and vomiting (unrelated to the migraine) develop.

1. Cafergot Tablets (Ergotamine tartrate and caffeine). Alliance Pharmaceuticals. UK Summary of product characteristics, March 2009.
2. Deseril (Methysergide maleate). Alliance Pharmaceuticals. UK Summary of product characteristics, December 2006.
3. Cafergot Tablets (Ergotamine tartrate and caffeine). Novartis. US Prescribing information, March 2003.
4. Migranal (Dihydroergotamine mesylate). Valeant Pharmaceuticals Inc. US Prescribing information, June 2007.
5. Migril (Ergotamine tartrate, cyclizine hydrochloride and caffeine). Wockhardt UK Ltd. UK Summary of product characteristics, March 2008.
6. Ergomar (Ergotamine tartrate). Rosedale Therapeutics. US Prescribing information, August 2007.

Ergot derivatives + Ergot derivatives

The concurrent use of methysergide and other ergot derivatives can increase the risk of severe and persistent spasm of major arteries in some patients.

Clinical evidence

A man developed loss of temperature sensitivity over the right side of his face and arm, as well as vertigo, dysphagia and hoarseness, 7 days after starting to take methysergide 2 mg three times daily and 500 micrograms of subcutaneous **ergotamine tartrate** at night. Continued use resulted in impaired pain, touch and temperature sensation over the right side of his face, shoulder and arm. Arteriography demonstrated left vertebral artery occlusion and right vertebral arterial spasm. These symptoms, apart from the loss of temperature sensitivity, resolved when the drugs were stopped.[1] Another man treated for cluster headaches with methysergide 2 mg, intramuscular **ergotamine tartrate** and pizotifen developed ischaemia of the right foot, with impalpable popliteal and pedal pulses. Arteriography showed that blood flow to the arteries of the right leg was reduced.[1]

Another report describes prolonged myocardial ischaemia in a patient with cluster headaches when a single 2-mg dose of **ergotamine tartrate** was added to methysergide 2 mg three times daily. Sublingual glyceryl trinitrate relieved the pain.[2]

A further case report describes a woman who developed gangrene of both big toes following surgical treatment of bilateral hallux valgus (bone swellings). Before the time of operation, and for 20 days afterwards, she took 6 tablets of *Bellergal* (total of **ergotamine tartrate** 1.8 mg, alkaloids of belladonna 600 micrograms, phenobarbital 120 mg daily) and methysergide maleate 6 mg daily. One toe was subsequently removed by amputation, the other recovered slowly following cessation of the **ergotamine** and methysergide.[3]

Mechanism

Cluster headaches are associated with abnormal dilatation of the carotid arteries, which can be constricted by ergot derivatives. In the cases cited it would seem that combined vasoconstrictor effects caused arterial spasm elsewhere in the body, resulting in serious tissue ischaemia. Parenteral ergotamine increases the risk of arterial spasm.

Importance and management

Direct information seems to be limited to these cases. Cardiovascular complications can occur with ergot derivatives given alone, but these cases suggest that their concurrent use may unpredictably increase the risk in some patients. Clearly they should be used together with great caution, or avoided.

The manufacturer of methysergide contraindicates its use with vasoconstrictive drugs including ergot alkaloids.[4] Many manufacturers of other ergot alkaloids (**dihydroergotamine**, ergotamine) say that they should not be used with other ergot alkaloids (including **methysergide**). In addition, the manufacturers of dihydroergotamine[5,6] suggest that it should not be used within 24 hours of ergot-type medications.

Note that drugs such as bromocriptine are also ergot derivatives, and it is similarly recommended that their use with other ergot derivatives should be avoided, see 'Bromocriptine and other dopamine agonists + Ergot derivatives', p.791.

1. Joyce DA, Gubbay SS. Arterial complications of migraine treatment with methysergide and parenteral ergotamine. *BMJ* (1982) 285, 260–1.
2. Galer BS, Lipton RB, Solomon S, Newman LC, Spierings ELH. Myocardial ischemia related to ergot alkaloids: a case report and literature review. *Headache* (1991) 31, 446–50.
3. Vaughan-Lane T. Gangrene induced by methysergide and ergotamine. J Bone Joint Surg Br. (1979) 61–B, 213–14.
4. Deseril (Methysergide maleate). Alliance Pharmaceuticals. UK Summary of product characteristics, December 2006.
5. Migranal (Dihydroergotamine mesylate). Valeant Pharmaceuticals Inc. US Prescribing information, June 2007.
6. D.H.E. 45. (Dihydroergotamine mesylate). Novartis Pharmaceuticals Corporation. US Prescribing information, April 2001.

Ergot derivatives + Glyceryl trinitrate (Nitroglycerin)

The ergot derivatives such as dihydroergotamine would be expected to oppose the anti-anginal effects of glyceryl trinitrate. Nevertheless, an *animal* study has not borne out this expectation.

Clinical evidence, mechanism, importance and management

There seem to be no clinical reports of adverse interactions between the ergot derivatives and glyceryl trinitrate, but as **ergot** causes vasoconstriction and can provoke angina it would be expected to oppose the effects of glyceryl trinitrate when used as a vasodilator for the treatment of angina.[1] Nevertheless, a study in *animals* suggested that **dihydroergotamine** would not worsen exercise-induced angina pectoris, and that the antianginal efficacy of glyceryl trinitrate would not be neutralised by pretreatment with **dihydroergotamine**.[2]

However, glyceryl trinitrate has been shown to increase the bioavailability of **dihydroergotamine** (by up to 370% in one case) in subjects with orthostatic hypotension, which would increase its vasoconstrictor effects.[1] The clinical outcome of concurrent use is therefore uncertain, especially as glyceryl trinitrate has been successfully used to relieve pain and arterial spasm related to the use of ergot derivatives (see 'Ergot derivatives + Ergot derivatives', p.682, and 'Ergot derivatives + Beta blockers', p.681). Note that ergot derivatives are generally regarded as contraindicated in those with ischaemic heart disease.

1. Bobik A, Jennings G, Skews H, Esler M, McLean A. Low oral bioavailability of dihydroergotamine and first-pass extraction in patients with orthostatic hypotension. *Clin Pharmacol Ther* (1981) 30, 673–9.
2. Schneider W, Krumpl G, Mayer N, Raberger G. The effects of nitroglycerin on exercise-induced regional myocardial contractile dysfunction are not diminished by pretreatment with dihydroergotamine. *Br J Pharmacol* (1987) 92, 87–95.

Ergot derivatives + Macrolides

Ergot toxicity can develop rapidly in patients taking ergotamine or dihydroergotamine if they are given erythromycin or troleandomycin. Cases of toxicity have also been reported with clarithromycin, josamycin, and oleandomycin; midecamycin and telithromycin are predicted to interact similarly. No cases of toxicity appear to have been described with azithromycin, dirithromycin, or spiramycin, and none would be expected.

Clinical evidence

(a) Clarithromycin

A 59-year-old woman took **ergotamine tartrate** 2 mg for a typical migraine headache. After 2 hours her tongue became swollen, painful and bluish in colour. She was moderately hypertensive (BP 200/110 mmHg), and her fingers and toes were cold and cyanotic (blue); this was diagnosed as ergotism. She had taken this dose of **ergotamine** many times previously without problems, but on this occasion she had been taking clarithromycin 500 mg twice daily for the previous 5 days. Other evidence suggests that this patient may possibly have been unusually sensitive to vascular occlusion.[1] The authors of this report briefly quote another case, originating from the manufacturers of clarithromycin, of a possible interaction with **dihydroergotamine**, although this was complicated by the concurrent use of other medications (not named) used in the management of AIDS.[1] A woman who had previously uneventfully taken *Cafergot* (**ergotamine tartrate** 1 mg, caffeine 100 mg) for migraine developed ergotism (leg pain, cold and cyanosed limbs, and impalpable pulses) within 3 days of starting to take clarithromycin (dosage not stated). The authors postulated that smoking and the use of oxymetazoline (both of which have vasoconstrictor effects) may also have had some part to play.[2]

(b) Erythromycin

A woman who had regularly and uneventfully taken *Migral* (**ergotamine tartrate** 2 mg, cyclizine hydrochloride 50 mg, caffeine 100 mg) on a number of previous occasions, took one tablet during a course of treatment with erythromycin 250 mg every 6 hours. Within 2 days she developed severe ischaemic pain in her arms and legs during exercise, with a burning sensation in her feet and hands. When admitted to hospital 10 days later, her extremities were cool and cyanosed. Her pulse could not be detected in the lower limbs.[3]

Eight other cases of acute ergotism have been reported[4-11] in which patients were taking **ergotamine tartrate** or **dihydroergotamine** and erythromycin. The reaction has been reported to develop within a few hours,[7] but it may take several days to occur.[10] One case appeared to occur when the erythromycin was started 3 days after the last dose of **dihydroergotamine**.[5]

A study involving 9 healthy subjects found that erythromycin increased the mean maximum plasma level and AUC of α-**dihydroergocryptine** by 9.5-fold and greater than 13-fold, respectively.[12]

(c) Josamycin

An isolated report describes a 33-year-old woman who developed severe ischaemia of the legs within 3 days of starting to take josamycin 2 g daily and **ergotamine tartrate** 300 micrograms. Her legs and feet were cold, white and painful, and most of her peripheral pulses were impalpable.[13]

(d) Midecamycin diacetate

After 12 healthy subjects took midecamycin diacetate 800 mg twice daily for 8 days, the peak level of a single 9-mg dose of **dihydroergotamine** were raised 3 to 40-fold.[14]

(e) Oleandomycin

A case of ergotism has been reported in a 45-year-old woman who had been taking **ergotamine** 4 mg daily for 5 years and recently also oleandomycin.[15]

(f) Troleandomycin

A 40-year-old woman who had been taking **dihydroergotamine**, 90 drops daily, for 3 years without problems, developed cramp in her legs within a few hours of starting to take troleandomycin 250 mg four times a day. Five days later she was admitted to hospital as an emergency, with severe ischaemia of her arms and legs. Her limbs were cold and all her peripheral pulses were impalpable.[16]

There are reports of several other patients who had taken normal doses of **ergotamine tartrate** or **dihydroergotamine** for months or years without problems, who then developed severe ergotism within hours or days of starting to take normal doses of troleandomycin.[17-24] This resulted in a myocardial infarction in one patient.[25]

Mechanism

Erythromycin and troleandomycin are potent inhibitors of the cytochrome P450 isoenzyme CYP3A4, an enzyme involved in the metabolism of ergot derivatives.[26,27] Clarithromycin and oleandomycin are also known to inhibit CYP3A4. As a result the ergot is poorly metabolised and accumulates in the body. This leads to increased vasoconstriction and ultimately ischaemia. Josamycin, midecamycin and **roxithromycin** have a lower affinity for CYP3A4 than erythromycin or troleandomycin and are therefore less likely to interact,[26,27] although interactions have been reported. **Azithromycin**, **dirithromycin** and **spiramycin** have little or no effect on CYP3A4.[27]

Importance and management

The interactions of ergot derivatives with erythromycin and troleandomycin are well documented, well established, and clinically important. Although information about clarithromycin and oleandomycin appears to be confined to case reports, they would be expected to interact similarly. The concurrent use of all of these macrolides and ergot derivatives should be avoided. Some of the cases cited were effectively treated with sodium nitroprusside or naftidrofuryl oxalate.[1,5,7-9,22] Note that **telithromycin**, is also a relatively potent inhibitor of CYP3A4 and the UK manufacturer contraindicates, and the US manufacturer advises against its use with ergot derivatives such as ergotamine and dihydroergotamine.[28,29]

Josamycin, midecamycin, and roxithromycin are less likely to interact because they have a much lower affinity for CYP3A4. Nevertheless, there has been a report of ergotism with josamycin, and the rise in dihydroergotamine levels seen with midecamycin would be expected to be clinically relevant.

Azithromycin, dirithromycin and spiramycin would not be expected to interact because they do not inhibit CYP3A4. Nevertheless, ergot alkaloids are contraindicated with azithromycin,[30,31] because clinically important interactions have been seen between ergot derivatives and other

macrolide antibacterials.[32,33] However, there seems so far to be no direct evidence of any adverse interactions between ergot alkaloids and azithromycin, and the US manufacturer says that concurrent use can be undertaken with careful monitoring.[34]

1. Horowitz RS, Dart RC, Gomez HF. Clinical ergotism with lingual ischemia induced by a clarithromycin-ergotamine interaction. *Arch Intern Med* (1996) 156, 456–8.
2. Ausband SC, Goodman PE. An unusual case of clarithromycin associated ergotism. *J Emerg Med* (2001) 21, 411–13.
3. Francis H, Tyndall A, Webb J. Severe vascular spasm due to erythromycin-ergotamine interaction. *Clin Rheumatol* (1984) 3, 243–6.
4. Lagier G, Castot A, Riboulet G, Boesh C. Un cas d'ergotisme mineur semblant en rapport avec une potentialisation de l'ergotamine par l'éthylsuccinate d'érythromycine. *Therapie* (1979) 34, 515–21.
5. Neveux E, Lesgourgues B, Luton J-P, Guilhaume B, Bertagna, Picard J. Ergotisme aigu par association proprionate d'érythromycine-dihydroergotamine. *Nouv Presse Med* (1981) 10, 2830.
6. Collet AM, Moncharmont D, San Marco JL, Eissinger F, Pinot JJ, Laselve L. Ergotisme iatrogène: rôle de l'association tartrate d'ergotamine-propionate d'érythromycine. *Sem Hop Paris* (1982) 58, 1624–6.
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12. de Mey C, Althaus M, Ezan E, Retzow A. Erythromycin increases plasma concentrations of α-dihydroergocryptine in humans. *Clin Pharmacol Ther* (2001) 70, 142–8.
13. Grolleau JY, Martin M, de la Guerrande B, Barrier J, Peltier P. Ergotism aigu lors d'une association josamycine/tartrate d'ergotamine. *Therapie* (1981) 36, 319–21.
14. Couet W, Mathieu HP, Fourtillan JB. Effect of ponsinomycin on the pharmacokinetics of dihydroergotamine administered orally. *Fundam Clin Pharmacol* (1991) 5, 47–52.
15. Monsarrat M, Lefebvre D, Parraguette J, Vaysse C, Bastide G. Ergotisme aigu par association ergotamine-oleandomycine. *Nouv Presse Med* (1982) 11, 603.
16. Franco A, Bourlard P, Massot C, Lecoeur J, Guidicelli H, Bessard G. Ergotisme aigu par association dihydroergotamine-triacétyloléandomycine. *Nouv Presse Med* (1978) 7, 205.
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19. Dupuy JC, Lardy P, Seaulau P, Kervoelen P, Paulet J. Spasmes artériels systémiques. Tartrate d'ergotamine. *Arch Mal Coeur* (1979) 72, 86–91.
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23. Chignier E, Riou R, Descotes J, Meunier P, Courpron P, Vignon G. Ergotisme iatrogène aigu par association médicamenteuse diagnostiqué par exploration non invasive (vélocimétrie à effet Doppler). *Nouv Presse Med* (1978) 7, 2478.
24. Bacourt F, Couffinhal J-C. Ischémie des membres par association dihydroergotamine-triacétyloléandomycine. Nouvelle observation. *Nouv Presse Med* (1978) 7, 1561.
25. Baudouy PY, Mellat M, Velleteau de Moulliac M. Infarctus du myocarde provoqué par l'association tartrate d'ergotamine-troléandomycine. *Rev Med Interne* (1988) 9, 420–2.
26. Pessayre D, Larrey D, Funck-Brentano C, Benhamou JP. Drug interactions and hepatitis produced by some macrolide antibiotics. *J Antimicrob Chemother* (1985) 16 (Suppl A), 181–94.
27. von Rosenstiel N-A, Adam D. Macrolide antibacterials. Drug interactions of clinical significance. *Drug Safety* (1995) 13, 105–22.
28. Ketek (Telithromycin). Sanofi-Aventis. UK Summary of product characteristics, June 2009.
29. Ketek (Telithromycin). Sanofi-Aventis. US Prescribing information, June 2009.
30. Zithromax (Azithromycin). Pfizer Ltd. UK Summary of product characteristics, March 2008.
31. Migril (Ergotamine tartrate, cyclizine hydrochloride and caffeine). Wockhardt UK Ltd. UK Summary of product characteristics, March 2008.
32. Hopkins S. Clinical toleration and safety of azithromycin. *Am J Med* (1991) 91 (Suppl 3A), 40S–45S.
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34. Zithromax (Azithromycin). Pfizer Inc. US Prescribing information, January 2009.

Ergot derivatives + Protease inhibitors

A patient receiving indinavir rapidly developed ergotism after taking normal doses of ergotamine. Several other patients taking ritonavir (sometimes with another protease inhibitor) and ergotamine have developed the same interaction. A patient taking nelfinavir developed peripheral arterial vasoconstriction after also taking ergotamine. Other ergot derivatives and protease inhibitors are expected to interact similarly.

Clinical evidence

(a) Indinavir

An HIV-positive man who had been taking lamivudine, stavudine, co-trimoxazole and indinavir (2.4 g daily) for more than a year was given *Gynergene caféiné* (**ergotamine tartrate** 1 mg with caffeine 100 mg) for migraine. He took two doses on two consecutive days, and 5 days later presented with numbness and cyanosis of the toes of his left foot. The next day he complained of intermittent claudication of his left leg, and 6 days later was admitted to hospital because of worsening symptoms and night cramps. Examination showed a typical picture of ergotism, with vasospasm and reduced blood flow in the popliteal, tibial and femoral arteries. He was given heparin and buflomedil (a vasodilator), and recovered after 3 days.[1]

See *Ritonavir with other protease inhibitors*, below, for details regarding a fatality involving the use of indinavir and ritonavir with ergotamine.

(b) Nelfinavir

A 40-year-old HIV-positive woman twice took **ergotamine** 2 mg for a migraine while also taking nelfinavir, zidovudine and lamivudine. On the first occasion she developed pain and cyanosis in her toes, and on the second occasion she developed cyanosis and oedema in her hands and feet, causing pain so severe that she was unable to walk. On both occasions peripheral arterial pulses were not palpable. Although she recovered spontaneously on both occasions, the authors caution concurrent use due to the extremely severe potential effects.[2]

See also *Ritonavir with other protease inhibitors*, below.

(c) Ritonavir

A 63-year-old man with AIDS, who had taken **ergotamine tartrate** 1 to 2 mg daily for migraine headaches over the last 5 years, had his treatment with zidovudine, zalcitabine and co-trimoxazole changed to zidovudine, didanosine and ritonavir 600 mg every 12 hours. Within 10 days he developed paraesthesias, coldness, cyanosis and skin paleness of both arms, and when admitted to hospital his axillary, brachial, radial and ulnar pulses were found to be absent. An arterial doppler test showed the absence of blood flow in both his radial and ulnar arteries and he was diagnosed as having ergotism. The **ergotamine** and ritonavir were stopped, and he recovered when given prostaglandin E1 and calcium nadroparin.[3]

A case report describes irreversible coma in a 34-year-old woman who was taking ritonavir 600 mg twice daily, lamivudine and stavudine. She presented with dizziness, loss of vision, headache, vomiting, diarrhoea and a feeling of cold in her left foot after having taken three tablets of **ergotamine** 1 mg in the preceding 4 days. Peripheral pulses were absent in her extremities. After an initial period of recovery she again experienced a loss of consciousness, with signs of stenosis and vasospasm with cerebral hypoperfusion. Despite treatment with alprostadil, and discontinuation of ritonavir her condition deteriorated, and 2 years after the initial presentation, she remained in coma vigil (a state of altered consciousness).[4]

At least 4 other cases of ergotism have been reported in patients taking ritonavir after taking ergot derivatives:[5-8] one required surgical amputation of the toes.[6] Ergotism developed in two of the patients within a few hours to 24 hours of taking a single 1- or 2-mg dose of **ergotamine tartrate**,[5,7] and in the others within about 4 to 15 days.[6,8] One was taking a combination drug (**ergotamine tartrate** 300 micrograms, belladonna extract 200 micrograms and phenobarbital 20 mg) twice daily for gastric discomfort,[6] and another received 10 mg of ergotamine rectally over 4 days.[8]

(d) Ritonavir with other protease inhibitors

A 49-year-old man taking ritonavir 200 mg twice daily and **indinavir** 800 mg twice daily (with stavudine and lamivudine) took 3 *Cafergot* tablets (**ergotamine tartrate** 1 mg and caffeine 100 mg) for a headache. However, his headache worsened, he developed progressive lower extremity weakness, severe peripheral vasoconstriction, labile hypertension and livedo reticularis (skin discoloration due to underlying capillary changes). He lapsed into coma and on day 5 was declared brain dead.[9]

A 31-year-old man, taking ritonavir 400 mg twice daily (and also taking pizotifen, **nelfinavir**, stavudine, lamivudine, co-trimoxazole and venlafaxine), developed severe burning and numbness in both feet, and paraesthesias in his hands, after taking 4 tablets of **ergotamine** 1 mg and caffeine 100 mg over 10 days. He was diagnosed as having ergotism. The drugs were stopped and he was treated effectively with intravenous alprostadil and heparin.[10]

Another man receiving ritonavir and **saquinavir** experienced numbness in his hands and feet, cyanosis of his extremities, and nausea and vomiting after taking **ergotamine** [4 mg]. Four days after taking the ergotamine he was found to have no pulses (by Doppler) in any extremity and ergot toxicity was diagnosed. He was given heparin, rifampicin (rifampin), nitrate vasodilators, calcium-channel blockers and prostaglandins; pulses re-

turned in his hands after 24 hours and in his feet after 48 hours. The patient recovered with gangrene of all his toes, one of which required amputation. Treatment included rifampicin to induce liver enzymes and therefore increase the metabolism of the ergotamine.[11]

At least two other cases of ergotism have been reported in patients taking ergot derivatives with ritonavir and another protease inhibitor (**amprenavir**,[12] unspecified[13]).

Mechanism

Protease inhibitors can, to varying degrees, reduce the metabolism of ergotamine (and other ergot derivatives) by inhibiting the cytochrome P450 isoenzyme CYP3A4. Therefore ergotamine levels are increased, which may result in toxicity. Ergotamine poisoning causes arterial spasm, which reduces and even shuts down the flow of blood in arteries.

Importance and management

Information appears to be limited to these reports, but what happened is consistent with the way other drugs that are CYP3A4 inhibitors can interact with ergot derivatives (see 'Ergot derivatives + Macrolides', p.683). This interaction would appear to be established, and is clearly clinically important. It would be prudent for any patient taking indinavir or ritonavir, and probably nelfinavir, to avoid the concurrent use of ergotamine or any other ergot derivative, such as **dihydroergotamine** or **methysergide**.

Information about possible interactions between ergot derivatives and other protease inhibitors seems to be limited, but as the protease inhibitors all inhibit CYP3A4 they would be expected to interact similarly, particularly if ritonavir is given as a pharmacokinetic enhancer. The manufacturers of protease inhibitors (including amprenavir, **atazanavir**, **darunavir**, **fosamprenavir**, indinavir, **lopinavir**, nelfinavir, ritonavir, saquinavir, **tipranavir**) generally contraindicate their use with ergot derivatives.

1. Rosenthal E, Sala F, Chichmanian R-M, Batt M, Cassuto J-P. Ergotism related to concurrent administration of ergotamine tartrate and indinavir. *JAMA* (1999) 281, 987.
2. Mortier E, Pouchot J, Vinceneux P, Lalande M. Ergotism related to interaction between nelfinavir and ergotamine. *Am J Med* (2001) 110, 594.
3. Caballero-Granado FJ, Viciana P, Cordero E, Gómez-Vera MJ, del Nozal M, López-Cortés LF. Ergotism related to concurrent administration of ergotamine tartrate and ritonavir in an AIDS patient. *Antimicrob Agents Chemother* (1997), 41,1207.
4. Pardo Rey C, Yebra M, Borrallo M, Vega A, Ramos A, Montero MC. Irreversible coma, ergotamine, and ritonavir. *Clin Infect Dis* (2003) 37, e72–3.
5. Montero A, Giovannoni AG, Tvrde PL. Leg ischemia in a patient receiving ritonavir and ergotamine. *Ann Intern Med* (1999) 130, 329–30.
6. Liaudet L, Buclin T, Jaccard C, Eckert P. Severe ergotism associated with interaction between ritonavir and ergotamine. *BMJ* (1999) 318, 771.
7. Blanche P, Rigolet A, Gombert B, Ginsburg C, Salmon D, Sicard D. Ergotism related to a single dose of ergotamine tartrate in an AIDS patient treated with ritonavir. *Postgrad Med J* (1999) 75, 546–7.
8. Spiegel M, Schmidauer C, Kampfl A, Sarcletti M, Poewe W. Cerebral ergotism under treatment with ergotamine and ritonavir. *Neurology* (2001) 57, 743–4.
9. Tribble MA, Gregg CR, Margolis DM, Amirkhan R, Smith JW. Fatal ergotism induced by an HIV protease inhibitor. *Headache* (2002) 42, 694–5.
10. Phan TG, Agaliotis D, White G, Britton WJ. Ischaemic peripheral neuritis secondary to ergotism associated with ritonavir therapy. *Med J Aust* (1999) 171, 502, 504.
11. Richardson JD, Sorensen S. Rifampin to treat ritonavir ergotamine drug interaction. *Clin Infect Dis* (1999) 29, 1002.
12. Vila A, Mykietiuk A, Bonvehì P, Temporiti E, Urueña A, Herrera F. Clinical ergotism induced by ritonavir. *Scand J Infect Dis* (2001) 33, 788–9.
13. Baldwin ZK, Ceraldi CC. Ergotism associated with HIV antiviral protease inhibitor therapy. *J Vasc Surg* (2003) 37, 676–8.

Ergot derivatives + Tetracyclines

Five patients taking ergotamine or dihydroergotamine developed ergotism when they also took doxycycline or tetracycline.

Clinical evidence

A woman who had previously taken **ergotamine tartrate** successfully and uneventfully for 16 years was given **doxycycline** and **dihydroergotamine** 30 drops three times a day. Five days later her hands and feet became cold and reddened, and she was diagnosed as having a mild form of ergotism.[1]

Other cases of ergotism, some of them more severe, have been described in two patients taking **ergotamine tartrate** and **doxycycline**,[2,3] and in 3 patients taking **tetracycline**-containing preparations.[4,5]

Mechanism

Unknown. One suggestion is that these antibacterials may inhibit the metabolism and clearance of ergotamine in the liver, thereby prolonging its stay in the body and enhancing its activity.[1] One of the patients had a history of alcoholism[2] and two of them were in their eighties,[5] so impaired liver function may have played a part.

Importance and management

Information is very limited indeed. The incidence and general importance of this interaction is uncertain, but it seems likely to be small. However, note that one of the manufacturers of ergotamine[6] actually recommends that the concurrent use of 'tetracycline' should be avoided. Impaired liver function may possibly be a contributory factor in this interaction and it may be prudent to monitor patients with this risk factor more closely.

1. Amblard P, Reymond JL, Franco A, Beani JC, Carpentier P, Lemonnier D, Bessard G. Ergotisme. Forme mineure par association dihydroergotamine-chlorhydrate de doxycycline, étude capillaroscopique. *Nouv Presse Med* (1978) 7, 4148–9.
2. Dupuy JC, Lardy P, Seaulau P, Kervoelen P, Paulet J. Spasmes artériels systémiques. Tartrate d'ergotamine. *Arch Mal Coeur* (1979) 72, 86–91.
3. Van Gestel R, Noirhomme P. Ergotism aigu par association de tartrate d'ergotamine et de doxycycline. *Louvain Med* (1984) 103, 207–8.
4. L'Yvonnet M, Boillot A, Jacquet AM, Barale F, Grandmottet P, Zurlinden B, Gillet JY. A propos d'un cas exceptionnel d'intoxication aigue par un dérivé de l'ergot de seigle. *Gynecologie* (1974) 25, 541–3.
5. Sibertin-Blanc M. Les dangers de l'ergotisme a propos de deux observations. *Arch Med Ouest* (1977) 9, 265–6.
6. Cafergot Tablets (Ergotamine tartrate and caffeine). Alliance Pharmaceuticals. UK Summary of product characteristics, March 2009.

Ergot derivatives; Dihydroergotamine + Heparin

The use of dihydroergotamine with heparin has resulted in ergotism. In some cases, amputation of the affected limb was necessary. The rate of absorption and peak levels of subcutaneous dihydroergotamine are reduced by heparin.

Clinical evidence, mechanism, importance and management

There have been several reports of ergotism following the combined use of **dihydroergotamine** and heparin for thromboembolic prophylaxis. In a retrospective review of 61 092 Austrian patients attending trauma units who received **dihydroergotamine** and heparin prophylaxis, complications attributable to ergotism were seen in 142 patients. In 7 patients amputation was necessary and in a further 7 cases immediate opening of the vessel and catheter dilatation was successful.[1] Other published reports support this interaction,[2,3] including a report of two patients who experienced fatal myocardial infarctions, attributed to coronary artery spasm as a complication of prophylaxis with **dihydroergotamine** and heparin.[4]

It has been found that the use of heparin results in a 25% increase in the AUC of subcutaneous **dihydroergotamine**. Giving the two drugs at the same injection site reduced the rate of dihydroergotamine absorption by 63%, delayed the time to peak levels by 110%, and reduced the peak levels by 15%. **Dihydroergotamine** had no effect on the pharmacokinetics of heparin.[5]

Because of the risk of peripheral ischaemia, the combination of **dihydroergotamine** and heparin is no longer widely used for thromboembolic prophylaxis. If the combination is used, the patient must be closely observed for any sign of vascular spasm.

1. Gatterer R. Ergotism as complication of thromboembolic prophylaxis with heparin and dihydroergotamine. *Lancet* (1986) II, 638–639.
2. Warmuth-Metz M. Ergotismus der unteren Extremität als Folge einer DHE-Heparin-Thromboseprophylaxe. *Radiologe* (1988) 28, 491–3.
3. Jahn R. Ergotismus – ein Risiko bei der Thromboseprophylaxe? *Zentralbl Chir* (1985) 110, 482–5.
4. Rem JA, Gratzl O, Follath F, Pult I. Ergotism as complication of thromboembolic prophylaxis with heparin-dihydroergotamine. *Lancet* (1987) I, 219.
5. Schran HF, Bitz DW, DiSerio FJ, Hirsh J. The pharmacokinetics and bioavailability of subcutaneously administered dihydroergotamine, heparin and the dihydroergotamine-heparin combination. Thromb Res. (1983) 31, 51–67.

Triptans + Azoles

Ketoconazole and fluconazole increase the AUC of eletriptan by about sixfold and twofold, respectively. Almotriptan is less affected; ketoconazole raises its AUC by about 60%. Itraconazole is predicted to interact in the same way as ketoconazole.

Clinical evidence

(a) Almotriptan

In a randomised, crossover study, 16 healthy subjects were given **ketoconazole** 400 mg daily on days 1 to 3, with a single 12.5-mg dose of almotriptan on day 2. Ketoconazole increased the AUC and maximum plasma levels of almotriptan by 57% and 61%, respectively. The renal clearance of almotriptan was also reduced, by approximately 16%.[1]

(b) Eletriptan

A pharmacokinetic study by the manufacturers of eletriptan found that **ketoconazole** 400 mg increased the maximum serum levels and AUC of eletriptan 2.7-fold, and 5.9-fold, respectively, and prolonged its half-life from 4.8 to 8.3 hours. **Fluconazole** caused a lesser 40% increase in the maximum serum levels of eletriptan, and doubled its AUC.[2,3]

Mechanism

Ketoconazole is a potent inhibitor of the cytochrome P450 isoenzyme CYP3A4, by which eletriptan is metabolised. Ketoconazole therefore inhibits the metabolism of eletriptan, which results in raised eletriptan levels. Fluconazole is a less potent inhibitor of CYP3A4 than ketoconazole, and therefore has a more modest effect. Almotriptan is also metabolised by CYP3A4, but this is not its only route of metabolism, and therefore inhibition of CYP3A4 by ketoconazole has a less dramatic effect on its levels.

Importance and management

Although studies are limited, these interactions are established. In the study with almotriptan and ketoconazole adverse events were not significantly altered, and so no almotriptan dosage adjustment is considered necessary when using this combination.[1] Ketoconazole dramatically raises eletriptan levels, and therefore the manufacturers advise that concurrent use should be avoided.[2,3] In addition, the US manufacturer recommends that eletriptan should not be given within 72 hours of ketoconazole.[2]

Itraconazole is expected to interact in the same way as ketoconazole, and therefore the same precautions should be taken.

Fluconazole is a less potent inhibitor of CYP3A4 and therefore may be used with caution. Other triptans would be expected to have little or no interaction with the azoles as they are not predominantly metabolised by CYP3A4 (see 'Table 16.2', (p.680)).

1. Fleishaker JC, Herman BD, Carel BJ, Azie NE. Interaction between ketoconazole and almotriptan in healthy volunteers. *J Clin Pharmacol* (2003) 43, 423–7.
2. Relpax (Eletriptan hydrobromide). Pfizer Inc. US Prescribing information, April 2007.
3. Relpax (Eletriptan hydrobromide). Pfizer Ltd. UK Summary of product characteristics, February 2008.

Triptans + Beta blockers

The plasma levels of rizatriptan are almost doubled by propranolol. No clinically important interaction occurs between other triptans and beta blockers.

Clinical evidence, mechanism, importance and management

(a) Almotriptan

Twelve healthy subjects were given **propranolol** 80 mg twice daily for 7 days followed by a single 12.5-mg dose of almotriptan. Although some small changes were noted in the pharmacokinetics of almotriptan (e.g. AUC increased by 7%), these were not considered to be clinically significant and concurrent use of the combination was well tolerated.[1]

(b) Eletriptan

In an interaction study, 12 healthy subjects were given a single 80-mg dose of eletriptan after taking **propranolol** 80 mg twice daily for 7 days. It was found that the eletriptan AUC was increased by 30%, and the half-life increased from 4.9 to 5.2 hours. However, these changes were not considered to be clinically significant, and no significant blood pressure changes or any adverse events were seen, when compared with taking eletriptan alone.[2,3]

The UK manufacturer reports that no evidence of an interaction was seen in clinical studies where eletriptan was taken with beta blockers.[3]

(c) Frovatriptan

A single 2.5-mg oral dose of frovatriptan was given to 12 healthy subjects after they had taken **propranolol** 80 mg twice daily for 7 days. The AUC and maximum levels of frovatriptan were increased by 25% and 23%, respectively. However, these changes are small, and no changes occurred in the ECGs and vital signs of the subjects. Therefore the pharmacokinetic interaction was not thought to be of clinical significance.[4]

(d) Naratriptan

The US manufacturer of naratriptan reports that, from population pharmacokinetic analyses, beta blockers did not affect the clearance of naratriptan, and the efficacy of naratriptan was unaffected by the concurrent use of beta blockers.[5] The UK manufacturer similarly says that there is no evidence of interactions with beta blockers (none specifically named).[6]

(e) Rizatriptan

A series of double-blind, placebo-controlled studies were conducted in a total of 51 healthy subjects who were given a single 10-mg dose of rizatriptan after they had taken **propranolol** 60 or 120 mg twice daily, **nadolol** 80 mg daily, or **metoprolol** 100 mg daily, for 7 days.[7] **Nadolol** and **metoprolol** had no effect on the pharmacokinetics of rizatriptan. However, **propranolol** raised the AUC and the maximum plasma concentration of rizatriptan by 1.67 and 1.75-fold, respectively; in one subject there was a fourfold increase in the AUC. Adjusting the dose of **propranolol** and separating the administration by 2 hours had little effect on this interaction.[7] The AUC of the active *N*-monodesmethyl metabolite of rizatriptan was not affected by **propranolol**.[7]

In vitro studies have similarly shown that **propranolol** markedly inhibits the metabolism of rizatriptan, whereas **atenolol**, **nadolol** and **timolol** do not affect the metabolism of rizatriptan.[7]

The manufacturers recommend that a 5-mg dose of rizatriptan (rather than the more usual 10 mg) should be used in the presence of **propranolol**, with a maximum of two[8] or three doses in 24 hours.[9] In the UK, they also state that administration should be separated by at least 2 hours,[8] although the rationale for this is less clear given that the above study found that such a dose separation did not appear to modify the interaction. No reduction in the rizatriptan dosage would seem to be needed in the presence of **atenolol**, **metoprolol**, **nadolol** or **timolol**.

(f) Sumatriptan

In a study in 10 healthy subjects, **propranolol** 80 mg twice daily for 7 days did not alter the pharmacokinetics of a single 300-mg dose of sumatriptan given on day 7. There was no significant effect on pulse rate or blood pressure.[10] The manufacturer says that the efficacy of sumatriptan was unaffected by the concurrent use of beta blockers.[11]

(g) Zolmitriptan

In a randomised, crossover study, 12 healthy subjects were given **propranolol** 160 mg or a placebo daily for 7 days, with a single 10-mg oral dose of zolmitriptan on day 7. **Propranolol** increased the maximum serum levels and the AUC of zolmitriptan by 56% and 37%, respectively, and reduced the extent of its conversion to its active metabolite, probably due to inhibition of, or competition for, metabolism by cytochrome P450 isoenzymes. However, the higher zolmitriptan levels were not associated with a greater rise in blood pressure and it was concluded that no clinically important changes in the therapeutic effects of zolmitriptan are likely, nor are any adjustments in its dosage needed.[12]

The manufacturer says there is no evidence that the concurrent use of beta blockers, has any effect on the efficacy or unwanted effects of zolmitriptan.[13]

1. Fleishaker JC, Sisson TA, Carel BJ, Azie NE. Lack of pharmacokinetic interaction between the antimigraine compound, almotriptan, and propranolol in healthy volunteers. *Cephalalgia* (2001) 21, 61–65.
2. Milton KA, Tan L, Love R. The pharmacokinetic and pharmacodynamic interactions of oral eletriptan and propranolol in healthy volunteers. *Cephalalgia* (1998) 18, 412.
3. Relpax (Eletriptan hydrobromide). Pfizer Ltd. UK Summary of product characteristics, February 2008.
4. Buchan P, Ward C, Stewart AJ. The effect of propranolol on the pharmacokinetic and safety profiles of frovatriptan. *Headache* (1999) 39, 345.
5. Amerge (Naratriptan hydrochloride). GlaxoSmithKline. US Prescribing information, October 2007.
6. Naramig (Naratriptan hydrochloride). GlaxoSmithKline UK. UK Summary of product characteristics, October 2008.
7. Goldberg MR, Sciberras D, De Smet M, Lowry R, Tomasko L, Lee Y, Olah TV, Zhao J, Vyas KP, Halpin R, Kari PH, James I. Influence of β-adrenoceptor antagonists on the pharmacokinetics of rizatriptan, a 5-$HT_{1B/1D}$ agonist: differential effects of propranolol, nadolol and metoprolol. *Br J Clin Pharmacol* (2001) 52, 69–76.

8. Maxalt (Rizatriptan benzoate). Merck Sharp & Dohme Ltd. UK Summary of product characteristics, April 2003.
9. Maxalt (Rizatriptan benzoate). Merck & Co., Inc. US Prescribing information, February 2008.
10. Scott AK, Walley T, Breckenridge AM, Lacey LF, Fowler PA. Lack of an interaction between propranolol and sumatriptan. *Br J Clin Pharmacol* (1991) 32, 581–4.
11. Imitrex Tablets (Sumatriptan succinate). GlaxoSmithKline. US Prescribing information, October 2007.
12. Peck RW, Seaber EJ, Dixon R, Gillotin CG, Weatherley BC, Layton G, Posner J. The interaction between propranolol and the novel antimigraine agent zolmitriptan (311C90). *Br J Clin Pharmacol* (1997) 44, 595–9.
13. Zomig Tablets (Zolmitriptan). AstraZeneca UK Ltd. UK Summary of product characteristics, January 2008.

Triptans + Ergot derivatives

Theoretically additive vasoconstriction may occur when ergot derivatives and triptans are given together, although this has been demonstrated only in one study with sumatriptan. However, one isolated case report describes myocardial infarction in a woman taking sumatriptan and methysergide.
No important additive effect has been seen in pharmacodynamic studies with ergot derivatives and almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan or zolmitriptan, although minor increases in blood pressure were reported with eletriptan.

Clinical evidence

(a) Almotriptan

The manufacturer of almotriptan says that no additive vasospastic effects were seen in a clinical study in 12 healthy subjects given almotriptan and **ergotamine**.[1] However, they do note that such effects are theoretically possible.

(b) Eletriptan

The manufacturer reports that when oral **ergotamine** with caffeine was given 1 hour and 2 hours after eletriptan, minor additive increases in blood pressure were seen.[2]

(c) Frovatriptan

In a randomised, crossover study, 12 healthy subjects were given a single 5-mg dose of oral frovatriptan, a single 2-mg sublingual dose of **ergotamine**, or both drugs together. **Ergotamine** reduced the maximum levels and AUC of frovatriptan by about 25%, which was modest. However, frovatriptan had no effect on **ergotamine** pharmacokinetics, and no clinically significant changes in the haemodynamics or the ECGs of the subjects were noted.[3]

(d) Naratriptan

A study in 12 healthy subjects found that 1 mg of intramuscular **dihydroergotamine** reduced the AUC and the maximum serum levels of a single 2.5-mg dose of naratriptan by 15% and 20%, respectively, but this was not considered to be clinically relevant. Concurrent use was well tolerated and no clinically significant blood pressure, heart rate or ECG effects were seen.[4]

(e) Rizatriptan

In a pharmacodynamic study in 16 healthy subjects additive vasospastic effects were not observed when oral rizatriptan 10 mg was given with intravenous **ergotamine** 250 micrograms.[5,6]

(f) Sumatriptan

A study in 38 migraine sufferers found that 1 mg of intravenous **dihydroergotamine** caused a maximum increase in blood pressure of 13/9 mmHg, while 2 or 4 mg of subcutaneous sumatriptan caused a smaller rise in blood pressure of 7/6 mmHg. When both drugs were given together the blood pressure rises were no greater than with **dihydroergotamine** alone.[7] A clinical study found that the adverse event profile of subcutaneous sumatriptan was not affected by the concurrent use of oral **dihydroergotamine**.[8] However, another pharmacodynamic study found that subcutaneous sumatriptan and intravenous **ergotamine** had additive vasoconstrictive effects (as assessed by decreases in toe-arm systolic blood pressure gradients).[9]

Myocardial infarction has been reported in a 43-year-old woman after she took two 2-mg doses of **methysergide** 12 hours apart, followed by sumatriptan 6 mg subcutaneously. Severe chest pain and tightness with breathlessness began 15 minutes later, and results of various tests were consistent with 'coronary spasm on an area of atherosclerosis'.[10]

(g) Zolmitriptan

In a randomised, placebo-controlled study, 12 healthy subjects were given 5 mg of oral **dihydroergotamine** twice daily for 10 days, with oral zolmitriptan 10 mg (four times the usual dose) on day 10. No significant changes in blood pressure, ECGs, or zolmitriptan pharmacokinetics were seen, and concurrent use was well tolerated.[11] Another randomised, placebo-controlled study in 12 healthy subjects looked at the effects of oral zolmitriptan 20 mg (eight times the usual dose) given with oral **ergotamine** 2 mg (contained in *Cafergot* tablets; **ergotamine** 1 mg with caffeine 100 mg). Using a very detailed and thorough range of techniques, no clinically relevant cardiovascular changes were found, even at this large dose of zolmitriptan, and concurrent use was generally well tolerated. No important changes in zolmitriptan pharmacokinetics were seen.[12]

Mechanism

Vasoconstriction is a well known adverse effect of ergot derivatives, and coronary vasoconstriction may also occur rarely with the triptans. (Note that in 1992, soon after the marketing of sumatriptan, the CSM in the UK had received 34 reports of chest pain or tightness caused by sumatriptan, possibly due to coronary vasoconstriction.[13]) It is therefore theoretically possible that the drugs may have additive vasoconstrictive effects, although there is little evidence of this in practice.

Importance and management

Due to the theoretical risk of additive vasoconstriction, and possible significant coronary vasoconstriction ergot derivatives are generally contraindicated with the triptans.

The UK manufacturer of sumatriptan says that ergotamine should not be given less than 6 hours after taking the triptan, and recommends that the triptan should not be taken less than 24 hours after taking ergotamine.[14] The same recommendations are made by the UK manufacturers of almotriptan,[1] rizatriptan,[5] and zolmitriptan.[15] The UK manufacturers of eletriptan,[2] and frovatriptan,[16] recommend that ergot derivatives are not given for a minimum of 24 hours (not just 6 hours) after these triptans, and in general, in the US, it is recommended that triptans and ergotamine or ergot-type medication should not be taken within 24 hours of each other. In the absence of specific guidance for individual triptans, it would seem prudent to follow this advice.

1. Almogran (Almotriptan hydrogen malate). Organon Laboratories Ltd. UK Summary of product characteristics, April 2007.
2. Relpax (Eletriptan hydrobromide). Pfizer Ltd. UK Summary of product characteristics, February 2008.
3. Buchan P, Ward C, Oliver SD. Lack of clinically significant interactions between frovatriptan and ergotamine. *Cephalalgia* (1999) 19, 364.
4. Kempsford RD, Nicholls B, Lam R, Wintermute S. A study to investigate the potential interaction of naratriptan and dihydroergotamine. 8th International Headache Congress, Amsterdam, June 1997.
5. Maxalt (Rizatriptan benzoate). Merck Sharp & Dohme Ltd. UK Summary of product characteristics, April 2003.
6. Tfelt-Hansen P, Seidelin K, Stepanavage M, Lines C. The effect of rizatriptan, ergotamine, and their combination on human peripheral arteries: a double-blind, placebo-controlled, crossover study in normal subjects. Br J Clin Pharmacol. (2002) 54, 38–44.
7. Fowler PA, Lacey LF, Thomas M, Keene ON, Tanner RJN, Baber NS. The clinical pharmacology, pharmacokinetics and metabolism of sumatriptan. *Eur Neurol* (1991) 31, 291–4.
8. Henry P, d'Allens H, and the French Migraine Network Bordeaux-Lyon-Grenoble. Subcutaneous sumatriptan in the acute treatment of migraine in patients using dihydroergotamine as prophylaxis. *Headache* (1993) 33, 432–5.
9. Tfelt-Hansen P, Sperling B, Winter PDO'B. Transient additional effect of sumatriptan on ergotamine-induced constriction of peripheral arteries in man. *Clin Pharmacol Ther* (1992) 51, 149.
10. Liston H, Bennett L, Usher B, Nappi J. The association of the combination of sumatriptan and methysergide in myocardial infarction in a premenopausal woman. *Arch Intern Med* (1999) 159, 511–13.
11. Veronese L, Gillotin C, Marion-Gallois R, Weatherley BC, Thebault JJ, Guillaume M, Peck RW. Lack of interaction between oral dihydroergotamine and the novel antimigraine compound zolmitriptan in healthy volunteers. *Clin Drug Invest* (1997) 14, 217–20.
12. Dixon RM, Meire HB, Evans DH, Watt H, On N, Posner J, Rolan PE. Peripheral vascular effects and pharmacokinetics of the antimigraine compound, zolmitriptan, in combination with oral ergotamine in healthy volunteers. *Cephalalgia* (1997) 17, 639–46.
13. Committee on Safety of Medicines. Sumatriptan (Imigran) and chest pain. *Current Problems* (1992) 34, 2.
14. Imigran Tablets (Sumatriptan succinate). GlaxoSmithKline UK. UK Summary of product characteristics, June 2008.
15. Zomig Tablets (Zolmitriptan). AstraZeneca UK Ltd. UK Summary of product characteristics, January 2008.
16. Migard (Frovatriptan succinate monohydrate). A. Menarini Pharma UK SRL. UK Summary of product characteristics, July 2008.

Triptans + Flunarizine

Flunarizine did not alter the pharmacokinetics or pharmacodynamics of sumatriptan in one study. Flunarizine does not appear to interact with eletriptan.

Clinical evidence, mechanism, importance and management

(a) Eletriptan

The manufacturer notes that although no formal interaction studies have been carried out, there was no evidence of an interaction between eletriptan and flunarizine in clinical studies.[1]

(b) Sumatriptan

A double-blind study in healthy subjects found that flunarizine 10 mg daily for 8 days had no effect on the pharmacokinetics of a single dose of sumatriptan, and the combination caused no significant changes in blood pressure, ECG or heart rate.[2]

1. Relpax (Eletriptan hydrobromide). Pfizer Ltd. UK Summary of product characteristics, February 2008.
2. Van Hecken AM, Depré M, De Schepper PJ, Fowler PA, Lacey LF, Durham JM. Lack of effect of flunarizine on the pharmacokinetics and pharmacodynamics of sumatriptan in healthy volunteers. *Br J Clin Pharmacol* (1992) 34, 82–4.

Triptans + Macrolides

Erythromycin markedly raises the plasma levels of eletriptan; clarithromycin, josamycin and troleandomycin are predicted to interact similarly. Erythromycin is predicted to raise almotriptan levels. Clarithromycin does not significantly alter the pharmacokinetics of sumatriptan.

Clinical evidence

(a) Eletriptan

A clinical pharmacokinetic study by the manufacturer of eletriptan[1] found that **erythromycin** 1 g increased the maximum serum levels and AUC of eletriptan twofold and 3.6-fold, respectively, and prolonged its half-life from 4.6 to 7.1 hours.

(b) Sumatriptan

A study in which 24 healthy subjects were given sumatriptan 50 mg on the morning of the fourth day of a course of **clarithromycin** 500 mg twice daily, found that **clarithromycin** did not significantly affect the pharmacokinetics of sumatriptan.[2]

Mechanism

The macrolides are, to varying degrees, inhibitors of the cytochrome P450 isoenzyme CYP3A4, by which eletriptan is metabolised. Therefore erythromycin reduces eletriptan metabolism and raises its plasma levels. Sumatriptan is not metabolised by CYP3A4 and therefore does not interact with clarithromycin.

Importance and management

Information is limited but an interaction between eletriptan and erythromycin appears to be established. Because of the elevated levels seen, the UK manufacturer advises against their concurrent use.[1] Similarly, other drugs that are moderate to potent CYP3A4 inhibitors, including **clarithromycin**[1,3] **josamycin**,[1] and troleandomycin,[3] are predicted to raise serum eletriptan levels, and should also not be used with eletriptan. The US manufacturer recommends that eletriptan should not be given within 72 hours of potent CYP3A4 inhibitors, and they specifically name **clarithromycin** and **troleandomycin**.[3] Note that the macrolides differ in their ability to inhibit CYP3A4, see 'Ergot derivatives + Macrolides', p.683.

Almotriptan is also metabolised, at least in part, by CYP3A4. The US manufacturer therefore reasonably predicts that its levels may be raised by erythromycin.[4] However, note that, based on its interaction with 'ketoconazole', (p.685), dosage adjustments would not be expected to be necessary.

Other triptans would be expected to have little or no interaction with the macrolides as they are not predominantly metabolised by CYP3A4 (see 'Table 16.2', (p.680)).

1. Relpax (Eletriptan hydrobromide). Pfizer Ltd. UK Summary of product characteristics, February 2008.
2. Moore KHP, Leese PT, McNeal S, Gray P, O'Quinn S, Bye C, Sale M. The pharmacokinetics of sumatriptan when administered with clarithromycin in healthy volunteers. *Clin Ther* (2002) 24, 583–94.
3. Relpax (Eletriptan hydrobromide). Pfizer Inc. US Prescribing information, April 2007.
4. Axert (Almotriptan malate). Ortho-McNeil Pharmaceutical Inc. US Prescribing Information, May 2007.

Triptans + MAOIs

Moclobemide (a RIMA) markedly inhibits the metabolism of rizatriptan, modestly inhibits the metabolism of zolmitriptan, and approximately doubles the bioavailability of sumatriptan. Moclobemide has no clinically significant pharmacokinetic effect on almotriptan, and is not expected to affect the pharmacokinetics of eletriptan, frovatriptan, or naratriptan. Non-selective MAOIs (e.g. phenelzine) would be expected to behave similarly.
Selegiline (an MAO-B inhibitor) does not alter the pharmacokinetics of sumatriptan or zolmitriptan, and would not be expected to alter the pharmacokinetics of the other triptans.
Some have suggested that there may be a pharmacodynamic interaction between MAOIs (both selective and non-selective) and triptans, which may result in serotonin syndrome.

Clinical evidence

(a) Almotriptan

In a study, 12 healthy subjects were given **moclobemide** 150 mg twice daily for 8 days with a single 12.5-mg dose of almotriptan on day 8. The AUC of almotriptan was increased by 37%, its clearance was decreased by 27% and its half-life was increased by 24%, but this was not considered to be clinically significant.[1]

(b) Frovatriptan

A study in 9 healthy subjects given a single 2.5-mg oral dose of frovatriptan after taking **moclobemide** 150 mg twice daily for 7 days did not find any pharmacokinetic changes, or any alterations in the vital signs and ECGs of the subjects.[2]

(c) Rizatriptan

In a randomised, placebo-controlled study, 12 healthy subjects were given **moclobemide** 150 mg three times daily for 4 days, with a single 10-mg dose of rizatriptan on day 4. **Moclobemide** increased the AUCs of rizatriptan and its active (but minor) metabolite by 2.2- and 5.3-fold, respectively, and increased their maximum serum levels by 1.4- and 2.6-fold, respectively. Despite these rises, the concurrent use of these drugs was well tolerated and any adverse effects were mild and similar to those seen when rizatriptan was given with placebo.[3]

(d) Sumatriptan

Three groups of 14 subjects were given placebo, **moclobemide** 150 mg three times daily, or **selegiline** 5 mg twice daily for 8 days, with subcutaneous sumatriptan 6 mg on day 8. No statistically significant differences in pulse rates or blood pressures were seen between any of the groups. However, the AUC of sumatriptan in the **moclobemide**-treated group was approximately doubled (129% increase), its clearance was reduced by 56%, and its half-life increased by 52%. The pharmacokinetic changes seen in the **selegiline** group were not consistent. There were no differences in the adverse events experienced by any of the three groups.[4]

A comprehensive search of the literature, and reports from proprietary manufacturers, identified published reports of 31 patients taking sumatriptan and MAOIs concurrently, but no adverse events were reported.[5] Furthermore, a patient taking **moclobemide** 300 mg three times daily had no adverse effects when given oral sumatriptan 100 mg on six occasions.[6] However, a patient who had taken an overdose of **moclobemide**, together with sumatriptan, sertraline, and citalopram developed serotonin syndrome.[7]

(e) Zolmitriptan

In a series of randomised studies, 12 healthy subjects were given **selegiline** 10 mg daily or **moclobemide** 150 mg twice daily for 7 days, with a single 10-mg oral dose of zolmitriptan on day 7.[8] **Moclobemide** increased

the AUCs of zolmitriptan and its active metabolite, by 26% and threefold, respectively.[9]

In another study, **selegiline** had no effect on the pharmacokinetics of zolmitriptan or its metabolites, apart from a small (7%) reduction in its renal clearance.[8]

Mechanism

Almotriptan, rizatriptan, sumatriptan and zolmitriptan are substrates of MAO-A. Therefore moclobemide, an inhibitor of MAO-A, can reduce their metabolism, resulting in raised levels. The effect differs between the triptans as less than half of a dose of almotriptan is metabolised by MAO-A,[10] whereas MAO-A is the principal enzyme concerned with the metabolism of rizatriptan[3] and sumatriptan.[11] Frovatriptan is not metabolised by MAO-A, and therefore its pharmacokinetics are not affected by moclobemide.

Importance and management

The interactions of moclobemide with **rizatriptan** or **sumatriptan** are established, and clinically relevant. The UK and US manufacturers contraindicate their use both during, and for 2 weeks after, the use of both non-selective MAOIs (e.g. phenelzine) and moclobemide because of the risks of coronary vasospasm.[12-15]

The interaction with **zolmitriptan** is modest, although levels of its active metabolite are more markedly raised. The US manufacturer contraindicates its use both during, and for 2 weeks after, the use of moclobemide,[16] whereas the UK manufacturer restricts the dose of zolmitriptan to 5 mg in 24 hours.[9] In the absence of any direct information it would seem prudent to apply these warnings to the use of non-selective MAOIs.

The interaction of moclobemide with **almotriptan** is slight, and no dosage adjustments would be expected to be necessary with any selective or non-selective MAOI.

Moclobemide did not affect the pharmacokinetics of **frovatriptan**, and would not be expected to affect the pharmacokinetics of **eletriptan** or **naratriptan**, as they, like frovatriptan, are not metabolised by MAO-A, see 'Table 16.2', (p.680). Similarly, non-selective inhibitors of MAO would not be expected to interact.

Selegiline, a selective inhibitor of MAO-B, does not affect the pharmacokinetics of sumatriptan or zolmitriptan, and would not be expected to alter the metabolism of any other triptan. Other MAO-B inhibitors, such as rasagiline, would also therefore not be expected to interact. However, note that the MAO-B selectivity of selegiline is lost at doses above 10 mg daily.

One isolated UK manufacturer of selegiline contraindicates its use with triptans and recommends a time interval of 24 hours between discontinuation of selegiline and initiation of serotonin agonists.[17] This is possibly because of a theoretical possibility of 'serotonin syndrome', (p.9), developing on concurrent use. The manufacturers of almotriptan,[18] and frovatriptan,[19] also warn of the possibility of serotonin syndrome with MAOIs. The syndrome is rare and it may (so it has been suggested[20]) sometimes be an idiosyncratic reaction.

1. Fleishaker JC, Ryan KK, Jansat JM, Carel BJ, Bell DJA, Burke MT, Azie NE. Effect of MAO-A inhibition on the pharmacokinetics of almotriptan, an antimigraine agent in humans. *Br J Clin Pharmacol* (2001) 51, 437–41.
2. Buchan P, Ward C, Freestone S. Lack of interaction between frovatriptan and monoamine oxidase inhibitor. *Cephalalgia* (1999) 19, 364.
3. van Haarst AD, van Gerven JMA, Cohen AF, De Smet M, Sterrett A, Birk KL, Fisher AL, De Puy ME, Goldberg MR, Musson DG. The effects of moclobemide on the pharmacokinetics of the 5-$HT_{1B/1D}$ agonist rizatriptan in healthy volunteers. *Br J Clin Pharmacol* (1999) 48, 190–96.
4. Glaxo Pharmaceuticals UK Limited. A study to determine whether the pharmacokinetics, safety or tolerability of subcutaneously administered sumatriptan (6 mg) are altered by interaction with concurrent oral monoamine oxidase inhibitors. Data on file (Protocol C92–050), 1993.
5. Gardner DM, Lynd LD. Sumatriptan contraindications and the serotonin syndrome. *Ann Pharmacother* (1998) 32, 33–38.
6. Blier P, Bergeron R. The safety of concomitant use of sumatriptan and antidepressant treatments. *J Clin Psychopharmacol* (1995) 15, 106–9.
7. Höjer J, Personne M, Skagius A-S, Hansson O. Serotoninergt syndrom: flera allvarliga fall med denna ofta förbisedda diagnos. *Lakartidningen* (2002) 99, 2054–5, 2058–60.
8. Rolan P. Potential drug interactions with the novel antimigraine compound zolmitriptan (Zomig™, 311C90). *Cephalalgia* (1997) 17 (Suppl 18), 21–7.
9. Zomig Tablets (Zolmitriptan). AstraZeneca UK Ltd. UK Summary of product characteristics, January 2008.
10. Axert (Almotriptan malate). Ortho-McNeil Pharmaceutical Inc. US Prescribing Information, May 2007.
11. Dixon CM, Park GR, Tarbit MH. Characterization of the enzyme responsible for the metabolism of sumatriptan in human liver. *Biochem Pharmacol* (1994) 47, 1253–7.
12. Maxalt (Rizatriptan benzoate). Merck Sharp & Dohme Ltd. UK Summary of product characteristics, April 2003.
13. Maxalt (Rizatriptan benzoate). Merck & Co., Inc. US Prescribing information, February 2008.
14. Imigran Tablets (Sumatriptan succinate). GlaxoSmithKline UK. UK Summary of product characteristics, June 2008.
15. Imitrex Tablets (Sumatriptan succinate). GlaxoSmithKline. US Prescribing information, October 2007.
16. Zomig (Zolmitriptan). AstraZeneca Pharmaceuticals LP. US Prescribing information, October 2008.
17. Zelapar (Selegiline hydrochloride). Cephalon Ltd. UK Summary of product characteristics, September 2008.
18. Almogran (Almotriptan hydrogen malate). Organon Laboratories Ltd. UK Summary of product characteristics, April 2007.
19. Migard (Frovatriptan succinate monohydrate). A. Menarini Pharma UK SRL. UK Summary of product characteristics, July 2008.
20. Mathew NT, Tietjen GE, Lucker C. Serotonin syndrome complicating migraine pharmacotherapy. *Cephalalgia* (1996) 16, 323–7.

Triptans + Paracetamol (Acetaminophen)

Paracetamol causes a slight increase in zolmitriptan levels and zolmitriptan causes a slight reduction in the rate and extent of paracetamol absorption, but this does not appear to be clinically relevant. Sumatriptan also delays paracetamol absorption.

Clinical evidence, mechanism, importance and management

In a randomised, crossover study, 15 healthy subjects were given a single 10-mg dose of **zolmitriptan**, alone or with 1 g of paracetamol. Paracetamol increased the maximum plasma levels and AUC of **zolmitriptan** by 11%, while reducing its renal clearance by 9%. The paracetamol maximum plasma levels and AUC were reduced by 31% and 11%, respectively, and absorption was delayed (time to achieve maximum plasma levels increased from 45 minutes to 3 hours). The presence of oral metoclopramide 10 mg did not affect the interaction between **zolmitriptan** and paracetamol.[1] The authors considered that the small changes in pharmacokinetics seen were of no clinical relevance.[1]

Similarly, in a study in 9 migraine patients, pretreatment with oral **sumatriptan** 100 mg delayed paracetamol absorption and reduced its maximum plasma concentration by 50%, but the total absorption of paracetamol over 8 hours was not significantly altered.[2] It has been suggested that **sumatriptan** and **zolmitriptan** might have some inhibitory effect on gastric emptying thereby slowing the absorption of paracetamol,[1,2] and although this appears to occur, it does not appear to be clinically relevant.

1. Seaber EJ, Ridout G, Layton G, Posner J, Peck RW. The novel anti-migraine compound zolmitriptan (Zomig 311C90) has no clinically significant interactions with paracetamol or metoclopramide. *Eur J Clin Pharmacol* (1997) 53, 229–34.
2. Rani PU, Naidu MUR, Rao TRK, Das SM, Shobha JC, Sekhar KR, Sekhar EC, Kumar TV. Sumatriptan delays paracetamol absorption in migraine patients. *Clin Drug Invest* (1996) 11, 300–4.

Triptans + Pizotifen

Pizotifen does not alter the pharmacokinetics or pharmacodynamics of sumatriptan or zolmitriptan, and does not alter the efficacy of acute sumatriptan for migraine. It seems unlikely that any of the other triptans will interact with pizotifen.

Clinical evidence

(a) Sumatriptan

Pizotifen 500 micrograms three times daily for 8 days was found to have no significant effect on the pharmacokinetics of sumatriptan in 14 healthy subjects. In addition, no significant changes in blood pressure or heart rate occurred.[1] In a clinical study, pizotifen prophylaxis did not alter the efficacy of acute sumatriptan for migraine relief. In this study, the combination was associated with more weight gain than sumatriptan alone, an effect that was attributed solely to the pizotifen.[2]

(b) Zolmitriptan

In a placebo-controlled, randomised study, 12 healthy subjects were given pizotifen 1.5 mg daily for 8 days, with oral zolmitriptan 10 mg on day 8. Pizotifen did not significantly alter the pharmacokinetics of zolmitriptan, and no clinically relevant changes in heart rates or ECGs or blood pressures were seen as a result of concurrent use.[3]

Mechanism, importance and management

Although the information is limited, it shows that no sumatriptan or zolmitriptan dosage adjustments are expected to be needed if used with pizo-

tifen, and concurrent use appears safe. On the basis of the information about sumatriptan and zolmitriptan it seems unlikely that any of the other triptans will interact.

1. Fowler PA, Lacey LF, Thomas M, Keene ON, Tanner RJN, Baber NS. The clinical pharmacology, pharmacokinetics and metabolism of sumatriptan. *Eur Neurol* (1991) 31, 291–4.
2. Cleland PG, Barnes D, Elrington GM, Loizou LA, Rawes GD. Studies to assess if pizotifen prophylaxis improves migraine beyond the benefit offered by acute sumatriptan therapy alone. *Eur Neurol* (1997) 38, 31–8.
3. Seaber EJ, Gillotin C, Mohanlal R, Layton G, Posner J, Peck R. Lack of interaction between pizotifen and the novel antimigraine compound zolmitriptan in healthy volunteers. *Clin Drug Invest* (1997) 14, 221–5.

Triptans + Protease inhibitors

Protease inhibitors such as ritonavir, indinavir or nelfinavir would be expected to markedly increase the levels of eletriptan. Ritonavir is also expected to increase the levels of almotriptan.

Clinical evidence, mechanism, importance and management

The manufacturers state that the concurrent use of eletriptan and ritonavir, indinavir, or nelfinavir should be avoided, because these protease inhibitors are potent inhibitors of the cytochrome P450 isoenzyme CYP3A4, an enzyme involved in the metabolism of eletriptan. Concurrent use would therefore be expected to markedly increase eletriptan levels.[1,2] In addition, the US manufacturer recommends that eletriptan should not be given within 72 hours of ritonavir and nelfinavir.[2] This predicted interaction is based on the known interaction with 'erythromycin', (p.688), and 'ketoconazole', (p.685). Similar predictions are made by the manufacturer of almotriptan; they advise that increased exposure to almotriptan may be expected with the use of ritonavir.[3] It is unclear what the clinical significance of this effect may be.

1. Relpax (Eletriptan hydrobromide). Pfizer Ltd. UK Summary of product characteristics, February 2008.
2. Relpax (Eletriptan hydrobromide). Pfizer Inc. US Prescribing information, April 2007.
3. Axert (Almotriptan malate). Ortho-McNeil Pharmaceutical Inc. US Prescribing Information, May 2007.

Triptans + SSRIs or SNRIs

The SSRIs normally appear not to interact with the triptans, but there are a few rare cases of dyskinesias when sumatriptan was given with an SSRI, and there is some evidence to suggest that serotonin syndrome may occasionally develop. The SNRIs venlafaxine, duloxetine and milnacipran are predicted to interact similarly. Fluvoxamine modestly inhibits the metabolism of frovatriptan, and may inhibit the metabolism of zolmitriptan.

Clinical evidence

The FDA in the US has reviewed 27 reports of serotonin syndrome associated with the concurrent use of an SSRI or SNRI (e.g. **duloxetine** or **venlafaxine**) and a triptan. Two reports described life-threatening events and 13 reports stated that the patients required hospitalisation. Some of the cases occurred in patients who had previously taken an SSRI or SNRI with a triptan without experiencing serotonin syndrome. In 8 cases, recent dose increases or the addition of another serotonergic drug had occurred around the time of symptom onset: the median time to onset was one day, with a range of 10 minutes to 6 days.[1] Reports describing interactions with specific triptans are outlined in the subsections below.

(a) Almotriptan

Fluoxetine 60 mg daily was given to 14 healthy subjects for 8 days, with a single 12.5-mg dose of almotriptan on day 8. **Fluoxetine** raised the maximum plasma levels of almotriptan by about 18%. The combination was well tolerated and caused no ECG changes, so no dose alterations were considered necessary.[2]

(b) Eletriptan

The manufacturer notes that although no formal interaction studies have been done, there was no evidence of an interaction between eletriptan and SSRIs in clinical studies, and that in population pharmacokinetic studies SSRIs appeared unlikely to alter the pharmacokinetics of eletriptan.[3] A retrospective review of seven double-blind studies identified 253 patients who had received eletriptan with an SSRI and 3908 patients who received eletriptan alone. There were no clinically significant differences with respect to the incidence of adverse effects between the two groups.[4]

(c) Frovatriptan

Fluvoxamine has been shown to increase the blood levels of frovatriptan by 27 to 49%.[5]

(d) Naratriptan

The UK manufacturer of naratriptan notes that there is no evidence of interactions with SSRIs.[6]

(e) Rizatriptan

In a placebo-controlled study, 12 healthy subjects were given a single 10-mg dose of rizatriptan after they took **paroxetine** 20 mg daily for 14 days. The plasma levels of rizatriptan and its active metabolite were not altered by **paroxetine**, and no adverse effects were seen. Safety evaluations included blood pressure, heart rate, temperature and a visual analogue assessment of mood. There was no evidence of serotonin syndrome.[7]

(f) Sumatriptan

A study in 11 healthy subjects found that **paroxetine** 20 mg daily for 16 days had no effect on the response to a 6-mg dose of subcutaneous sumatriptan, as measured by prolactin levels. The sumatriptan levels remained unaltered, its cardiovascular effects were unchanged and no clinically significant adverse effects occurred.[8] Other studies report that the concurrent use of sumatriptan and SSRIs (**fluoxetine** 20 to 60 mg daily, **fluvoxamine** 200 mg daily, **paroxetine** 20 to 50 mg daily, **sertraline** 50 to 100 mg daily) was successful and uneventful.[9,10] No adverse effects have been noted in 148 other patients.[11]

A prospective study of 12 339 individuals receiving sumatriptan by injection identified 14.5% of these (1784) who were also taking SSRIs (**fluoxetine** 8.3%, **sertraline** 5.5%, **paroxetine** 3.9%, other 0.4%) or **venlafaxine** 1.7%. Patients taking SSRIs were found to have a higher absolute frequency of adverse neurological effects, when compared with those not taking antidepressants (0.8% and 0.25%, respectively). Nevertheless, the authors concluded that there was no evidence of an interaction as the adverse events occurred more than 24 hours after sumatriptan was given.[12]

However, a case report describes a 65-year-old woman who had been taking **paroxetine** 20 mg [daily] for a number of years, who developed confusion, strange behaviour, sinus tachycardia, hypertension and hyperthermia shortly after starting sumatriptan. Serotonin syndrome was diagnosed, and she recovered completely when both drugs were withdrawn.[13]

Additionally, in Canada, post-marketing surveillance of the voluntary reports received by the manufacturers of **fluoxetine** identified 2 cases that showed good evidence, and another 4 cases that showed some, but not strong evidence, of reactions consistent with serotonin syndrome in patients also taking sumatriptan.[14] Other cases describe a decrease in the efficacy of sumatriptan with **fluoxetine**,[15] dyskinesias and dystonias with sumatriptan and **paroxetine**,[16] and twenty possible cases of serotonin syndrome with sumatriptan and SSRIs.[11,17]

The manufacturers of sumatriptan also say that they have rare post-marketing reports of weakness, hyperreflexia and incoordination following the use of sumatriptan and SSRIs.[18]

(g) Zolmitriptan

A placebo-controlled, crossover study in 20 subjects given **fluoxetine** 20 mg daily for 28 days, with zolmitriptan 10 mg on day 28, found that the pharmacokinetics of zolmitriptan were unaffected by **fluoxetine**.[19] Only very slight changes were seen in the pharmacokinetics of its active metabolite.[19] **Sertraline**, **paroxetine**, and **citalopram** are also not expected to alter the pharmacokinetics of zolmitriptan. However, **fluvoxamine**, a potent CYP1A2 inhibitor, is predicted to increase levels of zolmitriptan,[20] based on the known interaction with cimetidine (see 'Triptans; Zolmitriptan + Cimetidine', p.692).

Mechanism

Not understood. SSRIs increase the levels of 5-HT (serotonin) at post-synaptic receptors. In theory the triptans (5-HT_1 agonists) might possibly add to the effects of these increased levels of serotonin, but in practice it is questionable whether this is normally clinically relevant. Fluvoxamine probably inhibits the metabolism of frovatriptan[21] by cytochrome P450 isoenzyme CYP1A2, and is predicted to interact with zolmitriptan[20] by the same mechanism.

Importance and management

The weight of evidence suggests that the concurrent use of the triptans and SSRIs is normally uneventful, but adverse reactions do occur occasionally. SSRIs have frequently been prescribed with triptans and a drug interaction causing the serotonin syndrome appears to be extremely rare.[22,23] The authors of some of the references above concluded that their findings do not imply that concurrent use should be avoided, but that caution and close monitoring should be used.[11,14] Signs of serotonin syndrome include agitation, hyperthermia, tachycardia, weakness, hyperreflexia, and incoordination. Monitoring is particularly advisable during treatment initiation and dose increases. The FDA in the US recommends that patients given a triptan with an SSRI or SNRI should be informed of the possibility of serotonin syndrome and be carefully observed.[1] Similar advice is given by most US and UK manufacturers of SSRIs, SNRIs, and triptans; the exception being the UK manufacturers of sertraline, who cautiously state that, until further data are available, serotonergic drugs such as sumatriptan should not be used concurrently, due to a possible enhancement of 5-HT associated effects.[24,25] The manufacturer of **milnacipran** similarly states that it should not be used with triptans, and that one week should elapse after stopping milnacipran before starting a triptan.[26]

Fluvoxamine is predicted to have a pharmacokinetic interaction with zolmitriptan and therefore the manufacturer recommends a maximum dosage of 5 mg in 24 hours in the presence of fluvoxamine.[20] A similar pharmacokinetic interaction may also occur between fluvoxamine and frovatriptan, and the manufacturer advises caution and strict adherence to the recommended dose.[21]

1. FDA Information for Healthcare Professionals. Selective serotonin reuptake inhibitors (SSRIs) selective serotonin-norepinephrine reuptake inhibitors (SNRIs) 5-hydroxytryptamine receptor agonists (triptans). July 19, 2006. Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/ucm085845.htm (accessed 09/02/10).
2. Fleishaker JC, Ryan KK, Carel BJ, Azie NE. Evaluation of the potential pharmacokinetic interaction between almotriptan and fluoxetine in healthy volunteers. *J Clin Pharmacol* (2001) 41, 217–23.
3. Relpax (Eletriptan hydrobromide). Pfizer Ltd. UK Summary of product characteristics, February 2008.
4. Hettiarachchi J, Turrall K. Concomitant eletriptan and selective serotonin reuptake inhibitor therapy for migraine patients: a review of seven clinical studies. *Cephalalgia* (2001) 21, 431.
5. Wade A, Buchan P, Mant T, Ward C. Frovatriptan has no clinically significant interaction with fluvoxamine. *Cephalalgia* (2001) 21, 427.
6. Naramig (Naratriptan hydrochloride). GlaxoSmithKline UK. UK Summary of product characteristics, October 2008.
7. Goldberg MR, Lowry RC, Musson DG, Birk KL, Fisher A, DePuy ME, Shadle CR. Lack of pharmacokinetic and pharmacodynamic interaction between rizatriptan and paroxetine. *J Clin Pharmacol* (1999) 39, 192–9.
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13. Hendrix Y, van Zagten MSG. Het serotoninesyndroom bij gelijktijdig gebruik van paroxetine en sumatriptan. *Ned Tijdschr Geneeskd* (2005) 149, 888–90.
14. Joffe RT, Sokolov STH. Co-administration of fluoxetine and sumatriptan: the Canadian experience. *Acta Psychiatr Scand* (1997) 95, 551–2.
15. Szabo CP. Fluoxetine and sumatriptan: possibly a counterproductive combination. *J Clin Psychiatry* (1995) 56, 37–8.
16. Abraham JT, Brown R, Meltzer HY. Clozapine treatment of persistent paroxysmal dyskinesia associated with concomitant paroxetine and sumatriptan use. *Biol Psychiatry* (1997) 42, 144–6.
17. Mathew NT, Tietjen GE, Lucker C. Serotonin syndrome complicating migraine pharmacotherapy. *Cephalalgia* (1996) 16, 323–7.
18. GlaxoWellcome. Personal communication, August 1997.
19. Smith DA, Cleary EW, Watkins S, Huffman CS, Polvino WJ. Zolmitriptan (311C90) does not interact with fluoxetine in healthy volunteers. *Int J Clin Pharmacol Ther* (1998) 36, 301–5.
20. Zomig Tablets (Zolmitriptan). AstraZeneca UK Ltd. UK Summary of product characteristics, January 2008.
21. Migard (Frovatriptan succinate monohydrate). A. Menarini Pharma UK SRL. UK Summary of product characteristics, July 2008.
22. Tepper S, Allen C, Sanders D, Greene A, Boccuzzi S. Coprescription of triptans with potentially interacting medications: a cohort study involving 240 268 patients. *Headache* (2003) 43, 44–8.
23. Shapiro RE, Tepper SJ. The serotonin syndrome, triptans, and the potential for drug–drug interactions. *Headache* (2007) 47, 266–9.
24. Lustral (Sertraline hydrochloride). Pfizer Ltd. UK Summary of product characteristics, January 2009.
25. Sertraline Tablets (Sertraline hydrochloride). Wockhardt UK Ltd. UK Summary of product characteristics, January 2009.
26. Ixel (Milnacipran). Pierre Fabre Médicament. French Summary of Product Characteristics, February 2003.

Triptans + St John's wort (*Hypericum perforatum*)

Serotonin syndrome has been reported in a patient taking eletriptan and St John's wort.

Clinical evidence

A 28-year-old woman who had been taking fluoxetine 60 mg daily for one year for an eating disorder, and St John's wort (dose and frequency not stated) for one month, suffered a loss of consciousness, convulsions, and mental confusion after **eletriptan** 40 mg daily was started 3 days earlier for a recurrent migraine. Previous use of **eletriptan** and fluoxetine had not resulted in any reported adverse effects. After admission to hospital, the patient developed acute rhabdomyolysis and transient mild acute renal failure. Serotonin syndrome was diagnosed, all medications were stopped, and the symptoms gradually resolved over 10 days.[1]

Mechanism

Additive serotonergic effects are the likely explanation for the case report above as serotonin syndrome has been reported with both St John's wort[2] and with the triptans alone.

Importance and management

The CSM/MCA in the UK note that potentiation of serotonergic effects have been identified between the triptans and St John's wort leading to an increased risk of adverse effects. They advise that patients taking triptans should not take St John's wort preparations.[3,4] However, most UK manufacturers of triptans simply warn about the potential increase in undesirable effects. The possible concern is that concurrent use may result in the development of serotonin syndrome. For more information on serotonin syndrome, see under 'Additive or synergistic interactions', (p.9).

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2. Demott K. St. John's wort tied to serotonin syndrome. *Clin Psychiatry News* (1998) 26, 28.
3. Committee on Safety of Medicines/Medicines Control Agency. Reminder: St John's Wort (*Hypericum perforatum*) interactions. *Current Problems* (2000) 26, 6–7.
4. Henderson L, Yue QY, Bergquist C, Gerden B, Arlett P. St John's wort (*Hypericum perforatum*): drug interactions and clinical outcomes. *Br J Clin Pharmacol* (2002) 54, 349–56.

Triptans + Tobacco

The clearance of naratriptan, and possibly frovatriptan, is modestly increased by smoking. However, this is unlikely to be clinically relevant. One large study found no evidence of an interaction between smoking and sumatriptan.

Clinical evidence

(a) Frovatriptan

In a retrospective analysis of pharmacokinetic data from phase I studies, there was a trend for a lower frovatriptan AUC and maximum plasma level in smokers, when compared with non-smokers. The clearance tended to be higher but the half-life did not differ.[1]

(b) Naratriptan

The manufacturer notes that smoking increases the clearance of naratriptan by 30%.[2]

(c) Sumatriptan

A prospective study of 12 339 individuals receiving sumatriptan by injection identified 18.3% of these (2262) who were current smokers. There was no evidence of an interaction between sumatriptan and tobacco smoking.[3]

Mechanism

Tobacco smoke is known to induce the cytochrome P450 isoenzyme CYP1A2, which metabolises both naratriptan and frovatriptan to some extent. **Zolmitriptan** is also a substrate of CYP1A2, but the effect of smoking does not appear to have been studied.

Importance and management

Although data are limited, the possible small changes in the pharmacokinetics of frovatriptan and naratriptan with smoking are unlikely to be clinically relevant.

1. Buchan P. Effects of alcohol, smoking and oral contraceptives on the pharmacokinetics of frovatriptan. *Eur J Neurol* (2000) 7 (Suppl 3), 86–7.
2. Amerge (Naratriptan hydrochloride). GlaxoSmithKline. US Prescribing information, October 2007.
3. Putnam GP, O'Quinn S, Bolden-Watson CP, Davis RL, Gutterman DL, Fox AW. Migraine polypharmacy and the tolerability of sumatriptan: a large-scale, prospective study. *Cephalalgia* (1999) 19, 668–75.

Triptans + Verapamil

Verapamil markedly raises the plasma levels of eletriptan, but only slightly increases the plasma levels of almotriptan.

Clinical evidence, mechanism, importance and management

(a) Almotriptan

In a crossover study, 12 healthy subjects were given a single 12.5-mg dose of almotriptan, either alone or after they had taken sustained-release verapamil 120 mg twice daily for 7 days. Verapamil increased the AUC and maximum plasma level of almotriptan by about 20% and 24%, respectively. However, the only effect this caused was a slight increase in systolic BP (8 mmHg), which occurred 2 hours after the dose. It was suggested that verapamil might inhibit the metabolism of almotriptan by the cytochrome P450 isoenzyme CYP3A4.[1] The pharmacokinetic changes are slight, and no dosage adjustments or particular precautions would appear to be necessary on concurrent use.

(b) Eletriptan

In a clinical study, verapamil 480 mg markedly raised the maximum plasma levels and AUC of eletriptan by 2.2-fold and 2.7-fold, respectively.[2,3] The UK manufacturer states that these increases are not considered to be clinically significant as there were no associated increases in blood pressure or adverse events, when compared with eletriptan alone.[2]

1. Fleishaker JC, Sisson TA, Carel BJ, Azie NE. Pharmacokinetic interaction between verapamil and almotriptan in healthy volunteers. *Clin Pharmacol Ther* (2000) 67, 498–503.
2. Relpax (Eletriptan hydrobromide). Pfizer Ltd. UK Summary of product characteristics, February 2008.
3. Relpax (Eletriptan hydrobromide). Pfizer Inc. US Prescribing information, April 2007.

Triptans; Sumatriptan + Butorphanol

Sumatriptan given by injection appears not to interact with butorphanol nasal spray, but if both drugs are given sequentially by nasal spray a modest reduction in butorphanol absorption may occur.

Clinical evidence, mechanism, importance and management

No pharmacokinetic interactions or change in adverse effects were found to occur when 24 healthy subjects were given a single 1-mg dose of butorphanol tartrate nasal spray and a 6-mg subcutaneous dose of sumatriptan succinate. It was concluded that concurrent use during acute migraine attacks need not be avoided.[1]

In another study, 19 healthy subjects were given a 1-mg dose of butorphanol nasal spray either 1 or 30 minutes after a 20-mg dose of sumatriptan nasal spray. When butorphanol was given 1 minute after sumatriptan the AUC and maximum plasma levels of butorphanol were reduced by about 29% and 38%, respectively. When butorphanol was given 30 minutes after sumatriptan no significant pharmacokinetic interaction was noted. It was suggested that sumatriptan may cause a transient vasoconstriction of nasal blood vessels, leading to reduced butorphanol absorption. It would therefore seem wise to separate administration to ensure that the full effects of butorphanol are achieved.[2]

1. Srinivas NR, Shyu WC, Upmalis D, Lee JS, Barbhaiya RH. Lack of pharmacokinetic interaction between butorphanol tartrate nasal spray and sumatriptan succinate. *J Clin Pharmacol* (1995) 35, 432–7.
2. Vachharajani NN, Shyu W-C, Nichola PS, Boulton DW. A pharmacokinetic interaction study between butorphanol and sumatriptan nasal sprays in healthy subjects: importance of the timing of butorphanol administration. *Cephalalgia* (2002) 22, 282–7.

Triptans; Sumatriptan + Loxapine

An isolated report describes a woman taking loxapine who developed a severe dystonic reaction when she was given sumatriptan.

Clinical evidence, mechanism, importance and management

A woman was taking loxapine 10 mg twice daily for psychotic target symptoms, benzatropine for the prophylaxis of extrapyramidal effects, carbamazepine for mood stabilisation, and *Fiorcet* (paracetamol (acetaminophen), caffeine, and butalbital) for migraine headaches. Two days after the loxapine dosage was raised to 35 mg daily she was given a single 6-mg subcutaneous dose of sumatriptan for a migraine headache. Within 15 minutes she developed torticollis, which was treated with intramuscular benzatropine and intravenous diphenhydramine.

The authors of the report suggest that this reaction was possibly caused by the additive dystonic effects of the loxapine and sumatriptan, despite the presence of the benzatropine. Dystonia is not an uncommon extrapyramidal reaction associated with antipsychotics, and neck stiffness and dystonia are recognised adverse effects of sumatriptan, but of low incidence.[1] This seems to be the first and only report of this apparent interaction, and therefore its general significance is unclear.

1. Garcia G, Kaufman MB, Colucci RD. Dystonic reaction associated with sumatriptan. *Ann Pharmacother* (1994) 28, 1199.

Triptans; Sumatriptan + Naproxen

A study in 12 healthy subjects found that a single 500-mg dose of naproxen had no significant effect on the pharmacokinetics of a single 100-mg oral dose of sumatriptan.[1] A 12-month tolerability study found that a tablet containing both sumatriptan and naproxen was well tolerated for the treatment of acute migraine attacks, and the adverse events did not differ from those expected for the individual components alone.[2]

1. Srinivasu P, Rambhau D, Rao BR, Rao YM. Lack of pharmacokinetic interaction between sumatriptan and naproxen. *J Clin Pharmacol* (2000) 40, 99–104.
2. Winner P, Cady RK, Ruoff GE, Frishberg BM, Alexander WJ, Zhang Y, Kori SH, Lener SE. Twelve-month tolerability and safety of sumatriptan-naproxen sodium for the treatment of acute migraine. *Mayo Clin Proc* (2007) 82, 61–8.

Triptans; Sumatriptan + Topiramate

Topiramate does not affect the pharmacokinetics of oral or subcutaneous sumatriptan to a clinically relevant extent.

Clinical evidence, mechanism, importance and management

In a study, 24 healthy subjects were given topiramate 50 mg every 12 hours increased to 100 mg every 12 hours for a total of 7 days, with a single 100-mg oral dose of sumatriptan on day 7. It was found that topiramate reduced the AUC of sumatriptan by 10%, but this was not considered to be clinically relevant. Topiramate had no effect on the AUC of a 6 mg subcutaneous dose of sumatriptan. The clearance of topiramate appeared to be reduced, when data from this study was compared with that from historical controls, but the magnitude of the effect was not stated.[1] The clinical significance of this effect is unclear.

1. Bialer M, Doose DR, Murthy B, Curtin C, Wang S-S, Twyman RE, Schwabe S. Pharmacokinetic interactions of topiramate. Clin Pharmacokinet. (2004) 43, 763–80.

Triptans; Zolmitriptan + Cimetidine

Cimetidine moderately raises the plasma levels of zolmitriptan.

Clinical evidence, mechanism, importance and management

The manufacturer of zolmitriptan notes that the half-life of zolmitriptan was increased by 44% and the AUC was increased by 48% when it was

given after cimetidine.[1] They suggest that this may be because of the inhibitory effect of cimetidine on the cytochrome P450 isoenzyme CYP1A2, an enzyme involved in the metabolism of zolmitriptan. The UK manufacturer recommends a maximum dose of zolmitriptan of 5 mg in 24 hours in patients taking cimetidine.[1] The US manufacturer makes no recommendation on dose.[2]

1. Zomig Tablets (Zolmitriptan). AstraZeneca UK Ltd. UK Summary of product characteristics, January 2008.

2. Zomig (Zolmitriptan). AstraZeneca Pharmaceuticals LP. US Prescribing information, October 2008.

Triptans; Zolmitriptan + Metoclopramide

Metoclopramide does not affect the pharmacokinetics of zolmitriptan.

Clinical evidence, mechanism, importance and management

In a randomised, crossover study, 15 healthy subjects were given a single 10-mg dose of zolmitriptan, alone or with metoclopramide 10 mg. Metoclopramide had no effect on the pharmacokinetics of zolmitriptan,[1] so dosage adjustments would not appear to be necessary when giving these two drugs.

1. Seaber EJ, Ridout G, Layton G, Posner J, Peck RW. The novel anti-migraine compound zolmitriptan (Zomig 311C90) has no clinically significant interactions with paracetamol or metoclopramide. *Eur J Clin Pharmacol* (1997) 53, 229–34.

Triptans; Zolmitriptan + Quinolones

The quinolone antibacterials are predicted to increase levels of zolmitriptan by inhibiting the cytochrome P450 isoenzyme CYP1A2, an enzyme involved in its metabolism.[1] This is based on the known interaction of zolmitriptan with 'cimetidine', (p.692). The UK manufacturer recommends a maximum dose of zolmitriptan of 5 mg in 24 hours in patients taking quinolone antibacterials such as ciprofloxacin. Note that the quinolones differ in their ability to inhibit CYP1A2; their effects on caffeine may give a useful guide to their potency in this respect, see 'Caffeine + Quinolones', p.1422.

1. Zomig Tablets (Zolmitriptan). AstraZeneca UK Ltd. UK Summary of product characteristics, January 2008.

Triptans; Zolmitriptan + Xylometazoline

In a clinical study in 18 healthy subjects, the rate or extent of absorption of intranasal zolmitriptan 5 mg was not affected when it was given 30 minutes after xylometazoline nasal spray.[1] This suggests that nasal vasoconstriction does not affect absorption of intranasal zolmitriptan.

1. Nairn K, Kemp JV, Dane AL, Roberts DW, Dixon R. Evaluation of the effect of xylometazoline on the absorption of zolmitriptan nasal spray. *Clin Drug Invest* (2002) 22, 703–7.

17

Antineoplastics

The antineoplastic drugs (also called cytotoxics or sometimes cytostatics) are used in the treatment of malignant disease, alone or in conjunction with radiotherapy, surgery, or immunosuppressants. They also find application in the treatment of a number of autoimmune disorders such as rheumatoid arthritis and psoriasis, and a few are used with other immunosuppressant drugs (ciclosporin, corticosteroids) to prevent transplant rejection. These other drugs are dealt with under the section on 'immunosuppressants', (p.1209).

Of all the drugs discussed in this publication, the antineoplastic drugs are amongst the most toxic and have a narrow therapeutic index. This means that quite small increases in their levels can lead to the development of serious and life-threatening toxicity. A list of the antineoplastics and other drugs that are used in the treatment of malignancy that are featured in this section appear in 'Table 17.1', (p.695), grouped by their primary mechanism of action. This table also includes a number of hormone antagonists that are used in the treatment of cancer.

Unlike most of the other interaction monographs in this publication, some of the information on the antineoplastic drugs is derived from *animal* experiments and *in vitro* studies, so that confirmation of their clinical relevance is still needed. The reason for including these data is that the antineoplastic drugs as a group do not lend themselves readily to the kind of clinical studies that can be undertaken with many other drugs, and there would seem to be justification in this instance for including indirect evidence of this kind. The aim is not to make definite predictions, but to warn users of the interaction possibilities.

Table 17.1 Antineoplastics and other drugs used in the treatment of cancer

Action	*Drugs*
Alkylating agents, and drugs that appear to have an alkylating action	
Nitrosoureas	Carmustine, Lomustine, Streptozocin
Platinum compounds	Carboplatin, Cisplatin, Oxaliplatin
Others	Altretamine, Busulfan, Chlorambucil, Chlormethine (Mechlorethamine), Cyclophosphamide, Dacarbazine, Estramustine, Ifosfamide, Melphalan, Temozolomide, Thiotepa
Antimetabolites	
Folate antagonists	Methotrexate, Pemetrexed, Raltitrexed
Podophylotoxin derivatives	Etoposide, Teniposide
Purine analogues	Azathioprine, Cladribine, Clofarabine, Fludarabine, Mercaptopurine, Nelarabine, Tioguanine
Pyridmidine analogues	Capecitabine, Carmofur, Cytarabine, Fluorouracil, Gemcitabine, Tegafur
Mitotic inhibitors	
Taxanes	Docetaxel, Paclitaxel
Topoisomerase I inhibitors	Irinotecan, Topotecan
Vinca alkaloids	Vinblastine, Vincristine, Vindesine, Vinorelbine
Cytotoxic antibiotics	
Anthracyclines	Aclarubicin, Amrubicin, Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Mitoxantrone
Others	Bleomycin, Dactinomycin, Mitomycin
Anti-androgens	Bicalutamide, Flutamide, Nilutamide
Anti-oestrogens	
Aromatase inhibitors	Aminoglutethimide, Anastrozole, Exemestane, Formestane, Letrozole
Oestrogen-receptor antagonists	Fulvestrant, Tamoxifen, Toremifene
Tyrosine kinase inhibitors	Dasatinib, Erlotinib, Gefitinib, Imatinib, Lapatinib, Nilotinib, Sorafenib, Sunitinib
Monoclonal antibodies	Alemtuzumab, Bevacizumab, Cetuximab, Panitumumab, Rituximab, Trastuzumab
Photosensitisers	5-Aminolevulinic acid, Porfimer sodium, Temoporfin
Miscellaneous	Amsacrine, Asparaginase (Colaspase, Crisantaspase, Pegaspargase), Bexarotene, Bortezomib, Enzastaurin, Hydroxycarbamide, Lenalidomide, Mitotane, Pentostatin, Procarbazine, Thalidomide, Tipifarnib, Trabectedin, Tretinoin, Vorinostat

Alemtuzumab + Miscellaneous

Six infection-related deaths occurred in a study of consolidation therapy with alemtuzumab after induction therapy with fludarabine and rituximab. After alemtuzumab, at least 12 months should elapse before live vaccines are given.

Clinical evidence, mechanism, importance and management

(a) Fludarabine with Rituximab

In a clinical study in patients with chronic lymphocytic leukaemia, there were six infection-related deaths out of 51 patients given consolidation alemtuzumab therapy after an induction regimen of **fludarabine** and **rituximab**.[1,2] In this study, patients received up to 6 cycles of intravenous fludarabine 25 mg/m^2 with intravenous rituximab (escalated to 375 mg/m^2) daily for 5 days every 4 weeks. Four months after their last dose of fludarabine, patients with a complete response or stable disease started subcutaneous alemtuzumab (escalated to 30 mg) three times weekly for 6 weeks. Of the six patients who died, five had achieved a complete remission after induction therapy. The infections occurred both during the use of alemtuzumab and for up to 16 months afterwards. The study was subsequently amended to restrict the use of alemtuzumab to those with a partial response to **fludarabine** and **rituximab**, with close monitoring for infection.

It is thought that the immunosuppressive properties of these drugs were additive, and that there was insufficient time allowed before alemtuzumab was given for recovery from immunosuppression from the induction therapy.[1] Note that this use of alemtuzumab is outside the current licensed indications, and this combination should not be given to patients outside the context of a clinical study.[1,2]

(b) Vaccines, live

The manufacturer advises that vaccination with live viral vaccines should not be undertaken within at least 12 months of the use of alemtuzumab, although there are no specific data on this.[3]

1. Bayer HealthCare. Important safety information. Six infection-related deaths reported after treatment with MabCampath® (alemtuzumab) following fludarabine+rituximab induction in patients with B-Cell chronic lymphocytic leukaemia (CLL). Letter to Healthcare Professionals, February 2008.
2. Lin TS, Donohue KA, Lucas MS, Byrd JC, Bengtson EM, Peterson BL, Larson RA (Cancer and Leukemia Group B USA). Consolidation therapy with subcutaneous (SC) alemtuzumab results in severe infectious toxicity in previously untreated CLL patients who achieve a complete response (CR) after fludarabine and rituximab (FR) induction therapy: interim safety analysis of the CALGB study 10101. *Blood* (2007) 110, abstract 755.
3. MabCampath (Alemtuzumab). Genzyme Therapeutics. UK Summary of product characteristics, December 2008.

Altretamine (Hexamethylmelamine) + Antidepressants

Severe orthostatic hypotension has been described in patients given altretamine with either phenelzine, amitriptyline or imipramine.

Clinical evidence, mechanism, importance and management

Four patients experienced very severe orthostatic hypotension (described by the authors as potentially life-threatening) when they were given altretamine 150 to 250 mg/m^2 with either **phenelzine** 60 mg daily, **amitriptyline** 50 mg daily or **imipramine** 50 to 150 mg daily.[1] They experienced incapacitating dizziness, severe lightheadedness, and/or fainting within a few days of taking both drugs. Standing blood pressures as low as 50/30 mmHg and 60/40 mmHg were recorded. The reasons for this hypotensive effect are not known. One of the patients had no problems when **imipramine** was replaced by **nortriptyline** 50 mg daily. One other patient who had also taken altretamine with antidepressants reported dizziness, while another noted non-specific discomfort. The incidence of this interaction is unknown, but it is clear that the concurrent use of altretamine and **tricyclics** or **MAOIs** should be closely monitored.

1. Bruckner HW, Schleifer SJ. Orthostatic hypotension as a complication of hexamethylmelamine antidepressant interaction. *Cancer Treat Rep* (1983) 67, 516.

Altretamine (Hexamethylmelamine) + Pyridoxine (Vitamin B_6)

Pyridoxine reduced the neurotoxicity associated with altretamine, but also reduced its effectiveness.

Clinical evidence, mechanism, importance and management

In a large randomised study in women with advanced ovarian cancer the neurotoxicity associated with altretamine and cisplatin chemotherapy was reduced by pyridoxine, but the response duration was also reduced.[1] In this study, cisplatin was given on day 1 (37.5 or 75 mg/m^2) and altretamine 200 mg/m^2 daily was given on days 8 to 21, and half the patients also received pyridoxine 100 mg three times daily on days 1 to 21. It is unclear how pyridoxine reduced the activity of this regimen, but the use of pyridoxine should probably be avoided in patients receiving altretamine.

1. Wiernik PH, Yeap B, Vogel SE, Kaplan BH, Comis RL, Falkson G, Davis TE, Fazzini E, Cheuvart B, Horton J. Hexamethylmelamine and low or moderate dose cisplatin with or without pyridoxine for treatment of advanced ovarian carcinoma: a study of the Eastern Cooperative Oncology Group. *Cancer Invest* (1992) 10, 1–9.

9-Aminocamptothecin + Antiepileptics; Enzyme-inducing

Carbamazepine, phenobarbital, and phenytoin can lower the levels of 9-aminocamptothecin.

Clinical evidence, mechanism, importance and management

A study in 59 patients with glioblastoma multiforme or recurrent high grade astrocytomas found that the steady-state plasma levels of 9-aminocamptothecin were reduced to about one-third in 29 of the patients also taking antiepileptics (**carbamazepine**, **phenobarbital**, **phenytoin**, sodium valproate). The incidence of myelosuppression was greater in those not taking antiepileptics.[1] A further study also found that the clearance of 9-aminocamptothecin was increased by **carbamazepine** and **phenytoin**.[2] The reason for the reduced 9-aminocamptothecin levels is not known, but it seems likely that it was due to the enzyme-inducing activity of **carbamazepine**, **phenobarbital** and **phenytoin**. These results suggest that higher than usual doses of 9-aminocamptothecin are possibly needed in the presence of these antiepileptics. **Fosphenytoin** and **primidone**, which are metabolised to phenytoin and phenobarbital, respectively, would be expected to interact similarly.

1. Grossman SA, Hochberg F, Fisher J, Chen T-L, Kim L, Gregory R, Grochow LB, Piantadosi S. Increased 9-aminocamptothecin dose requirements in patients on anticonvulsants. *Cancer Chemother Pharmacol* (1998) 42, 118–26.
2. Minami H, Lad TE, Nicholas MK, Vokes EE, Ratain MJ. Pharmacokinetics and pharmacodynamics of 9-aminocamptothecin infused over 72 hours in phase II studies. *Clin Cancer Res* (1999) 5, 1325–30.

Aminoglutethimide + Danazol

Danazol may reduce the efficacy of aminoglutethimide.

Clinical evidence, mechanism, importance and management

In a randomised study, giving danazol with aminoglutethimide in women with breast cancer, reduced the response rate compared with the use of aminoglutethimide alone. It was found that danazol suppresses sex hormone-binding globulin leading to increased free oestradiol, which counteracts the oestradiol suppressive effect of aminoglutethimide.[1] Danazol should probably not be given with anti-oestrogenic treatments.

1. Dowsett M, Murray RML, Pitt P, Jeffcoate SL. Antagonism of aminoglutethimide and danazol in the suppression of serum free oestradiol in breast cancer patients. *Eur J Cancer Clin Oncol* (1985) 21, 1063–8.

Aminoglutethimide + Diuretics

A single case report describes hyponatraemia, which occurred after a patient had taken aminoglutethimide and bendroflumethiazide for 10 months.

Clinical evidence, mechanism, importance and management

A woman who had been taking **bendroflumethiazide** 10 mg daily and potassium chloride 578 mg for several years for hypertension and mild cardiac decompensation, was given aminoglutethimide 1 g daily, and hydrocortisone 60 mg daily, for breast cancer. After 10 months of treatment she was hospitalised with severe hyponatraemia, which resolved when all the drugs were withdrawn. No significant change in electrolytes occurred over 3 months when the aminoglutethimide and hydrocortisone were used alone, but serum sodium fell again when the diuretic was restarted. The serum sodium levels were subsequently maintained by the addition of fludrocortisone 100 micrograms daily.[1] The hyponatraemia was thought to be caused by the combined inhibitory effect of the aminoglutethimide on aldosterone production (which normally retains sodium in the body) and the sodium loss caused by the diuretic. Plasma electrolytes should be monitored when aminoglutethimide is used, and this would seem particularly important if it is given with any diuretic.

1. Bork E, Hansen M. Severe hyponatremia following simultaneous administration of aminoglutethimide and diuretics. *Cancer Treat Rep* (1986) 70, 689–90.

5-Aminolevulinic acid + St John's wort (*Hypericum perforatum*)

An isolated case report describes a severe phototoxic reaction attributed to a synergistic effect of oral 5-aminolevulinic acid and St John's wort.

Clinical evidence

A 47-year-old woman who was taking St John's wort (*Hyperiforce*, dose not stated) experienced a phototoxic reaction on skin areas exposed to light 6 hours after receiving oral 5-aminolevulinic acid 40 mg/kg. She developed a burning erythematous rash and severe swelling of the face, neck and hands. Treatment with oral corticosteroids resulted in complete resolution after skin desquamation.[1]

Mechanism

It was suggested that there was a synergistic photosensitivity reaction between the two drugs.

Importance and management

This appears to be the only report of such an effect, but bear it in mind in the event of an unexpected adverse reaction to oral 5-aminolevulinic acid. Note that this photosensitiser and its derivative methyl aminolevulinate are more usually applied topically, and in this situation, any interaction is unlikely to be important.

1. Ladner DP, Klein SD, Steiner RA, Walt H. Synergistic toxicity of <delta>-aminolaevulinic acid-induced protoporphyrin IX used for photodiagnosis and hypericum extract, a herbal antidepressant. *Br J Dermatol* (2001) 144, 901–22.

Anastrozole + Miscellaneous

Cimetidine and quinapril do not affect anastrozole levels. Anastrozole does not appear to interact with aspirin, digoxin or oral antidiabetics. It also appears to have no effect on cytochrome P450 enzymes, so it is unlikely to interact with drugs that are affected by inducers or inhibitors of this enzyme system.

Clinical evidence, mechanism, importance and management

In a pharmacokinetic study, 10 elderly women with breast cancer were given anastrozole 1 mg daily for 10 weeks and 5 of them who also had hypertension were additionally given **quinapril**, after week 4, for 28 days. **Quinapril** did not affect plasma anastrozole levels and dose adjustment is not required during concurrent use.[1]

A clinical study with **cimetidine** found that it does not affect the pharmacokinetics of anastrozole.[2] This provides some evidence that anastrozole might not be affected by other drugs that inhibit cytochrome P450 isoenzymes, although cimetidine is only a weak non-specific inhibitor of this enzyme system. Another clinical study found that anastrozole does not affect the pharmacokinetics of **antipyrine** (**phenazone**),[3] a non-specific marker of cytochrome P450 induction or inhibition. This suggests that anastrozole is probably unlikely to interact with those drugs that are known to be affected by inducers and inhibitors of this enzyme system.

The UK manufacturer of anastrozole notes that in clinical studies there was no evidence of any interactions between anastrozole and commonly used drugs;[4] **aspirin**, **digoxin**, and **oral antidiabetics** were specifically mentioned in the early product information.[5]

1. Repetto L, Vannozzi O, Hazini A, Sestini A, Pietropaolo M, Rosso R. Anastrozole and quinapril can be safely coadministered to elderly women with breast cancer and hypertension: a pharmacokinetic study. *Ann Oncol* (2003) 14, 1587–90.
2. Zeneca. Effect of cimetidine on anastrozole pharmacokinetics. Data on file, 1995.
3. Zeneca. Effect of anastrozole treatment on antipyrine pharmacokinetics in postmenopausal female volunteers. Data on file, 1995.
4. Arimidex (Anastrozole). AstraZeneca UK Ltd. UK Summary of product characteristics, March 2009.
5. Arimidex (Anastrozole) Monograph. Zeneca. September 1995.

Anthracyclines + Ciclosporin

High-dose ciclosporin increases the serum levels and the myelotoxicity of doxorubicin. An isolated report describes severe neurotoxicity and coma in a patient who had taken ciclosporin and was subsequently given doxorubicin. Ciclosporin can also increase the levels of daunorubicin, epirubicin, idarubicin and mitoxantrone.

Clinical evidence

(a) Daunorubicin

In a randomised study in patients receiving daunorubicin, ciclosporin significantly reduced the frequency of resistance to induction therapy (31% versus 47%) and increased relapse-free and overall survival. Ciclosporin recipients had higher steady-state serum levels of daunorubicin and its active metabolite, daunorubicinol.[1]

(b) Doxorubicin

Eight patients with small cell lung cancer were given an initial course of doxorubicin (25 to 70 mg/m^2 over one hour) and a subsequent ciclosporin-modulated doxorubicin course (ciclosporin 6 mg/kg bolus, then 16 mg/kg daily for 2 days) for multidrug-resistant tumour modulation. All of the patients were also given cyclophosphamide and vincristine. Ciclosporin increased the AUC of doxorubicin by 48%, and increased the AUC of its active metabolite, doxorubicinol, by 443%. The myelotoxicity was increased by concurrent use: the leucocyte count fell by 84% after doxorubicin and by 91% after doxorubicin with ciclosporin, and the platelet counts fell by 36% and 73%, respectively. The patients had significant weight loss and severe myalgias.[2]

Three preliminary phase I studies[3-5] are consistent with this report. In these studies, ciclosporin was found to increase the doxorubicin AUC by 40 to 73%, and the doxorubicinol AUC by 250 to 285%. However, no evidence of increased cardiotoxicity was found in a study of 23 patients given ciclosporin and doxorubicin.[6]

A heart transplant patient was given ciclosporin 2 mg/kg daily for 22 months. The ciclosporin was stopped and he was given doxorubicin 60 mg, vincristine 2 mg, cyclophosphamide 600 mg and prednisone 80 mg to treat Burkitt's lymphoma stage IVB. Eight hours later he developed disturbances of consciousness, which lead to stage I coma, from which he spontaneously recovered 12 hours later. A week later a similar course of chemotherapy was started, and 10 to 15 minutes later he lost consciousness and generalised tonic clonic seizures progressively developed. He died 8 days later without recovering consciousness.[7]

(c) Epirubicin

Preliminary evidence suggests that ciclosporin can markedly increase the AUC of epirubicin (up to about fourfold) and increase bone marrow suppression in response to epirubicin.[5] In one study in 20 patients ciclosporin did not increase the cardiotoxicity of epirubicin .[6]

(d) Idarubicin

In 9 patients the concurrent use of ciclosporin and idarubicin increased the AUC of idarubicin and its active metabolite, idarubicinol, by 77% and 181%, respectively, when compared with 11 patients receiving idarubicin alone.[8] Unacceptable toxicity occurred when idarubicin 9 or 12 mg/m^2 daily was given with ciclosporin 16 mg/kg daily, when compared with idarubicin 12 mg/m^2 alone: 3 of 7 patients given the combination died. Increases in the AUC of idarubicin and idarubicinol produced by ciclosporin have also been reported elsewhere.[9]

(e) Mitoxantrone

The pharmacokinetics of mitoxantrone 10 mg/m^2 daily were compared with mitoxantrone 6 mg/m^2 (a 40% reduction in dose) with high-dose ciclosporin in children. The ciclosporin recipients had a 42% reduction in mitoxantrone clearance, a 12% increase in mitoxantrone AUC, and similar toxicity.[10]

Mechanism

Uncertain. One reason may be that ciclosporin affects P-glycoprotein in the biliary tract so that the clearance of these anthracyclines in the bile is reduced. An additional reason may be that ciclosporin inhibits the metabolism of anthracycline metabolites, such as doxorubicinol, so that they accumulate.[2] The increased levels of both would explain the increases in toxicity. It is not clear why such severe neurotoxicity was seen in one patient.

Importance and management

An established and clinically important interaction. Ciclosporin alters the pharmacokinetics of the anthracyclines resulting in increased levels. This pharmacokinetic interaction has complicated study into the value of using ciclosporin to modulate multidrug resistance in tumours and thereby improve the response to chemotherapy. In the case of anthracyclines and 'etoposide', (p.724), any benefit could simply be attributed to dose intensification. Consequently, some have suggested reducing the dose of the anthracycline.[10] The use of high-dose ciclosporin for multidrug-resistant tumour modulation remains experimental and should only be used in clinical studies. Concurrent use should be very well monitored. More study is needed to find out the possible effects of low-dose ciclosporin.

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Anthracyclines + Taxanes

Toxicity associated with combinations of paclitaxel with doxorubicin or epirubicin depends on the order of administration. Some modest pharmacokinetic changes may occur when paclitaxel and epirubicin are given together. The combination of doxorubicin and paclitaxel is more cardiotoxic than doxorubicin alone: paclitaxel increases doxorubicin levels but doxorubicin does not alter paclitaxel levels. Docetaxel may modestly affect the pharmacokinetics of epirubicin and doxorubicin.

Clinical evidence

(a) Doxorubicin

1. Docetaxel. The pharmacokinetics of doxorubicin 50 mg/m^2, given as a 30-minute infusion, were unaffected when it was given immediately before or one hour before a one-hour infusion of docetaxel 75 mg/m^2 when compared with administration alone. However, the AUC of docetaxel was increased, both when given immediately before and one hour after doxorubicin, by 50% and 75%, respectively.[1] A retrospective review of patients who were given doxorubicin followed one hour later by docetaxel found that the clearance of docetaxel was about 20% lower than in patients who had received docetaxel alone, whereas the clearance of doxorubicin did not differ when given with docetaxel.[2]

In a study, 627 patients with breast cancer were given doxorubicin 50 mg/m^2 with docetaxel 75 mg/m^2, or doxorubicin 60 mg/m^2 with cyclophosphamide 600 mg/m^2, postoperatively for 4 courses to assess disease-free survival at 5 years. The study was terminated prematurely because of the high risk of life-threatening complications in the patients given doxorubicin with docetaxel (2 deaths associated with drug toxicity and one case of perforated peritonitis in a patient with febrile neutropenia). The incidence of febrile neutropenia was 41% and 7% in the doxorubicin with docetaxel, and doxorubicin with cyclophosphamide groups, respectively.[3]

A woman with recurrence of breast cancer developed pseudomembranous colitis (non-*Clostridium difficile*) and cholestatic jaundice 6 days after completing her first cycle of treatment with doxorubicin and docetaxel and again 4 days after the second cycle, about one month later.[4]

2. Paclitaxel. Early studies in patients with breast cancer found a higher frequency of toxicity (particularly mucositis) when paclitaxel was given immediately before doxorubicin (given as 24-hour and 48-hour infusions, respectively) rather than the other way around.[5] A subsequent study with similar effects revealed that doxorubicin clearance was reduced by one-third if paclitaxel was given first.[6] In another study the peak plasma levels of doxorubicin were increased when it was given by bolus injection 15 minutes after a 3-hour infusion of paclitaxel rather than the other way around. The effect was non-linear and dependent on the dose of paclitaxel.[7] The same authors had already found that this regimen produced a higher than expected incidence of cardiac toxicity, which was not affected by sequence with the short interval between administration.[8] Subsequent studies[9,10] have found that this schedule results in unacceptable cardiotoxicity when the total cumulative doxorubicin dose exceeds 340 to 380 mg/m^2. When a bolus dose of doxorubicin was given 15 or 30 minutes before a 3-hour infusion of paclitaxel, the levels of doxorubicin were higher than when the interval was 24 hours.[7,11] Moreover, when paclitaxel and doxorubicin were given together as a 3-hour infusion the levels of doxorubicin were lower than when a bolus dose of doxorubicin was given 15 minutes before a 3-hour paclitaxel infusion.[7] Similarly, in another study, the pharmacokinetics of each drug were found to be unchanged when they were given simultaneously as a 72-hour infusion.[12]

(b) Doxorubicin, liposomal

In 10 patients the AUC of intravenous pegylated liposomal doxorubicin (*Caelyx*) 30 to 35 mg/m^2 was increased by a mean of 80% when it was given immediately before intravenous **paclitaxel** 70 or 175 mg/m^2 compared with when it was given alone. Peak plasma levels of doxorubicin were also increased and clearance was reduced by 71%. In 9 other patients given *Caelyx* then **docetaxel** 30 or 60 mg/m^2, the AUC of doxorubicin was increased by 12% and clearance reduced by only 16%.[13]

(c) Epirubicin

The pharmacokinetics of epirubicin were compared in 4 patients with breast cancer given intravenous epirubicin 90 mg/m^2 alone and in 16 patients given the same dose of epirubicin followed immediately by either **paclitaxel** 175 mg/m^2 as a 3-hour infusion or **docetaxel** 70 mg/m^2 as a one-hour infusion. No effect on epirubicin levels was detected, but the concentrations of epirubicin metabolites (epirubicinol and deoxydoxorubicinone) were increased by both **paclitaxel** and **docetaxel**.[14] In a subsequent study, 21 patients were given the same regimen of epirubicin followed immediately by **paclitaxel** and 18 patients were given the drugs in the reverse order. Non-haematological toxicity was unaffected by the order of administration, but when **paclitaxel** was given first the neutrophil

and platelet nadir was lower and neutrophil recovery was slower. The AUC for epirubicin was also higher when **paclitaxel** was given first, but the pharmacokinetics of **paclitaxel** were unaffected.[15]

In one study, 21 women with breast cancer were given intravenous epirubicin 90 mg/m^2 followed 15 minutes later by a 3-hour intravenous infusion of **paclitaxel** 175 mg/m^2 (6 patients), 200 mg/m^2 (9 patients), or 225 mg/m^2 (6 patients). Six women were given **paclitaxel** 200 mg/m^2 30 hours after epirubicin. A significant increase in the AUC of epirubicin occurred with **paclitaxel** 200 mg/m^2 (23%) and 225 mg/m^2 (34%) and increases in the AUC of the metabolite of epirubicin (epirubicinol) occurred at all dose levels of **paclitaxel**, compared with those found when epirubicin was given 30 hours before **paclitaxel**.[16] In another study, exposure to epirubicin metabolites, but not epirubicin itself, was increased when it was given 15 minutes before a 3-hour infusion of **paclitaxel**, when compared with a regimen using a 24-hour interval between the two drugs. In addition, the neutrophil nadir was lower, and the clearance of **paclitaxel** was 30% slower with the former regimen, but cardiac toxicity was uncommon.[17]

Conversely, a study of the concurrent use of **docetaxel** and epirubicin did not find that the sequence of drug administration affected the pharmacokinetics of epirubicin, nor was there any difference in toxicity.[18] In another study, 16 patients with breast cancer had a transient but significant increase in epirubicin plasma levels during the subsequent infusion (after an interval of one hour) of **docetaxel** 75 mg/m^2, which was not seen if the **docetaxel** was given within 10 minutes of epirubicin.[19] A study in 43 patients who received **docetaxel**, cyclophosphamide and epirubicin found an increase in the plasma levels of epirubicinol, but this was only seen during the **docetaxel** infusion, after which levels returned to normal. The pharmacokinetics of **docetaxel** were not significantly different from historical data on its use alone.[20]

Mechanism

Studies in *mice* have found that the taxanes docetaxel and paclitaxel, and the vehicle used for paclitaxel, *Cremophor*, may all modify the distribution and metabolism of doxorubicin increasing its levels in the heart, liver and kidneys. This may contribute to the cardiac toxicity seen during use with paclitaxel.[21] Similarly, *in vitro* studies in human myocardial tissue found that paclitaxel and docetaxel increased the conversion of doxorubicin to doxorubicinol, the metabolite that is thought to be responsible for cardiotoxicity.[22] An *in vitro* study on the effect of paclitaxel and *Cremophor* on epirubicin metabolism in human blood found that paclitaxel slightly decreased the production of epirubicinol. A marked inhibition of epirubicinol production occurred in the presence of *Cremophor*, but because of the low volume of distribution of *Cremophor* this is not likely to be of clinical significance.[16] In addition, *in vitro* studies have shown that the taxanes may reduce the biliary excretion of doxorubicin and epirubicin by inhibiting P-glycoprotein,[7] and inhibition of epirubicinol excretion via competition for P-glycoprotein by paclitaxel and *Cremophor* may be significant.[16]

The case of pseudomembranous colitis and cholestatic jaundice in one patient was attributed to the combination of docetaxel and doxorubicin, but the patient was also receiving long-term treatment with erythromycin and omeprazole which may have contributed to the interaction by inhibiting docetaxel metabolism by the cytochrome P450 isoenzyme CYP3A.[4]

Importance and management

The effect of paclitaxel on doxorubicin appears to be established, and various strategies have been suggested to reduce the cardiotoxicity of this combination. These include giving doxorubicin at least 24 hours before paclitaxel; reducing the cumulative dose of doxorubicin; or adding the cytoprotective drug dexrazoxane.[23] Epirubicin is considered less cardiotoxic than doxorubicin, and may be an alternative in some situations. However, it still appears preferable to give the anthracycline before the taxane. Docetaxel appears to have little clinically relevant effect on doxorubicin or epirubicin pharmacokinetics, but doxorubicin might increase docetaxel levels. Further study is needed on the optimum scheduling of anthracyclines and taxanes to maximise efficacy and minimise toxicity.

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Anthracyclines; Aclarubicin + Other antineoplastics

Myelosuppression is among the adverse effects of aclarubicin. The concurrent use of other drugs with similar myelosuppressant actions may be expected to have additive effects. Previous treatment with nitrosoureas (not specifically named) or mitomycin has been shown to increase the severity of the myelosuppression.[1,2]

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Anthracyclines; Daunorubicin + Protease inhibitors

The pharmacokinetics of liposomal daunorubicin did not appear to be affected by ritonavir- or indinavir-based antiretroviral regimens.

Clinical evidence, mechanism, importance and management

In a study of the effects of the protease inhibitors **ritonavir** or **indinavir** on the pharmacokinetics of liposomal daunorubicin 40 mg/m^2 twice weekly in patients with Kaposi's sarcoma, the AUC of daunorubicin and its active metabolite, daunorubicinol, did not differ between 6 patients taking a **ritonavir**-based regimen or 9 patients taking an **indinavir**-based regimen, when compared with 6 other patients not taking a protease inhibitor. In patients for whom data were available before starting the protease inhibitor, the daunorubicin AUC was unchanged by **indinavir** in 3 patients, but was reduced by 30% after starting the **ritonavir** in 2 patients. The antiretroviral regimens used were **indinavir** 800 mg three times daily plus dual NRTIs or **ritonavir** 400 mg or 600 mg twice daily plus NRTIs. The protease inhibitors had been taken for at least a month before the pharmacokinetics of daunorubicin were assessed. The potential impact of daunorubicin on the pharmacokinetics of the antiretrovirals was not assessed. Two patients in this study were taking **ritonavir-boosted saquinavir** 600 mg three times daily with the same schedule of liposomal daunorubicin, however the number of patients was considered too small to draw any conclusions about a possible interaction.[1]

These data suggest that indinavir and ritonavir do not alter the pharmacokinetics of liposomal daunorubicin to a clinically relevant extent, and therefore no daunorubicin dose adjustment is needed on concurrent use.

For mention that protease inhibitor regimens have been associated with an increased risk of infection when used with various antineoplastic regimens, see 'Antineoplastics + Protease inhibitors', p.703.

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Anthracyclines; Doxorubicin + Barbiturates

The effects of doxorubicin may be reduced by the barbiturates.

Clinical evidence, mechanism, importance and management

A comparative study in patients given doxorubicin found that those also taking barbiturates had a doxorubicin plasma clearance that was 50% higher than those who were not taking barbiturates (318 mL/minute compared with 202 mL/minute).[1] This clinical study is in agreement with previous studies in *mice*.[2] A possible explanation is that the barbiturate increases the metabolism of the doxorubicin. It seems possible that the dose of doxorubicin will need to be increased in barbiturate-treated patients to achieve maximal therapeutic effects.

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Anthracyclines; Doxorubicin + Tamoxifen

Tamoxifen appears to have no significant effect on the pharmacokinetics of doxorubicin.

Clinical evidence, mechanism, importance and management

A pharmacokinetic study in patients with non-Hodgkin's lymphoma receiving CHOP (cyclophosphamide, vincristine, prednisone and doxorubicin 37.5 to 50 mg/m^2) found that the addition of tamoxifen 480 mg daily for 5 days had no significant effect on the AUC or total clearance of doxorubicin.[1]

For the possible additive thromboembolic effect of doxorubicin and tamoxifen, see 'Antineoplastics + Tamoxifen', p.704.

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Anthracyclines; Doxorubicin + Toremifene

In a study, 6 patients were given high-dose oral toremifene 600 mg daily for 5 days, with doxorubicin 60 mg/m^2 intravenously on day 5. The pharmacokinetics of doxorubicin were not affected by toremifene when compared with a single intravenous dose of doxorubicin 60 mg/m^2 given alone.[1] Usual doses of toremifene would not be expected to interact with doxorubicin.

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Anthracyclines; Epirubicin + Cimetidine

Cimetidine can increase the exposure to epirubicin.

Clinical evidence, mechanism, importance and management

In a study in 8 patients, cimetidine 400 mg twice daily increased the AUC of epirubicin by 50%. At the same time the AUCs of two metabolites of epirubicin, epirubicinol and 7-deoxydoxorubicinol aglycone, increased by 41% and 357%, respectively. Liver blood flow also increased by 17%.[1] The mechanism for this effect is unknown. More study of this interaction is needed but be aware of the possibility that cimetidine may increase the exposure to epirubicin; monitor the patient closely and adjust the epirubicin dose if needed. Cimetidine is available without a prescription in some countries so that patients may unwittingly increase the toxicity of epirubicin.

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Antineoplastics + Amphotericin B

Amphotericin B may delay the clearance of methotrexate, and there may be an increased risk of renal impairment. Similarly, the use of conventional amphotericin B with nephrotoxic antineoplastics such as cisplatin and ifosfamide may increase the risk of renal impairment.

Clinical evidence

Two children had delayed clearance of pulse **methotrexate** (1 g/m^2 over 24 hours) while they were receiving amphotericin B. **Methotrexate** levels were about 300 to 500% higher 48 hours after **methotrexate** when they were receiving amphotericin B, compared with **methotrexate** alone.[1] In a study, **methotrexate** clearance in 18 children given high-dose **methotrexate** (1 g/m^2 intravenously) was significantly correlated with the glomerular filtration rate (GFR). Concurrent amphotericin B in 6 of the children significantly decreased the GFR.[2] A history of heavy amphotericin B treatment (greater than 30 mg/kg) correlated with decreased **methotrexate** clearance in 24 children with relapsed leukaemia.[3]

A multivariate analysis in patients receiving high-dose **cisplatin** with saline hydration and mannitol diuresis found that the concurrent use of amphotericin B was a predictor of renal failure.[4]

Mechanism

Amphotericin B may cause renal impairment, which can result in delayed methotrexate clearance. Both cisplatin and amphotericin B are nephrotoxic, and their effects might be expected to be additive.

Importance and management

Evidence regarding an interaction between amphotericin B and methotrexate appears to be limited. Nevertheless, the adverse effects of methotrexate should be carefully monitored (e.g. patient reported symptoms, LFTs, renal function, blood counts) in patients taking amphotericin B or those previously extensively treated with the drug. In patients taking large doses of methotrexate (i.e. not the weekly doses given for conditions such as rheumatoid arthritis), the monitoring of methotrexate levels is recommended.

Similarly, evidence for an interaction between cisplatin and amphotericin B is limited, but what happens is in line with the known nephrotoxic effects of both drugs. The manufacturer of conventional amphotericin B states that nephrotoxic antineoplastics should not be given concurrently except with great caution.[5] Of the antineoplastics, cisplatin, **ifosfamide** and methotrexate are well known for their nephrotoxicity. Liposomal amphotericin B is licensed for use in the empirical treatment of presumed fungal infections in febrile neutropenic patients. It is therefore likely to be used in patients who have received antineoplastics and who may have antineoplastic-induced renal impairment. The manufacturer notes that it has been used successfully in a large number of patients with pre-existing renal impairment. Nevertheless, renal function should still be closely monitored in these patients.[6]

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Antineoplastics + Aprepitant

Aprepitant had no effect on the pharmacokinetics of single intravenous doses of docetaxel or vinorelbine. The activation of cyclophosphamide and thiotepa was slightly lower in patients receiving aprepitant. Etoposide and paclitaxel have been commonly used with aprepitant without any dose adjustment. Fosaprepitant is rapidly converted to aprepitant after intravenous administration, and is therefore expected to share the same interactions.

Clinical evidence

(a) Cyclophosphamide

The rate of auto-induction of cyclophosphamide was 23% lower and exposure to the active metabolite, 4-hydroxycyclophosphamide, was 5% lower in 6 patients receiving aprepitant with a 4-day course of high-dose CTC (cyclophosphamide, thiotepa, carboplatin) when compared with 49 patients receiving high-dose CTC without aprepitant.[1]

(b) Docetaxel

Aprepitant 125 mg given one hour before docetaxel on day one, then 80 mg daily on days 2 and 3 had no effect on the pharmacokinetics of a single 60- to 100-mg/m^2 infusion of docetaxel in 10 patients with cancer, and did not alter the toxicity profile. Each subject acted as their own control.[2]

(c) Thiotepa

The formation clearance of thiotepa was 33% lower and exposure to the active metabolite, TEPA (triethylenephosphamide), was 20% lower in 6 patients receiving aprepitant with a 4-day course of high-dose CTC (cyclophosphamide, thiotepa, carboplatin) when compared with 49 patients receiving high-dose CTC without aprepitant.[1]

(d) Vinorelbine

In a pharmacokinetic study, in 12 patients with cancer, aprepitant 125 mg on day one and 80 mg daily on days 2 and 3 had no effect on the pharmacokinetics of intravenous vinorelbine 25 mg/m^2 given on day one or day 8.[3]

Mechanism

In the short-term, aprepitant is an inhibitor of the cytochrome P450 isoenzyme CYP3A4, and might therefore reduce the activation of antineoplastics activated by this isoenzyme (cyclophosphamide, thiotepa), or increase the toxicity of antineoplastics metabolised by this enzyme (docetaxel, irinotecan). There is some evidence that aprepitant has a greater effect on CYP3A4 substrates when they are given orally rather than intravenously (see 'midazolam', (p.840)), so this might explain the findings with the intravenous antineoplastics studied.[2]

Importance and management

The studies cited above suggest that clinically relevant pharmacokinetic interactions between aprepitant and intravenous cyclophosphamide, docetaxel, thiotepa and vinorelbine are unlikely: in each case the effects found were modest. However, a degree of caution may be warranted if any of these antineoplastics are given orally, as greater effects may result (see *Mechanism*). These findings suggest that, despite aprepitant being an inhibitor of CYP3A4, it is unlikely to have any clinically relevant effect on the pharmacokinetics of intravenously antineoplastics that are substrates of this isoenzyme. Nevertheless, the manufacturers of aprepitant and fosaprepitant recommend caution when these drugs are used with antineoplastics that are metabolised by CYP3A4.[4-7] In the UK they limit this to antineoplastics given orally (**etoposide** and vinorelbine are named);[4,6] however, in addition, they particularly caution use with **irinotecan** (given intravenously), because of the possibility of increased toxicity with this drug.[4,6] In the US, the manufacturer mentions that **etoposide**, **paclitaxel** and vinorelbine were commonly given with aprepitant without dose adjustment for potential interactions. They recommend particular caution with **vinblastine**, **vincristine** and **ifosfamide**, as only a few patients have received these drugs with aprepitant, and with other antineoplastics principally metabolised by CYP3A4 that have not yet been studied (**imatinib** and **irinotecan** are named).[5,7]

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4. Emend (Aprepitant). Merck Sharp & Dohme Ltd. UK Summary of product characteristics, July 2009.
5. Emend (Aprepitant). Merck & Co., Inc. US Prescribing information, July 2009.
6. IVEMEND (Fosaprepitant dimeglumine). Merck Sharp & Dohme Ltd. UK Summary of product characteristics, August 2009.
7. Emend for Injection (Fosaprepitant dimeglumine). Merck & Co., Inc. US Prescribing information, October 2009.

Antineoplastics + Calcium-channel blockers

Verapamil can increase the efficacy of doxorubicin in tissue culture systems and increase doxorubicin levels in patients. D-verapamil can alter the pharmacokinetics of epirubicin and possibly increase its bone marrow depressant effects.

The absorption of verapamil can be modestly reduced by antineoplastic regimens containing cyclophosphamide, vincristine and procarbazine, or vindesine, doxorubicin and cisplatin.

Clinical evidence, mechanism, importance and management

(a) Antineoplastic regimens

A study in 9 patients with a variety of malignant diseases found that treatment with antineoplastics reduced the absorption of a single 160-mg oral dose of **verapamil**. The **verapamil** AUC in 8 patients was reduced by 40% (range 7 to 58%), but one patient conversely had a 26% increase. Five patients received a modified COPP regimen (**cyclophosphamide**, **vincristine**, **procarbazine**, prednisone) and 4 patients received VAC (**vindesine**, **doxorubicin**, **cisplatin**).[1]

It is believed that these antineoplastics damage the lining of the upper part of the small intestine, which impairs the absorption of **verapamil**. The clinical relevance of this reduction does not appear to have been studied but it seems likely that at least some patients will be affected. Therefore it would seem prudent to monitor concurrent use for verapamil efficacy.

(b) Doxorubicin

The efficacy of doxorubicin was increased by **verapamil** and **nicardipine** in doxorubicin-resistant tissue culture systems, while **nifedipine** had only minimal activity.[2] A study in 5 patients with small cell lung cancer given doxorubicin, vincristine, etoposide and cyclophosphamide found that when they were given **verapamil** 240 to 480 mg daily the AUC of doxorubicin was doubled, its peak serum levels were raised and its clearance was reduced. No increased toxicity was seen in this study.[3] However, although another study found no increase in doxorubicin acute toxicities, intravenous **verapamil** caused an unacceptable degree of cardiac adverse effects (heart block, hypotension, and/or heart failure) when given in doses to attain plasma levels four times the normal upper limit.[4]

(c) Epirubicin

When used to reduce multidrug resistance in patients with advanced colorectal cancer receiving epirubicin, the D-isomer of **verapamil** appears to increase the bone marrow depressant toxicity of epirubicin.[5] Another study found that **D-verapamil** halved the AUC and half-life of epirubicin, and increased its clearance,[6] while yet another study did not find these changes but found that the production of the metabolites of epirubicin was increased.[7] These changes should be taken into account if both drugs are used. More study is needed to evaluate the possible advantages and disadvantages of giving these drugs together.

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Antineoplastics + Colony-stimulating factors

Because of the increased risk of myelosuppression, colony-stimulating factors such as filgrastim and lenograstim should not be given at the same time as myelosuppressive cytotoxic antineoplastics.

Clinical evidence, mechanism, importance and management

Colony-stimulating factors such as filgrastim and lenograstim promote the growth of myeloid cell lines. Because rapidly dividing myeloid cells have increased sensitivity to cytotoxic chemotherapy, the manufacturers have advised that these drugs should not be used from 24 hours before until 24 hours after cytotoxic chemotherapy.[1-3] In support of this, the manufacturer of filgrastim notes that preliminary evidence confirmed that the severity of neutropenia could be exacerbated when patients were given **fluorouracil** and filgrastim concurrently.[2]

Note also that there is some evidence that colony-stimulating factors may potentiate the pulmonary toxicity of 'bleomycin', (p.707), and 'cyclophosphamide', (p.716).

1. Granocyte (Lenograstim). Chugai Pharma UK Ltd. UK Summary of product characteristics, May 2009.
2. Neupogen (Filgrastim). Amgen Ltd. UK Summary of product characteristics, February 2009.
3. Neupogen (Filgrastim). Amgen Inc. US Prescribing information, September 2007.

Antineoplastics + 5-HT$_3$-receptor antagonists

Ondansetron does not appear to affect the pharmacokinetics of cyclophosphamide and cisplatin to a clinically relevant extent. Ondansetron does not appear to affect the pharmacokinetics of carmustine or the *in vitro* activity of epirubicin, bleomycin, cisplatin or estramustine. Cisplatin and fluorouracil do not affect the pharmacokinetics of ondansetron. In *in vitro* studies granisetron potentiated the cytotoxic effects of epirubicin, had an additive effect on bleomycin and estramustine activity and appeared not to affect the metabolism of docetaxel and paclitaxel.

Clinical evidence, mechanism, importance and management

(a) Granisetron

1. Cytotoxicity. In an *in vitro* study, granisetron significantly potentiated the cytotoxic effects of **epirubicin** on fibroblasts, and the effect of granisetron on the cytotoxic effects of **bleomycin** and **estramustine** in lung cancer cells appeared to be additive. The clinical relevance of the effects of granisetron on **epirubicin** is not known.[1]

2. Electrocardiac effects. A review of the ECGs of 30 patients who had received granisetron and **doxorubicin** or **epirubicin** found that the antineoplastics did not cause any further change in the PR interval above that which was caused by granisetron alone. There were no clinically significant cardiac effects reported.[2]

3. Pharmacokinetics. An *in vitro* study found that granisetron did not affect the metabolism of **docetaxel** or **paclitaxel**,[3] nor did a study in 6 patients demonstrate any change in the pharmacokinetics or bone-marrow suppressant effect of **docetaxel** when given with granisetron.[4]

(b) Ondansetron

1. Cytotoxicity. An *in vitro* study found that ondansetron did not affect the cytotoxic effects of **bleomycin**, **epirubicin**, **estramustine** or **cisplatin** in fibroblasts and lung cancer cells.[1]

2. Nephrotoxicity. In a small retrospective review of patients who had received cisplatin, there was a decreased incidence of nephrotoxicity (an increase in serum creatinine of about 44 micromol/L or more) in those patients who had also received ondansetron.[5] The mechanism for this association is unclear. The data from these sorts of analyses require confirmation in a controlled study, because it is possible that the findings are due to chance alone. The general relevance of this report is therefore uncertain.

3. Pharmacokinetics. The pharmacokinetics of high-dose **cyclophosphamide**, **cisplatin** and **carmustine** in 23 patients given ondansetron, lorazepam and diphenhydramine as antiemetics were compared with those in 129 patients who received prochlorperazine instead of ondansetron. It was found that the AUCs of **cyclophosphamide** and **cisplatin**, but not that of **carmustine**, were lower (by 15% and 19%, respectively) in the ondansetron group.[6] Similarly, in another study, the pharmacokinetics of antineoplastics were analysed in 54 patients with breast cancer who were receiving high-dose **cyclophosphamide**, **cisplatin** and **carmustine** with lorazepam and ondansetron, with or without prochlorperazine, and compared with 75 matched control patients whose had been given prochlorperazine and lorazepam. In those given ondansetron the median AUC of **cyclophosphamide** was 17% lower, the **cisplatin** AUC was about 10% higher and the **carmustine** AUC was unchanged.[7]

In a crossover study in 10 patients, who received intravenous **cyclophosphamide** 600 mg/m^2 and **epirubicin** 90 mg/m^2 and either oral ondansetron 16 mg or placebo, found that the pharmacokinetic parameters of **cyclophosphamide** or its metabolite were not significantly altered by ondansetron although there was considerable variation between subjects. It was concluded that ondansetron can be safely given with **cyclophosphamide**.[8]

No significant changes in the pharmacokinetics of ondansetron occurred in 20 patients with cancer taking **cisplatin** 20 to 40 mg/m^2 and/or **fluorouracil** 1 g/m^2 for 5 days but the clearance was lower than in healthy subjects.[9]

Information seems to be limited to these studies, but any pharmacokinetic effects appear to be small, and unlikely to be clinically relevant.

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Antineoplastics + Megestrol

In one clinical study megestrol reduced the response rates to etoposide with cisplatin but in another had no effect on response rates to alternating cycles of cyclophosphamide, doxorubicin and vincristine, and etoposide with cisplatin.

Clinical evidence

A study in 243 patients with advanced small-cell lung cancer (SCLC) given **etoposide** and **cisplatin** found that patients who also received megestrol acetate 800 mg daily had increased non-fluid body-weight and significantly less nausea and vomiting. Although the one-year survival rate was similar in both groups patients who received megestrol had a significantly worse response rate to **cisplatin** (68% compared with 80%) and a higher incidence of thromboembolic events. However the megestrol recipients did have poorer quality of life (a prognostic factor) at the beginning of the study and this may have influenced the findings.[1] In a similar study, megestrol acetate had no effect on response rates, symptom profile or overall survival in patients with SCLC receiving chemotherapy (alternating cycles of **cyclophosphamide**, **doxorubicin** and **vincristine**, and **etoposide** with **cisplatin** for a maximum of 6 cycles). In this study, megestrol acetate was given at a dose of 160 mg three times daily for 8 days starting 3 days before each cycle of chemotherapy.[2]

Mechanism

An *in vitro* study found that megestrol may antagonise the antineoplastic activity of cisplatin by up-regulating cellular detoxification mechanisms.[3]

Importance and management

The authors of the first study suggest that megestrol acetate should not be used routinely at the time of chemotherapy.[1] Be aware that the use of megestrol may antagonise the antitumour activity of cisplatin. More study is needed.

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Antineoplastics + Propofol

There are two isolated reports of severe pain occurring when patients who had previously received intravenous chemotherapy were given intravenous propofol via hand veins, and one report of excessive bradycardia after a bolus dose of propofol in a child receiving cytarabine.

Clinical evidence

Although pain on injection of propofol is well known, one group of workers noted that, on a number of occasions, patients previously given intravenous chemotherapy had marked pain, both at the site of injection and up the arm, when given propofol via hand veins.[1] This would seem to link with a report of a 15-year-old girl with acute lymphoblastic leukaemia who had been given several injections of **cyclophosphamide**, **methotrexate** and **vincristine** during the previous 6 months, and who was cannulated in her hand and given an infusion of *Plasmalyte B*. An injection of 60 micrograms of fentanyl via this cannula was painful and 20 mg of lidocaine helped, but 20 mg of propofol caused extreme pain. A further 20 mg of lidocaine was given and the propofol administration was stopped, but the pain continued. The whole hand became blue and congested, and blood began to move backwards up the drip tubing. The venous congestion gradually subsided over the next 15 minutes.[2] The authors recommended that propofol should be avoided in patients who have recently had intravenous chemotherapy.[2]

A report describes a child being given **cytarabine** and **daunorubicin** who developed significant bradycardia after receiving a bolus dose of propofol.[3]

Mechanism

Both cytarabine and propofol may cause bradycardia by blocking the sinoatrial node, and an additive or synergistic effect may have caused the bradycardia in the child described above.[3]

Importance and management

The general applicability of these reports remains to be determined. The use of propofol alone may cause pain and it should be noted that the manufacturer of propofol recommends that local pain associated with propofol during the induction phase can be minimised by the use of the larger veins on the forearm and antecubital fossa.[4]

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4. Diprivan (Propofol). AstraZeneca UK Ltd. UK Summary of product characteristics, July 2009.

Antineoplastics + Protease inhibitors

There is limited evidence that the incidence of chemotherapy-induced toxicities (with CDE or CHOP regimens) might be increased by protease inhibitor-based antiretroviral therapy; however, there is also limited evidence of a lack of increased toxicity. Cyclophosphamide clearance might be modestly reduced by protease inhibitor-based therapy, whereas doxorubicin pharmacokinetics do not seem to be affected. Indinavir levels were modestly increased by CHOP chemotherapy (cyclophosphamide, doxorubicin and vincristine).

Clinical evidence

(a) CDE

When compared with historical controls, the mucositis experienced by 12 patients who were receiving **saquinavir** and CDE (**cyclophosphamide**, **doxorubicin** and **etoposide**) was more severe than without **saquinavir** (grade 3 or 4, 67% versus 12%). However, the use of **saquinavir** was not associated with an effect on haematological toxicity (myelosuppression, neutropenia). All patients also received stavudine and 10 also received didanosine.[1]

In a retrospective study in 46 patients with HIV-associated non-Hodgkin's lymphoma who had been receiving CDE, the incidence of neutropenia and infection in those also taking protease inhibitor-based antiretroviral regimens was compared with that of regimens without protease inhibitors. Eleven patients were taking protease inhibitor-based antiretroviral treatment (not specifically named) and 35 were receiving non-protease inhibitor regimens (mostly NNRTI-based). There was a higher incidence of infections requiring hospitalisation in the group taking a protease inhibitor than in the NNRTI-based treatment group (48% compared with 25%). There was a similar difference in the incidence of grade 4 neutropenia (54% compared with 38%), and day-10 and day-14 neutrophil counts were significantly lower in patients receiving protease inhibitors, resulting in delays in giving chemotherapy in 16% of cycles (compared with 9% with NNRTIs). Overall, however, there was no difference in response rate, disease-free survival or overall survival between the two groups.[2]

Conversely, in an earlier study in 98 patients who had received CDE for HIV-associated non-Hodgkin's lymphoma, those patients receiving a protease inhibitor and two nucleoside analogues experienced less toxicity (including grade 4 neutropenia and infections) than the 43 patients who received didanosine alone (these were patients treated early on in the study, before combined antiretroviral regimens became accepted practice).[3]

(b) CHOP

When compared with historical controls, the clearance of cyclophosphamide, as part of CHOP (**cyclophosphamide**, **doxorubicin** and **vincristine**) was about 35 to 40% lower in a study in patients taking stavudine, lamivudine and **indinavir**. There was no significant difference in the clearance of doxorubicin, and no significant difference in **indinavir** levels. Excessive haematological toxicity was not noted when compared with historical controls.[4]

Conversely, in a retrospective study, there was a higher incidence of anaemia, a need for colony-stimulating factor support, and neurotoxicity in patients who received antiretrovirals (most including protease inhibitors) with CHOP compared with those receiving CHOP alone.[5] Nevertheless, in a subsequent crossover study by this research group, no significant changes were noted in the pharmacokinetics of doxorubicin, given as part of CHOP, during a cycle when given with antiretrovirals, when compared with a cycle when no antiretrovirals were given. In addition, when analysed by the protease inhibitors given, **indinavir**, **nelfinavir**, or **saquinavir**, the pharmacokinetics of doxorubicin did not differ.[6]

In a prospective study, in 7 patients receiving indinavir-based antiretroviral therapy the **indinavir** AUC was 38% higher when they were receiving CHOP than when they were not (either before CHOP or 2 weeks after the last CHOP cycle). However, the **indinavir** plasma levels with CHOP were the same as those expected from historical controls given indinavir alone, whereas the levels of **indinavir** given without CHOP were lower than expected. There was a trend towards higher **nelfinavir** plasma levels in 3 patients who also received CHOP when compared with **nelfinavir** alone.[7]

(c) Hyper-CVAD

In a study in patients with AIDS-associated Burkitt lymphoma or acute lymphoblastic leukaemia, the incidence of toxicity with the use of hyper-CVAD (**cyclophosphamide**, **dexamethasone**, **doxorubicin** and **vincristine** alternating with **methotrexate** and **cytarabine**) given with antiretrovirals (including **amprenavir**, **indinavir**, **nelfinavir**, or **ritonavir**) was similar to that usually seen with this regimen when used in HIV-negative patients.[8]

Mechanism

Unknown. It has been speculated that protease inhibitors might reduce the metabolism or transport of antineoplastics by inhibiting cytochrome P450 enzymes or P-glycoprotein, and thereby increase the toxicity of chemotherapy.[2]

Importance and management

No interaction is established. None of these studies on the possible effect of protease inhibitors on the toxicity of CDE or CHOP were randomised prospective studies, therefore the findings are difficult to interpret, especially as they differ in whether they found toxicity to be increased, and which toxicities in particular were assessed. There is limited evidence that cyclophosphamide clearance might be modestly reduced by protease inhibitor-based therapy, although the relevance of this is uncertain since no increase in toxicity was noted. In one prospective study, the pharmacokinetics of doxorubicin were not altered by protease inhibitor-based antiretroviral regimens. In another, indinavir levels appeared to be modestly raised by CHOP, but the increase seen was unlikely to be clinically relevant.

For the lack of effect of protease inhibitors on the pharmacokinetics of liposomal daunorubicin, see 'Anthracyclines; Daunorubicin + Protease inhibitors', p.700. For limited evidence that the toxicity of taxanes and irinotecan might be increased by protease inhibitors, see 'Taxanes + Protease inhibitors', p.769, and 'Irinotecan + Protease inhibitors', p.740.

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Antineoplastics + Semaxanib

The combination of semaxanib, cisplatin and gemcitabine has caused an unexpectedly high incidence of thromboembolic events.

Clinical evidence, mechanism, importance and management

The pharmacokinetics of semaxanib (SU5416), **cisplatin** and **gemcitabine** were unaltered when they were given together in a phase I study but investigation of the combination was terminated after 8 of the 19 patients had thromboembolic events (transient ischaemic attacks, cerebrovascular accidents, deep vein thromboses). **Gemcitabine** 1250 mg/m^2 was given on day one, immediately followed by **cisplatin** 80 mg/m^2, then semaxanib 85 mg/m^2 (escalated to 145 mg/m^2 in some patients). **Gemcitabine** then semaxanib were given on day 8, and semaxanib alone on days 4, 11, 15, and 18. The cycle was repeated every 3 weeks.[1] The incidence of thromboembolic events in this study (42%) was much higher than that seen with **cisplatin** and **gemcitabine** (0%) or semaxanib alone (2.2%), and was thought to be a result of the drug combination.[1] **Cisplatin** in particular, due to its effects on platelets and its vasoconstrictive effects, may be the drug interacting with the semaxanib.[2] Preliminary results of other studies of semaxanib with: **irinotecan**; **fluorouracil** and folinic acid; **irinotecan**, **fluorouracil** and folinic acid; or **paclitaxel** and **carboplatin** did not report this complication.[3-6] The authors of the first study[1] caution against further clinical studies of antineoplastics with angiogenesis inhibitors such as semaxanib until the exact cause of the thromboembolic events has been elucidated.

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Antineoplastics + Tamoxifen

Antineoplastics and tamoxifen are associated with an increased risk of thrombosis and there is the possibility that their combined use may further increase this risk.

Clinical evidence

A retrospective analysis of data from various Eastern Cooperative Oncology Group studies suggested that venous thromboembolic complications were more common in women given tamoxifen with adjuvant chemotherapy (CMF; **cyclophosphamide**, **methotrexate**, **fluorouracil**) than women given CMF alone (3.8% versus 0% in one study).[1] In another study of patients given tamoxifen 30 mg daily for 2 years the incidence of thromboembolic events was 2.6% compared with 13.6% in those also given 8 cycles of CMF. The authors of this study considered the rate of thromboembolic events with the combination to be higher than that usually seen

with CMF, and suggested that this occurred as a result of an interaction between tamoxifen and CMF.[2] In contrast, in another study, in the first 12 weeks of therapy, thrombosis occurred in 5 of 103 patients given tamoxifen with chemotherapy (**cyclophosphamide**, **methotrexate**, **fluorouracil**, **vincristine**, prednisone, **doxorubicin**) compared with 4 of 102 given the same chemotherapy alone, suggesting that tamoxifen made no significant contribution to the rate of thromboembolic events.[3]

Mechanism

Tamoxifen alone is known to carry a small risk of thromboembolic events when used for primary prevention of breast cancer,[4] which may be a result of tamoxifen causing an increased calcium uptake by platelets, leading to platelet activation.[5] Antineoplastic chemotherapy also increases the risk of thrombosis,[3] and cancer *per se* increases the risk, as does surgery for cancer.[6]

Importance and management

To what extent, if any, tamoxifen further increases the risk of thrombosis with cytotoxic antineoplastics is unclear from the above studies. However, some authors recommend that serious consideration be given to the use of prophylactic anticoagulants if adjuvant CMF is given with tamoxifen in women with breast cancer,[2] and the UK manufacturer endorses this for any adjuvant chemotherapy.[7] This may be prudent with antineoplastic chemotherapy in any case.

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6. Rickles FR, Levine MN. Venous thromboembolism in malignancy and malignancy in venous thromboembolism. *Haemostasis* (1998) 28 (Suppl 3), 43–9.
7. Nolvadex D (Tamoxifen). AstraZeneca UK Ltd. UK Summary of product characteristics, June 2008.

Antineoplastics + Vaccines

The immune response of the body is suppressed by cytotoxic antineoplastics. The effectiveness of vaccines may be poor, and generalised infection may occur in patients immunised with live vaccines.

Clinical evidence, mechanism, importance and management

As cytotoxic antineoplastics are immunosuppressant, they reduce the response of the body to immunisation. A study[1] in 53 patients with Hodgkin's disease found that chemotherapy reduced the antibody response to a **pneumococcal vaccine** by 60% when measured 3 weeks after immunisation. The patients were taking **chlormethine** (mechlorethamine), **vincristine**, prednisone and **procarbazine**. A few of them had also been given **bleomycin**, **vinblastine** or **cyclophosphamide**. Subtotal radiotherapy reduced the response by a further 15%.

The response to **influenza immunisation** in children with various malignancies was also markedly suppressed by chemotherapy. The regimen included prednisone and the cytotoxic drugs **mercaptopurine**, **methotrexate**, and **vincristine**. Some of them were also given **dactinomycin** and **cyclophosphamide**.[2] In another study only 9 out of 17 children with leukaemia or other malignant diseases and taking **methotrexate**, **cyclophosphamide**, **mercaptopurine** and prednisone developed a significant response to immunisation with **inactivated measles vaccine**.[3]

Furthermore, immunisation with **live vaccines** may result in a potentially life-threatening infection. For example, a woman taking **methotrexate** 15 mg once a month for psoriasis developed a generalised vaccinial infection after vaccination against **smallpox**.[4] Studies in *animals* given **smallpox vaccine** confirmed that they were more susceptible to infection if they had been given **methotrexate**, **mercaptopurine** or **cyclophosphamide**.[5]

Live vaccines should not be given to patients who are receiving cytotoxics or other immunosuppressant antineoplastics. The UK Department of Health states that live vaccines should not be given during or within at least 6 months of treatment with immunosuppressive chemotherapy or radiotherapy for malignant disease.[6] Attenuated vaccines are also unlikely to be used during cytotoxic chemotherapy, but, bear in mind that they might have reduced efficacy if they have to be given.

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5. Rosenbaum EH, Cohen RA, Glatstein HR. Vaccination of a patient receiving immunosuppressive therapy for lymphosarcoma. *JAMA* (1966) 198, 737–40.
6. Department of Health. Immunisation Against Infectious Disease 2006: "The Green Book". Available at: http://www.dh.gov.uk/en/Policyandguidance/Healthandsocialcaretopics/Greenbook/DH_4097254 (accessed 29/01/10).

Bevacizumab + Miscellaneous

Bevacizumab did not alter the pharmacokinetics of capecitabine, cisplatin, interferon alfa-2a, irinotecan and its active metabolite, SN-38, or oxaliplatin. A possible association between the use of bevacizumab with sunitinib and microangiopathic haemolytic anaemia has been suggested. There might be an increased risk of congestive heart failure in patients receiving bevacizumab who have previously received cardiotoxic antineoplastics such as the anthracyclines.

Clinical evidence, mechanism, importance and management

(a) Anthracyclines

A case report describes a patient who, after being given bevacizumab and capecitabine, developed severe cardiac failure. She had previously received two different courses of **epirubicin**-based chemotherapy, and also radiotherapy.[1]

Bevacizumab use alone can cause congestive heart failure, principally in patients with metastatic breast cancer, as in this case. The manufacturer notes that the previous use of an anthracycline and/or chest radiation might be a risk factor.[2] Bear this possibility in mind when using bevacizumab. The relation of capecitabine to this case is unknown.

(b) Capecitabine

The manufacturer states that in a study in patients with metastatic colorectal cancer given capecitabine with oxaliplatin, the pharmacokinetics of capecitabine were not significantly altered when bevacizumab was given.[2] For a case of heart failure in a patient receiving capecitabine and bevacizumab, see *Anthracyclines*, above.

(c) Interferon

Bevacizumab had no effect on the pharmacokinetics of interferon alfa-2a in patients with renal cancer.[2]

(d) Irinotecan and IFL

The manufacturers note that, in a specific drug interaction study, bevacizumab did not appear to significantly alter the pharmacokinetics of irinotecan and its active metabolite, SN-38.[2,3] However, the manufacturer of irinotecan states that bevacizumab appeared to increase the plasma levels of SN-38, the active metabolite of irinotecan, by about 33% in patients who received bevacizumab with **irinotecan**, **fluorouracil** and **folinic acid** (IFL), compared with IFL alone, but because there was a wide variability between patients, it is uncertain if this was due to bevacizumab. Nevertheless, more irinotecan dose reductions were needed in the bevacizumab recipients.[4] In addition, there was no difference in the clearance of bevacizumab when it was given with bolus IFL, when compared with its use alone.[2]

(e) Platinum compounds

The manufacturer states that in a study in patients with metastatic colorectal cancer also given capecitabine the pharmacokinetics of **oxaliplatin** were not significantly altered when it was given with bevacizumab. In addition, the pharmacokinetics of **cisplatin** were not affected by bevacizumab in patients with lung cancer.[2]

(f) Sunitinib

In two studies in patients with metastatic renal carcinoma, 7 of 19 patients given bevacizumab 10 mg/kg every 2 weeks and sunitinib 50 mg daily developed microangiopathic haemolytic anaemia, which was reversible upon discontinuation of bevacizumab and sunitinib.[2] It is unclear whether this was related to an interaction of the two drugs, or an adverse effect of either drug alone. Bear the possibility of this effect in mind if these two drugs are used together.

1. Fraile Gil S, Hidalgo Correas FJ, Lara Álvarez MA, Garrote Martínez FJ. Insuficiencia cardiaca grave por bevacizumab en paciente tratado con antraciclinas. *Farm Hosp* (2007) 31, 256–7.
2. Avastin (Bevacizumab). Roche Products Ltd. UK Summary of product characteristics, July 2009.
3. Avastin (Bevacizumab). Genentech, Inc. US Prescribing information, July 2009.
4. Campto (Irinotecan hydrochloride trihydrate). Pfizer Ltd. UK Summary of product characteristics, May 2009.

Bexarotene + Miscellaneous

Gemfibrozil raises bexarotene plasma levels. The manufacturers warn that, theoretically, inhibitors of CYP3A4 (azoles, grapefruit juice, protease inhibitors and some macrolides) may possibly raise bexarotene levels, whereas CYP3A4 inducers (phenytoin, phenobarbital, rifampicin (rifampin)) may possibly reduce them. They also suggest that the efficacy of hormonal contraceptives may be reduced, and increased blood glucose-lowering effects may occur with insulin or oral antidiabetic drugs. Food increases the oral absorption of bexarotene. No interaction seems to occur between bexarotene and atorvastatin or levothyroxine.
Systemic drug interactions are unlikely to occur with topical bexarotene, but it should not be used with topical diethyltoluamide.

Clinical evidence, mechanism, importance and management

(a) CYP3A4 inducers, inhibitors and substrates

Because it is known that bexarotene is metabolised by the cytochrome P450 isoenzyme CYP3A4, the manufacturers point out that there is a theoretical risk that drugs that inhibit CYP3A4 might increase bexarotene levels when it is given orally. They name **clarithromycin**, **erythromycin**, **itraconazole**, **ketoconazole**, **protease inhibitors** and **grapefruit juice**. They also suggest that CYP3A4 inducers, namely **dexamethasone**, **phenytoin** [and therefore probably **fosphenytoin**], **phenobarbital** [and therefore probably **primidone**] and **rifampicin** (**rifampin**), may theoretically increase the metabolism of bexarotene and reduce its levels.[1,2] Note, however, that **dexamethasone** does not usually cause a clinically relevant interaction by this mechanism.

The US manufacturer notes that, based on interim data, the concurrent use of bexarotene capsules and **tamoxifen** reduced the plasma concentrations of tamoxifen by about 35%.[2] They say that this is an indication that bexarotene might induce CYP3A4,[2] and that it may theoretically increase the metabolism of other substances metabolised by CYP3A4 such oral or other systemic **hormonal contraceptives**, thereby reducing both their serum levels and their efficacy.[1,2] For this reason they advise the use of additional non-hormonal contraception (e.g. a barrier method) to avoid the risk of contraceptive failure. They point out that this is particularly important because if failure were to occur, the foetus might be exposed to the teratogenic effects of bexarotene.[1,2]

Due to the low systemic exposure to bexarotene after *topical* use, any increases that occur with CYP3A4 inhibitors are unlikely to be sufficient to result in adverse effects with a low to moderate intensity topical bexarotene regimen.[3]

(b) Diethyltoluamide (DEET)

The manufacturers advise that patients using bexarotene gel should avoid the use of insect repellents containing diethyltoluamide because *animal* studies have shown increased diethyltoluamide toxicity.[3]

(c) Food

Oral administration of bexarotene 75 to 300 mg with a fat-containing meal resulted in an increase in the AUC and maximum plasma level of bexarotene of 35% and 48%, respectively, compared with administration with a glucose solution.[1] It is therefore recommended that bexarotene capsules are taken with food.[1,2]

(d) Other drugs

A population analysis of patients with cutaneous T-cell lymphoma found that the concurrent use of **gemfibrozil** in 3 patients substantially increased the plasma levels of bexarotene after oral administration, and caused dose-limiting hypertriglyceridaemia. The reasons for this effect are unknown, although it was suggested that inhibition of CYP3A4 by **gemfibrozil** may be partially responsible.[4] The manufacturers state that the concurrent use of gemfibrozil with oral bexarotene is not recommended,[1,2] but note that fibrates are not generally recognised as inhibitors of this isoenzyme, see 'Lipid regulating drugs', (p.1313). Under similar conditions, they say that bexarotene levels were not affected by **atorvastatin** or **levothyroxine**. Changes in thyroid function caused by bexarotene have been successfully treated with **thyroid hormones**.[1,2,4]

The manufacturers recommend that because bexarotene is related to **vitamin A**, any **vitamin A** supplements should be limited to 15 000 units or less daily to avoid potentially additive toxic effects.[1-3] They also say that, although no cases of hypoglycaemia have been seen, because of the known mode of action of bexarotene, it should be used with caution if given with **insulin** or drugs that enhance insulin secretion (e.g. **sulfonylureas**) or insulin sensitisers (e.g. **thiazolidinediones**).[1,2] For a list of these drugs see 'Table 13.1', (p.534).

1. Targretin Capsules (Bexarotene). Cephalon Ltd. UK Summary of product characteristics, April 2009.
2. Targretin Capsules (Bexarotene). Eisai Inc. US Prescribing information, May 2007.
3. Targretin Gel (Bexarotene). Eisai Inc. US Prescribing information, January 2007.
4. Talpur R, Ward S, Apisarnthanarax N, Breuer-McHam J, Duvic M. Optimizing bexarotene therapy for cutaneous T-cell lymphoma. *J Am Acad Dermatol* (2002) 47, 672–84.

Bicalutamide + CYP3A4 inhibitors or substrates

Bicalutamide is a weak inhibitor of CYP3A4, as assessed by a minor to modest increase in the AUC of midazolam, and is unlikely to result in clinically relevant interactions with CYP3A4 substrates. Nevertheless, the UK manufacturer contraindicates concurrent use with astemizole, cisapride and terfenadine, and cautions use with ciclosporin and calcium-channel blockers. Theoretically, inhibitors of CYP3A4 might increase bicalutamide levels, but there is no evidence of this.

Clinical evidence, mechanism, importance and management

(a) CYP3A4 inhibitors

Bicalutamide is extensively metabolised by the cytochrome P450 enzyme system, possibly by CYP3A4.[1] Although there are no specific data, the manufacturer advises caution when bicalutamide is given with other drugs that may inhibit drug oxidation. They suggest that bicalutamide plasma levels may be increased, which could increase the risk of adverse effects. They specifically name **cimetidine** and **ketoconazole**.[2] However, steady-state levels of bicalutamide are known to vary up to about 15-fold,[1] and there is just one recommended dose of bicalutamide.[2] Any effect of a weak inhibitor of CYP3A4 such as **cimetidine** is therefore very unlikely to be clinically relevant. There does not appear to be any published evidence of any interactions of bicalutamide with drugs that are known inhibitors of CYP3A4.

(b) CYP3A4 substrates

In vitro, the active isomer of bicalutamide is an inhibitor of various cytochrome P450 isoenzymes, particularly CYP3A4. In an early 12-week study with **phenazone** (largely used as an investigational marker drug of enzyme induction or inhibition), there were only minor changes in phenazone pharmacokinetics (half-life reduced by 16% with bicalutamide 50 mg, AUC reduced by 19% with bicalutamide 150 mg. This suggests that clinically bicalutamide has little effect on the cytochrome P450 system.[3]

In a further study, a single oral dose of **midazolam** was given to men who had been randomised to receive bicalutamide 150 mg twice daily or placebo at least 3 months previously.[1] The mean AUC of midazolam was 27% higher,[1] with a maximum increase of 80%,[2] in the bicalutamide recipients, although this difference was not statistically significant.[1] Midazolam is used as a probe drug to assess the effects of CYP3A4, and this study therefore suggests that, clinically, bicalutamide is only a weak CYP3A4 inhibitor, and is unlikely to cause clinically relevant interactions with substrates of this isoenzyme. Nevertheless, the UK manufacturer suggests that an interaction might occur with drugs that have a narrow

therapeutic range. They specifically contraindicate the concurrent use of **astemizole**, **cisapride** and **terfenadine**. They advise caution when bicalutamide is given with **ciclosporin**, and suggest that plasma concentrations of **ciclosporin** should be monitored closely both during and after concomitant treatment. They also advise caution with **calcium-channel blockers**.[2] The US manufacturer[4] advises caution with drugs that are substrates of CYP3A4; however, this seems over cautious. There does not appear to be any published evidence of any interactions of bicalutamide with drugs that are substrates of CYP3A4.

1. Cockshott ID. Bicalutamide: clinical pharmacokinetics and metabolism. *Clin Pharmacokinet* (2004) 43, 855–78.
2. Casodex Tablets (Bicalutamide). AstraZeneca UK Ltd. UK Summary of product characteristics, October 2009.
3. Kaisary A, Klarskov P, McKillop D. Absence of hepatic enzyme induction in prostate cancer patients receiving 'Casodex' (bicalutamide). *Anticancer Drugs* (1996) 7, 54–9.
4. Casodex (Bicalutamide). AstraZeneca. US Prescribing information, December 2008.

Bicalutamide + Food

In a study in 15 healthy subjects, there was no clinically relevant difference in bicalutamide pharmacokinetics when a single 50-mg dose of bicalutamide was taken after an overnight fast or after a high-fat cooked breakfast.[1] Bicalutamide can therefore be taken with or without meals.

1. Cockshott ID, Oliver SD, Young JJ, Cooper KJ, Jones DC. The effect of food on the pharmacokinetics of the bicalutamide ('Casodex') enantiomers. *Biopharm Drug Dispos* (1997) 18, 499–507.

Bicalutamide + Tamoxifen and other anti-oestrogens

Tamoxifen and anastrozole do not appear to alter bicalutamide levels.

Clinical evidence, mechanism, importance and management

The mean trough levels of *R*- and *S*-bicalutamide did not differ between 7 men taking bicalutamide 150 mg daily alone and men also taking tamoxifen 20 mg daily (7 subjects) or anastrozole 1 mg daily (7 subjects). The plasma levels of tamoxifen and anastrozole were similar to those usually seen. The findings of this small study suggest that tamoxifen and anastrozole do not have a marked effect on bicalutamide pharmacokinetics, although a more minor effect cannot be ruled out.[1]

1. Boccardo F, Rubagotti A, Conti G, Potenzoni D, Manganelli A, Del Monaco D. Exploratory study of drug plasma levels during bicalutamide 150 mg therapy co-administered with tamoxifen or anastrozole for prophylaxis of gynecomastia and breast pain in men with prostate cancer. *Cancer Chemother Pharmacol* (2005) 56, 415–20.

Bleomycin + Cisplatin

Cisplatin can increase the pulmonary toxicity of bleomycin by reducing its renal excretion. Digital ischaemia and arterial thrombosis have also been described in patients receiving both drugs.

Clinical evidence

Thirty patients with carcinoma of the cervix and 15 patients with germ cell tumours were given combination chemotherapy including bleomycin and cisplatin. Cisplatin was given by infusion on day one, followed by bleomycin given intramuscularly every 12 hours for 4 days or by continuous infusion over 72 hours. Nine of the patients with normal renal function and no previous pulmonary disease developed serious pulmonary toxicity and 6 died from respiratory failure.[1]

In a study of 18 patients given cisplatin and bleomycin for the treatment of disseminated testicular non-seminoma, 2 patients developed pneumonitis, and it was found that the cisplatin-induced reduction in renal function was paralleled by an increase in bleomycin-induced pulmonary toxicity.[2] Similar results were found by the same group in a much larger study of 54 patients.[3] A study in 2 children found that the total plasma clearance of bleomycin was halved (from 39 to 18 mL/minute/m^2) when they were also given cisplatin in cumulative doses exceeding 300 mg/m^2. The renal clearance in one of the children fell by 73% (from 30 to 8.2 mL/minute/m^2) although there was no evidence of severe bleomycin toxicity in either child.[4] Two cases of fatal bleomycin toxicity have been described in patients with cisplatin-induced renal impairment.[5,6]

A case report describes arterial thrombosis associated with pathological vascular changes in the arteries of a man receiving cisplatin, bleomycin and etoposide.[7] Another man developed fatal thrombotic microangiopathy (characterised by microangiopathic haemolytic anaemia, thrombocytopenia, renal impairment), which was attributed to the use of bleomycin and cisplatin.[8]

In an earlier study, digital ischaemia occurred in 41% of patients given cisplatin, bleomycin and vinblastine, compared with 21% of patients given only cisplatin and vinblastine.[9]

Mechanism

Renal excretion accounts for almost half of the total body clearance of bleomycin. Cisplatin is nephrotoxic and reduces the glomerular filtration rate so that the clearance of bleomycin is reduced. The accumulating bleomycin apparently causes the pulmonary toxicity.

Importance and management

Pulmonary toxicity with bleomycin and cisplatin is an established reaction with a potentially serious, sometimes fatal, outcome. Concurrent use should be very closely monitored and renal function checked. One of the problems is that levels of creatinine may not accurately indicate the extent of renal damage both during and after cisplatin treatment. The renal toxicity of cisplatin may also develop rapidly. Other toxic effects on the vascular system can also occur.

1. Rabinowits M, Souhami L, Gil RA, Andrade CAV, Paiva HC. Increased pulmonary toxicity with bleomycin and cisplatin chemotherapy combinations. *Am J Clin Oncol* (1990) 13, 132–8.
2. van Barneveld PWC, Sleijfer D Th, van der Mark Th W, Mulder NH, Donker AJM, Meijer S, Schraffordt Koops H, Sluiter HJ, Peset R. Influence of platinum-induced renal toxicity on bleomycin-induced pulmonary toxicity in patients with disseminated testicular carcinoma. *Oncology* (1984) 41, 4–7.
3. Sleijfer S, van der Mark TW, Schraffordt Koops H, Mulder NH. Enhanced effects of bleomycin on pulmonary function disturbances in patients with decreased renal function due to cisplatin. *Eur J Cancer* (1996) 32A, 550–2.
4. Yee GC, Crom WR, Champion JE, Brodeur GM, Evans WE. Cisplatin-induced changes in bleomycin elimination. *Cancer Treat Rep* (1983) 67, 587–9.
5. Bennett WM, Pastore L, Houghton DC. Fatal pulmonary bleomycin toxicity in cisplatin-induced acute renal failure. *Cancer Treat Rep* (1980) 64, 921–4.
6. Perry DJ, Weiss RB, Taylor HG. Enhanced bleomycin toxicity during acute renal failure. *Cancer Treat Rep* (1982) 66, 592–3.
7. Garstin IWH, Cooper GG, Hood JM. Arterial thrombosis after treatment with bleomycin and cisplatin. *BMJ* (1990) 300, 1018.
8. Fields SM, Lindley CM. Thrombotic microangiopathy associated with chemotherapy: case report and review of the literature. *DICP Ann Pharmacother* (1989) 23, 582–8.
9. Vogelzang NJ, Bosl GJ, Johnson K, Kennedy BJ. Raynaud's phenomenon : a common toxicity after combination chemotherapy for testicular cancer. *Ann Intern Med* (1981) 95, 288–92.

Bleomycin + Colony-stimulating factors

The concurrent use of granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor has been linked with an increased occurrence of bleomycin-induced pulmonary toxicity.

Clinical evidence, mechanism, importance and management

Pulmonary toxicity that developed at low cumulative bleomycin doses (70 to 130 units/m^2) in at least 3 of 5 patients given standard ABVD treatment (doxorubicin, bleomycin, vinblastine, and dacarbazine) was attributed by the author of the report to the synergistic action of the concurrent use of **G-CSF** (granulocyte colony-stimulating factor).[1] In another report 8 out of 40 patients with malignant non-Hodgkin's lymphoma given **G-CSF** developed drug-induced pneumonia. Three of these patients were given chemotherapy regimens including bleomycin (MACOB-B, COP-BLAM III), and all 3 died of respiratory failure. None of 35 other patients, similarly treated but without **G-CSF**, developed pneumonia.[2] Non-infectious interstitial pneumonitis developed in a patient given doxorubicin, cyclophosphamide, bleomycin, vinblastine, methotrexate and prednisone with **GM-CSF** (granulocyte-macrophage colony-stimulating factor).[3] Five further reports have identified a total of 23 other patients who developed bleomycin-pulmonary toxicity probably potentiated by **G-CSF** or **GM-CSF**, including at least 7 fatalities.[4-8]

In contrast, analysis of two placebo-controlled studies of the use of adjuvant **G-CSF** (**filgrastim** or **lenograstim**) with combination chemother-

apy including bleomycin found no evidence of an increase in pulmonary complications. Overall 7 of 139 patients given placebo and 9 of 139 given **G-CSF** had pulmonary complications possibly related to bleomycin.[9,10] Similarly, another retrospective analysis found that 34% of patients given bleomycin and **G-CSF** developed pulmonary toxicity, compared with 33% of those given bleomycin alone.[11]

These interactions are not firmly established, but good pulmonary function monitoring appears to be advisable when colony-stimulating factors are used with antineoplastics causing pulmonary toxicity, such as bleomycin. If interstitial pneumonia occurs, the drugs should be discontinued and high-dose corticosteroids started immediately.[7]

1. Matthews JH. Pulmonary toxicity of ABVD chemotherapy and G-CSF in Hodgkin's disease: possible synergy. *Lancet* (1993) 342, 988.
2. Iki S, Yoshinaga K, Ohbayashi Y, Urabe A. Cytotoxic drug-induced pneumonia and possible augmentation by G-CSF — clinical attention. *Ann Hematol* (1993) 66, 217–18.
3. Philippe B, Couderc LJ, Balloul-Delclaux E, Janvier M, Caubarrere I. Pulmonary toxicity of chemotherapy and GM-CSF. *Respir Med* (1994) 88, 715.
4. Dirix LY, Schrijvers D, Druwè P, Van Den Brande J, Verhoeven D, Van Oosterom AT. Pulmonary toxicity and bleomycin. *Lancet* (1994) 344, 56.
5. Lei KIK, Leung WT, Johnson PJ. Serious pulmonary complications in patients receiving recombinant granulocyte colony-stimulating factor during BACOP chemotherapy for aggressive non-Hodgkin's lymphoma. *Br J Cancer* (1994) 70, 1009–13.
6. Katoh M, Shikoshi K, Takada M, Umeda M, Tsukahara T, Kitagawa S, Shirai T. Development of interstitial pneumonitis during treatment with granulocyte colony-stimulating factor. *Ann Hematol* (1993) 67, 201–2.
7. Niitsu N, Iki S, Muroi K, Motomura S, Murakami M, Takeyama H, Ohsaka A, Urabe A. Interstitial pneumonia in patients receiving granulocyte colony-stimulating factor during chemotherapy: survey in Japan 1991–96. *Br J Cancer* (1997) 76, 1661–6.
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10. Bastion Y, Coiffier B. Pulmonary toxicity of bleomycin: is G-CSF a risk factor? *Lancet* (1994) 344, 474.
11. Saxman SB, Nichols CR, Einhorn LH. Pulmonary toxicity in patients with advanced-stage germ cell tumors receiving bleomycin with and without granulocyte colony stimulating factor. *Chest* (1997) 111, 657–60.

Bleomycin + Oxygen

Serious and potentially fatal pulmonary toxicity can develop in patients given bleomycin who are exposed to conventional oxygen concentrations during anaesthesia.

Clinical evidence

Five patients given bleomycin, exposed to oxygen concentrations of 35 to 42% during and immediately following anaesthesia, developed a severe respiratory distress syndrome and died. Bleomycin-induced pneumonitis and lung fibrosis were diagnosed at post-mortem. Another group of 12 matched patients who underwent the same procedures but with lower oxygen concentrations (22 to 25%) had an uneventful postoperative course.[1]

Another comparative study[2] similarly demonstrated that adult respiratory distress syndrome (ARDS) in patients receiving bleomycin was reduced by a technique allowing the use of lower oxygen concentrations of 22 to 30%. Bleomycin-induced pulmonary toxicity, apparently related to oxygen concentrations, has also been described in other case reports.[3-7] Studies in *animals* have also confirmed that the severity of bleomycin-induced pulmonary toxicity is increased by oxygen.[8-10] However, in two other series of patients given bleomycin and undergoing surgery there was no obvious increase in pulmonary complications despite the use of usual concentrations of oxygen.[11,12]

Mechanism

Not understood. One suggestion is that bleomycin-injured lung tissue is less able to scavenge free oxygen radicals, which may be present, and damage occurs as a result.[3]

Importance and management

An established, well-documented, serious and potentially fatal interaction. It is advised that any patient receiving bleomycin and undergoing general anaesthesia should have their inspired oxygen concentrations limited to less than 30%, and the fluid replacement should be carefully monitored to minimise the crystalloid load. This is clearly very effective because one author has treated 700 patients following these guidelines without a single case of pulmonary failure.[13] It has also been suggested that reduced oxygen levels should be continued during the recovery period and at any time during hospitalisation.[3] If an oxygen concentration equal to or greater than 30% has to be used, the short-term use of prophylactic corticosteroids should be considered. Intravenous corticosteroids should be given at once if bleomycin toxicity is suspected.[3]

1. Goldiner PL, Carlon GC, Cvitkovic E, Schweizer O, Howland WS. Factors influencing postoperative morbidity and mortality in patients treated with bleomycin. *BMJ* (1978) 1, 1664–7.
2. El-Baz N, Ivankovich AD, Faber LP, Logas WG. The incidence of bleomycin lung toxicity after anesthesia for pulmonary resection: a comparison between HFV and IPPV. *Anesthesiology* (1984) 61, A107.
3. Gilson AJ, Sahn SA. Reactivation of bleomycin lung toxicity following oxygen administration. A second response to corticosteroids. *Chest* (1985) 88, 304–6.
4. Cersosimo RJ, Matthews SJ, Hong WK. Bleomycin pneumonitis potentiated by oxygen administration. *Drug Intell Clin Pharm* (1985) 19, 921–3.
5. Hulbert JC, Grossman JE, Cummings KB. Risk factors of anesthesia and surgery in bleomycin-treated patients. *J Urol (Baltimore)* (1983) 130, 163–4.
6. Donohue JP, Rowland RG. Complications of retroperitoneal lymph node dissection. *J Urol (Baltimore)* (1981) 125, 338–40.
7. Ingrassia TS, Ryu JH, Trastek VF, Rosenow EC. Oxygen-exacerbated bleomycin pulmonary toxicity. *Mayo Clin Proc* (1991) 66, 173–8.
8. Toledo CH, Ross WE, Hood I, Block ER. Potentiation of bleomycin toxicity by oxygen. *Cancer Treat Rep* (1982) 66, 359–62.
9. Berend N. The effect of bleomycin and oxygen on rat lung. *Pathology* (1984) 16, 136–9.
10. Rinaldo J, Goldstein RH, Snider GL. Modification of oxygen toxicity after lung injury by bleomycin in hamsters. *Am Rev Respir Dis* (1982) 126, 1030–3.
11. Douglas MJ, Coppin CML. Bleomycin and subsequent anesthesia: a retrospective study at Vancouver General Hospital. *Can Anaesth Soc J* (1980) 27, 449–52.
12. Mandelbaum I, Williams SD, Einhorn LH. Aggressive surgical management of testicular carcinoma metastatic to lungs and mediastinum. *Ann Thorac Surg* (1980) 30, 224–9.
13. Goldiner PL. Editorial comment. *J Urol (Baltimore)* (1983) 130, 164.

Bortezomib + Ciclosporin

Preliminary evidence suggests that patients who have received long-term ciclosporin might be at increased risk of severe neuropathy when given bortezomib.

Clinical evidence

In a review of 24 patients with multiple myeloma who had received bortezomib after relapse following allografting, the incidence of severe peripheral neuropathy was far higher than usually seen in non-transplant patients. Fourteen patients developed neurotoxicity; in 7 patients it was severe and 6 patients required treatment discontinuation as the neurotoxicity did not resolve following a bortezomib dose reduction. In an analysis of possible risk factors, prolonged ciclosporin use (median of 15 months) was found to be a risk factor for the development of severe neurotoxicity.[1]

Mechanism

Ciclosporin can cause neurotoxicity. Bortezomib is also very commonly associated with peripheral neuropathy, which can be dose-limiting. It was suggested that long-term ciclosporin might have caused subclinical neurotoxicity that became apparent after bortezomib was given.[1]

Importance and management

An interaction between bortezomib and ciclosporin is not established, but until more is known, be aware of the possibility of this effect if bortezomib is used in patients taking ciclosporin. The authors also suggest considering using a lower bortezomib dose in these patients.[1] Note that, any patients receiving bortezomib should be carefully monitored for symptoms of neuropathy such as a burning sensation, hyperaesthesia, hypoaesthesia, paraesthesia, discomfort, neuropathic pain or weakness. Patients experiencing new or worsening peripheral neuropathy should undergo neurological evaluation and may require the dose and schedule of bortezomib to be modified.

1. Giaccone L, Sorasio R, Patriarca F, Mattei D, Montefusco V, Peccatori J, Carnevale-Schianca F, Petrucci MT, Milone G, Guidi S, Rotta M, Fanin R, Corradini P, Boccadoro M, Bruno B. Bortezomib after allografting in multiple myeloma: association between neurotoxicity and cyclosporine treatment. *Biol Blood Marrow Transplant* (2007) 13, 497–9.

Bortezomib + Miscellaneous

Plasma levels of bortezomib were modestly increased by ketoconazole, and are predicted to be similarly affected by other potent CYP3A4 inhibitors. Omeprazole did not alter bortezomib levels, and no clinically relevant effect was seen with melphalan plus prednisone. Cases of hyper- and hypoglycaemia have been reported in clinical studies in patients taking antidiabetics and bortezomib. Hypotension is common in patients taking bortezomib,

and the effects may be additive if used with antihypertensives or other drugs that can cause hypotension.

Clinical evidence, mechanism, importance and management

(a) Antidiabetics

The manufacturers note that during clinical studies with bortezomib, some patients who were taking oral antidiabetics (none specifically named) experienced hyper- or hypoglycaemia.[1,2] Bortezomib commonly causes hyperglycaemia (sometimes requiring treatment discontinuation[2]) and uncommonly causes hypoglycaemia,[1] and it is therefore likely that this is a drug-disease interaction rather than a drug-drug interaction. The manufacturers advise that patients taking oral antidiabetics may require close monitoring of their blood glucose and adjustment of the dose of antidiabetic drugs accordingly.[1,2]

(b) CYP2C19 inhibitors and substrates

In *in vitro* studies bortezomib is metabolised by cytochrome P450 isoenzymes, including CYP2C19. However, the pharmacokinetics of bortezomib were unaltered in 17 patients who also received **omeprazole**, an inhibitor of CYP2C19.[1,2] Nevertheless, the UK manufacturer continues to advise that patients should be monitored carefully when given bortezomib with other drugs which are inhibitors of CYP2C19, and they name **fluoxetine**.[1] However, note that of the SSRIs, only **fluvoxamine** is an established CYP2C19 inhibitor. For a list of CYP2C19 inhibitors, see 'Table 1.3', (p.6).

The US manufacturer predicts that exposure to CYP2C19 substrates may be increased on the basis of *in vitro* data showing that bortezomib is an inhibitor of this isoenzyme.[2] This requires confirmation.

(c) CYP3A4 inducers

Bortezomib has been shown *in vitro* to be metabolised by cytochrome P450 isoenzymes, including CYP3A4. The manufacturers advise that in the absence of any studies investigating the interaction of bortezomib with inducers of CYP3A4, patients taking such drugs should be closely monitored.[1,2] They specifically name **rifampicin** (**rifampin**).[1]

(d) CYP3A4 inhibitors

The manufacturers note that the AUC of bortezomib was increased by 35% in 12 patients who also took **ketoconazole**, a known inhibitor of the cytochrome P450 isoenzyme CYP3A4. They advise close monitoring when bortezomib is given with **ketoconazole** or other drugs that inhibit CYP3A4, and name **ritonavir**.[1,2] For a list of CYP3A4 inhibitors, see 'Table 1.4', (p.6).

(e) Drugs causing hypotension

Bortezomib commonly causes orthostatic/postural hypotension, which may occur throughout treatment, and not just during administration. The manufacturers advise caution when treating patients receiving drugs known to be associated with hypotension. They say that management of orthostatic hypotension may include adjustment of **antihypertensives**. Patients should be instructed to seek medical advice if they experience symptoms of dizziness, light-headedness or fainting spells.[1,2]

(f) Melphalan with Prednisone

The manufacturers note that data from 21 patients show that the concurrent use of bortezomib with melphalan and prednisone resulted in an increase in the AUC of bortezomib of 17%, which is not considered to be clinically relevant.[1,2] Bortezomib is often used with melphalan and prednisone in patients with multiple myeloma.

1. Velcade (Bortezomib mannitol boronic ester). Janssen-Cilag Ltd. UK Summary of product characteristics, November 2009.
2. Velcade (Bortezomib). Millennium Pharmaceuticals, Inc. US Prescribing information, June 2008.

Busulfan + Azoles

Itraconazole, but not fluconazole, modestly reduces the clearance of busulfan. There is some limited evidence to suggest that the use of busulfan with ketoconazole may increase the risk of hepatic veno-occlusive disease.

Clinical evidence, mechanism, importance and management

The pharmacokinetics of busulfan were compared in 26 bone marrow transplant patients, who had received busulfan without concurrent antifungal therapy, in 13 similar patients given busulfan with **itraconazole**, and in another 13 patients given busulfan with **fluconazole**. The busulfan clearance was decreased by 20% by **itraconazole** (probably because **itraconazole** inhibits the metabolism of busulfan by the liver) but busulfan clearance was not affected by the **fluconazole**.[1] The expected rise in serum busulfan levels is only likely to be moderate, but until more information is available it would be prudent to monitor for any signs of increased busulfan toxicity if **itraconazole** is used, but no special precautions seem to be needed with **fluconazole**. Concurrent **ketoconazole** has been identified as a possible risk factor for hepatic veno-occlusive disease after the use of high-dose busulfan.[2] Further study is needed to confirm or refute this.

1. Buggia I, Zecca N, Alessandrino EP, Locatelli F, Rosti G, Bosi A, Pession A, Rotoli B, Majolino I, Dallorso A, Regazzi MB. Itraconazole can increase systemic exposure to busulfan in patients given bone marrow transplantation. *Anticancer Res* (1996) 16, 2083–8.
2. Méresse V, Hartmann O, Vassal G, Benhamou E, Valteau-Couanet D, Brugieres L, Lemerie J. Risk factors for hepatic veno-occlusive disease after high-dose busulfan-containing regimens followed by autologous bone marrow transplantation: a study in 136 children. *Bone Marrow Transplant* (1992) 10, 135–41.

Busulfan + Benzodiazepines

Diazepam and lorazepam do not appear to alter the pharmacokinetics of busulfan.

Clinical evidence, mechanism, importance and management

In a study in patients receiving high-dose busulfan, no pharmacokinetic changes were seen in 8 patients given **diazepam**, apart from a steady decline in steady-state serum levels in just one.[1] Similarly, in another study, **lorazepam** did not alter the absorption and clearance of high-dose busulfan in children undergoing stem-cell transplantation.[2] Benzodiazepines may therefore be a suitable alternative to phenytoin for seizure prophylaxis during high-dose busulfan treatment.[2]

1. Hassan M, Öberg G, Björkholm M, Wallin I, Lindgren M. Influence of prophylactic anticonvulsant therapy on high-dose busulphan kinetics. *Cancer Chemother Pharmacol* (1993) 33, 181–6.
2. Chan KW, Mullen CA, Worth LL, Choroszy M, Koontz S, Tran H, Slopis J. Lorazepam for seizure prophylaxis during high-dose busulfan administration. *Bone Marrow Transplant* (2002) 29, 963–5.

Busulfan + Ketobemidone

Ketobemidone may increase busulfan levels.

Clinical evidence, mechanism, importance and management

A patient with acute myeloid leukaemia was given busulfan 1 mg/kg four times daily for 4 days followed by cyclophosphamide for 2 days before bone marrow transplantation. At the time he was also receiving ketobemidone 1 g daily for a rectal fissure. Busulfan plasma levels after the first dose were elevated (AUC increased by about one-third). Later, when the dose of ketobemidone was reduced and morphine substituted, busulfan levels decreased.[1] The authors suggest that ketobemidone should not be used with high-dose busulfan unless monitoring is possible: dose adjustments may be required to prevent busulfan toxicity. An alternative analgesic should be considered.

1. Hassan M, Svensson J-O, Nilsson C, Hentschke P, AL-Shurbaji A, Aschan J, Ljungman P, Ringdén O. Ketobemidone may alter busulfan pharmacokinetics during high-dose therapy. *Ther Drug Monit* (2000) 22, 383–5.

Busulfan + Metronidazole

Metronidazole increases the trough levels of high-dose busulfan, and increases its toxicity.

Clinical evidence

In a study, patients were given oral high-dose busulfan 1 mg/kg every six hours for 4 days (adjusted to achieve a target trough level) as part of a stem cell transplant procedure. It was found that the dose-adjusted trough

levels of busulfan were 87% higher in 5 patients who also received metronidazole 400 mg three times daily than in 10 patients who did not take metronidazole. Furthermore, all 5 patients who had received metronidazole with busulfan developed elevated liver function tests and mucositis, and three developed veno-occlusive disease (moderate to severe in two, with one death). In the 10 patients who did not receive metronidazole, only 3 had elevated liver function tests, one had mucositis, and none had veno-occlusive disease.[1]

In a further group of 9 patients who received busulfan alone for 2 days then in combination with metronidazole for 2 days the trough level of busulfan increased by 78% when given metronidazole.[1]

Mechanism

The reason why metronidazole might increase busulfan levels is unknown, but it might be something to do with glutathione depletion.[1]

Importance and management

Although information is limited, this pharmacokinetic interaction would appear to be established and clinically important. The authors considered that metronidazole should not be given at the same time as high-dose busulfan,[1] and this would appear to be prudent, and is included in some manufacturers' advice.[2] If the drugs are used together in a patient taking conventional dose busulfan, one manufacturer recommends weekly blood counts to detect any increase in toxicity.[2].

1. Nilsson C, Aschan J, Hentschke P, Ringdén O, Ljungman P, Hassan M. The effect of metronidazole on busulfan pharmacokinetics in patients undergoing hematopoietic stem cell transplantation. *Bone Marrow Transplant* (2003) 31, 429–35.
2. Myleran (Busulfan). GlaxoSmithKline UK. UK Summary of product characteristics, October 2006.

Busulfan + Paracetamol (Acetaminophen)

Paracetamol is predicted to decrease the clearance of busulfan

Clinical evidence, mechanism, importance and management

Busulfan is conjugated with glutathione as part of its metabolism, and, as paracetamol is known to reduce the blood levels of glutathione it is predicted to reduce the clearance of busulfan. The manufacturers of busulfan therefore advise caution when paracetamol is given during the 72-hour period before busulfan is given, and during the use of busulfan.[1,2] Note that the clinical relevance of this proposed interaction is unclear, and only the manufacturers of intravenous busulfan appear to mention it.

1. Busilvex (Busulfan). Pierre Fabre Ltd. UK Summary of product characteristics, July 2008.
2. IVBusulfex (Busulfan). Otsuka America Pharmaceutical, Inc. US Prescribing information, August 2009.

Busulfan + Phenytoin

Phenytoin modestly increases the clearance of busulfan and lowers its levels. Subtherapeutic levels of phenytoin may occur in the presence of busulfan.

Clinical evidence

Seven patients receiving high-dose busulfan (1 mg/kg four times daily for 4 days) before bone marrow transplantation had a 19% increase in busulfan clearance, a 16% lower AUC and a shorter half-life (reduced from 3.94 to 3.03 hours) when they were given phenytoin 2.5 to 5 mg/kg daily. A continuous decline in the steady-state plasma levels of busulfan was also seen in 4 of the patients.[1]

In a study in 51 patients given busulfan and prophylactic phenytoin 300 mg daily for 5 days, 3 patients developed convulsions, and plasma phenytoin levels analysed in 2 of them were found to be subtherapeutic.[2]

Mechanism

It seems likely that phenytoin (a well recognised enzyme inducer) increases the metabolism of busulfan by the liver (possibly by induction of glutathione-S-transferase), thereby decreasing its levels. In an *animal* study, phenytoin was found to reduce the myelosuppressive effects of busulfan.[3]

Importance and management

Evidence for an interaction between phenytoin and busulfan appears to be limited to these two reports. However, the effects of phenytoin on busulfan are in line with the way phenytoin is known to interact with a number of other drugs, so an interaction would appear to be established. The authors of one study suggest that antiepileptics with fewer enzyme-inducing properties than phenytoin should be used as prophylaxis if busulfan is given for bone marrow transplant pretreatment.[1] One UK manufacturer recommends prophylaxis with a benzodiazepine rather than phenytoin if high-dose busulfan is given.[4] Clobazam has been suggested as a possible alternative to phenytoin.[5] Lorazepam and diazepam appear not to interact with busulfan (see 'Busulfan + Benzodiazepines', p.709) and they may therefore be suitable alternatives. The UK manufacturer of parenteral busulfan found no evidence that phenytoin increased its clearance, and notes that all adult patients given busulfan also received phenytoin.[6] However, the US manufacturer of parenteral busulfan gives a dose assuming that phenytoin will also be given, and notes that if other antiepileptics are used instead, the busulfan plasma levels may be increased and monitoring is recommended.[7]

To overcome the problem of reduced phenytoin levels, the authors recommended a loading dose of phenytoin 18 mg/kg on the day before the first dose of busulfan, then 300 mg daily until 48 hours after the last busulfan dose. A further loading dose was given if the phenytoin level was subtherapeutic 48 hours after the initial dose (required in 35% of patients).[2]

1. Hassan M, Öberg G, Björkholm M, Wallin I, Lindgren M. Influence of prophylactic anticonvulsant therapy on high-dose busulphan kinetics. *Cancer Chemother Pharmacol* (1993) 33, 181–6.
2. Grigg AP, Shepherd JD, Phillips GL. Busulphan and phenytoin. Ann Intern Med (1989) 111, 1049–50. Correction. *Ann Intern Med* (1989) 112, 313.
3. Fitzsimmons WE, Ghalie R, Kaizer H. The effect of hepatic enzyme inducers on busulfan neurotoxicity and myelotoxicity. *Cancer Chemother Pharmacol* (1990) 27, 226–8.
4. Myleran (Busulfan). GlaxoSmithKline UK. UK Summary of product characteristics, October 2006.
5. Schwarer AP, Opat SS, Watson AL, Cole-Sinclair MF. Clobazam for seizure prophylaxis during busulfan chemotherapy. *Lancet* (1995) 346, 1238.
6. Busilvex (Busulfan). Pierre Fabre Ltd. UK Summary of product characteristics, July 2008.
7. IVBusulfex (Busulfan). Otsuka America Pharmaceutical, Inc. US Prescribing information, August 2009.

Busulfan + Tioguanine

The long-term use of busulfan with tioguanine appears to increase the risk of nodular regenerative hyperplasia of the liver, portal hypertension and oesophageal varices.

Clinical evidence, mechanism, importance and management

Five patients receiving continuous busulfan 2 mg and tioguanine 80 mg five days weekly for chronic myeloid leukaemia (CML) developed oesophageal varices and abnormal liver function tests. Three of them had gastrointestinal haemorrhages and one died. Liver biopsy of 4 of the patients showed nodular regenerative hyperplasia, which was the cause of portal hypertension and varices.[1] A later analysis of the Medical Research Council study comparing busulfan with busulfan and tioguanine in 675 patients with CML, revealed a total of 18 cases of portal hypertension and oesophageal varices (including 4 described in the first report[1]), all 18 of which occurred in patients receiving both drugs. In addition, there was no survival advantage with the combination.[2] The risk of portal hypertension may be related to the long-term use of tioguanine, or to its combination with busulfan. It has been suggested that this drug combination should not be routinely used for the long-term maintenance of CML.[2]

1. Key NS, Kelly PMA, Emerson PM, Chapman RWG, Allan NC, McGee JO'D. Oesophageal varices associated with busulphan-thioguanine combination therapy for chronic myeloid leukaemia. *Lancet* (1987) 2, 1050–2.
2. Shepherd, PCA, Fooks J, Gray R, Allan NC. Thioguanine used in maintenance therapy of chronic myeloid leukaemia causes non-cirrhotic portal hypertension. *Br J Haematol* (1991) 79, 185–92.

Cetuximab + Irinotecan

No pharmacokinetic interaction occurs between cetuximab and irinotecan.

Clinical evidence, mechanism, importance and management

Cetuximab is used with irinotecan in the treatment of metastatic colorectal cancer. In a study, 14 patients with advanced epidermal growth factor responsive (EGFR) positive adenocarcinoma were given either irinotecan 350 mg/m^2 every 3 weeks and cetuximab 400 mg/m^2 at week 2 then 250 mg/m^2 each week, or cetuximab each week starting at week one and irinotecan starting at week 4. There was at least a one-hour period between the end of the cetuximab infusion and the start of the irinotecan infusion. No evidence was found of a pharmacokinetic interaction between cetuximab and irinotecan, nor was there any significant increase in serious toxicities for the combination, when compared with treatment with either drug alone.[1] Similar results were found in a crossover study in 8 patients who received irinotecan 350 mg/m^2 every 3 weeks and cetuximab 400 mg/m^2 on day 2, then 250 mg/m^2 each week.[2]

1. Delbaldo C, Pierga J-Y, Dieras V, Faivre S, Laurence V, Vedovato J-C, Bonnaay M, Mueser M, Nolting A, Kovar A, Raymond E. Pharmacokinetic profile of cetuximab (Erbitux) alone and in combination with irinotecan in patients with advanced EGFR-positive adenocarcinoma. *Eur J Cancer* (2005) 41, 1739–45.
2. Ettlinger DE, Mitterhauser M, Wadsak W, Ostermann E, Farkouh A, Schueller J, Czejka M. *In vivo* disposition of irinotecan (CPT-11) and its metabolites in combination with the monoclonal antibody cetuximab. *Anticancer Res* (2006) 26, 1337–42.

Chlorambucil + Prednisone

An isolated report describes seizures in a patient, which were possibly caused by the use of chlorambucil with prednisone.

Clinical evidence, mechanism, importance and management

A patient with non-Hodgkin's lymphoma experienced a syncopal episode with generalised tonic-clonic seizures 8 days after completing an initial 5-day course of chlorambucil 12 mg daily and prednisone 50 mg daily. The seizures were controlled with intravenous clonazepam. Four weeks later, on the third day of a second course, she again had generalised tonic-clonic seizures, which resolved spontaneously.

Chlorambucil-induced seizures have occurred in children with nephrotic syndrome. Cases in adults usually involve high-dose chlorambucil or are in patients with a history of seizures. The seizures in this patient may have been due to the additive effects of both drugs in reducing the seizure threshold.[1]

Note that chlorambucil and prednisone or prednisolone have been widely used together, but this case report highlights the need to assess the risk of seizures when giving drugs that lower the seizure threshold.

1. Jourdan E, Topart D, Pinzani V, Jourdan J. Chlorambucil/prednisone-induced seizures in a patient with non-Hodgkin's lymphoma. *Am J Hematol* (2001) 67, 147.

Cisplatin and other platinum compounds + Aminoglycosides

The renal toxicity of cisplatin is potentiated by aminoglycosides such as gentamicin and tobramycin. In one retrospective analysis in patients taking cisplatin, hearing loss was not associated with the concurrent use of ototoxic drugs, including tobramycin.

Clinical evidence

(a) Hypomagnesaemia

Both cisplatin and the aminoglycosides can cause excessive loss of magnesium, and it has been suggested that combined use increases this loss.[1]

(b) Nephrotoxicity

Early after the introduction of cisplatin it became apparent that aminoglycosides could increase the nephrotoxicity of this drug. In one report, 4 patients given cisplatin, in doses ranging from low to very high (eight doses of 0.5 mg/kg, one or two doses of 3 mg/kg or a single-dose of 5 mg/kg), and who were subsequently given **gentamicin** and cefalotin developed acute and fatal renal failure. Autopsy revealed extensive renal tubular necrosis.[2] Two similar cases of severe renal toxicity, attributed to the use of **gentamicin** and cefalotin in patients who had previously been given cisplatin, are described elsewhere.[3,4] Another patient given cisplatin and **gentamicin** developed acute renal failure.[5] A further 3 patients given cisplatin then **gentamicin** or **tobramycin** had greater decreases in creatinine levels than 12 others receiving cisplatin alone.[5] A retrospective comparative study confirmed that the incidence of abnormal renal function was higher in patients who had received cisplatin and an aminoglycoside than in patients who had received cisplatin alone (12 of 17 versus 19 of 50 patients, respectively), but the renal impairment was described as usually mild and not clinically significant.[6] Similarly, a brief report stated that aminoglycoside use was associated with a greater decline in renal function in children receiving high-dose cisplatin.[7] There is also evidence from a study in children to show that previous treatment with cisplatin is a risk factor for the delayed elimination of aminoglycosides (**gentamicin**, **amikacin**, **tobramycin**).[8]

Conversely, in another study, aminoglycosides were not found to be a significant factor in the development of renal impairment after the use of high-dose cisplatin-based therapy, and use of appropriate supportive care (hydration and mannitol diuresis) probably played a part in this.[9]

(c) Ototoxicity

In one small retrospective analysis of patients with cancer, the risk of developing hearing loss after low-dose, slow-infusion cisplatin did not correlate significantly with the concurrent use of other ototoxic drugs, such as furosemide or **tobramycin**.[10] Enhanced renal toxicity and ototoxicity have been reported in *guinea pigs* given cisplatin and **kanamycin** for 2 weeks.[11] In another *animal* study **gentamicin** was given for 14 days. A single dose of cisplatin given early in the course enhanced the ototoxic effects of **gentamicin** but no increase in ototoxicity occurred when cisplatin was given at the end of the **gentamicin** course.[12]

Mechanism

Cisplatin (and other platinum compounds such as **carboplatin**) are nephrotoxic and it would appear that its damaging effects on the kidney are additive with the nephrotoxic effects of the aminoglycoside. Both gentamicin and cisplatin may cause ototoxicity.[13] Previous exposure to cisplatin may delay the elimination of the aminoglycosides.

Importance and management

An established and potentially serious interaction. However, aminoglycosides remain an important group of antibacterials for the empirical treatment of febrile neutropenia in patients receiving chemotherapy,[14,15] including cisplatin-based regimens. However, in selecting an initial antibacterial regimen, it has been suggested that concurrent use of some drugs, including cisplatin and aminoglycosides, should be avoided if possible because of additive renal toxicity.[16] Good supportive care is required (e.g. pre and post-treatment hydration with mannitol diuresis), and renal function should be well monitored. Audiometric tests should be carried out when cisplatin is used, particularly when other ototoxic drugs are also given. Similar precautions would seem advisable with **carboplatin**.

1. Flombaum CD. Hypomagnesemia associated with cisplatin combination chemotherapy. *Arch Intern Med* (1984) 144, 2336–7.
2. Gonzalez-Vitale JC, Hayes DM, Cvitkovic E, Sternberg SS. Acute renal failure after *cis*-Dichlorodiammineplatinum (II) and gentamicin-cephalothin therapies. *Cancer Treat Rep* (1978) 62, 693–8.
3. Salem PA, Jabboury KW, Khalil MF. Severe nephrotoxicity: a probable complication of cis-dichlorodiammineplatinum (II) and cephalothin-gentamicin therapy. *Oncology* (1982) 39, 31–2.
4. Leite JBF, De Campelo Gentil F, Burchenal J, Marques A, Teixeira MIC, Abrão FA. Insuficiênza renal aguda após o uso de cis-diaminodicloroplatina, gentamicina e cefalosporina. *Rev Paul Med* (1981) 97, 75–7.
5. Dentino M, Luft FC, Yum MN, Williams SD, Einhorn LH. Long term effect of cis-diamminedichloride platinum (CDDP) on renal function and structure in man. *Cancer* (1978) 41, 1274–81.
6. Haas A, Anderson L, Lad T. The influence of aminoglycosides on the nephrotoxicity of *cis*-diamminedichloroplatinum in cancer patients. *J Infect Dis* (1983) 147, 363.
7. Pearson ADJ, Kohli M, Scott GW, Craft AW. Toxicity of high dose cisplatinum in children — the additive role of aminoglycosides. *Proc Am Assoc Cancer Res* (1987) 28, 221.
8. Christensen ML, Stewart CF, Crom WR. Evaluation of aminoglycoside disposition in patients previously treated with cisplatin. *Ther Drug Monit* (1989) 11, 631–6.
9. Cooper BW, Creger RJ, Soegiarso W, Mackay WL, Lazarus HM. Renal dysfunction during high-dose cisplatin therapy and autologous hematopoietic stem cell transplantation: effect of aminoglycoside therapy. *Am J Med* (1993) 94, 497–504.
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11. Schweitzer VG, Hawkins JE, Lilly DJ, Litterst CJ, Abrams G, Davis JA, Christy M. Ototoxic and nephrotoxic effects of combined treatment with *cis*-diamminedichloroplatinum and kanamycin in the guinea pig. *Otolaryngol Head Neck Surg* (1984) 92, 38–49.
12. Riggs LC, Brummett RE, Guitjens SK, Matz GJ. Ototoxicity resulting from combined administration of cisplatin and gentamicin. *Laryngoscope* (1996) 106, 401–6.
13. Lautermann J, Dehne N, Schacht J, Jahnke K. Aminoglykosid- und cisplatin-Ototoxizität: von der Grundlagenforschung zur Klinik. *Laryngorhinootologie* (2004) 83, 317–23.
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Cisplatin + Cannabis

A case report describes a fatal stroke when a young man receiving cisplatin smoked cannabis.

Clinical evidence, mechanism, importance and management

A 27-year-old man who smoked cannabis and tobacco daily developed tinnitus and paraesthesias after receiving the first course of chemotherapy consisting of cisplatin, etoposide and bleomycin for testicular cancer. Following the second course of chemotherapy, the patient reported distal paresis of the right arm and, 2 days later, about 30 minutes after cannabis inhalation, he developed headache, paresis of his right leg and aphasia. A large thrombus was found in the carotid artery. The patient died the next day. He had no cardiovascular risk factors apart from the smoking (about 4 cigarettes per day).[1]

Cisplatin is known to carry a small risk of stroke, and cases have also been reported for cannabis smoking alone. In this case it was suggested that the use of cannabis may have also contributed to the adverse outcome in this patient.[1] It might be prudent for patients receiving cisplatin to avoid smoking cannabis.

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Cisplatin + Diuretics

A single report describes the development of renal failure in a patient given furosemide and other antihypertensives during the use of cisplatin. However, note that furosemide can be used to promote diuresis in patients given cisplatin to reduce the risk of nephrotoxicity. A small retrospective review found that cisplatin-induced nephrotoxicity was associated with hydrochlorothiazide use. Although *animal* studies show that the damaging effects of cisplatin on the ear can be markedly increased by the concurrent use of etacrynic acid or furosemide a retrospective analysis in patients did not find this effect.

Clinical evidence, mechanism, importance and management

(a) Nephrotoxicity

1. Loop diuretics. Three hours after receiving intravenous cisplatin 70 mg/m^2 a patient experienced severe nausea and vomiting and his blood pressure rose from 150/90 mmHg to 248/140 mmHg. This was managed with **furosemide** 40 mg intravenously, hydralazine 10 mg intramuscularly, diazoxide 300 mg intravenously and propranolol 20 mg orally twice daily for 2 days. Nine days later the patient had evidence of renal impairment (creatinine raised from about 88 micromol/L to 283 micromol/L), which resolved within 3 weeks. The patient was subsequently similarly treated on two occasions with cisplatin and again developed hypertension, but no treatment was given and there was no evidence of renal impairment.[1]

The reasons for the renal impairment are not known, but a study in *rats*[2] indicates that kidney damage may possibly be related to the concentrations of cisplatin, and that **furosemide** can increase cisplatin levels in the kidney. However, another study in patients found that there was no difference in the toxicity or pharmacokinetics of cisplatin when **furosemide** was used to induce diuresis, compared with mannitol.[3] Two other studies have also found that **furosemide** does not alter cisplatin pharmacokinetics.[4,5] Another study found that sodium chloride solution with or without **furosemide** was associated with less cisplatin nephrotoxicity than sodium chloride solution with mannitol.[6]

For **furosemide**, information seems to be limited to the case cited and its general clinical importance is uncertain. Although mannitol is by far the more usual drug used to induce diuresis during the use of cisplatin in order to reduce the risk of nephrotoxicity, **furosemide** may also be used for this indication.[7]

2. Thiazides. A retrospective review of 62 patients who had received cisplatin found that there was an association between those patients who had also received **hydrochlorothiazide**, and those who developed nephrotoxicity (an increase in serum creatinine of about 44 micromol/L or more). All 5 patients who had taken **hydrochlorothiazide** developed nephrotoxicity after one cycle of cisplatin.[8] It was suggested that hydrochlorothiazide and cisplatin might have additive effects on renal magnesium wasting. The mechanism for any of these associations is unclear.

The data from these sorts of analyses require confirmation in a controlled study, because it is possible that the findings are due to chance alone. The general relevance of this report is therefore uncertain.

(b) Ototoxicity

Both cisplatin and loop diuretics (particularly **etacrynic acid**) given alone can be ototoxic in man. A study[9] in *guinea pigs* found that when cisplatin 7 mg/kg or **etacrynic acid** 50 mg/kg were given alone their ototoxic effects were reversible, but when given together the damaging effects on the ear were profound, prolonged and possibly permanent. Similarly, while cisplatin-induced ototoxicity was potentiated by **furosemide** in *guinea pigs* in one study[10] in another this was only seen when a very high dose of **furosemide** was used.[11] In one small retrospective analysis of patients with cancer, the risk of developing hearing loss after low-dose slow-infusion cisplatin did not correlate significantly with concurrent use of other ototoxic drugs, such as **furosemide**.[12] Audiometric tests should be carried out when cisplatin is used, and this is of particular importance when other ototoxic drugs are also given.

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11. Laurell G, Engström B. The combined effect of cisplatin and furosemide on hearing function in guinea pigs. *Hear Res* (1989) 38, 19–26.
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Cisplatin + H_2-receptor antagonists

Cimetidine and ranitidine probably do not have a clinically relevant effect on the renal clearance of cisplatin.

Clinical evidence, mechanism, importance and management

Some *animal* studies have shown that organic cations such as **cimetidine** and **ranitidine** may compete with the renal tubular transport of cisplatin and thus could be useful in reducing cisplatin nephrotoxicity.[1,2] However, in a study of 10 children receiving cisplatin, **ranitidine** had no effect on the total body disposition or renal clearance of cisplatin. This finding and further studies in *dogs* showed that cisplatin may not share transport systems with organic cations to a clinically relevant extent.[3] Although information is limited, it appears that there is no pharmacokinetic interaction between cisplatin and **cimetidine** or **ranitidine**.

1. Klein J, Bentur Y, Cheung D, Moselhy G, Koren G. Renal handling of cisplatin: interactions with organic anions and cations in the dog. *Clin Invest Med* (1991) 14, 388–94.

2. Haragsim L, Zima T, Němeček K. Nephrotoxic effects of platinum cytostatics–preventive effects of nifedipine and cimetidine. *Sb Lek* (1994) 95, 173–83.
3. Ito S, Weitzman S, Klein J, Greenberg M, Lau R, Atanakovic G, Koren G. Lack of cisplatin-ranitidine kinetic interactions: *in vivo* study in children, and *in vitro* study using dog renal brush border membrane vesicles. *Life Sci* (1998) 62, PL387–PL392.

Cisplatin + Probenecid

The available clinical data suggest that the nephrotoxicity of cisplatin is reduced by probenecid, but uncertainty remains.

Clinical evidence, mechanism, importance and management

In a randomised study in patients with cancer, probenecid 2 to 4 g daily reduced the fractional clearance of free platinum after a single 60- to 100-mg/m^2 dose of cisplatin given as a 24-hour infusion, and no cases of renal impairment were seen.[1] Similarly, in a further phase I dose-escalation study, no renal impairment was seen in patients given cisplatin at doses from 100 to 160 mg/m^2 when they were also given probenecid 1 g every 6 hours for 12 doses (beginning 24 hours before the cisplatin infusion, and continuing for 24 hours after).[2] It was concluded that probenecid may protect against cisplatin-induced renal toxicity. An earlier study in *rats* had also suggested that giving probenecid before cisplatin reduced nephrotoxicity, as assessed by blood urea levels and serum creatinine.[3] Subsequently, a study in *dogs* has found that probenecid decreases the renal clearance of free cisplatin,[4] and another study in *mice* found that probenecid reduces the renal tubular damage seen with cisplatin alone.[5]

Conversely, some researchers have suggested that the combination of probenecid and cisplatin is potentially more toxic than cisplatin alone. They found that probenecid increased the fractional clearance of free platinum from cisplatin in *rats*, and that pretreatment with probenecid increased nephrotoxicity, as assessed by blood urea levels.[6] Other authors similarly reported that probenecid increased cisplatin clearance in *rats*.[7]

It is unclear why some *animal* studies show that probenecid increases cisplatin-induced nephrotoxicity whereas others show a decrease. Although the available clinical data suggest that there is a decrease, some uncertainty remains. The combination should be used with caution.

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3. Ross DA, Gale GR. Reduction of the renal toxicity of *cis*-dichlorodiammineplatinum (II) by probenecid. *Cancer Treat Rep* (1979) 63, 781–7.
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Cyclophosphamide + Allopurinol

There is some evidence to suggest that the incidence of serious bone marrow depression caused by cyclophosphamide can be increased by allopurinol, but this was not confirmed in a controlled study.

Clinical evidence

A retrospective epidemiological survey of patients in four hospitals who, over a 4-year period, had been taking cyclophosphamide, found that the incidence of serious bone marrow depression was 58% in 26 patients who had also taken allopurinol, and 19% in 32 patients who had not taken allopurinol.[1] A pharmacokinetic study in 9 patients with malignant disease and 2 healthy subjects found that while taking allopurinol 600 mg daily the concentration of the cytotoxic metabolites of cyclophosphamide increased by an average of about 38% (range 2 to 110%).[2] Another pharmacokinetic study reported that the half-life of cyclophosphamide was more than twofold longer in 3 children also receiving allopurinol 300 mg/m^2, when compared with that in children not given allopurinol.[3] However, another study found that although allopurinol pre-treatment increased the half-life of cyclophosphamide, the plasma alkylating activity and urinary metabolite and cyclophosphamide excretion were unchanged.[4] Moreover, a randomised controlled study,[5] designed as a follow-up to the survey cited above,[1] failed to confirm that allopurinol increased the toxicity of cyclophosphamide in 81 patients with Hodgkin's or non-Hodgkin's lymphoma. In this study, there was no difference in nadirs for white blood cells and platelets during 3 cycles of cyclophosphamide-containing chemotherapy in 44 patients receiving allopurinol and in 37 patients not receiving allopurinol.

Mechanism

Not understood. Cyclophosphamide itself is inactive, but it is converted by the liver into cytotoxic metabolites.[4] Allopurinol or its metabolite oxypurinol may inhibit their renal excretion, or may alter hepatic metabolism.[2,3]

Importance and management

This interaction is not established with any certainty. The authors of the randomised study consider that, if necessary, allopurinol can be safely used to prevent hyperuricaemia with the chemotherapy regimens used for lymphomas,[5] and allopurinol is standardly given for the prevention of tumour lysis syndrome.[6]

1. Boston Collaborative Drug Surveillance Programme. Allopurinol and cytotoxic drugs. Interaction in relation to bone marrow depression. *JAMA* (1974) 227, 1036–40.
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Cyclophosphamide + Amiodarone

Early-onset pulmonary toxicity occurred in one patient taking amiodarone after high-dose cyclophosphamide was given. Fatal pulmonary toxicity occurred in another patient taking amiodarone after a single dose of cyclophosphamide.

Clinical evidence

A patient with dendritic cell carcinoma who had been taking amiodarone for 18 months, and who had received 6 cycles of chemotherapy including cyclophosphamide over the previous 12 months, was admitted to hospital with progressive shortness of breath 18 days after being given a single 4-g/m^2 dose of cyclophosphamide. He was found to have interstitial pneumonitis and a lung biopsy indicated drug-induced pulmonary toxicity. The patient's condition improved rapidly over the following 10 days with discontinuation of amiodarone and treatment with prednisolone 60 mg daily. Over the previous year he had also received vincristine, etoposide and prednisone, cisplatin, cytarabine and dexamethasone as part of his chemotherapy.[1] Similarly, another patient with non-Hodgkin's lymphoma, who had been taking amiodarone 300 mg twice daily for 4 years, developed acute respiratory distress 2 days after being given a single dose of cyclophosphamide. This was eventually fatal. Autopsy revealed lung damage consistent with the effects of amiodarone and cyclophosphamide, with the cyclophosphamide the major cause. Other drugs used as part of the chemotherapy regimen were rituximab, doxorubicin, vincristine and prednisone.[2]

Mechanism

Pulmonary toxicity may occur in about 10% of patients given amiodarone.[3,4] Pulmonary toxicity due to cyclophosphamide may occur between one to 6 months after exposure or occur as a more insidious form after about 6 months. The early onset of symptoms in the patients described above suggests accelerated mechanisms of pulmonary toxicity. Both cyclophosphamide and amiodarone pulmonary toxicity appear to be enhanced by oxygen and the combination of cyclophosphamide with amiodarone may enhance oxidative stress and therefore pulmonary toxicity.

Importance and management

Although information seems to be limited to the two case reports cited, the potential for both cyclophosphamide and amiodarone to cause pulmonary toxicity is established. Be alert to the possibility of enhanced pulmonary toxicity if these drugs are given together.

1. Bhagat R, Sporn TA, Long GD, Folz RJ. Amiodarone and cyclophosphamide: potential for enhanced lung toxicity. *Bone Marrow Transplant* (2001) 27, 1109–1111.
2. Gupta S, Mahipal A. Fatal pulmonary toxicity after a single dose of cyclophosphamide. *Pharmacotherapy* (2007) 27, 616–18.
3. Martin WJ, Rosenow EC. Amiodarone pulmonary toxicity. Recognition and pathogenesis (Part 1). *Chest* (1988) 93, 1067–75.
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Cyclophosphamide + Azathioprine

A report describes liver damage in four patients given cyclophosphamide and who had previously taken azathioprine. However, other studies have found that liver function improved when cyclophosphamide was substituted for azathioprine.

Clinical evidence, mechanism, importance and management

Four patients (two with systemic lupus erythematosus, one with Sjögren's syndrome, and one with Wegener's granulomatosis) developed liver injury when given cyclophosphamide and 3 of them had liver cell necrosis. All had previously been taking azathioprine and 2 of them had received cyclophosphamide previously without apparent liver damage. It was suggested that azathioprine and cyclophosphamide may have interacted.[1] However, in a retrospective study of heart transplant recipients, substitution of cyclophosphamide for azathioprine was associated with improvement in liver function tests in 29 patients with suspected azathioprine-induced liver impairment.[2] In a similar report 10 patients with kidney transplants who developed hepatic impairment while taking azathioprine, had an improvement in liver function when the treatment was changed to cyclophosphamide.[3]

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Cyclophosphamide or Ifosfamide + Azoles

Fluconazole and itraconazole both inhibit the metabolism of cyclophosphamide, but itraconazole might cause greater increases in cyclophosphamide toxicity. Ketoconazole inhibits the metabolism of ifosfamide: efficacy could be reduced.

Clinical evidence

(a) Cyclophosphamide

Twenty-two children with established cyclophosphamide metabolism profiles, who were not receiving other treatment known to affect drug metabolism, were included in a retrospective case series investigation. The clearance of cyclophosphamide was reduced by 43% in 9 children who were given oral or intravenous **fluconazole** 5 mg/kg daily compared with the remaining 13 children who did not receive **fluconazole**.[1] A study in patients given either intravenous or oral **fluconazole** 400 mg daily or **itraconazole** (either 200 mg daily intravenously or 2.5 mg/kg three times daily orally) for prophylaxis after allogeneic stem cell transplantation found that those given **itraconazole** developed higher bilirubin and creatinine levels in the first 20 days after transplantation than those given **fluconazole**. Highest values were in patients who received **itraconazole** with cyclophosphamide. In this study, analysis of cyclophosphamide pharmacokinetics in 9 **itraconazole** recipients and 140 **fluconazole** recipients revealed that **itraconazole** recipients had a 20% greater clearance of cyclophosphamide than fluconazole recipients, leading to greater exposure to the active metabolite of cyclophosphamide, 4-hydroxycyclophosphamide, and its metabolites.[2]

(b) Ifosfamide

Eight patients undergoing chemotherapy were also given (for the first or second cycle of treatment) **ketoconazole** 200 mg twice daily for 4 days starting one day before ifosfamide. The concurrent use of **ketoconazole** modestly decreased the clearance of ifosfamide by 11%, increased its AUC by 14%, and increased urinary elimination by 26%. The fraction of ifosfamide metabolised to the inactive, neurotoxic, dechloroethylated metabolite was not affected, whereas the fraction metabolised to the active, hydroxylated metabolite was modestly decreased.[3]

Mechanism

Cyclophosphamide is oxidised to the active metabolite 4-hydroxycyclophosphamide by the cytochrome P450 isoenzymes CYP2B6, CYP3A4, CYP2C9, and CYP2A6, and then 4-hydroxycyclophosphamide undergoes further metabolism to produce several toxic metabolites. It is also metabolised by CYP3A4 to an inactive metabolite, deschloroethylcyclophosphamide (DCCP). Itraconazole is a more potent inhibitor of CYP3A4 than fluconazole, but unlike itraconazole, fluconazole can also inhibit CYP2C9. It has been suggested that inhibition of CYP2C9 by fluconazole may decrease the formation of 4-hydroxycyclophosphamide and result in increased levels of DCCP and fewer toxic metabolites.[2] Further study is required to determine whether the inhibition of active metabolite formation by fluconazole reduces the therapeutic effect of cyclophosphamide.[1]

Ketoconazole is an inhibitor of the cytochrome P450 isoenzyme CYP3A4, an enzyme that is involved in the production of active and inactive-toxic metabolites of ifosfamide. See *Mechanism*, under 'Cyclophosphamide or Ifosfamide + Barbiturates', below, for more on the balance of production of these metabolites.

Importance and management

Until more is known it may be prudent to encourage caution when azoles are used in patients receiving cyclophosphamide, other than therapies established in randomised clinical studies, being alert for unexpected toxicity or reduced efficacy.

In the clinical study cited, ketoconazole modestly decreased the proportion of ifosfamide undergoing activation. It was suggested that concurrent use should be avoided, as it might result in decreased ifosfamide efficacy,[3] although this is not established.

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Cyclophosphamide or Ifosfamide + Barbiturates

Evidence suggests that neither the toxicity nor the therapeutic effects of cyclophosphamide and ifosfamide are significantly altered by the concurrent use of barbiturates. However, an isolated report describes a girl taking phenobarbital who developed encephalopathy when given ifosfamide.

Clinical evidence

(a) Cyclophosphamide

In 4 patients **phenobarbital** 180 mg daily in divided doses for 10 days increased the mean plasma levels of cyclophosphamide total metabolites by 50% and increased their rate of urinary excretion.[1] Similarly, another study in 11 patients given cyclophosphamide reported that the peak level of normustard-like substances was increased by 50% after pretreatment with **phenobarbital**.[2] Similar changes in cyclophosphamide pharmacokinetics have been described in *animal* studies, and these have generally also shown that **phenobarbital** has no effect on the antitumour activity of cyclophosphamide (one study is cited as an example[3]) although some have shown a reduction in its effects (one study is cited as an example[4]). Another study found that the auto-induction of cyclophosphamide clearance in a patient taking **phenobarbital** with subsequent chemotherapy courses was similar to that in patients not taking **phenobarbital**.[5]

Cyclophosphamide was reported to inhibit the clearance and increase the effects of **pentobarbital** in a study in *rats*.[6]

(b) Ifosfamide

A 15-year-old girl who had been taking **phenobarbital** for epilepsy since infancy developed confusion and gradually became unconscious 6 hours after being given a first dose of ifosfamide for metastatic rhabdomyosarcoma. Her chemotherapy regimen was ifosfamide 3 g/m^2, mesna 3.6 g/m^2, vincristine 2 mg and dactinomycin. An EEG revealed signs of severe diffuse encephalopathy. She remained unconscious for 24 hours but was asymptomatic after 48 hours.[7] In a pharmacokinetic study, **phenobarbital** 60 mg daily for 3 days had no effect on the pharmacokinetics of high-dose ifosfamide (4 g/m^2 over one hour each day for 3 days). The AUC for ifosfamide decreased from day one to day 3 irrespective of **phenobarbital** use.[8]

Mechanism

Cyclophosphamide and ifosfamide are prodrugs that undergo hepatic metabolism, and it seems that they are able to induce their own metabolism. Cyclophosphamide appears to be hydroxylated by the cytochrome P450 subfamilies CYP2B and CYP2C, in particular, to form active metabolites, whereas ifosfamide appears to be principally hydroxylated by CYP3A. Both drugs also undergo dechloroethylation to produce inactive but neurotoxic metabolites, which can cause encephalopathy. For cyclophosphamide, this seems to be primarily catalysed by CYP3A, whereas for ifosfamide both CYP3A and CYP2B appear to be involved. Ifosfamide has a higher incidence of encephalopathy than cyclophosphamide.[9] Phenobarbital and other barbiturates are inducers of both CYP2B and CYP3A. Therefore it is unlikely that barbiturates will generally alter the balance between dechloroethylation and hydroxylation for cyclophosphamide,[3] although there is some evidence from *animal* studies they may do so for ifosfamide.[10]

Importance and management

The relationship between the case of encephalopathy and the use of ifosfamide with phenobarbital is not established, but it serves to emphasise the need for particular caution and good monitoring if concurrent use is undertaken. Although barbiturates can cause an increase in the rate of metabolism of cyclophosphamide, this does not appear to alter the AUC and the efficacy of this drug.

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Cyclophosphamide or Ifosfamide + Benzodiazepines

***Animal* studies suggest that the benzodiazepines may possibly increase the metabolic activation and the toxicity of high doses of cyclophosphamide and ifosfamide. However, diazepam did not alter the pharmacokinetics of high-dose cyclophosphamide in a clinical study. Note also that lorazepam is widely used for chemotherapy-induced nausea and vomiting.**

Clinical evidence, mechanism, importance and management

Studies in *mice* found that pretreatment with benzodiazepines (**chlordiazepoxide**, **diazepam**, **oxazepam**) increased the levels of the active metabolites and the lethality of high-dose cyclophosphamide[1] and similarly increased the levels of active metabolites and enhanced the toxicity of high-dose ifosfamide.[2] However, a clinical study found that the prophylactic use of **diazepam** 5 mg daily as an antiepileptic had no effect on the pharmacokinetics of very high-dose cyclophosphamide (60 mg/kg intravenously over 2 hours for 2 days) or its neurotoxic (dechloroethylated) metabolites in 3 patients receiving cyclophosphamide and busulfan before bone marrow transplantation.[3]

In the *animal* studies, it was suggested that benzodiazepines may induce the liver enzymes concerned with the metabolism of cyclophosphamide and ifosfamide to its active cytotoxic products.

There are very limited data on this potential interaction. The widespread use of the benzodiazepine **lorazepam** in antiemetic regimens for chemotherapy-induced nausea and vomiting suggest that a significant increase in toxicity or alteration in efficacy of cyclophosphamide and ifosfamide does not occur clinically, but there do not appear to be any studies directly addressing this question.

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Cyclophosphamide + Busulfan

The levels of cyclophosphamide may be increased, and those of its active metabolite decreased, if it is given within 24 hours of busulfan.

Clinical evidence, mechanism, importance and management

In one study, the ratio of the AUC of cyclophosphamide and that of its active metabolite 4-hydroxycyclophosphamide (HCY) was higher in patients also receiving phenytoin and busulfan than in those receiving irradiation (suggesting reduced cyclophosphamide activation), but variability between patients was high.[1] In a similar study, 23 bone marrow transplant patients were pretreated with busulfan 4 mg/kg daily for 4 days, followed by cyclophosphamide 60 mg/kg daily for 2 days. The interval between the last dose of busulfan and starting cyclophosphamide was 24 to 50 hours in 12 patients [group A] and 7 to 15 hours in the remaining 11 [group B]. Nine others pretreated with cyclophosphamide and total body irradiation acted as the controls. In group A the AUCs of cyclophosphamide and HCY were similar to those in the controls but in group B the AUC of cyclophosphamide was more than doubled and the AUC of HCY significantly lower (representing a reduced ratio of HCY to cyclophosphamide). In addition group B had greater toxicity.[2]

Busulfan may directly inhibit the hepatic activation of cyclophosphamide or may act indirectly by depleting glutathione. Phenytoin (given in the first study) induces the metabolism of cyclophosphamide (see 'Cyclophosphamide or Ifosfamide + Phenytoin', p.718).

It seems therefore that if the cyclophosphamide is given at least 24 hours after the last busulfan dose, its serum levels will not be greatly affected, whereas if the interval is short, activation may be decreased and toxicity increased. Further study is required to determine the optimum timing to achieve maximum efficacy and minimum drug toxicity while taking into account other concurrent medication such as phenytoin.

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Cyclophosphamide + Chloramphenicol

Some limited evidence suggests that chloramphenicol may reduce the production of the active metabolites of cyclophosphamide.

Clinical evidence, mechanism, importance and management

Cyclophosphamide itself is inactive, but after administration it is metabolised to active alkylating metabolites. A study in *animals*[1] found that pretreatment with chloramphenicol reduced the effects of cyclophosphamide and reduced the production of its active metabolites. Although another *animal* study also found a reduction in the lethality of cyclophosphamide with chloramphenicol, the immunosuppressive effect of cyclophosphamide was unchanged.[2] A study in 4 patients found that chloramphenicol 1 g twice daily for 12 days prolonged the mean serum half-life of a single intravenous dose of cyclophosphamide from 7.5 hours to 11.5 hours, but did not significantly affect the AUC of the metabolites.[3]

Chloramphenicol is an inhibitor of the cytochrome P450 isoenzyme subfamily CYP2B, which is partially responsible for the activation of cyclophosphamide. It therefore seems possible that a reduction in the activity of cyclophosphamide may occur, but the extent to which this affects treatment with cyclophosphamide is uncertain. Concurrent use need not be avoided, but be alert for evidence of a reduced response.

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Cyclophosphamide or Ifosfamide + Cisplatin

The renal toxicity of ifosfamide may be greater when used with cisplatin or in those who have had previously been given cisplatin. Ifosfamide may increase the hearing loss due to cisplatin.

Clinical evidence

(a) Nephrotoxicity

A comparative study in 36 children with malignant solid tumours taking a range of drugs including some known to be potentially nephrotoxic (high dose methotrexate, aminoglycosides, cyclophosphamide), indicated that the previous use of cisplatin increased their susceptibility to ifosfamide toxicity (neurotoxicity, severe leucopenia or acute renal tubular damage).[1] Similarly, in another study the cumulative cisplatin dose given before high-dose ICE (ifosfamide, carboplatin, and etoposide) was found to be a strong risk factor for the development of nephrotoxicity.[2] The nephrotoxicity may not be reversible; 3 cases requiring long-term haemodialysis have been described.[3]

Other studies also suggested that the concurrent use of ifosfamide with cisplatin appeared to increase nephrotoxicity; one found an increase in depletion of phosphate reabsorption,[4] whereas the other found increased microglobulin excretion.[5]

(b) Ototoxicity

A retrospective comparative study found that when ifosfamide was given with cisplatin, the hearing loss caused by cisplatin was exacerbated.[6]

Mechanism

Both cisplatin and ifosfamide are commonly associated with nephrotoxicity. It is thought that concurrent or possibly previous use of cisplatin damages the renal tubules so that the clearance of the ifosfamide metabolites is reduced and their toxic effects are thereby increased. Damaged renal tubules may also be less capable of converting mesna to its active kidney-protecting form. The increase in the hearing loss is not understood.

Importance and management

These interactions appear to be established. The authors of the paper cited[1] point out that the majority of patients who develop toxicity have persistently high urinary NAG concentrations (*N*-acetyl-β-D-glucosaminidase, an enzyme released by renal tubular cells), even though serum creatinine levels remain within the acceptable range for ifosfamide treatment. They suggest that evidence of subclinical renal tubular damage should be sought for by monitoring the excretion of urinary NAG. Note that cisplatin and ifosfamide are widely used in combination, and the related drug **cyclophosphamide** is also routinely used with cisplatin. Amifostine may be useful in reducing the nephrotoxicity of this combination.[7] The authors who reported on hearing loss advised that serial audiograms should be done in patients given both drugs.[6]

1. Goren MP, Wright RK, Pratt CB, Horowitz ME, Dodge RK, Viar MJ, Kovnar EH. Potentiation of ifosfamide neurotoxicity, hematotoxicity, and tubular nephrotoxicity by prior *cis*-diamminedichloroplatinum(II) therapy. *Cancer Res* (1987) 47, 1457–60.
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3. Martinez F, Deray G, Cacoub P, Beaufils H, Jacobs C. Ifosfamide nephrotoxicity: deleterious effect of previous cisplatin administration. *Lancet* (1996) 348, 1100–1.
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7. Hartmann JT, Fels LM, Knop S, Stolte H, Kanz L, Bokemeyer C. A randomized trial comparing the nephrotoxicity of cisplatin/ifosfamide-based combination chemotherapy with or without amifostine in patients with solid tumors. *Invest New Drugs* (2000) 18, 281–9.

Cyclophosphamide + Colony-stimulating factors

Granulocyte colony-stimulating factor (G-CSF) used with cyclophosphamide has been associated with an increased occurrence of pulmonary toxicity.

Clinical evidence, mechanism, importance and management

A one-year-old boy with a neuroblastoma Evans stage III died of respiratory failure after being given **filgrastim** (a **G-CSF**) and normal doses of cyclophosphamide and doxorubicin. The authors of the report suggest that the pulmonary toxicity of the cyclophosphamide (normally only seen with high cumulative doses) is potentiated by **filgrastim**.[1] Six of 53 patients given CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) and **G-CSF** developed pulmonary toxicity, which was considered a much higher incidence than is usually seen with CHOP alone. The development of toxicity correlated with the mean peak leucocyte count.[2] Another 10 cases of interstitial pneumonitis have occurred with cyclophosphamide-based regimens (not including bleomycin or methotrexate) and **G-CSF**.[3,4]

These interactions are not firmly established, but good pulmonary function monitoring appears to be advisable when colony-stimulating factors are used with antineoplastics causing pulmonary toxicity, such as cyclophosphamide. If interstitial pneumonitis occurs, the drugs should be discontinued and high-dose corticosteroids started immediately.[2] Note however, because of the increased risk of myelosuppression, colony stimulating factors should not be given within 24 hours of myelosuppressive chemotherapy, see 'Antineoplastics + Colony-stimulating factors', p.702.

1. van Woensel JBM, Knoester H, Leeuw JA, van Aalderen WMC. Acute respiratory insufficiency during doxorubicin, cyclophosphamide, and G-CSF therapy. *Lancet* (1994) 344, 759–60.
2. Yokose N, Ogata K, Tamura H, An E, Nakamura K, Kamikubo K, Kudoh S, Dan K, Nomura T. Pulmonary toxicity after granulocyte colony-stimulating factor-combined chemotherapy for non-Hodgkin's lymphoma. *Br J Cancer* (1998) 77, 2286–90.
3. Niitsu N, Iki S, Muroi K, Motomura S, Murakami M, Takeyama H, Ohsaka A, Urabe A. Interstitial pneumonia in patients receiving granulocyte colony-stimulating factor during chemotherapy: survey in Japan 1991–96. *Br J Cancer* (1997) 76, 1661–6.
4. Hasegawa Y, Ninomiya J, Kamoshita M, Ohtani K, Kobayashi T, Kojima J, Nagasawa T, Abe T. Interstitial pneumonitis related to granulocyte colony-stimulating factor administration following chemotherapy for elderly patients with non-Hodgkin's lymphoma. *Intern Med* (1997) 36, 360–4.

Cyclophosphamide or Ifosfamide + Corticosteroids

There is limited and conflicting evidence on the effect of prednisone and prednisolone on the metabolic activation of cyclophosphamide. Synergistic increases in enzyme induction may occur if cyclophosphamide is given with dexamethasone. Dexamethasone does not appear to alter ifosfamide metabolism.

Clinical evidence

(a) Dexamethasone

In an *in vitro* study it was noted that the combination of cyclophosphamide with dexamethasone resulted in a greater induction of the cytochrome P450 isoenzyme CYP3A4 than with cyclophosphamide alone; the extent of induction being dependent on baseline CYP3A4 activity.[1] In *rats*,[2] dexamethasone pretreatment caused a fourfold increase in the AUC of the inactive, neurotoxic, dechloroethylated metabolite of cyclophosphamide, and caused a 60% decrease in the AUC of the active, hydroxylated metabolite. In an earlier study in patients receiving high-dose cyclophosphamide and dexamethasone for 2 days, the total clearance of both cyclophosphamide and dexamethasone were higher on the second day than the first day, with higher concentrations of cyclophosphamide metabolites.[3]

In *rats*, dexamethasone pretreatment had no net impact on the fraction of ifosfamide undergoing activation.[4] Similarly, in a clinical study, ifosfamide metabolism was no different when patients were given dexamethasone 4 mg every 8 hours with ifosfamide for 3 days than when they received ifosfamide alone.[5]

(b) Prednisone or Prednisolone

In an early study, single doses of prednisone were found to inhibit the metabolic activation of cyclophosphamide,[6,7] whereas another study briefly mentioned that massive single doses of prednisolone given just before cyclophosphamide did not inhibit cyclophosphamide metabolism.[8] Longer-term prednisone treatment (50 mg daily for 1 to 2 weeks) increased the rate of activation of cyclophosphamide in the first study.[6,7] Conversely, another study in 7 patients with systemic vasculitis given prednisone 1 mg/kg daily and cyclophosphamide 600 mg/m^2 intravenously every 3 weeks for 6 cycles found that, by the last cycle, the AUC of cyclophosphamide had significantly increased, while that of its active metabolites had significantly decreased.[9]

Mechanism

Cyclophosphamide and ifosfamide are prodrugs that undergo hepatic metabolism to active and inactive-neurotoxic metabolites, and it appears they induce their own metabolism (see also 'Cyclophosphamide or Ifosfamide + Barbiturates', p.714). Corticosteroids are said to be inducers of the cytochrome P450 isoenzyme CYP3A4. For cyclophosphamide, the CYP3A subfamily is thought to be principally involved in the production of inactive-neurotoxic metabolites, whereas, for ifosfamide, CYP3A catalyses both the production of active and inactive-neurotoxic metabolites. On this basis, corticosteroids are predicted decrease the efficacy and increase the neurotoxicity of cyclophosphamide (although this does not take account of auto-induction), whereas for ifosfamide they would not be expected to alter the balance between efficacy and toxicity.

Importance and management

The documentation is very limited. It appears that dexamethasone does not have any appreciable effect on the metabolism of ifosfamide. The information about cyclophosphamide is conflicting, and the clinical importance of any changes remains to be established. However, it should be noted that prednisone and prednisolone have a long established use as part of chemotherapy regimens including cyclophosphamide and are also often combined in various autoimmune diseases, and dexamethasone is widely used as an antiemetic with cancer chemotherapy.

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3. Moore MJ, Hardy RW, Thiessen JJ, Soldin SJ, Erlichman C. Rapid development of enhanced clearance after high-dose cyclophosphamide. *Clin Pharmacol Ther* (1988) 44, 622–8.
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7. Faber OK, Mouridsen HT, Skovsted L. The biotransformation of cyclophosphamide in man: influence of prednisone. *Acta Pharmacol Toxicol (Copenh)* (1974) 35, 195–200.
8. Bagley CM, Bostick FW, DeVita VT. Clinical pharmacology of cyclophosphamide. *Cancer Res* (1973) 33, 226–33.
9. Belfayol-Pisanté L, Guillevin L, Tod M, Fauvelle F. Possible influence of prednisone on the pharmacokinetics of cyclophosphamide in systemic vasculitis. *Clin Drug Invest* (1999) 18, 225–31.

Cyclophosphamide + H_2-receptor antagonists

Ranitidine, and probably famotidine, appear not to increase the bone marrow toxicity of cyclophosphamide. *Animal* studies suggest that cimetidine might.

Clinical evidence, mechanism, importance and management

A study in 7 patients with cancer found that although oral **ranitidine** 300 mg daily significantly prolonged the half-life and increased the AUC of intravenous cyclophosphamide 600 mg/m^2, it did not significantly affect the AUCs of the two major alkylating metabolites of cyclophosphamide, nor did it affect its bone marrow toxicity (leucopenia, granulocytopenia). The authors of the study concluded that **ranitidine** can safely be given with cyclophosphamide.[1] The same authors previously reported that **cimetidine**, when given with cyclophosphamide, increased the AUC of total alkylating metabolites of cyclophosphamide, and resulted in greater toxicity to normal bone marrow, but increased survival in leukaemia-bearing *mice*.[2,3] Other studies in *mice* have found that **cimetidine**, but not **famotidine**, increases the toxicity of cyclophosphamide to normal bone marrow cells.[4]

Cimetidine inhibits the cytochrome P450 isoenzyme CYP2C9, which has a minor role in the activation of cyclophosphamide (see 'Cyclophosphamide or Ifosfamide + Barbiturates', p.714). These results suggest that no special precautions are likely to be needed when **ranitidine** or **famotidine** are given with cyclophosphamide. The relevance of the findings with **cimetidine** is uncertain.

1. Alberts DS, Mason-Liddil N, Plezia PM, Roe DJ, Dorr RT, Struck RF, Phillips JG. Lack of ranitidine effects on cyclophosphamide bone marrow toxicity or metabolism: a placebo-controlled clinical trial. *J Natl Cancer Inst* (1991) 83, 1739–43.
2. Dorr RT, Alberts DS. Cimetidine enhancement of cyclophosphamide antitumour activity. *Br J Cancer* (1982) 45, 35–43.
3. Dorr RT, Soble MJ, Alberts DS. Interaction of cimetidine but not ranitidine with cyclophosphamide in mice. *Cancer Res* (1986) 46, 1795–9.
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Cyclophosphamide + Indometacin

A single case report describes acute water intoxication when a patient taking indometacin was given low-dose intravenous cyclophosphamide.

Clinical evidence, mechanism, importance and management

A patient with multiple myeloma taking indometacin 50 mg every 8 hours, developed acute water intoxication and salt retention after being given a single bolus intravenous injection of cyclophosphamide 500 mg (less than 10 mg/kg). The reasons for this effect are not understood, but it is suggested that it was due to the additive or synergistic effects of the two drugs, because water intoxication had not been noted before with this low-dose of cyclophosphamide.[1] There do not appear to be any further reports or studies on this potential interaction but water intoxication has subsequently been reported with low-dose intravenous cyclophosphamide alone.[2] The evidence does not justify any special precautions when both drugs are used.

1. Webberley M J, Murray J A. Life-threatening acute hyponatraemia induced by low dose cyclophosphamide and indomethacin. *Postgrad Med J* (1989) 65, 950–2.
2. McCarron MO, Wright GD, Roberts SD. Water intoxication after low dose cyclophosphamide. *BMJ* (1995) 311, 292.

Cyclophosphamide + Metronidazole

A case report describes encephalopathy in a girl given cyclophosphamide and metronidazole.

Clinical evidence, mechanism, importance and management

After the fourth dose of pulse intravenous cyclophosphamide, a 9-year-old girl developed pancytopenia and gastrointestinal bleeding. She was then given metronidazole for presumptive *Clostridium difficile* colitis. Within 6 hours she developed encephalopathy with seizures and visual hallucina-

tions, requiring antipsychotics. Metronidazole is thought to cause disulfiram-like reactions by inhibiting aldehyde dehydrogenase (see 'Alcohol + Metronidazole and related drugs', p.76), and it was suggested that inhibition of this enzyme may cause toxic metabolites of cyclophosphamide to accumulate (see also 'Cyclophosphamide or Ifosfamide + Barbiturates', p.714).[1] This appears to be the only report of this potential interaction, and its general relevance is unclear.

1. Pinsk MN, Renton K, Crocker JFS, Acott PD. A proposed drug interaction leading to cyclophosphamide-induced encephalopathy. *Pediatr Res* (2002) 51, 437A.

Cyclophosphamide + Pentostatin

Two patients had an acute and fatal cardiovascular collapse when pentostatin was added to high-dose cyclophosphamide. Some studies have found the combination to be effective and safe in patients with chronic lymphocytic leukaemia.

Clinical evidence, mechanism, importance and management

A clinical study that was started to find out if pentostatin would improve the immunosuppressive effects of an ablative regimen of high-dose cyclophosphamide, carmustine and etoposide in bone marrow transplant patients was stopped when acute and fatal cardiovascular collapse developed in the first 2 patients. Both patients had been given cyclophosphamide 800 mg/m^2 and etoposide 200 mg/m^2, both every 12 hours for 8 doses, and carmustine 112 mg/m^2 daily for 4 doses. On day 3 pentostatin 4 mg/m^2, given over 4 hours, was added. Within 8 to 18 hours after completion of chemotherapy both patients developed confusion, hypothermia, hypotension, respiratory distress, pulmonary oedema, and eventually fatal ventricular fibrillation within 45 to 120 minutes of the first symptoms. A later study in *rats* similarly found that pentostatin markedly increased the acute toxicity of cyclophosphamide. The reasons for this cardiotoxicity are not understood. Neither of the 2 patients had previously shown any evidence of cardiac abnormalities.[1] In view of these findings, the UK manufacturer advises against the use of pentostatin with high-dose cyclophosphamide.[2]

Note that pentostatin 4 mg/m^2 plus cyclophosphamide 600 mg/m^2, with or without subsequent rituximab 375 mg/m^2, has been used for chronic lymphocytic leukaemia[3-5] or Waldenstrom's macroglobulinaemia[6] with acceptable toxicity, and without any cases similar to that described in the first report.[1]

1. Gryn J, Gordon R, Bapat A, Goldman N, Goldberg J. Pentostatin increases the acute toxicity of high dose cyclophosphamide. *Bone Marrow Transplant* (1993) 12, 217–20.
2. Nipent (Pentostatin). Hospira UK Ltd. UK Summary of product characteristics, January 2009.
3. Weiss MA, Maslak PG, Jurcic JG, Scheinberg DA, Aliff TB, Lamanna N, Frankel SR, Kossman SE, Horgan D. Pentostatin and cyclophosphamide: an effective new regimen in previously treated patients with chronic lymphocytic leukemia. *J Clin Oncol* (2003) 21, 1278–84.
4. Lamanna N, Kalaycio M, Maslak P, Jurcic JG, Heaney M, Brentjens R, Zelenetz AD, Horgan D, Gencarelli A, Panageas KS, Scheinberg DA, Weiss MA. Pentostatin, cyclophosphamide, and rituximab is an active, well-tolerated regimen for patients with previously treated chronic lymphocytic leukaemia. *J Clin Oncol* (2006) 24, 1575–81.
5. Kay NE, Geyer SM, Call TG, Shanafelt TD, Zent CS, Jelinek DF, Tschumper R, Bone ND, Dewald GW, Lin TS, Heerema NA, Smith L, Grever MR, Byrd JC. Combination chemoimmunotherapy with pentostatin, cyclophosphamide, and rituximab shows significant clinical activity with low accompanying toxicity in previously untreated B chronic lymphocytic leukaemia. *Blood* (2007) 109, 405–11.
6. Hensel M, Villalobos M, Kornacker M, Krasniqi F, Ho AD. Pentostatin/cyclophosphamide with or without rituximab: an effective regimen for patients with Waldenström's macroglobulinaemia/lymphoplasmacytic lymphoma. *Clin Lymphoma Myeloma* (2005) 6, 131–5.

Cyclophosphamide or Ifosfamide + Phenytoin

Phenytoin increases the metabolism of cyclophosphamide and ifosfamide, but the clinical relevance of this is uncertain. Efficacy and toxicity has been suggested to be both unchanged and increased.

Clinical evidence

(a) Cyclophosphamide

In another case report, a 42-year-old man received two courses of CTC (high-dose cyclophosphamide, thiotepa and carboplatin) with phenytoin 150 mg twice daily started 5 days before the second course for seizures. When compared with the first course, phenytoin appeared to cause a 51% increase in the AUC of 4-hydroxycyclophosphamide, the active metabolite of cyclophosphamide, and a sixfold increase in its maximum plasma level. In addition, the AUC of cyclophosphamide was reduced by 67%. On the basis of these data, the dose of cyclophosphamide was almost halved for the remaining 2 days of this course of chemotherapy, and this resulted in plasma levels within the therapeutic range.[1]

In a small pharmacokinetic study, the use of prophylactic phenytoin increased the formation of *S*-dechloroethylated cyclophosphamide in 3 patients receiving cyclophosphamide and busulfan compared with 3 patients given diazepam with the same cytotoxic regimen.[2] In yet another study, the ratio of the AUC of active 4-hydroxycyclophosphamide to cyclophosphamide was 166% higher in patients receiving phenytoin and busulfan than in those receiving irradiation.[3] It is likely that phenytoin was responsible for this effect because busulfan alone decreases cyclophosphamide metabolism (see 'Cyclophosphamide + Busulfan', p.715). In an earlier study, in patients receiving enzyme-inducing drugs (2 of whom received phenytoin), the peak plasma levels of the alkylating metabolites of cyclophosphamide were raised, but declined rapidly, so that the overall exposure was not different from those not taking these drugs.[4] Another study reported that a patient taking phenytoin had a high clearance rate for cyclophosphamide during her first chemotherapy course, and that autoinduction of cyclophosphamide clearance was not apparent during her second course.[5]

(b) Ifosfamide

A child taking phenytoin and also given ifosfamide and etoposide had a neurotoxic reaction. The plasma levels of the dechloroethylated metabolites of ifosfamide were subsequently found to be markedly altered compared with those previously seen in 14 other children receiving the same chemotherapy but not taking phenytoin. The child recovered uneventfully after 3 days, and achieved clinical remission (she had not responded to first-line chemotherapy).[6]

Mechanism

The alteration in the pattern of ifosfamide metabolites suggested that phenytoin had induced the activity of the cytochrome P450 isoenzyme CYP2B6, and to a lesser extent CYP3A4.[6] The pattern of the increase in cyclophosphamide clearance is also consistent with induction of CYP2B and CYP3A.[2] See also *Mechanism*, under 'Cyclophosphamide or Ifosfamide + Barbiturates', p.714, for more detail on the metabolism of cyclophosphamide and its metabolites.

Importance and management

The alteration in the metabolism of cyclophosphamide and ifosfamide caused by phenytoin is not surprising, but the clinical importance of any changes remains to be established. The authors of the study from the 1970s concluded that phenytoin was unlikely to have much effect on the antitumour and toxic effects of cyclophosphamide.[4] Conversely, the authors of the more recent studies suggest that phenytoin may increase the therapeutic efficacy of cyclophosphamide and ifosfamide.[2,6] Moreover, the authors of the latest case report suggest that it is preferable to avoid using phenytoin with cyclophosphamide. They suggest that, when concurrent use is unavoidable, the starting dose of cyclophosphamide should be reduced, and the levels of active metabolite should be monitored to guide further doses.[1] Further study is needed.

Note that reduced phenytoin levels and seizures have been reported in a patient receiving chemotherapy including cyclophosphamide, see 'Table 14.1', (p.594).

1. de Jonge ME, Huitema ADR, van Dam SM, Beijnen JH, Rodenhuis S. Significant induction of cyclophosphamide and thiotepa metabolism by phenytoin. *Cancer Chemother Pharmacol* (2005) 55, 507–510.
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6. Ducharme MP, Bernstein ML, Granvil CP, Gehrcke B, Wainer IW. Phenytoin-induced alteration in the *N*-dechloroethylation of ifosfamide stereoisomers. *Cancer Chemother Pharmacol* (1997) 40, 531–3.

Cyclophosphamide or Ifosfamide + Rifampicin (Rifampin)

Rifampicin induced the metabolism of cyclophosphamide and ifosfamide *in vitro*. For ifosfamide, this did not improve the ratio of active to inactive-toxic metabolites in a clinical study.

Clinical evidence, mechanism, importance and management

In a clinical study, rifampicin doubled the clearance of ifosfamide. In this study, patients were given rifampicin 300 mg twice daily for 3 days before ifosfamide, for 3 days concurrently for one cycle, and then for another cycle they were given the ifosfamide alone. The fraction of ifosfamide metabolised to the inactive-neurotoxic, dechloroethylated metabolite was increased, but elimination of this metabolite was also increased resulting in reduced exposure. The fraction of ifosfamide metabolised to the active, hydroxylated metabolite, and its exposure, were not altered appreciably.[1]

An *in vitro* study in human liver cells found that rifampicin was a potent inducer of the activation (hydroxylation) of cyclophosphamide and ifosfamide.[2] Rifampicin is a clinically relevant inducer of the cytochrome P450 isoenzymes CYP3A4 and CYP2B6, which are involved in the metabolism of cyclophosphamide and ifosfamide (see also 'Cyclophosphamide or Ifosfamide + Barbiturates', p.714). In the clinical study cited,[1] rifampicin did not have a positive effect on the proportion of ifosfamide undergoing activation. In addition, as rifampicin increased metabolism overall, there is the possibility of decreased efficacy,[1] although this remains to be shown.

1. Kerbusch T, Jansen RLH, Mathôt RAA, Huitema ADR, Jansen M, van Rijswijk REN, Beijnen JH. Modulation of the cytochrome P450–mediated metabolism of ifosfamide by ketoconazole and rifampin. *Clin Pharmacol Ther* (2001) 70, 132–41.
2. Chang TKH, Yu L, Maurel P, Waxman DJ. Enhanced cyclophosphamide and ifosfamide activation in primary human hepatocyte cultures: response to cytochrome P-450 inducers and autoinduction by oxazaphosphorines. *Cancer Res* (1997) 57, 1946–54.

Cyclophosphamide + Sulfonamides

Some very limited evidence suggests that sulfaphenazole may modestly inhibit the metabolism of cyclophosphamide to its active metabolite.

Clinical evidence, mechanism, importance and management

A study in 7 patients given a 50-mg dose of cyclophosphamide with **sulfaphenazole** 1 g twice daily for 9 to 14 days found that the half-life of cyclophosphamide was unchanged in 3 patients, longer in 2 patients, and shorter in 2 patients.[1] **Sulfaphenazole** and **sulfamethoxazole** are inhibitors of the cytochrome P450 isoenzyme CYP2C9, which shows genetic polymorphism (i.e. some people produce very little, while others produce larger quantities). This enzyme has a minor role in the metabolism (and therefore activation) of cyclophosphamide, and the extent of its involvement varies between patients. For example, an *in vitro* study found that **sulfaphenazole** inhibited cyclophosphamide activation by 17 to 27% in one human liver sample, but insignificant inhibition occurred in two other samples.[2] Thus, sulfonamides such as **sulfaphenazole** and **sulfamethoxazole** may moderately inhibit the activation of cyclophosphamide in some patients, but the clinical relevance of this is uncertain. Note that **co-trimoxazole** is sometimes used for prophylaxis of infection in patients receiving chemotherapy. One study found that this did not *increase* the myelotoxicity of CAE (cyclophosphamide, doxorubicin, and etoposide).[3]

1. Faber OK, Mouridsen HT, Skovsted L. The effect of chloramphenicol and sulphaphenazole on the biotransformation of cyclophosphamide in man. *Br J Clin Pharmacol* (1975) 2, 281–5.
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3. de Jongh CA, Wade JC, Finley RS, Joshi JH, Aisner J, Wiernik PH, Schimpff SC. Trimethoprim/sulfamethoxazole versus placebo: a double-blind comparison of infection prophylaxis in patients with small cell carcinoma of the lung. *J Clin Oncol* (1983) 1, 302–7.

Cyclophosphamide or Ifosfamide + Taxanes

The clearance of ifosfamide is higher when it is given after docetaxel. This results in less toxicity, but the effect on efficacy is unknown. Ifosfamide did not alter the pharmacokinetics of docetaxel. Results from one study indicate that docetaxel pharmacokinetics are unaltered by cyclophosphamide. The sequence of ifosfamide followed by paclitaxel was antagonistic *in vitro*, and there is some evidence to suggest that the toxicity associated with combinations of paclitaxel and cyclophosphamide is dependent on the order of administration.

Clinical evidence, mechanism, importance and management

(a) Docetaxel

The AUCs of ifosfamide and its metabolites were lower when ifosfamide was given immediately after docetaxel than when it was given 24 hours before docetaxel, due to increased clearance. Docetaxel pharmacokinetics were unaltered by ifosfamide.[1] This supports the evidence that the maximum tolerated dose of ifosfamide is greater when it is given after docetaxel.[2] The mechanism of this effect is unknown, but it has been suggested[3] that docetaxel may competitively inhibit the activation of ifosfamide by the cytochrome P450 isoenzyme CYP3A4. These results show that the toxicity, and possibly efficacy, of the combination are schedule-dependent, but more study is needed to determine this.

In a phase I study, the pharmacokinetics of docetaxel were not altered by pretreatment with an intravenous bolus dose of cyclophosphamide.[4]

(b) Paclitaxel

In vitro studies in human liver microsomes found that additive or synergistic cytotoxicity occurred when activated ifosfamide (hydroxyifosfamide) and paclitaxel were given together or when paclitaxel was given first followed by hydroxyifosfamide. In contrast pronounced antagonism was seen when hydroxyifosfamide was given before paclitaxel.[5] The mechanism for this effect is unknown. These results suggest that the scheduling of this combination may be important for efficacy.

A study in patients given paclitaxel as a 24-hour infusion and cyclophosphamide as an infusion over one hour found that neutropenia and thrombocytopenia were more severe when paclitaxel preceded cyclophosphamide.[6] Similarly, in another study, the concurrent use of a continuous 72-hour infusion of paclitaxel and a daily bolus of cyclophosphamide had acceptable toxicity. However, when the cyclophosphamide was given as a single intravenous dose after the end of the 72-hour paclitaxel infusion, severe haematological and gastrointestinal toxicity occurred.[7] Whether the clinical efficacy of this combination is also altered by the schedule and sequence has not been determined.

1. Schrijvers D, Pronk L, Highley M, Bruno R, Locci-Tonelli D, De Bruijn E, Van Oosterom AT, Verweij J. Pharmacokinetics of ifosfamide are changed by combination with docetaxel. *Am J Clin Oncol* (2000) 23, 358–63.
2. Pronk L, Schrijvers D, Schellens JHM, De Bruijn EA, Planting ASTh, Locci-Tonelli D, Groult V, Verweij J, Van Oosterom AT. Phase I study on docetaxel and ifosfamide in patients with advanced solid tumours. *Br J Cancer* (1998) 77, 153–8.
3. Ando Y. Possible metabolic interaction between docetaxel and ifosfamide. *Br J Cancer* (2000) 82, 497.
4. Vasey PA, Roché H, Bisset D, Terret C, Vernillet L, Riva A, Ramazeilles C, Azli N, Kaye SB, Twelves CJ. Phase I study of docetaxel in combination with cyclophosphamide as first-line chemotherapy for metastatic breast cancer. *Br J Cancer* (2002) 87, 1072–8.
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7. Tolcher AW, Cowan KH, Noone MH, Denicoff AM, Kohler DR, Goldspiel BR, Barnes CS, McCabe M, Gossard MR, Zujewski J, O'Shaughnessy J. Phase I study of paclitaxel in combination with cyclophosphamide and granulocyte colony-stimulating factor in metastatic breast cancer patients. *J Clin Oncol* (1996) 14, 95–102.

Cyclophosphamide + Thiotepa

Pretreatment with thiotepa may inhibit the metabolism of cyclophosphamide to its active metabolite and decrease both its efficacy and toxicity. Cyclophosphamide might slightly increase the metabolism of thiotepa to TEPA (triethylenephosphamide), but the relevance of this is uncertain.

Clinical evidence

(a) Effect on cyclophosphamide

The proportion of cyclophosphamide excreted unchanged in the urine (i.e. never metabolically activated) was found to be higher when cyclophos-

phamide was given as a 96-hour infusion with thiotepa and novobiocin than when it was given alone. The authors suggested that the potential of thiotepa to inhibit the metabolism of cyclophosphamide should be investigated.[1] Later, other authors observed that the concentration of the active metabolite of cyclophosphamide, 4-hydroxycyclophosphamide, decreased sharply after thiotepa was given to 20 patients.[2] In a study to investigate this effect further, 3 patients were given high-dose cyclophosphamide 1 or 1.5 g/m^2 as a one-hour infusion, followed by carboplatin and thiotepa for 4 days. The order of infusion was reversed on one treatment day in each of 4 courses. Giving thiotepa one hour before cyclophosphamide resulted in decreases in the peak plasma levels and AUC of 4-hydroxycyclophosphamide of 62% and 26%, respectively, when compared with thiotepa given one hour after cyclophosphamide.[2]

(b) Effect on thiotepa

In an *in vitro* study using human microsomes, cyclophosphamide had no effect on the metabolism of thiotepa to TEPA (triethylenephosphamide) by cytochrome P450 at therapeutic concentrations.[2,3] However, the metabolism of thiotepa to TEPA was modestly increased in the presence of cyclophosphamide in two patients who received treatment with thiotepa and carboplatin with and then without cyclophosphamide.[4] A subsequent population pharmacokinetic modelling study found that incorporation of induction of thiotepa metabolism by cyclophosphamide improved the model. According to this model, the total clearance of thiotepa is increased by 10 to 25% with cyclophosphamide.[4]

Mechanism

In human microsomes, thiotepa was found to inhibit the conversion of cyclophosphamide to its active metabolite, 4-hydroxycyclophosphamide,[2] most likely because it is a potent inhibitor of the cytochrome P450 isoenzyme CYP2B6.[5] See also *Mechanism*, under 'Cyclophosphamide or Ifosfamide + Barbiturates', p.714, for further detail on the metabolism of cyclophosphamide and its metabolites. Cyclophosphamide may have induced the metabolism of thiotepa by cytochrome P450 enzymes, but the exact enzymes involved are not clear.[4]

Importance and management

These results suggest that thiotepa can decrease both the efficacy and toxicity of cyclophosphamide, and that the order of administration may be of critical importance. The authors of one study question the practice of giving cyclophosphamide and thiotepa simultaneously.[2] Cyclophosphamide may also slightly increase the metabolism of thiotepa to an active metabolite, although the clinical relevance of this remains to be determined.[4]

1. Chen T-L, Passos-Coelho JL, Noe DA, Kennedy MJ, Black KC, Colvin M, Grochow LB. Nonlinear pharmacokinetics of cyclophosphamide in patients with metastatic breast cancer receiving high-dose chemotherapy followed by autologous bone marrow transplantation. *Cancer Res* (1995) 55, 810–16. Correction. ibid.1600.
2. Huitema ADR, Kerbusch T, Tibben MM, Rodenhuis S, Beijnen JH. Reduction of cyclophosphamide bioactivation by thioTEPA: critical sequence-dependency in high-dose chemotherapy regimens. *Cancer Chemother Pharmacol* (2000) 46, 119–27.
3. Van Maanen MJ, Huitema ADR, Beijnen JH. Influence of co-medicated drugs on the biotransformation of thioTEPA to TEPA and thioTEPA-mercapturate. *Anticancer Res* (2000) 20, 1711–16.
4. de Jonge ME, Huitema ADR, Rodenhuis S, Beiknen JH. Integrated population pharmacokinetic model of both cyclophosphamide and thiotepa suggesting a mutual drug-drug interaction. *J Pharmacokinet Pharmacodyn* (2004) 31, 135–56.
5. Rae JM, Soukhova NV, Flockhart DA, Desta Z. Triethylenethiophosphoramide is a specific inhibitor of cytochrome P450 2B6: implications for cyclophosphamide metabolism. *Drug Metab Dispos* (2002) 30, 525–30.

Cytarabine + Dipyridamole

A fatal case of increased cytarabine toxicity has been attributed to the concurrent use of dipyridamole.

Clinical evidence

A case report describes a 52-year-old man who experienced a relapse of acute myeloid leukaemia and was given idarubicin daily for 3 days and cytarabine daily for 7 days. Amikacin and cefepime were also given for febrile neutropenia. In addition he was given dipyridamole 75 mg three times daily for 5 days for occlusion of the peroneal and tibialis anterior arteries. His liver function deteriorated, most notably his bilirubin increased almost 10-fold by day 5, and he died 10 days after starting treatment due to multiple organ failure.[1]

Mechanism

Dipyridamole is reported to inhibit the nucleoside transporter responsible for the extracellular transport of cytarabine and its metabolites, thus increasing the intracellular retention of cytarabine within the hepatocytes.[1] One *in vitro* study in *mouse* leukaemic cells has shown that use of dipyridamole *after* cytarabine resulted in an increase in cytarabine retention and an increase in cytotoxicity.[2] However, in a similar study using human acute myeloid leukaemia blasts, dipyridamole had little effect, possibly because these cells had few nucleoside transport carriers.[3] In yet another *in vitro* study, *pretreatment* with dipyridamole inhibited the uptake of cytarabine into both normal and leukaemic *mouse* and human cells, which suggests that dipyridamole may reduce the toxicity of cytarabine when used first.[4]

Importance and management

This appears to be the only report of an interaction between dipyridamole and cytarabine, but consider an interaction as a possible cause should unexpected toxicity occur in patients receiving both drugs.

1. Babaoglu MO, Karadag O, Saikawa Y, Altundag K, Elkiran T, Yasar U, Bozkurt A. Hepatotoxicity due to a possible interaction between cytosine arabinoside and dipyridamole: a case report. *Eur J Clin Pharmacol* (2004) 60, 455–6.
2. Yang J-L, White JC, Capizzi RL. Enhanced retention of cytosine arabinoside and its metabolites and synergistic cytotoxicity by sequential treatment with dipyridamole in L5178Y leukaemia. *Cancer Chemother Pharmacol* (1990) 26, 135–8.
3. Yang J-L, White JC, Capizzi RL. Modulation of the cellular pharmacokinetics of ara-CTP in human leukemic blasts by dipyridamole. *Cancer Chemother Pharmacol* (1992) 29, 236–40.
4. King ME, Naporn A, Young B, Howell SB. Modulation of cytarabine uptake and toxicity by dipyridamole. *Cancer Treat Rep* (1984) 68, 361–6.

Dasatinib + Miscellaneous

The AUC of dasatinib was markedly increased by ketoconazole, a CYP3A4 inhibitor, and markedly reduced by rifampicin (rifampin), a CYP3A4 inducer. Other CYP3A4 inhibitors and inducers are expected to interact similarly. Dasatinib modestly increased simvastatin levels, and may increase the levels of other substrates of CYP3A4. Antacids and drugs that reduce gastric pH reduce the absorption of dasatinib. Dasatinib commonly causes thrombocytopenia and bleeding, and its effects may be additive with antiplatelet drugs and anticoagulants and NSAIDs. Dasatinib prolongs the QT interval and its effect may be additive when given with other drugs that also prolong the QT interval.

Clinical evidence, mechanism, importance and management

(a) Anticoagulants, Antiplatelet drugs and NSAIDs

Dasatinib adverse effects reported in clinical studies include haemorrhages, with severe gastrointestinal haemorrhage occurring in 4% of patients, and CNS bleeds (some of which were fatal) in less than 1% of patients.[1,2] Most of these effects are thought to be due to dasatinib-induced thrombocytopenia, which is a dose-limiting toxicity.[2] In general, patients were excluded from clinical studies if they were taking antiplatelet drugs or anticoagulants, and in the cases where they were permitted, it was only if the platelet count was above 50×10^9/L.[1,2] Similarly, NSAIDs were only permitted when platelet count was above 50×10^9/L.[1,2] The manufacturers therefore advise caution when drugs that have antiplatelet or anticoagulant activity are given with dasatinib.[1,2] This seems a sensible precaution.

(b) CYP3A4 inducers

The manufacturer reports that **rifampicin** (**rifampin**) 600 mg daily for 8 days, markedly decreased the AUC of dasatinib, by 82%. They predict that other CYP3A4 inducers may also reduce dasatinib levels, and specifically name **carbamazepine**, **dexamethasone**, **phenobarbital** [and therefore probably **primidone**], **phenytoin** [and therefore probably **fosphenytoin**], **rifabutin**, and **St John's wort**.[1,2] They advise that the use of potent inhibitors of CYP3A4 should be avoided,[1,2] or, if this is not possible, the dose of dasatinib should be increased, and the patient monitored for toxicity.[2]

(c) CYP3A4 inhibitors

In a study in 18 patients with solid tumours, **ketoconazole** 200 mg twice daily with dasatinib 20 mg daily markedly increased the dasatinib maximum level and AUC by four- and fivefold, respectively.[2] Dasatinib has been shown *in vitro* to be a substrate of CYP3A4 and ketoconazole inhib-

its this isoenzyme. Other drugs that are potent inhibitors of CYP3A4 would be expected to interact similarly, and the manufacturers advise against concurrent use. They specifically mention **atazanavir**, **clarithromycin**, **erythromycin**, **indinavir**, **itraconazole**, **nefazodone**, **nelfinavir**, **ritonavir**, **saquinavir**, **telithromycin** and **voriconazole**[1,2] (for a list of CYP3A4 inhibitors, see 'Table 1.4', (p.6)). They advise that if an alternative is not suitable, the dose of dasatinib should be reduced to 20 mg daily. If this is not tolerated, then treatment with dasatinib should be interrupted until one week after the inhibitor is stopped.[2]

(d) CYP3A4 substrates

Following a single 100-mg dose of dasatinib, the AUC and maximum plasma concentration of **simvastatin** were increased by 20% and 37%, respectively. It is possible that the effect might be greater after multiple dasatinib doses.[1] Dasatinib is an inhibitor of CYP3A4,[1,2] of which simvastatin is a substrate. Dasatinib may therefore increase the plasma levels of other drugs that are substrates of CYP3A4, and the manufacturers recommend caution with CYP3A4 substrates that have a narrow therapeutic range. They specifically mention **alfentanil**, **astemizole**, **ciclosporin**, **cisapride**, **ergot derivatives**, **fentanyl**, **pimozide**, **quinidine**, **sirolimus**, **tacrolimus** and **terfenadine**.[1,2]

(e) Drugs that prolong the QT interval

The manufacturer warns that dasatinib may cause prolongation of the QT interval (a mean increase of 4 to 6 milliseconds was seen in clinical studies, and QTc prolongation has been reported as an adverse effect).[2] Therefore, they recommend that dasatinib should be used with caution with other drugs that may also prolong the QT interval, or with cumulative high-dose **anthracycline** chemotherapy.[1,2]

(f) Drugs that reduce gastric pH

1. Antacids. The solubility of dasatinib is altered by changes in pH. In a single-dose study, the AUC and maximum plasma level of dasatinib 50 mg were reduced by 55% and 58%, respectively, when it was given at the same time as 30 mL of an **aluminium/magnesium hydroxide** antacid. However, when the antacid was given 2 hours before dasatinib, there was no change in the pharmacokinetics of dasatinib.[1,2] Therefore, if needed, antacids may be given 2 hours before or 2 hours after a dose of dasatinib.[1]

2. H_2-receptor antagonists or Proton pump inhibitors. In a single-dose study, **famotidine**, given 10 hours before dasatinib markedly reduced the exposure to dasatinib by 61%. This is thought to be because the acid suppressant effect of famotidine decreases the solubility of dasatinib. The H_2-receptor antagonists and proton pump inhibitors should therefore be avoided in patients taking dasatinib. The manufacturers advise that antacids (see above) should be used instead.[1,2]

(g) Grapefruit juice

The US manufacturer predicts that grapefruit juice may increase the plasma levels of dasatinib and advises avoidance.[2] Grapefruit is a modest CYP3A4 inhibitor, having the greatest effect on drugs that are poorly bioavailable. Until more is known about its possible effect on dasatinib, given the marked effect of the CYP3A4 inhibitor, ketoconazole, see *CYP3A4 inhibitors*, above, this seems a sensible precaution.

1. Sprycel (Dasatinib). Bristol-Myers Squibb Pharmaceuticals Ltd. UK Summary of product characteristics, July 2009.
2. Sprycel (Dasatinib). Bristol-Myers Squibb Company. US Prescribing information, June 2009.

Enzastaurin + Antineoplastics

Capecitabine, cisplatin and gemcitabine did not alter the pharmacokinetics of enzastaurin, and enzastaurin did not appear to alter the pharmacokinetics of these antineoplastics.

Clinical evidence, mechanism, importance and management

In a study in 30 patients who received enzastaurin alone, followed by enzastaurin, **gemcitabine**, and **cisplatin**, the pharmacokinetics of enzastaurin were not altered to a clinically significant extent by cisplatin and gemcitabine. The pharmacokinetics of gemcitabine or cisplatin were not affected by enzastaurin, when compared with historical data.[1] Similarly, in a study in patients who received enzastaurin alone, or enzastaurin with **capecitabine**, there were no significant changes in the pharmacokinetics of enzastaurin in the 6 patients for whom pharmacokinetic data were available. In addition, the pharmacokinetics of capecitabine were similar to those previously reported for capecitabine alone.[2]

1. Rademaker-Lakhai JM, Beerepoot LV, Mehra N, Radema SA, van Maanen R, Vermaat JS, Witteveen EO, Visseren-Grul CM, Musib L, Enas N, van Hal G, Beijnen JH, Schellens JHM, Voest EE. Phase I pharmacokinetic and pharmacodynamic study of the oral protein kinase C β-inhibitor enzastaurin in combination with gemcitabine and cisplatin in patients with advanced cancer. *Clin Cancer Res* (2007) 13, 4474–5.
2. Camidge DR, Eckhardt SG, Gore L, O'Bryant CL, Leong S, Basche M, Holden SN, Musib L, Baldwin J, Darstein C, Thornton D, Finn RS, Britten CD. A phase I safety, tolerability, and pharmacokinetic study of enzastaurin combined with capecitabine in patients with advanced solid tumors. Anti-Cancer Drugs (2008) 19, 77–84.

Erlotinib + Antiepileptics; Enzyme-inducing

Enzyme-inducing antiepileptics reduce the plasma levels of erlotinib. A single case report describes increased phenytoin levels in a patient given erlotinib.

Clinical evidence

(a) Effect on erlotinib levels

As part of a study in 33 patients with glioma, the pharmacokinetics of erlotinib 100 mg daily increasing to 500 mg daily were compared in patients taking enzyme-inducing antiepileptics and those not taking these antiepileptics. There was a 33 to 71% lower exposure to erlotinib when it was given with an enzyme-inducing antiepileptic drug. Antiepileptic drugs taken were **carbamazepine**, **oxcarbazepine**, **phenytoin**, **fosphenytoin**, **phenobarbital** and **primidone**. Patients taking these drugs tolerated a higher dose of erlotinib.[1]

(b) Effect on antiepileptic levels

A case report describes a 52-year-old woman, stable taking **phenytoin** 100 mg twice daily, with a plasma level of 5 to 6 mg/dL, who experienced signs of **phenytoin** toxicity, and an elevated plasma **phenytoin** level (19.8 mg/dL) after starting to take erlotinib 150 mg daily. Despite a reduction in her **phenytoin** dose, to 100 mg daily alternating with 200 mg daily, her **phenytoin** level rose to 25.3 mg/dL. Three weeks after a further reduction in her **phenytoin** dose, to 100 mg daily, the phenytoin level was 13.5 mg/dL.[2]

Mechanism

Erlotinib is a substrate of the cytochrome P450 isoenzyme CYP3A4, and therefore its levels are reduced by the enzyme-inducing antiepileptics, which induce this isoenzyme. The reason for the increase in phenytoin levels is uncertain as erlotinib would not be expected to alter the pharmacokinetics of phenytoin by inhibiting CYP2C9, by which phenytoin is metabolised.

Importance and management

The effect of enzyme-inducing antiepileptics is established, and likely to be clinically important. The manufacturers of erlotinib recommend using alternatives to these antiepileptics if possible.[3,4] If this is not possible, the starting dose of erlotinib should be increased (the UK manufacturers suggest 300 mg) with close monitoring, and, if tolerated, further increased after 2 weeks, to a maximum of 450 mg.[3,4] When stopping the enzyme-inducing drug, they recommend immediately reducing the erlotinib dose to the indicated starting dose.[3] The authors of the glioma study suggest that, for further studies in this disease, the dose of erlotinib should be at least 500 mg daily in those already taking enzyme-inducing antiepileptics and 200 mg daily in those patients not taking these drugs.[1] Note that, **primidone** is metabolised to phenobarbital, and **fosphenytoin** is metabolised to phenytoin, and so similar precautions may be prudent with these drugs.

The case of raised phenytoin levels with erlotinib appears to be the only report of such an interaction, and its general relevance is unclear.[2]

1. Prados MD, Lamborn KR, Chang S, Burton E, Butowski N, Malec M, Kapadia A, Rabbitt J, Page MS, Fedoroff A, Xie D, Kelley SK. Phase 1 study of erlotinib HCl alone and combined with temozolomide in patients with stable or recurrent malignant glioma. *Neuro-oncol* (2006) 8, 67–78.
2. Grenader T, Gipps M, Shavit L, Gabizon A. Significant drug interaction: phenytoin toxicity due to erlotinib. *Lung Cancer* (2007) 57, 404–6.
3. Tarceva (Erlotinib). OSI Pharmaceuticals, Inc., and Genentech, Inc. US Prescribing information, April 2009.
4. Tarceva (Erlotinib). Roche Products Ltd. UK Summary of product characteristics, May 2009.

Erlotinib + Antineoplastics

Temozolomide appears to have dose-related effects on erlotinib levels. Erlotinib pharmacokinetics are not affected by carboplatin, gemcitabine, docetaxel or paclitaxel, but capecitabine may increase erlotinib exposure, although this was not seen in a pharmacokinetic study. The pharmacokinetics of gemcitabine and carboplatin were not affected to a clinically relevant extent by erlotinib. The effect of erlotinib on docetaxel pharmacokinetics is unclear.

Clinical evidence, mechanism, importance and management

(a) Capecitabine

The manufacturer notes that erlotinib has no effect on the pharmacokinetics of capecitabine, but the AUC of erlotinib may be increased by capecitabine (amount not stated).[1] However, a study in which patients received capecitabine, docetaxel and erlotinib found no clinically significant changes in the pharmacokinetics of erlotinib when it was given with these two cytotoxics.[2]

(b) Carboplatin

In a study in patients given paclitaxel and carboplatin the AUC of platinum was increased by about 10% when erlotinib was given, but this is not considered to be clinically significant. The pharmacokinetics of erlotinib were not altered by carboplatin when compared with historical controls.[1,3]

(c) Gemcitabine

The manufacturer notes that there was no change in the pharmacokinetics of gemcitabine or erlotinib on concurrent use in a phase 1 study.[1,4]

(d) Taxanes

In a study in which patients received capecitabine, **docetaxel** and erlotinib, there was no change in the pharmacokinetics of erlotinib when it was given with these two cytotoxics. A trend towards a modest reduction in the AUC and maximum concentration of **docetaxel** (with capecitabine) was seen when erlotinib was also given compared with docetaxel and capecitabine without erlotinib. However, the authors state that this did not confirm an interaction due to variability in docetaxel pharmacokinetics. The relevance of this is therefore uncertain and further study is needed.[2]

The pharmacokinetics of **paclitaxel** were not altered by erlotinib in a study in patients given **paclitaxel** and carboplatin, nor were the pharmacokinetics of erlotinib affected by **paclitaxel** when compared with historical controls.[1,3]

(e) Temozolomide

As part of a phase I study, 16 patients with glioma were given erlotinib 100 mg daily increasing to 250 mg daily alone, and 14 patients were given erlotinib with temozolomide 150 mg/m^2 increasing to 200 mg/m^2 for 5 days in each 28 day cycle. There was some variability in the pharmacokinetics of erlotinib between the patients taking the combination and those taking erlotinib alone at the different dose levels. For example, at the lowest dose of erlotinib 100 mg daily, the group also taking temozolomide (3 patients) had a 49% lower maximum plasma level of erlotinib, and almost 50% lower AUC of both erlotinib and its metabolite OSI-420. Whereas, at a dose of erlotinib of 200 mg daily, the difference was reversed with the temozolomide group (3 patients) having a 45% higher AUC of erlotinib. However, with erlotinib 150 mg and 250 mg no differences were apparent.[5] The reason for these paradoxical findings is unclear, and could be attributed to the small group sizes and an imbalance in some factor between the groups. Further study is needed to assess whether an interaction actually occurs and if it does, the clinical significance of this.

1. Tarceva (Erlotinib). Roche Products Ltd. UK Summary of product characteristics, May 2009.
2. Twelves C, Trigo JM, Jones R, De Rosa F, Rakhit A, Fettner S, Wright T, Baselga J. Erlotinib in combination with capecitabine and docetaxel in patients with metastatic breast cancer: a dose escalation study. Eur J Cancer (2008) 44, 419–26.
3. Patnaik A, Wood D, Tolcher AW, Hamilton M, Kreisberg JI, Hammond LA, Schwartz G, Beeram M, Hidalgo M, Mita MM, Wolf J, Nadler P, Rowinsky EK. Phase I, pharmacokinetic, and biological study of erlotinib in combination with paclitaxel and carboplatin in patients with advanced solid tumours. *Clin Cancer Res* (2006) 12, 7406–13.
4. Tarceva (Erlotinib). OSI Pharmaceuticals, Inc., and Genentech, Inc. US Prescribing information, April 2009.
5. Prados MD, Lamborn KR, Chang S, Burton E, Butowski N, Malec M, Kapadia A, Rabbitt J, Page MS, Fedoroff A, Xie D, Kelley SK. Phase 1 study of erlotinib HCl alone and combined with temozolomide in patients with stable or recurrent malignant glioma. *Neuro-oncol* (2006) 8, 67–78.

Erlotinib + Food

Food increases the extent of absorption of erlotinib.

Clinical evidence, mechanism, importance and management

In a pharmacokinetic study, 18 healthy subjects received a single 150-mg dose of erlotinib after a 10-hour fast and 4 hours before food, or with a high-fat, high-calorie breakfast. When taken with food, the maximum plasma concentration and AUC of erlotinib were increased by 52% and 97%, respectively. The effects of food on multiple doses of erlotinib were then investigated in 22 healthy subjects who took erlotinib 100 mg daily for 7 days after either a 10-hour fast and 4 hours before food, or with a high-fat, high-calorie breakfast. At day 7 of the study, there was a 34% increase in AUC of erlotinib when it was taken with food, but this was not statistically significant.[1]

It is thought that the increase in exposure to erlotinib is due to increased absorption in the presence of food.[1] However, this appears to be less significant after multiple dosing. Nevertheless, it is recommended that erlotinib is taken on an empty stomach, at least one hour before or 2 hours after any food.[2,3]

1. Ling J, Fettner S, Lum BL, Riek M, Rakhit A. Effect of food on the pharmacokinetics of erlotinib, an orally active epidermal growth factor receptor tyrosine-kinase inhibitor, in healthy individuals. Anti-Cancer Drugs (2008) 19, 209–16.
2. Tarceva (Erlotinib). OSI Pharmaceuticals, Inc., and Genentech, Inc. US Prescribing information, April 2009.
3. Tarceva (Erlotinib). Roche Products Ltd. UK Summary of product characteristics, May 2009.

Erlotinib + Miscellaneous

The metabolism of erlotinib is markedly affected by drugs that are potent inhibitors (such as ketoconazole) or inducers (such as rifampicin) of CYP3A4. CYP1A2 inhibitors such as ciprofloxacin also increase erlotinib exposure. Drugs that decrease gastric acidity (omeprazole, ranitidine) decrease erlotinib exposure.

Clinical evidence, mechanism, importance and management

(a) CYP1A2 inhibitors

The AUC of erlotinib was increased by 39% when it was given with **ciprofloxacin**, but its maximum plasma level was increased by just 17%.[1,2] The AUC and maximum plasma levels of the active metabolite of erlotinib were increased by 60% and 48%, respectively.[2] Erlotinib is partially metabolised by the cytochrome P450 isoenzyme CYP1A2, of which ciprofloxacin is a moderate inhibitor.

The UK manufacturer notes that the clinical relevance of these pharmacokinetic changes is unclear, but advises caution when **ciprofloxacin** or potent inhibitors of CYP1A2 are given with erlotinib, and they specifically name **fluvoxamine**.[2] It may be necessary to reduce the dose of erlotinib if adverse effects occur.[1,2] This seems a sensible precaution. For a list of CYP1A2 inhibitors, see 'Table 1.2', (p.4).

(b) CYP3A4 inducers

Pretreatment with **rifampicin** (**rifampin**) 600 mg daily for 7 days reduced the AUC of erlotinib by about 66%.[1,2] In another study, the AUC of a single 450-mg dose of erlotinib, taken after 11 days of treatment with **rifampicin** was about 57% of that of erlotinib 150 mg taken without rifampicin.[1,2] Rifampicin is a potent inducer of the metabolism of erlotinib, probably because of its effects on the cytochrome P450 isoenzyme CYP3A4.

The manufacturers advise that alternative treatments with no CYP3A4-inducing activity should be considered. If this is not possible, the starting dose of erlotinib should be increased (the UK manufacturers suggest 300 mg) with close monitoring, and if tolerated, further increased after 2 weeks, to a maximum of 450 mg.[1,2] When stopping the enzyme-inducing drug, they recommend immediately reducing the erlotinib dose to the indicated starting dose.[1] They also advise caution with other CYP3A4 inducers, and specifically name **rifabutin**,[1] **rifapentine**,[1] and **St John's wort**.[1,2] For a list of CYP3A4 inducers, see 'Table 1.4', (p.6).

(c) CYP3A4 inhibitors

In a study, 12 healthy subjects were given **ketoconazole** 200 mg twice daily for 5 days, with a single 100-mg dose of erlotinib on day 2. The AUC of erlotinib was increased by 86% and its maximum plasma level was

increased by 52%. There was no change in the elimination half-life. For the active metabolite, OSI-420, the AUC was 30% higher but the maximum level was 23% lower.[3]

Erlotinib is a substrate for the cytochrome P450 isoenzyme CYP3A4, of which ketoconazole is an inhibitor. The lack of change in elimination half-life suggests that ketoconazole increases erlotinib bioavailability, and it is possible that P-glycoprotein inhibition may also be involved.

This interaction is established, and the marked increase in erlotinib levels is likely to be clinically important. The manufacturers advise caution on concurrent use, and recommend that the dose of erlotinib should be reduced if severe adverse reactions occur when given with any potent CYP3A4 inhibitors. They specifically name **clarithromycin**,[1,2] **erythromycin**,[2] **grapefruit** and **grapefruit juice**,[1] **itraconazole**,[1,2] **ketoconazole**,[1,2] **nefazodone**,[1] **protease inhibitors**[2] (**atazanavir**, **indinavir**, **nelfinavir**, **ritonavir**, **saquinavir**)[1], **telithromycin**,[1] **troleandomycin**[1] and **voriconazole**.[1,2] For a list of CYP3A4 inhibitors, see 'Table 1.4', (p.6).

(d) CYP3A4 substrates

The manufacturer states that erlotinib did not alter the clearance of **midazolam**, a substrate of CYP3A4, but the bioavailability of oral **midazolam** was reduced by up to 24%.[2] *In vitro*, erlotinib is a moderate inhibitor of CYP3A4,[2] therefore this finding is the opposite of that expected, and the mechanism is not clear. However, this modest reduction in the AUC of midazolam is not clinically relevant, and suggests that clinically relevant interactions with other drugs that are substrates of CYP3A4 are unlikely.[2]

(e) Drugs that affect gastrointestinal pH

Omeprazole reduces the AUC and maximum plasma concentration of erlotinib by 46% and 61%, respectively.[1,2] The time taken to reach maximum plasma levels and the half-life of erlotinib were unaffected by **omeprazole**.[2] Similarly, giving erlotinib with **ranitidine** 300 mg decreased the erlotinib AUC and maximum levels by 33% and 54%, respectively.[2] However, when erlotinib was given 2 hours before or 10 hours after **ranitidine** 150 mg twice daily, the erlotinib AUC and maximum levels decreased by only 15% and 17%, respectively.[2]

Drugs that reduce gastric acidity are thought to reduce the solubility of erlotinib (which has a decreased solubility above pH 5), thereby reducing its absorption. Therefore, the manufacturers of erlotinib advise against the concurrent use of **proton pump inhibitors** and **H_2-receptor antagonists**.[1,2] If the use of **ranitidine** is essential, administration should be separated with the erlotinib taken 2 hours before or 10 hours after the ranitidine.[2] Although **antacids** are also predicted to interact, antacid interactions can usually be minimised by separation of administration. The manufacturer recommends that, if treatment with **antacids** is essential, they should be taken at least 4 hours before or 2 hours after erlotinib.[2]

(f) NSAIDs

Infrequent cases of gastrointestinal bleeding have been reported in patients taking erlotinib, and some cases have occurred in patients also taking NSAIDs.[1,2]

(g) P-glycoprotein inhibitors

Erlotinib is a substrate for the drug transporter protein P-glycoprotein. The manufacturer suggests that drugs that are inhibitors of P-glycoprotein may alter the pharmacokinetics (absorption and/or distribution) of erlotinib. They specifically mention **ciclosporin** and **verapamil**, and advise caution.[2] Note that, many CYP3A4 inhibitors, see (a) above, are also inhibitors of P-glycoprotein, and both mechanisms may be involved in their interactions with erlotinib.

(h) Warfarin

Raised INRs and infrequent bleeding have been reported in patients taking warfarin with erlotinib. Patients taking these drugs, and other coumarins, should be closely monitored for INR changes.[1,2]

1. Tarceva (Erlotinib). OSI Pharmaceuticals, Inc., and Genentech, Inc. US Prescribing information, April 2009.
2. Tarceva (Erlotinib). Roche Products Ltd. UK Summary of product characteristics, May 2009.
3. Rakhit A, Pantze MP, Fettner S, Jones HM, Charoin J-E, Riek M, Lum BL, Hamilton M. The effects of CYP3A4 inhibition on erlotinib pharmacokinetics: computer-based simulation (SimCYP™) predicts in vivo metabolic inhibition. Eur J Clin Pharmacol (2008) 64, 31–41.

Erlotinib + Tobacco

Smoking increases the metabolism of erlotinib.

Clinical evidence

In a study, 12 smokers and 14 non-smokers were given oral erlotinib 150 mg on day one and 300 mg on day 15. The subjects who smoked had lower maximum plasma levels of erlotinib; 35% lower after the 150 mg dose and 20% lower after the 300 mg dose. The AUC of erlotinib was also reduced, by 65% and 57%, respectively.[1]

In addition, the manufacturer notes that in a phase 3 study, the steady-state trough plasma concentrations of erlotinib were about twofold less in smokers than in former smokers or patients who had never smoked, and erlotinib clearance was 24% higher.[2]

Mechanism

Cigarette smoking induces the cytochrome P450 isoenzymes CYP1A1 and CYP1A2, which are involved in the metabolism of erlotinib.

Importance and management

Consideration should be given to the smoking status of a patient when planning treatment with erlotinib.[1] The manufacturer says that these decreases are likely to be clinically important, and that patients should be encouraged to stop smoking[2,3] as early as possible before starting treatment with erlotinib.[3] In patients who continue to smoke, the dose of erlotinib should be cautiously increased to a maximum of 300 mg. In patients who stop smoking during treatment, the erlotinib dose should be immediately reduced to the recommended starting dose.[2]

1. Hamilton M, Wolf JL, Rusk J, Beard SE, Clark GM, Witt K, Cagnoni PJ. Effects of smoking on the pharmacokinetics of erlotinib. *Clin Cancer Res* (2006) 12, 2166–71.
2. Tarceva (Erlotinib). OSI Pharmaceuticals, Inc., and Genentech, Inc. US Prescribing information, April 2009.
3. Tarceva (Erlotinib). Roche Products Ltd. UK Summary of product characteristics, May 2009.

Estramustine + ACE inhibitors

Angioedema occurred in a man taking cilazapril after starting estramustine. The concurrent use of estramustine and ACE inhibitors might increase the risk of angioedema.

Clinical evidence, mechanism, importance and management

A patient who had taken an ACE inhibitor for 20 years experienced four episodes of swelling of the tongue and epiglottis over a period of 40 days, approximately 2 months after starting to take estramustine. Three of the episodes resolved after hydrocortisone was given; one episode was unresponsive to hydrocortisone and required a tracheotomy. After stopping the estramustine and while continuing the **cilazapril**, the patient experienced no further episodes of angioedema. He had never had angioedema while taking the ACE inhibitor.[1]

Angioedema is a rare adverse effect of both estramustine and the ACE inhibitors, and it is possible that concurrent use might increase the risk. The UK manufacturer of estramustine notes that, in many of the reported cases of angioedema with estramustine, including a fatal one, patients were also taking ACE inhibitors.[2] They recommend that treatment with estramustine should be stopped immediately if angioedema occurs.[2]

1. Kamata Y, Iwamoto M, Kamimura T, Kanashiki E, Yoshio T, Okazaki H, Morita T, Minota S. Repeated massive tongue swelling due to the combined use of estramustine phosphate and angiotensin-converting enzyme inhibitor. *J Investig Allergol Clin Immunol* (2006) 16, 388–90.
2. Estracyt (Estramustine sodium phosphate). Pharmacia Ltd. UK Summary of product characteristics, November 2008.

Estramustine + Calcium compounds

The absorption of estramustine is reduced by milk, foods, and drugs containing calcium.

Clinical evidence

A randomised three-way crossover study in 6 patients with prostate cancer found that the absorption of single-doses of estramustine disodium (equivalent to 140 mg of estramustine) was reduced by 59% when taken with 200 mL of **milk**, and by 33% when taken with a standardised breakfast (2 pieces of white bread with margarine, ham, tomato, marmalade and water). Peak serum estramustine levels were reduced by 68% and 43%, respectively.[1]

Mechanism

In vitro studies suggest that estramustine combines with calcium ions in milk and food to form a poorly-soluble complex that is not as well absorbed as the parent compound.[1]

Importance and management

An established interaction although the information is limited. The manufacturers recommend that estramustine should be taken at least one hour before or 2 hours after meals, and that it should not be taken at the same time as milk, milk products, calcium-rich foods, or drugs containing calcium (such as **calcium-containing antacids**).[2,3]

1. Gunnarsson PO, Davidsson T, Andersson S-B, Backman C, Johansson S-Å. Impairment of estramustine phosphate absorption by concurrent intake of milk and food. *Eur J Clin Pharmacol* (1990) 38, 189–93.
2. Estracyt (Estramustine sodium phosphate). Pharmacia Ltd. UK Summary of product characteristics, November 2008.
3. Emcyt (Estramustine phosphate sodium). Pfizer. US Prescribing information, June 2007.

Estramustine + Clodronate

Clodronate markedly increases the levels of estramustine.

Clinical evidence, mechanism, importance and management

In 12 patients, the bioavailability of estramustine was increased by about 80% when clodronate 800 mg four times daily was given with estramustine 280 mg twice daily for 5 days. The serum levels and AUC of clodronate were not changed by estramustine.[1] Documentation appears to be limited to this study. However, the toxicity of estramustine should be more closely monitored if clodronate is also given. The effects of other bisphosphonates do not appear to have been studied.

1. Kylmälä T, Castrén-Kortekangas P, Seppänen J, Ylitalo P, Tammela TLJ. Effect of concomitant administration of clodronate and estramustine phosphate on their bioavailability in patients with metastasized prostate cancer. *Pharmacol Toxicol* (1996) 79, 157–60.

Etoposide + Antiepileptics; Enzyme-inducing

Etoposide clearance appears to be increased by phenobarbital, phenytoin, and probably carbamazepine, and this may result in reduced efficacy.

Clinical evidence, mechanism, importance and management

The clearance of etoposide was found to be highly variable in children given etoposide 320 to 500 mg/m^2 over 6 hours on alternate days for a total of 3 doses. However, it was 77% higher in 7 children taking antiepileptics (**phenobarbital**, **phenytoin** or both) than in 22 others not taking antiepileptics.[1] In a retrospective survey, long-term antiepileptic use (**phenytoin**, **phenobarbital**, **carbamazepine**, or a combination) was associated with worse event-free survival, and greater haematological and/or CNS relapse in children receiving chemotherapy for B-lineage acute lymphoblastic leukaemia. The authors considered that the increased clearance of etoposide induced by the antiepileptics was a likely factor in these findings.[2] Be alert for the possible need to give larger doses of etoposide if these antiepileptics (and probably **primidone**, which is metabolised to phenobarbital, or **fosphenytoin**, which is metabolised to phenytoin) are used. More study is needed to establish the magnitude and clinical effects of the interaction.

Note that reduced valproate levels and phenytoin levels have been reported in patients receiving chemotherapy including etoposide, see 'Antiepileptics + Antineoplastics; Cytotoxic', p.593.

1. Rodman JH, Murry DJ, Madden T, Santana VM. Altered etoposide pharmacokinetics and time to engraftment in pediatric patients undergoing autologous bone marrow transplantation. *J Clin Oncol* (1994) 12, 2390–7.
2. Relling MV, Pui C-H, Sandlund JT, Rivera GK, Hancock ML, Boyett JM, Schuetz EG, Evans WE. Adverse effect of anticonvulsants on efficacy of chemotherapy for acute lymphoblastic leukaemia. *Lancet* (2000) 356, 285–90.

Etoposide + Atovaquone

The concurrent use of atovaquone with etoposide may modestly increase exposure to the metabolite, etoposide catechol.

Clinical evidence, mechanism, importance and management

A study in 9 children with acute lymphoblastic leukaemia or non-Hodgkin's lymphoma found that the AUC of etoposide and its metabolite, etoposide catechol, were slightly increased, by 9% and 28%, respectively, following atovaquone 45 mg/kg daily, when compared with co-trimoxazole (trimethoprim with sulfamethoxazole) 150/750 mg/m^2 daily. The mechanism by which this occurs is unclear, but the authors suggested that atovaquone may affect the metabolism of etoposide by the cytochrome P450 isoenzyme CYP3A4 or its transport by P-glycoprotein.[1] The authors considered that an interaction with co-trimoxazole was unlikely, so used it as a control; however, ideally this requires confirmation. The relevance of the minor changes seen is unclear. The authors note that the risk of etoposide-related secondary acute myeloid leukaemia has been linked to minor changes in therapy, therefore, they advise caution if atovaquone is given with etoposide, particularly if it is used with other substrates of CYP3A4 or P-glycoprotein.[1] They also say it may be possible to avoid the interaction by separating the administration by one to 2 days,[1] but this requires confirmation.

1. van de Poll MEC, Relling MV, Schuetz EG, Harrison PL, Hughes W, Flynn PM. The effect of atovaquone on etoposide pharmacokinetics in children with acute lymphoblastic leukemia. *Cancer Chemother Pharmacol* (2001) 47, 467–72.

Etoposide + Ciclosporin

High-dose ciclosporin markedly raises etoposide levels and increases the suppression of white blood cell production. Severe toxicity has been reported in one patient.

Clinical evidence

In a comparative study, 16 patients with multidrug-resistant advanced cancer were given 20 paired courses of etoposide alone or with ciclosporin. Ciclosporin levels were measured at the end of a 2-hour infusion: ciclosporin levels of greater than 2000 nanograms/mL were defined as high-dose and ciclosporin levels less than 2000 nanograms/mL were defined as low-dose. High and low-dose ciclosporin, respectively, increased the etoposide AUC by 80% and 50%, decreased the total clearance by 38% and 28%, increased its half-life by 108% and 40%, reduced the leucocyte count nadir by 64% and 37%, and altered the volume of distribution at steady state by 46% and 1.4%.[1] The patients were given 150 to 200 mg/m^2 of etoposide daily as a 2-hour intravenous infusion for 3 consecutive days and ciclosporin in doses ranging from 5 to 21 mg/kg daily as a 3-day continuous infusion.[1]

In another study, 18 children with recurrent or refractory tumours who had previously received etoposide were given high-dose ciclosporin (either a continuous infusion of 15 mg/kg per 24 hours for 60 hours (13 patients) or 30 mg/kg over 3 hours on 3 consecutive days (5 patients) with etoposide 150 mg/m^2 over one hour for 3 days, starting one hour after the beginning of the ciclosporin infusion. The AUC and half-life of etoposide were increased by 89% and 78%, respectively, and the clearance was decreased by 48%.[2] In a further study in children, the pharmacokinetics of etoposide 100 mg/m^2 daily were compared with etoposide 60 mg/m^2 (a 40% reduction in dose) with high-dose ciclosporin. Despite the dose reduction, recipients of ciclosporin had a 71% reduction in etoposide clearance and a 47% increase in the etoposide AUC, although toxicity was similar.[3]

The leukaemic cells in the bone marrow of a patient with acute T-lymphocyte leukaemia were totally cleared when ciclosporin 8.3 mg/kg orally twice daily was given with etoposide 100 to 300 mg daily for 2 to 5 days, but the adverse effects were severe (mental confusion, renal and hepatic toxicity). The patient died from respiratory failure precipitated by a chest infection.[4]

A patient with chronic myeloid leukaemia who had responded poorly to treatment with etoposide, mitoxantrone and cytarabine for blast crisis, returned to the chronic phase when given etoposide with ciclosporin.[5] An *in vitro* study by the same authors showed that etoposide was partially toxic to blast cells but that its effect on blast cells was increased sixfold when it was given with ciclosporin.[5]

Mechanism

It is suggested that the ciclosporin inhibits the metabolism of etoposide by cytochrome P450 isoenzymes,[6] and inhibits hepatic P-glycoprotein, as

well as some unknown non-renal clearance mechanism.[1] The total effect is to cause the retention of etoposide in the body, thereby increasing its effects.

Importance and management

An established interaction. Ciclosporin alters the pharmacokinetics of etoposide resulting in increased levels. This pharmacokinetic interaction has complicated the study of the value of using ciclosporin to modulate multidrug resistance in tumours to improve the response to chemotherapy: any benefit could just be attributed to dose intensification. Consequently, some,[1-3] including one manufacturer,[7] have suggested reducing the dose of etoposide by 40% or 50% in the presence of ciclosporin.[1-3] In one study, a continuous infusion of ciclosporin was better tolerated than an intermittent regimen, but it was associated with similar hepatic and renal impairment as the short schedule (transient hyperbilirubinaemia, and elevated creatinine or urea).[2] The use of high-dose ciclosporin for multidrug-resistant tumour modulation remains experimental and should only be undertaken in clinical studies. Concurrent use should be very well monitored. More study is needed to find out the possible effects of low-dose ciclosporin.

1. Lum BL, Kaubisch S, Yahanda AM, Adler KM, Jew L, Ehsan MN, Brophy NA, Halsey J, Gosland MP, Sikic BI. Alteration of etoposide pharmacokinetics and pharmacodynamics by cyclosporine in a phase I trial to modulate multidrug resistance. *J Clin Oncol* (1992) 10, 1635–42.
2. Bisogno G, Cowie F, Boddy A, Thomas HD, Dick G, Pinkerton CR. High-dose cyclosporin with etoposide—toxicity and pharmacokinetic interaction in children with solid tumours. *Br J Cancer* (1998) 77, 2304–9.
3. Lacayo NJ, Lum BL, Becton DL, Weinstein H, Ravindranath Y, Chang MN, Bomgaars L, Lauer SJ, Sikic BI. Pharmacokinetic interactions of cyclosporine with etoposide and mitoxantrone in children with acute myeloid leukemia. *Leukemia* (2002) 16, 920–7.
4. Kloke O, Osieka R. Interaction of cyclosporin A with antineoplastic agents. *Klin Wochenschr* (1985) 63, 1081–2.
5. Maia RC, Noronha H, Vasconcelos FC, Rumjanek VM. Interaction of cyclosporin A and etoposide. Clinical and *in vitro* assessment in blast phase of chronic myeloid leukaemia. *Clin Lab Haematol* (1997) 19, 215–7.
6. Kawashiro T, Yamashita K, Zhao X-J, Koyama E, Tani M, Chiba K, Ishizaki T. A study on the metabolism of etoposide and possible interaction with antitumor or supporting agents by human liver microsomes. *J Pharmacol Exp Ther* (1998) 386, 1294–1300.
7. Eposin (Etoposide). Medac GmbH. UK Summary of product characteristics, January 2005.

Etoposide + Cisplatin and other platinum compounds

The clearance of etoposide may be modestly reduced by carboplatin and cisplatin.

Clinical evidence, mechanism, importance and management

(a) Carboplatin

In one study in 4 patients, the pharmacokinetics of etoposide were unchanged when carboplatin was also given.[1] However, in another study of 14 young patients receiving etoposide and carboplatin the clearance of etoposide was lower than in previous reports in adults and children. They had been given an escalating dose regimen starting with etoposide 960 mg/m^2, and increasing to 1200 mg/m^2, and 1500 mg/m^2, given in three divided doses on alternate days, with carboplatin 400 to 700 mg/m^2 given on the other days, followed by autologous marrow rescue. The authors point out that the dose and the timing of carboplatin may be important determinants for any interaction.[2] In yet another study,[3] carboplatin did not affect the pharmacokinetics of etoposide during the first cycle of chemotherapy (etoposide was given on days 1, 2 and 3, and carboplatin on day 2, and the AUC of etoposide was compared for days 1 and 2). However, during a second cycle of chemotherapy, the etoposide AUC was 8% higher on day 2 than day 1. These changes were considered unlikely to be clinically important.[3]

(b) Cisplatin

A study in 17 children with neuroblastoma found that when intravenous cisplatin 90 mg/m^2 was given immediately before etoposide, the clearance of etoposide 780 mg/m^2 fell by 20% and its serum levels rose. However, after a cumulative dose of 360 mg/m^2 cisplatin had no effect on the clearance of etoposide.[4] In another study, cisplatin did not affect the pharmacokinetics of etoposide during the first cycle of chemotherapy (etoposide was given on days 1, 2 and 3, and cisplatin on day 2, and the AUC of etoposide was compared for days 1 and 2). However, during a second cycle of chemotherapy, the etoposide AUC was 28% higher on day 3 than day 1. These changes were considered unlikely to be clinically important.[3]

1. Newell DR, Eeles RA, Gumbrell LA, Boxall FE, Horwich A, Calvert AH. Carboplatin and etoposide pharmacokinetics in patients with testicular teratoma. *Cancer Chemother Pharmacol* (1989) 23, 376–72.
2. Rodman JH, Murry DJ, Madden T, Santana VM. Altered etoposide pharmacokinetics and time to engraftment in pediatric patients undergoing autologous bone marrow transplantation. *J Clin Oncol* (1994) 12, 2390–7.
3. Thomas HD, Porter DJ, Bartelink I, Nobbs JR, Cole M, Elliott S, Newell DR, Calvert AH, Highley M, Boddy AV. Randomized cross-over clinical trial to study potential pharmacokinetics interactions between cisplatin or carboplatin and etoposide. *Br J Clin Pharmacol* (2002) 53, 83–91.
4. Relling MV, McLeod HL, Bowman LC, Santana VM. Etoposide pharmacokinetics and pharmacodynamics after acute and chronic exposure to cisplatin. *Clin Pharmacol Ther* (1994) 56, 503–11.

Etoposide + CYP3A4 inducers or inhibitors

Ketoconazole modestly increased the AUC and decreased the clearance of etoposide in one study. Etoposide clearance was markedly increased by prednisone in one study. Etoposide bioavailability was modestly (and unexpectedly) decreased by grapefruit juice.

Clinical evidence

(a) CYP3A4 inducers

In a study, 102 children with acute lymphoblastic leukaemia were given **prednisone** 40 mg/m^2 daily for 28 days with etoposide 300 mg/m^2 on day 29. Forty-eight of the children with high risk disease were given continuation therapy and received etoposide 300 mg/m^2 at week 54, two weeks or more after the last **prednisone** dose. Etoposide clearance was 62% higher on day 29 than at week 54 and the AUC for the catechol metabolite was significantly lower (27%) on day 29 compared with week 54.[1]

(b) CYP3A4 inhibitors

1. Grapefruit juice. In a single-dose study, 6 patients were given etoposide 50 mg intravenously or orally, either alone or after drinking 100 mL of **grapefruit juice**. The bioavailability of oral etoposide was unexpectedly *reduced* by about 25% by **grapefruit juice**, but there was wide inter-individual variation in the findings.[2]

2. Ketoconazole. In a study in 27 patients, ketoconazole 200 mg daily was given with oral etoposide (escalating doses of 50 mg every other day increasing to 50 mg alternating with 100 mg daily) in cycles of 3 out of 5 weeks. The median AUC of etoposide was increased by about 20%, and its clearance reduced by about 18%, and inter-individual variation was greater than seen with etoposide alone. However, the toxicity profile of etoposide did not appear to be altered by ketoconazole, when compared with historical data.[3]

Mechanism

Etoposide is a substrate for the cytochrome P450 isoenzyme CYP3A4. *In vitro* studies using human liver microsomes showed that ketoconazole, **prednisolone**, **troleandomycin**, **verapamil** and **vincristine** can inhibit the metabolism (3′-demethylation) of etoposide by CYP3A4.[4] The clinical study found that ketoconazole modestly inhibited etoposide metabolism; however, unexpectedly, grapefruit juice (another CYP3A4 inhibitor) appeared to decrease etoposide bioavailability. The reason for this is unknown, but may be a concentration effect, or an effect via P-glycoprotein. Also, somewhat in contrast to the *in vitro* findings, prednisone (a metabolite of prednisolone) induced etoposide metabolism, but note that corticosteroids are more usually known to be clinical inducers of CYP3A4 and possibly also P-glycoprotein.

Importance and management

There seems to be little clinical confirmation that the potential interactions with CYP3A4 inhibitors or inducers, other than prednisone have clinical relevance, but good monitoring would be a prudent precaution. Ketoconazole had only a modest and variable effect on etoposide, and grapefruit juice seemed to reduce rather than increase oral etoposide bioavailability. Further study is needed.

For mention that the protease inhibitors (CYP3A4 inhibitors) have been associated with an increased risk of infection when used with various antineoplastic regimens, including those containing etoposide, see also 'Antineoplastics + Protease inhibitors', p.703.

1. Kishi S, Yang W, Boureau B, Morand S, Das S, Chen P, Cook EH, Rosner GL, Schuetz E, Pui C-H, Relling MV. Effects of prednisone and genetic polymorphisms on etoposide disposition in children with acute lymphoblastic leukaemia. *Blood* (2004) 103, 67–72.
2. Reif S, Nicolson MC, Bisset D, Reid M, Kloft C, Jaehde U, McLeod HL. Effect of grapefruit juice intake on etoposide bioavailability. *Eur J Clin Pharmacol* (2002) 58, 491–4.
3. Yong WP, Desai AA, Innocenti F, Ramirez J, Shepard D, Kobayashi K, House L, Fleming GF, Vogelzang NJ, Schilsky RL, Ratain MJ. Pharmacokinetic modulation of oral etoposide by ketoconazole in patients with advanced cancer. *Cancer Chemother Pharmacol* (2007) 60, 811–19.
4. Kawashiro T, Yamashita K, Zhao X-J, Koyama E, Tani M, Chiba K, Ishizaki T. A study on the metabolism of etoposide and possible interactions with antitumor or supporting agents by human liver microsomes. *J Pharmacol Exp Ther* (1998) 386, 1294–1300.

Etoposide + Food

In 8 patients with extensive small cell lung carcinoma the pharmacokinetics of a 100-mg oral dose of etoposide were unaffected when it was taken with a full breakfast, when compared with the fasting state.[1] However, the UK manufacturer recommends that oral etoposide should be taken on an empty stomach.[2]

1. Harvey VJ, Slevin ML, Joel SP, Johnston A, Wrigley PFM. The effect of food and concurrent chemotherapy on the bioavailability of oral etoposide. *Br J Cancer* (1985) 52, 363–7.
2. Vepesid Capsules (Etoposide). Bristol-Myers Pharmaceuticals. UK Summary of product characteristics, March 2008.

Etoposide + Levamisole

The manufacturers of an intravenous etoposide *phosphate* product warn that the administration with drugs known to inhibit phosphatase activity (they name levamisole) should be undertaken with caution.[1,2] This is presumably because this might reduce the conversion of etoposide phosphate to etoposide in the plasma. There does not seem to be any information on whether this interaction is clinically relevant.

1. Etopophos Injection (Etoposide phosphate). Bristol-Myers Squibb Pharmaceuticals Ltd. UK Summary of product characteristics, September 2007.
2. Etopophos Injection (Etoposide phosphate). Bristol-Myers Squibb Company. US Prescribing information, March 2005.

Etoposide + Other antineoplastics

The use of doxorubicin with cyclophosphamide has no clinically relevant effects on the pharmacokinetics of oral or intravenous etoposide. Similarly, cyclophosphamide with methotrexate, doxorubicin with procarbazine and procarbazine alone do not affect the pharmacokinetics of oral etoposide.

Clinical evidence, mechanism, importance and management

(a) Cyclophosphamide with Doxorubicin

A pharmacokinetic study in 7 patients with small cell lung cancer given cyclophosphamide 800 mg/m^2, doxorubicin 40 mg/m^2 and etoposide 100 mg/m^2 (all given intravenously) found that the protein binding, metabolism and renal clearance of etoposide were unaffected by the other antineoplastics.[1] Similarly, another study found only modest changes in the pharmacokinetics of intravenous etoposide when it was given with cyclophosphamide and doxorubicin, compared with use alone, and these changes were considered unlikely to be clinically relevant. Specifically, the AUC of etoposide was 9% higher and the clearance was 10% lower on day one of the CAE cycle (cyclophosphamide, doxorubicin, and etoposide) compared with days 2 and 3 (etoposide alone).[2] This is a commonly used regimen, and these data suggest there is no pharmacokinetic interaction.

(b) Cyclophosphamide with Methotrexate

No changes in etoposide pharmacokinetics were seen when oral etoposide 100 mg was given immediately after oral cyclophosphamide 100 mg/m^2 and oral methotrexate 12.5 mg/m^2 in 8 patients with small cell lung cancer.[3]

(c) Doxorubicin with Procarbazine

No changes in etoposide pharmacokinetics were seen when oral etoposide 400 mg was given 15 minutes after intravenous doxorubicin 35 mg/m^2 with oral procarbazine 60 mg/m^2 or after oral procarbazine alone, when compared with etoposide alone.[3]

(d) Imatinib

For the possible effect of imatinib on etoposide, see 'Imatinib + Antineoplastics', p.734.

(e) Platinum compounds

For the lack of effect of platinum derivatives on etoposide pharmacokinetics, see 'Etoposide + Cisplatin and other platinum compounds', p.725.

1. Van Hoogenhuijze J, Lankelma J, Stam J, Pinedo HM. Unchanged pharmacokinetics of VP-16-213 (etoposide, NSC 141540) during concomitant administration of doxorubicin and cyclophosphamide. *Eur J Cancer Clin Oncol* (1987) 23, 807–11.
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Exemestane + CYP3A4 inducers or inhibitors

Ketoconazole appears not to interact with exemestane. Rifampicin reduces exemestane levels and other CYP3A4 inducers are predicted to interact similarly.

Clinical evidence, mechanism, importance and management

The manufacturers say that *in vitro* evidence shows that while exemestane is metabolised by both the cytochrome P450 isoenzyme CYP3A4 and aldoketoreductases, a clinical study found that **ketoconazole** (a specific inhibitor of CYP3A4) had no significant effects on the pharmacokinetics of exemestane. The manufacturers therefore suggest that interactions with CYP3A4 inhibitors are unlikely.[1,2]

However, in an interaction study the potent enzyme inducer **rifampicin** (**rifampin**) reduced the AUC and maximum plasma levels of exemestane by 54% and 41%, respectively.[1,2] The manufacturers therefore caution the use of exemestane with CYP3A4 inducers such as **carbamazepine**, **phenobarbital**, **phenytoin** and **St John's wort**,[1,2] and the US manufacturer recommends that the dose of exemestane should be doubled to 50 mg daily in patients taking CYP3A4 inducers such as **rifampicin** (**rifampin**) and **phenytoin**.[2] The clinical relevance of these potential interactions is unknown, but it would seem prudent to monitor the outcome of concurrent use for both exemestane efficacy and toxicity, if the dose is increased. Note that, **primidone** is metabolised to phenobarbital, and **fosphenytoin** is metabolised to phenytoin, and so similar precautions may be prudent with these drugs.

1. Aromasin (Exemestane). Pharmacia Ltd. UK Summary of product characteristics, May 2009.
2. Aromasin (Exemestane). Pfizer. US Prescribing information, October 2008.

Exemestane + Food

Food increases the bioavailability of exemestane.

Clinical evidence, mechanism, importance and management

In a single-dose study in 12 healthy postmenopausal women, a high-fat meal increased the AUC of exemestane 25 mg by 40%, but had no significant effect on its maximum plasma levels. In addition, its pharmacodynamics (estrone sulfate suppressant effect) were unaffected.[1] The manufacturers recommend that exemestane is taken after food.[2,3]

1. Valle M, Di Salle E, Jannuzzo MG, Poggesi I, Rochetti M, Spinelli R, Verotta D. A predictive model for exemestane pharmacokinetics/ pharmacodynamics incorporating the effect of food and formulation. *Br J Clin Pharmacol* (2005) 59, 355–64.
2. Aromasin (Exemestane). Pharmacia Ltd. UK Summary of product characteristics, May 2009.
3. Aromasin (Exemestane). Pfizer. US Prescribing information, October 2008.

Fludarabine + Busulfan

In 16 patients with haematological malignancies the pharmacokinetics of intravenous fludarabine were unaltered by oral high-dose busulfan.[1]

1. Bonin M, Pursche S, Bergeman T, Leopold T, Illmer T, Ehninger G, Schleyer E, Bornhauser M. F-ara-A pharmacokinetics during reduced-intensity conditioning therapy with fludarabine and busulfan. *Bone Marrow Transplant* (2007) 39, 201–6.

Fludarabine + Dipyridamole

Because fludarabine phosphate is an analogue of adenine, the UK manufacturers warn that drugs that are adenosine uptake inhibitors, such as dipyridamole, may prevent the uptake of fludarabine into cells and reduce its efficacy.[1,2] Until more is known, some caution would seem to be appropriate on concurrent use.

1. Schering Health Care Ltd. Personal communication, February 1995.
2. Fludara Tablets (Fludarabine phosphate). Genzyme Therapeutics. UK Summary of product characteristics, February 2009.

Fludarabine + Food

Food does not affect the pharmacokinetics of oral fludarabine.

Clinical evidence, mechanism, importance and management

In a randomised, crossover study, 16 patients were given fludarabine 90 mg orally either on a full stomach or after fasting on the first day of their chemotherapy cycle, followed 2 days later by intravenous fludarabine 25 mg/m^2 daily for 4 days. There was no clinically significant effect of food on the pharmacokinetics of oral fludarabine.[1] The manufacturer advises that oral fludarabine may be taken with or without food.[2]

1. Oscier D, Orchard JA, Culligan D, Cunningham D, Johnson S, Parker A, Klein M, Gieschen H. The bioavailability of oral fludarabine phosphate is unaffected by food. *Hematol J* (2001) 2, 316–21.
2. Fludara Tablets (Fludarabine phosphate). Genzyme Therapeutics. UK Summary of product characteristics, February 2009.

Fludarabine + Pentostatin

When fludarabine phosphate and pentostatin were used in the treatment of chronic lymphoid leukaemia, 4 out of 6 patients developed pulmonary toxicity consistent with interstitial pneumonitis, and 3 of them died.[1] Pentostatin should therefore not be given with fludarabine.[2,3]

1. Schering Health Care Ltd. Personal communication, February 1995.
2. Fludara Tablets (Fludarabine phosphate). Genzyme Therapeutics. UK Summary of product characteristics, February 2009.
3. Fludara (Fludarabine phosphate). Bayer HealthCare Pharmaceuticals Inc. US Prescribing information, February 2009.

Fludarabine with Cytarabine + Voriconazole

A case of fatal peripheral neuropathy was tentatively attributed to the use of voriconazole with fludarabine and cytarabine.

Clinical evidence, mechanism, importance and management

A patient experienced severe peripheral neuropathy, which progressed to poor respiratory effort and death, after receiving treatment with cytarabine, fludarabine and tretinoin. During his first course he had developed probable pulmonary invasive fungal infection, and was treated with broad-spectrum antibacterials and liposomal amphotericin B. He then started taking prophylactic voriconazole, which was stopped after a total of 7 days, two days after starting his second course of chemotherapy, because he again had a fever. After 14 days, severe distal peripheral neuropathy became apparent, which progressed, and he died after 23 days.[1] The exact cause of the neurological effects was not clear. Both cytarabine and fludarabine uncommonly cause neurological toxicity, and it has been reported with the combination.[1] In the case described, it was considered that voriconazole might have altered the metabolism of the antineoplastics, and increased the risk of toxicity.[1] However, neither cytarabine nor fludarabine are metabolised by the cytochrome P450 system, which voriconazole inhibits. The clinical relevance of this single case report is uncertain and no general recommendations can be made.

1. Osborne WL, Holyoake TL, McQuaker IG, Parker AN. Fatal peripheral neuropathy following FLA chemotherapy. *Clin Lab Haematol* (2004) 26, 295–6.

Fluorouracil + Allopurinol

Allopurinol has been studied as a modulator of the effects of fluorouracil, but has not gained an established clinical use in this setting.

Clinical evidence, mechanism, importance and management

Some early studies found that allopurinol 300 mg two to four times daily allowed the usual maximum tolerated dose of fluorouracil to be increased up to twofold.[1-3] The hope was that allopurinol would prove useful to decrease the toxicity and/or improve the activity of fluorouracil. However, most studies have found no increase in response rates in colorectal cancer with allopurinol,[4,5] even when the fluorouracil dose was escalated,[2,4] and some have also found no reduction in toxicity.[5-7] These are by no means all the studies, and are just cited as examples. Allopurinol mouthwash has also been investigated to reduce the incidence of stomatitis with fluorouracil. Some controlled studies have found a benefit,[8] whereas others have not.[9] Allopurinol clearly modulates some of the effects of fluorouracil; however, this has not been shown to be obviously beneficial or harmful in the clinical setting.

1. Howell SB, Wung WE, Taetle R, Hussain F, Romine JS. Modulation of 5-fluorouracil toxicity by allopurinol in man. *Cancer* (1981) 48, 1281–9.
2. Fox RM, Woods RL, Tattersall MHN, Piper AA, Sampson D. Allopurinol modulation of fluorouracil toxicity. *Cancer Chemother Pharmacol* (1981) 5, 151–5.
3. Woolley PV, Ayoob MJ, Smith FP, Lokey JL, DeGreen P, Marantz A, Schein PS. A controlled trial of the effect of 4-hydroxypyrazolopyrimidine (allopurinol) on the toxicity of a single bolus dose of 5-fluorouracil. *J Clin Oncol* (1985) 3, 103–9.
4. Tsavaris N, Bacoyannis C, Milonakis N, Sarafidou M, Zamanis N, Magoulas D, Kosmidis P. Folinic acid plus high-dose 5-fluorouracil with allopurinol protection in the treatment of advanced colorectal carcinoma. *Eur J Cancer* (1990) 26, 1054–6.
5. Merimsky O, Inbar M, Chaitchik S. Treatment of advanced colorectal cancer by 5-fluorouracil–leucovorin combination with or without allopurinol: a prospective randomized study. *Anticancer Drugs* (1991) 2, 447–51.
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7. Garewal H, Ahmann FR. Failure of allopurinol to provide clinically significant protection against the hematologic toxicity of a bolus 5-FU schedule. *Oncology* (1986) 43, 216–18.
8. Porta C, Moroni M, Nastasi G. Allopurinol mouthwashes in the treatment of 5-fluorouracil-induced stomatitis. *Am J Clin Oncol* (1994) 17, 246–7.
9. Loprinzi CL, Cianflone SG, Dose AM, Etzell PS, Burnham NL, Therneau TM, Hagen L, Gainey DK, Cross M, Athmann LM, Fischer T, O'Connell MJ. A controlled evaluation of an allopurinol mouthwash as prophylaxis against 5-fluorouracil–induced stomatitis. *Cancer* (1990) 65, 1879–82.

Fluorouracil + Aminoglycosides; Oral

Neomycin can delay the gastrointestinal absorption of fluorouracil, but the clinical importance of this is uncertain.

Clinical evidence, mechanism, importance and management

Some preliminary information from a study in 12 patients treated for metastatic adenocarcinoma found that the use of oral **neomycin** 500 mg four times daily for a week delayed the absorption of fluorouracil, but the effects were generally too small to reduce the therapeutic response, except possibly in one patient.[1] It seems probable that this interaction occurs because **neomycin** can induce a malabsorption syndrome. If **neomycin**, and most probably also **paromomycin** or **kanamycin**, are used in patients receiving fluorouracil, the possibility of this interaction should be borne in mind.

1. Bruckner HW, Creasey WA. The administration of 5-fluorouracil by mouth. *Cancer* (1974) 33, 14–18.

Fluorouracil + Cisplatin and other platinum compounds

Giving low-dose cisplatin with a fluorouracil infusion markedly increased toxicity in one study. Cardiotoxicity may possibly be increased if high doses of cisplatin are given with fluorouracil. Oxaliplatin appears to moderately raise fluorouracil levels, without increasing its toxicity.

Clinical evidence, mechanism, importance and management

(a) Cisplatin

In 18 patients with advanced cancers giving low-dose cisplatin 20 mg/m^2 weekly with continuous ambulatory fluorouracil infusions of 300 mg/m^2 daily considerably increased the toxicity (nausea, vomiting, anorexia, diarrhoea, stomatitis, myelosuppression). More than half of the patients developed multiple toxicities, and severe toxicity occurred in two-thirds of the patients. Leucopenia occurred in 28% given both drugs whereas it was virtually nonexistent with fluorouracil alone. Toxicity requiring treatment interruption or dose reduction was seen in 55% of patients receiving fluorouracil alone, and this rose to 94% in the presence of cisplatin.[1]

In another study, signs of cardiotoxicity (chest pain, ST-T wave changes, arrhythmias) were seen in 12 of 80 patients given fluorouracil with cisplatin for carcinoma of the head, neck, oesophagus and stomach.[2] Studies in humans and *rats* have shown that there is a prolonged elevation of filterable platinum levels associated with the concurrent use of cisplatin and fluorouracil.[3]

The combination of a platinum compound and fluorouracil is widely used, but the optimum schedule to improve activity and reduce toxicity is not firmly established. In one study of bolus cisplatin and continuous infusion fluorouracil, modifying the dose of fluorouracil based on its AUC reduced toxicity while still maintaining response rates.[4] In another study, cisplatin pharmacokinetics were said to be optimum when it was given as a continuous infusion with a continuous infusion of fluorouracil.[5] Further study is needed.

(b) Oxaliplatin

In one study, 28 patients with advanced or metastatic colorectal cancer were given fluorouracil alone, or immediately following an 85 mg/m^2 dose of oxaliplatin given over 2 hours. Oxaliplatin did not significantly affect the pharmacokinetics of fluorouracil (either 2 cycles of a 400 mg/m^2 bolus followed by a 46-hour infusion of 2400 mg/m^2 given to 10 patients, with pharmacokinetic sampling over 46 hours; or a single cycle of a 400 mg/m^2 bolus followed by 600 mg/m^2 over 22 hours given to 18 patients, with pharmacokinetic sampling over 22 hours).[6] Similarly, a study in which patients received fluorouracil 200 mg/m^2 daily as a continuous infusion, and oxaliplatin 30 mg/m^2 daily as a 12-hour infusion on days one to 4 of each 14 day cycle found that the pharmacokinetics of both oxaliplatin or fluorouracil were unaffected by concurrent use.[7] However, in another study, 29 patients with advanced colorectal cancer were given fluorouracil in a dose adjusted to give levels of 2.5 to 3 mg/L (dose range 750 to 3500 mg/m^2 per week) either alone, or immediately after a 2-hour infusion of oxaliplatin 130 mg/m^2. In this study pharmacokinetic samples were taken on days one, 8 and 15. Oxaliplatin raised the plasma levels of fluorouracil by about one-third, with the effect appearing to last for 15 days; however, fluorouracil toxicity was not increased.[8]

The combination of fluorouracil and oxaliplatin is widely used, but one of the studies cited here suggests that the schedules could still be adjusted to optimise efficacy and minimise toxicity.[8] As of 2005, the recommended schedule for use of oxaliplatin in the management of colon and colorectal cancer is that it is given before fluorouracil.[9]

1. Jeske J, Hansen RM, Libnoch JA, Anderson T. 5-Fluorouracil infusion and low-dose weekly cisplatin: an analysis of increased toxicity. *Am J Clin Oncol* (1990) 13, 485–8.
2. Jeremic B, Jevremovic S, Djuric L, Mijatovic L. Cardiotoxicity during chemotherapy treatment with 5-fluorouracil and cisplatin. *J Chemother* (1990) 2, 264–7.
3. Belliveau JF, Posner MR, Crabtree GW, Weitberg AB, Wiemann MC, Cummings FJ, O'Leary GP, Ingersoll E, Calabresi P. Clinical pharmacokinetics of 3-day continuous infusion cisplatin and daily bolus 5-fluorouracil. *Eur J Clin Pharmacol* (1991) 40, 115–17.
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9. National Institute for Clinical Excellence. Irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer. (Issued August 2005). Available at http://www.nice.org.uk/nicemedia/pdf/TA93Guidance.pdf (accessed 29/01/10).

Fluorouracil + Dipyridamole

One study suggested that *intravenous* dipyridamole may reduce the steady-state plasma levels of fluorouracil, whereas others found that *oral* dipyridamole caused no important changes in fluorouracil pharmacokinetics.

Clinical evidence, mechanism, importance and management

Numerous preclinical studies found that dipyridamole enhanced the activity of fluorouracil, leading to its investigation as a biomodulator.[1] However, unexpectedly, in one phase I study of the combination, the use of dipyridamole was associated with a lower steady state plasma level of fluorouracil, suggesting an increase of about 30% in the total body clearance or volume of distribution of fluorouracil.[2] In this study, 47 patients with advanced cancer were given fluorouracil in escalating doses ranging from 185 mg/m^2 daily to 3600 mg/m^2 daily with or without dipyridamole as a continuous infusion of 7.7 mg/kg daily for 72 hours.[2] In contrast, in a later randomised study, oral dipyridamole 75 mg three times daily for 5 days did not significantly alter the pharmacokinetics of fluorouracil, except for prolonging the half-life and slightly increasing the dose-intensity: over 5 cycles the average dose of fluorouracil was 479 mg/m^2 alone, compared with 533 mg/m^2 in the presence of dipyridamole. In this study, oral dipyridamole did not improve the antineoplastic activity of fluorouracil with folinic acid.[3] Similarly, another clinical study found that oral dipyridamole did not significantly alter the pharmacokinetics of fluorouracil.[4] Thus, despite the promise of preclinical studies, the benefits of combining dipyridamole with fluorouracil have not been realised clinically.

1. Grem JL. Biochemical modulation of fluorouracil by dipyridamole: preclinical and clinical experience. *Semin Oncol* (1992) 19 (Suppl 3), 56–65.
2. Trump DL, Egorin MJ, Forrest A, Willson JKV, Remick S, Tutsch KD. Pharmacokinetic and pharmacodynamic analysis of fluorouracil during 72-hour continuous infusion with and without dipyridamole. *J Clin Oncol* (1991) 9, 2027–35.
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Fluorouracil + Folic acid

Two patients developed severe fluorouracil toxicity while taking multivitamin preparations containing folic acid.

Clinical evidence

A woman who underwent surgery for carcinoma of the rectum was, a month later, given intravenous fluorouracil 500 mg/m^2 daily for 5 days. At the end of this chemotherapy she was admitted to hospital with anorexia, severe mouth ulceration, bloody diarrhoea and vaginal bleeding, which was interpreted as fluorouracil toxicity. Her concurrent medication included folic acid 5 mg daily (in *Multi-B forte*) along with loperamide, sulfasalazine, vitamins B_{12} and K, and HRT. A month later, when she was given fluorouracil without the folic acid, her treatment was well tolerated and without toxicity. A man similarly treated with fluorouracil for colonic cancer was admitted to hospital 2 days later with severe mouth ulceration and bloody diarrhoea. He too was found to be taking a multivitamin preparation, containing folic acid 500 micrograms (amount taken daily not known). Subsequent courses of fluorouracil at the same dose, but without the folic acid, were well tolerated.[1]

Mechanism

It would seem that folic acid increases fluorouracil inhibition of thymidine formation which is important for DNA synthesis, and thereby increases fluorouracil toxicity.

Importance and management

Direct information seem to be limited to these two cases and a case of fatal toxicity associated with concurrent folic acid and capecitabine, a prodrug of fluorouracil (see 'Fluorouracil prodrugs; Capecitabine + Folinates', p.731) but the interaction would appear to be established. What happened is consistent with the way folinic acid, another source of folate, is used therapeutically to increase the potency of fluorouracil. Patients given fluorouracil should therefore not be given folic acid, and should be told to avoid multivitamin preparations containing folic acid to prevent the development of severe fluorouracil adverse effects.

1. Mainwaring P, Grygiel JJ. Interaction of 5-fluorouracil with folates. *Aust N Z J Med* (1995) 25, 60.

Fluorouracil + Gemcitabine

Pharmacokinetic analysis has shown that gemcitabine enhances the systemic exposure of fluorouracil in patients with pancreatic carcinoma given folinic acid, fluorouracil, and gemcitabine.[1,2] In addition, *in vitro*, gemcitabine increases both the accumulation of fluorouracil and its cytotoxicity.[1] The use of fluorouracil with gemcitabine is being investigated for its therapeutic potential, particularly in pancreatic cancer.

1. Francini G, Correale P, Cetta F, Zuckermann M, Cerretani D, Micheli V, Bruni G, Clerici M, Pozzessere D, Petrioli R, Marsili S, Messinese S, Sabatino M, Giorgio G. Effects of gemcitabine on 5-fluorouracil activity, pharmacokinetics and pharmacodynamics in vitro and in cancer patients. *Gastroenterology* (2002) 122 (Suppl 1), A308.
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Fluorouracil + H_2-receptor antagonists

Some data indicate that four weeks, but not one week, of treatment with cimetidine can markedly increase plasma fluorouracil levels. The combination may have increased activity in colorectal cancer.

Clinical evidence, mechanism, importance and management

A study in 6 patients with carcinoma given fluorouracil (15 mg/kg daily for 5 days, repeated every 4 weeks) found that **cimetidine** 1 g daily for 4 weeks increased the AUC and peak plasma levels of fluorouracil by 72% and 74%, respectively, when fluorouracil was given orally. When fluorouracil was given intravenously, **cimetidine** increased its AUC by 27% and reduced its total body clearance by 28%. In this small group, no increased toxicity was noted. The pharmacokinetics of fluorouracil were unaltered when **cimetidine** was given for only one week.[1] **Cimetidine** had similar effects in *animal* studies but **ranitidine** had no effect on fluorouracil metabolism.[2] It is suggested that **cimetidine** reduces the hepatic metabolism of fluorouracil.[1,2] At least three clinical studies have shown some treatment benefits from giving fluorouracil with long-term **cimetidine** in colorectal cancer.[3-5] However, this benefit has been attributed to immunomodulation[3] or inhibition of adhesion,[4] rather than any pharmacokinetic interaction. Whatever the mechanism, it appears that **cimetidine** can increase the activity of fluorouracil. Concurrent treatment should be undertaken with care. **Cimetidine** can be obtained without a prescription in some countries, therefore patients may unwittingly increase the toxicity of fluorouracil. **Ranitidine** does not appear to interact.

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2. Dilloway MR, Lant AF. Effect of H_2-receptor antagonists on the pharmacokinetics of 5-fluorouracil in the rat and monkey. *Biopharm Drug Dispos* (1991) 12, 17–28.
3. Links M, Clingan PR, Phadke K, O'Baugh J, Legge J, Adams WJ, Ross WB, Morris DL. A randomized trial of cimetidine with 5-fluorouracil and folinic acid in metastatic colorectal cancer. *Eur J Surg Oncol* (1995) 21, 523–5.
4. Matsumoto S, Imaeda Y, Umemoto S, Kobayashi K, Suzuki H, Okamoto T. Cimetidine increases survival of colorectal cancer patients with high levels of sialyl Lewis-X and sialyl Lewis-A epitope expression on tumour cells. *Br J Cancer* (2002) 86, 159–60.
5. Yoshimatsu K, Ishibashi K, Hashimoto M, Umehara A, Yokomizo H, Yoshida K, Fujimoto T, Iwasaki K, Ogawa K. Effect of cimetidine with chemotherapy on stage IV colorectal cancer. *Gan To Kagaku Ryoho* (2003) 30, 1794–7.

Fluorouracil + Interferon alfa

Interferon alfa has increased plasma fluorouracil levels in some, but not other, studies.

Clinical evidence, mechanism, importance and management

In a pharmacokinetic study, 26 patients with colorectal cancer were given a 5-day continuous infusion of fluorouracil 750 mg/m^2 daily repeated in week 4 followed by a bolus intravenous injection of 750 mg/m^2 weekly with or without subcutaneous interferon alfa-2a (*Roferon*) 9 million units three times a week. There was considerable within-patient variation but no significant differences in steady-state plasma levels were found between the two groups.[1] Similarly, others have also reported that interferon alfa does not significantly alter fluorouracil pharmacokinetics;[2,3] however, other studies[4-8] have found a significant increase in the peak levels of fluorouracil and/or its AUC when interferon alfa is given. Despite promising early pre-clinical and clinical data indicating that interferon may improve the response to fluorouracil, this has not yet been demonstrated in randomised studies.[9]

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8. Schüller J, Czejka M. Pharmacokinetic interaction of 5-fluorouracil and interferon alpha-2b with or without folinic acid. *Med Oncol* (1995) 12, 47–53.
9. Makower D, Wadler S. Interferons as biomodulators of fluoropyrimidines in the treatment of colorectal cancer. *Semin Oncol* (1999) 26, 663–71.

Fluorouracil + Metronidazole

The toxicity, but not the efficacy of fluorouracil, is increased by metronidazole.

Clinical evidence

A marked increase in fluorouracil toxicity was noted in 27 patients with metastatic colorectal cancer when they were given intravenous metronidazole 750 mg/m^2 one hour before receiving intravenous fluorouracil 600 mg/m^2 five days per week, every 4 weeks. Granulocytopenia occurred in 74% of patients, nausea and vomiting in 48%, anaemia in 41%, stomatitis and oral ulceration in 34%, and thrombocytopenia in 19%.[1] A related pharmacokinetic study in 10 patients found that metronidazole reduced the clearance of fluorouracil by 27% over the 5-day period and increased the AUC by 34%. *In vitro* studies with human colon cancer cells did not show any increased efficacy.[1]

Studies using another nitroimidazole, **misonidazole**, in patients with colorectal cancer also found an increased incidence and severity of gastrointestinal toxicity with concurrent use,[2,3] a slightly increased incidence of leucopenia[2] and a reduction in the clearance of fluorouracil.[3]

Mechanism

Metronidazole reduces the clearance of fluorouracil, thereby increasing its toxic effects.

Importance and management

Information is limited but the interaction between fluorouracil and metronidazole appears to be established. It was hoped that metronidazole or misonidazole (no longer in clinical use) might increase the efficacy of fluorouracil. However, the studies above show that the toxicity of fluorouracil is increased without an obvious increase in its therapeutic efficacy. Care should be taken if metronidazole is required for its antimicrobial effects in a patient receiving fluorouracil. Whether other nitroimidazoles (e.g. tinidazole) behave similarly appears not to have been studied.

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2. Spooner D, Bugden RD, Peckham MJ, Wist EA. The combination of 5-fluorouracil with misonidazole in patients with advanced colorectal cancer. *Int J Radiat Oncol Biol Phys* (1982) 8, 387–9.
3. McDermott BJ, Van den Berg HW, Martin WMC, Murphy RF. Pharmacokinetic rationale for the interaction of 5-fluorouracil and misonidazole in humans. *Br J Cancer* (1983) 48, 705–10.

Fluorouracil + Miscellaneous

A retrospective analysis of studies in a total of 250 patients given fluorouracil for the treatment of gastrointestinal cancer found that chlorprothixene, cinnarizine, prochlorperazine, sodium pentobarbital, thiethylperazine, trimethobenzamide (in antiemetic doses) did not significantly increase toxicity or decrease therapeutic effects of fluorouracil, when compared with a placebo.[1]

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Fluorouracil prodrugs + Food

Food modestly to markedly reduces the AUC and plasma levels of capecitabine, but has a minor to modest effect on the pharmacokinetics of the active metabolites. Food markedly reduces the plasma levels and modestly reduces the AUC of fluorouracil derived from tegafur.

Clinical evidence, mechanism, importance and management

(a) Capecitabine

In a crossover study in 11 patients with colorectal cancer, oral capecitabine was given either after an overnight fast, or 30 minutes after breakfast. When normalised to a dose of capecitabine of 1255 mg/m^2, the time to reach maximum plasma levels was prolonged from 30 minutes to 2 hours when capecitabine was taken with food, and the maximum plasma level and AUC were reduced by 60% and 31%, respectively. The maximum plasma level and AUC of fluorouracil derived from capecitabine were reduced by 33% and 16%, respectively. The clinical relevance of these findings remains to be determined.[1] Note that, it is recommended that capecitabine is taken within 30 minutes after a meal,[1-3] because this is how it was used in clinical efficacy studies.[1]

(b) Tegafur with uracil

In a crossover study, 22 patients received a single 200-mg dose of *Uftoral* (tegafur with uracil) with a single 30-mg dose of folinic acid after an overnight fast, or 5 minutes after a high-fat breakfast. The maximum plasma level and AUC of fluorouracil derived from tegafur were reduced by 70% and 37%, respectively, when tegafur with uracil was given with food, and the time to maximum fluorouracil levels was delayed from 30 minutes to 2 hours.[4] This reduction is quite marked, and might result in reduced efficacy. It is recommended that tegafur with uracil is taken one hour before or one hour after meals,[5] as was the procedure in clinical efficacy studies.[4]

1. Reigner B, Verweij J, Dirix L, Cassidy J, Twelves C, Allman D, Weidekamm E, Roos B, Banken L, Utoh M, Osterwalder B. Effect of food on the pharmacokinetics of capecitabine and its metabolites following oral administration in cancer patients. *Clin Cancer Res* (1998) 4, 941–8.
2. Xeloda (Capecitabine). Roche Products Ltd. UK Summary of product characteristics, October 2008.
3. Xeloda (Capecitabine). Roche Laboratories Inc. US Prescribing information, April 2006.
4. Damle B, Ravandi F, Kaul S, Sonnichsen D, Ferreira I, Brooks D, Stewart D, Alberts D, Pazdur R. Effect of food on the oral bioavailability of UFT and leucovorin in cancer patients. *Clin Cancer Res* (2001) 7, 517–23.
5. Uftoral (Tegafur and uracil). Merck Serono. UK Summary of product characteristics, April 2009.

Fluorouracil prodrugs + Sorivudine

Marked and rapidly fatal toxicity, attributed to fluorouracil toxicity, has been seen in patients given tegafur or other fluorouracil prodrugs with sorivudine.

Clinical evidence

In 1993, the Japanese Ministry of Health reported that 15 Japanese patients with cancer and a viral disease died several days after being given a fluorouracil prodrug (e.g. **tegafur**) and sorivudine. Before death most of them developed severe toxicity including severe anorexia, marked damage to the bone marrow with decreases in white cell and platelet counts, and marked atrophy of the intestinal membrane, with diarrhoea and loss of blood. Eight other patients given both drugs developed symptoms of severe toxicity.[1,2]

Mechanism

Sorivudine appears to be converted in the gut to a metabolite (BVU or bromovinyluracil) that is a potent inhibitor of dihydropyrimidine dehydrogenase (DPD), an enzyme involved in the metabolism of fluorouracil (which is derived from tegafur and other fluorouracil prodrugs).[1,3] There is some evidence that DPD activity is genetically determined, and that there are poor fluorouracil metabolisers with low DPD activity, who would be expected to be more susceptible to this interaction.[4]

Importance and management

Information appears to be limited to these reports but the interaction appears to be established and of clinical importance. The concurrent use of inhibitors of dihydropyrimidine dehydrogenase (such as sorivudine and **brivudine**) with oral fluorouracil prodrugs such as **capecitabine**[5] and **tegafur**[6] is contraindicated. The manufacturers of tegafur with uracil suggest that it should not be given until 4 weeks after brivudine is stopped, to allow recovery of enzyme activity.[6] Note that sorivudine was withdrawn from the market following confirmation of this interaction.

1. Okuda H, Nishiyama T, Ogura K, Nagayama S, Ikeda K, Yamaguchi S, Nakamura Y, Kawaguchi Y, Watabe T. Lethal drug interactions of sorivudine, a new antiviral drug, with oral 5-fluorouracil prodrugs. *Drug Metab Dispos* (1997) 25, 270–3.
2. Diasio RB. Sorivudine and 5-fluorouracil; a clinically significant drug-drug interaction due to inhibition of dihydropyrimidine dehydrogenase. *Br J Clin Pharmacol* (1998) 46, 1–4.
3. Watabe T, Okuda H, Ogura K. Lethal drug interactions of the new antiviral, sorivudine, with anticancer prodrugs of 5-fluorouracil. *Yakugaku Zasshi* (1997) 117, 910–21. (In Japanese).
4. Watabe T, Ogura K, Nishiyama T. Molecular toxicological mechanism of the lethal interactions of the new antiviral drug, sorivudine, with 5-fluorouracil prodrugs and genetic deficiency of dihydropyrimidine dehydrogenase. *Yakugaku Zasshi* (2002) 122, 527–35.
5. Xeloda (Capecitabine). Roche Products Ltd. UK Summary of product characteristics, October 2008.
6. Uftoral (Tegafur and uracil). Merck Serono. UK Summary of product characteristics, April 2009.

Fluorouracil prodrugs + Taxanes

There are no clinically significant pharmacokinetic interactions between capecitabine and paclitaxel, and probably not between capecitabine and docetaxel. A case report describes hand-foot syndrome in a patient who received docetaxel two days after stopping tegafur with uracil.

Clinical evidence, mechanism, importance and management

(a) Capecitabine

1. Docetaxel. A study in patients with advanced solid tumours found that the use of capecitabine with docetaxel resulted in an almost twofold decrease in the maximum plasma concentration and AUC of fluorouracil. The authors suggest that more study is needed to assess the significance of this finding. Other pharmacokinetic parameters of capecitabine were not affected by docetaxel, and the pharmacokinetics of docetaxel were not significantly affected by capecitabine or its metabolites.[1]

Another study in similar patients also found that capecitabine did not alter the pharmacokinetics of docetaxel.[2] However, in a multiple regression analysis, the clearance of docetaxel appeared to be modestly increased in 32 patients who had received treatment with capecitabine and docetaxel when compared with 27 other patients who had received docetaxel alone,[3] but this was probably not clinically significant.

2. Paclitaxel. In a study in 17 patients, the concurrent use of paclitaxel and capecitabine did not significantly alter the pharmacokinetics of either drug.[4]

(b) Tegafur with uracil

A 30-year old patient received treatment with **docetaxel** 50 mg/m^2 two days after stopping tegafur with uracil, which she had been taking for the previous 14 months. Seven days later she developed hand-foot syndrome which increased to such an extent that she could not walk due to severe pain. A later subsequent dose of **docetaxel** did not result in hand-foot syndrome. Both fluoropyrimidines and taxanes have been associated with hand-foot syndrome. The authors suggested that a longer period of time is required between the two drugs to reduce the risk of this adverse effect occurring.[5] However, the combination of tegafur and docetaxel is being investigated, and other fluoropyrimidines are used with docetaxel in established regimens, suggesting that any additive interaction is rare.

1. Pronk LC, Vasey P, Sparreboom A, Reigner B, Planting AST, Gordon RJ, Osterwalder B, Verweij J. A phase I and pharmacokinetic study of the combination of capecitabine and docetaxel in patients with advanced solid tumours. *Br J Cancer* (2000) 83, 22–9.
2. Ramanathan RK, Ramalingam S, Egorin MJ, Belani P, Potter DM, Fakih M, Jung LL, Strychor S, Jacobs SA, Friedland DM, Shin DM, Chatta GS, Tutchko S, Zamboni WC. Phase I study of weekly (day 1 and 8) docetaxel in combination with capecitabine in patients with advanced solid malignancies. *Cancer Chemother Pharmacol* (2005) 55, 354–60.
3. Rudek MA, Sparreboom A, Garrett-Mayer ES, Armstrong DK, Wolff AC, Verweij J, Baker SD. Factors affecting pharmacokinetic variability following doxorubicin and docetaxel-based therapy. *Eur J Cancer* (2004) 40, 1170–8.
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5. Kanaji N, Bandoh S. Hand-foot syndrome associated with uracil/tegafur and docetaxel in a patient with lung cancer. *Nihon Kokyuki Gakkai Zasshi* (2007) 45, 474–8.

Fluorouracil prodrugs; Capecitabine + Allopurinol

The activity of capecitabine is predicted to be decreased by allopurinol.

Clinical evidence, mechanism, importance and management

Capecitabine is a prodrug, which is activated by several enzymatic steps to produce active fluorouracil within the body. Because allopurinol is reported to modulate fluorouracil, with possible decreased efficacy (although note an adverse effect is not established, see 'Fluorouracil + Allopurinol', p.727), the UK manufacturers of capecitabine say that the concurrent use of allopurinol should be avoided.[1]

1. Xeloda (Capecitabine). Roche Products Ltd. UK Summary of product characteristics, October 2008.

Fluorouracil prodrugs; Capecitabine + Antacids

The absorption of capecitabine was not affected by an aluminium/magnesium hydroxide antacid.

Clinical evidence, mechanism, importance and management

A study in 12 patients found that 20 mL of an **aluminium/magnesium hydroxide** antacid (*Maalox*) caused a small increase in the plasma levels of a single 1250-mg/m^2 oral dose of capecitabine and one metabolite (5′-DFCR) but it had no effect on the other 3 major metabolites (5′-DFUR, 5-FU and FBAL).[1] There would therefore seem to be no reason for taking special precautions if capecitabine and an antacid of this type are used concurrently.

1. Reigner B, Clive S, Cassidy J, Jodrell D, Schulz R, Goggin T, Banken L, Roos B, Utoh M, Mulligan T, Weidekamm E. Influence of the antacid Maalox on the pharmacokinetics of capecitabine in cancer patients. *Cancer Chemother Pharmacol* (1999) 43, 309–15.

Fluorouracil prodrugs; Capecitabine + Folinates

A patient died after treatment with capecitabine possibly because the concurrent use of folic acid enhanced capecitabine toxicity. The maximum tolerated dose of capecitabine is decreased by folinic acid.

Clinical evidence, mechanism, importance and management

(a) Folic acid

A 51-year-old woman with metastatic breast cancer started treatment with capecitabine 2500 mg/m^2 daily for 14 days every 21 days. Treatment was stopped after 8 days because she developed diarrhoea, vomiting and hand-foot syndrome. She improved with parenteral hydration and symptomatic treatment, but 3 weeks later still had diarrhoea, leg oedema and hand-foot syndrome. She was found to have been taking folic acid 15 mg daily for several weeks before starting capecitabine and had continued to take it during and after capecitabine treatment. The patient's condition improved when the folic acid was stopped, but she then developed diarrhoea and fever followed by necrotic colitis and she died from septic shock and vascular collapse. It is possible that the concurrent use of folic acid enhanced the toxicity of capecitabine.[1]

(b) Folinic acid

Studies in patients with refractory advanced cancer have found that folinic acid 30 mg twice daily does not have a major effect on the pharmacokinetics of capecitabine.[2] However, the pharmacodynamics of capecitabine were affected as determined by the more frequent occurrence of dose-limiting gastrointestinal disorders or hand-foot syndrome.[2] The UK manufacturers say that the maximum tolerated capecitabine dose when used alone in the intermittent regimen is 3 g/m^2, but this is reduced to 2 g/m^2 if folinic acid 30 mg twice daily is also given.[3]

1. Clippe C, Freyer G, Milano G, Trillet-Lenoir V. Lethal toxicity of capecitabine due to abusive folic acid prescription? *Clin Oncol* (2003) 15, 1–2.
2. Cassidy J, Dirix L, Bissett D, Reigner B, Griffin T, Allman D, Osterwalder B, Van Oosterom AT. A phase I study of capecitabine in combination with oral leucovorin in patients with intractable solid tumours. *Clin Cancer Res* (1998) 4, 2755–61.
3. Xeloda (Capecitabine). Roche Products Ltd. UK Summary of product characteristics, October 2008.

Fluorouracil prodrugs; Capecitabine + Miscellaneous

The maximum tolerated dose of capecitabine is decreased by interferon alfa. No pharmacokinetic interaction appears to occur between capecitabine and oxaliplatin.

Clinical evidence, mechanism, importance and management

(a) Interferon alfa

The UK manufacturer[1] says that the maximum tolerated capecitabine dose when used alone is 3 g/m^2, but when combined with interferon alfa-2a (3 million units/m^2 daily) the maximum tolerated dose is 2 g/m^2. Capecitabine is a prodrug of fluorouracil, the activity of which is thought to be modulated by interferon alfa. See also 'Fluorouracil + Interferon alfa', p.729.

(b) Oxaliplatin

The manufacturer notes there were no changes in the pharmacokinetics of capecitabine and its metabolites, or of platinum when capecitabine was given with oxaliplatin.[1]

1. Xeloda (Capecitabine). Roche Products Ltd. UK Summary of product characteristics, October 2008.

Fluorouracil prodrugs; Capecitabine + Vinorelbine

The concurrent use of vinorelbine and capecitabine does not appear to affect the pharmacokinetics of either drug.

Clinical evidence, mechanism, importance and management

A study in which 44 patients received escalating doses of oral capecitabine for 14 days every 3 or 4 weeks and vinorelbine weekly, or on days one and 8 of a 3- or 4-week cycle, found that the pharmacokinetics of vinorelbine were unaffected by capecitabine, when compared with historical data. The pharmacokinetics of capecitabine and its metabolites were highly variable, but were unchanged by the use of vinorelbine. Although the AUC of

fluorouracil was lower on day one, (when capecitabine was given with vinorelbine) than on day 7 (when capecitabine was given alone), this was expected after repeated dosing of capecitabine, and was not considered to have been affected by vinorelbine.[1] No pharmacokinetic drug interaction appears to occur.

1. Nolè F, Catania C, Sanna G, Imadalou K, Munzone E, Adamoli L, Longerey B, Blanchot G, Goldhirsch A. Dose-finding and pharmacokinetic study of an all-oral combination regimen of oral vinorelbine and capecitabine for patients with metastatic breast cancer. *Ann Oncol* (2006) 19, 322–9.

Fluorouracil prodrugs; Tegafur + Miscellaneous

Tegafur is partially metabolised by CYP2A6, and the manufacturer advises caution with CYP2A6 inhibitors (e.g. tranylcypromine and methoxsalen).

Clinical evidence, mechanism, importance and management

In vitro studies indicate that tegafur is partially metabolised by the cytochrome P450 isoenzyme CYP2A6.[1,2] In one report, a patient who was a CYP2A6 poor metaboliser (that is lacking in this isoenzyme) had fourfold higher levels of tegafur than other patients.[3] Therefore, it is possible that tegafur might not be as effective in patients such as this, or if it is given with drugs that are inhibitors of CYP2A6, because of reduced metabolism to active fluorouracil. In addition, the toxicity profile might be different. However, tegafur is also metabolised to fluorouracil by cytosolic thymidine phosphorylase and some other isoenzymes (e.g. CYP1A2 and CYP2C8), so it is likely that fluorouracil can still be produced in the absence of CYP2A6.[1,4] Nevertheless, the manufacturer advises that tegafur should not be used in patients with a known deficiency of hepatic CYP2A6,[1] although note that they do not advise testing for this, and a patient's P450 phenotype is rarely known outside of the clinical research situation. The manufacturer also advises caution if tegafur is given with other drugs that are substrates or inhibitors of CYP2A6. They specifically name **coumarin**, **methoxsalen** and the azole antifungals **clotrimazole**, **ketoconazole**, and **miconazole**.[1] The clinical relevance of any of these interactions and of CYP2A6 metaboliser status remains to be determined. However, note that important pharmacokinetic interactions do not usually occur between two drugs that are just substrates for the same isoenzyme, and so no interaction would be expected with **coumarin**. Moreover, **ketoconazole** did not inhibit the formation of fluorouracil from tegafur *in vitro*,[2] and is therefore unlikely to do so clinically. **Methoxsalen** is an inhibitor of CYP2A6,[5] and so might theoretically interact with tegafur, but as it has a specialist use in phototherapy it is unlikely to be used with tegafur. Another CYP2A6 inhibitor is the MAOI, **tranylcypromine**.

1. Uftoral (Tegafur and uracil). Merck Serono. UK Summary of product characteristics, April 2009.

2. Komatsu T, Yamazaki H, Shimada N, Nakajima M, Yokoi T. Roles of cytochromes P450 1A2, 2A6, and 2C8 in 5-fluorouracil formation from tegafur, an anticancer prodrug, in human liver microsomes. *Drug Metab Dispos* (2000) 28, 1457–63.

3. Daigo S, Takahashi Y, Fujieda M, Ariyoshi N, Yamazaki H, Koizumi W, Tanabe S, Saigenji K, Nagayama S, Ikeda K, Nishioka Y, Kamataki T. A novel mutant allele of the CYP2A6 gene (CYP2A6*11) found in a cancer patient who showed poor metabolic phenotype towards tegafur. *Pharmacogenetics* (2002) 12, 299–306.

4. Komatsu T, Yamazaki H, Shimada N, Nagayama S, Kawaguchi Y, Nakajima M, Yokoi T. Involvement of microsomal cytochrome P450 and cytosolic thymidine phosphorylase in 5-fluorouracil formation from tegafur in human liver. *Clin Cancer Res* (2001) 7, 675–81.

5. Kharasch ED, Hankins DC, Taraday JK. Single-dose methoxsalen effects on human cytochrome P-450 2A6 activity. *Drug Metab Dispos* (2000) 28, 28–33.

Fulvestrant + Miscellaneous

The pharmacokinetics of intravenous fulvestrant were not affected by rifampicin (rifampin), an inducer of the cytochrome P450 isoenzyme CYP3A4, or ketoconazole, an inhibitor of CYP3A4. In addition, intramuscular fulvestrant did not affect the pharmacokinetics of midazolam, a substrate of CYP3A4. It is therefore unlikely that fulvestrant will be affected by drug interactions involving this isoenzyme.[1]

1. Robertson JFR, Harrison M. Fulvestrant: pharmacokinetics and pharmacology. *Br J Cancer* (2004) 90 (Suppl. 1), S7–S10.

Gefitinib + Miscellaneous

The pharmacokinetics of gefitinib are affected by the concurrent use of drugs that induce (e.g. rifampicin) or inhibit (e.g. itraconazole) CYP3A4. Inhibitors of CYP2D6 may increase levels of gefitinib. Based on data with metoprolol, gefitinib is not expected to affect the pharmacokinetics of drugs that are metabolised by CYP2D6. The concurrent use of cisplatin, carboplatin or paclitaxel with gefitinib did not affect the pharmacokinetics of either drug. High-dose gefitinib slightly increased the exposure to gemcitabine. Anastrozole and tamoxifen do not alter gefitinib levels.

Clinical evidence, mechanism, importance and management

(a) Anastrozole

In a study in which 53 patients received gefitinib alone or with anastrozole, the authors briefly mention that the pharmacokinetics of gefitinib were not affected by anastrozole. The addition of anastrozole did not exacerbate the adverse effects of gefitinib.[1]

A case report describes an increase in liver transaminases in a woman given gefitinib and anastrozole, which resolved when gefitinib was stopped and recurred on rechallenge. However, the authors concluded that this was likely to be an adverse effect of gefitinib, and not due to a pharmacokinetic drug interaction with anastrozole.[2] Note that, although anastrozole weakly inhibited the cytochrome P450 isoenzyme CYP3A4 *in vitro*, (gefitinib is a CYP3A4 substrate), this was not considered likely to be important at clinically attainable levels.[3]

(b) Carboplatin and Paclitaxel

In 24 patients with advanced non-small cell lung cancer there was no change in the pharmacokinetics of carboplatin or paclitaxel when gefitinib 250 or 500 mg daily was also given. There was a slight increase in exposure to gefitinib, but no increase in toxicity was noted.[4]

(c) Cisplatin and Gemcitabine

Eighteen patients were given gemcitabine 1250 mg/m^2 on day one and 8 of a 21-day cycle, with cisplatin 80 mg/m^2 on day one, and gefitinib 250 mg or 500 mg daily. The pharmacokinetics of gefitinib were unchanged by the combination chemotherapy, and cisplatin pharmacokinetics were not affected by gefitinib. However, the exposure to gemcitabine was slightly increased when gefitinib was also given (day 8) at only the 500 mg dose, when compared with gemcitabine with cisplatin or with both cisplatin and gefitinib.[4]

(d) CYP2D6 inhibitors

The manufacturer predicts that potent inhibitors of the cytochrome P450 isoenzyme CYP2D6 may increase gefitinib levels. They advise that patients should be closely monitored for adverse effects. Note that, *in vitro* studies have shown that gefitinib is metabolised to its major metabolite by CYP2D6, and that exposure to gefitinib was twofold higher in CYP2D6 poor metabolisers (that is, those lacking this isoenzyme) than in CYP2D6 extensive metabolisers (those with normal levels of this isoenzyme).[5]

(e) Itraconazole and other CYP3A4 inhibitors

In a randomised, crossover study, 48 healthy subjects were given gefitinib 250 mg or 500 mg, alone and on day 4 of a 12-day course of itraconazole 200 mg daily. Itraconazole increased the maximum plasma concentration of gefitinib 250 mg and 500 mg by 51% and 32%, respectively, and increased the AUC of these two doses by 78% and 61%, respectively.[6] Itraconazole is a potent inhibitor of the cytochrome P450 isoenzyme CYP3A4, by which gefitinib is partly metabolised. Concurrent use therefore raises gefitinib levels. It seems likely that other potent inhibitors of CYP3A4 will also increase the levels of gefitinib and might increase its toxicity.[5,7] The manufacturers specifically name the azoles **ketoconazole**, **posaconazole**, and **voriconazole**; the macrolides **clarithromycin** and **telithromycin**, and **protease inhibitors**.[5,7] Monitor patients carefully when taking CYP3A4 inhibitors with gefitinib. For a list of CYP3A4 inhibitors, see 'Table 1.4', (p.6).

(f) Metoprolol and other CYP2D6 substrates

In a study, 15 patients were given gefitinib 500 mg daily for 28 days, with a single 50-mg dose of metoprolol on day 15. The maximum plasma concentration of metoprolol was increased by about 10% by gefitinib. There was a 35% increase in the AUC of metoprolol, but this was not statistically

significant.[6]These changes are not clinically relevant, and it was suggested that gefitinib is unlikely to have a clinically relevant effect on the pharmacokinetics of CYP2D6 substrates. Nevertheless, the UK manufacturer warns that such an increase may be relevant for CYP2D6 substrates with a narrow therapeutic index and that a dose modification may be necessary;[5] this seems extremely cautious.

(g) Rifampicin (Rifampin) and other CYP3A4 inducers

In a study, 18 healthy subjects were given rifampicin 600 mg daily for 16 days, with a single 500-mg dose of gefitinib on day 10. Rifampicin reduced the maximum plasma concentration of gefitinib by 65%, and reduced its AUC by 83%, when compared with gefitinib alone.[6] The US manufacturer advises that, in the absence of severe adverse reactions, the usual daily dose of gefitinib should be increased to 500 mg daily in patients taking potent CYP3A4 inducers, such as rifampicin or **phenytoin**.[7] In contrast, the UK manufacturer states that inducers of CYP3A4 should be avoided. They additionally name **barbiturates**, **carbamazepine** and **St John's wort**.[5] For a list of CYP3A4 inducers, see 'Table 1.4', (p.6).

(h) Tamoxifen

In a study, 18 healthy male subjects were given tamoxifen 60 mg daily for 4 days then 20 mg daily for at least 10 days with a single 250-mg dose of gefitinib on day 14. The pharmacokinetics of gefitinib were not significantly altered by tamoxifen.[8]

1. Polychronis A, Sinnett HD, Hadjiminas D, Singhal H, Mansi JL, Shivapatham D, Shousha S, Jiang J, Peston D, Barrett N, Vigushin D, Morrison K, Beresford E, Ali S, Slade MJ, Coombes RC. Preoperative gefitinib versus gefitinib and anastrozole in postmenopausal patients with oestrogen-receptor positive and epidermal-growth-factor-receptor-positive primary breast cancer: a double-blind placebo-controlled phase II randomised trial. *Lancet Oncol* (2005) 6, 383–91.
2. Carlini P, Papaldo P, Fabi A, Felici A, Ruggeri EM, Milella M, Ciccarese M, Nuzzo C, Cognetti F, Ferretti G. Liver toxicity after treatment with gefitinib and anastrozole: drug-drug interactions through cytochrome p450? *J Clin Oncol* (2006) 24, e60–e61.
3. Grimm SW, Dyroff MC. Inhibition of human drug metabolizing cytochromes P450 by anastrozole, a potent and selective inhibitor of aromatase. *Drug Metab Dispos* (1997) 25, 598–602.
4. Hammond LA. Pharmacokinetic evaluation of gefitinib when administered with chemotherapy. *Clin Lung Cancer* (2003) 5 (Suppl. 1), S18–S21.
5. Iressa (Gefitinib). AstraZeneca UK Ltd. UK Summary of product characteristics, June 2009.
6. Swaisland HC, Ranson M, Smith RP, Leadbetter J, Laight A, McKillop D, Wild MJ. Pharmacokinetic drug interactions of gefitinib with rifampicin, itraconazole and metoprolol. *Clin Pharmacokinet* (2005) 44, 1067–81.
7. Iressa (Gefitinib). AstraZeneca. US Prescribing information, June 2005.
8. Cantarini MV, Macpherson MP, Marshall AL, Robinson AV, Bailey CJ. A phase I study to determine the effect of tamoxifen on the pharmacokinetics of a single 250 mg oral dose of gefitinib (IRESSA) in healthy male volunteers. *Cancer Chemother Pharmacol* (2005) 56, 557–62.

Gemcitabine + Anthracyclines

The concurrent use of gemcitabine and doxorubicin or epirubicin does not appear to affect the pharmacokinetics of either drug. An *in vitro* study found that the efficacy of the combination of gemcitabine and epirubicin may be schedule-dependent.

Clinical evidence, mechanism, importance and management

(a) Doxorubicin

The pharmacokinetics of gemcitabine did not differ when it was given immediately before doxorubicin, when compared with historical data of its use alone in patients with breast cancer.[1] Similarly the pharmacokinetics of gemcitabine were unchanged when it was given with paclitaxel the day after liposomal doxorubicin, when compared with historical data.[2] Another study also found that when doxorubicin was given immediately before gemcitabine on day one, the pharmacokinetics of gemcitabine were unaltered, when compared with gemcitabine alone on day 8. However, the activation of gemcitabine to its phosphorylated forms in peripheral blood mononuclear cells was reduced by doxorubicin. As the combination was poorly tolerated and no more effective than doxorubicin alone, the authors suggested that this sequence of dosing should not be further investigated in sarcomas.[3]

(b) Epirubicin

Gemcitabine pharmacokinetics were unchanged by the concurrent use of epirubicin and paclitaxel in patients with breast cancer,[4] and gemcitabine did not alter the interaction between epirubicin and paclitaxel (see 'Anthracyclines + Taxanes', p.698).

An *in vitro* study using human bladder cancer cells found that both gemcitabine and epirubicin alone exerted a cytotoxic effect but the efficacy of the combination of epirubicin and gemcitabine depended on the schedule used. When the drugs were given concurrently or if gemcitabine was given before epirubicin, there was an antagonistic interaction. There was synergistic cytotoxic activity when epirubicin was used before gemcitabine. This schedule is being investigated in clinical studies.[5]

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Gemcitabine + Cisplatin and other platinum compounds

The toxicity and pharmacokinetics of gemcitabine combined with platinum drugs such as cisplatin is dependent upon the order in which they are given.

Clinical evidence, mechanism, importance and management

(a) Carboplatin

Gemcitabine 1 g/m^2 on days one, 8, and 15 has been given with carboplatin (maximum tolerated dose, giving an AUC of 5.2 mg/mL per minute) on day one, in a monthly cycle. No difference was detected in toxicity or tolerated dose when the gemcitabine was given before or after the carboplatin.[1] However, subsequent authors reported that this same dose schedule, with carboplatin given immediately after the gemcitabine, caused unexpected and severe thrombocytopenia, and could not be recommended.[2] Nevertheless, in clinical use,[3] it is recommended that carboplatin is given after gemcitabine 1 g/m^2.

(b) Cisplatin

When gemcitabine was given 4 hours before or after cisplatin there were no major differences in the plasma pharmacokinetics of gemcitabine, deaminated gemcitabine and platinum. Similarly, cisplatin given 24 hours before gemcitabine did not significantly change gemcitabine and deaminated gemcitabine levels, although there was a trend towards an increased AUC of gemcitabine triphosphate.[4] Gemcitabine given 24 hours before cisplatin decreased the platinum AUC twofold,[4] and caused the least leucopenia of the schedules.[5] Anaemia, thrombocytopenia, nausea and vomiting, and fatigue were not sequence dependent.[5] On the basis of these findings, the authors further evaluated the schedule of cisplatin given 24 hours before gemcitabine but found no clear evidence for the best sequence of these drugs.[6] Note that the combination of cisplatin and gemcitabine is commonly used for the treatment of various cancers, usually with cisplatin given after gemcitabine on the same day.[3]

(c) Oxaliplatin

The pharmacokinetics of gemcitabine 800 to 1500 mg/m^2 and its main metabolite did not appear to be affected by oxaliplatin 70 to 100 mg/m^2 when oxaliplatin was given immediately after gemcitabine once every 2 weeks.[7] Similarly, in a study in 10 patients with advanced solid tumours,[8] the pharmacokinetics of gemcitabine did not differ when it was given immediately before oxaliplatin on day one and when it was given alone on day 8. Furthermore, in a study in which 10 patients received either gemcitabine followed 24 hours later by oxaliplatin, or the two drugs in the reverse order, the sequence of administration had no effect on the pharmacokinetics of either gemcitabine or oxaliplatin.[9]

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Gemcitabine + Taxanes

One study found that giving paclitaxel before gemcitabine increased gemcitabine levels, but other studies did not find a pharmacokinetic interaction. Gemcitabine distribution may be altered by docetaxel, but docetaxel pharmacokinetics are not affected by gemcitabine. The clinical response to the combination of gemcitabine and a taxane may depend on the sequence of administration.

Clinical evidence, mechanism, importance and management

(a) Docetaxel

In a study of gemcitabine and docetaxel, given on days one and 8 of a 21 day cycle, drug toxicity and pharmacokinetics were unaffected by the relative order of their administration.[1] However, in another study, it appeared that while docetaxel pharmacokinetics were unaffected, the distribution of gemcitabine was altered by docetaxel, although there was no clear relationship between this and toxicity.[2]

A favourable response rate of 43% was reported in a study in which 35 patients with sarcomas were given gemcitabine 675 mg/m^2 over 90 minutes on days one and 8, followed by docetaxel 100 mg/m^2, given over 60 minutes, on day 8. The possible synergistic antitumour effect may have been secondary to both the prolonged gemcitabine infusion and the sequence of drug administration.[3] More study is needed.

(b) Paclitaxel

A study in 18 patients with non small cell lung cancer found that when they were given gemcitabine 1000 mg/m^2 on days one and 8 and paclitaxel 150 to 200 mg/m^2 on day one as a 3-hour infusion immediately before the gemcitabine, the plasma levels of gemcitabine and the AUC of its deaminated metabolite were unchanged, as was the AUC of paclitaxel. However, paclitaxel increased gemcitabine triphosphate levels, potentially improving efficacy.[4] In a study in 14 patients with non small cell lung cancer, gemcitabine 800 mg/m^2 was given on days one and 8 of a 21-day cycle and paclitaxel 110 mg/m^2 was given 3 hours before the second dose of gemcitabine on day 8. When paclitaxel was given first the clearance, volume of distribution and interpatient pharmacokinetic variability of gemcitabine were decreased. Plasma levels of gemcitabine were increased by 25%, but there was no correlation between these changes and toxicity, and the clinical significance of the interaction is uncertain.[5] In another study, no pharmacokinetic interactions were detected between gemcitabine and paclitaxel given weekly, although gemcitabine showed saturation kinetics at higher doses.[6,7] Another study in patients with advanced breast cancer given gemcitabine, epirubicin and paclitaxel also found no pharmacokinetic interaction between gemcitabine and paclitaxel:[8] a similar lack of pharmacokinetic interaction was found in a further study in patients receiving liposomal doxorubicin, gemcitabine and paclitaxel.[9]

The high overall response rate of 71% in a phase II study[10] in patients with advanced breast cancer given gemcitabine and paclitaxel, prompted an *in vitro* study,[11] which found that giving paclitaxel followed by gemcitabine resulted in synergistic cytotoxic activity, whereas gemcitabine followed by paclitaxel had antagonistic activity. Phase III studies are being carried out to further evaluate the effects of order of administration of these drugs in patients with metastatic breast cancer.[12] As of 2009, paclitaxel is given before gemcitabine, with both drugs given on the same day.[13,14]

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Hydroxycarbamide + Interferon alfa

When hydroxycarbamide is used with interferon alfa, the risk of vasculitis might be increased.

Clinical evidence, mechanism, importance and management

Hydroxycarbamide alone has been associated with cutaneous vasculitic ulceration and gangrene, and interferons alone have also been associated with vasculitis. In one review of serious vasculopathic adverse effects associated with interferon alfa in 13 patients, 5 patients were also taking hydroxycarbamide, 4 of whom had digital ulcerations and gangrene, and one of whom had pulmonary vasculitis. Most cases improved on stopping interferon alfa and adding immunosuppressants. The authors considered that the distribution of the ulcers was different from that seen with hydroxycarbamide alone. They say that whether the use of hydroxycarbamide, concurrently or use at any time, can potentiate these vascular events is a matter of debate.[1] Nevertheless, the manufacturer of hydroxycarbamide notes that the risk of cutaneous vasculitis may be increased when interferon is given with or before hydroxycarbamide,[2,3] and one UK manufacturer of interferon alfa also includes a similar warning.[4] Bear this possibility in mind. Hydroxycarbamide should be stopped if cutaneous vasculitic ulcers occur.[2,3]

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3. Hydrea (Hydroxyurea). Bristol-Myers Squibb Company. US Prescribing information, December 2006.
4. IntronA (Interferon alfa-2b). Schering-Plough Ltd. UK Summary of product characteristics, March 2009.

Imatinib + Antineoplastics

Data from *animal* studies suggest that imatinib markedly increases etoposide levels and modestly increases ifosfamide levels. The use of imatinib with asparaginase might be associated with increased hepatotoxicity.

Clinical evidence, mechanism, importance and management

(a) Asparaginase

The UK manufacturer states that the concurrent use of imatinib with asparaginase could be associated with increased hepatotoxicity. They therefore recommend caution with concurrent use.[1]

(b) Etoposide and Ifosfamide

In a study in *mice*, a fivefold increase in the maximum plasma levels of etoposide and a 60% increase in the maximum plasma level of ifosfamide occurred when they were given by intraperitoneal injection with imatinib, compared with when they were given alone. In a further study, there was a 3.4-fold increase in the $AUC_{0\text{-}3}$ of etoposide when it was given with imatinib. In yet another study, the AUC of etoposide was increased by 92% and its clearance reduced by about 50% when it was given with imatinib. In a lymphoma model, an increased antitumour effect was observed with the combination, but this was not seen in a small cell lung cancer model.[2]

Imatinib is an inhibitor of the cytochrome P450 isoenzyme CYP3A4, and it seems likely that it increased the levels of etoposide and ifosfamide, which are metabolised by this isoenzyme, by this mechanism.

Although these data are from *animals*, and therefore preliminary, they suggest that caution is necessary if imatinib were used, particularly with etoposide, and possibly with ifosfamide.

1. Glivec (Imatinib mesilate). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, April 2009.
2. Rezaï K, Lokiec F, Grandjean I, Weill S, de Cremoux P, Bordier V, Ekue R, Garcia M, Poupon M-F, Decaudin D. Impact of imatinib on the pharmacokinetics and *in vivo* efficacy of etoposide and/or ifosfamide. *BMC Pharmacol* (2007) 7, 13.

Imatinib + CYP3A4 inducers

Rifampicin (rifampin) and enzyme-inducing antiepileptics (e.g. carbamazepine, phenobarbital) markedly lower serum imatinib levels, and St John's wort (*Hypericum perforatum*) modestly lowers imatinib levels; other CYP3A4 inducers are predicted to do the same.

Clinical evidence

(a) Enzyme-inducing antiepileptics

The manufacturer reports that, in a study in patients with malignant gliomas, the AUC of imatinib was 73% lower in patients taking enzyme-inducing antiepileptics (such as **carbamazepine**, **oxcarbazepine** and **phenytoin**) than in patients not taking these drugs.[1]

(b) Rifampicin (Rifampin)

In a study in healthy subjects, rifampicin 600 mg daily for 11 days decreased the maximum serum levels and AUC of a 400-mg dose of imatinib given on day 8 by 54% and 74%, respectively.[2]

(c) St John's wort (Hypericum perforatum)

In a study in 12 healthy subjects, the pharmacokinetics of a single dose of imatinib was determined before and on day 12 of two weeks of treatment with St John's wort (*Hypericum perforatum*) extract (Kira [LI 160], Lichtwer Pharma) 300 mg three times daily. The AUC and maximum plasma level of imatinib was decreased by 30% and 15%, respectively. Imatinib clearance was increased by 43% and its half-life was decreased from 12.8 hours to 9 hours.[3] Similar results were found in another study.[4]

Mechanism

Rifampicin is a known potent inducer of many cytochrome P450 isoenzymes, including CYP3A4, by which imatinib is metabolised. Therefore rifampicin increases imatinib metabolism and decreases its levels. Enzyme-inducing antiepileptics interact similarly. St John's wort induces intestinal CYP3A4 and it therefore also modestly reduces imatinib levels.

Importance and management

Subtherapeutic levels of imatinib may occur if rifampicin or the enzyme-inducing antiepileptics [**carbamazepine**, **phenobarbital** (and therefore **primidone**), **phenytoin** (and therefore **fosphenytoin**)], are given. The manufacturers therefore reasonably recommend caution, and suggest that concurrent use with potent enzyme-inducing drugs should be avoided.[1,5] They also name **dexamethasone**,[1,5] and **rifabutin**,[5] (but note that, clinically, these drugs generally appear to have weak effects on this isoenzyme). If concurrent use cannot be avoided, it would be prudent to monitor the outcome, and increase the imatinib dose as necessary. An increase of at least 50% has been suggested by the US manufacturer.[5]

St John's wort has smaller effects, but they may be sufficient to impair the effects of imatinib, and are more likely to be variable, and it has therefore been suggested that concurrent use should also be avoided.[1,3]

1. Glivec (Imatinib mesilate). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, April 2009.
2. Bolton AE, Peng B, Hubert M, Krebs-Brown A, Capdeville R, Keller U, Seiberling M. Effect of rifampicin on the pharmacokinetics of imatinib mesylate (Gleevec, STI571) in healthy subjects. *Cancer Chemother Pharmacol* (2004) 53, 102–6.
3. Frye RF, Fitzgerald SM, Lagattuta TF, Hruska MW, Egorin MJ. Effect of St John's wort on imatinib mesylate pharmacokinetics. *Clin Pharmacol Ther* (2004) 76, 323–9.
4. Smith P. The influence of St John's wort on the pharmacokinetics and protein binding of imatinib mesylate. *Pharmacotherapy* (2004) 24, 1508–14.
5. Gleevec (Imatinib mesylate). Novartis Pharmaceuticals Corporation. US Prescribing information, May 2009.

Imatinib + CYP3A4 inhibitors

Single-dose ketoconazole modestly raised single-dose imatinib levels; however, ritonavir (given for three days) had little effect on imatinib levels at steady-state. There is a case report of an adverse skin reaction attributed to a pharmacokinetic interaction between voriconazole and imatinib.

Clinical evidence

(a) Ketoconazole

In a single-dose study in 14 healthy subjects, the maximum serum levels and AUC of imatinib rose by 26% and 40%, respectively, when ketoconazole 400 mg was given at the same time as imatinib 200 mg.[1]

(b) Ritonavir

In a study, 11 patients who had been taking imatinib 400 to 800 mg daily for at least 2 month were also given ritonavir 600 mg daily for 3 days, with a 50% reduction in the imatinib dose. Unexpectedly, the dose-normalised pharmacokinetics of imatinib were unaltered by ritonavir. However, the AUC of the active metabolite of imatinib was increased by about 40%.[2]

(c) Voriconazole

A patient with chronic myeloid leukaemia developed a pustular eruption while taking imatinib 800 mg daily, 12 weeks after starting to take voriconazole for pulmonary aspergillosis. His imatinib plasma levels were about twice the predicted levels while taking both drugs. His condition improved within 3 weeks of stopping both voriconazole and imatinib, and did not recur with the use of voriconazole alone.[3]

Mechanism

Ketoconazole, voriconazole, and ritonavir are potent inhibitors of the cytochrome P450 isoenzyme CYP3A4, which is involved in the metabolism of imatinib. The single-dose study with ketoconazole appears to confirm that CYP3A4 inhibitors increase imatinib levels. However, the multiple-dose study with ritonavir did not find this. This might be because imatinib is also a CYP3A4 inhibitor, so at steady-state it is less affected by other CYP3A4 inhibitors. However, it could also be due to specific effects of ritonavir, which can act as a CYP3A4 inducer. Further studies are needed. Adverse skin reactions occur frequently with imatinib and may be associated with high doses of imatinib and/or increased levels due to an interaction with CYP3A4 inhibitors, such as voriconazole.[3]

Importance and management

The pharmacokinetic interaction has not been fully established. The single-dose study with ketoconazole suggests a moderate increase in single-dose imatinib levels, which could possibly be greater with multiple-dose ketoconazole. However, the ritonavir study shows minimal effect on imatinib at steady-state. Further studies are needed to assess the extent and clinical relevance of these pharmacokinetic interactions at steady-state. At present, the manufacturers advise caution with ketoconazole and with other CYP3A4 inhibitors (examples listed are **atazanavir**, **clarithromycin**, **erythromycin**, **indinavir**, **itraconazole**, **nefazodone**, **nelfinavir**, **ritonavir**, **saquinavir**, **telithromycin** and **voriconazole**),[4,5] and the US manufacturer advises avoidance of **grapefruit juice**.[5] For a list of CYP3A4 inhibitors see 'Table 1.4', (p.6). The authors of the one case report suggest

monitoring plasma levels of imatinib to identify patients at risk of severe toxicity.[3]

1. Dutriex C, Peng B, Mehring G, Hayes M, Capdeville R, Porkony R, Seiberling M. Pharmacokinetic interaction between ketoconazole and imatinib mesylate (Glivec) in healthy subjects. *Cancer Chemother Pharmacol* (2004) 54, 290–4.
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3. Gambillara E, Laffitte E, Widmer N, Decosterd LA, Duchosal MA, Kovacsovics T, Panizzon RG. Severe pustular eruption associated with imatinib and voriconazole in a patient with chronic myeloid leukaemia. *Dermatology* (2005) 211, 363–5.
4. Glivec (Imatinib mesilate). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, April 2009.
5. Gleevec (Imatinib mesylate). Novartis Pharmaceuticals Corporation. US Prescribing information, May 2009.

Imatinib + Miscellaneous

In one case, adverse cutaneous drug reactions developed when lansoprazole was used with imatinib. In two cases, relapse during treatment with imatinib occurred in patients who also abused cocaine. One patient who took paracetamol with imatinib developed acute liver failure. Interactions are predicted to occur with warfarin. Imatinib is an inhibitor of CYP3A4, and caution is recommended with CYP3A4 substrates that have a narrow therapeutic window.

Clinical evidence, mechanism, importance and management

(a) Cocaine

Two patients with chronic myeloid leukaemia took imatinib and achieved a complete haematological response after 3 and 7 weeks, but then relapsed after 12 and 14 weeks and also experienced more severe imatinib adverse effects. Both patients had started to abuse cocaine 2 to 4 weeks before they relapsed. It was suggested that cocaine might have interfered with imatinib metabolism; however, the mechanism for this possible interaction is unclear.[1]

(b) CYP3A4 substrates

Imatinib is an inhibitor of the cytochrome P450 isoenzyme CYP3A4, as shown by the fact that it raises 'simvastatin', (p.1337), levels. The manufacturers of imatinib therefore predict that it may raise the levels of other CYP3A4 substrates and they mention **triazolo-benzodiazepines** (e.g. **triazolam**, **midazolam**)[2,3] and dihydropyridine calcium-channel blockers. They specifically advise caution with CYP3A4 substrates that have a narrow therapeutic index,[2,3] and name, **alfentanil**, **di[hydro]ergotamine**, **ergotamine**, **fentanyl**, **pimozide**, **quinidine** and some immunosuppressants [this would be expected to include ciclosporin and tacrolimus].[3] The clinical relevance of these interactions is not known, but caution would be appropriate.

(c) Lansoprazole

A patient with a recurrence of a gastrointestinal stromal tumour was given imatinib 400 mg daily without adverse effect. However, after 2 months, lansoprazole 15 mg daily was also given for dyspepsia and the patient developed bilateral eyelid oedema with hyperaemic conjunctivae and labial oedema. Both drugs were stopped, but on reintroduction the symptoms reappeared and she developed Stevens-Johnson syndrome. Both drugs were again stopped and she recovered after treatment with methylprednisolone and desloratadine for one month. Two months later, she took a single dose of lansoprazole on the day before taking imatinib 300 mg daily (with prednisone and desloratadine). One day later she developed eyelid and labial oedema and a generalised rash. She recovered after imatinib was stopped.[4]

Although the adverse effects could be attributed to either imatinib or lansoprazole alone, the authors suggested it was possible that the effects may have been the result of an interaction in which the levels of imatinib were increased by lansoprazole, which they said is a weak inhibitor of CYP3A4.[4] However, CYP3A4 inhibition was based on *in vitro* data, which indicated that clinically relevant CYP3A4 inhibition is unlikely. This has been borne out by the fact that lansoprazole has not caused interactions with CYP3A4 substrates in clinical use. Therefore, this mechanism seems unlikely.

(d) Paracetamol (Acetaminophen)

During clinical studies one patient regularly taking paracetamol for fever, died of acute liver failure 11 days after starting to take imatinib.[5] The manufacturers report that imatinib inhibits paracetamol *O*-glucuronidation *in vitro*. Although this potential interaction has not been studied in humans, the manufacturers recommend caution during concurrent use, especially with high doses of paracetamol.[2,3]

(e) Warfarin

The manufacturers say that patients needing anticoagulation should be given low-molecular-weight or standard **heparin** instead of warfarin. This recommendation is based on an observation in one patient[6] and *in vitro* studies[2,3] that show that imatinib can inhibit the cytochrome P450 isoenzyme CYP2C9, by which warfarin is extensively metabolised. There seems to be no other evidence that a clinically relevant interaction is likely to occur. However, note that, from a disease perspective, when treating venous thromboembolic disease in patients with cancer, warfarin is generally inferior (higher risk of major bleeds and recurrent thrombosis) to low-molecular-weight heparins.[7]

1. Breccia M, Gentilini F, Alimena G. Cocaine abuse may influence the response to imatinib in CML patients. *Haematologica* (2007) 92, e41–e42.
2. Glivec (Imatinib mesilate). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, April 2009.
3. Gleevec (Imatinib mesylate). Novartis Pharmaceuticals Corporation. US Prescribing information, May 2009.
4. Severino G, Chillotti C, De Lisa R, Del Zompo M, Ardau R. Adverse reactions during imatinib and lansoprazole treatment in gastrointestinal stromal tumors. *Ann Pharmacother* (2005) 39, 162–4.
5. Talpaz M, Silver RT, Druker B, Paquette R, Goldman JM, Reese SF, Capdeville R. A phase II study of STI 571 in adult patients with Philadelphia chromosome positive chronic myeloid leukaemia in accelerated phase. *Blood* (2000) 96 (Suppl 1), 469a.
6. Novartis Pharmaceuticals UK Limited. Personal communication, December 2001.
7. Baglin TP, Keeling DM, Watson HG; British Committee for Standards in Haematology. Guidelines on oral anticoagulation (warfarin): third edition–2005 update. *Br J Haematol* (2006) 132, 277–85.

Irinotecan + Antiepileptics

In patients with malignant gliomas, enzyme-inducing antiepileptics (carbamazepine, phenobarbital, phenytoin) markedly increase the clearance of irinotecan and its active metabolite. A number of case reports support these suggestions. Limited evidence suggests that non-enzyme inducing antiepileptics (particularly gabapentin) might also be associated with modestly increased irinotecan clearance. One case report with valproate found hepatotoxicity and *decreased* active irinotecan metabolite levels.

Clinical evidence

(a) Enzyme-inducing antiepileptics

In a study in adult patients with malignant glioma, the clearance of irinotecan was 60% higher in 18 patients taking enzyme-inducing antiepileptics (**phenytoin**, **carbamazepine**, **phenobarbital**, or combinations) than in 22 patients who were not taking these drugs. The maximum tolerated dose of irinotecan in these patients was double that in those not receiving enzyme-inducing antiepileptics, but there was no relationship between the dose and the AUC of the active metabolite, SN-38.[1] In a similar study in paediatric patients, the clearance of irinotecan lactone was 49% higher and the AUC of the lactone forms of irinotecan and SN-38 were 27% and 51% lower, respectively, in 10 children taking enzyme-inducing antiepileptics than in 21 children not taking these antiepileptics.[2] The enzyme-inducing antiepileptics used were **phenytoin** alone in 6 children, **carbamazepine**, **oxcarbazepine** and **phenobarbital** in one child each, and **phenytoin** with **carbamazepine** in one child. In a subsequent study by these authors, increasing the dose of irinotecan increased the AUC of the active metabolite, SN-38, in 3 of 5 children taking stable doses of enzyme-inducing antiepileptics, but no increase was seen in 2 children, despite a three- to fourfold increase in the irinotecan dose.[3]

1. Carbamazepine. In a preliminary report of studies in patients with malignant glioma, the clearance of irinotecan was increased almost twofold in the presence of carbamazepine. The peak plasma levels and AUCs of irinotecan and SN-38 were significantly decreased.[1]

2. Phenobarbital. In a preliminary report of studies in patients with malignant glioma, the clearance of irinotecan was increased by about 70% in the presence of phenobarbital. The AUC and peak plasma levels of irinotecan and SN-38 were significantly decreased.[1]

In a phase I study in patients given ciclosporin and irinotecan, giving phenobarbital 90 mg daily for 2 weeks before irinotecan allowed a dose escalation of irinotecan from 75 mg/m^2 to 144 mg/m^2. Phenobarbital increased

irinotecan clearance by 27% and reduced the AUC of SN-38 by 75%, when compared to irinotecan pharmacokinetics in patients given irinotecan with ciclosporin. Further clinical studies are needed to assess the effects of phenobarbital on the antitumour response and toxicity of irinotecan.[4]

3. Phenytoin. A 14-year-old girl with glioblastoma was given irinotecan 20 to 60 mg/m^2 daily for 5 days on 2 consecutive weeks every 21 days for 2 cycles. During the first cycle she also received phenytoin 300 mg and dexamethasone 6 mg daily. Irinotecan clearance was increased 2.5-fold compared with that in other patients receiving irinotecan alone, and there was decreased exposure to the active metabolite of irinotecan, SN-38. The effect on clearance decreased slowly over 8 days after stopping phenytoin.[5] Another patient taking phenytoin and irinotecan was found to have much lower AUCs for irinotecan and SN-38, when compared with data from patients not taking phenytoin.[6] Similarly, a third patient had a three-fold increase in irinotecan clearance and about a 60% reduction in the AUCs of irinotecan and SN-38 after starting phenytoin.[7] In a preliminary report of studies in patients with malignant glioma, the clearance of irinotecan was increased about twofold in the presence of phenytoin. The peak plasma levels and AUCs of irinotecan and SN-38 were significantly decreased.[1]

(b) Non-enzyme-inducing antiepileptics

A preliminary report of studies in patients with malignant gliomas found that in patients also taking non-enzyme-inducing antiepileptics (**gabapentin**, **lamotrigine**, **levetiracetam**, **tiagabine**, **topiramate**, **valproate**, or **zonisamide**, mostly in combination) there was a small but statistically significant increase (about 40%) in irinotecan clearance when compared with patients not taking any antiepileptics. The authors said that this was especially so for **gabapentin**. They also noted that in the four patients taking **valproate** (also in combination with other non-enzyme-inducing antiepileptics), there was no difference in irinotecan clearance or the AUC of SN-38.[1]

1. Valproate. A patient who was taking sodium valproate 600 mg and received an irinotecan 600 mg infusion, experienced dose-limiting hepatotoxicity. During a subsequent, uneventful, course, the dose of irinotecan was reduced to 300 mg, and in further courses the valproate was discontinued and the irinotecan dose returned to 600 mg. Pharmacokinetic analysis found that during valproate treatment the AUC of SN-38, the active metabolite of irinotecan, was 42% lower, and there were no changes in the pharmacokinetics of the valproate.[8] Conversely, preclinical data from *rats*[9] found that sodium valproate increased the AUC of SN-38 because valproate inhibits its subsequent glucuronidation.[1]

Mechanism

Irinotecan (which is inactive) is metabolised to an inactive metabolite by the cytochrome P450 isoenzyme CYP3A. In addition, the active metabolite SN-38 (which is formed by carboxylesterases) is inactivated by glucuronidation (UGT1A1). Enzyme-inducing antiepileptics probably induce both of these routes of metabolism, leading to decreased exposure to the active metabolite.[6,9]

Conversely, *animal* data show that valproate inhibits glucuronidation and therefore is likely to increase the AUC of the active metabolite of irinotecan, SN-38,[9] although a decrease was seen in the one case report of this interaction.

Importance and management

An established interaction. The enzyme-inducing antiepileptics induce the metabolism of irinotecan and reduce the availability of its active metabolite, SN-38. Increasing the dose of irinotecan may not increase the exposure to SN-38. Further study is needed to establish the most appropriate dose of irinotecan to use in patients requiring treatment with these drugs. The manufacturers advise that their use with irinotecan should be avoided,[10,11] and that, where possible, non-enzyme-inducing drugs should be substituted at least 2 weeks before irinotecan is given.[11] This would seem prudent. Note that as **fosphenytoin** is metabolised to phenytoin, and **primidone** is metabolised to phenobarbital, similar advice should probably apply.

With valproate, the apparently conflicting information from the *animal* study, and the case study in a single patient is difficult to interpret. It would seem wise to monitor patients carefully for any signs of toxicity or treatment failure.

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2. Crews KR, Stewart CF, Jones-Wallace D, Thompson SJ, Houghton PJ, Heideman RL, Fouladi M, Bowers DC, Chintagumpala MM, Gajjar A. Altered irinotecan pharmacokinetics in pediatric high-grade glioma patients receiving enzyme-inducing anticonvulsant therapy. *Clin Cancer Res* (2002) 8, 2202–9.
3. Gajjar A, Chintagumpala MM, Bowers DC, Jones-Wallace D, Stewart CF, Crews KR. Effect of intrapatient dosage escalation of irinotecan on its pharmacokinetics in pediatric patients who have high grade gliomas and receive enzyme-inducing anticonvulsant therapy. *Cancer* (2003) 97 (Suppl), 2374–80.
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6. Mathijssen RHJ, Sparreboom A, Dumez J, van Oosterom AT, de Bruijn EA. Altered irinotecan metabolism in a patient receiving phenytoin. *Anticancer Drugs* (2002) 13, 139–40.
7. Murry DJ, Cherrick I, Salama V, Berg S, Bernstein M, Kuttesch N, Blaney SM. Influence of phenytoin on the disposition of irinotecan: a case report. *J Pediatr Hematol Oncol* (2002) 24, 130–3.
8. de Jong FA, van der Bol JM, Mathijssen RHJ, Loos WJ, Mathôt RAA, Kitzen JJEM, van den Bent MJ, Verweij J. Irinotecan chemotherapy during valproic acid treatment. Pharmacokinetic interaction and hepatotoxicity. *Cancer Biol Ther* (2007) 6, 1368–74.
9. Gupta E, Wang X, Ramirez J, Ratain MJ. Modulation of the glucuronidation of SN-38, the active metabolite of irinotecan, by valproic acid and phenobarbital. *Cancer Chemother Pharmacol* (1997) 39, 440–4.
10. Campto (Irinotecan hydrochloride trihydrate). Pfizer Ltd. UK Summary of product characteristics, May 2009.
11. Camptosar (Irinotecan hydrochloride). Pfizer Inc. US Prescribing information, July 2008.

Irinotecan + Azoles

Ketoconazole markedly increases the levels of the active metabolite of irinotecan. Other azoles may interact similarly.

Clinical evidence

A study in 7 patients found that ketoconazole 200 mg given one hour before and 23 hours after an infusion of irinotecan 100 mg/m^2 decreased the dose-normalised AUC of the inactive metabolite APC by 87% and increased the AUC of the active metabolite, SN-38, by 109%, when compared with irinotecan 350 mg/m^2 given alone. There was no difference in degree of myelosuppression despite the large reduction in the irinotecan dose.[1]

Mechanism

Ketoconazole is a potent inhibitor of the cytochrome P450 isoenzyme CYP3A4, which is involved in the metabolism of irinotecan (itself inactive) to its inactive metabolite APC. More irinotecan would therefore be available to be metabolised by carboxylesterases to the active moiety SN-38. Ketoconazole had no effect on the subsequent glucuronidation of SN-38.[1] Other azoles are, to varying degrees, inhibitors of CYP3A4, and would therefore be expected to interact similarly.

Importance and management

The pharmacokinetic interaction between ketoconazole and irinotecan is established, and likely to be clinically important. Excess toxicity (potentially fatal[1]) would be expected if the dose of irinotecan were not markedly reduced on concurrent use. The manufacturers of irinotecan recommend that the concurrent use of ketoconazole should be avoided.[2,3] The US manufacturers recommend stopping ketoconazole at least one week before starting irinotecan.[3] It is likely that other drugs that are potent inhibitors of CYP3A4, such as **itraconazole** and possibly some other azoles (see 'azole antifungals', (p.233)), will also affect the metabolism of irinotecan, and the UK manufacturer advises avoidance of all potent CYP3A4 inhibitors.[2]

1. Kehrer DFS, Mathijssen RHJ, Verweij J, de Bruijn P, Sparreboom A. Modulation of irinotecan metabolism by ketoconazole. *J Clin Oncol* (2002) 20, 3122–9.
2. Campto (Irinotecan hydrochloride trihydrate). Pfizer Ltd. UK Summary of product characteristics, May 2009.
3. Camptosar (Irinotecan hydrochloride). Pfizer Inc. US Prescribing information, July 2008.

Irinotecan + Cannabis

The pharmacokinetics of irinotecan are not altered by a herbal tea containing cannabis.

Clinical evidence

In a crossover study, 24 patients were given intravenous irinotecan 600 mg before and 12 days after starting a 15-day course of 200 mL daily of a herbal tea containing cannabis 1 g/L. This was prepared from medicinal-grade cannabis (*Cannabis sativa* L. Flos, Bedrocan®) containing the cannabinoids Δ^9-tetrahydrocannabinol 18% and cannabidiol 0.8%. The clearance and the AUC of irinotecan and its metabolites, SN-38 and SN-38G, were not significantly altered by the presence of cannabis.[1]

Mechanism

Irinotecan is metabolised by the cytochrome P450 isoenzyme CYP3A4, and this does not appear to be affected by oral cannabis.

Importance and management

This study suggests that cannabis taken orally will not affect the pharmacokinetics of irinotecan. No dose adjustments are likely to be needed if irinotecan is given with cannabis tea. It is not known if this applies to other drugs metabolised by CYP3A4, or to other preparations and routes of administration of cannabis.

1. Engels FK, de Jong FA, Sparreboom A, Mathot RA, Loos WJ, Kitzen JJEM, de Bruijn P, Verweij J, Mathijssen RHJ. Medicinal cannabis does not influence the clinical pharmacokinetics of irinotecan and docetaxel. *Oncologist* (2007) 12, 291–300.

Irinotecan + Celecoxib

Celecoxib slightly increased irinotecan clearance in one study, and decreased it in another.

Clinical evidence, mechanism, importance and management

In a phase I study in patients given docetaxel followed by irinotecan on days one and 8 of a 21-day cycle, the addition of celecoxib 400 mg twice daily started on day 2 appeared to slightly increase the clearance of irinotecan by 18% and decreased the AUC of its active metabolite, SN-38, by 22% (day one of the first cycle compared with day one of the second cycle). Docetaxel pharmacokinetics were unaffected.[1] Conversely, in a similar study in 4 patients given FOLFIRI (irinotecan, fluorouracil and folinic acid), the addition of continuous celecoxib 400 mg twice daily started on day 2 appeared to slightly decrease the clearance of irinotecan by 31% and of SN-38 by 18%.[2] The reason for these changes is unclear. The authors considered that the changes are probably not large enough to be of clinical significance.[1,2]

1. Argiris A, Kut V, Luong L, Avram MJ. Phase I and pharmacokinetic study of docetaxel, irinotecan, and celecoxib in patients with advanced non-small cell lung cancer. *Invest New Drugs* (2006) 24, 203–12.
2. Javle MM, Cao S, Durrani FA, Pendyala L, Lawrence DD, Smith PF, Creaven PJ, Noel DC, Iyer RV, Rustum YM. Celecoxib and mucosal protection: translation from an animal model to a phase I clinical trial of celecoxib, irinotecan, and 5-fluorouracil. *Clin Cancer Res* (2007) 13, 965–71.

Irinotecan + Ciclosporin

Ciclosporin reduces the clearance of irinotecan and increases the exposure of its active metabolite, SN-38, but ciclosporin appears to reduce irinotecan-induced gastrointestinal toxicity.

Clinical evidence

In a phase I study in patients with refractory solid tumours or lymphomas, ciclosporin 5 to 10 mg/kg was given as a 6-hour infusion beginning 3 hours before irinotecan (initial dose 25 mg/m^2 increased to 72 mg/m^2 weekly). Ciclosporin increased the AUC of SN-38 (the active metabolite of irinotecan) by 23 to 630% and reduced irinotecan clearance by 39 to 64%, when compared with historical controls.[1] Similar pharmacokinetic findings have been reported in further phase I and II studies using intravenous or oral ciclosporin, and these studies have generally found a reduction in the irinotecan-induced gastrointestinal toxicity (diarrhoea), when compared with historical controls.[2-4]

Mechanism

The effects of ciclosporin on irinotecan pharmacokinetics may be due to inhibition of irinotecan- and SN-38-related biliary transporters,[1,3] and this suggestion is supported by a study in *rats*.[5] It is suggested that this results in a reduction in the gastrointestinal toxicity of irinotecan.

Importance and management

Ciclosporin clearly alters the pharmacokinetics of irinotecan. In the studies described, ciclosporin was being used to try to improve the toxicity profile of irinotecan without affecting its efficacy. If this is confirmed, this will be of clinical benefit rather than an adverse drug interaction. However, bear this pharmacokinetic interaction in mind if irinotecan is used in a patient already taking ciclosporin for other reasons: in this situation, the toxicity profile and drug levels might be different from that expected.

1. Innocenti F, Undevia SD, Ramírez J, Mani S, Schilsky RL, Vogelzang NJ, Prado M, Ratain MJ. A phase I trial of pharmacologic modulation of irinotecan with cyclosporine and phenobarbital. *Clin Pharmacol Ther* (2004) 76, 490–502.
2. Desai AA, Kindler HL, Taber D, Agamah E, Mani S, Wade-Oliver K, Ratain MJ, Vokes EE. Modulation of irinotecan with cyclosporine: a phase II trial in advanced colorectal cancer. *Cancer Chemother Pharmacol* (2005) 56, 421–6.
3. Chester JD, Joel SP, Cheeseman SL, Hall GD, Braun MS, Perry J, Davis T, Button CJ, Seymour MT. Phase I and pharmacokinetic study of intravenous irinotecan plus oral ciclosporin in patients with fluorouracil-refractory metastatic colon cancer. *J Clin Oncol* (2003) 21, 1125–32.
4. Vasudev NS, Jagdev S, Anthoney DA, Seymour MT. Intravenous irinotecan plus oral ciclosporin. *Clin Oncol* (2005) 19, 646–9.
5. Gupta E, Safa AR, Wang X, Ratain MJ. Pharmacokinetic modulation of irinotecan and metabolites by cyclosporin A. *Cancer Res* (1996) 56, 1309–14.

Irinotecan + Dexamethasone

In one small study, dexamethasone did not appear to alter the pharmacokinetics of irinotecan or its active metabolite, SN-38.

Clinical evidence, mechanism, importance and management

In a study in paediatric patients with gliomas, there did not appear to be any differences in irinotecan pharmacokinetics (in the AUC of irinotecan and its active metabolite, SN-38, and in the clearance of irinotecan) between 17 patients receiving dexamethasone (1 to 16 mg daily) and 4 patients not receiving dexamethasone. None of these 21 patients were taking enzyme-inducing antiepileptics.[1] Although this study was small and non-randomised, it provides some reassurance that dexamethasone might not have an important effect on irinotecan pharmacokinetics.

1. Crews KR, Stewart CF, Jones-Wallace D, Thompson SJ, Houghton PJ, Heideman RL, Fouladi M, Bowers DC, Chintagumpala MM, Gajjar A. Altered irinotecan pharmacokinetics in pediatric high-grade glioma patients receiving enzyme-inducing anticonvulsant therapy. *Clin Cancer Res* (2002) 8, 2202–9.

Irinotecan + Fluorouracil

Some studies suggest that giving fluorouracil after irinotecan reduces the conversion of irinotecan to its active metabolite, whereas others have found no interaction.

Clinical evidence, mechanism, importance and management

A study in 33 patients with metastatic colorectal cancer found that the toxicity and pharmacokinetics of irinotecan given with fluorouracil depended upon the order of administration of the two drugs.[1] When irinotecan was given before fluorouracil, the AUC of the major active metabolite of irinotecan, SN-38, was about 40% lower, and toxicity was lower. In this study, patients were randomised to receive a 60-minute infusion of irinotecan (150 mg/m^2 starting dose, escalated by 50 mg/m^2 increments) immediately before or after a 48-hour infusion of fluorouracil 3500 mg/m^2 modulated by folinic acid in the first cycle, then given in the reverse sequence in the second cycle. Similarly, in a study using historical controls, the AUC of SN-38 was about 28% lower and the AUC of irinotecan about 35% higher when irinotecan was given over 90 minutes immediately before a 7-day fluorouracil infusion, compared with irinotecan alone.[2]

In contrast, a study found that fluorouracil did not substantially affect the metabolism of irinotecan to SN-38. The AUC of irinotecan and SN-38 did not differ between irinotecan alone, irinotecan immediately followed by folinic acid and fluorouracil, and irinotecan immediately after folinic acid and fluorouracil. In this study, irinotecan 100 to 150 mg/m^2 was given as

a 90-minute infusion, and fluorouracil 210 to 500 mg/m^2 by rapid intravenous injection.[3] Similarly, preliminary reports from another research group found that the clearance of irinotecan did not differ when it was given one day before or one day after 5 daily bolus doses of fluorouracil.[4,5]

From this information it is unclear whether or not fluorouracil alters the pharmacokinetics of irinotecan. A key difference between the main studies is the use of bolus[3] or continuous infusion[1] fluorouracil. The combination is in established clinical usage, where the recommendation is to give irinotecan before fluorouracil and folinic acid.[6,7] This combination has been shown to be more effective than fluorouracil and folinic acid alone.[6,7] Whether this is the optimal schedule remains to be determined.

1. Falcone A, Di Paolo A, Masi G, Allegrini G, Danesi R, Lencioni M, Pfanner E, Comis S, Del Tacca M, Conte P. Sequence effect of irinotecan and fluorouracil treatment on pharmacokinetics and toxicity in chemotherapy-naive metastatic colorectal cancer patients. *J Clin Oncol* (2001) 19, 3456–62.
2. Sasaki Y, Ohtsu A, Shimada Y, Ono K, Saijo N. Simultaneous administration of CPT-11 and fluorouracil: alteration of the pharmacokinetics of CPT-11 and SN-38 in patients with advanced colorectal cancer. *J Natl Cancer Inst* (1994) 86 1096–8.
3. Salz LB, Kanowitz J, Kemeny NE, Schaaf L, Spriggs D, Staton BA, Berkery R, Steger C, Eng M, Dietz A, Locker P, Kelsen DP. Phase I clinical and pharmacokinetic study of irinotecan, fluorouracil, and leucovorin in patients with advanced solid tumors. *J Clin Oncol* (1996) 14, 2959–67.
4. Grossin F, Barbault H, Benhammouda A, Rixe O, Antoine E, Auclerc G, Weil M, Nizri D, Farabos C, Mignard D, Mahjoubi M, Khayat D, Bastian G. A phase I pharmacokinetics study of concomitant CPT-11 and 5FU combination. *Proc Am Assoc Cancer Res* (1996) 37, 168.
5. Benhammouda A, Bastian G, Rixe O, Antoine E, Gozy M, Auclerc G, Grossin F, Nizri D, Gil-Delgado M, Weil M, Bismuth H, Mignard DM, Mahjoubi M, Lenseigne S, Khayat D. A phase I pharmacokinetic study of CPT-11 and 5-FU combination. *Proc Am Soc Clin Oncol* (1997) 16, 202a.
6. Campto (Irinotecan hydrochloride trihydrate). Pfizer Ltd. UK Summary of product characteristics, May 2009.
7. Camptosar (Irinotecan hydrochloride). Pfizer Inc. US Prescribing information, July 2008.

Irinotecan + Fluorouracil prodrugs; Capecitabine

The pharmacokinetics of irinotecan and its active metabolite do not appear to be affected by capecitabine.

Clinical evidence, mechanism, importance and management

Irinotecan was given to 12 patients on days one and 8 of a 21-day cycle, alone, and with capecitabine on days one to 14. Capecitabine did not alter the pharmacokinetics of irinotecan or its active metabolite SN-38 (AUC, maximum levels unchanged). The time to reach maximum plasma levels of the active metabolite SN-38 was increased from 0.88 hours to 1.23 hours, suggesting a slight delay in conversion of irinotecan to SN-38.[1] Another study in 10 patients who received a weekly infusion of irinotecan for 6 weeks, and oral capecitabine twice daily for 2 weeks, starting the day after the first irinotecan infusion, also indicated that capecitabine might delay the conversion of irinotecan to SN-38, but that there was no significant effect on other irinotecan pharmacokinetic.[2]

Both irinotecan and capecitabine require activation by carboxylesterases, and it had been suggested that this might result in a pharmacokinetic interaction. The studies here suggest that no interaction of clinical relevance occurs.

1. Goel S, Desai K, Karri S, Gollamudi R, Chaudhary I, Bulgaru A, Kaubisch A, Goldberg G, Einsetin M, Camacho F, Baker S, Mani S. Pharmacokinetic and safety study of weekly irinotecan and oral capecitabine in patients with advanced solid cancers. *Invest New Drugs* (2007) 25, 237–45.
2. Czejka M, Schueller J, Hauer K, Ostermann E. Pharmacokinetics and metabolism of irinotecan combined with capecitabine in patients with advanced colorectal cancer. *Anticancer Res* (2005) 25, 2985–90.

Irinotecan + Food

In a study in 25 patients who received an *oral* preparation of irinotecan, formulated as a semi-solid matrix capsule, the pharmacokinetics of irinotecan and its active metabolite, SN-38, did not differ when the oral preparation was taken either with food or after an overnight fast.[1]

1. Soepenberg O, Dumez H, Verweij J, de Jong FA, de Jonge MJA, Thomas J, Eskens FALM, van Schaik RHN, Selleslach J, ter Steeg J, Lefebvre P, Assadourian S, Sanderink G-J, Sparreboom A, van Oosterom AT. Phase I pharmacokinetic, food effect, and pharmacogenetic study of oral irinotecan given as semisolid matrix capsules in patients with solid tumours. *Clin Cancer Res* (2005) 11, 1504–11.

Irinotecan + Gemcitabine

Gemcitabine appears not to alter the pharmacokinetics of the active metabolite of irinotecan.

Clinical evidence, mechanism, importance and management

In a phase I, dose-escalation study, a 24-hour infusion of gemcitabine, given before a 24-hour infusion of irinotecan, appeared to increase the AUC and maximum plasma levels of irinotecan at higher doses of gemcitabine. However, the pharmacokinetics of the active metabolite of irinotecan, SN-38, did not appear to be affected.[1]

1. Saif MW, Sellers S, Li M, Wang W, Cusimano L, Wang H, Zhang R. A phase I study of biweekly administration of 24-h gemcitabine followed by 24-h irinotecan in patients with solid tumours. *Cancer Chemother Pharmacol* (2007) 60, 871–82.

Irinotecan + Ifosfamide

Ifosfamide appears to markedly reduce the level of SN-38, the active metabolite of irinotecan, when ifosfamide is given daily immediately after irinotecan.

Clinical evidence, mechanism, importance and management

The pharmacokinetics of irinotecan were investigated in 3 paediatric patients who received irinotecan 20 mg/m^2 daily for 5 days, and ifosfamide 2.65 g/m^2 daily immediately after irinotecan on days one to 3. In all 3 patients, the AUC of the active metabolite of irinotecan, SN-38, was markedly lower on day 3 when compared with day one; in 2 patients the plasma levels of SN-38 were below the limit of detection. In two of the patients, the AUC of SN-38 on day 12 was still below that measured on day one. The AUC of the major inactive metabolite (APC) was also significantly reduced on day 3, but returned to day one levels by day 12. The study was stopped in view of the low exposure to SN-38.[1]

The reason for this possible interaction is unknown, but it was suggested that ifosfamide might have induced the metabolism of irinotecan.[1]

The authors concluded that the use of daily ifosfamide with daily irinotecan in a protracted regimen such as this should be avoided, because of this marked reduction in the levels of the active irinotecan metabolite. They note that other administration schedules might not cause the same interaction.[1]

1. Crews KR, Stewart CF, Liu T, Rodriguez-Galindo C, Santana VM, Daw NC. Effect of fractionated ifosfamide on the pharmacokinetics of irinotecan in pediatric patients with osteosarcoma. *J Pediatr Hematol Oncol* (2004) 26, 764–7.

Irinotecan + Milk thistle

Milk thistle does not appear to affect the pharmacokinetics of irinotecan.

Clinical evidence, mechanism, importance and management

A pharmacokinetic study was undertaken in 6 patients who were receiving intravenous irinotecan 125 mg/m^2 weekly for 4 weeks, followed by a 2-week rest period. Four days before the second dose of irinotecan, a 14-day course of 200 mg milk thistle seed extract (containing silymarin 80%) three times daily was started. The pharmacokinetics of irinotecan and its metabolites did not differ between week one (no milk thistle), week two (4 days of milk thistle) or week three (12 days of milk thistle).[1] No dose alterations would therefore be expected to be needed if milk thistle (standardised with silymarin 80%) is given with irinotecan.

1. van Erp NPH, Baker SD, Zhao M, Rudek MA, Guchelaar H-J, Nortier JWR, Sparreboom A, Gelderblom H. Effect of milk thistle (*Silybum marianum*) on the pharmacokinetics of irinotecan. *Clin Cancer Res* (2005) 11, 7800–6.

Irinotecan + Miscellaneous

Preclinical data suggest that vinorelbine and physostigmine may decrease the formation of the active metabolite of irinotecan, SN-38.

Clinical evidence, mechanism, importance and management

In studies in human liver microsomes, **nifedipine**, **clonazepam**, **methylprednisolone**, **omeprazole**, and **vinorelbine** had significant effects on the metabolism of irinotecan. However, only the effect of **vinorelbine** occurred at a concentration considered clinically relevant.[1] Similarly, of various potential carboxylesterase inhibitors, only **physostigmine** was considered sufficiently potent to possibly inhibit irinotecan activation.[2] Further study is needed to assess the clinical relevance of these findings.

1. Charasson V, Haaz M-C, Robert J. Determination of drug interactions occurring with the metabolic pathways of irinotecan. *Drug Metab Dispos* (2002) 30, 731–3.
2. Slatter JG, Su P, Sams JP, Schaaf LJ, Wienkers LC. Bioactivation of the anticancer agent CPT-11 to SN-38 by human hepatic microsomal carboxylesterases and the *in vitro* assessment of potential drug interactions. *Drug Metab Dispos* (1997) 25, 1157–64.

Irinotecan + Oxaliplatin

An isolated report suggests that the cholinergic toxicity associated with irinotecan may be enhanced by oxaliplatin.

Clinical evidence, mechanism, importance and management

One of 15 patients given a one-hour infusion of irinotecan 80 mg/m^2 following an 2-hour infusion of oxaliplatin 85 mg/m^2 experienced hypersalivation and abdominal pain, which was successfully treated with atropine. In this patient, symptoms did not recur during subsequent treatment with irinotecan alone, nor when drugs were separated by one day, but rechallenge with the original regimen again produced cholinergic toxicity.[1] Two studies have found that the combination of irinotecan with oxaliplatin does not appear to alter the pharmacokinetics of either drug.[2,3]

The cholinergic effects in the patient may have been due to a pharmacodynamic interaction.[4] It has been suggested that the cholinergic effects of irinotecan, which is a potent inhibitor of acetylcholinesterase,[5] may be enhanced by oxaliplatin, which may, like other alkylating drugs, inhibit acetylcholinesterase.[4]

The clinical relevance of this report is unknown. The combination of irinotecan and oxaliplatin has been extensively evaluated in clinical studies, and this appears to be the only report of this problem. However, it has been noted that the prophylactic use of atropine with irinotecan could mask any increased cholinergic toxicity.[4,6]

1. Valencak J, Raderer M, Kornek GV, Henja MH, Scheithauer W. Irinotecan-related cholinergic syndrome induced by coadministration of oxaliplatin. *J Natl Cancer Inst* (1998) 90, 160.
2. Wasserman E, Cuvier C, Lokiec F, Goldwasser F, Kalla S, Méry-Mignard D, Ouldkaci M, Besmaine A, Dupont-André G, Mahjoubi M, Marty M, Misset JL, Cvitkovic E. Combination of oxaliplatin plus irinotecan in patients with gastrointestinal tumors: results of two independent phase I studies with pharmacokinetics. *J Clin Oncol* (1999) 17, 1751–9.
3. Gil-Delgado MA, Bastian G, Guijnet F, Spano JP, Taillibert S, Rocher MA, Castaing D, Adam R, Urien S, Bismuth H, Khayat D. Oxaliplatin plus irinotecan and FU-FOL combination and pharmacokinetic analysis in advanced colorectal cancer patients. *Am J Clin Oncol* (2004) 27, 294–8.
4. Dodds HM, Bishop JF, Rivory LP. More about: irinotecan-related cholinergic syndrome induced by coadministration of oxaliplatin. *J Natl Cancer Inst* (1999) 91, 91–2.
5. Dodds HM, Rivory LP. The mechanism of the inhibition of acetylcholinesterase by irinotecan (CPT-11)–a lead in explaining the cholinergic toxicity of CPT-11 and its time-course. *Proc Am Assoc Cancer Res* (1998) 39, 327.
6. Cvitkovic E, Marty M, Wasserman E, Cuvier C, Goldwasser F, Misset JL. Re: irinotecan-related cholinergic syndrome induced by coadministration of oxaliplatin. *J Natl Cancer Inst* (1998) 90, 1016–17.

Irinotecan + Protease inhibitors

Ritonavir-boosted lopinavir markedly increased levels of the active metabolite of irinotecan, SN-38, in one study. Other protease inhibitors would be expected to interact similarly.

Clinical evidence

A patient taking antiretrovirals including **ritonavir**-boosted **lopinavir** 135/400 mg twice daily received irinotecan 150 mg/m^2 alone after a 2-day protease inhibitor washout then irinotecan at a reduced dose of 75 mg/m^2 with his antiretrovirals. The dose-normalised AUC of the active metabolite of irinotecan, SN-38, was increased by 121%, and the AUC of the inactive metabolite, APC, was reduced by 93%. In this patient, a 50% reduction in irinotecan dose was necessary for the second cycle because of grade 2 neutropenia, and, because grade 2 neutropenia occurred again during the second cycle, no further irinotecan was given.[1]

Similar pharmacokinetic findings were later reported by the same researchers in 7 patients taking **ritonavir**-boosted **lopinavir** and irinotecan: this study found a 204% increase in the AUC of SN-38 and an 81% decrease in the AUC of APC. There was also a decrease in formation of the inactive glucuronide metabolite of SN-38.[2]

Mechanism

It appears that the metabolism of irinotecan to its inactive metabolite by the cytochrome P450 isoenzyme CYP3A4 was inhibited by the protease inhibitors. Therefore more irinotecan is available to be metabolised by carboxylesterases to the active metabolite, SN-38.[1] In addition, protease inhibitors inhibit glucuronosyltransferases, which are involved in the inactivation of SN-38, also resulting in greater SN-38 levels.

Importance and management

Although information is limited, what is known suggests that protease inhibitors are likely to markedly increase the AUC of the active metabolite of irinotecan. These changes suggest that an irinotecan dose reduction may be necessary to avoid toxicity. Note that the US manufacturer of **atazanavir** contraindicates concurrent use with irinotecan because of this predicted interaction.[3]

1. Corona G, Vaccher E, Cattarossi G, Sartor I, Toffoli G. Potential hazard of pharmacokinetic interactions between lopinavir-ritonavir protease inhibitors and irinotecan. *AIDS* (2005) 19, 2043–55.
2. Corona G, Vaccher E, Sandron S, Sartor I, Tirelli U, Innocenti F, Toffoli G. Lopinavir-ritonavir dramatically affects the pharmacokinetics of irinotecan in HIV patients with Kaposi's sarcoma. Clin Pharmacol Ther (2008) 83, 601–6.
3. Reyataz (Atazanavir sulfate). Bristol-Myers Squibb. US Prescribing information, November 2009.

Irinotecan + Rifampicin (Rifampin)

A single case report found that rifampicin reduced the formation of the active metabolite of irinotecan.

Clinical evidence

A case report describes a 54-year-old man with small cell lung cancer and *Mycobacterium* infection who was uneventfully treated with rifampicin 450 mg daily, isoniazid, streptomycin and pyrazinamide. After 2 weeks of antimycobacterial treatment he was given 4 cycles of irinotecan 75 mg/m^2 on days one and 8, and cisplatin 60 mg/m^2 on day one, and during the first cycle rifampicin was stopped for a 4-day period. There was no difference in the pharmacokinetic profile of irinotecan with or without concurrent rifampicin; however, the AUC of the active metabolite of irinotecan, SN-38, and of its inactive glucuronide metabolite were reduced by 20% and 58%, respectively, in the presence of rifampicin.[1]

Mechanism

Irinotecan is metabolised by the cytochrome P450 isoenzyme CYP3A4 to an inactive metabolite, and rifampicin probably induces this pathway of metabolism. This would result in less irinotecan being available for conversion to the active metabolite SN-38.

Importance and management

The reduction in the levels of active metabolite of irinotecan in this patient taking rifampicin was only modest. However, note that the effects of rifampicin can persist for some time after it is stopped and therefore a 4-day period may not have been sufficient for any effect to have completely reversed. The UK manufacturer of irinotecan notes that the use of irinotecan with potent enzyme-inducers such as rifampicin should be avoided.[2] If concurrent use is unavoidable, it would seem wise to bear in mind the possibility of reduced irinotecan efficacy, and to closely monitor the patient accordingly.

1. Yonemori K, Takeda Y, Toyota E, Kobayashi N, Kudo K. Potential interactions between irinotecan and rifampin in a patient with small-cell lung cancer. *Int J Clin Oncol* (2004) 9, 206–9.
2. Campto (Irinotecan hydrochloride trihydrate). Pfizer Ltd. UK Summary of product characteristics, May 2009.

Irinotecan + Selenium

Selenium at a dose of 2.2 mg daily does not appear to alter the pharmacokinetics of irinotecan, nor does it attenuate the toxicity of irinotecan.

Clinical evidence, mechanism, importance and management

In a study in 13 patients with metastatic or unresectable solid tumours **selenomethionine**, at a dose of elemental selenium 2.2 mg daily, was given with irinotecan weekly, in escalating doses from 125 mg/m^2 to 160 mg/m^2 for 4 weeks of a 6-week cycle. Irinotecan doses above the previously recommended maximum tolerated dose were still considered intolerable, with 3 of 4 patients receiving a dose of 160 mg/m^2 developing dose-limiting diarrhoea. There were no significant alterations in the pharmacokinetics of irinotecan or its metabolites, SN-38 and SN-38G. It was suggested that higher doses of selenomethionine should be investigated to see if they protect against irinotecan toxicity.[1]

1. Fakih MG, Pendyala L, Smith PF, Creaven PJ, Reid ME, Badmaev V, Azrak RG, Prey JD, Lawrence D, Rustum YM. A phase I and pharmacokinetic study of fixed-dose selenomethionine and irinotecan in solid tumors. *Clin Cancer Res* (2006) 12, 1237–44.

Irinotecan + Sodium bicarbonate

Oral alkalinisation with sodium bicarbonate, and the concurrent use of domperidone and magnesium oxide, did not affect the pharmacokinetics of irinotecan or its metabolites, and patients tended to have less diarrhoea.

Clinical evidence, mechanism, importance and management

Ten patients with colorectal cancer who had not previously been treated with irinotecan were given irinotecan 120 mg/m^2 intravenously every 2 weeks until disease progression occurred. The study was a crossover design and patients also received oral alkalinisation with sodium bicarbonate 3 g daily, and also domperidone 30 mg daily, magnesium oxide up to 3 g daily and at least 1.5 litres of water daily, with either the first or second course of irinotecan. Sodium bicarbonate was given to alkalinise the gastrointestinal contents, domperidone to increase gastrointestinal motility, and magnesium oxide for its laxative effects. The aim was to try to reduce the delayed toxic effect of irinotecan on the bowel that can lead to severe diarrhoea.

The AUC of irinotecan and its inactive metabolite, SN-38G, were equivalent between the two groups, and there was no significant change in the AUC of the active metabolite, SN-38. The incidence of diarrhoea tended to be lower with oral alkalinisation (0 of 10 patients) than without (3 of 10 patients), although this was not significant, but there were no differences in the incidence of nausea and vomiting, anorexia and alopecia with or without oral alkalinisation. Concurrent alkalinisation is therefore unlikely to affect the efficacy of irinotecan and may reduce the incidence of delayed diarrhoea.[1]

Note that the current recommended treatment for delayed diarrhoea is prompt treatment with loperamide and fluid and electrolyte replacement.[2,3] The use of drugs with laxative properties [which would include magnesium oxide] should be avoided in case they exacerbate the diarrhoea.[3] Although oral alkalinisation is not an accepted from of therapy with irinotecan, it is worth knowing that sodium bicarbonate and domperidone did not alter the pharmacokinetics of irinotecan.

1. Tamura T, Yasutake K, Nishisaki H, Nakashima T, Horita K, Hirohata S, Ishii A, Hamano K, Aoyama N, Shirasaka D, Kamigaki T, Kasuga M. Prevention of irinotecan-induced diarrhoea by oral sodium bicarbonate and influence on pharmacokinetics. *Oncology* (2004) 67, 327–37.
2. Campto (Irinotecan hydrochloride trihydrate). Pfizer Ltd. UK Summary of product characteristics, May 2009.
3. Camptosar (Irinotecan hydrochloride). Pfizer Inc. US Prescribing information, July 2008.

Irinotecan + Sorafenib

Sorafenib increases the levels of irinotecan and its major active metabolite. Irinotecan increases sorafenib levels.

Clinical evidence

In a phase I dose-escalation study, sorafenib 100 mg, 200 mg or 400 mg twice daily was given continuously from day 4 of the first cycle with irinotecan 125 mg/m^2 weekly for 4 out of 6 weeks as an intravenous infusion.[1,2] The pharmacokinetics of irinotecan and its major active metabolite, SN-38, were not affected by sorafenib at the two lower doses (100 mg and 200 mg twice daily). In addition, sorafenib pharmacokinetics at these dose levels were not affected by irinotecan.[1,2] However, the maximum plasma level of sorafenib was increased by 78% and its AUC was increased by 68% in the patients who received the highest dose of sorafenib (400 mg twice daily) with irinotecan 125 mg/m^2, but this was not seen with a lower fixed dose of irinotecan 140 mg. At both doses of irinotecan, the patients who had received the highest dose of sorafenib experienced a 26 to 42% increase in the AUC of irinotecan, and a 67 to 120% increase in the AUC of SN-38.[2]

Mechanism

In vitro, sorafenib strongly inhibits the glucuronidation of SN-38 by UGT1A1,[1] which would result in reduced metabolism of this active metabolite of irinotecan.

Importance and management

Usual clinical doses of irinotecan and sorafenib appear likely to increase the levels of each other, with a marked increase in levels of the active metabolite of irinotecan. The clinical significance of this finding is unknown, but increased toxicity might be expected. The authors of the study suggest that the dose of irinotecan for concurrent use should be 125 mg/m^2 or 140 mg, with close monitoring for toxicity.[2] The manufacturers of sorafenib recommend caution on concurrent use.[3,4]

1. Mross K, Steinbild S, Baas F, Reil M, Buss P, Mersmann S, Voliotis D, Schwartz B, Brendel E. Drug-drug interaction pharmacokinetic study with the Raf kinase inhibitor (RKI) BAY 43-9006 administered in combination with irinotecan (CPT-11) in patients with solid tumors. *Int J Clin Pharmacol Ther* (2003) 41, 618–19.
2. Mross K, Steinbild S, Baas F, Gmehling D, Radtke M, Voliotis D, Brendel E, Christensen O, Unger C. Results from an *in vitro* and a clinical/pharmacological phase I study with the combination irinotecan and sorafenib. *Eur J Cancer* (2007) 43, 55–63.
3. Nexavar (Sorafenib tosylate). Bayer plc. UK Summary of product characteristics, July 2009.
4. Nexavar (Sorafenib tosylate). Bayer Pharmaceuticals Corp. US Prescribing information, February 2009.

Irinotecan + St John's wort (*Hypericum perforatum*)

St John's wort increases the metabolism of irinotecan, which may decrease its activity.

Clinical evidence

In a randomised, crossover study, St John's wort decreased the plasma levels of the active metabolite of irinotecan, SN-38, by 42%. Myelosuppression was also reduced; with irinotecan alone the leucocyte and neutrophil counts decreased by 56% and 63%, respectively, but in the presence of St John's wort the decreases were only 8.6% and 4.3%, respectively. In this study, irinotecan was given as a single 350-mg/m^2 intravenous dose every 3 weeks, and during one cycle a St John's wort preparation was given three times daily, beginning 14 days before and stopping 4 days after the irinotecan.[1]

Mechanism

St John's wort induces the cytochrome P450 isoenzyme CYP3A4 and P-glycoprotein, which are both involved in the metabolism and transport of irinotecan. The evidence suggests that St John's wort increases the metabolism of irinotecan to an unknown inactive metabolite, rather than the active SN-38, thereby reducing its effects.[1]

Importance and management

The evidence appears to be limited. Irinotecan has a narrow therapeutic range, and as irinotecan is a prodrug that is metabolised to its active metabolite SN-38, the lower levels of SN-38 suggest that its activity will be reduced in the presence of St John's wort. It would therefore seem sensible to warn patients who are about to receive irinotecan to avoid St John's

wort. It seems likely that **topotecan**, a related drug that is also a substrate for CYP3A4, will be similarly affected, but evidence for this is lacking.

1. Mathijssen RHJ, Verweij J, de Bruijn P, Loos WJ, Sparreboom A. Effects of St John's wort on irinotecan metabolism. *J Natl Cancer Inst* (2002) 94, 1247–9.

Irinotecan + Temozolomide

Temozolomide does not appear to alter the pharmacokinetics of irinotecan or its active metabolite. Irinotecan does not alter the pharmacokinetics of temozolomide.

Clinical evidence, mechanism, importance and management

In a study in paediatric patients, there was no change in the pharmacokinetics of irinotecan, its active metabolite SN-38, or temozolomide when oral temozolomide 100 mg/m^2 daily was given one hour before irinotecan 10 or 15 mg/m^2 daily, both for 5 days.[1] Similarly, the pharmacokinetics of irinotecan and its active metabolite, SN-38, in 6 patients also taking enzyme-inducing antiepileptic drugs were not affected by temozolomide, when compared to historical data from patients taking irinotecan and enzyme-inducing antiepileptic drugs.[2] For details of the interaction of irinotecan with enzyme-inducing antiepileptic drugs see 'Irinotecan + Antiepileptics', p.736.

1. Wagner LM, Crews KR, Iacono LC, Houghton PJ, Fuller CE, McCarville MB, Goldsby RE, Albritton K, Stewart CF, Santana VM. Phase I trial of temozolomide and protracted irinotecan in pediatric patients with refractory solid tumors. *Clin Cancer Res* (2004) 10, 840–8.
2. Loghin ME, Prados MD, Wen P, Junck L, Lieberman F, Fine H, Fink KL, Metha M, Kuhn J, Lamborn K, Chang SM, Cloughesy T, DeAngelis LM, Robins IH, Aldape KD, Yung WK. Phase I study of temozolomide and irinotecan for recurrent malignant gliomas in patients receiving enzyme-inducing antiepileptic drugs: a North American brain tumor consortium study. *Clin Cancer Res* (2007) 13, 7133–8.

Irinotecan + Thalidomide

Thalidomide has both slightly increased and decreased irinotecan levels and slightly decreased the levels of the active metabolite of irinotecan.

Clinical evidence, mechanism, importance and management

Patients with solid tumours given irinotecan 350 mg/m^2 on day one of a 3-week cycle were also given thalidomide 400 mg daily from days one to 14 of the first cycle. Thalidomide slightly increased the AUC of irinotecan by 21% (not statistically significant) and its SN-38-glucuronide metabolite by 28%, but decreased the AUC of the active SN-38 metabolite of irinotecan by 26%. There was no difference in the toxicities seen when irinotecan was given with or without thalidomide.[1] In another study, patients were given intravenous irinotecan 125 mg/m^2 on days one and 8 of a 21-day cycle with oral thalidomide 200 mg or 400 mg given daily from day 3, at least one hour before the irinotecan. There was no change in the AUC of the active metabolite of irinotecan, SN-38, in 17 evaluable patients, although the maximum plasma levels of irinotecan and SN-38 were reduced by about 12%.[2] These changes are modest, and unlikely to be clinically relevant, but ideally this needs establishing in larger studies.

1. Allegrini G, Di Paolo A, Cerri E, Cupini S, Amatori F, Masi G, Danesi R, Marcucci L, Bocci G, Del Tacca M, Falcone A. Irinotecan in combination with thalidomide in patients with advanced solid tumors: a clinical study with pharmacodynamic and pharmacokinetic evaluation. *Cancer Chemother Pharmacol* (2006) 58, 585–93.
2. Villalona-Calero M, Schaaf L, Phillips G, Otterson G, Panico K, Duan W, Kleiber B, Shah M, Young D, Wu W-H, Kuhn J. Thalidomide and celecoxib as potential modulators of irinotecan's activity in cancer patients. *Cancer Chemother Pharmacol* (2007) 59, 23–33.

Irinotecan + Tobacco

Retrospective data suggests that tobacco smoking might increase the clearance of irinotecan and reduce the levels of its active metabolite, its toxicity, and presumably therefore, its efficacy.

Clinical evidence

In a retrospective analysis, the pharmacokinetics of irinotecan were compared between 49 patients who were smokers and 141 patients who were non-smokers, and who had received intravenous irinotecan 175 to 350 mg/m^2 (or a fixed dose of 600 mg) once every 3 weeks. The clearance of irinotecan was 18% faster in the group of patients who smoked, and these patients had a 40% lower AUC of the active metabolite of irinotecan, SN-38, and also had more extensive conversion of the active metabolite, SN-38, to the inactive glucuronide (SN-38G). Smokers experienced significantly less haematological toxicity than non-smokers (grade 3 to 4 neutropenia 6% versus 38%), possibly as a result of the increased rate of clearance.[1]

Mechanism

Uncertain. Irinotecan is metabolised to inactive metabolites by the cytochrome P450 subfamily CYP3A, which, although not the most commonly implicated isoenzyme in interactions involving tobacco smoking, may be induced by some of the components of tobacco smoke, resulting in increased clearance of irinotecan. In addition, smoking might induce glucuronyltransferases (which are responsible for glucuronidation of the active SN-38 metabolite).[1]

Importance and management

The findings of this retrospective analysis suggest that smoking might reduce the efficacy of irinotecan. However, the evidence is insufficient to make recommendations regarding smoking cessation or an increased irinotecan dose.[1] Further study is required.

1. van der Bol JM, Mathijssen RHJ, Loos WJ, Friberg LE, van Schaik RHN, de Jonge MJA, Planting AST, Verweij J, Sparreboom A, de Jong FA. Cigarette smoking and irinotecan treatment: pharmacokinetic interaction and effects on neutropenia. *J Clin Oncol* (2007) 25, 2719–26.

Lapatinib + Antineoplastics

Lapatinib pharmacokinetics are not affected by fluorouracil, irinotecan or oxaliplatin, and fluorouracil and oxaliplatin pharmacokinetics are not affected by lapatinib. Lapatinib increased levels of the active metabolite of irinotecan, SN-38, and a reduction in the dose of the FOLFIRI regimen was required.

Clinical evidence, mechanism, importance and management

(a) Fluorouracil, Folinic acid and Irinotecan

The pharmacokinetics of lapatinib 1.25 g daily were unaffected when it was given with the FOLFIRI regimen (irinotecan, folinic acid and fluorouracil). In addition, there was no change in the steady-state level of fluorouracil or of the pharmacokinetics of irinotecan. However, there was a 41% increase in the AUC of the active metabolite of irinotecan, SN-38, and a 32% increase in its maximum level. A variety of mechanisms might be responsible for this effect, such as inhibition of transporters including OATP1B1 and P-glycoprotein. In this study, toxicity necessitated dose reductions rather than the planned dose escalations, and the optimally tolerated regimen was found to be FOLFIRI at 60% of the standard doses.[1] Bear these findings in mind if lapatinib is used with irinotecan.

(b) Fluorouracil, Folinic acid and Oxaliplatin

In 19 patients the pharmacokinetics of lapatinib 1.5 g daily were unaffected when it was given just before starting oxaliplatin in the FOLFOX4 regimen (**oxaliplatin**, folinic acid and **fluorouracil**), when compared with days when lapatinib was given alone. In addition, lapatinib had no effect on the pharmacokinetics of **fluorouracil** or **oxaliplatin**.[2] Lapatinib can be given with the full-dose FOLFOX regimen.

1. Midgley RS, Kerr DJ, Flaherty KT, Stevenson JP, Pratap SE, Koch KM, Smith DA, Versola M, Fleming RA, Ward C, O'Dwyer PJ, Middleton MR. A phase I and pharmacokinetic study of lapatinib in combination with infusional 5-fluorouracil, leucovorin and irinotecan. *Ann Oncol* (2007) 18, 2025–9.
2. Siegel-Lakhai WS, Beijnen JH, Vervenne WL, Boot H, Keessen M, Versola M, Koch KM, Smith DA, Pandite L, Richel DJ, Schellens JHM. Phase I pharmacokinetic study of the safety and tolerability of lapatinib (GW572016) in combination with oxaliplatin/fluorouracil/leucovorin (FOLFOX4) in patients with solid tumours. *Clin Cancer Res* (2007) 13, 4495–4502.

Lapatinib + Food

Food increases the bioavailability of lapatinib.

Clinical evidence, mechanism, importance and management

In a randomised, crossover study, 22 patients with cancer were given a single 1.5-g dose of lapatinib after a high-fat meal, a low-fat meal, or in the fasted state. The high-fat meal increased the AUC and maximum plasma concentration of lapatinib 4.2-fold and 3.1-fold, respectively, when compared with the fasted state. The low-fat meal increased the AUC and maximum plasma concentration of lapatinib by about 2.5-fold, when compared with the fasted state.[1]

This increase would be expected to be of clinical relevance, and therefore the manufacturers recommend taking lapatinib at least one hour before or one hour after food.[2,3]

Consider also 'Lapatinib + Miscellaneous', below, for the effects of grapefruit juice on lapatinib.

1. GlaxoSmithKline Clinical Trials Register. A phase I, open-label, three-period, randomized, crossover study to evaluate the effect of food on the pharmacokinetics of GW572016 in cancer patients with a continuation phase to evaluate the safety of GW572016 administered once daily. GSK Study ID EGF10032. Available at http://www.gsk-clinicalstudyregister.com (accessed 04/02/10).
2. Tykerb (Lapatinib). GlaxoSmithKline. US Prescribing information, July 2008.
3. Tyverb (Lapatinib ditosylate monohydrate). GlaxoSmithKline UK. UK Summary of product characteristics, June 2008.

Lapatinib + Miscellaneous

Ketoconazole increases lapatinib levels and carbamazepine reduces lapatinib levels. Other potent CYP3A4 inducers and inhibitors are predicted to interact similarly. Lapatinib is predicted to raise the levels of CYP3A4 substrates, but some evidence with midazolam suggests that this may not be clinically relevant. Additive QT prolongation may occur if lapatinib is given with other drugs that prolong the QT interval, and drugs that raise gastric pH may reduce lapatinib absorption. In theory lapatinib may affect the levels of P-glycoprotein substrates (such as digoxin), and have its levels affected by inducers and inhibitors of this drug transporter, but there is no clinical evidence to establish the relevance of these predictions.

Clinical evidence, mechanism, importance and management

(a) CYP2C8 and CYP3A4 substrates

In vitro, lapatinib is an inhibitor of CYP2C8 and CYP3A4, and the manufacturers therefore advise caution when it is given with other drugs that have a narrow therapeutic margin and are substrates of these isoenzymes. They specifically name **cisapride**, **pimozide** and **quinidine** (CYP3A4 substrates) and **repaglinide** (CYP2C8 substrate).[1,2] However, a study in 23 cancer patients found that lapatinib 1.5 g daily did not affect the pharmacokinetics of either oral or intravenous **midazolam**, a probe substrate of CYP3A4.[3] It therefore seems unlikely that lapatinib will have a clinically relevant effect on these drugs.

See 'Table 1.3', (p.6), for a list of substrates of CYP2C8.

(b) CYP3A4 inducers

A study in 23 healthy subjects who received **carbamazepine** 100 mg twice daily for 3 days followed by 200 mg twice daily for a further 17 days, with a single dose of lapatinib 250 mg on day 1 and day 21, found that the AUC and maximum plasma concentration of lapatinib were reduced by 72% and 58%, respectively.[4] Lapatinib is a substrate of the cytochrome P450 isoenzyme CYP3A4, and the manufacturer therefore advises that the concurrent use of **carbamazepine** and other strong inducers of CYP3A4 should be avoided. They specifically mention **dexamethasone**,[1] **phenobarbital**, **phenytoin**, **rifabutin**, **rifampicin** (**rifampin**), **rifapentine**, and **St John's wort**.[1,2] If concurrent use is necessary, the dose of lapatinib should be gradually increased to 4.5 g daily, depending on patient tolerability. The lapatinib dose should be reduced when the inducing drug is stopped.[1] However, note that clinically relevant interactions occurring as a result of dexamethasone inducing CYP3A4 appear rare.

For a list of CYP3A4 inducers, see 'Table 1.4', (p.6).

(c) CYP3A4 inhibitors

A randomised, crossover study in 22 healthy subjects found that **ketoconazole** 200 mg twice daily for 7 days increased the AUC and maximum plasma concentration of a single 100-mg dose of lapatinib taken on day 4 by 3.6-fold and 2.2-fold, respectively.[5] Lapatinib is a substrate of the cytochrome P450 isoenzyme CYP3A4, and the manufacturers therefore advise that the concomitant use of **ketoconazole**, and other strong inhibitors of CYP3A4 should be avoided. They specifically name the protease inhibitors **atazanavir**, **indinavir**, **nelfinavir**, **ritonavir**, and **saquinavir**; the macrolides **clarithromycin** and **telithromycin**; and the azoles **itraconazole**, **posaconazole**, and **voriconazole**.[1,2] If concurrent use with a strong inhibitor of CYP3A4 is unavoidable, a dose reduction of lapatinib to 500 mg daily should be considered.[1,2] A period of 1 week should be observed before increasing the lapatinib dose after stopping the CYP3A4 inhibitor.[1] The UK manufacturer also advises caution with moderate inhibitors of CYP3A4, which in practice probably means monitoring closely for lapatinib adverse effects. **Grapefruit juice** is also a CYP3A4 inhibitor and the manufacturers suggest that concurrent use should be avoided,[1,2] presumably as the effects of different grapefruit juice products may be variable.

For a list of CYP3A4 inhibitors, see 'Table 1.4', (p.6).

(d) Drugs that affect gastric pH

As lapatinib solubility is pH dependent, the UK manufacturer advises that drugs that increase gastric pH may reduce the bioavailability of lapatinib and should be avoided. This advice would apply to **antacids**, **H_2-receptor antagonists** and **proton pump inhibitors**; however, there does not appear to be any specific clinical data to confirm this prediction.[2]

(e) Drugs that prolong the QT interval

Lapatinib has been shown to prolong the QTc interval by more than 60 milliseconds in 13 of 81 patients, using Fridericia's correction. The manufacturers therefore advise caution when patients take lapatinib with antiarrhythmic drugs or other drugs that cause QT prolongation, and cumulative high-dose **anthracycline** treatment.[1]

Similar caution therefore seems appropriate with other drugs known to cause QT-prolongation, see 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290.

(f) P-glycoprotein inhibitors and substrates

Lapatinib is a substrate of P-glycoprotein, and the manufacturers therefore advise that caution is warranted with drugs that are inhibitors of P-glycoprotein as increased levels of lapatinib are likely to result.[1,2] See 'Table 1.6', (p.8), for a list of drugs that are inhibitors of P-glycoprotein.

As lapatinib is also an inhibitor of P-glycoprotein, it is predicted to increase the levels of P-glycoprotein substrates (**digoxin** is specifically named) and therefore caution is recommended. However there is no clinical information to clarify the relevance of this prediction.[1,2]

1. Tykerb (Lapatinib). GlaxoSmithKline. US Prescribing information, July 2008.
2. Tyverb (Lapatinib ditosylate monohydrate). GlaxoSmithKline UK. UK Summary of product characteristics, June 2008.
3. GlaxoSmithKline Clinical Trials Register. A four-way cross-over study to examine the effects of lapatinib on the pharmacokinetics of orally and intravenously administered midazolam in cancer patients. Available at: http://www.gsk-clinicalstudyregister.com/files/pdf/20663.pdf (accessed 29/01/10).
4. GlaxoSmithKline Clinical Trials Register. An open-label, fixed sequence, two period study to evaluate the potential induction of GW572016 metabolism by carbamazepine. GSK Study ID EGF10018. Available at: http://www.gsk-clinicalstudyregister.com (accessed 04/02/10).
5. GlaxoSmithKline Clinical Trials Register. An open-label, two-way randomized crossover study to evaluate the potential inhibition of GW572016 metabolism by ketoconazole. GSK Study ID EGF10013. Available at: http://www.gsk-clinicalstudyregister.com/files/pdf/23309.pdf (accessed 29/01/10).

Lenalidomide + Miscellaneous

Lenalidomide may slightly increase digoxin levels. The concurrent use of lenalidomide and drugs that may increase the risk of thromboembolism (combined hormonal contraceptives, HRT, epoetins) should be avoided, or undertaken with caution. No interaction is anticipated when lenalidomide is taken with warfarin.

Clinical evidence, mechanism, importance and management

(a) Digoxin

The maximum level of a single 500-microgram dose of digoxin was very slightly increased by 14% by lenalidomide 10 mg daily, and the AUC of digoxin was unchanged.[1] This increase is not clinically relevant, but, as doses of lenalidomide can be higher than this (up to 25 mg daily), the possibility that higher doses might have a greater clinically relevant effect cannot be entirely excluded.[2] Note that lenalidomide is normally given with dexamethasone, consider also 'Digoxin and related drugs + Drugs that lower potassium levels', p.1099.

(b) Epoetins

Patients given lenalidomide and dexamethasone for multiple myeloma have an increased risk of deep vein thrombosis and pulmonary embolism. The use of epoetins may further increase this risk and therefore the UK manufacturer advises that these drugs should be used with caution.[2]

(c) Hormonal contraceptives

Lenalidomide is structurally related to thalidomide and may therefore be teratogenic. The manufacturers therefore give detailed advice about the use of adequate contraceptive measures.[1,2] However, the UK manufacturer considers that the increased risk of thromboembolic events in patients receiving lenalidomide might be further increased by the use of combined hormonal contraceptives, so they contraindicate these contraceptives. They recommend that, if a hormonal contraceptive is required, progestogen-only contraceptives should be used, and they specifically recommend implants, injections, the levonorgestrel intra-uterine system or oral desogestrel.[2] However, the US manufacturer makes no mention of this theoretical interaction, and does not exclude the use of combined hormonal contraceptives.[1] Moreover, the UK manufacturer suggests that, as lenalidomide should be taken with dexamethasone, the possibility that contraceptive efficacy of oral contraceptives may be reduced cannot be excluded, because dexamethasone is a weak to moderate inducer of the cytochrome P450 isoenzyme CYP3A4, by which contraceptive steroids are metabolised.[2] Nevertheless, they do not suggest any changes in their recommended hormonal contraceptives on the basis of this interaction. Note that, although this is a theoretical possibility there appear to be no examples of dexamethasone interacting with hormonal contraceptives in this way.

(d) Hormone replacement therapy

Patients receiving lenalidomide and dexamethasone for multiple myeloma have an increased risk of deep vein thrombosis and pulmonary embolism. The use of hormone replacement therapy may further increase this risk and therefore the UK manufacturer advises that it should be used with caution.[2]

(e) Warfarin

Lenalidomide 10 mg daily did not affect the pharmacokinetics of a single dose of warfarin, nor were the pharmacokinetics of lenalidomide affected by a single 25-mg dose of warfarin.[1,2] However, the UK manufacturer mentions that an interaction cannot be excluded in clinical use, because dexamethasone is also given, and the effect of dexamethasone on warfarin is unknown.[2] Consider also 'Coumarins and related drugs + Corticosteroids or Corticotropin', p.450.

1. Revlimid (Lenalidomide). Celgene Corp. US Prescribing information, January 2009.
2. Revlimid (Lenalidomide). Celgene Ltd. UK Summary of product characteristics, August 2009.

Letrozole + Cimetidine

In 17 healthy subjects the pharmacokinetics of a single 2.5-mg dose of letrozole were unchanged by cimetidine 400 mg every 12 hours.[1]

1. Morgan JM, Palmisano M, Spencer S, Hirschhorn W, Piraino AJ, Rackley RJ, Choi L. Pharmacokinetic effect of cimetidine on a single 2.5-mg dose of letrozole in healthy subjects. *J Clin Pharmacol* (1996) 36, 852.

Melphalan + Cimetidine

Cimetidine modestly reduces the bioavailability of melphalan.

Clinical evidence, mechanism, importance and management

A study in 8 patients with multiple myeloma or monoclonal gammopathy found that pretreatment with cimetidine 1 g daily for 6 days reduced the bioavailability of a 10-mg oral dose of melphalan by 30%. The melphalan half-life was reduced from 1.94 hours to 1.57 hours. The interindividual variation in melphalan pharmacokinetics was high.[1] Note that, because of the variability in melphalan absorption, the dose of oral melphalan is usually cautiously increased until myelosuppression is seen, to ensure therapeutic levels. Therefore, this modest interaction with cimetidine is unlikely to have many clinical consequences.

1. Sviland L, Robinson A, Proctor SJ, Bateman DN. Interaction of cimetidine with oral melphalan. *Cancer Chemother Pharmacol* (1987) 20, 173–5.

Melphalan + Food

The absorption of melphalan can be reduced by food.

Clinical evidence, mechanism, importance and management

A study in 10 patients with multiple myeloma found that the half-life of oral melphalan 5 mg/m^2 was unaffected when it was taken with a standardised breakfast, but its AUC was reduced by 39%. In one patient, no melphalan was detectable in the plasma when it was given with food. In 8 of the patients who had also been given intravenous melphalan at the same dose, the bioavailability of oral melphalan was calculated to be 85% (range 26 to 96%) when fasting and 58% (7 to 99%) when given with food.[1] A similar reduction in absorption was noted in a study in 5 patients who were given melphalan orally with food, compared with doses given while fasting, or intravenously.[2]

The authors of these studies recommend that melphalan should not be taken with food,[1] or that it should be taken first thing in the morning on an empty stomach.[2] However, the manufacturers make no specific recommendations about intake in relation to food.[3,4] They note that absorption after oral administration is highly variable, and that the dose should be adjusted based on frequent monitoring of blood counts.[4]

1. Reece PA, Kotasek D, Morris RG, Dale BM, Sage RE. The effect of food on oral melphalan absorption. *Cancer Chemother Pharmacol* (1986) 16, 194–7.
2. Bosanquet AG, Gilby ED. Comparison of the fed and fasting states on the absorption of melphalan in multiple myeloma. *Cancer Chemother Pharmacol* (1984) 12, 183–6.
3. Alkeran Tablets (Melphalan). GlaxoSmithKline UK. UK Summary of product characteristics, July 2007.
4. Alkeran (Melphalan). GlaxoSmithKline. US Prescribing information, October 2008.

Melphalan + Interferon alfa

Interferon alfa modestly decreases the AUC of melphalan, but melphalan cytotoxicity is possibly increased because of interferon-induced fever.

Clinical evidence, mechanism, importance and management

In 10 myeloma patients, the AUC of melphalan 250 microgram/kg was reduced by 13% when it was given 5 hours after the administration of human interferon alfa (7×10^6 units/m^2), possibly due to fever caused by the interferon.[1] The clinical importance of this is uncertain but the authors of the report suggest that, despite this small reduction in the AUC, the cytotoxicity of the melphalan may be increased by the fever. The use of interferon alfa with melphalan and prednisone in multiple myeloma has been associated with more adverse effects.[2-4]

1. Ehrsson H, Eksborg S, Wallin I, Österborg A, Mellstedt H. Oral melphalan pharmacokinetics: influence of interferon-induced fever. *Clin Pharmacol Ther* (1990) 47, 86–90.
2. Österborg A, Björkholm M, Björeman M, Brenning G, Carlson K, Celsing F, Gahrton G, Grimfors G, Gyllenhammar J, Hast R. Natural interferon-α in combination with melphalan/prednisone versus melphalan/prednisone in the treatment of multiple myeloma stages II and III: a randomized study from the Myeloma Group of Central Sweden. *Blood* (1993) 81, 1428–34.
3. Cooper MR, Dear K, McIntyre OR, Ozer H, Ellerton J, Canellos G, Bernhardt B, Duggan D, Faragher D, Schiffer C. A randomized clinical trial comparing melphalan/prednisone with or without interferon alfa-2b in newly diagnosed patients with multiple myeloma: a Cancer and Leukemia Group B study. *J Clin Oncol* (1993) 11, 155–60.
4. The Nordic Myeloma Study Group. Interferon-α 2b added to melphalan-prednisone for initial and maintenance therapy in multiple myeloma: a randomized, controlled trial. *Ann Intern Med* (1996) 124, 212–22.

Methotrexate + Amiodarone

An isolated case report tentatively attributes the development of methotrexate toxicity to the concurrent use of amiodarone.

Clinical evidence, mechanism, importance and management

An elderly woman, whose psoriasis was effectively controlled for 2 years with methotrexate, developed ulceration of the psoriatic plaques within

2 weeks of starting treatment with amiodarone. The reason for this effect is not understood. A modest increase in her dose of furosemide is a suggested contributory factor because it might have interfered with the excretion of the methotrexate.[1] This appears to be an isolated case, and therefore no general recommendations can be made.

1. Reynolds NJ, Jones SK, Crossley J, Harman RRM. Methotrexate induced skin necrosis: a drug interaction with amiodarone? *BMJ* (1989) 299, 980–1.

Methotrexate + Antibacterials; Aminoglycosides, oral

Limited evidence suggests that the gastrointestinal absorption of methotrexate can be reduced by paromomycin, neomycin and possibly other oral aminoglycosides, but increased by kanamycin.

Clinical evidence

A study in 10 patients with small cell bronchogenic carcinoma taking methotrexate found that when they were also given a range of oral anti-infectives (**paromomycin**, vancomycin, polymyxin B, nystatin) the urinary recovery of methotrexate was reduced by over one-third (from 69% to 44%).[1] The **paromomycin** was believed to have been responsible. In another study the concurrent use of **neomycin** 500 mg four times daily for 3 days reduced the AUC of methotrexate and its 72-hour cumulative excretion by 50%.[2] In contrast, the same report suggests that **kanamycin** can *increase* the absorption of methotrexate, but no details are given.

Mechanism

Oral aminoglycosides reduce the activity of the gut flora, which metabolise methotrexate, so that more is available for absorption. However, paromomycin[3] and neomycin, in common with other oral aminoglycosides, can cause a malabsorption syndrome, which reduces drug absorption and presumably negates any effect altering the gut flora has. Kanamycin may possibly be different because it causes less malabsorption.

Importance and management

The documentation of these interactions is sparse, but it would seem prudent to be on the alert for a reduction in the response to methotrexate if patients are given oral aminoglycosides such as paromomycin or neomycin. An increased response may possibly occur with kanamycin. No interaction would be expected if aminoglycosides are given parenterally.

1. Cohen MH, Creaven PJ, Fossieck BE, Johnston AV, Williams CL. Effect of oral prophylactic broad spectrum nonabsorbable antibiotics on the gastrointestinal absorption of nutrients and methotrexate in small cell bronchogenic carcinoma patients. *Cancer* (1976) 38, 1556–9.
2. Shen DD, Azarnoff D. Clinical pharmacokinetics of methotrexate. *Clin Pharmacokinet* (1978) 3, 1–13.
3. Keusch GT, Troncale FJ, Buchanan RD. Malabsorption due to paromomycin. *Arch Intern Med* (1970) 125, 273–6.

Methotrexate + Antibacterials; Cefotiam

Pancytopenia and pseudomembraneous colitis occurred when a patient taking low-dose methotrexate and loxoprofen was given cefotiam.

Clinical evidence, mechanism, importance and management

An elderly woman who had been taking low-dose methotrexate 5 mg weekly and loxoprofen for one month developed acute pyelonephritis. Intravenous cefotiam was started, and on day 7 she developed severe watery diarrhoea. Analysis showed pancytopenia and *Clostridium difficile* infection. Methotrexate and cefotiam were stopped, and vancomycin started, and the patient recovered.[1] It was suggested that the combination of the antineoplastic drug and the antibacterial increased the risk of *Clostridium difficile* diarrhoea. In addition, the NSAID (see 'Methotrexate + NSAIDs, Aspirin or other Salicylates', p.752) and renal impairment from the pyelonephritis could have contributed to the methotrexate toxicity.[1] This appears to be an isolated case, and any interaction between methotrexate and cefotiam is not established.

1. Nanke Y, Kotake S, Akama H, Tomii M, Kamatani N. Pancytopenia and colitis with *Clostridium difficile* in a rheumatoid arthritis patient taking methotrexate, antibiotics and non-steroidal anti-inflammatory drugs. *Clin Rheumatol* (2001) 20, 73–5.

Methotrexate + Antibacterials; Ciprofloxacin

A report describes two patients who developed methotrexate toxicity when they were given ciprofloxacin.

Clinical evidence

Two patients with osteosarcoma, receiving high-dose methotrexate 12 g/m^2 per course, were given ciprofloxacin 500 mg twice daily, either during or 2 days before the start of the methotrexate course. Methotrexate elimination was delayed, resulting in raised serum levels, severe cutaneous toxicity and renal impairment. The first patient also had hepatic injury and haematological toxicity. Increased folinic acid rescue normalised methotrexate levels after several days. In earlier courses without ciprofloxacin in the first patient and subsequent courses without ciprofloxacin in the second patient, methotrexate elimination was normal.[1] This preliminary report has subsequently been published in full.[2,3]

Mechanism

Not fully understood. Ciprofloxacin may displace methotrexate from its plasma-protein binding sites resulting in a rise in levels of unbound methotrexate. Ciprofloxacin may also cause a decrease in the renal clearance of methotrexate.

Importance and management

Information about an interaction between methotrexate and ciprofloxacin appears to be limited to one report, but it would seem prudent to monitor for raised methotrexate levels if concurrent use is necessary. More study is needed.

1. Dalle JH, Auvrignon A, Vassal G, Leverger G. Possible ciprofloxacin-methotrexate interaction: a report of 2 cases. *Intersci Conf Antimicrob Agents Chemother* (2000) 40, 477.
2. Dalle JH, Auvrignon A, Vassal G, Leverger G, Kalifa C. Interaction méthotrexate–ciprofloxacine: à propos de deux cas d'intoxication sévère. *Arch Pediatr* (2001) 8, 1078–81.
3. Dalle J-H, Auvrignon A, Vassal G, Leverger G. Interaction between methotrexate and ciprofloxacin. *J Pediatr Hematol Oncol* (2002) 24, 321–2.

Methotrexate + Antibacterials; Co-trimoxazole or Trimethoprim

Several cases of severe bone marrow depression (some of which were fatal) have been reported in patients given low-dose methotrexate and trimethoprim or co-trimoxazole (sulfamethoxazole with trimethoprim). Pancytopenia has also been reported in a few patients given co-trimoxazole shortly after stopping methotrexate.

Clinical evidence

A 61-year-old patient with rheumatoid arthritis, taking methotrexate 7.5 mg weekly, developed generalised bone marrow hypoplasia over 2 months after a 10-day course of treatment with co-trimoxazole for a urinary tract infection. She had taken a total of 775 mg of methotrexate when the hypoplasia appeared.[1] Twelve other cases of severe bone marrow depression, four of them fatal,[2-4] have been described in patients taking low-dose weekly methotrexate with co-trimoxazole[2,5-9] or trimethoprim.[3,7,10,11] Life-threatening complications (no details given) are said to have occurred in two other patients taking low-dose methotrexate with unnamed sulfonamides.[12] A 10-year (1981 to 1991) regional survey in Ottawa identified co-trimoxazole as one of four factors associated with serious pancytopenia in patients taking low-dose methotrexate. The other factors were elevated BUN or creatinine levels, increased mean corpuscular volumes and increasing age.[13]

Three cases of severe pancytopenia, one of them fatal, have been reported in patients given treatment dose co-trimoxazole for pneumocystis pneumonia shortly after stopping low-dose methotrexate.[14-16] A fatal case

of severe agranulocytosis and toxic epidermal necrolysis occurred in a patient receiving co-trimoxazole for prophylaxis of pneumocystis pneumonia after high-dose methotrexate.[17]

Mechanism

Not fully understood. Both drugs can suppress the activity of dihydrofolate reductase and it seems possible that they can act additively to produce folate deficiency, which could lead to some of the bone marrow changes seen. There may also be a pharmacokinetic mechanism. An early study found that the concurrent use of co-trimoxazole had no effect on the pharmacokinetics of methotrexate in children;[18] however, another study reported that co-trimoxazole caused an increase in 'free' methotrexate from about 37% to 52% while the renal clearance was more than halved.[19] This was calculated to increase the exposure to methotrexate by 66%.[19] Another sulfonamide, **sulfafurazole** (sulfisoxazole),[20] has been found to cause a small reduction in the clearance of methotrexate by the kidneys.

Importance and management

Information seems to be limited to the reports cited but the interactions between methotrexate and co-trimoxazole or trimethoprim are established. Low-dose co-trimoxazole is commonly given without problem to patients taking methotrexate as prophylaxis of pneumocystis pneumonia. This type of patient should be having regular blood monitoring as a matter of course. However, the situation with higher doses of either drug is potentially more hazardous. Some have recommended avoiding the combination. If both drugs must be used, the haematological picture should be very closely monitored because the outcome can be life-threatening.

1. Thomas MH, Gutterman LA. Methotrexate toxicity in a patient receiving trimethoprim-sulfamethoxazole. *J Rheumatol* (1986) 13, 440–1.
2. Groenendal H, Rampen FHJ. Methotrexate and trimethoprim-sulphamethoxazole — a potentially hazardous combination. *Clin Exp Dermatol* (1990) 15, 358–60.
3. Steuer A, Gumpel JM. Methotrexate and trimethoprim: a fatal interaction. *Br J Rheumatol* (1998) 37, 105–6.
4. Bartha P, Bron R, Levy Y. Fatal pancytopenia and methotrexate-trimethoprim-sulfamethoxazole interaction. *Harefuah* (2004) 143, 398–400.
5. Thevenet JP, Ristori JM, Cure H, Mizony MH, Bussiere JL. Pancytopénie au cours due traitement d'une polyarthrite rheumatoïde par méthotrexate après administration de triméthoprime-sulfaméthoxazole. *Presse Med* (1987) 16, 1487.
6. Maricic M, Davis M, Gall EP. Megaloblastic pancytopenia in a patient receiving concurrent methotrexate and trimethoprim-sulphamethoxazole treatment. *Arthritis Rheum* (1986) 29, 133–5.
7. Jeurissen ME, Boerbooms AM, van de Putte LB. Pancytopenia and methotrexate with trimethoprim-sulfamethoxazole. *Ann Intern Med* (1989) 111, 261.
8. Liddle BJ, Marsden JR. Drug interactions with methotrexate. *Br J Dermatol* (1989) 120, 582–3.
9. Govert JA, Patton S, Fine RL. Pancytopenia from using trimethoprim and methotrexate. *Ann Intern Med* (1992) 117, 877–8.
10. Ng HWK, Macfarlane AW, Graham RM, Verbov JL. Near fatal drug interactions with methotrexate given for psoriasis. *BMJ* (1987) 295, 752–3.
11. Saravana S, Lalukotta K. Myelotoxicity due to methotrexate—an iatrogenic cause. *Eur J Haematol* (2003) 71, 315–16.
12. Zachariae H. Methotrexate and non-steroidal anti-inflammatory drugs. *Br J Dermatol* (1992) 126, 95.
13. Al-Awadhi A, Dale P, McKendry RJR. Pancytopenia associated with low dose methotrexate therapy. A regional survey. *J Rheumatol* (1993) 20, 1121–5.
14. Dan M, Shapira I. Possible role of methotrexate in trimethoprim- sulfamethoxazole-induced acute megaloblastic anemia. *Isr J Med Sci* (1984) 20, 262–3.
15. Kobrinsky NL, Ramsay NKC. Acute megaloblastic anemia induced by high-dose trimethoprim-sulfamethoxazole. *Ann Intern Med* (1981) 94, 780–1.
16. Chevrel G, Brantus JF, Sainte-Laudy, Miossec P. Allergic pancytopenia to trimethoprim-sulphamethoxazole for *Pneumocystis carinii* pneumonia following methotrexate treatment for rheumatoid arthritis. *Rheumatology (Oxford)* (1999) 38, 475–6.
17. Yang CH, Yang LJ, Jaing TH, Chan HL. Toxic epidermal necrolysis following combination of methotrexate and trimethoprim-sulfamethoxazole. *Int J Dermatol* (2000) 39, 621–3.
18. Beach BJ, Woods WG, Howell SB. Influence of co-trimoxazole on methotrexate pharmacokinetics in children with acute lymphoblastic leukemia. *Am J Pediatr Hematol Oncol* (1981) 3, 115–19.
19. Ferrazzini G, Klein J, Sulh H, Chung D, Griesbrecht E, Koren G. Interaction between trimethoprim-sulfamethoxazole and methotrexate in children with leukemia. *J Pediatr* (1990) 117, 823–6.
20. Liegler DG, Henderson ES, Hahn MA, Oliverio VT. The effect of organic acids on renal clearance of methotrexate in man. *Clin Pharmacol Ther* (1969) 10, 849–57.

Methotrexate + Antibacterials; Penicillins

Reduced methotrexate clearance and acute methotrexate toxicity has been attributed to the concurrent use of various penicillins (amoxicillin, benzylpenicillin, carbenicillin, dicloxacillin, flucloxacillin, mezlocillin, oxacillin, penicillin, phenoxymethylpenicillin, piperacillin, ticarcillin) in a small number of case reports.

Clinical evidence

Reduced methotrexate clearance and acute methotrexate toxicity has been attributed to the concurrent use of various penicillins in a number of patients. See 'Table 17.2', (p.747), for details.

A survey of the Wyeth/Lederle safety database in 1996 identified two additional unpublished cases of methotrexate toxicity (aplastic anaemia, thrombocytopenia, pneumonitis) in patients who had recently started penicillins.[1]

Mechanism

It is thought that weak acids such as the penicillins can possibly successfully compete with methotrexate in the kidney tubules for excretion so that the methotrexate is retained, thereby increasing its effects and its toxicity.[2] However, this was not demonstrated in a study with flucloxacillin,[3] and the mechanism has been disputed.[4]

Importance and management

Information seems to be limited to the reports given here, which would seem to indicate that serious interactions between methotrexate and penicillins are uncommon. It is not known why only a few patients have been affected and what other factors may have contributed, but the problem does not seem to be confined to patients receiving high-dose methotrexate. There is not enough evidence to forbid concurrent use (although some have advised against it[5]), but close monitoring is obviously advisable. One published recommendation is to carry out twice-weekly platelet and white cell counts for 2 weeks initially, with the measurement of methotrexate levels if toxicity is suspected. Folinic acid (leucovorin) rescue should be available.[6]

For the general guidelines given by the CSM in the UK on the use of methotrexate alone, see under *Importance and management* in 'Methotrexate + NSAIDs, Aspirin or other Salicylates', p.752.

1. Wyeth/Lederle. Personal communication, July 1996.
2. Iven H, Brasch H. Influence of the antibiotics piperacillin, doxycycline, and tobramycin on the pharmacokinetics of methotrexate in rabbits. *Cancer Chemother Pharmacol* (1986) 17, 218–22.
3. Herrick AL, Grennan DM, Giriffen K, Aarons L, Gifford LA. Lack of interaction between flucloxacillin and methotrexate in patients with rheumatoid arthritis. *Br J Clin Pharmacol* (1996) 41, 223–7.
4. Herrick AL, Grennan DM, Aarons L. Lack of interaction between methotrexate and penicillins. *Rheumatology (Oxford)* (1999) 38, 284–5.
5. Dawson JK, Abernethy VE, Lynch MP. Methotrexate and penicillin interaction. *Br J Rheumatol* (1998) 37, 807.
6. Mayall B, Poggi G, Parkin JD. Neutropenia due to low-dose methotrexate therapy for psoriasis and rheumatoid arthritis may be fatal. *Med J Aust* (1991) 155, 480–4.

Methotrexate + Antibacterials; Pristinamycin

An isolated report describes severe methotrexate toxicity in a patient also given pristinamycin.

Clinical evidence

A 13-year-old boy with acute lymphoblastic leukaemia had a relapse and began a series of regimens with high-dose methotrexate in combination with other drugs, including dexamethasone, mercaptopurine, vincristine, cytarabine and asparaginase, tioguanine and ifosfamide. During a late cycle when he was also taking pristinamycin 2 g daily for a staphylococcal infection, the clearance of methotrexate was markedly decreased (half-life prolonged from 6 hours to 203 hours). He developed severe methotrexate toxicity (oral mucositis, anusitis, balanitis, neutropenia and thrombocytopenia) and was given folinic acid rescue and haemodialysis.[1]

Mechanism

Not understood, but on the basis of experimental evidence the authors of the report excluded the possibilities of renal impairment or reduction of liver metabolism caused by the pristinamycin.[1]

Importance and management

This appears to be the first and only report of an interaction between methotrexate and pristinamycin. Its general importance is unknown but the au-

Table 17.2 Reports of reduced methotrexate clearance during penicillin use

Methotrexate	*Penicillin (dose)*	*Indication (number of patients)*	*Outcome*	*Refs*
High-dose intravenous regimen (with folinic acid rescue)				
Infusion of 8 g/m^2 over 6 hours	Amoxicillin (1 g every 6 hours orally)	Osteogenic sarcoma (1)	56% reduction in methotrexate clearance; prolonged and marked enhancement of methotrexate plasma levels; acute and subacute methotrexate toxicity	1
Infusion of 6 g/m^2 (10.8 g) over one hour, then 1.2 g/m^2 per hour for 23 hours	Carbenicillin (30 g daily)	Acute lymphoblastic leukaemia (1)	Elevated plasma methotrexate levels and decreased methotrexate clearance	2
Bolus of 15 to 60 mg/m^2, then 15 to 60 mg/m^2 infusion over 36 hours	Dicloxacillin (not stated) (Indometacin also given)	Oesophageal cancer (1)	93% reduction in methotrexate clearance; prolonged folinic acid rescue necessary	3
Infusion of 12 g/m^2 over 4 hours	Mezlocillin (330 mg/kg daily)	Osteogenic sarcoma (1)	Reduced methotrexate clearance; increased gastrointestinal toxicity	4
Infusion of 15 g over 6 hours	Oxacillin (1 g every 8 hours starting 6 hours after methotrexate infusion)	Osteogenic sarcoma (1)	Plasma methotrexate levels 53-fold higher than in previous cycles without oxacillin; fatal acute toxicity (renal failure and aplastic anaemia)	5
Bolus of 15 to 60 mg/m^2, then 15 to 60 mg/m^2 infusion over 36 hours	Penicillin [sic] (not stated)	Breast cancer (1)	36% reduction in methotrexate clearance; prolonged folinic acid rescue necessary	3
Bolus of 15 to 60 mg/m^2, then 15 to 60 mg/m^2 infusion over 36 hours	Piperacillin (not stated)	Chronic myeloid leukaemia (1)	67% reduction in methotrexate clearance; prolonged folinic acid rescue necessary	3
Infusion of 3 g/m^2 over 6 hours	Piperacillin (1 g every 6 hours intravenously)	Non-Hodgkin's lymphoma (1)	Reduced methotrexate clearance	6
High-dose methotrexate as part of CODOX-M regimen (Cyclophosphamide, Doxorubicin, Vincristine)	Piperacillin/tazobactam (not stated)	Burkitt's lymphoma (1)	Methotrexate clearance reduced by 97%. Plasma methotrexate levels remained at 0.2 micromols/L (reference less than 0.05 micromols/L) for 8 days until piperacillin stopped	7
Bolus of 15 to 60 mg/m^2, then 15 to 60 mg/m^2 infusion over 36 hours	Ticarcillin (not stated)	Acute myeloid leukaemia (1)	60% reduction in methotrexate clearance; prolonged folinic acid rescue necessary	3
Low-dose regimen				
7.5 mg weekly	Amoxicillin 500 mg orally three times daily for 7 days; from day 17, intravenous flucloxacillin 2 g every 4 hours, plus intravenous benzylpenicillin 2 million units every 4 hours	Rheumatoid arthritis	Neutropenia and thrombocytopenia probably as a result of reduced methotrexate clearance; folinic acid given, but patient died	8
10 mg weekly	Amoxicillin (route and dose not stated)	Not given (1)	Severe pancytopenia, sepsis, melaena, mucositis. Treatment also included aspirin and celecoxib. Treated with folinic acid and blood transfusion, but patient died	9
7.5 mg weekly	Co-amoxiclav (amoxicillin and clavulanic acid)	Psoriasis (1)	Neutropenia and thrombocytopenia, probably as a result of reduced methotrexate clearance	8
5 mg weekly	Flucloxacillin (4 g four times daily, intravenously then orally)	Rheumatoid arthritis (1)	Suspected methotrexate-induced pneumonitis	10
5 to 15 mg weekly	Flucloxacillin (500 mg four times daily orally)	Rheumatoid arthritis (10, and 10 not given flucloxacillin)	No significant effect on methotrexate pharmacokinetics	10
2.5 mg three times each week	Flucloxacillin (1 g every 6 hours intravenously) plus piperacillin (2 g every 6 hours intravenously)	Psoriasis (1)	Neutropenia and thrombocytopenia, probably as a result of reduced methotrexate clearance; folinic acid given, but patient died	8
5 mg twice weekly	Piperacillin (intravenous; dose not stated)	Psoriasis (1)	Neutropenia and thrombocytopenia, probably as a result of reduced methotrexate clearance; folinic acid given, but patient died	8

Continued

Table 17.2 Reports of reduced methotrexate clearance during penicillin use (continued)

Methotrexate	*Penicillin (dose)*	*Indication (number of patients)*	*Outcome*	*Refs*
Other regimen				
Intravenous 50 mg weekly	Phenoxymethylpenicillin 250 mg on alternate days	Dermatomyositis (also treated with prednisone; and prostatic cancer treated with diethylstilbestrol (stilboestrol); also receiving furosemide)	Methotrexate toxicity within a week of starting phenoxymethylpenicillin; treated with folinic acid and fluid replacement (and nafcillin and tobramycin)	11

1. Ronchera CL, Hernández T, Peris JE, Torres F, Granero L, Jiménez NV, Plá JM. Pharmacokinetic interaction between high-dose methotrexate and amoxycillin. *Ther Drug Monit* (1993) 15, 375–9.
2. Gibson DL, Bleyer AW, Savitch JL. Carbenicillin potentiation of methotrexate plasma concentration during high dose methotrexate therapy. American Society of Hospital Pharmacists. Mid year clinical meeting abstracts, New Orleans, Dec 1981. p. 111.
3. Bloom EJ, Ignoffo RJ, Reis CA, Cadman E. Delayed clearance (CL) of methotrexate (MTX) associated with antibiotics and anti-inflammatory agents. *Clin Res* (1986) 34, 560A.
4. Dean R, Nachman J, Lorenzana AN. Possible methotrexate-mezlocillin interaction. *Am J Pediatr Hematol Oncol* (1992) 14, 88–9.
5. Titier K, Lagrange F, Péhourcq F, Moore N, Molimard M. Pharmacokinetic interaction between high-dose methotrexate and oxacillin. *Ther Drug Monit* (2002) 24, 570–2.
6. Yamamoto K, Sawada Y, Matsushita U, Moriwaki K, Bessho F, Iga T. Delayed elimination of methotrexate associated with piperacillin administration. *Ann Pharmacother* (1997) 31, 1261–2.
7. Zarychanski R, Wlodarczyk K, Ariano R, Bow E. Pharmacokinetic interaction between methotrexate and piperacillin/tazobactam resulting in prolonged toxic concentrations of methotrexate. *J Antimicrob Chemother* (2006) 58, 228–30.
8. Mayall B, Poggi G, Parkin JD. Neutropenia due to low-dose methotrexate therapy for psoriasis and rheumatoid arthritis may be fatal. *Med J Aust* (1991) 155, 480–4.
9. Lim AYN, Gaffney K, Scott DGI. Methotrexate-induced pancytopenia: serious and under-reported? Our experience of 25 cases in 5 years. *Rheumatology* (2005) 44, 1051–5.
10. Herrick AL, Grennan DM, Griffen K, Aarons L, Gifford LA. Lack of interaction between flucloxacillin and methotrexate in patients with rheumatoid arthritis. *Br J Clin Pharmacol* (1996) 41, 223–7.
11. Nierenberg DW, Mamelok RD. Toxic reaction to methotrexate in a patient receiving penicillin and furosemide: a possible interaction. *Arch Dermatol* (1983) 119, 449–50.

thors strongly advise the avoidance of pristinamycin in patients taking methotrexate.[1]

1. Thyss A, Milano G, Renée N, Cassuto-Viguier E, Jambou P, Soler C. Severe interaction between methotrexate and a macrolide-like antibiotic. *J Natl Cancer Inst* (1993) 85, 582–3.

Methotrexate + Antibacterials; Tetracyclines

Two case reports describe the development of methotrexate toxicity in patients also given tetracycline or doxycycline.

Clinical evidence, mechanism, importance and management

A man stable taking methotrexate 25 mg weekly for psoriasis was also given **tetracycline** 500 mg four times daily for a mycoplasmal infection. Within 5 days he developed recurrent fever, ulcerative stomatitis and diarrhoea, his white cell count fell to 1000, and his platelet count fell to 30 000 (units not stated, previous counts not given). These are all signs of methotrexate toxicity. The problem resolved when methotrexate was withdrawn, but the psoriasis returned.[1] A 17-year-old girl with osteosarcoma of the femur was given **doxycycline** 100 mg every 12 hours for an abscess in her left eye at the same time as her eleventh cycle of high-dose methotrexate with folinic acid rescue. She had elevated plasma methotrexate levels and she developed haematological toxicity and severe vomiting; requiring antiemetics, continued folinic acid, a prolonged stay in hospital and postponement of her next dose of methotrexate. **Doxycycline** had not been taken during the first 10 cycles of methotrexate and the pharmacokinetic changes and symptoms seen in the eleventh cycle were attributed to the concurrent use of **doxycycline**.[2] It was suggested that displacement of the methotrexate from its binding sites may be part of the explanation for the raised methotrexate levels. There appears to be the only two clinical reports of this interaction on record. Concurrent use need not be avoided, but it should be well monitored.

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2. Tortajada-Ituren JJ, Ordovás-Baines JP, Llopis-Salvia P, Jiménez-Torres NV. High-dose methotrexate-doxycycline interaction. *Ann Pharmacother* (1999) 33, 804–8.

Methotrexate + Antibacterials; Vancomycin

Delayed methotrexate excretion and toxicity were seen when high-dose methotrexate was given to two patients recently treated with vancomycin. No significant interaction was found in eight other patients.

Clinical evidence, mechanism, importance and management

Two patients treated with a chemotherapy regimen containing high-dose methotrexate, cisplatin, doxorubicin and ifosfamide had delayed methotrexate excretion and methotrexate toxicity during a cycle soon after they had received vancomycin. Methotrexate levels took 170 to 231 hours to fall to 200 micromol/mL, and toxicity (mucositis) occurred. Subclinical renal impairment was found, which subsequently improved. In previous and subsequent cycles, where vancomycin was not given, serum methotrexate levels in both patients fell to 200 micromol/mL within 48 to 96 hours.[1] It was suggested that vancomycin caused subclinical nephrotoxicity, which resulted in delayed excretion of methotrexate, which is primarily renally excreted.[1] However, in another report of 8 patients who had received high-dose methotrexate following the use of vancomycin (all but one within 10 days) for previous neutropenia, there was no significant interaction in the absence of overt renal impairment. It was suggested that the difference in outcome may be due to slightly lower methotrexate doses and the fact that the drug regimen in the 8 patients did not include ifosfamide which, particularly in combination with cisplatin, may cause cumulative renal tubular damage.[2]

Vancomycin is commonly used in oncology patients with febrile neutropenia, and this appears to be the first report of this interaction. The authors of this report[1] suggest that it would be prudent to measure glomerular filtration rate with an EDTA renal scan before giving high-dose methotrexate to patients recently treated with vancomycin, to allow modification of the methotrexate dose if necessary.[1] However, the authors of the second report disagree and suggest such monitoring cannot be supported by their findings.[2] Further study is needed.

1. Blum R, Seymour JF, Toner G. Significant impairment of high-dose methotrexate clearance following vancomycin administration in the absence of overt renal impairment. *Ann Oncol* (2002) 13, 327–30.
2. Shamash J, Joel S, Lundholm L, Millard L, Oliver T. High-dose methotrexate clearance following prior vancomycin administration: no significant interaction in the absence of overt renal impairment. *Ann Oncol* (2003) 14, 169–70.

Methotrexate + Antiepileptics; Enzyme-inducing

Enzyme-inducing antiepileptics appear to increase the clearance of methotrexate given as a 24-hour infusion, and their use is asso-

ciated with lower efficacy of combination therapy for B-lineage leukaemia.

Clinical evidence, mechanism, importance and management

In a retrospective survey, long-term antiepileptic use (**phenytoin**, **phenobarbital**, **carbamazepine**, or a combination) was associated with worse event-free survival, and greater haematological relapse and CNS relapse in children receiving chemotherapy for B-lineage acute lymphoblastic leukaemia. Faster clearance of high-dose methotrexate given as a 24-hour infusion was found in those receiving these enzyme-inducing antiepileptics; however, the clearance of short 4 to 6-hour methotrexate infusions and weekly low-dose methotrexate did not appear to be affected.[1] Further study is needed.

Note that reduced phenytoin ,carbamazepine and valproate levels, but unaltered phenobarbital levels, have been reported in various case reports of patients receiving chemotherapy including methotrexate, see 'Table 14.1', (p.594).

1. Relling MV, Pui C-H, Sandlund JT, Rivera GK, Hancock ML, Boyett JM, Schuetz EG, Evans WE. Adverse effect of anticonvulsants on efficacy of chemotherapy for acute lymphoblastic leukaemia. *Lancet* (2000) 356, 285–90.

Methotrexate + Ascorbic acid (Vitamin C)

A study in a single patient found that the urinary excretion of methotrexate was not significantly changed by large amounts of vitamin C.

Clinical evidence, mechanism, importance and management

Vitamin C 1 g three times daily was found to have no effect on the urinary excretion of intravenous methotrexate 45 mg, given to a woman with breast cancer, despite the urine becoming more acidic at pH 5.9 (see also 'Methotrexate + Urinary alkalinisers', p.758). She was also receiving oral cyclophosphamide, propranolol, amitriptyline, perphenazine and prochlorperazine.[1] Although this is an isolated report, it appears that vitamin C is unlikely to affect methotrexate excretion.

1. Sketris IS, Farmer PS, Fraser A. Effect of vitamin C on the excretion of methotrexate. *Cancer Treat Rep* (1984) 68, 446–7.

Methotrexate + Caffeine

Caffeine may theoretically reduce the efficacy of low-dose methotrexate given for rheumatoid arthritis.

Clinical evidence

A study in 39 patients who had recently started taking methotrexate 7.5 mg weekly found that patients with a self-reported high caffeine intake (more than 180 mg of caffeine daily, 13 patients) had less relief in their symptoms of rheumatoid arthritis, such as swollen joints and joint pain, and smaller reductions from baseline in their erythrocyte sedimentation rate (ESR), a marker for inflammation, than patients with a low caffeine intake (less than 120 mg of caffeine daily, 13 patients).[1] A survey of 91 patients taking methotrexate 5 to 15 mg weekly for rheumatoid arthritis found that patients who were regular coffee drinkers (more than 7 cups a week) had a higher rate of methotrexate discontinuation (due to treatment failure in 80% of cases).[2]

In contrast, an analysis of data in a cohort study in 264 patients taking long-term methotrexate for rheumatoid arthritis found that the consumption of caffeinated beverages did not appear to affect the efficacy of methotrexate for rheumatoid arthritis in either low, moderate or high consumers of caffeinated drinks. The average dose of methotrexate was 16 mg weekly and the average intake of caffeine from caffeinated drinks was 212 mg daily. No difference in inflammatory markers or worsening of rheumatoid arthritis was found between the low-caffeine intake group and the high-caffeine intake group.[3] Similarly, a survey in 64 patients taking methotrexate (mean dose 13 mg weekly) for psoriasis and psoriatic arthritis found no effect on the efficacy or dose requirements of methotrexate between low caffeine intake (less than 120 mg daily) and high caffeine intake (more than 180 mg daily).[4]

Mechanism

It is not known exactly how methotrexate produces its effects in rheumatoid arthritis, but one theory is that it possibly increases the levels of adenosine by blocking a step in purine biosynthesis, leading to accumulation of adenosine, which results in anti-inflammatory effects.[1] Methotrexate also inhibits the enzyme 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) transformylase, raising levels of AICAR, which in turn increases adenosine levels. It may also contribute to the phosphorylation of adenosine nucleotides creating an accumulation of adenosine in tissues.[1,3] Caffeine is an adenosine receptor antagonist and therefore could reverse the effects of methotrexate.

Importance and management

There is limited information available regarding a potential interaction between caffeine consumption and methotrexate. The cohort study results and one patient survey seem to indicate that caffeine intake is not an issue, even with a high intake, whereas one study and another survey did find reduced efficacy in those with a higher caffeine intake. However, these results, particularly the surveys, were limited by a number of factors, including subjective reporting of caffeine consumption, lack of caffeine blood levels, and uncontrolled ingestion of both drugs. One UK manufacturer of intravenous methotrexate (licenced for rheumatoid arthritis) recommends avoiding the excessive consumption of caffeine-containing drinks.[5] There do not appear to be any case reports or studies indicating treatment failure as a result of high caffeine intake in patients receiving chemotherapy with high-dose methotrexate. More study is needed, but bear in mind that a high caffeine intake may be a factor in a reduced benefit from low-dose methotrexate given for rheumatoid arthritis.

1. Nesher G, Mates M, Zevin S. Effect of caffeine consumption on efficacy of methotrexate in rheumatoid arthritis. *Arthritis Rheum* (2003) 48, 571–2.
2. Silke C, Murphy MS, Buckley T, Busteed S, Molloy MG, Phelan M. The effect of caffeine ingestion on the efficacy of methotrexate. *Rheumatology (Oxford)* (2001) 40, 34.
3. Benito-Garcia E, Heller JE, Chibnik LB, Maher NE, Matthews HM, Bilics JA, Weinblatt ME, Shadick NA. Dietary caffeine intake does not affect methotrexate efficacy in patients with rheumatoid arthritis. *J Rheumatol* (2006) 33, 1275–81.
4. Swanson DL, Barnes SA, Mengden Koon SJ, el-Azhary RA. Caffeine consumption and methotrexate dosing requirement in psoriasis and psoriatic arthritis. *Int J Dermatol* (2007) 46, 157–9.
5. Metoject (Methotrexate). Medac GmbH. UK Summary of product characteristics, November 2008.

Methotrexate + Chloroquine or Hydroxychloroquine

Single-dose chloroquine caused a moderate decrease in the AUC of methotrexate in one study, but another study in children found no interaction. Conversely, hydroxychloroquine caused a minor increase in the AUC of methotrexate in one study. Methotrexate does not appear to alter hydroxychloroquine pharmacokinetics.

Clinical evidence, mechanism, importance and management

Eleven patients with rheumatoid arthritis taking methotrexate 15 mg weekly were studied after they took a single dose of methotrexate alone and after they took methotrexate with a single 250-mg dose of **chloroquine**. The chloroquine *reduced* the maximum plasma levels of methotrexate by 20% and its AUC by 28%.[1] In contrast, in a study in patients with juvenile arthritis taking long-term methotrexate 150 micrograms/kg, the addition of **chloroquine** 4 mg/kg had no significant effect on the pharmacokinetics of methotrexate, when compared with similar patients taking methotrexate alone.[2]

In a randomised, crossover study in 10 healthy subjects, **hydroxychloroquine** 200 mg *increased* the AUC of methotrexate 15 mg by 52%, and slightly decreased the maximum methotrexate level by 17%.[3] In a population pharmacokinetic analysis the clearance of **hydroxychloroquine** did not appear to differ between 49 patients also taking methotrexate and 74 patients taking hydroxychloroquine alone.[4]

The reasons for the pharmacokinetic changes seen in some studies are unknown: just why the findings of these studies differ is unclear and their clinical relevance is uncertain. However, the changes seen were small, and the combination of methotrexate and chloroquine (or hydroxychloroquine) is used in the management of rheumatoid arthritis.

1. Seideman P, Albertioni F, Beck O, Eksborg S, Peterson C. Chloroquine reduces the bioavailability of methotrexate in patients with rheumatoid arthritis. A possible mechanism of reduced hepatotoxicity. *Arthritis Rheum* (1994) 37, 830–3.

2. Kimura E, Oga S, Periera RMR. Comparative study of the pharmacokinetics of MTX in juvenile idiopathic arthritis patients receiving long-term MTX monotherapy or MTX plus chloroquine. *J Clin Pharm Ther* (2007) 32, 579–84.
3. Carmichael SJ, Beal J, Day RO, Tett SE. Combination therapy with methotrexate and hydroxychloroquine for rheumatoid arthritis increases exposure to methotrexate. *J Rheumatol* (2002) 29, 2077–83.
4. Carmichael SJ, Charles B, Tett SE. Population pharmacokinetics of hydroxychloroquine in patients with rheumatoid arthritis. *Ther Drug Monit* (2003) 25, 671–81.

Methotrexate + Cisplatin

The risk of methotrexate toxicity appears to be markedly increased by the previous use of cisplatin. Methotrexate may inhibit the clearance of cisplatin.

Clinical evidence, mechanism, importance and management

Six out of 106 patients developed clinical signs of methotrexate toxicity and died 6 to 13 days after receiving standard doses of methotrexate (20 to 50 mg/m^2) in the absence of signs of renal impairment, and despite having previously been given methotrexate without serious toxicity. On this occasion all had previously been given cisplatin. Four of the patients were regarded as low-risk (i.e. methotrexate toxicity was not considered likely as they did not have renal or hepatic impairment, and their general condition was good).[1] A study in children and adolescents suggested that those who had received a cumulative dose of cisplatin greater than 360 mg/m^2 had delayed methotrexate clearance and a greater risk of methotrexate toxicity.[2] Similarly, a further report by the same authors, in 14 patients receiving high-dose methotrexate,[3] indicated that previous treatment with one course of cisplatin sharply increased the serum levels of methotrexate, particularly if the cumulative cisplatin dose exceeded 400 mg/m^2.

The picture is not totally clear but it seems possible that the previous use of cisplatin causes kidney damage that may not necessarily be detectable with the usual creatinine clearance tests. The effect is to cause a marked reduction in the clearance of the methotrexate. The serum methotrexate levels of such patients should be closely monitored so that any delay in its clearance is detected early and folinic acid rescue can be given.[2] This appears to prevent serious toxicity.[1-3]

There is also a report that suggests that methotrexate inhibits the renal clearance of cisplatin. The renal clearance of platinum in 4 of 5 patients with non-small-cell lung cancer given cisplatin 50 mg/m^2 and methotrexate 40 mg/m^2 was reduced in the first 6 hours after administration (50% lower in the first 3 hours). Apart from a transient increase in serum urea nitrogen and creatinine in one patient, there was no sign of nephrotoxicity with concurrent use.[4]

1. Haim N, Kedar A, Robinson E. Methotrexate-related deaths in patients previously treated with *cis*-diamminedichloride platinum. *Cancer Chemother Pharmacol* (1984) 13, 223–5.
2. Crom WR, Pratt CB, Green AA, Champion JE, Crom DB, Stewart CF, Evans WE. The effect of prior cisplatin therapy on the pharmacokinetics of high-dose methotrexate. *J Clin Oncol* (1984) 2, 655–61.
3. Crom WR, Teresi ME, Meyer WH, Green AA, Evans WE. The intrapatient effect of cisplatin therapy on the pharmacokinetics of high-dose methotrexate. *Drug Intell Clin Pharm* (1985) 19, 467.
4. Preiss R, Brovtsyn VK, Perevodchikova NI, Bychkov MB, Hüller H, Belova LA, Michailov P. Effect of methotrexate on the pharmacokinetics and renal clearance of cisplatin. *Eur J Clin Pharmacol* (1988) 34, 139–44.

Methotrexate + Colestyramine

The serum levels of methotrexate, given by infusion, were markedly reduced by colestyramine in several patients.

Clinical evidence

An 11-year-old girl with osteosarcoma who developed colitis when given high-dose intravenous methotrexate, was subsequently given colestyramine 2 g every 6 hours from 6 to 48 hours after the methotrexate. Serum methotrexate levels at 24 hours were approximately halved. A marked fall in serum methotrexate levels was seen in another patient similarly treated.[1] Colestyramine also reduced methotrexate levels in cases of toxicity in two other patients.[2,3]

Mechanism

Methotrexate undergoes enterohepatic recirculation, that is to say it is excreted into the gut in the bile and re-absorbed further along the gut. If colestyramine is given orally, it can bind strongly to the methotrexate in the gut, thereby preventing its reabsorption and, as a result, its serum levels fall.[1,4]

Importance and management

The documentation seems to be limited. In the cases cited[1-3] the colestyramine was deliberately used to reduce serum methotrexate levels. However, in some circumstances it might represent an unwanted interaction. As methotrexate is excreted into the gut in the bile, separating the oral doses of colestyramine and methotrexate may not necessarily prevent their coming into contact and interacting together. Monitor concurrent use.

1. Erttmann R, Landbeck G. Effect of oral cholestyramine on the elimination of high-dose methotrexate. *J Cancer Res Clin Oncol* (1985) 110, 48–50.
2. Shinozaki T, Watanabe H, Tomidokoro R, Yamamoto K, Horiuchi R, Takagishi K. Successful rescue by oral cholestyramine of a patient with methotrexate nephrotoxicity: nonrenal excretion of serum methotrexate. *Med Pediatr Oncol* (2000) 34, 226–8.
3. Fernández Megía MJ, Alós Almiñana M, Terol Castera MJ. Manejo de la intoxicación por metotrexato: a propósito de un caso. *Farm Hosp* (2004) 28, 371–4.
4. McAnena OJ, Ridge JA, Daly JM. Alteration of methotrexate metabolism in rats by administration of an elemental liquid diet. II. Reduced toxicity and improved survival using cholestyramine. *Cancer* (1987) 59, 1091–7.

Methotrexate + Corticosteroids

Methotrexate clearance may be modestly reduced by the long-term use of prednisolone, but methotrexate does not alter prednisolone pharmacokinetics. Limited evidence suggests methotrexate may alter prednisone levels. Dexamethasone may increase the acute hepatotoxicity of high-dose methotrexate.

Clinical evidence, mechanism, importance and management

There is some evidence to suggest that **prednisolone** may reduce the clearance of methotrexate: patients taking long-term **prednisolone** 15 mg daily had a 20% lower clearance of intramuscular methotrexate 10 mg and a 30% higher AUC than patients given **prednisolone** 15 mg daily for just 4 days before the methotrexate, or those not given corticosteroids.[1] In another study, methotrexate had no effect on **prednisolone** pharmacokinetics in 7 patients, or **methylprednisolone** pharmacokinetics in one patient.[2] The preliminary findings of another study suggested that methotrexate may increase plasma methylprednisolone levels in response to a dose of **prednisone**: in 2 of 4 patients given methotrexate, plasma methylprednisolone levels remained stable despite a decrease in the **prednisone** dose.[3] These findings require confirmation. Their clinical relevance is uncertain.

Dexamethasone may increase the acute hepatotoxicity of high-dose methotrexate. A retrospective comparison in children with brain tumours given methotrexate alone (24 patients), or with **dexamethasone** (33 patients), found that no serious brain oedema occurred in either of the groups and there were no differences in bone marrow toxicity or mucositis, but liver enzymes were significantly higher in the **dexamethasone** group, indicating liver toxicity (AST levels 76 units/L compared with 19 units/L, ALT levels 140 units/L compared with 39 units/L). This effect was not due to differences in serum methotrexate levels.[4] The authors recommend that **dexamethasone** should not be included in high-dose methotrexate protocols for children with brain tumours when they are not glucocorticoid dependent.[4]

1. Lafforgue P, Monjanel-Mouterde S, Durand A, Catalin J, Acquaviva PC. Is there an interaction between low doses of corticosteroids and methotrexate in patients with rheumatoid arthritis? A pharmacokinetic study in 33 patients. *J Rheumatol* (1993) 20, 263–7.
2. Glynn-Barnhart AM, Erzurum SC, Leff JA, Martin RJ, Cochran JE, Cott GR, Szefler SJ. Effect of low-dose methotrexate on the disposition of glucocorticoids and theophylline. *J Allergy Clin Immunol* (1991) 88, 180–6.
3. Sockin SM, Ostro MG, Goldman MA, Bloch KJ. The effect of methotrexate on plasma prednisolone levels in steroid dependent asthmatics. *J Allergy Clin Immunol* (1992) 89, 286.
4. Wolff JEA, Hauch H, Kühl J, Egeler RM, Jürgens H. Dexamethasone increases hepatotoxicity of MTX in children with brain tumours. *Anticancer Res* (1998) 18, 2895–9.

Methotrexate + Diuretics

Some very limited evidence suggests that triamterene may possibly increase the bone marrow suppressive effects of methotrexate. It seems doubtful if thiazides interact adversely with methotrexate.

Clinical evidence, mechanism, importance and management

A 57-year-old woman who had been treated for several years with daily doses of diclofenac 150 mg, atenolol 50 mg and **triamterene** with **hydrochlorothiazide** 50/25 mg, for rheumatoid arthritis and hypertension, additionally started taking methotrexate 5 mg weekly. After 2 months she was admitted to hospital with pancytopenia, extensive mucosal ulceration and renal impairment. The authors point out that **triamterene** is structurally similar to folate and has anti-folate activity, which may therefore have been additive with the effects of methotrexate,[1] but the diclofenac may also have contributed (see 'Methotrexate + NSAIDs, Aspirin or other Salicylates', p.752). In 1998, the manufacturer of methotrexate noted there were two other reports of pancytopenia in patients taking methotrexate and **triamterene**, but again the patients were also taking an NSAID.[2] These cases are isolated, and none of them can be directly attributed to an interaction. Nevertheless, it may be prudent to consider the use of triamterene as a possible cause of otherwise unexplained methotrexate toxicity.

A study in 9 patients found that **furosemide** and **hydroflumethiazide** did not effect the urinary clearance of methotrexate.[3] However, a study in women with breast cancer, taking methotrexate, **cyclophosphamide** and **fluorouracil** found that the concurrent use of a **thiazide diuretic** appeared to increase the myelosuppressant effects of the chemotherapy, but it is not clear which of the antineoplastics might have been affected.[4] This appears to be the only evidence of an interaction between the thiazides and methotrexate. An interaction is not established.

1. Richmond R, McRorie ER, Ogden DA, Lambert CM. Methotrexate and triamterene — a potentially fatal combination. *Ann Rheum Dis* (1997) 56, 209–10.
2. Wyeth/Lederle. Data on file, September 1998.
3. Kristensen LØ, Weismann K, Hutters L. Renal function and the rate of disappearance of methotrexate from serum. *Eur J Clin Pharmacol* (1975) 8, 439–44.
4. Orr LE. Potentiation of myelosuppression from cancer chemotherapy and thiazide diuretics. *Drug Intell Clin Pharm* (1981) 15, 967–70.

Methotrexate + Fluorouracil

Two patients taking low-dose methotrexate had a toxic skin reaction when they started to use a cream containing fluorouracil. The activity of systemic treatment with methotrexate and fluorouracil are said to be dependent on the order in which the two drugs are given.

Clinical evidence, mechanism, importance and management

(a) Topical fluorouracil

Two patients with rheumatoid arthritis taking low-dose methotrexate 7.5 to 12.5 mg weekly for 6 to 14 months were given 2% fluorouracil cream for actinic keratosis. Within 2 to 3 days both patients developed erythema, blister formation and necrosis. The cream was stopped and the lesions healed over the next 2 to 3 weeks.[1] It would seem that topical fluorouracil should be avoided in patients taking methotrexate.

(b) Systemic fluorouracil

In vitro and *animal* data indicate that methotrexate and fluorouracil can be mutually antagonistic under certain conditions.[2-4] Other studies indicate that the sequence (methotrexate first)[5,6] is important for additive or synergistic activity. However, the combination of cyclophosphamide, methotrexate and fluorouracil (CMF) has been the most commonly used adjuvant therapy in breast cancer, and the sequence of administration is said not to be important.[7]

1. Blackburn WD, Alarcón GS. Toxic response to topical fluorouracil in two rheumatoid arthritis patients receiving low dose weekly methotrexate. *Arthritis Rheum* (1990) 33, 303–4.
2. Tattersall MHN, Jackson RC, Connors TA, Harrap KR. Combination chemotherapy: the interaction of methotrexate and 5-fluorouracil. *Eur J Cancer* (1973) 9, 733–9.
3. Maugh TH. Cancer chemotherapy: an unexpected drug interaction. *Science* (1976) 194, 310.
4. Waxman S, Bruckner H. Antitumour drug interactions: additional data. *Science* (1976) 194, 672.
5. Bertino JR, Sawicki WL, Lindquist CA, Gupta VS. Schedule-dependent antitumor effects of methotrexate and 5-fluorouracil. *Cancer Res* (1977) 37, 327–8.
6. Brown I, Ward HWC. Therapeutic consequences of antitumour drug interactions: methotrexate and 5-fluorouracil in the chemotherapy of C3H mice with transplanted mammary adenocarcinoma. *Cancer Lett* (1978) 5, 291–7.
7. Summerhayes M, Daniels S, eds. Practical Chemotherapy: A Multidisciplinary Guide. 1st ed. UK: Radcliffe Medical Press; 2003 P. 91.

Methotrexate + Folinates

Folic acid or folinic acid are sometimes added to low-dose methotrexate for rheumatoid arthritis or psoriasis to reduce adverse effects. Folinic acid is frequently used as an antidote to high-dose methotrexate.

Clinical evidence, mechanism, importance and management

Methotrexate acts as a folic acid antagonist by reversibly binding to the enzyme dihydrofolate reductase, so blocking the conversion of folic acid to tetrahydrofolate. Therefore folic acid and folinic acid (a derivative of tetrahydrofolate) would be expected to interfere with both the toxic and therapeutic effects of methotrexate.

Folic acid or folinic acid are commonly used to reduce the adverse effects of low-dose methotrexate used for rheumatoid arthritis and psoriasis, although the optimum doses and schedules to maximise tolerability and efficacy remain to be determined.

Similarly, folinic acid is used in conjunction with high-dose methotrexate for various cancers to minimise toxicity, when it is typically started 24 hours after methotrexate administration (folinic acid or 'leucovorin' rescue). In this setting, the antidote effect is clearly influenced by the dose of folinate in relation to the dose of methotrexate, and the timing of folinate administration in relation to methotrexate administration.

Patients taking methotrexate for any indication should avoid the inadvertent or unsupervised use of folates, which are commonly found in multivitamin preparations.

Methotrexate + Food

The absorption of low-dose oral methotrexate does not appear to be significantly affected by food.

Clinical evidence, mechanism, importance and management

In 10 children with lymphoblastic leukaemia the peak serum levels of a 15-mg/m^2 oral dose of methotrexate (measured at 1.5 hours) were reduced by about 40% when the methotrexate was taken with a milky meal (milk, cornflakes, sugar, white bread and butter). The $AUC_{0\text{-}4}$ was reduced by about 25%. A smaller reduction in methotrexate absorption was seen when it was taken after a citrus meal (orange juice, fresh orange, white bread, butter and jam).[1] However, a 4-hour study is too short to assess the extent of the total absorption. Another study, in 16 children given methotrexate 8 to 22.7 mg/m^2, found that the peak levels and AUC were not significantly affected if methotrexate was given before a meal.[2] A further study in 12 healthy subjects found that a high fat-content breakfast delayed the absorption of methotrexate 7.5 mg orally by about 30 minutes but the extent of the absorption was unchanged.[3] It would therefore appear that methotrexate may be taken without regard to meals.

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Methotrexate + Isoniazid

It is possible that the risk of liver function abnormalities seen with either methotrexate or isoniazid is increased when the two drugs are given together. One small review suggested this may be the case, but other larger reviews have not confirmed these findings.

Clinical evidence

In a review of clinical studies of tumour necrosis factor (TNF) antagonists given to patients already taking methotrexate or **sulfasalazine** for rheumatoid arthritis, 8 patients were identified who were also given prophylactic isoniazid 300 mg daily for inactive (latent) tuberculosis (positive PPD skin test). Of these, 4 patients (50%) developed mild to severe hepatic impairment within 7 to 16 weeks, and in three cases this resolved on discon-

tinuation of isoniazid. In one case, excessive alcohol consumption might have been a contributory factor. Two cases (one mild, one severe) occurred in 5 patients taking methotrexate, and 2 cases (one moderate and one severe) occurred in 3 patients taking **sulfasalazine**.[1]

In contrast, when 77 patients with rheumatoid arthritis were given methotrexate with isoniazid prophylaxis for 3 years, two patients stopped treatment due to increases in AST and ALT, but the incidence of hepatotoxic effects was no different to that found in the control group.[2] In a retrospective review of the records of 44 patients taking methotrexate for rheumatoid arthritis and given prophylactic isoniazid for inactive tuberculosis (38 patients) or isoniazid, **pyrazinamide**, rifampicin and ethambutol for a history of active tuberculosis (6 patients), just 5 patients (11.3%) had elevated liver function tests. None of these were more than twice the upper limit of normal, and all abnormalities resolved without intervention. None of the patients included in this study had experienced liver function abnormalities while taking methotrexate alone.[3] For comparison, the authors of this study[3] mention that in one large study, raised liver function tests (three times the upper limit of normal), occurred in 7.5% of patients treated with methotrexate for rheumatoid arthritis.

Mechanism

Both isoniazid and methotrexate are known to be hepatotoxic, and it has been suggested that the risk might be increased by combined use. Sulfasalazine is also hepatotoxic, as is rifampicin and, particularly, pyrazinamide.

Importance and management

An increased risk of hepatotoxicity during the concurrent use of methotrexate and isoniazid is not established, and this possible risk is not a reason to avoid the combination. Monitoring of liver function is recommended during long-term methotrexate use, and is also recommended for isoniazid. This would appear to be sufficient to identify any adverse hepatic effects.

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Methotrexate + Miscellaneous

***Animal* studies suggested that the toxicity of methotrexate might be increased by the use of chloramphenicol, aminosalicylic acid, sodium salicylate, sulfamethoxypyridazine, tetracycline or tolbutamide, but confirmation of this in man has only been seen with the salicylates, sulphonamides, and possibly tetracycline.**

Clinical evidence, mechanism, importance and management

Some lists, reviews and books on interactions say that **chloramphenicol**, aminosalicylic acid, sodium salicylate, sulfamethoxypyridazine, tetracycline or **tolbutamide** interact with methotrexate, apparently based largely on the preliminary findings of a study in which male *mice* were treated for 5 days with each of 4 doses of methotrexate (1.53 to 12.25 mg/kg intravenously) and immediately afterwards with non-toxic intraperitoneal doses of the drugs listed. These drugs were said to decrease the lethal dose and/or decrease the survival time of the *mice*.[1] That is to say, the toxicity of the methotrexate was increased. The reasons are not understood, but it is suggested that displacement of the methotrexate from its plasma protein binding sites could result in a rise in the levels of unbound and active methotrexate, and in the case of sodium salicylate to a decrease in renal clearance.

These *animal* studies were done in 1968. Since then the clinical importance of the interaction with salicylates has been confirmed (see 'Methotrexate + NSAIDs, Aspirin or other Salicylates', below); there are a few cases involving sulfonamides (see 'Methotrexate + Antibacterials; Co-trimoxazole or Trimethoprim', p.745); and there are two isolated case reports of an interaction with tetracyclines (see 'Methotrexate + Antibacterials; Tetracyclines', p.748), but there appears to be no direct clinical evidence of interactions between methotrexate and **chloramphenicol** or **tolbutamide**. The results of *animal* experiments cannot be applied directly and uncritically to man and it now seems probable that some of these suggested or alleged interactions are more theoretical than real.

1. Dixon RL. The interaction between various drugs and methotrexate. *Toxicol Appl Pharmacol* (1968) 12, 308.

Methotrexate + Nitrous oxide

Methotrexate-induced stomatitis and other toxic effects may be increased by the use of nitrous oxide.

Clinical evidence, mechanism, importance and management

A study in which intravenous methotrexate, cyclophosphamide and fluorouracil (CMF) were used within 36 hours of mastectomy suggested that stomatitis may be caused by a toxic interaction between methotrexate and nitrous oxide used during anaesthesia. Stomatitis was much more common in those receiving CMF within 6 hours of surgery.[1-3] A possible reason is that the effects of methotrexate on tetrahydrofolate metabolism are increased by nitrous oxide, and this has been confirmed in *animals*.[4] It was found that the incidence of stomatitis, severe leucopenia, thrombocytopenia, and of severe systemic and local infections could be reduced by giving calcium folinate (leucovorin) and intravenous hydration.[2,3] Alternatively, the use of nitrous oxide shortly before methotrexate administration should be avoided.[4]

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Methotrexate + NSAIDs, Aspirin or other Salicylates

Increased methotrexate toxicity, sometimes life-threatening, has been seen in a few patients also taking NSAIDs, whereas other patients have taken an NSAID and methotrexate uneventfully. The pharmacokinetics of methotrexate can also be changed by some NSAIDs, aspirin or other salicylates. The development of toxicity may be dose related: the risk appears to be lowest in those taking low-dose methotrexate for psoriasis or rheumatoid arthritis who have normal renal function.

Clinical evidence

(a) Aminophenazone

Megaloblastic pancytopenia occurred in a woman with rheumatoid arthritis who took methotrexate 15 mg weekly with aminophenazone 1 to 1.5 g daily.[1]

(b) Aspirin and other salicylates

A study in 15 patients with rheumatoid arthritis given a single 10-mg bolus dose of methotrexate, either with or without aspirin 975 mg four times daily, found that the methotrexate clearance was reduced by aspirin (systemic clearance about 16%, renal clearance of unbound methotrexate about 30%). Also, the unbound fraction of methotrexate was higher during aspirin use. Despite these changes no acute toxicity was seen.[2] Another study found that aspirin did not affect the pharmacokinetics of methotrexate.[3] A further study found that, although aspirin did not alter the pharmacokinetics of methotrexate, it did increase the AUC of the metabolite 7-hydroxymethotrexate.[4]

A study in 4 patients found that the renal clearance of methotrexate was reduced by 35% by an infusion of **sodium salicylate** (2 g initially, then 33 mg/minute).[5] A further study found that **choline magnesium trisalicylate** reduced methotrexate clearance by 24 to 41%, and increased the

unbound fraction by 28%, when compared with paracetamol (acetaminophen).[6]

Lethal pancytopenia in 2 patients given methotrexate and aspirin prompted a retrospective survey of the records of other patients given intra-arterial infusions of methotrexate 50 mg daily for 10 days, for epidermoid carcinoma of the oral cavity. Six out of 7 who developed rapid and serious pancytopenia were found to have taken aspirin or other salicylates.[7] There are other case reports[8,9] of methotrexate toxicity in patients taking salicylates but whether a causal relationship exists is uncertain. It has been suggested that pneumonitis in patients receiving low-dose methotrexate may have resulted from the concurrent use of aspirin 4 to 5 g daily.[10]

See also the report about the comparative use of aspirin and other NSAIDs in the section *NSAIDs in general*, below.

(c) Azapropazone

A woman who had been taking methotrexate 25 mg weekly for 4 years for psoriasis had acute toxicity (oral and genital ulceration, bone marrow failure) shortly after starting to take azapropazone (reducing from a dose of 2.4 g on the first day, 1.8 g on the second day to 1.2 g daily for a week). She was also taking aspirin 300 mg daily.[11,12]

(d) Bromfenac

In a short-term study, 10 patients taking methotrexate weekly were given bromfenac 50 mg three times daily for 6 days. No significant changes were seen in either the pharmacokinetics of bromfenac or methotrexate. However, the AUC of the major metabolite of methotrexate, 7-hydroxymethotrexate, was increased by 30% and its renal clearance was reduced by 16%. Eight of the patients had mild to moderate adverse effects and one patient had to withdraw because of moderate hypertension. No patient had any clinically important abnormal laboratory test results.[13] Note that systemic bromfenac has been withdrawn from the market because of reports of hepatic toxicity.

(e) Celecoxib

Fourteen female patients with rheumatoid arthritis taking methotrexate 5 to 20 mg weekly for at least 3 months were also given celecoxib 200 mg or a placebo twice daily for a week. It was found that the maximum serum levels of the methotrexate, its AUC, renal clearance, and other pharmacokinetic parameters were unchanged by celecoxib.[14] The authors note that, in clinical studies, celecoxib was taken in combination with low-dose methotrexate for up to 12 weeks by over 450 patients, and the incidence of adverse effects was similar to that in patients taking methotrexate with placebo.[14]

(f) Diclofenac

A study found that diclofenac 100 mg daily did not affect the pharmacokinetics of methotrexate.[3] Five patients taking low-dose methotrexate 7.5 to 12.5 mg weekly for psoriasis or rheumatoid arthritis developed serious/fatal neutropenias. These cases probably involved other drug interactions, but diclofenac may have been an additional factor in two of them.[15] Methotrexate pneumonitis occurred in a patient who had taken methotrexate 10 mg weekly for 4 weeks. He was also taking diclofenac 75 mg twice daily, although the relevance of this to the adverse reaction is uncertain.[16] Other cases involving diclofenac are mentioned in the sections on *indometacin* and *ketoprofen*, below.

(g) Dipyrone (Metamizole sodium)

A study in a patient with osteosarcoma found that dipyrone 4 g daily more than doubled the methotrexate AUC during the first cycle of high-dose methotrexate treatment.[17]

(h) Etodolac

A pharmacokinetic study in patients with rheumatoid arthritis found that etodolac 600 mg daily did not affect the AUC of methotrexate, but the duration of exposure was lengthened (mean residence time increased from 8.5 hours to 11.4 hours). No clinical toxicity was seen.[18]

(i) Etoricoxib

A study in patients taking methotrexate 7.5 to 20 mg weekly for rheumatoid arthritis found that the addition of etoricoxib 60, 90 or 120 mg daily had no effect on the methotrexate AUC or on its renal clearance. However, another similar study found that etoricoxib 120 mg daily increased the methotrexate AUC by 28% and reduced its clearance by 13%.[19]

(j) Flurbiprofen

A study in 6 patients taking methotrexate 10 to 25 mg weekly found no important changes in methotrexate levels when they were also given flurbiprofen 100 mg three times daily.[20] In another study in 10 patients with rheumatoid arthritis taking methotrexate 7.5 to 17.5 mg weekly and flurbiprofen 3 mg/kg daily, methotrexate oral and renal clearance were similarly unaffected by flurbiprofen.[21]

A case report describes an elderly woman who had been taking methotrexate 2.5 mg three times a week for 3 years for rheumatoid arthritis, who developed haematemesis, neutropenia and thrombocytopenia (diagnosed as methotrexate toxicity) within 1 to 2 weeks of starting to take flurbiprofen 100 mg daily.[22]

(k) Ibuprofen

A study in 7 patients found that the clearance of oral methotrexate 7.5 to 15 mg was halved by ibuprofen 40 mg/kg daily, when compared with paracetamol (acetaminophen).[23] In a related study the clearance of methotrexate was reduced by 40% by ibuprofen.[6] Another study in 6 patients with rheumatoid arthritis taking methotrexate 10 to 25 mg weekly found that ibuprofen 800 mg three times daily had no effect on the pharmacokinetics of methotrexate.[20] Similar findings have been reported by other workers.[3]

A patient taking methotrexate who was given ibuprofen required prolonged folinic acid rescue because the clearance of methotrexate had fallen by two-thirds.[24] Another patient receiving high-dose methotrexate (7.5 g/m^2) had severe methotrexate-induced nephrotoxicity and delayed excretion of methotrexate while taking ibuprofen 400 mg every 4 hours.[25] A report attributes pancytopenia and resulting pneumocystis pneumonia in a 16-year-old patient taking methotrexate 5 to 10 mg weekly to the concurrent use of ibuprofen 600 mg twice daily (and also prednisolone 1 mg daily).[26]

(l) Indometacin

In a child taking methotrexate 7.5 mg/m^2 weekly for 9 months, the AUC of methotrexate was increased by 140% when indometacin and aspirin were also given.[27] Another study found that indometacin did not affect the pharmacokinetics of methotrexate.[3]

Two patients given sequential intermediate-dose methotrexate and fluorouracil, who were also taking indometacin 75 to 100 mg daily, died from acute drug toxicity, which the authors of the report attributed to indometacin-associated renal failure.[28] Another case of acute renal failure has been described,[29] but there were no cases of toxicity in 4 other patients taking methotrexate with either paracetamol (acetaminophen) or indometacin.[9] An elderly woman taking indometacin 50 mg daily rectally and **diclofenac** 100 mg daily intravenously died after being given a single 10-mg intramuscular dose of methotrexate.[30]

(m) Ketoprofen

In a study in 10 patients with rheumatoid arthritis taking methotrexate 7.5 to 17.5 mg weekly and ketoprofen 3 mg/kg daily, the methotrexate oral and renal clearance and the fraction of methotrexate unbound were unaffected by ketoprofen.[21] Similarly, in another study in 18 patients with rheumatoid arthritis who were given intravenous methotrexate 15 mg weekly, ketoprofen had no significant effect on the AUC, half-life, or clearance of methotrexate and its major metabolite, 7-hydroxymethotrexate.[31] However, a retrospective study of 118 cycles of *high-dose* methotrexate (800 to 8300 mg/m^2; mean 3200 mg/m^2) in 36 patients found that 4 out of the 9 patients who developed severe methotrexate toxicity had also taken ketoprofen 150 to 200 mg daily for 2 to 15 days. Three of them died. A marked and prolonged rise in serum methotrexate levels was observed. Another patient who had methotrexate toxicity had also been given **diclofenac** 150 mg (in one day).[32] The authors of this report state that ketoprofen should not be given at the same time as high-dose methotrexate, but it may be safe to give it 12 to 24 hours after the methotrexate because 50% of the methotrexate is excreted by the kidneys within 6 to 12 hours. This was tried in two patients without adverse effects.[32]

(n) Lumiracoxib

In a double-blind, placebo-controlled study in patients with rheumatoid arthritis given methotrexate 7.5 to 15 mg weekly, lumiracoxib 400 mg daily for 7 days had no significant effects on the pharmacokinetics of methotrexate.[33]

(o) Meloxicam

Thirteen patients with rheumatoid arthritis were given intravenous methotrexate 15 mg before and after taking meloxicam 15 mg daily for a week.

The pharmacokinetics of methotrexate were unaffected by meloxicam and no increase in toxicity was seen.[34]

(p) Naproxen

Naproxen had no significant effect on the AUC, half-life, or clearance of methotrexate and its major metabolite 7-hydroxymethotrexate in 18 patients with rheumatoid arthritis given intravenous methotrexate 15 mg weekly.[31] Other studies have found that naproxen did not affect the pharmacokinetics of methotrexate and/or 7-hydroxymethotrexate.[3,35,36]

In contrast, a study found that the clearance of methotrexate was decreased by 22% by naproxen.[6,23] A further study in 9 children taking methotrexate 0.22 to 1.02 mg/kg weekly found that the clearance of methotrexate was increased in 4 children by more than 30% when they were given naproxen 14.6 to 18.8 mg/kg daily. There was also a 30% or more change in the pharmacokinetics of naproxen in 6 of the patients, but as both increases and decreases in clearance occurred, the significance of these findings are uncertain.[37] In addition, two children taking methotrexate for 1 and 2 years had increases in the AUC of methotrexate of 22% and 71% when given naproxen with aspirin or indometacin, respectively.[27] A woman died of gross methotrexate toxicity apparently exacerbated by the concurrent use of naproxen,[38] and a report attributes pneumonitis in a patient taking methotrexate 7.5 to 10 mg weekly to the concurrent use of naproxen (initially 1 g then 500 mg) daily.[39] A further report describes an infant who developed severe hepatitis while taking methotrexate and naproxen for juvenile idiopathic arthritis. Following intravenous folinic acid and cessation of methotrexate and naproxen her liver function normalised. The role of naproxen is unclear, but the authors consider that the toxicity of methotrexate may have been synergistic with naproxen.[40]

(q) Parecoxib

Studies in patients with rheumatoid arthritis found that oral valdecoxib 40 mg twice daily had no clinically significant effect on the plasma levels of methotrexate given weekly by the intramuscular route [dose not stated].[41] Note that valdecoxib is the main metabolite of parecoxib.

(r) Phenylbutazone

Two patients taking methotrexate for psoriasis developed methotrexate toxicity and skin ulceration shortly after starting to take phenylbutazone 200 to 600 mg daily. One of them died from septicaemia following bone marrow depression.[42]

(s) Piroxicam

No effect on the pharmacokinetics of either free or bound methotrexate was seen in 20 patients with rheumatoid arthritis taking methotrexate 10 mg weekly when they were given piroxicam 20 mg daily for at least 15 days.[43] In another study in 10 patients with rheumatoid arthritis taking methotrexate 7.5 to 17.5 mg weekly, methotrexate oral and renal clearance were unaffected by piroxicam 20 mg daily.[21]

(t) Rofecoxib

Rofecoxib 12.5 to 50 mg daily had no effect on the AUC and renal clearance of methotrexate or 7-hydroxymethotrexate in 19 patients taking methotrexate 7.5 to 20 mg weekly.[44] However, the authors note that in previous evaluations (data on file), higher than therapeutic doses of rofecoxib (75 mg and 250 mg) were associated with a 23% and 40% increase in the AUC of methotrexate, and an 11% and 40% decrease in its renal clearance, respectively.[44]

(u) Sulindac

Sulindac (mean dose 400 mg daily) had no effect on the pharmacokinetics of a single 10-mg/m^2 intravenous dose of methotrexate, but it slightly increased the AUC of the 7-hydroxymethotrexate metabolite.[4]

(v) Tolmetin

Three children taking methotrexate for between 6 months and 1 year had increases in the AUC of methotrexate of 42% when given tolmetin, and of 18% and 25% when given tolmetin with aspirin.[27]

(w) NSAIDs in general

In a study of 34 patients with rheumatoid arthritis taking methotrexate 5 or 10 mg/m^2 (to nearest 2.5 mg) weekly, 12 patients also took **aspirin** (average 4.5 g daily) and 22 took other NSAIDs. Twenty-one of the 34 also took prednisone. Toxicity, sometimes serious (5 patients withdrawn), was common, but no clinical differences between **aspirin** or other NSAIDs with respect to this toxicity was seen during 12 months of concurrent use.[45]

A preliminary report of a study in 87 patients receiving long-term treatment with methotrexate (mean weekly dose 8.19 mg), most of whom were also taking unspecified NSAIDs, found that the majority (72%) experienced no untoward effects and in the rest adverse effects were only relatively mild.[46] The concurrent use of methotrexate and NSAIDs in more than 450 patients with psoriatic arthritis or rheumatoid arthritis was said to be without clinical interaction problems.[47]

In a review of the records of 315 patients with rheumatoid arthritis taking low-dose methotrexate, 13 patients had low platelet counts. The thrombocytopenia was believed to have resulted from an interaction with an NSAID, or in some patients, a multiple drug interaction. If multiple drug interactions were not involved, the authors found that if the NSAID was given on a separate day, or doses spaced according to the NSAID half-life, treatment could be re-introduced avoiding the problems of thrombocytopenia.[48]

Mechanism

Methotrexate is largely cleared unchanged from the body by renal excretion. The NSAIDs as a group inhibit the synthesis of the prostaglandins (PGE_2) resulting in a fall in renal perfusion, which could lead to a rise in serum methotrexate levels, accompanied by increased toxicity. In addition, salicylates competitively inhibit the tubular secretion of methotrexate, which would further reduce its clearance.[5] NSAIDs can also cause renal impairment, which would allow the methotrexate to accumulate. The pyrazolone derivatives and related drugs (e.g. azapropazone, metamizole sodium, phenylbutazone, aminophenazone), in particular, can cause bone marrow depression, which could be additive with that of methotrexate. Protein binding displacement of methotrexate or its metabolite (7-hydroxymethotrexate) have also been suggested as possible additional mechanisms.[49,50] There is also some evidence that 7-hydroxymethotrexate is cleared more slowly in the presence of NSAIDs.[4]

Importance and management

The evidence presented here clearly shows that a few patients taking methotrexate have developed very serious toxicity, apparently due to the concurrent use of NSAIDs, whereas many other patients have experienced no problems at all. There is also other evidence that the pharmacokinetics of the methotrexate are changed (in particular reduced clearance) by some NSAIDs (aspirin, choline magnesium trisalicylate, etodolac, ibuprofen, metamizole sodium, rofecoxib (at higher than therapeutic doses), sodium salicylate, tolmetin), which might be expected to increase its toxicity.

The consensus of opinion seems to be that the risks are greatest with high-dose methotrexate (150 mg or more daily to treat neoplastic diseases) and in patients with impaired renal function, but less in those given low doses (5 to 25 mg weekly) for psoriasis or rheumatoid arthritis and with normal renal function. The manufacturers of methotrexate and the CSM in the UK do not advise the avoidance of NSAIDs (except azapropazone and non-prescription aspirin and ibuprofen), even though their use is a recognised additional risk factor for toxicity. Instead their advice is that the methotrexate dose should be well monitored, which implies that the precautions for methotrexate use should be stepped up. The advice of the CSM is that any patient given methotrexate alone should have a full blood count, renal and liver function tests before starting treatment. These should be repeated weekly until therapy is stabilised, and thereafter every 2 to 3 months. Patients should be told to report any sign or symptom suggestive of infection, particularly sore throat (which might possibly indicate that white cell counts have fallen) or dyspnoea or cough (suggestive of pulmonary toxicity).[51] Aminophenazone or metamizole sodium can cause agranulocytosis on their own (and they consequently have limited use) so their use with methotrexate should be avoided.

Some of the NSAIDs cited here have not been reported to interact (celecoxib, lumiracoxib, meloxicam, piroxicam), and information about some other NSAIDs seems to be lacking, but the same general precautions indicated above should be followed with all NSAIDs just to be on the safe side.

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Methotrexate + Paracetamol (Acetaminophen)

Paracetamol appears not to interact with methotrexate.

Clinical evidence, mechanism, importance and management

A study in patients with rheumatoid arthritis found that the clearance of oral methotrexate 7.5 to 15 mg was unaffected by the concurrent use of paracetamol.[1] In a study of patients with psoriasis taking methotrexate in doses of up to 25 mg weekly, no cases of toxicity occurred in 4 patients also taking paracetamol or indometacin.[2] In one study, methotrexate clearance was reduced by NSAIDs but not by paracetamol, which was included in the study as a control.[3]

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Methotrexate + Probenecid

Probenecid markedly increases serum methotrexate levels.

Clinical evidence

The concurrent use of oral or intravenous probenecid 500 mg to 1 g and methotrexate 200 mg/m^2 as an intravenous bolus resulted in serum methotrexate levels in 4 patients that were more than four times higher than in 4 other patients who had not been given probenecid (methotrexate levels 400 micrograms/L compared with 90 micrograms/L, measured 24-hours post-dose).[1] A three to fourfold increase in serum methotrexate levels at 24 hours was also seen in 4 patients given probenecid.[2] In another 4 patients, pretreatment with probenecid (500 mg every 6 hours for 5 doses) doubled serum methotrexate levels.[3] Severe and life-threatening pancytopenia occurred when a woman taking low-dose methotrexate 7.5 mg weekly for rheumatoid arthritis was given probenecid. She also had renal impairment, hypoalbuminaemia and was taking salsalate (a salicylic acid derivative).[4]

Mechanism

Probenecid inhibits the renal excretion of methotrexate in both *monkeys* and *rats*[5,6] and this probably also happens in man. Changes in the protein binding of methotrexate may also have some part to play.[7] The increased methotrexate levels increase the risk of serious bone marrow depression.

Importance and management

An established and clinically important interaction. A marked increase in both the therapeutic and toxic effects of methotrexate can occur, apparently even with low doses if other risk factors are present.[4] Anticipate the need to reduce the dose of methotrexate and monitor the effects well if probenecid is used concurrently. If this is not possible, avoid the combination.

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Methotrexate + Proton pump inhibitors

The excretion of methotrexate is reported to have been reduced in several patients given omeprazole and a few patients given lansoprazole. However, similar elevations in methotrexate levels in another patient were independent of omeprazole use. One patient had myalgia and elevated 7-hydroxymethotrexate levels when given methotrexate with pantoprazole.

Clinical evidence

(a) Lansoprazole

In a study in 76 patients with solid tumours treated with high-dose methotrexate infusions (300 mg/m^2 to 12 g/m^2 over 1 to 24 hours), the clearance of methotrexate and its metabolite 7-hydroxymethotrexate was significantly decreased and its plasma levels significantly increased in the 3 patients who were also given lansoprazole 30 mg daily.[1]

(b) Omeprazole

In a study in 76 patients with solid tumours, receiving high-dose methotrexate infusions (300 mg/m^2 to 12 g/m^2 over 1 to 24 hours), the clearance of methotrexate and its metabolite 7-hydroxymethotrexate was significantly decreased and the plasma levels significantly increased in the 10 patients who had also been given omeprazole 20 to 40 mg daily.[1] A number of case reports support this finding. In one, a man with Hodgkin's disease developed osteosarcoma and was given cyclophosphamide, bleomycin, dactinomycin and methotrexate, followed by folinic acid rescue. He was also taking a number of other drugs, including omeprazole. During the first cycle of treatment his serum methotrexate levels remained elevated for several days, and suspicion fell on the omeprazole, which was stopped. The patient's serum methotrexate levels then fell rapidly, and during the following three cycles the methotrexate pharmacokinetics were normal.[2] In another case, an 11-year-old boy with osteoblastic osteosarcoma was given high-dose methotrexate 15 g as a 4-hour infusion. He was also given omeprazole 20 mg twice daily (for about one week before the methotrexate), megestrol acetate, sucralfate and folinic acid rescue. Methotrexate elimination was delayed and so further folinic acid was given. When later cycles of methotrexate were given, with ranitidine instead of omeprazole, the elimination of methotrexate was normal. The elimination half-life of the initial phase after the first dose given with omeprazole was 65% longer, when compared with that of the second dose without omeprazole.[3] In a third report, a 15-year-old boy experienced methotrexate toxicity, and elevated levels of methotrexate despite being given folinic acid, when he was also taking omeprazole. His symptoms of methotrexate resolved rapidly once omeprazole was stopped. He had experienced no toxicity in a previous cycle when he had taken ranitidine.[4]

In contrast to these findings, a case report describes a man with chondroblastic osteosarcoma, who had been taking omeprazole, and who was given high-dose methotrexate 20 g over 6 hours with hydration, urinary alkalinisation and, after 24 hours, folinic acid rescue. The folinic acid dose was adjusted in response to elevated methotrexate levels and omeprazole was stopped. A second dose of methotrexate 2 weeks later, this time without omeprazole, resulted in similar elevated methotrexate levels. Thus the elevated methotrexate levels in this patient could not be attributed to the concurrent use of omeprazole.[5]

(c) Pantoprazole

Severe generalised myalgia occurred in a man taking pantoprazole 20 mg daily after he received intramuscular methotrexate 15 mg weekly. The symptoms subsided and eventually disappeared when the pantoprazole was replaced with ranitidine. The symptoms reappeared in response to rechallenge with pantoprazole, and the AUC of 7-hydroxymethotrexate was found to be increased by about 70%, although the AUC of methotrexate was unchanged.[6]

Mechanism

Proton pump inhibitors may affect renal, and possibly hepatic, clearance of methotrexate by inhibition of methotrexate transporter proteins.[1,7] It has been suggested that omeprazole may inhibit the activity of a hydrogen-ion dependent mechanism in the kidney, on which methotrexate depends for its excretion, so that its renal clearance is reduced.[2] It has also been suggested that the situation with lansoprazole may be similar, but that pantoprazole may differ because at about the pH found in the renal tubules (pH 5), pantoprazole is more slowly activated than omeprazole.[3] However, a case of an interaction with pantoprazole has also been reported.[6]

Importance and management

Information seems to be limited to these few reports and, with the exception of one case report, they all found that proton pump inhibitors reduced the clearance of methotrexate. Any changes in methotrexate kinetics are important in terms of the potential for increased toxicity. The authors of one study in which the levels of methotrexate and its active metabolite were increased during the concurrent use of omeprazole or lansoprazole advise against concurrent use.[1] Further, the authors of one report recommend that if omeprazole is necessary for a patient about to receive methotrexate, then omeprazole should be discontinued 4 to 5 days before methotrexate administration.[3] The situation with other proton pump inhibitors may be similar. Ranitidine was found to be a suitable alternative in two of the cases.[3,6] Note that the risks would appear to be most significant with high-dose methotrexate, but the case report involving a 15 mg weekly dose of methotrexate introduces a note of caution in all patients.

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Methotrexate + Retinoids

The levels of methotrexate may be increased by etretinate, and cases of severe liver toxicity have been reported.

Clinical evidence

(a) Acitretin

In a review of the medical records of 18 patients who had taken methotrexate and acitretin for psoriasis, two patients (both of whom had consumed alcohol during their treatment) developed mildly raised liver function tests, four patients experienced at least one elevated gamma-glutamyl transferase level, and no patient discontinued treatment due to abnormal laboratory results.[1]

(b) Etretinate

A man was given a 48-hour infusion of methotrexate 10 mg every week, for chronic discoid psoriasis but when he was also given etretinate 30 mg daily his serum methotrexate levels almost doubled. Concentrations at 12 and 24 hours during the infusion were 0.11 mmol/L, compared with 0.07 mmol/L and 0.05 mmol/L before the etretinate.[2] A later study[3] in patients with psoriasis found that those receiving etretinate had 38% higher maximum plasma levels of methotrexate, but no difference in the clearance or elimination half-life of methotrexate (i.e. no methotrexate accumulation).

Severe toxic hepatitis has been reported in a number of cases when both etretinate and methotrexate were given.[4-6] It may take several months to develop.[6] The author of two of these cases stated that these occurred in a total of just 10 patients given both drugs, whereas they not seen any cases of severe toxic hepatitis in 531 patients given methotrexate alone or in 110 patients given etretinate alone.[4]

Mechanism

Not understood. Both etretinate and methotrexate can cause hepatotoxicity. The increased incidence of toxic hepatitis seen with etretinate and methotrexate may possibly be related to the increased maximum methotrexate plasma levels.

Importance and management

Although methotrexate and etretinate have been used together with success for psoriasis,[7-9] the risk of severe drug-induced hepatitis seems to be increased. One author says that he has decided not to use this combination in future.[4] Concurrent use should clearly be undertaken with great care. Etretinate has been largely superseded by acitretin (a metabolite of etretinate, which has a shorter half-life), but some, including the manufacturers, consider that the concurrent use of methotrexate and acitretin should also be avoided.[10-12] However, some do use this combination.[1] If the combination is used, it would be prudent to increase the frequency of monitoring of liver function tests.

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11. Neotigason (Acitretin). Actavis UK Ltd. UK Summary of product characteristics, October 2008.
12. Soriatane (Acitretin). Stiefel Labs, Inc. US Prescribing information, September 2008.

Methotrexate + Sulfasalazine

The pharmacokinetics of methotrexate are unaffected by sulfasalazine. Clinical studies in patients with rheumatoid arthritis suggest that the combination of methotrexate and sulfasalazine may result in folate-deficiency anaemias.

Clinical evidence, mechanism, importance and management

A study in 15 patients with rheumatoid arthritis found that when sulfasalazine 2 g was given with methotrexate 7.5 mg weekly, the pharmacokinetics of methotrexate remained unchanged. Similarly, methotrexate did not alter the trough levels of sulfasalazine.[1] Although this study suggests that there is no reason to avoid the concurrent use of sulfasalazine and methotrexate, clinical studies in patients with rheumatoid arthritis have found that concurrent use does not significantly increase therapeutic efficacy and seems to increase the development of folate-deficiency anaemias.[2] The results of an *in vitro* study suggest this may be because sulfasalazine is a potent inhibitor of the reduced folate carrier-mediated cellular uptake of methotrexate and folinate.[3] An alternative explanation is that both sulfasalazine and methotrexate promote enhanced adenosine release, which may suppress inflammation, and the combination of two drugs with the same mechanism of action may not improve the therapeutic response of either.[4]

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Methotrexate + Tacrolimus

Limited evidence suggests that tacrolimus does not affect methotrexate levels.

Clinical evidence, mechanism, importance and management

In a study in 3 bone marrow transplant patients given tacrolimus 30 micrograms/kg daily from the day before transplantation and low-dose methotrexate 15 mg/m^2 on day one, and 10 mg/m^2 on days 3, 6 and 11, methotrexate levels at 24 hours post-dose remained below the range requiring folinic acid, suggesting that no interaction of clinical significance had occurred.[1] In a later, similar report from this research group, in a total of 40 patients, tacrolimus did not appear to affect methotrexate levels.[2]

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2. Wingard JR, Nash RA, Ratanatharathorn V, Fay JW, Klein JL, Przepiorka D, Maher RM, Devine SM, Boswell G, Bekersky I, Fitzsimmons W. Lack of interaction between tacrolimus (FK506) and methotrexate in bone marrow transplant recipients. *Bone Marrow Transplant* (1997) 20, 49–51.

Methotrexate + Taxanes

Docetaxel does not alter methotrexate pharmacokinetics. Methotrexate does not appear to alter paclitaxel pharmacokinetics.

Clinical evidence, mechanism, importance and management

(a) Docetaxel

In a study in 6 patients, the pharmacokinetics of methotrexate and its metabolite, 7-hydroxymethotrexate, were unaltered when methotrexate 30 mg/m^2 was given immediately before or 24 hours before an infusion of docetaxel 75 mg/m^2, compared with methotrexate 30 mg/m^2 given alone.[1]

(b) Paclitaxel

The pharmacokinetics of paclitaxel did not appear to be changed when a 24-hour infusion of paclitaxel was started 24 hours after a bolus of methotrexate, when compared with historical data of paclitaxel alone. Myelosuppression was severe in this study.[2]

1. Sparreboom A, Loos WJ, Nooter K, Stoter G, Verweij J. Liquid chromatographic analysis and preliminary pharmacokinetics of methotrexate in cancer patients co-treated with docetaxel. *J Chromatogr B Biomed Sci Appl* (1999) 735, 111–19.
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Methotrexate + Theophylline

Methotrexate causes a modest reduction in theophylline clearance. Theophylline may reduce methotrexate-induced neurotoxicity, but there is the possibility that it may also reduce methotrexate efficacy.

Clinical evidence

(a) Effects on theophylline

In 8 patients with severe, steroid-dependent asthma, the apparent clearance of theophylline (given as oral aminophylline, choline theophyllinate or theophylline) was reduced by 19% after 6 weeks of treatment with intramuscular methotrexate 15 mg weekly. Three patients complained of nausea and the theophylline dose was reduced in one of them as the theophylline level was more than 20 micrograms/mL.[1]

(b) Effects on methotrexate

Four of 6 patients aged 3 to 16 years with acute lymphoblastic leukaemia and high-dose methotrexate-induced neurotoxicity had a complete resolution of their symptoms when they were given a 2.5-mg/kg aminophylline infusion over one hour. The other 2 patients had some improvement in symptoms. One patient also had symptom relief with rapid-release theophylline.[2] Similar results were reported in another child who developed

neurotoxicity after receiving high-dose methotrexate. In this case, aminophylline was reported not to alter methotrexate levels.[3] A patient with methotrexate-induced leukoencephalopathy recovered after being given a combination of intravenous folinic acid with intravenous aminophylline 145 mg daily for 7 days.[4]

Mechanism

It is not known why theophylline clearance is altered by methotrexate. Methotrexate neurotoxicity may be linked with increased levels of adenosine. Theophylline is a competitive antagonist for adenosine receptors at serum concentrations within the therapeutic range used in respiratory disease.[2]

Importance and management

The clinical importance of the small reduction in theophylline clearance is uncertain, although it may be worth bearing this in mind in patients maintained at the higher end of the therapeutic levels for theophylline, as they may be more likely to develop toxicity. One UK manufacturer of methotrexate (licensed for rheumatoid arthritis) recommends monitoring theophylline levels with concurrent use, and avoiding excessive consumption of theophylline-containing drinks; however, this recommendation appears to be based on studies and surveys that looked at the effects of caffeine intake in patients taking low-dose, weekly methotrexate for rheumatoid arthritis or psoriasis.[5,6] Consider also, 'Methotrexate + Caffeine', p.749.

Aminophylline may reduce methotrexate-induced neurotoxicity, and, although there is some evidence that theophylline does not alter the cytotoxic effects of methotrexate, this requires confirmation.[2]

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5. Metoject (Methotrexate). Medac GmbH. UK Summary of product characteristics, November 2008.
6. Medac UK. Personal Communication, March 2007.

Methotrexate + Urinary alkalinisers

Alkalinisation of the urine increases the urinary excretion of methotrexate.

Clinical evidence, mechanism, importance and management

Methotrexate is much more soluble in alkaline than in acidic fluids, therefore urinary alkalinisers such as **sodium bicarbonate** and **acetazolamide** (and ample fluids) are often given to patients receiving high-dose methotrexate to prevent the precipitation of methotrexate in the renal tubules, which would cause damage. However alkalinisation also increases the loss of methotrexate in the urine because at high pH values more of the drug exists in the ionised form, which is not readily reabsorbed by the tubules. This increased clearance was clearly shown in about 70 patients in whom alkalinisation of the urine (to pH greater than 7) with **sodium bicarbonate** and hydration reduced the serum methotrexate levels at 48 hours and 72 hours by 73% and 76%, respectively.[1] In this instance the interaction was being exploited therapeutically to avoid toxicity. This interaction has also been shown by others.[2,3] However, the possible consequences should be recognised if concurrent use is undertaken in other situations (e.g. if sodium bicarbonate is given as an antacid).

For the effects of acidic urine on methotrexate excretion see 'Methotrexate + Ascorbic acid (Vitamin C)', p.749.

1. Nirenberg A, Mosende C, Mehta BM, Gisolfi AL, Rosen G. High dose methotrexate with citrovorum factor rescue: predictive value of serum methotrexate concentrations and corrective measures to avert toxicity. *Cancer Treat Rep* (1977) 61, 779–83.
2. Sand TE, Jacobsen S. Effect of urine pH and flow on renal clearance of methotrexate. *Eur J Clin Pharmacol* (1981) 19, 453–6.
3. Shamash J, Earl H, Souhami R. Acetazolamide for alkalinisation of urine in patients receiving high-dose methotrexate. *Cancer Chemother Pharmacol* (1991) 28, 150–1.

Mitomycin + Doxorubicin

An increased incidence of cardiotoxicity has been seen in patients receiving mitomycin who were previously or simultaneously given doxorubicin.

Clinical evidence, mechanism, importance and management

Fourteen out of 91 patients (15.3%) with advanced breast cancer who had previously not responded to doxorubicin developed congestive heart failure when they were later given a combination of intravenous mitomycin 20 mg/m^2 every 4 to 6 weeks and megestrol acetate 160 mg daily. None of them had any pre-existing heart disease. This compares with only 3 out of 89 patients (3.5%) from another group who had received doxorubicin but no mitomycin. The maximum cumulative dose of doxorubicin was 450 mg/m^2 and all of the patients had also been given cyclophosphamide. Some of them also received other drugs during the doxorubicin phase. These included fluorouracil, methotrexate, tegafur and vincristine. The heart failure developed slowly (mean time of 8.5 months) compared with those in the control group (1.5 months).[1]

Other studies have also suggested that the combination of mitomycin and doxorubicin may increase cardiotoxicity.[2,3] In a randomised study, 2 of 39 patients given doxorubicin 45 mg/m^2 every 3 weeks and mitomycin 10 mg/m^2 every 6 weeks developed cardiomyopathy, compared with none of 42 patients given doxorubicin 75 mg/m^2 every 3 weeks alone.[4]

The reasons for this apparent synergistic cardiotoxicity are not understood, but it may be related to free radical generation. This interaction is not established with certainty. The authors of one report suggest that its incidence is probably less than 10%, and that it does not occur until a cumulative mitomycin dose of 30 mg/m^2 or more.[3] It may be prudent to monitor patients given mitomycin more closely if they have previously received anthracyclines.[1] Note that the combination (FAM, fluorouracil, doxorubicin and mitomycin) has been widely used for gastric cancer.

1. Buzdar AU, Legha SS, Tashima CK, Hortobagyi GN, Yap HY, Krutchik AN, Luna MA, Blumenschein GR. Adriamycin and mitomycin C: possible synergistic cardiotoxicity. *Cancer Treat Rep* (1978) 62, 1005–8.
2. Villani F, Comazzi R, Lacaita G, Guindani A, Genitoni V, Volonterio A, Brambilla MC. Possible enhancement of the cardiotoxicity of doxorubicin when combined with mitomycin C. *Med Oncol Tumor Pharmacother* (1985) 2, 93–7.
3. Verweij J, Funke-Küpper AJ, Teule GJJ, Pinedo HM. A prospective study on the dose dependency of cardiotoxicity induced by mitomycin C. *Med Oncol Tumor Pharmacother* (1988) 5, 159–63.
4. Andersson M, Daugaard S, von der Maase H, Mouridsen HT. Doxorubicin versus mitomycin versus doxorubicin plus mitomycin in advanced breast cancer: a randomized study. *Cancer Treat Rep* (1986) 70, 1181–6.

Mitomycin + Fluorouracil

Rarely, serious and potentially life-threatening intravascular haemolysis and renal failure may develop after the long-term use of mitomycin and fluorouracil.

Clinical evidence, mechanism, importance and management

Two patients developed chronic haemolysis and progressive renal impairment after the long-term use of mitomycin and fluorouracil following partial or total gastrectomy for gastric cancer. The haemolysis was exacerbated by blood transfusions. The authors of the report[1] suggested that these two cases were extreme examples of a syndrome that was becoming increasingly apparent in their pretransfusion patients, after the maintenance use of these drugs for 6 months or more. A similar syndrome occurred in 2 other patients, one with gastric carcinoma and one without, when given these two drugs.[2,3] This severe and potentially fatal syndrome has also been seen with mitomycin alone.[4,5] Its incidence is not known, but note that a regimen of fluorouracil, doxorubicin and mitomycin (FAM) has been widely used in gastric cancer and there are only a few reports of this syndrome. The authors of one report suggest that the drugs should be stopped at the first sign of intravascular haemolysis, persistent proteinuria and rising urea levels (two consecutive values above 8 mmol/L).[1] The syndrome has also occurred when tamoxifen was given to patients who had been treated with mitomycin, see 'Mitomycin + Tamoxifen', p.759.

1. Jones BG, Fielding JW, Newman CE, Howell A, Brookes VS. Intravascular haemolysis and renal impairment after blood transfusion in two patients on long-term 5-fluorouracil and mitomycin-C. *Lancet* (1980) i, 1275–7.
2. Krauss S, Sonoda T, Solomon A. Treatment of advanced gastrointestinal carcinoma with 5-fluorouracil and mitomycin C. *Cancer* (1979) 43, 1598–1603.

3. Lempert KD. Haemolysis and renal impairment syndrome in patients on 5-fluorouracil and mitomycin-C. *Lancet* (1980) ii, 369–70.
4. Rumpf KW, Reiger J, Lankisch PG, von Heyden HW, Nagel GA, Scheler F. Mitomycin-induced haemolysis and renal failure. *Lancet* (1980) ii, 1037–8.
5. Schiebe ME, Hoffmann W, Belka C, Bamberg M. Mitomycin C-related hemolytic uremic syndrome in cancer patients. *Anticancer Drugs* (1998) 9, 433–5.

Mitomycin + Furosemide

A study in 5 patients with advanced solid tumours receiving mitomycin C 10 mg/m^2 found that furosemide given as a 40 mg intravenous bolus either 120 minutes or 200 minutes after the mitomycin had no effect on its pharmacokinetics.[1]

1. Verweij J, Kerpel-Fronius S, Stuurman M, de Vries J, Pinedo HM. Absence of interaction between furosemide and mitomycin C. *Cancer Chemother Pharmacol* (1987) 19, 84–6.

Mitomycin + Tamoxifen

Haemolytic anaemia, thrombocytopenia and renal impairment, leading to potentially fatal haemolytic uraemic syndrome, has occurred in a few patients given tamoxifen with, or shortly after, mitomycin.

Clinical evidence, mechanism, importance and management

After a woman with metastatic breast cancer who had previously been given mitomycin, mitoxantrone and methotrexate, developed rapidly fatal acute renal failure 21 days after starting tamoxifen, a retrospective survey was undertaken of other patients who had also received all four of these drugs.[1] Nine out of 94 patients (9.6%) developed anaemia, thrombocytopenia and renal impairment, compared with none in another group of 45 patients not given tamoxifen. One of the 9 died from renal failure. The doses used were mitomycin 7 mg/m^2 intravenously every 42 days for four courses; mitoxantrone 7 mg/m^2 and methotrexate 35 mg/m^2 intravenously every 21 days for eight courses; and tamoxifen 20 mg orally daily.[1] A few other reports describe cases of haemolytic uraemic syndrome in patients given mitomycin and tamoxifen.[2-4]

The authors of the first study suggested that this haemolytic uraemic syndrome was due to a combination of subclinical endothelial damage induced by mitomycin, and a thrombotic effect on platelets caused by tamoxifen.[1] They advise the avoidance of tamoxifen with or shortly after mitomycin unless concurrent use can be carefully monitored. Erythropoietin may be useful in managing the syndrome.[4] This syndrome has also occurred rarely with mitomycin alone, and when mitomycin was given with fluorouracil, see 'Mitomycin + Fluorouracil', p.758.

1. Montes A, Powles TJ, O'Brien MER, Ashley SE, Luckit J, Treleaven J. A toxic interaction between mitomycin C and tamoxifen causing the haemolytic uraemic syndrome. *Eur J Cancer* (1993) 29A, 1854–7.
2. Ellis PA, Luckitt J, Treleaven J, Smith IE. Haemolytic uraemic syndrome in a patient with lung cancer: further evidence for a toxic interaction between mitomycin-C and tamoxifen. *Clin Oncol (R Coll Radiol)* (1996) 8, 402–3.
3. Arola O, Aho H, Asola M, Kauppila M, Nikkanen V, Voipio-Pulkki LM. Hemolyyttis-ureeminen oireyhytmä-mitomysiinihoidon vakava komplikaatio. *Duodecim* (1997) 113, 1923–9.
4. O'Brien MER, Casey S, Treleaven J, Powles TJ. Use of erythropoietin in the management of the haemolytic uraemic syndrome induced by mitomycin C/tamoxifen. *Eur J Cancer* (1994) 30A, 894–5.

Mitotane + Miscellaneous

The manufacturer advises that mitotane might reduce the plasma levels of drugs that are cytochrome P450 substrates. The absorption of mitotane may be increased when taken with food.

Clinical evidence, mechanism, importance and management

(a) Cytochrome P450 substrates

The manufacturer advises that mitotane may induce the activity of cytochrome P450 isoenzymes.[1,2] This appears to be based on a case report of decreased efficacy of warfarin (see 'Coumarins + Antineoplastics; Miscellaneous cytotoxics', p.432), and on studies in *rats*.[3] On this basis, the manufacturers give a general caution about the concurrent use of drugs influenced by hepatic enzyme induction.[1,2] However, if mitotane were an important enzyme inducer it might have been expected to have come to light by now, but there do not appear to be any case reports supporting this effect, other than the one case already mentioned with warfarin. On the basis of this proposed interaction, the UK manufacturer specifically recommends caution with **antiepileptics**, **griseofulvin**, **rifabutin**, **rifampicin**, and **St John's wort** (*Hypericum perforatum*).[1] However, most of these drugs are also enzyme inducers, with some being potent (e.g. rifampicin), and the effect of adding another modest enzyme-inducer is probably unlikely to be clinically relevant.

In summary, there is too little information available to warrant a general caution for the use of mitotane with all cytochrome P450 substrates that have a narrow therapeutic index. Further study is needed.

(b) Food

The UK manufacturer notes that the absorption of mitotane was increased when it was given with food (although they say the relative bioavailability was not calculated), and they say that mitotane should be preferably taken with meals.[1] The US information does not mention this effect, nor give any advice about administration in relation to meals.[2]

1. Lysodren (Mitotane). HRA Pharma UK Ltd. UK Summary of product characteristics, April 2009.
2. Lysodren (Mitotane). Bristol-Myers Squibb Company. US Prescribing information, February 2009.
3. EMEA Scientific discussion. 2005, 1–45. Available at: http://www.emea.europa.eu/humandocs/PDFs/EPAR/lysodren/071204en6.pdf (accessed 29/01/10).

Mitotane + Spironolactone

In an isolated report, the effects of mitotane appeared to be inhibited by spironolactone in a patient with Cushing's disease.

Clinical evidence, mechanism, importance and management

A woman with Cushing's disease taking chlorpropamide, digoxin and furosemide was given spironolactone 50 mg four times daily to control hypokalaemia. She was also given mitotane 3 g daily for 5 months to control the elevated cortisol levels, but this had no effect.[1] When an interaction was suspected (on the basis of *animal* studies[1]) it was decided to withdraw the spironolactone, whereupon severe nausea and profuse diarrhoea developed within 24 to 48 hours, suggesting mitotane toxicity. This subsided, and then redeveloped when the mitotane was stopped, and then restarted a week later. The mechanism of this apparent interaction is not understood. It would seem that mitotane can become ineffective in the management of Cushing's syndrome in the presence of spironolactone. The UK manufacturer of mitotane contraindicates its use with spironolactone,[2] while the US manufacturer does not mention this interaction.[3]

1. Wortsman J, Soler NG. Mitotane. Spironolactone antagonism in Cushing's syndrome. *JAMA* (1977) 238, 2527.
2. Lysodren (Mitotane). HRA Pharma UK Ltd. UK Summary of product characteristics, April 2009.
3. Lysodren (Mitotane). Bristol-Myers Squibb Company. US Prescribing information, February 2009.

Nilotinib + Miscellaneous

Rifampicin (rifampin), a CYP3A4 inducer, decreases nilotinib levels and ketoconazole, a CYP3A4 inhibitor, increases nilotinib levels. Other inducers and inhibitors of CYP3A4 are predicted to interact similarly. Additive QT prolongation may occur on the concurrent use of nilotinib and drugs that prolong the QT interval. Nilotinib increases midazolam levels, and is predicted to increase the levels of other CYP3A4 substrates. Food increases the absorption of nilotinib. No clinically relevant interaction appears to occur between nilotinib and esomeprazole, and no interaction is expected with other proton pump inhibitors.

Clinical evidence, mechanism, importance and management

(a) CYP2C9 substrates

In a single-dose study in healthy subjects, nilotinib had no effect on the pharmacokinetics or anticoagulant response to **warfarin** (a known substrate of CYP2C9).[1] Nevertheless, as **warfarin** is also (in part) metabolised by CYP3A4, which nilotinib modestly inhibits, the manufacturers of nilotinib advise caution on concurrent use and suggest that alternative anticoagulant drugs should be used.[1,2] Note that, from a disease perspective,

when treating venous thromboembolic disease in patients with cancer, **warfarin** is generally inferior (higher risk of major bleeds and recurrent thrombosis) to low-molecular-weight heparins.

The manufacturers of nilotinib[1,2] also advise caution if it is given with other drugs that are substrates of CYP2C9, particularly those with narrow therapeutic margins, although given the study with warfarin, this seems unlikely to be necessary.

(b) CYP2D6 substrates

In vitro studies have suggested that nilotinib is an inhibitor of the cytochrome P450 isoenzyme CYP2D6 and it may therefore increase the plasma levels of drugs that are substrates of this enzyme. The manufacturers advise caution when giving nilotinib with drugs that are substrates of CYP2D6, particularly those with narrow therapeutic margins.[1] For a list of drugs that are substrates of CYP2D6, see 'Table 1.3', (p.6).

(c) CYP3A4 inducers

In a study in healthy subjects, **rifampicin** (**rifampin**) 600 mg daily for 12 days reduced the AUC and peak levels of nilotinib by about 80% and 64%, respectively.[1,2] Nilotinib is metabolised by the cytochrome P450 isoenzyme CYP3A4, and therefore its levels may be reduced by drugs that induce this isoenzyme, such as **rifampicin**. The manufacturers of nilotinib advise against the concurrent use of drugs that are potent inducers of CYP3A4, and they specifically name **carbamazepine**, **dexamethasone**, **phenytoin**, **rifampicin** (**rifampin**), **rifabutin**, **rifapentine**, **phenobarbital**, and **St John's wort**.[1,2] Note however that clinically relevant interactions occurring as a result of **dexamethasone** inducing CYP3A4 are rare. The US manufacturer of nilotinib states that if it the concurrent use of a potent CYP3A4 inducer is necessary, the dose of nilotinib may need to be increased. The nilotinib dose should be readjusted when the CYP3A4 inducer is stopped.[1] For a list of drugs that are inducers of CYP3A4, see 'Table 1.4', (p.6).

(d) CYP3A4 inhibitors

In a study in healthy subjects, **ketoconazole** 400 mg daily for 6 days increased the AUC of nilotinib threefold.[1,2] Nilotinib is metabolised by the cytochrome P450 isoenzyme CYP3A4 and its levels may be increased by drugs that inhibit this isoenzyme, such as **ketoconazole**. The manufacturers of nilotinib advise against the concurrent use of drugs that are potent inhibitors of CYP3A4, and they specifically name **atazanavir**, **clarithromycin**, **grapefruit products**, **itraconazole**, **indinavir**, **ketoconazole**, **nefazodone**, **nelfinavir**, **ritonavir**, **saquinavir**, **telithromycin**, and **voriconazole**.[1,2] If treatment with a potent CYP3A4 inhibitor is cannot be avoided, nilotinib should be withheld, or, if this is not possible, both manufacturers advise close monitoring for QT prolongation: nilotinib prolongs the QT interval, and this effect may be greater at higher nilotinib levels. The US manufacturers also state that the dose of nilotinib should be reduced to 400 mg daily, half of the normal daily dose.[1,2] The US manufacturer further advises that a washout period should be allowed when the potent CYP3A4 inhibitor is stopped before the dose of nilotinib is readjusted.[1] Increased exposure to nilotinib may also occur with moderate inhibitors of CYP3A4, and the UK manufacturer advises that an alternative drug with no or only minimal CYP3A4 inhibition should be considered.[2] For a list of drugs that are inhibitors of CYP3A4, see 'Table 1.4', (p.6).

(e) CYP3A4 substrates

In a single-dose study in healthy subjects, nilotinib increased the exposure to oral **midazolam** by 30%.[1,2]. Nilotinib is an inhibitor of the cytochrome P450 isoenzyme CYP3A4, by which **midazolam** is metabolised; however, the study with **midazolam** suggests that its effects are modest. The manufacturers therefore caution the concurrent use of nilotinib with drugs that are substrates of CYP3A4, particularly those with narrow therapeutic margins. The UK manufacturer names **astemizole**, **terfenadine**, **cisapride**, **pimozide**, **quinidine**, and **ergot alkaloids** (e.g. **ergotamine**, **dihydroergotamine**).[2] For a list of drugs that are substrates of CYP3A4, see 'Table 1.4', (p.6).

(f) Cytochrome P450 substrates; Miscellaneous

In vitro studies have shown that nilotinib is an inhibitor and inducer of the cytochrome P450 isoenzyme CYP2C8,[1,2] and an inducer of CYP2B6.[1] In the absence of any specific information, the manufacturers advise that nilotinib has the potential to alter the pharmacokinetics of drugs that are metabolised by these isoenzymes.[1] For a list of drugs that are substrates of CYP2B6 and CYP2C8, see 'Table 1.3', (p.6).

(g) Drugs that affect gastric pH

It is suggested that drugs that suppress gastric acid may lead to lower exposure to nilotinib as the solubility of nilotinib is pH-dependent, with lower solubility at higher pH. In a study in healthy subjects, **esomeprazole** 40 mg daily for 5 days modestly reduced the AUC and maximum plasma levels of nilotinib by 34% and 27%, respectively, despite a marked increase in gastric pH. The manufacturers advise that nilotinib may be given with **esomeprazole** or other **proton pump inhibitors** as needed.[2]

(h) Drugs that prolong the QT interval

In an analysis of ECG recordings from 119 patients given nilotinib, it was found that the Fridericia-corrected QTc (QTcF) interval increased by 5 to 15 milliseconds.[3] In a study in patients with chronic myeloid leukaemia, nilotinib increased the QTcF by 6 to 8 milliseconds and no episodes of torsade de pointes were reported.[2] The US manufacturer advises avoiding the concurrent use of drugs that prolong the QT interval, whereas the UK manufacturer advises caution on concurrent use.[1,2] They specifically name **amiodarone**, **chloroquine**, **clarithromycin**, **disopyramide**, **halofantrine**, **haloperidol**, **methadone**, **moxifloxacin**, **pimozide**, **procainamide**, **quinidine** and **sotalol**. If concurrent use is necessary, nilotinib should be stopped,[1] or, if this is not possible, the manufacturers advise close monitoring for QT prolongation.[1,2] Consider also, 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290.

(i) Food

In a study in healthy subjects, a high-fat meal increased the AUC of nilotinib by 82%, when the dose was given 30 minutes after the meal, when compared with the fasting state. The bioavailability of nilotinib is reported to be increased by 29% and 15%, respectively, when it is taken 30 minutes or 2 hours after food.[2] The manufacturers therefore recommend that nilotinib is taken on an empty stomach, at least one hour before and 2 hours after food.[1,2]

(j) P-glycoprotein inhibitors and substrates

Nilotinib is an inhibitor and substrate of P-glycoprotein. The US manufacturer therefore predicts that the concurrent use of nilotinib with drugs that are substrates of P-glycoprotein may lead to an increase in their levels, and that inhibitors of P-glycoprotein will increase nilotinib levels, and they caution concurrent use;[1] however, the clinical relevance of this prediction needs confirming. For a list of drugs that inhibit and are substrates of P-glycoprotein, see 'Table 1.6', (p.8).

1. Tasigna (Nilotinib hydrochloride monohydrate). Novartis Pharmaceuticals Corp. US Prescribing information, August 2009.
2. Tasigna (Nilotinib hydrochloride monohydrate). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, August 2009.
3. Kantarjian H, Giles F, Wunderle L, Bhalla K, O'Brien S, Wassmann B, Tanaka C, Manley P, Rae P, Mietlowski W, Bochinski K, Hochhaus A, Griffin JD, Hoelzer D, Albitar M, Dugan M, Cortes J, Alland L, Ottmann OG. Nilotinib in imatinib-resistant CML and Philadelphia chromosome-positive ALL. *N Engl J Med* (2006) 354, 2542–51.

Nitrosoureas + Cimetidine

The bone marrow depressant effects of carmustine and lomustine are possibly increased by cimetidine.

Clinical evidence

Nine patients given **carmustine** 80 mg/m^2 daily for 3 days, cimetidine 300 mg four times daily for one to 4 weeks, steroids, and cranial irradiation over 6 weeks, had marked leucopenia during the first cycle. Bone marrow aspirates confirmed the marked decrease in granulocytic elements in 2 patients. In comparison, 31 patients similarly treated, but without cimetidine, had no significant white cell depression.[1,2]

Neutropenia was found in a man taking regular cimetidine, phenytoin, phenobarbital, and dexamethasone, 53 days after he was given **lomustine** 120 mg, and 16 days after he was given **lomustine** 160 mg. The cimetidine was discontinued and the neutropenia rapidly reversed within 14 days. The neutrophil nadir from the **lomustine** 160 mg dose occurred after a further 16 to 19 days and was much less severe than the first episode.[3]

Mechanism

Studies in *animals* suggest that cimetidine impairs the clearance of carmustine.[4]

Importance and management

Information appears to be limited to the reports cited, but it seems to be an established reaction. Patients given both lomustine or carmustine and cimetidine should be closely monitored for changes in blood cell counts. Because of its immunomodulatory effects, cimetidine has been used as an adjunct to carmustine in the treatment of malignant melanoma, but this did not improve outcomes.[5]

1. Selker RG, Moore P, LoDolce D. Bone-marrow depression with cimetidine plus carmustine. *N Engl J Med* (1978) 299, 834.
2. Volkin RL, Shadduck RK, Winkelstein A, Zeigler ZR, Selker RG. Potentiation of carmustine-cranial irradiation-induced myelosuppression by cimetidine. *Arch Intern Med* (1982) 142, 243–5.
3. Hess WA, Kornblith PL. Combination of lomustine and cimetidine in the treatment of a patient with malignant glioblastoma: a case report. *Cancer Treat Rep* (1985) 69, 733.
4. Dorr RT, Soble MJ. H_2-Antagonists and carmustine. *J Cancer Res Clin Oncol* (1989) 115, 41–6.
5. Morton RF, Creagan ET, Schaid DJ, Kardinal CG, McCormack GW, McHale MS, Wiesenfeld M. Phase II trial of recombinant leukocyte A interferon (IFN-α2A) plus 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) and the combination cimetidine with BCNU in patients with disseminated malignant melanoma. *Am J Clin Oncol* (1991) 14, 152–5.

Nitrosoureas; Lomustine + Phenobarbital

***Animal* studies have shown that the antitumour effects and the toxicity of lomustine are markedly reduced by phenobarbital. It is suggested that the metabolism of lomustine is accelerated by the enzyme-inducing effects of phenobarbital.[1] There appears to be no clinical data confirming this; nevertheless, it would be prudent to bear the possibility of an interaction in mind if both drugs are given.**

1. Siemann DW. Effect of pretreatment with phenobarbital or SKF 525A on the toxicity and antitumor activity of lomustine. *Cancer Treat Rep* (1983) 67, 259–65.

Nitrosoureas; Lomustine + Theophylline

A single case report describes thrombocytopenia and bleeding, which was attributed to the concurrent use of lomustine and theophylline.

Clinical evidence, mechanism, importance and management

An woman with asthma taking theophylline and given lomustine, prednisone and vincristine for medulloblastoma, developed severe nose bleeding and thrombocytopenia 3 weeks after the third cycle of chemotherapy.[1] This was attributed to the concurrent use of lomustine and theophylline. The suggested explanation for this effect is that theophylline inhibited the activity of phosphodiesterase within the platelets, thereby increasing cyclic AMP levels and disrupting normal platelet function (which seems to be supported by an experimental study[2]) while lomustine causes thrombocytopenia. What is known is far too limited to act as more than a warning of the possibility of increased thrombocytopenia during the concurrent use of theophylline and lomustine.

1. Zeltzer PM, Feig SA. Theophylline-induced lomustine toxicity. *Lancet* (1979) ii, 960–1.
2. DeWys WD, Bathina S. Synergistic anti-tumour effect of cyclic AMP elevation (induced by theophylline) and cytotoxic drug treatment. *Proc Am Assoc Cancer Res* (1978) 19, 104.

Panitumumab + Antineoplastics

The efficacy of panitumumab was reduced and the toxicity increased when it was given with bevacizumab-containing chemotherapy regimens. When panitumumab was given with irinotecan, bolus fluorouracil plus folinic acid (IFL) there was a high incidence of severe diarrhoea.

Clinical evidence

(a) Bevacizumab with chemotherapy

In an interim analysis of a study of 823 patients randomised to receive bevacizumab plus **oxaliplatin**-based regimens, with or without panitumumab, there was an increased incidence of adverse effects (skin toxicity, diarrhoea, infections, pulmonary embolism), a shortened progression-free survival time (10 months versus 11.4 months) and increased deaths (from pulmonary embolism) in those receiving panitumumab.[1] In a smaller cohort receiving panitumumab with bevacizumab plus **irinotecan**-based regimens similar increased toxicity without improved efficacy was seen. Patients receiving panitumumab received a lower dose-intensity of the cytotoxics (**oxaliplatin**, **irinotecan**, **fluorouracil**) because of the toxicities experienced.[2]

(b) IFL and FOLFIRI

A high incidence of severe (grade 3 to 4) diarrhoea (58%) was noted when panitumumab was given to 19 patients who also received the IFL regimen (irinotecan, bolus fluorouracil and folinic acid): the concurrent use of these drugs was considered to be poorly tolerated.[3] In another arm of this study a 25% incidence of grade 3 diarrhoea was seen when panitumumab was added to the FOLFIRI regimen (irinotecan, folinic acid and infusional fluorouracil).[3]

Mechanism

Unknown. A pharmacokinetic interaction would not be anticipated.

Importance and management

Panitumumab is currently indicated for use only as monotherapy after the failure of chemotherapy.[2,4] One study shows that the effect of combining it with another monoclonal antibody, bevacizumab, plus chemotherapy is detrimental, and this combination should not be used. A high incidence of severe diarrhoea was also seen in the study with IFL, and the UK manufacturer advises against using this combination.[4]

1. Hecht JR, Mitchell E, Chidiac T, Scroggin C, Hagenstad C, Spigel D, Marshall J, Cohn A, McCollum D, Stella P, Deeter R, Shahin S, Amado RG. A randomized phase IIIB trial of chemotherapy, bevacizumab, and panitumumab compared with chemotherapy and bevacizumab alone for metastatic colorectal cancer. J Clin Oncol (2009) 27, 672–80.
2. Vectibix (Panitumumab). Amgen Inc. US Prescribing information, July 2009.
3. Berlin J, Posey J, Tchekmedyian S, Hu E, Chan D, Malik I, Yang L, Amado RG, Hecht JR. Panitumumab with irinotecan/leucovorin/5-fluorouracil for first-line treatment of metastatic colorectal cancer. *Clin Colorectal Cancer* (2007) 6, 427–32.
4. Vectibix (Panitumumab). Amgen Ltd. UK Summary of product characteristics, April 2009.

Pemetrexed + Aspirin or NSAIDs

NSAIDs are predicted to decrease the renal excretion of pemetrexed. However, aspirin and ibuprofen had little effect on pemetrexed clearance in patients with normal renal function.

Clinical evidence

In a study in 27 patients with advanced cancer, aspirin 325 mg every 6 hours for 9 doses, starting 2 days before pemetrexed, and with the last dose one hour before an infusion of pemetrexed 500 mg/m^2, had no effect on the pharmacokinetics of pemetrexed.[1] In a similar study, **ibuprofen** 400 mg four times daily caused a slight 16% decrease in the clearance of pemetrexed, and increased its AUC by 20%.[1]

Mechanism

Pemetrexed is largely cleared unchanged from the body by renal excretion. The NSAIDs as a group inhibit the synthesis of the prostaglandins (PGE_2) resulting in a fall in renal perfusion, which could lead to a rise in serum pemetrexed levels, accompanied by increased toxicity.

Importance and management

The modest increase in pemetrexed exposure seen with ibuprofen 1.6 g daily or aspirin 1.3 g daily is unlikely to be clinically relevant in patients with *normal renal function*, and they may be used in these patients. However, the effects of higher doses of aspirin or ibuprofen are not known, and they could be greater. Because of this, in patients with normal renal function, the manufacturer recommends caution when pemetrexed is used with high doses of NSAIDs (e.g. ibuprofen greater than 1.6 g daily) or high-dose aspirin (greater than 1.3 g daily).[2] Moreover, in patients with *mild to moderate renal impairment*, the manufacturer recommends that NSAIDs with short half-lives such as ibuprofen and higher dose aspirin should be completely avoided from 2 days before to 2 days after pemetrexed use.[2,3]

Because of the lack of data on pemetrexed clearance with NSAIDs with

longer half-lives (e.g. **piroxicam**), the manufacturer recommends that all patients taking these NSAIDs should stop them from 5 days before to 2 days after pemetrexed.[2,3]

1. Sweeney CJ, Takimoto CH, Latz JE, Baker SD, Murry DJ, Krull JH, Fife K, Battiato L, Cleverly A, Chaudhary AK, Chaudhuri T, Sandler A, Mita AC, Rowinsky EK. Two drug interaction studies evaluating the pharmacokinetics and toxicity of pemetrexed when coadministered with aspirin or ibuprofen in patients with advanced cancer. *Clin Cancer Res* (2006) 12, 536–42.
2. Alimta (Pemetrexed disodium). Eli Lilly and Company Ltd. UK Summary of product characteristics, September 2009.
3. Alimta (Pemetrexed disodium). Eli Lilly and Company. US Prescribing information, July 2009.

Pemetrexed + Gemcitabine

The concurrent use of pemetrexed and gemcitabine does not affect the pharmacokinetics of either drug.

Clinical evidence, mechanism, importance and management

In one study in 4 patients, the pharmacokinetics of pemetrexed were not affected when pemetrexed was given 90 minutes after gemcitabine on day one, when compared with its use alone on day 8.[1] Similarly, another report describes a study in 14 patients in which there was no pharmacokinetic interaction between pemetrexed and gemcitabine when a single dose of pemetrexed was given immediately after gemcitabine (gemcitabine 1.25 g/m^2 was given on days 1 and 8 of a 21-day cycle, with pemetrexed 500 mg/m^2 on day 8, for 84 cycles).[2]

1. Adjei AA, Erlichman C, Sloan JA, Reid JM, Pitot HC, Goldberg RM, Peethambaram P, Atherton P, Hanson LJ, Alberts SR, Jett J. Phase I and pharmacologic study of sequences of gemcitabine and the multitargeted antifolate agent in patients with advanced solid tumors. *J Clin Oncol* (2000) 18, 1748–57.
2. Adjei AA. Clinical studies of pemetrexed and gemcitabine combinations. *Ann Oncol* (2006) 17, v29–v32.

Pemetrexed + Irinotecan

The concurrent use of pemetrexed and irinotecan does not appear to affect the pharmacokinetics of either drug.

Clinical evidence, mechanism, importance and management

In a dose-finding study in 51 patients, when irinotecan 175 mg/m^2 to 350 mg/m^2 was given after pemetrexed 300 mg/m^2 to 500 mg/m^2, there did not appear to be any change in the pharmacokinetics of either drug, when compared with historical data for either drug alone.[1]

1. Rowinsky EK, Beeram M, Hammond LA, Schwartz G, De Bono J, Forouzesh B, Chu Q, Latz JE, Hong S, John W, Nguyen B. A phase I and pharmacokinetic study of pemetrexed plus irinotecan in patients with advanced solid malignancies. *Clin Cancer Res* (2007) 13, 532–9.

Pemetrexed + Miscellaneous

Caution is recommended if pemetrexed is given with nephrotoxic drugs such as the aminoglycosides, cisplatin, loop diuretics, and ciclosporin, and drugs that are secreted by the renal tubules, such as probenecid and penicillin. No pharmacokinetic interaction occurs between pemetrexed and cisplatin.

Clinical evidence, mechanism, importance and management

(a) Cisplatin

The US manufacturer states that there is no pharmacokinetic interaction between pemetrexed and cisplatin,[1] but there is the possibility that cisplatin-induced nephrotoxicity could decrease pemetrexed clearance and increase its toxicity.[1,2] However, it should be noted that the use of pemetrexed with cisplatin is indicated for mesothelioma.[1,2]

(b) Folic acid and Vitamin B_{12}

Oral folic acid and intramuscular vitamin B_{12} do not alter the pharmacokinetics of pemetrexed[1] and because these vitamins were found to decrease pemetrexed toxicity, it is recommended that all patients receiving pemetrexed should receive folic acid and B_{12} supplements.[1,2]

(c) Nephrotoxic drugs

The manufacturers consider that the concurrent use of nephrotoxic drugs could potentially decrease the clearance of pemetrexed and therefore increase its toxicity.[1,2] In the UK, the manufacturer specifically mentions **aminoglycosides**, **loop diuretics**, **platinum compounds** (see also *Cisplatin*, above) and **ciclosporin**, and recommends caution on concurrent use, and, if necessary, close monitoring of creatinine clearance.[2]

(d) Probenecid and other drugs secreted by the renal tubules

It is possible that drugs that are secreted by the renal tubules (e.g. probenecid, **penicillin**) could decrease the clearance of pemetrexed, which is also secreted by this mechanism. For this reason, the manufacturer recommends caution on concurrent use, and, if necessary, close monitoring of creatinine clearance.[2]

1. Alimta (Pemetrexed disodium). Eli Lilly and Company. US Prescribing information, July 2009.
2. Alimta (Pemetrexed disodium). Eli Lilly and Company Ltd. UK Summary of product characteristics, September 2009.

Procarbazine + Antiepileptics; Enzyme-inducing

The use of phenytoin, phenobarbital or carbamazepine might increase the risk of procarbazine hypersensitivity reactions, and at high doses of procarbazine, a few cases of severe hepatotoxicity were seen with phenytoin and carbamazepine plus zolpidem. The pharmacokinetics of procarbazine did not appear to differ when given with phenytoin, phenobarbital or carbamazepine.

Clinical evidence

A retrospective study of the records of 83 patients with primary brain tumours who were given procarbazine between 1981 and 1996 found that 20 of them had experienced procarbazine hypersensitivity reactions. Of these 20, 95% had also taken antiepileptics, compared with 71% of those not developing hypersensitivity. In addition, there was a significant dose-response association between the development of hypersensitivity reactions and the serum levels of the antiepileptics used (**phenytoin**, **phenobarbital**, or **carbamazepine**, with or without valproate).[1]

In a prospective study, the pharmacokinetics of procarbazine did not differ between 31 patients taking enzyme-inducing antiepileptics (**carbamazepine**, **oxcarbazepine**, **phenobarbital** or **phenytoin**) and 18 patients taking non-enzyme-inducing antiepileptics or no antiepileptics. Procarbazine was given daily for 5 days every 4 weeks at a starting dose of 200 mg/m^2 escalated to the maximum tolerated dose. At procarbazine doses of 393 mg/m^2 and 429 mg/m^2, there were two cases of severe hepatic dysfunction in patients taking **phenytoin** (one of which was fatal), and one in a patient taking **carbamazepine** and **zolpidem** (this resolved on stopping the **zolpidem**). In addition, at a dose of procarbazine 343 mg/m^2, there was one case of liver dysfunction in a patient not taking enzyme-inducing antiepileptics, at which point the study was halted. In this study, the concurrent use of **dexamethasone** with or without enzyme-inducing antiepileptics also did not affect procarbazine pharmacokinetics.[2]

Mechanism

It was suggested that the enzyme-inducing antiepileptics may increase the metabolism of procarbazine to metabolites causing hypersensitivity.[1] However, no change in the pharmacokinetics of procarbazine itself was seen; suggesting this is unlikely.[2] Procarbazine clearly inhibited its own metabolism, which suggests that it might also inhibit the metabolism of the antiepileptics and this might have increased the risk of hepatotoxicity. However, hepatotoxicity may have also been a result of the high dose of procarbazine. Further study is needed.[2]

Importance and management

Enzyme-inducing antiepileptics do not appear to alter the pharmacokinetics of procarbazine, and, in clinical practice, the dose of procarbazine is not modified in patients taking these drugs.[2] There is some evidence that the incidence of procarbazine-induced hypersensitivity is higher in patients receiving enzyme-inducing antiepileptics. In one dose-finding study, an unexpectedly high incidence of hepatotoxicity was seen with

high-dose procarbazine, and a possible interaction with enzyme-inducing antiepileptics could not be ruled out.

1. Lehmann DF, Hurteau TE, Newman N, Coyle TE. Anticonvulsant usage is associated with an increased risk of procarbazine hypersensitivity reactions in patients with brain tumours. *Clin Pharmacol Ther* (1997) 62, 225–9.
2. Grossman SA, Carson KA, Batchelor TT, Lesser G, Mikkelsen T, Alavi JB, Phuphanich S, Hammour T, Fisher JD, Supko JG. The effect of enzyme-inducing antiseizure drugs on the pharmacokinetics and tolerability of procarbazine hydrochloride. *Clin Cancer Res* (2006) 12, 5174–81.

Procarbazine + Chlormethine (Mechlorethamine)

A report suggests that, in two patients, the use of high doses of procarbazine with chlormethine may result in neurological toxicity.

Clinical evidence, mechanism, importance and management

Two patients with acute myelogenous leukaemia admitted to hospital for bone marrow transplantation and who were given *high doses* of procarbazine 12.5 mg/kg and 15 mg/kg with chlormethine 0.75 mg/kg and 1 mg/kg on the same day became lethargic, somnolent and disorientated for about a week. Two other patients who received the same drugs, but not on the same day, had no neurological complications. In addition, only one of 45 patients given high-dose procarbazine alone had similar persistent lethargy. Although no interaction has been proved, the authors suggest that the chlormethine may have enhanced the neurotoxic effects of the procarbazine, and advise that it would be prudent to avoid high-doses of these drugs on the same day.[1] Note that lower doses of the combination have been widely used in the MOPP regimen (mechlorethamine, vincristine, procarbazine, and prednisone) without problems.

1. Weiss GB, Weiden PL, Thomas ED. Central nervous system disturbances after combined administration of procarbazine and mechlorethamine. *Cancer Treat Rep* (1977) 61, 1713–14.

Procarbazine + Miscellaneous

The effects of drugs that can cause CNS depression or lower blood pressure may possibly be increased by the presence of procarbazine. Some caution might be appropriate with tricyclics, as procarbazine is a weak MAOI.

Clinical evidence, mechanism, importance and management

(a) Antihypertensives

In one early clinical study, 4 of 48 patients developed postural hypotension when given procarbazine. In addition, another patient with hypertension (180/110 mmHg) had a progressive fall in blood pressure (to 110/80 mmHg) while taking procarbazine.[1] Additive hypotensive effects may therefore be expected if procarbazine is given to patients taking antihypertensives.

(b) CNS depressants

Procarbazine can cause CNS depression ranging from mild drowsiness to profound stupor. In early clinical studies, the incidence was variously reported as 8%, 14%, and 31% (when combined with prochlorperazine).[1-3] Additive CNS depression may therefore be expected if other drugs possessing CNS-depressant activity are given with procarbazine. The US manufacturer names **barbiturates**, **antihistamines**, **narcotics** and **phenothiazines**.[4]

(c) Prochlorperazine

An isolated report describes an acute dystonic reaction (difficulty in speaking or moving, intermittent contractions of muscles on the left side of the neck) in a patient taking procarbazine with prochlorperazine.[5] Prochlorperazine was thought to have contributed to the sedative effects of procarbazine in one early clinical study.[3]

(d) Tricyclics

Procarbazine is a weak inhibitor of MAO (see 'Procarbazine + Sympathomimetics', p.763), and it could therefore theoretically interact with tricyclics, in a similar way to the conventional 'MAOIs', (p.1391). On this basis, the US manufacturer specifically advises avoiding the concurrent use of tricyclics such as amitriptyline and imipramine,[4] whereas the UK manufacturer advises caution.[6]

1. Samuels ML, Leary WV, Alexanian R, Howe CD, Frei E. Clinical trials with N-isopropyl-α-(2-methylhydrazino)-p-toluamide hydrochloride in malignant lymphoma and other disseminated neoplasia. *Cancer* (1967) 20. 1187–94.
2. Stolinsky DC, Solomon J, Pugh RP, Stevens AR, Jacobs EM, Irwin LE, Wood DA, Steinfeld JL, Bateman JR. Clinical experience with procarbazine in Hodgkin's disease, reticulum cell sarcoma, and lymphosarcoma. *Cancer* (1970) 26, 984–90.
3. Brunner KW, Young CW. A methylhydrazine derivative in Hodgkin's disease and other malignant neoplasms: therapeutic and toxic effects studied in 51 patients. *Ann Intern Med* (1965) 63, 69–86.
4. Matulane (Procarbazine hydrochloride). Sigma-tau Pharmaceuticals, Inc. US Prescribing information, February 2004.
5. Poster DS. Procarbazine-prochlorperazine interaction: an underreported phenomenon. *J Med* (1978) 9, 519–24.
6. Procarbazine (Procarbazine hydrochloride). Cambridge Laboratories. UK Summary of product characteristics, August 2006.

Procarbazine + Sympathomimetics

Despite warnings, it seems doubtful that the weak MAO-inhibitory properties of procarbazine can, under normal circumstances, cause a hypertensive reaction with tyramine-rich foods or sympathomimetic drugs.

Clinical evidence, mechanism, importance and management

The manufacturers say that procarbazine is a weak inhibitor of MAO and therefore predict that interactions with certain foods and drugs may occur in rare cases.[1,2] This is apparently based on the results of *animal* studies, which show that the monoamine oxidase inhibitory properties of procarbazine are weaker than pheniprazine.[3] There seem to be no formal reports of hypertensive reactions in patients taking procarbazine who have eaten tyramine-containing foods (e.g. cheese) or after using indirectly-acting sympathomimetic amines (e.g. **phenylpropanolamine**, **amfetamines**, etc.). The only account traced is purely anecdotal and unconfirmed: one author states that he can recall one patient who had a vivid reaction to wine and chicken livers when taking MOPP (mechlorethamine, vincristine, procarbazine, and prednisone) several years earlier.[4] A practical way to deal with this interaction problem has been suggested by a practitioner in an oncology unit:[4] patients taking procarbazine should ideally be given a list of the potentially interacting foodstuffs (see 'MAOIs or RIMAs + Tyramine-rich foods', p.1395), with a warning about the nature of the possible reaction but also with the advice that it very rarely occurs. The foods may continue to be eaten, but patients should start with small quantities to ensure that they still agree with them. Those taking MOPP should also be told that any reaction is most likely to occur during the second week of a 14-day course of treatment with procarbazine, and during the week after it has been stopped.

1. Procarbazine (Procarbazine hydrochloride). Cambridge Laboratories. UK Summary of product characteristics, August 2006.
2. Matulane (Procarbazine hydrochloride). Sigma-tau Pharmaceuticals, Inc. US Prescribing information, February 2004.
3. De Vita VT, Hahn MA, Oliverio VT. Monoamine oxidase inhibition by a new carcinostatic agent. N-isopropyl-α-(2–methylhydrazino)-p-toluamide (MIH). *Proc Soc Exp Biol Med* (1965) 120, 561–5.
4. Maxwell MB. Reexamining the dietary restrictions with procarbazine (an MAOI). *Cancer Nurs* (1980) 3, 451–7.

Raltitrexed + Miscellaneous

On theoretical grounds the manufacturers say that folinic acid and folic acid may possibly interfere with the action of raltitrexed. Warfarin and NSAIDs do not appear to interact with raltitrexed.

Clinical evidence, mechanism, importance and management

(a) Folinates

The antimetabolite, raltitrexed, is a folate analogue and is a potent and specific inhibitor of the enzyme thymidylate synthase. Inhibition of this enzyme ultimately interferes with the synthesis of deoxyribonucleic acid (DNA) leading to cell death. The intracellular polyglutamation of raltitrexed leads to the formation of even more potent inhibitors of thymidylate synthase. Folate (methylene tetrahydrofolate) is a co-factor required by thymidylate synthase and therefore theoretically folinic acid or folic acid

may interfere with the action of raltitrexed. Clinical interaction studies have not yet been undertaken to confirm these predicted interactions.[1]

(b) Warfarin and NSAIDs

The manufacturers say that no specific clinical interaction studies have been conducted, but a review of the clinical study database did not reveal any evidence of interactions between raltitrexed and warfarin, NSAIDs or other drugs.[1]

1. Tomudex (Raltitrexed). AstraZeneca UK Ltd. UK Summary of product characteristics, August 2008.

Sorafenib + Antineoplastics

Sorafenib may increase docetaxel and doxorubicin levels. Unexpectedly severe toxicity was seen when sorafenib was given with bevacizumab, which limited the dose of both drugs. Variable effects on the pharmacokinetics of fluorouracil have been seen. Sorafenib does not alter the pharmacokinetics of gemcitabine or oxaliplatin, or of paclitaxel when stopped for three days around its administration.

Clinical evidence, mechanism, importance and management

(a) Bevacizumab

In a dose-finding study, the maximum tolerated doses of sorafenib and bevacizumab were lower when they were given together compared with either drug alone. Unexpectedly severe toxicity was seen, in particular hypertension, proteinuria and thrombocytopenia. Three-quarters of patients required a further reduction in their sorafenib dose to 200 mg daily.[1]

(b) Docetaxel

Sorafenib 200 mg or 400 mg twice daily on days 2 to 19 of a 21-day cycle increased the AUC and maximum concentration of docetaxel 75 or 100 mg/m^2 given on day one every 21 days, by 36 to 80%, and by 16 to 32%, respectively.[2,3] The manufacturer therefore recommends caution on the concurrent use of these drugs.[2,3]

(c) Doxorubicin

A modest 21% increase in the AUC of doxorubicin occurred when it was given with sorafenib. The manufacturers therefore recommend caution on the concurrent use of these drugs.[2,3]

(d) Fluorouracil

The AUC of fluorouracil has been reported both to increase by up to 47% and to decrease by 10% when given with sorafenib. The manufacturer therefore advises caution on the concurrent use of these drugs.[3]

(e) Gemcitabine

In a phase I study The pharmacokinetics of gemcitabine and sorafenib were not significantly altered in 27 patients who received gemcitabine weekly and sorafenib daily from day 2.[4]

(f) Oxaliplatin

In clinical studies sorafenib did not affect the pharmacokinetics of oxaliplatin.[2,3]

(g) Paclitaxel

Sorafenib is predicted to inhibit the metabolism of paclitaxel by the cytochrome P450 isoenzyme CYP2C8. In one clinical study, there was no change in the pharmacokinetics of paclitaxel when sorafenib was stopped for 3 days around the administration of paclitaxel.[3]

1. Azad NS, Posadas EM, Kwitkowski VE, Steinberg SM, Jain L, Annunziata CM, Minasian L, Sarosy G, Kotz HL, Premkumar A, Cao L, McNally D, Chow C, Chen HX, Wright JJ, Figg WD, Kohn EC. Combination targeted therapy with sorafenib and bevacizumab results in enhanced toxicity and antitumor activity. J Clin Oncol (2008) 26, 3709–14.
2. Nexavar (Sorafenib tosylate). Bayer plc. UK Summary of product characteristics, July 2009.
3. Nexavar (Sorafenib tosylate). Bayer Pharmaceuticals Corp. US Prescribing information, February 2009.
4. Siu LL, Awada A, Takimoto CH, Piccart M, Schwartz B, Giannaris T, Lathia C, Petrenciuc O, Moore MJ. Phase I trial of sorafenib and gemcitabine in advanced solid tumors with an expanded cohort in advanced pancreatic cancer. *Clin Cancer Res* (2006) 12, 144–51.

Sorafenib + Miscellaneous

Sorafenib levels were modestly reduced by rifampicin (a potent enzyme inducer) and might be similarly affected by other inducers of cytochrome P450 isoenzymes. Ketoconazole (a CYP3A4 inhibitor) had no clinically relevant effect on sorafenib pharmacokinetics, suggesting that other CYP3A4 inhibitors are unlikely to interact. Sorafenib did not alter the pharmacokinetics of midazolam, dextromethorphan or omeprazole, but is predicted to inhibit the metabolism of CYP2B6 and CYP2C8 substrates.
Isolated cases of raised INRs and bleeding have been reported in patients taking warfarin with sorafenib, but no INR changes were seen in a study in patients.

Clinical evidence, mechanism, importance and management

(a) Cytochrome P450 inducers

A 5-day course of **rifampicin** (**rifampin**) reduced the AUC of a single dose of sorafenib by an average of 37%. Other inducers of cytochrome P450 isoenzymes and/or glucuronidation, such as **St John's wort**, **carbamazepine**, **phenytoin**, **phenobarbital** and **dexamethasone**, may also reduce sorafenib levels.[1,2] Sorafenib is given as a standard dose, and is not titrated to effect. The clinical relevance of this reduction is unknown, but the US manufacturer recommends avoiding strong enzyme inducers.[2] They say that, if an enzyme inducer is required, consideration can be given to increasing the dose of sorafenib with close monitoring for adverse effects.[2]

(b) CYP3A4 inhibitors

In a study in 15 healthy subjects, **ketoconazole** 400 mg daily for 7 days had no effect on the AUC or maximum level of a low 50-mg dose of sorafenib given on day 4. However, ketoconazole markedly inhibited the formation of the metabolite, sorafenib *N*-oxide. **Ketoconazole** is a known inhibitor of the cytochrome P450 isoenzyme CYP3A4, by which sorafenib is metabolised to its *N*-oxide metabolite. Nevertheless, because the exposure to sorafenib did not increase, it is likely the glucuronidation metabolic pathway compensated.[3] The pharmacokinetics of sorafenib are linear at clinical doses, therefore higher doses of sorafenib are also unlikely to be affected by ketoconazole.[3] The findings of this study suggest that no pharmacokinetic interaction is likely with other CYP3A4 inhibitors as a result of this mechanism.

(c) Cytochrome P450 substrates

Sorafenib did not alter the pharmacokinetics of **dextromethorphan**, **midazolam**, and **omeprazole**, used as substrates for the cytochrome P450 isoenzymes CYP2D6, CYP3A4 and CYP2C19, respectively. Pharmacokinetic interactions with drugs that are substrates of these isoenzymes are therefore not anticipated.[1]

In vitro studies have shown that sorafenib inhibits CYP2B6 and CYP2C8, but the clinical relevance of this is unclear. The manufacturers warn that the plasma levels of substrates of CYP2B6 (the UK manufacturer names **bupropion**, **cyclophosphamide**, **efavirenz**, **ifosfamide** and **methadone**) and of CYP2C8 (the UK manufacturer names **amodiaquine** and **repaglinide**) may be increased by sorafenib.[1,2] Until more is known, this warning seems prudent. Be alert for any increase in the adverse effects of these drugs in patients also given sorafenib. For a list of substrates of CYP2B6 and CYP2C8 see 'Table 1.3', (p.6).

(d) Warfarin

A study in patients given sorafenib and taking warfarin found that the INR did not differ between those patients taking sorafenib and those not taking sorafenib, despite previous *in vitro* evidence that sorafenib inhibits the cytochrome P450 isoenzyme CYP2C9, the main isoenzyme involved in the metabolism of warfarin.[1,2]

However, raised INRs and infrequent bleeding have been reported in patients taking warfarin with sorafenib. The manufacturers therefore advise that the INR should be closely monitored in patients taking these drugs together.[1,2] Note that, from a disease perspective, when treating venous thromboembolic disease in patients with cancer, warfarin is generally inferior (higher risk of major bleeds and recurrent thrombosis) to low-molecular-weight heparins.[4]

1. Nexavar (Sorafenib tosylate). Bayer plc. UK Summary of product characteristics, July 2009.
2. Nexavar (Sorafenib tosylate). Bayer Pharmaceuticals Corp. US Prescribing information, February 2009.
3. Lathia C, Lettieri J, Cihon F, Gallentine M, Radtke M, Sundaresan P. Lack of effect of ketoconazole-mediated CYP3A inhibition on sorafenib clinical pharmacokinetics. *Cancer Chemother Pharmacol* (2006) 57, 685–92.
4. Baglin TP, Keeling DM, Watson HG, for the British Committee for Standards in Haematology. Guidelines on oral anticoagulation (warfarin): third edition – 2005 update. *Br J Haematol* (2006) 132, 277–85.

Streptozocin + Phenytoin

A single case report indicates that phenytoin can reduce or abolish the effects of streptozocin.

Clinical evidence, mechanism, importance and management

A patient with an organic hypoglycaemic syndrome, due to a metastatic apud cell carcinoma of the pancreas, who was taking streptozocin 2 g daily with phenytoin 400 mg daily for 4 days, did not have the expected response to streptozocin until phenytoin was withdrawn.[1] It would seem that the phenytoin inhibited the effects of the streptozocin by some mechanism as yet unknown. Although this is an isolated case report its authors recommend that concurrent use should be avoided.

1. Koranyi L, Gero L. Influence of diphenylhydantoin on the effect of streptozotocin. *BMJ* (1979) 1, 127.

Sunitinib + Food

Food does not affect the pharmacokinetics of sunitinib.

Clinical evidence, mechanism, importance and management

In a randomised study, 16 healthy subjects were given a single 50-mg dose of sunitinib following a 10 hour fast, or within 30 minutes of a high-fat, high-calorie breakfast. The rate of formation of the active metabolite, SU12662, was decreased resulting in a 23% reduction in its maximum concentration. However as the overall bioavailability of both sunitinib and the active metabolite were unaffected by food, the reduction in the maximum levels of the active metabolite is not thought to be clinically relevant. No difference in adverse effects was reported between the two groups.[1] Sunitinib may therefore be taken with or without food.[2]

1. Bello CL, Sherman L, Zhou J, Verkh L, Smeraglia J, Mount J, Klamerus KJ. Effect of food on the pharmacokinetics of sunitinib malate (SU11248), a multi-targeted receptor tyrosine kinase inhibitor: results from a phase I study in healthy subjects. *Anticancer Drugs* (2006) 17, 353–8.
2. Sutent (Sunitinib malate). Pfizer Ltd. UK Summary of product characteristics, October 2009.

Sunitinib + Miscellaneous

Ketoconazole increases sunitinib levels, and rifampicin reduces sunitinib levels. Other potent CYP3A4 inhibitors and inducers are expected to interact similarly. Sunitinib may have additive QT prolonging effects if it is given with other drugs that prolong the QT interval.

Clinical evidence, mechanism, importance and management

(a) CYP3A4 inducers

A study in healthy subjects found that **rifampicin** (**rifampin**) reduced the total AUC and maximum plasma concentration of sunitinib and its primary metabolite by 46% and 23%, respectively. Therefore, the manufacturers advise that the concurrent use of sunitinib and CYP3A4 inducers should be avoided.[1,2] They specifically mention **carbamazepine**,[1,2] **dexamethasone**,[1,2] **phenobarbital**,[1,2] **phenytoin**,[1,2] **rifabutin**,[2] **rifapentine**,[2] and **St John's wort**.[1] If concurrent use is necessary, the manufacturers advise increasing the dose of sunitinib in 12.5 mg increments to a maximum of 87.5 mg daily;[1,2] however, the US manufacturer advises that patients should not take **St John's wort** with sunitinib due to the unpredictable nature of the interaction.[2] Note that clinically relevant interactions occurring as a result of dexamethasone inducing CYP3A4 appear rare.

(b) CYP3A4 inhibitors

A study in healthy subjects found that **ketoconazole** increased the total AUC and maximum plasma concentration of sunitinib and its primary metabolite by 51% and 49%, respectively. Sunitinib was given as a single dose (amount not stated). Sunitinib is metabolised by the cytochrome P450 isoenzyme CYP3A4, and its metabolite is further metabolised by CYP3A4. Based on the results seen with ketoconazole, the manufacturers of sunitinib advise avoiding the concurrent use of potent CYP3A4 inhibitors. They specifically mention **atazanavir**,[2] **clarithromycin**,[1,2] **erythromycin**,[1] **grapefruit juice**,[1] **indinavir**,[2] **itraconazole**,[1,2] **nelfinavir**,[2] **ritonavir**,[1,2], **saquinavir**,[2] **telithromycin**,[2] and **voriconazole**.[2]. If concurrent use is necessary, the dose of sunitinib should be reduced to a minimum of 37.5 mg daily, based on tolerability.[1,2]

(c) Drugs that prolong the QT interval

Sunitinib has been shown to prolong the QTc interval in 24 patients, using Fridericia's correction, at twice the usual therapeutic concentrations, but none of these patients were noted to experience a cardiac arrhythmia.[1] Torsades de pointes has been reported in less than 0.1% of patients taking sunitinib.[1,2] The manufacturers advise caution in patients taking sunitinib with antiarrhythmic drugs (presumably class Ia and class III antiarrhythmics). This caution should probably also be extended to other drugs known to prolong the QT interval, see 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290.

1. Sutent (Sunitinib malate). Pfizer Ltd. UK Summary of product characteristics, October 2009.
2. Sutent (Sunitinib malate). Pfizer Inc. US Prescribing information, May 2008.

Tamoxifen + Acitretin

A patient taking tamoxifen developed bradycardia and a prolonged QT interval when also taking acitretin.

Clinical evidence, mechanism, importance and management

A case report describes a woman taking tamoxifen 20 mg daily who experienced symptomatic bradycardia and QT prolongation 3 weeks after starting acitretin 50 mg daily for 14 days then 30 mg daily during radiation therapy. On stopping the acitretin and later the tamoxifen, her ECG returned to normal and her symptoms resolved.[1] It was suggested that the acitretin might have inhibited the metabolism of tamoxifen, thus increasing the plasma levels of tamoxifen to a level at which QT prolongation became symptomatic. However, this seems unlikely.

The clinical relevance of this isolated report is uncertain. Bear it in mind in the event of an unexpected response to treatment.

1. Slovacek L, Ansorgova V, Macingova Z, Haman L, Petera J. Tamoxifen-induced QT interval prolongation. J Clin Pharm Ther (2008) 33, 453–5.

Tamoxifen + Aromatase inhibitors

Aminoglutethimide markedly increases tamoxifen clearance and reduces its serum levels. Anastrozole, exemestane and letrozole do not appear to affect tamoxifen levels. Tamoxifen modestly reduces anastrozole and letrozole levels, but it does not alter aminoglutethimide or exemestane levels, or anastrozole, exemestane or letrozole effects.

Clinical evidence

(a) Aminoglutethimide

In 6 menopausal women with breast cancer, aminoglutethimide 250 mg four times daily for 6 weeks markedly reduced the serum levels of tamoxifen 20 to 80 mg daily and most of its metabolites. The clearance of the tamoxifen was increased 3.2-fold and the tamoxifen AUC was reduced by 73% (range 56 to 80%). Tamoxifen did not alter the pharmacokinetics of aminoglutethimide.[1]

(b) Anastrozole

In a double-blind, placebo-controlled study in 34 women with breast cancer, who had been taking tamoxifen 20 mg daily for at least 10 weeks, the addition of anastrozole 1 mg daily for 28 days did not affect the pharmacokinetics of tamoxifen.[2] Although the estradiol suppressant effects of anastrozole 1 mg daily did not appear to be affected by tamoxifen 20 mg daily in two studies,[2,3] in one of these studies, anastrozole levels were decreased by 27% by tamoxifen.[3]

(c) Exemestane

In a study in 32 women who had been taking tamoxifen 20 mg daily for at least 4 months, exemestane 25 mg daily for 8 weeks had no effect on the pharmacokinetics of tamoxifen or the formation of tamoxifen metabolites.[4]

Tamoxifen did not affect the plasma levels of exemestane in a pilot study

in 18 postmenopausal women given exemestane 25 mg daily for 14 days, then exemestane and tamoxifen 20 mg daily for 4 weeks. In addition, tamoxifen did not affect the pharmacodynamics (estrone, estrone sulfate and estradiol suppression) of exemestane.[5]

(d) Letrozole

In 12 women, letrozole levels were reduced by 38% (range 0 to 70%) 6 weeks after tamoxifen 20 mg daily was added to letrozole 2.5 mg daily. This reduction persisted after 4 to 8 months; however, the estradiol suppressant effects of letrozole did not appear to be affected.[6] In 18 women, the pharmacokinetics of tamoxifen 20 mg daily were not affected by letrozole 2.5 mg daily.[7]

Mechanism

It is likely that aminoglutethimide, an enzyme inducer, increases the metabolism of the tamoxifen by the liver, thereby increasing its loss from the body. It is not known how tamoxifen reduces anastrozole and letrozole levels, although it may also be by enzyme induction.[6]

Importance and mechanism

Theoretically, the combination of an oestrogen antagonist such as tamoxifen and an aromatase inhibitor should provide additional benefit in the treatment of hormone-dependent cancers; however, no clinical studies have yet found this to be so. The pharmacokinetic interactions described above may partly explain this. It may be preferable to use these drugs sequentially rather than concurrently.[6]

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Tamoxifen and other anti-oestrogens + HRT

In one cohort study, HRT did not increase the risk of recurrent breast cancer in women taking tamoxifen. HRT is reported to oppose the lipid-lowering effects of tamoxifen.

Clinical evidence, mechanism, importance and management

(a) Anti-oestrogenic effects

In a cohort study of the use of HRT in the management of menopausal symptoms in women treated for breast cancer, the use of continuous combined HRT (an oestrogen plus a progestogen) was not associated with an increased risk of breast cancer recurrence in women taking tamoxifen.[1] This is of interest because HRT increases the risk of oestrogen receptor-positive breast cancer and might therefore be expected to oppose the effects of anti-oestrogens such as tamoxifen in the treatment and prevention of breast cancer. For this reason, HRT and other oestrogens are often considered to be contraindicated in women taking anti-oestrogens such as **anastrozole**,[2] **exemestane**,[3,4] **letrozole**, tamoxifen and **toremifene**. The cohort study described[1] suggests that there need not be a complete restriction on their concurrent use, but ideally randomised prospective studies are required to confirm this. Note that adding low-dose tamoxifen to HRT is being tried as a way of reducing the risks of HRT. In one study in 210 healthy postmenopausal women taking HRT for menopausal symptoms, the addition of tamoxifen 5 mg daily appeared to have a favourable effect on markers of breast cancer risk without appreciably increasing menopausal symptoms.[5]

(b) Cardiovascular effects

A large-scale comparative study was undertaken over a 12-month period in groups of women taking tamoxifen alone, HRT alone, or tamoxifen with transdermal HRT to see whether the cardiovascular risk factors (low-density lipoprotein cholesterol, high-density lipoprotein-cholesterol levels, platelet counts) were changed by concurrent use. It was found that the decrease in total and LDL-cholesterol levels due to the tamoxifen was unchanged in current HRT users, but reduced by two-thirds in women taking tamoxifen who then started HRT.[6] In another study in 210 healthy postmenopausal women taking HRT for menopausal symptoms, the addition of low-dose tamoxifen 5 mg daily for 12 months appeared to have a beneficial effect on some markers of cardiovascular disease (C-reactive protein and antithrombin) but not others (lipids and fibrinogen).[5]

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Tamoxifen + Medroxyprogesterone

Medroxyprogesterone reduces the levels of tamoxifen and its desmethyl metabolite.

Clinical evidence, mechanism, importance and management

In 20 women with breast cancer taking tamoxifen 20 mg twice daily, the addition of medroxyprogesterone acetate 500 mg twice daily only slightly reduced the tamoxifen serum levels over a 6-month period, but considerably reduced the levels of the desmethyl metabolite of tamoxifen, presumably because of some effect on the metabolism of the tamoxifen by the liver.[1] The clinical importance of this interaction is unclear.

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Tamoxifen + Rifampicin (Rifampin)

Rifampicin increases the metabolism of tamoxifen.

Clinical evidence, mechanism, importance and management

In 10 healthy *men* rifampicin 600 mg daily for 5 days reduced the AUC of a single 80-mg dose of tamoxifen by 86%, reduced its peak plasma levels by 55%, and reduced its half-life by 44%. Similarly, the AUC of *N*-demethyltamoxifen was reduced by 62%.[1]

It is likely that rifampicin induces the metabolism of tamoxifen by the cytochrome P450 isoenzyme CYP3A4, thereby reducing its levels. These findings suggest that the efficacy of tamoxifen may be reduced by rifampicin. However, there is some *in vitro* evidence that suggests that tamoxifen and rifampicin have additive antineoplastic effects in pancreatic carcinoma cell lines.[2] Also, tamoxifen induces its own metabolism on long-term use.[3] Thus, further study is needed to assess the clinical impact of the long-term concurrent use of these drugs.

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Tamoxifen + SSRIs

Paroxetine reduces the metabolism of tamoxifen to one of its active metabolites. One small case-control study found that inhibitors of CYP2D6 such as some SSRIs did not increase the recurrence of breast cancer in tamoxifen users, and another reported the same finding for citalopram or escitalopram.

Clinical evidence

Twelve women taking tamoxifen 20 mg daily were also given **paroxetine** 10 mg daily for 4 weeks, and plasma levels of tamoxifen and its metabolites were measured.[1] Before **paroxetine**, the plasma levels of the 4-hydroxy-*N*-desmethyl-tamoxifen metabolite (endoxifen) were about 12 times higher than those of the 4-hydroxy-tamoxifen metabolite. **Paroxetine** reduced endoxifen levels by 56%, but those of *N*-desmethyl-tamoxifen, and 4-hydroxy-tamoxifen were unchanged. The reduction in endoxifen levels was greatest in those who were CYP2D6 extensive metabolisers (that is, those with normal levels of this isoenzyme). In a further study by the same research group, 80 women starting tamoxifen 20 mg daily had plasma levels of tamoxifen measured after one and 4 months.[2] These were then correlated with CYP2D6 metaboliser phenotype and the concurrent use of CYP2D6 inhibitors (taken by 24 women). In women who were CYP2D6 extensive metabolisers, the use of CYP2D6 inhibitors was associated with a 58% lower endoxifen level, which was substantially lower in those taking **paroxetine** (a moderate CYP2D6 inhibitor), but only slightly reduced by venlafaxine, and intermediate in those taking **sertraline** (a weak CYP2D6 inhibitor).[2]

However, a case-control study of 28 women taking tamoxifen with recurrences of oestrogen receptor positive breast cancer found that there was no difference in the number of women taking CYP2D6 inhibitors (said to be **fluoxetine**, **paroxetine**, **sertraline**) between cases and controls (women taking tamoxifen with no recurrence). Similarly, there were no differences for CYP2C9 inhibitors (said to include **paroxetine** and **sertraline**).[3] Moreover, in another similar case-control study, there was no difference in incidence of use of **citalopram** or its isomer **escitalopram** between 184 women with breast cancer recurrence and 184 matched controls.[4]

Mechanism

Endoxifen and 4-hydroxy-tamoxifen are more active anti-oestrogens than tamoxifen.[1] Tamoxifen is metabolised to 4-hydroxy-tamoxifen and *N*-desmethyl-tamoxifen principally by the cytochrome P450 subfamily CYP3A,[1] although others have found that other isoenzymes are involved,[5] and to endoxifen by CYP2D6.[1] Of the SSRIs, paroxetine and fluoxetine are moderate inhibitors of CYP2D6, whereas citalopram and sertraline only weakly inhibit CYP2D6. However, tamoxifen resistance may be more to do with altered oestrogen receptor sensitivity than reduced levels of tamoxifen metabolites.[3] Further it has been suggested that the plasma levels of tamoxifen and metabolites found in one study[1] would be sufficient to block oestrogen binding to oestrogen receptors so that a decrease in endoxifen levels would not substantially affect anti-oestrogen activity.[6]

Importance and management

Although information is limited, it is established that moderate inhibitors of CYP2D6 such as paroxetine can alter the metabolism of tamoxifen to its active metabolites. However, the effect this has on the clinical efficacy of tamoxifen remains to be established. The case-control studies suggest the effect is not great for SSRIs as a whole or for citalopram or escitalopram (although it should be noted that these are weak inhibitors of CYP2D6). At present, there is insufficient evidence to recommend caution when giving SSRIs with tamoxifen, but further study is clearly needed.

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Taxanes + Amifostine

Amifostine had no effect on docetaxel and paclitaxel pharmacokinetics, except in one study which found that amifostine extended paclitaxel plasma circulation time. Amifostine appears not to reduce the toxicity of these taxanes.

Clinical evidence, mechanism, importance and management

In a randomised study, amifostine did not alter the response to, or the pharmacokinetics of, **paclitaxel**, neither did it protect against **paclitaxel**-related neurotoxicity or myelotoxicity.[1] Another study in 8 patients has confirmed that amifostine (750 mg/m^2 as a 15-minute infusion 30 minutes before **paclitaxel**) had no effect on the pharmacokinetics of **paclitaxel** 135 to 200 mg/m^2. Six of the patients were also taking epirubicin and cisplatin.[2] Although the preliminary findings of an earlier study had suggested that pre-treatment with amifostine reduced the AUC of **paclitaxel** by 29%,[3] the full report of this study concluded that amifostine had no clinically relevant effect on **paclitaxel** pharmacokinetics.[4] In a study in which patients were given amifostine 500 mg as an infusion over 15 minutes just before low-dose **paclitaxel** 80 mg/m^2 as a one-hour infusion, amifostine reduced maximum plasma levels by about 20%. The AUC of paclitaxel was not affected, but the paclitaxel plasma circulation time was prolonged.[5]

Amifostine had no effect on the pharmacokinetics of **docetaxel**, and it did not reduce **docetaxel**-induced myelotoxicity.[6]

The finding in two of these studies[1,6] that the toxicity of taxanes was not reduced by amifostine does not support earlier *in vitro* data where amifostine protected normal tissue from **paclitaxel** toxicity.[7]

Most studies show no beneficial or adverse consequences from giving amifostine with the taxanes. Further study is needed to evaluate the possible effects of amifostine on taxane plasma circulation time.

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Taxanes + Ciclosporin

Ciclosporin increases the levels of docetaxel and paclitaxel after *oral* administration.

Clinical evidence

(a) Docetaxel

One study found that the bioavailability of docetaxel after oral administration of the intravenous formulation was increased from 8% to 90% by oral ciclosporin 15 mg/kg.[1] In this study, the AUC of ciclosporin was about 50% higher than expected from previously published data, when it was given with oral docetaxel.[2]

(b) Paclitaxel

In 5 patients the plasma levels of paclitaxel were below therapeutic concentrations when they were given an oral dose (intravenous formulation) of paclitaxel 60 mg/m^2 followed by intravenous doses of 175 mg/m^2 for subsequent courses. However, therapeutic levels above 100 micromol/mL (a ninefold increase) were achieved in 9 patients who received the same regimen with ciclosporin 15 mg/kg.[3]

Mechanism

Oral paclitaxel and docetaxel have poor oral bioavailability because of a high affinity for P-glycoprotein in the gastrointestinal tract, and possibly also pre-systemic metabolism by the cytochrome P450 isoenzyme CYP3A4. Ciclosporin is a known P-glycoprotein inhibitor, and thereby increases their oral absorption, and might also interact via CYP3A4. It was suggested that docetaxel might increase ciclosporin levels because they are both substrates for CYP3A4, but this sort of competition for metabolism does not usually result in clinically relevant interactions.

Importance and management

The use of oral docetaxel or paclitaxel is not established, therefore the pharmacokinetic interaction with ciclosporin has little general relevance. The suggestion that oral docetaxel might increase ciclosporin levels requires confirmation in a prospective study.

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Taxanes + Cisplatin and other platinum compounds

The toxicity of paclitaxel given with cisplatin appears to be dependent on the order of administration, with more severe myelosuppression occurring if cisplatin is given first. There does not appear to be any sequence dependent interaction for the combination of docetaxel with carboplatin or docetaxel with cisplatin. Paclitaxel may reduce the thrombocytopenia associated with carboplatin. The combination of carboplatin with paclitaxel appears to be more neurotoxic than carboplatin with docetaxel.

Clinical evidence, mechanism, importance and management

(a) Carboplatin

Several clinical studies have found that the severity of thrombocytopenia with the combination of **paclitaxel** and carboplatin was less than that expected with carboplatin alone.[1-5] This does not appear to be due to any changes in carboplatin pharmacokinetics. In one study, patients were given carboplatin as a 30-minute infusion, either alone or immediately after **paclitaxel** 175 mg/m^2 as a 3-hour infusion. It was found that the pharmacokinetics of carboplatin were not significantly affected by **paclitaxel**.[6] Similarly, a pharmacokinetic interaction was not noted when **paclitaxel** and carboplatin were given in either order in another study.[1] Other studies found the AUC of carboplatin to be similar to that predicted, despite the presence of paclitaxel.[2,5] Although one study found the AUC of carboplatin to be about 12% lower in the presence of **paclitaxel**,[4] the same researchers also found that the AUC associated with a 50% decrease in platelet count increased by 68% (i.e. more carboplatin is needed to cause the same degree of thrombocytopenia), which suggests a pharmacodynamic basis for the attenuated toxicity of the combination.[7] Other researchers also reported that the AUC of carboplatin causing a 50% reduction in platelets was about 6.3 mg/mL per minute when given with **paclitaxel** compared with historical data of 4 mg/mL per minute when given alone.[8] Although thrombocytopenia may be lower than expected, myelosuppression (in the form of neutropenia) is a dose-limiting toxicity of the combination of carboplatin and **paclitaxel**.[1-4] In one study, patients given **paclitaxel** with carboplatin experienced significantly greater neurotoxicity than those given **docetaxel** with carboplatin, but the regimens were similar in efficacy.[9] Further, there appear to be no pharmacokinetic interactions between carboplatin and **docetaxel**.[10,11]

(b) Cisplatin

Early studies of the combination of cisplatin and **paclitaxel** found that the degree of myelosuppression was sequence dependent. When cisplatin was given first, a greater degree of myelosuppression was seen.[12] Pharmacokinetic studies suggest that sequence-dependent differences in myelosuppression may be due to a 25% reduction in **paclitaxel** clearance when cisplatin is given first.[12] For this reason, the manufacturers recommend that **paclitaxel** is given before cisplatin.[13,14] There is also some evidence that *myelosuppression* is greater for the combination when **paclitaxel** is given over 24 hours as opposed to 3 hours.[13] When **paclitaxel** is given with cisplatin, *neurotoxicity* (peripheral neuropathy) is common,[13] and there is some evidence that this is more severe if the **paclitaxel** is given over 3 hours as opposed to over 24 hours.[15] In one study,[16] neurotoxicity was unexpectedly severe when **paclitaxel** alone was used in patients who had relapsed after treatment with cisplatin; however, this was not the case in another similar study.[17] There is also some retrospective evidence that the use of paclitaxel with cisplatin may increase *nephrotoxicity* when compared with cisplatin alone.[18]

In contrast to **paclitaxel**, early studies did not reveal any obvious sequence dependent toxicity for the combination of **docetaxel** and cisplatin.[19] In addition, cisplatin did not cause any significant changes in **docetaxel** pharmacokinetics.[19,20] A more recent analysis confirmed that cisplatin was not associated with any changes in docetaxel clearance.[21]

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Taxanes + Protease inhibitors

Life-threatening haematological toxicities have been reported in a few patients taking protease inhibitors when given paclitaxel, and a couple of cases have been reported for docetaxel. Nelfinavir and ritonavir appear to inhibit the clearance of paclitaxel, although one case report did not find this. Protease inhibitors are also predicted to inhibit the metabolism of docetaxel.

Clinical evidence

(a) Docetaxel

An HIV-positive 64-year-old woman taking **nelfinavir** was given trastuzumab and docetaxel 36 mg/m^2 for breast cancer. Three days later she was hospitalised with early, severe myelosuppression, which was attributed to an interaction between the nelfinavir and docetaxel, and she died from sepsis.[1]

A 40-year-old HIV-positive man taking **ritonavir**-boosted **lopinavir** developed febrile neutropenia 8 days after a single 25-mg/m^{2}dose of docetaxel; microbiological tests were negative.[2]

(b) Paclitaxel

In a study of paclitaxel 100 mg/m^2 given every 2 weeks for the treatment of HIV-related Kaposi's sarcoma, there was no difference in haematological toxicity (including severe or life-threatening haematological toxicity) or other toxicities between patients taking protease inhibitors (mostly **indinavir**, but also **saquinavir**, **ritonavir**, or **nelfinavir**) and those not taking a protease inhibitor in each of the first 10 cycles. Grade 4 neutropenia was reported in 35% of patients. In this study, of 107 patients, 82 received protease inhibitor-based antiretroviral regimens, and protease inhibitor use had a favourable impact on survival. Nevertheless, paclitaxel-related adverse effects contributed to the deaths of 4 patients, all of whom were receiving multiple other drugs including protease inhibitor-based antiretroviral regimens and co-trimoxazole.[3]

A number of case reports describe unexpected paclitaxel-related toxicity with protease inhibitors. A 39-year-old woman taking **lopinavir** was given carboplatin and paclitaxel 175 mg/m^2 for adenocarcinoma. Five days later she was hospitalised with early, severe myelosuppression, which was attributed to an interaction between lopinavir and paclitaxel, and she later died.[1] In another report, an HIV-positive patient who was taking **ritonavir**-boosted **lopinavir**, delavirdine and didanosine was also given paclitaxel 100 mg/m^2 for Kaposi's sarcoma. Within 3 days he developed myalgia and arthralgia, and 8 days after treatment developed fever, tachycardia and a productive cough. He was treated with antibacterials and G-CSF, but later died. Findings at post mortem included severe oesophageal mucositis, *Streptococcus viridans* pneumonia and a massive saddle embolism (an embolism that sits across two vessels).[4] A second patient taking **indinavir**, **ritonavir**, lamivudine and stavudine developed severe leucopenia and thrombocytopenia within 7 days of being given paclitaxel 100 mg/m^2 for Kaposi's sarcoma, and again after a second course of paclitaxel. Further courses of paclitaxel were tolerated by giving a reduced dose of 60 mg/m^2 of paclitaxel with G-CSF.[4] Similar cases have been reported in 2 patients receiving paclitaxel 100 mg/m^2 every other week for Kaposi's sarcoma when their antiretroviral regimens were changed from **indinavir** or **nelfinavir** with NRTIs to **saquinavir**, delavirdine and didanosine. One of these patients also received intermittent fluconazole.[5]

The UK manufacturer of paclitaxel briefly mentions that studies in patients with Kaposi's sarcoma, who were taking multiple other drugs, suggest that the systemic clearance of paclitaxel was significantly lower in the presence of **nelfinavir** and **ritonavir**, but not with **indinavir**.[6] In one published study, the pharmacokinetics of paclitaxel did not differ in 4 patients receiving **indinavir**, compared with 5 patients not taking protease inhibitors.[7] In contrast, in one case, the clearance of paclitaxel was modestly *increased* and its AUC slightly reduced when it was given with protease inhibitors or nevirapine. This patient, over a number of cycles of paclitaxel, variously received paclitaxel alone, with **ritonavir**, **indinavir**, and two NRTIs, with **ritonavir**, **saquinavir**, and two NRTIs, or with **nevirapine** and two NRTIs. However, the pharmacokinetics of paclitaxel during any of these regimens did not differ from each other and were not significantly different from historical data from HIV-negative patients, and the pharmacokinetics of saquinavir, ritonavir, indinavir or nevirapine also did not differ from historical data.[8]

Mechanism

Uncertain. Paclitaxel is metabolised by the cytochrome P450 isoenzymes CYP2C8 and CYP3A4, whereas docetaxel is principally metabolised by CYP3A4. Protease inhibitors such as ritonavir and indinavir are known to inhibit CYP3A4, which might result in increased taxane levels and toxicity, but, docetaxel is more likely to be affected by this mechanism than paclitaxel. Nevertheless, additional use of a CYP2C8 inhibitor (such as trimethoprim as part of co-trimoxazole, as is common in HIV infection) could result in an interaction with paclitaxel.

Importance and management

Evidence is limited, nevertheless the UK manufacturers advise caution when docetaxel or paclitaxel is given to patients also receiving protease inhibitors.[6] Monitor patients receiving protease inhibitors closely for severe myelosuppression, peripheral neuropathy and mucositis. The interaction may be modified by the presence of other drugs: the NNRTI delavirdine is a known inhibitor of CYP3A4, but nevirapine (and also efavirenz) is usually an *inducer* of CYP3A4 and might therefore *decrease* taxane levels.

1. Parameswaran R, Sweeney C, Einhorn LH. Interaction between highly active antiretroviral therapy (HAART) and taxanes: a report of two cases. *Proc Am Soc Clin Oncol* (2002) 21, abstract 2194.
2. Loulergue P, Mir O, Allali J, Viard J-P. Possible pharmacokinetic interaction involving ritonavir and docetaxel in a patient with Kaposi's sarcoma. AIDS (2008) 22, 1237–9.
3. Tulpule A, Groopman J, Saville MW, Harrington W, Friedman-Kien A, Espina BM, Garces C, Mantelle L, Mettinger K, Scadden DT, Gill PS. Multicenter trial of low-dose paclitaxel in patients with advanced AIDS-related Kaposi sarcoma. *Cancer* (2002) 95, 147–54.
4. Bundow D, Aboulafia DM. Potential drug interaction with paclitaxel and highly active antiretroviral therapy in two patients with AIDS-associated Kaposi sarcoma. *Am J Clin Oncol* (2004) 27, 81–4.
5. Schwartz JD, Howard W, Scadden DT. Potential interaction of antiretroviral therapy with paclitaxel in patients with AIDS-related Kaposi's sarcoma. *AIDS* (1999) 13, 283–4.
6. Paclitaxel. Medac GmbH. UK Summary of product characteristics, September 2007.
7. Duchin K, Sun J, Tan M, Ilaw M, Cabriales S, Espina BM, East D, Tulpule A, Gill PS. Pharmacokinetics of low-dose Paxene (paclitaxel) in patients with refractory or relapsed AIDS-related Kaposi's sarcoma [abstract no. 829]. 33rd Annual Meeting of the American Society of Clinical Oncology;1997 May 17-20; Denver.
8. Nannan Panday VR, Hoetelmans RMW, van Heeswijk RPG, Meenhorst PL, Inghels M, Mulder JW, Beijnen JH. Paclitaxel in the treatment of human immunodeficiency virus 1-associated Kaposi's sarcoma – drug-drug interactions with protease inhibitors and a nonnucleoside reverse transcriptase inhibitor: a case report study. *Cancer Chemother Pharmacol* (1999) 43, 516–9.

Taxanes; Docetaxel + Cannabis

The pharmacokinetics of docetaxel are not altered by a herbal tea containing cannabis.

Clinical evidence

In a study investigating the effects of cannabis on docetaxel pharmacokinetics, 12 patients were given 200 mL of a herbal tea containing cannabis 1 g/L each day for 15 days. The tea was prepared from medicinal-grade cannabis (*Cannabis sativa* L. Flos, Bedrocan®) containing the cannabinoids Δ^9-tetrahydrocannabinol 18% and cannabidiol 0.8%. The clearance and the AUC of docetaxel given on day 12 of the cannabis tea were not significantly altered, when compared with docetaxel given before the cannabis tea. The dose of docetaxel used was 180 mg, reduced to 135 mg in 3 patients who experienced dose-related docetaxel toxicity.

Mechanism

Docetaxel is metabolised by the cytochrome P450 isoenzyme CYP3A4, and this does not appear to be affected by oral cannabis.

Importance and management

This study suggests that cannabis taken orally will not affect the pharmacokinetics of docetaxel. No dose adjustments are likely to be needed if docetaxel is given with cannabis tea.[1] It is not known if this applies to other

drugs metabolised by CYP3A4, or to other preparations and routes of administration of cannabis.

1. Engels FK, de Jong FA, Sparreboom A, Mathot RA, Loos WJ, Kitzen JJEM, de Bruijn P, Verweij J, Mathijssen RHJ. Medicinal cannabis does not influence the clinical pharmacokinetics of irinotecan and docetaxel. *Oncologist* (2007) 12, 291–300.

Taxanes; Docetaxel + CYP3A4 inhibitors, inducers or substrates

Ketoconazole (a CYP3A4 inhibitor) halved the clearance of docetaxel, and would be expected to increase the risk of neutropenia. Other CYP3A4 inhibitors would also be expected to raise docetaxel levels, whereas potent CYP3A4 inducers (such as rifampicin (rifampin) and the barbiturates) would be expected to reduce docetaxel levels Prednisone did not alter docetaxel pharmacokinetics.

Clinical evidence, mechanism, importance and management

(a) CYP3A4 inducers

Docetaxel is known to be principally metabolised by CYP3A4. An *in vitro* study found that hyperforin, a constituent of **St John's wort** induced docetaxel metabolism in a dose-dependent manner by 2.6- to 7-fold when compared with controls. In the same study, **rifampicin** (**rifampin**) increased docetaxel metabolism by 6.8- to 32-fold when compared with controls.[1] Similarly, microsomes prepared from the livers of 3 patients taking **pentobarbital** and/or **phenobarbital** are reported to have strikingly induced docetaxel metabolism *in vitro*.[2]

Although there are no clinical data to back up these findings, the fact that the CYP3A4 inhibitor ketoconazole markedly reduced the clearance of docetaxel in patients (see *CYP3A4 inhibitors*, below) suggests that clinically relevant increases in docetaxel clearance are likely with potent inducers of CYP3A4. If potent inducers of CYP3A4 have to be used with docetaxel, it might be prudent to increase the dose of docetaxel, carefully monitoring for toxicity. For a list of CYP3A4 inducers, see 'Table 1.4', (p.6).

(b) CYP3A4 inhibitors

In a study in 7 patients, **ketoconazole**, 200 mg daily for 3 days, started one hour before an infusion of docetaxel 10 mg/m^2, reduced the clearance of docetaxel by 49%, which could increase the risk of neutropenia.[3] This interaction was expected, because, the metabolism of docetaxel is mainly mediated by the cytochrome P450 isoenzyme CYP3A subfamily, which is inhibited by ketoconazole.

The pharmacokinetic interaction with ketoconazole is clinically important. The manufacturers[4,5] advise caution with any potent CYP3A4 inhibitors: the UK manufacturer notes that reduced tolerance may occur even at lower doses of docetaxel.[4] In addition to ketoconazole, the manufacturers specifically name **itraconazole**, **erythromycin**, and **troleandomycin**,[4,5] For a list of CYP3A4 inhibitors, see 'Table 1.4', (p.6).

(c) CYP3A4 substrates

The manufacturers state that *in vitro* studies have shown that the metabolism of docetaxel can be modified by drugs that are metabolised by CYP3A4, and they name **terfenadine**.[4,5] However, pharmacokinetic drug interactions do not usually occur clinically between drugs that just share the same metabolic route.

(d) Prednisone

The manufacturers note that, in a study in patients with metastatic prostatic cancer, **prednisone** did not significantly affect the pharmacokinetics of docetaxel.[4,5] Microsomes prepared from the liver of a single patient who had been taking **prednisone** for a year did not inhibit docetaxel metabolism *in vitro*.[2] It was suggested that prednisone might induce the metabolism of docetaxel by CYP3A4, but this effect was not seen. No clinically relevant pharmacokinetic interaction therefore occurs, and no docetaxel dose adjustment would be expected to be needed on concurrent use.

1. Komoroski BJ, Parise RA, Egorin MJ, Strom SC, Venkataramanan R. Effect of the St. John's wort constituent hyperforin on docetaxel metabolism by human hepatocyte cultures. *Clin Cancer Res* (2005) 11, 6972–9.
2. Royer I, Monsarrat B, Sonnier M, Wright M, Cresteil T. Metabolism of docetaxel by human cytochromes P450: Interactions with paclitaxel and other antineoplastic drugs. *Cancer Res* (1996) 56, 58–65.
3. Engels FK, ten Tije AJ, Baker SD, Lee CKK, Loos WJ, Vulto AG, Verweij J, Sparreboom A. Effect of cytochrome P450 3A4 inhibition on the pharmacokinetics of docetaxel. *Clin Pharmacol Ther* (2004) 75, 448–54.
4. Taxotere (Docetaxel). Sanofi-Aventis. UK Summary of product characteristics, December 2008.
5. Taxotere (Docetaxel). Sanofi-Aventis US LLC. US Prescribing information, November 2008.

Taxanes; Docetaxel + Tipifarnib

There was no pharmacokinetic interaction between tipifarnib and docetaxel in one study.

Clinical evidence, mechanism, importance and management

In a dose-finding study, docetaxel was given intravenously on day one of a 21-day cycle and oral tipifarnib 200 or 300 mg twice daily was given for 7 or 14 days starting one hour before docetaxel. There was no change in the pharmacokinetics of docetaxel or tipifarnib when compared with docetaxel given alone on day one or tipifarnib given alone on day 3.[1]

1. Awada A, Zhang S, Gil T, de Valeriola D, Lalami Y, De Porre P, Piccart-Gebhart MJ. A phase I clinical and pharmacokinetic study of tipifarnib in combination with docetaxel in patients with advanced solid malignancies. *Curr Med Res Opin* (2007) 23, 991–1003.

Taxanes; Paclitaxel + Clindamycin

Clindamycin does not appear to alter the pharmacokinetics of paclitaxel to a clinically significant extent.

Clinical evidence, mechanism, importance and management

In a study in 16 patients given intravenous paclitaxel 175 mg/m^2 over 3 hours, intravenous clindamycin 600 mg or 1.2 g over 30 minutes started 2.5 hours after the paclitaxel slightly reduced the $AUC_{0–4}$ and maximum plasma level of paclitaxel by about 11% when compared with placebo.[1]

Paclitaxel is highly bound to alpha-1-acid glycoprotein (AGP), and levels of this protein are increased in some cancers, which might contribute to reduced efficacy. Clindamycin was predicted to displace the AGP binding of paclitaxel, and might therefore alter paclitaxel pharmacokinetics.[1] However, the slight pharmacokinetic interaction seen in this study is not likely to be clinically relevant.

1. Fruscio R, Lissoni AA, Frapolli R, Corso S, Mangioni C, D'Incalci M, Zucchetti M. Clindamycin-paclitaxel pharmacokinetic interaction in ovarian cancer patients. *Cancer Chemother Pharmacol* (2006) 58, 319–25.

Taxanes; Paclitaxel + CYP3A4 inducers

Phenytoin, carbamazepine, and phenobarbital increase the clearance of paclitaxel and increase its maximum tolerated dose. Other CYP3A4 inducers are also predicted to decrease paclitaxel levels.

Clinical evidence, mechanism, importance and management

In a study in patients with glioblastoma multiforme the maximum tolerated dose of paclitaxel was 43% higher in patients receiving enzyme-inducing antiepileptics (**phenytoin**, **carbamazepine**, and **phenobarbital**) than in those not receiving them.[1] Another study in patients with recurrent malignant gliomas reported the same finding: a 50% increase in the maximum tolerated dose coupled with a 104% increase in the plasma clearance of paclitaxel in those taking enzyme-inducing antiepileptics. In addition, this study reported that the dose-limiting toxicity differed: central neurotoxicity in those taking enzyme-inducing antiepileptics and myelosuppression and/or gastrointestinal toxicity in those not taking these antiepileptics.[2]

It is probable that enzyme-inducing antiepileptics increase the metabolism of paclitaxel, and therefore it is likely that patients taking these antiepileptics will require an increase in their paclitaxel dose. The manufacturers suggest caution with all inducers of CYP3A4, and they specifically name the enzyme-inducing antiepileptics **carbamazepine**, **phenobarbital**, and **phenytoin**, and also the NNRTIs, **efavirenz** and **nevirapine**, and **rifampicin** (**rifampin**).[3,4] Close monitoring would be appropriate. Similar caution is probably warranted with **primidone**, which is metabolised to phenobarbital, and **fosphenytoin**, which is metabolised to phenytoin. For a list of inducers of CYP3A4, see 'Table 1.4', (p.6).

1. Fetell MR, Grossman SA, Fisher JD, Erlanger B, Rowinsky E, Stockel J, Piantadosi S. Preirradiation paclitaxel in glioblastoma multiforme: efficacy, pharmacology, and drug interactions. New approaches to Brain Tumor Therapy Central Nervous System Consortium. *J Clin Oncol* (1997) 15, 3121–8.
2. Chang SM, Kuhn JG, Rizzo J, Robins HI, Schold SC, Spence AM, Berger MS, Mehta MP, Bozik ME, Pollack I, Gilbert M, Fulton C, Rankin C, Malec M, Prados MD. Phase I study of paclitaxel in patients with recurrent malignant glioma: a North American Brain Tumor Consortium report. *J Clin Oncol* (1998) 16, 2188–94.
3. Paclitaxel. Medac GmbH. UK Summary of product characteristics, September 2007.
4. Taxol (Paclitaxel). Bristol-Myers Squibb Company. US Prescribing information, July 2007.

Taxanes; Paclitaxel + CYP3A4 inhibitors

In one patient fluconazole reduced the clearance of paclitaxel, whereas in two patients ketoconazole did not affect the pharmacokinetics of paclitaxel. CYP3A4 inhibitors are predicted to increase paclitaxel levels.

Clinical evidence

(a) Fluconazole

The clearance of paclitaxel was assessed in one patient who had taken fluconazole (dose not stated) for 2 weeks up until one day before his first cycle of paclitaxel and then 3 weeks later during his second cycle of paclitaxel. The clearance of paclitaxel was 44% lower after the use of fluconazole, and levels of the metabolites of paclitaxel formed by the action of CYP3A4 were lower.[1]

(b) Ketoconazole

Five women with ovarian cancer were given 3-hour infusions of paclitaxel 175 mg/m^2 every 21 days. In two of them, it was found that when single 200-mg oral doses of ketoconazole were given 3 hours before or 3 hours after the paclitaxel, the serum levels of the paclitaxel and its principal metabolite (6-alpha-hydroxypaclitaxel) remained unchanged.[2]

Mechanism

Paclitaxel is principally metabolised by the cytochrome P450 isoenzyme CYP2C8, and to a lesser extent by CYP3A4. Ketoconazole is a potent inhibitor of CYP3A4, and the findings of the study with this drug suggest that CYP3A4 inhibition alone might not affect paclitaxel levels. However, this study used a single low-dose of ketoconazole given just 3 hours before or after the paclitaxel, and it is possible that a longer course with a higher dose might have interacted. The data from the single case with fluconazole, which is a modest inhibitor of CYP3A4, suggest that CYP3A4 might be important, at least in some individuals.

Importance and management

Information is limited and not conclusive. Based on the study with ketoconazole, the UK manufacturer states that ketoconazole can be given without any paclitaxel dose adjustments.[3] However, they still continue to advise caution with other drugs that are inhibitors of CYP3A4, as does the US manufacturer.[4] They specifically name **erythromycin** and **fluoxetine** (but note that fluoxetine is usually considered a weak inhibitor of CYP3A4). Until more is known, some caution would appear to be appropriate with all moderate to potent CYP3A4 inhibitors. Note that interactions have, on occasion, been seen with the protease inhibitors (see 'Taxanes + Protease inhibitors', p.769), which are known potent CYP3A4 inhibitors. For a list of CYP3A4 inhibitors, see 'Table 1.4', (p.6).

1. Sonnichsen DS, Liu Q, Schuetz EG, Schuetz JD, Pappo A, Relling MV. Variability in human cytochrome P450 paclitaxel metabolism. *J Pharmacol Exp Ther* (1995) 275, 566–75.
2. Jamis-Dow CA, Pearl ML, Watkins PB, Blake DS, Klecker RW, Collins JM. Predicting drug interactions in vivo from experiments in vitro: human studies with paclitaxel and ketoconazole. *Am J Clin Oncol* (1997) 20, 592–99.
3. Paclitaxel. Medac GmbH. UK Summary of product characteristics, September 2007.
4. Taxol (Paclitaxel). Bristol-Myers Squibb Company. US Prescribing information, July 2007.

Taxanes; Paclitaxel + Miscellaneous

***In vitro* studies with human liver tissue suggest that no metabolic interactions are likely to occur between paclitaxel and cimetidine, dexamethasone or diphenhydramine. *In vitro* data also suggest that *Cremophor* may inhibit the intracellular uptake and metabolism of paclitaxel. CYP2C8 inhibitors (e.g. gemfibrozil) are predicted to raise paclitaxel levels.**

Clinical evidence, mechanism, importance and management

(a) Cimetidine, Dexamethasone, Diphenhydramine

On the basis of an *in vitro* study using human liver slices and human liver microsomes,[1] it has been concluded that the metabolism of paclitaxel is unlikely to be altered by cimetidine, dexamethasone or diphenhydramine, all of which are frequently given to prevent the hypersensitivity reactions associated with paclitaxel or its vehicle, see *Cremophor*, below. The UK manufacturers say that paclitaxel clearance in patients is not affected by cimetidine premedication.[2] Nevertheless, some authors[3] have advised caution when using cimetidine with paclitaxel, because they have found profound neutropenia, which they attributed to a possible pharmacokinetic interaction. Cimetidine is known to inhibit the cytochrome P450 isoenzyme CYP3A4, which is responsible, in part, for the metabolism of paclitaxel. However, cimetidine is a weak inhibitor of CYP3A4 (and some other isoenzymes not involved in paclitaxel metabolism), and an interaction with CYP3A4 inhibitors is not established (see 'Taxanes; Paclitaxel + CYP3A4 inhibitors', p.771. A pharmacokinetic interaction between cimetidine and paclitaxel is therefore seems unlikely.

(b) Cremophor

In vitro, *Cremophor* was found to inhibit the metabolism of paclitaxel in human liver microsomes,[1] which might be expected to increase its toxicity. The concentration used in the *in vitro* study may be achieved clinically in patients given paclitaxel with *Cremophor* as the vehicle.[4] This may be worth bearing in mind if other drugs formulated with *Cremophor* are given with paclitaxel.

(c) CYP2C8 inhibitors

Although there do not appear to be any clinical pharmacokinetic data on the use of paclitaxel with CYP2C8 inhibitors, the manufacturers advise caution,[2,5] presumably because of the possibility of raised paclitaxel levels. They specifically name **gemfibrozil**. Note that **trimethoprim** is also a clinically relevant CYP2C8 inhibitor.

1. Jamis-Dow CA, Klecker RW, Katki AG, Collins JM. Metabolism of taxol by humans and rat liver in vitro: a screen for drug interactions and interspecies differences. *Cancer Chemother Pharmacol* (1995) 36, 107–14.
2. Paclitaxel. Medac GmbH. UK Summary of product characteristics, September 2007.
3. Clouse T, Geisler JP, Manahan KJ, Gudenkauf TJ, Linnemeier G, Wiemann MC. Should we be using cimetidine to premedicate patients receiving docetaxel or paclitaxel? *Gynecol Oncol* (2004) 95, 270–1.
4. Rischin D, Webster LK, Millward MJ, Linahan BM, Toner GC, Woollett AM, Morton CG, Bishop JF. Cremophor pharmacokinetics in patients receiving 3-, 6-, and 24-hour infusions of paclitaxel. *J Natl Cancer Inst* (1996) 88, 1297–1301.
5. Taxol (Paclitaxel). Bristol-Myers Squibb Company. US Prescribing information, July 2007.

Taxanes; Paclitaxel + Quinine

One study found that quinine markedly reduced the plasma levels of paclitaxel.

Clinical evidence, mechanism, importance and management

In a study in 12 patients, paclitaxel levels at the end of a 20 to 24-hour infusion of paclitaxel 120 mg/m^2 given on day 2 were 40% lower when given with oral quinine 400 mg three times daily for 4 days started on day one. In one patient the paclitaxel levels were undetectable at this time point. Paclitaxel clearance was estimated to have increased twofold, but the reasons for this are unclear. Quinine was used as a chemosensitiser in this study, on the basis of *in vitro* findings, but was not very effective.[1] The pharmacokinetic interaction was unexpected, and its clinical relevance is unclear. Bear the possibility of an interaction in mind in the unlikely event that quinine is used with paclitaxel.

1. Miller TP, Chase EM, Dorr R, Dalton WS, Lam KS, Salmon SE. A phase I/II trial of paclitaxel for non-Hodgkin's lymphoma followed by paclitaxel plus quinine in drug-resistant disease. *Anticancer Drugs* (1998) 9, 135–40.

Taxanes; Paclitaxel + Verapamil

High-dose *R*-verapamil reduced the clearance of paclitaxel and increased the incidence of haematological toxicity.

Clinical evidence

In a crossover study in which 24 patients were given paclitaxel up to 200 mg/m^2 over 3 hours every 21 days alone, or with high-dose oral

R-verapamil (up to 250 mg/m^2 every 4 hours for 12 doses starting 24 hours before the paclitaxel), haematological toxicity was greater in those cycles when *R*-verapamil had also been given. In a subset of 6 patients, the pharmacokinetics of paclitaxel were assessed: the AUC and maximum plasma level of paclitaxel were increased by 90% and 122%, respectively, when *R*-verapamil was also given.[1]

Mechanism

Paclitaxel is a substrate of P-glycoprotein. It seems likely that *R*-verapamil inhibits the efflux of paclitaxel by this transporter protein.[1]

Importance and management

The clinical significance of this finding is unclear as the use of just the *R*-isomer of verapamil in such high doses is generally limited to investigational use only. However, bear in mind the possibility that verapamil might modestly increase paclitaxel levels.

1. Tolcher AW, Cowan KH, Solomon D, Ognibene F, Goldspiel B, Chang R, Noone MH, Denicoff AM, Barnes CS, Gossard MR, Fetsch PA, Berg SL, Balis FM, Venzon DJ, O'Shaughnessy JA. Phase I crossover study of paclitaxel with r-verapamil in patients with metastatic breast cancer. *J Clin Oncol* (1996) 14, 1173–84.

Temozolomide + Miscellaneous

Valproic acid may slightly reduce the clearance of temozolomide. Carbamazepine, H_2-receptor antagonists, dexamethasone, phenobarbital, phenytoin, prochlorperazine and ondansetron did not affect the clearance of temozolomide. Food, but not ranitidine, slightly reduces the extent of absorption of temozolomide.

Clinical evidence, mechanism, importance and management

(a) Antiepileptics

The manufacturer notes that the concurrent use of **carbamazepine**, **dexamethasone**, **H_2-receptor antagonists**, **ondansetron**, **phenobarbital**, **phenytoin** or **prochlorperazine** did not affect the clearance of temozolomide, based on an analysis of population pharmacokinetics from phase II studies.[1,2] **Valproic acid** modestly reduces the oral clearance of temozolomide by 5%, however, the manufacturer states that clinical relevance of this small reduction is unclear.[2]

(b) Food

The manufacturer notes that food slightly reduces the temozolomide AUC by 9% and maximum plasma concentration by 33%. They recommend that it should be given without food.[1,2]

(c) Ranitidine

In a study in 12 patients given temozolomide 150 mg/m^2 daily, ranitidine 150 mg twice daily had no effect on the absorption or plasma pharmacokinetics of temozolomide, or that of its active metabolite.[3]

1. Temodal (Temozolomide). Schering-Plough Ltd. UK Summary of product characteristics, June 2009.
2. Temodar (Temozolomide). Schering Corporation. US Prescribing information, March 2009.
3. Beale P, Judson I, Moore S, Statkevich P, Marco A, Cutler D, Reidenberg P, Brada M. Effect of gastric pH on the relative oral bioavailability and pharmacokinetics of temozolomide. *Cancer Chemother Pharmacol* (1999) 44, 389–94.

Teniposide + Antiepileptics; Enzyme-inducing

Carbamazepine, phenytoin and phenobarbital markedly increase the clearance of teniposide. A reduction in its effects has been noted in B-lineage leukaemia.

Clinical evidence, mechanism, importance and management

In 6 children with acute lymphocytic leukaemia the clearance of teniposide was increased two- to threefold (from 13 to 32 mL/minute per m^1) when they also took **phenytoin** or **phenobarbital**.[1] Another patient had a twofold increase in teniposide clearance when **carbamazepine** was given.[1] In a retrospective survey, long-term antiepileptic use (**phenytoin**, **phenobarbital**, **carbamazepine**, or a combination) was associated with worse event-free survival, and greater haematological relapse and CNS relapse in children receiving chemotherapy for B-lineage acute lymphoblastic leukaemia. In this study, faster clearance of teniposide was found in those receiving the antiepileptics.[2]

These effects probably occur because these antiepileptics are potent liver enzyme inducers, which may increase the metabolism of teniposide by the liver and thereby reduce its levels. The authors of these reports therefore conclude that an increased dose of teniposide will be needed in the presence of these antiepileptics to achieve systemic exposure to the drug comparable to that achievable in their absence.[1] It may be preferable to use alternative antiepileptics (that are not enzyme inducers) in patients requiring teniposide.[2] Note that **primidone** is metabolised to phenobarbital, and **fosphenytoin** is metabolised to phenytoin, and therefore these drugs may be expected to interact similarly.

1. Baker DK, Relling MV, Pui C-H, Christensen ML, Evans WE, Rodman JH. Increased teniposide clearance with concomitant anticonvulsant therapy. *J Clin Oncol* (1992) 10, 311–5.
2. Relling MV, Pui C-H, Sandlund JT, Rivera GK, Hancock ML, Boyett JM, Schuetz EG, Evans WE. Adverse effect of anticonvulsants on efficacy of chemotherapy for acute lymphoblastic leukaemia. *Lancet* (2000) 356, 285–90.

Thalidomide + Doxorubicin

The concurrent use of thalidomide and chemotherapy regimens containing doxorubicin appears to be associated with an increased risk of deep-vein thrombosis in patients with multiple myeloma.

Clinical evidence, mechanism, importance and management

In a randomised study in 100 patients with newly diagnosed multiple myeloma given induction chemotherapy (dexamethasone, vincristine, doxorubicin, cyclophosphamide, etoposide and cisplatin) with or without thalidomide, deep-vein thrombosis developed in 14 of the 50 patients (28%) given thalidomide compared with 2 of 50 patients (4%) not given thalidomide.[1] In a further study by the same authors, 232 patients with multiple myeloma were given DT-PACE (dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, etoposide) if they had preceding standard dose therapy but no previous autotransplantation, or with DCEP-T (dexamethasone, cyclophosphamide, etoposide, cisplatin, thalidomide) for relapse after transplantation. Deep-vein thrombosis developed in 31 of 192 patients (16%) given the doxorubicin-containing regimen (DT-PACE) and only 1 of 40 (2.5%) given the regimen without doxorubicin (DCEP-T).[2]

In patients with multiple myeloma, the risk of deep-vein thrombosis appears to be increased when thalidomide is given with combination chemotherapy containing doxorubicin. Various strategies are recommended to reduce this risk of thrombosis including low-molecular-weight heparin, warfarin, and low-dose aspirin.[3]

1. Zangari M, Anaissie E, Barlogie B, Badros A, Desikan R, Gopal AV, Morris C, Toor A, Siegel E, Fink L, Tricot G. Increased risk of deep-vein thrombosis in patients with multiple myeloma receiving thalidomide and chemotherapy. *Blood* (2001) 98, 1614–5.
2. Zangari M, Siegel E, Barlogie B, Anaissie E, Saghafifar F, Fassas A, Morris C, Fink L, Tricot G. Thrombogenic activity of doxorubicin in myeloma patients receiving thalidomide: implications for therapy. *Blood* (2002) 100, 1168–71.
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Thalidomide + Epoetins

A higher than expected incidence of thromboembolic events occurred in one study in patients with myelodysplastic syndrome treated with thalidomide and darbepoetin alfa; however, this was not noted in a retrospective analysis of patients with multiple myeloma given thalidomide with epoetin, although cases of DVT have been reported with epoetin alfa and thalidomide.

Clinical evidence

A phase II study to investigate the efficacy and tolerability of the concurrent use of thalidomide 100 mg daily and subcutaneous **darbepoetin alfa** 2.25 micrograms/kg per week in patients with myelodysplastic syndrome was discontinued because of an unexpectedly high incidence of thromboembolic events. Of the first 7 patients enrolled in the study, two devel-

oped deep-vein thrombosis (DVT) and one died of pulmonary embolism.[1]

In contrast to these findings, in a retrospective analysis of patients with multiple myeloma who had been taking thalidomide, thromboses were reported in 4 of 49 patients (8.1%) also given **epoetin** and in 14 of 150 patients not given **epoetin** (9.3%). These results suggest that epoetin might not increase the risk of thrombosis in patients with multiple myeloma receiving thalidomide.[2] Nevertheless, two patients with myeloid cancers who had been taking thalidomide and dexamethasone for 5 to 6 months, developed DVTs 4 and 6 weeks, respectively, after starting treatment with **epoetin alfa** for anaemia.[3]

Mechanism

Both thalidomide and epoetins increase the risk of thromboembolism, and the risk might be increased with concurrent use. There seems to be a particular risk of thrombosis when using epoetins in patients with cancer.[4]

Importance and management

There is little information on the possible increased risk of thrombosis if epoetins are used with thalidomide in myeloid cancers. The authors of the first study recommended careful monitoring and possibly thromboprophylaxis (heparin or warfarin) in patients with myelodysplastic syndrome given both thalidomide and epoetin. This seems prudent.

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Thalidomide + Interferon alfa

Severe bone marrow depression was reported in a patient given thalidomide with peginterferon alfa.

Clinical evidence, mechanism, importance and management

A patient with multiple myeloma in remission after an autologous stem cell transplantation was given thalidomide 200 mg daily. Five weeks after also being given **peginterferon alfa-2b**, severe reversible bone marrow hypoplasia developed. **Peginterferon** was probably responsible for the bone marrow depression. However, thalidomide may also cause bone marrow depression and it was suggested that the severe suppression in this patient may have been due to the combined effects of the **peginterferon** and thalidomide.[1] This should be considered in patients given both drugs.

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Thalidomide + Miscellaneous

Rifampicin and phenobarbital did not appear to alter thalidomide clearance in one study. Thalidomide increases the sedative effect of other CNS depressants. Thalidomide does not alter the pharmacokinetics of digoxin, although additive bradycardia is expected with other drugs that slow heart rate. Peripheral neuropathy is common with thalidomide, and other drugs that have this effect might have an additive effect with thalidomide.

Clinical evidence, mechanism, importance and management

(a) CNS depressants

Animal studies have shown an increase in CNS depressant activity when thalidomide was given with **alcohol**, **barbiturates**, **chlorpromazine** and **reserpine**.[1] In clinical use, thalidomide frequently causes drowsiness, and the manufacturers advise caution with these drugs[2,3] and also with **anxiolytics**, **hypnotics**, **antipsychotics**, **antihistamines**, and **opioids**, because of the possibility of enhanced sedation.[3]

(b) Cytochrome P450 isoenzyme inducers

There was no clear relationship between thalidomide clearance and the concurrent use of enzyme inducers such as **rifampicin** (**rifampin**), or **phenobarbital** in a study in patients with glioma.[4] For the possible additive CNS depressant effect with barbiturates, see *CNS depressants*, above.

(c) Digoxin

In a study in 18 healthy subjects, multiple-doses of thalidomide 200 mg did not affect the pharmacokinetics of a single 500-microgram dose of digoxin, nor were the pharmacokinetics of thalidomide altered by this dose of digoxin.[3] However, see also *Other drugs*, below.

(d) Other drugs

Thalidomide can cause clinically relevant bradycardia, and patients should be monitored for this effect, which may require a dose reduction or discontinuation of thalidomide.[3] The UK manufacturer of thalidomide therefore cautions its use with other drugs that can cause bradycardia, and they name drugs that are known to induce torsade de pointes (unspecified), **beta blockers** and **anticholinesterases**.

Thalidomide very commonly causes peripheral neuropathy, which can be severe, and may require dose modification.[2,3] Because of this, the manufacturers recommend caution with other drugs that can cause peripheral neuropathy,[2,3] and the UK manufacturer specifically mentions **vincristine** and **bortezomib**.[3] However, in a review of 24 patients with multiple myeloma who had received **bortezomib** after relapse following allografting, the incidence of severe peripheral neuropathy was far higher than usually seen in non-transplant patients. Fourteen patients developed neurotoxicity; in 7 patients it was severe and 6 patients required treatment discontinuation as the neurotoxicity did not resolve following a **bortezomib** dose reduction. In an analysis of possible risk factors, previous treatment with thalidomide use (a drug with known potential to cause peripheral neuropathy) was not found to increase the risk of peripheral neuropathy.[5]

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3. Thalidomide Celgene (Thalidomide). Celgene Ltd. UK Summary of product characteristics, August 2009.
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Thiopurines + Allopurinol

The haematological effects of azathioprine and mercaptopurine are markedly increased by allopurinol.

Clinical evidence

(a) Azathioprine

A patient taking allopurinol 300 mg daily for gout was also given azathioprine 100 mg daily to treat autoimmune haemolytic anaemia. Within 10 weeks his platelet count fell from 236×10^9/L to 45×10^9/L, his white cell count fell from 9.4×10^9/L to 0.8×10^9/L and his haemoglobin concentration fell from 11.5 g/dL to 5.3 g/dL.[1]

A number of other reports similarly describe reversible bone marrow toxicity associated with anaemia, pancytopenia, leucocytopenia and thrombocytopenia in patients given azathioprine with allopurinol,[1-9] and in one case a fatality occurred as a result of neutropenia and septicaemia.[8] In a retrospective analysis of 24 patients who had received both azathioprine and allopurinol, 11 developed leucopenia, 7 developed moderate anaemia, and 5 developed thrombocytopenia. Only 14 of the patients had received a greater than two-thirds reduction in their azathioprine dose when allopurinol was started, but despite this, some of these patients still developed haematological toxicity.[10]

(b) Mercaptopurine

In early studies, allopurinol 200 to 300 mg reduced the effective dose of mercaptopurine by about fourfold in 7 patients with chronic granulocytic leukaemia or variants.[11]

Profound pancytopenia developed in the first 3 of 13 children given mercaptopurine 2.5 mg/kg daily and allopurinol 10 mg/kg daily, but when the mercaptopurine dose was halved, toxicity was manageable in the remaining 9 children.[12] Severe leucopenia and thrombocytopenia occurred in another patient given allopurinol with standard-dose mercaptopurine.[13]

A pharmacokinetic study found that allopurinol caused a fivefold increase in the AUC and in peak plasma levels of mercaptopurine when the mercaptopurine was given *orally*. The bioavailability of mercaptopurine increased from 12% to 59%.[14] This did not occur when the mercaptopurine was given *intravenously*.[14,15]

Mechanism

Azathioprine is firstly metabolised in the liver to mercaptopurine and then enzymatically oxidised in the liver and intestinal wall by xanthine oxidase to an inactive compound (6-thiouric acid), which is excreted. Allopurinol inhibits first-pass metabolism by xanthine oxidase so that mercaptopurine accumulates, blood levels rise and its toxic effects develop (leucopenia, thrombocytopenia, etc.).

Importance and management

A well documented, well established, clinically important and potentially life-threatening interaction. The doses of azathioprine and mercaptopurine should be reduced by about two-thirds or three-quarters when given orally to reduce the development of toxicity. Despite taking these precautions toxicity may still be seen[10] and very close haematological monitoring is advisable if concurrent use is necessary. On the basis of two studies[14,15] it would seem that this precaution might not be necessary if mercaptopurine is given intravenously, but note that parenteral mercaptopurine is not routinely available.

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Thiopurines + 5-Aminosalicylates

The haematological toxicity of azathioprine and mercaptopurine may be increased by mesalazine, olsalazine or sulfasalazine. Balsalazide may be less likely to interact but this requires confirmation.

Clinical evidence

(a) Balsalazide

The frequency of clinically important neutropenia did not increase in 10 patients with Crohn's disease receiving **azathioprine** or **mercaptopurine** when they were given balsalazide 6.75 g daily for 8 weeks, but increases in whole blood 6-thioguanine nucleotide concentrations were seen.[1]

(b) Mesalazine

A 13-year-old boy with severe ulcerative pancolitis and cholangitis was given prednisone 60 mg daily, ursodeoxycholic acid 15 mg/kg daily and mesalazine 25 mg/kg daily. When **azathioprine** 2 mg/kg daily was added in an attempt to reduce the prednisone dose, he developed marked and prolonged **azathioprine** toxicity (severe pancytopenia), which was attributed to an interaction resulting from abnormally high, persistent levels of an **azathioprine** metabolite.[2] In another study, there was a trend towards an increased rate of clinically important neutropenia in 10 patients with Crohn's disease receiving **azathioprine** or **mercaptopurine** when they were given mesalazine 4 g daily for 8 weeks. One patient was withdrawn from the study after 6 weeks because of leucopenia. Increases in whole blood 6-thioguanine nucleotide concentrations were also seen.[1]

(c) Olsalazine

A case report describes a patient with Crohn's disease who had two separate episodes of bone marrow suppression while receiving **mercaptopurine** 50 to 75 mg daily and olsalazine 1 to 1.75 g daily. It was found necessary to reduce the **mercaptopurine** dose on the first occasion and to withdraw both drugs on the second.[3]

(d) Sulfasalazine

A decrease in leucocyte counts was seen in 4 patients taking **azathioprine** (2.1 to 3.3 mg/kg daily) after the addition of sulfasalazine. This lasted several months in one patient, and was transitory in two. The fourth patient developed agranulocytosis after 4 days, which required treatment discontinuation. When the drugs were later resumed at a lower dose, no reduction in leucocyte counts occurred.[4] Another report describes 38 patients taking **azathioprine** (mean dose 92.8 mg) and sulfasalazine (mean dose 2.1 g) for rheumatoid or psoriatic arthritis. Some patients did well, but in general the combination was poorly tolerated, and only 45% continued treatment after 6 months. Reasons for withdrawal included rash (3 patients), gastrointestinal upset (7 patients), leucopenia (one patient) and nephrotic syndrome (one patient).[5] In another study, there was a trend towards an increased rate of clinically important neutropenia in 12 patients with Crohn's disease receiving **azathioprine** or **mercaptopurine** when they were given sulfasalazine 4 g daily for 8 weeks. One patient withdrew from the study after 6 weeks because of leucopenia. Increases in whole blood 6-thioguanine nucleotide concentrations were also found.[1]

Mechanism

The metabolism of azathioprine and mercaptopurine depends on *S*-methylation by thiopurine methyltransferase (TPMT) and oxidation by xanthine oxidase. An *in vitro* study using recombinant TPMT found that both sulfasalazine and its metabolites inhibit the activity of TPMT.[6] Therefore if these drugs are used together, the clearance of azathioprine and mercaptopurine may be reduced by the sulfasalazine, resulting in an increase in their toxicity (there is only a small margin between their therapeutic and toxic levels). About 11% of patients may be at particular risk because of genetic polymorphism whereby they have TPMT enzyme activity that is only half that of the rest of the population.[1,6] *In vitro* studies confirmed that mesalazine,[7] olsalazine and its metabolite olsalazine-*O*-sulfate[3,7] and balsalazide[7] are inhibitors of recombinant TPMT. In patients, increased levels of 6-thioguanine nucleotide are probably due to inhibition of TPMT.[1] It is suggested that the reported *in vitro* concentration (IC_{50}) of balsalazide required to halve the TPMT activity is about 1000 times higher than peak plasma levels after therapeutic doses and therefore an interaction is unlikely. Mesalazine and olsalazine peak levels may also be less than the IC_{50} concentrations, but peak plasma levels of sulfasalazine are close to IC_{50} concentrations.[8]

Importance and management

These reports underline the importance of taking particular care if azathioprine or mercaptopurine is used with balsalazide, mesalazine, olsalazine, or sulfasalazine. Balsalazide may be less likely to interact, but this requires confirmation.[1] Some have postulated that the interaction may actually benefit patients, as increased whole blood 6-thioguanine nucleotide or mild leucopenia is associated with a greater chance of remission in those taking azathioprine or mercaptopurine.[1,9] Additional monitoring of white blood cell counts is required when starting the combination.[9]

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Thiopurines; Azathioprine + Co-trimoxazole or Trimethoprim

There is some evidence that the risk of haematological toxicity may be increased in renal transplant patients taking azathioprine if they are given co-trimoxazole or trimethoprim, particularly for extended periods. However, other evidence suggests that the drugs may be used together safely, and the combination is commonly used in practice.

Clinical evidence

The observation that haematological toxicity often seemed to occur in renal transplant patients given azathioprine and co-trimoxazole, prompted a retrospective survey of the records of 40 patients. It was found that there was no difference in the incidence of thrombocytopenia and neutropenia in those given azathioprine, either alone, or with co-trimoxazole, (trimethoprim 160 to 320 mg and sulfamethoxazole 800 mg to 1.6 g daily) for a short time (6 to 16 days), but a significant increase occurred in the incidence and duration of thrombocytopenia and neutropenia if both drugs were given together for 22 days or more.[1]

Another report describes a marked fall in white cell counts in renal transplant recipients during the concurrent use of azathioprine with either co-trimoxazole (described as frequent) or trimethoprim (3 cases).[2] In one case the fall occurred within 5 days and was managed by temporarily withdrawing the azathioprine and reducing the trimethoprim dose from 300 mg daily to 100 mg daily.[2]

Conversely, in an early study, there was no difference in the incidence of leucopenia when renal transplant recipients were given co-trimoxazole or other antibacterials.[3] Similarly, in 252 renal transplant patients given continuous prophylaxis with co-trimoxazole or **sulfafurazole** for 12 to 25 months, toxicity was minimal: leucopenia occurred only occasionally and was reversed by temporarily withholding azathioprine. This was needed in a similar number of patients with each antibacterial.[4] In another placebo-controlled study in heart transplant recipients taking triple therapy including azathioprine; co-trimoxazole prophylaxis for 4 months did not alter total white blood cell counts: leucopenia did not occur and no change in the dose of azathioprine was required.[5]

Mechanism

Not understood. It seems possible that the bone marrow depressant effects of azathioprine, trimethoprim and sulfamethoxazole may be additive. In addition, in some patients impaired renal function may allow co-trimoxazole levels to become elevated, and haemodialysis may deplete folate levels, which could exacerbate the anti-folate effects of the co-trimoxazole. Trimethoprim has been shown to inhibit renal tubular creatinine secretion.[6]

Importance and management

Information appears to be limited and the interaction is not established. Although there is some evidence of an increased risk of haematological toxicity in renal transplant patients taking azathioprine if they are given co-trimoxazole or trimethoprim, this has not been shown in all studies. Two of the early studies suggested that the incidence of leucopenia with co-trimoxazole was related to the time after transplantation, and it improved if the dose of azathioprine was decreased or temporarily suspended.[3,7] Prophylaxis with co-trimoxazole post-transplant is commonly used in some centres.

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Thiopurines; Azathioprine + Myelosuppressive drugs

Azathioprine commonly causes myelosuppression and this effect might be enhanced by other myelosuppressive drugs.

Clinical evidence, mechanism, importance and management

Azathioprine commonly causes dose-related myelosuppression, and full blood counts should be regularly monitored when this drug is used. The manufacturers note that the concurrent use of other drugs that may have a myelosuppressive effect might lead to exaggerated leucopenia.[1,2] The UK manufacturer specifically states that, where possible such use should be avoided, and they name **penicillamine** as an example.[1] Note that the myelosuppressive effect of **penicillamine** mainly results in thrombocytopenia and less frequently neutropenia, and its use also requires monitoring of full blood counts. This advice therefore seems prudent.

The UK manufacturer also says that it has been suggested that **cimetidine** and **indometacin** may have myelosuppressive effects, which may be enhanced by azathioprine.[1] Leucopenia is a rare adverse effect of cimetidine and an infrequent adverse effect of indometacin. However, there appear to be no published clinical reports of any interactions of these drugs with azathioprine. In one *animal* study, cimetidine did *not* increase the haematopoietic toxicity of azathioprine or delay bone marrow recovery after cimetidine.[3] Whether there is a real additional risk from using drugs such as cimetidine and indometacin with azathioprine is unknown, but the likelihood seems small.

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Thiopurines; Mercaptopurine + Doxorubicin

One study suggested that the hepatotoxicity of *intravenous* mercaptopurine can be increased by doxorubicin.

Clinical evidence, mechanism, importance and management

One report describes 11 patients who developed liver damage after being given *intravenous* mercaptopurine 500 mg/m^2 daily for 5 days, with doxorubicin 50 mg/m^2 on the first day. The frequency and severity of liver damage was greater than the authors had previously seen with mercaptopurine alone. They suggested that doxorubicin potentiated the hepatotoxicity of mercaptopurine.[1] Mercaptopurine is no longer commonly used *intravenously*, and the dose given in this study is much higher than that currently used *orally*. The general applicability of this study is therefore unknown.

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Thiopurines; Mercaptopurine + Food

Some studies have shown that breakfast, usually including milk, may modestly reduce and delay the absorption of mercaptopurine, whereas others have not found this effect. A case report describes increased mercaptopurine dose requirements when it was taken with milk.

Clinical evidence

A study in 17 children with acute lymphoblastic leukaemia found that the absorption of mercaptopurine 5 mg/m^2 was reduced if it was given 15 minutes after a standard breakfast of 250 mL of **milk** and 50 g of biscuits, when compared with fasting. The AUC was reduced by 26%, the maximum plasma levels by 36%, and the time to maximum plasma levels delayed from 1.2 hours to 2.3 hours.[1] Some individuals had more marked effects than others; 11 subjects had a decrease in absorption, whereas 6 subjects had no change or a small increase.[1] Similarly, in another study in 7 children, peak plasma mercaptopurine levels were lower and were delayed when it was given with a standard breakfast (orange juice, cereal, toast) compared with those after an overnight fast.[2] Moreover, a case report describes a 4-year-old child who required a 60% increase in his calculated dose of mercaptopurine when he took it with **milk**, but no change when he took it with water lightly flavoured with fruit squash.[3]

In contrast, in a study in 10 children, mercaptopurine levels varied widely between individuals and there was no clear effect of food. The peak plasma levels were increased only 11% (range 67% decrease to 81% increase), and the AUC was increased by a mean of 3% (range 53% decrease to 86% increase) when given in the fasting state compared with after breakfast (not standardised, but consisting mainly of milk or yogurt plus cereal, or sandwiches).[4] Similarly, a further study in 15 children taking mercaptopurine found that there was a non-significant 20 to 22% decrease in the maximum plasma levels or AUC of mercaptopurine when it was taken after a standardised breakfast (milk, bread, ham, cheese) compared with after a 12 hour fast, and there was a delay in reaching the maximum plasma levels when mercaptopurine was taken after food. Again, there was wide inter-individual variation in these parameters.[5]

Mechanism

Not understood. Delayed gastric emptying is a suggested reason.[1] Alternatively, it has been suggested that xanthine oxidases in milk might inactivate mercaptopurine.[6]

Importance and management

Mercaptopurine levels vary widely, and it is not established whether food or milk is a clear factor in this variation. Some have suggested that mercaptopurine should be taken before food or without milk to optimise its absorption,[2,3,6] and the UK Acute Lymphoblastic Leukaemia (UK ALL) study requires doses to be taken at least one hour after the evening meal without milk products,[7] whereas others do not consider the evidence sufficient to make a recommendation.[4] Note that the manufacturers of mercaptopurine do not include any specific instructions regarding food or milk intake.[8,9]

1. Riccardi R, Balis FM, Ferrara P, Lasorella A, Poplak DG, Mastrangelo R. Influence of food intake on bioavailability of oral 6-mercaptopurine in children with acute lymphoblastic leukaemia. *J Pediatr Hematol Oncol* (1986) 3, 319–24.
2. Burton NK, Barnett MJ, Aherne GW, Evans J, Douglas I, Lister TA. The effect of food on the oral administration of 6-mercaptopurine. *Cancer Chemother Pharmacol* (1986) 18, 90–1.
3. Sofianou-Katsoulis A, Khakoo G, Kaczmarski R. Reduction in bioavailability of 6-mercaptopurine on simultaneous administration with cow's milk. *Pediatr Hematol Oncol* (2006) 23, 485–7.
4. Lönnerholm G, Kreuger A, Lindström B, Myrdal U. Oral mercaptopurine in childhood leukemia: influence of food intake on bioavailability. *Pediatr Hematol Oncol* (1989) 6, 105–12.
5. Lafolie P, Björk O, Hayder S, Åhström L, Peterson C. Variability of 6-mercaptopurine pharmacokinetics during oral maintenance therapy of children with acute leukaemia. *Med Oncol Tumor Pharmacother* (1989) 6, 259–65.
6. de Lemos ML, Hamata L, Jennings S, Leduc T. Interaction between mercaptopurine and milk. *J Oncol Pharm Pract* (2007) 13, 237–40.
7. Medical Research Council. Working party on leukaemia in children. UK national randomised trial for children and young adults with acute lymphoblastic leukaemia (ALL) UKALL 2003. Version 7, 2009. Available at: http://www.ctsu.ox.ac.uk/projects/leuk/ukall2003 (accessed 29/01/10)
8. Purinethol (Mercaptopurine). Gate Pharmaceuticals. US Prescribing information, February 2007.
9. Puri-Nethol (Mercaptopurine). GlaxoSmithKline UK. UK Summary of product characteristics, October 2009.

Thiopurines; Mercaptopurine + Methotrexate

Methotrexate can increase the bioavailability of mercaptopurine, but the contribution this makes to their synergistic action in the maintenance of remission of leukaemia is unclear.

Clinical evidence

(a) Oral mercaptopurine

In 14 children receiving maintenance therapy for leukaemia, oral low-dose methotrexate 20 mg/m^2 increased the AUC and peak plasma levels of mercaptopurine 75 mg/m^2 by 31% and 26%, respectively.[1] In another study, 10 children with acute lymphoblastic leukaemia in remission were given mercaptopurine 25 mg/m^2 daily and intravenous infusions of high-dose methotrexate 2 or 5 g/m^2 every other week for consolidation therapy. It was found that methotrexate 2 or 5 g/m^2 increased the AUC of mercaptopurine by 69% and 93%, respectively, and raised the maximum serum levels of mercaptopurine by 108% and 121%, respectively.[2] Nevertheless, the risk of relapse of leukaemia did not appear to be related to the pharmacokinetics of methotrexate or mercaptopurine, which showed considerable inter- and intrapatient variability, in one study in children.[3]

(b) Intravenous mercaptopurine

One report suggests that, with high dose induction therapy, the combination of mercaptopurine and methotrexate may not be synergistic. In this study, children with newly diagnosed acute lymphoblastic leukaemia were given *intravenous* mercaptopurine 1 g/m^2 over 6 hours, either alone, or after low-dose oral methotrexate (6 doses of 30 mg/m^2), or high-dose intravenous methotrexate (1 g/m^2 over 24 hours). Methotrexate increased the plasma levels of mercaptopurine, but, unexpectedly, it was also found that thioguanine nucleotide levels in bone marrow leukaemic lymphoblasts were 13-fold lower during methotrexate use. It is not known whether methotrexate would reduce thiopurine metabolite levels in leukaemic lymphoblasts when mercaptopurine is given as continuation therapy where the leukaemic burden is less substantial than in newly diagnosed cases. In addition, the changes in leukocyte counts over 3 days suggested that mercaptopurine alone had little effect, and although methotrexate caused a reduction in intracellular thiopurine metabolite levels, it produced a greater decrease in leukocytes than mercaptopurine alone. It was concluded that, in this particular study, the antileukaemic effect was primarily due to methotrexate.[4]

Mechanism

The reasons for the pharmacokinetic interaction are not understood, although it is thought that methotrexate is a xanthine oxidase inhibitor, which may therefore inhibit the metabolism of mercaptopurine.[1,2,5]

Importance and management

The combination of methotrexate and mercaptopurine has an established place in the maintenance therapy of leukaemia once it is in remission after successful induction and consolidation therapy. The pharmacokinetic findings may be part of the explanation for the benefits of combined use, although biochemical mechanisms may be more important.[5]

1. Balis FM, Holcenberg JS, Zimm S, Tubergen D, Collins JM, Murphy RF, Gilchrist GS, Hammond D, Poplack DG. The effect of methotrexate on the bioavailability of oral 6-mercaptopurine. *Clin Pharmacol Ther* (1987) 41, 384–7.
2. Innocenti F, Danesi R, Di Paolo A, Loru B, Favre C, Nardi M, Bocci G, Nardini D, Macchia P, Del Tacca M. Clinical and experimental pharmacokinetic interaction between 6-mercaptopurine and methotrexate. *Cancer Chemother Pharmacol* (1996) 37, 409–14.
3. Balis FM, Holcenberg JS, Poplack DG, Ge J, Sather HN, Murphy RF, Ames MM, Waskerwitz MJ, Tubergen DG, Zimm S, Gilchrist GS, Bleyer WA. Pharmacokinetics and pharmacodynamics of oral methotrexate and mercaptopurine in children with lower risk acute lymphoblastic leukemia: a joint Children's Cancer Group and Pediatric Oncology Branch study. *Blood* (1998) 92, 3569–77.
4. Dervieux T, Hancock ML, Pui C-H, Rivera GK, Sandlund JT, Ribeiro RC, Boyett J, Evans WE, Relling MV. Antagonism by methotrexate on mercaptopurine disposition in lymphoblasts during up-front treatment of acute lymphoblastic leukemia. *Clin Pharmacol Ther* (2003) 73, 506–16.
5. Giverhaug T, Loennechen T, Aarbakke J. The interaction of 6-mercaptopurine (6-MP) and methotrexate (MTX). *Gen Pharmacol* (1999) 33, 341–6.

Thiotepa + Phenytoin

The metabolism of thiotepa to its active metabolite, TEPA (triethylenephosphamide), was increased by phenytoin in one patient.

Clinical evidence

A 42-year-old man received two courses of CTC (high-dose cyclophosphamide, thiotepa and carboplatin), with phenytoin 150 mg twice daily started 5 days before the second course, for seizures. When compared with the first course, phenytoin caused a 115% increase in the AUC of TEPA (triethylenephosphamide), the active metabolite of thiotepa, and a 29% reduction in the AUC of thiotepa. On the basis of these data, the dose of thiotepa was reduced by about one-third for the remaining 2 days of the course, and this resulted in plasma levels within the therapeutic range.[1]

Mechanism

Phenytoin probably induces the cytochrome P450 isoenzyme CYP2B6, which is involved in the metabolism of thiotepa.

Importance and management

This appears to be the only case report of such an interaction, but it would seem prudent to monitor the effects of concurrent use, and reduce the dose of thiotepa if necessary.

1. de Jonge ME, Huitema ADR, van Dam SM, Beijnen JH, Rodenhuis S. Significant induction of cyclophosphamide and thiotepa metabolism by phenytoin. *Cancer Chemother Pharmacol* (2005) 55, 507–510.

Topotecan + Amifostine

In 10 women with ovarian cancer, amifostine, given daily for 5 days before topotecan, did not significantly affect the pharmacokinetics of topotecan.[1]

1. Zackrisson A-L, Malmström H, Peterson C. No evidence that amifostine influences the plasma pharmacokinetics of topotecan in ovarian cancer patients. *Eur J Clin Pharmacol* (2002) 58, 103–8.

Topotecan + Amrubicin

A study in which 9 patients were given topotecan as an infusion on days one to 5 of a 4-week cycle, with amrubicin on days 3 to 5 of each cycle, found that amrubicin did not affect the pharmacokinetics of topotecan.[1]

1. Shibayama T, Hotta K, Takigawa N, Tada A, Ueoka H, Harita S, Kiura K, Tabata M, Segawa Y, Nogami N, Kuyama S, Shinkai T, Tanimoto M. A phase I and pharmacological study of amrubicin and topotecan in patients of small-cell lung cancer with relapsed or extensive-disease small-cell lung cancer. *Lung Cancer* (2006) 53, 189–95.

Topotecan + Miscellaneous

Ciclosporin and elacridar markedly increase the AUC of oral topotecan, and other inhibitors of P-glycoprotein and BCRP transporters are predicted to interact similarly. Food did not alter the extent of absorption of oral topotecan. Corticosteroids, co-trimoxazole, granisetron, morphine, and ondansetron are not expected to significantly alter the pharmacokinetics of intravenous topotecan.

Clinical evidence, mechanism, importance and management

(a) Ciclosporin

The manufacturer reports that giving oral ciclosporin 15 mg/kg within 4 hours of oral topotecan increased the AUC of the metabolite topotecan lactone and total topotecan by 2- and 2.5-fold, respectively. This is likely to be because ciclosporin is an inhibitor of P-glycoprotein and the cytochrome P450 isoenzyme CYP3A4, which affect the transport and metabolism of topotecan, thereby increasing its oral bioavailability. Patients should be carefully monitored for topotecan adverse effects if inhibitors of P-glycoprotein are used with oral topotecan.[1]

(b) Elacridar

Studies have shown that elacridar (an investigational drug) markedly increased the oral bioavailability of topotecan from 40% to 100%, but had little effect on intravenous topotecan.[2,3] In these studies, a reduced dose of topotecan was used,[2,3] and elacridar use actually appeared to be associated with a reduced incidence of dose-limiting diarrhoea, when compared with historical data.[3] Elacridar is a P-glycoprotein inhibitor and also an inhibitor of the BCRP transporter protein, for which topotecan is a substrate. Patients should be carefully monitored for adverse reactions if inhibitors of BCRP are used with oral topotecan.[1]

(c) Food

The AUC of oral topotecan was found to be similar when it was taken either in the fasted state or after a high-fat meal, although the time to maximum plasma levels was delayed from 1.5 hours to 3 hours.[4] The manufacturer advises that oral topotecan can be taken with or without food.[1]

(d) Other drugs

The UK manufacturer reports that, in a population pharmacokinetic analysis, the pharmacokinetics of intravenous topotecan did not appear to be significantly affected by **granisetron**, **ondansetron**, **morphine** or **corticosteroids**.[1] Similarly, in a population pharmacokinetic analysis of intravenous topotecan in children, **dexamethasone** and **co-trimoxazole** (**sulfamethoxazole**/**trimethoprim**) did not appear to alter the clearance of topotecan.[5]

1. Hycamtin Hard Capsule (Topotecan hydrochloride). GlaxoSmithKline UK. UK Summary of product characteristics, December 2008.
2. Kruijtzer CM, Beijnen JH, Rosing H, ten Bokkel Huinink WW, Schot M, Jewell RC, Paul EM, Schellens JH. Increased oral bioavailability of topotecan in combination with the breast cancer resistance protein and P-glycoprotein inhibitor GF120918. *J Clin Oncol* (2002) 20, 2943–50.
3. Kuppens IE, Witteveen EO, Jewell RC, Radema SA, Paul EM, Mangum SG, Beijnen JH, Voest EE, Schellens JH. A phase I, randomized, open-label, parallel cohort, dose-finding study of elacridar (GF120918) and oral topotecan in cancer patients. *Clin Cancer Res* (2007) 13, 3276–85.
4. Herben VM, Rosing H, ten Bokkel Huinink WW, van Zomeren DM, Batchelor D, Doyle E, Beusenberg FD, Beijnen JH, Schellens JH. Oral topotecan: bioavailability and effect of food co-administration. *Br J Cancer* (1999) 80, 1380–6.
5. Schaiquevich P, Panetta JC, Iacono LC, Freeman BB 3rd, Santana VM, Gajjar A, Stewart CF. Population pharmacokinetic analysis of topotecan in pediatric cancer patients. *Clin Cancer Res* (2007) 13, 6703–11.

Topotecan + Phenytoin

Phenytoin may possibly increase topotecan clearance.

Clinical evidence, mechanism, importance and management

When a 5-year-old child with medulloblastoma received a course of topotecan, with phenytoin, the total clearance of topotecan was increased by 47%, when compared with a cycle of topotecan without phenytoin.[1] Similarly, in a population pharmacokinetic analysis of studies of intravenous topotecan in children, topotecan clearance was significantly higher in those receiving phenytoin (estimated mean increase of 80%).[2]

Evidence is limited, but the case report and the pharmacokinetic data suggest that an increased topotecan dose may possibly be needed in the presence of phenytoin. It would seem prudent to monitor topotecan efficacy more closely if phenytoin is given.

1. Zamboni WC, Gajjar AJ, Heideman RL, Beijnen JH, Rosing H, Houghton PJ, Stewart CF. Phenytoin alters the disposition of topotecan and *N*-desmethyl topotecan in a patient with medulloblastoma. *Clin Cancer Res* (1998) 4, 783–9.
2. Schaiquevich P, Panetta JC, Iacono LC, Freeman BB, Santana VM, Gajjar A, Stewart CF. Population pharmacokinetic analysis of topotecan in pediatric cancer patients. *Clin Cancer Res* (2007) 13, 6703–11.

Topotecan + Probenecid

In *mice*, probenecid markedly inhibited the renal tubular secretion of topotecan, which led to an increase in topotecan systemic exposure.[1] The clinical relevance of this finding is unknown, but it would seem prudent to monitor for topotecan adverse effects in patients also given probenecid. More study is needed to confirm a clinically relevant interaction.

1. Zamboni WC, Houghton PJ, Johnson RK, Hulstein JL, Crom WR, Cheshire PJ, Hanna SK, Richmond LB, Luo X, Stewart CL. Probenecid alters topotecan systemic and renal disposition by inhibiting renal tubular secretion. *J Pharmacol Exp Ther* (1998) 284, 89–94.

Topotecan + Ranitidine

Ranitidine does not alter the pharmacokinetics of topotecan.

Clinical evidence, mechanism, importance and management

In 18 patients with solid tumours, the pharmacokinetics of topotecan (given in initial doses of 2.3 mg/m^2 daily for 5 days, repeated every 3 weeks) and its active metabolite, topotecan lactone, were not affected by the previous use of ranitidine 150 mg twice daily for 4 days.[1] No special precautions would seem necessary if ranitidine or other drugs that increase gastric pH are given with oral topotecan.

1. Akhtar S, Beckman RA, Mould DR, Doyle E, Fields SZ, Wright J. Pretreatment with ranitidine does not reduce the bioavailability of orally administered topotecan. *Cancer Chemother Pharmacol* (2000) 46, 204–10.

Toremifene + Antiepileptics; Enzyme-inducing

Carbamazepine, phenobarbital and possibly phenytoin can reduce the serum levels of toremifene.

Clinical evidence, mechanism, importance and management

A pharmacokinetic study of toremifene in two groups of 10 patients (a control group and a group of patients taking antiepileptics) found that the AUC and half-life of a single 120-mg dose of toremifene were approximately halved in the antiepileptic group. The antiepileptics used were **carbamazepine** alone (3 patients) or with clonazepam (3 patients), or **phenobarbital** alone (3 patients) or with **phenytoin** (1 patient). This interaction is thought to occur because these antiepileptics induce the liver enzymes (almost certainly the cytochrome P450 isoenzyme CYP3A4) by which toremifene is metabolised, resulting in increased toremifene clearance.[1] The UK manufacturers of toremifene have therefore reasonably suggested that the toremifene dose may need to be doubled in the presence of these antiepileptics.[2] **Primidone** is metabolised to phenobarbital, and **fosphenytoin** is metabolised to phenytoin. Similar precautions may therefore be prudent in patients taking these drugs.

1. Anttila M, Laakso S, Nyländen P, Sotaniemi EA. Pharmacokinetics of the novel antiestrogenic agent toremifene in subjects with altered liver and kidney function. *Clin Pharmacol Ther* (1995) 57, 628–35.
2. Fareston (Toremifene citrate). Orion Pharma UK Ltd. UK Summary of product characteristics, January 2009.

Toremifene + Miscellaneous

Based on theoretical considerations, the manufacturers advise care when toremifene is given with thiazides. CYP3A inhibitors such as erythromycin, ketoconazole, and troleandomycin would be expected to increase toremifene levels.

Clinical evidence, mechanism, importance and management

(a) CYP3A inhibitors

The manufacturers of toremifene note that it is mainly metabolised by the cytochrome P450 isoenzymes CYP3A4, CYP3A5, and CYP3A6 so it is suggested that drugs that can inhibit these enzymes (such as **erythromycin**, **troleandomycin**, and **ketoconazole**) may possibly increase its effects.[1,2] Although the clinical relevance of these interactions has not been established, note that CYP3A4 *inducers* (see 'Toremifene + Antiepileptics; Enzyme-inducing', above, and 'Toremifene + Rifampicin (Rifampin)', below) have been found to interact, so a pharmacokinetic interaction with CYP3A inhibitors would be expected. For a list of CYP3A4 inhibitors, see 'Table 1.4', (p.6).

(b) Thiazides

Hypercalcaemia is a recognised adverse effect of toremifene, and it is suggested that drugs such as the **thiazides**, which decrease renal calcium excretion, may increase the risk of hypercalcaemia.[1,2] This warning is based on indirect evidence and theoretical considerations so its clinical importance awaits confirmation.

1. Fareston (Toremifene citrate). Orion Pharma UK Ltd. UK Summary of product characteristics, January 2009.
2. Fareston (Toremifene citrate). GTx, Inc. US Prescribing information, December 2004.

Toremifene + Rifampicin (Rifampin)

Rifampicin increases the metabolism of toremifene, and might be expected to reduce its efficacy.

Clinical evidence, mechanism, importance and management

A study in 9 healthy men found that rifampicin 600 mg daily for 5 days reduced the AUC, peak plasma levels, and half-life of a single 120-mg dose of toremifene by 87%, 55%, and 44%, respectively. Similarly, the AUC of the metabolite *N*-demethyltoremifene was reduced by 80%.[1] Rifampicin may therefore reduce the efficacy of toremifene.[1] It would therefore seem prudent to monitor concurrent use for toremifene efficacy.

1. Kivistö KT, Villikka K, Nyman L, Anttila M, Neuvonen PJ. Tamoxifen and toremifene concentrations in plasma are greatly decreased by rifampin. *Clin Pharmacol Ther* (1998) 64, 648–54.

Trabectedin + Miscellaneous

Trabectedin is mainly metabolised by CYP3A4 and therefore inhibitors of this isoenzyme are predicted to raise its levels, whereas inducers of this isoenzyme are predicted to reduce its levels. Trabectedin is also a substrate for P-glycoprotein, and therefore inhibitors of this transporter are expected to raise trabectedin levels. The concurrent use of trabectedin with statins is expected to increase the risks of rhabdomyolysis, and the concurrent use of hepatotoxic drugs is expected to increase the risks of hepatotoxicity. Trabectedin may reduce the absorption of phenytoin. The use of live vaccines should be avoided.

Clinical evidence, mechanism, importance and management

(a) Alcohol

The manufacturer warns that because of the risk of additive hepatotoxicity, the use of trabectedin with hepatotoxic drugs is not recommended. They specifically advise that alcohol consumption must be avoided during treatment with trabectedin.[1]

(b) CYP3A4 inducers and inhibitors

Trabectedin is mainly metabolised by the cytochrome P450 isoenzyme CYP3A4. The manufacturer therefore predicts that inducers of this enzyme (they name **phenobarbital**, **rifampicin** (**rifampin**) and **St John's wort**) may decrease trabectedin levels, and that inhibitors of this isoenzyme (they name **ketoconazole**, **fluconazole**, **ritonavir**, **aprepitant** and **clarithromycin**) may increase trabectedin levels.[1]

Patients should be monitored to ensure that the trabectedin is effective if inducers of CYP3A4 are taken concurrently (see also *Phenytoin*, below). The manufacturers advise that potent CYP3A4 inhibitors should be avoided, but suggest that, if concurrent use cannot be avoided, patients should be closely monitored for trabectedin toxicity and consideration should be given to reducing its dose.[1]

(c) P-glycoprotein inhibitors

Trabectedin is a substrate of P-glycoprotein. The manufacturer therefore advises caution when inhibitors of P-glycoprotein are given to patients taking trabectedin. They specifically name **ciclosporin** and **verapamil**.[1]

(d) Phenytoin

The manufacturer warns that trabectedin may reduce the absorption of phenytoin and therefore increase the risk of seizures. This is predicted on the basis that trabectedin is a cytotoxic and can damage the gastric mucosa and may therefore reduce phenytoin absorption.[2] They therefore do not recommend the combination.[1] There are a few cases of this having occurred with other cytotoxics, see 'Antiepileptics + Antineoplastics; Cytotoxic', p.593; however, it is by no means an established interaction mechanism, and therefore the advice seems over cautious. Note that phenytoin would also be predicted to decrease trabectedin levels, see *CYP3A4 inducers*, above. If both drugs are required, it would seem prudent to monitor phenytoin levels more closely and monitor for trabectedin efficacy.

(e) Statins

In rare cases trabectedin has been associated with rhabdomyolysis. The manufacturers therefore advise caution if other drugs that cause rhabdomyolysis are also given, and they specifically name the statins.[1]

(f) Vaccines

The manufacturer warns that patients receiving trabectedin should not also receive live attenuated vaccines, presumably because of the risks of a generalised infection developing. They specifically contraindicate **yellow fever vaccine**.[1]

1. Yondelis (Trabectedin). Pharma Mar, S.A. UK Summary of product characteristics, October 2009.
2. PharmaMar S. A. Personal communication, March 2009.

Tretinoin + Antifibrinolytics

In acute promyelocytic leukaemia the combination of tretinoin and antifibrinolytics such as tranexamic acid and aprotinin has been associated with fatal thrombotic complications.

Clinical evidence, mechanism, importance and management

In an analysis of 31 patients with acute promyelocytic leukaemia (APL) treated over a 7-year period, **tranexamic acid** 1 to 2 g daily for 6 days was given for prophylaxis of haemorrhage to 15 of 24 patients receiving tretinoin and chemotherapy, 4 of 4 receiving tretinoin only and 2 of 3 receiving chemotherapy only. Seven of the patients receiving tretinoin died during the study period and 4 of them, who had received the combination of tretinoin and **tranexamic acid**, died within 42 days (early deaths). Three of the early deaths were attributed to thrombotic complications.[1] Another earlier report describes a similar fatal case of thromboembolism in a patient given tretinoin and **tranexamic acid**,[2] and another in a patient given tretinoin and **aprotinin**.[3] A further report describes acute renal cortex necrosis as a result of arterial thrombosis in a patient given tretinoin and **tranexamic acid**.[4] Tretinoin alone causes a procoagulant tendency in APL, and this may be exacerbated by use of antifibrinolytics. Although antifibrinolytics and chemotherapy may be safely used concurrently in APL, the combination of tretinoin and antifibrinolytics can cause fatal thrombotic complications and should be used with caution. The use of blood, platelets and plasma rather than **tranexamic acid** for prophylaxis of haemorrhage has been advocated for APL patients.[1]

1. Brown JE, Olujohungbe A, Chang J, Ryder WDJ, Chopra R, Scarffe JH. All-*trans* retinoic acid (ATRA) and tranexamic acid: a potentially fatal combination in acute promyelocytic leukaemia. *Br J Haematol* (2000) 110, 1010–12.
2. Hashimoto S, Koike T, Tatewaki W, Seki Y, Sato N, Azegami T, Tsukada N, Takahashi H, Kimura H, Ueno M, Arakawa M, Shibata A. fatal thromboembolism in acute promyelocytic leukemia during all-*trans* retinoic acid therapy combined with antifibrinolytic therapy for prophylaxis of hemorrhage. *Leukemia* (1994) 8, 1113–15.
3. Mahendra P, Keeling DM, Hood IM, Baglin TP, Marcus RE. Fatal thromboembolism in acute promyelocytic leukaemia treated with a combination of all-trans retinoic acid and aprotinin. *Clin Lab Haematol* (1996) 18, 51–2.
4. Levin M-D, Betjes MGH, v d Kwast TH, Wenberg BL, Leebeek FWG. Acute renal cortex necrosis caused by arterial thrombosis during treatment for acute promyelocytic leukemia. *Haematologica* (2003) 88, ECR21.

Tretinoin + Azoles

The metabolism of tretinoin can be inhibited by fluconazole and ketoconazole, and a case report describes tretinoin toxicity as a result of this interaction.

Clinical evidence

(a) Fluconazole

In 2 patients taking tretinoin, a loading dose of fluconazole 400 mg then 200 mg daily thereafter, increased the tretinoin AUC about two- to four-fold, after the second fluconazole dose, when compared with the AUC 8 days after starting tretinoin, but tretinoin levels were similar to those on the first day of use.[1] A 4-year-old boy with acute promyelocytic leukaemia was given induction chemotherapy consisting of cytarabine, daunorubicin and tretinoin 45 mg/m^2 daily in two divided doses. Febrile neutropenia was treated with meropenem and amphotericin B for periods up to day 20. On day 20 he started antifungal prophylaxis with fluconazole 100 mg daily. The next day he complained of headache and a week later he had headache, vomiting and papilloedema. His CT scan was normal. Pseudotumor cerebri was diagnosed and symptoms of increased intracranial pressure resolved within a day of stopping tretinoin. Restarting tretinoin on day 30 at 75% of the previous dose resulted in headache and vomiting, and the treatment was continued from day 35 with an even lower dose (30%), which caused headache but only one episode of vomiting. Fluconazole was stopped on day 41 and within 24 hours the patient had improved clinically with the headache and vomiting fully resolved. He was then able to tolerate the full dose of tretinoin without adverse effects.[2]

(b) Ketoconazole

In 6 patients with lung cancer,[3] a single 400-mg dose of ketoconazole given one hour before tretinoin on day 29 increased the AUC of tretinoin by 115% (compared with day 28 when tretinoin was given alone), but a 200 mg dose of ketoconazole had little effect on the AUC of tretinoin. Ketoconazole had no effect on the AUC of tretinoin when given on day 2 (compared with tretinoin alone on day one).

Mechanism

Fluconazole inhibits the cytochrome P450 isoenzymes CYP3A4 and CYP2C9, and ketoconazole inhibits CYP3A4. *In vitro* both these azoles inhibited the oxidative metabolism of tretinoin, with ketoconazole being more potent.[1] Tretinoin induces its own metabolism over time, and the effect of these azoles is not as great on the first day of tretinoin administration as after a week or more of use.[1,3]

Importance and management

Although it has been suggested that drugs such as fluconazole and ketoconazole may be useful in overcoming clinical resistance to tretinoin,[1,3] it has also been suggested that the concurrent use of tretinoin with drugs that affect its metabolism should be avoided if possible, or patients should be carefully monitored.[2] Given the reaction described in the case report of the child, this seems advisable.

1. Schwartz EL, Hallam S, Gallagher RE, Wiernik PH. Inhibition of all-trans retinoic acid metabolism by fluconazole in vitro and in patients with acute promyelocytic leukaemia. *Biochem Pharmacol* (1995) 50, 923–8.
2. Vanier KL, Mattiussi AJ, Johnston DL. Interaction of all-trans-retinoic acid with fluconazole in acute promyelocytic leukaemia. *J Pediatr Hematol Oncol* (2003) 25, 403–4.
3. Rigas JR, Francis PA, Muindi JRF, Kris MG, Huselton C, DeGrazia F, Orazem JP, Young CW, Warrell RP. Constitutive variability in the pharmacokinetics of the natural retinoid, all-trans-retinoic acid, and its modulation by ketoconazole. *J Natl Cancer Inst* (1993) 85, 1921–6.

Vinca alkaloids + Antiepileptics; Enzyme-inducing

Carbamazepine and phenytoin appear to reduce the plasma levels of vincristine, and may reduce its efficacy. Other vinca alkaloids may interact similarly.

Clinical evidence, mechanism, importance and management

The systemic clearance of vincristine 2 mg was 63% higher and the AUC was 43% lower in 9 patients receiving **carbamazepine** or **phenytoin** than in 6 patients not taking antiepileptics. In this study, patients were being treated with procarbazine, lomustine and vincristine for brain tumours.[1] In a retrospective survey, long-term antiepileptic use (**phenytoin**, **phenobarbital**, **carbamazepine**, or a combination) was associated with worse event-free survival, and greater haematological relapse and CNS relapse in children receiving chemotherapy for B-lineage acute lymphoblastic leukaemia. The authors considered that the increased clearance of vincristine induced by the antiepileptics was a likely factor in these findings.[2]

These enzyme-inducing antiepileptics increase the metabolism of vincristine by the cytochrome P450 isoenzyme CYP3A4. Other vinca alkaloids are also metabolised by this route. However, *in vitro* studies have shown that **phenytoin** may potentiate the antineoplastic (antimitotic) effects of the vinca alkaloids.[3,4] Thus, further study is required to determine the overall effect of **phenytoin** on the efficacy and toxicity of vincristine and other vinca alkaloids. **Carbamazepine** and **phenobarbital** would be expected to reduce the efficacy of vincristine. Therefore it would seem prudent to monitor concurrent use for efficacy. Also note that **primidone** is metabolised to phenobarbital and **fosphenytoin** is metabolised to phenytoin, and these drugs may therefore be expected interact with the vinca alkaloids.

Note that a number of case reports have described reduced phenytoin

levels in patients receiving chemotherapy including vinca alkaloids, see 'Table 14.1', (p.594).

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Vinca alkaloids + Azoles

Itraconazole can increase the toxicity of vincristine, and there is some limited evidence that this is particularly likely with the oral liquid formulation and at higher doses. There are case reports of itraconazole increasing the toxicity of vinblastine, vindesine, and vinorelbine. One case report describes a similar interaction between posaconazole and vincristine. Voriconazole is expected to interact similarly, although this was not seen in one study with vincristine.

Clinical evidence

(a) Vinblastine

Acute neurotoxicity and myelotoxicity occurred in a boy with Hodgkin's lymphoma receiving vinblastine, doxorubicin and methotrexate when he was also given **itraconazole**. The toxicity did not occur when he was given the same chemotherapy without **itraconazole**.[1]

(b) Vincristine

1. Itraconazole. Four out of 14 adults with acute lymphoblastic leukaemia (ALL) given induction chemotherapy with weekly injections of vincristine (with prednisone, daunorubicin and asparaginase) and antifungal prophylaxis with oral itraconazole capsules 400 mg daily, developed severe and early vincristine-induced neurotoxicity (paraesthesia and muscle weakness of the hands and feet, paralytic ileus, mild laryngeal nerve paralysis). The degree and early onset of these neurotoxic reactions were unusual, and were all reversible except for mild paraesthesia in one patient. The complications were more serious than in a previous series of 46 patients given vincristine without itraconazole (29% compared with 6%).[2] Similarly, five consecutive children with ALL enrolled in an open study of prophylactic oral itraconazole 2.5 mg/kg daily (presumably as a liquid formulation) developed severe vincristine toxicity (constipation, abdominal pain, hypertension, ileus, hyponatraemia, seizures) attributed to the concurrent use of itraconazole. They were also receiving nifedipine, which is known to reduce the clearance of vincristine (see 'Vinca alkaloids; Vincristine + Nifedipine', p.782), and which may have made things worse.[3] Since these two reports, cases of severe vincristine neurotoxicity have been reported in five other children[4-8] and two adults[9] with ALL when they were given oral (liquid formulation where stated[8,9]) or intravenous[6] itraconazole. In a further series of 9 children given weekly vincristine and oral itraconazole 5 mg/kg (liquid formulation), all developed increased vincristine toxicity, with 4 patients experiencing seizures.[10] Similarly, in yet another study, 5 of 7 adults given vincristine as part of CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) for lymphoma developed vincristine neurotoxicity when receiving oral itraconazole 200 mg daily as a solution. Of note, none of the patients who received vincristine and itraconazole 200 mg daily as capsules developed neurotoxicity.[11]

2. Posaconazole. A patient given posaconazole 400 mg twice daily who also received four doses of vincristine 2 mg at weekly intervals developed bilateral foot paraesthesias and was unable to walk unassisted. Treatment with posaconazole and any vinca alkaloids was stopped, but the patient showed little signs of improvement 5 months later.[12]

3. Voriconazole. None of eight patients who received antifungal prophylaxis with voriconazole 200 mg twice daily during the initial phase of treatment for acute lymphoblastic leukaemia with vincristine and other chemotherapy developed neurotoxicity.[13]

(c) Vindesine

Two cases of vindesine-associated neuropathy were reported in two adult patients. In the first case, paralytic ileus developed 9 days after the patient started to take **itraconazole** solution; vindesine was given 2 and 9 days after **itraconazole** was started. On stopping the **itraconazole**, his symptoms improved rapidly. The second case was that of a 37-year-old woman who received vindesine on days one, 8 and 15. Intravenous **itraconazole** was given from day 9, and 5 days after this she developed symptoms of neurotoxicity, which resolved rapidly on stopping **itraconazole** and vindesine.[14]

(d) Vinorelbine

A 72-year-old man with fungal pneumonia and lung cancer received **itraconazole** (dose not stated) and vinorelbine with cisplatin. After chemotherapy he developed constipation, oral mucositis, leucopenia, progressively deteriorated and died 12 days later.[15]

Mechanism

The reasons for these interactions are not understood, but it has been suggested that itraconazole inhibits the metabolism of vincristine by the cytochrome P450 isoenzyme CYP3A subfamily.[2] Another possible explanation is that itraconazole inhibits P-glycoprotein,[2] and increased vincristine neurotoxicity may be the result of the inhibition of this pump in endothelial cells of the blood-brain barrier.[16] All of the other clinically used vinca alkaloids (vinblastine, vindesine and vinorelbine) are known to be metabolised by CYP3A4, and vinblastine is also a substrate for P-glycoprotein.

Of the other azoles, ketoconazole is also a potent inhibitor of CYP3A4, whereas fluconazole is a moderate inhibitor of CYP3A4 and a potent inhibitor of CYP2C9 (which is not involved in the metabolism of vinca alkaloids). Both of the newer azoles, posaconazole and voriconazole, inhibit CYP3A4.

Importance and management

The interaction of **itraconazole** with vincristine appears to be well documented. The authors of many of the reports[2,4,8-10] suggest that itraconazole should be avoided in patients taking vincristine, or that it should be interrupted when vincristine is given.[6,7] There is some evidence that the liquid oral formulations may be more likely to interact (because of higher oral bioavailability for a given dose)[11] and that the interaction may be dose related (less likely with 200 mg daily than 400 mg daily as capsules[11] and less likely with monthly vincristine than weekly vincristine[4]). Although less well documented; itraconazole may interact similarly with vinblastine, vindesine and vinorelbine. Some UK[17] and US[18] manufacturers advise caution if vinorelbine, is given with itraconazole and **ketoconazole**. The manufacturers of vindesine also note that concurrent use of CYP3A inhibitors may result in early onset or increased severity of vindesine adverse effects.[19]

Data for other azoles is sparse. Some limited evidence indicates that fluconazole did not interact.[10,16] Of the newer azoles, the manufacturer of **posaconazole** advises avoidance of concurrent use with vinca alkaloids (vincristine and vinblastine are named), but if they are given, then dose adjustments of the vinca alkaloids should be considered.[20] Similarly, the manufacturers of **voriconazole** advise caution if it is given to patients receiving vinca alkaloids (vincristine and vinblastine are named) because of the risk of neurotoxicity.[21,22] The US manufacturer of voriconazole recommends that dose adjustments of the vinca alkaloids should be considered.[22]

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3. Murphy JA, Ross LM, Gibson BES. Vincristine toxicity in five children with acute lymphoblastic leukaemia. *Lancet* (1995) 346, 443.
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19. Eldisine (Vindesine). Genus Pharmaceuticals Ltd. UK Summary of product characteristics, July 2008.
20. Noxafil (Posaconazole). Schering-Plough Ltd. UK Summary of product characteristics, November 2009.
21. VFEND (Voriconazole). Pfizer Ltd. UK Summary of product characteristics, September 2009.
22. VFEND (Voriconazole). Pfizer Inc. US Prescribing information, December 2009.

Vinca alkaloids + Macrolides

Erythromycin increased the toxicity of vinblastine in three patients. Other macrolides are predicted to interact similarly with the vinca alkaloids, but limited evidence suggests that not all patients are affected.

Clinical evidence

Three patients with renal cell carcinoma given ciclosporin 10 or 13 mg/kg daily and **erythromycin** 1 g daily for 3 days developed severe toxicity when given **vinblastine** 7 to 10 mg/m^2 on the third day. Ciclosporin was used as a modifier of multidrug resistance and **erythromycin** was given to achieve higher ciclosporin levels at a lower dose (see 'Ciclosporin + Antibacterials; Macrolides', p.1218). To rule out increased ciclosporin toxicity, one patient was given **erythromycin** without ciclosporin but he still developed **vinblastine** toxicity (severe neutropenia, constipation, myositis, severe myalgia) typical of much higher doses of **vinblastine**. Of the other 2 patients, only negligible toxicity developed in one when he was later given **vinblastine** alone, and the other had received ciclosporin and **vinblastine** on two previous occasions without problems.[1] Other authors report that they have used **clarithromycin** with standard doses of vinca alkaloids in at least 6 patients without any evidence of increased toxicity.[2]

Mechanism

Uncertain, but erythromycin inhibits the cytochrome P450 isoenzyme CYP3A4, which is concerned with the metabolism of vinblastine and other vinca alkaloids. This would be expected to reduce their metabolism resulting in an increase in toxicity.

Importance and management

Information about an interaction between vinca alkaloids and macrolides seems to be limited to this report. On the basis of their findings the authors suggest that erythromycin should be avoided at the time of vinblastine infusion.[1] Use with clarithromycin may be safe,[2] although given that clarithromycin is known to inhibit CYP3A4, by which the vinca alkaloids are metabolised, this needs establishing. The UK manufacturers of **vincristine**, **vindesine** and **vinorelbine** have warned that caution should be exercised in patients taking any drugs known to inhibit the CYP3A subfamily[3-5] because of the risk of an earlier onset and/or increased severity of adverse effects.[3,4] This would be expected to include a number of macrolides (notably, clarithromycin, erythromycin and **telithromycin**). Note that itraconazole, another CYP3A4 inhibitor, is known to increase the toxicity of the vinca alkaloids, see 'Vinca alkaloids + Azoles', p.780.

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2. Torresin A, Cassola G, Penco G, Crisalli MP, Piersantelli N. Vinca alkaloids and macrolides in human immunodeficiency virus-related malignancies: a safe association. *Cancer Chemother Pharmacol* (1996) 39, 176–7.
3. Eldisine (Vindesine). Genus Pharmaceuticals Ltd. UK Summary of product characteristics, July 2008.
4. Vincristine sulphate. Hospira UK Ltd. UK Summary of product characteristics, January 2008.
5. Navelbine (Vinorelbine tartrate). Pierre Fabre Ltd. UK Summary of product characteristics, August 2009.

Vinca alkaloids + Mitomycin

A syndrome of acute pulmonary toxicity, characterised by severe shortness of breath, can occur when vinblastine, vindesine or vinorelbine is given with mitomycin. Fatalities have occurred.

Clinical evidence, mechanism, importance and management

There are numerous reports describing acute lung disease in patients given mitomycin with vinca alkaloids, which appears to be different to the chronic pulmonary fibrosis seen with mitomycin alone. Sudden onset of acute shortness of breath has been described shortly after administration of the vinca alkaloid as part of a vinca alkaloid and mitomycin-containing regimen. Chest radiographs have shown diffuse lung damage characterised by interstitial infiltrates and pulmonary oedema. The acute syndrome has usually improved over 24 hours, although some patients have chronic respiratory impairment (60% in one case series[1]). Fatalities have occurred.[2-4] The syndrome has been reported with mitomycin and **vinblastine**,[1-9] **vindesine**[1,8,10-12] or intravenous **vinorelbine**.[12-15] The incidence is reported to be about 3 to 6%.[1,7,12]

The potential hazards of combining these drugs should be recognised, and in view of the unpredictability of the reaction, close observation of patients receiving this combination is recommended.[1,3] If the reaction occurs, supportive measures such as supplemental oxygen and mechanical ventilation may be needed. Corticosteroids are also often used in an attempt to treat the acute symptoms, and to possibly decrease the risk of chronic respiratory impairment.[1] In patients who have developed acute pulmonary toxicity, the use of both mitomycin and vinca alkaloids should subsequently be avoided.[1]

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Vinca alkaloids + Protease inhibitors

Severe neutropenia has been seen in two patients given vinblastine and antiretroviral regimens including ritonavir-boosted lopinavir.

Clinical evidence, mechanism, importance and management

A 55-year-old HIV-positive man who was taking zidovudine, lamivudine, abacavir, nevirapine and **ritonavir**-boosted **lopinavir** experienced unexpected severe gastrointestinal and haematological toxicities and moderate renal failure after the second and third intravenous injections of vinblastine 10 mg given to treat multicentric Castleman's disease (MCD). Subsequently, the antiretrovirals were stopped and the patient did not experience these toxicities when vinblastine was given alone. When the MCD was under control, the antiretrovirals were restarted, and the vinblastine dose reduced to 3 mg every 3 weeks without problems.[1] A second HIV-positive patient who was taking a **lopinavir**/**ritonavir**-based antiretroviral regimen developed life-threatening neutropenia when given ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) for Hodgkin's lymphoma. Further vinblastine treatment was successfully given by interrupting the protease inhibitors around the time the chemotherapy was given.[2]

It was suggested that the metabolism of vinblastine by the cytochrome P450 isoenzyme CYP3A was inhibited by ritonavir, resulting in increased toxicity.

These appear to be the only cases so far of a possible interaction. Nevertheless, it would now be prudent to carefully monitor any patient taking a ritonavir-based antiretroviral regimen who receives vinblastine. Note that, many manufacturers of vinca alkaloids advise caution if these drugs are given with CYP3A4 inhibitors because of the risks of toxicity. This would be expected to include the protease inhibitors.

For mention that protease inhibitor regimens have been associated with an increased risk of infection when used with various antineoplastic regimens, including those containing vincristine, see 'Antineoplastics + Protease inhibitors', p.703.

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Vinca alkaloids; Vinblastine + Bleomycin

The combination of vinblastine and bleomycin, with or without cisplatin, commonly causes Raynaud's phenomenon. Rarely, it also appears to cause serious life-threatening cardiovascular toxicity.

Clinical evidence, mechanism, importance and management

Five patients (aged 23 to 58 years) treated for germ cell tumours died from unexpected acute life-threatening vascular events (myocardial infarction, rectal infarction, cerebrovascular accident) after treatment with VBP (vinblastine, bleomycin, cisplatin). A survey of the literature by the authors of this paper revealed 14 other cases of both acute and long-term cardiovascular problems (myocardial infarction, coronary heart disease, cerebrovascular accident) in patients given VBP.[1]

Raynaud's phenomenon is common, occurring in one-third to one-half of those given vinblastine and bleomycin or VBP,[2,3] and there is evidence that blood vessels are pathologically altered.[2] Cisplatin may contribute to the effect.[3] Analysis of late vascular toxicity after chemotherapy for testicular cancer revealed that the use of VBP carried a higher risk of Raynaud's phenomenon than BEP (bleomycin with etoposide and cisplatin).[4]

The use of the VBP (PVB) regimen has largely been replaced by the BEP (PEB) regimen, because of its reduced toxicity.

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3. Hansen SW. Late-effects after treatment for germ-cell cancer with cisplatin, vinblastine, and bleomycin. *Dan Med Bull* (1992) 39, 391–9.
4. Berger CC, Bokemeyer C, Schneider M, Kuczyk MA, Schmoll H-J. Secondary Raynaud's phenomenon and other late vascular complications following chemotherapy for testicular cancer. *Eur J Cancer* (1995) 31A, 2229–38.

Vinca alkaloids; Vincristine + Asparaginase

An isolated case report suggests that vincristine neurotoxicity may possibly have been increased by the subsequent use of asparaginase.[1,2] The UK manufacturer recommends that vincristine should be given 12 to 24 hours before asparaginase.[3] Regimens including both drugs are commonly used in treating leukaemia.

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2. Hildebrand J, Kenis Y. Additive toxicity of vincristine and other drugs for the peripheral nervous system. *Acta Neurol Belg* (1971) 71, 486–91.
3. Vincristine sulphate. Hospira UK Ltd. UK Summary of product characteristics, January 2008.

Vinca alkaloids; Vincristine + Isoniazid

Some limited evidence suggests that vincristine neurotoxicity may possibly be increased by isoniazid.

Clinical evidence, mechanism, importance and management

An 85-year-old woman with Hodgkin's disease was given COPP and ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine), alternating every 28 days. She started COPP (cyclophosphamide and 2 mg vincristine on day one, with procarbazine and prednisone days one to 14) and was also given isoniazid 300 mg daily as prophylaxis of tuberculosis. Five days after the start of this treatment she experienced tingling in her fingers and weakness in her legs, which was interpreted by the authors of this report as being vincristine toxicity (paraesthesia of the feet and/or hands being a recognised early sign of vincristine toxicity) brought about by the concurrent use of isoniazid. Their reasoning was that such a small dose of vincristine on its own was unlikely to cause severe neurotoxicity of this kind, but it is not clear why isoniazid should apparently interact like this. The authors suggest that the age of this patient and the fact that she had diabetes (well controlled) may have contributed to this increase in vincristine neurotoxicity.[1]

This report is consistent with another much earlier report of 2 patients who also developed peripheral neurotoxicity when they were given vincristine after starting to take isoniazid and pyridoxine, the cumulative doses of vincristine being 11 mg and 11.2 mg, respectively.[2,3] Similarly, another case describes severe neurotoxicity with an overdose of isoniazid and high-dose vincristine.[4]

These reports appear to be the only ones implicating isoniazid in an increase in vincristine toxicity, but they serve to emphasise the importance of very close neurological supervision in anyone given both drugs.

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Vinca alkaloids; Vincristine + Nifedipine

Nifedipine reduces the clearance of vincristine.

Clinical evidence, mechanism, importance and management

In a study in 12 patients, nifedipine reduced the clearance of a single 2-mg intravenous dose of vincristine by 68%, and increased its AUC threefold, when compared with 14 patients receiving vincristine alone. Nifedipine was given at a dose of 10 mg three times daily for 3 days before and 7 days after vincristine was given. However, no important adverse effects were noted in either group of patients, suggesting that these pharmacokinetic changes did not markedly increase vincristine toxicity.[1] Further study is needed to establish any interaction.

1. Fedeli L, Colozza M, Boschetti E, Sabalich I, Aristei C, Guerciolini R, Del Favero A, Rossetti R, Tonato M, Rambotti P, Davis S. Pharmacokinetics of vincristine in cancer patients treated with nifedipine. *Cancer* (1989) 64, 1805–11.

Vinca alkaloids; Vinorelbine + Cisplatin

The pharmacokinetics of intravenous vinorelbine were not altered by cisplatin in one study. The incidence of granulocytopenia is reported to be higher when vinorelbine is given with cisplatin than when given alone.

Clinical evidence, mechanism, importance and management

The pharmacokinetics of vinorelbine did not differ between 4 patients who received a single 30-mg/m^2 infusion of vinorelbine given over 15 minutes and 4 patients who were also given a single 80-mg/m^2 dose of cisplatin given one hour after the start of the vinorelbine infusion.[1]

The incidence of granulocytopenia is reported to be higher when vinorelbine is given with cisplatin, than when given alone.[2,3] In one large clinical study, the incidence of grade 3 to 4 granulocytopenia was 79% in patients receiving intravenous vinorelbine 30 mg/m^2 weekly with cisplatin (120 mg/m^2 on days one and 29, and then every 6 weeks) compared with an incidence of 53% in patients receiving vinorelbine 30 mg/m^2 weekly alone.[3] However, the combination regimen improved survival.

The combination of vinorelbine and cisplatin is in established use. Note that close monitoring for granulocytopenia and appropriate dose adjustment or a delay in treatment is important if granulocytopenia develops with vinorelbine alone.

1. Levêque D, Jehl F, Quoix E, Breillout F. Clinical pharmacokinetics of vinorelbine alone and combined with cisplatin. *J Clin Pharmacol* (1992) 32, 1096–8.
2. Navelbine (Vinorelbine tartrate). Pierre Fabre Ltd. UK Summary of product characteristics, August 2009.
3. Navelbine (Vinorelbine tartrate). Pierre Fabre Pharmaceuticals Inc. US Prescribing information, October 2007.

Vinca alkaloids; Vinorelbine + Rifampicin (Rifampin)

The manufacturers advise that the pharmacokinetics of vinorelbine may be altered if it is given with rifampicin.

Clinical evidence, mechanism, importance and management

In a small study in 4 *pigs*, there was no difference in the clearance of vinorelbine when a single intravenous dose of 500 micrograms/kg was given alone or on the day 7 of intravenous rifampicin 600 mg daily. The AUC and maximum level of vinorelbine were increased by about 66% by rifampicin, but this was not statistically significant,[1] possibly because of the small sample size. The pig was chosen for this study because porcine CYP3A is reportedly similar to that of humans.[1]

Vinorelbine is known to be metabolised by the cytochrome P450 isoenzyme CYP3A4, of which rifampicin is a known potent inducer, therefore rifampicin would be expected to increase the clearance of vinorelbine and reduce its levels. The manufacturers of vinorelbine advise caution with potent inducers of the CYP3A subfamily,[2,3] which would include rifampicin. Until more is known, this seems prudent.

1. Leveque D, Wisniewski S, Renault C, Peter JD, Le Corre P, Monteil H, Jehl F. The effect of rifampin on the pharmacokinetics of vinorelbine in the micropig. *Anticancer Res* (2003) 23, 2741–4.
2. Navelbine (Vinorelbine tartrate). Pierre Fabre Ltd. UK Summary of product characteristics, August 2009.
3. Navelbine (Vinorelbine tartrate). Pierre Fabre Pharmaceuticals Inc. US Prescribing information, October 2007.

Vorinostat + Antineoplastics

Use of paclitaxel and carboplatin with vorinostat modestly increased vorinostat levels in one study. Paclitaxel levels were unaffected.

Clinical evidence, mechanism, importance and management

In a study in 28 patients with solid tumours, the AUC and half-life of vorinostat were increased by 37% and 61%, respectively, when given with **carboplatin** and **paclitaxel**. In this study, patients received intravenous **paclitaxel** 175 mg/m^2 increased to 200 mg/m^2 over 3 hours then **carboplatin** (dose adjusted to reach a target exposure) as a 30-minute infusion every 3 weeks. Oral vorinostat 200 mg daily for 14 days was given, starting 4 days before chemotherapy in the first cycle, then in increasing doses of 300 mg daily then 400 mg daily for 14 days starting on day one for subsequent cycles. The pharmacokinetics of **paclitaxel** were unaffected by vorinostat when compared with historical data, but the pharmacokinetics of **carboplatin** were not assessed. The incidence of grade 4 neutropenia was higher in this study (50%) than historical data for **carboplatin** with **paclitaxel**.[1]

The reason for the apparent alteration in vorinostat pharmacokinetics is uncertain. There was no definite relationship between vorinostat dose and the incidence of neutropenia, but it is possible that the use of vorinostat with paclitaxel contributed to this. Further study is needed to establish the effects of concurrent use.

1. Ramalingam SS, Parise RA, Ramananthan RK, Lagattuta TF, Musguire LA, Stoller RG, Potter DM, Argiris AE, Zwiebel JA, Egorin MJ, Belani CP. Phase I and pharmacokinetic study of vorinostat, a histone deacetylase inhibitor, in combination with carboplatin and paclitaxel for advanced solid malignancies. *Clin Cancer Res* (2007) 16, 3605–10.

Vorinostat + Food

The absorption of oral vorinostat is modestly increased by food.

Clinical evidence, mechanism, importance and management

The pharmacokinetics of vorinostat were investigated in 23 patients who received a single 400-mg oral dose of vorinostat in the fasted state, and again after a standardised high-fat meal. There was a 38% increase in the AUC of vorinostat when taken with food, and a delay of 2.5 hours in reaching the maximum plasma levels. This modest effect of food was not considered to be clinically relevant.[1] However, note that the manufacturer advises that the daily dose is taken with food, as this is how the clinical studies were conducted.[2]

1. Rubin EH, Agrawal NGB, Friedman EJ, Scott P, Mazina KE, Sun L, Du L, Ricker JL, Frankel SR, Gottesdiener KM, Wagner JA, Iwamoto M. A study to determine the effects of food and multiple dosing on the pharmacokinetics of vorinostat given orally to patients with advanced cancer. *Clin Cancer Res* (2006) 12, 7039–45.
2. Zolinza (Vorinostat). Merck & Co., Inc. US Prescribing information, September 2009.

Vorinostat + Miscellaneous

Severe thrombocytopenia and gastrointestinal bleeding have been reported in patients who took vorinostat and valproic acid. Increased INRs have occurred in patients taking vorinostat with coumarins.

Clinical evidence, mechanism, importance and management

(a) Valproate

The manufacturer notes that severe thrombocytopenia and gastrointestinal bleeding have been reported in patients who took vorinostat and other drugs that are histone deacetylase inhibitors. They specifically name **valproic acid**.[1] Note that thrombocytopenia is common with vorinostat alone.

(b) Warfarin and related drugs

The manufacturer notes that prolongation of the prothrombin time and raised INRs have been observed in patients receiving vorinostat with coumarin anticoagulants. They recommend close monitoring of the prothrombin time and INR in these patients.[1]

1. Zolinza (Vorinostat). Merck & Co., Inc. US Prescribing information, September 2009.

18

Antiparkinsonian and related drugs

The drugs in this section are considered together because their major therapeutic application is in the treatment of Parkinson's disease, although some of the related antimuscarinic (anticholinergic) drugs included here are also used for other conditions. Parkinson's disease is named after Dr James Parkinson who originally described the four main signs of the disease, namely rigidity, tremor, dystonias and dyskinesias (movement disorders). Similar symptoms may also be displayed as the unwanted adverse effects of certain drugs.

The basic cause of the disease lies in the basal ganglia of the brain, particularly the striatum and the substantia nigra, where the normal balance between dopaminergic nerve fibres (those that use dopamine as the chemical transmitter) and cholinergic nerve fibres (those that use acetylcholine as the transmitter) is lost, because the dopaminergic fibres degenerate. As a result the cholinergic fibres end up in relative excess. Much of the treatment of Parkinson's disease is based on an attempt to redress the balance, and there are several groups of drugs that can be used to this end. These are listed in 'Table 18.1', (below), and discussed below.

Levodopa

Levodopa can pass the blood-brain barrier (unlike dopamine), where it is converted into dopamine, and thus acts by 'topping up' the CNS dopaminergic system. Levodopa is most usually given with **carbidopa** or **benserazide** (dopa-decarboxylase inhibitors), which prevent the 'wasteful' peripheral metabolism of levodopa. This allows lower doses of levodopa to be given, which results in fewer adverse effects.

Amantadine

Amantadine may augment dopaminergic activity in the brain.

Dopamine agonists

Bromocriptine, cabergoline, pergolide, ropinirole and similar drugs act as dopamine agonists and so also have the effect of increasing dopaminergic activity in the brain.

Entacapone and Tolcapone

The catechol-*O*-methyltransferase (COMT) inhibitors work by inhibiting the peripheral metabolism of levodopa by COMT. Note that this enzyme is the major metabolising enzyme for levodopa when a decarboxylase inhibitor (e.g. benserazide) is being used.

Rasagiline and Selegiline

The selective irreversible MAO-B inhibitors enhance dopamine activity by preventing dopamine degradation. These drugs sometimes interact like non-selective MAOIs, and the reader is cross-referred to the information under MAOIs when appropriate. Selegiline undergoes rapid first-pass metabolism to produce amfetamine metabolites. A buccal tablet has been developed, which markedly reduces this first-pass metabolism, and is consequently given as a smaller dose.

Antimuscarinics

Benzhexol, orphenadrine, procyclidine and other antimuscarinic (anticholinergic) drugs work by correcting the relative cholinergic excess.

The interactions that affect the antimuscarinic effects of these drugs are discussed in this section. However, the antimuscarinics also affect the actions of other drugs (such as the centrally-acting anticholinesterases) and these are therefore discussed elsewhere in the publication.

Table 18.1 Antiparkinsonian drugs

Group	*Drugs*
Dopaminergic drugs	
Amino-acid precursor of dopamine	Levodopa
Levodopa combined with a peripheral dopa-decarboxylase inhibitor	Co-beneldopa (levodopa with benserazide) Co-careldopa (levodopa with carbidopa)
COMT-inhibitors	Entacapone, Tolcapone
Dopamine agonists	
Ergot derivatives	Bromocriptine, Cabergoline, Lisuride, Pergolide
Non-ergot dopamine agonists	Piribedil, Pramipexole, Quinagolide, Ropinirole, Rotigotine
Other dopamine agonists	Apomorphine
MAO-B inhibitors	Rasagiline, Selegiline
Other	Amantadine
Other	
Peripheral dopa-decarboxylase inhibitors	Benserazide, Carbidopa
Antimuscarinics	Benzatropine, Biperiden, Bornaprine, Dexetimide, Metixene, Orphenadrine, Procyclidine, Profenamine, Trihexyphenidyl, Tropatepine

Amantadine + Co-trimoxazole

An interaction between amantadine and co-trimoxazole is thought to have caused acute confusion in an elderly man, and amantadine toxicity in a patient with end-stage renal disease. However, in both cases other factors could have been responsible for the adverse reactions.

Clinical evidence, mechanism, importance and management

An 84-year-old man with parkinsonism, COPD and chronic atrial fibrillation, had been taking amantadine 100 mg twice daily and digoxin 125 micrograms daily for at least 2 years. Within 72 hours of starting co-trimoxazole twice daily for bronchitis he became mentally confused, incoherent and combative. He also had cogwheel rigidity and a resting tremor. Within 24 hours of stopping the amantadine and co-trimoxazole, the patient's mental status returned to normal.[1] The reasons for this reaction are not understood, but on the basis of *animal* studies, the authors suggest that the **trimethoprim** component of co-trimoxazole may have competed with amantadine for renal secretion. This resulted in an accumulation of amantadine and led to the adverse effects seen.[1] This interaction is more likely in the elderly because ageing results in a decreased clearance of these and many other drugs. However, it should be noted that both drugs can cause some mental confusion, and also that mental confusion is not an uncommon symptom of infection in the elderly. Another case of amantadine toxicity has been reported in a 27-year-old woman with end-stage renal disease who was also taking co-trimoxazole. As in the other case the authors suggest that the **trimethoprim** component of co-trimoxazole may have competed with amantadine for renal secretion. However, they also note that amantadine toxicity occurred 5 days after the amantadine dose was increased, and during an episode of acute renal failure, which could also account for the toxicity.[2]

These seem to be the only reports of a possible interaction, and therefore their general importance remains uncertain.

1. Speeg KV, Leighton JA, Maldonado AL. Case report: toxic delirium in a patient taking amantadine and trimethoprim-sulfamethoxazole. *Am J Med Sci* (1989) 298, 410–12.
2. Michalski LS, Hantsch CE, Hou SH. Amantadine toxicity in a renal transplant patient. Abstracts of the 2003 North American Congress of Clinical Toxicology Annual Meeting, 93.

Amantadine + Diuretics

A patient has been described who developed amantadine toxicity when given hydrochlorothiazide with triamterene, and another patient taking amantadine developed myoclonic jerks after starting to take spironolactone and altizide.

Clinical evidence

Amantadine toxicity (ataxia, agitation, hallucinations) developed in a patient within a week of starting to take two tablets of *Dyazide* (**hydrochlorothiazide** with **triamterene**) daily. The symptoms rapidly disappeared when all the drugs were withdrawn. In a later study the amantadine plasma levels of this patient rose by about 50% (from 156 to 243 nanograms/mL) after taking the diuretic for 7 days.[1] A further case describes myoclonic jerks in a 64-year-old man after the addition of **spironolactone** and **altizide** to established treatment for Parkinson's disease, which included levodopa with benserazide, amantadine, orphenadrine, imipramine and diazepam. The diuretics were stopped, but the myoclonic jerks only resolved after the amantadine was also stopped.[2]

Mechanism

Uncertain. Amantadine is largely excreted unchanged in the urine and it seems probable that these diuretics reduce its renal clearance.[1]

Importance and management

Published information about an adverse interaction between amantadine and diuretics appears to be limited. There seems to be little reason for avoiding concurrent use, but bear these cases in mind in the event of an unexpected response to treatment.

1. Wilson TW, Rajput AH. Amantadine–Dyazide interaction. *Can Med Assoc J* (1983) 129, 974–5.
2. Chevalier JF, Renier E, Brion S. Œdème et myoclonies chez un parkinsonien traité par Mantadix®. Problème des associations médicamenteuses. *Encephale* (1980) 6, 381–4.

Amantadine + MAOIs or MAO-B inhibitors

An isolated report describes a rise in blood pressure in a patient taking amantadine within 72 hours of taking phenelzine. The use of selegiline with amantadine may increase adverse effects.

Clinical evidence, mechanism, importance and management

A 49-year-old woman taking amantadine 200 mg daily, haloperidol 5 mg daily and flurazepam 30 mg at night was given **phenelzine** 15 mg twice daily for depression. Within 72 hours her blood pressure rose from 140/90 mmHg to 160/110 mmHg. The **phenelzine** was withdrawn, and 24 hours later, the amantadine and haloperidol were withdrawn. The blood pressure remained elevated for a further 72 hours.[1] In contrast, a woman is reported to have successfully and uneventfully taken amantadine 200 mg daily for Parkinson's disease and **phenelzine** 45 mg daily for depression.[2]

The first case appears to be the only reported interaction with amantadine. Its general importance is therefore uncertain, but bear it in mind in case of an unusual response to treatment.

One manufacturer of **selegiline** states that concurrent use of amantadine can lead to an increased occurrence of adverse effects,[3] but no further information is given.

1. Jack RA, Daniel DG. Possible interaction between phenelzine and amantadine. *Arch Gen Psychiatry* (1984) 41, 726.
2. Greenberg R, Meyers BS. Treatment of major depression and Parkinson's disease with combined phenelzine and amantadine. *Am J Psychiatry* (1985) 142, 273–4.
3. Zelapar (Selegiline hydrochloride). Cephalon Ltd. UK summary of product characteristics, September 2008.

Amantadine + Miscellaneous

Amantadine has antimuscarinic adverse effects and therefore may interact in the same way as the antimuscarinics.

Clinical evidence, mechanism, importance and management

The adverse effects of amantadine resemble those of antimuscarinic drugs. The manufacturers of amantadine note[1,2] that it may interact with a number of drugs, presumably somewhat based on the way these antimuscarinics are known to interact. They name alcohol (consider 'Alcohol + Antimuscarinics', p.51), antimuscarinics (consider 'Antimuscarinics + Antimuscarinics', p.786), antipsychotics (consider 'Antipsychotics + Antimuscarinics', p.833), and levodopa (consider 'Levodopa + Antimuscarinics', p.796).

1. Symmetrel (Amantadine hydrochloride). Alliance Pharmaceuticals. UK Summary of product characteristics, January 2008.
2. Symmetrel (Amantadine hydrochloride). Endo Pharmaceuticals Inc. US Prescribing information, May 2007.

Amantadine + Phenylpropanolamine

The use of amantadine in a patient also taking phenylpropanolamine resulted in psychosis, and concurrent use in another patient resulted in intense and recurrent déjà vu experiences.

Clinical evidence, mechanism, importance and management

A case report describes the development of severe psychosis in a woman within 7 to 8 days of starting amantadine 100 mg [frequency unclear but possibly twice daily] and phenylpropanolamine 80 mg daily. The reasons are not known, but both drugs alone, and in high doses sometimes cause psychosis, and concurrent use may enhance this effect.[1] Another report describes intense and recurrent déjà vu experiences in a 39-year-old man taking amantadine 100 mg twice daily and phenylpropanolamine 25 mg twice daily during a viral infection. These experiences stopped the day he discontinued the drugs. He had previously taken phenylpropanolamine

without this effect. The authors considered the déjà vu experiences to be related to increased dopamine activity caused by both drugs.[2]

Concurrent use need not be avoided, but remain aware of the potential for this interaction.

1. Stroe AE, Hall J, Amin F. Psychotic episode related to phenylpropanolamine and amantadine in a healthy female. *Gen Hosp Psychiatry* (1995) 17, 457–8.
2. Taiminen T, Jääskeläinen SK. Intense and recurrent déjà vu experiences related to amantadine and phenylpropanolamine in a healthy male. *J Clin Neurosci* (2001) 8, 460–2.

Amantadine + Quinidine or Quinine

In a single-dose study, quinidine and quinine modestly reduced the loss of amantadine in the urine in men, but not women.

Clinical evidence, mechanism, importance and management

Single-dose studies into the renal excretion of amantadine in healthy subjects found that quinine sulfate 200 mg and quinidine sulfate 200 mg reduced the renal clearance of oral amantadine 3 mg/kg by about 30%, but only in male subjects.[1] Whether the long-term use of these drugs would therefore cause a clinically relevant rise in serum amantadine levels is uncertain. However, the absence of any clinical reports suggests it is unlikely. Nevertheless, be aware that amantadine toxicity (e.g. headache, nausea, or dizziness) could possibly result from the concurrent use of quinine or quinidine.

1. Gaudry SE, Sitar DS, Smyth DD, McKenzie JK, Aoki FY. Gender and age as factors in the inhibition of renal clearance of amantadine by quinine and quinidine. *Clin Pharmacol Ther* (1993) 54, 23–7.

Amantadine + Tobacco

Amantadine clearance was not altered by tobacco smoking in one study.

Clinical evidence, mechanism, importance and management

The elimination of a single 3-mg/kg dose of amantadine was compared between heavy smokers (20 or more cigarettes daily) and non-smokers.

Although a higher apparent volume of distribution was noted in the heavy smokers, renal and plasma clearances were unchanged, suggesting that no interaction of note occurs.[1]

1. Wong LTY, Sitar DS, Aoki FY. Chronic tobacco smoking and gender as variables affecting amantadine disposition in healthy subjects. *Br J Clin Pharmacol* (1995) 39, 81–4.

Antimuscarinics + Antimuscarinics

Additive antimuscarinic effects, both peripheral and central, can develop if two or more drugs with antimuscarinic effects are used together. The outcome may be harmful.

Clinical evidence, mechanism, importance and management

The antimuscarinic (sometimes called anticholinergic) effects of some drugs are exploited therapeutically. These include antimuscarinic bronchodilators, gastrointestinal antispasmodics, mydriatics, urological antimuscarinics, and drugs such as **trihexyphenidyl** and **benzatropine** (see 'Table 18.1', (p.784)), which are used for the control of parkinsonian symptoms. Other drugs, such as some antiemetics, sedating antihistamines, antipsychotics, and tricyclic antidepressants, (see 'Table 18.2', (below)), may also possess some antimuscarinic effects that are unwanted and troublesome, but usually not serious, unless they are worsened by the addition of another drug with similar properties.

The easily recognised and common peripheral antimuscarinic effects are blurred vision, dry mouth, constipation, difficulty in urination, reduced sweating and tachycardia. Central effects include confusion, disorientation, visual hallucinations, agitation, irritability, delirium, memory problems, belligerence and even aggressiveness. Problems are most likely to arise in patients with particular physical conditions such as glaucoma, prostatic hypertrophy or constipation, in whom antimuscarinic drugs should be used with caution, if at all. It has been pointed out that the antimuscarinic adverse effects can mimic the effects of normal ageing.

'Table 18.1', (p.784) and 'Table 18.2', (below) list many of the drugs with antimuscarinic effects, which may be expected to be additive if used together, but apart from some reports describing life-threatening reactions (see 'Antipsychotics + Antimuscarinics', p.833) there are very few reports describing this simple additive interaction, probably because the outcome is so obvious. Many of these interactions are therefore theoretical but their probability is high.

Some drugs with only minimal antimuscarinic properties sometimes cause difficulties if given with other antimuscarinics. A patient taking **isopropamide iodide** developed urinary retention needing catheterisation, only when **trazodone** 75 mg daily was also taken, but not when either drug was taken alone.[1] **Trazodone** is usually regarded as having minimal antimuscarinic effects. Another case describes acute psychosis in an elderly woman taking **hyoscine** and **meclozine**, both of which have antimuscarinic effects.[2]

If the central antimuscarinic effects caused by the use of antimuscarinic drugs are not clearly recognised for what they are, there is the risk that antipsychotics may be prescribed to treat them. Many antipsychotics also have antimuscarinic adverse effects so that matters are simply made worse. If the patient then demonstrates dystonias, akathisia, tremor and rigidity, even more antimuscarinics may be added to control the extrapyramidal effects, which merely adds to the continuing downward cycle of drug-induced problems.

In addition to the obvious and very well recognised drugs with antimuscarinic effects, a study of the 25 drugs most commonly prescribed for the elderly identified detectable antimuscarinic activity (using an antimuscarinic radioreceptor assay) in 14 of them, 9 of which (**codeine**, **digoxin**, **dipyridamole**, **isosorbide dinitrate**, **nifedipine**, **prednisolone**, **ranitidine**, **theophylline**, and **warfarin**) produced levels of antimuscarinic activity that have been shown to cause significant impairment in tests of memory and attention in the elderly.[3] Thus the problem may not necessar-

Table 18.2 Drugs with antimuscarinic effects (main or adverse effects)

Group	*Drugs*
Antiarrhythmics	Disopyramide, Propafenone
Antiemetics	Cyclizine, Dimenhydrinate, Hyoscine (Scopolamine), Meclozine
Antihistamines	Brompheniramine, Chlorphenamine, Cyproheptadine, Diphenhydramine, Hydroxyzine, Promethazine, Tripelennamine, Triprolidine
Antiparkinsonian drugs (Antimuscarinics)	see Table 18.1, p.784
Antipsychotics	Chlorpromazine, Chlorprothixene, Clozapine, Loxapine, Mesoridazine, Perphenazine, Pimozide, Thioridazine, Trifluoperazine
Antispasmodics	Anisotropine, Atropine, Belladonna alkaloids, Dicycloverine (Dicyclomine), Flavoxate, Hyoscine (Scopolamine), Hyoscyamine, Isopropamide, Propantheline
Antiulcer drugs	Clidinium, Hexocyclium, Isopropamide, Mepenzolate, Methanthelinium, Oxyphencyclimine, Pirenzepine, Tridihexethyl
Bronchodilators	Ipratropium, Tiotropium
Cycloplegic mydriatics	Atropine, Cyclopentolate, Homatropine, Hyoscine (Scopolamine), Tropicamide
Muscle relaxants	Baclofen, Cyclobenzaprine, Orphenadrine
Peripheral vasodilator	Papaverine
Tricyclic and related antidepressants	Amitriptyline, Amoxapine, Clomipramine, Desipramine, Doxepin, Imipramine, Maprotiline, Protriptyline, Nortriptyline, Trimipramine
Urinary antimuscarinics	Darifenacin, Oxybutynin, Solifenacin, Tolterodine, Trospium

After Barkin RL, Stein ZLG. *South Med J* (1989) 82, 1547, and others.
The categorization is not exclusive; some of these drugs are used for a range of effects. There are many other antimuscarinic drugs.

ily be confined to those drugs that have well recognised antimuscarinic properties.

1. Chan CH, Ruskiewicz RJ. Anticholinergic side effects of trazodone combined with another pharmacologic agent. *Am J Psychiatry* (1990) 147, 533.
2. Osterholm RK, Camoriano JK. Transdermal scopolamine psychosis. *JAMA* (1982) 247, 3081.
3. Tune L, Carr S, Hoag E, Cooper T. Anticholinergic effects of drugs commonly prescribed for the elderly: potential means for assessing risk of delirium. *Am J Psychiatry* (1992) 149, 1393–4.

Antimuscarinics + Areca (Betel nuts)

The control of the extrapyramidal (parkinsonian) adverse effects of fluphenazine and flupenthixol with procyclidine was lost in two patients when they began to chew areca.

Clinical evidence

An Indian patient receiving depot fluphenazine (50 mg every 3 weeks) for schizophrenia, and with mild parkinsonian tremor controlled with **procyclidine** 5 mg twice daily, developed marked rigidity, bradykinesia and jaw tremor when he began to chew areca. The symptoms were so severe he could barely speak. When he stopped chewing areca his stiffness and abnormal movements disappeared. Another patient receiving depot flupenthixol developed marked stiffness, tremor and akathisia when he began to chew areca, despite taking up to 20 mg of **procyclidine** daily. The symptoms vanished within 4 days of stopping the areca.[1]

Mechanism

Areca contains arecoline, an alkaloid with cholinergic activity, which could therefore oppose the antimuscarinic (anticholinergic) actions of procyclidine. As the procyclidine was being used to control the extrapyramidal adverse effects of the two antipsychotics, opposing its action allowed the adverse effects to re-emerge and worsen.

Importance and management

Direct information seems to be limited to this report but the interaction would seem to be established and clinically important. Patients taking antimuscarinic drugs for the control of drug-induced extrapyramidal (parkinsonian) adverse effects, or Parkinson's disease, should avoid areca (betel nuts). Betel is traditionally chewed by those from the continent of Asia, and the East Indies. The authors of this report suggest that a dental inspection for the characteristic red stains of the areca may possibly provide a simple explanation for the sudden and otherwise mysterious deterioration in the symptoms of patients. Symptoms seem to develop over a period of 2 weeks, and resolve fairly rapidly (within a week).

1. Deahl M. Betel nut-induced extrapyramidal syndrome: an unusual drug interaction. *Mov Disord* (1989) 4, 330–3.

Antimuscarinics + SSRIs

Nine patients developed delirium when given fluoxetine, paroxetine or sertraline with benzatropine, in the presence of an antipsychotic (usually perphenazine or haloperidol).

Clinical evidence

Five patients became confused and developed delirium when given an antipsychotic, an SSRI (4 taking **fluoxetine** and one taking **paroxetine**) and **benzatropine**. No peripheral antimuscarinic toxicity was seen. The delirium developed within 2 days in two cases, but took several weeks to appear in another. The authors also very briefly mention two other patients who became delirious when given an unnamed antipsychotic and either **sertraline** or **paroxetine** with **benzatropine**.[1] Another case describes delirium in a 17-year-old boy, 8 days after **paroxetine** was added to his medication, which included **benzatropine** and haloperidol. Serum levels of **benzatropine** were markedly increased.[2] A further case report describes delirium in a 26-year-old woman taking **sertraline** 200 mg daily, haloperidol up to 9 mg daily, and lithium 900 mg daily after **benzatropine** 5 mg daily was added to her medication, to treat an episode of parkinsonism.[3] In contrast, another report describes 12 patients taking **fluoxetine** and perphenazine who also received **benzatropine** 1 mg daily without showing signs of delirium.[4,5]

The manufacturers note that **paroxetine** 30 mg daily increased the AUC, maximum and minimum plasma levels of **procyclidine** 5 mg daily by 35%, 37%, and 67%, respectively.[6]

Mechanism

The authors of the first report attributed these effects to an interaction between the SSRIs and benzatropine, speculating that the SSRIs may have inhibited the metabolism of the benzatropine thereby increasing its toxicity. Alternatively they suggest a possible additive central antimuscarinic effect. It is noteworthy that 4 of the first group of patients were given perphenazine and one haloperidol,[1] which have been involved in additive antimuscarinic interactions (see 'Antipsychotics + Antimuscarinics', p.833). Also note that adverse interactions have been reported with the use of haloperidol and SSRIs, see 'Haloperidol + SSRIs', p.887.

Importance and management

The general clinical importance of this interaction is uncertain, but it would seem prudent to be alert for evidence of confusion and possible delirium in patients given SSRIs with benzatropine, particularly if they are also taking other psychotropics that may have antimuscarinic actions. The authors of the first report say that they have not seen delirium with combinations of SSRIs (not named) and other antimuscarinic drugs such as **biperiden** and **diphenhydramine**.[1] If antimuscarinic effects are seen in patients taking paroxetine and procyclidine, the dose of procyclidine should be reduced.[6,7]

1. Roth A, Akyol S, Nelson JC. Delirium associated with the combination of a neuroleptic, an SSRI, and benztropine. *J Clin Psychiatry* (1994) 55, 492–5.
2. Armstrong SC, Schweitzer SM. Delirium associated with paroxetine and benztropine combination. *Am J Psychiatry* (1997) 154, 581–2.
3. Byerly MJ, Christensen RC, Evans DL. Delirium associated with a combination of sertraline, haloperidol, and benztropine. *Am J Psychiatry* (1996) 153, 965–6.
4. Rothschild AJ, Samson JA, Bessette MP, Carter-Campbell JT. Efficacy of the combination of fluoxetine and perphenazine in the treatment of psychotic depression. *J Clin Psychiatry* (1993) 54, 338–42.
5. Rothschild AJ. Delirium: an SSRI-benztropine adverse effect? *J Clin Psychiatry* (1995) 56, 537.
6. Paxil (Paroxetine hydrochloride). GlaxoSmithKline. US Prescribing information, August 2009.
7. Kemadrin (Procyclidine hydrochloride). GlaxoSmithKline UK. UK Summary of product characteristics, May 2008.

Apomorphine + Antihypertensives

The hypotensive adverse effects of apomorphine may possibly be increased by nitrates, calcium-channel blockers and alpha blockers. There is some evidence that ACE inhibitors, beta blockers and diuretics do not generally increase the risk of hypotension with apomorphine.

Clinical evidence

(a) ACE inhibitors

A single 5-mg sublingual dose of apomorphine produced no clinically relevant changes in heart rate or blood pressure in 25 patients taking ACE inhibitors [not specifically named]. One patient experienced symptomatic hypotension.[1]

(b) Alpha blockers

A single 5-mg sublingual dose of apomorphine caused a greater decrease in systolic blood pressure from supine to standing in 24 patients taking alpha blockers [not specifically named] when compared with placebo (decrease in systolic blood pressure of 23 mmHg versus 13 mmHg at 40 minutes post dose). One patient experienced symptomatic hypotension.[1]

(c) Beta blockers

A single 5-mg sublingual dose of apomorphine produced no clinically relevant changes in heart rate or blood pressure in 26 patients taking beta blockers [not specifically named]. One patient experienced syncope and one had symptomatic hypotension.[1]

(d) Calcium-channel blockers

A single 5-mg sublingual dose of apomorphine caused a greater decrease in systolic blood pressure from supine to standing in 26 patients taking calcium-channel blockers [not specifically named] when compared with pla-

cebo (decreased in systolic blood pressure of 17 mmHg versus 11 mmHg at 20 minutes post dose).[1]

(e) Diuretics

A single 5-mg sublingual dose of apomorphine produced no clinically relevant changes in heart rate or blood pressure in 21 patients taking diuretics [not specifically named]. One patient experienced symptomatic hypotension.[1]

(f) Nitrates

1. Short-acting. A single 5-mg sublingual dose of apomorphine produced no clinically relevant changes in heart rate or blood pressure in 20 patients taking short-acting nitrates. The apomorphine was given 30 minutes before the patient took their short-acting nitrate. Two patients experienced symptomatic hypotension after their sublingual glyceryl trinitrate.[1]

2. Long-acting. A single 5-mg sublingual dose of apomorphine caused a greater decrease in systolic blood pressure from supine to standing in 20 patients taking long-acting nitrates when compared with placebo (decrease in systolic blood pressure of 12 mmHg versus 6 mmHg at 50 minutes post dose). Two patients experienced symptomatic hypotension.[1]

Mechanism

Apomorphine alone may cause postural hypotension, and this is potentially additive with the effects of vasoactive antihypertensives and nitrates.

Importance and management

A potentially clinically relevant interaction resulting in orthostatic hypotension may occur when sublingual apomorphine is given to patients taking calcium-channel blockers or alpha blockers. Similarly, symptomatic hypotension on standing may be more common in patients taking nitrates. Note that the 5-mg dose used in the study was slightly higher than the recommended 2- to 3-mg sublingual dose commonly used for erectile dysfunction. All the patients who had symptomatic hypotension experienced a prodrome of symptoms such as nausea, dizziness, pallor, and/or sweating.[1] The manufacturer of apomorphine used subcutaneously for Parkinson's disease suggests caution in patients taking antihypertensives[2] and on the basis of the study mentioned above[1], particular caution should be taken with nitrates. In practice, this means telling patients what may possibly happen and what to do if adverse effects occur (i.e. do not attempt to stand up, but lie down and raise their legs until the symptoms resolve). Note that apomorphine should be given with caution to patients with cardiovascular disease.[2]

1. Fagan TC, Buttler S, Marbury T, Taylor A, Edmonds A, and the SL APO study group. Cardiovascular safety of sublingual apomorphine in patients on stable doses of oral antihypertensive agents and nitrates. *Am J Cardiol* (2001) 88, 760–6.
2. APO-go Ampoules (Apomorphine hydrochloride). Britannia Pharmaceuticals Ltd. UK Summary of product characteristics, July 2009.

Apomorphine + COMT inhibitors

Entacapone had no effect on the pharmacokinetics or efficacy of apomorphine in a single-dose study. Similarly, tolcapone had no relevant effect on the pharmacokinetics of a single dose of apomorphine.

Clinical evidence

(a) Entacapone

In a placebo-controlled, crossover study in 24 patients with Parkinson's disease a single dose of entacapone 200 mg or 400 mg given 30 minutes before a subcutaneous injection of apomorphine had no effect on the pharmacokinetics of apomorphine. In addition, entacapone had no effect on measures of apomorphine efficacy (tapping test and incidence of dyskinesias).[1]

(b) Tolcapone

In 5 patients with Parkinson's disease, tolcapone 200 mg three times daily for 5 days then 200 mg one hour before sublingual apomorphine 40 mg caused a non-significant increase in the AUC of apomorphine of about 13%.[2]

Mechanism

In vitro and *animal* data suggested that the enzyme catechol-*O*-methyl transferase (COMT) is involved in the metabolism of apomorphine[3] and that COMT inhibitors might increase apomorphine bioavailability. However, the single dose studies above suggest that this metabolic pathway for apomorphine may not be important in humans.

Importance and management

The evidence from these single-dose studies suggest that there is no pharmacokinetic interaction between entacapone or tolcapone and apomorphine, and that the drugs can be used together without alteration of the apomorphine dose. However, further data are required from longer-term concurrent use to confirm this. Until more is known, increased monitoring during concurrent use of COMT inhibitors and apomorphine may be prudent, in order to detect any apomorphine adverse effects that may develop.

1. Zijlmans JCM, Debilly B, Rascol O, Lees AJ, Durif F. Safety of entacapone and apomorphine coadministration in levodopa-treated Parkinson's disease patients: pharmacokinetic and pharmacodynamic results of a multicenter, double-blind, placebo-controlled, cross-over study. *Mov Disord* (2004) 19, 1006–11.
2. Ondo WG, Hunter C, Vuong KD, Jankovic VJ. The pharmacokinetic and clinical effects of tolcapone on a single dose of apomorphine in Parkinson's disease. *Parkinsonism Relat Disord* (2000) 6, 237–40.
3. Coudoré F, Durif F, Duroux E, Eschalier A, Fialip J. Effect of tolcapone on plasma and striatal apomorphine disposition in rats. *Neuroreport* (1997) 8, 877–80.

Apomorphine + Hormonal contraceptives

The sedative effects of apomorphine were decreased by an oral combined hormonal contraceptive in one study.

Clinical evidence, mechanism, importance and management

A study in a group of 9 women found that the sedative effects of a single 5-micrograms/kg subcutaneous dose of apomorphine were decreased when they were taking an oral combined hormonal contraceptive (**ethinylestradiol** 30 micrograms, **levonorgestrel** 150 or 250 micrograms).[1] The clinical importance of this is uncertain.

1. Chalmers JS, Fulli-Lemaire I, Cowen PJ. Effects of the contraceptive pill on sedative responses to clonidine and apomorphine in normal women. *Psychol Med* (1985) 15, 363–7.

Apomorphine + Miscellaneous

The concurrent use of apomorphine and other drugs used for erectile dysfunction or dopamine antagonists is not recommended. Domperidone and prochlorperazine are said not to interact when apomorphine is used for erectile dysfunction, and domperidone is the recommended antiemetic when apomorphine is used for Parkinson's disease. There have been reports of profound hypotension when ondansetron was used with apomorphine. There appears to be no evidence that antidepressants or antiepileptics interact adversely with apomorphine.

Clinical evidence, mechanism, importance and management

(a) Antidepressants

An analysis of phase II/III studies found no difference in the efficacy of sublingual apomorphine for erectile dysfunction in patients receiving antidepressants, nor was there any significant difference in the adverse effects reported, when compared with the general study population.[1] In a study in 7 patients with Parkinson's disease, **fluoxetine** 20 mg given twice daily for about 11 days did not alter the apomorphine-induced decrease in parkinsonian motor disability, but it did result in an improvement in the dyskinesias induced by apomorphine.[2]

(b) Antiemetics

The small doses of apomorphine used for erectile dysfunction (2 to 3 mg) do not normally cause vomiting, but nausea does occur in about 7% of patients and the manufacturer reported that interaction studies and/or clinical experience has shown that **domperidone**, **ondansetron** or **prochlorperazine** can safely be given as antiemetics in this patient group (but see below for use in Parkinson's disease).[3] Studies with other antiemetics have not been carried out, so concurrent use was not recommended.[3]

Note that **prochlorperazine** should not be given if apomorphine is used for Parkinson's disease, as its dopamine antagonist actions can worsen the disease. It is possible that the use of the dopamine antagonist, **metoclopramide**, may diminish the effects of apomorphine[4] (see also 'Levodopa + Antiemetics', p.796). Because apomorphine is highly emetogenic at the doses required for the treatment of Parkinson's disease (1 to 4 mg/hour by subcutaneous infusion), patients with Parkinson's disease requiring apomorphine should be pretreated with **domperidone** 20 mg three times daily for at least 2 days.[5] Rarely, extrapyramidal adverse effects have been reported with **ondansetron**,[6] which may be of relevance in patients with Parkinson's disease. However, the US manufacturer of apomorphine injection, indicated for the management of Parkinson's disease, contraindicates the concurrent use of 5-HT_3 receptor antagonists based on reports of profound hypotension and loss of consciousness when **ondansetron** was given with apomorphine; they name **alosetron**, **dolasetron**, **granisetron**, **ondansetron** and **palonosetron**.[4]

(c) Antiepileptics

The manufacturer of a preparation of apomorphine used for erectile dysfunction noted that no studies about interactions between apomorphine and antiepileptics have been undertaken, but clinical experience in erectile dysfunction suggests that no interaction occurs.[3]

(d) Antipsychotics

The manufacturer of a preparation of apomorphine used for erectile dysfunction, advised that apomorphine should not be given with centrally-acting dopamine antagonists[3] because potentially they may antagonise the effects of apomorphine. Such drugs would include some antipsychotics. Some manufacturers recommend that if neuroleptics are necessary in patients with Parkinson's disease receiving dopamine agonists, the dopamine agonist should be progressively reduced (and then stopped[7]), as sudden withdrawal may cause neuroleptic malignant syndrome.[5,7]

The manufacturer of *APO-go* specifically notes that there is a potential interaction between **clozapine** and apomorphine, although they say that **clozapine** may also be used to reduce the symptoms of neuropsychiatric complications of Parkinson's disease.[5]

(e) Other dopamine agonists

One manufacturer advised that apomorphine, used for erectile dysfunction, should not be given with other centrally-acting dopamine agonists.[3] See 'Table 18.1', (p.784) for a list of these drugs.

(f) Other drugs used for erectile dysfunction

One manufacturer reported that although no formal studies had been done with a combination of apomorphine and other drugs used for erectile dysfunction, there seemed to be no evidence of problems, nevertheless concurrent use was not recommended.[3] Other drugs used for this condition include **alprostadil**, **moxisylyte**, **papaverine**, **phentolamine**, and the **phosphodiesterase type-5 inhibitors** such as **sildenafil**. A study using a combination of up to three of apomorphine, **papaverine** and **phentolamine**, found that the lowest incidence of treatment-related adverse effects occurred with apomorphine and **phentolamine** (9.8%), a higher incidence with **papaverine** and **phentolamine** (16.7%) and the highest incidence with all three drugs (17.5%).[8]

1. Heaton J, Sleep D, Perdok R, Rescek ME. Uprima (apomorphine SL) 2 and 3 mg is well-tolerated and effective in men with erectile dysfunction (ED) concurrently taking antidepressant medication. *Eur Urol Suppl* (2002) (Suppl 1), 153.
2. Durif F, Vidailhet M, Bonnet AM, Blin J, Agid Y. Levodopa-induced dyskinesias are improved by fluoxetine. *Neurology* (1995) 45, 1855–8.
3. Uprima (Apomorphine hydrochloride). Abbott Laboratories Ltd. UK Summary of product characteristics, September 2004.
4. Apokyn (Apomorphine hydrochloride). Tercica Inc. US Prescribing information, April 2009.
5. APO-go Ampoules (Apomorphine hydrochloride). Britannia Pharmaceuticals Ltd. UK Summary of product characteristics, July 2009
6. Zofran (Ondansetron hydrochloride dihydrate). GlaxoSmithKline UK. UK Summary of product characteristics, October 2009.
7. Britannia Pharmaceuticals Ltd. Personal Communication, March 2006.
8. Lammers PI, Rubio-Aurioles E, Castell R, Castaneda J, Ponce de Leon R, Hurley D, Lipezker M, Loehr LA, Lowrey F. Combination therapy for erectile dysfunction: a randomized, double blind, unblinded active-controlled, cross-over study of the pharmacodynamics and safety of combined oral formulations of apomorphine hydrochloride, phentolamine mesylate and papaverine hydrochloride in men with moderate to severe erectile dysfunction. *Int J Impot Res* (2002) 14, 54–9.

Bromocriptine and other dopamine agonists + ACE inhibitors

A single report describes severe hypotension when a patient taking lisinopril was given pergolide. Dopamine agonists are well known to be associated with hypotensive reactions during the first few days of treatment.

Clinical evidence

A man successfully treated for hypertension with **lisinopril** 10 mg daily experienced a severe hypotensive reaction within 4 hours of taking a single 50-microgram dose of **pergolide** for periodic leg movements during sleep. He needed hospitalisation and treatment with intravenous fluids.[1]

Mechanism

All dopamine agonists can cause hypotensive reactions during the first few days of treatment. It is not clear whether this patient was extremely sensitive to pergolide or whether what occurred was due to an interaction. However, it is not unreasonable to assume that the hypotensive effects of dopamine agonists and ACE inhibitors might be additive.

Importance and management

Evidence for an interaction between the dopamine agonists and ACE inhibitors appears to be limited to this isolated case, but what happened is in line with the known effects of both classes of drug. Postural hypotension on starting dopamine agonists is a well recognised adverse effect, but this appears to be the only report that this might be of more concern in patients taking antihypertensives. The manufacturers of pergolide recommend caution when it is given with antihypertensives because of the risk of postural and/or sustained hypotension. The authors of the case report suggest that in patients taking antihypertensives the initial dose of pergolide should be 25 micrograms.[1] It would seem prudent to exercise extra caution with the initial use of pergolide and other dopamine agonists in patients taking ACE inhibitors.

1. Kando JC, Keck PE, Wood PA. Pergolide-induced hypotension. *Ann Pharmacother* (1990) 24, 543.

Bromocriptine and other dopamine agonists + Antiemetics

Domperidone and metoclopramide would be expected to reduce the prolactin-lowering effect of bromocriptine. The hypotensive effect of bromocriptine has also been reduced by metoclopramide and domperidone. Metoclopramide, but not domperidone, would be expected to reduce the antiparkinsonian effect of any dopamine agonist.

Metoclopramide does not affect the overall bioavailability of bromocriptine. The pharmacokinetics of ropinirole or rotigotine are not affected by domperidone.

Clinical evidence, mechanism, importance and management

(a) Effect on Parkinson's disease

Dopamine agonists frequently cause nausea and vomiting on starting treatment. The manufacturers of bromocriptine,[1] **lisuride**,[2] and **pergolide**[3] state that, if necessary, this may be reduced by taking a peripheral dopamine antagonist such as **domperidone**. **Metoclopramide** is not considered a suitable antiemetic for use in Parkinson's disease because it crosses the blood brain barrier and has central dopamine antagonist effects, and may therefore reduce the efficacy of dopamine agonists in this condition, see also 'Levodopa + Antiemetics', p.796. In a single-dose study in 10 patients with Parkinson's disease, giving **metoclopramide** before bromocriptine resulted in a slight reduction in clinical response to bromocriptine in some patients.[4] The manufacturers of **cabergoline**,[5] **ropinirole**,[6] and **rotigotine**[7] advise against the use of metoclopramide for this reason.

(b) Pharmacokinetic effects

In a study, 7 healthy subjects were given a single 7.5-mg dose of bromocriptine alone or with a single 500-microgram/kg intravenous dose of **metoclopramide**, after a standardised breakfast and after an overnight fast. The bioavailability of bromocriptine was unaffected by the concurrent use of **metoclopramide**, but the time to reach the maximum plasma level of bromocriptine, after fasting, was reduced by 30% by metoclopramide.[8]

In a study in 10 patients with Parkinson's disease, giving a single 60-mg dose of **metoclopramide** before single doses of up to 100 mg of bromocriptine caused a slight increase in peak plasma bromocriptine levels in some patients, which occurred a little earlier than when bromocriptine was given alone. However, these changes did not result in any change in clinical outcomes.[4]

In a single-dose study in 9 healthy subjects, giving **domperidone** 20 mg one hour before **ropinirole** 800 micrograms did not alter the pharmacokinetics of **ropinirole**.[9]

In a crossover study, 16 healthy subjects applied a **rotigotine** patch 2 mg/24 hours daily for 4 days with or without **domperidone** 10 mg three times daily for 5 days. The pharmacokinetics of rotigotine were not affected by concurrent domperidone, and no dose adjustment is likely to be required on concurrent use.[10]

(c) Prolactin-lowering effect

Both **domperidone** and **metoclopramide** are dopamine antagonists and can raise prolactin levels, sometimes causing galactorrhoea, gynaecomastia or mastalgia.[11,12] They would therefore be expected to reduce the prolactin-lowering effect of bromocriptine.[1] However, an early study in 10 patients with Parkinson's disease given single doses of bromocriptine 12.5 to 100 mg found that pretreatment with a single 60-mg dose of **metoclopramide** had no consistent effect on plasma bromocriptine levels or on the clinical or hormonal response,[4] although this does not seem to have been studied in a multiple dose study. Further, in a single-dose study in 9 healthy subjects, a single 20-mg dose of **domperidone** increased the plasma level of prolactin whereas a single 800-microgram dose of **ropinirole** given alone reduced it. Giving **ropinirole** one hour after **domperidone** tended to blunt the response of prolactin to domperidone, but the differences were small and not likely to be clinically significant.[9] Nevertheless, it would be prudent to monitor the efficacy of bromocriptine and other dopamine agonists used for their effect on prolactin if **domperidone** or **metoclopramide** are required.

(d) Other effects

In a placebo-controlled study, 9 patients with hypertension received a single 2.5-mg dose of bromocriptine after taking **metoclopramide** 30 mg daily for one week. Bromocriptine alone reduced blood pressure from 163/93 mmHg to 143/82 mmHg, three hours after administration, but this hypotensive effect was not seen after pretreatment with **metoclopramide**. Plasma renin activity and plasma aldosterone levels were reduced after taking bromocriptine alone, but after pretreatment with **metoclopramide**, bromocriptine did not cause any significant changes in these hormonal parameters.[13] Similar results were seen in a study in which a single 2.5-mg dose of bromocriptine was given after the subjects took **domperidone** 30 mg daily for a week.[14]

In a placebo-controlled, crossover study, 9 healthy subjects took a single 20-mg dose of **domperidone** followed, one hour later, by a single 800-microgram dose of **ropinirole**. There was no significant difference in the effects on supine blood pressure when each drug was taken alone or together, but pretreatment with **domperidone** prevented orthostatic reactions to **ropinirole** in all but one subject.[9]

1. Parlodel (Bromocriptine mesilate). Meda Pharmaceuticals. UK Summary of product characteristics, November 2007.
2. Lisuride. Cambridge Laboratories. UK Summary of product characteristics, January 2001.
3. Celance (Pergolide mesilate). Eli Lilly and Company Ltd. UK Summary of product characteristics, August 2009.
4. Price P, Debono A, Parkes JD, Marsden CD, Roenthaler J. Plasma bromocriptine levels, clinical and growth hormone responses in parkinsonism. *Br J Clin Pharmacol* (1978) 6, 303–9.
5. Cabaser (Cabergoline). Pharmacia Ltd. UK Summary of product characteristics, December 2008.
6. Requip (Ropinirole hydrochloride). GlaxoSmithKline UK. UK Summary of product characteristics, September 2009.
7. Neupro (Rotigotine). UCB Pharma Ltd. UK Summary of product characteristics, August 2009.
8. Kopitar Z, Vrhovac B, Povšič L, Plavšić F, Francetić I, Urbančič J. The effect of food and metoclopramide on the pharmacokinetics and side effects of bromocriptine. *Eur J Drug Metab Pharmacokinet* (1991) 16, 177–81.
9. de Mey C, Enterling D, Meineke I, Yeulet S. Interactions between domperidone and ropinirole, a novel dopamine D_2-receptor agonist. *Br J Clin Pharmacol* (1991) 32, 483–8.
10. Braun M, Cawello W, Boekens H, Horstmann R. Influence of domperidone on pharmacokinetics, safety and tolerability of the dopamine agonist rotigotine. Br J Clin Pharmacol (2009) 67, 209–15.
11. Motilium Suppositories (Domperidone). Winthrop Pharmaceuticals UK Ltd. UK Summary of product characteristics, January 2009.
12. Metoclopramide injection (Metoclopramide hydrochloride). Hameln Pharmaceuticals Ltd. UK Summary of product characteristics, December 2008.
13. Luchsinger A, Grilli M, Forte P, Morales E, Velasco M. Metoclopramide blocks bromocriptine induced antihypertensive effect in hypertensive patients. *Int J Clin Pharmacol Ther* (1995) 33, 509–512.
14. Luchsinger A, Grilli M, Velasco M. Metoclopramide and domperidone block the antihypertensive effect of bromocriptine in hypertensive patients. *Am J Ther* (1998) 5, 81–8.

Bromocriptine and other dopamine agonists + Antipsychotics

Many antipsychotics are dopamine antagonists. Therefore if they are given with dopamine agonists, such as bromocriptine, the effects of both drugs may be expected to be reduced. In particular the antipsychotics are associated with extrapyramidal adverse effects, which would be expected to oppose the effects of bromocriptine and related drugs in treating Parkinsonian symptoms. Case reports describe a reduction in prolactin-lowering effects and the emergence of schizophrenic symptoms in patients given an antipsychotic with a dopamine agonist.

Clinical evidence, mechanism, importance and management

(a) Effect on antipsychotic drug activity

A woman with schizoaffective schizophrenia, taking **molindone** 100 mg and imipramine 200 mg daily, relapsed within 5 days of starting to take bromocriptine 2.5 mg three times daily for amenorrhoea and galactorrhoea.[1] Within 3 days of stopping the bromocriptine the symptoms of relapse (agitation, delusions, and auditory hallucinations) vanished. The reason suggested by the authors of the report is that the bromocriptine (a dopamine agonist) opposed the actions of the antipsychotic medication (dopamine antagonists) thereby allowing the schizophrenia to re-emerge. Limited evidence suggests that levodopa may antagonise the effects of antipsychotics (see 'Levodopa + Antipsychotics', p.797), which adds weight to this theory.

(b) Effect on prolactin levels

A case of reduced prolactin levels has been reported in a man taking **fluphenazine** and **benzatropine** who was given bromocriptine to treat a pituitary tumour. His prolactin level became undetectable, and his psychiatric status was unchanged, although no reduction in tumour size was seen with the bromocriptine.[2] The prolactin levels of a patient with a prolactin-secreting pituitary adenoma fell from almost 8000 nanograms/mL to 400 nanograms/mL when bromocriptine was started, but increased again to 1000 nanograms/mL when he started to take **thioridazine** 25 mg twice daily. As the **thioridazine** dose was increased to 200 mg daily, his prolactin level increased further, to 2000 nanograms/mL, and his visual fields deteriorated. Normal vision returned within 5 days of stopping the **thioridazine**, and his prolactin levels fell to below 500 nanograms/mL.[3]

Other dopamine agonists used for their prolactin-lowering effects would be expected to be similarly affected.

(c) Extrapyramidal effects

Many antipsychotics have dopamine antagonist properties and can cause movement disorders (extrapyramidal effects). For this reason, these drugs can reduce the efficacy of dopamine agonists used in Parkinson's disease, and exacerbate the disorder. This interaction is well established for levodopa: see 'Levodopa + Antipsychotics', p.797, which discusses the relative tendency for various classical and atypical antipsychotics to cause this effect. It would equally well be anticipated for any dopamine agonist.

If an antipsychotic is required for psychosis in Parkinson's disease, the risk-benefit ratio should be carefully assessed, and an antipsychotic chosen that has a lower risk of extrapyramidal effects such as an atypical antipsychotic.

1. Frye PE, Pariser SF, Kim MH, O'Shaughnessy RW. Bromocriptine associated with symptom exacerbation during neuroleptic treatment of schizoaffective schizophrenia. *J Clin Psychiatry* (1982) 43, 252–3.
2. Kellner C, Harris P, Blumhardt C. Concurrent use of bromocriptine and fluphenazine. *J Clin Psychiatry* (1985) 46, 455.
3. Robbins RK, Kern PA, Thompson TL. Interactions between thioridazine and bromocriptine in a patient with a prolactin-secreting pituitary adenoma. *Am J Med* (1984) 76, 921–3.

Bromocriptine and other dopamine agonists + Azoles

Two patients taking cabergoline had improvements in their Parkinson's disease symptoms while taking itraconazole. In one case a 300% increase in cabergoline levels occurred, and the other patient reduced the dose of her medications without adversely affecting disease control. All azoles may interact to a greater or

lesser extent. Bromocriptine is predicted to interact in the same way as cabergoline.

Clinical evidence

A man with Parkinson's disease taking cabergoline 4 mg daily and selegiline 5 mg twice daily was prescribed pulse itraconazole (200 mg twice daily for one week out of four) for a fungal nail infection. At the end of the first week the patient reported improvements in his parkinsonism, which was confirmed by clinical investigation. The improvement gradually decreased during the weeks without itraconazole, and re-emerged while taking the itraconazole. Analysis of cabergoline blood levels found a 300% increase in levels after he had taken itraconazole for a week.[1]

Another similar patient taking cabergoline 2 mg twice daily, selegiline, entacapone, and levodopa with carbidopa, experienced symptoms of overdose (hyperkinesia of the extremities) 3 days after starting itraconazole 200 mg twice daily. She reduced the dose of her Parkinson's medication, and had marked improvement in her usual Parkinson's symptoms, which then gradually reduced after stopping the itraconazole. This was repeated following two additional periods of itraconazole use.[1]

Mechanism

Cabergoline is metabolised by the cytochrome P450 isoenzyme CYP3A4. Itraconazole is a potent inhibitor of this isoenzyme, and would therefore be expected to increase cabergoline levels.

Importance and management

Although evidence is limited, this interaction would be predicted on the basis of the known pharmacokinetics of cabergoline and enzyme-inhibitory effects of itraconazole. It would be prudent to monitor toxicity and efficacy in any patient taking cabergoline requiring itraconazole, or similar potent inhibitors of CYP3A4, which include a number of the azole antifungals. Bromocriptine is metabolised in a similar way to cabergoline, and would be expected to interact similarly. The manufacturer of bromocriptine advises caution on the concurrent use of azole antifungals.[2]

1. Christensen J, Dupont E, Østergaard K. Cabergoline plasma concentration is increased during concomitant treatment with itraconazole. *Mov Disord* (2002) 17, 1360–2.
2. Parlodel (Bromocriptine mesilate). Meda Pharmaceuticals. UK Summary of product characteristics, November 2007.

Bromocriptine and other dopamine agonists + Ergot derivatives

Because cabergoline is an ergot derivative, the manufacturers have looked at what happens if other ergot derivatives are used concurrently, but have so far found no evidence of changes in the efficacy or safety of cabergoline. Nevertheless they do not recommend their concurrent use during long-term treatment with cabergoline.[1] Similarly, the manufacturer of bromocriptine does not recommend concurrent use of other ergot derivatives during the puerperium.[2] It would seem prudent to use similar caution with other dopamine agonists that are ergot derivatives (e.g. lisuride, pergolide), although there appears to be no information available. See also 'Ergot derivatives + Ergot derivatives', p.682, for a description of a number of adverse effects that have occurred as a result of the concurrent use of two ergot derivatives.

1. Dostinex (Cabergoline). Pharmacia Ltd. UK Summary of product characteristics, April 2009.
2. Parlodel (Bromocriptine mesilate). Meda Pharmaceuticals. UK Summary of product characteristics, November 2007.

Bromocriptine and other dopamine agonists + Food

Food does not alter the pharmacokinetics of bromocriptine, cabergoline or lisuride and has little effect on the extent of absorption of ropinirole.

Clinical evidence

(a) Bromocriptine

In a study in 7 healthy subjects, taking a single 7.5-mg dose of bromocriptine after breakfast did not alter the bromocriptine AUC, when compared with the fasted state, although it slightly reduced the maximum plasma level.[1]

(b) Cabergoline

In a study in healthy subjects, the pharmacokinetics of cabergoline did not change when a single 1-mg dose of cabergoline was taken after breakfast, when compared with the fasting state.[2]

(c) Lisuride

Thirty healthy subjects were given lisuride 200 micrograms orally while fasting or with food. It was found that food did not significantly modify either the pharmacokinetics or the pharmacodynamics of lisuride.[3]

(d) Ropinirole

In a study, 12 patients who had achieved ropinirole steady-state levels took a single 2-mg dose after an overnight fast, or after a high-fat breakfast. The mean maximum ropinirole plasma levels were reduced by about 25%, and the median time to reach maximum plasma levels was delayed from 1.25 hours to 4 hours, in the presence of food. The $AUC_{0\text{-}8}$ was reduced by 11% after a high-fat breakfast. The effect of these changes on the patients' Parkinson's disease was not monitored.[4] A study involving 20 patients with Parkinson's disease who received ropinirole 8 mg as a prolonged-release tablet, after fasting or after a high-fat breakfast, found that the AUC and maximum plasma levels of ropinirole were similar when given in the fed or fasted state. Reports of adverse effects were similar between the two groups.[5]

Mechanism

None.

Importance and management

Food had no effect on the pharmacokinetics of the dopamine agonists studied. Food decreased the rate of absorption of ropinirole, but had little effect on the extent of absorption. The manufacturers of bromocriptine, cabergoline, lisuride and ropinirole recommend that they are taken with food.[6-9] These drugs commonly cause nausea and vomiting, especially when they are newly started, and taking them with food may improve tolerability.[7-9] As **rotigotine** is given transdermally, food is not expected to affect its pharmacokinetics.[10]

1. Kopitar Z, Vrhovac B, Povšič L, Plavšić F, Francetić I, Urbančič J. The effect of food and metoclopramide on the pharmacokinetics and side effects of bromocriptine. *Eur J Drug Metab Pharmacokinet* (1991) 16, 177–81.
2. Persiani S, Rocchetti M, Pacciarini MA, Holt B, Toon S, Strolin-Benedetti M. The effect of food on cabergoline pharmacokinetics and tolerability in healthy volunteers. *Biopharm Drug Dispos* (1996) 17, 443–55.
3. Gandon JM, Le Coz F, Kühne G, Hümpel M, Allain H. PK/PD interaction studies of lisuride with erythromycin and food in healthy volunteers. *Clin Pharmacol Ther* (1995) 57, 191.
4. Brefel C, Thalamas C, Rayet S, Lopez-Gil A, Fitzpatrick K, Bullman S, Citerone DR, Taylor AC, Montastruc JL, Rascol O. Effect of food on the pharmacokinetics of ropinirole in parkinsonian patients. *Br J Clin Pharmacol* (1998) 45, 412–15.
5. Tompson DJ, Vearer D. Steady-state pharmacokinetic properties of a 24-hour prolonged-release formulation of ropinirole: results of two randomized studies in patients with Parkinson's disease. *Clin Ther* (2007) 29, 2654–66.
6. Lisuride. Cambridge Laboratories. UK Summary of product characteristics, January 2001.
7. Parlodel (Bromocriptine mesilate). Meda Pharmaceuticals. UK Summary of product characteristics, November 2007.
8. Cabaser (Cabergoline). Pharmacia Ltd. UK Summary of product characteristics, December 2008.
9. Requip (Ropinirole hydrochloride). GlaxoSmithKline UK. UK Summary of product characteristics, September 2009.
10. Neupro (Rotigotine). UCB Pharma Ltd. UK Summary of product characteristics, August 2009.

Bromocriptine and other dopamine agonists + Macrolides

Erythromycin markedly increases bromocriptine levels, and a case of toxicity has been reported. Bromocriptine toxicity also occurred in a patient given josamycin. Clarithromycin increases cabergoline levels, and erythromycin would be expected to interact similarly. Erythromycin has no effect on lisuride levels.

Clinical evidence

(a) Bromocriptine

1. Erythromycin. In 5 healthy subjects, erythromycin estolate 250 mg four times daily for 4 days increased the peak plasma levels and the AUC of a single 5-mg oral dose of bromocriptine by about 360% and 268%, respectively.[1] Another report describes 2 women taking levodopa with carbidopa and bromocriptine for parkinsonism in whom the disease was better controlled when erythromycin was added. Bromocriptine plasma levels were found to be 40 to 50% higher while they were taking erythromycin.[2] An elderly woman taking levodopa and bromocriptine 15 mg developed psychotic symptoms when she took erythromycin, which were attributed to bromocriptine toxicity.[3]

2. Josamycin. An elderly man with Parkinson's disease, which was well-controlled for 10 months with levodopa with benserazide, bromocriptine 70 mg daily and domperidone, was given josamycin 2 g daily for a respiratory infection. Shortly after the first dose he became drowsy with visual hallucinations, and began to have involuntary movements of his limbs, similar to the dystonic and dyskinetic movements seen in choreoathetosis. These adverse effects (interpreted as bromocriptine toxicity) disappeared within a few days of withdrawing the josamycin.[4]

(b) Cabergoline

In a crossover study, 10 healthy subjects received cabergoline 1 mg daily with or without **clarithromycin** 200 mg twice daily for 6 days. The AUC of cabergoline was increased by 162% and its maximum plasma level increased by 176%. The study was repeated with 7 patients with Parkinson's disease already taking cabergoline, and this found that **clarithromycin** increased the average plasma level of cabergoline by about 70%. Three of the patients experienced an improvement in their Parkinson's disease symptoms; none of the patients had adverse effects.[5]

(c) Lisuride

Twelve healthy subjects were given lisuride 200 micrograms orally or 50 micrograms as a 30 minute intravenous infusion after taking **erythromycin** (dose unknown) twice daily for 4 days. Preliminary results showed that **erythromycin** did not significantly modify either the pharmacokinetics or the pharmacodynamics of the lisuride.[6]

Mechanism

The ergot dopamine agonists, bromocriptine and cabergoline, undergo extensive metabolism, most likely by the cytochrome P450 isoenzyme CYP3A4. Erythromycin and clarithromycin (and potentially other macrolides, see 'Ergot derivatives + Macrolides', p.683) inhibit this metabolism, thus significantly elevating bromocriptine and cabergoline plasma levels.[1] *In vitro* study has suggested that bromocriptine is also a substrate of OATP-C (organic anion transporting polypeptide C), which may be inhibited by erythromycin, resulting in reduced hepatic uptake and thus metabolism of bromocriptine.[7] It is also possible that P-glycoprotein may be involved in the transport of these ergot dopamine agonists and that inhibition of P-glycoprotein-mediated excretion by macrolides such as clarithromycin may result in increased plasma levels.[5]

Importance and management

Information seems to be limited to these reports, but the pharmacokinetic interaction would appear to be established. Concurrent use should be well monitored if any of these macrolides (clarithromycin, erythromycin, josamycin) is added to bromocriptine or cabergoline treatment. Note that **azithromycin** does not normally cause enzyme inhibition and so may not interact. Moderately increased levels may be therapeutically advantageous, but grossly elevated levels can be toxic. The authors of one report[1] suggest reducing the bromocriptine dose, while in another case the dose was reduced by 50% to avoid toxicity.[3] The manufacturer of cabergoline advises avoiding the concurrent use of macrolides, and specifically names erythromycin.[8] Preliminary data suggest that dose adjustments are not needed if lisuride is given with erythromycin.

1. Nelson MV, Berchou RC, Kareti D, LeWitt PA. Pharmacokinetic evaluation of erythromycin and caffeine administered with bromocriptine. *Clin Pharmacol Ther* (1990) 47, 694–7.
2. Sibley WA, Laguna JF. Enhancement of bromocriptine clinical effect and plasma levels with erythromycin. *Excerpta Med* (1981) 548, 329–30.
3. Alegre M, Noé E, Martínez Lage JM. Psicosis por interacción de eritromicina con bromocriptina en enfermedad de Parkinson. *Neurologia* (1997) 12, 429.
4. Montastruc JL, Rascol A. Traitement de la maladie de Parkinson par doses élevées de bromocriptine. Interaction possible avec la josamycine. *Presse Med* (1984) 13, 2267–8.
5. Nakatsuka A, Nagai M, Yabe H, Nishikawa N, Nomura T, Moritoyo H, Moritoyo T, Nomoto M. Effect of clarithromycin on the pharmacokinetics of cabergoline in healthy controls and in patients with Parkinson's disease. *J Pharmacol Sci* (2006) 100, 59–64.
6. Gandon JM, Le Coz F, Kühne G, Hümpel M, Allain H. PK/PD interaction studies of lisuride with erythromycin and food in healthy volunteers. *Clin Pharmacol Ther* (1995) 57, 191.
7. Lu W-J, Huang K, Lai M-L, Huang J-D. Erythromycin alters the pharmacokinetics of bromocriptine by inhibition of organic anion transporting polypeptide C-mediated uptake. *Clin Pharmacol Ther* (2006) 80, 421–2.
8. Cabaser (Cabergoline). Pharmacia Ltd. UK Summary of product characteristics, December 2008.

Bromocriptine and other dopamine agonists + Proton pump inhibitors

A single case describes worsening mobility, which was attributed to an interaction between lansoprazole and bromocriptine. The same patient later received bromocriptine and omeprazole without problems. No pharmacokinetic interaction occurred when omeprazole was taken with rotigotine.

Clinical evidence, mechanism, importance and management

(a) Bromocriptine

A 73-year-old man taking levodopa with benserazide and bromocriptine for Parkinson's disease was given **lansoprazole** 15 mg daily to treat reflux oesophagitis. Two days later, the patient exhibited akinesia (more motor difficulties and slowness in movements) associated with frequent falls. **Lansoprazole** was discontinued, and the symptoms had resolved by the following day. About 3 months later the patient took **omeprazole** 20 mg daily, which caused no aggravation of Parkinson's disease over the following 6 months. The authors attribute this case to a possible interaction between **lansoprazole** and bromocriptine,[1] although any mechanism is unclear, especially as **omeprazole** was given without problems. This single unexplained case seems unlikely to be of general significance.

(b) Rotigotine

The pharmacokinetics of rotigotine were unaltered by **omeprazole** 40 mg daily, in healthy subjects.[2]

1. Anglès A, Bagheri H, Saivin S, Montastruc JL. Interaction between lansoprazole and bromocriptine in a patient with Parkinson's disease. *Therapie* (2002) 57, 408–10.
2. Neupro (Rotigotine). UCB Pharma Ltd. UK Summary of product characteristics, August 2009.

Bromocriptine + Griseofulvin

Evidence from a single patient, who was taking bromocriptine for acromegaly, suggests that the effects of bromocriptine can be opposed by griseofulvin.

Clinical evidence, mechanism, importance and management

In a study of the effects of bromocriptine used for the treatment of acromegaly, one patient who initially had a good response to bromocriptine developed resistance to the drug. After a number of months it was found that this patient had subsequently been given griseofulvin 500 mg daily for the treatment of a fungal nail infection. When the griseofulvin was stopped, the bromocriptine was again effective.[1] The mechanism of this interaction and its general importance are unknown.

1. Schwinn G, Dirks H, McIntosh C, Köbberling J. Metabolic and clinical studies on patients with acromegaly treated with bromocriptine over 22 months. *Eur J Clin Invest* (1977) 7, 101–7.

Bromocriptine + Nasal decongestants and related drugs

Adverse effects, including hypertension, severe headache, seizures and psychosis, have been seen in patients taking phenylpropanolamine, pseudoephedrine or isometheptene with or shortly after the use of bromocriptine.

Clinical evidence

Two healthy women who had given birth 3 to 4 days previously, developed severe headaches while taking bromocriptine 2.5 mg twice daily for

milk suppression. After additionally taking three 65-mg doses of **isometheptene mucate**, the headache of one of them markedly worsened, and hypertension with life-threatening ventricular tachycardia and cardiac dysfunction developed. The other woman took two 75-mg doses of **phenylpropanolamine**, and developed grand mal seizures and cerebral vasospasm.[1]

A 32-year-old woman took two 5-mg doses of bromocriptine for milk suppression without any adverse effects following the birth of a child. Within 2 hours of taking a third dose with **phenylpropanolamine** 50 mg she awoke with a very severe headache and was found to have a blood pressure of 240/140 mmHg. She was given 5 mg of intramuscular morphine and her blood pressure became normal within 24 hours. Another 5-mg dose of bromocriptine taken 48 hours after the original dose of **phenylpropanolamine** had the same effect, but the blood pressure rise was less severe (160/120 mmHg).[2]

A case report describes a 37-year-old woman who took bromocriptine for 17 days. Nine days later, she took *Rinurel*, a preparation for colds containing **phenylpropanolamine**, and 90 minutes later she developed a severe headache: cerebral haemorrhagic lesions were detected. It was thought that the phenylpropanolamine was mainly responsible for the vascular effects, but it was also suggested that the recent use of bromocriptine may have contributed to this effect.[3]

A woman who had recently given birth and who had taken bromocriptine 2.5 mg twice daily for 9 days without problems became psychotic shortly after starting to take **pseudoephedrine** 60 mg four times daily.[4]

Mechanism

Not understood. Severe hypertension occasionally occurs with either bromocriptine or phenylpropanolamine given alone. Shortly after giving birth some individuals show increased vascular reactivity, and it could be that all of these factors conspired together to cause the adverse effects seen.[2] Psychosis occasionally occurs after giving birth or with bromocriptine alone, so that in the latter case the addition of pseudoephedrine may have been coincidental.[4]

Importance and management

Direct information seems to be limited to these cases, but the severity of the reactions suggests that it might be prudent for postpartum patients to avoid indirectly-acting sympathomimetics like these (e.g. phenylpropanolamine, ephedrine, pseudoephedrine) while taking bromocriptine. Note that bromocriptine is not recommended for the routine suppression of lactation postpartum.

1. Kulig K, Moore LL, Kirk M, Smith D, Stallworth J, Rumack B. Bromocriptine-associated headache: possible life-threatening sympathomimetic interaction. *Obstet Gynecol* (1991) 78, 941–3.
2. Chan JCN, Critchley JAJH, Cockram CS. Postpartum hypertension, bromocriptine and phenylpropanolamine. *Drug Invest* (1994) 8, 254–6.
3. Veyrac G, Huguenin H, Guillon B, Chiffoleau A, Thajte N, Bourin M, Jolliet P. Hémorragie cérébroméningée et angiopathie cérébrale aiguë associées à la prise de phénylpropanolamine: un nouveau cas. *Therapie* (2001) 56, 323–7.
4. Reeves RR, Pinkofsky HB. Postpartum psychosis induced by bromocriptine and pseudoephedrine. *J Fam Pract* (1997) 45, 164–6.

Bromocriptine + Octreotide

Octreotide modestly increases the bioavailability of bromocriptine, whereas bromocriptine does not appear to alter octreotide pharmacokinetics.

Clinical evidence, mechanism, importance and management

The concurrent use of bromocriptine 5 mg twice daily and subcutaneous octreotide 200 micrograms twice daily increased the bioavailability of bromocriptine by about 40%, without altering its clearance or half-life. The pharmacokinetics of octreotide were unchanged.[1] This effect may contribute to the increased efficacy of concurrent use in acromegaly, which has been seen in some studies. It seems unlikely that any particular precautions are necessary on concurrent use.

1. Fløgstad AK, Halse J, Grass P, Abisch E, Djøseland O, Kutz K, Bodd E, Jervell J. A comparison of octreotide, bromocriptine, or a combination of both drugs in acromegaly. *J Clin Endocrinol Metab* (1994) 79, 461–5.

Cabergoline + Grapefruit juice

Grapefruit juice increases cabergoline levels.

Clinical evidence, mechanism, importance and management

When 5 patients with Parkinson's disease were given grapefruit juice (quantity not specified) with cabergoline, the plasma levels of cabergoline were increased by about 70%. No adverse events were reported by the patients.[1]

Grapefruit juice is an inhibitor of the cytochrome P450 isoenzyme CYP3A4 in the gut, which is involved in the metabolism of cabergoline. Therefore the concurrent use of grapefruit reduces the metabolism of cabergoline in the gut, increasing its bioavailability.

Evidence for an interaction appears to be limited to this study, but the interaction is established. However, there appear to be no reports of adverse effects in patients receiving grapefruit juice and cabergoline, so its clinical relevance is not established. The authors suggest that, as cabergoline has a large therapeutic index, concurrent use need not be avoided, and may even be beneficial.[1]

1. Nagai M, Nakatsuka A, Yabe H, Moritoyo T, Nomoto M. Effect of grapefruit juice on cabergoline pharmacokinetics in patients with Parkinson's disease. *Clin Pharmacol Ther* (2005) 77, P84.

COMT inhibitors + Inotropes and Vasopressors

Entacapone potentiated the increase in heart rate and arrhythmogenic effects of isoprenaline (isoproterenol) and adrenaline (epinephrine) in a study in healthy subjects. Therefore, the manufacturers of entacapone and tolcapone issue a caution about the concurrent use of adrenaline, isoprenaline, and a number of other inotropes and vasopressors.

Clinical evidence

In a study in healthy subjects, the maximal increase in heart rate during an infusion of **adrenaline** (**epinephrine**) was about 80% greater (25 bpm versus 14 bpm) after pretreatment with a single 400-mg dose of **entacapone**. Similarly, the maximal increase in heart rate during **isoprenaline** (**isoproterenol**) infusion was about 50% greater (40 bpm versus 27 bpm) after pretreatment with the same dose of **entacapone**. Moreover, more subjects experienced palpitations when pretreated with **entacapone**, and this study was terminated early because of two cases of ventricular arrhythmias, one requiring treatment with propranolol. There was no change in blood pressure, nor any increase in plasma levels of the **adrenaline** or **isoprenaline**.[1]

Mechanism

Tolcapone and entacapone inhibit the enzyme catechol-*O*-methyl transferase (COMT), which is concerned with the metabolism of drugs such as adrenaline (epinephrine) and isoprenaline (isoproterenol). There is therefore a possibility of increased plasma levels and related adverse effects of these drugs.

Importance and management

The evidence from this single-dose study confirms the theoretical prediction that COMT inhibitors might potentiate the effects of adrenaline (epinephrine). Because of this, the manufacturers of entacapone and tolcapone suggest caution if drugs known to be metabolised by COMT are given to patients taking COMT inhibitors.[2-5] Adrenaline (epinephrine), **dobutamine**, **dopamine**, isoprenaline (isoproterenol) and **noradrenaline** (**norepinephrine**), are specifically named in one or more of the lists,[2-5] and one manufacturer of entacapone also lists **bitolterol** and **isoetarine** (**isoetharine**), which are usually used in asthma, and specifically includes the inhaled route of administration.[5]

1. Illi A, Sundberg S, Ojala-Karlsson P, Korhonen P, Scheinin M, Gordin A. The effect of entacapone on the disposition and hemodynamic effects of intravenous isoproterenol and epinephrine. *Clin Pharmacol Ther* (1995) 58, 221–7.
2. Tasmar (Tolcapone). Meda Pharmaceuticals. UK Summary of product characteristics, January 2009.
3. Tasmar (Tolcapone). Valeant Pharmaceuticals North America. US Prescribing information, June 2009.

4. Comtess (Entacapone). Orion Pharma (UK) Ltd. UK Summary of product characteristics, September 2008.
5. Comtan (Entacapone). Novartis. US Prescribing information, March 2009.

COMT inhibitors + MAOIs

In a single-dose study, there was no adverse effect on heart rate or blood pressure when entacapone was given with moclobemide. The COMT inhibitors may be used with the MAO-B inhibitors (such as selegiline). However, the manufacturers of entacapone and tolcapone contraindicate concurrent use of non-selective MAOIs or a combination of both a RIMA and an MAO-B inhibitor.

Clinical evidence

In a single-dose, placebo-controlled study, **moclobemide** 150 mg did not change the heart rate or blood pressure at rest or during exercise, when given with **entacapone** 200 mg, compared with either drug alone or placebo. In addition, the plasma concentrations of endogenous noradrenaline (norepinephrine) and adrenaline (epinephrine) were not altered.[1] In 13 patients with Parkinson's disease, the addition of **selegiline** 10 mg daily to treatment with **entacapone** 200 mg three or four times daily, and levodopa with benserazide 200/50 mg three or four times daily, did not result in any clinically significant changes in haemodynamic parameters or adverse effects.[2]

Mechanism

Monoamine oxidase and COMT are the two major enzyme systems involved in the metabolism of catecholamines. Therefore it is theoretically possible that the combination of a COMT inhibitor and a non-selective MAOI would result in inhibition of the normal metabolism of catecholamines, with an increase in their effects (e.g. hypertension). Using an MAO-B inhibitor with a RIMA is similar to giving a non-selective MAOI and therefore using these two drugs with a COMT inhibitor would also be likely to inhibit the normal metabolism of catecholamines.

Importance and management

The results of the single-dose study with entacapone and moclobemide suggest that no adverse haemodynamic interaction occurs. Nevertheless, this finding needs confirmation in a clinical setting. Until further information is available, caution would be advisable on concurrent use. The manufacturers of entacapone and **tolcapone** contraindicate or advise against the use of non-selective MAOIs (e.g. **phenelzine**, **tranylcypromine**)[3-6] and combinations of both a RIMA [e.g. moclobemide] plus an MAO-B inhibitor (e.g. **selegiline**).[3,5] However, they state that **selegiline** alone is compatible with the COMT inhibitors provided not more than 10 mg daily is used.[3,5] At this dose, **selegiline** is likely to remain selective for MAO-B.

1. Illi A, Sundberg S, Ojala-Karlsson P, Scheinin M, Gordin A. Simultaneous inhibition of catechol-*O*-methyltransferase and monoamine oxidase A: effects on hemodynamics and catecholamine metabolism in healthy volunteers. *Clin Pharmacol Ther* (1996) 59, 450–7.
2. Lyytinen J, Kaakkola S, Ahtila S, Tuomainen P, Teräväinen H. Simultaneous MAO-B and COMT inhibition in L-dopa-treated patients with Parkinson's disease. *Mov Disord* (1997) 12, 497–505.
3. Tasmar (Tolcapone). Meda Pharmaceuticals. UK Summary of product characteristics, January 2009.
4. Tasmar (Tolcapone). Valeant Pharmaceuticals North America. US Prescribing information, June 2009.
5. Comtess (Entacapone). Orion Pharma (UK) Ltd. UK Summary of product characteristics, September 2008.
6. Comtan (Entacapone). Novartis. US Prescribing information, March 2009.

COMT inhibitors + Nasal decongestants

A single case report describes severe hypertension in a patient given entacapone and intravenous ephedrine. Tolcapone did not alter the effect of ephedrine in one study.

Clinical evidence

(a) Entacapone

A 76-year-old woman with Parkinson's disease taking levodopa with carbidopa and entacapone 200 mg five times daily, was given 3 mg of intravenous **ephedrine** during cataract surgery to correct a low blood pressure of 85/35 mmHg. Her blood pressure immediately rose to 225/125 mmHg. The patient needed several doses of hydralazine over the following 140 minutes before her blood pressure returned to normal.[1]

(b) Tolcapone

The manufacturer notes that tolcapone did not alter the effect of **ephedrine** (route of administration not stated) on haemodynamic parameters or plasma catecholamine levels, either at rest or during exercise.[2,3]

Mechanism

COMT inhibitors may inhibit the normal metabolism of ephedrine (and the catecholamines it releases at adrenergic nerve endings), which could result in a marked exaggeration of its normal effects.[1]

Importance and management

The single case report with entacapone and intravenous ephedrine appears to be the only evidence that COMT inhibitors could potentiate the effect of indirectly-acting sympathomimetics such as ephedrine. The manufacturer of tolcapone states that ephedrine and tolcapone can be used concurrently.[2,3] Nevertheless, some caution may be warranted with intravenous ephedrine.

1. Renfrew C, Dickson R, Schwab C. Severe hypertension following ephedrine administration in a patient receiving entacapone. *Anesthesiology* (2000) 93, 1562.
2. Tasmar (Tolcapone). Meda Pharmaceuticals. UK Summary of product characteristics, January 2009.
3. Tasmar (Tolcapone). Valeant Pharmaceuticals North America. US Prescribing information, June 2009.

COMT inhibitors + Tricyclic and related antidepressants

Entacapone and imipramine did not interact adversely in a single-dose study. Similarly, in another study, tolcapone and desipramine did not interact adversely.

Clinical evidence

(a) Entacapone

In a single-dose, crossover study, 12 healthy women were given entacapone 200 mg with **imipramine** 75 mg, either drug alone, or placebo. Although both drugs can impair the inactivation of catecholamines the study found no evidence that concurrent use had any relevant effect on haemodynamics or on free adrenaline (epinephrine) or noradrenaline (norepinephrine) plasma levels. The combination was well tolerated in all subjects.[1]

(b) Tolcapone

In one study, healthy subjects were given **desipramine** 25 mg three times daily for 3 days then 50 mg three times daily for 10 days. For the last 5 days they were also given levodopa with carbidopa 100/25 mg three times daily and either a placebo or tolcapone 200 mg three times daily. The addition of tolcapone to the use of levodopa with carbidopa and **desipramine** did not lead to any changes in haemodynamics or catecholamine levels, or to any changes in **desipramine** pharmacokinetics.[2]

Mechanism

Both COMT inhibitors and drugs with noradrenaline re-uptake inhibitory activity (e.g. the tricyclics) can impair the inactivation of catecholamines, so in theory the effects of catecholamines may be increased by concurrent use. However, this did not appear to occur in the above studies.

Importance and management

In these pharmacological studies, no important interaction between entacapone and imipramine or between tolcapone and desipramine was detected. Nevertheless, the manufacturer of entacapone says there is limited clinical experience of the use of entacapone with tricyclic antidepressants, and they therefore recommend caution.[3] Similarly, the manufacturers of tolcapone suggest that caution should be exercised with desipramine[4,5] and any drugs that are potent noradrenaline uptake inhibitors such as **maprotiline** and **venlafaxine**.[4]

1. Illi A, Sundberg S, Ojala-Karlsson P, Scheinin M, Gordin A. Simultaneous inhibition of catecholamine-*O*-methylation by entacapone and neuronal uptake by imipramine: lack of interactions. *Eur J Clin Pharmacol* (1996) 51, 273–6.

2. Jorga KM, Fotteler B, Modi M, Rabbia M. Effect of tolcapone on the haemodynamic effects and tolerability of desipramine. *Eur Neurol* (2000) 44, 94–103.
3. Comtess (Entacapone). Orion Pharma (UK) Ltd. UK Summary of product characteristics, September 2008.
4. Tasmar (Tolcapone). Meda Pharmaceuticals. UK Summary of product characteristics, January 2009.
5. Tasmar (Tolcapone). Valeant Pharmaceuticals North America. US Prescribing information, June 2009.

COMT inhibitors; Entacapone + Iron compounds

Entacapone formed chelates with iron *in vitro*.

Clinical evidence, mechanism, importance and management

An *in vitro* study[1] found that entacapone formed chelates with iron. Although the clinical relevance of this does not appear to have been assessed, the UK manufacturer recommends that entacapone and iron compounds should be taken at least 2 to 3 hours apart.[2]

1. Orama M, Tilus P, Taskinen J, Lotta T. Iron (III)-chelating properties of the novel catechol *O*-methyltransferase inhibitor entacapone in aqueous solution. *J Pharm Sci* (1997) 86, 827–31.
2. Comtess (Entacapone). Orion Pharma (UK) Ltd. UK Summary of product characteristics, September 2008.

COMT inhibitors; Tolcapone + Clozapine

A case report describes neuroleptic malignant-like syndrome and acute hepatitis in a patient who took tolcapone and clozapine.

Clinical evidence, mechanism, importance and management

A case report describes a 70-year-old woman taking levodopa with benserazide who developed a neuroleptic malignant-like syndrome, with a temperature of 40.5°C, coma, and muscular rigidity, and fulminant hepatitis about 2 weeks after starting to take tolcapone, and about 10 days after also starting to take clozapine. Twelve hours after stopping tolcapone and clozapine her temperature normalised, and within 2 days she had regained consciousness. Clozapine was restarted with no recurrence of these symptoms.[1] Tolcapone alone can cause increases in liver transaminases, hepatocellular injury, and a neuroleptic malignant-like syndrome, and therefore an interaction is not established.

1. Blum MW, Siegel AM, Meier R, Hess K. Neuroleptic malignant-like syndrome and acute hepatitis during tolcapone and clozapine medication. *Eur Neurol* (2001) 46, 158–60.

Levodopa + Antacids

Antacids do not appear to interact significantly with immediate-release levodopa, but they may reduce the bioavailability of modified-release preparations of levodopa.

Clinical evidence

(a) Immediate-release levodopa

One study found that 15 mL of an **aluminium/magnesium hydroxide** antacid, given 30 minutes before levodopa, to a patient with a prolonged gastric emptying time, caused a threefold increase in levodopa serum levels, which was associated with a marked improvement in symptoms.[1] Another patient was able to reduce his levodopa dose when taking antacids, without affecting symptom control.[1] A further study found that the maximum plasma concentration of levodopa was raised by 20% when 20 mL of an antacid was given before the levodopa.[2]

However, when 8 patients (only 3 with Parkinson's disease) were given *Mylanta* (containing **aluminium/magnesium hydroxide** and simeticone), 30 minutes before, and/or with levodopa, only occasional increases in bioavailability were seen. One of the 3 patients with Parkinson's disease who had shown improved bioavailability while taking antacids had his levodopa dose lowered and continued to take *Mylanta*, but the parkinsonian symptoms worsened and the levodopa was increased back to the original dose.[3] Another study, in 15 patients taking dopamine agonists (e.g. bromocriptine) and levodopa with carbidopa who were given six 30-mL doses of **aluminium hydroxide** daily, inferred that the antacid had no significant effect on levodopa bioavailability, because of the lack of clinical fluctuations in effect.[4]

(b) Sustained-release levodopa

In a study in healthy subjects, using *Madopar HBS*, a sustained-release preparation of levodopa with benserazide, the concurrent use of an unnamed antacid reduced the levodopa bioavailability by about one-third.[5] The manufacturer of *Madopar CR* states that antacids reduce the bioavailability of levodopa from the controlled-release preparation in comparison with conventional *Madopar*.[6]

Mechanism

The small intestine is the major site of absorption for levodopa, and delayed gastric emptying appears to result in low plasma levodopa levels, probably because levodopa can be metabolised in the stomach. In theory, antacids may reduce gastric emptying time, and increase levodopa absorption.[1] It is not known why antacids reduced absorption from the slow-release preparation.[5]

Importance and management

The overall picture is that the concurrent use of antacids need not be avoided with standard preparations of levodopa (with a dopa-decarboxylase inhibitor), although some individuals may be affected so the outcome should be monitored. With modified-release preparations it would seem advisable to avoid concurrent administration (one to 2 hours is usually enough in other similar cases of interactions with antacids). Again, the outcome should be monitored.

1. Rivera-Calimlim L, Dujovne CA, Morgan JP, Lasagna L, Bianchine JR. Absorption and metabolism of L-dopa by the human stomach. *Eur J Clin Invest* (1971) 1, 313–20.
2. Pocelinko R, Thomas GB, Solomon HM. The effect of an antacid on the absorption and metabolism of levodopa. *Clin Pharmacol Ther* (1972) 13, 149.
3. Leon AS, Spiegel HE. The effect of antacid administration on the absorption and metabolism of levodopa. *J Clin Pharmacol* (1972) 12, 263–7.
4. Lau E, Waterman K, Glover R, Schulzer M, Calne DB. Effect of antacid on levodopa therapy. *Clin Neuropharmacol* (1986) 9, 477–9.
5. Malcolm SL, Allen JG, Bird H, Quinn NP, Marion MH, Marsden CD, O'Leary CG. Single-dose pharmacokinetics of Madopar HBS in patients and effect of food and antacid on the absorption of Madopar HBS in volunteers. *Eur Neurol* (1987) 27 (Suppl 1), 28–35.
6. Madopar CR (Levodopa and Benserazide hydrochloride). Roche Products Ltd. UK Summary of product characteristics, April 2009.

Levodopa + Anticholinesterases; Centrally acting

Reports describe cases of a worsening of Parkinson's disease in a few patients given donepezil, rivastigmine or tacrine. Other centrally acting anticholinesterases may exacerbate or induce extrapyramidal symptoms, including worsening of Parkinson's disease. In contrast, one study found that donepezil did not affect the control of Parkinson's disease.

Clinical evidence

(a) Donepezil

In a placebo-controlled study in 23 patients with Parkinson's disease taking levodopa with carbidopa, donepezil 5 mg daily for 15 days caused a modest 30% increase in the $AUC_{0\text{-}4}$ of levodopa. There was no change in carbidopa pharmacokinetics, and the pharmacokinetics of donepezil did not differ between the patients with Parkinson's disease and a control group of healthy subjects. There was no obvious difference in adverse effects between patients with Parkinson's disease and the control subjects, and no evidence that donepezil significantly altered motor activity in patients taking levodopa with carbidopa.[1] This latter finding is in contrast to a report that found a worsening of Parkinson's disease, which responded to levodopa with carbidopa, in 3 of 9 patients who had taken donepezil for 24 weeks.[2]

(b) Rivastigmine

A case report describes a 71-year-old woman taking levodopa with carbidopa and tolcapone, who experienced a worsening of her Parkinson's disease after taking a single 3-mg dose of rivastigmine. She became anxious and dysphoric, had severe bradykinesia and rigidity, and felt nauseous. Note that this dose is higher than the usual starting dose of rivastigmine, and this may have contributed to the effects seen.[3]

(c) Tacrine

The mild parkinsonism of an elderly woman with Alzheimer's disease worsened, leading to severe tremor, stiffness and gait dysfunction within 2 weeks of doubling her tacrine dose from 10 mg to 20 mg four times daily. This improved when levodopa with carbidopa was started, but the tremor returned when tacrine was increased to 30 mg four times daily. The symptoms disappeared when the tacrine dose was reduced to 20 mg four times daily.[4]

Mechanism

Parkinsonism is due to an imbalance between two neurotransmitters, dopamine and acetylcholine, in the basal ganglia of the brain. Centrally acting anticholinesterases increase the amount of acetylcholine in the brain, which could lead to an exacerbation of parkinsonian symptoms. Levodopa improves the situation by increasing the levels of dopamine. It is not known why donepezil modestly increased the levels of levodopa.

Importance and management

Direct information seems to be limited, but the reports of worsening Parkinson's disease are consistent with the known pharmacology of these drugs and the biochemical pathology of Parkinson's disease. Be aware that if centrally acting anticholinesterases are given to any patient with parkinsonism, whether taking levodopa or any other anti-parkinson drug, the disease may possibly worsen. The antiparkinson drug dose may need increasing and/or the dose of the anticholinesterase may need reducing.

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4. Ott BR, Lannon MC. Exacerbation of parkinsonism by tacrine. *Clin Neuropharmacol* (1992) 15, 322–5.

Levodopa + Antiemetics

Although metoclopramide can increase the rate of levodopa absorption, it may also antagonise its effects by aggravating symptoms of Parkinson's disease, although some studies have found no evidence of this effect. Phenothiazine antiemetics such as prochlorperazine are also generally considered to be contraindicated in Parkinson's disease. In one small study, promethazine did not affect the control of Parkinson's disease in patients taking levodopa. Domperidone is the antiemetic of choice to prevent and treat nausea and vomiting caused by levodopa. Other antiemetics that are generally considered useful include cyclizine and 5-HT_3 receptor antagonists.

Clinical evidence, mechanism, importance and management

(a) Domperidone

Domperidone is a dopamine antagonist similar to metoclopramide.[1] However, as it acts on the dopamine receptors in the stomach wall, and unlike metoclopramide, it does not readily cross the blood-brain barrier, it does not appear to oppose the effects of levodopa within the brain, although some extrapyramidal symptoms have been observed. It may even slightly increase the bioavailability and effects of levodopa (by stimulating gastric emptying).[2] Domperidone can therefore be used to control the nausea and vomiting associated with levodopa treatment of Parkinson's disease.

(b) Metoclopramide

Metoclopramide is a dopamine antagonist that can cause extrapyramidal disturbances (parkinsonian symptoms), especially in children and young adults, and possibly also in the elderly, where the effects may be misdiagnosed as Parkinson's disease.[3] On the other hand, metoclopramide stimulates gastric emptying, which can result in an increase in the bioavailability of levodopa.[4,5] The outcome of these two effects (possible antagonism resulting in aggravation of Parkinson's disease, or potentiation resulting in increased bioavailability) is uncertain, and it is generally considered that metoclopramide should be avoided in Parkinson's disease. However, in one open study, metoclopramide 30 to 60 mg daily in divided doses for a range of 4 to 16 weeks caused no change in mean total disability scores in 10 patients with Parkinson's disease taking levodopa.[6] Similarly, in a controlled study in 7 patients, the incidence and severity of levodopa-induced involuntary movements were unchanged and additional acute dyskinesias did not appear when metoclopramide was also given.[6] Furthermore, in a retrospective analysis, by the same authors, there was no worsening of parkinsonian symptoms in 40 patients with Parkinson's disease taking levodopa who were also given metoclopramide up to 80 mg daily.[7] Nevertheless, if alternative antiemetics are unsuitable for a patient with Parkinson's disease and consequently metoclopramide is given, it would seem prudent to monitor the outcome closely.

(c) Phenothiazine antiemetics

Phenothiazines block the dopamine receptors in the brain and can therefore upset the balance between cholinergic and dopaminergic components within the striatum and substantia nigra. As a consequence they may not only induce the development of extrapyramidal (parkinsonian) symptoms, but they can aggravate parkinsonism and antagonise the effects of levodopa used in its treatment. See 'Levodopa + Antipsychotics', p.797. Phenothiazines, used in smaller doses as antiemetics, such as **prochlorperazine**,[8,9] can also behave in this way. For this reason, drugs of this kind are generally regarded as contraindicated in patients with Parkinson's disease, and there are other more suitable alternatives, see *Non-interacting antiemetics*, below. However, one small controlled study found that **promethazine** (a phenothiazine derivative with few extrapyramidal effects) did not change the total disability score or alter the incidence or severity of levodopa-induced involuntary movements in 6 patients with Parkinson's disease taking levodopa.[6]

(d) Non-interacting antiemetics

Antiemetics that are generally considered useful in patients with Parkinson's disease include **cyclizine** and 5-HT_3 antagonists such as **granisetron** and **ondansetron**,[3] which do not affect dopamine, and **domperidone** as discussed above. However, note that rare cases of extrapyramidal adverse effects have been reported with **ondansetron**, which may be of relevance in patients with Parkinson's disease.[10]

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4. Berkowitz DM, McCallum RW. Interaction of levodopa and metoclopramide on gastric emptying. *Clin Pharmacol Ther* (1980) 27, 414–20.
5. Mearrick PT, Wade DN, Birkett DJ, Morris J. Metoclopramide, gastric emptying and L-dopa absorption. *Aust N Z J Med* (1974) 4, 144–8.
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7. Tarsy D, Parkes JD, Marsden CD. Metoclopramide in parkinsonism. *Lancet* (1975) 1, 1244–5.
8. Duvoisin RC. Diphenidol for levodopa induced nausea and vomiting. *JAMA* (1972) 221, 1408.
9. Campbell JB. Long-term treatment of Parkinson's disease with levodopa. *Neurology* (1970) 20, 18–22.
10. Zofran (Ondansetron hydrochloride dihydrate). GlaxoSmithKline UK. UK Summary of product characteristics, October 2009.

Levodopa + Antimuscarinics

Antimuscarinics and other drugs with antimuscarinic effects, such as the tricyclics, may modestly reduce the rate, and possibly the extent, of absorption of levodopa. One case describes levodopa toxicity, which occurred after the withdrawal of an antimuscarinic.

Clinical evidence

A study in 6 healthy subjects and 6 patients with Parkinson's disease found that **trihexyphenidyl** 2 mg twice daily for 3 days lowered the peak plasma levels of a 500-mg dose of levodopa by 42% in the healthy subjects and by 17% in the patients, although the interaction was present in only about half of the subjects. The AUC was reduced in both groups by less than 20%.[1] Similarly, a study in 10 healthy subjects found that the initial levodopa plasma levels were lowered when a single 250-mg dose of levodopa was taken 90 minutes after a single 5-mg dose of **trihexyphenidyl**. The absorption of levodopa was slower, but the overall bioavailability was not significantly altered. Carbidopa 100 mg was given one hour before the levodopa, and a 50-mg dose was given 5 hours after the levodopa.[2]

A study in 6 patients with Parkinson's disease taking levodopa with car-

bidopa or benserazide found that **orphenadrine** caused either a delay, a reduction, or an increase in levodopa absorption in 3 patients.[3] A patient who needed 7 g of levodopa daily while taking **homatropine** developed levodopa toxicity when the **homatropine** was withdrawn, and he was subsequently restabilised on only 4 g of levodopa daily.[4]

A study in 4 healthy subjects[5] found that **imipramine** 25 mg four times daily for 3 days reduced the peak plasma concentration of a single 500-mg dose of levodopa by about 50%, but did not appear to alter the extent of absorption. See also 'Levodopa + Tricyclic antidepressants', p.806, for other non-antimuscarinic interactions of the tricyclics.

Mechanism

The small intestine is the major site of absorption for levodopa. Delayed gastric emptying, which can be caused by antimuscarinics, appears to result in lower plasma levodopa levels and thus lower brain levodopa levels. This is because the gastric mucosa has more time to metabolise the levodopa to dopamine and therefore less is available for absorption.[6]

Importance and management

Antimuscarinics are commonly given with levodopa, and they are of established benefit. However, limited evidence suggests they might sometimes reduce levodopa efficacy. Levodopa preparations are now more usually given in conjunction with a dopa decarboxylase inhibitor to minimise metabolism in the gastric mucosa. This would be expected to minimise the effects of any interaction. However, note that two of the above studies included a dopa-decarboxylase inhibitor, yet still found an effect on levodopa absorption. There is certainly no need to avoid concurrent use, but it would be prudent to be alert for any evidence of a reduced levodopa response if antimuscarinics are added, or for levodopa toxicity if they are withdrawn.

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2. Roberts J, Waller DG, Renwick AG, O'Shea N, Macklin BS, Bulling M. The effects of co-administration of benzhexol on the peripheral pharmacokinetics of oral levodopa in young volunteers. *Br J Clin Pharmacol* (1996) 41, 331–7.
3. Contin M, Riva R, Martinelli P, Procaccianti G, Albani F, Baruzzi A. Combined levodopa-anticholinergic therapy in the treatment of Parkinson's disease. *Clin Neuropharmacol* (1991) 14, 148–55.
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5. Morgan JP, Rivera-Calimlim L, Messiha F, Sundaresan PR, Trabert N. Imipramine-mediated interference with levodopa absorption from the gastrointestinal tract in man. *Neurology* (1975) 25, 1029–34.
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Levodopa + Antipsychotics

Phenothiazines, butyrophenones, thioxanthenes and pimozide can oppose the effects of levodopa because of their dopamine antagonist properties, causing deterioration of motor function in Parkinson's disease. The antipsychotic effects and extrapyramidal adverse effects of these drugs can be opposed by levodopa. Of the atypical antipsychotics, risperidone and olanzapine cause deterioration in motor function in Parkinson's disease. Ziprasidone and paliperidone may act similarly, and there have been reports of mild motor deterioration with quetiapine. Clozapine does not have this effect.

Clinical evidence, mechanism, importance and management

(a) Classical antipsychotics

Phenothiazines (e.g. fluphenazine, perphenazine, prochlorperazine, and trifluoperazine), **butyrophenones** (e.g. droperidol and haloperidol), **thioxanthenes** (e.g. flupentixol and zuclopenthixol) and pimozide block the dopamine receptors in the brain and can therefore upset the balance between cholinergic and dopaminergic components within the striatum and substantia nigra. As a consequence they may not only induce the development of extrapyramidal (parkinsonian) symptoms, but they can aggravate parkinsonism and antagonise the effects of levodopa used in its treatment.[1-5] For this reason drugs of this kind are generally regarded as contraindicated in patients being treated for Parkinson's disease, or only used with great caution in carefully controlled conditions. The extrapyramidal symptoms that frequently occur with the **phenothiazines** have in the past been treated without much success with levodopa. However, the levodopa may also antagonise the antipsychotic effects of the **phenothiazines**,[6] and other dopamine-antagonist antipsychotics. Phenothiazines used as antiemetics may also act in this way. Consider also 'Levodopa + Antiemetics', p.796.

(b) Atypical antipsychotics

Of the atypical antipsychotics, both **risperidone** and **olanzapine** have caused deterioration of motor function in patients with Parkinson's disease.[7,8] **Paliperidone**, the active metabolite of risperidone, is expected to have similar effects.[9,10] There have also been reports of deterioration in motor function with **quetiapine**, but in general this effect seems to be mild[7] and, in patients with Parkinson's disease, quetiapine appears to be better tolerated than risperidone or olanzapine.[8] There is far less experience with **ziprasidone**, but it may have a propensity to cause extrapyramidal adverse effects that is similar to **olanzapine**.

Low-dose **clozapine** appears to cause little deterioration in motor function, and may improve tremor. It is therefore a preferred antipsychotic for patients with Parkinson's disease and levodopa-induced psychosis. Note that individual reports and studies of the use of these antipsychotics in patients with Parkinson's disease are numerous. Reviews on the topic have been published.[7,8]

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8. Zahodne LB, Fernandez HH. Pathophysiology and treatment of psychosis in Parkinson's disease: a review. Drugs Aging (2008) 25, 665–82.
9. Invega (Paliperidone). Janssen-Cilag Ltd. UK Summary of product characteristics, November 2009.
10. Invega (Paliperidone). Janssen Pharmaceuticals Inc. US Prescribing information, July 2009.

Levodopa + Ascorbic acid (Vitamin C)

Ascorbic acid does not appear to alter the pharmacokinetics of levodopa.

Clinical evidence, mechanism, importance and management

In a study, 67 elderly patients with Parkinson's disease took a single dose of levodopa 100 mg with carbidopa 10 mg alone, and with a single 200-mg dose of ascorbic acid. The AUC, maximum plasma levels, and time to reach maximum levodopa plasma levels were increased when ascorbic acid was also given, but these increases were not statistically significant. However, there was a trend towards a larger effect in those patients with lower baseline levodopa bioavailability.[1] Based on the available evidence, there would appear to be no reason for patients taking levodopa to avoid modest doses of ascorbic acid.

1. Nagayama H, Hamamoto M, Ueda M, Nito C, Yamaguchi H, Katayama Y. The effect of ascorbic acid on the pharmacokinetics of levodopa in elderly patients with Parkinson disease. *Clin Neuropharmacol* (2004) 27, 270–3.

Levodopa + Baclofen

Unpleasant adverse effects (hallucinations, confusion, headache, nausea) and worsening of the symptoms of parkinsonism have occurred in patients taking levodopa who were given baclofen.

Clinical evidence

Twelve patients with parkinsonism taking levodopa with a dopa-decarboxylase inhibitor were also given baclofen. The eventual baclofen dose was intended to be 90 mg daily, but the adverse effects were considerable (visual hallucinations, a toxic confusional state, headaches, nausea) so that only 2 patients reached this dose, and 2 patients withdrew because they

could not tolerate these adverse effects. The mean dose for those who continued was 45 mg daily. Rigidity was aggravated by an average of 46% and functional capacity deteriorated by 21%.[1]

A patient with Parkinson's disease taking levodopa with carbidopa, orphenadrine and diazepam became acutely confused, agitated, incontinent and hallucinated when given a third dose of baclofen (in all 15 mg). The baclofen was stopped, but on the following night she again hallucinated and became confused. The next day she was given two 2.5-mg doses of baclofen but she became anxious and hallucinated with paranoid ideas.[2]

Mechanism

Not understood. The toxicity seen appears to be an exaggeration of the known adverse effects of baclofen.

Importance and management

Information appears to be limited to these reports, but they suggest that baclofen should be used very cautiously in patients taking levodopa.

1. Lees AJ, Shaw KM, Stern GM. Baclofen in Parkinson's disease. *J Neurol Neurosurg Psychiatry* (1978) 41, 707–8.
2. Skausig OB, Korsgaard S. Hallucinations and baclofen. *Lancet* (1977) 1, 1258.

Levodopa + Benzodiazepines and related drugs

On rare occasions it seems that the therapeutic effects of levodopa can be reduced by chlordiazepoxide, diazepam or nitrazepam.

Clinical evidence

Various benzodiazepines (dose unstated) were given to 8 patients with Parkinson's disease taking levodopa. In 5 of the patients (3 taking **chlordiazepoxide**, one taking **nitrazepam**, one taking **oxazepam**) no interactions were seen. However, the other 3 patients (one taking **diazepam**, 2 taking **nitrazepam**) experienced transient disturbances in the control of their Parkinson's disease, which lasted up to 3 weeks in the case of the patient taking **diazepam**.[1] Other cases of a reversible loss of control of Parkinson's disease have been seen in 3 patients taking **diazepam**[2] and 4 patients taking **chlordiazepoxide**.[3,4] In one further case, a patient taking **chlordiazepoxide** experienced falls associated with a worsening of parkinsonian symptoms while taking **chlordiazepoxide**. She recovered 5 days after the **chlordiazepoxide** was withdrawn.[5]

In contrast, a case-control study of patients with Parkinson's disease taking levodopa did not find a statistically significant increase in the required dose of antiparkinsonian drug treatment in the 180 days after starting a benzodiazepine.[6]

Mechanism

Not understood, although *animal* studies have shown that benzodiazepines can decrease the levels of dopamine in the striatum.[6]

Importance and management

Not established. Given the widespread use of benzodiazepines in patients taking levodopa,[7] any major or common interaction would be expected to have come to light by now. It would therefore seem that any interaction is fairly rare, and on the basis of one of the reports cited above, possibly only transient. There is no need to avoid concurrent use, but bear these reports in mind in the case of an unexpected response to treatment.

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5. Yosselson-Superstine S, Lipman AG. Chlordiazepoxide interaction with levodopa. *Ann Intern Med* (1982) 96, 259–60.
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7. van de Vijver DAMC, de Boer A, Herings RMC, Roos RAC, Porsius AJ. Increased use of psychotropic drugs by patients with Parkinson's disease. *Br J Clin Pharmacol* (1999) 47, 476P.

Levodopa + Beta blockers

The concurrent use of levodopa and beta blockers normally appears to be favourable, but be aware that, as with all antihypertensives, additive hypotensive effects can occur.

Clinical evidence, mechanism, importance and management

Most of the effects of the concurrent use of levodopa and beta blockers seem to be favourable, although additive hypotension can be a problem. Dopamine derived from levodopa stimulates beta-receptors in the heart, which can cause arrhythmias.[1] These receptors are blocked by **propranolol** and other beta blockers. An enhancement of the effects of levodopa and a reduction in tremor has been described in 23 out of 25 patients taking **propranolol**,[2] but not in 9 patients taking **oxprenolol**,[3] or in another placebo-controlled study in 18 patients taking **propranolol**.[4] Early evidence found that growth hormone levels were substantially raised by **propranolol**[5,6] or **practolol**[6] [now withdrawn due to fatal reactions] in conjunction with levodopa, but no clinical relevance for this has been demonstrated.

1. Goldberg LI, Whitsett TL. Cardiovascular effects of levodopa. *Clin Pharmacol Ther* (1971) 12, 376–82.
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4. Marsden CD, Parkes JD, Rees JE. Propranolol in Parkinson's disease. *Lancet* (1974) ii, 410.
5. Camanni F, Massara F. Enhancement of levodopa-induced growth-hormone stimulation by propranolol. *Lancet* (1974) i, 942.
6. Lotti G, Delitala G, Masala A. Enhancement of levodopa-induced growth-hormone stimulation by practolol. *Lancet* (1974) 2, 1329.

Levodopa + Bromocriptine and other dopamine agonists

The concurrent use of levodopa and dopamine agonists can increase efficacy and adverse effects in Parkinson's disease. Bromocriptine may sometimes alter levodopa levels and levodopa may lower bromocriptine levels. There appears to be no pharmacokinetic interaction between levodopa and cabergoline, pramipexole or ropinirole. An isolated report describes the development of serotonin syndrome when levodopa with carbidopa was added to treatment with bromocriptine.

Clinical evidence

(a) Bromocriptine

A study in 20 patients with Parkinson's disease taking levodopa with carbidopa found that overall there was no difference in plasma levodopa levels after bromocriptine was also taken, although some patients had either significant elevations or significant reductions in levels. However, the only adverse clinical change found was an increase in dyskinesias in the patients with elevated levodopa levels.[1] An earlier study found no pharmacokinetic interaction between levodopa with carbidopa and bromocriptine, but it should be noted that this was a single-dose study and may not reflect long-term concurrent use.[2] A further study in 7 patients with Parkinson's disease taking long-term levodopa with benserazide found that the addition of bromocriptine, 15 mg daily in three divided doses for 6 months, had no effect on the pharmacokinetics of levodopa.[3] Steady-state bromocriptine plasma levels were found to be reduced by levodopa in a study in 10 patients with Parkinson's disease. The patients normally took levodopa, but this was withheld to give baseline bromocriptine pharmacokinetics.[4]

A patient with parkinsonism, who had been taking bromocriptine 60 mg daily for nearly 3 years, was also given levodopa with carbidopa (250/25 mg daily increasing over a week to 750/75 mg) while the bromocriptine dose was reduced to 20 mg daily. On the seventh day he started shivering, and developed myoclonus of the trunk and limbs, hyperreflexia, patellar clonus, tremor, diaphoresis, anxiety, diarrhoea, tachycardia and had a temperature of 37.9°C with a blood pressure of 180/100 mmHg. Serotonin syndrome was suspected. The patient responded to treatment with the 5-HT antagonist methysergide.[5]

A case of pathological gambling in a 54-year-old woman was attributed to the concurrent use of bromocriptine and levodopa with carbidopa.[6]

(b) Cabergoline

Levodopa with carbidopa 250/25 mg daily did not cause a clinically significant change in the pharmacokinetics of cabergoline 2 mg daily when the combination was given to patients newly diagnosed with Parkinson's disease. Similarly, cabergoline (in increasing doses up to 4 mg daily) for 8 weeks had no effect on the absorption, AUC or elimination half-life of levodopa in another group of patients with fluctuating Parkinson's disease who were taking levodopa with carbidopa.[7]

(c) Pergolide

The manufacturer notes that the use of pergolide in patients taking levodopa may cause and/or exacerbate pre-existing states of dyskinesia, confusion, and hallucinations. Also, they say that stopping pergolide abruptly in patients taking levodopa may precipitate the onset of hallucinations and confusion.[8]

(d) Pramipexole

Patients taking a stable dose of levodopa with carbidopa were given increasing doses of pramipexole or placebo for 7 weeks. Pramipexole 1.5 mg daily and 4.5 mg daily had no effect on levodopa bioavailability.[9] Several cases of pathological gambling have been reported in patients taking pramipexole, usually in association with levodopa.[10]

(e) Ropinirole

In patients taking a stable dose of levodopa with a dopa-decarboxylase inhibitor, ropinirole had no effect on the pharmacokinetics of levodopa, except for a small clinically irrelevant 16% increase in its maximum level. Levodopa also had no effect on the pharmacokinetics of ropinirole in another group of patients.[11] Similarly, in a single-dose study in healthy subjects, levodopa with benserazide had no significant effect on the pharmacokinetics of ropinirole.[12]

(f) Rotigotine

The manufacturer of rotigotine reports that levodopa and carbidopa had no effect on the pharmacokinetics of rotigotine and similarly, rotigotine had no effect on the pharmacokinetics of either levodopa or carbidopa. However, as with other dopamine agonists, rotigotine may cause and/or exacerbate dyskinesia in patients taking levodopa and may potentiate the dopaminergic adverse reactions of levodopa.[13]

Mechanism

Additive dopaminergic effects would be expected. Serotonin syndrome is thought to occur because of increased stimulation of the 5-HT receptors in the brainstem and spinal cord. A syndrome resembling neuroleptic malignant syndrome (which has similar symptoms to serotonin syndrome) can occur when a dopamine agonist like bromocriptine is withdrawn abruptly. It is therefore possible that the effects of reducing the bromocriptine dose were additive with those of levodopa, which can displace serotonin from the nerve endings.[5]

Importance and management

The concurrent use of levodopa and dopamine agonists can increase efficacy in Parkinson's disease, but adverse effects such as hallucinations and dyskinesias may also be increased, and the dose of both drugs should be gradually adjusted to optimise therapy. The manufacturer of ropinirole suggests a total reduction in the levodopa dose of about 20%.[14] If the decision is made to withdraw the dopamine agonist, this should be done slowly, over several days.

Serotonin syndrome described with levodopa and bromocriptine appears to be an isolated incident and not of general importance. A number of cases of pathological gambling have been reported in patients taking dopamine agonists with levodopa. It has been suggested that pathological gambling may be a class effect of dopamine agonists, although levodopa may have contributed in patients receiving both drugs.[10]

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4. Rabey JM, Oberman Z, Scharf M, Isakov A, Bar M, Graff E. The influence of levodopa in the pharmacokinetics of bromocriptine in Parkinson's disease. *Clin Neuropharmacol* (1989) 12, 440–7.
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6. Polard E, Trioux E, Flet L, Colin F, Allain H. Ludopathie induite par la lévodopa associée à la bromocriptine. *Presse Med* (2003) 32, 1223.
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13. Neupro (Rotigotine). UCB Pharma Ltd. UK Summary of product characteristics, August 2009.
14. Requip (Ropinirole hydrochloride). GlaxoSmithKline UK. UK Summary of product characteristics, September 2009.

Levodopa + Caffeine

Caffeine increased the rate of absorption of levodopa, but not its overall bioavailability.

Clinical evidence, mechanism, importance and management

In a crossover study, 12 patients with Parkinson's disease were given a single 200-mg dose of caffeine or placebo 15 minutes before receiving levodopa 250 mg with carbidopa 25 mg. The rate of absorption of levodopa was increased by caffeine, with maximum levodopa plasma levels being achieved at one hour, compared with 1.5 hours when taken with placebo. There was also a shortening of the time to detect a motor response to levodopa when caffeine was taken. However, the maximum plasma levels and the $AUC_{0\text{-}3}$ of levodopa were not significantly altered by caffeine.[1]

A study in 4 patients with Parkinson's disease investigated the therapeutic benefit of adding caffeine to levodopa with carbidopa. Doses of up to 1.4 g of caffeine daily did not potentiate the antiparkinsonian action of levodopa, but there was an increase in the duration of involuntary movements during the use of high doses of caffeine, and signs or symptoms of caffeine toxicity appeared in all 6 patients.[2]

These studies suggest that caffeine need not be avoided in patients taking levodopa, but high doses may increase movement disorders in response to levodopa. If this becomes troublesome, it may be prudent to try to decrease caffeine intake.

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2. Shoulson I, Chase TN. Caffeine and the antiparkinsonian response to levodopa or piribedil. *Neurology* (1975) 25, 722–4.

Levodopa + Clonidine

Limited evidence suggests that clonidine may oppose the effects of levodopa. Be aware that, as with the use of all antihypertensives with levodopa, additive hypotensive effects may occur.

Clinical evidence

A study in 2 patients taking levodopa with carbidopa found that the concurrent use of clonidine (up to 1.5 mg daily for 10 to 24 days) caused a worsening of parkinsonism (an exacerbation of rigidity and akinesia). The concurrent use of antimuscarinic drugs reduced the effects of this interaction.[1]

Another report on 10 hypertensive and 3 normotensive patients with Parkinson's disease, 9 of them taking levodopa and 4 of them not, suggested that the concurrent use of clonidine did not affect the control of the parkinsonism. However, 2 patients stopped taking clonidine because of an increase in tremor and gait disturbances.[2]

Mechanism

Not understood. One suggestion is that clonidine opposes the antiparkinson effects by stimulating alpha-receptors in the brain. Another idea is that clonidine directly stimulates post-synaptic dopaminergic receptors.

Importance and management

Information seems to be limited to these reports. Be alert for a reduction in the control of the Parkinson's disease during the concurrent use of levodopa and clonidine. The effects of this interaction appear to be reduced if antimuscarinic drugs are also being used.[1] Also note, that as with all antihypertensives, additive hypotensive effects may occur.

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Levodopa + COMT inhibitors

Entacapone and tolcapone increase the AUC of levodopa given with benserazide or carbidopa. This may require a reduction in the levodopa dose to avoid symptoms of dopamine excess when first starting the COMT inhibitor. Tolcapone increases the levels of benserazide, but neither entacapone nor tolcapone alters carbidopa pharmacokinetics.

Clinical evidence

(a) Levodopa

Entacapone[1-3] and **tolcapone**[4,5] have been shown to increase the AUC and/or prolong the elimination half-life of levodopa (given with benserazide or carbidopa) without significantly altering the maximum levodopa level. However, in some studies, the maximum levodopa plasma levels have also been increased by **entacapone** or **tolcapone**.[6,7]

COMT inhibitors can therefore improve the clinical condition of patients with Parkinson's disease, which is mainly seen as a decrease in 'off' time.[8] However, as levodopa levels are raised, there may be an accompanying increase in the adverse effects of levodopa (e.g. dyskinesias, nausea, vomiting, orthostatic hypotension, hallucinations).[9-11]

(b) Benserazide or Carbidopa

The effects of COMT inhibitors on the pharmacokinetics of dopa-decarboxylase inhibitors have also been studied. Neither **entacapone**[2] nor **tolcapone**[12] altered the pharmacokinetics of carbidopa. However, **tolcapone** increased the plasma levels of benserazide in patients with Parkinson's disease.[13] The benserazide levels remained within the usual range in patients taking levodopa with benserazide 25 mg and **tolcapone** 200 mg three times daily. However, with a 50-mg dose of benserazide the AUC of benserazide was increased 4.8-fold with standard-release preparation and 2.3-fold with a controlled-release preparation.[13]

Mechanism

When levodopa is given with a dopa-decarboxylase inhibitor such as carbidopa or benserazide, COMT becomes the major enzyme for metabolising levodopa, so inhibiting COMT delays the breakdown of levodopa.

Importance and management

When starting a COMT inhibitor, all patients should be informed of the symptoms of excess levodopa, and what to do if they occur. The manufacturers of entacapone suggest that if entacapone is started, the daily dose of levodopa should be reduced by about 10 to 30% (within the first few days or weeks) to accommodate these potential adverse effects.[10,14] This can be done by either extending the dosing intervals and/or by reducing the amount of levodopa per dose. Patients taking levodopa with benserazide may require a greater dose reduction than those taking levodopa with carbidopa because entacapone increases the bioavailability of standard levodopa with benserazide preparations by 5 to 10% more than standard levodopa with carbidopa.[10] The manufacturers of tolcapone say that the average reduction in the daily dose of levodopa required on starting tolcapone was 30%, and that greater than 70% of patients taking levodopa doses above 600 mg daily required such a reduction.[11,15] The clinical significance of the increase in benserazide levels is unknown, but the manufacturers advise good monitoring for benserazide adverse effects.[15]

1. Myllylä VV, Sotaniemi KA, Illi A, Suominen K, Keränen T. Effect of entacapone, a COMT inhibitor, on the pharmacokinetics of levodopa and on cardiovascular responses in patients with Parkinson's disease. *Eur J Clin Pharmacol* (1993) 45, 419–23.
2. Keränen T, Gordin A, Harjola V-P, Karlsson M, Korpela K, Pentikäinen PJ, Rita H, Seppälä L, Wikberg T. The effect of catechol-*O*-methyl transferase inhibition by entacapone on the pharmacokinetics and metabolism of levodopa in healthy volunteers. *Clin Neuropharmacol* (1993) 16, 145–56.
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9. Ruottinen HM, Rinne UK. Entacapone prolongs levodopa response in a one month double blind study in parkinsonian patients with levodopa related fluctuations. *J Neurol Neurosurg Psychiatry* (1996) 60, 36–40.
10. Comtess (Entacapone). Orion Pharma (UK) Ltd. UK Summary of product characteristics, September 2008.
11. Tasmar (Tolcapone). Valeant Pharmaceuticals North America. US Prescribing information, June 2009.
12. Jorga KM, Nicholl DJ. COMT inhibition with tolcapone does not affect carbidopa pharmacokinetics in parkinsonian patients on levodopa/carbidopa (Sinemet). *Br J Clin Pharmacol* (1999) 48, 449–52.
13. Jorga KM, Larsen JP, Beiske A, Schleimer M, Fotteler B, Schmitt M, Moe B. The effect of tolcapone on the pharmacokinetics of benserazide. *Eur J Neurol* (1999) 6, 211–19.
14. Comtan (Entacapone). Novartis. US Prescribing information, March 2009.
15. Tasmar (Tolcapone). Meda Pharmaceuticals. UK Summary of product characteristics, January 2009.

Levodopa + Dacarbazine

An isolated report describes a reduction in the effects of levodopa caused by dacarbazine.

Clinical evidence, mechanism, importance and management

A patient who had been treated surgically for melanoma, continued to receive dacarbazine 200 mg intravenously daily, intermittently, for sporadic positive melanuria. He later developed Parkinson's disease, and was given levodopa, which had no effect on his melanoma. However, each time he was given dacarbazine he complained that the effects of the levodopa with benserazide were reduced and his Schwab and England score (measures of activities of daily living) fell by as much as 25%. A subsequent double-blind study in this patient, using a modified Columbia Score, confirmed this.[1] The reasons are not understood, but as the serum dopamine levels remained unchanged it is suggested that competition between the two drugs at the blood-brain barrier may be the explanation.[1] Be alert for the need to modify levodopa treatment if dacarbazine is used concurrently. However, note also that the manufacturers contraindicate levodopa in those with a history of malignant melanoma because there is some suggestion that levodopa may activate this malignancy,[2] although some consider that, from the available evidence, this is unlikely.[3]

1. Merello M, Esteguy M, Perazzo F, Leiguarda R. Impaired levodopa response in Parkinson's disease during melanoma therapy. *Clin Neuropharmacol* (1992) 15, 69–74.
2. Madopar Capsules (Levodopa and Benserazide hydrochloride). Roche Products Ltd. UK Summary of product characteristics, April 2009.
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Levodopa + Food

The fluctuations in response to levodopa experienced by some patients may be due to the timing of meals and the type of diet, particularly the protein content, both of which can reduce the effects of levodopa. The effects of levodopa can be reduced by the amino acid methionine, and the blood levels of levodopa can be reduced by the amino acid tryptophan.

Clinical evidence

(a) Effects of meals

A study in patients with Parkinson's disease taking levodopa found that if taken with a meal, the mean absorption of levodopa from the gut and its peak plasma levels were reduced by 27% and 29%, respectively, and the peak plasma level was delayed by 34 minutes.[1] Other studies have found that the absorption of levodopa is delayed and peak plasma levels are reduced if the levodopa is taken with food rather than when fasting.[2-4]

(b) Effects of protein

1. Levodopa levels. A study in healthy subjects found that a low-protein meal (protein 10.5 g) caused a small reduction in levodopa absorption when compared with the fasting state, but also found that a high-protein meal (protein 30.5 g) was no different to the fasting state.[5] In another study, the protein content of the diet appeared to have little effect on levodopa pharmacokinetics.[6]

In contrast, other studies have found that a high daily intake of protein reduces the effects of levodopa (with or without a dopa-decarboxylase inhibitor), compared with a lower intake of protein.[7-9]

2. Subjective or clinical response. A study in 20 patients with Parkinson's disease who took levodopa with carbidopa four times daily with no-, low-, or high-protein snacks, each for one day, found no difference in markers of their Parkinson's disease (such as functional activity, dyskinesias, mental status).[10]

In a study, 11 patients with Parkinson's disease followed a restricted-protein diet in which they ingested up to about 10 g of protein during the day, but their intake was unrestricted during the evening. After following this diet for 6 weeks, 7 patients reported an improvement in their daytime mobility, and 6 patients indicated that they would continue with such a diet.[11]

A case report describes a patient with Parkinson's disease, receiving levodopa with carbidopa, who was admitted to an intensive care unit and developed severe rigidity after he was given continuous **enteral nutrition** with 1.4 g/kg of protein daily, despite continuing with his antiparkinsonian medication via the gastric tube. The protein content of the feed was reduced to 900 mg/kg per day, and given as bolus doses, with the levodopa given between the boluses. His parkinsonian symptoms improved with this feeding regime.[12]

(c) Effects of specific amino acids

A study found that the clinical response to a constant intravenous infusion of levodopa in 4 patients was unchanged by **glycine** and **lysine** but was reduced by **phenylalanine**, **leucine** and **isoleucine**, although the plasma levodopa levels remained unchanged.[1]

Fourteen patients taking levodopa for Parkinson's disease were given a **low-methionine** diet (0.5 g daily) for a period of 8 days. Seven patients were given additional **methionine** (4.5 g daily), while the other 7 were given placebo. Five out of the 7 given **methionine** 4.5 g daily had a definite worsening of their symptoms (gait, tremor, rigidity, etc.). The symptoms subsided when the **methionine** was withdrawn, although this took 7 to 10 days in one patient. Three out of the 7 given placebo (while following the low-methionine diet) had some subjective improvement.[13]

The blood levels of levodopa were markedly reduced in healthy subjects when levodopa 500 mg was taken with 1 g of **tryptophan**.[14] The clinical importance of this was not assessed.

(d) Broad bean pods (Vicia faba)

In a study, patients who took levodopa with carbidopa or benserazide additionally ate a portion (approximately 250 g) of cooked broad beans at least twice a day for up to 3 months. Three patients completed diary cards, and it was found that their 'on' periods were prolonged. One patient experienced an improvement in his 'on' periods each day even when he ate the broad beans on alternate days, and another patient reduced his dose of levodopa with carbidopa, from 500/50 mg to 375/37.5 mg each day.[15]

(e) Dietary fibre

In a study, 16 patients with Parkinson's disease and severe constipation took dietary fibre, to achieve a diet high in insoluble fibre (mean 28 g daily), with their usual medications. Plasma levodopa levels were increased significantly after increasing the fibre content of the diet, and there was improvement in constipation and motor function.[16]

Mechanism

Meals that delay gastric emptying increase the potential for peripheral metabolism of levodopa in the gut, which reduces the amount available for absorption. Conversely, a diet high in insoluble fibre may possibly increase levodopa absorption due to improved gastrointestinal motility. In addition some large neutral amino acids arising from the digestion of proteins can compete with levodopa for transport into the brain so that the therapeutic response may be reduced, whereas other amino acids do not have this effect.[1,5,8,17] Broad bean pods have been shown to contain a significant amount of levodopa, which may have contributed to the beneficial effect.

Importance and management

An established interaction, but unpredictable. As the fluctuations in the response of patients to levodopa may be influenced by what is eaten and when, a change in the pattern of drug and food administration on a trial-and-error basis may be helpful. Note that the manufacturer of *Madopar* recommends taking this preparation with food or slowly increasing the dose in the early stages of treatment to control anorexia, nausea, vomiting, and diarrhoea.[18] Multiple small doses of levodopa and distributing the intake of proteins may also diminish the effects of these interactions. Diets that conform to the recommended daily allowance of protein (said to be 800 mg/kg in this report) are reported to reduce this adverse drug-food interaction.[8]

The amino acid methionine is used therapeutically, and although information about its interaction with levodopa is very limited, the available data indicate that large doses of methionine should be avoided in patients taking levodopa.

1. Anon. Timing of meals may affect clinical response to levodopa. *Am Pharm* (1985) 25, 34–5.
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3. Baruzzi A, Contin M, Riva R, Procaccianti G, Albani F, Tonello C, Zoni E, Martinelli P. Influence of meal ingestion time on pharmacokinetics of orally administered levodopa in Parkinsonian patients. *Clin Neuropharmacol* (1987) 10, 527–37.
4. Crevoisier C, Zerr P, Calvi-Gries F, Nilsen T. Effects of food on the pharmacokinetics of levodopa in a dual-release formulation. *Eur J Pharm Biopharm* (2003) 55, 71–6.
5. Robertson DRC, Higginson I, Macklin BS, Renwick AG, Waller DG, George CF. The influence of protein containing meals on the pharmacokinetics of levodopa in healthy volunteers. *Br J Clin Pharmacol* (1991) 31, 413–17.
6. Simon N, Gantcheva R, Bruguerolle B, Viallet F. The effects of a normal protein diet on LevoDOPA plasma kinetics in advanced Parkinson's disease. *Parkinsonism Relat Disord* (2004) 10, 137–42.
7. Gillespie NG, Mena I, Cotzias GC, Bell MA. Diets affecting treatment of parkinsonism with levodopa. *J Am Diet Assoc* (1973) 62, 525–8.
8. Juncos JL, Fabbrini G, Mouradian MM, Serrati C, Chase TN. Dietary influences on the antiparkinsonian response to levodopa. *Arch Neurol* (1987) 44, 1003–1005.
9. Carter JH, Nutt JG, Woodward WR, Hatcher LF, Trotman TL. Amount and distribution of dietary protein affects clinical response to levodopa in Parkinson's disease. *Neurology* (1989) 39, 552–6.
10. Bozek CB, Suchowersky O, Purves S, Calne S, Calne DB. Sinemet in Parkinson's disease: efficacy with and without food. *Clin Neuropharmacol* (1986) 9, 196–9.
11. Paré S, Barr SI, Ross SE. Effect of daytime protein restriction on nutrient intakes of free-living Parkinson's disease patients. *Am J Clin Nutr* (1992) 55, 701–7.
12. Cooper MK, Brock DG, McDaniel CM. Interaction between levodopa and enteral nutrition. Ann Pharmacother (2008) 42, 439–42.
13. Pearce LA, Waterbury LD. L-methionine: a possible levodopa antagonist. *Neurology* (1974) 24, 640–1.
14. Weitbrecht W-U, Weigel K. Der einfluß von L-tryptophan auf die L-dopa-resorption. *Dtsch Med Wochenschr* (1976) 101, 20–2.
15. Apaydin H, Ertan S, Özekmekçi S. Broad bean (*Vicia faba*) – a natural source of L-dopa – prolongs "on" periods in patients with Parkinson's disease who have "on-off" fluctuations. *Mov Disord* (2000) 15, 164–6.
16. Astarloa R, Mena MA, Sánchez V, de la Vega L, de Yébenes JG. Clinical and pharmacokinetic effects of a diet rich in insoluble fiber on Parkinson disease. *Clin Neuropharmacol* (1992) 15, 375–80.
17. Daniel PM, Moorhouse SR, Pratt OE. Do changes in blood levels of other aromatic aminoacids influence levodopa therapy? *Lancet* (1976) i, 95.
18. Madopar Capsules (Levodopa and Benserazide hydrochloride). Roche Products Ltd. UK Summary of product characteristics, April 2009.

Levodopa + Indinavir

An isolated report describes a man taking levodopa who developed severe dyskinesias when given indinavir.

Clinical evidence, mechanism, importance and management

A 66-year-old man with idiopathic Parkinson's disease and AIDS was free of dyskinesias when taking levodopa with a dopa-decarboxylase inhibitor, although he had unpredictable fluctuations. One month after starting indinavir 2.4 g daily, lamivudine and zidovudine, he developed severe peak-dose dyskinesias, and the 'on' periods lasted all day, with no fluctuations. The antivirals were stopped and the dyskinesias improved within 5 days. Each antiviral was then given separately for 2 weeks. Only indinavir induced dyskinesias, which started after 3 days of concurrent use.[1]

The mechanism of this interaction is uncertain, but may be related to the

inhibition of cytochrome P450 by protease inhibitors such as indinavir.[1]

This appears to be the only report of this possible interaction. Bear in mind the possibility that the levodopa dose may need to be decreased if a protease inhibitor such as indinavir is required.

1. Caparros-Lefebvre D, Lannuzel A, Tiberghien F, Strobel M. Protease inhibitors enhance levodopa effects in Parkinson's disease. *Mov Disord* (1999) 14, 535.

Levodopa + Iron compounds

Ferrous sulfate can reduce the bioavailability of levodopa and carbidopa, and may possibly reduce the control of Parkinson's disease.

Clinical evidence

A study in 9 patients with Parkinson's disease found that a single 325-mg dose of **ferrous sulfate** reduced the AUC of levodopa by 30% and reduced the AUC of carbidopa by more than 75%. There was a trend towards an increase in disability, suggesting a worsening of disease, but this did not reach statistical significance. Some, but not all of the patients had some deterioration in the control of their disease.[1]

In another study, 8 healthy subjects were given a single 250-mg dose of levodopa, with and without a single 325-mg dose of **ferrous sulfate**, and the plasma levodopa levels were measured for the following 6 hours. Peak plasma levodopa levels and the levodopa AUC were reduced by 55% and 51%, respectively. Those subjects who had the highest peak levels and greatest absorption when given levodopa alone, had the greatest reductions when they were also given **ferrous sulfate**.[2]

Mechanism

Ferrous iron rapidly oxidises to ferric iron at the pH values found in the gastrointestinal tract. Ferric iron binds strongly to carbidopa and levodopa to form chelation complexes that are poorly absorbed.[2-4]

Importance and management

Information appears to be limited to these single-dose and *in vitro* studies. The importance of this interaction in patients taking both drugs long-term does not appear to have been studied, but the extent of the reductions in absorption (30 to 50%), and the hint of worsening control,[1] suggests that this interaction may be of clinical importance in some patients. Be alert for any evidence of this. Separating the administration of the iron and levodopa as much as possible is likely to prove effective, as this appears to be an absorption interaction.

1. Campbell NRC, Rankine D, Goodridge AE, Hasinoff BB, Kara M. Sinemet-ferrous sulphate interaction in patients with Parkinson's disease. *Br J Clin Pharmacol* (1990) 30, 599–605.
2. Campbell NRC, Hasinoff B. Ferrous sulfate reduces levodopa bioavailability: chelation as a possible mechanism. *Clin Pharmacol Ther* (1989) 45, 220–5.
3. Campbell RRA, Hasinoff B, Chernenko G, Barrowman J, Campbell NRC. The effect of ferrous sulfate and pH on L-dopa absorption. *Can J Physiol Pharmacol* (1990) 68, 603–7.
4. Greene RJ, Hall AD, Hider RC. The interaction of orally administered iron with levodopa and methyldopa therapy. *J Pharm Pharmacol* (1990) 42, 502–4.

Levodopa + Isoniazid

There is evidence that isoniazid can reduce the control of Parkinson's disease in patients taking levodopa. An isolated case report describes hypertension, tachycardia, flushing and tremor in a patient, which was attributed to the use of levodopa with isoniazid.

Clinical evidence

Following the observation that levodopa-induced dyskinesias were reduced by isoniazid in one patient, a further study was undertaken in 20 other patients taking levodopa with a dopa-decarboxylase inhibitor. It was found that isoniazid (average dose 290 mg daily, range 100 to 800 mg daily) reduced the dyskinesias of 18 of the 20 patients. However, the reduction in dyskinesias was accompanied by an intolerable worsening of parkinsonism, shown by decreased mobility and greater 'off' periods. The reduction in mobility was so severe that the isoniazid had to be stopped immediately in several cases and was discontinued after an average of 5.2 weeks in all the patients. Control of parkinsonism was then restored.[1] Another patient taking levodopa with carbidopa similarly had a deterioration in the control of parkinsonism within one to 2 weeks of starting isoniazid with rifampicin (*Rifinah*). When the antitubercular drugs were stopped, the patient's motor performance improved ('on' period lengthened by 75%), the levodopa AUC rose by 37%, its half-life doubled, and its maximum plasma levels fell by 33%.[2]

An isolated report describes a patient taking levodopa who developed hypertension, agitation, tachycardia, flushing and severe non-parkinsonian tremor after starting to take isoniazid. He recovered when the isoniazid was stopped.[3]

Mechanism

Not understood. Metabolic studies in one patient suggest that isoniazid inhibits dopa-decarboxylase,[2] although other mechanisms have been proposed.[1,2] The isolated case of hypertension and tachycardia is also not understood, but it has been suggested that it may have been due to a weak monoamine oxidase inhibitory effect of the isoniazid metabolites. See 'MAOIs or RIMAs + Levodopa', p.1377, for further explanation.

Importance and management

Information seems to be limited to the reports cited. If concurrent use is thought to be necessary, be alert for any evidence of a reduction in the control of the parkinsonism, and be aware that drug treatment may need to be modified. One of the reports suggests that it may take 15 to 20 days or more for the deterioration in parkinsonian symptoms to occur.[1] The isolated case seems not to be of general importance.

1. Gershanik OS, Luquin MR, Scipioni O, Obeso JA. Isoniazid therapy in Parkinson's disease. *Mov Disord* (1988) 3, 133–9.
2. Wenning GK, O'Connell MT, Patsalos PN, Quinn NP. A clinical and pharmacokinetic case study of an interaction of levodopa and antituberculous therapy in Parkinson's disease. *Mov Disord* (1995) 10, 664–7.
3. Morgan JP. Isoniazid and levodopa. *Ann Intern Med* (1980) 92, 434.

Levodopa + MAO-B inhibitors

No serious interaction usually occurs between levodopa and selegiline, although the dose of levodopa may need to be reduced when selegiline is added. Levodopa does not affect rasagiline clearance.

Clinical evidence

(a) Rasagiline

The manufacturer notes that levodopa had no effect on rasagiline clearance.[1]

(b) Selegiline

The combination of levodopa and selegiline has been very extensively used. No serious hypertensive reactions of the kind seen with non-selective MAOIs (see 'MAOIs or RIMAs + Levodopa', p.1377) seem to occur. No adverse pharmacokinetic interactions have been reported,[2,3] and serious adverse interactions are said to be lacking.[4,5] Many studies have reported the beneficial effects of this combination,[6-11] but one has suggested that it may result in increased mortality in patients with early, mild Parkinson's disease.[12] Although no clear reason for this increase in mortality could be found, it appeared that patients receiving selegiline with levodopa were more likely to have possible dementia and have had recent falls, postural dizziness, and shortness of breath.[13] Urinary retention has also been suggested as being associated with this drug combination.[14] Selegiline potentiates the effects of levodopa, so the usual adverse effects (dyskinesias, nausea, agitation, confusion, hallucinations, headache, postural hypotension, cardiac arrhythmias, and vertigo) may be increased, particularly if the levodopa dose is too high.[15]

Mechanism

MAO-B inhibitors prevent the metabolism of dopamine, therefore additive dopaminergic effects occur with levodopa.

Importance and management

No adverse interactions usually occur if levodopa and selegiline are given concurrently. However, the manufacturers say that after adding selegiline a reduction in the dose of levodopa is usually required to avoid symptoms

of levodopa excess (about 10 to 30% is suggested).[15-17] Reduction of the levodopa dose should be gradual, in steps of 10% every 3 to 4 days.[16] It has been suggested that the concurrent use is probably best avoided in patients with postural hypotension, frequent falls, confusion and dementia.[13]

1. Azilect (Rasagiline mesilate). Teva Pharmaceuticals Ltd. UK Summary of product characteristics, November 2009.
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15. Eldepryl (Selegiline hydrochloride). Orion Pharma (UK) Ltd. UK Summary of product characteristics, June 2009.
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Levodopa + Methyldopa

Methyldopa can increase the effects of levodopa and permit a reduction in the dose in some patients taking levodopa alone, but the benefit may only be temporary and dyskinesias may be worsened in some patients. This interaction would not be expected to be significant in a patient taking levodopa with benserazide or carbidopa but this does not appear to have been studied. A small increase in the hypotensive actions of methyldopa may also occur.

Clinical evidence

(a) Effects on the response to levodopa

A double-blind, crossover study in 10 patients with Parkinson's disease who had been taking levodopa alone for 12 to 40 months, found that the optimum daily dose of levodopa fell by 68% with methyldopa 1.92 g daily, and by 50% with methyldopa 800 mg daily.[1]

Other reports in patients taking levodopa alone describe reductions in the levodopa dose of up to 30%[2] and 70%[3] during the concurrent use of methyldopa. Another report states that the control of Parkinson's disease improved during the concurrent use of methyldopa in some patients taking levodopa alone, but the dyskinesias were worsened in others.[4] Similar findings have been reported elsewhere: in some cases an initial improvement was followed by a loss of benefit.[5] Methyldopa on its own can cause a reversible parkinsonian-like syndrome.[6-8]

(b) Effects on the response to methyldopa

A study in 18 patients with Parkinson's disease taking levodopa alone found that the concurrent use of levodopa and methyldopa lowered the blood pressure. The doses used did not affect the systolic blood pressure when given alone, whereas daily doses of 1 to 2.5 g of levodopa with methyldopa 500 mg caused a 12/6 mmHg fall in blood pressure. No change in the control of the Parkinson's disease was seen, but the study lasted only a few days.[9] In a study of 41 patients who took methyldopa in daily doses of 125 mg to 1.25 g with levodopa 1 g to 7 g daily, two patients experienced a significant drop in blood pressure.[5]

Mechanism

Methyldopa inhibits the breakdown of levodopa outside the brain (by dopa decarboxylase) so that more is available to exert its therapeutic effects.

The increased hypotension may simply be due to the additive effects of the two drugs.

Importance and management

Well documented. Concurrent use need not be avoided but the outcome should be well monitored. In patients taking levodopa alone, the use of methyldopa may allow a reduction in the dose of the levodopa (the reports cited[1-3] give figures of 30 to 70%) and may enhance the control of Parkinson's disease, but it should also be borne in mind that in some patients dyskinesias may be worsened. However, in the presence of carbidopa or benserazide the dopa decarboxylase effects of methyldopa would be expected to be less significant and so it seems unlikely that a dose reduction of levodopa would be required. The increased hypotensive effects seem to be small, but they too should be checked.

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8. Strang RR. Parkinsonism occurring during methyldopa therapy. *Can Med Assoc J* (1966) 95, 928–9.
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Levodopa + Methylphenidate

Methyldopa does not appear to affect the levels of levodopa or the response to levodopa.

Clinical evidence, mechanism, importance and management

A study in 12 patients with Parkinson's disease who took methylphenidate 400 micrograms/kg three times daily in addition to their normal antiparkinsonian medicines which included levodopa, found that methylphenidate had no clinically significant effect on the response to levodopa as measured by tapping speed, a walking test or the presence of dyskinesia. Methylphenidate did not significantly alter the plasma levels of levodopa.[1]

1. Nutt JG, Carter JH, Carlson NE. Effects of methylphenidate on response to oral levodopa. A double-blind clinical trial. *Arch Neurol* (2007) 64, 319–23.

Levodopa + Mirtazapine

An isolated report describes the development of serious psychosis, which was attributed to an interaction between levodopa and mirtazapine.

Clinical evidence, mechanism, importance and management

A 44-year-old woman taking levodopa with carbidopa, pergolide, selegiline and memantine for Parkinson's disease, started taking mirtazapine, in increasing doses rising from 15 to 60 mg daily over 24 days, for depression, labile mood, anxiety, social withdrawal and sleep disturbance. She initially improved, but then major depression and psychosis developed, and on day 26 she attempted self-strangulation. She recovered when the mirtazapine, memantine and selegiline were stopped and low-dose clozapine started. The authors concluded that the reaction was attributable to dopamine-induced psychosis triggered by the addition of mirtazapine to levodopa.[1] This appears to be an isolated case, and as such, no general conclusions can be drawn.

1. Normann C, Hesslinger B, Frauenknecht S, Berger M, Walden J. Psychosis during chronic levodopa therapy triggered by the new antidepressive drug mirtazapine. *Pharmacopsychiatry* (1997) 30, 263–5.

Levodopa + Papaverine

Case reports describe a deterioration in the control of parkinsonism when patients taking levodopa were given papaverine, but a controlled study did not find an interaction.

Clinical evidence

(a) Levodopa effects reduced

A woman with long-standing parkinsonism, well controlled with levodopa (and the later addition of carbidopa), began to have a steady worsening of her parkinsonism within a week of starting papaverine 100 mg daily for cerebral vascular insufficiency. The deterioration continued until the papaverine was withdrawn. The normal response to levodopa returned within a week. Four other patients had a similar response.[1] Two other similar cases have been described in another report.[2]

(b) Levodopa effects unchanged

A double-blind, crossover study in 9 patients with parkinsonism, taking levodopa (range 100 to 750 mg daily) with a dopa-decarboxylase inhibitor, did not find any changes in disease control when they also took papaverine hydrochloride 150 mg daily for 3 weeks. Two patients were also taking bromocriptine 40 mg daily and two patients were also taking trihexyphenidyl 15 mg daily.[3]

A study in 6 healthy subjects, who took a single 500-mg dose of levodopa before and after taking papaverine 150 mg twice daily for 2 weeks, found that papaverine did not affect the increase in serum growth hormone and the decrease in prolactin levels caused by levodopa.[4]

Mechanism

Not understood. One suggestion is that papaverine blocks the dopamine receptors in the striatum of the brain, thereby inhibiting the effects of the levodopa.[1,5] Another is that papaverine may have a reserpine-like action on the vesicles of adrenergic neurones[1,6] (i.e. it can deplete dopamine stores).

Importance and management

Direct information seems to be limited to the reports cited. Concurrent use can apparently be uneventful. However, in the light of the reports of adverse interactions it would be prudent to monitor the outcome closely. Carefully controlled studies can provide a good picture of the general situation, but may not necessarily identify the occasional patient who may be affected by an interaction.

1. Duvoisin RC. Antagonism of levodopa by papaverine. *JAMA* (1975) 231, 845.
2. Posner DM. Antagonism of levodopa by papaverine. *JAMA* (1975) 233, 768.
3. Montastruc JL, Rascol O, Belin J, Ane M, Rascol A. Does papaverine interact with levodopa in Parkinson's disease? *Ann Neurol* (1987) 22, 558–9.
4. Cooper DS, Jacobs LS. Failure of papaverine to alter L-dopa-influenced GH and PRL secretion. *J Clin Endocrinol Metab* (1977) 44, 585–7.
5. Gonzalez-Vegas JA. Antagonism of dopamine-mediated inhibition in the nigro-striatal pathway: a mode of action of some catatonia-inducing drugs. *Brain Res* (1974) 80, 219–28.
6. Cubeddu L, Weiner N. Relationship between a granular effect and exocytotic release of norepinephrine by nerve stimulation. *Pharmacologist* (1974) 16, 190.

Levodopa + Penicillamine

Penicillamine can raise levodopa levels in a few patients. This may improve the control of the parkinsonism but the adverse effects of levodopa may also be increased.

Clinical evidence, mechanism, importance and management

A patient with Parkinson's disease taking levodopa with a dopa-decarboxylase inhibitor [probably carbidopa] had a 60% increase in his levodopa plasma levels after taking penicillamine 600 mg daily. This resulted in improved control of symptoms but with an increase in dyskinesia. It was noted that this patient had slightly low serum copper and ceruloplasmin levels.[1] In another study 2 patients with Parkinson's disease taking levodopa also improved when they also took penicillamine, but levodopa levels were apparently not measured. Again it was noted that the patients had slightly low copper and ceruloplasmin levels. In another 4 similar patients the effects of penicillamine on levodopa seemed absent in the presence of normal copper and ceruloplasmin levels.[2] The authors of this report[2] attribute the improvement in parkinsonism to the copper chelating properties of penicillamine. However, the authors of the other report[1] suggest that the effect of penicillamine would not be this rapid, and suggested that penicillamine must be affecting levodopa pharmacokinetics.

This limited evidence suggests that the concurrent use of levodopa and penicillamine need not be avoided, and in some patients parkinsonian symptoms may be improved. However, if both drugs are given, monitor the effects as an increase in the adverse effects of levodopa is also possible.

1. Mizuta E, Kuno S. Effect of D-penicillamine on pharmacokinetics of levodopa in Parkinson's disease. *Clin Neuropharmacol* (1993) 16, 448–50.
2. Sato M, Yamane K, Oosawa Y, Tanaka H, Shirata A, Nagayama T, Maruyama S. Two cases of Parkinson's disease whose symptoms were markedly improved by D-penicillamine. A study with emphasis on cases displaying a slightly low level of serum copper and ceruloplasmin. *Neurol Ther Chiba* (1992) 9, 555–9.

Levodopa + Phenylbutazone

A single case report describes antagonism of the effects of levodopa by phenylbutazone.

Clinical evidence, mechanism, importance and management

A patient (who was very sensitive to levodopa) found that he was only able to prevent the involuntary movements of his tongue, jaw, neck and limbs caused by levodopa, by taking frequent small doses (125 mg) of levodopa. He was able to suppress the levodopa adverse effects with phenylbutazone. However, the phenylbutazone also lessened the therapeutic effect of the levodopa.[1] The reason is not understood. This interaction has not been confirmed, and its general importance is not known.

1. Wodak J, Gilligan BS, Veale JL, Dowty BJ. Review of 12 months' treatment with L-dopa in Parkinson's disease, with remarks on unusual side effects. *Med J Aust* (1972) 2, 1277–82.

Levodopa + Phenytoin

The therapeutic effects of levodopa can be reduced or abolished by phenytoin.

Clinical evidence, mechanism, importance and management

A study in 5 patients taking levodopa 630 to 4600 mg (four also taking carbidopa 150 to 225 mg daily) for Parkinson's disease, found that when they also took phenytoin in doses of up to 500 mg daily for 5 to 19 days the levodopa-induced dyskinesias were relieved, but the beneficial effects of the levodopa on parkinsonism were reduced or abolished. The patients became slow, rigidity re-emerged, and some of them became unable to get out of a chair. Within 2 weeks of stopping the phenytoin, their parkinsonism was again well controlled by the levodopa.[1] Despite many suggestions, the mechanism of this interaction is not understood. Information relating to a reduction in efficacy of levodopa seems to be limited to this study, nevertheless it would seem prudent to monitor concurrent use for any evidence of reduced levodopa efficacy.

1. Mendez JS, Cotzias GC, Mena I, Papavasiliou PS. Diphenylhydantoin blocking of levodopa effects. *Arch Neurol* (1975) 32, 44–6.

Levodopa + Pyridoxine (Vitamin B_6)

The effects of levodopa are reduced or abolished by pyridoxine, but this interaction does not occur when levodopa is given with the dopa-decarboxylase inhibitors carbidopa or benserazide, as is usual clinical practice.

Clinical evidence

A study in 25 patients taking levodopa alone found that if they were given high doses of pyridoxine (750 mg to 1 g daily), the effects of the levodopa were reduced within 24 hours, and were completely abolished within 3 to 4 days. Daily doses of pyridoxine 50 to 100 mg also reduced or abolished the effects of levodopa, and an increase in the signs and symptoms of parkinsonism occurred in 8 out of 10 patients taking only 5 to 10 mg of pyridoxine daily.[1]

The antagonism of the effects of levodopa (given without a dopa-decar-

boxylase inhibitor) by pyridoxine has been described in numerous other reports.[1-6]

In contrast, a study in 15 patients with Parkinson's disease taking long-term levodopa found that a single 250-mg oral dose of levodopa produced a peak dopa level of 600 nanograms/mL. When pyridoxine 50 mg was also given, the peak plasma levels of dopa fell by almost 70%. When the levodopa was given with carbidopa 50 mg the peak plasma dopa levels were 1300 nanograms/mL, and were not significantly affected by pyridoxine.[6] The results from a subset of these patients have been reported elsewhere.[7] The absence of an interaction in the presence of a dopa-decarboxylase inhibitor is confirmed in another report.[8]

Mechanism

The conversion of levodopa to dopamine within the body requires the presence of pyridoxal-5-phosphate (derived from pyridoxine) as a co-factor. When dietary amounts of pyridoxine are high, the peripheral metabolism of levodopa by dopa-decarboxylase is increased so that less is available for entry into the CNS, and its effects are reduced accordingly. Pyridoxine may also alter levodopa metabolism by Schiff-base formation. However, in the presence of dopa-decarboxylase inhibitors such as carbidopa or benserazide, this peripheral metabolism of levodopa is reduced and much larger amounts are available for entry into the CNS, even if quite small doses are given. Therefore, even in the presence of large amounts of pyridoxine, the peripheral metabolism remains unaffected and the serum levels of levodopa are virtually unaltered.

Importance and management

A clinically important, well documented and well established interaction, but principally of historical interest now as levodopa is rarely used alone. The problem of this interaction can be totally solved by giving levodopa with a dopa-decarboxylase inhibitor such as carbidopa or benserazide. In the rare cases that levodopa is used alone, pyridoxine in doses as low as 5 mg daily can reduce the effects of levodopa and should therefore be avoided. Warn patients about proprietary pyridoxine-containing preparations such as multivitamins and supplements. Some breakfast cereals are fortified with pyridoxine and other vitamins, but the amounts are usually too small to matter (e.g. a 30 g serving of Kellogg's Corn Flakes or Rice Krispies (UK products) contains only about 0.5 mg of pyridoxine). There is no good clinical evidence to suggest that a low-pyridoxine diet is desirable, and indeed it may be harmful as the normal dietary requirements are about 2 mg daily.

1. Duvoisin RC, Yahr MD, Coté LD. Pyridoxine reversal of L-dopa effects in parkinsonism. *Trans Am Neurol Assoc* (1969) 94, 81–4.
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6. Mars H. Levodopa, carbidopa, and pyridoxine in Parkinson disease: metabolic interactions. *Arch Neurol* (1974) 30, 444–7.
7. Mars H. Metabolic interactions of pyridoxine, levodopa, and carbidopa in Parkinson's disease. *Trans Am Neurol Assoc* (1973) 98, 241–5.
8. Papavasiliou PS, Cotzias GC, Düby SE, Steck AJ, Fehling C, Bell MA. Levodopa in parkinsonism: potentiation of central effects with a peripheral inhibitor. *N Engl J Med* (1972) 285, 8–14.

Levodopa + Rauwolfia alkaloids

The effects of levodopa are opposed by rauwolfia alkaloids such as reserpine.

Clinical evidence, mechanism, importance and management

Reserpine and other rauwolfia alkaloids deplete the brain of monoamines, including dopamine, thereby reducing their effects.[1] This can lead to parkinsonian-like symptoms, and may oppose the actions of levodopa. There are not only sound pharmacological reasons for believing this to be an interaction of clinical importance, but a reduction in the antiparkinsonian activity of levodopa has been observed in patients given **reserpine**.[2] The rauwolfia alkaloids should be avoided in patients with Parkinson's disease, whether or not they are taking levodopa.

1. Bianchine JR, Sunyapridakul L. Interactions between levodopa and other drugs: significance in the treatment of Parkinson's disease. *Drugs* (1973) 6, 364–88.
2. Yahr MD. Personal communication, February 1977.

Levodopa + Spiramycin

The plasma levels of levodopa (given with carbidopa) are reduced by spiramycin, thereby reducing its therapeutic effects.

Clinical evidence

The observation of a patient with Parkinson's disease taking levodopa with carbidopa whose condition became less well-controlled when spiramycin was taken, prompted further study. Levodopa 250 mg with carbidopa 25 mg was given to 7 healthy subjects after they had taken spiramycin 1 g twice daily for 3 days. The spiramycin reduced the AUC of levodopa by 57%, and its maximum plasma levels fell by about 20%, which was not statistically significant. The relative bioavailability of levodopa was only 43%. The plasma levels of the carbidopa were barely detectable.[1]

Mechanism

Not fully established. In some way spiramycin markedly reduces the absorption of carbidopa, possibly by forming a non-absorbable complex in the gut or by accelerating its transit through the gut. As a result, not enough carbidopa is absorbed to inhibit the peripheral metabolism of the levodopa by dopa-decarboxylase, so that the effects of the levodopa are reduced.[1]

Importance and management

Information is very limited, but the interaction appears to be established and of clinical importance. The management of this interaction is unclear, but as it appears to be due to an effect on absorption it would seem prudent to try to separate the dosing of these two drugs by as much as possible, although this may be difficult with some levodopa regimens. Monitor the outcome of concurrent use on the control of Parkinson's disease. It is not known whether other macrolide antibacterials behave in a similar way, or whether spiramycin affects levodopa with benserazide. More study is needed.

1. Brion N, Kollenbach K, Marion MH, Grégoire A, Advenier C, Pays M. Effect of a macrolide (spiramycin) on the pharmacokinetics of L-dopa and carbidopa in healthy volunteers. *Clin Neuropharmacol* (1992) 15, 229–35.

Levodopa + SSRIs and related antidepressants

The use of an SSRI is often beneficial in parkinsonian patients taking levodopa, to treat the depression associated with the disease. However, sometimes parkinsonian symptoms are worsened.

Clinical evidence

A number of reviews have been published about the extrapyramidal effects of SSRIs.[1,2] A retrospective study of patients taking levodopa, found that 15 patients taking an SSRI (**fluoxetine**, **fluvoxamine**, **paroxetine**) required faster increases in their antiparkinsonian drugs than 31 patients taking a tricyclic antidepressant, or 304 patients taking antiparkinsonian drugs only.[3] However, a retrospective study of the effect of SSRIs or serotonergic antidepressants, in patients taking levodopa, found that the change in antiparkinsonian medication in 90 patients taking SSRIs was similar to that in 99 patients taking tricyclic antidepressants. Furthermore, initiation of antidepressants with a high inhibition of serotonin reuptake was not associated with a change in antiparkinsonian drug treatment compared with antidepressants with a low inhibition of serotonin reuptake.[4] Other cases and studies outlined below have shown conflicting outcomes.

(a) Citalopram

A case report describes an 81-year-old woman who experienced an increase in the duration of her tremor and 'off' periods 2 days after starting to take citalopram 20 mg daily. She was also taking levodopa with benserazide 1 g daily and alprazolam 1.5 mg daily. One month after stopping citalopram, her parkinsonian symptoms had improved.[5]

A study in 44 patients with Parkinson's disease taking levodopa with carbidopa, 30 of whom received citalopram 10 mg daily increasing to 20 mg daily, found an improvement in bradykinesia in those patients taking citalopram.[6]

(b) Fluoxetine

Four patients taking levodopa 375 to 990 mg daily, a dopa-decarboxylase inhibitor (drug and dose not stated) and amantadine (dose not stated), had a deterioration in the control of their parkinsonism when they were also given fluoxetine 20 mg daily for 8 to 11 weeks. The fluoxetine was withdrawn and their motor performance was restored. The antidepressant efficacy of fluoxetine was not found to be substantial in any of the 4 patients.[7] A case report describes a 34-year-old woman whose dystonia was well controlled by levodopa with carbidopa 100/25 mg three times daily. Five days after starting to take fluoxetine 20 mg daily her dystonia and torticollis returned. Two days after stopping the fluoxetine her symptoms started to improve, and had resolved in about a week.[8] Another patient taking levodopa developed frequent hallucinations after the addition of fluoxetine. They resolved when the fluoxetine was withdrawn.[9]

In a retrospective study of 23 parkinsonian patients who were given fluoxetine up to 40 mg daily, 20 patients had no change in the control of their parkinsonism but 3 others experienced a worsening in their Parkinson's disease signs.[10]

However, in a study, 14 patients with Parkinson's disease whose treatment included levodopa, started to take fluoxetine 20 mg daily for one month. One patient dropped out because of intolerable asthenia. Of the remaining 13 patients there was no change in rigidity or bradykinesia, but tremor was significantly reduced.[11]

(c) Nefazodone

A case report describes a 70-year-old man whose Parkinson's disease was well controlled by levodopa with benserazide and bromocriptine, but when he started to take nefazodone, he developed severe bradykinesia, rigidity, gait instability and akathisia. He stopped taking nefazodone, and the dose of levodopa with benserazide was increased to 500 mg daily with improvement in his condition.[12] However, in a small study, nefazodone was found to be of benefit in treating depression in 9 patients taking levodopa for Parkinson's disease, and motor symptoms also improved.[13]

(d) Paroxetine

In a placebo-controlled study in 14 patients with Parkinson's disease, paroxetine 10 mg daily for 5 days and then 20 mg daily for 9 days did not significantly alter the response to an infusion of levodopa 1 mg/kg per hour given for 2 hours. Several patients reported a reduction in their sense of balance, and one patient fell, resulting in a pelvic fracture.[14]

A case report describes visual hallucinations in a 79-year-old woman taking levodopa with carbidopa when she started to take paroxetine 20 mg daily. The hallucinations stopped when paroxetine was withdrawn.[15] It has been suggested that the hallucinations may have been related to the Parkinson's disease and use of levodopa, rather than an interaction with paroxetine.[16]

(e) Sertraline

A review of 101 patients receiving treatment for Parkinson's disease and who also took an antidepressant, identified 5 patients who experienced a worsening of their Parkinson's disease, possibly attributed to the use of an SSRI. Three of these patients were taking sertraline, one **fluoxetine**, and one took **fluoxetine** followed by sertraline. Four of the 5 patients who experienced a worsening of their symptoms were also taking selegiline.[17] See also 'MAO-B inhibitors + SSRIs or SNRIs', p.808 for details of possible interactions between selegiline and the SSRIs.

(f) Venlafaxine

A case report describes a 32-year-old woman who took levodopa with carbidopa 50/1.25 mg twice daily to treat tremor, dystonia and rigidity. She started to take venlafaxine, and within 4 days her dystonia and trembling returned. Two days after stopping the venlafaxine her symptoms started to improve, and had resolved in about a week.[8]

Mechanism

Not understood. The mechanism is likely to involve a complex interaction between various neurotransmitters.[2] Extrapyramidal effects are rare but recognised adverse effects of SSRIs.[1,2]

Importance and management

Although the information is conflicting, it seems that in some cases parkinsonism can be worsened by SSRIs, venlafaxine or nefazodone. Concurrent use is valuable and need not be avoided, but monitor the outcome and withdraw the antidepressant if necessary.

1. Anonymous. Extrapyramidal effects of SSRI antidepressants. *Prescrire Int* (2001) 10, 118–19.
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9. Lauterbach EC. Dopaminergic hallucinosis with fluoxetine in Parkinson's disease. *Am J Psychiatry* (1993) 150, 1750.
10. Caley CF, Friedman JH. Does fluoxetine exacerbate Parkinson's disease? *J Clin Psychiatry* (1992) 53, 278–282.
11. Montastruc J-L, Fabre N, Blin O, Senard J-M, Rascol O, Rascol A. Does fluoxetine aggravate Parkinson's disease? A pilot prospective study. *Mov Disord* (1995) 10, 355–7.
12. Benazzi F. Parkinson's disease worsened by nefazodone. *Int J Geriatr Psychiatry* (1997) 12, 1195.
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16. Jansen Steur ENH. Hallucinaties veroorzaakt door paroxetine bij gebruik van de combinatie levodopa-carbidopa. *Ned Tijdschr Geneeskd* (2002) 146, 1056–7.
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Levodopa + Tetrabenazine

Tetrabenazine may interfere with the effects of levodopa.

Clinical evidence, mechanism, importance and management

Caution is advised when tetrabenazine is given with levodopa, because it can deplete dopamine and can cause parkinsonian adverse effects. Tetrabenazine may therefore be expected to diminish the effects of levodopa and interfere with its use in the management of Parkinson's disease. One manufacturer of levodopa states that concurrent use should be avoided where possible, but if both drugs are considered essential, extreme care should be exercised and patients should be monitored for any signs of potentiation, antagonism or other unusual adverse effects.[1]

1. Madopar Capsules (Levodopa and Benserazide hydrochloride). Roche Products Ltd. UK Summary of product characteristics, April 2009.

Levodopa + Tricyclic antidepressants

The concurrent use of levodopa and the tricyclics is usually uneventful although two unexplained hypertensive crises have occurred when imipramine or amitriptyline was given with levodopa and carbidopa.

Clinical evidence

A hypertensive crisis (blood pressure 210/110 mmHg) associated with agitation, tremor and generalised rigidity developed in a woman taking 6 tablets of levodopa 100 mg with carbidopa 10 mg daily the day after she started to take **imipramine** 25 mg three times daily. The **imipramine** was stopped and she recovered over the following 24 hours. The same reaction occurred again when she was later accidentally given **amitriptyline** 25 mg three times daily.[1] A similar hypertensive reaction (a rise in blood pressure from 190/110 mmHg to 270/140 mmHg) occurred over 34 hours in another woman taking **amitriptyline** 20 mg at night when she was given levodopa 50 mg with carbidopa 5 mg and metoclopramide 10 mg, both three times daily. This resolved when all the drugs were stopped.[2]

Mechanism

Not understood.

Importance and management

Information seems to be limited to these reports. Concurrent use is normally successful and uneventful.[3-5] However, be alert for the possibility of a hypertensive reaction, which resolves if the tricyclic antidepressant is withdrawn. See also 'Levodopa + Antimuscarinics', p.796 for interactions due to the antimuscarinic adverse effects of tricyclic antidepressants.

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2. Rampton DS. Hypertensive crisis in a patient given Sinemet, metoclopramide, and amitriptyline. *BMJ* (1977) 3, 607–8.
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5. van Wieringen A, Wright J. Observations on patients with Parkinson's disease treated with L-dopa. I. Trial and evaluation of L-dopa therapy. *S Afr Med J* (1972) 46, 1262–6.

MAO-B inhibitors + Dextromethorphan

The manufacturer of rasagiline[1] suggests that its use with dextromethorphan should be avoided. Similarly, some consider that patients taking selegiline should try to avoid dextromethorphan.[2] These warnings are based on the serious adverse reactions (serotonin syndrome or similar) that have rarely occurred when dextromethorphan has been used with non-selective MAOIs, see 'MAOIs or RIMAs + Dextromethorphan', p.1375. The likelihood of any interaction with MAO-B inhibitors would appear to be very small, but because of the potential severity, some caution would appear to be prudent.

1. Azilect (Rasagiline mesilate). Teva Pharmaceuticals Ltd. UK Summary of product characteristics, November 2009.
2. Jacob JE, Wagner ML, Sage JI. Safety of selegiline with cold medications. *Ann Pharmacother* (2003) 37, 438–41.

MAO-B inhibitors + MAOIs or RIMAs

Marked orthostatic hypotension has been seen in two patients taking iproniazid or tranylcypromine with trifluoperazine when they were given selegiline. When moclobemide is given with selegiline, restriction of dietary tyramine is necessary, and there may be an increased risk of hypotensive reactions. Some manufacturers of MAO-B inhibitors contraindicate the concurrent use of MAOIs or RIMAs.

Clinical evidence, mechanism, importance and management

(a) MAOIs

In a pilot study, one patient taking **iproniazid** 150 mg daily developed severe orthostatic hypotension on two occasions within an hour of taking **selegiline** 5 mg. Two other patients (one taking **tranylcypromine** with trifluoperazine and one taking **tranylcypromine** with trifluoperazine and **isocarboxazid**) did not have this reaction to **selegiline** 5 mg twice daily. The authors mention another patient who similarly developed postural hypotension on two occasions within 2 hours of taking **selegiline** 5 mg. He had stopped taking **tranylcypromine** with trifluoperazine, 4 weeks previously.[1] This evidence suggests that **selegiline** should be given with caution to patients taking, or who have recently stopped, non-selective MAOIs. One UK manufacturer of **selegiline**[2] and the manufacturer of **rasagiline**[3] contraindicate the concurrent use of non-selective MAOIs. The manufacturer of rasagiline includes **St John's wort** (*Hypericum perforatum*) in this contraindication, because they state that it has MAO inhibitory properties.[3] At least 14 days should elapse between stopping **rasagiline** or **selegiline** and starting an MAOI.[2,3]

(b) RIMAs

A study in 24 healthy subjects, designed to assess the safety and tolerability of giving **moclobemide** 100 to 400 mg and **selegiline** 5 mg twice daily, sequentially or concurrently, found that the adverse effects were no greater under steady-state conditions than with either drug alone, but the sensitivity to tyramine was considerably increased. The mean tyramine sensitivity factor for **moclobemide** alone was 2 to 3, for **selegiline** alone was 1.4, and for **moclobemide** with **selegiline** was 8 to 9 (and even 18 in one subject).[4,5] The reason for this effect is, that when taken together, the **moclobemide** inhibits MAO-A while **selegiline** inhibits MAO-B, so that little or no MAO activity remains available to metabolise the tyramine. However, unexpectedly, the combined effect was more than additive.[5] **Selegiline** had no effect on the pharmacokinetics of **moclobemide**.[6] In a clinical study using tyramine restriction, one of 5 subjects taking **selegiline** and one of 5 subjects taking **selegiline** with **moclobemide** reported symptomatic hypotension, and there was no increase in blood pressure in any patient.[7]

In practical terms this means that patients taking **moclobemide** with **selegiline** should be given the same dietary restrictions for tyramine-rich foods and drinks (see 'MAOIs or RIMAs + Tyramine-rich drinks', p.1393, and 'MAOIs or RIMAs + Tyramine-rich foods', p.1395), that relate to the non-selective MAOIs such as phenelzine and tranylcypromine.[5] However, because of the potential risks the manufacturer of **moclobemide**[8] contraindicates the concurrent use of **selegiline**. It has been suggested that if **selegiline** is replaced by **moclobemide**, the dietary restrictions can be relaxed after a wash-out period of about 2 weeks. If switching from **moclobemide** to **selegiline**, a wash-out period of one to 2 days is sufficient.[4]

1. Pare CMB, Al Mousawi M, Sandler M, Glover V. Attempts to attenuate the 'cheese effect'. Combined drug therapy in depressive illness. *J Affect Disord* (1985) 9, 137–41.
2. Zelapar (Selegiline hydrochloride). Cephalon Ltd. UK Summary of product characteristics, September 2008.
3. Azilect (Rasagiline mesilate). Teva Pharmaceuticals Ltd. UK Summary of product characteristics, November 2009.
4. Dingemanse J. An update of recent moclobemide interaction data. *Int Clin Psychopharmacol* (1993) 7, 167–80.
5. Korn A, Wagner B, Moritz E, Dingemanse J. Tyramine pressor sensitivity in healthy subjects during combined treatment with moclobemide and selegiline. *Eur J Clin Pharmacol* (1996) 49, 273–8.
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7. Jansen Steur ENH, Ballering LAP. Moclobemide and selegiline in the treatment of depression in Parkinson's disease. *J Neurol Neurosurg Psychiatry* (1997) 63, 547.
8. Manerix (Moclobemide). Meda Pharmaceuticals. UK Summary of product characteristics, September 2009.

MAO-B inhibitors + Nasal decongestants

An isolated report describes a hypertensive crisis, which was attributed to an interaction between selegiline, ephedrine, and maprotiline. Selegiline does not appear to affect the pharmacokinetics of pseudoephedrine or phenylpropanolamine.

Clinical evidence

An isolated case report describes a man taking **selegiline** 10 mg daily, levodopa with carbidopa, lisuride, maprotiline 75 mg daily, and theophylline with **ephedrine** 180/32 mg daily who developed hypertensive crises (blood pressure up to 300/150 mmHg), intense vasoconstriction, confusion, abdominal pain, sweating, and tachycardia (110 bpm) within 2 days of raising the dose of theophylline with **ephedrine** to 270/48 mg daily. All of the drugs were stopped, and the patient was treated with intravenous nicardipine. He recovered uneventfully.[1]

In a study, 10 healthy subjects received **selegiline** via a transdermal patch delivering 6 mg/24 hours, applied daily, and **pseudoephedrine** 60 mg up to three times daily, for 3 days. **Selegiline** did not cause any significant changes in the cardiovascular pharmacodynamics or the pharmacokinetics of **pseudoephedrine**. In a separate part of this study, 11 healthy subjects received **selegiline** via a transdermal patch delivering 6 mg/24 hours and **phenylpropanolamine** 25 mg up to six times daily. Selegiline did not cause any clinically significant changes in the pharmacodynamics or pharmacokinetics of **phenylpropanolamine**.[2]

Mechanism

It is thought that this reaction described in the case report occurred as a result of excess sympathomimetic amines: ephedrine is an indirectly-acting sympathomimetic that causes increased release of noradrenaline; selegiline has some MAO-A inhibitory activity and may therefore inhibit noradrenaline metabolism; and maprotiline inhibits reuptake of noradrenaline.[1] Compare also 'MAOIs or RIMAs + Sympathomimetics; Indirectly-acting', p.1388 and 'MAOIs or RIMAs + Tricyclic and related antidepressants', p.1391.

Importance and management

This appears to be the only report of a hypertensive reaction in a patient taking selegiline and ephedrine, and the concurrent maprotiline was also implicated in this reaction. In general, if selegiline is used at recommended doses it is selective for MAO-B and no restrictions are required in the use of nasal decongestants with indirect sympathomimetic actions, such as ephedrine and pseudoephedrine. Nevertheless, this report suggests that, rarely, interactions are still possible, and some consider that patients taking selegiline should try to avoid pseudoephedrine or other related drugs.[2,3] The manufacturers of both **rasagiline**[4] and selegiline[5] suggest avoiding the concurrent use of sympathomimetics such as those present in decongestants or cold medications containing ephedrine or pseudoephedrine.[4]

1. Lefebvre H, Noblet C, Moore N, Wolf LM. Pseudo-phaeochromocytoma after multiple drug interactions involving the selective monoamine oxidase inhibitor selegiline. *Clin Endocrinol (Oxf)* (1995) 42, 95–9.
2. Azzaro AJ, VanDenBerg CM, Ziemniak J, Kemper EM, Blob LF, Campbell BJ. Evaluation of the potential for pharmacodynamic and pharmacokinetic drug interactions between selegiline transdermal system and two sympathomimetic agents (pseudoephedrine and phenylpropanolamine) in healthy volunteers. *J Clin Pharmacol* (2007) 47, 978–90.
3. Jacob JE, Wagner ML, Sage JI. Safety of selegiline with cold medications. *Ann Pharmacother* (2003) 37, 438–41.
4. Azilect (Rasagiline mesilate). Teva Pharmaceuticals Ltd. UK Summary of product characteristics, November 2009.
5. Zelapar (Selegiline hydrochloride). Cephalon Ltd. UK Summary of product characteristics, September 2008.

MAO-B inhibitors + Pethidine (Meperidine)

A case of fluctuating stupor and agitation, with muscle rigidity, sweating and a raised temperature has been reported when pethidine was used with selegiline. Rasagiline is expected to interact similarly.

Clinical evidence, mechanism, importance and management

A patient taking **selegiline** 5 mg twice daily, pergolide, levodopa with carbidopa, imipramine and desipramine was given pethidine beginning on postoperative day one for 4 days in doses of 75 to 150 mg daily. On the second day he became increasingly restless and irritable, progressing to delirium on the fourth day, with fluctuations between stupor and severe agitation associated with muscular rigidity, sweating and a raised temperature. The patient remained normotensive. Both pethidine and then **selegiline** were stopped, with full recovery.[1] This case is similar to various cases described with non-selective MAOIs and pethidine, see 'MAOIs or RIMAs + Opioids; Pethidine (Meperidine)', p.1381. The US manufacturer of selegiline states that other serious reactions including death have occurred when **selegiline** was given with pethidine.[2]

On the basis of this evidence the manufacturers of **selegiline**[2,3] and **rasagiline**[4] contraindicate the concurrent use of **pethidine**, which is a prudent precaution. Some manufacturers of **rasagiline** additionally say that pethidine should not be given until 14 days after stopping **rasagiline**,[4] which makes sense because they are irreversible inhibitors of MAO-B. One UK manufacturer of **selegiline** also contraindicates concurrent use with all opioids,[3] which is probably unnecessary, based on the evidence with non-selective MAOIs, see 'MAOIs or RIMAs + Opioids; Pethidine (Meperidine)', p.1381. Another UK manufacturer of **selegiline** cautions that **tramadol** may potentially interact,[5] which seems a possibility based on evidence of an interaction between tramadol and non-selective MAOIs, see 'MAOIs or RIMAs + Opioids; Tramadol', p.1382.

1. Zornberg GL, Bodkin JA, Cohen BM. Severe adverse interaction between pethidine and selegiline. *Lancet* (1991) 337, 246.
2. Selegiline hydrochloride tablets USP. Apotex Inc. US Prescribing information, June 2009.
3. Zelapar (Selegiline hydrochloride). Cephalon Ltd. UK Summary of product characteristics, September 2008.
4. Azilect (Rasagiline mesilate). Teva Pharmaceuticals Ltd. UK Summary of product characteristics, November 2009.
5. Eldepryl (Selegiline hydrochloride). Orion Pharma (UK) Ltd. UK Summary of product characteristics, June 2009.

MAO-B inhibitors + SSRIs or SNRIs

A few cases of serotonin syndrome and other serious CNS disturbances have been seen when selegiline was given with fluoxetine or venlafaxine. Other SSRIs and SNRIs are expected to interact similarly. Rasagiline is expected to interact in the same way as selegiline.

Clinical evidence

(a) Citalopram

In a double-blind, randomised study, 18 healthy subjects were given citalopram 20 mg or placebo daily for 10 days, with **selegiline** 10 mg daily added for a further 4 days. There was no evidence of changes in vital signs or in the frequency of adverse events, but the bioavailability of **selegiline** was slightly reduced by about 30% by citalopram. The authors of this report concluded that no clinically relevant interaction occurred between **selegiline** and citalopram.[1]

(b) Fluoxetine

A woman with Parkinson's disease taking **selegiline**, bromocriptine and levodopa with carbidopa was also given fluoxetine 20 mg. Several days later she developed episodes of shivering and sweating in the mid-afternoon, which lasted several hours. Her hands became blue, cold and mottled and her blood pressure was elevated (200/120 mmHg). These episodes disappeared when both fluoxetine and **selegiline** were stopped, and did not reappear when the fluoxetine alone was restarted.[2] A case of mild serotonin syndrome has been described in a woman taking levodopa and **selegiline**, which developed a few days after she started fluoxetine,[3] and a possible case of serotonin syndrome has been described in another patient taking selegiline and fluoxetine.[4] A further case of serotonin syndrome, which was fatal, developed in a patient taking levodopa with carbidopa and fluoxetine when **selegiline** was added and the dose of levodopa increased.[5] Other patients have become hyperactive and apparently manic,[2,6] have developed ataxia,[7] or developed a tonic-clonic seizure and headache, flushes, palpitations, and a blood pressure of 250/130 mmHg (a pseudophaeochromocytoma syndrome),[8] all after the concurrent use of fluoxetine and **selegiline**.

These reports contrast with a retrospective study of 23 patients with parkinsonism, who received both **selegiline** and fluoxetine without any serious adverse effects occurring, although worsening confusion was noted in 5 patients.[9]

(c) Fluvoxamine

The manufacturer of **selegiline** notes that serious reactions similar to those seen with fluoxetine have occurred in patients receiving **selegiline** and fluvoxamine.[10] Fluvoxamine may be expected to inhibit the metabolism of **rasagiline**, see 'MAO-B inhibitors; Rasagiline + Miscellaneous', p.810.

(d) Paroxetine

A retrospective study of patients with Parkinson's disease taking **selegiline** 5 to 10 mg daily (and other antiparkinsonian drugs such as levodopa with carbidopa, bromocriptine, amantadine, pergolide, and antimuscarinics) noted that the addition of paroxetine 10 to 40 mg daily caused no adverse effects and the patients appeared to obtain overall benefit, including some improvement in parkinsonian symptoms.[11] However, the manufacturers of **selegiline** note that serious reactions similar to those seen with fluoxetine have occurred in patients receiving **selegiline** and paroxetine.[10,12]

(e) Sertraline

A retrospective study of patients with Parkinson's disease taking **selegiline** 5 to 10 mg daily (and other antiparkinsonian drugs such as levodopa with carbidopa, bromocriptine, amantadine, pergolide, and antimuscarinics) noted that the addition of sertraline 25 to 100 mg daily caused no adverse effects and the patients appeared to obtain overall benefit, including some improvement in parkinsonian symptoms.[11] However, the manufacturers of **selegiline** note that serious reactions similar to those seen with concurrent fluoxetine have occurred in patients receiving **selegiline** and sertraline.[10,12]

108 (f) Venlafaxine

A man developed serotonin syndrome 15 days after stopping **selegiline** 50 mg [daily] and within 30 minutes of starting venlafaxine 37.5 mg.[13]

Mechanism

Not fully understood. In some cases the symptoms seen appear to be consistent with serotonin syndrome, which is typified by CNS irritability, increased muscle tone, shivering, altered consciousness and myoclonus, and appears to be associated with the use of more than one serotonergic drug, see *Serotonin syndrome*, under 'Additive or synergistic interac-

tions', (p.9). This syndrome has also occurred when non-selective MAOIs were given with SSRIs or venlafaxine (see 'MAOIs or RIMAs + SSRIs', p.1384, and 'MAOIs or RIMAs + SNRIs', p.1383). Note that selegiline may have some non-selective MAOI activity, especially at higher doses.

Importance and management

The possibility of serotonin syndrome or similar occurring with selegiline and SSRIs or venlafaxine would appear to be established, although the incidence is very rare. Nevertheless, the manufacturers of selegiline recommend that these drug combinations should be avoided.[10,12,14] In addition, selegiline should not be started for 5 weeks after stopping fluoxetine, 2 weeks after stopping sertraline, and one week after stopping other SSRIs, and SSRIs should not be started for 2 weeks after stopping selegiline.[10,14]

Similarly, the manufacturers of **rasagiline** recommend avoiding the concurrent use of fluoxetine and fluvoxamine. Rasagiline should not be started for 5 weeks after stopping fluoxetine, and fluoxetine or fluvoxamine should not be started for 2 weeks after stopping rasagiline.[15]

For more information about serotonin syndrome, including signs and symptoms, and management, see under 'Additive or synergistic interactions', (p.9).

1. Laine K, Anttila M, Heinonen E, Helminen A, Huupponen R, Mäki-Ikola O, Reinikainen K, Scheinin M. Lack of adverse interactions between concomitantly administered selegiline and citalopram. *Clin Neuropharmacol* (1997) 20, 419–33.
2. Suchowersky O, deVries JD. Interaction of fluoxetine and selegiline. *Can J Psychiatry* (1990) 35, 571–2.
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4. Ritter JL, Alexander B. Retrospective study of selegiline-antidepressant drug interactions and a review of the literature. *Ann Clin Psychiatry* (1997) 9, 7–13.
5. Bilbao Garay J, Mesa Plaza N, Castilla Castellano V, Dhimes Tejada P. Síndrome serotoninérgico: presentación de un caso de evolución letal y revisión de la literatura. *Rev Clin Esp* (2002) 202, 209–11.
6. Kurlan R, Dimitsopulos T. Selegiline and manic behavior in Parkinson's disease. *Arch Neurol* (1992) 49, 1231.
7. Jermain DM, Hughes PL, Follender AB. Potential fluoxetine-selegiline interaction. *Ann Pharmacother* (1992) 26, 1300.
8. Montastruc JL, Chamontin B, Senard JM, Tran MA, Rascol O, Llau ME, Rascol A. Pseudophaeochromocytoma in parkinsonian patient treated with fluoxetine plus selegiline. *Lancet* (1993) 341, 555.
9. Waters CH. Fluoxetine and selegiline — lack of significant interaction. *Can J Neurol Sci* (1994) 21, 259–61.
10. Eldepryl (Selegiline hydrochloride). Orion Pharma (UK) Ltd. UK Summary of product characteristics, June 2009.
11. Toyama SC, Iacono RP. Is it safe to combine a selective serotonin reuptake inhibitor with selegiline? *Ann Pharmacother* (1994) 28, 405–6.
12. Selegiline hydrochloride tablets, USP. Apotex Inc. US prescribing information, June 2009.
13. Gitlin MJ. Venlafaxine, monoamine oxidase inhibitors, and the serotonin syndrome. *J Clin Psychopharmacol* (1997) 17, 66–67.
14. Zelapar (Selegiline hydrochloride). Cephalon Ltd. UK Summary of product characteristics, September 2008.
15. Azilect (Rasagiline mesilate). Teva Pharmaceuticals Ltd. UK Summary of product characteristics, November 2009.

MAO-B inhibitors + Tricyclic and related antidepressants

The concurrent use of selegiline and tricyclics may lead to adverse effects such as serotonin syndrome. Trazodone may interact similarly, although evidence for this is lacking. Rasagiline is expected to interact in the same way as selegiline.

Clinical evidence

(a) Trazodone

A retrospective study of patients with Parkinson's disease taking **selegiline** 5 to 10 mg daily (and other antiparkinson drugs such as levodopa with carbidopa, bromocriptine, amantadine, pergolide, and antimuscarinics) noted that the addition of trazodone 25 to 150 mg daily caused no adverse effects and the patients appeared to obtain overall benefit, including some improvement in parkinsonian symptoms.[1]

(b) Tricyclic antidepressants

Between 1989 and 1994 the FDA in the US received 16 reports of adverse interactions between **selegiline** and tricyclic antidepressants, which were attributed to serotonin syndrome.[2] The manufacturers of **selegiline** very briefly describe severe CNS toxicity in one patient given **selegiline** and **amitriptyline** (hyperpyrexia and death), and in another given **selegiline** and **protriptyline** (tremor, agitation, restlessness, followed by unresponsiveness and death).[3-5] They state that related adverse events including hypertension, syncope, asystole, diaphoresis, seizures, changes in behavioural and mental status, and muscular rigidity have also been reported in some patients receiving **selegiline** and various tricyclics.[3,4] A further report describes serotonin syndrome in a woman given **nortriptyline** with **selegiline**.[6] Another report describes hypomania occurring in a woman taking **selegiline** and **nortriptyline**;[7] the contribution of a drug interaction is unclear in this case. However, these warnings need to be balanced by other reports indicating that these reactions are uncommon. One study based on the findings of 47 investigators treating 4 568 patients with **selegiline** and antidepressants [not specifically named but possibly including the tricyclics and related antidepressants] found that only 11 patients (0.24%) experienced symptoms considered to represent serotonin syndrome, and only 2 patients (0.04%) experienced symptoms considered to be serious.[8] Another small retrospective study designed to evaluate the tolerability and efficacy of combining **selegiline** and tricyclic antidepressants (not specifically named) identified 28 patients who had taken both drugs.[2] In total, 17 patients definitely benefited and 6 patients possibly benefited from taking the combination. Another retrospective study of 25 occasions of the use of a tricyclic with **selegiline** found no cases of serotonin syndrome.[9]

Mechanism

Not fully understood. In some cases the symptoms seen appear to be consistent with serotonin syndrome, which is typified by CNS irritability, increased muscle tone, shivering, altered consciousness and myoclonus, and appears to be associated with the use of more than one serotonergic drug, see *Serotonin syndrome*, under 'Additive or synergistic interactions', (p.9). This syndrome has also occurred with non-selective MAOIs and tricyclics or trazodone (see 'MAOIs or RIMAs + Tricyclic and related antidepressants', p.1391, and 'MAOIs + Trazodone', p.1390). Note that selegiline may have some non-selective MAOI activity, especially at high doses.

Importance and management

Evidence for an interaction between the tricyclic and related antidepressants and selegiline is sparse, and needs to be balanced by the reports of safe and uneventful concurrent use. If the decision is made to use selegiline with any of the tricyclic antidepressants, the outcome should be well monitored, but the likelihood of problems seems to be small. Nevertheless, some manufacturers of selegiline advise avoiding tricyclic antidepressants.[4,5] Similarly, the manufacturers of **rasagiline** advise caution if it is given with antidepressants.[10] This caution should also apply to the use of trazodone, as studies will not always identify rare adverse effects.

1. Toyama SC, Iacono RP. Is it safe to combine a selective serotonin reuptake inhibitor with selegiline? *Ann Pharmacother* (1994) 28, 405–6.
2. Yu LJ, Zweig RM. Successful combination of selegiline and antidepressants in Parkinson's disease. *Neurology* (1996) 46 (2 Suppl), A374.
3. Eldepryl (Selegiline hydrochloride). Orion Pharma (UK) Ltd. UK Summary of product characteristics, June 2009.
4. Selegiline hydrochloride tablets, USP. Apotex Inc. US prescribing information, June 2009.
5. Zelapar (Selegiline hydrochloride). Cephalon Ltd. UK Summary of product characteristics, September 2008.
6. Hinds NP, Hillier CEM, Wiles CM. Possible serotonin syndrome arising from an interaction between nortriptyline and selegiline in a lady with parkinsonism. *J Neurol* (2000) 247, 811.
7. Kurlan R, Dimitsopulos T. Selegiline and manic behavior in Parkinson's disease. *Arch Neurol* (1992) 49, 1231.
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10. Azilect (Rasagiline mesilate). Teva Pharmaceuticals Ltd. UK Summary of product characteristics, November 2009.

MAO-B inhibitors + Tyramine-rich foods

No dietary restrictions are required with the doses of rasagiline and selegiline recommended for use in Parkinson's disease. An isolated report describes a hypertensive reaction in a patient taking selegiline 20 mg daily. Thus, at higher doses of selegiline, restriction of the amount of tyramine in the diet may be necessary.

Clinical evidence

(a) Rasagiline

In a study in which 72 patients with Parkinson's disease were given rasagiline, there was no statistically significant change in the cardiovascular response to a single 50-mg or 75-mg dose of tyramine when compared with 38 patients not taking rasagiline. Three patients taking rasagiline and one taking placebo experienced an asymptomatic increase in systolic blood pressure of 30 mmHg or more, after the tyramine challenge.[1]

The manufacturer notes that the results of four tyramine challenge studies, together with the results of home monitoring of blood pressure after meals (from 464 patients taking rasagiline 0.5 or 1 mg daily or placebo without tyramine restrictions), and the lack of reported problems in clinical studies without tyramine restriction, indicate that no dietary restrictions are necessary with rasagiline.[2]

(b) Selegiline

1. Oral selegiline. The pressor response to oral tyramine was not altered by pretreatment with selegiline 10 mg daily in healthy subjects and patients with Parkinson's disease.[3] However, another study[4] found that selegiline 5 mg daily for at least 14 days reduced the dose of oral tyramine required to achieve the cardiovascular threshold (increase in systolic blood pressure of greater than 30 mmHg, a diastolic blood pressure greater than 100 mmHg or a fall in heart rate of greater than 20%) by a factor of 2.8. Nevertheless, this reduction was less than that found with the RIMA moclobemide (4.3) and the MAOI phenelzine (10.3).[4] In other studies, higher doses of selegiline (20 or 30 mg daily) increased the sensitivity to oral tyramine by 2- to 4.5-fold.[5,6] A patient taking selegiline 20 mg daily was reported to have had a hypertensive reaction (severe headache and rise in blood pressure) after eating macaroni and cheese,[7] but this appears to be the only published report of this type of hypertensive reaction with selegiline.

2. Buccal and transdermal selegiline. The dose of tyramine required to elicit a pressor effect was not altered by pretreatment with buccal selegiline 1.25 mg in healthy subjects.[8] Similarly, the pressor response to tyramine up to 200 mg was not significantly altered by pretreatment with a single 24-hour application of transdermal selegiline 7.8 mg/24 hour in healthy subjects.[9] Another study in 12 healthy subjects who applied selegiline transdermal patches 6 mg/24 hours daily for 13 days, in order to achieve steady-state levels, similarly found no clinically significant blood pressure response to meals containing up to 400 mg of tyramine.[10] A study by the same authors, in which the use of selegiline was extended to 33 days also found no clinically meaningful change in the pressor sensitivity to tyramine.[11]

Mechanism

Rasagiline and selegiline specifically inhibit MAO-B, which leaves MAO-A still available to metabolise any tyramine in foodstuffs. However, at higher doses the selectivity of selegiline diminishes, and inhibition of the metabolism of tyramine is more likely. Nevertheless, the 2- to 4.5-fold increase in effect of tyramine seen with selegiline 5 to 30 mg daily is still less than that seen with the non-selective MAOIs, see 'MAOIs or RIMAs + Tyramine-rich foods', p.1395.

Importance and management

The absence of an interaction between rasagiline or selegiline and tyramine is well established, and the manufacturer of rasagiline states that no dietary tyramine restrictions are necessary.[2] Similarly, at the recommended doses of conventional or buccal selegiline used in Parkinson's disease the manufacturers say that no dietary restrictions are necessary,[12-14] and this is supported by the scarcity of any published reports of reactions. If higher doses of selegiline are used, MAO-B selectivity may be lost, and patients should be advised to avoid large amounts of tyramine-rich foods. This is reflected by the advice given by one manufacturer of a transdermal selegiline patch who suggests that restrictions on tyramine ingestion are only necessary with a daily dose of 9 mg/24 hours or more.[15] For a list of the possible tyramine-content of some foods, see 'Table 32.3', (p.1396).

1. deMarcaida JA, Schwid SR, White WB, Blindauer K, Fahn S, Kieburtz K, Stern M, Shoulson I, and the Parkinson Study Group TEMPO and PRESTO Tyramine Substudy Investigators and Coordinators. Effects of tyramine administration in Parkinson's disease patients treated with selective MAO-B inhibitor rasagiline. *Mov Disord* (2006) 21, 1716–1721.
2. Azilect (Rasagiline mesilate). Teva Pharmaceuticals Ltd. UK Summary of product characteristics, November 2009.
3. Elsworth JD, Glover V, Reynolds GP, Sandler M, Lees AJ, Phuapradit P, Shaw KM, Stern GM, Kumar P. Deprenyl administration in man: a selective monoamine oxidase B inhibitor without the 'cheese effect'. *Psychopharmacology (Berl)* (1978) 57, 33–8.
4. Warrington SJ, Turner P, Mant TGK, Morrison P, Haywood G, Glover V, Goodwin BL, Sandler M, St John-Smith P, McClelland GR. Clinical pharmacology of moclobemide, a new reversible monoamine oxidase inhibitor. *J Psychopharmacol* (1991) 5, 82–91.
5. Prasad A, Glover V, Goodwin BL, Sandler M, Signy M, Smith SE. Enhanced pressor sensitivity to oral tyramine challenge following high dose selegiline treatment. *Psychopharmacology (Berl)* (1988) 95, 540–3.
6. Bieck PR, Antonin KH. Tyramine potentiation during treatment with MAO inhibitors: brofaromine and moclobemide vs irreversible inhibitors. *J Neural Transm* (1989) (Suppl 28), 21–31.
7. McGrath PJ, Stewart JW, Quitkin FM. A possible l-deprenyl induced hypertensive reaction. *J Clin Psychopharmacol* (1989) 9, 310–11.
8. Clarke A, Johnson ES, Mallard N, Corn TH, Johnston A, Boyce M, Warrington S, MacMahon DG. A new low-dose formulation of selegiline: clinical efficacy, patient preference and selectivity for MAO-B inhibition. *J Neural Transm* (2003) 110, 1273–8.
9. Barrett JS, Hochadel TJ, Morales RJ, Rohatagi S, DeWitt KE, Watson SK, Darnow J, Azzaro AJ, DiSanto AR. Pressor response to tyramine after single 24-hour application of a selegiline transdermal system in healthy males. *J Clin Pharmacol* (1997) 37, 238–47.
10. Blob LF, Sharoky M, Campbell BJ, Kemper EM, Gilmor M, VanDenBerg CM, Azzaro AJ. Effects of a tyramine-enriched meal on blood pressure response in healthy male volunteers treated with selegiline transdermal system 6 mg/24 hour. *CNS Spectr* (2007) 12, 25–34.
11. Azzaro AJ, VanDenBerg CM, Blob LF, Kemper EM, Sharoky M, Oren DA, Campbell BJ. Tyramine pressor sensitivity during treatment with the selegiline transdermal system 6 mg/24 h in healthy subjects. *J Clin Pharmacol* (2006) 46, 933–44.
12. Eldepryl (Selegiline hydrochloride). Orion Pharma (UK) Ltd. UK Summary of product characteristics, June 2009.
13. Zelapar (Selegiline hydrochloride). Cephalon Ltd. UK Summary of product characteristics, September 2008.
14. Selegiline hydrochloride tablets USP. Apotex Inc. US Prescribing information, June 2009.
15. Emsam (Selegiline). Somerset Pharmaceuticals Inc. US Prescribing information, May 2009.

MAO-B inhibitors; Rasagiline + Miscellaneous

Ciprofloxacin increases the AUC of rasagiline by inhibiting CYP1A2. Other inhibitors of CYP1A2 are predicted to interact similarly. There is a theoretical possibility that tobacco smoke, may reduce the plasma levels of rasagiline. Rasagiline does not affect the pharmacokinetics of theophylline.

Clinical evidence, mechanism, importance and management

(a) CYP1A2 inhibitors

The manufacturer notes that concurrent use of rasagiline and **ciprofloxacin** increased the AUC of rasagiline by 83%.[1] **Ciprofloxacin** inhibits the cytochrome P450 isoenzyme CYP1A2, which is the major enzyme responsible for the metabolism of rasagiline. The clinical relevance of this increase has not been assessed, but until more is known caution is warranted. Be alert for rasagiline adverse effects (e.g. headache, dyspepsia). This caution should be extended to other potent inhibitors of CYP1A2, such as **enoxacin**. Note that fluvoxamine is also a CYP1A2 inhibitor, but concurrent use with, and for 2 weeks after, rasagiline should be avoided, see 'MAO-B inhibitors + SSRIs or SNRIs', p.808.

(b) Theophylline

The manufacturer reports that the pharmacokinetics of neither rasagiline nor theophylline, a substrate of cytochrome P450 isoenzyme CYP1A2, were altered when the two drugs were given together.[1] Rasagiline would not be expected to affect the metabolism of other drugs by this route.

(c) Tobacco

Rasagiline is a substrate of the cytochrome P450 isoenzyme CYP1A2, and the manufacturer advises that the plasma levels of rasagiline may be lowered in patients who smoke, due to the inducing effect of tobacco smoke on CYP1A2.[1] Bear this theoretical interaction in mind if rasagiline seems less effective than anticipated.

1. Azilect (Rasagiline mesilate). Teva Pharmaceuticals Ltd. UK Summary of product characteristics, November 2009.

MAO-B inhibitors; Selegiline + Alprazolam

In a study in 12 healthy subjects, the concurrent use of transdermal selegiline patches 6 mg/24 hours and alprazolam

500 micrograms three times daily did not affect the steady-state pharmacokinetics of either drug.[1]

1. Azzaro AJ, Ziemniak J, Kemper E, Campbell BJ, VanDenBerg C. Selegiline transdermal system: an examination of the potential for CYP450-dependent pharmacokinetic interactions with 3 psychotropic medications. *J Clin Pharmacol* (2007) 47, 146–58.

MAO-B inhibitors; Selegiline + Antipsychotics

When healthy subjects were given selegiline transdermal patches 6 mg/24 hours either alone, or with olanzapine 5 mg daily or risperidone 1 mg twice daily, the steady-state pharmacokinetics of olanzapine, risperidone and selegiline were not affected.[1]

1. Azzaro AJ, Ziemniak J, Kemper E, Campbell BJ, VanDenBerg C. Selegiline transdermal system: an examination of the potential for CYP450-dependent pharmacokinetic interactions with 3 psychotropic medications. *J Clin Pharmacol* (2007) 47, 146–58.

MAO-B inhibitors; Selegiline + Cocaine

Cocaine and selegiline appear not to interact adversely.

Clinical evidence, mechanism, importance and management

In a study to establish the safety of using selegiline to prevent relapse in cocaine addiction, 5 otherwise healthy intravenous cocaine users were given 0, 20 and 40 mg intravenous doses of cocaine one hour apart after receiving selegiline 10 mg or placebo orally. The cocaine increased the heart rate, blood pressure, pupil diameter and subjective indices of euphoria as expected. However, the presence of selegiline reduced pupillary diameter, but did not alter the pupil dilation or other effects normally caused by cocaine.[1] In another study, transdermal selegiline did not alter the pharmacokinetics of intravenous cocaine in cocaine-dependent subjects. Some physiological effects (blood pressure and heart rate) and subjective effects of cocaine were attenuated by selegiline.[2]

The authors of the first study[1] concluded that concurrent use is safe and unlikely to increase the reinforcing effects of cocaine.

1. Haberny KA, Walsh SL, Ginn DH, Wilkins JN, Garner JE, Setoda D, Bigelow GE. Absence of acute cocaine interactions with the MAO-B inhibitor selegiline. *Drug Alcohol Depend* (1995) 39, 55–62.
2. Houtsmuller EJ, Notes LD, Newton T, van Sluis N, Chiang N, Elkashef A, Bigelow GE. Transdermal selegiline and intravenous cocaine: safety and interactions. *Psychopharmacology (Berl)* (2004) 172, 31–40.

MAO-B inhibitors; Selegiline + Dopamine agonists

No pharmacokinetic interaction occurs between selegiline and cabergoline, pramipexole or ropinirole.

Clinical evidence, mechanism, importance and management

(a) Cabergoline

In a study in 6 subjects with Parkinson's disease, no pharmacokinetic interaction was found to occur between cabergoline 1 mg daily and selegiline 10 mg daily after 22 days of concurrent use.[1]

(b) Pramipexole

The manufacturer of pramipexole says that no pharmacokinetic interaction occurs with selegiline.[2]

(c) Ropinirole

The manufacturer of ropinirole notes that a population pharmacokinetic analysis showed a lack of relevant effects of selegiline on ropinirole.[3]

1. Dostert P, Benedetti MS, Persiani S, La Croix R, Bosc M, Fiorentini F, Deffond D, Vernay D, Dordain G. Lack of pharmacokinetic interaction between the selective dopamine agonist cabergoline and the MAO-B inhibitor selegiline. *J Neural Transm* (1995) 45 (Suppl), 247–57.
2. Mirapexin (Pramipexole dihydrochloride monohydrate). Boehringer Ingelheim Ltd. UK Summary of product characteristics, October 2009.
3. SmithKline Beecham. Personal Communication, September 1996.

MAO-B inhibitors; Selegiline + Hormonal contraceptives or HRT

In a small study, the bioavailability of selegiline was markedly higher (mean of about 20-fold) in women taking oral combined hormonal contraceptives than in those not taking contraceptives. A controlled study found that the effect of HRT was more modest.

Clinical evidence

(a) Combined oral contraceptives

The AUCs of single doses of selegiline 5 to 40 mg were 16- to 45-fold higher in 4 women taking oral combined hormonal contraceptives than in 4 women who were not taking contraceptives. Three subjects were taking **ethinylestradiol/gestodene** 30/75 micrograms, and one was taking a triphasic preparation of **ethinylestradiol/levonorgestrel**.[1]

(b) HRT

In a crossover study in 12 young healthy women, the AUC of a single 10-mg dose of selegiline was increased by 60% (which was not statistically significant) following 10 days of HRT (containing **estradiol valerate/levonorgestrel** 2 mg/250 micrograms). There was marked variability in selegiline levels with two women having a threefold increase in AUC, and 3 having a decrease. Other changes in pharmacokinetics of selegiline or its metabolites were small.[2]

Mechanism

It was suggested that the combined hormonal contraceptive inhibited the first pass metabolism of selegiline and so markedly increased its bioavailability.[1] However, this was not found for HRT containing a different estrogenic hormone.

Importance and management

Although data are limited, it appears that combined hormonal contraceptives may markedly increase the bioavailability of selegiline. One UK manufacturer advises caution with concurrent use,[3] and the other suggests the combination should be avoided.[4] Although the short-term use of HRT also increased the AUC of selegiline, the changes were modest and were not considered clinically relevant. Nevertheless, the results perhaps need confirming with longer term concurrent use. One UK manufacturer of selegiline also advises the avoidance of concurrent HRT.[4]

1. Laine K, Anttila M, Helminen A, Karnani H, Huupponen R. Dose linearity study of selegiline pharmacokinetics after oral administration: evidence for strong drug interaction with female sex steroids. *Br J Clin Pharmacol* (1999) 47, 249–54.
2. Palovaara S, Anttila M, Nyman L, Laine K. Effect of concomitant hormone replacement therapy containing estradiol and levonorgestrel on the pharmacokinetics of selegiline. *Eur J Clin Pharmacol* (2002) 58: 259–63.
3. Eldepryl (Selegiline hydrochloride). Orion Pharma (UK) Ltd. UK Summary of product characteristics, June 2009.
4. Zelapar (Selegiline hydrochloride). Cephalon Ltd. UK Summary of product characteristics, September 2008.

MAO-B inhibitors; Selegiline + Itraconazole

The concurrent use of selegiline and itraconazole does not appear to alter the pharmacokinetics of either drug.

Clinical evidence, mechanism, importance and management

In a randomised, placebo-controlled, crossover study, 12 healthy subjects were given selegiline 10 mg after taking itraconazole 200 mg daily for 4 days. Itraconazole did not have any significant effects on the pharmacokinetics of selegiline, although the AUC of desmethylselegiline, a primary metabolite, was increased by 11%. The pharmacokinetics of

itraconazole were also unaffected. There would appear to be no reason for avoiding concurrent use.[1]

1. Kivistö KT, Wang J-S, Backman JT, Nyman L, Taavitsainen P, Anttila M, Neuvonen PJ. Selegiline pharmacokinetics are unaffected by the CYP3A4 inhibitor itraconazole. *Eur J Clin Pharmacol* (2001) 57, 37–42.

MAO-B inhibitors; Selegiline + Metamfetamine

Selegiline does not alter the pharmacokinetics of metamfetamine.

Clinical evidence, mechanism, importance and management

In a study, 5 subjects who used metamfetamine at least twice a week, took selegiline 5 mg twice daily for 12 days, and 4 subjects took placebo. During this time they received intravenous metamfetamine 15 mg and 30 mg given 2 days apart. When compared with placebo, selegiline did not affect either the pharmacokinetics of metamfetamine and its metabolite, d-amfetamine or the cardiovascular effects of metamfetamine. Subjects reported greater metamfetamine-associated "bad effects" while taking selegiline than while taking placebo, but other subjective effects were not altered.[1]

1. Newton TF, De La Garza R, Fong T, Chiang N, Holmes TH, Bloch DA, Anderson A, Elkashef A. A comprehensive assessment of the safety of intravenous methamphetamine administration during treatment with selegiline. *Pharmacol Biochem Behav* (2005) 82, 704–11.

Piribedil + Clonidine

Clonidine is reported to oppose the effects of piribedil.

Clinical evidence, mechanism, importance and management

A study in 5 patients taking piribedil found that the concurrent use of clonidine (up to 1.5 mg daily for 10 to 24 days) caused a worsening of parkinsonism (an exacerbation of rigidity and akinesia). The concurrent use of antimuscarinic drugs reduced the effects of this interaction.[1] The reason is uncertain, and the general relevance of this small study is unclear.

1. Shoulson I, Chase TN. Clonidine and the anti-parkinsonian response to L-dopa or piribedil. *Neuropharmacology* (1976) 15, 25–7.

Pramipexole + Drugs that alter its renal clearance

Cimetidine, and possibly amantadine modestly reduce the clearance of pramipexole. Probenecid had a minor effect on pramipexole clearance in one study.

Clinical evidence, mechanism, importance and management

A study in 12 healthy subjects found that multiple doses of **cimetidine** reduced the total oral clearance of a single 250-microgram dose of pramipexole by about 35% and increased its half-life by 40%. A similar reduction in the renal clearance of pramipexole was noted. The authors suggest that **cimetidine** reduces the renal excretion of pramipexole by inhibiting the active renal organic cation transport system.[1] The manufacturers say that **cimetidine** and other drugs that are eliminated by this route such as **amantadine** may interact with pramipexole to reduce excretion of either or both drugs.[2] The clinical significance of these interactions is uncertain, and as yet there appear to be no reports of any adverse interactions. Nevertheless, the manufacturers suggest a reduction of the pramipexole dose should be considered when **amantadine** or **cimetidine** are given with pramipexole.[2]

In a study in 12 healthy subjects, multiple doses of **probenecid** reduced the clearance of a single 250-microgram dose of pramipexole by 10%.[1] This change is not clinically relevant.

1. Wright CE, Lasher Sisson T, Ichhpurani AK, Peters GR. Influence of probenecid (PR) and cimetidine (C) on pramipexole (PX) pharmacokinetics. *Clin Pharmacol Ther* (1996) 59, 183.
2. Mirapexin (Pramipexole dihydrochloride monohydrate). Boehringer Ingelheim Ltd. UK Summary of product characteristics, October 2009.

Ropinirole + CYP1A2 inhibitors

Ciprofloxacin increased the AUC of ropinirole by 84%, by inhibiting CYP1A2: other CYP1A2 inhibitors are predicted to interact similarly.

Clinical evidence

In a study in 12 patients **ciprofloxacin** 500 mg twice daily increased the AUC of ropinirole 2 mg three times daily by 84% and increased the maximum plasma level by 60%.[1]

Mechanism

Ropinirole is principally metabolised by the cytochrome P450 isoenzyme CYP1A2, of which ciprofloxacin is a known inhibitor.

Importance and management

Although the clinical relevance of this pharmacokinetic interaction has not been assessed, it would seem possible that the effects of ropinirole may be increased. The manufacturers suggest that if a known potent inhibitor of CYP1A2 is stopped or started in a patient taking ropinirole, adjustment of the ropinirole dose may be required.[1,2] The UK manufacturer specifically mentions **cimetidine** (which is not usually considered a potent CYP1A2 inhibitor) and **fluvoxamine** in addition to ciprofloxacin.[2] Note that enoxacin is usually also considered to be a potent CYP1A2 inhibitor.

1. Requip (Ropinirole hydrochloride). GlaxoSmithKline. US Prescribing information, May 2009.
2. Requip (Ropinirole hydrochloride). GlaxoSmithKline UK. UK Summary of product characteristics, September 2009.

Ropinirole + Miscellaneous

Estrogens (HRT) may reduce the clearance and tobacco smoking may increase the clearance of ropinirole.

Clinical evidence, mechanism, importance and management

(a) Oestrogens

Population pharmacokinetic analysis of clinical study data showed that estrogens (mainly ethinylestradiol[1]) used in HRT reduced ropinirole clearance by one-third.[1-4] In another analysis it was found that women taking HRT received a slightly lower daily dose of ropinirole than those not taking HRT, with no difference in adverse effects.[4] Therefore, in women already receiving HRT, ropinirole treatment may be started using the usual dose titration.[1,3] However, it is suggested that an adjustment [reduction] in the ropinirole dose may be needed if HRT is started.[1,3]

(b) Tobacco

The manufacturer notes that, in a study in patients with restless leg syndrome, 7 tobacco smokers were found to have a 38% lower ropinirole AUC and a 30% lower maximum level than 11 non-smokers.[1] Tobacco induces the cytochrome P450 isoenzyme CYP1A2, by which ropinirole is extensively metabolised. Because the dose of ropinirole is titrated to effect, this interaction is unlikely to be clinically relevant, except perhaps if patients stop or start smoking while taking ropinirole, when further dose titration may be necessary.

(c) Other drugs

The manufacturer notes that population analysis revealed that **amantadine**, **antimuscarinics**, **antihistamines**, **benzodiazepines**, **ibuprofen**, **thiazides**, **tricyclic antidepressants**, and **trihexyphenidyl** did not have any relevant effects on the pharmacokinetics and/or clearance of ropinirole.[1,2,5]

1. Requip (Ropinirole hydrochloride). GlaxoSmithKline. US Prescribing information, May 2009.
2. SmithKline Beecham. Personal Communication, September 1996.
3. Requip (Ropinirole hydrochloride). GlaxoSmithKline UK. UK Summary of product characteristics, September 2009.
4. SmithKline Beecham. Personal Communication, May 1999.
5. Kaye CM, Nicholls B. Clinical pharmacokinetics of ropinirole. *Clin Pharmacokinet* (2000) 39, 243–54.

19

Antiplatelet drugs and Thrombolytics

Platelets usually circulate in the plasma in an inactive form, but following injury to blood vessels they become activated and adhere to the site of injury. Platelet aggregation then occurs, which contributes to the haemostatic plug. Platelet aggregation involves the binding of fibrinogen with a glycoprotein IIb/IIIa receptor on the platelet surface. The activated platelets secrete substances such as adenosine diphosphate (ADP) and thromboxane A_2 that result in additional platelet aggregation and also cause vasoconstriction. Finally a number of platelet-derived factors stimulate production of thrombin and hence fibrin through the coagulation cascade (see 'The blood clotting process', (p.405)). Opposing this process is the fibrinolysis pathway, which is initiated during clot formation by a number of mediators such as tissue plasminogen activator (tPA) and urokinase. These proteins convert plasminogen to plasmin, which in turn degrades fibrin, the main component of the clot.

Antiplatelet drugs (see 'Table 19.1', (below)) reduce platelet aggregation and are used to prevent thromboembolic events. They act through a wide range of mechanisms including:

- prevention of thromboxane A_2 synthesis or inhibition of thromboxane receptors e.g. aspirin inhibits platelet cyclo-oxygenase, preventing the synthesis of thromboxane A_2
- interference with adenosine diphosphate mediated platelet activation e.g. thienopyridines; inhibition of adenosine reuptake e.g. dipyridamole; interference with adenosine metabolism by inhibiting cyclic adenosine monophosphate (cAMP) phosphodiesterase e.g. cilostazol
- interference in the final step in platelet aggregation by stopping fibrinogen binding with the glycoprotein IIb/IIIa receptor on the platelet surface e.g. abciximab

Therefore some antiplatelet drugs can have beneficial additive effects with other antiplatelet drugs that act via different mechanisms. Furthermore, other drugs such as dextrans, heparin, some prostaglandins and sulfinpyrazone also have some antiplatelet activity. It should be noted that the additive bleeding effects of using two drugs with antiplatelet and/or thrombolytic properties should always be considered, and patients monitored appropriately. Consideration should also be given when using these types of drugs with other drugs that may cause bleeding such as 'NSAIDs', (p.158) or 'SSRIs', (p.817).

Thrombolytics (see 'Table 19.1', (below)) are used in the treatment of thromboembolic disorders. Thrombolytics activate plasminogen to form plasmin, which is a proteolytic enzyme that degrades fibrin and therefore produces clot dissolution.

This section is primarily concerned with those interactions where the activities of antiplatelet drugs or thrombolytics are changed by the presence of another drug. Note that the interactions of high-dose aspirin are covered under analgesics.

Table 19.1 Antiplatelet drugs and thrombolytics

Group	*Drugs*
Antiplatelet drugs	
Adenosine reuptake inhibitors/Phosphodiesterase inhibitors	Cilostazol, Dipyridamole
Cyclo-oxygenase inhibitors	Aspirin, Indobufen, Triflusal
Glycoprotein IIb/IIIa-receptor antagonists	Abciximab, Eptifibatide, Tirofiban
Thienopyridines (inhibitors of adenosine diphosphate mediated platelet aggregation)	Clopidogrel, Prasugrel, Ticlopidine
Thromboxane receptor antagonists	Picotamide
Miscellaneous	Ditazole, Trapidil
Thrombolytics	
Thrombolytics	Alteplase, Anistreplase, Defibrotide, Reteplase, Streptokinase, Tenecteplase, Urokinase

Anagrelide + Miscellaneous

Anagrelide should not be used with other phosphodiesterase III inhibitors (e.g. milrinone) because of the potential for increased inotropic effects. Inhibitors of CYP1A2 (e.g. fluvoxamine) are predicted to increase anagrelide levels, and substrates of CYP1A2 (e.g. theophylline) are predicted to be affected by anagrelide. Some caution might be required with concurrent aspirin. Food delays the absorption of anagrelide, but does not affect the systemic exposure. Isolated reports suggested that sucralfate and hydroxycarbamide may interact with anagrelide. Allopurinol, digoxin, furosemide, iron, paracetamol (acetaminophen), ranitidine and warfarin are not expected to interact with anagrelide.

Clinical evidence, mechanism, importance and management

(a) Aspirin

A study found that the concurrent use of single doses of anagrelide 1 mg and aspirin 900 mg were generally well tolerated and no clinically significant pharmacokinetic interaction occurred. No changes in the bleeding time, aPTT or PT were seen.[1] Nevertheless, anagrelide was found to have additive antiplatelet effects with aspirin *in vitro*, and the manufacturer recommends that the risk/benefit ratio should be assessed before aspirin is used with anagrelide in patients with a high platelet count (greater than 1500 x 10^9/L) and/or a history of haemorrhage.[2]

(b) CYP1A2 inhibitors and substrates

Anagrelide is principally metabolised by the cytochrome P450 isoenzyme CYP1A2. Drugs that are inhibitors of this isoenzyme are therefore predicted to reduce the clearance of anagrelide, and the manufacturers specifically name **fluvoxamine**[1,2] and **omeprazole**.[2] Be aware that increased effects, both beneficial and adverse, might occur. However, note that **omeprazole** is only a weak CYP1A2 inhibitor, and would not be expected to have much effect on anagrelide. **Grapefruit juice** has also been predicted to interact via this mechanism,[2] but again, it appears to have little clinically relevant effect on CYP1A2. For a list of CYP1A2 inhibitors, see 'Table 1.2', (p.4).

Anagrelide is a weak inhibitor of CYP1A2, and therefore the manufacturers suggest that it might interact with CYP1A2 substrates, such as **theophylline**.[1,2] The clinical significance of this is unknown, but it seems likely to be small.

(c) Hydroxycarbamide

In a preclinical study in *dogs*, there was no pharmacokinetic interaction between hydroxycarbamide and anagrelide, therefore no clinical pharmacokinetic interaction is expected.[2] A patient taking hydroxycarbamide for 7 years developed severe hypersensitivity pneumonitis soon after anagrelide was started.[3] The clinical significance of this isolated case is unknown, although there has been another case report of hypersensitivity pneumonitis with anagrelide alone.[4]

(d) Phosphodiesterase inhibitors

Anagrelide is a cyclic AMP phosphodiesterase III inhibitor, and consequently has positive inotropic effects. The manufacturer recommends against its concurrent use with other phosphodiesterase III inhibitors, because of the potential increased inotropic effects, and they specifically mention **amrinone**, **cilostazol**, **enoximone**, **milrinone**, and **olprinone**.[2]

(e) Sucralfate

An isolated case report suggested that sucralfate may interfere with the absorption of anagrelide,[1] however the clinical significance of this is unclear. If an interaction is suspected, it is usual practice to separate administration by 2 hours.

(f) Other medications

The US manufacturer notes that although no formal drug interaction studies have been performed, **allopurinol**, **furosemide**, **iron**, **paracetamol** (acetaminophen), and **ranitidine** did not appear to interact with anagrelide in clinical studies.[1] The manufacturer briefly mentions that there was no pharmacokinetic interaction between **digoxin** or **warfarin** and anagrelide.[1,2] Food delays the absorption of anagrelide, but does not alter the overall amount absorbed.[2] The interaction is not clinically relevant.[1,2]

1. Agrylin (Anagrelide hydrochloride). Shire US Inc. US Prescribing information, December 2004.
2. Xagrid (Anagrelide hydrochloride). Shire Pharmaceuticals, Ltd. UK Summary of product characteristics, January 2008.
3. Raghavan M, Mazer MA, Brink DJ. Severe hypersensitivity pneumonitis associated with anagrelide. *Ann Pharmacother* (2003) 37, 1228–31.
4. Spencer EM, Lawrence DS. 'Double hit' from streptococcal pneumonia and hypersensitivity pneumonitis associated with anagrelide. *Clin Lab Haematol* (2006) 28, 63–5.

Antiplatelet drugs + Antacids

***Maalox* causes a moderate decrease in the absorption of ticlopidine. An aluminium/magnesium-containing antacid did not affect the absorption of clopidogrel in one study.**

Clinical evidence, mechanism, importance and management

(a) Clopidogrel

In a randomised study, 12 healthy subjects were given two 400-mg tablets of *Maalox* (**aluminium**/**magnesium hydroxide**) followed, one hour later, by a single 75-mg dose of clopidogrel. The maximum levels and AUC (only 9 subjects assessed) of the major carboxylic acid metabolite of clopidogrel were not significantly affected, suggesting that clopidogrel absorption was not altered by the antacid.[1]

(b) Dipyridamole

See 'Dipyridamole + Drugs that affect gastric pH', p.825, for the suggestion that antacids can affect the absorption of dipyridamole from some dosage forms.

(c) Ticlopidine

In a study in 12 healthy subjects the extent of absorption of a single 250-mg dose of ticlopidine was decreased by about 20% by 30 mL of *Maalox* [**aluminium**/**magnesium hydroxide**].[2] These modest changes are unlikely to be of much clinical importance.

1. McEwen J, Strauch G, Perles P, Pritchard G, Moreland TE, Necciari J, Dickinson JP. Clopidogrel bioavailability: absence of influence of food or antacids. *Semin Thromb Hemost* (1999) 25 (Suppl 2), 47–50.
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Antiplatelet drugs + Aspirin

There is an increased risk of bleeding if clopidogrel is given with aspirin, but their concurrent use can be beneficial. Ticlopidine increases the antiaggregant effects of aspirin and there is an increased risk of bleeding on concurrent use. Cilostazol appears not to interact to a clinically relevant extent with low-dose aspirin, and the addition of dipyridamole to aspirin does not appear to increase the incidence of bleeding.

Clinical evidence, mechanism, importance and management

(a) Cilostazol

In a randomised, placebo-controlled study in 11 healthy subjects, giving aspirin 325 mg daily for 5 days with cilostazol 100 mg twice daily increased the inhibition of ADP-induced platelet aggregation by 23 to 35%, when compared with the use of cilostazol alone. Aspirin also appeared to cause a minor 22% increase in the AUC of cilostazol. However, there were no statistically significant additive effects on arachidonic acid-induced platelet aggregation, and no clinically relevant effects on prothrombin times, aPTT or bleeding times.[1] The US manufacturer reports that in 8 randomised, placebo-controlled studies, in a total of 201 patients receiving cilostazol and aspirin, the incidence of bleeding was no greater than that seen with aspirin and placebo. The most frequent doses and mean duration of aspirin therapy were 75 to 81 mg daily for 137 days (107 patients) and 325 mg daily for 54 days (85 patients).[2]

These studies suggest that no special precautions are needed if cilostazol is used concurrently with low-dose aspirin, although note that the UK manufacturer of cilostazol recommends that, when given with cilostazol, the daily dose of aspirin should not exceed 80 mg.[3]

(b) Clopidogrel

A variety of studies have investigated the beneficial effects of using the combination of aspirin with clopidogrel. Although these studies were pri-

marily designed to assess the benefits of concurrent use they did also report on bleeding events. The key findings were:

- In patients with recent acute coronary syndrome (CURE): an increase in major bleeding events following the use of clopidogrel 75 mg daily with aspirin 75 to 325 mg daily compared with aspirin alone (3.7% versus 2.7%, respectively).[4]
- In patients with recent stroke or transient ischaemic attack (MATCH): an increase in life-threatening bleeding events following the use of clopidogrel 75 mg daily with aspirin 75 mg daily, when compared with aspirin alone (2.6% versus 1.3%, respectively).[5]
- In patients with clinically evident cardiovascular disease or multiple atherosclerotic risk factors (CHARISMA): an increase in the risk of moderate and severe bleeding following the use of clopidogrel 75 mg daily with aspirin 75 to 162 mg daily, when compared with aspirin alone (moderate 2.1% and 1.3%, respectively, severe 1.7% and 1.3%, respectively).[6]

Other studies designed to assess the risk of bleeding when aspirin was given with clopidogrel found the following results:

- A retrospective, population based, case-control study identified 1443 cases of significant upper gastrointestinal bleeding; 380 of these patients were taking antiplatelet and/or anticoagulant drugs. The study found that the adjusted odds ratio for serious upper gastrointestinal bleeding with clopidogrel alone was 1.1 but that this rose to 7.4 in patients taking clopidogrel with aspirin.[7]
- Another study in 3335 patients with atrial fibrillation found that the rates of major bleeding were similar to that of oral anticoagulation, but a higher rate of minor bleeds occurred with clopidogrel and aspirin combined (relative risk of 1.23).[8]
- A study in 7 healthy subjects found that clopidogrel 75 mg and aspirin 150 mg daily for 2 days caused a significant 3.4-fold increase in bleeding time relative to baseline, and when the clopidogrel dose was increased to 300 mg there was a 5-fold increase in bleeding time.[9]

Furthermore, a number of case reports describe adverse effects when using the combination:

- Spontaneous haemarthrosis of the knee has been associated with the concurrent use of aspirin and clopidogrel in one patient.[10]
- A report describes two surgical cases, which were complicated by bleeding associated with the combination of aspirin and clopidogrel. In both cases the bleeding was delayed, in that it was not obvious until the end of surgery, causing unanticipated surgical re-exploration.[11]
- Further reports describe increased perioperative bleeding in patients taking both aspirin and clopidogrel.[12,13]

The manufacturer of clopidogrel warns that the concurrent use of clopidogrel and aspirin should be undertaken with caution because of the increased risk of bleeding, although this combination is recommended for use in patients with acute coronary syndromes for up to one year. They recommend that, in patients taking clopidogrel, the dose of aspirin should not exceed 100 mg daily as higher doses are associated with higher bleeding risks.[14] For patients undergoing surgery, it has been suggested that, if possible, the combined use of clopidogrel and aspirin should be discontinued about 5 days before the surgery to minimise the risks of bleeding.[4,12,15] The manufacturers say that if an antiplatelet effect is not necessary, clopidogrel should be discontinued 5 to 7 days before surgery,[14,16] although note that this needs to be balanced against the possible adverse effects of stopping such treatment, such as recurrent myocardial infarction or in-stent stenosis.

(c) Dipyridamole

A study in 10 healthy subjects found that dipyridamole 50 mg three times daily given with a single 180-mg dose of aspirin, or dipyridamole 75 mg three times daily given with aspirin 120 mg maximally inhibited platelet functions but did not prolong the bleeding time.[17] Two major studies in stroke patients (ESPRIT and ESPS-2) reported no significant increase in bleeding with combined use of aspirin and dipyridamole, when compared with aspirin alone, and the combination was beneficial in reducing the risk of further stroke.[18,19] The manufacturer of dipyridamole states that the addition of dipyridamole to aspirin does not increase the incidence of bleeding events.[20] However, be aware that the manufacturer of *Asasantin* (dipyridamole 200 mg with aspirin 25 mg) recommends caution when taking this product with other antiplatelet drugs because of the possible risk of increased bleeding.[21]

(d) Ticlopidine

Aspirin combined with ticlopidine appears to inhibit platelet aggregation more than either drug alone.[22,23] The rate of haemorrhagic complications at 30 days in the STARS study for ticlopidine 250 mg twice daily with low-dose aspirin was 5.5% compared with 1.8% for aspirin alone.[24] The US manufacturer of ticlopidine warns that its use with aspirin increases the risk of bleeding and that the safety of combined use beyond 30 days has not been established. They recommend that clinical monitoring is advisable.[24]

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Antiplatelet drugs + Food

Food increases the bioavailability of cilostazol, which may increase the incidence of adverse effects. Food increases the absorption of clopidogrel and ticlopidine.

Clinical evidence, mechanism, importance and management

(a) Cilostazol

A randomised, crossover study in 15 healthy subjects found that giving a single 100-mg dose of cilostazol within 10 minutes of a high-fat meal caused an increase in the rate and extent of cilostazol absorption. The maximum plasma level of cilostazol was increased by about 95%, the AUC was increased by 25%, and the half-life decreased from 15.1 to 5.4 hours, when compared with the fasted state.[1] The manufacturers recommend that cilostazol should be taken 30 minutes before or 2 hours after food, because the increase in maximum plasma levels of cilostazol when taken with food may be associated with an increased incidence of adverse effects.[2,3]

(b) Clopidogrel

Two studies in 12 healthy subjects, one group with an average age of 67 years and the other with an average age of 23 years, found that the bioavailability of the carboxylic acid metabolite of clopidogrel (a major metabolite used as a marker of absorption) remained unchanged when a single 75-mg dose of clopidogrel was taken in the fasting state or with food.[4] In another small study in 12 healthy subjects, food delayed the absorption of a single dose of clopidogrel, and increased its maximum concentration and AUC by about sixfold and ninefold, respectively.[5] The clinical significance of this increase is unclear as clopidogrel and its carboxylic acid metabolite are not active. Furthermore, neither study measured levels of the *active* thiol metabolite. The UK manufacturers currently recommend that clopidogrel may be taken without regard to food intake.[6]

(c) Ticlopidine

In a study in 12 healthy subjects the extent of absorption of a single 250-mg dose of ticlopidine was increased by 20% and occurred more rapidly when ticlopidine was taken after food, when compared with the fasting state.[7] These modest changes are unlikely to be of much clinical importance, and, although it is suggested that ticlopidine is taken with food, this is to minimise gastric intolerance.[7,8]

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Antiplatelet drugs + Ginkgo (*Ginkgo biloba*)

Ginkgo has been associated with platelet, bleeding, and clotting disorders, and there are isolated reports of serious adverse reactions after its concurrent use with antiplatelet drugs such as aspirin, clopidogrel, and ticlopidine.

Clinical evidence

A study in 10 healthy subjects found no significant increase in the antiplatelet effects of single doses of **clopidogrel** 75 mg or **cilostazol** 100 mg when a single dose of ginkgo 120 mg was added. However, the bleeding time was significantly increased when **cilostazol** was combined with ginkgo, although none of the subjects developed any significant adverse effects.[1] Another study[2] in 8 healthy subjects found that ginkgo 40 mg three times daily had no significant effect on the pharmacokinetics of a single dose of **ticlopidine** 250-mg taken on day 4.

A randomised, double-blind study in 55 patients with established peripheral artery disease (PAD) or with risk factors for developing PAD, found that the addition of ginkgo extract 300 mg (EGb 761) in divided doses to **aspirin** 325 mg daily did not have a significant effect on platelet aggregation. Five of the patients taking combined therapy reported nosebleeds or minor bleeding; however, 4 patients from the **aspirin**-only group also reported minor bleeding.[3] Similarly, a study in 41 healthy subjects found that 120-mg ginkgo coated-tablets (EGb 761) twice daily had no effect on the antiplatelet activity of **aspirin** 500 mg daily given for seven days. Minor bleeding was seen in a few subjects but this was attributed to the use of **aspirin**.[4] In an analysis of supplement use, 23% of 123 patients were currently taking supplements, and 4 patients were found to be taking ginkgo and **aspirin**. However, no problems from this use were found on review of the patients' notes.[5]

Nevertheless, a number of cases of clinically significant bleeding have been reported. A 70-year-old man developed spontaneous bleeding from the iris into the anterior chamber of his eye within one week of starting to take a ginkgo supplement (*Ginkoba*) tablet twice daily. He experienced recurrent episodes of blurred vision in one eye lasting about 15 minutes, during which he could see a red discoloration through his cornea. Each tablet contained 40 mg of concentrated (50:1) extract of ginkgo. He was also taking **aspirin** 325 mg daily, which he had taken uneventfully for 3 years since having coronary bypass surgery. He stopped taking the ginkgo but continued with the **aspirin**, and 3 months later had experienced no recurrence of the bleeding.[6] Another case reports persistent postoperative bleeding from a hip arthroplasty wound, which continued despite stopping **aspirin**. On closer questioning, the patient had continued to take ginkgo extract 120 mg daily postoperatively. The oozing from the wound gradually reduced when the ginkgo was stopped.

A search of Health Canada's database of spontaneous adverse reactions for the period January 1999 to June 2003 found 21 reports of suspected adverse reactions associated with ginkgo. Most of these involved platelet, bleeding, and clotting disorders. One report of a fatal gastrointestinal haemorrhage was associated with **ticlopidine** and ginkgo, both taken over 2 years along with other medications. Another report was of a stroke in a patient taking multiple drugs, including **clopidogrel**, **aspirin**, and a herbal product containing ginkgo.[7]

Mechanism

The reason for the bleeding is not known, but ginkgo extract contains ginkgolide B, which is a potent inhibitor of platelet-activating factor *in vitro*, which is needed for arachidonate-independent platelet aggregation. However, in one controlled study in healthy subjects, taking a ginkgo preparation alone for two weeks had no effect on platelet function.[8] Nevertheless, there are case reports of ginkgo supplements, on their own, being associated with prolonged bleeding times,[9-11] left and bilateral subdural haematomas,[9,12] a right parietal haematoma,[13] a retrobulbar haemorrhage,[14] post-laparoscopic cholecystectomy bleeding,[15] and subarachnoid haemorrhage.[10] Therefore it seems that the effects of ginkgo and conventional antiplatelet drugs can be additive, leading to bleeding complications on rare occasions.

Importance and management

The evidence from these case reports is too slim to advise patients taking aspirin, clopidogrel, or ticlopidine to avoid ginkgo, but some do recommend caution,[7] which seems prudent, especially as this is generally advised with most combinations of conventional antiplatelet drugs. There may also be a theoretical risk of increased bleeding if ginkgo is taken with other antiplatelet drugs; interactions have been reported with NSAIDs, some of which have antiplatelet effects (see 'NSAIDs + Ginkgo (*Ginkgo biloba*)', p.164).

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Antiplatelet drugs + NSAIDs

The manufacturers of clopidogrel warn about possible gastrointestinal bleeding if it is used with naproxen or other NSAIDs. There is also an increased risk of bleeding if ticlopidine is given with NSAIDs.

Clinical evidence, mechanism, importance and management

(a) Clopidogrel

A double-blind, placebo-controlled study in 30 healthy subjects given **naproxen** 250 mg twice daily, found that the addition of clopidogrel 75 mg daily increased faecal blood loss, when compared with **naproxen** alone. Six subjects receiving both drugs had their bleeding time prolonged by a factor of more than 5, which was greater than expected (clopidogrel alone prolongs bleeding by a factor of about 2) and one subject had subcutaneous haemorrhages of moderate intensity after taking clopidogrel with **naproxen**.[1] A retrospective study of patient records in the UK found that the adjusted rate ratio for the risk of gastrointestinal bleeding in patients taking clopidogrel with an NSAID increased from 1.67 for clopidogrel alone to 2.9 when clopidogrel was taken with an NSAID or 2.6 when clopidogrel was taken with a coxib.[2]

A case report describes intracerebral haemorrhage in an 86-year-old woman who had been taking **celecoxib** 200 mg daily with clopidogrel 75 mg daily for 3 weeks. The authors comment that there may possibly have been a pharmacokinetic interaction between clopidogrel and **celecoxib** [a metabolite of clopidogrel may inhibit CYP2C9, by which **celecoxib** is metabolised, although interaction have not been found between clopidogrel and other CYP2C9 substrates], although the haemorrhage could have been secondary to other factors, such as age, or the individual drugs.[3]

The manufacturers advise caution if NSAIDs, including coxibs, and clopidogrel are given together.[4,5] Note that, due to an increased thrombotic risk, the use of a coxib is contraindicated in those with ischaemic heart disease, cerebrovascular disease, and peripheral artery disease; and some evidence suggests that **diclofenac**, and high doses of **ibuprofen**, may similarly be associated with an increased risk of thrombotic events.[6] The use of an antiplatelet drug may indicate the presence of one of these conditions, and therefore the concurrent use of an NSAID should be considered carefully.

(b) Ticlopidine

The US manufacturer of ticlopidine states that drugs which might induce lesions with a propensity to bleed (such as ulcers) should be used with caution and also that ticlopidine potentiates the effect of NSAIDs on platelet aggregation. The safety of concurrent use of ticlopidine with NSAIDs has not been established,[7] and therefore caution should be used when prescribing an NSAID in patients taking ticlopidine. See above under clopidogrel, for comment on the use of NSAIDs in patients with coronary or cerebrovascular disease.

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Antiplatelet drugs + Policosanol

Policosanol has antiplatelet effects, which may be additive with those of other antiplatelet drugs.

Clinical evidence

In a randomised study, four groups, each containing 10 or 11 subjects, were given placebo, policosanol 20 mg daily, **aspirin** 100 mg daily, or both drugs together, for 7 days. Adrenaline-induced platelet aggregation was reduced in the group given **aspirin** and policosanol by about 35% more than in the group given **aspirin** alone: the effects of **aspirin** and policosanol were approximately additive. Furthermore, collagen-induced platelet aggregation was reduced in the group given **aspirin** and policosanol by about 10% more than in the group given **aspirin** alone. One patient taking both drugs suffered from bleeding gums. There was no significant effect on coagulation time.[1] A 3-year study, primarily designed to assess the safety and efficacy of policosanol in patients taking beta blockers, included 32 patients taking antiplatelet drugs (mainly **aspirin**). No adverse effects related to bleeding were reported.[2]

Mechanism

Additive antiplatelet effects.

Importance and management

The concurrent use of two conventional antiplatelet drugs is not uncommon, and so concurrent use of policosanol and aspirin need not be avoided. However, because platelet aggregation was reduced significantly, and a bleeding event was experienced, caution is perhaps warranted when taking policosanol supplements with aspirin or any other antiplatelet drug.

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Antiplatelet drugs + SSRIs

The bleeding risk associated with antiplatelet drugs such as aspirin, clopidogrel, dipyridamole, and ticlopidine may be further increased by concurrent use of an SSRI, although the data appears to be conflicting.

Clinical evidence

A retrospective study[1] of the UK general practice research database identified 1651 cases of upper gastrointestinal bleeding diagnosed between 1993 and 1997. The concurrent use of an SSRI significantly increased the risk of bleeding threefold, when compared with 10 000 control patients. In addition, the concurrent use of an SSRI with **aspirin** was associated with a relative excess risk of upper gastrointestinal bleeding of 3.5.

Another retrospective study found that the observed-expected ratio of an upper gastrointestinal bleed was 3.6 in patients taking an SSRI (17 320 patients), 2.5 in patients taking low-dose **aspirin** (26,762 patients), but increased to 5.2 in patients taking both an SSRI and low-dose **aspirin** (2 640 patients).[2] A retrospective case-control study in 579 patients diagnosed with gastrointestinal bleeding (upper and lower) found that the concurrent use of SSRIs with low-dose **aspirin** increased the risk of gastrointestinal bleeding above the risk found with each drug separately (odds ratio 2.1 for the combination, compared with 1.8 and 1.5 for **aspirin** and an SSRI, respectively).[3]

In contrast, a case-control study of hospital admissions for gastrointestinal bleeding reported no substantial increase in the risk of a gastrointestinal bleed in patients taking an SSRI. Furthermore, an interaction with low-dose **aspirin** was not seen.[4] Some workers have agreed with these results and found no evidence to suggest that SSRIs are more likely to cause gastrointestinal bleeding than other drugs.[5] In the SADHART study, which looked at the efficacy and cardiac safety of **sertraline** in the treatment of depression in patients with acute coronary syndromes, bleeding was not reported as an adverse effect of concurrent treatment, even though 170 of the 186 patients randomised to treatment with sertraline were also taking **aspirin**. Thirty-five (19%) of the **sertraline** group were taking other antiplatelet drugs such as **clopidogrel** and **ticlopidine**.[6] A substudy of SADHART, which included 25 patients taking **sertraline**, found that the use of **sertraline** was associated with a decrease in platelet/endothelial activation, suggesting that **sertraline** did not have an additional antiplatelet effect.[7] Similarly, a randomised, placebo-controlled study in patients with

coronary artery disease found no increased risk in reported bleeding in those taking **citalopram** 20 to 40 mg daily, when compared with placebo. Of the patients taking **citalopram**, 80% were also taking **aspirin** and 25% were taking other antiplatelet drugs (not specified).[8] A study in 20 healthy male smokers found that **paroxetine** 20 mg daily for 21 days did not produce an increase in the platelet inhibition produced by **aspirin** 100 mg daily from days 18 to 21.[9]

Mechanism

Serotonin is not synthesised by platelets but is taken up into platelets from the bloodstream. At therapeutic doses SSRIs can block this uptake, leading to serotonin depletion within the platelet. Serotonin released from platelets has an important role in regulating the haemostatic response to injury as it potentiates platelet aggregation. Therefore SSRIs may impair the haemostatic function of the platelets, which may increase the risk of bleeding,[10] especially in the presence of other antiplatelet drugs.

Importance and management

There appears to be an association between the use of antidepressant drugs that interfere with serotonin reuptake and the occurrence of bleeding, including gastrointestinal bleeding. **Citalopram**, **fluoxetine**, **fluvoxamine**, paroxetine, and sertraline have all been reported to cause bleeding.[10] It therefore seems reasonable to anticipate that the risks of bleeding with an antiplatelet drug may be increased by an SSRI. However, the overall evidence for an increased risk of bleeding when giving an SSRI with an antiplatelet drug, such as aspirin or clopidogrel, is conflicting, with some studies demonstrating an increased risk and others suggesting no additional antiplatelet effect occurs.

The manufacturers advise caution in patients taking SSRIs with aspirin or other drugs that affect coagulation or platelet function,[11] and this would seem prudent. This is especially important in patients taking combinations of antiplatelet drugs, such as aspirin and clopidogrel for acute coronary syndromes or coronary stents, where the risk of bleeding from this combination alone appears to be significant, see 'Antiplatelet drugs + Aspirin', p.814. Consideration should be given to the prescribing of gastroprotective drugs in those at high risk of gastrointestinal bleeding, such as elderly patients or those with a history of gastrointestinal bleeding. Note that this advice would also apply to those patients taking analgesic-dose aspirin with an SSRI.

For a discussion on the theoretical pharmacokinetic interaction of fluoxetine and fluvoxamine with clopidogrel, see 'Clopidogrel + Proton pump inhibitors and other CYP2C19 inhibitors', p.821.

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8. Lespérance F, Frasure-Smith N, Koszycki D, Laliberté M-A, van Zyl LT, Baker B, Swenson JR, Ghatavi K, Abramson BL, Dorian P, Guertin M-C for the CREATE investigators. Effects of citalopram and interpersonal psychotherapy on depression in patients with coronary artery disease: the Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) trial. *JAMA* (2007) 297, 367–79.
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10. De Abajo FJ, Montero D, García Rodríguez LA, Madurga M. Antidepressants and risk of upper gastrointestinal bleeding. *Basic Clin Pharmacol Toxicol* (2006) 98, 304–10.
11. Asasantin Retard (Dipyridamole with Aspirin). Boehringer Ingelheim Ltd. UK Summary of product characteristics, December 2007.

Aspirin + Fish oils

The concurrent use of aspirin and fish oil caused at least additive effects on bleeding time in healthy subjects, but in one clinical study there was no increase in incidence of bleeding episodes.

Clinical evidence

In a study in 8 healthy subjects, aspirin (325 mg on day one followed by 80 mg daily on days 2 and 3) prolonged the bleeding time by a mean of 2.2 minutes, whereas fish oil 4.5 g daily for 14 days had a non-significant effect (bleeding times increased by a mean of just 0.6 minutes). The combination prolonged bleeding time by a mean of 5 minutes, although this was stated to be not significantly different from a purely additive (43%) effect.[1] In this and a later study by the same researchers, fish oil did not increase the antiplatelet effect of aspirin.[1,2]

In a large placebo-controlled, randomised study of the effect of fish oils taken with either aspirin or warfarin over 9 months, there was no difference in the frequency of bleeding episodes between 119 patients taking aspirin 300 mg daily and fish oil 4 g daily and 106 taking aspirin alone (10 episodes versus 8 episodes, respectively).[3]

For a case of life-threatening bleed after a minor fall in a patient who had been taking omega-3 fatty acids 6 g daily, together with aspirin and warfarin for a year, see 'Coumarins + Fish oils', p.459.

Mechanism

Fish oils contain omega-3 fatty acids particularly **eicosapentaenoic acid** and **docosahexaenoic acid**. These are considered to have some antiplatelet activity, and may prolong the bleeding time. Theoretically, this effect might be additive with other antiplatelet drugs such as aspirin.

Importance and management

It appears that the concurrent use of aspirin and fish oils might increase bleeding times, particularly at high doses of fish oils, but one moderately large study found no evidence of increased incidence of bleeding episodes in clinical use. The manufacturer[4] of one product, *Omacor* (omega-3-acid ethyl esters), notes that at high doses of 4 g daily it may increase bleeding time, and advises caution in patients at a high risk of bleeding, but the only example they give is with anticoagulants. Some caution might be appropriate.

Note that this product is also licensed to be used with other standard therapies including antiplatelets as adjuvant treatment after myocardial infarction, but at a lower dose of just 1 g daily.[2]

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4. Omacor (Omega-3-acid ethyl esters 90). Solvay Healthcare Ltd. UK Summary of product characteristics, March 2008.

Cilostazol + Clopidogrel

Clopidogrel slightly increases the levels of cilostazol, without altering platelet count, aPTT, or prothrombin time. The addition of cilostazol to clopidogrel (with aspirin) does not appear to increase the risk of major or minor bleeding in some patient groups.

Clinical evidence, mechanism, importance and management

The concurrent use of cilostazol 150 mg twice daily and clopidogrel 75 mg daily for 5 days increased the AUC of cilostazol by only 9%, but increased the AUC of the dehydro metabolite of cilostazol by 24% (this metabolite has 3 to 4 times the potency of cilostazol in inhibiting platelet aggregation). No changes in platelet count, prothrombin time or aPTT were seen. However, clopidogrel alone prolonged bleeding time, and it was not possible to determine whether there was an additive effect with cilostazol.[1]

The DECLARE-Long study evaluated the efficacy of cilostazol 100 mg twice daily with clopidogrel 75 mg and aspirin 200 mg daily (triple thera-

py), in 250 patients with drug-eluting stents by comparing treatment with 250 similar patients taking just aspirin and clopidogrel (dual therapy). No major bleeding requiring transfusion occurred in either the triple or dual therapy group. Only 2 patients in the triple therapy group developed minor bleeding (ecchymoses) compared with 4 in the dual therapy group. However, the incidence of rash and gastrointestinal adverse effects was more common in the group that also took cilostazol (24 compared with 5 patients). There was also a higher discontinuation rate in the triple therapy patients.[2]

The CREST study also found no significant difference in bleeding rates (major or minor) between 354 patients taking aspirin, clopidogrel and cilostazol after percutaneous coronary intervention compared with those taking aspirin and clopidogrel (351 patients). Compliance with the triple therapy was similar to dual therapy and the only increased adverse effect reported in the triple therapy group was headache.[3]

A study found that the addition of cilostazol to aspirin and clopidogrel significantly increased the inhibition of ADP-induced platelet aggregation in patients undergoing primary percutaneous coronary intervention, although cilostazol had no significant additive effect on aspirin-induced antiplatelet activity. There was no major bleeding and no discontinuation of cilostazol because of adverse drug reactions.[4] Similar findings were reported in another study.[5]

Although it appears that the addition of cilostazol to clopidogrel therapy may not increase the risk of bleeding, the UK manufacturer suggests caution if cilostazol is given with any drug that inhibits platelet aggregation, and says that consideration should be given to monitoring the bleeding time at intervals.[1] This would seem prudent until more data, particularly in those patient groups at higher risk of bleeding, are available.

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Cilostazol + Miscellaneous

Erythromycin, diltiazem and ketoconazole, all inhibitors of the cytochrome P450 isoenzyme CYP3A4, increase the plasma levels of cilostazol. Other inhibitors of CYP3A4 are predicted to interact similarly, but grapefruit juice does not appear to significantly interact. Inducers of CYP3A4 (such as rifampicin (rifampin)) may also, in theory, alter cilostazol pharmacokinetics. Cilostazol is predicted to increase the levels of substrates of CYP3A4 (e.g. cisapride). Quinidine, an inhibitor of CYP2D6, does not appear to affect the pharmacokinetics of cilostazol and it is therefore suggested that other CYP2D6 inhibitors or substrates will not interact. Cilostazol appears not to interact to a clinically relevant extent with tobacco smoke.

Clinical evidence, mechanism, importance and management

(a) CYP3A4 and CYP2C19 inducers

The manufacturers of cilostazol state that the effect of inducers of the cytochrome P450 isoenzymes CYP3A4 and CYP2C19 (they name **carbamazepine**, **phenytoin**, **rifampicin** (**rifampin**) and **St John's wort**) on the pharmacokinetics of cilostazol has not been evaluated. In view of the effects of CYP3A4 inhibitors (see below) the manufacturers advice, to monitor concurrent use for an alteration in the antiplatelet effects of cilostazol, appears prudent.[1]

(b) CYP3A4 inhibitors

A study in 16 healthy subjects found that **erythromycin** 500 mg three times daily increased the maximum plasma level and the AUC of a single 100-mg oral dose of cilostazol by 47% and 73%, respectively. **Erythromycin** inhibits the cytochrome P450 isoenzyme CYP3A4, by which cilostazol is metabolised, thereby raising its plasma levels.[2] Other macrolide antibacterials e.g. **clarithromycin** (but not **azithromycin**) would be expected to have a similar effect.[3]

Diltiazem is also a moderate inhibitor of CYP3A4. When **diltiazem** 180 mg daily was given with cilostazol 100 mg twice daily, the AUC of cilostazol was increased by about 40%.[1,3]

In a single-dose study, **ketoconazole** 400 mg caused a greater than twofold increase in the AUC of cilostazol.[1] Other potent CYP3A4 inhibitors such as **itraconazole** are expected to interact similarly.[3]

In view of these effects the manufacturers suggest reducing the dose of cilostazol to 50 mg twice daily in the presence of CYP3A4 inhibitors such as the **macrolides** (e.g. **erythromycin**), **diltiazem**, some **azoles** (**itraconazole**, **ketoconazole**, **fluconazole**, **miconazole**) and the **protease inhibitors**.[1,3] The US manufacturer suggests that other CYP3A4 inhibitors, such as **SSRIs** (**fluoxetine**, **fluvoxamine**, **sertraline**) and **nefazodone**, may also interact.[3] Note that the SSRIs are, at worst, weak inhibitors of this isoenzyme, and therefore a clinically relevant interaction seems unlikely.

(c) CYP3A4 substrates

The UK manufacturer advises caution when cilostazol is given with drugs that are substrates of CYP3A4, especially those with a narrow therapeutic index. They specifically mention **cisapride**, **halofantrine**, **pimozide** and **ergot alkaloids** [**ergot derivatives**].[1] Further study is needed to establish these predicted interactions, although note that cilostazol has been seen to increase the levels of the CYP3A4 substrate lovastatin, see 'Statins + Cilostazol', p.1328.

(d) Grapefruit juice

The US manufacturer reports that grapefruit juice (a moderate inhibitor of CYP3A4) increased the maximum levels of cilostazol by approximately 50%, but had no clinically significant effect on the AUC.[3] However, the UK manufacturer says that 240 mL of grapefruit juice did not have a notable effect on the pharmacokinetics of a single 100-mg dose of cilostazol.[1] There has been a single, published case report of an interaction between grapefruit juice and cilostazol. A patient taking aspirin 100 mg daily and cilostazol 100 mg twice daily developed purpura, which resolved when the patient stopped drinking grapefruit juice. Neither aspirin nor cilostazol were stopped, and no dosage adjustments of either drug were made.[4] The general significance of this case is unclear, particularly as no pharmacokinetic data were reported confirming an increase in cilostazol levels. At present there appears to be no good evidence for avoiding the concurrent intake of grapefruit juice with cilostazol. However, bear the case report in mind, particularly in patients taking combinations of antiplatelet drugs who develop signs of bleeding.

(e) Quinidine

A crossover study in 22 healthy subjects found that the pharmacokinetics of a single 100-mg dose of cilostazol were unaffected by pretreatment with two 200-mg doses of quinidine sulfate, one taken 25 hours previously and the other taken one hour previously. Quinidine inhibits the activity of the cytochrome P450 isoenzyme CYP2D6, and it appears that this enzyme does not play a significant role in the metabolism of cilostazol or its primary metabolites.[5]

(f) Tobacco smoking

The manufacturer reports that population pharmacokinetic analysis suggests that tobacco smoking reduces the exposure to cilostazol by about 20%,[1,3] but this is unlikely to have much, if any, clinical relevance.

1. Pletal (Cilostazol). Otsuka Pharmaceuticals (UK) Ltd. UK Summary of product characteristics, November 2008.
2. Suri A, Forbes WP, Bramer SL. Effects of CYP3A inhibition on the metabolism of cilostazol. *Clin Pharmacokinet* (1999) 37 (Suppl 2), 61–8.
3. Pletal (Cilostazol). Otsuka America Pharmaceutical, Inc. US Prescribing information, May 2007.
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5. Bramer SL, Suri A. Inhibition of CYP2D6 by quinidine and its effects on the metabolism of cilostazol. *Clin Pharmacokinet* (1999) 37 (Suppl 2), 41–51.

Cilostazol + Proton pump inhibitors

Omeprazole, a CYP2C19 inhibitor, increases the bioavailability of cilostazol and its active metabolite. Other CYP2C19 inhibitors (such as esomeprazole) are predicted to interact similarly.

Clinical evidence

In a crossover study in 20 healthy subjects, **omeprazole** 40 mg daily for one week increased the AUC of a single 100-mg dose of cilostazol by a modest 26%.[1] More importantly, the AUC of 3,4-dehydro-cilostazol (a metabolite with 4 to 7 times the activity of cilostazol) was increased by 69%.[1-3] The AUC of the other active cilostazol metabolite (with low activity) was reduced by 31%.[1,3] The manufacturer notes this results in an overall increase in pharmacological activity of 42% when compared with cilostazol alone.[3]

Mechanism

Cilostazol is partially metabolised by the cytochrome P450 isoenzyme CYP2C19, and therefore omeprazole, an inhibitor of this isoenzyme, may inhibit the metabolism of cilostazol, and may possibly also affect the elimination of its active metabolites.

Importance and management

The clinical relevance of the pharmacokinetic interaction between cilostazol and omeprazole is uncertain, but some caution would seem prudent. The manufacturer suggests that the interaction could have the potential to increase cilostazol adverse effects, and they say that the dose of cilostazol could be reduced to 50 mg twice daily in patients also taking omeprazole or other CYP2C19 inhibitors (such as **esomeprazole**), based on individual assessment of efficacy and tolerability.[2,3] For a list of CYP2C19 inhibitors, see 'Table 1.3', (p.6).

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2. Pletal (Cilostazol). Otsuka America Pharmaceutical, Inc. US Prescribing information, May 2007.
3. Pletal (Cilostazol). Otsuka Pharmaceuticals (UK) Ltd. UK Summary of product characteristics, November 2008.

Clopidogrel + Azoles

In one study, ketoconazole modestly reduced the formation of the active metabolite of clopidogrel, and reduced its antiplatelet effect. Fluconazole and voriconazole are predicted to have a similar effect. In one study itraconazole reduced the antiplatelet effect of clopidogrel, but only in a subgroup of patients.

Clinical evidence

(a) Itraconazole

In a study to determine the effect of itraconazole on clopidogrel inhibition of platelet aggregation, 32 healthy subjects took itraconazole 200 mg daily, starting 4 days before clopidogrel was given (300 mg as a loading dose followed by 75 mg daily for 6 days). The antiplatelet effect of clopidogrel was also determined when subjects took clopidogrel alone. Platelet aggregation was significantly reduced by itraconazole, but only in the 16 subjects who were CYP3A5 non-expressor genotypes (that is, those lacking this isoenzyme), and not in the 16 subjects who were CYP3A5 expressors.[1]

(b) Ketoconazole

In a controlled study, 18 healthy subjects received clopidogrel (300 mg on day one followed by 75 mg daily for 5 days) alone and then with ketoconazole 400 mg daily, which was started 3 days before the clopidogrel. Ketoconazole reduced the AUC of the active metabolite of clopidogrel by 22% and 29%, after the loading and maintenance doses of clopidogrel, respectively. Inhibition of platelet aggregation (IPA) was also significantly reduced with ketoconazole, from 43% to 15% at 4 hours after the loading dose, and from 50% to 17% at 24 hours after the last maintenance dose. Of the 19 subjects, 14 had an IPA of less than 20% following the loading dose, a level seen in non-responders to clopidogrel.[2]

Mechanism

Formation of the active metabolite of clopidogrel is dependent on metabolism by the cytochrome P450 isoenzyme CYP2C19 and possibly also CYP3A4, and is therefore likely to be reduced by azoles that inhibit these isoenzymes. Ketoconazole is an inhibitor of CYP3A4 and CYP3A5,[2] and itraconazole is principally a CYP3A4 inhibitor. The interaction with itraconazole appeared to occur only in those without CYP3A5 activity, which suggests that CYP3A5 may be involved in the formation of the active metabolite of clopidogrel in the presence of CYP3A4 inhibition.[1] This appeared to be confirmed by a further study in patients given clopidogrel after stent implantation, which found a greater risk of atherothrombotic events in those without CYP3A5 activity.[1] Azoles that are inhibitors of CYP2C19 are also predicted to interact.

Importance and management

Evidence for an interaction between clopidogrel and the azoles appears to be limited to these two studies. The clinical relevance of the pharmacokinetic interaction with ketoconazole is unclear, but the level of inhibition of platelet aggregation in about three-quarters of healthy subjects taking ketoconazole with clopidogrel was below the level at which patients are classed as non-responders to clopidogrel, suggesting it may be important. The data with itraconazole suggest that the interaction with CYP3A4 inhibitors might be important in those lacking CYP3A5. Until more is known, some caution may be appropriate with azoles that are potent inhibitors of CYP3A4. Note that the US manufacturer advises the avoidance of ketoconazole with clopidogrel[3] (but on the basis that it is a CYP2C19 inhibitor; however, studies with CYP2C19 substrates suggests that it is not an inhibitor of this isoenzyme, see 'Azoles + Proton pump inhibitors', p.246).

The interaction of clopidogrel with CYP2C19 inhibitors is more extensively investigated than that with CYP3A4 inhibitors (see 'Clopidogrel + Proton pump inhibitors and other CYP2C19 inhibitors', p.821), and the manufacturers advise that the concurrent use of CYP2C19 inhibitors should be discouraged, and, of the azoles, they specifically name **fluconazole** and **voriconazole**.[3,4]

1. Suh J-W, Koo B-K, Zhang S-Y, Park K-W, Cho J-Y, Jang I-J, Lee D-S, Sohn D-W, Lee M-M, Kim H-S. Increased risk of atherothrombotic events associated with cytochrome P450 3A5 polymorphism in patients taking clopidogrel. *CMAJ* (2006) 174, 1715–22.
2. Farid NA, Payne CD, Small DS, Winters KJ, Ernest CS, Brandt JT, Darstein C, Jakubowski JA, Salazar DE. Cytochrome *P*450 3A inhibition by ketoconazole affects prasugrel and clopidogrel pharmacokinetics and pharmacodynamics differently. *Clin Pharmacol Ther* (2007) 81, 735–41.
3. Plavix (Clopidogrel bisulfate). Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership. US Prescribing information, October 2009.
4. Plavix Film-coated Tablets (Clopidogrel hydrogen sulphate). Bristol-Myers Squibb Pharmaceuticals Ltd. UK Summary of product characteristics, August 2009.

Clopidogrel + Miscellaneous

No adverse interactions appear to occur with clopidogrel and atenolol, cimetidine, digoxin, insulin, nifedipine, oestrogens, phenobarbital, phenytoin or tolbutamide.

Clinical evidence, mechanism, importance and management

No clinically significant pharmacodynamic interactions were seen when clopidogrel was given with **atenolol**, **nifedipine** or a combination of **atenolol** and **nifedipine**,[1] and the activity of clopidogrel was not altered by the concurrent use of **oestrogen**[2] or **phenobarbital**.[2] Another study found that clopidogrel does not alter the plasma levels of **digoxin** and that the pharmacodynamics of clopidogrel do not appear to be affected by **digoxin**.[3] One study found that the inhibition of platelet aggregation by clopidogrel was not reduced by **acetylcysteine**.[4]

Data from CAPRIE and other clinical studies showed that **ACE inhibitors**, **antidiabetics** (**insulin** and **tolbutamide** named),[2] **antiepileptics** (**phenytoin** named),[2] **beta blockers**, **calcium-channel blockers**, **coronary or peripheral vasodilators**, **diuretics** and **HRT** have been safely given with clopidogrel.[5]

No special precautions would therefore seem necessary when clopidogrel is given with any of these drugs.

1. Forbes CD, Lowe GDO, Maclaren M, Shaw BG, Dickinson JP, Kieffer G. Clopidogrel compatibility with concomitant cardiac co-medications: a study of its interactions with a beta-blocker and a calcium uptake antagonist. *Semin Thromb Hemost* (1999) 25 (Suppl 2), 55–9.
2. Plavix (Clopidogrel hydrogen sulphate). Sanofi Pharma Bristol-Myers Squibb SNC. UK Summary of product characteristics, August 2009.
3. Peeters PAM, Crijns HJMJ, Tamminga WJ, Jonkman JHG, Dickinson JP, Necciari J. Clopidogrel, a novel antiplatelet agent, and digoxin: absence of pharmacodynamic and pharmacokinetic interaction. *Semin Thromb Hemost* (1999) 25 (Suppl 2), 51–4.

4. Campbell CL, Berger PB, Nuttall GA, Orford JL, Santrach PJ, Oliver WC, Ereth MH, Thompson CM, Murphy MK, McGlassen DL, Schrader LM, Steinhubl SR. Can *N*-acetylcysteine reverse the antiplatelet effects of clopidogrel? An in vivo and vitro study. *Am Heart J* (2005) 150, 796–9.

5. Morais J, on behalf of the CAPRIE investigators. Use of concomitant medications in the CAPRIE trial: clopidogrel is unlikely to be associated with clinically significant drug interactions. *Eur Heart J* (1998) 19 (Abstract Suppl), 5.

Clopidogrel + Proton pump inhibitors and other CYP2C19 inhibitors

Information from controlled studies suggests that high-dose omeprazole almost halves exposure to the active metabolite of clopidogrel and reduces the antiplatelet action of clopidogrel by 30%. However, preliminary findings from one large clinical study found no reduction in clopidogrel efficacy with omeprazole 20 mg daily. Nevertheless, reduced efficacy has been seen in some, but not all, retrospective analyses.

In one controlled study, lansoprazole showed a trend towards a reduction in the antiplatelet action of clopidogrel, and some, but not all, retrospective analyses also show reduced efficacy. There is no information from *controlled* studies on the effect of other proton pump inhibitors. In one study, esomeprazole and pantoprazole did not appear to alter clopidogrel antiplatelet effects; however, some, but not all, retrospective analyses have shown poorer cardiovascular outcomes with both these proton pump inhibitors and also rabeprazole.

Clopidogrel slightly increases omeprazole exposure in CYP2C19 extensive metabolisers.

Clinical evidence

A. Pharmacokinetics and antiplatelet effects

(a) Controlled studies

1. Lansoprazole. In a randomised study, 24 healthy subjects were given lansoprazole 30 mg daily with a single 300-mg dose of clopidogrel on day 7. Lansoprazole had no effect on the AUC and maximum levels of the *inactive* carboxylic acid metabolite of clopidogrel, a major metabolite formed by esterases and used as a marker of absorption. The authors state that this study did not look at the effect of lansoprazole on the pharmacokinetics of the *active* metabolite of clopidogrel, because an assay was not available at the time. Lansoprazole tended to slightly reduce the effects of clopidogrel on platelet aggregation, but the effect was only statistically significant at 24 hours after the single dose of clopidogrel (39% versus 49%). A post-hoc analysis suggested that this effect was more pronounced in the subjects that had the greatest antiplatelet response to clopidogrel.[1]

2. Omeprazole. The manufacturer notes that, in a crossover study in 72 healthy subjects given a 300-mg loading dose of clopidogrel then clopidogrel 75 mg daily for 5 days, high-dose omeprazole 80 mg daily for 5 days, taken at the same time as clopidogrel, reduced the exposure to the active metabolite of clopidogrel by about 45%. In addition, the mean inhibition of platelet aggregation was reduced by 47% at 24 hours and reduced by 30% on day 5, when compared with clopidogrel alone. Similar results were seen in a further study when the daily dose of omeprazole and clopidogrel were taken 12 hours apart.[2]

In a randomised, placebo-controlled study in 124 patients undergoing elective coronary stent insertion and taking aspirin 75 mg daily and clopidogrel (300 mg loading dose followed by 75 mg daily), 64 patients were also given omeprazole 20 mg daily for 7 days. On day 7, the group given omeprazole were found to have a higher platelet reactivity index when compared with placebo recipients (51% compared with 40%, respectively), indicating a reduced antiplatelet effect.[3] The authors note that a platelet reactivity index of greater than 50% indicates a poor response to clopidogrel. On this basis, 61% of omeprazole recipients were considered to have had a poor response to clopidogrel, compared with 27% in the placebo group.[3] Note that, in this study, CYP2C19 metaboliser status was unknown,[4] although given that it was a large randomised study in a specific population, a difference between the groups would not usually be expected.

In a pharmacokinetic study in healthy subjects, clopidogrel (a 300-mg loading dose and then 75 mg daily for 3 days) modestly increased the AUC of a single 40-mg dose of omeprazole given on day 4 by 30% and decreased its clearance by 22% in CYP2C19 extensive metabolisers (that is, those with normal levels of this isoenzyme), but had no effect in CYP2C19 poor metabolisers (that is, those lacking or totally deficient in this isoenzyme). The degree of inhibition was modest, and omeprazole exposure in CYP2C19 extensive metabolisers given clopidogrel was still lower than in CYP2C19 poor metabolisers (with or without clopidogrel). The effect of omeprazole on clopidogrel was not assessed.[5]

(b) Non-randomised studies

1. Esomeprazole. A study in patients taking aspirin 100 mg daily with clopidogrel 75 mg daily for at least 5 days (average 3 months) included 74 patients taking esomeprazole. The study found no difference in the platelet reactivity index or ADP-induced platelet aggregation when these patients were compared with 74 patients not taking a proton pump inhibitor.[6] Similarly, in a study of patients with coronary artery disease taking both aspirin and clopidogrel, the proportion of patients having a poor antiplatelet response to clopidogrel was similar in 42 patients taking esomeprazole and in patients not taking a proton pump inhibitor (about 20% in both groups).[7]

2. Omeprazole. In a study in patients with coronary artery disease taking both aspirin and clopidogrel, the proportion of patients having a poor antiplatelet response to clopidogrel was about 13% higher in the 64 patients taking omeprazole, when compared with patients taking esomeprazole or pantoprazole, or not taking a proton pump inhibitor (about 33% versus 20%).[7]

3. Pantoprazole. In a study in patients taking aspirin 100 mg daily with clopidogrel 75 mg daily for at least 5 days (average 3 months) included 152 patients taking pantoprazole. This study found that there was no difference in the platelet reactivity index or ADP-induced platelet aggregation in the patients taking pantoprazole when compared with 74 patients not taking a proton pump inhibitor.[6] Similarly, in a study of patients with coronary artery disease taking both aspirin and clopidogrel, the proportion of patients having a poor antiplatelet response to clopidogrel was similar in 162 patients taking pantoprazole and those patients not taking a proton pump inhibitor (about 20% in both groups).[7]

4. Unspecified proton pump inhibitors. In a study, the platelet reactivity index was measured in 105 consecutive patients taking aspirin and clopidogrel to investigate its relationship with various other concurrent drugs. A higher platelet reactivity index (indicating a poor response to aspirin and clopidogrel) was found in the 24 patients taking proton pump inhibitors, when compared with the 81 patients not taking proton pump inhibitors (about 61% versus 50%).[8] Similarly, in a post-hoc analysis of a clinical study in patients given a 600-mg loading dose of clopidogrel then clopidogrel 150 mg daily (PRINCIPLE-TIMI 44), mean inhibition of platelet aggregation was lower in those patients also taking a proton pump inhibitor. The proportion of patients with reduced platelet responsiveness to clopidogrel was twofold higher in patients taking a proton pump inhibitor than in patients not taking a proton pump inhibitor, when assessed at 24 hours after the 600-mg loading dose of clopidogrel.[9]

B. Clinical outcomes

Note that, at present, there are no data from placebo-controlled, randomised studies on the effect of any proton pump inhibitors on the long-term cardiovascular efficacy of clopidogrel, apart from preliminary data from the halted Cogent study, see *Prospective studies*, below. All other data available are retrospective analyses, and, as it is impossible to control for all possible confounders, definitive conclusions cannot be drawn from these studies. Note that there is also some information showing that the clinical benefit of clopidogrel depends on CYP2C19 genotype,[2] which partly supports the proposed mechanism of the interaction by CYP2C19 inhibition.

(a) Prospective studies

A preliminary analysis of data from the COGENT-1 study found that, of the 3 627 patients enrolled, there appeared to be no clinically significant difference in the incidence of all cardiovascular events as well as myocardial infarction or in the need for revascularisation between the patients taking clopidogrel and omeprazole 20 mg daily and those patients taking clopidogrel but not omeprazole, for a mean follow-up of 133 days.[10] However, note that this large, phase III clinical study was unfinished due to bankruptcy, and was primarily designed to investigate the gastrointestinal benefits of a combined preparation of omeprazole and clopidogrel, rather than to investigate a drug interaction between omeprazole and clopidogrel and its possible effects on cardiovascular outcomes.

(b) Retrospective studies

1. Poorer outcomes with all proton pump inhibitors. A large, retrospective, cohort study in patients taking clopidogrel who were hospitalised with acute coronary syndrome, investigated the use of proton pump inhibitors to establish if concurrent use was associated with an increase in adverse cardiovascular outcomes. In this study, the 5 244 patients taking a proton pump inhibitor with clopidogrel were reported to have a 9% additional increase in the rate of death or rehospitalisation for acute coronary syndrome compared with the 2 961 patients not taking a proton pump inhibitor (29.8% versus 20.8%), although the patients in the proton pump inhibitor group were older and had more co-morbid conditions. After adjusting for these confounding factors, the odds ratio was 1.25. Further analysis on the secondary outcomes reported that the rate of rehospitalisation for acute coronary syndrome was 14.6% in those taking a proton pump inhibitor with clopidogrel, compared with 6.9% for those patients not taking a proton pump inhibitor with clopidogrel, with an adjusted odds ratio of 1.86. The proton pump inhibitors given included **omeprazole** (59.7%), **rabeprazole** (2.9%), **lansoprazole** (0.4%) and **pantoprazole** (0.2%), and 36.7% of patients took more than one proton pump inhibitor during follow-up (that is, they switched between different proton pump inhibitors). Individual data for **lansoprazole** and **pantoprazole** were not analysed as the patient numbers were too small, but **omeprazole** and **rabeprazole** use were reported to have an increased risk of adverse outcomes (odds ratio 1.24 and 2.83, respectively). In patients discharged after an episode of acute coronary syndrome who were not given clopidogrel, the use of proton pump inhibitors was not associated with an increased risk of death or re-admission to hospital, suggesting that any effect was the result of an interaction, rather than a factor of proton pump inhibitor use.[11] Similarly, in a cohort study of 18 565 patients who were given clopidogrel, there was a slight increased risk of hospitalisation for myocardial infarction, or death (adjusted risk ratio of 1.26) in those taking a proton pump inhibitor (**omeprazole**, **esomeprazole**, **lansoprazole**, **pantoprazole**, **rabeprazole**) compared with patients not taking a proton pump inhibitor. This suggests that if an effect exists, it is unlikely to be greater than a 20% increased risk.[12] In an unpublished retrospective cohort study, there was an increased risk of hospitalisation for a major adverse cardiovascular event for all proton pump inhibitors compared with clopidogrel alone (25% versus 18%, hazard ratio 1.51). The most common proton pump inhibitors taken were **esomeprazole** (3 257 patients), **omeprazole** (2 307 patients) and **pantoprazole** (1 653 patients), with fewer patients taking **lansoprazole** (785 patients) or **rabeprazole** (298 patients). When the data was analysed by individual proton pump inhibitor, a similar increased risk was seen for **lansoprazole** (24%), **esomeprazole** (25%), **omeprazole** (25%), and **pantoprazole** (29%): the patient group taking **rabeprazole** was too small for individual statistical evaluation. No increased risk was found with in 472 patients taking an **H_2-receptor antagonist** (not specified), when compared with a control group not taking an **H_2-receptor antagonist** (9390 patients).[13]

2. Poorer outcomes with some proton pump inhibitors. In a retrospective case-control study in 734 patients taking clopidogrel post myocardial infarction and readmitted within 90 days with a further myocardial infarction, the concurrent use of a proton pump inhibitor (**lansoprazole**, **omeprazole**, **pantoprazole**, or **rabeprazole**; 194 cases) was associated with a 27% increased risk of re-infarction. When the data was analysed for **pantoprazole** separately (46 cases), there was no additional risk of myocardial infarction.[14] The remaining proton pump inhibitors as a group were associated with a 40% increased risk and the data for them were not analysed separately. However, the difference between the risk for pantoprazole and the other drugs was not statistically significant. The proton pump inhibitors were grouped like this on the basis of *in vitro* CYP2C19 inhibition data; however, see under *Mechanism*, below, for further discussion of the potential relevance of this. In this study, use of the **H_2-receptor antagonists**, **ranitidine**, **famotidine** and **nizatidine**, were not associated with an increased risk of re-infarction.

3. No effect of proton pump inhibitors. In a retrospective analysis of a large clinical study in patients taking clopidogrel (TRITON-TIMI 38), no association was found between proton pump inhibitor use and an increased incidence of cardiovascular death, myocardial infarction, stroke or coronary stent thrombosis. The most common proton pump inhibitors taken were **pantoprazole** (1 844 patients) and **omeprazole** (1 675 patients), with fewer patients taking **esomeprazole** (613 patients), **lansoprazole** (441 patients) and **rabeprazole** (66 patients).[9]

Mechanism

The mechanism for the interaction between the proton pump inhibitors and clopidogrel is unclear. At present, the most plausible mechanism is that omeprazole inhibits the conversion of clopidogrel to its active metabolite by the cytochrome P450 isoenzyme CYP2C19. *In vitro* data indicate that lansoprazole, esomeprazole and a metabolite of rabeprazole can all inhibit CYP2C19, but that pantoprazole does not significantly affect this isoenzyme.[15] However, *in vitro* inhibitory activity does not always translate to a clinically relevant effect *in vivo*: inhibition of CYP2C19 appears to occur between the known CYP2C19 substrate diazepam, and omeprazole and esomeprazole, but a significant interaction does not occur with rabeprazole, lansoprazole or pantoprazole (see 'Benzodiazepines + Proton pump inhibitors', p.860). Furthermore, CYP2C19 inhibition by the proton pump inhibitors is not entirely consistent with the available data for their suggested interaction with clopidogrel. For example, there are data suggesting that esomeprazole does not alter the antiplatelet effects of clopidogrel, and some evidence from retrospective studies that all proton pump inhibitors are associated with a similar risk of poorer outcomes in patients taking clopidogrel. However, if the proton pump inhibitors completely inhibited the activity of CYP2C19, this would effectively make CYP2C19 extensive metabolisers into poor metabolisers, who have been reported to have a reduced antiplatelet response to clopidogrel and a higher than expected rate of cardiovascular events.[2,16]

Others have suggested that P-glycoprotein may also possibly be involved;[4] *in vitro* data suggest that clopidogrel absorption may be reduced by P-glycoprotein inhibition,[17] and based on their interaction with digoxin, a key P-glycoprotein substrate (see 'Digoxin and related drugs + Proton pump inhibitors', p.1111), most proton pump inhibitors appear to affect this drug transporter protein, although the effect is mild.

Clopidogrel is a minor inhibitor of CYP2C19, by which omeprazole and many other proton pump inhibitors are partly metabolised. In this study, the metabolism of omeprazole to 5-hydroxyomeprazole by CYP2C19 was decreased, whereas its metabolism to omeprazole sulfone by CYP3A4 was unchanged.[5]

Importance and management

A pharmacokinetic interaction between high-dose **omeprazole** (80 mg daily) and clopidogrel appears to be established, roughly halving the levels of the active metabolite of clopidogrel and reducing its antiplatelet effects by 30%. Separating the dose of clopidogrel and omeprazole by 12 hours did not reduce or abolish the pharmacokinetic interaction in one study. However, what is not clearly established is to what degree this might reduce the clinical efficacy of clopidogrel, and to what extent it applies to more commonly used doses of omeprazole (20 mg daily). Limited evidence from one unfinished prospective, randomised controlled study suggests that omeprazole 20 mg daily has no effect on clopidogrel efficacy,[10] and data from retrospective analyses have varied from no effect to an increased risk of adverse cardiac outcomes, with the greatest effect being a 1.86-fold increased risk in the rate of rehospitalisation for acute coronary syndrome. This, coupled with the data showing a reduced clinical response to clopidogrel alone in patients who are CYP2C19 poor metabolisers, suggests that it is not unreasonable to suppose that omeprazole causes some reduction in the efficacy of clopidogrel.

Evidence for a class interaction between clopidogrel and the **proton pump inhibitors** is mostly based on retrospective data, some of which is contradictory, and does not appear to fit with the known CYP2C19 inhibitory activity of these proton pump inhibitors. On reviewing the available evidence, in November 2009 the FDA in the US recommended that omeprazole should be avoided in patients taking clopidogrel. A similar recommendation is made for **esomeprazole** on the basis that it is the *S*-isomer of omeprazole, and also inhibits CYP2C19.[18] At present, the FDA states that there is insufficient evidence to make specific recommendations about the concurrent use of clopidogrel with other proton pump inhibitors.[18] The EMEA and MHRA guidance[19-21] does not distinguish between the proton pump inhibitors. These bodies advise that proton pump inhibitors [as a class] should only be given with clopidogrel if it is considered essential (such as, where the risk of gastric disease is greater than the risk of a cardiac event). If a proton pump inhibitor is considered essential, based on the lack of a pharmacokinetic interaction with the known CYP2C19 substrate diazepam (consider 'Benzodiazepines + Proton pump inhibitors', p.860), **rabeprazole**, and possibly also **pantoprazole** or **lansoprazole**, would seem to be the most appropriate options. However, the effects or lack of effect of these individual proton pump inhibitors on clopidogrel efficacy

is not established, and more prospective studies are needed to investigate this.

H_2-receptor antagonists would seem to offer an alternative to the proton pump inhibitors, with **ranitidine**, **famotidine** or **nizatidine** not having been implicated in causing an interaction in a number of the retrospective analyses. Although the UK manufacturer of clopidogrel briefly reports that **cimetidine** has no significant effects on the antiplatelet activity of clopidogrel;[16] cimetidine is a known weak inhibitor of various cytochrome P450 isoenzymes, and is known to inhibit the metabolism of diazepam, a substrate of CYP2C19 (see 'Benzodiazepines and related drugs + H_2-receptor antagonists', p.849). Therefore, it may be prudent to avoid the use of cimetidine.

On the basis of the interaction with omeprazole, the FDA say that other drugs that inhibit CYP2C19 would also be expected to interact similarly, and concurrent use should be avoided. The US and UK manufacturers[2,16] list a number of drugs, including **cimetidine**, **etravirine**, **felbamate**, **fluoxetine**, **fluvoxamine**, **ticlopidine**, **moclobemide**, **ciprofloxacin**, **carbamazepine**, **oxcarbazepine** and **chloramphenicol**. However, not all of these drugs are proven, clinically relevant CYP2C19 inhibitors. Note that, **ticlopidine**, like clopidogrel, is a thienopyridine antiplatelet drug, and it is not usually used with clopidogrel because it has the same mechanism of action.

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Clopidogrel + Statins

Atorvastatin had no clinically relevant effect on the pharmacokinetics or antiplatelet effect of clopidogrel in controlled studies. Similarly, pravastatin, and possibly lovastatin and rosuvastatin, do not to alter the antiplatelet effect of clopidogrel. The data for simvastatin and fluvastatin are limited, with one study showing some reduction in antiplatelet effect. Nevertheless, clinical outcome data from retrospective analysis of large studies does not support an interaction with any of these other statins.
Isolated cases of rhabdomyolysis have been reported in patients taking statins (atorvastatin, lovastatin, simvastatin) and given clopidogrel.

Clinical evidence

A. Clopidogrel effects

(a) Atorvastatin

In 2003, a small non-randomised study reported that 19 patients taking atorvastatin 10 to 40 mg daily had lower antiplatelet activity of clopidogrel after undergoing coronary artery stenting when compared with 16 patients not receiving statins or 9 receiving **pravastatin**, and the effect appeared to be dose related.[1] Note that non-randomised comparisons like this cannot account for all differences between patients (e.g. genetic differences resulting in non-response to clopidogrel), and the smaller they are, the more likely that differences could bias the results. Since this original publication suggesting an interaction, numerous non-randomised and retrospective analyses have been conducted. Of studies looking at antiplatelet effects, one other non-randomised study found that the antiplatelet effects of clopidogrel were lower in those receiving atorvastatin,[2] whereas other non-randomised studies[3-5] and, more importantly, three randomised studies,[6-8] have not found any effect. However, of these randomised studies, one used a high dose of clopidogrel (600 mg)[6] and one used a low dose of atorvastatin (10 mg),[7] both factors that might minimise any interaction.

Platelet reactivity studies may not be directly relevant to clinical outcomes, so the efficacy of clopidogrel in relation to statin type has been retrospectively analysed from a number of studies and patient cohorts. Interpretation of this sort of study is complicated by the presence of unknown confounders. In one retrospective, observational review of prescribing data, a 1.49-fold higher rate of cardiovascular events at day 30 post-procedure was noted in patients taking atorvastatin with clopidogrel, when compared with control patients, about 55% of whom were taking other statins (mostly **pravastatin** or **simvastatin**).[9] However, note that simvastatin might also be anticipated to interact, based on the original proposed mechanism. Conversely, in all other analyses, use of atorvastatin, or any other statin studied, has not been associated with reduced efficacy in patients receiving clopidogrel.[10-15] For example, a retrospective examination of data from the CREDO study found no difference in one-year outcomes in patients given atorvastatin or **pravastatin**,[10] although there appeared to be a slightly better outcome in those given a statin that is not a CYP3A4 substrate (**fluvastatin**, **pravastatin**) compared with statins that are (**atorvastatin**, **cerivastatin**, **lovastatin**, **simvastatin**).[16,17] Furthermore, a prospective, cohort study in 1651 patients with acute coronary syndromes found that the use of clopidogrel with a statin was associated with *lower* 6-month mortality and morbidity compared with the use of clopidogrel in the absence of a statin. There was no significant difference in clinical benefit between a statin predominantly metabolised by the cytochrome P450 isoenzyme CYP3A4 or a statin not predominantly metabolised by CYP3A4.[12] Similarly, retrospective analysis of data from the CHARISMA study, which involved 15 603 patients and had a median duration of 28 months, also found no difference in terms of clinical outcomes between patients who received statins primarily metabolised by CYP3A4 and those who took statins not predominantly affected by CYP3A4. Also, those who took a statin had a lower risk of myocardial infarction, stroke or cardiovascular death, when compared with those who did not take a statin.[13] Similarly, there was no difference in clinical outcomes between those patients randomised to receive **atorvastatin** 80 mg daily or **pravastatin** 40 mg daily and also receiving clopidogrel in a retrospective analysis of the PROVE IT–TIMI 22 study.[14] In addition, one-year outcomes did not differ between statins (**atorvastatin**, **simvastatin**, **fluvastatin** and **pravastatin**) in the EXCELSIOR study.[15]

In 2008, a key randomised, crossover study was published, which conclusively demonstrates, that, if anything high-dose atorvastatin actually modestly *increases* the levels of the active metabolite of clopidogrel and slightly *increased* its antiplatelet effect. In this study, 31 healthy subjects received clopidogrel alone (300 mg loading dose then 75 mg daily for 10 days) with atorvastatin 80 mg daily started 6 days before the clopidogrel. Atorvastatin did not change the exposure (AUC) to the active metabolite of clopidogrel after the 300 mg dose, but, on day 10, there was a modest 28% increase in AUC of the active metabolite. The antiplatelet effect of clopidogrel was unchanged after the 300 mg dose, but tended to be increased on the final day. There was an increase of about 6 to 16%; differences which were statistically significant at some, but not all, time points.[18]

(b) Other statins metabolised by CYP3A4

In one crossover study in 20 healthy subjects given clopidogrel 75 mg daily, **simvastatin** 20 mg daily for 7 days reduced the antiplatelet response by about 31%, with just one subject then classified as a clopidogrel non-responder.[8] However, in a randomised study in patients, **simvastatin** (20 mg given 24 hours before the clopidogrel) did not alter the antiplatelet effects of clopidogrel after a 600 mg dose, when compared with placebo.[6] This study also found no effect of **lovastatin**.[6] Of non-randomised studies looking at antiplatelet effects, one found a lower antiplatelet response to clopidogrel after coronary artery stenting in those receiving simvastatin,[2] whereas, in another very similar study, no effect of **simvastatin** was detected.[5] Moreover, retrospective clinical outcome studies have shown no detrimental effect of simvastatin or lovastatin, see *Atorvastatin*, above. There are no studies on the effect of **simvastatin** or **lovastatin** on clopidogrel pharmacokinetics.

(c) Statins not principally metabolised by CYP3A4

There do not appear to be any studies suggesting that an interaction between clopidogrel and **pravastatin** occurs, and a number of studies showing no interaction. In one crossover study in 20 healthy subjects given clopidogrel 75 mg daily, neither **pravastatin** 40 mg daily nor **rosuvastatin** 10 mg daily for 7 days reduced the antiplatelet response of clopidogrel.[8] Similarly, in two randomised studies in patients, **pravastatin** (20 mg or 40 mg started 24 hours before the clopidogrel) did not alter the antiplatelet effects of clopidogrel after a 600 mg or 375 mg dose.[6,7] Similarly, in non-randomised studies, pravastatin did not affect the antiplatelet activity of clopidogrel.[1,5] Retrospective clinical outcome studies have shown no detrimental effect of **pravastatin**, see *Atorvastatin*, above. There are no studies on the effect of **pravastatin** on clopidogrel pharmacokinetics

In one crossover study in 20 healthy subjects given clopidogrel 75 mg daily, **fluvastatin** 80 mg daily for 7 days reduced the antiplatelet response by about 29%, with just two subjects then classified as clopidogrel non-responders.[8] However, in a randomised study in patients, **fluvastatin** (20 mg given 24 hours before the clopidogrel) did not alter the antiplatelet effects of clopidogrel after a 600 mg dose, when compared with placebo.[6] Similarly, one retrospective analysis found that **fluvastatin** did not affect the platelet activity of clopidogrel.[3] Clopidogrel had no effect on the pharmacokinetics of **fluvastatin** 80 mg daily in a controlled study in healthy subjects, and the antiplatelet effect of clopidogrel was similar to that expected for clopidogrel alone.[19] Moreover, retrospective clinical outcome studies have shown no detrimental effect of **fluvastatin**, see *Atorvastatin*, above.

B. Rhabdomyolysis

Isolated cases of rhabdomyolysis precipitated by clopidogrel have been reported. Two heart transplant patients taking **simvastatin** or **lovastatin**, together with ciclosporin for several years with no reported problems, developed rhabdomyolysis within 2 weeks of starting clopidogrel.[20] Another similar report describes a patient who was stable taking ciclosporin and **atorvastatin** who developed rhabdomyolysis when a 4-week course of clopidogrel was started.[21]

Mechanism

Clopidogrel is an inactive prodrug that is metabolised to its active metabolite by the cytochrome P450 isoenzyme system, with CYP2C19 known to be important, and possibly also CYP3A4 (see 'Clopidogrel + Azoles', p.820). Several statins (lovastatin, simvastatin, atorvastatin), are principally metabolised by CYP3A4 and it has been suggested that these statins may competitively inhibit the activation of clopidogrel,[1] and this was shown *in vitro* for atorvastatin lactone.[22] However, note that this is not an established mechanism for pharmacokinetic drug interactions, and substrates of CYP3A4 do not cause clinically relevant interactions unless they are also CYP3A4 inhibitors, which none of the statins are known to be. The well-designed pharmacokinetic study with atorvastatin conclusively shows that it does not inhibit the formation of the active metabolite of clopidogrel. In fact, it actually resulted in a modest increase in active metabolite levels, the mechanism for which is unknown.

One controlled study showed a reduction in antiplatelet effects of clopidogrel with simvastatin and fluvastatin. The mechanism for this is unknown.

Clopidogrel (a possible CYP2C9 inhibitor) does not alter the metabolism of fluvastatin (a CYP2C9 substrate).[19]

Importance and management

The possible interaction between clopidogrel and the statins has been the subject of much study and debate. The few studies showing a reduced antiplatelet effect of atorvastatin are all limited by their non-randomised design and small number of patients, and the findings could therefore easily be due to confounding by unknown factors. These sorts of studies are useful in generating hypotheses, but should not be used to guide clinical decisions.[23] A subsequent well-designed study has shown that atorvastatin 80 mg daily has no inhibitory effect on the pharmacokinetics and antiplatelet effects of clopidogrel, and, in fact, slightly increased the levels and activity of clopidogrel, although probably not to a clinically relevant extent. Therefore, no interaction would be expected in clinical use. This is supported by all of the retrospective analyses of clinical outcome data except one.

Apart from pravastatin, which also appears to have no effect on the antiplatelet action of clopidogrel, data for other statins are limited. Of some concern, in one controlled crossover study, the antiplatelet effect of clopidogrel was reduced with both simvastatin and fluvastatin (but not with atorvastatin, pravastatin or rosuvastatin), and further study into this is therefore needed. Nevertheless, all the available retrospective outcome data show no adverse effect of either simvastatin or fluvastatin.

The general significance of the case reports describing rhabdomyolysis, when clopidogrel was given to transplant patients who were stable taking a statin with ciclosporin, is unclear.

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Dipyridamole + Beta blockers

No adverse reactions normally occur in patients taking beta blockers who undergo dipyridamole–thallium-201 scintigraphy and echocardiography, but case reports suggest that very rarely bradycardia and asystole can occur.

Clinical evidence

A 71-year-old woman taking **nadolol** 120 mg daily and bendroflumethiazide, with a 3-week history of chest pain, was given a 300-mg dose of oral dipyridamole as part of a diagnostic dipyridamole-thallium imaging test for coronary artery disease. She was given thallium-201 intravenously, 50 minutes after the dipyridamole, but 3 minutes later, while exercising, she complained of chest pain and then had a cardiac arrest. She was given cardiopulmonary resuscitation and a normal cardiac rhythm was obtained after she was given intravenous aminophylline.[1]

Adverse interactions have been reported in another 3 patients taking beta blockers during diagnostic dipyridamole-thallium stress testing. One patient, who was taking **atenolol**, developed bradycardia and then asystole, another patient who was taking **metoprolol** developed bradycardia,[2] and a third patient, also taking **metoprolol**, developed sinus bradycardia and then asystole.[3] All three patients recovered when treated with aminophylline.[2,3]

These reports need to be set in a broad context. A very extensive study of high-dose dipyridamole echocardiography (10 451 tests in 9 122 patients) noted significant adverse effects in only 96 patients, with major adverse reactions occurring in just 7 patients. Three of the 7 developed asystole and two of these patients were taking unnamed beta blockers.[4] However, a further three case reports describe the development of asystole or symptomatic bradycardia during dipyridamole infusion in patients *not* taking beta blockers.[5,6]

Mechanism

Not established. One possible explanation is that both drugs have negative chronotropic effects on the heart.

Importance and management

The value and safety of dipyridamole perfusion scintigraphy and echocardiography have been very extensively studied in very large numbers of patients, and reports of bradycardia and asystole, attributed to an interaction between dipyridamole and beta blockers, are sparse. It would therefore appear to be a relatively rare interaction (if such it is).

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Dipyridamole + Drugs that affect gastric pH

The effective disintegration, dissolution and eventual absorption of dipyridamole formulated as a tablet or suspension depends upon having a low pH in the stomach. Drugs that raise the gastric pH significantly are expected to reduce the bioavailability of dipyridamole. Modified-release preparations of dipyridamole (that are buffered) do not appear to be affected.

Clinical evidence, mechanism, importance and management

The solubility of dipyridamole depends very much on pH. It is very soluble at low pH values and almost insoluble at neutral pH.[1] This indicates that dipyridamole needs a low pH in the stomach if solid formulations of the drug are to disintegrate and dissolve adequately. A study in 11 healthy elderly subjects (6 control subjects with a low fasting gastric pH and 5 achlorhydric subjects with fasting gastric pH greater than 5) found that elevated gastric pH reduced the absorption of a single 50-mg oral dose of dipyridamole. In addition, pretreatment with **famotidine** 40 mg increased the gastric pH to above 5 for at least 3 hours, which resulted in reduced dipyridamole absorption. The dipyridamole AUC was reduced by 37% (not statistically significant) and the maximum serum levels were significantly delayed and reduced.[2] In another study, 20 healthy subjects were given **lansoprazole** 30 mg daily for 5 days and then either:

- a single dose of an extended-release preparation of dipyridamole 200 mg with aspirin 25 mg (formulated with tartaric acid to improve bioavailability of dipyridamole if the gastric pH is elevated)
- or a conventional dipyridamole formulation (100 mg given with 81 mg of aspirin, followed 6 hours later by another dose of dipyridamole).

In the presence of **lansoprazole** (gastric pH greater than 4) the relative bioavailability of conventional dipyridamole tablets was about 50% of that with the buffered extended-release tablets.[3]

A consequential conclusion is that any drug that raises the stomach pH significantly would be likely to reduce the dissolution and absorption of dipyridamole *tablets* and *suspension*. It would therefore be reasonable to expect that proton pump inhibitors, H_2-receptor antagonists and antacids, which can raise the gastric pH, could interact to reduce the bioavailability of dipyridamole tablets and *suspension*. Further study is needed to find out whether this is a clinically relevant interaction or not, but note that the manufacturers advise that **antacids** may reduce the efficacy of dipyridamole tablets and suspension.[4,5]

Modified-release dipyridamole capsules (*Persantin Retard*, and the formulation containing aspirin, *Asasantin Retard*) do not appear to be affected[6] and may therefore be a suitable alternative in some patients.

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5. Dipyridamole Oral Suspension (Dipyridamole). Rosemont Pharmaceuticals Ltd. UK Summary of product characteristics, September 2007.
6. Boehringer Ingelheim. Personal communication, February 2008.

Dipyridamole + Irbesartan

A study in 13 patients with coronary artery disease found that irbesartan 150 mg daily reduced the extent and severity of perfusion defects after dipyridamole-induced stress.[1] The authors of this study suggest that irbesartan and other angiotensin II receptor antagonists should be stopped before dipyridamole-stress testing, as they may mask the true extent of the problems with myocardial blood flow. Note that it is generally recommended that the initial risk study be performed with patients off cardiac active medications,[2] and this study would seem to suggest that angiotensin II receptor antagonists should be included in this.

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Dipyridamole + Xanthines

Caffeine (in tea, coffee, cola, etc.) may interfere with dipyridamole–thallium-201 scintigraphy tests. Similarly, theophylline and aminophylline can also reduce some of the effects of dipyridamole.

Clinical evidence, mechanism, importance and management

In one patient, **caffeine** 4 mg/kg intravenously (roughly equivalent to 2 to 3 cups of coffee), given before dipyridamole–thallium-201 myocardial scintigraphy, caused a false-negative test result.[1] A further study in 8 healthy subjects confirmed that **caffeine** inhibits the haemodynamic response to an infusion of dipyridamole,[2] and another study similarly found that **caffeine** reduced myocardial blood flow in response to dipyridamole.[3]

Other xanthines appear to interact like **caffeine**. In one study oral **theophylline** markedly reduced the diagnostic accuracy of myocardial imaging using dipyridamole,[4] and intravenous **aminophylline** has been found to accelerate the myocardial washout rate of thallium-201 after a dipyridamole infusion.[5]

It appears that xanthine derivatives such as **caffeine** and **theophylline** might antagonise some of the haemodynamic effects of dipyridamole because they act as competitive antagonists of adenosine (an endogenous vasodilator involved in the action of dipyridamole).[1,2] Due to these opposing effects, parenteral **aminophylline** has been used to treat adverse events associated with intravenous dipyridamole,[6,7] and it is recommended that **aminophylline** should be made available before beginning dipyridamole myocardial imaging.[7,8]

Patients should therefore abstain from **caffeine** (tea, coffee, chocolate, cocoa, cola, caffeine-containing analgesics etc.)[1,2,8] and other xanthine derivatives, such as **theophylline**,[4] for 24 hours[2,7] before dipyridamole testing, and if during the test the haemodynamic response is low (e.g. no increase in heart rate) the presence of **caffeine** should be suspected.[2]

Adenosine, also used in cardiac radionuclide scans, may interact with caffeine in a similar way, see 'Adenosine + Xanthines', p.274.

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2. Smits P, Straatman C, Pijpers E, Thien T. Dose-dependent inhibition of the hemodynamic response to dipyridamole by caffeine. *Clin Pharmacol Ther* (1991) 50, 529–37.

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7. Persantin Ampoules (Dipyridamole). Boehringer Ingelheim Ltd. UK Summary of product characteristics, May 2007.

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Glycoprotein IIb/IIIa antagonists + Miscellaneous

The risk of bleeding with glycoprotein IIb/IIIa antagonists may be increased by heparin and thrombolytics, but low-dose thrombolytic therapy appears less likely to cause a problem. Increased bleeding may occur with other drugs that affect coagulation.

Clinical evidence, mechanism, importance and management

(a) Abciximab

Although the manufacturers of abciximab recommend the concurrent use of **heparin**, they also report that there is an increase in the incidence of bleeding.[1,2] In one study in patients with acute coronary syndrome without early revascularisation, the concurrent use of **low-molecular-weight heparin** was considered to be one of the factors that increased the risk of bleeding events with abciximab.[3] A study in patients receiving a single intravenous dose of **enoxaparin** 750 micrograms/kg with abciximab (250 micrograms/kg bolus followed by 125 nanograms/kg per minute as an infusion over 12 hours) found that abciximab had no significant effect on plasma antifactor Xa pharmacokinetics and antithrombin activity, suggesting that the pharmacokinetics of enoxaparin were not affected.[4]

Limited experience of abciximab in patients who have received **thrombolytics** suggests an increase in the risk of bleeding.[1,2] A retrospective analysis of 103 patients who presented with acute myocardial infarction and underwent angioplasty with adjunctive abciximab, found that there was a significant increase in major bleeding complications when abciximab was used with full-dose **alteplase**. A major bleed occurred in 5 of 22 (23%) patients who underwent angioplasty within 15 hours of receiving a thrombolytic, compared with 0 of 36 patients who underwent elective angioplasty more than 15 hours after fibrinolysis, and 1 of 45 (2%) without prior fibrinolysis.[5] However, the combination of abciximab with low-dose **reteplase** appeared not to result in the haemorrhagic complications associated with full-dose fibrinolytic therapy,[6] and no increase in bleeding complications were reported in studies using a reduced-dose of a thrombolytic with full-dose abciximab.[6,7]

The manufacturer of abciximab recommends caution when it is used with other drugs that affect haemostasis, such as **heparin**, **oral anticoagulants** such as **warfarin**, **thrombolytics**, antiplatelet drugs such as **dipyridamole**, **ticlopidine**, or **dextrans**, and **NSAIDs**.[1,2]

No adverse drug reactions were reported in clinical studies in patients given abciximab and also taking commonly used cardiovascular medications such as **ACE inhibitors**, **beta blockers**, **calcium-channel blockers** and **nitrates** (oral and intravenous).[1]

(b) Eptifibatide

In an acute myocardial infarction study involving 181 patients, eptifibatide at the highest infusion rates studied (1.3 and 2 micrograms/kg per minute) appeared to increase the risk of bleeding when given with **streptokinase** 1.5 million units over 60 minutes. In a percutaneous coronary intervention study and an acute myocardial infarction study there was no consistent evidence that eptifibatide increased the risk of major or minor bleeding associated with **alteplase**.[8,9] However, the manufacturers state that data on the use of eptifibatide in patients receiving thrombolytics are limited.

The UK manufacturer of eptifibatide reports that its concurrent use with **warfarin** and **dipyridamole** did not appear to increase the risk of major and minor bleeding. The use of **heparin** is recommended, but they warn that if eptifibatide is given with **heparin**, there must be careful monitoring, including the aPTT.

Caution must be employed when eptifibatide is used with drugs that affect haemostasis, including **clopidogrel**, **dipyridamole**, **ticlopidine**, **oral anticoagulants** or **thrombolytics**, **dextrans**, **adenosine**, **epoprostenol**, **NSAIDs**, and **sulfinpyrazone**.[8] Concurrent or planned use of another **glycoprotein IIb/IIIa inhibitor** is contraindicated.[8,9]

(c) Tirofiban

The manufacturers of tirofiban state that the safety of using tirofiban with **thrombolytic** therapy has not been established, although an increased risk of bleeding would be expected, and therefore they do not recommend concurrent use.[10]

The concurrent use of tirofiban with **enoxaparin** has been shown to have a similar efficacy as unfractionated **heparin** but a slightly higher bleeding risk.[11,12] Tirofiban is recommended for concurrent use with **heparin**; however there is an increased risk of bleeding with this combination, when compared with either drug alone.[10,13]

The following drugs had no clinically significant effects on the plasma clearance of tirofiban in the PRISM study: **ACE inhibitors** (**captopril**, **enalapril**), **aspirin**, **beta blockers** (including **acebutolol**, **atenolol**, **metoprolol**, **propranolol**), **benzodiazepines** (including **alprazolam**, **bromazepam**, **diazepam**, **lorazepam**, **oxazepam**, **temazepam**), **calcium-channel blockers** (**amlodipine**, **diltiazem**, **nifedipine**), **digoxin**, **docusate sodium**, **furosemide**, **glibenclamide** (**glyburide**), **heparin**, **insulin**,

metoclopramide, **morphine**, **nitrate** preparations, **paracetamol** (acetaminophen), **potassium chloride**, **ranitidine**, **statins** (**lovastatin**, **simvastatin**), and **sucralfate**.[13]

Tirofiban clearance appeared to be increased in patients taking **levothyroxine** or **omeprazole**, however the clinical significance of this is unknown.[13]

Caution should be used when tirofiban is used with other drugs that affect haemostasis, including **clopidogrel**, **ticlopidine**, **dipyridamole**, **oral anticoagulants** (e.g. **warfarin**), **epoprostenol** (prostacyclin), and **sulfinpyrazone**.[10]

1. ReoPro (Abciximab). Eli Lilly and Company Ltd. UK Summary of product characteristics, June 2005.
2. ReoPro (Abciximab). Centocor. US Prescribing information, November 2005.
3. Lenderink T, Boersma E, Ruzyllo W, Widimsky P, Ohman EM, Armstrong PW, Wallentin L, Simoons ML; GUSTO IV-ACS Investigators. Bleeding events with abciximab in acute coronary syndromes without early revascularization: an analysis of GUSTO IV-ACS. *Am Heart J* (2004) 147, 865–73.
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8. Integrilin (Eptifibatide). GlaxoSmithKline UK. UK Summary of product characteristics, March 2007.
9. Integrilin (Eptifibatide). Millennium Pharmaceuticals Inc. US Prescribing information, June 2006.
10. Aggrastat (Tirofiban hydrochloride). Merck Sharp & Dohme Ltd. UK Summary of product characteristics, April 2005.
11. Blazing MA, de Lemos JA, White HD, Fox KAA, Verheugt FWA, Ardissino D, DiBattiste PM, Palmisano J, Bilheimer DW, Snapinn SM, Ramsey KE, Gardner LH, Hasselblad V, Pfeffer MA, Lewis EF, Braunwald E, Califf RM for the A to Z investigators. Safety and efficacy of enoxaparin vs unfractionated heparin in patients with non-ST-segment elevation acute coronary syndromes who receive tirofiban and aspirin: a randomized controlled trial. *JAMA* (2004) 292, 55–64.
12. Petersen JL, Mahaffey KW, Hasselblad V, Antman EM, Cohen M, Goodman SG, Langer A, Blazing MA, Le-Moigne-Amrani A, de Lemos JA, Nessel CC, Harrington RA, Ferguson JJ, Braunwald E, Califf RM. Efficacy and bleeding complications among patients randomized to enoxaparin or unfractionated heparin for antithrombin therapy in non-ST-segment elevation acute coronary syndromes: a systematic overview. *JAMA* (2004) 292, 89–96.
13. Aggrastat (Tirofiban hydrochloride). Merck & Co. Inc. US Prescribing information, May 2002.

Prasugrel + Miscellaneous

The use of prasugrel with other drugs that affect bleeding (e.g. antiplatelet drugs, anticoagulants, NSAIDs) may increase the risk of bleeding.
The manufacturer suggests that prasugrel may alter the pharmacokinetics of cyclophosphamide and efavirenz.
Ketoconazole and rifampicin do not affect the pharmacokinetics of prasugrel. Other CYP3A4 inhibitors and inducers are therefore not expected to interact. Prasugrel does not have a clinically relevant effect on the pharmacokinetics of bupropion, digoxin, or warfarin; and atorvastatin, lansoprazole and ranitidine do not alter the pharmacokinetics and/or antiplatelet effects of prasugrel.

Clinical evidence, mechanism, importance and management

(a) Antiplatelet drugs

The concurrent use of low-dose **aspirin** and prasugrel is licensed for treating acute coronary syndromes. However, the manufacturer of prasugrel advises caution as there is a possible increased risk of bleeding in the presence of aspirin. Patients should be warned that they may bleed for longer than expected when taking prasugrel with aspirin and should be advised to report any unusual bleeding.[1]

The concurrent use of **clopidogrel** and prasugrel has not been specifically studied; however, the manufacturer logically advises that this combination may increase the risk of bleeding. As both drugs have the same mechanism of action, concurrent use is unlikely to be desirable, but if concurrent use is necessary, the patient should be monitored for signs of increased bleeding, and told to report any unexplained bruising or bleeding.[1] Similar advice would apply to **ticlopidine**.

The manufacturer of prasugrel notes that in phase III studies, no clinically significant interaction was reported when **glycoprotein IIb/IIIa-receptor antagonists** (unspecified) were given with prasugrel.[1] However, due to the actions of both drugs there is a possible increased risk of bleeding with combined use. Be aware of the potential for this interaction if bleeding occurs.

(b) Bivalirudin

The manufacturer of prasugrel notes that in phase III studies, no clinically significant interaction was reported when bivalirudin was given with prasugrel.[1] However, due to the actions of both drugs there is a possible increased risk of bleeding with combined use. Be aware of the potential for this interaction if bleeding occurs.

(c) Coumarins and related drugs

The manufacturer reports that prasugrel has no effect on the metabolism of ***S*-warfarin** by the cytochrome P450 isoenzyme CYP2C9. They advise that the use of prasugrel in patients also taking other **coumarins** has not been studied, and recommend caution on concurrent use due to the theoretical possibility of an increased risk of bleeding.[1] If concurrent use is necessary, the patient should be monitored for signs of increased bleeding, and told to report any unexplained bruising or bleeding.[1]

Due to the actions of both drugs there is a possible increased risk of bleeding with combined use of prasugrel and the **indanediones**. If prasugrel is given with an indanedione it would seem prudent to follow the same precautions advised for the coumarins.

(d) Digoxin

The manufacturer reports that prasugrel has no significant effect on the pharmacokinetics of digoxin.[1] Therefore no digoxin dosage adjustments are likely to be needed on concurrent use.

(e) Drugs that affect gastric pH

In a randomised study, 24 healthy subjects were given **lansoprazole** 30 mg daily for 7 days with a single 60-mg dose of prasugrel on day 7. **Lansoprazole** slightly reduced the AUC of the active metabolite of prasugrel by 12% (not clinically significant), and reduced its maximum concentration by 29%; however, the antiplatelet effect of prasugrel was unaffected.[2]

In a study in 23 healthy subjects, **ranitidine** had no statistically significant effect on the AUC or the maximum concentration of the active metabolite of prasugrel, and did not have a clinically relevant effect on platelet inhibition in response to prasugrel. In this study prasugrel was given as a single 60-mg loading dose, followed by 10 mg daily for 7 days, started on the second day of treatment with **ranitidine** 150 mg twice daily.[3]

These minor pharmacokinetic changes are not expected to be of clinical significance, and the manufacturer of prasugrel advises that it may be taken with **proton pump inhibitors** or **H_2-receptor antagonists**. However, they do suggest that a quicker onset of action may occur if the loading dose of prasugrel is taken without the use of a proton pump inhibitor.

(f) Drugs that are substrates of CYP2B6

In a study in 30 healthy subjects, prasugrel, given as a 60-mg loading dose, then 10 mg daily for 10 days, increased the AUC and maximum concentration of a single 150-mg dose of **bupropion** given on day 7 by a modest 18% and 14%, respectively. Prasugrel reduced the AUC and maximum concentration of the active hydroxyl metabolite of bupropion by 23% and 32%, respectively.[4] Bupropion and its hydroxyl metabolite are substrates of the cytochrome P450 isoenzyme CYP2B6. The authors of this paper and the manufacturer of prasugrel state that this weak inhibition of CYP2B6 is unlikely to be of clinical significance. However, they advise that caution may be needed in patients taking high doses of drugs with a narrow therapeutic margin and that are solely metabolised by CYP2B6, such as **cyclophosphamide** and **efavirenz**.[1] However, given the slight effects seen with bupropion a clinically relevant interaction seems unlikely, even with narrow therapeutic index drugs.

(g) Drugs that induce CYP3A4

The manufacturer of prasugrel reports that **rifampicin** 600 mg daily had no significant effect on the pharmacokinetics of prasugrel. Rifampicin is a potent inducer of the cytochrome P450 isoenzyme CYP3A4, which converts prasugrel to its active metabolite, and so it seemed possible that it may increase this metabolic conversion and therefore alter the efficacy of prasugrel. As no significant interaction appears to occur with rifampicin, the manufacturer advises that no significant interaction would be expected with other inducers of CYP3A4 (they name **carbamazepine**).[1] For a list of other known inducers of CYP3A4, see 'Table 1.4', (p.6). No prasugrel dosage adjustments are therefore likely to be needed if prasugrel is given with any CYP3A4 inducer.

(h) Drugs that inhibit CYP3A4

In a randomised study[5] in 18 healthy subjects given prasugrel 60 mg as a loading dose followed by 15 mg daily for 6 days, **ketoconazole** 400 mg daily for 10 days reduced the maximum concentration of the active metabolite of prasugrel by 34% to 46% but had no significant effect on the $AUC_{0\text{-}24}$. Ketoconazole is a potent inhibitor of the cytochrome P450 isoenzyme CYP3A4, which converts prasugrel to its active metabolite, and it seemed possible that it may reduce this metabolic conversion and therefore reduce the efficacy of prasugrel. However, no significant change in the antiplatelet effect of prasugrel was seen in this study,[5] and the manufacturer advises that other CYP3A4 inhibitors, they name the **azoles**, **ciprofloxacin**, **clarithromycin**, **diltiazem**, **grapefruit juice**, **protease inhibitors**, **telithromycin**, and **verapamil** are unlikely to have a significant pharmacokinetic effect on the active metabolite of prasugrel.[1] Therefore, no prasugrel dosage adjustments appear to be necessary when prasugrel is taken with ketoconazole or other inhibitors of CYP3A4.

Note that, despite its inclusion in the manufacturer's list, ciprofloxacin is not usually considered to be an inhibitor of CYP3A4.

(i) Heparin and Low-molecular-weight heparins

The manufacturer reports that a single 100-unit/kg bolus of intravenous heparin had no effect on the antiplatelet effect of prasugrel, and prasugrel did not affect the anticoagulant effect of heparin. In phase III studies, no clinically significant interaction was reported when low-molecular-weight heparins were given with prasugrel. However, the manufacturer advises that although prasugrel may be given with heparin, there is a possible increased risk of bleeding on concurrent use.[1] Be aware of the potential for this interaction if bleeding occurs.

(j) NSAIDs

The manufacturer notes that the use of prasugrel in patients taking long-term NSAIDs, including coxibs, has not been studied, and they therefore advise caution due to the potential increased risk of bleeding.[1]

(k) Statins

In a randomised study, 31 healthy subjects were given **atorvastatin** 80 mg daily for 16 days with prasugrel 60 mg as a loading dose on day 7 followed by 10 mg daily for 10 days. **Atorvastatin** had no effect on the AUC of the loading dose of prasugrel, and the AUC of the active metabolite of prasugrel was only slightly increased (by 17%) by day 16. The rate of bleeding associated with the use of prasugrel was not affected by the concurrent use of **atorvastatin**, and its effects on platelet inhibition were also unchanged.[6] No clinically relevant interaction would therefore be expected if **atorvastatin** is given with prasugrel.

Note that, although there appear to be no other drug interaction studies, the manufacturer of prasugrel states that it may be given with statins.

1. Efient (Prasugrel hydrochloride). Eli Lilly and Company Ltd. UK Summary of product characteristics, September 2009.
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Ticlopidine + Codergocrine mesilate (Ergoloid mesylates)

Codergocrine mesilate reduces the bioavailability of a single dose of ticlopidine.

Clinical evidence, mechanism, importance and management

A study in 8 healthy subjects found that codergocrine mesilate 1.5 mg three times daily for 4 days decreased both the AUC and maximum level of a single 250-mg dose of ticlopidine by about 30%. It was suggested that codergocrine mesilate inhibits the human organic anion transporting polypeptide B (OATP-B)-mediated absorption of ticlopidine from the intestine.[1] However, *in vitro* data from the same study suggested that *Ginkgo biloba* also inhibits OATP-B, but *Ginkgo biloba* did not alter ticlopidine levels in an *in vivo* study, see 'Antiplatelet drugs + Ginkgo (*Ginkgo biloba*)', p.816.

The general significance of this study in patients is unclear; however, bear the potential for an interaction in mind, particularly in patients where reductions in the levels of ticlopidine may be critical, such as those with drug-eluting stents.

1. Lu W-J, Huang J-D, Lai M-L. The effects of ergoloid mesylates and Ginkgo biloba on the pharmacokinetics of ticlopidine. *J Clin Pharmacol* (2006) 46, 628–34.

Ticlopidine + Miscellaneous

Ticlopidine-induced increases in bleeding times are opposed by methylprednisolone and prednisolone but its effects on platelet function are not affected. Ticlopidine decreases the clearance of phenazone (antipyrine), which suggests that it has mild enzyme-inhibiting effects. Beta blockers, calcium-channel blockers and diuretics are reported not to interact with ticlopidine.

Clinical evidence, mechanism, importance and management

(a) Corticosteroids

A study involving 14 healthy subjects found that a single 20-mg intravenous injection of **methylprednisolone**, or oral **prednisolone** 15 mg twice daily for 7 days, decreased the prolongation of bleeding times caused by ticlopidine 250 to 500 mg twice daily for 7 days. However, the antiplatelet effects of ticlopidine were not affected.[1] The clinical importance of this interaction is therefore uncertain.

(b) Phenazone (Antipyrine)

A study in 10 healthy subjects found that ticlopidine 250 mg twice daily for 3 weeks decreased the clearance of phenazone (a marker of enzyme inhibition or induction). The AUC increased by 14% and the half-life increased by 27%, suggesting that ticlopidine has some mild enzyme-inhibiting effects.[2] This is consistent with the way ticlopidine appears to inhibit the metabolism of 'theophylline', (p.1436).

(c) Non-interacting drugs

The manufacturer of ticlopidine reports that, in clinical studies in which ticlopidine was given with **beta blockers**, **calcium-channel blockers** and **diuretics** [none of the individual drugs named], no clinically significant adverse interactions were reported.[3]

1. Thébault J, Blatrix C, Blanchard J, Panak E. A possible method to control prolongations of bleeding time under antiplatelet therapy with ticlopidine. *Thromb Haemost* (1982) 48, 6–8.
2. Knudsen JB, Bastain W, Sefton CM, Allen JG, Dickinson JP. Pharmacokinetics of ticlopidine during chronic oral administration to healthy volunteers and its effects on antipyrine pharmacokinetics. *Xenobiotica* (1992) 22, 579–89.
3. Ticlid (Ticlopidine hydrochloride). Roche Laboratories Inc. US Prescribing information, March 2001.

Thrombolytics + Aspirin

Patients with acute ischaemic stroke treated with streptokinase have an increased risk of early death due to cerebral haemorrhage if they are also given aspirin.

Clinical evidence, mechanism, importance and management

A post hoc analysis of 313 patients with acute ischaemic stroke given intravenous **streptokinase** 1.5 million units found that the addition of oral aspirin 300 mg daily, started at the same time as **streptokinase**, increased the risk of early death. The combined regimen significantly increased early fatalities (from day 3 to 10) with 53 deaths occurring out of 156 patients (34%), compared with 30 of 157 (19%) who received **streptokinase** alone. This was mainly due to cerebral causes (42 versus 24) and associated with intracranial haemorrhage (25 versus 11).[1] Other studies have also reported less favourable results, and therefore **streptokinase** is not recommended in the management of acute stroke.[2,3]

Alteplase has been shown to improve the outcome in acute ischaemic stroke and is now recommended management for selected patients, as is aspirin.[2-4] This combination is still associated with an increased risk of

bleeding, therefore treatment with aspirin should not be initiated within the first 24 hours after treatment with **alteplase** in acute stroke patients.[5]

1. Ciccone A, Motto C, Aritzu E, Piana A, Candelise L, on behalf of the MAST-I Collaborative Group. Negative interaction of aspirin and streptokinase in acute ischemic stroke: further analysis of the Multicenter Acute Stroke Trial-Italy. *Cerebrovasc Dis* (2000) 10, 61–4.
2. Wardlaw JM, del Zoppo G, Yamaguchi T, Berge E. Thrombolysis for acute ischaemic stroke (review). Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2003 (accessed 14/04/08).
3. Albers GW, Amarenco P, Easton JD, Sacco RL, Teal P. Antithrombotic and thrombolytic therapy for ischemic stroke: the seventh ACCP conference on antithrombotic and thrombolytic therapy. *Chest* (2004) 126, 483S–512S.
4. National Institute for Health and Clinical Excellence (NICE). Alteplase for the treatment of acute ischaemic stroke. Available at: http://www.nice.org.uk/nicemedia/pdf/TA122QRGFINAL.pdf (accessed 29/01/10).
5. Actilyse (Alteplase). Boehringer Ingelheim Ltd. UK Summary of product characteristics, March 2007.

Thrombolytics; Alteplase + Glyceryl trinitrate (Nitroglycerin)

Glyceryl trinitrate may reduce the thrombolytic efficacy of alteplase, but this is not thought to be clinically relevant.

Clinical evidence, mechanism, importance and management

In a randomised study, 60 patients with acute anterior myocardial infarction were given intravenous alteplase 100 mg over 3 hours, as well as heparin and aspirin. In addition, 27 of the patients were also given intravenous glyceryl trinitrate 100 micrograms/minute for 8 hours. Patients receiving both alteplase and glyceryl trinitrate had signs of reperfusion less often (56%) than the patients who received alteplase alone (76%). In the combined treatment group time to reperfusion was also longer (37.8 versus 19.6 minutes) and the incidence of coronary artery re-occlusion was higher (53% versus 24%). Giving alteplase with glyceryl trinitrate produced plasma levels of tissue plasminogen activator (tPA) antigen that were about two-thirds lower than when alteplase was given alone.[1] Impaired thrombolysis has been found in another study[2] and also in an earlier study in *dogs*.[3]

It was postulated that glyceryl trinitrate increased hepatic blood flow and therefore increased the metabolism of alteplase, which resulted in reduced plasma tPA levels.[1] However, an *in vitro* study found that glyceryl trinitrate enhanced the degradation of alteplase, and therefore a mechanism other than increased hepatic blood flow seems likely to be involved.[4] Given the results of subsequent major studies on thrombolytics in patients with myocardial infarction, where most patients also received intravenous or sublingual nitrates it seems unlikely that this interaction is generally significant.

1. Romeo F, Rosano GMC, Martuscelli E, De Luca F, Bianco C, Colistra C, Comito M, Cardona N, Miceli F, Rosano V, Mehta JL. Concurrent nitroglycerin administration reduces the efficacy of recombinant tissue-type plasminogen activator in patients with acute anterior wall myocardial infarction. *Am Heart J* (1995) 130, 692–7.
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3. Mehta JL, Nicolini FA, Nichols WW, Saldeen TGP. Concurrent nitroglycerin administration decreases thrombolytic potential of tissue-type plasminogen activator. *J Am Coll Cardiol* (1991) 17, 805–11.
4. White CM, Fan C, Chen BP, Kluger J, Chow MSS. Assessment of the drug interaction between alteplase and nitroglycerin: an in vitro study. *Pharmacotherapy* (2000) 20, 380–2.

Thrombolytics; Streptokinase + Other thrombolytics

The thrombolytic effects of streptokinase and anistreplase are likely to be reduced or abolished if either drug is given some time after a dose of streptokinase, because of persistently high levels of streptokinase antibodies. There is also an increased risk of hypersensitivity reactions. This may also be true for urokinase.

Clinical evidence

A study in 25 patients who had been given streptokinase for acute myocardial infarction, found that 12 weeks later, 24 patients had enough anti-streptokinase antibodies in circulation to neutralise an entire 1.5 million unit dose of streptokinase. After 4 to 8 months, 18 out of 20 patients still had enough antibodies to neutralise half of a 1.5 million unit dose of streptokinase.[1] Further study has suggested that, after streptokinase use, anti-streptokinase antibodies fall within 24 hours, but then increase gradually and are significantly raised by 4 days after treatment. The antibody titres reach a peak (approximately 200 times that of pretreatment levels) after 2 weeks and then subsequently decline, but remain above baseline values for at least one year.[2] Studies in patients given streptokinase[3-7] or **anistreplase**[7] have variously found that:

- antibody levels return to their pretreatment range in 92% of patients approximately 12 months after treatment,[7]
- neutralising antibody titres return to control levels by 2 years,[6]
- antibody titres may remain high enough to neutralise the effects of streptokinase for several years after a dose,[3,4]
- high titres may persist for up to 7.5 years.[5]

Increased titres of streptokinase antibodies have also been seen in patients receiving topical streptokinase for wound care,[8] intrapleural streptokinase for pleural effusions,[9] and following streptococcal infections.[10] Apart from the reduced thrombolytic effect, repeated dosing[11] or high pretreatment anti-streptokinase antibody titres[12] may increase the risk of allergic reactions.

Anistreplase, like its parent drug streptokinase, has been shown to be neutralised by anti-streptokinase antibodies.[13,14]

Of 6 patients given **urokinase** 1.5 million units infused over 30 minutes for recurrent myocardial infarction, rigors occurred in 4 patients and 2 of these also had bronchospasm; they had all previously received streptokinase.[15]

Mechanism

Streptokinase use causes the production of anti-streptokinase antibodies. These persist in the circulation so that the clot-dissolving effects of another dose of streptokinase given many months later may be ineffective, or less effective, because it becomes bound and neutralised by the antibodies. Many people already have a very low titre of antibodies resulting from previous streptococcal infections, yet this does not usually appear to influence thrombolysis.[16]

Importance and management

The interaction that results in neutralisation of the thrombolytics is established and clinically important. One author[17] suggests that therapy should not be repeated within one year as it would not be effective. Given that it has been suggested that the neutralising effects may be very persistent, it would seem prudent, if subsequent treatment is needed, to use a thrombolytic with less antigenic effects, such as alteplase. The BNF in the UK states that streptokinase should not be used again beyond 4 days of the first use of either streptokinase or anistreplase.[18] The American College of Cardiology/American Heart Association guidelines recommend avoiding the readministration of streptokinase,[19] and the European Society of Cardiology specifically contraindicates the use of streptokinase or anistreplase in patients who have previously been treated with either drug.[20] In addition, the manufacturer recommends avoidance of streptokinase in patients who have had recent streptococcal infections that have produced high anti-streptokinase titres, such as acute rheumatic fever or acute glomerulonephritis.[10]

Little is known about the increased risk of hypersensitivity reactions.

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20

Antipsychotics, Anxiolytics and Hypnotics

The interactions where the effects of antipsychotic, anxiolytic and hypnotic drugs are affected are covered in this section but there are other monographs elsewhere in this publication where the effects of other drugs are altered by benzodiazepines or related drugs, or antipsychotics.

Antipsychotics

The antipsychotics are represented by chlorpromazine (and other phenothiazines), haloperidol (and other butyrophenones), thioxanthenes, and the atypical, or newer, antipsychotic drugs, such as clozapine, olanzapine, risperidone and its main metabolite, paliperidone (9-hydroxyrisperidone), and ziprasidone. Their major use is in the treatment of psychoses such as schizophrenia and mania; a list of these drugs is given in 'Table 20.1', (below). Some of the antipsychotics are also used as antiemetics, and for motor tics and hiccups.

Many of the interactions of the older antipsychotics are pharmacodynamic, relating to their effect on dopamine, whilst several of the newer atypical antipsychotics are metabolised to a significant extent by cytochrome P450 isoenzymes. The concurrent use of other drugs that are inhibitors or inducers of these isoenzymes may result in large changes in plasma levels. Furthermore, lifestyle factors, such as tobacco smoking and caffeine intake can have an effect on the pharmacokinetics of some of these drugs, leading to adverse effects or lack of therapeutic effect following lifestyle changes.

Anxiolytics and Hypnotics

Anxiolytics include the benzodiazepines (e.g. diazepam, alprazolam, lorazepam), buspirone and other drugs used to treat psychoneuroses such as anxiety and tension, and are intended to induce calm without causing drowsiness and sleep. Hypnotics include benzodiazepines such as nitrazepam or temazepam and non-benzodiazepines such as zaleplon, zolpidem or zopiclone; however, the difference in action between anxiolytics and hypnotics is mainly one of degree and, in general, the same drug or group of drugs can have both effects.

Anxiolytics and hypnotics may impair judgement and increase reaction time and they can interact with other drugs, such as 'alcohol', (p.56), that affect the CNS, see 'CNS depressants + CNS depressants', p.1553. Some of the benzodiazepines and related drugs are also used as antiepileptics. 'Table 20.1', (below) contains a list of the benzodiazepines and other anxiolytics and hypnotics.

Table 20.1 Antipsychotics, anxiolytics, and hypnotics

Group	*Drugs*
Antipsychotics	
Atypical antipsychotics	Amisulpride, Aripiprazole, Clozapine, Olanzapine, Paliperidone, Quetiapine, Risperidone, Sertindole, Ziprasidone, Zotepine
Phenothiazines	Butaperazine, Chlorpromazine, Cyamemazine, Fluphenazine, Levomepromazine, Mesoridazine, Metopimazine, Pericyazine, Perphenazine, Prochlorperazine, Promazine, Thioridazine, Trifluoperazine
Butyrophenones	Benperidol, Bromperidol, Droperidol, Haloperidol, Melperone, Pipamperone
Thioxanthenes	Chlorprothixene, Flupentixol, Tiotixene, Zuclopenthixol
Miscellaneous	Loxapine, Molindone, Pimozide, Ritanserin, Sulpiride
Anxiolytics and hypnotics	
Benzodiazepines	Alprazolam, Bromazepam, Brotizolam, Chlordiazepoxide, Clobazam, Clonazepam, Clorazepate, Clotiazepam, Diazepam, Estazolam, Etizolam, Flunitrazepam, Flurazepam, Ketazolam, Loprazolam, Lorazepam, Lormetazepam, Medazepam, Midazolam, Nitrazepam, Oxazepam, Oxazolam, Quazepam, Temazepam, Triazolam
Miscellaneous	Buspirone, Clomethiazole, Cloral betaine, Cloral hydrate, Eszopiclone, Glutethimide, Hydroxyzine, Meprobamate, Promethazine, Ramelteon, Tandospirone, Triclofos, Zaleplon, Zolpidem, Zopiclone

(a) Benzodiazepines

Many benzodiazepines undergo phase I metabolism by *N*-dealkylation and hydroxylation and many of the metabolites are active. They may then undergo phase II conjugation, mainly to form glucuronides before being excreted. For example, diazepam is metabolised to nordazepam (desmethyldiazepam), temazepam and oxazepam. The metabolism of diazepam in the liver is also mediated by cytochrome P450 isoenzymes, particularly CYP2C19 and to a lesser extent CYP3A4, and diazepam is excreted mainly as free or conjugated metabolites.

The triazolo- and related benzodiazepines, such as alprazolam, midazolam and triazolam, are mainly metabolised by hydroxylation, mediated by CYP3A4, to active compounds, which then rapidly undergo glucuronide conjugation.

Therefore, drugs that affect CYP2C19 may interact with benzodiazepines such as diazepam and those that affect CYP3A4 may interact with midazolam or triazolam.

Benzodiazepines such as lorazepam, oxazepam and temazepam, which are mainly conjugated without prior phase I metabolism, are less likely to be involved in interactions with inhibitors or inducers of cytochrome P450. Benzodiazepines themselves do not significantly induce cytochrome P450 isoenzymes, so interactions involving enhanced metabolism of other drugs are not usual.

(b) Non-benzodiazepine hypnotics

Zaleplon, zolpidem and zopiclone are non-benzodiazepine hypnotics, but they act at the benzodiazepine receptor. They are metabolised by several cytochrome CYP450 isoenzymes and it has been suggested that because of this, other drugs that affect a particular isoenzyme such as CYP3A4, may have less effect on their metabolism. However, their pharmacokinet-

ics are affected by potent CYP3A4 inducers such as rifampicin (rifampin) and by potent CYP3A4 inhibitors such as the azole antifungals.

(c) Miscellaneous anxiolytics and hypnotics

Buspirone is an azapirone anxiolytic that does not act on benzodiazepine receptor sites and lacks sedative, antiepileptic and muscle relaxant properties. It enhances the activity of specific dopaminergic and noradrenergic pathways, and also affects serotonin and acetylcholine systems of the brain. Buspirone is metabolised by hepatic CYP3A4.

Clomethiazole is a hypnotic and sedative with anticonvulsant effects. It is extensively metabolised in the liver.

Ramelteon is a melatonin receptor agonist, but has no appreciable affinity for the GABA-receptor complex, or for dopamine, noradrenaline, serotonin or acetylcholine receptors. Ramelteon is metabolised primarily by oxidation and then by glucuronidation. Ramelteon is primarily metabolised by CYP1A2 in the liver.

Antipsychotics + Antimuscarinics

Antipsychotics and antimuscarinics are very often given together advantageously and uneventfully, but occasionally serious and even life-threatening interactions occur. These include heat stroke in hot and humid conditions, severe constipation and adynamic ileus, and atropine-like psychoses. Antimuscarinics used to counteract the extrapyramidal adverse effects of antipsychotics may also reduce or abolish their therapeutic effects.

Clinical evidence

The use of antipsychotics with antimuscarinics can result in a generalised, low grade, but not usually serious, additive increase in the antimuscarinic effects of these drugs (blurred vision, dry mouth, constipation, difficulty in urination, see 'Antimuscarinics + Antimuscarinics', p.786). However, sometimes serious intensification takes place. For the sake of clarity these effects have been subdivided here into (a) heat stroke, (b) constipation and adynamic ileus, (c) atropine-like psychoses, (d) antagonism of antipsychotic effects and (e) miscellaneous effects.

(a) Heat stroke

Three patients were admitted to hospital in Philadelphia for drug-induced hyperpyrexia during a hot and humid period. In each case their skin and mucous membranes were dry and they were tachycardic (120 bpm). There was no evidence of infection.[1]

Drug combinations implicated in reports of heat stroke, some of them fatal, include:[1-5]

- **chlorpromazine** and **benzatropine**
- **chlorpromazine** and **trifluoperazine**
- **chlorpromazine**, **amitriptyline** and **benzatropine**
- **chlorpromazine**, **chlorprothixene** and **benzatropine**
- **chlorpromazine**, **fluphenazine**, **trihexyphenidyl** and **benzatropine**
- **chlorpromazine**, **trifluoperazine** and **benzatropine**
- **haloperidol** and **benzatropine**
- **promazine** and **benzatropine**.

The danger of heat stroke in patients taking **atropine** or **atropine-like compounds** was recognised in the 1920s, and the warning has been repeated many times.[6,7]

(b) Constipation and adynamic ileus

Paralytic ileus with faecal impaction (fatal in 6 cases) has been reported in a number of patients taking:

- **chlorpromazine** and **amitriptyline**,[8] **imipramine**,[9] **nortriptyline**,[10] or **trihexyphenidyl**[9]
- **haloperidol** and **benzatropine**[11]
- **levomepromazine** and **imipramine** with **benzatropine**[9]
- **levomepromazine** and **trihexyphenidyl**[9]
- **mesoridazine** and **benzatropine**[12]
- **thioridazine** and **imipramine** with **trihexyphenidyl**[9]
- **trifluoperazine** and **benzatropine**[13] or **trihexyphenidyl**[9]
- **trifluoperazine** and **benzatropine** with **methylphenidate**.[14]

Severe constipation also occurred in a woman given **thioridazine**, **biperiden** and **doxepin**.[15]

(c) Atropine-like psychoses

In a double-blind study 3 patients given a **phenothiazine** and **benzatropine** for the parkinsonian adverse effects, developed an intermittent toxic confusional state (marked disturbance of short-term memory, impaired attention, disorientation, anxiety, visual and auditory hallucinations) with peripheral antimuscarinics signs.[16] Similar reactions occurred in 3 elderly patients given **imipramine** or **desipramine**, with **trihexyphenidyl**,[17] and in another man given **chlorpromazine**, **benzatropine** and **doxepin**.[15]

(d) Antagonism of antipsychotic effects

A study in psychiatric patients given **chlorpromazine** 300 to 800 mg daily found that when **trihexyphenidyl** 6 to 10 mg daily was added, the plasma **chlorpromazine** levels were reduced from a range of 100 to 300 nanograms/mL to less than 30 nanograms/mL. When the **trihexyphenidyl** was withdrawn the plasma **chlorpromazine** levels rose again and clinical improvement was seen.[18,19]

Other studies confirm that **trihexyphenidyl**[20,21] and **orphenadrine**[22] reduce the plasma levels and effects of **chlorpromazine**. In another study, patients with schizophrenia taking **chlorpromazine**, **levomepromazine**, **thioridazine**, or **haloperidol** and in some cases also taking small doses of **trifluoperazine**, **fluphenazine**, **thioproperazine**, **perphenazine** or **tiotixene** were all taking either **benzatropine**, **trihexyphenidyl** or **procyclidine** for extrapyramidal symptoms. These antimuscarinic antiparkinsonian drugs were gradually withdrawn in the fifth study week. Plasma levels of the antipsychotics increased during the next 12 weeks after which a plateau was reached, suggesting that the antimuscarinic drugs reduced plasma levels of the antipsychotics.[23] In contrast to these reports, another found that **trihexyphenidyl** increased **chlorpromazine** levels by 41% in 20 young schizophrenics, but no clinical change was seen. The levels dropped again over the first 4 weeks of treatment.[24] Some of the beneficial actions of **haloperidol** on social avoidance behaviour are lost during concurrent treatment with **benzatropine**, but cognitive integrative function is unaffected.[25] Other studies found that the effects of **chlorpromazine** on social, affective and cognitive dysfunctions in patients with schizophrenia were reversed by **benzatropine**[26]and that **benzatropine**[27] and **trihexyphenidyl**[28] diminished the effects of **chlorpromazine** to a greater extent than those of **haloperidol**.

A study to investigate any possible interaction between **procyclidine** 5 to 15 mg daily and **chlorpromazine**, **fluphenazine** or **haloperidol** found that the addition of **procyclidine** caused a transient fall in the serum levels of **chlorpromazine**, whilst the fall in levels of **fluphenazine** and **haloperidol** was maintained for the 4-week treatment period with **procyclidine**. Two patients in the **haloperidol** group experienced a worsening of symptoms whilst taking **procyclidine**.[29]

(e) Miscellaneous effects

A study in psychotic patients found that the addition of **biperiden** 2 mg three times daily or **orphenadrine** 50 mg three times daily for 3 weeks had no effect on the steady-state levels of **perphenazine** 24 to 48 mg daily.[30] A study in patients with schizophrenia found that **biperiden** 6 mg daily or **trihexyphenidyl** 8 mg daily had no effect on steady-state plasma levels of **bromperidol** or its reduced metabolite.[31]

An isolated report describes the development of a hypoglycaemic coma in a non-diabetic patient given **chlorpromazine** and **orphenadrine**.[32]

Mechanism

Antimuscarinic (anticholinergic) drugs inhibit the parasympathetic nervous system, which innervates the sweat glands, so that when the ambient temperature rises the major heat-losing mechanism of the body can be partially or wholly lost.[33] Phenothiazines, thioxanthenes and butyrophenones may also have some antimuscarinic effects, but additionally they impair (to a varying extent) the hypothalamic thermoregulatory mechanisms that control the body's ability to keep a constant temperature when exposed to heat or cold. Thus, when the ambient temperature rises, the body temperature also rises. The tricyclics can similarly disrupt temperature control. Therefore in very hot and humid conditions, when the need to reduce the temperature is great, the additive effects of these drugs can make patients unable to control their temperature,[4] which can be fatal.

Antimuscarinic drugs also reduce peristalsis, which in the extreme can result in total gut stasis. Additive effects can occur if two or more antimuscarinic drugs are taken.

The toxic psychoses described resemble the CNS effects of atropine or belladonna poisoning and appear to result from the additive effects of the drugs used.

The mechanism for antipsychotic antagonism is not understood. *Animal* studies suggest that the site of interaction is in the gut.[19]

Importance and management

Established and well-documented interactions. While antipsychotics and antimuscarinics (including **tricyclics**, which have antimuscarinic adverse effects) have been widely used together with apparent advantage and without problems, prescribers should be aware that low-grade antimuscarinic toxicity can easily go undetected, particularly in the elderly because the symptoms can be so similar to the general complaints of this group. Also be aware of the serious problems that can sometimes develop, particularly if high doses are used.

- Warn patients to minimise outdoor exposure and/or exercise in hot and humid climates, particularly if they are taking high doses of antipsychotic/antimuscarinic drugs.
- Be alert for severe constipation and for the development of complete gut stasis, which can be fatal.

- Be aware that the symptoms of central antimuscarinic psychosis can be confused with the basic psychotic symptoms of the patient. Withdrawal of one or more of the drugs, or a dosage reduction and/or appropriate symptomatic treatment can be used to control these interactions.
- Ensure that the concurrent use of antimuscarinics to control the extrapyramidal adverse effects of neuroleptics is necessary[34,35] and be aware that the therapeutic effects may possibly be reduced as a result.

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Antipsychotics + Coffee or Tea

Tea and coffee can cause some drugs to precipitate out of solution *in vitro*, but so far there is no clinical evidence to show that this normally affects the bioavailability of these drugs nor that it has a detrimental effect on treatment.

Clinical evidence, mechanism, importance and management

A single report describes 2 patients whose schizophrenia was said to have been exacerbated by an increased consumption of tea and coffee.[1] Subsequent *in vitro* studies[2-6] found that a number of drugs (**chlorpromazine**, **promethazine**, **fluphenazine**, orphenadrine, **promazine**, **prochlorperazine**, **trifluoperazine**, **thioridazine**, **loxapine**, **haloperidol**, **droperidol**) form a precipitate with tea or coffee due to the formation of a drug-tannin complex, which was thought might possibly lower the absorption of these drugs in the gut. Studies with *rats* also found that tea abolished the cataleptic effects of **chlorpromazine**, which did not appear to be related to the presence of caffeine.[7] However, the drug-tannin complex gives up the drug into solution if it becomes acidified, as in the stomach.[6] Moreover, a clinical study of this interaction in 16 patients found that the plasma levels of **chlorpromazine**, **fluphenazine**, **trifluoperazine** and **haloperidol** were unaffected by the consumption of tea or coffee. Their behaviour also remained unchanged.[8] Similarly, a study in 12 healthy subjects concluded that there was no significant decrease in the plasma levels of a single 5-mg dose of **fluphenazine** given with either tea, coffee, or water.[9] Therefore there appears to be little or no direct evidence that this physicochemical interaction is normally of any clinical importance.

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Antipsychotics + Lithium

Chlorpromazine levels can be reduced to subtherapeutic concentrations by lithium. The development of severe extrapyramidal adverse effects or severe neurotoxicity has been seen in one or more patients given lithium with various antipsychotics. Sleepwalking has been described in some patients taking chlorpromazine-like drugs and lithium.

Clinical evidence

(a) Chlorpromazine

In a double-blind study in psychiatric patients it was found that chlorpromazine 400 to 800 mg daily, a dose that normally produced plasma levels of 100 to 300 nanograms/mL, only produced levels of 0 to 70 nanograms/mL when lithium carbonate was also given.[1] Other studies confirm that normal therapeutic levels of lithium carbonate reduce plasma chlorpromazine levels.[2,3] The peak serum levels and AUC of chlorpromazine were reduced by 40% and 26%, respectively, in healthy subjects given lithium carbonate.[2]

A paranoid schizophrenic taking chlorpromazine 200 to 600 mg daily for 5 years with no extrapyramidal symptoms developed stiffness of his face, arms and legs, and parkinsonian tremor of both hands within one day of starting to take lithium 900 mg daily. His lithium blood level after 3 days was 0.5 mmol/L. He was later given lithium 1.8 g daily (blood level 1.17 mmol/L), chlorpromazine 200 mg daily and benzatropine 2 mg daily, which improved his condition, but he still complained of stiffness and had a persistent hand tremor.[4]

A number of other reports describe the emergence of severe extrapyramidal adverse effects when chlorpromazine was given with lithium.[5-7] Ventricular fibrillation, thought to be caused by chlorpromazine toxicity, occurred in a patient taking lithium when both drugs were suddenly withdrawn.[8] Severe neurotoxicity has also been seen in a handful of other patients taking lithium and chlorpromazine.[9,10]

(b) Haloperidol

A large-scale retrospective study of the literature over the period 1966 to 1996 using the Medline database identified 41 cases of neurotoxic adverse effects in 41 patients with low therapeutic concentrations of lithium. Of these patients, 10 were taking haloperidol.[9]

Another retrospective study using both Medline and the spontaneous reporting system of the FDA in the US, over the period 1969 to 1994, identified 237 cases of severe neurotoxicity involving lithium, of which 59 also involved the concurrent use of haloperidol.[11,12]

Other reports describe encephalopathic syndromes (lethargy, fever, tremulousness, confusion, extrapyramidal and cerebellar dysfunction),[13] neuromuscular symptoms, impaired consciousness and hyperthermia,[14] delirium, severe extrapyramidal symptoms and organic brain damage in patients taking haloperidol with lithium.[15-26] In one study it was found that of the 13 patients who were taking haloperidol, 5 developed neurotoxic reactions, and they were receiving higher doses of haloperidol (average dose was 59 mg) than the 8 patients who did not develop such symptoms (average dose was 34.9 mg).[27] The sudden emergence of extrapyramidal or other adverse effects with lithium and haloperidol has also been described in other studies.[9,15,28]

In contrast to the reports cited above, there are others describing successful and uneventful use.[13,29-32] A retrospective search of Danish hospital records found that 425 patients had taken both drugs and none of them had developed serious adverse reactions.[33]

A small rise in serum lithium levels occurs in the presence of haloperidol, but it is almost certainly of little or no clinical significance.[34]

(c) Other antipsychotics

A large-scale retrospective study of the literature over the period 1966 to 1996 using the Medline database identified 41 cases of neurotoxic adverse effects in 41 patients with low, therapeutic concentrations of lithium. Of these patients, 51.2% were also taking at least one antipsychotic drug.[9] Another retrospective study using both Medline and the spontaneous reporting system of the FDA in the US, over the period 1969 to 1994, identified 237 cases of severe neurotoxicity involving lithium, with 188 involving lithium with antipsychotics.[11,12] The sudden emergence of extrapyramidal or other adverse effects has also been described in other studies. The antipsychotics implicated in this interaction with lithium are **bromperidol**,[11,12] **chlorprothixene**,[11,12] **clopenthixol**,[9] **flupentixol**,[15,28,35] **fluphenazine**,[9,11,12,15,28,36] **levomepromazine**,[9,11,12] **loxapine**,[11,12,37,38] **mesoridazine**,[11,12] **molindone**,[11,12] **perphenazine**,[11,12,28] **pipotiazine**,[39] **prochlorperazine**,[11,12] **sulpiride**,[40] **thioridazine**,[9,11,12,28,41,42] **tiotixene**,[9,11,12,16,28] **trifluoperazine**,[11,12] and **zuclopenthixol**.[9] Examples of some cases are cited in a little more detail below.

A study in 10 patients taking **fluphenazine**, **haloperidol** or **tiotixene** found that the addition of lithium worsened their extrapyramidal symptoms.[43] Neurotoxicity (tremor, rigidity, ataxia, tiredness, vomiting, confusion) attributed to an interaction between lithium and **fluphenazine** has been described in another patient. He previously took **haloperidol** and later took **chlorpromazine** with lithium, without problem.[44] Irreversible brain damage has been reported in a patient taking **fluphenazine decanoate** and lithium.[45] Severe neurotoxic complications (seizures, encephalopathy, delirium, abnormal EEGs) developed in 4 patients taking **thioridazine** 400 mg daily or more and lithium. Serum lithium levels remained below 1 mmol/L. Lithium and other phenothiazines had been taken by 3 of the patients for extended periods without problems, and the fourth subsequently took lithium and **fluphenazine** without problems.[46] In one study the concurrent use of lithium and **chlorpromazine**, **perphenazine**, or **thioridazine** was associated with sleep-walking episodes in 9% of patients.[47] A retrospective review of 39 patients with a diagnosis of neurotoxicity caused by treatment with lithium and an antipsychotic, found that the onset of symptoms varied from 24 hours to 3 months after taking the two drugs together, with an average delay of 12.7 days.[28]

A study in 8 patients found a fourfold increase in the half-life of **molindone** when lithium was also given.[48]

Mechanism

Not understood. One suggestion to account for the reduced serum levels of chlorpromazine, which is based on *animal* studies,[49,50] is that chlorpromazine can be metabolised in the gut. Therefore, if lithium delays gastric emptying, more chlorpromazine will be metabolised before it reaches the circulation. Just why severe neurotoxicity and other adverse effects sometimes develop in patients taking lithium and antipsychotics is not understood. It is the subject of considerable discussion and debate.[9,11,12,51,52]

Importance and management

Information about the reduction in chlorpromazine levels caused by lithium is limited, but it would seem to be an established interaction of clinical importance. Serum chlorpromazine levels below 30 nanograms/mL have been shown to be ineffective, whereas clinical improvement is usually associated with levels within the 150 to 300 nanogram/mL range.[53] Thus a fall in levels to below 70 nanograms/mL, as described in one study, would be expected to result in a reduced therapeutic response to chlorpromazine. Therefore the effects of concurrent use should be closely monitored and the chlorpromazine dosage increased if necessary.

The development of severe neurotoxic or severe extrapyramidal adverse effects with combinations of antipsychotics and lithium appears to be uncommon and unexplained but be alert for any evidence of toxicity if lithium is given with any of these drugs. One recommendation is that the onset of neurological manifestations, such as excessive drowsiness or movement disorders, warrants electroencephalography without delay and withdrawal of the drugs, especially as irreversible effects have been seen. A review[54] suggests that the concurrent use of haloperidol seems to be safe if lithium levels are below 1 mmol/L. It is not known whether this also applies to other antipsychotics.

At the moment there seems to be no way of identifying the apparently small number of patients who are particularly at risk, but possible likely factors include a previous history of extrapyramidal reactions with antipsychotics and the use of large doses of the antipsychotic.

Note that the interactions of **atypical antipsychotics** with lithium are covered elsewhere.

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Antipsychotics + Orlistat

No changes in the plasma levels of haloperidol or clozapine were seen when orlistat was also given.

Clinical evidence, mechanism, importance and management

In a study, 8 patients who had experienced weight gain as a result of treatment with **haloperidol** (2), **clozapine** (2), clomipramine (3), desipramine (1), or carbamazepine (2), were given orlistat 120 mg three times daily for 8 weeks. There were no significant changes in the plasma levels of the antipsychotic drugs, and steatorrhoea, which occurred in three patients, had no effect on their bioavailability.[1] Although an interaction appears to be unlikely, due to the small numbers involved in the study, this needs confirmation.

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Aripiprazole + Miscellaneous

Aripiprazole plasma levels are increased by inhibitors of CYP3A4 and decreased by inducers of CYP3A4. Quinidine increases aripiprazole levels. The manufacturers advise caution with drugs that can prolong the QT interval. Food, famotidine, and lorazepam do not have a clinically relevant effect on the pharmacokinetics of aripiprazole, and aripiprazole does not affect the pharmacokinetics of dextromethorphan, lamotrigine, lorazepam, omeprazole, and warfarin.

Clinical evidence, mechanism, importance and management

(a) CYP3A4 inducers

In a study, 6 patients were given aripiprazole 30 mg daily and **carbamazepine** in doses to produce trough serum levels of 8 to 12 mg/L. After 4 to 6 weeks of concurrent use, the peak plasma levels and AUC of aripiprazole were reduced by 66% and 71%, respectively. The apparent oral clearance of aripiprazole was increased about fourfold.[1] Analysis of results from a routine therapeutic monitoring service found **carbamazepine** lowered the dose-adjusted serum level of aripiprazole by 88% in one patient.[2]

It is recommended that the dose of aripiprazole is doubled when it is taken with **carbamazepine**.[1,3,4] Other potent inducers of CYP3A4 (the UK manufacturers name **efavirenz**, **nevirapine**, **phenytoin**, **phenobarbital**, **primidone**, **rifabutin**, **rifampicin** and **St John's wort**) are expected to have similar effects and an increase in the dose of aripiprazole may also be necessary if these drugs are given.[3]

(b) CYP3A4 inhibitors

In a study in 24 healthy subjects, **itraconazole**, an inhibitor of CYP3A4, given in a dose of 100 mg daily for 7 days increased the peak levels, AUC and half-life of a single 3-mg dose of aripiprazole by 19%, 48% and 19%, respectively.[5]

Similarly, **ketoconazole**, another inhibitor of CYP3A4, given in a dose of 200 mg daily for 14 days increased the AUC and maximum plasma concentration of a single 15-mg dose of aripiprazole by 63% and 37%, respectively.[3,4] The UK manufacturers note that other potent inhibitors of CYP3A4, such as the **protease inhibitors** would be expected to produce similar or greater increases in aripiprazole levels to those seen with ketoconazole, and they recommend that the dose of aripiprazole should be halved with these drugs.[3] The dose of aripiprazole should also be increased again if the drug is stopped. Moderate inhibitors of CYP3A4, such as **diltiazem**, may produce more modest increases in aripiprazole levels,[3] and patients should be closely monitored for signs of aripiprazole toxicity, although an initial dose reduction of aripiprazole may not be required.

(c) Drugs that prolong the QT interval

The manufacturers report that in clinical studies the incidence of QT prolongation with aripiprazole was comparable to placebo. Nevertheless, they recommend caution when prescribing aripiprazole with other drugs that may prolong the QT interval or cause electrolyte disturbances.[3] See 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290, for a list.

(d) Famotidine

In a single-dose study, famotidine 40 mg reduced the rate of absorption of aripiprazole 15 mg, and reduced the peak level and AUC of aripiprazole by 37% and 13% respectively,[4] but these effects are not clinically significant.[3,4]

(e) Food

A study in 39 healthy subjects who took aripiprazole 15 mg either after fasting, or 5 minutes after a high-fat breakfast, found no significant changes in the pharmacokinetics of aripiprazole.[6]

(f) Haloperidol

A case report describes a 30-year-old man with schizophrenia who developed worsening psychotic symptoms while taking aripiprazole 10 mg daily and haloperidol 5 mg twice daily. The symptoms worsened when the aripiprazole dose was increased to 30 mg daily, and a doubling of the haloperidol dose only achieved a marginal improvement. His psychotic symptoms and agitation improved within 4 days of stopping aripiprazole. He was later discharged taking haloperidol, and had some extrapyramidal adverse effects and a raised prolactin level, which had been absent when taking the aripiprazole. It was suggested that aripiprazole, a partial D_2 agonist had interfered with the effects of haloperidol, a D_2 antagonist.[7]

(g) Lamotrigine

The manufacturers report that giving aripiprazole 10 to 30 mg daily to patients with bipolar disorder had no effect on the steady-state pharmacokinetics of lamotrigine 100 to 400 mg daily. The dose of lamotrigine does not need to be adjusted when aripiprazole is also given.[3,4]

(h) Lorazepam

A study in healthy subjects given lorazepam 2 mg and aripiprazole 15 mg, both by injection, found there were no clinically important changes in the pharmacokinetics of either drug. No dosage adjustment is required on combined use. However, the intensity of sedation with the combination was greater than that observed with aripiprazole alone and orthostatic hypotension was greater with the combination than with lorazepam alone.[4]

(i) Quinidine

Quinidine, an inhibitor of CYP2D6, has been found to increase the AUC of aripiprazole by 107%, although the maximum concentration was unchanged. It is recommended that the dose of aripiprazole is halved if quinidine is also given.[3,4]

(j) Other drugs

Aripiprazole 10 to 30 mg daily had no significant effects on the metabolism of **dextromethorphan** (CYP2D6 substrate), **warfarin** (CYP2C9 substrate) and **omeprazole** (CYP2C19 substrate). The manufacturers

therefore conclude that aripiprazole is unlikely to have clinically significant interactions with drugs that are substrates for these isoenzymes.[3,4]

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3. Abilify (Aripiprazole). Otsuka and Bristol-Myers Squibb. UK Summary of product characteristics, August 2009.
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7. Burke MJ, Lincoln J. Aripiprazole and haloperidol: a clinically relevant interaction with a dopamine antagonist and partial agonist. *Ann Clin Psychiatry* (2006) 18, 129–30.

Aripiprazole + Oxcarbazepine

An isolated case describes priapism in a patient taking oxcarbazepine, aripiprazole and lithium.

Clinical evidence, mechanism, importance and management

A case report describes a 16-year old patient who developed painless priapism after oxcarbazepine (total daily dose of 600 mg increased to 900 mg) was added to his established treatment with lithium and aripiprazole. On discontinuing the oxcarbazepine, the patient experienced no further episodes of priapism. Priapism is a known adverse effect of aripiprazole, and it is not known if priapism occurred as an adverse reaction to this drug, or whether an interaction with oxcarbazepine or lithium was responsible.[1] This is an isolated case, and as such no general recommendations can be made.

1. Negin B, Murphy TK. Priapism associated with oxcarbazepine, aripiprazole, and lithium. *J Am Acad Child Adolesc Psychiatry* (2005) 44, 1223–4.

Aripiprazole + SSRIs or SNRIs

Fluoxetine and probably paroxetine may cause clinically significant increases in aripiprazole levels. The concurrent use of aripiprazole with SSRIs or venlafaxine has led to adverse effects such as neuroleptic malignant syndrome and extrapyramidal symptoms.

Clinical evidence, mechanism, importance and management

A study analysing routine samples sent for aripiprazole monitoring noted that the plasma levels of aripiprazole were 44% higher in 5 patients taking inhibitors of the cytochrome P450 isoenzyme CYP2D6, which included 2 patients taking **fluoxetine**. However, note that they also included levomepromazine in this group, which is not known to be a potent CYP2D6 inhibitor, and may therefore have reduced the true increase seen with **fluoxetine**. Further, in 6 patients taking **escitalopram** or **citalopram** (also CYP2D6 inhibitors, but generally considered to be weaker than **fluoxetine**) the plasma levels of aripiprazole were found to be 39% and 34% higher, respectively, when compared with patients taking aripiprazole alone.[1]

The manufacturers recommend that the dose of aripiprazole should be halved if CYP2D6 inhibitors are given.[2,3] The UK manufacturer suggests that weaker inhibitors of this isoenzyme would only be expected to cause modest increases in aripiprazole levels, and therefore no dose adjustment would expected to be required.[2]

Two case reports describing extrapyramidal effects in association with aripiprazole attribute this effect to an interaction with antidepressants. In the first case, a patient taking **venlafaxine**, trazodone and clonazepam developed parkinsonian symptoms a few days after starting to take aripiprazole 15 mg daily. Her symptoms resolved on stopping the aripiprazole. In the second case, a patient taking **sertraline** 200 mg daily developed akathisia after starting to take aripiprazole 10 mg daily. This did not respond to a reduction of aripiprazole dose, but gradually resolved when the aripiprazole was withdrawn. The authors attributed these effects to an interaction due to the low incidence of extrapyramidal adverse effects with aripiprazole alone.[4]

Neuroleptic malignant syndrome developed in a patient within 2 weeks of starting aripiprazole 30 mg daily and **fluoxetine** 20 mg daily. The patient had stopped taking the aripiprazole 2 days before admission, **fluoxetine** was stopped on admission, and he recovered within one week with symptomatic treatment. The authors suggested that **fluoxetine** may have increased the risk of this syndrome developing by raising aripiprazole levels.[5]

The concurrent use of aripiprazole and an SSRI can be useful, but it would be prudent to be alert for adverse effects (e.g. constipation, anxiety, insomnia). With **paroxetine** and **fluoxetine**, dose reductions should be considered. An interaction resulting in adverse effects, such as extrapyramidal symptoms, is not established.

1. Castberg I, Spigset O. Effects of comedication on the serum levels of aripiprazole: evidence from a routine therapeutic drug monitoring service. *Pharmacopsychiatry* (2007) 40, 107–10.
2. Abilify (Aripiprazole). Otsuka and Bristol-Myers Squibb. UK Summary of product characteristics, August 2009.
3. Abilify (Aripiprazole). Otsuka and Bristol-Myers Squibb Company. US Prescribing information, November 2009.
4. Cohen ST, Rulf D, Pies R. Extrapyramidal side effects associated with aripiprazole coprescription in 2 patients. *J Clin Psychiatry* (2005) 66, 135–6.
5. Duggal HS, Kithas J. Possible neuroleptic malignant syndrome with aripiprazole and fluoxetine. *Am J Psychiatry* (2005) 162, 397–8.

Aripiprazole + Valproate

Valproate can modestly reduce aripiprazole levels.

Clinical evidence, mechanism, importance and management

Analysis of results from a routine therapeutic monitoring service found that valproate lowered the dose-adjusted serum level of aripiprazole by 24% in 9 patients.[1] Similarly, in a study in 6 healthy subjects, aripiprazole 30 mg daily for 5 weeks, with **valproate semisodium** (**divalproex sodium**) daily in doses to achieve a serum valproate levels of 50 to 125 mg/L, for weeks 3 to 5 of the study, decreased the maximum plasma concentrations of aripiprazole by 26%.[2] Aripiprazole and valproate share the same protein binding sites, and it was therefore considered likely that the valproate displaced bound aripiprazole leading to increased oral clearance. However, this change in valproate levels is not considered to be clinically significant, and aripiprazole dose adjustments are not expected to be necessary on concurrent use.

1. Castberg I, Spigset O. Effects of comedication on the serum levels of aripiprazole: evidence from a routine therapeutic drug monitoring service. *Pharmacopsychiatry* (2007) 40, 107–10.
2. Citrome L, Josiassen R, Bark N, Salazar DE, Mallikaarjun S. Pharmacokinetics of aripiprazole and concomitant lithium and valproate. *J Clin Pharmacol* (2005) 45, 89–93.

Barbiturates + Miscellaneous

Miconazole increases pentobarbital levels. The hypnotic effects of pentobarbital are reduced or abolished by the concurrent use of caffeine.

Clinical evidence, mechanism, importance and management

(a) Caffeine

In a placebo-controlled study in 34 patients, caffeine 250 mg and **pentobarbital** 100 mg were given together and alone. It was found that the hypnotic effects of **pentobarbital** were reduced in the presence of caffeine, and indistinguishable from those of placebo.[1] Caffeine stimulates the cerebral cortex and impairs sleep, whereas **pentobarbital** depresses the cortex and promotes sleep. These mutually opposing actions would seem to explain this interaction. This seems to be only direct study of this interaction, but it is well supported by common experience and the numerous studies of the properties of each of these compounds. Patients given barbiturate hypnotics should avoid caffeine-containing drinks (tea, coffee, cola drinks, etc.) or analgesics at or near bedtime if the hypnotic is to be effective.

(b) Miconazole

High-dose intravenous pentobarbital was given to 5 patients in intensive care to decrease intracranial pressure. When miconazole was also given, all patients had marked rises in plasma **pentobarbital** levels, and a 50 to 90% reduction in its total plasma clearance. This is thought to occur because miconazole inhibits the liver enzymes concerned with the metabolism of the barbiturate, thereby reducing its clearance from the body.[2] It would be prudent to monitor the effects of concurrent use to ensure that plasma barbiturate levels do not rise too high. Note that miconazole oral

gel can be absorbed in sufficient amounts to potentially interact and therefore some caution is also warranted with this product.

1. Forrest WH, Bellville JW, Brown BW. The interaction of caffeine with pentobarbital as a nighttime hypnotic. *Anesthesiology* (1972) 36, 37–41.
2. Heinemeyer G, Roots I, Schulz H, Dennhardt R. Hemmung der Pentobarbital-Elimination durch Miconazol bei Intesivtherapie des erhöhten intracraniellen Druckes. *Intensivmed* (1985) 22, 164–7.

Benzodiazepines + Acetazolamide

Although acetazolamide can be used to treat acute mountain sickness at very high altitudes, a case report suggests that it may potentiate the respiratory depressant effects of benzodiazepines such as triazolam. Acetazolamide did not improve symptoms of sleep apnoea worsened by flurazepam.

Clinical evidence, mechanism, importance and management

A study in elderly subjects found that sleep apnoea worsened in 4 of 10 subjects given a single 30-mg dose of **flurazepam** at night. These 4 subjects were then pretreated with acetazolamide 500 mg twice daily for 3 days, as acetazolamide has been found to improve sleep apnoea. A further dose of **flurazepam** 30 mg was given on the fourth night.[1] Treatment with acetazolamide did not block the benzodiazepine-associated increase in sleep apnoea in these subjects, possibly because the acetazolamide treatment period was not long enough.[1]

Acetazolamide is sometimes used by climbers at very high altitudes as a prophylactic against acute mountain sickness. Benzodiazepines are used in this situation to treat insomnia, which is common at high altitude. Benzodiazepines are believed to depress breathing because they reduce the normal respiratory response to hypoxia. This was demonstrated by a Japanese climber in the Himalayas who took acetazolamide 500 mg daily and **triazolam** 500 micrograms, and then needed to be reminded to hyperventilate in order to relieve his hypoxia while returning from a climb. The acetazolamide did not prevent, and may possibly have increased, the central ventilatory depression of the **triazolam**, possibly by increasing its delivery to the brain. The authors of the report advise against taking these two drugs together at high altitudes,[2] thus confirming a previous warning about the risks of taking benzodiazepines at high altitude.[3]

1. Guilleminault C, Silvestri R, Mondini S, Coburn S. Aging and sleep apnea: action of benzodiazepine, acetazolamide, alcohol, and sleep deprivation in a healthy elderly group. *J Gerontol* (1984) 39, 655–61.
2. Masuyama S, Hirata K, Saito A. 'Ondine's curse': side effect of acetazolamide? *Am J Med* (1989) 86, 637.
3. Sutton JR, Powles ACP, Gray GW, Houston CS. Insomnia, sedation, and high altitude cerebral oedema. *Lancet* (1979) i, 165.

Benzodiazepines + Alosetron

In a study in 12 healthy subjects, alosetron 1 mg twice daily for 2 days had no significant effect on the pharmacokinetics of a single 1-mg dose of alprazolam. No increase in adverse effects was noted with the combination.[1] No alprazolam dose adjustment therefore seems necessary on concurrent use. Note that this study suggests that alosetron is unlikely to affect the pharmacokinetics of similarly metabolised benzodiazepines (e.g. midazolam, triazolam), but this needs confirmation.

1. D'Souza DL, Levasseur LM, Nezamis J, Robbins DK, Simms L, Koch KM. Effect of alosetron on the pharmacokinetics of alprazolam. *J Clin Pharmacol* (2001) 41, 452–4.

Benzodiazepines + Amiodarone

An isolated report describes clonazepam toxicity, which was attributed to the concurrent use of amiodarone. Amiodarone is predicted to inhibit the metabolism of midazolam, triazolam, and possibly alprazolam.

Clinical evidence, mechanism, importance and management

A 78-year-old man with congestive heart failure and coronary artery disease was taking furosemide, potassium, and calcium supplements, a multivitamin preparation, and amiodarone 200 mg daily for sustained ventricular tachycardia. Two months after **clonazepam** 500 micrograms at night was added to treat restless leg syndrome he developed slurred speech, confusion, difficulty in walking, dry mouth and urinary incontinence. This was interpreted as **clonazepam** toxicity. The problems cleared when the **clonazepam** was stopped. The authors of the report suggest that the amiodarone may have inhibited the oxidative metabolism of the **clonazepam** by the liver, thereby allowing it to accumulate. They also point out that this patient may have been more sensitive to these effects because of a degree of hypothyroidism caused by the amiodarone. Hypothyroidism is known to decrease the metabolism of drugs that undergo oxidative metabolism by the liver.[1] This is an unconfirmed and isolated case and therefore its general importance is unknown.

Amiodarone is a known inhibitor of the cytochrome P450 isoenzyme, by which a number of benzodiazepines are metabolised. The UK manufacturer of amiodarone reasonably predicts that it may raise the levels of **midazolam** and **triazolam**.[2] **Alprazolam** may be similarly affected. It would therefore seem prudent to be alert for evidence of increased and/or prolonged sedation if patients taking amiodarone are given these benzodiazepines.

1. Witt DM, Ellsworth AJ, Leversee JH. Amiodarone–clonazepam interaction. *Ann Pharmacother* (1993) 27, 1463–4.
2. Cordarone X (Amiodarone hydrochloride). Sanofi-Aventis. UK Summary of product characteristics, March 2009.

Benzodiazepines + Antacids

Although antacids can moderately change the rate of absorption of chlordiazepoxide, clorazepate and diazepam, no adverse interaction of clinical importance has been reported.

Clinical evidence

In a three-period study, 10 healthy subjects were given **clorazepate** 7.5 mg at night, with either water, with *Maalox* (**aluminium/magnesium hydroxide** mixture) 30 mL, or with *Maalox* 30 mL three times daily before meals. The mean steady-state plasma levels of the active metabolite of clorazepate, desmethyldiazepam, were not affected by *Maalox*, although they varied widely between individuals.[1] This is in line with another report,[2] but contrasts with a single-dose study, in which the peak plasma concentration of desmethyldiazepam was delayed and reduced by about one-third by the use of *Maalox*. The $AUC_{0\text{-}48}$ was reduced by about 10%.[3]

In another study the absorption of a single dose of **chlordiazepoxide** was delayed by *Maalox*, but the total amount of drug absorbed was not significantly affected.[4] Similar results have been found with **diazepam** and **aluminium hydroxide**-containing antacids (*Maalox* and *Gelusil*).[5] Another study found that 40 mL of **Aluminium Hydroxide Gel BP** and 30 mL of **sodium citrate** (0.3 mmol/L) marginally hastened the sedative effect of **diazepam** 10 mg when used as an oral premedication before minor surgery. **Magnesium Trisilicate Mixture BPC** 30 mL tended to delay sedation with **diazepam**.[6]

Mechanism

The delay in the absorption of chlordiazepoxide and diazepam is attributed to the effect of the antacid on gastric emptying. Clorazepate on the other hand is a prodrug, which needs acid conditions in the stomach for conversion by hydrolysis and decarboxylation to its active form. Antacids are presumed to inhibit this conversion by raising the pH of the stomach contents.[7]

Importance and management

Most of the reports describe single-dose studies, but what is known suggests that no adverse interaction of any clinical importance is likely if antacids are given with chlordiazepoxide, clorazepate or diazepam. Whether the delay in absorption has an undesirable effect in those who only take benzodiazepines during acute episodes of anxiety, and who need rapid relief is uncertain. Information about other benzodiazepines is lacking. However, no special precautions would be expected to be necessary.

1. Shader RI, Ciraulo DA, Greenblatt DJ, Harmatz JS. Steady-state plasma desmethyldiazepam during long-term clorazepate use: effect of antacids. *Clin Pharmacol Ther* (1982) 31, 180–3.
2. Chun AHC, Carrigan PJ, Hoffman DJ, Kershner RP, Stuart JD. Effect of antacids on absorption of clorazepate. *Clin Pharmacol Ther* (1977) 22, 329–35.

3. Shader RI, Georgotas A, Greenblatt DJ, Harmatz JS, Allen MD. Impaired absorption of desmethyldiazepam from clorazepate by magnesium aluminum hydroxide. *Clin Pharmacol Ther* (1978) 24, 308–15.
4. Greenblatt DJ, Shader RI, Harmatz JS, Franke K, Koch-Weser J. Influence of magnesium and aluminum hydroxide mixture on chlordiazepoxide absorption. *Clin Pharmacol Ther* (1976) 19, 234–9.
5. Greenblatt DJ, Allen MD, MacLaughlin DS, Harmatz JS, Shader RI. Diazepam absorption: effect of antacids and food. *Clin Pharmacol Ther* (1978) 24, 600–9.
6. Nair SG, Gamble JAS, Dundee JW, Howard PJ. The influence of three antacids on the absorption and clinical action of oral diazepam. *Br J Anaesth* (1976) 48, 1175–80.
7. Abruzzo CW, Macasieb T, Weinfeld R, Rider JA, Kaplan SA. Changes in the oral absorption characteristics in man of dipotassium clorazepate at normal and elevated gastric *p*H. *J Pharmacokinet Biopharm* (1977) 5, 377–90.

Benzodiazepines + Antiepileptics; Miscellaneous

The use of benzodiazepines with antiepileptics is common and possibly accompanied by some changes in plasma levels, which are normally of limited clinical importance. Pharmacokinetic interactions have been reported between clobazam and felbamate, and clonazepam and lamotrigine.

Clinical evidence

(a) Felbamate

A retrospective study compared *N*-desmethylclobazam plasma level to dose ratios in patients taking **clobazam** and enzyme-inducing antiepileptics, without felbamate (group B, 28 patients) or with felbamate (group C, 16 patients). When compared with 22 patients (group A) receiving **clobazam** alone or with non-enzyme-inducing antiepileptics, the *N*-desmethylclobazam level to dose ratio of group B was increased twofold and the *N*-desmethylclobazam level to dose ratio of group C was increased fivefold,[1] suggesting that felbamate further increased the effect of enzyme-inducing antiepileptics on **clobazam** metabolism.

In a study in 18 healthy subjects, the pharmacokinetics of **clonazepam** 1 mg every 12 hours were not significantly altered by felbamate 1.2 g every 12 hours for 10 days.[2] No serious adverse reactions were reported.

(b) Lamotrigine

The plasma **clonazepam** levels in 4 of 8 patients fell by about 38% when they were also given lamotrigine.[3]

(c) Tiagabine

A single-dose study in healthy subjects did not find any clinically important pharmacodynamic or pharmacokinetic interactions between tiagabine and **triazolam**.[4]

Mechanism

Uncertain. It has been suggested that felbamate inhibits the clearance of *N*-desmethylclobazam.[1]

Importance and management

None of the interactions between the benzodiazepines and antiepileptics described here appear to be of major clinical importance, with the possible exception of the interaction between clobazam and felbamate. If these drugs are given be aware that additive sedative or other adverse effects may occur. There may also be a potential interaction between clonazepam and lamotrigine in some patients, but the clinical significance is not known.

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Benzodiazepines and related drugs + Antimuscarinics

Atropine and hyoscine do not affect the absorption or the sedative effects of diazepam but atropine may slow the absorption of zopiclone.

Clinical evidence, mechanism, importance and management

(a) Diazepam

A study in 8 healthy subjects given a single 10-mg oral dose of diazepam found that serum diazepam levels were not significantly changed by the concurrent use of **atropine** 1 mg or **hyoscine hydrobromide** 1 mg. Furthermore, the sedative effects of diazepam were not altered.[1]

(b) Zopiclone

In 12 healthy subjects the absorption of a single 7.5-mg dose of zopiclone was reduced by intravenous **atropine** 600 micrograms. Mean plasma zopiclone levels at one hour were reduced from 22.7 nanograms/mL to 6.5 nanograms/mL and at 2 hours from 49.3 nanograms/mL to 31.9 nanograms/mL by **atropine**. This was presumably to be due to altered gut motility.[2] The clinical importance of these findings is not known.

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Benzodiazepines and related drugs + Antipsychotics

Additive CNS depressant effects might be expected between antipsychotics and benzodiazepines or related drugs: sedation, respiratory depression and airways obstruction has been reported. In addition, hypotension, and rare cases of neuroleptic malignant syndrome have been reported in patients taking benzodiazepines and antipsychotics. The effects vary with different pairs, but the parenteral use of these drugs is frequent in the more severe cases. In one study the effect of lorazepam on psychomotor tests and memory was not affected by amisulpride.

Clinical evidence, mechanism, importance and management

A. Benzodiazepines

(a) Lorazepam

1. Amisulpride. A single-dose study in 18 healthy subjects found that amisulpride 50 mg or 200 mg did not potentiate or antagonise the effects of a single 2-mg dose of lorazepam on psychomotor performance or memory.[1]

2. Loxapine. A woman with a manic bipolar affective disorder was admitted to hospital and given lorazepam 2 mg with loxapine 25 mg. After 2 hours she was found to be lethargic with sonorous respirations, occasional episodes of apnoea and an irregular respiration as low as 4 breaths per minute. She was given oxygen and recovered spontaneously within 12 hours. She had experienced no previous problems with lorazepam, and had none when it was later given while she was taking perphenazine.[2] Two other cases have been reported where patients given intramuscular lorazepam 1 to 2 mg and oral loxapine 50 mg developed prolonged stupor, a significantly lowered respiration rate (8 breaths per minute), and in one case hypotension. Both showed signs of recovery within 3 to 5 hours and both had taken each of these drugs alone without problems.[3]

3. Promethazine. A case report describes a patient who developed neuroleptic malignant syndrome after treatment with promethazine and lorazepam. He had recently stopped taking haloperidol, trihexyphenidyl and chlorpromazine due to the development of extrapyramidal symptoms. The role of promethazine and lorazepam is unclear, but it was suggested that they had both reduced dopaminergic activity, and the lorazepam had additionally reduced cholinergic activity.[4]

4. Other antipsychotics. Hypotension, respiratory depression and/or sedation have been reported in patients given lorazepam and ‘clozapine’, (p.873) or ‘olanzapine’, (p.889).

(b) Other benzodiazepines

1. Alzheimer's disease deterioration. A study involving 224 patients diagnosed with probable Alzheimer's disease examined the effects of all prescribed drugs on the progression of the disease over a 12-month period. Overall, the 34 patients taking antipsychotic drugs and the 30 patients taking benzodiazepines or benzodiazepine-related drugs were more likely to have a faster rate of deterioration than those who were not taking these drugs (odds ratio 2.74 and 2.77, respectively). However, a higher risk of deterioration was observed in those who were taking both antipsychotic and benzodiazepines or benzodiazepine-related drugs (odds ratio 3.86). The decline in patients treated with antipsychotics and benzodiazepines appeared to be additive.[5]

2. Neuroleptic malignant syndrome. Three cases of neuroleptic malignant syndrome have been reported following the use of **diazepam** with **risperidone**; **clorazepate** with **zuclopenthixol**; and **clonazepam** with **tiapride**. In 2 cases this followed the abrupt withdrawal of long-term benzodiazepines. All 3 patients recovered, one without any treatment.[6] These reports are isolated and unexplained.

3. Obstruction of airways. A patient with catatonic schizophrenia was given intravenous **diazepam** 20 mg followed by intramuscular haloperidol 10 mg and **levomepromazine** 50 mg. Because of combative behaviour about 50 minutes later, he was given intravenous **flunitrazepam** 2 mg, and about 2 hours later another dose of both intravenous haloperidol 12 mg and **flunitrazepam** 5 mg. An hour after the last injection he became mildly cyanotic due to collapse of glossopharyngeal structures and excessive oral and nasal secretions, causing airways obstruction. Four other cases of airways obstruction associated with the combination of intramuscular **levomepromazine** in doses of 0.52 mg/kg or more and intravenous **flunitrazepam** or **diazepam** are also described. A subsequent review of all cases found that there were no cases of airways obstruction in patients who received haloperidol with either **levomepromazine** or a benzodiazepine. The interaction occurred immediately after the last intravenous injection in one patient and about 25 minutes after intramuscular **levomepromazine** but onset may be delayed up to 2 hours or more.[7]

B. Non-benzodiazepine hypnotics

(a) Zaleplon

A single 50-mg dose of **thioridazine** had no effect on the pharmacokinetics of zaleplon 20 mg, and the psychomotor tests showed only short-term additive effects lasting 1 to 4 hours.[8] These short-term CNS additive effects are small and unlikely to be clinically relevant, and so there would seem to be no reason for avoiding concurrent use.

(b) Zolpidem

Single-dose studies found that the pharmacokinetics of 20-mg doses of zolpidem were unaffected by 50 mg of **chlorpromazine**[9,10] or 2 mg of **haloperidol**.[9] The pharmacokinetics of both of these antipsychotics were unaffected by zolpidem, except that in one study the elimination half-life of **chlorpromazine** was increased from about 5 hours to 8 hours.[10] **Chlorpromazine** increased the sedative effects of zolpidem (as indicated by impaired performances of manual dexterity and Stroop's tests).[9,10] It seems likely that additive sedation will be seen with other sedative drugs.

(c) Zopiclone

No pharmacokinetic interaction was found when 12 healthy subjects were given a single 7.5-mg oral dose of zopiclone with **chlorpromazine** 50 mg. However, the overall performance in a number of psychomotor tests (including digit symbol substitution and simulated driving) was definitely impaired more by the combination of the drugs than by **chlorpromazine** alone. Zopiclone with **chlorpromazine** impaired memory and learning, and caused a marked impairment of the performance of the tests.[11] In practical terms this means that patients given **chlorpromazine** with zopiclone should be warned that drowsiness may persist the next day and they may be less able to drive or handle potentially hazardous machinery safely.

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Benzodiazepines + Aprepitant

Aprepitant inhibits the metabolism of oral midazolam resulting in increased levels. Aprepitant appears to have less effect on intravenous midazolam. A few days after aprepitant treatment is stopped a transient slight reduction in midazolam plasma levels may occur due to induction of its metabolism. Alprazolam and triazolam are expected to be affected similarly. Fosaprepitant is a prodrug of aprepitant, and may therefore be expected to share its interactions.

Clinical evidence

In a randomised study, 16 healthy subjects took either aprepitant 125 mg on day one followed by 80 mg daily for 4 days, or 40 mg on day one followed by 25 mg daily for 4 days, with a single 2-mg oral dose of midazolam on days one and 5. The aprepitant 40/25 mg dosing schedule had no significant effect on the pharmacokinetics of midazolam. However, the aprepitant 125/80 mg dosing schedule increased the AUC of oral midazolam by 126% and 229% on days one and 5, respectively, and increased the maximum plasma levels of midazolam by 46% and 94% on days one and 5, respectively.[1]

In a randomised, placebo-controlled study, 24 healthy subjects were given aprepitant 125 mg on day one then 80 mg daily for a further 2 days. A single 2-mg intravenous dose of midazolam was given on days 4, 8 and 15. The 3-day aprepitant regimen increased midazolam levels slightly on day 4 (AUC increased by 25% and clearance reduced by 20%), decreased midazolam levels slightly on day 8 (AUC decreased by 19% and clearance increased by 24%) and had almost no effect by day 15.[2] Another study also found that a single 125-mg oral dose of aprepitant modestly increased the AUC of intravenous midazolam by 47%.[3]

Mechanism

Aprepitant is a moderate (dose-dependent) inhibitor of the cytochrome P450 isoenzyme CYP3A4 by which midazolam is metabolised; concurrent use therefore results in increased midazolam levels. There appears to be a greater pharmacokinetic effect on oral midazolam than on intravenous midazolam indicating that aprepitant affects intestinal as well as hepatic CYP3A4 activity. Aprepitant is also a mild inducer of CYP3A4;[2,4] however, the induction is transient, with a maximal effect 3 to 5 days after the end of the usual prescribed 3 days of treatment.

Importance and management

Based on the way midazolam interacts with similarly potent inhibitors of CYP3A4, aprepitant may be expected to increase the drowsiness and length of sedation and amnesia in patients given midazolam. Consider reducing the midazolam dose in patients given aprepitant and monitor the outcome of concurrent use carefully. The manufacturers note that the potential effects of increased levels of other benzodiazepines metabolised via CYP3A4, such as **alprazolam** and **triazolam**, should be considered if they are given with aprepitant. They also state that the effects of aprepitant on plasma levels of intravenously administered CYP3A4 substrates are expected to be less than the effects on orally administered substrates.[4,5] Fosaprepitant is a prodrug of aprepitant, and may therefore be expected to share its interactions; similar precautions are therefore warranted.

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Benzodiazepines + Aspirin

The induction of anaesthesia with midazolam is more rapid in patients who have been pretreated with aspirin.

Clinical evidence

A study in patients about to undergo surgery found that pretreatment with aspirin 1 g (given as intravenous **lysine acetylsalicylate**) one minute before induction shortened the induction time with intravenous midazolam 300 micrograms/kg. Only 60% were 'asleep' within 3 minutes of receiving midazolam alone, but about 80% were 'asleep' within 3 minutes of receiving midazolam given after the aspirin pretreatment.[1]

Mechanism

Not understood. It has been suggested that aspirin increases the amount of free (and active) midazolam in the plasma because both drugs compete for the binding sites on the plasma albumins.[1,2]

Importance and management

Information is limited but what is known shows that the effects of midazolam are increased by aspirin, but the effects seem relatively modest, and, if the mechanism is correct, no greater effect would be expected on long-term concurrent use. Note also that regular aspirin use may increase the risk of bleeding during surgery, and in some situations this may justify avoidance of aspirin in the week before surgery.[3]

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Benzodiazepines and related drugs + Azoles

Fluconazole, itraconazole and ketoconazole very markedly increase the plasma levels of midazolam and triazolam, thereby increasing and prolonging their sedative and amnesic effects. Voriconazole and posaconazole also markedly increase midazolam levels. Similar but smaller effects are seen with itraconazole or ketoconazole and alprazolam and with itraconazole and brotizolam. Even less effect is seen with itraconazole and etizolam. Fluconazole and voriconazole increase the levels of diazepam, but itraconazole has only a minor effect.
Ketoconazole or itraconazole cause modest increases in the levels of the non-benzodiazepine hypnotics, zolpidem, eszopiclone, and zopiclone.
No important interaction appears to occur between fluconazole and bromazepam or zolpidem; between itraconazole and estazolam, quazepam or temazepam; and probably between ketoconazole and chlordiazepoxide.

Clinical evidence

A. Benzodiazepines

(a) Alprazolam

1. Itraconazole. In a study, 10 healthy subjects were given a single 800-microgram dose of alprazolam before and after itraconazole 200 mg daily for 6 days. The itraconazole increased the AUC and the half-life of alprazolam nearly threefold, and psychomotor function was impaired.[1]

2. Ketoconazole. A study in healthy subjects found that ketoconazole 200 mg twice daily decreased the clearance of alprazolam 1 mg by about two-thirds, and prolonged its half-life fourfold; the maximum plasma levels only slightly increased, but the AUC increased almost fourfold.[2]

(b) Bromazepam

In a study in 12 healthy subjects, **fluconazole** 100 mg daily for 4 days had no effect on the pharmacokinetics or pharmacodynamics of oral or rectal bromazepam.[3]

(c) Brotizolam

In a placebo-controlled study, 10 healthy subjects were given **itraconazole** 200 mg daily for 4 days with a single 500-microgram dose of brotizolam given on day 4. **Itraconazole** increased the $AUC_{0\text{-}24}$ and maximum plasma levels of brotizolam by about 2.5-fold and 25%, respectively. The elimination half-life of brotizolam was also increased, from 4.51 hours to 23.27 hours, and sedation was increased.[4]

(d) Chlordiazepoxide

In 12 healthy subjects, **ketoconazole** 400 mg daily for 5 days decreased the clearance of chlordiazepoxide 600 micrograms/kg by 38%.[5]

(e) Diazepam

1. Fluconazole. A study in healthy subjects found that fluconazole 400 mg on the first day and 200 mg on the second day increased the AUC of a single 5-mg oral dose of diazepam 2.5-fold and prolonged the half-life from 31 hours to 73 hours.[6]

2. Itraconazole. In a study in 10 healthy subjects, itraconazole 200 mg daily for 4 days slightly increased the AUC of a single 5-mg oral dose of diazepam by about 15%, but there was no clinically significant interaction as determined by psychomotor performance tests.[7]

3. Voriconazole. A study in healthy subjects found that voriconazole 400 mg twice daily on the first day and 200 mg twice daily on the second day increased the AUC of a single 5-mg oral dose of diazepam 2.2-fold and prolonged the half-life from 31 hours to 61 hours.[6]

(f) Estazolam

A placebo-controlled study in 10 healthy subjects[8] found that **itraconazole** 100 mg daily for 7 days did not affect the pharmacokinetics or pharmacodynamics of a single 4-mg dose of estazolam given on day 4.

(g) Etizolam

A placebo-controlled study in healthy subjects found that **itraconazole** 100 mg twice daily for 7 days increased the AUC of a single 1-mg dose of etizolam given on day 6 by about 50%. The elimination half-life of etizolam was also increased, from 12 hours to 17.3 hours.[9]

(h) Midazolam

1. Fluconazole. A study in 12 healthy subjects found that fluconazole 400 mg on the first day and then 200 mg daily for 5 days reduced the clearance of a single 7.5-mg oral dose of midazolam by 51%, and increased the AUC of midazolam approximately 3.5-fold. It was found that the subjects could hardly be wakened during the first hour after taking the midazolam.[10] Another study found that a single 150-mg dose of fluconazole increased the plasma levels of a single 10-mg dose of midazolam by about 40%.[11] Yet another study found that the route of administration of fluconazole (i.e. whether oral or intravenous) made little or no difference to the pharmacodynamic effects of midazolam.[12] Fluconazole 400 mg initially and then 200 mg daily given by infusion over 30 minutes caused a fourfold increase in the plasma levels of midazolam in intensive care unit patients receiving midazolam infusions. The interaction was most marked in patients with renal failure.[13] These reports contrast with another, which found that a single 150-mg dose of fluconazole only slightly increased the effects of a single 10-mg dose of midazolam.[14]

2. Itraconazole. When 9 healthy subjects were given oral midazolam 7.5 mg, before and after taking itraconazole 200 mg daily for 4 days, the AUC of midazolam was increased about tenfold, the peak plasma levels were increased about threefold, and the half-life was prolonged, from 2.8 hours to 7.9 hours. The subjects could hardly be wakened during the first hour after taking the midazolam and most of them experienced amnesia lasting several hours.[15] A later study found that itraconazole 100 mg daily for 4 days increased the AUC of oral midazolam sixfold and increased its peak plasma levels 2.5-fold.[16] A further study found that itraconazole 200 mg daily for 4 days increased the AUC of midazolam 7.5 mg eightfold when the midazolam was taken on day 4, and 2.6-fold when the midazolam was taken on day 8.[17]

Another study confirmed the marked effect of itraconazole on oral midazolam, but found that the effects of bolus doses of intravenous midazolam were not increased to a clinically significant extent, although their results suggested that long-term, high-dose infusions of midazolam need to be titrated according to effect to avoid overdose.[10] The manufacturer of midazolam reports that itraconazole increased the plasma levels of intravenous midazolam two- to threefold and its terminal half-life was increased 2.4-fold.[18]

3. Ketoconazole. When 9 healthy subjects were given oral midazolam 7.5 mg before and after taking ketoconazole 400 mg daily for 4 days, the AUC of midazolam was increased almost 17-fold, its peak plasma levels were increased about fourfold, and its half-life was prolonged, from 2.8 hours to 8.7 hours. The subjects could hardly be wakened during the first hour after taking the midazolam and most of them experienced amnesia lasting several hours.[15] A study in healthy subjects found that 3 doses of oral ketoconazole 200 mg increased the AUC of a single 6-mg dose of oral midazolam 16-fold, but only increased the AUC of a single 2-mg dose of intravenous midazolam fivefold.[19] Another study found that the increase in the AUC of oral and intravenous midazolam was significantly greater after ketoconazole 400 mg for 7 days (15-fold and 4.2-fold, respectively) than after ketoconazole 200 mg daily for 7 days (11-fold and 3.4-fold, respectively).[20] Ketoconazole has been shown to reduce the metabolism of midazolam and greatly prolong its effects in further studies.[21,22]

4. Posaconazole. In a study in healthy subjects, posaconazole 200 mg daily for 10 days increased the AUC of intravenous midazolam 50 micrograms/kg by 83%.[23] In another study, oral posaconazole 200 mg or 400 mg twice daily for 7 days increased the AUC of intravenous midazolam 4.6-fold and 6.2-fold, respectively. Similarly, both doses of posaconazole increased the AUC of a single 2-mg oral dose of midazolam 4.5-fold. In addition, posaconazole 200 mg or 400 mg prolonged the mean terminal half-life of midazolam from about 3 to 4 hours to 8 to 10 hours.[23]

5. Voriconazole. A study in 10 healthy subjects found that voriconazole 400 mg twice daily on the first day and 200 mg twice daily on the second day affected the pharmacokinetics of both intravenous and oral midazolam. Voriconazole reduced the clearance of intravenous midazolam 50 micrograms/kg by 72% and increased its half-life from 2.8 hours to 8.3 hours. Voriconazole increased the maximum plasma level and AUC of a single 7.5-mg oral dose of midazolam by 3.8-fold and 10.3-fold, respectively. The psychomotor effects of oral midazolam were profoundly increased by voriconazole, but the effects of small intravenous doses of midazolam were only weakly increased. However, the authors suggested that high intravenous doses or long-term infusions might result in long-lasting hypnotic effects.[24]

(i) Quazepam

Ten healthy subjects were given **itraconazole** 50 mg twice daily or placebo for 14 days, with a single 20-mg dose of quazepam on day 4. **Itraconazole** did not affect the pharmacokinetics of quazepam, but the maximum plasma level and AUC of its two active metabolites, 2-oxoquazepam and N-desalkyl-2-oxoquazepam were decreased. However, psychomotor tests were not affected by **itraconazole**.[25]

(j) Temazepam

In a study, 10 healthy subjects were given **itraconazole** 200 mg daily for 4 days, with a single 20-mg dose of temazepam on day 4. A very small increase in the temazepam AUC was seen, but the psychomotor tests carried out were unchanged.[26]

(k) Triazolam

1. Fluconazole. Eight healthy subjects were given fluconazole or a placebo daily for 4 days, with a single 250-microgram dose of oral triazolam on day 4. The AUC of triazolam was increased 1.6-fold, 2.1-fold, and 4.4-fold by 50 mg, 100 mg, and 200 mg fluconazole, respectively, and the maximum plasma triazolam levels were more than doubled by the 200-mg dose of fluconazole. The 100- and 200-mg doses of fluconazole both produced significant changes in the psychomotor tests of triazolam, but the 50-mg dose did not.[27]

2. Itraconazole. In a study in 9 healthy subjects, the AUC of a single 250-microgram dose of triazolam was increased about 28-fold by itraconazole 200 mg daily for 4 days. Peak plasma levels were increased threefold. Marked changes in psychomotor and other responses were also seen. The subjects had amnesia and were still very tired and confused as long as 17 hours after taking the triazolam.[28] Another study found that the interaction persists for several days after taking the itraconazole.[29]

3. Ketoconazole. A study in healthy subjects found that when they were given triazolam 125 micrograms, after ketoconazole 200 mg taken 17 hours and 1 hour earlier, the triazolam half-life was prolonged (from 4 hours to almost 18 hours in one subject) and the clearance was increased ninefold. Pharmacodynamic testing found an increase in the impairment of a digit-symbol substitution test, and there were increased effects on EEG beta activity.[30] In another study, the AUC of a single 250-microgram dose of triazolam was increased about 23-fold by ketoconazole 400 mg daily for 4 days. Peak plasma levels were increased threefold. Marked changes in psychomotor and other responses were seen. The subjects had amnesia and were still very tired and confused as long as 17 hours after taking the triazolam.[28] A further study similarly found that ketoconazole inhibited the metabolism of triazolam leading to an increase in its sedative effects.[31]

B. Non-benzodiazepine hypnotics

(a) Zolpidem

1. Fluconazole. In a placebo-controlled study in healthy subjects fluconazole 100 mg twice daily for 2 days had no significant effect on the pharmacokinetics of a single 5-mg dose of zolpidem given after the third dose of fluconazole.[32]

2. Itraconazole. In a placebo-controlled study, 10 healthy subjects were given itraconazole 200 mg daily for 4 days with a single 10-mg oral dose of zolpidem on day 4. The mean peak plasma levels of the zolpidem were increased by 10.5% and the AUC was increased by 34%, but the performance of a number of psychomotor tests (digit symbol substitution, critical flicker fusion, subjective drowsiness, postural sway) remained unaltered.[33] Another study similarly found that itraconazole did not interact with zolpidem to a clinically significant extent.[32]

3. Ketoconazole. A study in 12 healthy subjects found that ketoconazole 200 mg twice daily for 2 days increased the AUC of a single 5-mg oral dose of zolpidem by 70% and the subjects were more sedated, as shown by the digit symbol substitution test.[32]

4. Voriconazole. In a study in 10 healthy subjects, pretreatment with voriconazole 400 mg twice daily for one day and then 200 mg twice daily for the second day increased the AUC of a single 10-mg oral dose of zolpidem by 50%: its half-life was prolonged from 3.2 hours to 4.1 hours. Voriconazole appeared to increase drowsiness in the immediate period following administration of zolpidem, but no statistically significant differences in pharmacodynamic variables were seen.[34]

(b) Zopiclone or Eszopiclone

1. Itraconazole. In a placebo-controlled study, 10 healthy subjects were given itraconazole 200 mg daily for 4 days with a single 7.5-mg oral dose of zopiclone on day 4. Itraconazole increased the maximum plasma levels of zopiclone by 29% (from 49 to 63 nanograms/mL), increased its AUC by 73%, and prolonged its half-life from 5 hours to 7 hours. Despite these increases, there were no statistical or clinical differences between the performance of the psychomotor tests carried out during the placebo and itraconazole phases of the study.[35]

2. Ketoconazole. In a multiple-dose, crossover study in 18 healthy subjects ketoconazole 400 mg increased the AUC of eszopiclone 3 mg 2.2-fold and increased its maximum plasma level by 40%. The AUC of ketoconazole was decreased by 12% with concurrent eszopiclone, but this was not considered to be clinically significant.[36]

Mechanism

Itraconazole, ketoconazole, voriconazole and to a lesser extent fluconazole and posaconazole are inhibitors of the cytochrome P450 isoenzyme CYP3A4. The benzodiazepines and zopiclone and zolpidem are, to varying degrees, metabolised by CYP3A4, with the extent of the interaction related to how significant CYP3A4 is in their metabolism and how potent a CYP3A4 inhibitor the azole is. So, for example midazolam, which is predominantly metabolised by CYP3A4 is greatly affected by potent inhibitors (e.g. itraconazole), whereas CYP3A4 is not a significant route in the metabolism of temazepam, so it is only slightly affected. Other isoenzymes are also involved in the metabolism of zolpidem, and to some extent zopiclone, so they are only moderately affected by CYP3A4 inhibitors. Similarly, diazepam is extensively metabolised by CYP2C19 and also CYP3A4, and so itraconazole has only a minor effect; whereas

fluconazole and voriconazole, which inhibit both CYP2C19 and CYP3A4, can significantly decrease the elimination of diazepam.

The azoles inhibit CYP3A4 in the liver (hence intravenous benzodiazepines can be affected) but studies have also suggested that ketoconazole inhibits the metabolism of midazolam[19,21] and triazolam[31] by CYP3A4 in the gut wall, which explains why oral benzodiazepines are more affected than intravenous benzodiazepines.

Ketoconazole appears to partially inhibit the oxidation of chlordiazepoxide by the liver.[5]

Importance and management

The interactions between midazolam or triazolam and itraconazole or ketoconazole are established and clinically important. In very broad terms the dose of midazolam would need to be reduced by about 75% or more in the presence of these antifungals to avoid excessive sedation, and even then the effects would still be expected to be prolonged. Unless appropriate precautions are taken (very reduced doses with careful monitoring and management) these interactions can be dangerous; most manufacturers contraindicate the concurrent use of oral midazolam or triazolam with itraconazole or ketoconazole. Patients taking these azoles should be warned about the likelihood of increased and prolonged sedation and advised not to drive (for example) after receiving midazolam until completely recovered; one study found that patients are not likely to be capable of tasks such as driving for at least 6 hours after the dose of the benzodiazepine,[10] but it could be substantially longer especially after multiple doses of these azoles. There is some evidence that bolus doses of intravenous midazolam given in the presence of itraconazole or fluconazole are not increased to a clinically significant extent, and normal doses can be used.[16] However, where high doses of intravenous midazolam are used long term (e.g. during intensive care treatment) it has been suggested that the dose will need to be titrated to avoid long-lasting hypnotic effects.[10] These precautions appear to be equally applicable to voriconazole. The manufacturer of **miconazole** oral gel also contraindicates triazolam and oral midazolam.[37] This is probably because a large proportion of miconazole oral gel (both prescription and non-prescription doses) may be swallowed and therefore adequate systemic absorption may occur to produce an interaction.

Fluconazole interacts less significantly but even so, the midazolam or triazolam dose probably needs to be reduced, possibly by as much as half. Similarly, posaconazole may also increase midazolam levels and dose adjustments may be required.

The effects of alprazolam and brotizolam are increased and prolonged by ketoconazole and itraconazole, but the extent of this is less than that seen with midazolam or triazolam. However, dose reductions may still be necessary; most manufacturers suggest caution, but a few have contraindicated the concurrent use of these azoles and benzodiazepines. Alprazolam and brotizolam should also be used with caution with oral miconazole.[37]

Diazepam, in single doses, is not significantly affected by itraconazole, however, both fluconazole and voriconazole considerably increase exposure to diazepam and a dose reduction may be required. Zopiclone or eszopiclone are moderately affected by itraconazole and ketoconazole and it may be necessary to reduce the dose.

The effects of itraconazole on etizolam, quazepam, temazepam or zolpidem, ketoconazole on chlordiazepoxide or zolpidem, and voriconazole on zolpidem are small and seem unlikely to be clinically significant in most patients.

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Benzodiazepines + Beta blockers

Only small and clinically unimportant pharmacokinetic interactions occur between most benzodiazepines and beta blockers, but there is limited evidence that some psychomotor tests may possibly be impaired in patients taking benzodiazepines combined with beta blockers.

Clinical evidence, mechanism, importance and management

No significant *pharmacokinetic* interactions were reported to occur between:

- **alprazolam** and **propranolol**[1]
- **clorazepate** and **propranolol**[2]
- **diazepam** and **atenolol**[3] or **propranolol**[3]
- **lorazepam** and **metoprolol**[4] or **propranolol**[1]
- **oxazepam** and **labetalol**[5] or **propranolol**.[5]

Moderate changes, which seem unlikely to be clinically significant, were found between:

- **diazepam** and **propranolol** (diazepam clearance reduced by 17%)[1] or **metoprolol** (diazepam clearance reduced by 18%,[6] AUC increased by 25%[3])
- **bromazepam** and **metoprolol** (bromazepam AUC increased by 35%)[4] or **propranolol** (bromazepam half-life increased by 22%).[7]

However, studies of psychomotor performance have shown that simple reaction times with **oxazepam** given with either **propranolol** or **labetalol** are increased,[5] and those taking **diazepam** and **metoprolol** have a reduced kinetic visual acuity,[3,8] which is related to driving ability.[9] Moreover, choice reaction times at 2 hours were also found to be lengthened when taking **diazepam** and **metoprolol**, **propranolol** or **atenolol**, but at 8 hours they only persisted with **diazepam** and **metoprolol**.[8]

Information about interactions between the benzodiazepines and beta blockers is very limited indeed. The current evidence does not seem to justify any additional caution, but bear the possibility of an interaction in mind in case of an unexpected response to treatment.

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Benzodiazepines + Buspirone

No adverse interaction appears to occur if buspirone is given with alprazolam, flurazepam or triazolam. When buspirone is given with diazepam the adverse effects appear to be mild and short-lived.

Clinical evidence, mechanism, importance and management

In 12 healthy subjects, buspirone 10 mg every 8 hours increased the maximum plasma levels and AUC of **alprazolam** 1 mg every 8 hours by 7% and 8%, respectively. The maximum plasma levels of buspirone were not altered, but the AUC of buspirone was increased by 29%. However, these changes were within the normal pharmacokinetic variability of these drugs, and no unexpected adverse effects were seen.[1]

In 12 healthy subjects given **diazepam** 5 mg daily for 22 days, buspirone 15 mg every 8 hours for 12 days had no effect on the plasma levels of **diazepam**, but the levels of the metabolite nordiazepam were raised by about 20%. Concurrent use resulted in some mild adverse effects (headache, nausea, dizziness) in all subjects, and in two cases muscle twitching was seen. These symptoms subsided after a few days.[2]

The concurrent use of buspirone with either **flurazepam** or **triazolam** did not appear to prolong or intensify the sedative effects of either benzodiazepine.[3]

There would seem to be no reason for avoiding the concurrent use of these benzodiazepines and buspirone.

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Benzodiazepines and related drugs + Caffeine

Caffeine appears to antagonise the effects of the benzodiazepines (mainly sedative effects, but possibly also anxiolytic effects). The effects of zopiclone may be similarly antagonised.

Clinical evidence

(a) Benzodiazepines

In a study in healthy subjects, a single 250-mg or 500-mg dose of caffeine (added to decaffeinated coffee) counteracted the drowsiness and mental slowness induced by a single 10- to 20-mg dose of **diazepam**.[1] The same or a similar study has been reported elsewhere.[2] Conversely, in a study in 6 healthy subjects, the concurrent use of caffeine 6 mg/kg and **diazepam** 300 micrograms/kg did not antagonise the effects of either drug; however, caffeine caused a minor 22% reduction in **diazepam** levels.[3] In one study the sedative effects of **midazolam**[4] were moderately antagonised by caffeine 250 mg but not 125 mg, and there is also some evidence to suggest that caffeine and **clonazepam**[5] or **triazolam**[6] have mutually opposing effects.

No pharmacokinetic interaction appears to occur between caffeine and **midazolam**[7] or **alprazolam**.[8]

(b) Non-benzodiazepine hypnotics

Zopiclone 7.5 mg appears to counter the stimulant effects of **caffeine** 300 mg more easily than **caffeine** counters the sedative effects of **zopiclone**.[6] In one study, no pharmacokinetic interaction occurred between **zolpidem** 10 mg and **caffeine** 300 mg (added to decaffeinated coffee), and the hypnotic effects of **zolpidem** were unchanged.[9] However, a placebo-controlled, crossover study in 12 healthy subjects found that **caffeine** 250 mg and 500 mg reversed the pharmacodynamic effects (such as sedation, reduced tapping speed, reaction time) caused by **zolpidem** 7.5 mg. Even though the pharmacodynamic effects of **zolpidem** were reduced by **caffeine**, the AUC of **zolpidem** was *increased* by 41% by **caffeine** 500 mg, when compared with placebo.[10]

Mechanism

Uncertain. One suggestion is that caffeine can block adenosine receptors, leading to CNS stimulation, which would antagonise the CNS depressant effects of the benzodiazepines.[11] Another suggestion is that the stimulant effects of caffeine and the sedative effects of benzodiazepines are simply antagonistic.

Importance and management

The evidence suggests that caffeine, particularly at higher doses, at least partially reduces the sedative and performance-impairing effects of benzodiazepines and related hypnotics. This would appear to be a disadvantage at night, but may possibly be useful the next morning, although caffeine should not be considered an antidote to the residual effects of these hypnotics. The extent to which caffeine reduces the anxiolytic effects of the benzodiazepines remains uncertain (it needs assessment), but be alert for reduced benzodiazepine effects if both are used.

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Benzodiazepines + Calcium-channel blockers

Of the calcium-channel blockers, diltiazem and verapamil are known to inhibit CYP3A4, the route by which benzodiazepines such as midazolam and triazolam are metabolised. Increased effects, such as sedation, which have been marked in some cases, have been seen in patients given these drugs. Alprazolam would be expected to interact similarly. There appear to be no clinically significant interactions between other calcium-channel blockers and benzodiazepines.

Clinical evidence

(a) Diazepam

1. Diltiazem. In 6 healthy subjects, the concurrent use of single doses of diazepam 5 mg and diltiazem 60 mg did not significantly affect the plasma levels of either drug.[1] In another study, poor and extensive metabolisers of the cytochrome P450 isoenzyme CYP2C19 (that is, those lacking or deficient in this isoenzyme, and those with normal levels of this isoenzyme, respectively) were given diltiazem 200 mg daily for 3 days before and 7 days after a single 2-mg dose of diazepam. Diltiazem increased the AUC of diazepam by 25% in both poor and extensive metabolisers, when compared with placebo; however, the half-life of diazepam increased from 46 hours to 65 hours in extensive metabolisers and from 77 hours to 104 hours in poor metabolisers. The clinical effects of these pharmacokinetic changes were not assessed.[2]

2. Felodipine. In 12 healthy subjects, felodipine 10 mg daily for 12 days did not affect the pharmacokinetics of a 10-mg intravenous dose of diazepam, but the AUC and peak plasma levels of the diazepam metabolite, desmethyldiazepam, were raised by 14% and 16%, respectively.[3]

3. Nimodipine. In 24 healthy, elderly subjects the plasma levels of diazepam 10 mg daily and nimodipine 30 mg three times daily were unaffected by concurrent use, and no clinically relevant changes in haemodynamics, ECG recordings, clinical chemistry or haematology occurred.[4]

(b) Midazolam

1. Diltiazem. After taking diltiazem 60 mg three times daily for 2 days, 9 healthy female subjects were given midazolam 15 mg orally. The AUC of midazolam was increased fourfold, the maximum plasma levels doubled, and the half-life increased by 49%. It was almost impossible for the subjects to stay awake for 90 minutes after taking the midazolam. They suffered several hours of amnesia and there was a marked decrease in the performance of pharmacodynamic tests (digit symbol substitution, Maddox wing test).[5] Diltiazem 60 mg, given to 15 patients 2 hours before induction of anaesthesia with midazolam and alfentanil, increased the AUC and half-life of midazolam by 15% and 43%, respectively. Tracheal extubation was performed on average 2.5 hours later, when compared with placebo.[6]

2. Lercanidipine. Midazolam appears to increase the absorption of lercanidipine by 40%.[7] The clinical relevance of this interaction is as yet unclear.

3. Nitrendipine. A study in 9 healthy subjects found that the pharmacokinetics and pharmacodynamics of midazolam were unaffected by a single 20-mg dose of nitrendipine.[8]

4. Verapamil. After taking verapamil 80 mg three times daily for 2 days, 9 healthy female subjects were given midazolam 15 mg orally. The AUC of the midazolam was increased threefold, the maximum plasma levels were doubled, and the half-life increased by 41%. It was almost impossible for the subjects to stay awake for 90 minutes after taking the midazolam. They suffered several hours of amnesia and there was a marked decrease in the performance of pharmacodynamic tests (digit symbol substitution, Maddox wing test).[5] Another study found that verapamil 240 mg daily for 7 days decreased the oral clearance of midazolam fourfold and the systemic clearance was decreased by about 60%.[9]

(c) Temazepam

In 16 healthy insomniacs, **diltiazem** 40 mg had little or no effect on the hypnotic effects of temazepam.[10]

(d) Triazolam

1. Diltiazem. A study in 7 healthy subjects found that diltiazem 60 mg three times daily for 3 days increased the AUC of a single 250-microgram dose of triazolam 2.3-fold and almost doubled its peak plasma levels. Pharmacodynamic tests showed an increase in the sedative effects of triazolam.[11] Another study in 10 healthy subjects found that diltiazem 60 mg three times daily for 2 days increased the AUC of a single 250-microgram dose of triazolam 3.4-fold, and approximately doubled its maximum plasma level and half-life. The pharmacodynamic changes were briefly described as profound and prolonged.[12] In contrast, in another study, diltiazem 40 mg was found to have little or no effect on the hypnotic effects of triazolam in 16 healthy insomniacs.[10]

2. Isradipine. In 9 healthy subjects, isradipine 5 mg daily reduced the AUC of a single 250-microgram dose of triazolam by 20%, but no difference in the pharmacodynamic effects of triazolam were seen.[13]

Mechanism

The evidence suggests that diltiazem and verapamil inhibit the metabolism of midazolam and triazolam, by the cytochrome P450 isoenzyme CYP3A4, leading to increased plasma levels and increased effects. It appears that the intestine is the major site of the interaction between midazolam and verapamil.[9]

Importance and management

The interactions between midazolam and diltiazem or verapamil are established and clinically important. The authors of one report say that patients taking either diltiazem or verapamil are probably incapable of doing skilled tasks (e.g. car driving) for up to 6 hours after taking midazolam 15 mg, and possibly even after 8 to 10 hours. They suggest that the usual dose of midazolam should be reduced by at least 50% to avoid unnecessarily deep sleep and prolonged hypnosis, and they also point out that as the half-life of the midazolam is prolonged, the effects will persist regardless of the dose.[5] The effects are not so marked with intravenous midazolam, but the elimination of midazolam is still reduced and postoperative recovery may be delayed.[6] Similar precautions are likely to be needed for triazolam with diltiazem, and the interaction is also predicted to occur with triazolam and verapamil.[12] As **alprazolam** is also metabolised by CYP3A4, diltiazem and verapamil would also be expected to increase its levels; however, there do not appear to be any clinical reports of an interaction.

No special precautions appear to be necessary when other calcium-channel blockers are given with a benzodiazepine.

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Benzodiazepines and related drugs + Carbamazepine

The use of benzodiazepines with carbamazepine is common, and some evidence suggests that the effects of the benzodiazepines are sometimes reduced. Levels of alprazolam were reduced and levels of midazolam were markedly reduced and its effects almost abolished by carbamazepine. Single-dose studies have shown that the sedative effects of zopiclone and carbamazepine are additive; however it has been predicted that, when taken long-term, carbamazepine might reduce the effects of zopiclone.

Clinical evidence

A. Benzodiazepines

(a) Alprazolam

In a placebo-controlled, crossover study in 7 healthy subjects, carbamazepine 100 mg three times daily for 10 days increased the apparent oral clearance of a single 800-microgram dose of alprazolam 2.4-fold and reduced the elimination half-life from about 17 hours to 8 hours.[1] The plasma alprazolam levels of a patient with atypical bipolar disorder and panic attacks, taking alprazolam 7.5 mg daily, were reduced by more than 50% (from 43 to 19.3 nanograms/mL) when carbamazepine was given. This was accompanied by a deterioration in his clinical condition, which was managed with haloperidol.[2]

(b) Clobazam

A study in patients with epilepsy found that carbamazepine reduces the plasma levels of clobazam and increases the levels of *N*-desmethylclobazam (the principal metabolite).[3] Similar results are described in other studies in healthy subjects and patients with epilepsy taking clobazam and carbamazepine.[4,5]

A 66-year-old man taking carbamazepine and topiramate experienced fatigue, ataxia, impairment of gait and clumsiness while taking clobazam 10 mg daily. His symptoms resolved when the clobazam was stopped. When he was later given carbamazepine, topiramate, and clobazam 20 mg daily his carbamazepine level rose from 36.8 micromol/L to 41.9 micromol/L. Five days after the clobazam was stopped the carbamazepine level had returned to approximately the pre-clobazam level (35.5 micromol/L).[6] However, another study in 15 patients with epilepsy taking carbamazepine alone and another 7 patients taking carbamazepine with clobazam, found that carbamazepine levels were similar in both groups, despite patients receiving monotherapy taking a significantly lower dose of carbamazepine, but levels of carbamazepine metabolites, including the active carbamazepine-10,11-epoxide, were higher in those also taking clobazam. It was suggested that clobazam increased the metabolism of carbamazepine by about 50%.[7]

(c) Clonazepam

Clonazepam, in slowly increasing doses up to a maximum of 4 to 6 mg/day given over a 6-week period, had no effect on carbamazepine serum levels. Some patients were also taking phenobarbital.[8] A study in 7 healthy subjects found that carbamazepine 200 mg daily given over a 3-week period reduced the plasma levels of clonazepam 1 mg daily from a range of 4 to 7 nanograms/mL down to 2.5 to 4 nanograms/mL, and reduced the half-life of clonazepam by about one-third.[9] A retrospective analysis of this interaction in 183 patients found that clonazepam clearance was increased by 22% and carbamazepine clearance was decreased by 21% during concurrent use.[10]

(d) Diazepam

A study found that the plasma clearance of a single 10-mg intravenous dose of diazepam was threefold greater, and the half-life shorter in a group of 9 patients with epilepsy when compared with 6 healthy subjects. Seven of the patients with epilepsy were taking carbamazepine.[11]

(e) Etizolam

In healthy subjects, carbamazepine 200 mg daily for 6 days decreased the maximum plasma level and AUC of a single 1-mg dose of etizolam by about 20% and 42%, respectively. The elimination half-life was reduced from 11 hours to about 7 hours.[12]

(f) Midazolam

The pharmacokinetics and pharmacodynamics of a single 15-mg oral dose of midazolam were studied in 6 patients with epilepsy taking either carbamazepine, phenytoin or both drugs together, and in 7 control subjects not taking either antiepileptic. The AUC of midazolam in the patients with epilepsy was reduced to 6%, and the peak plasma levels to 7% of the value in the control subjects. The pharmacodynamic effects of the midazolam (subjective drowsiness, body sway with eyes closed and open, as well as more formal tests) were also reduced. Most of the patients did not notice any effects from taking midazolam, while the control subjects were clearly sedated for 2 to 4 hours, and also experienced amnesia after taking the midazolam.[13]

B. Non-benzodiazepine hypnotics

A crossover study in 12 healthy subjects given single oral doses of **zopiclone** 7.5 mg and carbamazepine 600 mg found only minor changes in the plasma levels of both drugs. **Zopiclone** levels were higher and carbamazepine levels slightly lower. Psychomotor tests confirmed that both drugs had sedative effects, which were additive, and in a simulated driving test it was found that co-ordination was impaired and reaction times prolonged.[14]

Mechanism

Alprazolam and midazolam are both metabolised by the cytochrome P450 isoenzyme CYP3A4, of which carbamazepine is a known inducer. Concurrent use therefore increases the metabolism of these benzodiazepines and decreases their levels.

Importance and management

The interaction between carbamazepine and midazolam appears to be of greatest clinical significance. Much larger doses of midazolam are likely to be required in the presence of carbamazepine, or an alternative sedative may be needed. **Triazolam** is predicted to interact like midazolam.[13] Alprazolam and etizolam interact similarly, but to a lesser extent. The dose of these drugs may also need to be increased to ensure adequate serum levels.

One small study[11] suggests that enzyme-inducing antiepileptic drugs including carbamazepine may increase the clearance of diazepam; however, the clinical relevance of this does not appear to have been assessed. Nevertheless, it would seem prudent to monitor concurrent use for reduced efficacy.

As *N*-desmethylclobazam retains some of the activity of clobazam the effects of carbamazepine on clobazam metabolism probably have little clinical significance. In addition, the case of carbamazepine toxicity appears to be isolated and is therefore probably of limited importance.

The pharmacokinetic changes seen with clonazepam seem likely to be too small to be clinically significant, but this needs confirmation.

Note that carbamazepine is also metabolised via CYP3A4 and it appears that some benzodiazepines such as clonazepam, which share the same metabolic pathway, may interfere with the metabolism of carbamazepine. However, the effects are small, and unlikely to be of clinical relevance in most patients.

The evidence for an interaction between zopiclone and carbamazepine is slim, and the effects of long-term use are unclear. Carbamazepine is a strong inducer of CYP3A4 (by which zopiclone is metabolised) and it has been predicted that the effect of long-term carbamazepine treatment might be a reduction in zopiclone plasma levels and hypnotic effects.[15] It would seem prudent to be alert for the need to increase the zopiclone dose in patients taking carbamazepine. More study of this potential interaction is needed.

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Benzodiazepines + Ciclosporin

No pharmacokinetic interaction appears to occur between intravenous midazolam and ciclosporin.

Clinical evidence, mechanism, importance and management

In a study in 9 transplant patients taking ciclosporin, the pharmacokinetics of a single 75-microgram/kg dose of intravenous midazolam did not differ from those of historical values in healthy subjects. In addition, the length of time of midazolam sedation did not differ from that expected. Midazolam did not appear to alter ciclosporin levels in these patients.[1] These findings suggest that there is no pharmacokinetic interaction between intravenous midazolam and oral ciclosporin. However, it might be prudent to confirm this with oral midazolam.

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Benzodiazepines + Corticosteroids

The metabolism of midazolam may possibly be increased in patients receiving long-term treatment with corticosteroids.

Clinical evidence, mechanism, importance and management

Intravenous **midazolam** 200 micrograms/kg was given to 8 patients receiving long-term treatment with corticosteroids (6 taking **prednisolone** 2.5 mg to 15 mg daily; 1 taking **betamethasone** 0.5 mg daily; one taking **methylprednisolone** 48 mg daily) and to 10 other patients not taking corticosteroids. In the patients taking corticosteroids the AUC of **midazolam** was decreased and the clearance increased, when compared with the patients not taking corticosteroids; however the differences were not statistically significant. The onset of anaesthesia between the two groups was also not notably different. It was suggested that the trend towards increased **midazolam** metabolism might be due to induction of the cytochrome P450 isoenzyme CYP3A4 and/or UDP-glucuronosyltransferase. Although the results with intravenous midazolam appeared not to be clinically significant, the authors suggested that the metabolism of oral **midazolam** might possibly be more markedly affected.[1] Other benzodiazepines metabolised in a similar way to midazolam (e.g. **alprazolam**, **triazolam**) may be similarly affected. However, further study is needed to establish if any effect is clinically relevant.

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Benzodiazepines + Dexamfetamine

Dexamfetamine reverses the sedative effects and some of the memory-impairing effects of triazolam. Alprazolam attenuates the behavioural effects of dexamfetamine, but oxazepam appears to have no effect on dexamfetamine pharmacodynamics.

Clinical evidence, mechanism, importance and management

A placebo-controlled study in 20 healthy subjects found that a single 20-mg/70 kg dose of dexamfetamine sulfate reversed the sedative effects of a single 250-microgram/70 kg dose of **triazolam**. The study also found that dexamfetamine selectively reversed some of the memory-impairing effects of **triazolam**.[1] Similar results were reported in a related study.[2]

In a study, 6 healthy subjects were trained to discriminate between placebo and dexamfetamine 15 mg. Pretreatment with single 500-microgram doses of **alprazolam** significantly attenuated the discriminative-stimulus effects of dexamfetamine, and some of the self-reported drug effects.[3] A further study in 6 healthy subjects found that **oxazepam** 20 mg was ineffective at modulating the discriminative-stimulus or subject-rated effects of dexamfetamine.[4]

It is thought that the behavioural effects of dexamfetamine are due to increased synaptic dopamine levels, which are under the inhibitory control of GABA systems, whereas benzodiazepines are $GABA_A$ receptor positive modulators. However, it appears that benzodiazepines differ in their ability to affect the behavioural effects of dexamfetamine.[3,4]

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Benzodiazepines + Disulfiram

The plasma levels of chlordiazepoxide, diazepam and possibly temazepam are increased by the use of disulfiram and some patients may experience increased drowsiness. Alprazolam, oxazepam and lorazepam appear to be either not affected, or only minimally affected, by disulfiram. The intensity of the disulfiram-alcohol reaction may possibly be decreased by diazepam.

Clinical evidence

A man taking disulfiram 200 mg daily developed confusion, drowsiness, slurred speech and an unsteady gait within a few days of starting to take **temazepam** 20 mg at night. This was interpreted as **temazepam** toxicity. The symptoms disappeared when both drugs were stopped.[1]

After taking disulfiram 500 mg daily for 14 to 16 days, the median plasma clearance of single doses of **chlordiazepoxide** and **diazepam** were reduced by 54% and 41%, respectively, and the half-lives were increased by 84% and 37%, respectively, although there was considerable interindividual variation. The plasma levels of **chlordiazepoxide** were approximately doubled. **Oxazepam** was also given after the use of disulfiram, but changes in **oxazepam** pharmacokinetics were minimal. There was no difference in the interaction between alcoholic subjects (without hepatic cirrhosis) and healthy subjects.[2] Other studies have found that the pharmacokinetics of **lorazepam**[3] and **alprazolam**[4] were unaffected by disulfiram.

It has been reported that the intensity of the disulfiram-alcohol reaction may be decreased by **diazepam**.[5]

Mechanism

Disulfiram inhibits the initial metabolism (*N*-demethylation and oxidation) of chlordiazepoxide and diazepam by the liver so that an alternative but slower metabolic pathway is used. This results in the accumulation of these benzodiazepines in the body. However, alprazolam is metabolised by hepatic microsomal oxidation, but does not appear to interact with disulfiram.[4]

The metabolism (glucuronidation) of oxazepam and lorazepam is minimally affected by disulfiram so that their clearance from the body remains largely unaffected.[2,3] The possible interaction between disulfiram and

temazepam is not understood, as temazepam is also mainly eliminated in the urine as the inactive glucuronide metabolite, and so its metabolism would not generally be expected to be affected by disulfiram.

Importance and management

There seems to be only one report (with temazepam) of a clinically significant interaction between disulfiram and the benzodiazepines, and this report is unconfirmed, as the patient did not take temazepam alone. The other reports only describe potential interactions that have been identified by single-dose studies. These do not necessarily reliably predict what will happen in practice. However, it seems possible that some patients will experience increased drowsiness, maybe due to this interaction or because drowsiness is a very common adverse effect of disulfiram. Reduce the dose of the benzodiazepine if necessary. Benzodiazepines that are metabolised by similar pathways to diazepam and chlordiazepoxide, may possibly interact in the same way, but this needs confirmation. Alprazolam, oxazepam and lorazepam appear to be non-interacting alternatives.

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Benzodiazepines + Ethambutol

Ethambutol appears not to affect the pharmacokinetics of diazepam.

Clinical evidence, mechanism, importance and management

A study in 6 patients, newly diagnosed with tuberculosis and taking ethambutol 25 mg/kg, found that although some of the pharmacokinetic parameters of **diazepam** were different to those obtained in healthy control subjects not taking ethambutol, the differences were not significant.[1] There seems to be nothing in the literature to suggest that ethambutol interacts with other benzodiazepines.

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Benzodiazepines + Food

Food can delay and reduce the hypnotic effects of flunitrazepam and loprazolam. Food can markedly enhance the absorption of quazepam. Food does not appear to have a clinically relevant effect on the overall bioavailability of alprazolam, diazepam or nitrazepam.

Clinical evidence, mechanism, importance and management

(a) Alprazolam

When compared with the fasting state, food had no effect on the extent of absorption of alprazolam 1 mg, formulated as an immediate-release orally disintegrating tablet. However, the maximum plasma level decreased by 23% and the time to maximum level increased from 2.5 to 4 hours. The clinical significance of this was thought to be minimal.[1]

(b) Diazepam

In a single-dose, crossover study, light food delayed the time to maximum plasma levels of diazepam by about one hour, but had no effect on its maximum plasma level or AUC, when compared with the fasting state. Light food did not appear to affect the CNS-depressant effects of diazepam.[2]

(c) Flunitrazepam

A study in 8 healthy subjects found that when they took a single 2-mg dose of flunitrazepam 2 hours after an evening meal (spaghetti, meat, salad, an apple and wine) and one hour before going to bed, the peak plasma levels of flunitrazepam were reduced by 63%. The time to reach these levels was delayed by 2.5 hours, and the absorption half-life was considerably prolonged.[3] It seems probable therefore that the onset of sleep with flunitrazepam may be delayed by food.

(d) Loprazolam

A study in 8 healthy subjects found that when they took a single 2-mg dose of loprazolam 2 hours after an evening meal (spaghetti, meat, salad, an apple and wine) and one hour before going to bed, the peak plasma levels of loprazolam were reduced by 41%. The time to reach these levels was delayed by 3.6 hours, and the absorption half-life was considerably prolonged.[3] It seems probable therefore that the onset of sleep with loprazolam may be delayed by food.

(e) Nitrazepam

In a single-dose, crossover study, light food delayed the time to maximum plasma levels of nitrazepam by about one hour, but had no effect on its maximum plasma level or AUC, when compared with the fasting state. Light food did not appear to affect the CNS-depressant effects of nitrazepam.[2]

(f) Quazepam

In a crossover study, 9 healthy subjects were given single 20-mg doses of quazepam immediately after a standard meal, and 3 hours after a standard meal. When compared with the fasting state, the peak plasma levels and $AUC_{0\text{-}8}$ for quazepam were increased 3-fold and 2.4-fold, respectively, when given 30 minutes after food, and by 2.5-fold and 2.1-fold, respectively, when given 3 hours after food. The CNS-depressant effects of quazepam were enhanced to a similar extent by administration 30 minutes or 3 hours after food.[4] In another study by the same authors, it was found that both low-fat and high-fat meals increased the absorption of quazepam.[5] A further study found that a light snack increased the bioavailability of quazepam and prolonged the reaction time at 4 and 6 hours after dosing.[2] However, another study found increases in the bioavailability when quazepam was taken 2 hours after food, but did not find any significant difference in the subjective effects of quazepam, such as drowsiness, malaise, and calmness, when compared with fasting.[6] It appears that food affects the absorption of quazepam and this effect may continue for at least 3 hours after food intake.[4] Some authorities have contraindicated the administration of quazepam with food;[4-6] however, it has also been suggested that, because of the good tolerability of quazepam, it may not be necessary to adjust the dose with meal content.[5] The US manufacturer does not suggest any restrictions concerning administration with food.[7]

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7. Doral (Quazepam). Questcor Pharmaceuticals, Inc. US Prescribing information, November 2007.

Benzodiazepines + Grapefruit and other fruit juices

Grapefruit juice can increase the bioavailability of oral diazepam, midazolam and triazolam. Quazepam levels are also raised by grapefruit juice.

Clinical evidence

(a) Diazepam

A study in 8 healthy subjects found that simultaneous administration of 250 mL of grapefruit juice increased the AUC and maximum plasma levels of a single 5-mg oral dose of diazepam 3.2-fold and 1.5-fold, respectively.[1]

(b) Midazolam

Grapefruit juice 200 mL was given to 8 healthy subjects followed 15 minutes later by 5 mg of intravenous midazolam or 60 minutes later by

15 mg of oral midazolam. The pharmacokinetics of intravenous midazolam remained unchanged, but the AUC of oral midazolam was increased by 52%, and its maximum plasma levels rose by 56%. These changes were also reflected in the psychometric measurements made.[2] Grapefruit juice resulted in a similar increase in the AUC of oral midazolam in another study.[3] A further study found that the AUC of oral midazolam increased by 65% when midazolam was given 2 hours after grapefruit juice, but when the midazolam was given 26 hours, 50 hours and 74 hours after grapefruit juice, its AUC was increased by 21%, 22% and 6%, respectively. Midazolam elimination half-life was not altered by grapefruit juice.[4]

A large-scale placebo-controlled study involving a total of 120 healthy young medical students used psychomotor tests to measure the effect of benzodiazepines with and without grapefruit juice. Subjects were given midazolam 10 mg or **triazolam** 250 micrograms with 300 mL of grapefruit juice or water. Only a minor increase in the benzodiazepine effects occurred with grapefruit juice, and these effects were of little or no practical importance.[5]

(c) Quazepam

A study in 9 healthy subjects found that 250 mL of grapefruit juice three times daily for 3 days increased the AUC of a single 15-mg oral dose of quazepam and its active metabolite, 2-oxoquazepam, by 38% and 28%, respectively, although these increases were not statistically significant. The pharmacodynamic effects of quazepam, such as sedation, were not enhanced by grapefruit juice.[6]

(d) Triazolam

A single oral 250-microgram dose of triazolam was given to 10 healthy subjects with either 250 mL of grapefruit juice or water. The mean AUC of the triazolam was increased by 50% by the grapefruit juice, the peak plasma levels were increased by 30%, and the time to peak plasma levels was prolonged from 1.5 hours to 2.5 hours. A slight decrease in psychomotor performance occurred (more drowsiness and tiredness).[7]

Another study of the interaction between triazolam and grapefruit juice found that the effects of grapefruit juice were much more pronounced when multiple doses of grapefruit juice were given. The triazolam AUC and half-life were increased by about 50% and 6 to 9%, respectively, when single doses of normal or double-strength grapefruit juice were given, and by about 150% and 50%, respectively, by multiple doses (3 times daily) of double-strength grapefruit juice. The effect of grapefruit juice on psychomotor tests was also greater after multiple dosing.[8] Similar increases in the AUC of triazolam were found in a study using normal-strength grapefruit juice three times daily for 3 days, and although grapefruit juice was not found to enhance the sedative effects of triazolam, it did result in deterioration of performance in the digit symbol substitution test.[6] However, in another study, 300 mL of grapefruit juice once daily for 10 days only increased the AUC of a single dose of oral triazolam by 60%, which was similar to the effects of exposure to a single dose of grapefruit juice.[9]

For another study in which grapefruit juice had little effect on the response to triazolam, see under *Midazolam*, above.

Mechanism

The evidence suggests that grapefruit juice inhibits the metabolism of these benzodiazepines by the cytochrome P450 isoenzyme CYP3A4, so that more is left to enter the circulation.[2] Single exposure to grapefruit juice appears to mainly impair enteric, but not hepatic, metabolism and recovery of enteric CYP3A function seems to be largely complete within 3 days.[4] In one study grapefruit juice was found to have a greater effect on the bioavailability and pharmacodynamics of triazolam than on quazepam. This was considered to be because triazolam is metabolised by CYP3A4, while quazepam is metabolised by CYP2C9 as well as by CYP3A4.[6]

Importance and management

Established interactions. These increases in bioavailability might be expected to increase the extent of the sedation and amnesia due to these benzodiazepines, but in young healthy adults this is apparently of little importance, although multiple doses of grapefruit juice may increase the risk of adverse effects. The clinical effects of the interaction with diazepam appear not to have been investigated. The effects of midazolam and triazolam may be more enhanced than those of other benzodiazepines, because these drugs are more dependent on CYP3A4 for their metabolism (see *Mechanism*, above).

Other fruit juices have been reported to affect CYP3A4 *in vitro*, but studies in healthy subjects have not found any clinically relevant pharmacokinetic interactions with midazolam and **cranberry juice**,[10] **pomegranate juice**[3] or **tangerine juice**.[11]

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Benzodiazepines and related drugs + H_2-receptor antagonists

The levels of many of the benzodiazepines and related drugs are raised by cimetidine, but normally this appears to be of little or no clinical importance and only the occasional patient may experience an increase in effects (sedation). The interactions with midazolam, and possibly zaleplon may be more significant, but this is not established. Famotidine, nizatidine and ranitidine do not normally appear to interact with most benzodiazepines.

Clinical evidence

A. Benzodiazepines

(a) Cimetidine

In 10 patients who took cimetidine 300 mg four times daily for 2 weeks the combined plasma level of **diazepam** and its active metabolite, desmethyldiazepam, was found to be increased by 57%, but reaction times and other motor and intellectual tests remained unaffected.[1] Other reports describe a rise in the plasma levels and/or AUC of **diazepam** (associated with increased sedation in one report[2]) due to cimetidine,[3-9] and generalised incoordination has also been described in one individual.[10]

Cimetidine also raises the plasma levels of **adinazolam**,[11] **alprazolam**,[12,13] **bromazepam**,[14] **chlordiazepoxide**,[15] **clobazam**[16,17] (this interaction was considered to be both clinically significant[16] and clinically irrelevant due to large interpatient variation in clobazam plasma levels[17]), **clorazepate**,[18] **flurazepam**,[19] **nitrazepam**,[20] and **triazolam**.[12,13,21,22] Liver cirrhosis increases the effects of cimetidine on the loss of **chlordiazepoxide**.[23]

Confusion has been reported in a 50-year-old man taking **clorazepate** when he was given cimetidine,[24] and increased sedation has been seen in some patients taking **adinazolam** and cimetidine.[11] Prolonged hypnosis in an elderly woman[25] and CNS toxicity (including lethargy and hallucinations) in a 49-year-old woman[26] have been attributed to an interaction between **triazolam** and cimetidine but this remains unconfirmed.

In contrast, cimetidine does not normally interact with **clotiazepam**,[27] **lormetazepam**,[28] **oxazepam**[19,29,30] or **temazepam**,[31,32] although prolonged post-operative sedation was seen in one patient given **oxazepam** and cimetidine.[33] Similarly, some studies suggest that no interaction occurs between **lorazepam** and cimetidine,[19,29] although one study found an increase in **lorazepam** levels, but this was only statistically significant with a 400-mg intravenous dose of cimetidine and not with a 200-mg dose.[3]

There is some controversy about whether or not **midazolam** is affected by cimetidine. An increase in sedation,[34,35] an increase in **midazolam**

levels[35-37] and no pharmacokinetic interaction[38] have been reported with the combination.

(b) Famotidine

Famotidine does not interact with **bromazepam**,[39] **clorazepate**,[39] **chlordiazepoxide**,[39] **diazepam**[9,40] or **triazolam**.[39]

(c) Nizatidine

Nizatidine does not interact significantly with **diazepam**.[41-43]

(d) Ranitidine

Ranitidine does not interact to a clinically significant extent with **adinazolam**,[44] **diazepam**[41,45] (although diminished absorption of diazepam may possibly occur),[46] **lorazepam**,[45] or **temazepam**,[32,47] but it can modestly increase the bioavailability (by about 10 to 30%) of oral **triazolam**:[48,49] this is unlikely to be clinically relevant.

There is some controversy about whether or not **midazolam** is affected by ranitidine. Increases in **midazolam** levels[36] and sedation[47,50] have been reported on a few occasions, but a lack of effect has also been documented.[34,37,38]

(e) Roxatidine

Roxatidine does not interact with **diazepam** or its active metabolite, desmethyldiazepam.[51]

B. Non-benzodiazepine hypnotics

(a) Cimetidine

Cimetidine increased plasma levels of a single dose of **zaleplon** by 85%.[52] There appeared to be no significant pharmacokinetic interaction between cimetidine and **zolpidem** in healthy subjects, although sleep duration tended to be prolonged.[53]

(b) Ranitidine

There appeared to be no significant pharmacokinetic interaction between ranitidine and **zolpidem**.[53] Ranitidine did not affect the hypnotic action of **zopiclone**.[47]

Mechanism

Cimetidine inhibits the liver enzymes concerned with the metabolism of diazepam, alprazolam, chlordiazepoxide, clorazepate, flurazepam, nitrazepam, triazolam, and zaleplon. As a result their clearance from the body is reduced and their plasma levels rise.

Lorazepam, oxazepam and temazepam are metabolised by a different metabolic pathway involving glucuronidation, which is not affected by cimetidine, and so they do not usually interact.

Ranitidine, famotidine and nizatidine appear not to inhibit liver microsomal enzymes. There is some evidence that ranitidine increases the absorption of triazolam, and possibly other benzodiazepines, due to changes in gastric pH,[49] although it has been suggested that this effect is negligible.[22] Cimetidine has been said to similarly affect the absorption of diazepam and lorazepam.[3]

Importance and management

The interactions between the benzodiazepines or related drugs and cimetidine are well documented (not all the references are listed here) but normally they appear to be of little clinical importance. However, a few patients may be adversely affected (increased effects, drowsiness, etc.) and this may possibly be more common with midazolam and the non-benzodiazepine hypnotic, zaleplon. If symptoms occur in any patient taking a benzodiazepine or related drug and cimetidine, reduce the benzodiazepine dose: a dose reduction of one-third or increased dosing intervals (twice daily instead of three times daily) have been suggested for alprazolam.[12] Alternatively, use a non-interacting benzodiazepine, such as lorazepam, lormetazepam, oxazepam or temazepam, or a non-interacting H_2-receptor antagonist such as ranitidine, famotidine, nizatidine or roxatidine.

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Benzodiazepines and related drugs + Hormonal contraceptives

Hormonal contraceptives can increase the effects of alprazolam, chlordiazepoxide, diazepam, nitrazepam and triazolam, and reduce the effects of oxazepam, lorazepam and temazepam. Chlordiazepoxide, diazepam, nitrazepam and meprobamate can possibly increase the incidence of break-through bleeding in patients taking hormonal contraceptives.

Clinical evidence

(a) Effects on benzodiazepines and related drugs

A controlled study found that the mean half-life of intravenous **chlordiazepoxide** 600 micrograms/kg was virtually doubled (20.6 hours compared with 11.6 hours) and the total clearance was almost two-thirds lower in 6 women taking oral hormonal contraceptives when compared with 6 women not taking oral hormonal contraceptives.[1]

Similar but less marked effects were found in other studies in women taking oral hormonal contraceptives given **chlordiazepoxide**,[2] **diazepam**,[3,4] and to an even lesser extent with **nitrazepam**[5] and **triazolam**.[6] Oral hormonal contraceptives have also been reported to inhibit[6] or to have no significant influence[7] on the metabolism of **alprazolam**. No clinically significant pharmacokinetic changes were seen when **bromazepam**,[8] **clotiazepam**,[9] **midazolam** (given orally,[10,11] intramuscularly,[12] or intravenously[10]) or **zolpidem**[13] were given with hormonal contraceptives.

A controlled study, comparing 7 women taking an oral hormonal contraceptive with 8 women not taking oral hormonal contraceptives found that the mean half-life of intravenous **lorazepam** 2 mg was over 50% shorter in the contraceptive group (6 hours compared with 14 hours) and the total clearance was over threefold greater.[1]

A smaller increase in the elimination rate was seen in other controlled studies in women taking oral hormonal contraceptives and **lorazepam**,[6,14] or **temazepam**,[6] and in two other studies small decreases in the half-life of **oxazepam** were observed.[1,14]

(b) Effects on contraceptives

A study in 72 patients taking oral combined hormonal contraceptives (*Rigevidon*, *Anteovin*) found that breakthrough bleeding occurred in 36% of patients while taking **chlordiazepoxide** 10 to 20 mg daily, **diazepam** 5 to 15 mg daily, **nitrazepam** 5 to 10 mg daily or **meprobamate** 200 to 600 mg daily, but no pregnancies occurred. Only three cases of bleeding occurred with **diazepam** or **nitrazepam**.[15] The average values for breakthrough bleeding with these two oral contraceptives were 9.1% for *Rigevidon* and 3.3% for *Anteovin* in the absence of other drugs. It was possible to establish a causal relationship between the bleeding and the use of the anxiolytic/hypnotic in 77% of the cases either by stopping the drug or by changing it for another.[15]

Mechanism

Hormonal contraceptives affect the metabolism of the benzodiazepines by the liver in different ways: oxidative metabolism is reduced (alprazolam, chlordiazepoxide, diazepam, etc.), whereas metabolism by glucuronide conjugation is increased (lorazepam, oxazepam, temazepam, etc.). Just why these hypnotics should cause breakthrough bleeding is not understood.

Importance and management

Established interactions, but of uncertain clinical importance. Long-term use of benzodiazepines that are highly oxidised (alprazolam, chlordiazepoxide, diazepam, nitrazepam, etc.) in women taking oral hormonal contraceptives should be monitored to ensure that the dose is not too high. Those taking benzodiazepines that are metabolised to glucuronides (lorazepam, oxazepam, temazepam, etc.) may possibly need a dose increase but this is not proven. Bromazepam, clotiazepam, midazolam and zolpidem appear not to interact. No firm conclusions could be drawn from the results of one study, which set out to evaluate the importance of this interaction.[16]

The increased incidence of breakthrough bleeding (more than one-third) due to these anxiolytics/hypnotics, is an unpleasant reaction, but no contraceptive failures have been reported.[15] Limited evidence from the study suggests that changing the anxiolytic/hypnotic or the contraceptive might avoid breakthrough bleeding. Note that the UK Family Planning Association[17] did not consider that additional contraceptive precautions were necessary with **clonazepam** or **clobazam** and it seems unlikely that they will be necessary with most benzodiazepines.

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Benzodiazepines + 5-HT_3-receptor antagonists

Granisetron does not appear to interact with lorazepam, and ondansetron does not appear to interact with temazepam.

Clinical evidence, mechanism, importance and management

Lorazepam 2.5 mg, given to 12 healthy subjects, clearly affected the performance of a number of psychometric tests. Statistically significant increases occurred in drowsiness, feebleness, muzziness, clumsiness, lethargy, mental slowness, relaxation, dreaminess, incompetence, sadness, and withdrawal. However, there was very little evidence that **granisetron** 160 micrograms/kg alone had any effect on the performance of these tests except that clumsiness and inattentiveness were increased, nor was there evidence that granisetron added to the effects of **lorazepam** when both drugs were taken concurrently.[1]

In a placebo-controlled, crossover study in 24 healthy subjects, **ondansetron** 8 mg did not affect the pharmacokinetics of **temazepam** 20 mg. The psychomotor performances of the subjects (subjective and ob-

jective sedation, memory and other measurements) were not influenced by the presence of the **ondansetron**.[2]

No additional special precautions would seem to be necessary if either of these pairs of drugs are given.

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Benzodiazepines + Influenza vaccines

The pharmacokinetics of alprazolam, chlordiazepoxide and lorazepam are not affected by influenza vaccination.

Clinical evidence, mechanism, importance and management

The pharmacokinetics of single doses of oral **alprazolam** 1 mg, or intravenous **lorazepam** 2 mg remained unaffected in healthy subjects when the benzodiazepines were given 7 and 21 days after 0.5 mL of an intramuscular trivalent influenza vaccine.[1] Similarly, in another study, neither **lorazepam** nor **chlordiazepoxide** metabolism was altered when they were given one and 7 days after a trivalent influenza vaccine.[2] There would seem to be no reason for avoiding the concurrent use of these drugs.

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Benzodiazepines + Isoniazid

Isoniazid reduces the clearance of both diazepam and triazolam. Some increase in their effects would be expected. No interaction occurs between isoniazid and oxazepam or clotiazepam.

Clinical evidence

A study in 9 healthy subjects found that isoniazid 90 mg twice daily for 3 days increased the half-life of a single 5- or 7.5-mg dose of **diazepam** from about 34 hours to 45 hours, and reduced its total clearance by 26%.[1] A study in 6 healthy subjects found that isoniazid 90 mg twice daily for 3 days, increased the half-life of a single 500-microgram dose of **triazolam** from 2.5 hours to 3.3 hours, increased its AUC by 46% and reduced its clearance by 42%.[2]

A study in 9 healthy subjects found that isoniazid 90 mg twice daily for 3 days had no effect on the pharmacokinetics of a single 30-mg oral dose of **oxazepam**.[2] Similarly, in another study, the pharmacokinetics of **clotiazepam** were not altered by isoniazid.[3]

Mechanism

What is known suggests that isoniazid acts as an enzyme inhibitor, decreasing the metabolism and loss of diazepam and triazolam from the body, thereby increasing and prolonging their effects. Oxazepam, which is metabolised by glucuronidation, would be unlikely to interact.

Importance and management

Information is limited but the interactions appear to be established. Their clinical importance is uncertain but be alert for the need to decrease the doses of diazepam and triazolam if isoniazid is started. There seems to be no direct information about other benzodiazepines, but those undergoing high first-pass extraction and/or liver microsomal metabolism (e.g. **alprazolam** or **triazolam**) may interact similarly. Oxazepam and clotiazepam appear not to interact.

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Benzodiazepines + Kava

A man taking alprazolam became semicomatose a few days after starting to take kava, which was suggested to be due to additive sedation. The pharmacokinetics of midazolam are not affected by kava.

Clinical evidence, mechanism, importance and management

(a) Alprazolam

A 54-year-old man taking alprazolam, cimetidine and terazosin was hospitalised in a lethargic and disorientated state 3 days after starting to take kava, which he had bought from a local health food store. He denied having overdosed with any of these drugs. The patient became alert again after several hours.[1] The reason for what happened is not known, but the suggested explanation is that the kava α-pyrones might have had additive sedative effects with those of the alprazolam.[1,2] This is an isolated case and its general importance is not known.

(b) Midazolam

In a study in 6 subjects, who regularly took 7 to 27 g of kavalactones weekly as an aqueous kava extract, there was no change in the metabolism of a single 8-mg oral dose of midazolam before or after they *stopped* kava for 30 days.[3] Similar results were found in a study in 12 healthy subjects given kava kava root extract 1 g twice daily for 28 days before receiving a single 8-mg dose of oral midazolam.[4] A pharmacokinetic interaction requiring a midazolam dose alteration therefore seems unlikely.

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Benzodiazepines and related drugs + Macrolides

The plasma levels and effects of midazolam, triazolam and zopiclone are increased and prolonged by erythromycin. The same interaction has been seen with clarithromycin, telithromycin and troleandomycin, and to a limited extent with josamycin and roxithromycin, but not with azithromycin. Alprazolam and brotizolam would be expected to be similarly affected by these macrolides. Other benzodiazepines such as diazepam, flunitrazepam, nitrazepam, and the related hypnotic, zaleplon, only appear to interact with erythromycin to a fairly modest extent, and temazepam and zolpidem appear not to interact.

Clinical evidence

A. Benzodiazepines

(a) Alprazolam

In a randomised study, 12 healthy subjects were given **erythromycin** 400 mg three times daily for 10 days with a single 800-microgram dose of alprazolam on day 8. The alprazolam AUC was increased 2.5-fold and the half-life increased from 16 hours to 40.3 hours. However, no increase in sedation was seen.[1]

(b) Brotizolam

A randomised study in healthy subjects found that **erythromycin** 400 mg three times daily for 7 days increased AUC of a single 500-microgram dose of brotizolam 2.5-fold. The elimination half-life was also increased from 9.4 hours to 20.7 hours. However, **erythromycin** did not affect the changes in psychomotor function associated with brotizolam.[2]

(c) Diazepam

In a crossover study, 6 healthy subjects were given a single 5-mg oral dose of diazepam after taking **erythromycin** 500 mg three times daily for one week. The diazepam $AUC_{0\text{-}42}$ was increased by a modest 15% and its pharmacodynamic effects were unchanged.[3]

(d) Flunitrazepam

In a crossover study, 5 healthy subjects were given a single 1-mg oral dose of flunitrazepam after taking **erythromycin** 500 mg three times daily for one week. The flunitrazepam AUC_{0-42} was increased by a modest 25%, and its pharmacodynamic effects were unchanged.[3]

(e) Midazolam

1. Azithromycin. A study in 64 healthy medical students found that azithromycin 750 mg had no effect on the metabolism of a 10- or 15-mg dose of midazolam, and did not alter the performance of a number of psychomotor tests.[4] A study in 10 healthy subjects given azithromycin 250 mg daily found that some small changes in the pharmacokinetics of midazolam 15 mg occurred (a possible small delay in its onset of action), but its pharmacodynamic effects were unaltered.[5] Other studies confirm that azithromycin does not interact with midazolam.[6,7]

2. Clarithromycin. In a study, 16 healthy subjects were given a concurrent oral 4 mg and intravenous 50 microgram/kg dose of midazolam, before and after they took clarithromycin 500 mg twice daily for 7 days. It was found that clarithromycin reduced the systemic clearance of midazolam by about 64%, which resulted in a doubling of the midazolam-induced sleeping time.[8] Similarly, a study in elderly subjects, aged 66 to 80 years, found that clarithromycin 500 mg twice daily for 7 days increased the AUC of intravenous midazolam about threefold and increased the AUC of oral midazolam eightfold.[9] Another study reported a similar interaction.[7]

3. Erythromycin. A study in 12 healthy subjects found that erythromycin 500 mg three times daily for 6 days almost tripled the peak plasma levels of a single 15-mg oral dose of midazolam, more than doubled its half-life and increased its AUC more than fourfold. The subjects could hardly be wakened during the first hour after being given the midazolam, and most experienced amnesia lasting several hours.[10] Another study found that the increase in dose-corrected AUCs for oral midazolam in subjects that had taken erythromycin 200 mg four times daily for 2, 4, or 7 days were 2.3-, 3.4- and 3.4-fold, respectively. It appeared that a plateau level of CYP3A4 inhibition could be achieved by 4 days or more of erythromycin treatment.[11] The manufacturer reports that erythromycin causes a twofold increase in the plasma levels and half-life of intravenous midazolam.[12]
The plasma levels of a 500-microgram/kg oral dose of midazolam, given to an 8-year-old boy as premedication before surgery, were approximately doubled when he was given intravenous erythromycin. He developed nausea and tachycardia, and after 40 minutes (by which point he had received 200 mg of erythromycin) he lost consciousness.[13] A patient in a coronary care unit given 300 mg of intravenous midazolam over 14 hours slept for about 6 days (apart from brief wakening when given flumazenil). The midazolam half-life was increased about tenfold. This was attributed to an interaction due to the combined effects of erythromycin 4 g daily and amiodarone 1.7 g over 3 days.[14,15] Other studies and reports have also described this interaction.[4,6,16,17]

4. Roxithromycin. In 10 healthy subjects roxithromycin 300 mg daily for 6 days increased the AUC of a single 15-mg dose of midazolam by about 47%, and lengthened the half-life from 1.7 hours to 2.2 hours. Only minor psychomotor changes were seen.[18] A modest increase in the effects of midazolam were seen in another study in subjects given roxithromycin 300 mg, but the effects were very much weaker than those seen with erythromycin.[17]

5. Telithromycin. When intravenous and oral midazolam were given with telithromycin, the AUC of midazolam was increased 2.2-fold and 6.1-fold, respectively. The midazolam half-life was increased about 2.5-fold.[19]

(f) Nitrazepam

When 10 healthy subjects were given **erythromycin** 500 mg three times daily for 4 days, the AUC of a single 5-mg dose of nitrazepam was increased by 25%, its peak plasma levels were increased by 30% and the time to peak concentration was reduced by over 50%. However, hardly any changes were seen in the psychomotor tests undertaken.[20]

(g) Temazepam

A randomised, study in 10 healthy subjects found that **erythromycin** 500 mg three times daily for 6 days had no significant effect on the pharmacokinetics or psychomotor effects of a single 20-mg dose of temazepam.[21]

(h) Triazolam

1. Azithromycin. A clinical study in 12 healthy subjects found that azithromycin did not affect the pharmacokinetics of a single 125-microgram dose of triazolam.[22] These results were supported by an *in vitro* study, which suggested that azithromycin was only a weak inhibitor of triazolam metabolism.[22]

2. Clarithromycin. An *in vitro* study found clarithromycin to be a relatively potent inhibitor of triazolam metabolism. These results were confirmed in practice with 12 healthy subjects, who were given both drugs. The oral clearance of triazolam was reduced by 77% by clarithromycin and the AUC was increased about fivefold, when compared with placebo.[22]

3. Erythromycin. A study in 16 healthy subjects found that erythromycin 333 mg three times daily for 3 days, reduced the clearance of a single 500-microgram dose of triazolam by about 50%, doubled its AUC, and increased its maximum plasma levels by about one-third (from 2.8 to 4.1 nanograms/mL).[23] Other reports confirm the marked decrease in triazolam clearance and an increase in its peak levels in the presence of erythromycin.[22,24] A patient with acute pneumonia and chronic renal failure taking erythromycin 600 mg daily developed visual hallucinations and abnormal body sensations each time a dose of triazolam and **nitrazepam** were taken. These symptoms had not occurred before the addition of erythromycin.[25]

4. Josamycin. A patient taking josamycin experienced confusion lasting about 24 hours after taking a single dose of triazolam.[26]

5. Roxithromycin. A single-dose study found that the psychomotor effects of triazolam were only slightly affected by roxithromycin 300 mg.[17]

6. Troleandomycin. Troleandomycin 2 g daily given to 7 healthy subjects for 7 days increased the peak triazolam levels by 107%, increased its AUC by 275% and prolonged its half-life from 1.81 hours to 6.48 hours. Apparent oral clearance was reduced by 74%. Marked psychomotor impairment and amnesia was seen.[27] Troleandomycin has been reported to interact similarly in a patient taking triazolam, causing an increase in its effects.[26] An *in vitro* study has shown troleandomycin to be a potent inhibitor of triazolam metabolism.[22]

B. Non-benzodiazepine hypnotics

(a) Zaleplon

The manufacturers of zaleplon note that a single 800-mg dose of **erythromycin** increased the maximum plasma levels of zaleplon by 34% and increased its AUC by 20%.[28,29]

(b) Zolpidem

In a study in 10 healthy subjects 4 doses of **clarithromycin** 500 mg had no effect on the pharmacokinetics of a single 5-mg dose of zolpidem or on its sedative effects. Clarithromycin pharmacokinetics were unaffected by zolpidem.[30]

(c) Zopiclone

Zopiclone 7.5 mg was given to 10 healthy subjects before and after they took **erythromycin** 500 mg three times daily for 6 days. **Erythromycin** increased the plasma levels of zopiclone fivefold at 30 minutes and twofold at one hour. Peak plasma levels rose by about 40% and occurred at 1 hour instead of 2 hours. The 1-hour and 2-hour AUCs were increased threefold and twofold, respectively, while the total AUC was increased by nearly 80%.[31] These pharmacokinetic changes were reflected in some small changes in a number of psychomotor tests.[31]

Mechanism

Some of the macrolides (notably clarithromycin, erythromycin and telithromycin) are moderate to potent inhibitors of the cytochrome P450 isoenzyme CYP3A4. They therefore inhibit the metabolism of some benzodiazepines by this route, causing an increase in their levels, and increasing and prolonging their effects. Benzodiazepines, such as midazolam, that are predominantly metabolised by CYP3A4 are affected more than those such as diazepam, where CYP3A4 plays only a minor part in the metabolism. Further, CYP3A4-mediated metabolism occurs in the liver and also in the intestines. Midazolam and triazolam undergo extensive first-pass metabolism (low bioavailability of about 40%) but alprazolam and brotizolam undergo less first-pass metabolism (bioavailabilities of about 90% and 70%, respectively). Erythromycin causes greater increases in the levels and AUCs of midazolam and triazolam than in those of alprazolam and brotizolam, and this may be related to the extent of first-pass metabolism.[2] The non-benzodiazepine hypnotics, zaleplon and zopiclone are, to

varying degrees, also metabolised by CYP3A4: they are therefore similarly affected by the macrolides.

Importance and management

The interactions of midazolam with clarithromycin, erythromycin and telithromycin appear to be established, and of clinical importance. Troleandomycin would be expected to interact similarly. The dose of midazolam should be reduced 50 to 75% when these antibacterials are used if excessive effects (marked drowsiness, memory loss) are to be avoided. Remember too that the hypnotic effects are also prolonged so that patients should be warned about hangover effects the following morning if they intend to drive. There is some evidence that the effects of single bolus doses of intravenous midazolam given in the presence of erythromycin are not increased to a clinically significant degree, and normal doses can be used, although the duration of effect may be prolonged. However, where high doses of intravenous midazolam are used long term (e.g. during intensive care treatment) one manufacturer of midazolam suggests[32] that the initial dose may need to be reduced by up to 50% and the dose will then need to be titrated to avoid long-lasting hypnotic effects. Triazolam appears to interact similarly, and similar precautions would seem advisable.

Limited information from single-dose studies suggests that erythromycin may increase the levels of alprazolam, brotizolam and zopiclone but only small pharmacodynamic changes were reported. Nevertheless, the extent of the pharmacokinetic effect is reasonably large, and a degree of caution is warranted as some patients may be affected. Clarithromycin, telithromycin and troleandomycin would be expected to interact similarly.

The manufacturers of zaleplon say that patients should be advised that increased sedation is possible with erythromycin,[28] although a dose adjustment is usually not required;[28,29] however the extent of the effect is small, and would not generally be expected to lead to a clinically relevant interaction.

Other macrolides appear not to interact (azithromycin) or only interact to a modest extent (roxithromycin) with midazolam and/or triazolam. Similarly modest effects would be expected with other benzodiazepines or related hypnotics partly metabolised by CYP3A4 (e.g. alprazolam, brotizolam).

Other benzodiazepines and related hypnotics not significantly metabolised by CYP3A4 (diazepam, flunitrazepam, nitrazepam, temazepam and zolpidem) have only minor or insignificant interactions with any of the macrolides, suggesting that no special precautions are necessary on their concurrent use.

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Benzodiazepines and related drugs + Melatonin

The CNS effects of benzodiazepines and related hypnotics, such as zolpidem, may be additive with those of melatonin.

Clinical evidence

In a well-controlled, single-dose study in 16 healthy subjects aged 55 years and older, giving prolonged-release melatonin 2 mg with **zolpidem** 10 mg at bedtime enhanced the impairment of cognitive function seen with **zolpidem** alone at one hour and 4 hours post-dose, but not the next morning. Melatonin alone had no effect on cognitive function. No pharmacokinetic interaction was found.[1]

Mechanism

The activity of melatonin is thought to involve similar interactions at the GABA receptors in the brain to benzodiazepines. It may therefore enhance the activity of benzodiazepines and related drugs.

Importance and management

The evidence available suggests that melatonin might enhance the sedative properties of benzodiazepines and related hypnotics such as zolpidem. Although in the study of zolpidem, the enhanced effect was not apparent the morning after dosing, it would be wise to be aware that increased drowsiness is a possibility if melatonin is also given, especially with longer-acting hypnotics.

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Benzodiazepines and related drugs + Metoclopramide

Intravenous, but not oral, metoclopramide increases the rate of absorption of diazepam and raises its maximum plasma levels. Intravenous metoclopramide increases the rate of absorption of zopiclone.

Clinical evidence, mechanism, importance and management

(a) Diazepam

Intravenous metoclopramide increased the peak plasma levels of diazepam by 38% and increased the rate of absorption (peak levels occurred at 30 minutes instead of 60 minutes),[1] but in another study in 6 healthy

subjects oral metoclopramide 10 mg did not increase the rate of absorption of oral diazepam 0.2 mg/kg.[2] The reason is not understood. The clinical importance of this interaction is not known, but it is probably small.

(b) Zopiclone

In a study in 12 healthy subjects, intravenous metoclopramide 10 mg increased the rate of absorption of a single 7.5-mg dose of oral zopiclone. This was presumably because metoclopramide alters gut motility. Metoclopramide almost doubled the mean plasma levels of zopiclone (from 22.7 to 44.4 nanograms/mL) at 1 hour, but the increase in zopiclone levels was only about 20% (from 49.3 to 59.6 nanograms/mL) at 2 hours.[3] The clinical importance of these findings is not known.

1. Gamble JAS, Gaston JH, Nair SG, Dundee JW. Some pharmacological factors influencing the absorption of diazepam following oral administration. *Br J Anaesth* (1976) 48, 1181–5.
2. Chapman MH, Woolner DF, Begg EJ, Atkinson HC, Sharman JR. Co-administered oral metoclopramide does not enhance the rate of absorption of oral diazepam. *Anaesth Intensive Care* (1988) 16, 202–5.
3. Elliott P, Chestnutt WN, Elwood RJ, Dundee JW. Effect of atropine and metoclopramide on the plasma concentrations of orally administered zopiclone. *Br J Anaesth* (1983) 55, 1159P–1160P.

Benzodiazepines + Metronidazole

Metronidazole does not affect the pharmacokinetics of alprazolam, diazepam, lorazepam, or midazolam.

Clinical evidence, mechanism, importance and management

A study in healthy subjects found that metronidazole 400 mg twice daily for 5 days had no effect on the pharmacokinetics of a single 100-microgram/kg intravenous dose of **diazepam**.[1] Another study in healthy subjects found that metronidazole 750 mg had no effect on the pharmacokinetics of **alprazolam** or **lorazepam**.[2] *In vivo* and *in vitro* studies have shown that metronidazole has no effect on the pharmacokinetics or pharmacodynamics of **midazolam**.[3] Although they do not appear to have been studied, interactions with other benzodiazepines seem unlikely.

1. Jensen JC, Gugler R. Interaction between metronidazole and drugs eliminated by oxidative metabolism. *Clin Pharmacol Ther* (1985) 37, 407–10.
2. Blyden GT, Greenblatt DJ, Scavone JM. Metronidazole impairs clearance of phenytoin but not of alprazolam or lorazepam. *Clin Pharmacol Ther* (1986) 39, 181.
3. Wang J-S, Backman JT, Kivistö KT, Neuvonen PJ. Effects of metronidazole on midazolam metabolism in vitro and in vivo. *Eur J Clin Pharmacol* (2000) 56, 555–9.

Benzodiazepines + Modafinil

Modafinil reduces triazolam levels. It may therefore also affect the metabolism of other similarly metabolised benzodiazepines such as midazolam and possibly alprazolam. Conversely, modafinil might increase diazepam levels.

Clinical evidence, mechanism, importance and management

In a placebo-controlled study, 34 healthy women (all taking an oral hormonal contraceptive containing ethinylestradiol and norgestimate) were given a single 125-microgram dose of **triazolam**, both before and on the last day of taking modafinil 200 mg daily for 7 days then 400 mg daily for 21 days. The AUC of **triazolam** was reduced by almost 60%, its maximum plasma level was reduced by 42%, and its elimination half-life was reduced by about one hour by modafinil.[1]

Modafinil is known to induce the cytochrome P450 isoenzyme CYP3A4, by which **triazolam** is metabolised, and it is therefore likely to reduce **triazolam** levels by this mechanism, particularly in the gastrointestinal tract.[1] It seems possible that other benzodiazepines metabolised by CYP3A4 (e.g. **midazolam** and possibly **alprazolam**) may be similarly affected. It would therefore seem prudent to monitor for a reduction in the sedative effects and a reduced duration of action of these benzodiazepines in patients taking modafinil: increase the dose if necessary.

Conversely, modafinil inhibits the cytochrome P450 isoenzyme CYP2C19. The manufacturers therefore predict that the elimination of **diazepam**, which is metabolised by this isoenzyme, may be reduced. They suggest that a dose reduction of **diazepam** may be necessary on concurrent use.[2,3]

1. Robertson P, Hellriegel ET, Arora S, Nelson M. Effect of modafinil on the pharmacokinetics of ethinyl estradiol and triazolam in healthy volunteers. *Clin Pharmacol Ther* (2002) 71, 46–56.
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Benzodiazepines and related drugs + Nefazodone

Nefazodone increases the plasma levels and effects of alprazolam, midazolam, triazolam and zopiclone, but not lorazepam.

Clinical evidence

A. Benzodiazepines

(a) Alprazolam

A placebo-controlled study in 12 healthy subjects found that nefazodone 200 mg twice daily caused an almost twofold increase in the plasma levels of alprazolam 1 mg twice daily taken for 7 days.[1] Another study found that nefazodone increased the mean AUC of alprazolam by 47%.[2] A further study reported impairment of psychomotor performance and increased sedation when nefazodone was given with alprazolam.[3] A case report describes a woman taking alprazolam who developed benzodiazepine withdrawal symptoms after nefazodone was withdrawn following several years of concurrent use. She needed an alprazolam dose increase from 500 micrograms daily to 4 mg daily to control her symptoms.[4]

(b) Lorazepam

A placebo-controlled study in healthy subjects given nefazodone 200 mg twice daily found no changes in the pharmacokinetics of lorazepam 2 mg twice daily.[5] Another study found that psychomotor performance was not further impaired and no additional sedation occurred when nefazodone was given with lorazepam.[3]

(c) Midazolam

A study in 10 healthy subjects found that both the AUC and the maximum plasma level of a single 10-mg oral dose of midazolam were increased about fivefold and twofold, respectively, when they took nefazodone 200 mg twice daily.[6]

(d) Triazolam

A study in 12 healthy subjects found that the maximum plasma levels, the half-life and the AUC of a single 250-microgram dose of triazolam were increased 1.7-fold, 4.6-fold, and 4-fold, respectively, by nefazodone 200 mg twice daily.[7] Another study found that impairment of psychomotor performance and increased sedation occurred when nefazodone was given with triazolam.[3]

B. Non-benzodiazepine hypnotics

An 86-year-old woman taking diltiazem, irbesartan, lorazepam, and pravastatin started taking nefazodone 50 mg twice daily, increasing to 500 mg daily in divided doses, for the treatment of a major depressive episode. Because of associated insomnia, **zopiclone** was added, starting at 15 mg each night, but this was reduced after 5 days to 7.5 mg because of morning drowsiness. Plasma levels of *S*-zopiclone and *R*-zopiclone were 107 nanograms/mL and 20.6 nanograms/mL, respectively, at this time. After several months, nefazodone was replaced by venlafaxine. The *S*-zopiclone and *R*-zopiclone levels were again measured and found to be only 16.9 nanograms/mL and 1.45 nanograms/mL, respectively.[8]

Mechanism

Nefazodone appears to inhibit the oxidative metabolism of alprazolam, midazolam, triazolam and zopiclone by the cytochrome P450 isoenzyme CYP3A4 so that they accumulate in the body. Lorazepam is unaffected because it is primarily excreted as a conjugate.

Importance and management

The interactions of nefazodone with alprazolam, midazolam, triazolam and zopiclone are established and clinically important; the practical consequences are that the effects of these drugs are expected to be increased to varying extents. Be alert for any evidence of any psychomotor impairment, drowsiness etc. and reduce the benzodiazepine dose if necessary. A substantial reduction (approximately 50%) in the initial dose of alprazolam might be required, and an even greater reduction might be needed for midazolam and triazolam; however, the manufacturer of triazolam[9]

contraindicates its concurrent use with nefazodone. Lorazepam does not interact with nefazodone. There seems to be no direct information about other benzodiazepines and related drugs.

1. Greene DS, Salazar DE, Dockens RC, Kroboth P, Barbhaiya RH. Coadministration of nefazodone and benzodiazepines: III. A pharmacokinetic interaction study with alprazolam. *J Clin Psychopharmacol* (1995) 15, 399–408.
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8. Alderman CP, Gebauer MG, Gilbert AL, Condon JT. Possible interaction of zopiclone and nefazodone. *Ann Pharmacother* (2001) 35, 1378–80.
9. Halcion (Triazolam). Pfizer Inc. US Prescribing information, December 2008.

Benzodiazepines + NNRTIs

Delavirdine is predicted to increase the levels of alprazolam, midazolam and triazolam. Etravirine is predicted to increase the levels of diazepam, and modestly decreases the levels of midazolam. Efavirenz and nevirapine may increase the metabolism of midazolam by induction of CYP3A4. However, efavirenz may also compete for metabolism by CYP3A4 and potentially *decrease* the metabolism of midazolam and triazolam.

Clinical evidence, mechanism, importance and management

(a) Delavirdine

Delavirdine is an inhibitor of the cytochrome P450 isoenzyme CYP3A4 and may increase the plasma levels of drugs that are metabolised by this route. Delavirdine is contraindicated with drugs that are highly dependent on CYP3A4 for clearance including **alprazolam**, **midazolam** and **triazolam**.[1]

(b) Efavirenz or Nevirapine

In a study, 90 HIV-positive patients not taking antiretrovirals (control group) and 56 similar patients already taking antiretrovirals, were given a 75-microgram dose of oral **midazolam**. When compared with the control group, the 1-hydroxymidazolam to **midazolam** ratio was fivefold higher in 28 patients receiving efavirenz, but 17-fold lower in 3 patients receiving efavirenz together with ritonavir (the ratio for ritonavir alone was 50-fold lower). Similarly, the 1-hydroxymidazolam to **midazolam** ratio was sevenfold lower in 3 patients receiving nevirapine together with ritonavir or nelfinavir or grapefruit juice. It appears that efavirenz and nevirapine *induce* the metabolism of midazolam by the cytochrome P450 isoenzyme CYP3A4, but the inhibition of CYP3A4 by ritonavir or nelfinavir offsets the inductive effects of efavirenz or nevirapine given concurrently.[2] Note that the manufacturers of efavirenz contraindicate its use with **midazolam** or **triazolam** as they suggest that competition for CYP3A4 by efavirenz could also result in *inhibition* of metabolism and the potential for prolonged sedation or respiratory depression.[3,4] However, note that competition for metabolism rarely results in clinically relevant increases in the levels of either of the two drugs involved.

A study in 12 subjects found that efavirenz 600 mg daily for 10 days increased the maximum plasma level of a single 2-mg dose of **lorazepam** by 16%[4] and the AUC by 7%.[3] These changes are not considered to be clinically significant and no dose adjustment is considered necessary for either efavirenz or **lorazepam**.[3]

(c) Etravirine

Etravirine is a weak inhibitor of the cytochrome P450 isoenzyme CYP2C19, by which **diazepam** is metabolised. The manufacturers of etravirine therefore predict that concurrent use will raise **diazepam** levels[5,6] (which would increase the risk of prolonged and/or excessive sedation). The UK manufacturer suggests that alternatives to **diazepam** should be considered,[5] whereas the US manufacturer suggests that a decrease in the dose of **diazepam** may be necessary.[6]

In a study, 12 healthy subjects were given a single dose of intravenous **midazolam** 250 micrograms/kg on day one and day 14 of a 14-day course of etravirine 200 mg twice daily. Etravirine modestly reduced the ratio of the AUC of **midazolam** to its metabolite, 1-hydroxymidazolam, by 37%.[7] However, this modest reduction in **midazolam** levels would not be expected to be of clinical significance in most patients.

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4. Sustiva (Efavirenz). Bristol-Myers Squibb Company. US Prescribing information, September 2009.
5. Intelence (Etravirine). Janssen-Cilag Ltd. UK Summary of product characteristics, November 2009.
6. Intelence (Etravirine). Tibotec, Inc. US Prescribing information, November 2009.
7. Schöller-Gyüre M, Kakuda TN, Stevens T, Aharchi F, De Smedt G, Peeters M, Hoetelmans RMW. Effect of etravirine on cytochrome P450 isoenzymes assessed by the Cooperstown 5+1 cocktail. 48th Annual ICAAC/ IDSA 46th General Meeting, Washington DC, 25th-28th October 2008.

Benzodiazepines and related drugs + NSAIDs

The interactions of the NSAIDs with the benzodiazepines are usually minor and of little clinical relevance; however, diclofenac appears to reduce the dose of midazolam needed to produce sedation and hypnosis, and in some cases feelings of dizziness may be increased.

Clinical evidence, mechanism, importance and management

(a) Diazepam

1. Diclofenac. In a study in 8 healthy subjects, diazepam increased the AUC of diclofenac by 60% and reduced its clearance by 36%.[1] The effects of diazepam on diclofenac appeared to depend on the time of administration and may reflect time-dependent effects of diazepam on gastrointestinal function. More study is needed to establish the mechanism and clinical relevance of this interaction.

2. Ibuprofen. A study in 8 healthy subjects investigating the effects of diazepam on ibuprofen pharmacokinetics found that the ibuprofen half-life was increased from 2.39 hours to 3.59 hours and its clearance was reduced by about one-third when diazepam and ibuprofen were given at 10 pm, but no effect was seen with morning dosing.[2] The clinical importance of this is uncertain.

3. Indometacin. Diazepam 10 to 15 mg impaired the performance of a number of psychomotor tests (digit symbol substitution, letter cancellation, tracking and flicker fusion) in 119 healthy medical students. It also caused subjective drowsiness, mental slowness and clumsiness. When indometacin 50 or 100 mg was given the effects were little different from diazepam alone, except that feelings of dizziness (common to both drugs) were increased and caused subjective clumsiness.[3]

4. Naproxen. A double-blind, crossover study did not find any clinically important changes in mood or attention in healthy subjects given naproxen and diazepam.[4] A single-dose study in 10 healthy subjects found that peak serum concentrations of naproxen 500 mg were reduced by 23%, the time to peak concentration was increased (from 1.36 hours to 2 hours) and the absorption rate constant was decreased by 40% by diazepam 10 mg. Other pharmacokinetic parameters were not affected.[5] No special precautions appear to be necessary on concurrent use.

5. Parecoxib. Valdecoxib, the active metabolite of parecoxib is an inhibitor of CYP2C19 and may possibly increase the serum levels of diazepam, see 'NSAIDs; Parecoxib + Miscellaneous', p.177.

(b) Midazolam

A clinical study found that **diclofenac** 75 mg given intravenously to 10 patients reduced the dose of intravenous midazolam needed to produce sedation and hypnosis by 35%, when compared with 10 control subjects not given **diclofenac**.[6] The clinical importance of this is uncertain.

A randomised, crossover study in 32 patients undergoing two surgical procedures for bilateral symmetrically impacted third molars, found that midazolam, in doses used for conscious sedation, had no effect on the potency or duration of action of **diflunisal** for postoperative pain relief.[7]

A study in 12 healthy adults found no significant changes in the pharmacokinetics of midazolam 70 micrograms/kg given an hour after a single 40-mg dose of intravenous **parecoxib**.[8] Valdecoxib, the active metabolite

of **parecoxib** is a substrate for the cytochrome P450 isoenzyme CYP3A4, but does not appear to affect the pharmacokinetics of midazolam, which is metabolised by CYP3A4.

(c) Oxazepam

In a study in 6 healthy subjects, **diflunisal** 500 mg twice daily decreased the peak plasma concentration and AUC of a single 30-mg dose of oxazepam by 38% and 16%, respectively; the AUC of oxazepam glucuronide increased by 70%. It was suggested that **diflunisal** displaced oxazepam from its plasma protein binding sites leading to a slightly increased presystemic hepatic extraction and a slightly decreased systemic availability. In addition, there appeared to be competition between the glucuronides of oxazepam and **diflunisal** for tubular secretion. The overall clinical significance was thought to be small.[9]

(d) Zaleplon

A randomised, single-dose study in 17 healthy subjects found that **ibuprofen** 600 mg had no effect on the pharmacokinetics of zaleplon 10 mg.[10]

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Benzodiazepines + Paracetamol (Acetaminophen)

Paracetamol reduces the urinary excretion of diazepam but diazepam plasma levels are little affected. Oxazepam does not affect the pharmacokinetics of paracetamol.

Clinical evidence, mechanism, importance and management

The 96-hour urinary excretion of a single 10-mg oral dose of **diazepam** and its metabolite, nordiazepam, were reduced from 44% to 12% and from 27% to 8%, respectively, in 2 female subjects, and from 11% to 4.5%, respectively, in a male subject, by a single 500-mg dose of paracetamol. The reasons for these changes are not understood. The plasma levels of **diazepam** and its metabolite were not significantly affected,[1] which suggests that these changes are of limited clinical relevance.

In a study, 7 healthy subjects received a single 500-mg intravenous dose of paracetamol alone, and with a single 30-mg dose of oral **oxazepam**. The pharmacokinetics of paracetamol and its metabolites were unaffected by **oxazepam**, and no adverse effects were observed.[2]

There would seem to be no reason for avoiding the concurrent use of these benzodiazepines and paracetamol. There seems to be no information about other benzodiazepines.

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2. Sonne J, Enghusen Poulsen H, Buch Andreasen P. Single dose oxazepam has no effect on acetaminophen clearance or metabolism. *Eur J Clin Pharmacol* (1986) 30, 127–9.

Benzodiazepines and related drugs + Phenobarbital or Primidone

The use of benzodiazepines with phenobarbital or primidone may possibly be accompanied by some changes in plasma levels, which are normally of limited clinical importance. However, additive adverse effects such as sedation may occur during initial use. More serious effects (hallucinations, violent behaviour) have been reported, but appear rare.

Clinical evidence

(a) Chlordiazepoxide

A single case report describes a man given phenobarbital, secobarbital and chlordiazepoxide who became drowsy, unsteady, and developed slurred speech, nystagmus, poor memory and hallucinations, all of which disappeared once the phenobarbital was withdrawn and the chlordiazepoxide dose reduced from 80 to 60 mg daily.[1]

(b) Clobazam

A study in patients with epilepsy receiving long-term clobazam, alone or with other antiepileptic drugs, found that phenobarbital slightly reduced the plasma levels of both clobazam and its active metabolite, *N*-desmethylclobazam.[2] Similarly, another study reported that phenobarbital reduced the plasma levels of clobazam by 63% and reduced *N*-desmethylclobazam by 31%, although the effect on *N*-desmethylclobazam was not statistically significant. The plasma levels of phenobarbital were not affected by clobazam.[3] A further study also found that clobazam plasma levels were decreased by phenobarbital, and that the ratio between *N*-desmethylclobazam and clobazam levels increased. Clobazam significantly reduced the apparent clearance of primidone.[4]

(c) Clonazepam

Clonazepam, in slowly increasing doses up to a maximum of 4 to 6 mg daily, given over a 6-week period to patients taking phenobarbital with or without carbamazepine, had no effect on phenobarbital levels.[5] A study in patients receiving various combinations of phenytoin, phenobarbital and primidone, found that their plasma levels were not significantly altered by the addition of clonazepam 3 mg daily for 4 weeks, but the levels of clonazepam were reduced in the presence of the other antiepileptics, particularly phenobarbital and primidone. Drowsiness occurred in 44 of 66 patients in the first week after clonazepam was added to their antiepileptic treatment, but this improved in most patients; after 2 to 3 weeks only 6 patients still reported drowsiness, together with ataxia and hypotonicity. Depression was reported in one patient and personality changes with irritability and violent behaviour was reported in another.[6] A study found that phenobarbital caused some small changes in the pharmacokinetics of a single dose of clonazepam but only the small increase in clearance was statistically significant.[7] In contrast, an analysis of the serum levels of antiepileptics in children found that those taking clonazepam had markedly higher levels of primidone, and toxicity was seen.[8]

(d) Clorazepate

A report suggested that the concurrent use of primidone and clorazepate may have been responsible for the development of irritability, aggression and depression in 6 of 8 patients.[9]

(e) Diazepam

Phenobarbital 100 mg daily for 8 days had no effect on the metabolism of diazepam in a group of healthy subjects.[10] Some modest additive CNS depression may possibly be expected, but the authors of this report make no comment about this.

(f) Nitrazepam

An analysis of the serum levels of antiepileptics in children found that those taking nitrazepam had lower levels of primidone.[8]

Mechanism

Uncertain. Simple additive effects in some cases or changes in the drug metabolism in others seem likely. Phenobarbital may increase the rate of metabolism of some benzodiazepines through induction of liver enzymes.

Importance and management

Phenobarbital may increase the clearance of benzodiazepines and related drugs, although none of the interactions described here appear to be of major clinical importance. However, caution might be necessary with benzodiazepines, such as **midazolam**, that are primarily metabolised by CYP3A4. Similarly, the manufacturer of **zopiclone** notes that the concurrent use of phenobarbital may decrease the plasma levels of **zopiclone** and a dose increase may be required.[11] Primidone levels may be affected by clobazam and clonazepam and one study reported increased toxicity in children. It may be prudent to be alert for primidone adverse effects

such as drowsiness, ataxia or dysarthria, and monitor levels should these develop.

Adverse effects such as sedation may be more evident when benzodiazepines are combined with barbiturates, particularly in the initial stages of treatment, and careful dose adjustment may be required.

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Benzodiazepines and related drugs + Phenytoin

Reports are inconsistent: benzodiazepines can cause phenytoin levels to increase (toxicity has been seen), decrease, or remain unaltered. In addition phenytoin may reduce clonazepam, diazepam, midazolam and oxazepam levels.

Clinical evidence

(a) Phenytoin levels increased

The observation that toxicity developed in patients taking phenytoin when they were given **chlordiazepoxide** or **diazepam** prompted a more detailed study. The plasma phenytoin levels of 25 patients taking phenytoin 300 or 400 mg daily and **chlordiazepoxide** or **diazepam** were 80 to 90% higher than those of 99 subjects taking phenytoin without a benzodiazepine.[1]

Further reports attribute increased phenytoin plasma levels and phenytoin toxicity to **chlordiazepoxide**,[2] **clobazam**,[3] **clonazepam**,[4-6] and **diazepam**.[7-9]

(b) Phenytoin levels decreased

The plasma phenytoin levels of 12 patients fell by about 30% over a 2-month period while they were taking **clonazepam** 1.5 to 12 mg daily. When data from another 12 patients were combined, the mean fall was only 18%.[10] Other studies describe similar findings with **clonazepam**[11] and **diazepam**.[12,13]

(c) Phenytoin levels unchanged

In one study, **alprazolam** did not affect the serum phenytoin levels in healthy subjects.[14] **Clonazepam** did not alter serum phenytoin levels in one study,[15] and another study concluded that **clonazepam** produced no predictable change in phenytoin levels, as phenytoin levels were increased in 9 patients, decreased in one patient, and unchanged in 3 patients.[16] A single-dose study in healthy subjects found no significant pharmacokinetic interaction between intravenous **diazepam** 10 mg and intravenous **fosphenytoin** 1.125 g (or the phenytoin formed by the hydrolysis of fosphenytoin).[17]

(d) Benzodiazepine levels reduced

A study in 5 patients given phenytoin 250 to 400 mg daily found that plasma **clonazepam** levels were reduced by more than 50%,[18] and another study found that phenytoin increased the clearance of **clonazepam** by about 50%.[19] In further studies, phenytoin reduced the plasma levels of **clobazam** and increased the levels of *N*-desmethylclobazam (the principal metabolite).[20,21] **Diazepam**[22] and **oxazepam**[23] may be similarly affected in patients with epilepsy given phenytoin.

The pharmacokinetics and pharmacodynamics of a single 15-mg oral dose of **midazolam** were studied in 6 patients with epilepsy taking carbamazepine, phenytoin, or both drugs together, and in 7 control subjects not taking either of these antiepileptics. The AUC of **midazolam** in the patients with epilepsy was reduced to 5.7%, and the peak plasma levels to 7.4%, of their value in the control subjects. The pharmacodynamic effects (subjective drowsiness, body sway with eyes closed and open, as well as more formal tests) were also reduced. Most of the patients did not notice any effects of the **midazolam**, while the control subjects were clearly sedated for 2 to 4 hours after taking the **midazolam**, and also experienced amnesia.[24]

Mechanism

The inconsistency of these reports is not understood. Benzodiazepine-induced changes in the metabolism of phenytoin[2,7,9,13] as well as alterations in the apparent volume of distribution have been suggested as possible mechanisms. Enzyme induction by phenytoin may possibly account for the reduction in plasma benzodiazepine levels.

Importance and management

A confusing picture. Concurrent use certainly need not be avoided (it has proved to be valuable in many cases) but monitor the outcome of concurrent use and consider monitoring plasma phenytoin levels so that undesirable changes can be detected. Only diazepam, chlordiazepoxide, clobazam and clonazepam have been implicated, but it seems possible that other benzodiazepines could also interact. One manufacturer of **temazepam** suggests that plasma phenytoin levels may be increased or decreased by temazepam and that phenytoin levels may need to be monitored during temazepam withdrawal. In addition, adverse effects may be more evident.[25]

Phenytoin may induce the metabolism of some benzodiazepines including clonazepam, diazepam, and midazolam causing a decrease in benzodiazepine levels. Similarly, the manufacturer of the non-benzodiazepine hypnotic, **zopiclone**,[26] suggests that its plasma levels may be decreased by phenytoin. If necessary, dose adjustments should be considered. Phenytoin may also cause an increase in the metabolic conversion of clobazam to the active metabolite *N*-desmethylclobazam.

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Benzodiazepines + Probenecid

Probenecid reduces the clearance of adinazolam, lorazepam and nitrazepam. Increased effects (e.g. sedation) may be expected. Probenecid does not appear to interact with temazepam.

Clinical evidence

(a) Adinazolam

In a single-dose study in 16 healthy subjects, probenecid 2 g increased the psychomotor effects of sustained-release adinazolam 60 mg. The tests used were symbol-digit substitution, digit span forwards and continuous performance tasks.[1] The peak plasma levels of adinazolam and its active metabolite, *N*-desmethyladinazolam, were increased by 37% and 49%, respectively, and the clearances were reduced by 16% and 53%, respectively, by probenecid. Both drugs have uricosuric actions, but when used together the effects appear not to be additive.[1]

(b) Lorazepam

In 9 healthy subjects, probenecid 500 mg every 6 hours approximately halved the clearance of a single 2-mg intravenous dose of lorazepam. The elimination half-life was more than doubled, from 14.3 hours to 33 hours.[2]

(c) Nitrazepam

In healthy subjects, probenecid 500 mg daily for 7 days reduced the clearance of nitrazepam by 25%.[3]

(d) Temazepam

In healthy subjects, probenecid 500 mg daily for 7 days did not significantly affect the clearance of temazepam.[3]

Mechanism

Probenecid inhibits the renal tubular clearance of many drugs and their metabolites, including some of the benzodiazepines. It also inhibits the glucuronidation of nitrazepam and lorazepam by the liver.[2,3] The overall result is that these benzodiazepines accumulate and their effects are increased. Temazepam, which also undergoes glucuronidation, was not affected, possibly as increased sulfation compensated.[3]

Importance and management

Established interactions but of uncertain clinical importance. Be alert for increases in the effects (sedation, antegrade amnesia) of adinazolam, lorazepam and possibly nitrazepam. Reduce the dose as necessary. Note that adinazolam is no longer available. There seems to be no direct information about other benzodiazepines, but those that are metabolised like lorazepam or nitrazepam may possibly interact. Temazepam does not appear to interact with probenecid.

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Benzodiazepines and related drugs + Protease inhibitors

Ritonavir, nelfinavir, saquinavir and ritonavir-boosted saquinavir, lopinavir and tipranavir reduce the metabolism and/or increase the bioavailability of midazolam. Ritonavir affects triazolam and, to a lesser extent, alprazolam and zolpidem. Increased sedative effects are predicted with several different pairs of protease inhibitors and benzodiazepines.

Clinical evidence

A. Benzodiazepines

(a) Alprazolam

A crossover study in 10 healthy subjects found that **ritonavir** 200 mg for 4 doses decreased the clearance of a single 1-mg dose of alprazolam by 59% and increased its AUC approximately 2.5-fold. The half-life of alprazolam was increased from 13.3 hours to 29.6 hours and the subjects experienced increased and prolonged sedation.[1] However, in another study when **ritonavir** 500 mg was given every 12 hours for 10 days, the AUC of a single dose of alprazolam *decreased* by 12%.[2,3]

(b) Midazolam

In a study, 90 HIV-positive patients not taking antiretrovirals (control group) and 56 similar patients taking antiretrovirals were given a 75-microgram oral dose of midazolam. The ratio of 1-hydroxymidazolam to midazolam, assessed 30 minutes after the midazolam dose, was found to be 13-fold lower in 18 patients taking **nelfinavir**, when compared with the control group. Similarly, the 1-hydroxymidazolam to midazolam ratio was 50-fold lower in 4 patients taking **ritonavir**, but less reduced in other patients who were also taking efavirenz or nevirapine.[4]

A randomised study in 12 healthy subjects found that **saquinavir** (soft-gel formulation) 1.2 g three times daily increased the bioavailability of oral midazolam from 41% to 90% and increased its AUC more than fivefold. Psychomotor tests showed impaired skills and greater sedation in the presence of **saquinavir**.[5] When intravenous midazolam was given with **saquinavir**, its sedative effects were only marginally altered.[5] However, a 32-year-old man with advanced HIV, taking zidovudine, lamivudine, co-trimoxazole and **saquinavir** 600 mg three times daily, did not wake spontaneously from a 5-mg intravenous dose of midazolam. He was given 300 micrograms of intravenous flumazenil to revert the prolonged sedation, but he was not free from sedation until 5 hours later. On a previous occasion, in the absence of **saquinavir**, he woke spontaneously 2 hours after the dose of midazolam.[6] The manufacturers of saquinavir note that in 16 healthy subjects, ritonavir-boosted **saquinavir** 100/1000 mg twice daily for 2 weeks increased the maximum levels and AUC of a single 7.5-mg oral dose of midazolam 4.3-fold and 12.4-fold, respectively.[7,8]

The manufacturer of **tipranavir** notes that ritonavir-boosted **tipranavir** increased the AUCs of intravenous and oral midazolam 2.8-fold and tenfold, respectively.[9] Similarly, the manufacturer of ritonavir-boosted **lopinavir** notes that, in a study in 14 healthy subjects, ritonavir-boosted **lopinavir** raised the AUC of intravenous and oral midazolam fourfold and 13-fold, respectively.[10]

(c) Triazolam

In a crossover study in 6 healthy subjects, **ritonavir** 200 mg for 4 doses reduced the clearance of triazolam 125 micrograms to less than 4% of control values, increased its AUC about 20-fold and increased its half-life from 3 hours to 41 hours, which resulted in increased and prolonged sedation.[11] A very brief case report also describes prolonged sedation in a patient given **ritonavir** and triazolam.[12]

B. Non-benzodiazepine hypnotics

A crossover study in 6 healthy subjects found that **ritonavir** 200 mg twice daily for 4 doses resulted in a 28% increase in the AUC of a single 5-mg dose of **zolpidem**. The reduction in the clearance of **zolpidem** was considered to be clinically unimportant.[11]

Mechanism

Alprazolam, midazolam and triazolam are metabolised by the cytochrome P450 isoenzyme CYP3A4, which is inhibited, to varying degrees, by the protease inhibitors. Benzodiazepine levels and effects are therefore

increased by the protease inhibitors. However, ritonavir may also induce CYP3A and although metabolism may be inhibited following the introduction of ritonavir, it appears that for some drugs, such as alprazolam, the inhibitory effects of ritonavir on CYP3A4 may decrease over time,[2,3] possibly reflecting the effect of induction from chronic exposure overcoming the inhibition due to acute exposure.[13] One study suggested that the enzyme-inducing effects of the protease inhibitors is diminished by efavirenz and nevirapine, which are known enzyme inducers.[4]

Zolpidem metabolism depends on several isoenzymes so inhibition of CYP3A4 alone may not produce clinically significant changes in its clearance.

Interactions between the protease inhibitors and the benzodiazepines that are metabolised mainly by glucuronidation, such as **lorazepam**, **oxazepam** or **temazepam**, are less likely, and reports are lacking. However, some protease inhibitors, such as ritonavir, also induce glucuronidation, and so in theory they may also affect the metabolism of these benzodiazepines.[2,14]

Importance and management

The interaction between the protease inhibitors and **midazolam** is established and of clinical importance. The UK manufacturers of the protease inhibitors contraindicate the concurrent use of *oral* midazolam, but advise that *intravenous* midazolam may be used with close monitoring within an intensive care unit or similar setting so that the appropriate management of respiratory depression is available. They also suggest that dose reductions should be considered. The authors of the study[5] suggest that continuous intravenous midazolam doses should be reduced by 50%, but do not consider dose adjustments for single intravenous doses necessary. **Triazolam** would be expected to interact in the same way as midazolam, and therefore the UK manufacturers generally contraindicate its use. The US manufacturers similarly contraindicate the concurrent use of midazolam and triazolam with protease inhibitors; however, they do not always differentiate between oral or intravenous midazolam. **Alprazolam** is contraindicated by the UK and US manufacturers of indinavir,[15,16] but cautioned by the manufacturers of saquinavir.[7,8] The manufacturer of ritonavir also suggests caution during the first several days when alprazolam is given with ritonavir, before induction of alprazolam metabolism develops.[2] Careful monitoring and dose adjustment will be required. It would seem prudent to apply some caution on the concurrent use of any protease inhibitor, as alprazolam is, in part, metabolised by the same route as midazolam.

Recommendations regarding other benzodiazepines vary slightly. **Clorazepate**, **diazepam**, **estazolam**, and **flurazepam** are contraindicated by the UK manufacturer of ritonavir[2] and indinavir,[15] but cautioned by the US manufacturer of ritonavir.[3] The US manufacturer of fosamprenavir and the UK and US manufacturers of saquinavir also suggest the possibility of an interaction with clorazepate, diazepam and flurazepam, and suggest that careful monitoring is needed, with dose adjustments as required.[7,8,17]

The manufacturers of ritonavir note that **zolpidem** may be given concurrently with careful monitoring for excessive sedative effects[2] and consideration of reducing the dose of zolpidem.[3] Similarly, the manufacturer of **zopiclone** warns that, as zopiclone is metabolised by CYP3A4, plasma levels of zopiclone may be increased when it is given with CYP3A4 inhibitors such as ritonavir, and a dose reduction of zopiclone may be required.[18]

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Benzodiazepines + Proton pump inhibitors

Gait disturbances (attributed to benzodiazepine toxicity) occurred in two patients given triazolam and lorazepam or flurazepam with omeprazole, and another patient taking diazepam and omeprazole became wobbly and sedated. Lansoprazole, pantoprazole, or rabeprazole appear not to interact to a clinically relevant extent with diazepam. Diazepam plasma levels are increased by esomeprazole.

Clinical evidence

(a) Esomeprazole

In a placebo-controlled study 10 healthy subjects took esomeprazole 30 mg daily for 9 days, with a single 100-microgram/kg intravenous infusion of **diazepam** on day 5. The AUC of **diazepam** was increased by 81%, its clearance was decreased by 45%, and the half-life was extended from 43 hours to 86 hours. However, increased plasma levels of **diazepam** were only observed 12 hours or more after dosing, at which point they were subtherapeutic, and thus the interaction was thought unlikely to be of clinical relevance. **Diazepam** did not appear to change the pharmacokinetics of esomeprazole.[1]

(b) Lansoprazole

Lansoprazole 60 mg daily for 10 days was found to have no effect on the pharmacokinetics of a single 100-microgram/kg intravenous dose of **diazepam**.[2]

(c) Omeprazole

Two elderly patients, both smokers, taking **triazolam** with **lorazepam**, or **flurazepam**, developed gait disturbances when they were given omeprazole 20 mg daily. They rapidly recovered when either the benzodiazepines or the omeprazole were stopped.[3] A brief report describes a patient taking omeprazole who became wobbly and sedated by small, unspecified doses of **diazepam**,[4] and another report describes a patient who developed toxic levels of nordiazepam and remained unconscious for 13 days after receiving a high dose of **clorazepate** (1.5 g over about 29 hours) and omeprazole 80 mg daily.[5]

One study in 8 healthy subjects found that omeprazole 40 mg daily for one week reduced the clearance of a single 100-microgram/kg intravenous dose of **diazepam** by 54%,[6] while another study found that omeprazole 20 mg reduced **diazepam** clearance by 27%.[7]

A further study found that omeprazole 40 mg reduced the oral clearance of **diazepam** by 38% in white American subjects but only by 21% in Chinese subjects.[8] Metaboliser status (see 'Genetic factors', (p.4)) was also found to be important in other studies of this interaction: only extensive metabolisers of CYP2C19 showed a significant decrease in **diazepam** clearance when given omeprazole.[9,10]

(d) Pantoprazole

In a placebo-controlled study in 12 healthy subjects, intravenous pantoprazole 240 mg for 7 days did not change the half-life, clearance and AUC of a 100-microgram/kg intravenous bolus dose of **diazepam**.[11]

(e) Rabeprazole

In a crossover study, rabeprazole 20 mg daily or placebo was given to 20 subjects for 35 days with a single 100-microgram/kg intravenous dose of **diazepam** on day 8. The subjects were also assessed for mephenytoin hydroxylator status [a measure of CYP2C19 activity, see 'Genetic factors', (p.4)] and 2 subjects were found to be poor metabolisers. No signif-

icant changes in the pharmacokinetics of the **diazepam** were seen with rabeprazole, either when analyses were conducted including all the subjects or when excluding the poor metabolisers.[12] Another study similarly found that rabeprazole does not affect the pharmacokinetics of **diazepam** in both poor and extensive metabolisers of CYP2C19.[9]

Mechanism

In vitro studies with human liver microsomes suggest that omeprazole inhibits diazepam metabolism because it inhibits the cytochrome P450 isoenzymes CYP3A and CYP2C19.[13] Studies in humans suggest that CYP2C19 may be the most important isoenzyme in this interaction.[8] Esomeprazole also inhibits CYP2C19.[1]

Omeprazole is not expected to interact with benzodiazepines that are mainly metabolised by glucuronide conjugation such as lorazepam.[3] The reaction involving lorazepam[3] may possibly not be an interaction (so it is suggested) but an adverse effect of giving sedating medications to markedly anaemic patients.[4]

Importance and management

Information is limited, but what is currently known suggests that patients given omeprazole, and possibly esomeprazole, with diazepam may experience increased benzodiazepine effects (sedation, unstable gait etc.). If this occurs the benzodiazepine dose should be reduced. Lansoprazole, pantoprazole and rabeprazole do not appear to interact with diazepam. There seems to be no information regarding other benzodiazepines.

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Benzodiazepines + Quinolones

Ciprofloxacin causes a marked reduction in the clearance of diazepam, but this does not appear to be clinically important in healthy subjects. Ciprofloxacin appears not to affect the pharmacokinetics of temazepam, and gatifloxacin appears not to interact with midazolam. Patients who are dependent on or withdrawing from long-term benzodiazepine use may possibly be more susceptible to CNS adverse effects of quinolones.

Clinical evidence and mechanism

(a) Ciprofloxacin

In a study in 10 healthy subjects, ciprofloxacin 500 mg twice daily for 3 days was found to have no effect on the pharmacokinetics of **diazepam**.[1] However, a later study in 12 healthy subjects found that ciprofloxacin 500 mg twice daily for 5 days increased the AUC of a single 5-mg intravenous dose of **diazepam** by 50%, reduced its clearance by 37% and doubled its half-life. These changes caused no significant alteration in the performance of a number of psychometric tests. It was suggested that the clearance of **diazepam** was reduced because ciprofloxacin inhibited the cytochrome P450-mediated metabolism of **diazepam**.[2] Another study by the same group found that ciprofloxacin 500 mg twice daily for 4 days does not interact with a single 10-mg oral dose of **temazepam**.[3]

(b) Gatifloxacin

In 14 healthy subjects gatifloxacin 400 mg daily for 5 days had no effect on the pharmacokinetics of **midazolam**. The pharmacokinetics of gatifloxacin were also unaffected by concurrent use.[4]

(c) Norfloxacin

A 44-year-old woman, who had undergone withdrawal from high doses of benzodiazepines 3 months previously, experienced an acute psychotic reaction within one hour of starting norfloxacin, and attempted suicide. Her condition quickly deteriorated and she developed repeated seizures progressing to status epilepticus. Her seizures were only controlled after norfloxacin was stopped.[5] Note that quinolones alone are known to cause psychiatric reactions and trigger seizures or lower the seizure threshold.

(d) Unnamed quinolones

Results from a survey of patients dependent on and withdrawing from benzodiazepines suggested an abnormally high incidence of adverse reactions to fluoroquinolones. Eleven participants reported severe or very severe adverse reactions, one participant reported a moderate adverse reaction and a further participant reported no reaction to fluoroquinolone treatment. All participants reported adverse effects similar to those of acute benzodiazepine withdrawal, which included depression, anxiety, psychosis, paranoia, severe insomnia, paraesthesia, tinnitus, hypersensitivity to light and sound, and tremors; four patients became acutely suicidal.[5] See also *Norfloxacin*, above

Importance and management

Ciprofloxacin may cause a reduction in the clearance of diazepam, but it seems unlikely that any marked increases in diazepam effects (drowsiness etc.) will occur in most patients. However, it may possibly be significant in those who have reduced renal or hepatic clearance (e.g. the elderly).[2] This needs confirmation.

Patients who are dependent on or withdrawing from chronic benzodiazepines may be more susceptible to adverse reactions to fluoroquinolones.[5]

1. Wijnands WJA, Trooster JFG, Teunissen PC, Cats HA, Vree TB. Ciprofloxacin does not impair the elimination of diazepam in humans. *Drug Metab Dispos* (1990) 18, 954–7.
2. Kamali F, Thomas SHL, Edwards C. The influence of steady-state ciprofloxacin on the pharmacokinetics and pharmacodynamics of a single dose of diazepam in healthy volunteers. *Eur J Clin Pharmacol* (1993) 44, 365–7.
3. Kamali F, Herd B, Edwards C, Nicholson E, Wynne H. The influence of ciprofloxacin on the pharmacokinetics and pharmacodynamics of a single dose of temazepam in the young and elderly. *J Clin Pharm Ther* (1994) 19, 105–9.
4. Grasela DM, LaCreta FP, Kollia GD, Randall DM, Uderman HD. Open-label, nonrandomized study of the effects of gatifloxacin on the pharmacokinetics of midazolam in healthy male volunteers. *Pharmacotherapy* (2000) 20, 330–5.
5. McConnell JG. Benzodiazepine tolerance, dependency, and withdrawal syndromes and interactions with fluoroquinolone antimicrobials. Br J Gen Pract (2008) 58, 365–6.

Benzodiazepines + Ramelteon

A study in 28 healthy subjects found that ramelteon 32 mg daily for 9 days had no effect on the pharmacokinetics of a single 10-mg oral dose of midazolam. No midazolam dose adjustments are therefore expected to be necessary on concurrent use.[1]

1. Karim A, Tolbert D, Cao C, Zhao Z, Sainati SM. The effect of multiple doses of ramelteon (TAK-375) on the single-dose pharmacokinetic profile of midazolam in healthy adult subjects. *Sleep* (2004) 27 (Abstract Suppl), A47.

Benzodiazepines + Reboxetine

There is no pharmacokinetic interaction between lorazepam and reboxetine, and reboxetine does not alter the pharmacokinetics of alprazolam.

Clinical evidence

(a) Alprazolam

In a study in 12 healthy subjects, reboxetine 4 mg twice daily had no effect on the clearance of a single 1-mg dose of alprazolam given on day 12. This study was summarised in a review paper.[1]

(b) Lorazepam

In a study in 6 healthy subjects, the AUC of lorazepam did not differ when a single 2.5-mg dose of lorazepam was given alone or with reboxetine 2 mg twice daily. There was a less than 10% change in the lorazepam maximum level and half-life.[2] In a further study in 6 healthy subjects, the pharmacokinetics of a single 4-mg dose of reboxetine were not altered by lorazepam 1 mg twice daily for 7 days.[3]

Mechanism

These studies suggest that reboxetine does not alter the glucuronidation of lorazepam or the metabolism of alprazolam by the cytochrome P450 isoenzyme CYP3A4.

Importance and management

These studies show that no pharmacokinetic interactions are anticipated between lorazepam or alprazolam and reboxetine. Nevertheless, the manufacturer notes that during the concurrent use of reboxetine and lorazepam, mild to moderate drowsiness and an orthostatic increase in heart rate was observed in healthy subjects,[4] but they do not say how frequently these occurred with either drug alone, and, specifically, whether the effects were actually increased on combined use.

1. Fleishaker JC. Clinical pharmacokinetics of reboxetine, a selective norepinephrine reuptake inhibitor for the treatment of patients with depression. *Clin Pharmacokinet* (2000) 39, 413–27.
2. Januzzo MG, Bosc M, Renoux A, Dostert P, Strolin Benedetti M. Effect of reboxetine on the pharmacokinetics of lorazepam in healthy volunteers. *Eur Neuropsychopharmacol* (1995) 5, 300–301.
3. Fiorentini F, Poggesi I, Januzzo MG, Seiberling M, Dostert P, Strolin Benedetti M. Effect of lorazepam on the pharmacokinetics of reboxetine in healthy volunteers. *Eur Neuropsychopharmacol* (1995) 5, 300.
4. Edronax (Reboxetine). Pharmacia Ltd. UK Summary of product characteristics, July 2008.

Benzodiazepines and related drugs + Rifampicin (Rifampin)

Rifampicin causes a very marked increase in the metabolism and/or clearance of diazepam, lorazepam, midazolam, nitrazepam, triazolam, zaleplon, zolpidem and zopiclone. Benzodiazepines and related drugs that are metabolised similarly are expected to interact in the same way. Temazepam pharmacokinetics are unchanged by rifampicin.

Clinical evidence

A. Benzodiazepines

(a) Diazepam

In 7 patients with tuberculosis who were given daily doses of isoniazid 500 mg to 2.2 g, rifampicin 450 to 600 mg and ethambutol 25 mg/kg, the mean half-life of diazepam was reduced from 58 hours to 14 hours and the clearance was increased fourfold, when compared with healthy control subjects.[1] In 21 healthy subjects rifampicin 600 mg or 1.2 g daily for 7 days increased the clearance of diazepam by about fourfold.[2]

(b) Lorazepam

In a study in healthy subjects, rifampicin increased the mean systemic clearance of intravenous lorazepam by approximately 140%, but interindividual variability occurred and clearance values were also affected by genetic variations in uridine diphosphate glucuronosyltransferase (UGT).[3]

(c) Midazolam

A pharmacokinetic study in 10 healthy subjects found that rifampicin 600 mg daily for 5 days reduced the AUC of a single 15-mg oral dose of midazolam by 96%, and reduced its half-life by almost two-thirds. The psychomotor effects of the midazolam (as measured by the digit symbol substitution test, Maddox wing test, postural sway and drowsiness) were almost totally lost.[4] The manufacturers note that rifampicin 600 mg daily for 7 days decreased the plasma concentrations of intravenous midazolam by about 60% and decreased its half-life by about 50 to 60%.[5]

(d) Nitrazepam

A study in healthy subjects found that rifampicin 600 mg daily for 7 days increased the total body clearance of nitrazepam by 83%.[6]

(e) Temazepam

A study found that the pharmacokinetics of temazepam were unchanged by rifampicin.[6]

(f) Triazolam

In a placebo-controlled study, 10 healthy subjects were given oral triazolam 500 micrograms before and after rifampicin 600 mg daily for 5 days. Rifampicin reduced the triazolam AUC by 95% and decreased its maximum plasma levels by 88%, when compared with placebo. The elimination half-life was reduced from 2.8 hours to 1.3 hours. Pharmacodynamic tests (drowsiness, sway, Maddox wing, etc.) showed that rifampicin abolished the effects of triazolam.[7]

B. Non-benzodiazepine hypnotics

(a) Zaleplon

A non-randomised, crossover study in healthy subjects found that rifampicin 600 mg daily for 14 days increased the clearance of a 10-mg dose of zaleplon 5.4-fold, decreasing its maximum plasma levels and AUC by 80%.[8]

(b) Zolpidem

In a randomised, placebo-controlled study, 8 healthy subjects were given rifampicin 600 mg daily for 5 days with a single 20-mg oral dose of zolpidem on day 6. It was found that the rifampicin reduced the zolpidem AUC by 73%, reduced its maximum plasma level by about 60% and reduced its half-life from 2.5 hours to 1.6 hours. A significant reduction in the effects of zolpidem was also seen, as measured by a number of psychomotor tests (digital symbol substitution, critical flicker fusion, subjective drowsiness, etc.).[9]

(c) Zopiclone

In a placebo-controlled study, 8 healthy subjects were given rifampicin 600 mg for 5 days, with a single 10-mg oral dose of zopiclone on day 6. The rifampicin reduced the AUC of zopiclone by 81%, decreased its peak plasma levels by 71% and reduced its half-life from 3.8 hours to 2.3 hours. A significant reduction in the effects of zopiclone was also seen, as measured by the performance of psychomotor tests.[10]

Mechanism

Rifampicin is a potent liver enzyme inducer, which increases the metabolism of several benzodiazepines and the non-benzodiazepine hypnotics, zaleplon, zolpidem and zopiclone, thereby decreasing their levels. The metabolism of midazolam by the cytochrome P450 isoenzyme CYP3A4 in both liver and gut is affected.[4] The enzyme-inducing effects of rifampicin seem to predominate if isoniazid (an enzyme inhibitor) is also present. Temazepam undergoes glucuronidation and seems to be unaffected by rifampicin. However, lorazepam glucuronidation appears to be induced by rifampicin, although lorazepam pharmacokinetics may also be influenced by drug transporter activity.[3]

Importance and management

The documentation of these interactions is limited but what has been reported is consistent with the way rifampicin interacts with many other drugs. The clinical importance of some of these interactions between the benzodiazepines and related drugs and rifampicin has not yet been assessed, but what is known suggests that the dose of diazepam and nitrazepam may need to be increased if rifampicin is given. Be alert for a reduction in the effects of other similarly metabolised benzodiazepines (e.g. **chlordiazepoxide**, **flurazepam**).

The effect of rifampicin on oral midazolam and triazolam is so large that they are likely to become ineffective and an alternative should be used instead. **Alprazolam** is also predicted to interact because CYP3A is involved with its metabolism.[11] The plasma levels and/or the pharmacodynamic effects of the non-benzodiazepine hypnotics, zaleplon, zolpidem and zopiclone, are also substantially reduced and a dose increase may be required.

Those benzodiazepines that, like temazepam, undergo glucuronidation (e.g. lorazepam, **oxazepam**) are not expected to be affected by rifampicin to such an extent as those metabolised primarily by hepatic microsomal oxidation, and may be useful alternatives; however, note that lorazepam has been seen to interact and so, until more is known, some caution may be warranted.

1. Ochs HR, Greenblatt DJ, Roberts G-M, Dengler HJ. Diazepam interaction with antituberculosis drugs. *Clin Pharmacol Ther* (1981) 29, 671–8.

2. Ohnhaus EE, Brockmeyer N, Dylewicz P, Habicht H. The effect of antipyrine and rifampin on the metabolism of diazepam. *Clin Pharmacol Ther* (1987) 42, 148–56.
3. Chung J-Y, Cho J-Y, Yu K-S, Kim J-R, Jung H-R, Lim K-S, Jang I-J, Shin S-G. Effect of the *UGT2B15* genotype on the pharmacokinetics, pharmacodynamics, and drug interactions of intravenous lorazepam in healthy volunteers. *Clin Pharmacol Ther* (2005) 77, 486–94.
4. Backman JT, Olkkola KT, Neuvonen PJ. Rifampin drastically reduces plasma concentrations and effects of oral midazolam. *Clin Pharmacol Ther* (1996) 59, 7–13.
5. Hypnovel (Midazolam hydrochloride). Roche Products Ltd. UK Summary of product characteristics, February 2008.
6. Brockmeyer NH, Mertins L, Klimek K, Goos M, Ohnhaus EE. Comparative effects of rifampin and/or probenecid on the pharmacokinetics of temazepam and nitrazepam. *Int J Clin Pharmacol Ther Toxicol* (1990) 28, 387–93.
7. Villikka K, Kivistö KT, Backman JT, Olkkola KT, Neuvonen PJ. Triazolam is ineffective in patients taking rifampin. *Clin Pharmacol Ther* (1997) 61, 8–14.
8. Darwish M. Overview of drug interaction studies with zaleplon. Poster presented at 13th Annual Meeting of Associated Professional Sleep Studies (APSS), Orlando, Florida, June 23rd, 1999.
9. Villikka K, Kivistö KT, Luurila H, Neuvonen PJ. Rifampicin reduces plasma concentrations and effects of zolpidem. *Clin Pharmacol Ther* (1997) 62, 629–34.
10. Villikka K, Kivistö KT, Lamberg TS, Kantola T, Neuvonen PJ. Concentrations and effects of zopiclone are greatly reduced by rifampicin. *Br J Clin Pharmacol* (1997) 43, 471–4.
11. Greenblatt DJ, von Moltke LL, Harmatz JS, Ciraulo DA, Shader RI. Alprazolam pharmacokinetics, metabolism, and plasma levels: clinical implications. *J Clin Psychiatry* (1993) 54, 10 (Suppl), 4–11.

Benzodiazepines + Rifaximin

In a study in healthy subjects, rifaximin 200 mg three times daily did not affect the pharmacokinetics of single oral or intravenous doses of midazolam.[1] Therefore, rifaximin does not appear to affect intestinal or hepatic CYP3A4 activity, and would therefore not be expected to affect the pharmacokinetics of other benzodiazepines metabolised in this way (e.g. alprazolam, triazolam). No dose adjustments of these benzodiazepines would therefore be necessary if rifaximin is also given.

1. Pentikis HS, Connolly M, Trapnell CB, Forbes WP, Bettenhausen DK. The effect of multiple-dose, oral rifaximin on the pharmacokinetics of intravenous and oral midazolam in healthy volunteers. *Pharmacotherapy* (2007) 27, 1361–9.

Benzodiazepines + Roflumilast

Roflumilast did not affect the pharmacokinetics of midazolam in one study.

Clinical evidence, mechanism, importance and management

In a study, 18 healthy subjects were given a single 2-mg oral dose of midazolam, and a single 1-mg intravenous dose of midazolam before and after taking roflumilast 500 micrograms daily for 14 days. Roflumilast did not affect the pharmacokinetics of midazolam.[1] Midazolam is used as a probe drug for the activity of the cytochrome P450 isoenzyme CYP3A4. These findings therefore suggest that roflumilast will not affect the metabolism of other benzodiazepines metabolised by this route (e.g. alprazolam and triazolam). No dose adjustments would therefore appear necessary if roflumilast is given with any of these benzodiazepines.

1. Nassr N, Lahu G, von Richter O, Reutter F, Knoerzer D, Zech K, Erb KA, Schug B, Blume H, Hermann R. Lack of a pharmacokinetic interaction between steady-state roflumilast and single-dose midazolam in healthy subjects. *Br J Clin Pharmacol* (2007) 63, 365–70.

Benzodiazepines and related drugs + SNRIs

Visual hallucinations have been seen in one patient given zolpidem and venlafaxine. No important interaction normally appears to occur between venlafaxine and alprazolam, diazepam or zaleplon. The pharmacokinetics of duloxetine are not affected by lorazepam or temazepam. However, there is limited evidence to suggest that sedation might initially be increased by the concurrent use of duloxetine and lorazepam.

Clinical evidence

(a) Duloxetine

In a placebo-controlled study, the pharmacokinetics of duloxetine 60 mg twice daily and **lorazepam** 2 mg twice daily were not affected by concurrent use. However, compared with **lorazepam** alone, the addition of duloxetine led to decreased vigilance on various psychomotor tests (such as digit symbol substitution test) during the first day of concurrent use, although this effect tended to lessen over the 4 days of the study.[1] The steady-state pharmacokinetics of duloxetine 20 mg at bedtime were not affected by **temazepam** 30 mg at bedtime.[2]

(b) Venlafaxine

A 27-year-old woman who had been taking venlafaxine 37.5 mg at night for a week and terfenadine for a few years started taking **zolpidem** 10 mg daily. After 2 days, and within 45 minutes of the **zolpidem** dose, she developed visual hallucinations, which lasted for 2 to 4 hours. A similar episode occurred 2 weeks later when she had discontinued the terfenadine.[3]

A study in 16 healthy subjects found that venlafaxine 75 mg twice daily reduced the AUC of a single 2-mg oral dose of **alprazolam** by 29% and reduced its half-life by 21%, and the performance of psychometric tests were only minimally changed.[4] A double-blind study in 18 healthy subjects taking venlafaxine 50 mg every 8 hours found that the concurrent use of **diazepam** 10 mg did not have a clinically significant effect on the pharmacokinetics of either drug, or their major active metabolites (*O*-desmethylvenlafaxine and desmethyldiazepam). **Diazepam** affected the performance of a series of pharmacodynamic tests, but the addition of venlafaxine had no further effects.[5]

The manufacturers of **zaleplon** describe a study in which a single dose of **zaleplon** 10 mg and extended-release venlafaxine 150 mg did not result in any significant changes in the pharmacokinetics of either **zaleplon** or venlafaxine.[6,7] Additionally, there was no pharmacodynamic interaction[7] with tests for memory and psychomotor performance being unaffected.[6]

Mechanism

Uncertain. Zolpidem alone is associated with hallucinations, and it has been suggested that a pharmacodynamic interaction between serotonin reuptake inhibition and zolpidem may lead to a prolongation of this effect in susceptible individuals.[3]

Importance and management

The studies suggest that no special precautions are necessary during the concurrent use of venlafaxine and alprazolam or diazepam, or between duloxetine and lorazepam or temazepam. However, a pharmacodynamic interaction may possibly occur and caution has been advised due to the potential for increased sedation.[1] Hallucinations have been seen with zolpidem alone, and they have also occurred, rarely, when zolpidem was given with some 'SSRIs', (below), which are related to venlafaxine. Reports of adverse effects such as these seem rare and the concurrent use of these drugs need not be avoided, but bear these possible interactions in mind if hallucinations or increased sedation occur.

1. Chalon S, Vandenhende F, Ertle S. Combined administration of duloxetine (DU) and lorazepam (LO): a pharmacokinetic and pharmacodynamic study. *Clin Pharmacol Ther* (2005) 77, P65.
2. Cymbalta (Duloxetine hydrochloride). Eli Lilly and Company. US Prescribing information, February 2009.
3. Elko CJ, Burgess JL, Robertson WO. Zolpidem-associated hallucinations and serotonin reuptake inhibition: a possible interaction. *Clin Toxicol* (1998), 36, 195–203.
4. Amchin J, Zarycranski W, Taylor KP, Albano D, Klockowski PM. Effect of venlafaxine on the pharmacokinetics of alprazolam. *Psychopharmacol Bull* (1998) 34, 211–19.
5. Troy SM, Lucki I, Peirgies AA, Parker VD, Klockowski PM, Chiang ST. Pharmacokinetic and pharmacodynamic evaluation of the potential drug interaction between venlafaxine and diazepam. *J Clin Pharmacol* (1995) 35, 410–19.
6. Sonata (Zaleplon). Meda Pharmaceuticals. UK Summary of product characteristics, March 2004.
7. Sonata (Zaleplon). King Pharmaceuticals, Inc. US Prescribing information, December 2007.

Benzodiazepines and related drugs + SSRIs

The metabolism of some benzodiazepines such as alprazolam, bromazepam and diazepam (and also possibly midazolam and triazolam) may be reduced by fluvoxamine. There is some evidence to suggest that fluoxetine may have some effect on the pharmacokinetics and psychomotor impairment caused by alprazolam and diazepam. On the whole, no clinically significant interaction appears to occur between other SSRIs and the benzodiazepines or related drugs such as cloral hydrate or zaleplon. However, there is limited evidence to support the suggestion that sedation may be increased by the concurrent use of SSRIs and benzodiazepines. Rare cases of hallucinations have been seen with zolpidem and some SSRIs. Symptoms of the serotonin syndrome have been reported in two patients taking paroxetine and benzodiazepines.

Clinical evidence

(a) Citalopram

1. Alprazolam. A general study in psychiatric patients found that when data on benzodiazepines was pooled, they caused a modest 23% increase in serum citalopram levels, which is almost certainly too small to be clinically relevant. Alprazolam was the only benzodiazepine to cause an elevation of citalopram levels (by 13%) when analysed alone.[1] In another study, citalopram was found to have no effect on alprazolam plasma levels, although the time to peak alprazolam levels was increased by 30 minutes.[2]

2. Triazolam. A study in 17 healthy subjects found no pharmacokinetic interaction between triazolam and citalopram.[3]

(b) Fluoxetine

1. Alprazolam. The concurrent use of fluoxetine 60 mg daily has been found to reduce the clearance of alprazolam 1 mg four times daily by about 21% and to increase its plasma levels by about 30%. These changes were accompanied by increased psychomotor impairment.[4] Another study also reported impaired alprazolam metabolism, although no significant changes in alprazolam pharmacodynamics were found.[2]

2. Diazepam. Fluoxetine 30 mg, given either as s single dose, or daily for 8 days, had no effect on the pharmacokinetics of diazepam 10 mg.[5] A later study by the same group, using 60 mg of fluoxetine suggested that the diazepam half-life and AUC were increased, possibly because the fluoxetine decreased the metabolism of diazepam. However, they concluded that this was not of any clinical significance.[6] Another study found that fluoxetine 60 mg alone did not affect psychomotor performance but fluoxetine 60 mg plus diazepam 5 mg significantly impaired the divided attention tracking test and vigilance test more than with diazepam 5 mg alone.[7]

3. Other benzodiazepines and related drugs. Other studies found that the pharmacokinetics of **clonazepam**,[8] **estazolam**,[9] **midazolam**,[10,11] **triazolam**,[12] and **zolpidem**[13,14] were not significantly affected by fluoxetine. Isolated cases of visual hallucinations lasting up to 7 hours have been reported in patients taking **zolpidem** who were also taking fluoxetine.[15] Marked drowsiness occurred for a whole day in a patient taking fluoxetine 20 mg daily after being given **cloral hydrate** 500 mg the night before. She later tolerated **cloral hydrate** 1 g in the absence of fluoxetine without adverse effects.[16]

(c) Fluvoxamine

1. Alprazolam. In 60 healthy subjects, fluvoxamine 50 mg daily for 3 days then 100 mg daily for 7 days, doubled the plasma levels of alprazolam 1 mg four times daily given on days 7 to 10. The alprazolam clearance was more than halved. Psychomotor performance and memory were found to be significantly worsened, even after only one day.[17] A study in 23 Japanese patients found that fluvoxamine increased the plasma levels of alprazolam by 58%. There was wide interpatient variability, possibly associated with differences in the cytochrome P450 isoenzyme CYP2C19 levels in these patients although it is unclear exactly what impact this isoenzyme has on the interaction.[18]

2. Bromazepam. In 12 healthy subjects, fluvoxamine 50 mg twice daily increased the plasma levels of a single 12-mg dose of bromazepam by 36% and increased the AUC almost 2.5-fold. Some increased impairment in cognitive function was seen.[19]

3. Cloral hydrate. Fluvoxamine has been found not to interact adversely with cloral hydrate.[20]

4. Diazepam. In 8 healthy subjects, fluvoxamine (50 mg on day one, 100 mg on day 2, then 150 mg daily thereafter) for 16 days decreased the clearance of a single 10-mg dose of diazepam given on day 4 by about 65%. The half-life was increased from 51 hours to 118 hours, and the AUC was increased threefold.[21]

5. Lorazepam. In 12 healthy subjects, fluvoxamine 50 mg twice daily caused a very small, non-significant, increase in the plasma levels and AUC of a single 4-mg dose of lorazepam.[19]

6. Midazolam. A study in 10 healthy subjects[11] found that fluvoxamine 50 mg twice daily for 8 days then 100 mg twice daily for 6 days had minimal effects on the pharmacokinetics of a single 10-mg dose of midazolam given on day 12.

7. Quazepam. A placebo-controlled study in 12 healthy subjects found that fluvoxamine 25 mg twice daily for 14 days had no effect on the pharmacokinetics of a single 20-mg dose of quazepam. However, formation of the metabolite, 2-oxoquazepam, was decreased, and there was a minor decrease in the sedative effects of quazepam at 4 hours, although these changes were considered to be of little clinical significance.[22]

(d) Paroxetine

1. Alprazolam. A randomised, placebo-controlled study in 22 healthy subjects reported no evidence for a pharmacokinetic or pharmacological interaction between paroxetine and alprazolam.[23]

2. Clonazepam. An isolated report describes worsening anxiety, agitation, mild abdominal cramps and diaphoresis in a woman taking paroxetine, shortly after starting clonazepam (dose stated as one tablet). This toxic response was suggested as being serotonin syndrome, although in fact many of the usual signs were absent and moreover, clonazepam has actually been used to treat the myoclonus that occurs in serotonin syndrome. The patient was effectively treated with **lorazepam**.[24]

3. Diazepam. No important changes in the pharmacokinetics of paroxetine were seen when 12 healthy subjects given paroxetine 30 mg daily were also given diazepam 5 mg three times a day. Adverse events were not increased by the combination.[25]

4. Etizolam. Another report describes a patient who was admitted to hospital with symptoms of serotonin syndrome within 6 days of starting daily treatment with paroxetine 20 mg, etizolam 1 mg and **brotizolam** 250 micrograms. Paroxetine was discontinued on day 6. Serotonin syndrome usually resolves within 24 hours of discontinuing the causative medication but symptoms in this patient continued for a total of 10 days.[26]

5. Oxazepam. One study found that paroxetine did not increase the impairment of a number of psychomotor tests caused by oxazepam.[27]

6. Zaleplon. In a double-blind study in healthy subjects it was found that paroxetine 20 mg for 9 days had no effect on the pharmacokinetics of zaleplon 20 mg, and psychomotor performance was unaffected by concurrent use.[28]

7. Zolpidem. An isolated report describes a healthy 16-year-old girl with depression who took paroxetine 20 mg daily for 3 days, and then on the evening of the third night a single 10-mg dose of zolpidem. Within one hour she began to hallucinate, then became disorientated and was unable to recognise members of her family. She recovered spontaneously within 4 hours.[29]

(e) Sertraline

1. Alprazolam. A pharmacokinetic study in 10 healthy subjects found that sertraline 50 to 150 mg daily had no effect on the pharmacokinetics of alprazolam 1 mg and did not potentiate the psychomotor impairment produced by alprazolam alone, although there was a decrease in peak performance in the manual tracking test.[30] Similarly, in 12 healthy subjects, sertraline 50 mg daily had no effect on the pharmacokinetics of alprazolam 1 mg daily after 2 weeks of concurrent use.[31]

2. Clonazepam. A study in 13 subjects given clonazepam 1 mg daily with sertraline 100 mg daily for 10 days found that sertraline did not significantly affect the pharmacokinetics of clonazepam. There was also no evidence that the addition of sertraline to clonazepam made the subjects more sedated or less able to carry out simple psychometric tests.[32]

3. Diazepam. In a placebo-controlled study, the systemic clearance of a single intravenous dose of diazepam was reduced by 13% after 21 days of sertraline treatment. This small effect was thought unlikely to be of clinical significance, although the effect of sertraline on repeated oral doses of diazepam was not studied.[33,34]

4. Zolpidem. Sertraline appears to have no clinically significant effects on the pharmacokinetics of zolpidem,[35] but isolated cases of visual hallucinations lasting up to 7 hours have been reported in patients taking zolpidem and sertraline.[15]

Mechanism

The evidence suggests that fluvoxamine inhibits the metabolism of benzodiazepines that undergo oxidation (e.g. alprazolam, bromazepam, diazepam) thereby increasing and prolonging their effects, but not those that are metabolised by glucuronidation (e.g. lorazepam). Fluoxetine is a weak inhibitor of CYP3A4, and it appears to inhibit the metabolism of alprazolam by this route.[2]

Importance and management

A well studied interaction, although the evidence regarding individual pairs of benzodiazepines and SSRIs is generally limited. The available data suggests that the doses of alprazolam, bromazepam and diazepam should be reduced, probably by half, in the presence of fluvoxamine to avoid adverse effects (drowsiness, reduced psychomotor performance and memory). Furthermore, some US manufacturers recommend avoiding the use of fluvoxamine with diazepam as substantial diazepam accumulation could occur. They also note that fluvoxamine has non-linear kinetics, and therefore the effects of higher doses of fluvoxamine such as 300 mg daily could be even more pronounced, particularly with long-term diazepam use.[36] Some manufacturers warn that the clearance of other oxidatively metabolised benzodiazepines (e.g. midazolam and **triazolam**) is likely to be decreased by fluvoxamine[36,37] and the dose of these benzodiazepines may need to be reduced;[37] however, one study with midazolam and fluvoxamine found only a minimal interaction. Fluvoxamine is unlikely to affect lorazepam and other benzodiazepines metabolised by glucuronidation (e.g. oxazepam, **temazepam**).[36]

Fluoxetine also appears to have some effect on the pharmacokinetics and pharmacodynamics of alprazolam and diazepam and so some caution would be prudent.

It seems unlikely that citalopram, paroxetine or sertraline will affect the pharmacokinetics of the benzodiazepines and they may therefore be a useful alternative to fluvoxamine. However, it should be noted that some of the studies found pharmacodynamic effects (that is, increased sedation or clumsiness) in the absence of a pharmacokinetic interaction. Patients should be advised to be alert for the possibility of these effects when first starting treatment.

The hallucinations seen with the SSRIs and zolpidem appear rare, and reactions of this kind have been seen with zolpidem alone. The concurrent use of these drugs need not be avoided, but bear this possible interaction in mind if hallucinations occur.

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Benzodiazepines and related drugs + St John's wort (*Hypericum perforatum*)

Long-term use of St John's wort decreases the plasma levels of alprazolam, midazolam and quazepam. Zopiclone is predicted to be similarly affected. St John's wort preparations taken as a single dose, or containing low-hyperforin levels, appear to have less of an effect.

Clinical evidence, mechanism, importance and management

(a) Alprazolam

In a study in 12 healthy subjects, St John's wort (*LI 160, Lichtwer Pharma*, 0.12 to 0.3% hypericin) 300 mg three times daily for 16 days with a single 2-mg dose of alprazolam on day 14. The AUC of alprazolam was halved by St John's wort and the clearance was increased by about twofold.[1]

In another study, alprazolam 1 or 2 mg was given to 7 healthy subjects on the third day of a 3-day treatment period with St John's wort (*Solaray*; hypericin content standardised at 0.3%) 300 mg three times daily. The pharmacokinetics of alprazolam were unchanged by St John's wort, but the authors note that 3 days may have been an insufficient time for St John's wort to fully induce cytochrome P450 isoenzymes.[2] In another study, 16 healthy subjects were given St John's wort extract 120 mg (*Esbericum* capsules; corresponding to 0.5 mg total hypericins and 1.76 mg hyperforin) twice daily for 10 days. A single 1-mg dose of alprazolam was given on the day before treatment with St John's wort and on the last day of treatment. St John's wort extract at this low dosage and low hyperforin content had no clinically relevant effects on the pharmacokinetics of alprazolam, when compared with 12 subjects given placebo.[3]

(b) Midazolam

An open-label study in 12 healthy subjects found that a single 900-mg dose of St John's wort had no significant effect on the pharmacokinetics of single doses of either *oral* midazolam 5 mg or *intravenous* midazolam 0.05 mg/kg, although there was a trend for increased oral clearance. However, St John's wort 300 mg three times daily for 14 or 15 days decreased the AUC and maximum plasma concentration of *oral* midazolam by about 50% and 40%, respectively. Intravenous midazolam was not significantly affected. Similar results were found in another six studies.[4-9] In one of the studies, although no serious adverse events occurred, 3 subjects reported that the sedative effects of midazolam were less noticeable when St John's wort was taken at the same time.[6]

(c) Quazepam

In a placebo-controlled study, 13 healthy subjects were given St John's wort (*TruNature*; hypericin content standardised at 0.3%) 300 mg three

times daily for 14 days with a single 15-mg dose of quazepam on day 14. St John's wort modestly decreased the AUC and maximum plasma levels of quazepam by 26% and 29%, respectively, but the pharmacodynamic effects of quazepam were not affected.[10]

Mechanism

Alprazolam, midazolam and quazepam are substrates of the cytochrome P450 isoenzyme CYP3A4. St John's wort appears to induce CYP3A4 thus increasing the metabolism of *oral* midazolam,[5-9,11] alprazolam,[1] and quazepam,[10] and reducing the bioavailability of these benzodiazepines.

Hyperforin appears to be the main active constituent that induces CYP3A4, because high-hyperforin extracts have more of an inducing effect than low-hyperforin extracts.[6-9]

Importance and management

Although not all the studies found an interaction between St John's wort and alprazolam or midazolam, those that did found a reduction in levels, which is in line with the known CYP3A4 inducing effects of St John's wort. The variable findings reported in the studies (some found no interaction) could be due to the preparation of St John's wort used and the duration of treatment.[2,9] Until more is known about the interacting constituents of St John's wort, and the amount necessary to provoke an interaction it would seem prudent to monitor patients receiving alprazolam and oral midazolam concurrently for any signs of reduced efficacy. Single doses of *intravenous* midazolam do not appear to be significantly affected. Note that triazolam is also a substrate of CYP3A4 and is likely to be affected in the same way as alprazolam and midazolam.

The non-benzodiazepine hypnotic, **zopiclone**, is also metabolised by CYP3A4 and the manufacturer of zopiclone suggests that the dose may need to be increased if St John's wort is also given.[12]

The modest reduction in quazepam levels did not reduce its efficacy; however, it may be prudent to bear the potential for an interaction in mind should a patient taking St John's wort have a reduced response to quazepam.

Those benzodiazepines that undergo glucuronidation, such as lorazepam, oxazepam and temazepam, would not be expected to be affected by St John's wort, and may be useful alternatives.

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Benzodiazepines + Statins

The long-term use of atorvastatin appears to decrease the clearance of intravenous midazolam.

Clinical evidence, mechanism, importance and management

In a study in 14 patients given intravenous **midazolam** during elective surgery, long-term **atorvastatin** therapy in 7 of the patients was found to decrease the plasma clearance of midazolam by one-third and increase the AUC of midazolam by about 40%. It was therefore suggested that, in patients receiving **atorvastatin** long-term, the potential for respiratory depression or prolonged sedation should be considered if high-dose **midazolam** is used.[1]

The reason for this effect is unclear. The effect of other statins and benzodiazepines does not appear to have been studied. Nevertheless, some caution would seem warranted with benzodiazepines that are metabolised in the same way as midazolam (e.g. **alprazolam**, **triazolam**).

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Benzodiazepines + Sucrose polyesters

Sucrose polyesters (e.g. *Olestra*) do not appear to interact with diazepam.

Clinical evidence, mechanism, importance and management

In a study in 8 healthy subjects, a single 5-mg dose of **diazepam** was given with 18 g of sucrose polyester (*Olestra*). Sucrose polyester had no effect on the pharmacokinetics of **diazepam**.[1] Sucrose polyesters are non-absorbable, non-calorific fat replacements. It has been concluded that sucrose polyesters are unlikely to reduce the absorption of oral drugs in general.[2]

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Benzodiazepines + Tadalafil

Tadalafil does not alter the pharmacokinetics of midazolam.

Clinical evidence, mechanism, importance and management

An open label study in 12 healthy subjects found that while taking tadalafil 10 mg daily for 14 consecutive days, the pharmacokinetics of a single 15-mg oral dose of **midazolam** were unchanged.[1] **Midazolam** is metabolised by the cytochrome P450 isoenzyme CYP3A4, and it was therefore concluded that the absence of any interaction shows that tadalafil does not inhibit or induce the activity of this isoenzyme.[1] No special precautions are therefore needed if **midazolam** is given with tadalafil.

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Benzodiazepines + Terbinafine

Terbinafine does not interact with midazolam or triazolam to a clinically relevant extent.

Clinical evidence, mechanism, importance and management

In studies in healthy subjects, terbinafine 250 mg daily for 4 days had no effect on the pharmacokinetics of a single 7.5-mg oral dose of **midazolam**[1] or a single 250-microgram oral dose of **triazolam**.[2] The performance of a number of psychomotor tests was unaffected by concurrent use. No special precautions would seem to be necessary if terbinafine is given with either of these drugs.

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Benzodiazepines and related drugs + Theophylline

Aminophylline and theophylline appear to antagonise the effects of the benzodiazepines (mainly sedative effects, but possibly also anxiolytic effects). Theophylline appears to reduce the levels of alprazolam.

Clinical evidence

In a comparative study, two groups of patients were given **alprazolam** 500 micrograms twice daily for 7 days. In one group there were 6 patients who had chronic obstructive pulmonary disease (COPD) and were taking theophylline; and in the other group there were 7 patients with chronic heart failure or atherosclerotic disease (one patient also with COPD) who were not taking theophylline. On day 7, those taking the theophylline were found to have trough serum **alprazolam** levels of 13.25 nanograms/mL, whereas in the group not taking theophylline, **alprazolam** trough levels were 43.92 nanograms/mL.[1] Note that the groups were not randomised, or equivalent in terms of disease state, and other medications taken, so other factors may have had a part to play in this finding.

A patient who was unrousable and unresponsive having been given **diazepam** 60 mg over 10 minutes and nitrous oxide/oxygen anaesthesia, rapidly returned to consciousness when given aminophylline 56 mg intravenously.[2] Other reports confirm this antagonism of **diazepam**-induced sedation, by low doses of aminophylline (60 mg to 4.5 mg/kg intravenously).[3-5] Further studies report that aminophylline and theophylline counteract the drowsiness and mental slowness induced by a single 10- to 20-mg dose of **diazepam**.[6-8] **Flunitrazepam**,[9] **lorazepam**,[10] and **midazolam**[11,12] also appear to be affected; however, there is some controversy about whether or not aminophylline antagonises the effects of **midazolam**.[13]

Mechanism

Uncertain. One suggestion is that the xanthines can block adenosine receptors,[3] which regulate the release of neurotransmitters, and may therefore lead to stimulant effects, which oppose the sedative effects of the benzodiazepines.

Importance and management

The documentation is somewhat sparse and there is a need for more study over the range of benzodiazepines, but the overall picture is that these interactions are established. The extent to which theophylline and aminophylline actually reduce the anxiolytic effects of the benzodiazepines remains uncertain (it needs assessment) but be alert for reduced benzodiazepine effects if either xanthine is used.

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Benzodiazepines and related drugs + Tobacco

Smokers may possibly need larger doses of some benzodiazepines or zolpidem than non-smokers.

Clinical evidence, mechanism, importance and management

Some studies have suggested that smoking does not affect the pharmacokinetics of **chlordiazepoxide**,[1] **clorazepate**,[2] **diazepam**,[3,4] **estazolam**,[5] **lorazepam**,[4] **midazolam**,[4] **quazepam**,[6] or **triazolam**,[7] but others have found that the clearance of **alprazolam**,[8] **clorazepate**,[9] **diazepam**,[10] **lorazepam**,[4,11] **oxazepam**[12,13] or **zolpidem**[14] is increased by smoking, although not all the changes were statistically significant,[4,8,10-12,14] often due to the small numbers of smokers involved in the studies. The Boston Collaborative Drug Surveillance Program reported a decreased frequency of drowsiness in smokers who took **diazepam** or **chlordiazepoxide**,[15] which confirmed the findings of a previous study.[16] It has also been noted that two heavy smokers had a very high clearance and did not experience any sedative effects following the use of **zolpidem**.[17]

The probable reason for the reduction in sedative effects with these drugs is that some of the components of tobacco smoke are enzyme inducers, which increase the rate at which the liver metabolises these benzodiazepines, thereby reducing their effects. The inference to be drawn is that smokers may possibly need larger doses than non-smokers to achieve the same therapeutic effects. Smoking also possibly reduces the drowsiness that the benzodiazepines and non-benzodiazepine hypnotics, such as **zolpidem**, can cause. However, one study suggested that caffeine intake,[16] and others have suggested age, may affect the response to benzodiazepines, so the picture is not altogether clear. Whether any of these interactions has much clinical relevance awaits assessment.

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15. Boston Collaborative Drug Surveillance Program. Clinical depression of the central nervous system due to diazepam and chlordiazepoxide in relation to cigarette smoking and age. *N Engl J Med* (1973) 288, 277–80.
16. Downing RW, Rickels K. Coffee consumption, cigarette smoking and reporting of drowsiness in anxious patients treated with benzodiazepines or placebo. *Acta Psychiatr Scand* (1981) 64, 398–408.
17. Harvengt C, Hulhoven R, Desager JP, Coupez JM, Guillet P, Fuseau E, Lambert D, Warrington SJ. Drug interactions investigated with zolpidem. In: Sauvanet JP, Langer SZ, Morselli PL, eds. Imidazopyridines in Sleep Disorders. New York: Raven Press, 1988: pp. 165–73.

Benzodiazepines + Ursodeoxycholic acid (Ursodiol)

Ursodeoxycholic acid does not appear to affect the pharmacokinetics of midazolam.

Clinical evidence, mechanism, importance and management

A placebo-controlled, crossover study in 14 healthy subjects found that ursodeoxycholic acid 100 mg three times daily for 9 days did not affect the pharmacokinetics or the pharmacodynamics of single doses of intravenous **midazolam** 5 micrograms/kg or oral midazolam 15 micrograms/kg. This suggests that ursodeoxycholic acid has no effect on both intestinal and hepatic CYP3A activities in healthy subjects.[1] Another study also reported

that ursodeoxycholic acid had no effect on the pharmacokinetics of a single 7.5-mg oral dose of **midazolam**.[2]

Other benzodiazepines do not appear to have been studied, but as **alprazolam** and **triazolam** are metabolised in a similar way to **midazolam**, they would also not be expected to interact with ursodeoxycholic acid.

1. Yan D, Yang Y, Uchida S, Misaka S, Luo J, Takeuchi K, Inui N, Yamada S, Ohashi K, Watanabe H. Effects of ursodeoxycholic acid on the pharmacokinetics and pharmacodynamics of intravenous and oral midazolam in healthy volunteers. Naunyn-Schmiedebergs Arch Pharmacol (2008) 377, 629–36.
2. Becquemont L, Glaeser H, Drescher S, Hitzl M, Simon N, Murdter TE, Heinkele G, Hofmann U, Schaefer C, Burk O, Verstuyft C, Eichelbaum M, Fromm MF. Effects of ursodeoxycholic acid on P-glycoprotein and cytochrome P450 3A4-dependent pharmacokinetics in humans. *Clin Pharmacol Ther* (2006) 79, 449–60.

Benzodiazepines and related drugs + Valproate

Valproate appears to increase the plasma levels of diazepam, lorazepam and possibly midazolam, while clobazam appears to raise valproate levels. Clonazepam clearance may increase and valproate clearance decrease during concurrent use, and increased adverse effects have been seen. An isolated case describes sleepwalking in a patient taking valproate and zolpidem.

Clinical evidence

A. Benzodiazepines

(a) Clobazam

In a study in patients with epilepsy, the plasma levels of clobazam appeared lower in the presence of antiepileptics including sodium valproate than when patients were given monotherapy, but sodium valproate did not affect the levels of the main metabolite of clobazam, *N*-desmethylclobazam.[1] A study in children found that clobazam caused an 11% increase in the serum levels of valproate, despite a reduction of at least 10% in the valproate dose.[2]

(b) Clonazepam

The addition of clonazepam to sodium valproate increased the unwanted effects (drowsiness, absence status) in 9 out of 12 paediatric and adolescent patients.[3] An analysis of the interaction between clonazepam and valproate in 317 patients with epilepsy found that concurrent use increased clonazepam clearance by 14% and decreased valproate clearance by 18%.[4]

(c) Diazepam

In 6 healthy subjects sodium valproate increased the serum levels of free diazepam twofold.[5] Valproate may slightly increase the sedative effects of diazepam.[6]

(d) Lorazepam

In healthy subjects, lorazepam 1 mg every 12 hours for 3 days had no effect on the pharmacokinetics of valproate semisodium 500 mg every 12 hours. Valproate semisodium increased the AUC and maximum plasma levels of lorazepam by 20% and 8%, respectively. Sedation scores were slightly increased by concurrent use, although this was not statistically significant.[7]

The clearance of a 2-mg intravenous bolus dose of lorazepam was decreased by 40% in 6 out of 8 healthy subjects while they were taking valproate 250 mg twice daily.[8] Similarly, in another study, valproate decreased the mean systemic clearance of intravenous lorazepam by 20%, but interindividual variability occurred and clearance values were also affected by variations in uridine diphosphate glucuronosyltransferase (UGT) genotype.[9] A woman taking valproate, phenytoin, and carbamazepine went into a coma after she received a total of 6 mg of intravenous lorazepam. She promptly recovered on stopping the valproate.[10] Valproate may slightly increase the sedative effects of lorazepam.[7]

B. Non-benzodiazepine hypnotics

A report describes a patient taking **zolpidem** 5 mg at night and citalopram 30 mg daily, who started sleepwalking when valproate 250 mg twice daily was started. The patient stopped the valproate and the sleepwalking episodes resolved. Later, the valproate was restarted causing the sleepwalking to recur. This time the symptoms resolved when the **zolpidem** was stopped.[11]

Mechanism

It seems that valproate reduces the glucuronidation of lorazepam,[7,8] thereby decreasing its clearance. Other benzodiazepines that are mainly metabolised by glucuronide conjugation, such as **oxazepam** and **temazepam** would be expected to be similarly affected. However, lorazepam pharmacokinetics may additionally be influenced by other factors including genetic polymorphism.[9] It is also thought that valproate may displace diazepam from plasma binding sites.[5] However, this mechanism alone rarely results in clinically significant interactions.

Importance and management

Evidence of an adverse interaction between valproate and the benzodiazepines and related hypnotics is sparse, and concurrent use is generally beneficial. Although potentially clinically significant effects (sedation, absence seizures) have been seen only rarely, it has been suggested that the combination of clonazepam and sodium valproate should be avoided.[3] However, a very brief letter points out that clonazepam and valproate can be given together in patients with absence seizures and some patients have an excellent response to the combination.[12] Nevertheless, the potential hazard should be borne in mind when concurrent use is considered.

It has been recommended that if clobazam is given with valproate it would be prudent to monitor for any increases in valproate serum levels.[2]

The increased levels of lorazepam seen with valproate are relatively modest; however the case report describing coma introduces a note of caution. The manufacturer of lorazepam advises that the dose of lorazepam should be halved in patients taking valproate.[13] Enhanced sedation has been briefly described during the concurrent use of valproate and unnamed benzodiazepines,[14] and diazepam. Be aware of this potential adverse effect when valproate is given with any benzodiazepine.

1. Bun H, Monjanel-Mouterde S, Noel F, Durand A, Cano J-P. Effects of age and antiepileptic drugs on plasma levels and kinetics of clobazam and N-desmethylclobazam. *Pharmacol Toxicol* (1990) 67, 136–40.
2. Theis JGW, Koren G, Daneman R, Sherwin AL, Menzano E, Cortez M, Hwang P. Interactions of clobazam with conventional antiepileptics in children. *J Child Neurol* (1997) 12, 208–13.
3. Jeavons PM, Clark JE, Maheshwari MC. Treatment of generalized epilepsies of childhood and adolescence with sodium valproate ('Epilim'). *Dev Med Child Neurol* (1977) 19, 9–25.
4. Yukawa E, Nonaka T, Yukawa M, Higuchi S, Kuroda T, Goto Y. Pharmacoepidemiologic investigation of a clonazepam-valproic acid interaction by mixed effect modeling using routine clinical pharmacokinetic data in Japanese patients. *J Clin Pharm Ther* (2003) 28, 497–504.
5. Dhillon S, Richens A. Valproic acid and diazepam interaction *in vivo*. *Br J Clin Pharmacol* (1982) 13, 553–60.
6. Diazepam Solution for Injection. Wockhardt UK Ltd. UK Summary of product characteristics, April 2008.
7. Samara EE, Granneman RG, Witt GF, Cavanaugh JH. Effect of valproate on the pharmacokinetics and pharmacodynamics of lorazepam. *J Clin Pharmacol* (1997) 37, 442–50.
8. Anderson GD, Gidal BE, Kantor ED, Wilensky AJ. Lorazepam-valproate interaction: studies in normal subjects and isolated perfused rat liver. *Epilepsia* (1994) 35, 221–5.
9. Chung J-Y, Cho J-Y, Yu K-S, Kim J-R, Jung H-R, Lim K-S, Jang I-J, Shin S-G. Effect of the *UGT2B15* genotype on the pharmacokinetics, pharmacodynamics, and drug interactions of intravenous lorazepam in healthy volunteers. *Clin Pharmacol Ther* (2005) 77, 486–94.
10. Lee S-A, Lee JK, Heo K. Coma probably induced by lorazepam–valproate interaction. *Seizure* (2002) 11, 124–5.
11. Sattar SP, Ramaswamy S, Bhatia SC, Petty F. Somnambulism due to probable interaction of valproic acid and zolpidem. *Ann Pharmacother* (2003) 37, 1429–33.
12. Browne TR. Interaction between clonazepam and sodium valproate. *N Engl J Med* (1979) 300, 679.
13. Ativan Injection (Lorazepam). Wyeth Pharmaceuticals. UK Summary of product characteristics, October 2009.
14. Völzke E, Doose H. Dipropylacetate (Dépakine®, Ergenyl®) in the treatment of epilepsy. *Epilepsia* (1973) 14, 185–93.

Benzodiazepines + Vinpocetine

Vinpocetine does not appear to interact adversely with oxazepam. Vinpocetine did not appear to affect the ability to sleep, or the short-term memory impairment, induced by flunitrazepam.

Clinical evidence, mechanism, importance and management

In a study in 16 healthy subjects, vinpocetine 10 mg three times daily for 7 days did not affect the steady-state plasma levels of **oxazepam** 10 mg three times daily.[1] There would therefore seem to be no reason for taking special precautions if these two drugs are given together.

A crossover study in 8 healthy subjects found that although vinpocetine 40 mg three times daily for 2 days improved short-term memory processes, it did not significantly affect **flunitrazepam**-induced impairment of

memory. **Flunitrazepam** either alone or in combination with vinpocetine appeared to improve patients' ability to sleep.[2]

1. Storm G, Oosterhuis B, Sollie FAE, Visscher HW, Sommer W, Beitinger H, Jonkman JHG. Lack of pharmacokinetic interaction between vinpocetine and oxazepam. *Br J Clin Pharmacol* (1994) 38, 143–6.
2. Bhatti JZ, Hindmarch I. Vinpocetine effects on cognitive impairments produced by flunitrazepam. *Int Clin Psychopharmacol* (1987) 2, 325–31.

Benzodiazepines; Diazepam + Misoprostol

A study in 12 subjects found that misoprostol 200 micrograms four times daily for 7 days had no effect on the steady-state plasma levels of diazepam 10 mg daily or on the plasma levels of the metabolite, nordiazepam.[1] Similar results were found in another study.[2] No dose adjustments of diazepam would therefore seem to be necessary if misoprostol is also given.

1. Lima DR, Santos RM, Werneck E, Andrade GN. Effect of orally administered misoprostol and cimetidine on the steady state pharmacokinetics of diazepam and nordiazepam in human volunteers. *Eur J Drug Metab Pharmacokinet* (1991) 16, 161–70.
2. Nicholson PA, Karim A, Smith M. Pharmacokinetics of misoprostol in the elderly, in patients with renal failure and when coadministered with NSAID or antipyrine, propranolol or diazepam. *J Rheumatol* (1990) 17 (Suppl 20), 33–7.

Benzodiazepines; Lorazepam + Colestyramine and Neomycin

The clearance of lorazepam is increased by colestyramine with neomycin.

Clinical evidence, mechanism, importance and management

A study in 7 healthy subjects found that neomycin 1 g every 6 hours, given with colestyramine 4 g every 4 hours, reduced the half-life of oral **lorazepam** from 15.8 hours to 11.7 hours, and increased the clearance of free **lorazepam** by 34%.[1] The reasons for these changes are not clear but parallel studies using intravenous **lorazepam**[1] suggested that neomycin and colestyramine may interfere with the enterohepatic circulation of **lorazepam**.

The clinical importance of this interaction is uncertain but probably small. Other benzodiazepines do not appear to have been studied.

1. Herman RJ, Duc Van Pham J, Szakacs CBN. Disposition of lorazepam in human beings: enterohepatic recirculation and first-pass effect. *Clin Pharmacol Ther* (1989) 46, 18–25.

Buspirone + Azoles

The plasma levels of buspirone are markedly increased by itraconazole. Ketoconazole is predicted to interact similarly.

Clinical evidence

In a placebo-controlled study, 8 healthy subjects were given buspirone 10 mg, before and after taking **itraconazole** 100 mg twice daily for 4 days. It was found that the buspirone maximum plasma levels and its AUC were increased 13-fold and 19-fold, respectively, by **itraconazole**. These increased buspirone levels caused a moderate impairment of psychomotor performance (digital symbol substitution, body sway, drowsiness, etc.) and an increase in adverse effects.[1]

Mechanism

Itraconazole is a potent inhibitor of the cytochrome P450 isoenzyme CYP3A4, by which buspirone is metabolised. Itraconazole therefore increases buspirone levels and effects.

Importance and management

Direct information appears to be limited to this study but the interaction would seem to be established. The dose of buspirone should be greatly reduced if itraconazole is given concurrently. The manufacturers recommend 2.5 mg daily[2] or twice daily.[3] **Ketoconazole** is predicted to interact similarly because it is also a potent CYP3A4 inhibitor.[1,2]

1. Kivistö KT, Lamberg TS, Kantola T, Neuvonen PJ. Plasma buspirone concentrations are greatly increased by erythromycin and itraconazole. *Clin Pharmacol Ther* (1997) 62, 348–54.
2. BuSpar (Buspirone hydrochloride). Bristol-Myers Squibb Company. US Prescribing information, March 2007.
3. Buspar (Buspirone hydrochloride). Bristol-Myers Pharmaceuticals. UK Summary of product characteristics, May 2008.

Buspirone + Calcium-channel blockers

Diltiazem and verapamil can markedly raise the plasma levels of buspirone, increasing the likelihood of adverse effects.

Clinical evidence, mechanism, importance and management

In a randomised study in 9 healthy subjects, **diltiazem** 60 mg three times daily for 5 doses increased the AUC of a single 10-mg dose of buspirone 5.5-fold and increased its maximum plasma level 4.1-fold.

When **verapamil** 80 mg three times daily was similarly given with buspirone, the buspirone AUC and maximum plasma level were both increased 3.4-fold.

The increased buspirone levels are thought to occur because both **diltiazem** and **verapamil** inhibit the cytochrome P450 isoenzyme CYP3A4, which is concerned with the metabolism of buspirone.[1]

The practical consequences of this interaction are that the effects of buspirone are likely to be increased by **diltiazem** and **verapamil**. Concurrent use need not be avoided but be alert for the need to reduce the buspirone dose. The US manufacturer suggests adjusting the dose according to response,[2] while the UK manufacturer suggests using a lower dose of buspirone e.g. 2.5 mg twice daily.[3] Information about other calcium-channel blockers appears to be lacking, but they do not usually appear to interact by inhibiting CYP3A4 (see 'Calcium-channel blockers', (p.1025)).

1. Lamberg TS, Kivistö KT, Neuvonen PJ. Effects of verapamil and diltiazem on the pharmacokinetics and pharmacodynamics of buspirone. *Clin Pharmacol Ther* (1998) 63, 640–5.
2. BuSpar (Buspirone hydrochloride). Bristol-Myers Squibb Company. US Prescribing information, March 2007.
3. Buspar (Buspirone hydrochloride). Bristol-Myers Pharmaceuticals. UK Summary of product characteristics, May 2008.

Buspirone + Disulfiram

An isolated report describes mania in an alcoholic patient taking buspirone 20 mg daily, possibly due to an interaction with disulfiram 400 mg daily;[1] however, buspirone on its own has also apparently caused mania.[2,3] Therefore an interaction is not established and no general recommendations can be made.

1. McIvor RJ, Sinanan K. Buspirone-induced mania. *Br J Psychiatry* (1991) 158, 136–7.
2. Price WA, Bielefeld M. Buspirone-induced mania. *J Clin Psychopharmacol* (1989) 9, 150–1.
3. McDaniel JS, Ninan PT, Magnuson JV. Possible induction of mania by buspirone. *Am J Psychiatry* (1990) 147, 125–6.

Buspirone + Grapefruit juice

Grapefruit juice can markedly increases the plasma levels of buspirone.

Clinical evidence, mechanism, importance and management

In a randomised, crossover study, 10 healthy subjects were given either double-strength grapefruit juice 200 mL or water 200 mL three times daily for 2 days. On the third day, a single 10-mg dose of buspirone was given with the grapefruit juice or water, and additional grapefruit juice or water ingested 30 and 90 minutes later. Grapefruit juice increased the peak plasma level and AUC of buspirone 4.3-fold and 9.2-fold, respectively. The time to peak buspirone level was also increased from 45 minutes to 3 hours. However, an increase in the pharmacodynamic effects of buspirone was seen only in the subjective overall drug effect. Grapefruit juice probably inhibited the metabolism of buspirone by the cytochrome P450 isoenzyme CYP3A4 in the gut. The authors of this study recommended that the concurrent use of buspirone and grapefruit juice should be avoided.[1] However, the UK manufacturer recommends that a lower dose of bus-

pirone e.g. 2.5 mg twice daily should be used with potent inhibitors of CYP3A4 such as grapefruit juice:[2] the US manufacturer suggests that patients should avoid drinking large quantities of grapefruit juice.[3]

1. Lilja JJ, Kivistö KT, Backman JT, Lamberg TS, Neuvonen PJ. Grapefruit juice substantially increases plasma concentrations of buspirone. *Clin Pharmacol Ther* (1998) 64, 655–60.
2. Buspar (Buspirone hydrochloride). Bristol-Myers Pharmaceuticals. UK Summary of product characteristics, May 2008.
3. BuSpar (Buspirone hydrochloride). Bristol-Myers Squibb Company. US Prescribing information, March 2007.

Buspirone + Macrolides

The plasma levels of buspirone are markedly increased by erythromycin.

Clinical evidence

In a placebo-controlled study buspirone 10 mg was given to 8 healthy subjects before and after they took **erythromycin** 500 mg three times daily for 4 days. It was found that the buspirone maximum plasma level and AUC were increased fivefold and sixfold, respectively, by **erythromycin**. The increased buspirone levels caused a moderate impairment of psychomotor performance (digital symbol substitution, body sway, drowsiness, etc.) and an increase in adverse effects.[1]

Mechanism

Erythromycin is an inhibitor of the cytochrome P450 isoenzyme CYP3A4, by which buspirone is metabolised. Erythromycin therefore increases buspirone levels and hence its effects.

Importance and management

Direct information appears to be limited to this study, but the interaction would seem to be established. The dose of buspirone should be reduced if erythromycin is given concurrently. The manufacturers suggest using a low dose of buspirone e.g. 2.5 mg twice daily,[2,3] adjusted according to response.[3]

Other macrolides (most notably **clarithromycin** and **telithromycin**) are also inhibitors of CYP3A4 and may therefore interact similarly.

1. Kivistö KT, Lamberg TS, Kantola T, Neuvonen PJ. Plasma buspirone concentrations are greatly increased by erythromycin and itraconazole. *Clin Pharmacol Ther* (1997) 62, 348–54.
2. Buspar (Buspirone hydrochloride). Bristol-Myers Pharmaceuticals. UK Summary of product characteristics, May 2008.
3. BuSpar (Buspirone hydrochloride). Bristol-Myers Squibb Company. US Prescribing information, March 2007.

Buspirone + Miscellaneous

Buspirone does not appear to interact with amitriptyline, cimetidine or terfenadine. Nefazodone greatly increases buspirone levels.

Clinical evidence, mechanism, importance and management

(a) Amitriptyline

In a study in healthy subjects, buspirone 15 mg every 8 hours, given with amitriptyline 25 mg every 8 hours for 10 days, had no significant effect on the steady-state plasma levels of amitriptyline or its metabolite, nortriptyline. No evidence of a pharmacodynamic interaction was seen.[1] There would seem to be no reason for avoiding concurrent use.

(b) Cimetidine

In 10 healthy subjects, cimetidine 1 g daily for 7 days had no effect on the plasma levels of buspirone 15 mg three times daily. Some small pharmacokinetic changes were seen, but the performance of three psychomotor function tests remained unaltered.[2] There would seem to be no reason for avoiding concurrent use.

(c) Nefazodone

Nefazodone 250 mg twice daily caused a 20-fold increase in the maximum plasma levels of buspirone 2.5 or 5 mg twice daily and a 50-fold increase in its AUC. Buspirone 5 mg twice daily raised the AUC of nefazodone by 23%, which is unlikely to be clinically significant. The manufacturers of buspirone have recommended that a lower dose of buspirone e.g. 2.5 mg daily[3] or twice daily[4] should be used if nefazodone is given.

(d) Terfenadine

A single 10-mg dose of buspirone was given to 10 healthy subjects after they had taken terfenadine 120 mg daily for 3 days. There were no significant effects on the pharmacokinetics or pharmacodynamics of buspirone.[5]

1. Gammans RE, Mayol RF, Labudde JA. Metabolism and disposition of buspirone. *Am J Med* (1986) 80 (Suppl 3B), 41–51.
2. Gammans RE, Pfeffer M, Westrick ML, Faulkner HC, Rehm KD, Goodson PJ. Lack of interaction between cimetidine and buspirone. *Pharmacotherapy* (1987) 7, 72–9.
3. BuSpar (Buspirone hydrochloride). Bristol-Myers Squibb Company. US Prescribing information, March 2007.
4. Buspar (Buspirone hydrochloride). Bristol-Myers Pharmaceuticals. UK Summary of product characteristics, May 2008.
5. Lamberg TS, Kivistö KT, Neuvonen PJ. Lack of effect of terfenadine on the pharmacokinetics of the CYP3A4 substrate buspirone. *Pharmacol Toxicol* (1999) 84, 165–9.

Buspirone + Protease inhibitors

Ritonavir, and possibly indinavir, are predicted to reduce the metabolism of buspirone. This resulted in Parkinson-like symptoms in one case.

Clinical evidence, mechanism, importance and management

A 54-year-old man who had been taking high-dose buspirone (40 mg every morning and 30 mg every evening) developed Parkinson-like symptoms about 6 weeks after starting to take **ritonavir** 400 mg and **indinavir** 400 mg, both twice daily. The dose of buspirone was reduced to 15 mg three times daily, **ritonavir** and **indinavir** were discontinued, and amprenavir 1.2 g twice daily was started. The Parkinson-like symptoms were reduced after about one week and completely resolved after 2 weeks.[1]

Buspirone is metabolised by the cytochrome P450 isoenzyme CYP3A4, and it is probable that **ritonavir** and **indinavir** inhibited the metabolism of buspirone resulting in toxic levels.

This appears to be an isolated case report,but it is in line with the way buspirone is known to interact with other CYP3A4 inhibitors. The manufacturer of buspirone usually recommends that a lower dose of buspirone (e.g. 2.5 mg twice daily in the UK) should be used with potent inhibitors of CYP3A4,[2] such as **ritonavir**. All protease inhibitors inhibit CYP3A4 to a greater or lesser extent, and therefore some caution would be prudent if buspirone is given with any protease inhibitor.

1. Clay PG, Adams MM. Pseudo-Parkinson disease secondary to ritonavir-buspirone interaction. *Ann Pharmacother* (2003) 37, 202–5.
2. Buspar (Buspirone hydrochloride). Bristol-Myers Pharmaceuticals. UK Summary of product characteristics, May 2008.

Buspirone + Rifampicin (Rifampin)

Rifampicin can cause a marked reduction in the plasma levels and effects of buspirone.

Clinical evidence

In a randomised study, a single 30-mg dose of buspirone was given to 10 healthy subjects, before and after they took rifampicin 600 mg daily for 5 days. It was found that rifampicin reduced the total AUC of buspirone by about 90% and reduced its peak plasma level by 84%. The pharmacodynamic effects of buspirone were reduced accordingly (as measured by digit symbol substitution, critical flicker fusion, body sway and visual analogue scales for subjective drowsiness).[1]

Mechanism

Not fully established, but it is almost certain that rifampicin induces the cytochrome P450 isoenzyme CYP3A4 in the gut and liver, which metabolises buspirone. Therefore the metabolism and clearance of buspirone are increased.

Importance and management

Direct information appears to be limited to this study, but it is consistent with the way rifampicin interacts with many other drugs. This interaction would appear to be clinically important. If both drugs are used in combi-

nation, the buspirone dose may need to be increased, although note that the extent of this interaction is so great that this may not be effective, and therefore it may be prudent to consider alternatives to buspirone, where possible.

1. Lamberg TS, Kivistö KT, Neuvonen PJ. Concentrations and effects of buspirone are considerably reduced by rifampicin. *Br J Clin Pharmacol* (1998) 45, 381–5.

Buspirone + SSRIs

Isolated reports describe symptoms of serotonin syndrome when buspirone was given with SSRIs, although in some cases there may have been other contributing factors. The combination of buspirone and fluoxetine can be effective, but seizures and worsening of symptoms have been reported. Fluvoxamine may increase the levels of buspirone, but may possibly reduce its effects.

Clinical evidence, mechanism, importance and management

(a) Citalopram

An isolated report describes the development of serotonin syndrome and hyponatraemia, thought to be caused by an interaction between citalopram and buspirone, which had been taken in higher doses than prescribed.[1] The general importance of this interaction when conventional doses are used is unknown.

(b) Fluoxetine

An isolated report describes serotonin syndrome in a 48-year-old man after his dose of clomipramine was increased to 250 mg daily and buspirone 5 mg three times daily and fluoxetine 20 mg daily were added to his treatment. As all three drugs can affect brain serotonin concentrations, buspirone was considered to be partially responsible.[2]

A 35-year-old man with a long history of depression, anxiety and panic started taking buspirone 60 mg daily. His anxiety abated, but because of worsening depression he was also given trazodone 200 mg daily for 3 weeks. This had little effect, so fluoxetine 20 mg daily was added. Within 48 hours his usual symptoms of anxiety had returned and persisted even when the dose of buspirone was raised to 80 mg daily. Stopping the buspirone did not increase his anxiety.[3] Another patient with obsessive-compulsive disorder taking fluoxetine experienced a marked worsening of his symptoms when buspirone 5 mg twice daily was added.[4] A patient taking fluoxetine 80 mg daily had a grand mal seizure 3 weeks after buspirone 30 mg daily was added. The drugs were stopped and an EEG showed no signs of epilepsy, so the seizure was attributed to a drug interaction.[5] Other reports describe the effective concurrent use of fluoxetine and buspirone in patients with treatment-resistant depression[6] and with obsessive-compulsive disorder.[7,8]

There would seem to be little reason for avoiding concurrent use, however bear these case reports of interactions in mind when both drugs are used.

(c) Fluvoxamine

Serotonin syndrome developed in a 48-year-old man taking fluvoxamine and haloperidol after buspirone and valproate semisodium were also given. The symptoms subsided within 24 to 36 hours after discontinuation of these medications. Buspirone affects 5-HT_{1A} receptors and so may contribute to the development of serotonin syndrome with fluvoxamine.[9]

A double-blind study in 9 healthy subjects found that after taking fluvoxamine (mean dose 127 mg daily, range 100 to 150 mg daily) for 3 weeks, the plasma levels of a single 30-mg dose of buspirone were increased almost threefold. Even so, the psychological responses to the buspirone were reduced.[10] However, a study in 10 healthy subjects given a single 10-mg dose of buspirone after taking fluvoxamine 100 mg daily for 5 days, found that although the pharmacokinetics of buspirone were altered (AUC increased 2.4-fold) the pharmacodynamic tests remained unchanged.[11]

It has been suggested that fluvoxamine inhibits the liver enzymes concerned with the metabolism of buspirone. Concurrent use need not be avoided but it would be wise to remain alert to the possibility of reduced buspirone effects until more is known.

(d) Paroxetine

A 52-year-old woman experienced symptoms of serotonin syndrome within a month of taking the combination of buspirone, paroxetine and paverine. The symptoms rapidly decreased after paroxetine was withdrawn.[12]

(e) Sertraline

Symptoms of serotonin syndrome occurred in a patient 11 days after buspirone, sertraline and loxapine were started for recurrent major depression. Buspirone was discontinued and the main symptoms resolved over the next day, although facial dyskinesias remained until the other two drugs were stopped. The patient had previously received buspirone together with **citalopram** or another serotonergic drug without any adverse effects. It was suggested that the concurrent use of drugs with serotonergic and antidopaminergic properties may have produced two different effects: serotonin syndrome and extrapyramidal adverse effects.[13]

1. Spigset O, Adielsson G. Combined serotonin syndrome and hyponatraemia caused by a citalopram–buspirone interaction. *Int Clin Psychopharmacol* (1997) 12, 61–3.
2. Nijhawan PK, Katz G, Winter S. Psychiatric illness and the serotonin syndrome: an emerging adverse drug effect leading to intensive care unit admission. *Crit Care Med* (1996) 24, 1086–9.
3. Bodkin JA, Teicher MH. Fluoxetine may antagonize the anxiolytic action of buspirone. *J Clin Psychopharmacol* (1989) 9, 150.
4. Tanquary J, Masand P. Paradoxical reaction to buspirone augmentation of fluoxetine. *J Clin Psychopharmacol* (1990) 10, 377.
5. Grady TA, Pigott TA, L'Heureux F, Murphy DL. Seizure associated with fluoxetine and adjuvant buspirone therapy. *J Clin Psychopharmacol* (1992) 12, 70–1.
6. Bakish D. Fluoxetine potentiation by buspirone: three case histories. *Can J Psychiatry* (1991) 36, 749–50.
7. Markovitz PJ, Stagno SJ, Calabrese JR. Buspirone augmentation of fluoxetine in obsessive-compulsive disorder. *Am J Psychiatry* (1990) 147, 798–800.
8. Jenike MA, Baer L, Buttolph L. Buspirone augmentation of fluoxetine in patients with obsessive compulsive disorder. *J Clin Psychiatry* (1991) 52, 13–14.
9. Baetz M, Malcolm D. Serotonin syndrome from fluvoxamine and buspirone. *Can J Psychiatry* (1995) 40, 428–9.
10. Anderson IM, Deakin JFW, Miller HEJ. The effect of chronic fluvoxamine on hormonal and psychological responses to buspirone in normal volunteers. *Psychopharmacology (Berl)* (1996) 128, 74–82.
11. Lamberg TS, Kivistö KT, Laitila J, Mårtensson K, Neuvonen PJ. The effect of fluvoxamine on the pharmacokinetics and pharmacodynamics of buspirone. *Eur J Clin Pharmacol* (1998) 54, 761–6.
12. Jägestedt M, von Bahr C. Kombination av serotonerga läkemedel gav kraftiga biverkningar. *Lakartidningen* (2004) 101, 1618–19.
13. Bonin B, Vandel P, Vandel S, Sechter D, Bizouard P. Serotonin syndrome after sertraline, buspirone and loxapine? *Therapie* (1999) 54, 269–71.

Buspirone + St John's wort (*Hypericum perforatum*)

Two patients taking buspirone developed marked CNS effects after starting to take herbal medicines including St John's wort.

Clinical evidence

A 27-year-old woman who had been taking buspirone 30 mg daily for over one month started to take St John's wort (*Hypericum 2000 Plus*, Herb Valley, Australia) three tablets daily. After 2 months she complained of nervousness, aggression, hyperactivity, insomnia, confusion and disorientation, which was attributed to serotonin syndrome. The St John's wort was stopped, the buspirone was increased to 50 mg daily and her symptoms resolved over a week.[1] A 42-year-old woman who was taking fluoxetine 20 mg twice daily and buspirone 15 mg twice daily started to develop symptoms of anxiety, with episodes of over-sleeping and memory deficits. It was discovered that she had been self-medicating with St John's wort, **ginkgo biloba** and **melatonin**. She was asked to stop the non-prescribed medication and her symptoms resolved.[2]

Mechanism

The exact mechanism of these interactions are not clear, but it seems most likely they were due to the additive effects of the buspirone and the herbal medicines, either through their effects on elevating mood or through excess effects on serotonin. Fluoxetine may have had a part to play in one of the cases. See 'SSRIs + St John's wort (*Hypericum perforatum*)', p.1492.

Importance and management

The clinical significance of these cases is unclear, but they highlight the importance of considering adverse effects from herbal medicines when they are used with conventional medicines.

1. Dannawi M. Possible serotonin syndrome after combination of buspirone and St John's wort. *J Psychopharmacol* (2002) 16, 401.
2. Spinella M, Eaton LA. Hypomania induced by herbal and pharmaceutical psychotropic medicines following mild traumatic brain injury. *Brain Inj* (2002) 16, 359–67.

Buspirone + Trazodone

The concurrent use of buspirone and trazodone may result in serotonin syndrome, and may possibly affect liver enzymes.

Clinical evidence, mechanism, importance and management

A report describes serotonin syndrome in a patient receiving several drugs including buspirone and trazodone.[1] Mild serotonin syndrome occurred in another patient receiving **tandospirone** (which is structurally related to buspirone) and trazodone.[2]

It was suggested that synergistic effects on the 5-HT system might be responsible, and/or an increase in the plasma levels of the drugs might occur due to a shared metabolic pathway.[2] A further report suggested that the concurrent use of buspirone and trazodone may have caused three- to sixfold elevations of ALT in a few patients. However, in a similar study no interactive effect on hepatic transaminases was identified.[3]

For more information on serotonin syndrome, see under 'Additive or synergistic interactions', (p.9). The clinical relevance of the effect on liver enzymes is unclear; note that trazodone is, rarely, known to cause hepatocellular damage, sometimes severe, when given alone.

1. Goldberg RJ, Huk M. Serotonin syndrome from trazodone and buspirone. *Psychosomatics* (1992) 33, 235–6.
2. Kaneda Y, Ohmori T, Okabe H. Possible mild serotonin syndrome related to co-prescription of tandospirone and trazodone. *Gen Hosp Psychiatry* (2001) 23, 98–101.
3. BuSpar (Buspirone hydrochloride). Bristol-Myers Squibb Company. US Prescribing information, March 2007.

Clomethiazole + Diazoxide

Clomethiazole and diazoxide, given to pregnant women in labour, can cause marked respiratory depression in their infants for up to 36 hours after birth.

Clinical evidence

An infusion of 0.8% clomethiazole, in a dose of 4 to 24 g, was given during labour to 21 pregnant women of 28 to 40 weeks gestation for eclampsia or pre-eclamptic toxaemia. Diazoxide 75 to 150 mg was also given intravenously to 14 of the women for hypertension. All 21 babies were born alive but 13 suffered hypotonia, hypoventilation or apnoea for 24 to 36 hours after birth. All of the neonates affected, apart from one, came from the group of mothers who had been given diazoxide. Three of them died of respiratory distress syndrome; one was only 28 weeks' gestation.[1]

Mechanism

Clomethiazole has some respiratory depressant effects, and is contraindicated in patients with respiratory deficiency, but it is not clear why, having passed across the placenta into the foetus, its effects should apparently be so markedly increased by diazoxide.

Importance and management

Although use of this drug combination in eclampsia is historical, the interaction is included on account of its severity. The author of the report says that the respiratory depression was managed successfully with intermittent positive pressure ventilation, provided that respiratory distress syndrome was not also present.[1]

1. Johnson RA. Adverse neonatal reaction to maternal administration of intravenous chlormethiazole and diazoxide. *BMJ* (1976) 1, 943.

Clomethiazole + Furosemide

Ten female patients aged 66 to 90 years were given clomethiazole edisilate syrup 500 mg each evening and 250 mg each morning as a sedative, with furosemide 20 to 80 mg. No significant changes in the plasma levels or effects of clomethiazole or furosemide were detected, and no other significant adverse reactions were seen.[1] No particular precautions therefore seem necessary on concurrent use.

1. Reid J, Judge TG. Chlormethiazole night sedation in elderly subjects receiving other medications. *Practitioner* (1980) 224, 751–3.

Clomethiazole + H_2-receptor antagonists

Increased sedation appears to occur when clomethiazole is given with cimetidine. Ranitidine does not appear to affect the pharmacokinetics of clomethiazole.

Clinical evidence, mechanism, importance and management

In a study in 8 healthy subjects, cimetidine 1 g daily for one week reduced the clearance of a single 768-mg dose of clomethiazole by 31% and prolonged its elimination half-life from 2.33 hours to 3.63 hours. Furthermore, clomethiazole produced a sleep duration of 30 to 60 minutes, but this was prolonged in most subjects to at least 2 hours after cimetidine. It was suggested that cimetidine inhibits the metabolism of clomethiazole and increases the bioavailability of the drug resulting in increased pharmacodynamic effects.[1] The clinical relevance of these relatively modest effects is probably small.

In two studies, each in 7 healthy subjects, ranitidine 150 mg twice daily did not significantly affect the pharmacokinetics of a single 768-mg dose of oral clomethiazole, or a single 192-mg dose of intravenous clomethiazole, given over 5 minutes.[2]

1. Shaw G, Bury RW, Mashford ML, Breen KJ, Desmond PV. Cimetidine impairs the elimination of chlormethiazole. *Eur J Clin Pharmacol* (1981) 21, 83–5.
2. Mashford ML, Harman PJ, Morphett BJ, Breen KJ, Desmond PV. Ranitidine does not affect chlormethiazole or indocyanine green disposition. *Clin Pharmacol Ther* (1983) 34, 231–3.

Clomethiazole + Miscellaneous

Carbamazepine increases the clearance of clomethiazole. Other enzyme inducers are expected to interact similarly.

Clinical evidence, mechanism, importance and management

The manufacturers of clomethiazole note that the clearance of intravenous clomethiazole was increased by 30% by **carbamazepine**, resulting in decreased plasma levels. Although this interaction has not been studied with oral clomethiazole, the concurrent use of **carbamazepine** would be expected to result in decreased clomethiazole bioavailability. Higher doses of clomethiazole may therefore be needed in the presence of **carbamazepine** or other potent inducers of the cytochrome P450 isoenzyme CYP3A4.[1] For a list of inducers of this isoenzyme see 'Table 1.4', (p.6).

1. Heminevrin Capsules (Clomethiazole). AstraZeneca UK Ltd. UK Summary of product characteristics, August 2009.

Clomethiazole + Propranolol

An isolated report describes marked bradycardia when an elderly woman taking propranolol started to take clomethiazole.

Clinical evidence, mechanism, importance and management

An 84-year-old woman taking propranolol 40 mg twice daily for hypertension underwent skin grafting. Her pulse was stable (54 to 64 bpm) until the thirteenth day after the operation when she took two oral doses of clomethiazole 192 mg, 9 hours apart. Three hours after taking the second dose, her heart rate fell to 43 bpm with a PR interval of 240 milliseconds, and by 5 hours after the dose her pulse rate was down to 36 bpm. Her pulse had risen to 70 bpm twelve hours after stopping both drugs, and had restabilised 2 days later at about 60 bpm with a PR interval of 200 milliseconds. At this time the propranolol was restarted, with haloperidol.[1] This interaction appears to be an isolated case and therefore probably of limited clinical significance.

1. Adverse Drug Reactions Advisory Committee. Chlormethiazole/propranolol interaction? *Med J Aust* (1979) 2, 553.

Clozapine + Antihypertensives

There are isolated cases of apparent hypotensive interactions in patients taking clozapine, and enalapril, lisinopril or propranolol. Additive hypotensive effects are possible with clozapine and any antihypertensive drug.

Clinical evidence, mechanism, importance and management

A patient taking **enalapril** 5 mg twice daily fainted within an hour of being given an initial 25-mg dose of clozapine. Later he was stabilised without problems taking **enalapril** 2.5 mg twice daily and clozapine, initially 12.5 mg daily, later rising to 800 mg daily. Another patient taking **enalapril** 5 mg daily fainted within 5 hours of being given clozapine 25 mg. He needed resuscitation, but was later treated with clozapine in doses up to 600 mg daily.[1] The clozapine blood levels of a 39-year-old man rose from 490 nanograms/mL to 966 nanograms/mL after the addition of **lisinopril** 5 mg daily. When the **lisinopril** dose was increased to 10 mg daily, the levels further rose to 1092 nanograms/mL. The dose of clozapine was reduced, and **lisinopril** replaced by diltiazem, after which his levels began to return to normal.[2]

Coma developed in a woman taking **propranolol** 40 mg daily 1.5 to 2 hours after she was given a single 150-mg dose of clozapine. She had stopped taking fluphenazine 24 hours earlier. The patient recovered, and was subsequently slowly titrated up to a daily clozapine dose of 100 mg in addition to the **propranolol**, without any problems. Although the authors state that an interaction between **propranolol** and clozapine was the likely cause of the coma, the effects of fluphenazine cannot be wholly ruled out.[3]

Clozapine has alpha-blocking effects and therefore may cause orthostatic hypotension. The manufacturers note that this is more likely in the presence of other antipsychotics or benzodiazepines and during initial titration with rapid dose increases. Because of the potential for additive effects they recommend caution when giving clozapine to patients taking any hypotensive drug.[4,5]

1. Aronowitz JS, Chakos MH, Safferman AZ, Lieberman JA. Syncope associated with the combination of clozapine and enalapril. *J Clin Psychopharmacol* (1994) 14, 429–30.
2. Abraham G, Grunberg B, Gratz S. Possible interaction of clozapine and lisinopril. *Am J Psychiatry* (2001) 158, 969.
3. Vetter PH, Proppe DG. Clozapine-induced coma. *J Nerv Ment Dis* (1992) 180, 58–9.
4. Clozaril (Clozapine). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, February 2009.
5. Clozaril (Clozapine). Novartis Pharmaceuticals Corporation. US Prescribing information, July 2009.

Clozapine + Antimuscarinics

The antimuscarinic effects of clozapine are additive with those of other antimuscarinic drugs, which has led to urinary retention and delirium.

Clinical evidence, mechanism, importance and management

The manufacturers of clozapine warn that the antimuscarinic effects of some drugs (such as those used to control hypersalivation[1]), may be additive with those of clozapine, which may lead to adverse effects such as dry mouth and constipation.[2,3] Confirmation of the clinical relevance of this proposed interaction was seen in a patient who developed severe urinary retention while taking clozapine and **meclozine**.[4]

Another case report describes a man with a schizoaffective disorder taking **nortriptyline**, **perphenazine** and propranolol was also given clozapine 150 mg daily. Some improvement was seen after 8 days, and over the next week the propranolol was gradually discontinued while the clozapine dosage was raised to 225 mg daily. The patient then began to complain of extreme fatigue and slurred speech, and by day 17 was delirious and confused. His serum **nortriptyline** levels were found to have doubled (from 93 to 185 nanograms/mL) from the time the clozapine was started. He recovered within 5 days of stopping all of the drugs, after which the clozapine was restarted.[5] The authors of the report interpreted the symptoms as an antimuscarinic delirium arising from the additive antimuscarinic effects of the clozapine, **nortriptyline** and **perphenazine**, made worse by the increased levels of **nortriptyline**.[5] Just why the **nortriptyline** levels rose is not clear, but one possible explanation is that the **nortriptyline** and clozapine compete for metabolism by the same liver enzymes, resulting in a reduction in the clearance of the **nortriptyline**.

However, **pirenzepine**, which has antimuscarinic activity, has been used to control clozapine-associated hypersalivation. In one study in 29 patients, there were no significant changes in the serum levels of clozapine or its metabolite desmethylclozapine (although levels were increased in 3 patients) when **pirenzepine** was also taken, and the risk of additional adverse effects was reportedly low.[6]

'Table 18.1', (p.784) and 'Table 18.2', (p.786) give lists of drugs that have antimuscarinic activity.

1. Davydov L, Botts SR. Clozapine-induced hypersalivation. *Ann Pharmacother* (2000) 34, 662–5.
2. Clozaril (Clozapine). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, February 2009.
3. Clozaril (Clozapine). Novartis Pharmaceuticals Corporation. US Prescribing information, July 2009.
4. Cohen MAA, Alfonso CA, Mosquera M. Development of urinary retention during treatment with clozapine and meclizine. *Am J Psychiatry* (1994) 151, 619–20.
5. Smith T, Riskin J. Effect of clozapine on plasma nortriptyline concentration. *Pharmacopsychiatry* (1994) 27, 41–2.
6. Schneider B, Weigmann H, Hiemke C, Weber B, Fritze J. Reduction of clozapine-induced hypersalivation by pirenzepine is safe. *Pharmacopsychiatry* (2004) 37, 43–5.

Clozapine + Azoles

Itraconazole and ketoconazole do not affect the pharmacokinetics of clozapine.

Clinical evidence, mechanism, importance and management

A double-blind study in 7 patients with schizophrenia taking clozapine found that giving **itraconazole** 200 mg daily for a week did not affect the serum levels of clozapine or its desmethylclozapine metabolite.[1]

In a study, 5 patients with schizophrenia were given a single 50-mg dose of clozapine before and after a 7-day course of **ketoconazole** 400 mg daily. **Ketoconazole** had no significant effect on the pharmacokinetics of clozapine.[2]

The authors of these reports conclude that the cytochrome P450 isoenzyme CYP3A4 is of only minor importance in clozapine metabolism, and that because no interaction takes place between clozapine and **itraconazole** or **ketoconazole**, these azoles and other inhibitors of CYP3A4 can be used with clozapine.[1,2] However, note that raised clozapine levels have been attributed to treatment with the CYP3A4 inhibitor, erythromycin, see 'Clozapine + Macrolides', p.876, and lowered clozapine levels have been seen with the CYP3A4 inducer phenytoin, see 'Clozapine + Phenytoin', p.878. This suggests that, in some circumstances at least, CYP3A4 may be important in clozapine metabolism, and so the potential for an interaction cannot entirely be dismissed.

1. Raaska K, Neuvonen PJ. Serum concentrations of clozapine and *N*-desmethylclozapine are unaffected by the potent CYP3A4 inhibitor itraconazole. *Eur J Clin Pharmacol* (1998) 54, 167–70.
2. Lane H-Y, Chiu C-C, Kazmi Y, Desai H, Lam YWF, Jann MW, Chang W-H. Lack of CYP3A4 inhibition by grapefruit juice and ketoconazole upon clozapine administration *in vivo*. *Drug Metabol Drug Interact* (2001) 18, 263–78.

Clozapine + Benzodiazepines

A handful of reports describe severe hypotension, respiratory depression, unconsciousness and respiratory arrest (fatal in one case) in patients taking benzodiazepines and clozapine. Dizziness and sedation are also increased.

Clinical evidence

A schizophrenic patient did not respond to treatment with fluphenazine, **diazepam**, **clobazam** and **lormetazepam** having taken the combination for several weeks. The fluphenazine was stopped and clozapine started at a dose of 25 mg at noon and 100 mg at night. Toxic delirium and severe hypersalivation developed 3 hours later. The patient collapsed (systolic blood pressure 50 mmHg, diastolic blood pressure unrecordable) and stopped breathing. Resuscitation was started, and the patient remained unconscious for 30 minutes. After a few drug-free days clozapine 12.5 mg was successfully re-introduced, and very slowly titrated upwards; a low benzodiazepine dosage was also given.[1]

Another patient taking clozapine died suddenly and unexpectedly during the night, apparently due to respiratory arrest, after being given three 2-mg intravenous doses of **lorazepam** the previous day.[2]

There are at least 6 other cases of severe hypotension, respiratory depres-

sion or loss of consciousness in patients taking clozapine and **flurazepam**, **lorazepam** or **diazepam**,[1,3-5] as well as other cases of marked sedation, hypersalivation, ataxia and delirium in patients taking **lorazepam** and clozapine.[6,7] Two of these reports[1,3] are from the same group of workers and it is not clear whether they are about the same or different patients.

Mechanism

Not understood. Clozapine on its own very occasionally causes respiratory arrest and hypotension.

Importance and management

Evidence for an interaction between benzodiazepine and clozapine appears to be limited to case reports. The authors of the first of these reports[1] say that the relative risk of a cardiovascular/respiratory reaction is only 2.1%. Another report[2] says that the death they reported is the only life-threatening event among 162 patients given clozapine and benzodiazepines between 1986 and 1991 so that the incidence of serious problems is quite low. Even so, concurrent use should be very well monitored for any evidence of CNS depression because of the severity of the reaction, even if it is rare.

1. Grohmann R, Rüther E, Sassim N, Schmidt LG. Adverse effects of clozapine. *Psychopharmacology (Berl)* (1989) 99, S101–S104.
2. Klimke A, Klieser E. Sudden death after intravenous application of lorazepam in a patient treated with clozapine. *Am J Psychiatry* (1994) 151, 780.
3. Sassim N, Grohmann R. Adverse drug reactions with clozapine and simultaneous application of benzodiazepines. *Pharmacopsychiatry* (1988) 21, 306–7.
4. Friedman LJ, Tabb SE, Worthington JJ, Sanchez CJ, Sved M. Clozapine – a novel antipsychotic agent. *N Engl J Med* (1991) 325, 518–9.
5. Tupala E, Niskanen L, Tiihonen J. Transient syncope and ECG changes associated with the concurrent administration of clozapine and diazepam. *J Clin Psychiatry* (1999) 60, 619–20.
6. Cobb CD, Anderson CB, Seidel DR. Possible interaction between clozapine and lorazepam. *Am J Psychiatry* (1991) 148, 1606–7.
7. Jackson CW, Markowitz JS, Brewerton TD. Delirium associated with clozapine and benzodiazepine combinations. *Ann Clin Psychiatry* (1995) 7, 139–41.

Clozapine + Caffeine

Caffeine increases serum clozapine levels, which may increase the incidence of its adverse effects.

Clinical evidence

A study in 12 healthy subjects[1] found that caffeine 400 mg to 1 g daily, raised the AUC and decreased the clearance of a single 12.5-mg dose of clozapine by 19% and 14%, respectively. A previous study in 7 patients had found that clozapine levels *decreased* by 47% when the subjects *avoided* caffeine for 5 days, and increased again when caffeine consumption was resumed.[2] In a crossover study, 6 coffee-drinking patients taking clozapine were given decaffeinated or caffeine-containing instant coffee for 7 days. The plasma levels of clozapine were 26% higher while the patients were taking caffeine-containing coffee.[3]

A patient taking clozapine for schizophrenia had an exacerbation of his psychotic symptoms, which was attributed to caffeinated coffee (5 to 10 cups daily). The problem resolved when the patient stopped drinking caffeine-containing beverages. He had previously not had any problems with caffeine while taking haloperidol 30 mg and procyclidine 30 mg daily.[4]

A 31-year-old woman taking clozapine 550 mg daily developed increased daytime sleepiness, sialorrhoea and withdrawn behaviour after taking caffeine (about 1.2 g daily as drinks and tablets). Her plasma clozapine levels fell from 1500 nanograms/mL to 630 nanograms/mL when her caffeine intake was stopped.[5]

A 66-year-old woman taking clozapine 300 mg daily developed supraventricular tachycardia (180 bpm) when she was given 500 mg of intravenous caffeine sodium benzoate to increase seizure length during an ECT session. Verapamil was needed to revert the arrhythmia. Before taking clozapine she had received caffeine sodium benzoate in doses of up to 1 g during ECT sessions without problems.[6]

Mechanism

It has been suggested that caffeine and clozapine compete for the same metabolic pathway (the cytochrome P450 isoenzyme CYP1A2) resulting in a reduction in clozapine metabolism and its accumulation. Consequently clozapine serum levels and effects increase.[1,2,7] In most cases the effects appear to be modest.

Importance and management

The interaction between caffeine and clozapine would appear to be established and of clinical relevance to some patients. However, it seems unlikely to be a problem if clozapine serum levels are established and well monitored, and caffeine intake remains fairly stable and moderate. Possible exceptions are if large doses of caffeine are given during ECT treatment or if for some other reason the caffeine intake suddenly markedly increases or decreases. Patients taking clozapine should probably avoid taking large doses of caffeine-containing herbal preparations.

1. Hägg S, Spigset O, Mjörndal T, Dahlqvist R. Effect of caffeine on clozapine pharmacokinetics in healthy volunteers. *Br J Clin Pharmacol* (2000) 49, 59–63.
2. Carrillo JA, Herraiz AG, Ramos SI, Benitez J. Effects of caffeine withdrawal from the diet on the metabolism of clozapine in schizophrenic patients. *J Clin Psychopharmacol* (1998) 18, 311–16.
3. Raaska K, Raitasuo V, Laitila J, Neuvonen PJ. Effect of caffeine-containing versus decaffeinated coffee on serum clozapine concentrations in hospitalised patients. *Basic Clin Pharmacol Toxicol* (2004) 94, 13–18.
4. Vainer JL, Chouinard G. Interaction between caffeine and clozapine. *J Clin Psychopharmacol* (1994) 14, 284–5.
5. Odom-White A, de Leon J. Clozapine levels and caffeine. *J Clin Psychiatry* (1996) 57, 175–6.
6. Beale MD, Pritchett JT, Kellner CH. Supraventricular tachycardia in a patient receiving ECT, clozapine, and caffeine. *Convuls Ther* (1994) 10, 228–31.
7. Carrillo JA, Jerling M, Bertilsson L. Comments to "Interaction between caffeine and clozapine". *J Clin Psychopharmacol* (1995) 15, 376–7.

Clozapine + Carbamazepine or Oxcarbazepine

Clozapine serum levels are approximately halved by carbamazepine. An isolated case of fatal pancytopenia has been seen in one patient taking clozapine and carbamazepine, and neuroleptic malignant syndrome occurred in another.

Clinical evidence

A study by a therapeutic drug monitoring service for clozapine found that the concentration/dose ratio of 17 patients taking carbamazepine was 50% of that found in 124 other patients taking clozapine alone.[1] This suggests that clozapine levels are decreased by carbamazepine. In another 12 patients, the serum levels of clozapine decreased by 47% when they were given carbamazepine. Oxcarbazepine did not interact.[2] The plasma clozapine levels of 2 patients who had been taking clozapine 600 or 800 mg daily and carbamazepine 600 or 800 mg daily for several months were *increased* from 1.4 to 2.4 micromol/L and from 1.5 to 3 micromol/L, respectively, within 2 weeks of *stopping* the carbamazepine.[3] Similarly, a case report describes 2 schizophrenic patients taking clozapine whose treatment was changed from carbamazepine to oxcarbazepine. After 3 weeks their plasma clozapine levels had risen from 1.4 to 1.7 micromol/L and from 1.5 to 2.5 micromol/L, respectively.[4]

A man with mania taking carbamazepine 1.2 g daily and lithium developed muscle rigidity, mild hyperpyrexia, tachycardia, sweating and somnolence (diagnosed as neuroleptic malignant syndrome) 3 days after his lithium was stopped and clozapine 25 mg daily started. The symptoms immediately improved when the clozapine was stopped.[5]

A patient taking carbamazepine, lithium, benzatropine and clonazepam developed fatal pancytopenia about 10 weeks after starting clozapine 400 mg daily.[6] A retrospective study of the records of other patients given clozapine and carbamazepine found a significant increase in granulopenia.[7] A previous report had not found this, due to a statistical error.[8]

Mechanism

Not established, but it seems likely that carbamazepine (a recognised potent enzyme inducer) increases the metabolism of clozapine by the liver, thereby reducing its effects. It has been suggested that this is because carbamazepine induces the activity of the cytochrome P450 isoenzyme CYP1A2.[1] Carbamazepine may also have an effect via CYP3A4. The case of pancytopenia may possibly have been due to the additive bone marrow depressant effects of the clozapine and carbamazepine.

Importance and management

The interaction between clozapine and carbamazepine is established and clinically important: one small sub-group analysis appears to suggest that treatment with clozapine is less effective if antiepileptics (including carbamazepine) are also taken.[9] The manufacturers of clozapine advise that carbamazepine should not be given with clozapine, although this is be-

cause of the risk of bone marrow suppression.[10,11] If both drugs are necessary, monitor for clozapine efficacy and be alert for the need to increase the clozapine dosage. Furthermore, it would seem essential to increase the frequency of monitoring associated with the use of clozapine (e.g. white cell counts).

1. Jerling M, Lindström L, Bondesson U, Bertilsson L. Fluvoxamine inhibition and carbamazepine induction of the metabolism of clozapine: evidence from a therapeutic drug monitoring service. *Ther Drug Monit* (1994) 16, 368–74.
2. Tiihonen J, Vartiainen H, Hakola P. Carbamazepine-induced changes in plasma levels of neuroleptics. *Pharmacopsychiatry* (1995) 28, 26–8.
3. Raitasuo V, Lehtovaara R, Huttunen MO. Carbamazepine and plasma levels of clozapine. *Am J Psychiatry* (1993) 150, 169.
4. Raitasuo V, Lehtovaara R, Huttunen MO. Effect of switching carbamazepine to oxcarbazepine on the plasma levels of neuroleptics: a case report. *Psychopharmacology (Berl)* (1994) 116, 115–16.
5. Müller T, Becker T, Fritze J. Neuroleptic malignant syndrome after clozapine plus carbamazepine. *Lancet* (1988) 2, 1500.
6. Gerson SL, Lieberman JA, Friedenberg WR, Lee D, Marx JJ, Meltzer H. Polypharmacy in fatal clozapine-associated agranulocytosis. *Lancet* (1991) 338, 262–3.
7. Langbehm DR, Alexander B. Increased risk of side-effects in psychiatric patients treated with clozapine and carbamazepine: a reanalysis. *Pharmacopsychiatry* (2000) 33,196.
8. Junghan U, Albers M, Woggon B. Increased risk of hematological side-effects in psychiatric patients treated with clozapine and carbamazepine? *Pharmacopsychiatry* (1993) 26, 262.
9. Wilson WH. Do anticonvulsants hinder clozapine treatment? *Biol Psychiatry* (1995) 37, 132–3.
10. Clozaril (Clozapine). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, February 2009.
11. Clozaril (Clozapine). Novartis Pharmaceuticals Corporation. US Prescribing information, July 2009.

Clozapine + Drugs that cause bone marrow suppression

The manufacturers caution the use of clozapine with other drugs that can cause bone marrow suppression. Low white cells counts have been seen in patients taking clozapine and co-trimoxazole, methazolamide, nitrofurantoin, olanzapine, or thiamazole.

Clinical evidence, mechanism, importance and management

Clozapine can cause blood dyscrasias and potentially fatal agranulocytosis, therefore the manufacturers contraindicate its use with other drugs that have a well-known potential to cause agranulocytosis.[1,2] A systematic review of MEDLINE reports in English or German of non-chemotherapy, drug-induced agranulocytosis published between January 1996 and December 2006, identified 11 drugs including clozapine where there were more than 10 reports of definite or probable drug-associated agranulocytosis. The other drugs were **benzylpenicillin** (long-term, high dose), **carbimazole**, **dapsone**, **dipyrone**, **procainamide**, **propylthiouracil**, **rituximab**, **sulfasalazine**, **thiamazole**, and **ticlopidine**.[3] Comments on this review have suggested additional drugs.[4-7]

The UK manufacturer lists **chloramphenicol**, **cytotoxics**, **penicillamine**, pyrazolone analgesics (e.g. **phenylbutazone**), and **sulfonamides** (e.g. **co-trimoxazole**) as drugs that should not be given with clozapine. Furthermore, because they cannot be stopped if an adverse reaction occurs, they advise against the use of **depot antipsychotics**.[1] There are several cases that confirm the clinical significance of these predicted interactions.

A woman was taking **thiamazole** for Graves' disease, at times with various different antipsychotics including haloperidol, flupentixol, zuclopenthixol and perphenazine for schizophrenia. Because of the severe extrapyramidal reactions and failure to control the schizophrenia, clozapine, increased over 5 days to 250 mg daily, was started instead. Within 5 days her white cell count had fallen to 2.2×10^9/L, which rose to 4×10^9/L, one month after both drugs were stopped. Later, after the **thiamazole** was stopped, she was given the same dose of clozapine without these adverse effects.[8]

A patient who had been taking clozapine 500 mg daily for 8 months developed granulocytopenia within 8 days of starting to take **nitrofurantoin** 200 mg daily.[9]

An 86-year old woman taking clozapine developed neutropenia 2 weeks after **methazolamide** was added for glaucoma. Both drugs were stopped and her white cell count recovered. She later restarted clozapine without problem and so the toxic effect was attributed to the combined use of the two drugs.[10]

A 47-year-old woman who had been uneventfully taking clozapine for 5 years developed neutropenia 4 days after **co-trimoxazole** was started. **Co-trimoxazole** was stopped and the white cell counts returned to normal over the next 2 weeks.[11]

Three patients had a delay in their recovery from clozapine-induced agranulocytosis when they were given **olanzapine**, and it has been suggested that **olanzapine** should therefore be avoided until the patient's haematological status has normalised.[12]

The manufacturers also suggest that carbamazepine should not be given with clozapine, because of the risks of bone marrow depression; cases of this adverse effect have been reported. See 'Clozapine + Carbamazepine or Oxcarbazepine', p.874.

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Clozapine + H_2-receptor antagonists

A case report describes increased serum clozapine levels and toxicity due to cimetidine. Another case report describes the use of cimetidine to increase levels of clozapine to the therapeutic range. Ranitidine does not appear to interact.

Clinical evidence

A man with chronic paranoid schizophrenia was taking atenolol and clozapine 900 mg daily. When **cimetidine** 400 mg twice daily was added for gastritis, his serum clozapine levels rose by almost 60% (from a range of 992 to 1081 nanograms/mL, up to a range of 1559 to 1701 nanograms/mL) but this did not result in any adverse effects. Within 3 days of raising the dosage of **cimetidine** to 400 mg three times daily he developed evidence of clozapine toxicity (marked diaphoresis, dizziness, vomiting, weakness, orthostatic hypotension), all of which resolved over 5 days when the clozapine dosage was lowered to 200 mg daily, and the **cimetidine** was stopped. The serum clozapine levels during this period were not reported. When **cimetidine** was replaced by **ranitidine** 150 mg twice daily his clozapine serum levels were not affected.[1]

Another patient with schizophrenia who was given clozapine, titrated to 400 mg daily, had clozapine and norclozapine levels of 120 nanograms/mL and 38 nanograms/mL, respectively. The patient refused to take a higher clozapine dose. **Cimetidine** 300 mg twice daily was started, both to treat gastro-oesophageal reflux and to increase clozapine levels. After one month of concurrent use, his clozapine and norclozapine levels had increased to 278 nanograms/mL and 122 nanograms/mL, respectively. Clozapine and norclozapine levels further increased to 502 nanograms/mL and 176 nanograms/mL when the dose of **cimetidine** was increased to 1.5 g daily. The symptoms of schizophrenia improved, but he also experienced increased salivation.[2]

Mechanism

The suggested reason for this interaction is that the cimetidine (a potent non-specific enzyme inhibitor) reduces the metabolism of clozapine by the liver so that it accumulates, causing toxicity. Ranitidine does not cause enzyme inhibition and therefore does not interact.

Importance and management

Information appears to be limited to these reports but it is consistent with the way that cimetidine interacts with many other drugs. If cimetidine is

given to a patient taking clozapine, it would seem prudent to monitor the outcome closely, being alert for clozapine adverse effects, and consider monitoring clozapine levels. Ranitidine, and possibly other H_2-receptor antagonists such as famotidine or nizatidine, which do not inhibit liver enzymes and therefore do not raise clozapine levels, would seem to be preferable and safer alternatives to cimetidine; however, this needs confirmation.

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Clozapine + Hormonal contraceptives

Two case reports describe raised clozapine levels with associated adverse effects in patients who also took oral hormonal contraceptives.

Clinical evidence, mechanism, importance and management

A 47-year-old smoker with paranoid schizophrenia taking clozapine 550 mg daily had a good therapeutic response at this dose, but also reported drowsiness, weakness and dizziness. The patient was also taking an oral combined hormonal contraceptive containing **norethisterone** 500 micrograms and **ethinylestradiol** 35 micrograms. Clozapine plasma levels ranged from 736 to 792 nanograms/mL (reference range 300 to 700 nanograms/mL). After 2 months she stopped taking her contraceptive and noted that the adverse effects of clozapine resolved: her clozapine levels were found to be 378 to 401 nanograms/mL. The patient did not stop smoking during this time.[1]

A second report describes a 33-year-old woman who had taken clozapine 500 mg daily for several months. Within one week of starting to take an oral hormonal contraceptive containing **ethinylestradiol**, she experienced marked drowsiness, anergy, dizziness, and orthostasis. Her blood level of clozapine had increased from 448 nanograms/mL to 1281 nanograms/mL. The oral contraceptive was stopped and after 3 days the clozapine level fell to 577 nanograms/mL. Several weeks later, the dose of clozapine was reduced to 200 mg daily, and she restarted the contraceptive: her clozapine level was 531 nanograms/mL.[2]

It was suggested that the hormonal contraceptive inhibited the cytochrome P450 isoenzymes CYP1A2, CYP2C19 and CYP3A4 resulting in raised clozapine plasma levels.[1,2] The authors note that slower titration and smaller doses of clozapine may be needed in patients taking hormonal contraceptives.[1,2] Further study is needed as these reports appear to be the only published cases of this interaction.

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Clozapine + Lamotrigine

An isolated case report suggests that lamotrigine may raise clozapine plasma levels. A study did not find an interaction.

Clinical evidence, mechanism, importance and management

A 35-year-old man, who had been taking clozapine for 3 years, became dizzy and sedated about one month after starting to take lamotrigine. His plasma clozapine levels were found to have increased to 1020 micrograms/L. When the lamotrigine was stopped his levels fell to 450 micrograms/L.[1]

In contrast, a study in 11 patients taking clozapine in doses of 200 mg to 500 mg daily, and who were also given lamotrigine in increasing doses over 8 weeks to 200 mg daily found no significant changes in the pharmacokinetics of clozapine.[2]

Evidence for an interaction between lamotrigine and clozapine appears to be limited to the isolated case report, the findings of which are in contrast to the study. Furthermore, there appears to be no pharmacokinetic mechanism for this interaction. The evidence is currently too slim to recommend any additional precautions if lamotrigine is given to a patient taking clozapine.

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2. Spina W, D'Arrigo C, Migliardi G, Santoro V, Muscatello MR, Micò U, D'Amico G, Perucca E. Effect of adjunctive lamotrigine treatment on the plasma concentrations of clozapine, risperidone and olanzapine in patients with schizophrenia or bipolar disorder. *Ther Drug Monit* (2006) 28, 599–602.

Clozapine + Macrolides

A study in healthy subjects found no evidence of an interaction between clozapine and erythromycin, but three case reports describe clozapine toxicity (e.g. seizures drowsiness, neutropenia) when the patients were given erythromycin.

Clinical evidence

A randomised, crossover study in 12 healthy subjects found that **erythromycin** 500 mg three times daily did not affect the pharmacokinetics of a single 12.5-mg dose of clozapine.[1]

In contrast, a man with schizophrenia taking clozapine 800 mg daily, was given **erythromycin** 250 mg four times daily for a fever and sore throat caused by pharyngitis. After a week he had a single tonic-clonic seizure and his serum clozapine levels were found to be 1300 micrograms/mL. Both drugs were stopped, and the clozapine restarted 2 days later, initially at only 400 mg daily, but then, after several weeks, the dose had increased to 800 mg daily, giving serum clozapine levels of 700 micrograms/mL.[2] Another man with schizophrenia taking clozapine 600 mg daily became drowsy, with slurred speech, incontinence, difficulty in walking and incoordination within 2 to 3 days of starting to take **erythromycin** 333 mg three times daily. His serum clozapine level was found to be 1150 micrograms/L and he had leucocytosis. He recovered when both drugs were stopped. When he later restarted treatment with the same clozapine dose, but without the **erythromycin**, his steady-state trough clozapine serum level was 385 micrograms/L.[3] Another case also describes a reduced white cell count when **erythromycin** was added to established treatment with clozapine, but no clozapine levels were available.[4]

Mechanism

Uncertain. One suggestion is that erythromycin might have inhibited the cytochrome P450 isoenzyme CYP3A4, which has a minor role in the metabolism of clozapine, leading to a reduced clearance, which resulted in increased serum clozapine levels and toxicity.[2,3] Clozapine is mainly metabolised by CYP1A2, which is not known to be affected by the macrolides.

Importance and management

Information appears to be limited to this study and the three case reports, but there are a number of case reports describing *reduced* clozapine levels with CYP3A4 *inducers*. This suggests that, in some circumstances at least, CYP3A4 may be important in clozapine metabolism, and so the potential for an interaction cannot entirely be dismissed. Some reports suggest that clozapine levels may be increased by bacterial infections and therefore it is possible that the effects seen were independent of erythromycin use. However, in one of these cases **roxithromycin** (which is known to interact similarly to erythromycin) was given,[5] and in the other, an effect of mirtazapine could not be ruled out.[6] Whatever the reason, cases of raised clozapine levels with erythromycin appear to be rare. Bear this interaction in mind if clozapine adverse effects (e.g. agitation, dizziness, sedation, hypersalivation) develop.

There does not appear to be any information about other macrolides. However, until the mechanism for this effect is established, it may be prudent to suspect an interaction if clozapine adverse effects develop in any patient taking a macrolide that inhibits CYP3A4 (e.g. **clarithromycin**, **telithromycin**).

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3. Cohen LG, Chesley S, Eugenio L, Flood JG, Fisch J, Goff DC. Erythromycin-induced clozapine toxic reaction. *Arch Intern Med* (1996) 156, 675–7.
4. Usiskin SI, Nicolson R, Lenane M, Rapoport JL. Retreatment with clozapine after erythromycin-induced neutropenia. *Am J Psychiatry* (2000) 157, 1021.

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Clozapine + Miscellaneous

There are isolated cases of apparent interactions between clozapine, and ampicillin, buspirone, haloperidol, loperamide, modafinil, nefazodone, nicotinic acid, tryptophan, or vitamin C. Grapefruit juice, influenza vaccine, reboxetine, and venlafaxine do not appear to interact with clozapine. Cocaine levels may be increased by clozapine.

Clinical evidence, mechanism, importance and management

(a) Ampicillin

An isolated report describes a 17-year-old taking clozapine (12.5 mg increased to 50 mg three times daily) who was given ampicillin 500 mg four times daily, starting on day 15 of clozapine treatment. On the next day the patient became easily distracted, very drowsy and salivated excessively. These adverse reactions stopped when the ampicillin was replaced by doxycycline.[1]

(b) Buspirone

A man who had been taking clozapine for a year developed acute and potentially lethal gastrointestinal bleeding and marked hyperglycaemia about 5 weeks after starting buspirone, and one week after the buspirone dosage was raised to 20 mg daily. No gut pathology (e.g. ulceration) was detected and there were no problems when he was subsequently given clozapine alone, so the reaction was attributed to the drug combination.[2]

(c) Cocaine

A single-dose study in 8 cocaine addicts found that clozapine caused a dose-dependent rise in the serum levels of a 2-mg/kg intranasal dose of cocaine. Cocaine levels rose by 6%, 49% and 67% after clozapine was given in doses of 12.5 mg, 25 mg or 50 mg, respectively. Subjective questioning revealed a reduction in the positive effects of cocaine. One subject also experienced a near-syncopal attack which required medical attention.[3]

(d) Grapefruit juice

Grapefruit juice did not affect the metabolism of clozapine in two studies in a total of 36 patients with schizophrenia.[4,5]

(e) Haloperidol

A 68-year-old man taking clozapine 600 mg daily and venlafaxine, lorazepam, aspirin, vitamin E and multivitamins, was given haloperidol 4 mg daily to control persistent paranoid delusions and hallucinations. After 27 days he was found collapsed and was lethargic, tachycardic, feverish and delirious. Neuroleptic malignant syndrome was suspected so the antipsychotics were withheld, and the patient recovered over the following 7 days. Clozapine was later re-started without a recurrence of symptoms.[6]
A case of elevated haloperidol levels has been reported in a 40-year-old man who was given haloperidol intramuscular injections 50 mg every 4 weeks. He was also given clozapine in increasing doses from 50 to 250 mg daily. Over this time his haloperidol levels increased from 12 nanogram/mL to 166 nanogram/mL, although it is not clear whether he had attained steady-state levels when the first measurement was reported.[7]

(f) Influenza vaccine

In an open-label study in 14 patients the metabolism of clozapine was not altered following a single intramuscular dose of influenza vaccine (*Influvac* 2001 to 2002 formula, Solvay).[8]

(g) Loperamide

A patient taking clozapine 500 mg daily died after taking loperamide 6 mg daily during an episode of food poisoning. The authors of the report attribute the death to toxic megacolon brought on by the additive effects of clozapine and loperamide on gut transit.[9] Toxic megacolon can sometimes occur with loperamide alone, especially in the presence of an infection, and clozapine can cause constipation by virtue of its antimuscarinic effects.

(h) Mirtazapine

A study in 9 patients taking clozapine in doses ranging from 100 to 650 mg daily found no significant change in the pharmacokinetics of clozapine after the addition of mirtazapine 30 mg daily.[10]

(i) Modafinil

A 42-year-old man taking clozapine 450 mg daily was given modafinil, titrated up to 300 mg daily, to combat sedation. After about one month of concurrent use he developed dizziness and an unsteady gait, and his clozapine serum level was found to be 1400 nanograms/mL. His clozapine level had been 761 nanograms/mL while taking clozapine 400 mg daily, and because the 50 mg clozapine dose increase was not thought large enough to almost double his clozapine level, an interaction with modafinil was suspected.[11]

(j) Nefazodone

A 40-year-old man who had been successfully treated with risperidone and clozapine 425 to 475 mg daily started taking nefazodone 200 mg daily, increasing to 300 mg daily, for the treatment of persistent depression. After one week on the higher dose he became dizzy and hypotensive and it was noted that his clozapine plasma level had risen from 133 to 233 nanograms/mL. This was thought to be due to an inhibitory effect of nefazodone on the cytochrome P450 isoenzyme CYP3A4.[12] In contrast, a small study in 6 patients taking clozapine found that the addition of nefazodone had no significant effects on the pharmacokinetics of clozapine.[13]

A possible case of neutropenia was attributed to the addition of nefazodone to sodium valproate and clozapine. The patient had been taking sodium valproate and clozapine for many months when nefazodone was started, in increasing doses up to 200 mg twice daily. Within one week her neutrophil count had dropped to 1.8×10^9/L, and remained low until the nefazodone was discontinued. The patient's clozapine level was reported to remain stable during this time and the patient had not had any previous episodes of leucopenia during treatment with clozapine.[14]

(k) Nicotinic acid/Tryptophan/Vitamin C

A man with schizophrenia taking tryptophan, lorazepam, vitamin C, benzatropine and nicotinic acid, developed a severe urticarial rash covering his face, neck and trunk 3 days after starting clozapine 150 mg daily. All of the drugs except lorazepam were stopped, and the rash subsided. It did not recur when clozapine was restarted, even at a dose of 600 mg daily, nor when small doses of benzatropine and fluphenazine were briefly added. The authors draw the inference that tryptophan, vitamin C and nicotinic acid may have been responsible for this alleged interaction with clozapine.[15]

(l) Reboxetine

A small study in 7 patients found that reboxetine 8 mg daily had no effect on the metabolism of clozapine or its major metabolite.[16]

(m) Ritonavir

Ritonavir is a potent inhibitor of the cytochrome P450 isoenzymes CYP3A4 and CYP2D6, and is therefore expected to increase plasma levels of clozapine. This may result in serious haematologic abnormalities, although there appear to be no published studies or case reports of this effect. The UK manufacturers of ritonavir therefore contraindicate concurrent use.[17]

(n) Venlafaxine

In 11 patients, venlafaxine in doses of up to 150 mg daily did not affect the pharmacokinetics of established clozapine treatment in doses of up to 950 mg daily.[18]

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2. Good MI. Lethal interaction of clozapine and buspirone? *Am J Psychiatry* (1997) 154, 1472–3.
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4. Lane H-Y, Chiu C-C, Kazmi Y, Desai H, Lam YWF, Jan MW, Chang W-H. Lack of CYP3A4 inhibition by grapefruit juice and ketoconazole upon clozapine administration *in vivo*. *Drug Metabol Drug Interact* (2001) 18, 263–78.
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17. Norvir Soft Capsules (Ritonavir). Abbott Laboratories Ltd. UK Summary of product characteristics, October 2009.
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Clozapine + Phenobarbital

Clozapine serum levels are possibly reduced by phenobarbital.

Clinical evidence

A patient had a seizure 10 days after his dose of clozapine was titrated up to 300 mg twice daily. Phenobarbital 60 mg daily was given to prevent further seizures and after 4 months the dose of clozapine was tapered down to 400 mg daily. When phenobarbital was gradually withdrawn the patient experienced moderate sedation and drowsiness and clozapine levels were found to have increased by about 75%, when compared with the levels found during the concurrent use of phenobarbital.[1] Similarly, mean clozapine plasma levels in 7 patients taking clozapine and phenobarbital were 35% lower than those of 15 patients taking clozapine alone.[2]

Mechanism

Not established, but it seems likely that phenobarbital (a recognised potent enzyme inducer) increased the metabolism of clozapine by the liver, thereby reducing its effects. It has been suggested that this is due to induction of the cytochrome P450 isoenzyme CYP1A2 and CYP3A4.

Importance and management

Evidence for an interaction between clozapine and phenobarbital is limited, but it appears to be clinically important: one sub-group analysis appears to suggest that treatment with clozapine is less effective if antiepileptics (including phenobarbital) are also taken.[3] Monitor clozapine efficacy and be alert for the need to increase the clozapine dose if phenobarbital is started. **Primidone** is metabolised in the body to phenobarbital. It would therefore be expected to interact similarly.

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Clozapine + Phenytoin

Clozapine serum levels are possibly reduced by phenytoin.

Clinical evidence

Two patients taking clozapine had reduced clozapine levels (falls of 65 to 85%) and worsening psychoses when phenytoin was also given.[1] Another patient developed neutropenia, which was attributed to the concurrent use of phenytoin and clozapine. When the phenytoin was stopped clozapine levels rose from 114 nanograms/mL to 137 nanograms/mL, suggesting a pharmacokinetic interaction,[2] rather than just additive adverse effects.

Mechanism

Not established, but it seems likely that phenytoin (a recognised potent enzyme inducer) increased the metabolism of clozapine by the liver, thereby reducing its effects. It has been suggested that this is due to induction of the cytochrome P450 isoenzyme CYP1A2 and possibly CYP3A4.

Importance and management

Evidence for an interaction between clozapine and phenytoin is limited, but it appears to be clinically important: one sub-group analysis appears to suggest that treatment with clozapine is less effective if antiepileptics (including phenytoin) are also taken.[3] Monitor clozapine efficacy and be alert for the need to increase the clozapine dose if phenytoin is given.

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Clozapine + Proton pump inhibitors

Omeprazole appears to reduce the serum levels of clozapine.

Clinical evidence, mechanism, importance and management

A retrospective study identified 13 patients taking clozapine and **omeprazole** in who the proton pump inhibitor was subsequently changed to **pantoprazole**. This resulted in an increase in the mean clozapine serum level from 445 nanograms/mL to 579 nanograms/mL in 3 non-smokers, but in the 10 smokers there was a slight *reduction* in levels, from 364 to 323 nanograms/mL. Both **omeprazole** and smoking are known to induce the cytochrome P450 isoenzyme CYP1A2, which is the major isoenzyme involved in the metabolism of clozapine. The authors suggest that when **omeprazole** was stopped in the non-smokers there was no CYP1A2 induction, hence clozapine levels rose, whereas in the smokers CYP1A2 induction continued, so their levels were only slightly affected by stopping **omeprazole**.[1]

A case report describes two patients (both smokers) whose clozapine levels were reduced, from 762 to 443 nanograms/mL and from 369 to 204 nanograms/mL, respectively, after **omeprazole** was started. However, no changes in clinical condition were noted.[2]

The interaction between clozapine and **omeprazole** appears to be relatively modest, with clozapine levels effectively reduced by about up to 45% by **omeprazole**. Nevertheless, it would seem prudent to monitor clozapine efficacy if **omeprazole** is started. Other proton pump inhibitors do not appear to have been studied.

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2. Frick A, Kopitz J, Bergemann N. Omeprazole reduces clozapine plasma concentrations. *Pharmacopsychiatry* (2003) 36, 121–3.

Clozapine + Quinolones

A small number of case reports suggest that ciprofloxacin may increase clozapine levels and cause clozapine toxicity. A study supports these observations.

Clinical evidence

An elderly man with multi-infarct dementia and behavioural disturbances, taking clozapine, glibenclamide (glyburide), trazodone and melatonin, was hospitalised for agitation on the last day of a 10-day course of **ciprofloxacin** 500 mg twice daily. When the **ciprofloxacin** course was completed, his plasma clozapine serum levels fell from 90 nanograms/mL to undetectable levels (lower limit of detection being 50 nanograms/mL).[1]

A 64-year-old woman with schizophrenia whose symptoms had been controlled with clozapine 125 mg twice daily for 5 years became dizzy and somnolent within a few days of starting **ciprofloxacin** 500 mg twice daily. Clozapine and norclozapine levels were found to be 1043 nanograms/mL and 432 nanograms/mL, respectively. It was thought that she was no longer able to tolerate the clozapine and it was discontinued and replaced with ziprasidone which did not control her psychotic symptoms. It was then suggested that the high clozapine levels and adverse effects could have been due to an interaction with **ciprofloxacin**. Ziprasidone was tapered and clozapine re-introduced and titrated back up to her original dose of 125 mg twice daily. Clozapine and norclozapine levels were found to be

686 nanograms/mL and 244 nanograms/mL and there were no symptoms of toxicity.[2] A woman who was taking clozapine developed a raised level (1498 nanograms/mL), confusion and irritability when she started to take **ciprofloxacin** for a urinary tract infection. Clozapine was stopped, and the symptoms resolved. Subsequently clozapine was re-introduced and a level of 787 nanograms/mL was achieved.[3]

In a study, 7 patients with schizophrenia taking clozapine were given **ciprofloxacin** 250 mg twice daily for 7 days. The mean serum clozapine and *N*-desmethylclozapine levels were increased by 29% and 31%, respectively, but no additional adverse effects were reported. Interindividual variation in serum levels was high, so it seems likely that some patients may demonstrate a clinically significant interaction.[4]

Mechanism

This interaction probably occurs because ciprofloxacin inhibits the cytochrome P450 isoenzyme CYP1A2, the major isoenzyme involved in the metabolism of clozapine. Clozapine metabolism is therefore reduced, resulting in elevated clozapine levels.

Importance and management

An interaction between clozapine and ciprofloxacin is established and clinically relevant. Monitor for clozapine adverse effects (e.g. agitation, dizziness, sedation, hypersalivation) if ciprofloxacin is added. There seem to be no other reports of an interaction between clozapine and other quinolones, but as they all inhibit CYP1A2 to a varying extent (see 'Theophylline + Quinolones', p.1452) some interaction seems possible.

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Clozapine + Rifampicin (Rifampin)

Case reports suggest that rifampicin reduces clozapine levels.

Clinical evidence

A schizophrenic patient taking clozapine developed tuberculosis and was given rifampicin, isoniazid and pyrazinamide. Within 2 to 3 weeks his trough serum clozapine levels had fallen dramatically from about 250 nanograms/mL to 40 nanograms/mL, but rose again rapidly when the rifampicin was replaced by ciprofloxacin.[1] A second case report describes a patient who was stable taking clozapine 300 mg daily, but who had symptoms of hypersalivation and sedation. He was given rifampicin 600 mg daily for tuberculosis, and after 2 weeks the adverse effects of clozapine began to resolve, but his psychosis started to re-emerge. His clozapine dose was increased to 550 mg daily without much improvement in his condition. Rifampicin was stopped after 6 months, at which point his psychotic symptoms markedly improved and the clozapine adverse effects of sedation and hypersalivation reappeared.[2]

Mechanism

Clozapine is metabolised by the cytochrome P450 isoenzyme CYP1A2, with some contribution from other isoenzymes, including CYP3A4. Rifampicin is a potent enzyme inducer, which affects both of these isoenzymes. It therefore seems likely that rifampicin increases clozapine metabolism leading to a decrease in its levels.

Importance and management

Evidence for an interaction between rifampicin and clozapine is limited, but the effects seen in the cases are consistent with the way rifampicin interacts with other drugs. Clozapine serum levels should be well monitored if rifampicin is added. The cases indicate that an increase in the dose of clozapine may not be successful in managing this interaction, and therefore it may be prudent to consider the use of other drugs. In the first case ciprofloxacin was successfully given, although note that this drug *increases* clozapine levels, see 'Clozapine + Quinolones', p.878.

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Clozapine + Risperidone

The concurrent use of clozapine and risperidone can be effective and well tolerated but two isolated reports describe a rise in serum clozapine levels when risperidone was added and the development of atrial ectopics. Dystonia has been seen when clozapine was replaced by risperidone.

Clinical evidence, mechanism, importance and management

A man with a schizoaffective disorder taking clozapine started to take risperidone, firstly 500 micrograms twice daily, and then after a week 1 mg twice daily. Clinical improvement was seen and it was found that after 2 weeks his serum clozapine levels had risen by 74%, from 344 nanograms/mL to 598 nanograms/mL, without any adverse effects.[1] The serum clozapine levels of another patient more than doubled when risperidone was given. No signs of clozapine toxicity were seen, but mild oculogyric crises were reported.[2] A patient with schizophrenia taking clozapine and trihexyphenidyl, who developed tachycardia of 120 bpm, which was controlled with propranolol, developed atrial ectopics when risperidone 1.5 mg daily was added. The ectopics stopped when the risperidone was withdrawn and started again when it was re-introduced. Clozapine plasma levels were normal throughout the duration of risperidone treatment.[3] Another report describes 4 patients developed dystonia after their treatment was changed from clozapine to risperidone.[4] A single case of agranulocytosis has been seen 6 weeks after risperidone was added to stable clozapine treatment. The patient needed 3 doses of G-CSF before the white cell count returned to normal.[5] Another case report describes neuroleptic malignant syndrome in a 20-year-old man within 2 days of clozapine being added to risperidone treatment. The drugs were stopped and he recovered over the following 10 days. He subsequently received clozapine alone without problem.[6]

Contrasting with these reports is a study in 12 patients with schizophrenia, which found that the addition of risperidone to clozapine was both effective and well tolerated, although 4 patients complained of mild akathisia. Serum clozapine levels were not significantly changed.[7] Furthermore, a retrospective study in 18 patients also found that risperidone did not alter clozapine serum levels.[8]

The suggested reason for the raised clozapine levels is that both drugs compete for metabolism by the cytochrome P450 isoenzyme CYP2D6 resulting in a reduction in the metabolism of the clozapine,[1,2] although this does not explain why only some patients are affected. The dystonias are attributed to cholinergic rebound and ongoing dopamine blockade caused by a rapid switch of medication. The recommendation is that withdrawal of clozapine should be tapered and possibly that an antimuscarinic drug should be given.[4] The raised clozapine levels seem to be isolated cases and are therefore of doubtful general significance.

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3. Chong SA, Tan CH, Lee HS. Atrial ectopics with clozapine-risperidone combination. *J Clin Psychopharmacol* (1997) 17, 130–1.
4. Simpson GM, Meyer JM. Dystonia while changing from clozapine to risperidone. *J Clin Psychopharmacol* (1996) 16, 260–1.
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Clozapine + SSRIs

Fluvoxamine dramatically raises clozapine levels; fluoxetine and paroxetine have more modest effects. Small increases in clozapine levels may occur with sertraline. Studies suggest that citalopram

generally does not interact, although one case report describes raised clozapine levels in a patient taking citalopram.

Clinical evidence

(a) Citalopram

A preliminary study in 5 patients found that their mean plasma clozapine levels were unchanged by citalopram.[1] Another study in 8 patients found similar results.[2] However, a patient who was stable taking clozapine developed sedation, hypersalivation and confusion shortly after he started to take citalopram 40 mg daily. When total clozapine serum levels were measured they were found to be 1097 nanograms/mL. The citalopram dose was reduced to 20 mg daily, the symptoms resolved over the following 2 weeks, and the total clozapine level dropped to 792 nanograms/mL.[3]

(b) Fluoxetine

Several studies and case reports have found increased clozapine levels of 30 to 75%, and increased levels of the metabolite norclozapine of 34 to 52% after fluoxetine was added to established clozapine treatment.[4-6] In two cases the levels of clozapine and norclozapine were raised more than fivefold by fluoxetine. One patient developed hypertension but the other experienced no troublesome adverse effects and his mood and psychotic symptoms improved.[7,8]

A patient who had been taking clozapine 500 mg and lorazepam 3 mg daily, developed myoclonic jerks of his whole body 79 days after fluoxetine 20 mg was added. These decreased over the next 2 days when the fluoxetine and lorazepam were stopped.[9] The death of a 44-year old patient who was taking clozapine and fluoxetine was felt to be due to an increase in clozapine levels caused by fluoxetine.[10] Another case report attributes an SSRI withdrawal reaction to an interaction between fluoxetine and clozapine, although it is unclear what part the clozapine had to play in this.[11]

In contrast, there are reports of successful use,[12] and no pharmacokinetic changes[13] when clozapine and fluoxetine were used together.

A case has also been reported of a patient with schizophrenia and depression, whose cognitive symptoms improved when he took clozapine and fluoxetine, but when treatment was changed to sertraline, this improvement was not sustained. The authors tentatively suggested that the fluoxetine elevated plasma clozapine levels by inhibition of CYP2D6, whereas this effect was not seen with sertraline as it is a much weaker inhibitor of this enzyme.[14] However, this explanation has been questioned, since the role of other drug metabolising enzymes was not considered.[15]

(c) Fluvoxamine

Up to tenfold elevations in plasma clozapine levels have been seen in several studies and case reports when clozapine was given with fluvoxamine.[16-27] These elevations occurred as early as 14 days after concurrent use began,[26] but were often not associated with any significant adverse effects, even after treatment had continued for a year in one patient.[19] Another study, which compared 12 patients taking clozapine with 11 patients taking clozapine and fluvoxamine, found that in the combined treatment group, clozapine doses were about half those used when clozapine was given alone. A trend towards decreased granulocyte levels was also seen in the clozapine with fluvoxamine group, but not when clozapine was used alone.[28]

Another patient had extremely high plasma clozapine levels of up to 4160 micrograms/L as a result of taking fluvoxamine.[29]

Other cases have also demonstrated worsening psychosis[30] or extrapyramidal adverse effects[31] (including, rigidity, tremors and akathisia) and sedation within days of giving fluvoxamine with clozapine.

A study in 68 patients taking either clozapine alone or clozapine and fluvoxamine found a trend towards less weight increase after 12 weeks of treatment in the group of patients also taking fluvoxamine. Those patients taking clozapine alone were found to have significantly higher glucose and triglyceride levels.[32] Note that fluvoxamine treatment alone can result in weight loss.

(d) Paroxetine

The serum levels of clozapine and norclozapine rose by 57% and 50%, respectively, in 16 schizophrenic patients after they took an average of 31.2 mg of paroxetine daily. One patient taking clozapine 300 mg daily developed reversible cerebral intoxication when given paroxetine 40 mg daily.[5] Another patient with a delusional disorder developed an antimuscarinic syndrome with doubled serum clozapine levels within about 3 weeks of the addition of paroxetine.[33] A further study in 9 patients found that the serum levels of clozapine and norclozapine rose by 31% and 20%, respectively, when paroxetine 20 to 40 mg daily was given for 3 weeks. Two patients experienced mild and transient sedation 2 to 3 days after starting paroxetine. The rise in clozapine levels was not associated with an increase in efficacy and was well tolerated.[34] In contrast, a study in 14 patients taking clozapine 2.5 to 3 mg/kg daily found that the addition of paroxetine 20 mg daily had no effect on the serum levels of clozapine.[24] This, or similar work, has been published elsewhere.[35]

An increase in the plasma levels of clozapine, thought to be due to concurrent treatment with paroxetine, has been suggested as the causative factor in the development of a fatal venous thromboembolism in a 47-year-old woman.[36]

A fatal case of neuroleptic malignant syndrome, which started to develop two days after the introduction of clozapine 25 mg daily to established treatment with paroxetine 20 mg daily, has been reported. The patient had previously taken clozapine alone with no problem.[37]

(e) Sertraline

In 10 patients with schizophrenia the serum levels of clozapine and norclozapine increased by 30% and 52%, respectively, when they started to take an average of 92.5 mg of sertraline daily.[5] Another patient taking clozapine 600 mg daily had a 40% reduction in total clozapine serum levels within one month of stopping sertraline 300 mg daily.[38]

The serum clozapine levels of a patient with schizophrenia doubled within a month of adding sertraline 50 mg daily and her psychosis worsened. When the sertraline was stopped she improved and her serum clozapine levels fell once again.[30] In contrast, a study in 8 patients who were taking clozapine 200 to 400 mg daily and were also given sertraline 50 to 100 mg per day for 3 weeks, found no significant changes in the levels of clozapine and its major metabolites.[34]

A case report describes sudden cardiac death in a 26-year-old man, which the authors attributed to an interaction between clozapine and sertraline.[39] However, this interaction has been questioned as it is said that the patient had other risk factors that were more likely to have caused the fatality.[40]

Mechanism

The SSRIs (including **escitalopram**) are known to inhibit the cytochrome P450 isoenzyme CYP2D6 to a varying extent. Fluvoxamine is also a potent inhibitor of CYP1A2. Both of these isoenzymes are involved in the metabolism of clozapine, the most significant being CYP1A2, so their inhibition causes clozapine levels to rise. The levels of clozapine and norclozapine rise together, and so it has been suggested that the metabolic step inhibited is after the *N*-dealkylation step.[5]

Importance and management

The interactions of the SSRIs with clozapine are established. Concurrent use need not be avoided, but it would be prudent to monitor the outcome closely when any SSRI is used with clozapine because of the rises in serum clozapine and norclozapine levels that can occur, and because of the rare potential for deterioration in clinical status. Adjust the clozapine dose as necessary. The authors of one study suggest particularly close monitoring if the clozapine dose exceeds 300 mg or 3.5 mg/kg daily.[5] The interaction is greatest with fluvoxamine, so other SSRIs may be a more prudent choice, although close monitoring is still required.

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Clozapine + Tobacco or Cannabis

Smoking tobacco appears to decrease clozapine levels and clozapine toxicity may occur due to increased levels on smoking cessation.

Clinical evidence

(a) Cannabis

A 37-year-old man who smoked both tobacco and cannabis daily, and took clozapine 700 mg daily, experienced elevated clozapine plasma levels and signs of clozapine toxicity, one month after he stopped smoking both tobacco and cannabis. One week after reducing the dose of clozapine to 500 mg daily, his psychotic symptoms disappeared and plasma levels returned to normal.[1]

(b) Tobacco

Although one group of workers found that smoking did not affect clozapine levels,[2] and another found only a trend towards a reduction in clozapine levels in smokers,[3] the majority of the available data supports an interaction between smoking and clozapine. Several studies have found that smokers had clozapine levels that were up to 50% lower than those of non-smokers.[4-6] One study in 11 patients found a mean *increase* in clozapine levels of about 72% on smoking *cessation*,[7] and a retrospective study found that the clozapine clearance was 86% higher in 9 smokers than in 3 non-smokers.[8] A study in 80 patients with schizophrenia, taking clozapine 25 mg to 700 mg daily, found that the concentration-dose ratio of clozapine in the 45 patients who smoked at least 15 cigarettes daily was 2.4-fold lower than in those patients who did not smoke.[9]

A number of case reports also support the existence of an interaction. One case report describes 2 patients with psychoses resistant to treatment with clozapine. Both patients were heavy smokers and one also consumed large amounts of caffeine, which would have been expected to increase plasma clozapine levels (see also 'Clozapine + Caffeine', p.874), but it was considered that the CYP1A2 induction due to smoking increased clearance of both clozapine and caffeine.[10] Two case reports describe elevations in clozapine plasma levels when the patients stopped smoking abruptly;[11,12] in one case this was associated with seizures. Another three case reports suggest that smoking cessation may have resulted in clozapine adverse effects, including seizures, although no plasma levels were available.[13-15]

A report describes a patient, stable while taking clozapine 500 mg daily, who used *Nicotrol* inhalers as a substitute for smoking when he was admitted to a 'smoke-free' hospital. He re-started smoking after discharge from hospital and his paranoid symptoms and hallucinations returned and his clozapine levels fell from 417 nanograms/mL to 192 nanograms/mL.[16]

Mechanism

Tobacco smoke contains aromatic hydrocarbons that are potent inducers of the cytochrome P450 isoenzyme CYP1A2, which is the major isoenzyme involved in clozapine metabolism. Smoking therefore increases clozapine metabolism and lower levels result. Nicotine patches and other nicotine products used as replacement therapy do not induce CYP1A2.[16]

Importance and management

An interaction between smoking and clozapine is established. It has been suggested that smoking 7 to 12 cigarettes daily is probably sufficient for maximum induction of clozapine metabolism and that a 50% lower starting dose is suggested for non-smokers.[5] In smokers who are resistant to clozapine, using single doses of clozapine at night when the patients are not smoking, or augmentation of treatment with another drug such as low-dose amisulpride has been suggested.[10] It has also been suggested that if a patient taking clozapine starts to smoke, a 50% increase in clozapine dose should be anticipated. Likewise, a patient who stops smoking may experience a 50% increase in clozapine levels within 2 to 4 weeks of stopping smoking. One report recommends that patients with high baseline clozapine levels should be monitored if they stop smoking.[7] In all cases, dose adjustments should be guided by the clinical status of the patient, and clozapine levels where available.[10,17]

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15. McCarthy RH. Seizures following smoking cessation in a clozapine responder. *Pharmacopsychiatry* (1994) 27, 210–11.
16. Sandson NB, Cozza KL, Armstrong C, Eckermann G, Fischer A, Phillips B. Clozapine case series. *Psychosomatics* (2007) 48, 170–5.
17. de Leon J. Atypical antipsychotic dosing: the effect of smoking and caffeine. *Psychiatr Serv* (2004) 55, 491–3.

Clozapine + Topiramate

Topiramate does not affect the plasma levels of clozapine.

Clinical evidence, mechanism, importance and management

In a study, 10 patients receiving long-term treatment with clozapine 250 mg to 500 mg daily were given topiramate in a dose that was increased gradually to 200 mg daily. The plasma levels of clozapine and its metabolite norclozapine were not significantly affected by topiramate and the combination was well tolerated.[1] This suggests that the dose of clozapine is unlikely to need adjusting if topiramate is also given.

1. Migliardi G, D'Arrigo C, Santoro V, Bruno A, Cortese L, Campolo D, Cacciola M, Spina E. Effect of topiramate on plasma concentrations of clozapine, olanzapine, risperidone, and quetiapine in patients with psychotic disorders. *Clin Neuropharmacol* (2007) 30, 107–13.

Clozapine + Valproate

Valproate may increase or decrease serum clozapine levels but the effects appear to be modest.

Clinical evidence

A controlled study in 11 patients found that when valproate (at an average dose of 1.06 g daily) was given with clozapine, the steady-state serum clozapine levels were increased by 39% and the levels of the demethylated metabolite of clozapine were increased by 23%. However, correction of these levels for dose and weight reduced the total clozapine metabolite values to only 6% above those of the controls. No increase in clozapine adverse effects was seen.[1] Another study found that the concurrent use of sodium valproate and clozapine had no significant effect on the pharmacokinetics of either drug.[2]

In contrast, a study in 4 schizophrenics taking clozapine 550 to 650 mg daily found that when valproate semisodium (divalproex sodium) 750 mg to 1 g daily was added, the serum clozapine levels began to fall, and by 3 weeks had dropped by an average of 41%. However, no deterioration in clinical condition occurred.[3] In another study in 7 patients given clozapine, the clozapine levels were decreased by a more modest 15% when valproic acid was given.[4] An isolated report describes a 37-year-old man taking clozapine, who developed sedation, confusion, slurred speech and impaired functioning on two occasions when valproate semisodium was added.[5] Clozapine levels were doubled in a patient after valproic acid treatment was stopped.[6] The authors of an analysis of reports on the use of mood stabiliser combinations obtained from a MEDLINE search noted that there may be additive adverse effects of weight gain and drowsiness with the combination of clozapine and valproate.[7]

Mechanism

Unclear. It has been suggested that valproate may increase the metabolism of clozapine, although it is unclear which pathway is affected. Alternatively it has been suggested that valproate impairs clozapine absorption.[6]

Importance and management

Evidence for an interaction between clozapine and valproate appears to be limited to these reports, and the situation is not entirely clear. A subgroup analysis of 20 patients who received clozapine and antiepileptics including valproate suggested that this group of patients showed less clinical improvement than patients who were not also taking an antiepileptic. However, the indication for the antiepileptic drug was not always clear and combined treatment may have been used in patients who were more severely ill, or less responsive to clozapine alone, and the effects of valproate were not separated from those of the enzyme-inducing antiepileptics, which are known to reduce clozapine levels.[8]

In general, the effects on clozapine levels in the case reports were relatively modest, and the studies suggesting a lack of interaction indicate that most patients are unlikely to experience a clinically relevant effect. Nevertheless, the isolated cases suggest that it may be prudent to be alert for additive adverse effects (such as weight gain and CNS depressant effects) if both drugs are given.

1. Centorrino F, Baldessarini RJ, Kando J, Frankenburg FR, Volpicelli SA, Puopolo PR, Flood JG. Serum concentrations of clozapine and its major metabolites: effects of cotreatment with fluoxetine or valproate. *Am J Psychiatry* (1994) 151, 123–5.
2. Facciolà G, Avenoso A, Scordo MG, Madia AG, Ventimiglia A, Perucca E, Spina E. Small effects of valproic acid on the plasma concentrations of clozapine and its major metabolites in patients with schizophrenic or affective disorders. *Ther Drug Monit* (1999) 21, 341–5.
3. Finley P, Warner D. Potential impact of valproic acid therapy on clozapine disposition. *Biol Psychiatry* (1994) 36, 487–8.
4. Longo LP, Salzman C. Valproic acid effects on serum concentrations of clozapine and norclozapine. *Am J Psychiatry* (1995) 152, 650.
5. Costello LE, Suppes T. A clinically significant interaction between clozapine and valproate. *J Clin Psychopharmacol* (1995) 15, 139–141.
6. Conca A, Beraus W, König P, Waschgler R. A case of pharmacokinetic interference in comedication of clozapine and valproic acid. *Pharmacopsychiatry* (2000) 33, 234–5.
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Flupentixol and related drugs + SSRIs

There is an isolated reported of parkinsonian-like symptoms in a patient taking amitriptyline, flupentixol, and fluoxetine. The pharmacokinetics of zuclopenthixol appear not to be affected by citalopram.

Clinical evidence, mechanism, importance and management

A study in schizophrenic patients found that over a 12-week period the serum levels of zuclopenthixol were not significantly altered by **citalopram** 40 mg daily.[1] Dose adjustments are therefore unlikely to be necessary on concurrent use.

Parkinson-like symptoms developed in a patient taking amitriptyline and flupenthixol when **fluoxetine** was given.[2] Movement disorders may occur simply as a result of the additive adverse effects of antipsychotics and SSRIs. **Fluoxetine** alone has been shown to occasionally cause movement disorders.[3,4] This appears to be an isolated case; however, bear it in mind if extrapyramidal effects become troublesome.

1. Syvälahti EKG, Taiminen T, Saarijärvi S, Lehto H, Niemi H, Ahola V, Dahl M-L, Salokangas RKR. Citalopram causes no significant alterations in plasma neuroleptic levels in schizophrenic patients. *J Int Med Res* (1997) 25, 24–32.
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3. Coulter DM, Pillans PI. Fluoxetine and extrapyramidal side effects. *Am J Psychiatry* (1995) 152, 122–5.
4. Bouchard RH, Pourcher E, Vincent P. Fluoxetine and extrapyramidal side effects. *Am J Psychiatry* (1989) 146, 1352–3.

Glutethimide + Tobacco

A study in 7 subjects found that glutethimide worsened psychomotor performance in smokers more than in non-smokers, possibly due to an increase in glutethimide absorption.[1] However there would seem to be no need for particular caution if smokers take glutethimide.

1. Crow JW, Lain P, Bochner F, Shoeman DW, Azarnoff DL. Glutethimide and 4-OH glutethimide: pharmacokinetics and effect on performance in man. *Clin Pharmacol Ther* (1977) 22, 458–64.

Haloperidol + Alosetron

A placebo-controlled study in 10 patients taking haloperidol found that alosetron 1 mg daily, given during weeks 2 and 3 of the

8-week study period, did not alter the pharmacokinetics of haloperidol.[1]

1. Gupta SK, Kunka RL, Metz A, Lloyd T, Rudolph G, Perel JM. Effect of alosetron (a new 5-HT_3 receptor antagonist) on the pharmacokinetics of haloperidol in schizophrenic patients. *J Clin Pharmacol* (1995) 35, 202–7.

Haloperidol + Amfetamines

Acute dystonia occurred in two healthy subjects when they were given haloperidol with dexamfetamine. Haloperidol inhibits the central stimulant effects of amfetamines.

Clinical evidence, mechanism, importance and management

Two healthy young women were given haloperidol 5 mg and **dexamfetamine** 5 mg as part of a neuropharmacological study. After 29 hours one of them developed stiffness of her neck and limbs, parkinsonian facies, her tongue protruded, and she had oropharyngeal spasm. After 34 hours the other woman developed an oculogyric crisis and acute dystonia of the neck with her back slightly arched. Both recovered rapidly after being given 10 mg of intramuscular procyclidine.[1]

The reasons for this interaction are not fully understood, but it may be due to acute dopamine receptor blockade with a secondary increase in dopamine release on supersensitive receptors. The general significance of these isolated cases is unclear.

The manufacturers of **amfetamine**, **dexamfetamine** and **lisdexamfetamine** note that haloperidol inhibits the central stimulant effects of amfetamines by blocking dopamine and noradrenaline re-uptake.[2-4] Therefore these amfetamines may be less effective in those taking haloperidol. Be alert for this effect on concurrent use.

1. Capstick C, Checkley S, Gray J, Dawe S. Dystonia induced by amphetamine and haloperidol. *Br J Psychiatry* (1994) 165, 276.
2. Adderall XR (Mixed salts of amphetamine and dextroamphetamine). Shire US Inc. US Prescribing information, March 2009.
3. Dexedrine (Dextroamphetamine sulfate). GlaxoSmithKline. US Prescribing information, July 2008.
4. Vyvanse (Lisdexamfetamine dimesylate). Shire US Inc. US Prescribing information, May 2009.

Haloperidol + Antacids

There seem to be no clinical studies or reports confirming the anecdotal evidence of a possible reduction in the effects of haloperidol by antacids.

Clinical evidence, mechanism, importance and management

In 1982 a questioner in a letter asked whether haloperidol interacts with antacids because he had a patient responding well to treatment with haloperidol who had begun to deteriorate when *Amphojel* (**aluminium hydroxide**) was added. In a written answer it was stated[1] that there are no reports of this interaction but several clinicians had said that based on clinical impressions oral haloperidol and antacids should not be given together.

With other antacid interactions separating the doses by as much as possible (1 to 2 hours) to avoid admixture in the gut usually minimises any effects. This may also prove of use if haloperidol appears to be less effective when an antacid is taken.

1. Goldstein BJ. Interaction of antacids with psychotropics. *Hosp Community Psychiatry* (1982) 33, 96.

Haloperidol and related drugs + Azoles

Itraconazole increases the plasma levels of haloperidol, and its metabolite, reduced haloperidol. Other azoles may have similar effects on both haloperidol and bromperidol.

Clinical evidence

(a) Bromperidol

A study in 8 patients found that the plasma levels of bromperidol 12 mg or 24 mg daily, were increased by **itraconazole** 200 mg daily for 7 days. The average increase was about 87%, but there was wide variation between patients, with some being unaffected and others having increases of up to 302%. Levels of the metabolite of bromperidol, reduced bromperidol, were similarly increased, by up to 415%.[1]

(b) Haloperidol

A study in 13 patients with schizophrenia taking haloperidol 6 mg or 12 mg twice daily found an increase in the levels of haloperidol and its metabolite, reduced haloperidol, when **itraconazole** 200 mg daily was given for 7 days. Haloperidol levels were increased by 30%, and levels of the metabolite, reduced haloperidol, were increased by 24%. There was also an increase in neurological adverse effects during **itraconazole** treatment.[2] In a randomised study 15 healthy subjects were given **itraconazole** 200 mg twice daily for 10 days with a single 5-mg dose of haloperidol on day 7. **Itraconazole** increased the AUC of haloperidol by 55% in the 8 subjects with normal levels of CYP2D6 and by 81% in those lacking or totally deficient in CYP2D6. No significant changes in QT prolongation were seen.[3]

Mechanism

It is likely that itraconazole inhibited the metabolism of bromperidol and haloperidol by the cytochrome P450 isoenzyme CYP3A4. The wide variation in results may be attributed to interindividual variation in CYP3A4 activity. This interaction may be of more importance in those patients who have less active CYP2D6, the predominant isoenzyme involved in the metabolism of haloperidol, because CYP3A4, which is inhibited by itraconazole, will then become more important in haloperidol metabolism.

Importance and management

The clinical significance of the raised butyrophenone levels is unclear, although one study found an increase in neurological adverse effects with haloperidol. It may be prudent to monitor concurrent use, decreasing the haloperidol or bromperidol dose if adverse effects (e.g. sedation, agitation, movement disorders) become troublesome. It is likely that other azoles that are potent inhibitors of CYP3A4, such as **ketoconazole**, would interact similarly, but this does not appear to have been studied. See 'azoles', (p.233), for more on the enzyme-inhibitory properties of the azoles.

1. Furukori H, Kondo T, Yasui N, Otani K, Tokinaga N, Nagashima U, Kaneko S, Inoue Y. Effects of itraconazole on the steady-state plasma concentrations of bromperidol and reduced bromperidol in schizophrenic patients. *Psychopharmacology (Berl)* (1999) 145, 189–92.
2. Yasui N, Kondo T, Otani K, Furukori H, Mihara K, Suzuki A, Kaneko S, Inoue Y. Effects of itraconazole on the steady-state plasma concentrations of haloperidol and its reduced metabolite in schizophrenic patients: in vivo evidence of the involvement of CYP3A4 for haloperidol metabolism. *J Clin Psychopharmacol* (1999) 19, 149–54.
3. Park J-Y, Shon J-H, Kim K-A, Jung H-J, Shim J-C, Yoon Y-R, Cha I-J, Shin J-G. Combined effects of itraconazole and CYP2D6*10 genetic polymorphism on the pharmacokinetics and pharmacodynamics of haloperidol in healthy subjects. *J Clin Psychopharmacol* (2006) 26, 135–42.

Haloperidol + Buspirone

Two studies found that buspirone can cause a rise in plasma haloperidol levels, while another study found that no interaction occurred.

Clinical evidence, mechanism, importance and management

A pharmacokinetic study in 27 schizophrenic patients taking haloperidol 10 to 40 mg daily found that buspirone 5 mg three times daily for 2 weeks, followed by 10 mg three times daily for 4 weeks, did not significantly affect the steady-state plasma levels of haloperidol.[1]

These findings contrast with those of a 6-week study, in which 6 out of 7 schizophrenics had 15 to 122% rises in their plasma haloperidol levels when they were given buspirone.[2] The authors also mention a single-dose study in healthy subjects, which found a 30% rise in haloperidol levels when subjects were given buspirone.[2]

It is not known why these findings differ, but since no adverse reactions have been reported, there would seem to be no reason for avoiding concurrent use. However, be aware that some patients seem to experience large rises in haloperidol levels, so consider this potential interaction if the ad-

verse effects of haloperidol (e.g. sedation, agitation, movement disorders) become troublesome.

1. Huang HF, Jann MW, Wei F-C, Chang T-P, Chen J-S, Juang D-J, Lin S-K, Lam YFW, Chien C-P, Chang W-H. Lack of pharmacokinetic interaction between buspirone and haloperidol in patients with schizophrenia. *J Clin Pharmacol* (1996) 36, 963–9.

2. Goff DC, Midha KK, Brotman AW, McCormick S, Waites M, Amico ET. An open trial of buspirone added to neuroleptics in schizophrenic patients. *J Clin Psychopharmacol* (1991) 11, 193–7.

Haloperidol and related drugs + Carbamazepine

Haloperidol plasma levels are roughly halved by carbamazepine; bromperidol levels are also reduced by carbamazepine. Haloperidol can raise carbamazepine levels. The plasma levels of haloperidol do not appear to be affected by oxcarbazepine.
Neurotoxicity and Stevens-Johnson syndrome have been seen in patients taking haloperidol and carbamazepine.

Clinical evidence

(a) Bromperidol

When 13 patients with schizophrenia taking bromperidol 12 or 24 mg daily were given carbamazepine 200 mg twice daily for 4 weeks, the plasma levels of bromperidol and reduced bromperidol (a metabolite) were decreased by 37% and 23%, respectively. Despite this fall in levels, the Clinical Global Impression scores (a measure of illness severity) fell slightly, suggesting an improvement in disease control.[1]

(b) Haloperidol

A study in 9 patients with schizophrenia taking haloperidol (average dose 30 mg daily) found a 55% reduction in plasma haloperidol levels (a mean fall from 45.5 to 21.2 nanograms/mL) when they were given carbamazepine for 5 weeks (precise dose not stated). They also took trihexyphenidyl 10 mg daily and oxazepam 30 mg at night, as necessary. Carbamazepine serum levels and the control of the disease remained unchanged.[2]

Other studies and reports have similarly found 40 to 60% falls in plasma haloperidol levels in patients taking carbamazepine,[3-7] with the occasional patient having undetectable levels.[4,8] Haloperidol clearance was found to be increased by 32% in a retrospective study in patients who were also taking enzyme-inducing antiepileptics, which included carbamazepine.[9] Decreases in plasma haloperidol levels of unspecified amounts have also been described in patients taking carbamazepine.[10-13] A study in 9 patients taking haloperidol 6 mg twice daily who were then given carbamazepine, with the daily dose increased at fortnightly intervals from 100 to 300 and to 600 mg, found a dose-dependent reduction in haloperidol levels. Mean plasma haloperidol levels were reduced by 25%, 61%, and 82%, respectively.[14] A few patients have had clinical worsening or increased adverse effects.[4-6,8] Three patients had two- to fivefold increases in plasma haloperidol levels and clinical improvement when carbamazepine 1.2 to 1.4 g daily was stopped, but extrapyramidal adverse effects developed within one to 30 days.[15] Three cases of neurotoxicity (drowsiness, slurred speech, confusion) have also been described in patients taking haloperidol and carbamazepine.[10,16,17] One study found that concurrent use increased the incidence of QT prolongation.[18]

A case report describes 3 schizophrenic patients taking haloperidol whose treatment was changed from carbamazepine to **oxcarbazepine**. After 2 weeks their plasma haloperidol levels had dramatically risen (from 6 to 18 nanomol/L, from 6 to 14 nanomol/L and from 17 to 27 nanomol/L). This was accompanied by severe extrapyramidal adverse effects, which necessitated dose reductions in 2 of the patients.[19]

A study in Japanese patients with schizophrenia found that haloperidol raised serum carbamazepine levels by about 30%, despite a 25% dose reduction.[11]

A patient taking haloperidol (and 'fluphenazine', (p.894)) developed Stevens-Johnson syndrome 12 days after starting to take carbamazepine. She had erythema multiforme skin lesions and at least two mucous membranes were affected. After treatment, she restarted her previous drugs, except carbamazepine, without problems.[20] Another case of Stevens-Johnson syndrome has been reported in a patient taking carbamazepine, lithium carbonate, haloperidol and trihexyphenidyl.[21]

Mechanism

Carbamazepine, is a recognised enzyme inducer, therefore it seems highly likely that the reduced plasma bromperidol and haloperidol levels occur because their metabolism by the liver is markedly increased by carbamazepine. Oxcarbazepine does not appear to interact, probably because it is not as potent an enzyme inducer as carbamazepine.

The reason for the raised carbamazepine levels with haloperidol is not understood.

Importance and management

The interactions of haloperidol with carbamazepine are well documented and appear to be clinically important, but only a few patients have been reported to show clinical worsening. Although there are advantages in adding carbamazepine to haloperidol in treating some patients[22] be alert for the need to increase the haloperidol dosage. A study, in which intramuscular haloperidol was used, recommended shortening the interval between injections rather than raising the dosage, but it was not stated by how much.[23] Remember too that if carbamazepine is withdrawn it may be necessary to reduce the haloperidol dosage. Also be alert for the development of dystonic reactions and for a rise in serum carbamazepine levels. Similar precautions may be needed with bromperidol, but this needs confirmation. Limited evidence suggest that no special precautions are necessary with oxcarbazepine.

Stevens-Johnson syndrome with carbamazepine alone is rare, and the risk appears to be mostly confined to the first 8 weeks of treatment.[24] It may be more common in patients being treated for conditions other than epilepsy.[25] It is not possible to say whether the concurrent use of haloperidol increases the risk of its development, but until more is known it would be prudent to monitor the outcome, particularly during the first 2 weeks of combined use.

1. Otani K, Ishida M, Yasui N, Kondo T, Mihara K, Suzuki A, Furukori H, Kaneko S, Inoue Y. Interaction between carbamazepine and bromperidol. *Eur J Clin Pharmacol* (1997) 53, 219–22.
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11. Iwahashi K, Miyatake R, Suwaki H, Hosokawa K, Ichikawa Y. The drug–drug interaction effects of haloperidol on plasma carbamazepine levels. *Clin Neuropharmacol* (1995) 18, 233–6.
12. Jann MW, Chang W-H, Lane H-Y. Differences in haloperidol epidemiologic pharmacokinetic studies. *J Clin Psychopharmacol* (2001) 21, 628–30.
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16. Kanter GL, Yerevanian BI, Ciccone JR. Case report of a possible interaction between neuroleptics and carbamazepine. *Am J Psychiatry* (1984) 141, 1101–2.
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Haloperidol + Chlorpromazine

Some patients may have a large increase in haloperidol levels when they are also given chlorpromazine.

Clinical evidence, mechanism, importance and management

Haloperidol was given to 43 patients in doses of 2 to 21 mg daily for 2 months, and then chlorpromazine 50 to 300 mg daily was added for a further 2 months. Haloperidol plasma levels were found to increase by an average of 29%, and levels of the metabolite, reduced haloperidol, were increased by 161%. However, the variation in effect was large.

Chlorpromazine was thought to raise haloperidol levels by inhibiting haloperidol metabolism by the cytochrome P450 isoenzyme CYP2D6. The large inter-individual variation suggested that differences in cytochrome P450 genotypes may affect haloperidol metabolism,[1] and therefore some patients may be at risk of developing adverse effects related to high haloperidol levels when taking chlorpromazine. Concurrent use need not be avoided, but consider this interaction if haloperidol adverse effects (e.g. sedation, agitation, movement disorders) become troublesome. Of more concern is the potential for additive effects on the QT interval, see 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290.

1. Suzuki Y, Someya T, Shimoda K, Hirokane G, Morita S, Yokono A, Inoue Y, Takahashi S. Importance of the cytochrome P450 2D6 genotype for the drug metabolic interaction between chlorpromazine and haloperidol. *Ther Drug Monit* (2001) 23, 363–8.

Haloperidol + Granisetron

Granisetron appears not to increase the adverse effects of haloperidol.

Clinical evidence, mechanism, importance and management

A study in 12 healthy subjects found that, while haloperidol 3 mg alone caused some impaired psychometric performance (increased drowsiness, muzziness, lethargy, mental slowness, etc.), the addition of granisetron 160 micrograms/kg did not seem to make performance significantly worse.[1] If both drugs are used, no additional precautions would seem necessary.

1. Leigh TJ, Link CGG, Fell GL. Effects of granisetron and haloperidol, alone and in combination, on psychometric performance and the EEG. *Br J Clin Pharmacol* (1992) 34, 65–70.

Haloperidol + Grapefruit juice

In a study in 12 patients with schizophrenia taking haloperidol 6 mg twice daily, the ingestion of 200 mL of regular-strength grapefruit juice three times daily for 7 days did not affect the pharmacokinetics of haloperidol.[1]

1. Yasui N, Kondo T, Suzuki A, Otani K, Mihara K, Furukori H, Kaneko S, Inoue Y. Lack of significant pharmacokinetic interaction between haloperidol and grapefruit juice. *Int Clin Psychopharmacol* (1999) 14, 113–8.

Haloperidol + Imipenem

Marked but transient hypotension was seen when three patients receiving intravenous imipenem were given low dose intravenous haloperidol.

Clinical evidence, mechanism, importance and management

Three patients in intensive care who were receiving intravenous imipenem 500 mg (with cilastatin) every 6 hours for 2, 3, and 7 days, respectively, developed a rapid and short-lived episode of hypotension when they were given a 2.5-mg dose of intravenous haloperidol. For example, the blood pressure of one of the patients fell from 117/75 mmHg to 91/49 mmHg. After 30 minutes her blood pressure had risen to 100/57 mmHg. No treatment for hypotension was given to any of the patients and the reaction was brief and self-limiting. Two of the patients were also taking famotidine and erythromycin. No acute ECG changes were seen.[1]

The reason for this fall in blood pressure is not understood, but the authors attribute what happened to the concurrent use of haloperidol and imipenem, although they point out that intravenous haloperidol alone can cause orthostatic hypotension. One suggestion is that competitive protein binding displacement might have transiently increased the levels of free haloperidol,[1] although this has been questioned. Furthermore, it has been suggested that the clinical condition of the patients may have had a greater part to play in the development of hypotension than any drug interaction.[2]

The authors advise that if haloperidol is used, low doses should be given, and the outcome well monitored. They say that no pressor agent was needed in these cases, but they suggest the possible use of metaraminol, phenylephrine or noradrenaline (norepinephrine) rather than dopamine, the vasopressor effects of which might be blocked or reversed by haloperidol.[1]

1. Franco-Bronson K, Gajwani P. Hypotension associated with intravenous haloperidol and imipenem. *J Clin Psychopharmacol* (1999) 19, 480–1.
2. Hauben M. Comments on "Hypotension associated with intravenous haloperidol and imipenem". *J Clin Psychopharmacol* (2001) 21, 345–7.

Haloperidol + Indometacin

Profound drowsiness and confusion have been described in patients given haloperidol with indometacin.

Clinical evidence, mechanism, importance and management

A crossover study in 20 patients, designed to find out the possible advantages of combining haloperidol 5 mg daily with indometacin 25 mg three times daily, was eventually abandoned because 13 patients (11 taking haloperidol and 2 taking placebo) failed to complete the study. Profound drowsiness or tiredness caused 6 of the haloperidol-treated patients to withdraw. The authors of this paper said that the concurrent use of indometacin produced drowsiness and confusion greater than anything expected with haloperidol alone, which was sufficiently severe that in some cases independent functioning was affected.[1]

Evidence for this interaction appears to be very limited. If concurrent use is thought appropriate, consider warning patients about this potentially severe effect. It might be wiser to avoid concurrent use because many patients requiring this type of treatment may not be hospitalised and under the day-to-day scrutiny of the prescriber.

1. Bird HA, Le Gallez P, Wright V. Drowsiness due to haloperidol/indomethacin in combination. *Lancet* (1983) i, 830–1.

Haloperidol + Nefazodone

Nefazodone does not appear to significantly affect the pharmacokinetics of haloperidol.

Clinical evidence, mechanism, importance and management

In a study in 12 healthy subjects taking haloperidol 5 mg daily, nefazodone 200 mg twice daily for about 7 days (to achieve steady-state pharmacokinetics), increased the AUC of haloperidol by 36% but its maximum plasma levels were unaltered. The pharmacokinetics of the nefazodone were unaltered.[1] It seems fairly unlikely that this change is enough to be of clinical relevance and therefore no dose adjustment seems necessary on concurrent use.

1. Barbhaiya RH, Shukla UA, Greene DS, Breuel H-P, Midha KK. Investigation of pharmacokinetic and pharmacodynamic interactions after coadministration of nefazodone and haloperidol. *J Clin Psychopharmacol* (1996) 16, 26–34.

Haloperidol + Phenobarbital and/or Phenytoin

Haloperidol plasma levels are roughly halved by phenobarbital and phenytoin.

Clinical evidence

A study in epileptic patients, 2 taking phenobarbital, 3 taking phenytoin, and 4 taking both drugs, found that after taking haloperidol 10 mg three times daily for 6 weeks their serum haloperidol levels were about half of those in a control group who were not taking antiepileptics (19.4 nanograms/mL compared with 36.6 nanograms/mL). Antiepileptic levels remained unchanged.[1] A patient had a marked rise in serum haloperidol levels and clinical improvement when phenytoin 300 mg daily was stopped.[2] Haloperidol clearance was increased by 32% in a study in patients who were also taking enzyme-inducing antiepileptics, which included phenobarbital or phenytoin.[3] A retrospective study found that phenobarbital reduced the haloperidol concentration/dose ratio, suggesting that phenobarbital may affect the metabolism of haloperidol.[4]

Mechanism

Phenobarbital and phenytoin are recognised enzyme inducers, therefore it seems highly likely that the reduced plasma haloperidol levels occur because its metabolism by the liver is markedly increased by these antiepileptics.

Importance and management

The interactions of haloperidol with phenytoin and phenobarbital are moderately well documented but their clinical effects do not seem to have been studied. Be alert for the need to increase the haloperidol dose if either of these antiepileptics is also given. The authors of one study suggest a two- to threefold increase in the haloperidol dose may be needed.[1] Another study, in which intramuscular haloperidol was used, recommended shortening the interval between injections rather than raising the dose, but it was not stated by how much.[5] Remember too that if the antiepileptics are withdrawn it may be necessary to reduce the haloperidol dose.

1. Linnoila M, Viukari M, Vaisanen K, Auvinen J. Effect of anticonvulsants on plasma haloperidol and thioridazine levels. *Am J Psychiatry* (1980) 137, 819–21.
2. Jann MW, Fidone GS, Hernandez JM, Amrung S, Davis CM. Clinical implications of increased antipsychotic plasma concentrations upon anticonvulsant cessation. *Psychiatry Res* (1989) 28, 153–9.
3. Yukawa E, Hokazono T, Funakoshi A, Yukawa M, Ohdo S, Higuchi S, Ichimaru R, Maki T, Matsunaga K, Anai M, Goto Y. Epidemiologic investigation of the relative clearance of haloperidol by mixed-effect modelling using routine clinical pharmacokinetic data in Japanese patients. *J Clin Psychopharmacol* (2000) 20, 685–90.
4. Hirokane G, Someya T, Takahashi S, Morita S, Shimoda K. Interindividual variation of plasma haloperidol concentrations and the impact of concomitant medications: the analysis of therapeutic drug monitoring data. *Ther Drug Monit* (1999) 21, 82–6.
5. Pupeschi G, Agenet C, Levron J-C, Barges-Bertocchio M-H. Do enzyme inducers modify haloperidol decanoate rate of release? *Prog Neuropsychopharmacol Biol Psychiatry* (1994) 18, 1323–32.

Haloperidol + Quinidine

Haloperidol levels can be markedly increased by quinidine.

Clinical evidence, mechanism, importance and management

An experimental study in 13 healthy subjects found that quinidine bisulfate 250 mg, taken about one hour before a single 5-mg dose of haloperidol approximately doubled the maximum plasma levels and the AUC of haloperidol. The reasons for this effect are not understood.[1] The clinical importance of this interaction has not been assessed, but it seems likely that the beneficial and adverse effects of haloperidol will be increased if quinidine is added.

Concurrent use need not be avoided, but consider this interaction if haloperidol adverse effects (e.g. sedation, agitation, movement disorders) become troublesome. Of more concern is the potential for additive effects on the QT interval, see 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290.

1. Young D, Midha KK, Fossler MJ, Hawes EM, Hubbard JW, McKay G, Korchinski ED. Effect of quinidine on the interconversion kinetics between haloperidol and reduced haloperidol in humans: implications for the involvement of cytochrome P450IID6. *Eur J Clin Pharmacol* (1993) 44, 433–8.

Haloperidol + Rifampicin (Rifampin) and/or Isoniazid

The serum levels of haloperidol can be reduced by rifampicin, and possibly raised by isoniazid.

Clinical evidence

A study in schizophrenic patients taking haloperidol, 7 of whom were also taking a range of antimycobacterial drugs (ethambutol, isoniazid, rifampicin), and 18 of whom were taking isoniazid only, found that those receiving multiple drugs including rifampicin had significantly lower haloperidol serum levels. The half-life of haloperidol in 2 patients taking rifampicin was 4.9 hours compared with 9.4 hours in 3 other patients not taking rifampicin.[1] Three of the patients taking isoniazid (without rifampicin or ethambutol) had *increased* serum haloperidol levels.[1]

The trough serum haloperidol levels of 15 schizophrenics fell to 37% of the expected level after they took rifampicin 600 mg daily for 7 days.[2] After 28 days the serum level had dropped further, to 30% of the expected level. In another group of 5 patients taking haloperidol and rifampicin, the serum haloperidol levels rose to 229% of the previous level 7 days after rifampicin was stopped, and to 329% 28 days after rifampicin was stopped.[2] The clinical effects of the haloperidol appeared to be reduced by the rifampicin.[2]

Mechanism

The likeliest explanation for the reduced haloperidol levels is that rifampicin, a recognised potent enzyme inducer, increases the metabolism and loss of haloperidol from the body.

Importance and management

The interaction between haloperidol and rifampicin would appear to be established and clinically important. Be alert for any evidence of reduced haloperidol effects if rifampicin alone is used, and possibly increased effects if isoniazid alone is used. Adjust the haloperidol dosage if necessary.

1. Takeda M, Nishinuma K, Yamashita S, Matsubayashi T, Tanino S, Nishimura T. Serum haloperidol levels of schizophrenics receiving treatment for tuberculosis. *Clin Neuropharmacol* (1986) 9, 386–97.
2. Kim Y-H, Cha I-J, Shim J-C, Shin J-G, Yoon Y-R, Kim Y-K, Kim J-I, Park G-H, Jang I-J, Woo J-I, Shin S-G. Effect of rifampin on the plasma concentration and the clinical effect of haloperidol concomitantly administered to schizophrenic patients. *J Clin Psychopharmacol* (1996) 16, 247–52.

Haloperidol + Risperidone

A case report describes neuroleptic malignant syndrome in a patient taking risperidone and haloperidol.

Clinical evidence, mechanism, importance and management

A case report describes a 57-year-old man who had been taking haloperidol 4 mg three times daily uneventfully for several years. At a review, his treatment was changed to risperidone, in increasing doses to 3 mg twice daily, and mirtazapine 15 mg at night. Despite being advised to stop haloperidol when he started risperidone, the patient continued to take haloperidol, and by the third day of concurrent use he had become pyrexial, and exhibited rigidity of his trunk and extremities. He was diagnosed as having neuroleptic malignant syndrome, and so he was given dantrolene, bromocriptine and lorazepam: he recovered over the next 2 months.

The effects seen in this patient were thought to be due to the additive dopamine antagonism caused by both the haloperidol and risperidone. Mirtazapine may have also contributed, although the patient only took two doses before he was admitted. The authors suggest that if antipsychotic treatment is to be changed, it is advisable to slowly reduce the dose of the old antipsychotic and, simultaneously, slowly increase the dose of the new drug to avoid the risk of a psychotic relapse, and the patient should be closely monitored during this time for signs of neuroleptic malignant syndrome.[1]

1. Reeves RR, Mack JE, Torres RA. Neuroleptic malignant syndrome during a change from haloperidol to risperidone. *Ann Pharmacother* (2001) 35, 698–701.

Haloperidol + Ritonavir

Ritonavir may raise haloperidol levels.

Clinical evidence, mechanism, importance and management

The manufacturers of ritonavir predict that antiretroviral doses of ritonavir may increase the plasma levels of haloperidol by inhibiting its metabolism

by the cytochrome P450 isoenzyme CYP2D6.[1] Haloperidol has been seen to interact in this way with other known CYP2D6 inhibitors (see 'Haloperidol + Quinidine', p.886). The manufacturers advise monitoring for haloperidol adverse effects (e.g. sedation, agitation, movement disorders) during concurrent use. This seems a prudent precaution.

1. Norvir Soft Capsules (Ritonavir). Abbott Laboratories Ltd. UK Summary of product characteristics, October 2009.

Haloperidol + SSRIs

Fluoxetine, fluvoxamine, and possibly sertraline may raise haloperidol levels, which may increase its adverse effects. A number of case reports describe extrapyramidal adverse effects following the use of fluoxetine and haloperidol.

Clinical evidence

(a) Citalopram

A study in schizophrenic patients found that, over a 12-week period, the serum levels of haloperidol were not significantly altered by citalopram 40 mg daily.[1]

(b) Fluoxetine

A woman taking haloperidol 2 to 5 mg daily for 2 years with only occasional mild extrapyramidal symptoms began to experience severe extrapyramidal symptoms (tongue stiffness, parkinsonism, akathisia) shortly after starting to take fluoxetine 40 mg twice daily and was virtually incapacitated for 3 days. Both drugs were stopped and she recovered over a period of one week.[2] Three other patients developed movement disorders after receiving both drugs:[3-5] in one case severe antimuscarinic adverse effects also occurred.[4]

A report describes 8 patients who had a 20% rise in plasma haloperidol levels when fluoxetine 20 mg daily was added. Although no overall increase in extrapyramidal effects was seen, one patient developed tremor, and another developed akathisia.[6] Similarly 15 patients had an increase of nearly 30% in their haloperidol plasma levels after fluoxetine was given, and 5 of 17 patients had aggravated parkinsonian symptoms.[7] Another report describes a more than 100% rise in plasma haloperidol levels, accompanied by clinical improvement, in 7 patients given fluoxetine 20 to 40 mg with haloperidol.[8]

(c) Fluvoxamine

A study in 12 patients with schizophrenia found that haloperidol levels were increased by 20%, 39%, and 60% by fluvoxamine 25, 75, and 150 mg daily, respectively, which suggested the extent of the interaction was related to the dose of fluvoxamine.[9] A study in 3 patients with schizophrenia found that the addition of fluvoxamine caused their serum haloperidol levels to rise, and when the fluvoxamine was stopped the levels fell. This was not a formal pharmacokinetic study, but while taking fluvoxamine 150 to 200 mg daily the haloperidol serum levels of one patient rose from 17 to 38 nanograms/mL. The fluvoxamine was then stopped and 54 days later his serum haloperidol levels had fallen to 9 nanograms/mL. This patient became lethargic and showed worsening of all of the clinical and cognitive functions assessed while taking these drugs.[10] It should be noted that all three patients were also taking benzatropine, which can caused additive antimuscarinic effects when given with SSRIs (see 'Antimuscarinics + SSRIs', p.787). Another limited study also observed a rise in the serum levels of haloperidol in patients taking fluvoxamine.[11]

(d) Paroxetine

In one study the sedative effects and impairment of psychomotor performance caused by haloperidol 3 mg were not increased by paroxetine 30 mg.[12]

(e) Sertraline

In a randomised, placebo-controlled study, 21 healthy subjects were given a single 2-mg dose of haloperidol on days 2 to 25. On days 9 to 25 the subjects were given sertraline, increased over 7 days to 200 mg daily. All subjects took psychomotor tests on days 1, 2 and 25 to assess the effect of haloperidol. Their cognitive function was impaired for 6 to 8 hours after taking haloperidol, but this effect had disappeared after 23 hours. Overall, sertraline did not appear to worsen the cognitive impairment caused by haloperidol.[13] Another study found similar pharmacodynamic results, and also found that the pharmacokinetics of haloperidol are unaffected by sertraline.[14] In contrast, a study in 16 hospitalised patients who were taking haloperidol found that the addition of sertraline 50 mg daily for 2 weeks resulted in an increase in plasma haloperidol concentrations, and a reduction in the plasma concentrations of the metabolite (reduced haloperidol).[15]

Mechanism

Movement disorders and raised haloperidol serum levels seem most common with fluoxetine, possibly because it inhibits the metabolism of haloperidol by the cytochrome P450 isoenzyme CYP2D6.[16] However, paroxetine also inhibits CYP2D6 and an interaction with haloperidol has not been reported, whereas sertraline has only weak effects on CYP2D6 and an interaction has been reported. Therefore the movement disorders may simply occur as a result of the additive adverse effects of antipsychotics and SSRIs. Fluoxetine alone has been shown to occasionally cause movement disorders.[3,17]

Importance and management

On the whole significant interactions between haloperidol and the SSRIs appear rare. The combination can be useful and so the isolated cases of extrapyramidal adverse effects should not prevent concurrent use. However, if extrapyramidal effects become troublesome bear this interaction in mind as a possible cause. The significance of the rise in haloperidol levels caused by fluoxetine and fluvoxamine is unclear; be aware that haloperidol adverse effects (e.g. sedation, agitation, movement disorders) may be increased in some patients and consider reducing the haloperidol dose if problems occur. Note that this pharmacokinetic interaction has also been predicted by the manufacturers of **escitalopram**.[18]

1. Syvälahti EKG, Taiminen T, Saarijärvi S, Lehto H, Niemi H, Ahola V, Dahl M-L, Salokangas RKR. Citalopram causes no significant alterations in plasma neuroleptic levels in schizophrenic patients. *J Int Med Res* (1997) 25, 24–32.
2. Tate JL. Extrapyramidal symptoms in a patient taking haloperidol and fluoxetine. *Am J Psychiatry* (1989) 146, 399–400.
3. Coulter DM, Pillans PI. Fluoxetine and extrapyramidal side effects. *Am J Psychiatry* (1995) 152, 122–5.
4. Benazzi F. Urinary retention with fluoxetine–haloperidol combination in a young patient. *Can J Psychiatry* (1996) 41, 606–7.
5. D'Souza DC, Bennett A, Abi-Dargham A, Krystal JH. Precipitation of a psychoneuromotor syndrome by fluoxetine in a haloperidol-treated schizophrenic patient. *J Clin Psychopharmacol* (1994) 14, 361–3.
6. Goff DC, Midha KK, Brotman AW, Waites M, Baldessarini RJ. Elevation of plasma concentrations of haloperidol after the addition of fluoxetine. *Am J Psychiatry* (1991) 148, 790–2.
7. Shim J-C, Kelly DL, Kim Y-H, Yoon Y-R, Park J-H, Shin J-G, Conley RR. Fluoxetine augmentation of haloperidol in chronic schizophrenia. *J Clin Psychopharmacol* (2003) 23, 520–2.
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9. Yasui-Furukori N, Kondo T, Mihara K, Inoue Y, Kaneko S. Fluvoxamine dose-dependent interaction with haloperidol and the effects on negative symptoms in schizophrenia. *Psychopharmacology (Berl)* (2004) 171, 223–7.
10. Daniel DG, Randolph C, Jaskiw G, Handel S, Williams T, Abi-Dargham A, Shoaf S, Egan M, Elkashef A, Liboff S, Linnoila M. Coadministration of fluvoxamine increases serum concentrations of haloperidol. *J Clin Psychopharmacol* (1994) 14, 340–3.
11. Vandel S, Bertschy G, Baumann P, Bouquet S, Bonin B, Francois T, Sechter D, Bizouard P. Fluvoxamine and fluoxetine: Interaction studies with amitriptyline, clomipramine and neuroleptics in phenotyped patients. *Pharmacol Res* (1995) 31, 347–53.
12. Cooper SM, Jackson D, Loudon JM, McClelland GR, Raptopoulos P. The psychomotor effects of paroxetine alone and in combination with haloperidol, amylobarbitone, oxazepam, or alcohol. *Acta Psychiatr Scand* (1989) 80 (Suppl 350), 53–5.
13. Williams SA, Wesnes K, Oliver SD, Rapeport WG. Absence of effect of sertraline on time-based sensitization of cognitive impairment with haloperidol. *J Clin Psychiatry* (1996) 57 (Suppl 1), 7–11.
14. Lee MS, Kim YK, Lee SK, Suh KY. A double-blind study of adjunctive sertraline in haloperidol-stabilized patients with chronic schizophrenia. *J Clin Psychopharmacol* (1998) 18, 399–403.
15. Lee M-S, Han C-S, You Y-W, Kim S-H. Co-administration of sertraline and haloperidol. *Psychiatry Clin Neurosci* (1998) 52, S193–8.
16. Özdemir V, Naranjo CA, Herrmann N, Reed K, Sellers EM, Kalow W. Paroxetine potentiates the central nervous system side effects of perphenazine: contribution of cytochrome P4502D6 inhibition in vivo. *Clin Pharmacol Ther* (1997) 62, 334–47.
17. Bouchard RH, Pourcher E, Vincent P. Fluoxetine and extrapyramidal side effects. *Am J Psychiatry* (1989) 146, 1352–3.
18. Cipralex (Escitalopram oxalate). Lundbeck Ltd. UK Summary of product characteristics, October 2008.

Haloperidol + Tobacco

Smokers of tobacco may possibly need larger doses of haloperidol than non-smokers.

Clinical evidence, mechanism, importance and management

Steady-state haloperidol levels were found to be lower in a group of 23 cigarette smokers than in another group of 27 non-smokers (16.83 nanograms/mL compared with 28.8 nanograms/mL) and the clearance was increased by 44%.[1] Other studies have broadly confirmed these findings.[2,3]

Although the reason for the reduction in haloperidol levels has not been established, it seems likely that some of the components of tobacco smoke act as enzyme inducers, which increase the rate at which the liver metabolises haloperidol, thereby reducing its serum levels and, possibly, clinical effects. Be alert for the need to increase the dose of haloperidol in patients who smoke, and reduce the dose if smoking is stopped.

1. Jann MW, Saklad SR, Ereshefsky L, Richards AL, Harrington CA, Davis CM. Effects of smoking on haloperidol and reduced haloperidol plasma concentrations and haloperidol clearance. *Psychopharmacology (Berl)* (1986) 90, 468–70.
2. Perry PJ, Miller DD, Arndt SV, Smith DA, Holman TL. Haloperidol dosing requirements: the contribution of smoking and nonlinear pharmacokinetics. *J Clin Psychopharmacol* (1993) 13, 46–51.
3. Pan L, Vander Stichele R, Rosseel MT, Berlo JA, De Schepper N, Belpaire FM. Effects of smoking, CYP2D6 genotype, and concomitant drug intake on the steady state plasma concentrations of haloperidol and reduced haloperidol in schizophrenic inpatients. *Ther Drug Monit* (1999) 21, 489–97.

Haloperidol + Topiramate

Topiramate slightly increases haloperidol levels.

Clinical evidence, mechanism, importance and management

In a study, healthy subjects were given topiramate 50 mg twice daily, titrated over 2 days to 100 mg twice daily. They were also given a single 5-mg dose of haloperidol 4 days before starting topiramate and on day 7 of topiramate use. Topiramate slightly increased the plasma levels of haloperidol and its reduced metabolite. The mean AUC of haloperidol and its active reduced metabolite were increased by 11% and 31%, respectively, suggesting that exposure to the active metabolite (which possesses 20 to 50% of the activity of haloperidol) was increased by topiramate.[1] In another study, the mean AUC of a single 2-mg dose of haloperidol was increased by 15% in the presence of topiramate 50 to 100 mg twice daily.[2]

Evidence for an interaction between haloperidol and topiramate appears to be limited, but an interaction is established. However, the rise in haloperidol levels is modest, and unlikely to be of clinical significance. Nevertheless, the authors of one of the studies suggest that a haloperidol dose adjustment [reduction] should be considered, if adverse effects occur during concurrent use.[1]

1. Bialer M, Doose DR, Murthy B, Curtin C, Wang S-S, Twyman RE, Schwabe S. Pharmacokinetic interactions of topiramate. *Clin Pharmacokinet* (2004) 43, 763–80.
2. Doose DR, Kohl KA, Desai-Krieger D, Natarajan J, van Kammen DP. No clinically significant effect of topiramate on haloperidol concentration. *Eur Neuropsychopharmacol* (1999) 9, S357.

Haloperidol + Valproate

No clinically relevant interaction appears to occur between haloperidol and valproate.

Clinical evidence, mechanism, importance and management

A study in 6 patients given haloperidol 6 to 10 mg daily found no significant interaction with valproic acid.[1] Similarly, haloperidol was not found to interact with valproate in two further studies,[2,3] although in one of these studies an increase of 64% in haloperidol plasma levels was seen, which was not considered to be clinically significant.[2]

Evidence for an interaction between haloperidol and valproate appears to be limited to these brief studies, but they suggest that a clinically relevant interaction is unlikely.

1. Ishizaki T, Chiba K, Saito M, Kobayashi K, Iizuka R. The effects of neuroleptics (haloperidol and chlorpromazine) on the pharmacokinetics of valproic acid in schizophrenic patients. *J Clin Psychopharmacol* (1984) 4, 254–61.
2. Hesslinger B, Normann C, Langosch JM, Klose P, Berger M, Walden J. Effects of carbamazepine and valproate on haloperidol plasma levels and on psychopathologic outcome in schizophrenic patients. *J Clin Psychopharmacol* (1999) 19, 310–15.
3. Normann C, Klose P, Hesslinger B, Langosch JM, Berger M, Walden J. Haloperidol plasma levels and psychopathology in schizophrenic patients with antiepileptic co-medication: a clinical trial. *Pharmacopsychiatry* (1997) 30, 204.

Haloperidol + Venlafaxine

Venlafaxine can increase the serum levels of haloperidol. This is consistent with an isolated report, which describes a man taking haloperidol who developed urinary retention when venlafaxine was added.

Clinical evidence, mechanism, importance and management

A study in 24 healthy subjects found that steady-state venlafaxine 75 mg every 12 hours reduced the renal clearance of a single 2-mg dose of haloperidol by 42%. This resulted in a 70% rise in the AUC of haloperidol and an 88% rise in its maximum serum levels.[1-3] This rise in haloperidol levels would seem to be consistent with an isolated report of a 75-year-old man taking haloperidol 1 mg and alprazolam 500 micrograms daily, who suddenly developed urinary retention when venlafaxine 37.5 mg daily was added. Urinary retention resolved spontaneously when all the drugs were stopped.[4]

It was suggested that venlafaxine inhibits the cytochrome P450 isoenzyme CYP2D6, which is concerned with the metabolism of haloperidol. As a result the serum levels of the haloperidol rise, thereby increasing its antimuscarinic effects,[4] which in this case resulted in urinary retention.

The evidence for an interaction between haloperidol and venlafaxine is limited but it appears to be established. Be aware that increased haloperidol adverse effects (e.g. sedation, agitation, movement disorders) may occur if venlafaxine is also given. It may be necessary to reduce the haloperidol dosage.

1. Efexor XL (Venlafaxine hydrochloride). Wyeth Pharmaceuticals. UK Summary of product characteristics, March 2008.
2. Wyeth, Personal communication, April 2001.
3. Effexor XR (Venlafaxine hydrochloride). Wyeth Pharmaceuticals Inc. US Prescribing information, July 2009.
4. Benazzi F. Urinary retention with venlafaxine-haloperidol combination. *Pharmacopsychiatry* (1997) 30, 27.

Loxapine + SSRIs

Galactorrhoea and amenorrhoea developed in a patient given loxapine and fluvoxamine.

Clinical evidence, mechanism, importance and management

A 38-year-old woman developed amenorrhoea, followed shortly by galactorrhoea, about 6 weeks after starting to take **fluvoxamine** and loxapine. The galactorrhoea resolved within 3 weeks of stopping the **fluvoxamine**, and menstruation occurred one week later. Her prolactin levels were found to be 80 micrograms/L (reference range 4 to 30 micrograms/L).[1]

Galactorrhoea is a known adverse effect of loxapine, and the SSRIs can increase prolactin levels,[2] which may have triggered this adverse effect.

The general relevance of this isolated case is unclear. Consider an interaction as a possible cause if a patient taking loxapine and an SSRI develops galactorrhoea.

1. Jeffries J, Bezchlibnyk-Butler K, Remington G. Amenorrhea and galactorrhea associated with fluvoxamine in a loxapine-treated patient. *J Clin Psychopharmacol* (1992) 12, 296–7.
2. Rosen RC, Lane RM, Menza M. Effects of SSRIs on sexual function: a critical review. *J Clin Psychopharmacol* (1999) 19, 67–85.

Molindone + SSRIs

An isolated report describes extrapyramidal adverse effects following the use of paroxetine with molindone.

Clinical evidence, mechanism, importance and management

An elderly woman taking molindone 10 mg twice daily developed severe and disabling extrapyramidal symptoms (severe bradykinesia, tremor, inability to feed herself, delirium) within about 2 weeks of starting **paroxetine** 10 mg daily. The symptoms resolved when molindone was stopped, and no problems occurred when **fluoxetine** alone was started.[1]

Movement disorders may just be a result of the additive adverse effects of molindone and SSRIs. **Fluoxetine** alone has been shown to occasionally cause movement disorders.[2,3]

The combination of an antipsychotic and an SSRI can be useful and so

the isolated case of extrapyramidal adverse effects should not prevent concurrent use. However, if extrapyramidal effects become troublesome bear this interaction in mind as a possible cause.

1. Malek-Ahmadi P, Allen SA. Paroxetine-molindone interaction. *J Clin Psychiatry* (1995) 56, 82–3.
2. Coulter DM, Pillans PI. Fluoxetine and extrapyramidal side effects. *Am J Psychiatry* (1995) 152, 122–5.
3. Bouchard RH, Pourcher E, Vincent P. Fluoxetine and extrapyramidal side effects. *Am J Psychiatry* (1989) 146, 1352–3.

Olanzapine + Carbamazepine or Oxcarbazepine

Carbamazepine appears to lower olanzapine levels, whereas oxcarbazepine does not appear to affect the pharmacokinetics of olanzapine.

Clinical evidence, mechanism, importance and management

(a) Carbamazepine

Multiple-dose studies in healthy subjects have shown that carbamazepine increases the metabolism of olanzapine. The clearance of olanzapine was increased by 44% and its elimination half-life was reduced 20% by carbamazepine, but these changes were not considered significant enough to necessitate dose adjustments.[1] In another study in healthy subjects, pretreatment with carbamazepine 200 mg twice daily for 2 weeks increased the clearance of a single 10-mg dose of olanzapine by 46%. The maximum plasma level and AUC were decreased by about 25% and 34%, respectively.[2] Another study found that 5 patients taking olanzapine and carbamazepine had a concentration/dose ratio 36% lower than 22 patients taking olanzapine alone.[3] A later study by the same authors found similar results, and also found that this increased olanzapine metabolism was probably due to an increase in glucuronidation, which was induced by the carbamazepine.[4]

A retrospective study identified 10 patients taking olanzapine and carbamazepine. The patients taking carbamazepine were taking olanzapine doses that were double those of subjects taking olanzapine alone. When corrected for dose it was found that the concentration/dose ratio of olanzapine was 71% lower in those also taking carbamazepine.[5] A 23 year-old woman required an olanzapine dose reduction from 15 mg daily to 10 mg daily to maintain similar serum olanzapine concentrations after discontinuing treatment with carbamazepine 600 mg per day.[6]

These findings suggest that, in some patients at least, the modest decreases in olanzapine levels caused by carbamazepine may be clinically relevant. It would seem prudent to monitor the outcome of concurrent use for olanzapine efficacy and adjust the olanzapine dose if necessary.

(b) Oxcarbazepine

A study in 13 patients taking olanzapine 5 to 20 mg daily found that the addition of oxcarbazepine for 5 weeks, at an initial dose of 300 mg daily increased to a range of 900 mg to 1.2 g after one week, had no significant effects on the pharmacokinetics of olanzapine. Concurrent use was generally well tolerated.[7] No particular additional monitoring or dose adjustment therefore appears necessary if oxcarbazepine and olanzapine are given concurrently.

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Olanzapine + Lamotrigine

Olanzapine reduces lamotrigine levels and lamotrigine may increase olanzapine levels.

Clinical evidence, mechanism, importance and management

A study in 43 healthy subjects found that steady-state olanzapine pharmacokinetics were not affected by lamotrigine 200 mg daily. However, the AUC and maximum plasma concentrations of lamotrigine were reduced by 24% and 20%, respectively. Although this reduction was not considered to be clinically significant, the authors suggested that interpatient variation indicated that some patients may require adjustment of their lamotrigine dose if olanzapine is started or discontinued.[1]

A further study in 14 healthy subjects given lamotrigine 50 mg daily, and a single 5-mg dose of olanzapine found no significant changes in the AUC and maximum plasma concentrations of lamotrigine when given with olanzapine, although the time to maximum plasma levels of lamotrigine was increased from 1.8 hours to 4.2 hours. This may be due to antimuscarinic effects of olanzapine slowing the gastrointestinal absorption of lamotrigine.[2] As only a single dose of olanzapine, and low doses of both drugs were used, the clinical significance of this finding is unclear.

A study in 14 patients taking olanzapine in doses of 10 mg to 20 mg daily, and who were also given lamotrigine in increasing doses over 8 weeks to 200 mg daily found no changes in the pharmacokinetics of olanzapine with a lamotrigine dose of 100 mg daily, but when the dose was increased to 200 mg daily, an increase of 16% in olanzapine plasma levels occurred. This increase would not be expected to be clinically significant.[3]

The effects found in these studies were small, and therefore suggest that dose adjustments are unlikely to be necessary if lamotrigine and valproate are given concurrently.

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Olanzapine + Miscellaneous

Activated charcoal causes a fall in olanzapine levels and venlafaxine moderately raise olanzapine levels. Additive dopaminergic effects have been seen in one patient taking olanzapine and haloperidol. Olanzapine appears not to interact to a clinically relevant extent with aluminium/magnesium hydroxide antacids, cimetidine or diazepam. However, excessive sedation and hypotension may occur if parenteral benzodiazepines are given with intramuscular olanzapine.

Clinical evidence, mechanism, importance and management

(a) Antacids

The manufacturers of olanzapine say that single doses of an **aluminium/magnesium-containing antacid** had no effect on the pharmacokinetics of olanzapine.[1] No special precautions would seem to be needed during concurrent use.

(b) Benzodiazepines

In vivo studies have found that no pharmacokinetic interaction occurs between olanzapine and **diazepam**.[1] This confirms *in vitro* studies using human liver microsomes,[1] which found that olanzapine did not inhibit the cytochrome P450 isoenzymes CYP3A4 or CYP2C19, which are concerned with the metabolism of **diazepam**. It was noted that mild increases in heart rate, sedation and dry mouth were seen in patients taking both drugs, but no dosage adjustments were thought to be necessary.[2] There would therefore appear to be no reason for avoiding concurrent use.

Similarly, intramuscular **lorazepam** 2 mg, given one hour after intramuscular olanzapine 5 mg increased the drowsiness seen with either drug alone. The pharmacokinetics of both drugs were not affected.[3,4] One case report describes hypotension occurring following the intramuscular use of a single 2-mg dose of **lorazepam** in a patient receiving intramuscular olanzapine 10 mg, the most recent dose being given 30 minutes before the **lorazepam**. His blood pressure dropped from 124/74 mmHg to 66/30 mm Hg; 12 hours later his blood pressure had returned to normal.[5] Intramuscular olanzapine has been associated with hypotension, bradycardia, respiratory depression, and rarely death, particularly in patients who have also received benzodiazepines. The manufacturers therefore say that

concurrent use is not recommended. If both drugs are needed, parenteral benzodiazepines should not be given for 1 hour after intramuscular olanzapine. If a parenteral benzodiazepine has already been given, intramuscular olanzapine should only be given with careful consideration and monitoring of sedation and respiration.[4]

(c) Charcoal, activated

The manufacturers report that activated charcoal reduces the bioavailability of oral olanzapine by 50 to 60%,[1,3] and recommend that administration be separated by 2 hours.[1]

(d) Cimetidine

The manufacturers say that cimetidine has no effect on the bioavailability of olanzapine.[1,3] No special precautions would seem to be needed during concurrent use.

(e) Haloperidol

A 67-year-old man with a long history of bipolar disorder was taking haloperidol 10 mg daily, with valproate and benzatropine. Because he had previously had parkinsonian symptoms, olanzapine was started, to be increased as the haloperidol was decreased. On day 6 his parkinsonian symptoms became particularly marked. The haloperidol was stopped and 2 days later the symptoms had resolved. It is thought that either the small amount of dopaminergic activity of olanzapine combined with that of the haloperidol brought on these symptoms, or that olanzapine affected the metabolism of haloperidol, resulting in increased levels and therefore greater dopaminergic activity.[6] The significance of this interaction is not clear, but it would be wise to be aware of it if both drugs are used.

(f) Venlafaxine

A retrospective study found that venlafaxine caused a modest 27% increase in olanzapine plasma levels. The clinical significance of this finding is unclear.[7] but probably small.

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3. Zyprexa (Olanzapine). Eli Lilly and Company. US Prescribing information, December 2009.
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Olanzapine + Probenecid

Probenecid may increase the AUC and maximum plasma levels of olanzapine.

Clinical evidence, mechanism, importance and management

Twelve healthy subjects were given a single 5-mg dose of olanzapine alone, or on day 2 of a 4-day course of probenecid 500 mg twice daily. The AUC and maximum plasma levels of olanzapine were increased by about 20%, but overall bioavailability was not affected. The probenecid is thought to have caused these small effects by reducing the glucuronidation of olanzapine.[1] As this was a single dose study, the clinical implications of this interaction when olanzapine is taken regularly, are unclear; however they are probably small

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Olanzapine + Quinolones

The olanzapine levels of a patient were reduced when ciprofloxacin was stopped. A patient taking olanzapine developed QT interval prolongation when intravenous ciprofloxacin was also given.

Clinical evidence

The olanzapine levels of a patient were rapidly reduced, by more than 50%, when **ciprofloxacin** 250 mg twice daily was stopped. On the day of the last dose of a 7-day course of **ciprofloxacin** her olanzapine plasma level was 32.6 nanograms/mL, but within 3 days it had fallen to 14.6 nanograms/mL.[1]

A case report describes a 70-year old woman taking azathioprine, olanzapine 10 mg daily and valsartan, who developed marked QTc interval prolongation after receiving intravenous **ciprofloxacin** 800 mg daily for 3 days. Her QTc interval returned to its initial value after **ciprofloxacin** was stopped.[2]

Mechanism

Olanzapine is metabolised by the cytochrome P450 isoenzyme CYP1A2, which can be inhibited by ciprofloxacin. Concurrent use therefore decreases olanzapine metabolism, which leads to increased olanzapine levels, and the adverse effects seen.

Importance and management

Evidence for an interaction between olanzapine and ciprofloxacin is limited, but what is known is in line with the way both drugs interact with other substances. An interaction is therefore established. The UK manufacturer of olanzapine recommends that a lower starting dose of olanzapine should be given to patients taking ciprofloxacin, and dose decrease should be considered if ciprofloxacin is started.[3] Note that other quinolones can inhibit CYP1A2 to varying degrees (for example see 'Theophylline + Quinolones', p.1452) and may therefore be expected to interact similarly.

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Olanzapine + Ritonavir

Ritonavir almost halves olanzapine levels.

Clinical evidence, mechanism, importance and management

In a study, 14 healthy non-smoking subjects were given a single 10-mg dose of olanzapine after they had taken ritonavir for 11 days (initially 300 mg twice daily, escalating to 500 mg twice daily). Ritonavir decreased the AUC and maximum plasma levels of olanzapine by 53% and 40%, respectively, and reduced its half-life from 32 hours to 16 hours.[1]

The authors suggest that ritonavir increased the metabolism of olanzapine by inducing the cytochrome P450 isoenzyme CYP1A2, which is the main metabolic route of olanzapine. They also suggest that ritonavir may have increased olanzapine glucuronidation, by inducing glucuronyltransferases, which may also have contributed to the decrease in olanzapine levels.

Evidence is limited to this one study, but ritonavir is an established enzyme inducer. It seems likely that increased olanzapine doses may be needed in the presence of ritonavir. If concurrent use is necessary monitor for olanzapine efficacy and increase the dose if necessary.

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Olanzapine + SSRIs

Fluvoxamine causes a rise in serum olanzapine levels, which is associated with increased adverse effects. Fluoxetine, paroxetine and sertraline appear to moderately raise olanzapine levels while citalopram appears to have no effect. A case of retarded ejaculation has been seen in one patient taking olanzapine and paroxetine, and the serotonin syndrome has been reported in patients taking citalopram or fluoxetine with olanzapine.

Clinical evidence

(a) Fluvoxamine

In a placebo-controlled study, 10 male smokers were given fluvoxamine 50 to 100 mg daily for 11 days, with olanzapine 2.5 to 7.5 mg daily on days 4 to 11. During the initial 4 days of concurrent use somnolence was increased by 19 to 115%, when compared to the group taking olanzapine and placebo, but the subjects accommodated to this over the next 4 days. Fluvoxamine increased the olanzapine maximum plasma levels and AUC by 84% and 119%, respectively, and the olanzapine clearance fell by 50%.[1] A retrospective study found that in patients taking fluvoxamine and olanzapine the concentration/dose ratio was 2.3-fold higher than those taking olanzapine alone.[2] In another study 10 schizophrenic patients were given fluvoxamine 50 mg daily from days 1 to 14 followed by fluvoxamine 100 mg daily from days 15 to 28. A single 10-mg dose of olanzapine was given on day 10 and again on day 24. The maximum plasma level of olanzapine was raised by 12% and 64% by 50 mg and 100 mg of fluvoxamine, respectively. Increased sedation was also seen, which was more frequent with fluvoxamine 100 mg daily.[3]

Other studies have found 50 to 81% increases in olanzapine levels with fluvoxamine 100 mg daily, and these increases took up to 8 weeks to occur. There was a marked variation between individuals in the extent of the interaction.[4-6] In one study, plasma levels of olanzapine were maintained when the dose of olanzapine was reduced by an average of 4.5 mg daily following the addition of fluvoxamine 25 mg daily.[7]

A number of case reports demonstrate the clinical relevance of this interaction. In one case, the olanzapine plasma levels of a 21-year-old woman were 6 times the recommended upper limit while she was taking fluvoxamine. During this time she developed rigidity and tremor. After the olanzapine dose was reduced from 15 mg to 5 mg daily the levels were still almost double the recommended level.[8] In another case, a patient taking fluvoxamine 200 mg daily developed hypersalivation (an adverse effect of olanzapine), without any extrapyramidal symptoms, when olanzapine 10 mg daily was also given..[9]

(b) Other SSRIs

In a study in 15 healthy nonsmokers, **fluoxetine** 60 mg daily for 8 days increased the maximum serum levels of a single 5-mg dose of olanzapine by 15%. In the same study, a single 60-mg dose of **fluoxetine** increased the maximum serum levels and AUC of a single 5-mg dose of olanzapine by 18%. No serious or unexpected adverse effects that could be attributed to an interaction were reported.[10] A case report describes a patient who had been taking **fluoxetine** 80 mg daily for several weeks with no adverse effects who developed serotonin syndrome within 3 weeks of starting to take olanzapine 5 mg daily. His symptoms resolved after discontinuing **fluoxetine**, and he was later able to tolerate a 20 mg daily dose of **fluoxetine** and olanzapine with no further adverse effects.[11] Serotonin syndrome has also been reported in a patient taking olanzapine, **citalopram** and lithium, see 'Lithium + Olanzapine', p.1363.

A patient taking fluvoxamine had olanzapine levels double the upper recommended limit; when **paroxetine** was substituted for fluvoxamine the olanzapine levels became almost normal.[8] Another patient taking **paroxetine** developed retarded ejaculation 2 months after he started to take olanzapine 15 mg daily. This adverse effect resolved when the olanzapine was given in divided doses.[12]

A retrospective study found that **sertraline** had no effect on the concentration/dose ratio of olanzapine, suggesting that it does not affect the pharmacokinetics of olanzapine.[2] Another study found that **paroxetine**, **fluoxetine** and **sertraline** increased olanzapine levels by about 32%, but **citalopram** had no effect.[6]

Mechanism

Fluvoxamine inhibits the cytochrome P450 isoenzyme CYP1A2, which is the major isoenzyme involved in the metabolism of olanzapine,[1] resulting in increased olanzapine levels and adverse effects. CYP2D6 also has a minor role in olanzapine metabolism. Many SSRIs can affect CYP2D6, with fluoxetine and paroxetine having the most potent effect. These SSRIs therefore raise olanzapine levels, but only to a very modest extent.

Importance and management

There is a good body of evidence that demonstrates that fluvoxamine can greatly raise olanzapine levels. The extent of the rise seen, and the case reports of adverse effects suggests that a lower dose of olanzapine is likely to be needed in the presence of fluvoxamine. Monitor for olanzapine adverse effects (e.g. somnolence, weight gain, dizziness). Other SSRIs do not appear to interact to any great extent, and olanzapine dose adjustments would not be expected to be necessary. However, the case report with paroxetine suggests that additive adverse effects are a possibility, and this should be borne in mind if adverse effects become troublesome.

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Olanzapine + Tobacco

Smoking tobacco increases the clearance of olanzapine.

Clinical evidence, mechanism, importance and management

Retrospective study has found that cigarette smoking reduces olanzapine levels,[1-3] in one study by 12%[1] and by about 50% in another,[3] and that smokers needed higher doses of olanzapine than non-smokers (10 mg compared with 12.5 mg) yet had lower olanzapine levels (60 nanomol/L compared with 92 nanomol/L).[4] Similarly, a study found that the clearance of olanzapine was about 50% greater in 274 smokers than in 249 non-smokers.[5] A further study in 17 psychiatric patients found that the olanzapine concentration-dose ratio was directly related to the activity of the cytochrome P450 isoenzyme CYP1A2: both CYP1A2 activity and olanzapine levels were sixfold higher in smokers than non-smokers.[6]

A case report describes a patient whose schizophrenia was successfully managed with olanzapine 15 mg daily whilst in hospital and smoking up to 12 cigarettes a day. However, on discharge his cigarette consumption increased to 80 per day, and his schizophrenic symptoms worsened. Olanzapine plasma levels reduced from 52 nanograms/mL to 30 nanograms/mL as his cigarette consumption increased to 80 per day.[7]

A patient taking olanzapine 30 mg daily developed extrapyramidal symptoms, probably as a result of increased plasma levels of olanzapine, following a reduction of his tobacco consumption. These effects improved following a reduction in his olanzapine dose to 20 mg daily.[8]

These findings suggest that the effects of olanzapine are reduced to some extent by smoking, but as the dose of olanzapine is individually titrated to effect it seems likely that routine dose adjustments will account for this interaction. However, if a patient decides to stop smoking, or begins to smoke more tobacco, it may be prudent to monitor the patient more closely, as dose decreases or increases may become necessary.

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Olanzapine + Topiramate

In a study, 12 patients receiving long-term treatment with olanzapine 10 mg to 20 mg daily were given topiramate in a dose that was increased gradually to 200 mg daily. Plasma levels of olanzapine were not significantly affected by topiramate and the combination was well tolerated.[1]

1. Migliardi G, D'Arrigo C, Santoro V, Bruno A, Cortese L, Campolo D, Cacciola M, Spina E. Effect of topiramate on plasma concentrations of clozapine, olanzapine, risperidone, and quetiapine in patients with psychotic disorders. *Clin Neuropharmacol* (2007) 30, 107–13.

Olanzapine + Tricyclic and related antidepressants

No pharmacokinetic interaction occurs between imipramine and olanzapine, and mirtazapine does not affect the pharmacokinetics of olanzapine. The additive effects of clomipramine and olanzapine were thought to have caused a seizure in one patient.

Clinical evidence, mechanism, importance and management

A randomised, crossover study in 9 healthy men who were given single doses of olanzapine 5 mg and **imipramine** 75 mg found no clinically relevant pharmacokinetic or pharmacodynamic interactions between the two drugs.[1] However, one case report describes seizures, thought to be caused by the additive effects of olanzapine and **clomipramine**. Neither drug alone had produced this reaction in the patient.[2]

A study in 7 patients with schizophrenia investigated the effect of adding **mirtazapine** 30 mg at bedtime, for 6 weeks, to treatment with olanzapine. **Mirtazapine** had a negligible effect on the metabolism of olanzapine and the combination was well tolerated.[3]

No dose adjustments would seem to be necessary if olanzapine is given with a tricyclic, but be aware that both olanzapine and the tricyclics have the potential to lower the seizure threshold and that their effects may be additive.

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Olanzapine + Valproate

Valproate appears to lower olanzapine levels, and the combination appears to increase the risk of hepatic injury in children.

Clinical evidence, mechanism, importance and management

A retrospective study identified 52 children (under 18-years-old) who were taking olanzapine alone (17 patients), valproate semisodium (divalproex sodium) alone (23 patients) or both drugs together (12 patients). At least one peak liver enzyme level (ALT, AST or lactate dehydrogenase) was found to be above the normal range in 59% of those taking olanzapine alone, in 26% of those taking valproate alone, and in 100% of the patients taking both drugs. Liver enzymes were persistently elevated in 42% of the patients taking both drugs, and 2 of these patients had levels that were three times the upper limit of normal. Treatment was discontinued due to pancreatitis in one and steatohepatitis in the other.

The authors of his study recommend measuring liver enzymes every 3 to 4 months for the first year of concurrent use, thereafter monitoring every 6 months if no adverse effects are detected.[1]

In 4 patients, a significant reduction in olanzapine plasma levels of between 32 and 79% was found when valproate was given. The authors suggested that this occurred due to the valproate inducing the enzymes involved in the metabolism of olanzapine.[2]

The authors of an analysis of reports on the use of mood stabiliser combinations noted that there may be additive adverse effects of weight gain and drowsiness when olanzapine is given with valproate.[3]

The clinical relevance of these two latter reports is uncertain.

1. Gonzalez-Heydrich J, Raches D, Wilens TE, Leichtner A, Mezzacappa E. Retrospective study of hepatic enzyme elevations in children treated with olanzapine, divalproex, and their combination. *J Am Acad Child Adolesc Psychiatry* (2003) 12, 1227–33.
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Paliperidone + Miscellaneous

The bioavailability of paliperidone may be increased by a high fat/high caloric meal, carbamazepine, St John's wort, rifampicin (rifampin) and valproate. Additive pharmacological effects can be expected if paliperidone is taken with other drugs that have a CNS depressant action, that prolong the QT interval, cause hypotension or lower seizure threshold.

Clinical evidence, mechanism, importance and management

Paliperidone (9-hydroxyrisperidone) is the active metabolite of risperidone.

(a) Antihypertensives

Paliperidone may cause orthostatic hypotension, and should therefore be given cautiously to patients also taking other drugs which can also cause this effect. The manufacturers specifically mention other **antipsychotics** and **tricyclic antidepressants**,[1] and **hypotensive** medication.[2]

(b) Carbamazepine

Carbamazepine 200 mg twice daily caused a 37% decrease in the mean steady-state AUC and peak levels of paliperidone. This is mainly due to a 35% increase in renal clearance of paliperidone associated with the induction of renal P-glycoprotein by carbamazepine. Higher doses of carbamazepine may produce greater decreases in paliperidone levels. The manufacturer advises that if carbamazepine is started, the dose of paliperidone should be re-evaluated and increased if necessary, with decreases in dose if carbamazepine is then discontinued. The induction effects of carbamazepine on paliperidone levels become maximal after 2 to 3 weeks.[1,2] Note that **rifampicin** (**rifampin**) and **St John's wort** (*Hypericum perforatum*) are also a P-glycoprotein inducers, and they may therefore be expected to interact similarly.[1]

(c) CNS depressants

Paliperidone can cause adverse effects on the CNS, and therefore its use with other drugs which have a CNS depressant activity is not recommended. The manufacturers specifically mention **anxiolytics**, **antipsychotics**, **hypnotics**, **opioids** and **alcohol**.[1,2]

(d) Drugs that lower seizure threshold

The manufacturer advises caution if paliperidone is used with other drugs known to lower the seizure threshold. The manufacturer specifically mentions **butyrophenones**, **mefloquine**, **phenothiazines**, **SSRIs**, **tramadol**, and **tricyclic antidepressants**.[1]

(e) Drugs that prolong the QT interval

Paliperidone may prolong the QT interval (12.3 millisecond increase in one study at twice the recommended exposure to paliperidone).[2] The manufacturers advise that the concurrent use of other drugs that prolong the QT interval should be avoided. They specifically mention **class Ia antiarrhythmics** (e.g. **disopyramide**, **quinidine**, **procainamide**), **class III antiarrhythmics** (e.g. **amiodarone**, **sotalol**), **antipsychotics** (e.g. **chlorpromazine**, **thioridazine**), antibacterials (e.g. **gatifloxacin**, **moxifloxacin**), **mefloquine**, and some antihistamines [presumably **terfenadine** and **astemizole**].[1,2]

(f) Food

Giving paliperidone with a high fat/high caloric meal increased its maximum levels and AUC by 50 to 60%, when compared with the fasting

state.[1] The UK manufacturer says that paliperidone should normally be consistently taken on an empty stomach, or with breakfast,[1] whereas the US manufacturer says that paliperidone may be taken without regard to food.[2]

(g) Trimethoprim

A randomised study in 30 healthy subjects who were given a single 6-mg dose of paliperidone alone, and after a 5-day course of trimethoprim 200 mg twice daily, found that trimethoprim did not affect the pharmacokinetics of paliperidone.[3]

(h) Valproate

Paliperidone does not appear to affect valproate levels. However, extended-release valproate semisodium (divalproex sodium) 500 mg twice daily increased the AUC and maximum levels of a 12 mg dose of paliperidone by 50%. The US manufacturer advises considering a dose reduction of paliperidone if both drugs are given.[2]

1. Invega (Paliperidone). Janssen-Cilag Ltd. UK Summary of product characteristics, November 2009.
2. Invega (Paliperidone). Janssen Pharmaceuticals Inc. US Prescribing information, July 2009.
3. Cleton A, Cleton A, Talluri K, Leempoels J, Thyssen A, Janssens L, Eerdekens M, Boom S. No pharmacokinetic interaction between trimethoprim and paliperidone ER in healthy subjects. *Clin Pharmacol Ther* (2006) 79, P22.

Perospirone + Miscellaneous

Perospirone levels are reduced by carbamazepine, and increased by itraconazole, possibly ketoconazole, and some macrolides.

Clinical evidence, mechanism, importance and management

(a) Carbamazepine

Carbamazepine reduced the plasma levels of a single 8-mg dose of perospirone to below the detection limit.[1] This is likely to be as a result of carbamazepine-induced induction of perospirone metabolism by CYP3A4.

(b) Itraconazole or Ketoconazole

Giving itraconazole 200 mg daily for 5 days, with a single 8-mg dose of perospirone on day 6 resulted in a 6-fold increase in perospirone maximum plasma levels. A similar increase in the AUC and the half-life of perospirone was also seen.[2] An *in vitro* study found that the metabolism of perospirone was markedly reduced by ketoconazole and it was estimated that *in vivo* perospirone clearance could be reduced by 64 to 90%.[3] As itraconazole and ketoconazole are potent inhibitors of CYP3A4, increases in levels of perospirone are likely due to inhibition of its metabolism. The authors of the *in vitro* study suggest that concurrent use of other inhibitors of CYP3A4, such as some **macrolides** may also increase levels of perospirone.[3]

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Phenothiazines + Antacids

Antacids containing aluminium/magnesium hydroxide or magnesium trisilicate can reduce the serum levels of chlorpromazine. *In vitro* studies suggest that this interaction may possibly also occur with other antacids and phenothiazines.

Clinical evidence

A study in 10 patients taking **chlorpromazine** 600 mg to 1.2 g daily found that 30 mL of *Aludrox* (**aluminium**/**magnesium hydroxide gel**) reduced the urinary excretion of **chlorpromazine** by 10 to 45%.[1]

A study was prompted by the observation of one psychiatric patient, taking **chlorpromazine** who relapsed within 3 days of starting to take an unnamed antacid. When 6 patients were given 30 mL of *Gelusil* (**aluminium hydroxide** with **magnesium trisilicate**) with **chlorpromazine** suspension, the serum **chlorpromazine** levels measured 2 hours later were reduced by about 20% (from 168 to 132 nanograms/mL).[2] *In vitro* studies have also found that other phenothiazines (**trifluoperazine**, **fluphenazine**, **perphenazine**, **thioridazine**) are adsorbed to a considerable extent onto a number of antacids (**magnesium trisilicate**, **bismuth subnitrate**, **aluminium hydroxide** with **magnesium carbonate**) but there do not appear to be any clinical studies of the possible clinical effects of these interactions.[3]

Mechanism

Chlorpromazine and other phenothiazines become adsorbed onto these antacids,[2,4] which would seem to account for the reduced bioavailability.

Importance and management

Information regarding an interaction between antacids and phenothiazines seems to be limited to the reports cited. Reductions of up to 45% in serum antipsychotic levels would be expected to be clinically important, but so far only one case describing reduced efficacy seems to have been reported.[2] Separating the doses as much as possible (1 to 2 hours) to avoid admixture in the gut should minimise any effects. In the case of chlorpromazine an alternative would be to use calcium carbonate-glycine or magnesium hydroxide gel, which seem to affect its gastrointestinal absorption to a lesser extent.[4] Other phenothiazines and antacids are known to interact *in vitro*,[3] but the clinical importance of these interactions awaits further study.

1. Forrest FM, Forrest IS, Serra MT. Modification of chlorpromazine metabolism by some other drugs frequently administered to psychiatric patients. *Biol Psychiatry* (1970) 2, 53–8.
2. Fann WE, Davis JM, Janowsky DS, Sekerke HJ, Schmidt DM. Chlorpromazine: effects of antacids on its gastrointestinal absorption. *J Clin Pharmacol* (1973) 13, 388–90.
3. Moustafa MA, Babhair SA, Kouta HI. Decreased bioavailability of some antipsychotic phenothiazines due to interactions with adsorbent antacid and antidiarrhoeal mixtures. *Int J Pharmaceutics* (1987) 36, 185–9.
4. Pinell OC, Fenimore DC, Davis CM, Moreira O, Fann WE. Drug-drug interaction of chlorpromazine and antacid. *Clin Pharmacol Ther* (1978) 23, 125.

Phenothiazines + Barbiturates

The levels of chlorpromazine, and possibly thioridazine, are decreased by phenobarbital. Phenothiazines also appear to reduce barbiturate levels. However, the clinical importance of these reductions is uncertain. Pentobarbital, promethazine and hyoscine in combination are said to increase the incidence of perioperative agitation.

Clinical evidence

(a) Phenothiazine levels reduced

A study in 12 patients with schizophrenia taking **chlorpromazine** 100 mg three times daily found that **phenobarbital** 50 mg three times daily reduced **chlorpromazine** plasma levels by 25 to 30%, which was accompanied by changes in certain physiological measurements, which clearly reflected a reduced response to chlorpromazine..[1]

In another study in 7 patients, the plasma levels of **thioridazine** were reduced by **phenobarbital**, but the clinical effects of this were uncertain.[2] However, another study found that **phenobarbital** caused no changes in serum **thioridazine** levels, but the levels of its active metabolite (mesoridazine) were reduced.[3]

(b) Phenobarbital levels reduced

A study in patients with epilepsy found that their serum phenobarbital levels fell by 29% when they were given phenothiazines, which included **chlorpromazine**, **thioridazine** or **mesoridazine**, and increased when the phenothiazine was withdrawn.[4] This study confirms another, in which **thioridazine** 100 to 200 mg daily was found to reduce serum phenobarbital levels by about 25%.[5]

(c) Pentobarbital

There is some limited evidence that the concurrent use of pentobarbital, **promethazine** and hyoscine increases the incidence of pre-operative, peri-operative and postoperative agitation, and it has been suggested that this triple combination should be avoided.[6]

Mechanism

Uncertain. The barbiturates are potent liver enzyme inducers, and so it is presumed that they increase the metabolism of the phenothiazines by the liver.

Importance and management

These interactions appear to be established, but the documentation is limited. Their importance is uncertain, but be alert for evidence of reductions in response to both drugs if a phenothiazine and a barbiturate are given, and to increased responses if one of the drugs is withdrawn. The only combinations implicated are phenobarbital with chlorpromazine, mesoridazine, and thioridazine, but it seems possible that other phenothiazines and barbiturates will behave similarly.

1. Loga S, Curry S, Lader M. Interactions of orphenadrine and phenobarbitone with chlorpromazine: plasma concentrations and effects in man. *Br J Clin Pharmacol* (1975) 2, 197–208.
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4. Haidukewych D, Rodin EA. Effect of phenothiazines on serum antiepileptic drug concentrations in psychiatric patients with seizure disorder. *Ther Drug Monit* (1985) 7, 401–4.
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Phenothiazines + Cannabis or Tobacco

Smokers of tobacco may possibly need larger doses of chlorpromazine, fluphenazine, or thioridazine than non-smokers. A similar effect may occur with chlorpromazine in cannabis smokers.

Clinical evidence

(a) Chlorpromazine

A comparative study found that the frequency of drowsiness in 403 patients taking chlorpromazine was 16% in non-smokers, 11% in light smokers, and 3% in heavy smokers (more than 20 cigarettes daily).[1] Another report describes a patient taking chlorpromazine who experienced increased sedation and dizziness and higher plasma chlorpromazine levels when he gave up smoking.[2] A study in 31 patients found that the clearance of chlorpromazine was increased by 38% by tobacco smoking, by 50% by cannabis smoking, and by 107% when both tobacco and cannabis were smoked.[3]

(b) Fluphenazine

A retrospective study in 40 psychiatric inpatients found that the plasma fluphenazine levels of non-smokers were more than double those of smokers (1.83 nanograms/mL compared with 0.89 nanograms/mL) when they were given oral fluphenazine hydrochloride. The clearance of both oral and intramuscular fluphenazine was 1.67-fold and 2.33-fold greater, respectively, in the smokers than in the non-smokers.[4] No behavioural differences were seen.[4]

(c) Thioridazine

A study in 76 patients taking thioridazine found that the dose-corrected steady-state plasma levels of thioridazine were significantly lower in smokers than in non-smokers (4 nanomol/L per mg compared with 7.4 nanomol/L per mg, respectively). Levels of the thioridazine metabolites, mesoridazine and sulforidazine, were also lower in smokers.[5]

Mechanism

Not established. The probable reason is that some of the components of tobacco smoke act as enzyme inducers, which increase the rate at which the liver metabolises these antipsychotics, thereby reducing their serum levels and clinical effects.

Importance and management

Established interactions but of uncertain clinical importance. Be alert for the need to increase the doses of these antipsychotics in patients who smoke, and reduce the doses if smoking is stopped.

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Phenothiazines + Carbamazepine or Oxcarbazepine

Fluphenazine levels are reduced by carbamazepine. The plasma levels of chlorpromazine do not appear to be affected by oxcarbazepine. The concurrent use of thioridazine and carbamazepine does not appear to affect the pharmacokinetics of either drug. Case reports describe Stevens-Johnson syndrome and neuroleptic malignant syndrome in patients taking phenothiazines with carbamazepine.

Clinical evidence

(a) Chlorpromazine

Oxcarbazepine was substituted for carbamazepine in 4 difficult to treat schizophrenic patients. All patients were also taking chlorpromazine, and in 3 cases other antipsychotic medication (lithium, zuclopenthixol or clozapine). After 3 weeks of taking the oxcarbazepine all 4 patients had rises in their chlorpromazine levels, of 28%, 63%, 76%, and 90%, respectively. In one case this rise was associated with increased extrapyramidal adverse effects.[1]

A case report describes a patient taking amoxapine and chlorpromazine 350 mg daily, who developed ataxia, nausea and agitation when carbamazepine, titrated to 900 mg daily, was started. The adverse effects were attributed to high levels of the carbamazepine metabolite carbamazepine-10,11-epoxide.[2] See also, *Trifluoperazine*, below.

(b) Fluphenazine

A patient receiving intramuscular fluphenazine decanoate 37.5 mg weekly had a rise in his serum fluphenazine levels from 0.6 nanograms/mL to 1.17 nanograms/mL 6 weeks after stopping carbamazepine 800 mg daily. A moderate improvement in his schizophrenic condition occurred.[3] See also, *Trifluoperazine*, below.

(c) Levomepromazine

A 54-year old man living in a psychiatric hospital, who had been taking haloperidol, levomepromazine, **sultopride**, and metixene long-term was prescribed carbamazepine 400 mg daily for impulsive behaviour. The following day he became unstable on his feet, and after 3 days could no longer walk by himself. He had a fever of 40°C, muscle rigidity, diaphoresis, and serum creatine phosphokinase was elevated to 923 units/L. He was diagnosed as having neuroleptic malignant syndrome, and recovered after body cooling and administration of fluids, with symptoms resolving over 12 days.[4]

(d) Thioridazine

Thioridazine 100 to 200 mg daily was found to have no effect on the steady-state levels of carbamazepine or carbamazepine-10,11-epoxide in 8 epileptic patients.[5] Carbamazepine had no significant effect on thioridazine plasma levels in 6 patients.[6]

(e) Trifluoperazine

Two patients taking **trifluoperazine** (with fluphenazine and chlorpromazine in one case) developed Stevens-Johnson syndrome within 8 to 14 days of starting to take carbamazepine. Both had erythema multiforme skin lesions and at least two mucous membranes were affected. After treatment, they restarted all their previous drugs, except carbamazepine, without problems.[7]

Mechanism

Carbamazepine is a recognised enzyme inducer, therefore it seems highly likely that the reduced plasma chlorpromazine levels occur because its metabolism by the liver is markedly increased by carbamazepine.

In the case describing neuroleptic malignant syndrome it was suggested that carbamazepine may have reduced levels of the antimuscarinic

(anticholinergic) antipsychotics (levomepromazine and sultopride), resulting in cholinergic rebound, and inducing NMS.[4]

Importance and management

Evidence appears to be limited to the reports cited, many of which suggest that no interaction normally occurs. Nevertheless, it would seem prudent to be alert for a diminished response to treatment with a phenothiazine if carbamazepine is added: it may be necessary to increase the dose of the phenothiazine. Oxcarbazepine does not appear to interact, probably because it is not an enzyme inducer.

The isolated case of high carbamazepine-10,11-epoxide levels in the patient taking chlorpromazine appears to be the only reported case of an interaction. Its general significance is therefore unknown. Similarly, the general relevance of the case of neuroleptic malignant syndrome is unknown.

Stevens-Johnson syndrome with carbamazepine alone is rare, and the risk appears to be mostly confined to the first 8 weeks of treatment.[8] It may be more common in patients being treated for conditions other than epilepsy.[9] It is not possible to say whether the concurrent use of antipsychotics increases the risk of its development, but until more is known it would be prudent to monitor the outcome, particularly during the first 2 weeks of combined use.

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9. Dhar S, Todi SK. Are carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis more common in nonepileptic patients? *Dermatology* (1999) 199, 194.

Phenothiazines + SSRIs

A number of case reports describe extrapyramidal adverse effects following the use of fluoxetine or paroxetine with phenothiazines. Thioridazine levels are increased by fluvoxamine, and predicted to be increased by fluoxetine, or paroxetine, which increases the risk of QT interval prolongation.

Clinical evidence

(a) Chlorpromazine

A study in patients with schizophrenia found that over a 12-week period the serum levels of chlorpromazine were not significantly altered by **citalopram** 40 mg daily.[1]

(b) Cyamemazine

A study in patients taking cyamemazine found that **fluvoxamine** 150 mg daily had no effect on cyamemazine serum levels, but the authors of the report also say that no firm conclusions should be drawn from this finding because the number of patients was too small.[2]

(c) Fluphenazine

A severe dystonic reaction (painful jaw tightness and throat 'closing up') occurred in a man taking **fluoxetine** 40 mg daily when he also took fluphenazine 2.5 mg on two consecutive nights.[3]

(d) Levomepromazine

A study in patients taking levomepromazine found that **fluvoxamine** 150 mg daily did not affect its serum levels, but the authors of the report also say that no firm conclusions should be drawn from this finding because the number of patients was too small.[2] A further study in 15 patients also found that levomepromazine 5 to 25 mg daily had no significant effect on the pharmacokinetics of **fluvoxamine**. Additionally, patients in this study found that the levomepromazine counteracted the insomnia caused by **fluvoxamine**.[4]

A study in three groups of 8 healthy subjects taking **citalopram** 40 mg daily for 10 days found that a single 50-mg oral dose of levomepromazine increased the initial steady-state levels of desmethylcitalopram, the primary metabolite of **citalopram** by 10 to 20%, which was not considered to be clinically significant.[5]

A study in patients with schizophrenia found that over a 12-week period the serum levels of levomepromazine were not significantly altered by **citalopram** 40 mg daily.[1]

(e) Metopimazine

A French regional pharmacovigilance centre reported 37 cases of extrapyramidal adverse effects linked to the concurrent use of an SSRI and a neuroleptic. In 2 cases metopimazine was given.[6]

(f) Pericyazine

A study describes a patient who developed extrapyramidal symptoms when given pericyazine and **fluoxetine**.[7]

(g) Perphenazine

1. Citalopram. A study in patients with schizophrenia found that, over a 12-week period, the serum levels of perphenazine were not significantly altered by citalopram 40 mg daily.[1]

2. Fluoxetine. The combination of perphenazine and fluoxetine was found to be effective in the treatment of psychotic depression in 30 patients, and the adverse effects (which included dry mouth, blurred vision, constipation, tremor or rigidity, orthostasis and hypotension) were thought to be easier to tolerate than an antipsychotic with a tricyclic antidepressant.[8] However, one woman developed marked extrapyramidal symptoms within 2 weeks of starting perphenazine 4 mg twice daily and fluoxetine 20 mg daily.[9]

3. Paroxetine. The effects of a single 100-microgram/kg oral dose of perphenazine on the performance of psychomotor tests were assessed after 4, 6, 8 and 10 hours in 5 subjects. The tests were then repeated after the subjects also took paroxetine 20 mg daily for 10 days. The scores for these tests were worsened by the perphenazine, when compared with a placebo, and further worsened by the presence of the paroxetine. In addition to over-sedation and impairment of the performance of psychomotor tests and memory, 2 of the subjects developed akathisia 10 hours after taking both drugs. The AUC of the perphenazine was increased sevenfold and its maximum plasma levels were increased sixfold.[10]

(h) Thioridazine

A study in patients with schizophrenia found that, over a 12-week period, the serum levels of thioridazine were not significantly altered by **citalopram** 40 mg daily.[1]

A study in 10 patients with schizophrenia found that when **fluvoxamine** 50 mg daily was added to established treatment with thioridazine 30 to 200 mg daily, thioridazine plasma levels were increased by 225%. There were no reported changes in either clinical status or adverse effects.[11]

(i) Trifluoperazine

A New Zealand study describes a patient who developed extrapyramidal symptoms when given trifluoperazine and **fluoxetine**.[7]

Mechanism

Fluoxetine and paroxetine can inhibit the metabolism of some phenothiazines by the cytochrome P450 isoenzyme CYP2D6.[10] Raised phenothiazine levels may increase the risk of phenothiazine adverse effects, such as movement disorders. However, movement disorders may just be a result of the additive adverse effects of antipsychotics and SSRIs. Furthermore, fluoxetine alone has been shown to occasionally cause movement disorders.[7,12]

Importance and management

On the whole significant interactions between the phenothiazines and SSRIs appear rare (although see thioridazine, below). The combination can be useful and so the isolated cases of extrapyramidal adverse effects should not prevent concurrent use. However, if extrapyramidal effects become troublesome bear this interaction in mind as a possible cause. The rise in **perphenazine** levels caused by paroxetine seems to result in a greater number of more serious adverse effects and so consideration should be given to reducing the dose of perphenazine if paroxetine is start-

ed. Citalopram may be a suitable alternative as it does not appear to affect perphenazine levels.

Note that, the US manufacturers of fluoxetine,[13] and paroxetine,[14] contraindicate the concurrent use of **thioridazine** as they suggest that its metabolism (by CYP2D6) may be inhibited by these SSRIs, leading to raised thioridazine levels and the risk of QT prolongation. The use of thioridazine is also contraindicated for 5 weeks after fluoxetine has been stopped.[13] The manufacturers of fluvoxamine also contraindicate concurrent use;[15] the study cited above found a large increase in thioridazine levels so this seems prudent. Smaller increases would be expected with other SSRIs, and it has been suggested that the dose of thioridazine may need to be adjusted [reduced] when it is given with **escitalopram**.[16]

SSRI antidepressants may lower the seizure threshold, and therefore concurrent use with other drugs, which can also lower the seizure threshold, such as phenothiazines, should be undertaken with caution.

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14. Paxil (Paroxetine hydrochloride). GlaxoSmithKline. US Prescribing information, August 2009.
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16. Cipralex (Escitalopram oxalate). Lundbeck Ltd. UK Summary of product characteristics, October 2008.

Phenothiazines + Trazodone

Undesirable hypotension occurred in two patients taking chlorpromazine or trifluoperazine with trazodone. Thioridazine causes a moderate rise in trazodone plasma levels. A fatal case of jaundice and hepatic encephalopathy has been reported with the use of trifluoperazine, thioridazine and trazodone.

Clinical evidence, mechanism, importance and management

A depressed patient taking **chlorpromazine** began to complain of dizziness and unstable gait within 2 weeks of starting to take trazodone 100 mg one to three times daily. His blood pressure had fallen to between 92/58 and 126/72 mmHg. Within 2 days of stopping the trazodone his blood pressure had restabilised.[1]

A patient taking **trifluoperazine** was given trazodone 100 mg daily and within 2 days she complained of dizziness and was found to have a blood pressure of 86/52 mmHg. Within one day of stopping the trazodone her blood pressure was back to 100/65 mmHg.[1] It would seem that the hypotensive adverse effects of the two drugs can be additive, although an interaction was not confirmed as the trazodone was not taken alone.

A study, undertaken to confirm the involvement of the cytochrome P450 isoenzyme CYP2D6 in the metabolism of trazodone, found that when 11 patients with depression were given trazodone 150 to 300 mg at bedtime for 18 weeks, and then with **thioridazine** 20 mg twice daily for one week, the plasma levels of the trazodone and its active metabolite, *m*-chlorophenylpiperazine, rose by 36% and 54%, respectively.[2] No adverse reactions were described. However, a case of fatal hepatic necrosis with cholestasis has been attributed to the concurrent use of trazodone and phenothiazines. A 72-year-old woman taking **trifluoperazine**, trazodone and lithium carbonate developed an elevated alanine aminotransferase level. **Trifluoperazine** was replaced with **thioridazine**, but 9 weeks later she became jaundiced and developed hepatic encephalopathy, and died 6 weeks after the onset of jaundice. The authors consider that the combination of the phenothiazines and trazodone were the cause of her hepatic necrosis: both phenothiazines and trazodone have been reported to individually cause hepatic adverse effects.[3]

Evidence for an interaction between trazodone and the phenothiazines appears to be limited. The isolated case of hepatic adverse effects is of unknown general importance, but it serves as a reminder to consider the additive adverse effects of drugs when prescribing them in combination. The reports of hypotensive effects are also isolated. It would seem prudent to warn patients of the possibility of additive hypotensive effects (e.g. dizziness, postural hypotension) and advise them to seek medical advice if this becomes troublesome.

1. Asayesh K. Combination of trazodone and phenothiazines: a possible additive hypotensive effect. *Can J Psychiatry* (1986) 31, 857–8.
2. Yasui N, Otani K, Kaneko S, Ohkubo T, Osanai T, Ishida M, Mihara K, Kondo T, Sugawara K, Fukushima Y. Inhibition of trazodone metabolism by thioridazine in humans. *Ther Drug Monit* (1995) 17, 333–5.
3. Hull M, Jones R, Bendall M. Fatal hepatic necrosis associated with trazodone and neuroleptic drugs. *BMJ* (1994) 309, 378.

Phenothiazines + Tricyclic antidepressants

The concurrent use of tricyclic antidepressants and phenothiazines is common, but the tricyclic levels are increased by many of the phenothiazines, and the levels of some phenothiazines are also increased by the tricyclics. It has been suggested that concurrent use might contribute to an increased incidence of tardive dyskinesia. Nevertheless, fixed-dose combined preparations are available. Tricyclics have also been shown to reverse the therapeutic effects of chlorpromazine. Occasionally the concurrent use of a tricyclic and a phenothiazine can lead to adverse effects such as faecal impaction.

Clinical evidence

(a) Effect of phenothiazines on tricyclic antidepressants

An extended study of 4 patients given intramuscular **fluphenazine decanoate** 12.5 mg weekly, with benzatropine 2 mg three times daily and **imipramine** 300 mg daily, found that the mean combined plasma concentrations of **imipramine** and its metabolite, desipramine, were 850 nanograms/mL. This appeared high, when compared with 60 other patients who were taking **imipramine** 225 mg daily and had levels of 180 nanograms/mL.[1]

A comparative study of 99 patients taking **amitriptyline** or **nortriptyline** alone, and 60 other patients also taking **perphenazine** 10 mg daily, found that although the tricyclic antidepressant dosages were the same, the plasma tricyclic antidepressant levels were up to 70% higher in those also taking **perphenazine**.[2]

Other studies have described increased tricyclic antidepressant levels with phenothiazines. There is currently evidence for this interaction between:

- **imipramine**,[3-5] and **chlorpromazine**
- **nortriptyline**,[6] and **levomepromazine**
- **amitriptyline**,[7] **imipramine**,[5,8,9] **desipramine**[10] or **nortriptyline**,[6,11-13] and **perphenazine**
- **desipramine**,[14] **imipramine**[15] or **nortriptyline**,[6] and **thioridazine**
- **nortriptyline**[16] and **thioridazine** (with paroxetine).

However, other studies have found no interaction between:

- **amitriptyline**[6,11,17] or **nortriptyline**,[18] and **perphenazine**
- **amitriptyline**[6] and **thioridazine**
- **amitriptyline**[6] and **levomepromazine**.

It should be noted that in the case of **amitriptyline**, although the levels were not affected, levels of nortriptyline, its metabolite, were raised.[6]

(b) Effect of tricyclic antidepressants on phenothiazines

In a controlled study in 8 patients with schizophrenia taking **butaperazine** 20 mg daily, the 6 patients taking **desipramine** 150 mg or more daily had a rise in serum **butaperazine** levels of between 50 and 300%. The other 2 patients, taking **desipramine** 100 mg or less, had no changes in **butaperazine** levels.[19] Other studies have found a rise in phenothiazine levels when tricyclic antidepressants are added. So far, interactions with **chlo-**

rpromazine and **amitriptyline**,[20] **imipramine**[20] or **nortriptyline**[21] have been documented. One study in 23 patients found transitory increases in the levels of **chlorpromazine**, **mesoridazine**, **methotrimeprazine**, **perphenazine**, **thioproperazine**, **thioridazine**, and **trifluoperazine** when **amitriptyline** was also given for 12 weeks.[22]

One study in 7 patients with chronic schizophrenia also reported that giving **nortriptyline** 50 mg three times daily to patients taking **chlorpromazine** 100 mg three times daily resulted in profound worsening of the clinical state, with marked increases in agitation and tension, despite the fact that the **chlorpromazine** levels were actually raised. The **nortriptyline** was withdrawn.[21] A temporary reversion to a disruptive behaviour pattern has been seen in other patients taking **chlorpromazine** when **amitriptyline** was given.[23] One patient experienced a severe catatonic reaction that was attributed to the use of **thioridazine** and **amitriptyline**,[24] and the case of a woman who became anxious with widely staring eyes, a persistent jerking of her head and at times the inability to speak was thought to be due to the use of **imipramine** and **chlorpromazine**.[25] Ventricular tachycardia has also been reported in a 38-year-old woman taking **desipramine** and **thioridazine**, which responded to treatment with lidocaine.[26]

(c) Other effects

The tricyclic antidepressants have antimuscarinic side effects, which can, in conjunction with the use of an antipsychotic, lead to life-threatening interactions. These are discussed further in the monograph 'Antipsychotics + Antimuscarinics', p.833.

Mechanism

The rise in the serum levels of both drugs is thought to be due to a mutual inhibition of the liver enzymes concerned with the metabolism of both drugs, which results in their accumulation.[3,4,8,19,21]

Importance and management

Established interactions, but the advantages and disadvantages of concurrent use are the subject of debate. These two groups of drugs are widely used together in the treatment of schizophrenic patients who show depression, and for mixed anxiety and depression. A number of fixed-dose combinations have been marketed (e.g. amitriptyline with perphenazine, and nortriptyline with fluphenazine). However, the safety of using both drugs together has been questioned.

One of the problems of phenothiazine use is the development of tardive dyskinesias, and some evidence suggests that the higher the dosage, the greater the incidence.[27] The symptoms can be transiently masked by increasing the dosage,[28] and so it has been suggested that the presence of a tricyclic antidepressant might not only be a factor causing tardive dyskinesia to develop, but might also mask the condition.[19,29] It has been recommended that the addition of full antidepressant doses of nortriptyline to average antipsychotic doses of chlorpromazine should be avoided because the therapeutic actions of the chlorpromazine may be reversed.[21] See also Antagonism of antipsychotic effects, under 'Antipsychotics + Antimuscarinics', p.833.

Attention has also been drawn to excessive weight gain associated with several months use of amitriptyline with thioridazine for the treatment of chronic pain,[30] but note that excessive weight gain is a recognised adverse effect of antipsychotics alone.

For reports of paralytic ileus with faecal impaction in patients taking chlorpromazine and amitriptyline, imipramine, or nortriptyline, thioridazine and imipramine, and levomepromazine with imipramine (and benzatropine); for reports of severe constipation in a patients given thioridazine and doxepin (with biperiden); and for reports of atropine-like psychoses in patients taking chlorpromazine and doxepin (with benzatropine) see, 'Antipsychotics + Antimuscarinics', p.833.

The tricyclic antidepressants and many antipsychotics increase the QT interval, see 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290, for further information.

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3. Gram LF, Overø KF. Drug interaction: inhibitory effect of neuroleptics on metabolism of tricyclic antidepressants in man. *BMJ* (1972) 1, 463–5.
4. Crammer JL, Rolfe B. Interaction of imipramine and chlorpromazine in man. *Psychopharmacologia* (1972) 26 (Suppl), 81.
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9. Gram LF. Effects of perphenazine on imipramine metabolism in man. *Psychopharmacol Comm* (1975) 1, 165–75.
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11. Linnet K. Comparison of the kinetic interactions of the neuroleptics perphenazine and zuclopenthixol with tricyclic antidepressives. *Ther Drug Monit* (1995) 17, 308–11.
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13. Overø KF, Gram LF, Hansen V. Interaction of perphenazine with the kinetics of nortriptyline. *Acta Pharmacol Toxicol (Copenh)* (1977) 40, 97–105.
14. Hirschowitz J, Bennett JA, Zemlan FP, Garver DL. Thioridazine effect on desipramine plasma levels. *J Clin Psychopharmacol* (1983) 3, 376–9.
15. Maynard GL, Soni P. Thioridazine interferences with imipramine metabolism and measurement. *Ther Drug Monit* (1996) 18, 729–31.
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18. Kragh-Sørensen P, Borgå O, Garle M, Bolvig Hansen L, Hansen CE, Hvidberg EF, Larsen N-E, Sjöqvist F. Effect of simultaneous treatment with low doses of perphenazine on plasma and urine concentrations of nortriptyline and 10-hydroxynortriptyline. *Eur J Clin Pharmacol* (1977) 11, 479–83.
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23. O'Connor JW. Personal communication, February 1983.
24. Witton K. Severe toxic reaction to combined amitriptyline and thioridazine. *Am J Psychiatry* (1965) 121, 812–13.
25. Kane FJ. An unusual reaction to combined imipramine-thorazine therapy. *Am J Psychiatry* (1963) 120, 186–7.
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Phenothiazines; Chlorpromazine + Antimalarials

Chloroquine, amodiaquine and *Fansidar* (sulfadoxine with pyrimethamine) can markedly increase serum chlorpromazine levels.

Clinical evidence

A total of 15 patients with schizophrenia taking **chlorpromazine** 400 or 500 mg daily for at least 2 weeks were given single doses of either **chloroquine sulfate** 400 mg, **amodiaquine hydrochloride** 600 mg or three tablets of *Fansidar* (**pyrimethamine** 25 mg with **sulfadoxine** 500 mg) one hour before the **chlorpromazine**. Serum **chlorpromazine** levels 3 hours later were found to be raised about threefold by the **chloroquine** and **amodiaquine**, and almost fourfold by the *Fansidar*. The plasma level of 7-hydroxychlorpromazine, one of the major metabolites of **chlorpromazine**, was also elevated, but not those of the other metabolite, chlorpromazine sulfoxide. The serum **chlorpromazine** levels of the patients given **chloroquine** or *Fansidar* were, to some extent, still elevated 4 days later. There was subjective evidence that the patients were more heavily sedated when given the antimalarials.[1]

Mechanism

Not understood. Both chloroquine and *Fansidar* have relatively long half-lives compared with amodiaquine, which may explain the persistence of their effects.

Importance and management

Direct information about this interaction seems to be limited to this study. Its clinical importance is uncertain but it seems possible that these antimalarials could cause chlorpromazine toxicity. Monitor the effects of concur-

rent use closely and anticipate the need to reduce the chlorpromazine dosage. More study is needed.

1. Makanjuola ROA, Dixon PAF, Oforah E. Effects of antimalarial agents on plasma levels of chlorpromazine and its metabolites in schizophrenic patients. *Trop Geogr Med* (1988) 40, 31–3.

Phenothiazines; Chlorpromazine + Cimetidine

One study found that chlorpromazine plasma levels are reduced by cimetidine, whereas a case report suggests that cimetidine may increase chlorpromazine levels.

Clinical evidence, mechanism, importance and management

A study in 8 patients taking chlorpromazine 75 to 450 mg daily found that cimetidine 1 g daily in divided doses for one week decreased their steady-state chlorpromazine plasma levels by one-third, from 37 to 24 micrograms/mL. A two-thirds reduction was noted in one patient.[1] The reasons for this effect are not understood but a decrease in chlorpromazine absorption from the gut has been suggested.[1]

In contrast, another report describes 2 patients with schizophrenia taking chlorpromazine 100 mg four times daily who became excessively sedated when they were given cimetidine 400 mg twice daily. The sedation disappeared when the chlorpromazine dosage was halved. When the cimetidine was later withdrawn it was found necessary to give the original chlorpromazine dosage.[2] Chlorpromazine levels were not measured.

There is no simple explanation for these discordant reports, but they emphasise the need to monitor the concurrent use of chlorpromazine and cimetidine. More study is needed. There seems to be no information about other phenothiazines.

1. Howes CA, Pullar T, Sourindhrin I, Mistra PC, Capel H, Lawson DH, Tilstone WJ. Reduced steady-state plasma concentrations of chlorpromazine and indomethacin in patients receiving cimetidine. *Eur J Clin Pharmacol* (1983) 24, 99–102.
2. Byrne A, O'Shea B. Adverse interaction between cimetidine and chlorpromazine in two cases of chronic schizophrenia. *Br J Psychiatry* (1989) 155, 413–15.

Phenothiazines; Chlorpromazine + Combined hormonal contraceptives

A case report describes a marked rise in serum chlorpromazine levels in a woman taking an oral combined hormonal contraceptive.

Clinical evidence, mechanism, importance and management

A case report describes a woman who had been taking chlorpromazine 100 mg three times daily for one week without problems when an oral combined hormonal contraceptive (**ethinylestradiol/norgestrel**) was started. Four days later she developed severe dyskinesias and tremor, and her chlorpromazine levels were found to have increased by about sixfold.[1] This case was briefly mentioned in an earlier report by the same authors.[2]

The reasons for the raised chlorpromazine levels are not understood, but increased absorption or reduced liver metabolism of the phenothiazine are suggested.[1,3]

There seem to be no other reports of adverse reactions between phenothiazines and contraceptives, and the available data are insufficient to justify any general precautions.

1. Chetty M, Miller R. Oral contraceptives increase the plasma concentrations of chlorpromazine. *Ther Drug Monit* (2001) 23, 556–8.
2. Chetty M, Miller R, Moodley SV. Smoking and body weight influence the clearance of chlorpromazine. *Eur J Clin Pharmacol* (1994) 46, 523–6.
3. El-Yousef MK, Manier DH. Estrogen effects on phenothiazine derivative blood levels. *JAMA* (1974) 228, 827–8.

Phenothiazines; Chlorpromazine + Tetrabenazine

An isolated report describes severe Parkinson-like symptoms when a woman with Huntington's chorea taking tetrabenazine was given chlorpromazine.

Clinical evidence, mechanism, importance and management

A woman with Huntington's chorea, successfully treated with tetrabenazine 100 mg daily for 9 years, became motionless, rigid, mute and only able to respond by blinking her eyes within one day of being given two intramuscular injections of chlorpromazine 25 mg. This was diagnosed as severe drug-induced parkinsonism, which rapidly responded to the withdrawal of both drugs and treatment with benzatropine given intramuscularly and orally. She had previously tolerated chlorpromazine well.[1] The reason for this reaction is not understood, and its general relevance is unclear, but probably small.

1. Moss JH, Stewart DE. Iatrogenic parkinsonism in Huntington's chorea. *Can J Psychiatry* (1986) 31, 865–6.

Phenothiazines; Fluphenazine + Ascorbic acid (Vitamin C)

A single case report describes a reduction in serum fluphenazine levels and signs of a reduction in its effects when a patient was also given ascorbic acid.

Clinical evidence, mechanism, importance and management

A man with a history of manic behaviour, taking fluphenazine 15 mg daily, had a 25% reduction in his plasma fluphenazine levels, from 0.93 nanograms/mL to 0.705 nanograms/mL, over a 13-day period while taking ascorbic acid 500 mg twice daily. This was accompanied by a deterioration in his behaviour.[1] The reason for this effect is not understood. There seem to be no other reports of this interaction with fluphenazine or any other phenothiazine so that this interaction would not appear to be of general importance.

1. Dysken MW, Cumming RJ, Channon RA, Davis JM. Drug interaction between ascorbic acid and fluphenazine. *JAMA* (1979) 241, 2008.

Phenothiazines; Fluphenazine + Spiramycin

Acute dystonia occurred when a man taking fluphenazine was also given spiramycin.

Clinical evidence, mechanism, importance and management

A man with a schizoaffective disorder taking lorazepam, orphenadrine, fluvoxamine and fluphenazine decanoate 12.5 mg every 2 weeks, developed acute and painful dystonia of the trunk, neck, right arm and leg about one week after his last fluphenazine injection and on the fourth day of taking spiramycin 6 million units daily for gingivitis. The problem resolved when he was given biperiden.[1] The reasons for this adverse reaction are not understood, nor is it entirely clear whether this was an interaction between fluphenazine and spiramycin, although the author suggested that a causal link existed. This seems to be the only report of an alleged interaction between fluphenazine and a macrolide antibacterial and it is therefore of little or no general importance.

1. Benazzi F. Spiramycin-associated acute dystonia during neuroleptic treatment. *Can J Psychiatry* (1997) 42, 665–6.

Phenothiazines; Perphenazine + Disulfiram

A single case report describes a man taking perphenazine whose psychotic symptoms re-emerged when he started to take disulfiram.

Clinical evidence, mechanism, importance and management

A man taking perphenazine 8 mg twice daily developed marked psychosis soon after starting to take disulfiram 100 mg daily.[1] His serum perphenazine levels had fallen from a range of 2 to 3 nanomol/L to less than 1 nanomol/L. Doubling the dosage of perphenazine had little effect, and no substantial clinical improvement or rise in serum levels occurred until he was given intramuscular perphenazine enantate 50 mg weekly, at which point the levels rose to about 4 nanomol/L. The results of clinical biochemical tests suggested that the disulfiram was acting as an enzyme

inducer, resulting in increased metabolism and clearance of the perphenazine. However, disulfiram normally acts as an enzyme *inhibitor*. Too little is known to assess the general importance of this interaction, and there seems to be no information about an interaction with other phenothiazines.

1. Hansen LB, Larsen N-E. Metabolic interaction between perphenazine and disulfiram. *Lancet* (1982) ii, 1472.

Phenothiazines; Promazine + Attapulgite-pectin

An attapulgite-pectin antidiarrhoeal preparation caused a small reduction in the absorption of promazine in one subject, but in a study, the overall excretion of promazine was only slightly altered.

Clinical evidence, mechanism, importance and management

A study in one healthy subject found that attapulgite-pectin reduced the absorption of a single 50-mg dose of promazine by about 25%, possibly due to adsorption of the phenothiazine onto the attapulgite.[1] Another study found that the presence of activated attapulgite reduced the initial rate of urinary excretion of a single 50-mg dose of promazine, but caused only a small decrease in the overall extent of excretion.[2]

The clinical importance of this interaction and whether other phenothiazines behave similarly does not appear to have been studied; however, the magnitude of the interaction appears small, and seems unlikely to be of clinical relevance. If a problem does occur, separating administration as much as possible (2 hours or more) to avoid admixture in the gut has been shown to minimise the effects of this type of interaction with other drugs.

1. Sorby DL, Liu G. Effects of adsorbents on drug absorption II. Effect of an antidiarrhea mixture on promazine absorption. *J Pharm Sci* (1966) 55, 504–10.
2. Sorby DL. Effects of adsorbents on drug absorption I. Modification of promazine absorption by activated attapulgite and activated charcoal. *J Pharm Sci* (1965) 54, 677–83.

Phenothiazines; Promethazine + Midodrine

An increased severity of akathisia was seen in one study when promethazine and midodrine were given together.

Clinical evidence, mechanism, importance and management

A placebo-controlled study in 9 healthy subjects who received a single 10-mg oral dose of midodrine followed one hour later by a single 25-mg intravenous dose of promethazine, found that the akathisia which occurred in 6 subjects taking both midodrine and promethazine was significantly more severe than the symptoms experienced in 4 subjects when they received promethazine alone.

It was suggested that as both drugs are metabolised by the cytochrome P450 isoenzyme CYP2D6, competition for metabolism by this isoenzyme reduced the clearance of promethazine.[1]

This appears to be an isolated report, and its general relevance is unclear. However, if patients taking both drugs develop akathisia it may be prudent to suspect an interaction as a possible cause.

1. Platts SH, Shi S-J, Meck JV. Akathisia with combined use of midodrine and promethazine. *JAMA* (2006) 295, 2000–1.

Phenothiazines; Thioridazine + Melatonin

The concurrent use of thioridazine and melatonin may lead to increased CNS effects.

Clinical evidence, mechanism, importance and management

In a single-dose controlled study, there was no pharmacokinetic interaction between thioridazine 50 mg and melatonin 2 mg. However, there was a possible pharmacodynamic interaction, with increased feelings of 'muzzy-headedness' when compared with thioridazine alone.[1,2] Patients should be warned of a possible additive effect.

1. Circadin (Melatonin). Lundbeck Ltd. UK Summary of product characteristics, March 2009.
2. EMEA Assessment report for Circadin. Procedure No. EMEA/H/C/695. 2007. Available at: http://www.emea.europa.eu/humandocs/PDFs/EPAR/circadin/H-695-en6.pdf (accessed 29/01/10).

Phenothiazines; Thioridazine + Naltrexone

Extreme lethargy occurred in two patients taking thioridazine when they were given naltrexone.

Clinical evidence, mechanism, importance and management

Two schizophrenic patients taking thioridazine 50 to 200 mg three times daily for at least one year took part in a pilot project to assess the efficacy of naltrexone for the treatment of tardive dyskinesias. Both patients tolerated the first challenge dose of intravenous naltrexone 800 micrograms without problems, but experienced extreme lethargy and slept almost continuously after the second naltrexone dose of 50 to 100 mg orally. The severe lethargy resolved within 12 hours of stopping the naltrexone.[1] The reasons for this reaction are not understood. Information seems to be limited to this report and the general importance of this interaction is unknown. Note that a case report has described excessive sleepiness and lethargy in a 58-year-old man who took a single 100-mg dose of naltrexone alone,[2] so an interaction is by no means established.

1. Maany I, O'Brien CP, Woody G. Interaction between thioridazine and naltrexone. *Am J Psychiatry* (1987) 144, 966.
2. Malcolm R, Gabel T, Morton A. Idiosyncratic reaction to naltrexone augmented by thioridazine. *Am J Psychiatry* (1988) 145, 773–4.

Phenothiazines; Thioridazine + Phenylpropanolamine

A single case report describes fatal ventricular fibrillation, which was attributed to the concurrent use of thioridazine and phenylpropanolamine.

Clinical evidence, mechanism, importance and management

A 27-year-old woman with schizophrenia who was taking thioridazine 100 mg daily and procyclidine 2.5 mg twice daily was found dead in bed 2 hours after taking a single capsule of *Contac C* (phenylpropanolamine 50 mg with chlorphenamine 4 mg). The principal cause of death was attributed to ventricular fibrillation.[1] Just why this happened is not understood but it is suggested that it may have been due to the combined effects of the thioridazine (known to be cardiotoxic and to cause T-wave abnormalities) and the phenylpropanolamine (possibly able to cause ventricular arrhythmias).

The general importance of this alleged interaction is uncertain but the authors of the report suggest that ephedrine-like drugs such as phenylpropanolamine should not be given to patients taking thioridazine or **mesoridazine**.

1. Chouinard G, Ghadirian AM, Jones BD. Death attributed to ventricular arrhythmia induced by thioridazine in combination with a single Contac C capsule. *Can Med Assoc J* (1978) 119, 729–31.

Phenothiazines; Thioridazine + Ritonavir

Antiretroviral doses of ritonavir (300 mg twice daily or more) may increase plasma levels of thioridazine by inhibition of the cytochrome P450 isoenzyme CYP2D6. Monitoring for thioridazine adverse effects is recommended during concurrent use.[1]

1. Norvir Soft Capsules (Ritonavir). Abbott Laboratories Ltd. UK Summary of product characteristics, October 2009.

Pimozide + CYP3A4 inhibitors

Inhibition of CYP3A4 results in markedly increased pimozide levels and increases the risk of QT interval prolongation and the development of life-threatening arrhythmias.

Clinical evidence, mechanism, importance and management

The sudden death of a patient taking pimozide and **clarithromycin** prompted a study of a possible interaction between the two drugs. Using

human liver microsomes it was found that pimozide is partly metabolised by the cytochrome P450 isoenzyme CYP3A, and that 2 micromol of **clarithromycin** inhibits this enzyme by at least 80%.[1] The practical consequences of this finding were seen in a later study in 12 healthy subjects, which found that **clarithromycin** 500 mg twice daily for 5 days more than doubled the AUC of a single 6-mg oral dose of pimozide and raised its maximum plasma levels by almost 50%. The QTc interval was prolonged by about 17 milliseconds with pimozide alone and by 24 milliseconds when **clarithromycin** was added.[2] The results were the same in both poor and extensive CYP2D6 metabolisers (see 'Genetic factors', (p.4)). CYP2D6 status was considered as this is the other main metabolic route of pimozide. The authors of this study concluded that **clarithromycin** can therefore increase the cardiotoxicity of pimozide during chronic use, irrespective of the CYP2D6 status of the patient.[2] Pimozide alone has been associated with ventricular arrhythmias, prolongation of the QT interval, T-wave changes and sudden and unexpected death, even in the young with no previous evidence of cardiac disease.[3,4] Due to the severity of this interaction the UK manufacturers contraindicate the use of macrolides with pimozide,[5] whereas the US manufacturers contraindicate pimozide with the named macrolides, **azithromycin**, **clarithromycin**, **dirithromycin**, **erythromycin** and **troleandomycin**.[6] However, note that **azithromycin** and **dirithromycin** do not usually interact with other drugs by inhibiting CYP3A4.

The use of many other inhibitors of the cytochrome P450 isoenzyme CYP3A4 with pimozide is also contraindicated as they are similarly expected to increase the plasma levels of pimozide, which is likely to result in QT prolongation and associated arrhythmias. The manufacturers specifically mention **azole antifungals**, **grapefruit juice**, **nefazodone**, **protease inhibitors**, and **zileuton**.[5,6] Drugs that are known to cause clinically relevant CYP3A4 inhibition are listed in 'Table 1.4', (p.6).

1. Flockhart DA, Richard E, Woosely RL, Pearle PL, Drici M-D. A metabolic interaction between clarithromycin and pimozide may result in cardiac toxicity. *Clin Pharmacol Ther* (1996) 59, 189.
2. Desta Z, Kerbusch T, Flockhart DA. Effect of clarithromycin on the pharmacokinetics and pharmacodynamics of pimozide in healthy poor and extensive metabolizers of cytochrome P450 2D6 (CYP2D6). *Clin Pharmacol Ther* (1999) 65, 10–20.
3. Committee on Safety of Medicines. Cardiotoxic effects of pimozide. *Current Problems* (1990) 29.
4. Flockhart DA, Drici M-D, Kerbusch T, Soukhova N, Richard E, Pearle PL, Mahal SK, Babb VJ. Studies on the mechanism of a fatal clarithromycin-pimozide interaction in a patient with Tourette syndrome. *J Clin Psychopharmacol* (2000) 20, 317–24.
5. Orap (Pimozide). Janssen-Cilag Ltd. UK Summary of product characteristics, February 2009.
6. Orap (Pimozide). Gate Pharmaceuticals. US Prescribing information, August 2005.

Pimozide + SSRIs

Pimozide levels are expected to rise when used with fluoxetine, paroxetine, or sertraline, which would increase the risk of potentially fatal torsade de pointes arrhythmias. Fluvoxamine is predicted to interact similarly. QT prolongation may occur with the concurrent use of pimozide and citalopram. The use of SSRIs and pimozide has also led to extrapyramidal adverse effects, oculogyric crises and sedation in rare cases.

Clinical evidence

(a) Fluoxetine

A patient taking fluoxetine and pimozide had a worsening of extrapyramidal symptoms, and another patient taking both drugs developed marked sinus bradycardia of 35 to 44 bpm with somnolence.[1] This report was the subject of later discussion on the mechanism of the interaction.[2,3] Another patient also developed extrapyramidal symptoms,[4] while a further patient became stuporous when given both drugs.[5]

(b) Paroxetine

A boy of about 10 years, with various disorders (motor tics, enuresis, attention deficit hyperactivity disorder, Tourettes's disorder, impulsivity, albinism) was treated for a year with pimozide 2 mg twice, and later three times daily.[6] Within 3 days of starting paroxetine 10 mg in the morning, he began to complain of his eyes hurting and his mother noted that about 4 hours after taking the paroxetine his eyes were rolled back in his head but the problem had resolved by the evening. This oculogyric crisis occurred on a further occasion, and so the paroxetine was stopped. There was no other evidence of either extrapyramidal or hyperserotonergic reactions. This case needs to be viewed in its particular context (oculogyric crises are associated with albinism) so that it may not be of general importance.

In a study, paroxetine 60 mg daily, caused a 151% rise in the AUC of a single 2-mg dose of pimozide and a 62% rise in its maximum plasma levels.[7]

(c) Sertraline

In a study in 15 healthy subjects, sertraline 200 mg daily increased the AUC and maximum plasma levels of a single 2-mg dose of pimozide by about 40%. No changes in the QTc interval were seen.[8]

A fatality has been reported with an overdose of moclobemide, sertraline and pimozide, with blood levels suggesting that none of the drugs individually would have been fatal.[9]

Mechanism

The SSRIs can, to varying degrees, inhibit the cytochrome P450 isoenzyme CYP2D6 (and fluvoxamine possibly also inhibits CYP3A4) by which pimozide is metabolised. Concurrent use would therefore be expected to lead to raised pimozide levels.

Importance and management

Evidence of an adverse interaction between the SSRIs and pimozide is limited; however, the interaction is potentially severe as raised pimozide levels can cause torsade de pointes arrhythmias, which can be fatal. The manufacturers of pimozide contraindicate its use with SSRIs, and in the UK they specifically name sertraline, paroxetine, and **citalopram**; which has been seen to cause QT prolongation with pimozide, and its isomer, **escitalopram**.[7] The US manufacturer additionally contraindicates **fluvoxamine**.[10] Neither manufacturer mentions fluoxetine (except with regard to the possibility of additive bradycardia[10]), but as it is known to have greater effects on CYP2D6 than either sertraline or citalopram, it would seem prudent to also consider it as contraindicated.

1. Ahmed I, Dagincourt PG, Miller LG, Shader RI. Possible interaction between fluoxetine and pimozide causing sinus bradycardia. *Can J Psychiatry* (1993) 38, 62–3.
2. Friedman EH. Re: bradycardia and somnolence after adding fluoxetine to pimozide regimen. *Can J Psychiatry* (1994) 39, 634.
3. Ahmed I. Re: bradycardia and somnolence after adding fluoxetine to pimozide regimen. *Can J Psychiatry* (1994) 39, 634.
4. Coulter DM, Pillans PI. Fluoxetine and extrapyramidal side effects. *Am J Psychiatry* (1995) 152, 122–5.
5. Hansen-Grant S, Silk KR, Guthrie S. Fluoxetine-pimozide interaction. *Am J Psychiatry* (1993) 150, 1751–2.
6. Horrigan JP, Barnhill LJ. Paroxetine–pimozide drug interaction. *J Am Acad Child Adolesc Psychiatry* (1994) 33, 1060–1.
7. Orap (Pimozide). Janssen-Cilag Ltd. UK Summary of product characteristics, February 2009.
8. Alderman J. Coadministration of sertraline with cisapride or pimozide: an open-label, nonrandomized examination of pharmacokinetics and corrected QT intervals in healthy adult volunteers. *Clin Ther* (2005) 27, 1050–63.
9. McIntyre IM, King CV, Staikos V, Gall J, Drummer OH. A fatality involving moclobemide, sertraline, and pimozide. *J Forensic Sci* (1997) 42, 951–3.
10. Orap (Pimozide). Gate Pharmaceuticals. US Prescribing information, August 2005.

Quetiapine + Antipsychotics

Haloperidol and risperidone do not appear to affect the pharmacokinetics of quetiapine, whereas thioridazine moderately reduces quetiapine levels. A case report describes a seizure in a patient taking olanzapine and quetiapine.

Clinical evidence, mechanism, importance and management

In 12 patients with schizophrenia or bipolar disorder taking quetiapine 300 mg twice daily, **thioridazine** 200 mg twice daily reduced the steady-state quetiapine AUC and its maximum plasma levels by about 41% and 48%, respectively. It was suggested that the decreased quetiapine levels were due to an increase in its metabolism, although the mechanism for this effect is unclear.[1] These reductions are only moderate, but until more information is available it would seem prudent to monitor concurrent use for efficacy, being alert for the need to raise the quetiapine dose.

Two groups of 12 patients with schizophrenia or bipolar disorder taking quetiapine 300 mg twice daily were also given **haloperidol** 7.5 mg twice daily or **risperidone** 3 mg twice daily for 9 days. These antipsychotics had no significant effect on the pharmacokinetics of quetiapine.[1] Quetiapine dose adjustments are therefore not expected to be necessary if either **haloperidol** or **risperidone** is given. However, a case report describes considerable QT prolongation in a patient who took quetiapine 2 g with **risperidone**. The authors consider this significant as the overdose was small, and because no QT prolongation was seen in toxicity studies of quetiapine when doses as large as 9.6 g were used,[2] although there is a sin-

gle case of a prolonged QTc interval associated with a quetiapine overdose of 9.6 g.[3]. As neither drug is commonly associated with QT prolongation, the general relevance of this case report is unknown.

Another case report describes a seizure lasting 30 to 60 seconds in a 27-year-old woman, which occurred one day after quetiapine 100 mg daily was added to treatment with **olanzapine** 15 mg daily and sertraline 100 mg daily.[4] The seizure was attributed to an interaction between quetiapine and **olanzapine**, although it seems possible that the sertraline also may have contributed. This case highlights the importance of considering seizure potential when prescribing multiple antipsychotic medications.

1. Potkin SG, Thyrum PT, Alva G, Bera R, Yeh C, Arvanitis LA. The safety and pharmacokinetics of quetiapine when coadministered with haloperidol, risperidone, or thioridazine. *J Clin Psychopharmacol* (2002) 22, 121–30.
2. Beelen AP, Yeo K-TJ, Lewis LD. Asymptomatic QTc prolongation associated with quetiapine fumarate overdose in a patient being treated with risperidone. *Hum Exp Toxicol* (2001) 20, 215–19.
3. Gajwani P, Pozuelo L, Tesar GE. QT interval prolongation associated with quetiapine (Seroquel) overdose. *Psychosomatics* (2000) 41, 63–5.
4. Hedges DW, Jeppson KG. New-onset seizure associated with quetiapine and olanzapine. *Ann Pharmacother* (2002) 36, 437–9.

Quetiapine + CYP3A4 inducers

The plasma levels of quetiapine are reduced by carbamazepine, and the clearance of quetiapine is increased by phenytoin. The barbiturates and rifampicin (rifampin) are predicted to interact similarly. Case reports suggest that quetiapine may increase carbamazepine-10,11-epoxide levels.

Clinical evidence

(a) Carbamazepine

In a study, 14 patients took quetiapine 300 mg twice daily for 28 days, with carbamazepine 200 mg three times daily for 20 days. It was found that the AUC and maximum plasma levels of quetiapine were reduced by 87% and 80%, respectively.[1]

A 52-year-old woman taking carbamazepine 700 mg twice daily was given quetiapine, increased to 700 mg daily over 5 weeks. At this point she was noted to have become more aggressive and agitated, and unsteady. Her carbamazepine level had increased from 7.7 micrograms/mL to 11.2 micrograms/mL and her level of the metabolite carbamazepine-10,11-epoxide had risen from 2.1 micrograms/mL to 5.2 micrograms/mL. Symptoms resolved when carbamazepine was replaced with **oxcarbazepine**. A second patient taking carbamazepine also had raised carbamazepine-10,11-epoxide levels after starting quetiapine, but was asymptomatic.[2]

(b) Phenytoin

When 17 patients taking quetiapine 250 mg three times daily were given phenytoin 100 mg three times daily for 10 days, the oral clearance of quetiapine was increased fivefold.[3]

Mechanism

Quetiapine is metabolised by the cytochrome P450 isoenzyme CYP3A4. Both carbamazepine and phenytoin are known potent inducers of this enzyme, and therefore concurrent use results in an increase in quetiapine clearance and a decrease in its metabolism.

The reason for the raised carbamazepine-10,11-epoxide levels is less clear. It has been suggested that quetiapine inhibits the metabolism (glucuronidation) of this metabolite.[2]

Importance and management

Although evidence suggesting that carbamazepine and phenytoin decrease quetiapine levels is limited, it is in line with the way these antiepileptics commonly interact, and is therefore established. It would seem prudent to monitor the outcome of concurrent use, and increase the quetiapine dose as necessary. The manufacturers of quetiapine reasonably predict that other potent CYP3A4 inducers, such as the **barbiturates** and **rifampicin** (**rifampin**), will interact similarly,[4,5] and therefore similar precautions are warranted.

The general relevance of the reports of increased carbamazepine-10,11-epoxide levels is unknown, and more study is warranted to establish an interaction. However, it would be prudent to consider monitoring carbamazepine-10,11-epoxide levels if adverse effects develop. Limited evidence suggests that oxcarbazepine may be an alternative if the interaction cannot be managed by carbamazepine dose reductions.

1. Grimm SW, Richtand NM, Winter HR, Stams KR, Reele SB. Effects of cytochrome P450 3A modulators ketoconazole and carbamazepine on quetiapine pharmacokinetics. *Br J Clin Pharmacol* (2006), 61, 58–69.
2. Fitzgerald BJ, Okos AJ. Elevation of carbamazepine-10,11-epoxide by quetiapine. *Pharmacotherapy* (2002) 22, 1500–1503.
3. Wong YWJ, Yeh C, Thyrum PT. The effects of concomitant phenytoin administration on the steady-state pharmacokinetics of quetiapine. *J Clin Psychopharmacol* (2001) 21, 89–93.
4. Seroquel (Quetiapine fumarate). AstraZeneca UK Ltd. UK Summary of product characteristics, September 2009.
5. Seroquel (Quetiapine fumarate). AstraZeneca. US Prescribing information, December 2009.

Quetiapine + CYP3A4 inhibitors

The plasma levels of quetiapine are increased by erythromycin and ketoconazole. Azoles, macrolides, and protease inhibitors are expected to interact similarly.

Clinical evidence

(a) Erythromycin

A study in 19 Chinese patients who received quetiapine 200 mg twice daily and erythromycin 500 mg three times daily found that erythromycin increased the maximum plasma concentration and AUC of quetiapine by 68% and 129%, respectively.[1]

(b) Ketoconazole

In a study, 12 healthy subjects were given ketoconazole 200 mg daily, with a single 25-mg dose of quetiapine on day 4. The AUC and maximum plasma levels of quetiapine were increased about 6.2-fold and 3.4-fold, respectively.[2]

Mechanism

Ketoconazole is a potent inhibitor of the cytochrome P450 isoenzyme CYP3A4 by which quetiapine is metabolised. Concurrent use therefore reduces quetiapine metabolism and increases its levels. Erythromycin is only a moderate inhibitor of this isoenzyme, and therefore has a more modest effect on quetiapine levels.

Importance and management

An interaction between quetiapine and ketoconazole or erythromycin is established. If quetiapine is given with either of these drugs it would seem prudent to monitor closely for quetiapine adverse effects (e.g. dizziness, anxiety, orthostatic hypotension). Expect to need to reduce the quetiapine dose, particularly with ketoconazole.

The manufacturers of quetiapine[3,4] reasonably predict that other **macrolides** and **azoles** will interact similarly, although note that they are likely to differ in the extent of the interaction. See 'azoles', (p.233), and 'Ergot derivatives + Macrolides', p.683, which can be used as a guide to the relative potency of these drugs on CYP3A4 substrates.

The **protease inhibitors** are also expected to dramatically raise quetiapine levels.[3,4]

1. Li K-Y, Li X, Cheng Z-N, Zhang B-K, Peng W-X, Li H-D. Effect of erythromycin on metabolism of quetiapine in Chinese suffering from schizophrenia. *Eur J Clin Pharmacol* (2005) 60, 791–5.
2. Grimm SW, Richtand NM, Winter HR, Stams KR, Reele SB. Effects of cytochrome P450 3A modulators ketoconazole and carbamazepine on quetiapine pharmacokinetics. *Br J Clin Pharmacol* (2006), 61, 58–69.
3. Seroquel (Quetiapine fumarate). AstraZeneca UK Ltd. UK Summary of product characteristics, September 2009.
4. Seroquel (Quetiapine fumarate). AstraZeneca. US Prescribing information, December 2009.

Quetiapine + Miscellaneous

Quetiapine does not appear to interact to a clinically relevant extent with cimetidine, fluoxetine, or lorazepam. Isolated cases of

adverse outcomes have been reported with diphenhydramine and lovastatin.

Clinical evidence, mechanism, importance and management

(a) Cimetidine

In a study in 7 men with psychotic disorders, quetiapine 150 mg three times daily was given with cimetidine 400 mg three times daily for 4 days. There were some slight alterations in the pharmacokinetics of the quetiapine, but these were within the intraindividual changes seen and so were not considered significant.[1] The dose of quetiapine does not need to be adjusted in patients given cimetidine.

(b) Diphenhydramine

A patient taking diphenhydramine 100 mg daily developed urinary retention when she increased her dose of quetiapine from 900 mg daily to 2.4 g daily. When the dose of quetiapine was reduced back to 900 mg daily, her urinary retention resolved. A further episode occurred when the patient again increased her quetiapine dose. Although quetiapine does not normally have antimuscarinic adverse effects at usual therapeutic doses, it is suggested by the authors that the likelihood of these adverse effects is increased at doses of quetiapine greater than 900 mg daily. This effect may have occurred as a result of additive antimuscarinic activity of both diphenhydramine and high-dose quetiapine.[2]

(c) Lorazepam

The pharmacokinetics and pharmacodynamic effects of a single 2-mg dose of lorazepam were studied in 10 men taking quetiapine 250 mg three times daily. It was found that the maximum serum lorazepam level was not significantly changed by quetiapine, and the alterations in the performance of a number of psychometric tests were small and considered not to be clinically relevant.[3]

(d) Lovastatin

A patient taking quetiapine 800 mg daily and sertraline 100 mg daily developed a prolonged QTc interval of 569 milliseconds after starting to take lovastatin 10 mg daily. Following a reduction in the lovastatin dose to 5 mg daily, her QTc interval returned to her baseline of 424 milliseconds. It is suggested that lovastatin competitively inhibited the metabolism of quetiapine by CYP3A4, as both drugs are substrates for this enzyme, resulting in increased quetiapine levels.[4] However, the full contribution of sertraline to this case was only briefly considered, and full details relating to the cardiac effects and calculation of the QTc interval are not given.[5]

(e) SSRIs

Fluoxetine 60 mg daily for 5 days had no clinically significant effect on the steady-state plasma levels of quetiapine 300 mg twice daily.[6] No dose adjustments would therefore appear to be necessary if **fluoxetine** and quetiapine are used concurrently.

1. Strakowski SM, Keck PE, Wong YWJ, Thyrum PT, Yeh C. The effect of multiple doses of cimetidine on the steady-state pharmacokinetics of quetiapine in men with selected psychotic disorders. *J Clin Psychopharmacol* (2002) 22, 201–5.
2. Sokolski KN, Brown BJ, Melden M. Urinary retention following repeated high-dose quetiapine. *Ann Pharmacother* (2004) 38, 899–900.
3. Potkin SG. The pharmacokinetics and pharmacodynamics of lorazepam given before and during treatment with ICI 204,636 (Seroquel) in men with selected psychotic disorders. (5077IL/0027). Zeneca Pharma. Data on file (Study 27).
4. Furst BA, Champion KM, Pierre JM, Wirshing DA, Wirshing WC. Possible association of QTc interval prolongation with co-administration of quetiapine and lovastatin. *Biol Psychiatry* (2002) 51, 264–5.
5. Geller W, Smith M, Winter H, Brecher M. Response: possible association of QTc interval prolongation with co-administration of quetiapine and lovastatin. *Biol Psychiatry* (2002) 52, 914.
6. Potkin SG, Thyrum PT, Alva G, Carreon D, Yeh C, Kalali A, Arvanitis LA. Effect of fluoxetine and imipramine on the pharmacokinetics and tolerability of the antipsychotic quetiapine. *J Clin Psychopharmacol* (2002) 22, 174–82.

Quetiapine + Topiramate

Topiramate does not affect the plasma levels of quetiapine.

Clinical evidence, mechanism, importance and management

In a study, 7 patients receiving long-term quetiapine 200 mg to 600 mg daily were given topiramate in a dose that was increased gradually to 200 mg daily. The plasma levels of quetiapine were not significantly affected by topiramate and the combination was well tolerated.[1] There would therefore appear to be no need to adjust the dose of quetiapine in patients also given topiramate.

1. Migliardi G, D'Arrigo C, Santoro V, Bruno A, Cortese L, Campolo D, Cacciola M, Spina E. Effect of topiramate on plasma concentrations of clozapine, olanzapine, risperidone, and quetiapine in patients with psychotic disorders. *Clin Neuropharmacol* (2007) 30, 107–13.

Quetiapine + Tricyclic and related antidepressants

Imipramine does not appear to affect the pharmacokinetics of quetiapine. Isolated cases of adverse outcomes have been reported in patients taking quetiapine with doxepin (and pantoprazole) or mirtazapine. The use of quetiapine may falsely elevate tricyclic levels by interfering with immunoassay results.

Clinical evidence

(a) Doxepin

A patient taking doxepin 150 mg daily and lorazepam 500 micrograms daily was admitted to hospital with confusion and depression. Quetiapine 750 mg daily and pantoprazole 40 mg daily were started, and the doses of his existing medication were adjusted to doxepin 100 mg daily and lorazepam 4.5 mg daily. At this point his quetiapine level was found to be 1838 to 1860 nanograms/mL, but as there was only slight improvement in the symptoms of schizophrenia, the dose of quetiapine was increased to 900 mg daily. Pantoprazole and doxepin were discontinued and the dose of lorazepam was reduced to 2 mg daily. At this point his quetiapine levels were found to be just 109 nanograms/mL. The lorazepam dose was decreased further to 500 micrograms daily and quetiapine levels were found to be 68 nanograms/mL.[1]

(b) Imipramine

Imipramine 75 mg twice daily for 5 days had no clinically significant effect on the steady-state plasma levels of quetiapine 300 mg twice daily.[2]

(c) Mirtazapine

An isolated case report describes increased prolactin levels after the introduction of mirtazapine 15 mg daily in a woman who was taking quetiapine 400 mg daily. Her prolactin level normalised when the mirtazapine was stopped, but rechallenge again produced an increase in prolactin levels, although this was transient and appeared to resolve within one month.[3]

Mechanism

The reasons for the elevated quetiapine levels are not known but the authors suggest that they may have been due to the concurrent use of doxepin and pantoprazole. As lorazepam was given continuously and was present when quetiapine levels were low, it was considered unlikely to be involved in the interaction.[1]

The authors of the case of raised prolactin levels suggest that the mirtazapine may have caused an increase in quetiapine-induced dopamine receptor blockade, or alternatively an agonist action at opioid receptors altered dopamine receptor function.[3]

Importance and management

Evidence for an interaction between the tricyclic and related antidepressants and mirtazapine appear to be limited to these disparate case reports, which are largely unexplained. The one pharmacokinetic study involving imipramine found no interaction. Therefore, in general, no particular precautions would appear necessary if quetiapine is given with a tricyclic antidepressant.

Immunoassay methods for identifying tricyclic antidepressants in blood and urine have given false positive results in the presence of quetiapine.[4-6] In one case, HPLC analysis gave normal results.[6]

1. Härtter S, Connemann B, Schönfeldt-Lecuona C, Sachse J, Hiemke C. Elevated quetiapine serum concentrations in a patient treated concomitantly with doxepin, lorazepam, and pantoprazole. *J Clin Psychopharmacol* (2004) 24, 568–71.
2. Potkin SG, Thyrum PT, Alva G, Carreon D, Yeh C, Kalali A, Arvanitis LA. Effect of fluoxetine and imipramine on the pharmacokinetics and tolerability of the antipsychotic quetiapine. *J Clin Psychopharmacol* (2002) 22, 174–82.
3. Orlandi V, Speca A, Salviati M, Biondi M. Abnormal prolactin elevation in a schizophrenic patient in treatment with quetiapine and mirtazapine. The role of the opioid system. *J Clin Psychopharmacol* (2003) 23, 677–9.

4. Hayes KM. Law , Burns MM. Quetiapine (Seroquel®) produces false positive tricyclic antidepressant screen. *Pediatr Res* (2003) 53, 104A.
5. Al-Mateen CS, Wolf CE. Falsely elevated imipramine levels in a patient taking quetiapine. *J Am Acad Child Adolesc Psychiatry* (2002) 41, 5–6.
6. Schussler JM, Juenke JM, Schussler I. Quetiapine and falsely elevated nortriptyline level. *Am J Psychiatry* (2003) 160, 589.

Quetiapine + Valproate

Valproate may modestly raise quetiapine levels.

Clinical evidence, mechanism, importance and management

An analysis of the plasma levels of quetiapine in 9 patients who were also taking valproate, found a 77% increase in the concentration dose ratio of quetiapine, when compared with those patients not taking valproate.[1] A study in 33 patients given quetiapine 150 mg twice daily or valproate semisodium (divalproex sodium) 500 mg twice daily either alone or concurrently found that valproate increased the maximum plasma levels of quetiapine by 17% but did not affect its AUC. Valproate levels and AUC were decreased by 11% by quetiapine. These changes were not statistically significant.[2]

The effect of valproate on quetiapine levels appears to be modest, but consider the possibility of an interaction if quetiapine adverse effects (e.g. dizziness, anxiety, orthostatic hypotension) are increased.

1. Aichhorn W, Marksteiner J, Walch T, Zernig G, Saria A, Kemmler G. Influence of age, gender, body weight and valproate comedication on quetiapine plasma concentrations. *Int Clin Psychopharmacol* (2006) 21, 81–5.
2. Winter HR, DeVane CL, Figueroa C, Ennis DJ, Hamer-Maansson JE, Davis PC, Smith MA. Open-label steady-state pharmacokinetic drug interaction study on co-administered quetiapine fumarate and divalproex sodium in patients with schizophrenia, schizoaffective disorder, or bipolar disorder. *Hum Psychopharmacol* (2007) 22, 469–76.

Ramelteon + Azoles

Fluconazole and ketoconazole increase the levels of ramelteon. Other azoles may interact similarly.

Clinical evidence, mechanism, importance and management

A study in 28 healthy subjects found that **fluconazole** 400 mg on day one then 200 mg daily for 3 days significantly increased the AUC and maximum plasma level of a single 16-mg dose of ramelteon, given on day 4, by about 150%.[1] Further study found that **ketoconazole** 200 mg daily for 4 days increased the AUC and maximum plasma concentration of single-dose ramelteon by 84% and 36%, respectively. As ramelteon undergoes extensive first-pass metabolism, these increases in systemic exposure were considered to be moderate, suggesting that neither CYP2C9 nor CYP3A4 is the predominant enzyme involved in the metabolism of ramelteon.[1] Nevertheless, the manufacturer suggests that ramelteon should be given with caution with strong CYP2C9 inhibitors such as **fluconazole** and strong CYP3A4 inhibitors such as **ketoconazole**.[2] It may therefore be prudent to be alert for an increase in the sedative effects, and the duration of effects, of ramelteon, and consider a reduction in dose if the effects become excessive. Information about other azoles generally appears to be lacking, but all of them, would be expected to interact to a greater or lesser extent. Note that a large proportion of **miconazole** oral gel (both prescription and non-prescription doses) may be swallowed and therefore adequate systemic absorption may occur to produce an interaction.

1. Karim A, Tolbert D, Cao C, Zhao Z, Sainati SM. Effects of fluconazole and ketoconazole on the pharmacokinetics of ramelteon (TAK-375) in normal healthy male and female subjects. *Sleep* (2004) 27 (Abstract Suppl), A53.
2. Rozerem (Ramelteon). Takeda Pharmaceuticals America, Inc. US Prescribing information, October 2008.

Ramelteon + Dextromethorphan

A study in 36 healthy subjects found that giving ramelteon 32 mg with dextromethorphan 30 mg had no effect on the pharmacokinetics of either drug.[1] Ramelteon does not, therefore, appear to affect the metabolism of CYP2D6 substrates (see 'Table 1.3', (p.6), for a list) and, therefore dose adjustments of these drugs would not be expected to be necessary if ramelteon is also given.

1. Tolbert D, Karim A, Cao C, Zhao Z, Johnson J, Sainati SM. Study to assess drug interaction between ramelteon (TAK-375) and dextromethorphan in healthy adults. *Sleep* (2004) 27 (Abstract Suppl), A50.

Ramelteon + Miscellaneous

Rifampicin (rifampin) and to a much lesser extent food, may decrease the efficacy of ramelteon. CYP1A2 inhibitors (such as some quinolones) are expected to increase ramelteon levels.

Clinical evidence, mechanism, importance and management

(a) CYP1A2 inhibitors

Ramelteon is metabolised by the cytochrome P450 isoenzyme CYP1A2. Based on the profound interaction with fluvoxamine (see 'Ramelteon + SSRIs', below) the manufacturer advises caution with other CYP1A2 inhibitors. Note that many of the quinolones can, to varying extents, inhibit CYP1A2, most notably **enoxacin** and **ciprofloxacin**. Concurrent use of these drugs and ramelteon should be closely monitored for increased sedation, and the dose of ramelteon reduced as necessary. A list of CYP1A2 inhibitors is given in 'Table 1.2', (p.4).

(b) Food

A high-fat meal increased the AUC of a single 16-mg dose of ramelteon by 31% and decreased the maximum plasma concentration by 22%, compared with the fasted state. The time to maximum plasma concentration was also delayed by about 45 minutes when ramelteon was given with food. The manufacturer therefore recommends that ramelteon should not be taken with or immediately after a high-fat meal.[1]

(c) Rifampicin (Rifampin)

Rifampicin 600 mg daily for 11 days decreased the total exposure to a single 32-mg dose of ramelteon and its active metabolite by about 80%. Efficacy may be reduced when ramelteon is used in combination with strong enzyme inducers such as rifampicin.[1]

1. Rozerem (Ramelteon). Takeda Pharmaceuticals America, Inc. US Prescribing information, October 2008.

Ramelteon + SSRIs

Fluvoxamine dramatically increases and fluoxetine modestly increases ramelteon levels.

Clinical evidence, mechanism, importance and management

A study in 28 healthy subjects found that **fluoxetine** 40 mg daily for 11 days increased the AUC and maximum plasma level of a single 16-mg dose of ramelteon by 50% and 40%, respectively. This increase in systemic exposure was not considered to be clinically important as ramelteon has high interindividual variability and a wide therapeutic window. No dose adjustment of ramelteon is considered to be necessary if **fluoxetine** is also taken.[1]

The manufacturer of ramelteon reports that the AUC and maximum plasma level of ramelteon were increased approximately 190-fold and 70-fold, respectively, by **fluvoxamine**. The manufacturer therefore contraindicates the use of ramelteon with **fluvoxamine**.[2]

The effects of other SSRIs do not appear to have been studied; however, **paroxetine** generally interacts in the same way as **fluoxetine**, and none of the other SSRIs would be expected to interact in the same way as **fluvoxamine**, as they are not CYP1A2 inhibitors.

1. Sainati SM, Karim A, Tolbert D, Cao C. Effects of multiple doses of fluoxetine on the systemic exposure of a single dose of ramelteon (TAK-375) in healthy adults. *Sleep* (2004) 27 (Abstract Suppl), A48.
2. Rozerem (Ramelteon). Takeda Pharmaceuticals America, Inc. US Prescribing information, October 2008.

Risperidone + Carbamazepine or Oxcarbazepine

Carbamazepine reduces risperidone levels, and risperidone may cause a small increase in carbamazepine levels. Oxcarbazepine dose not significantly affect the pharmacokinetics of risperidone.

Clinical evidence

(a) Carbamazepine

A 22-year-old man taking risperidone 4 mg daily and carbamazepine 600 mg daily for schizophrenia had lower than expected risperidone levels, so his risperidone dose was doubled and the carbamazepine tailed off. Ten days after carbamazepine had been discontinued it was noted that his plasma levels of the major active metabolite of risperidone, 9-hydroxyrisperidone, was 49 micrograms/L; it had only been 19 micrograms/L when he was taking carbamazepine.[1] There are 4 other cases of this interaction between risperidone and carbamazepine.[2-4] In one case, the addition of carbamazepine to established risperidone treatment resulted in a reduction in the risperidone and 9-hydroxyrisperidone levels of about 75% and 65%, respectively, accompanied by the return of the patients psychotic symptoms.[4] In two other cases, a 20-year-old and an 81-year-old man developed parkinsonian symptoms when carbamazepine was stopped. The symptoms resolved when the doses of risperidone were reduced by about two-thirds.[2]

These cases are supported by a study in 5 patients taking carbamazepine and risperidone for schizophrenia or bipolar disorders. The dose-normalised plasma level of risperidone and its active metabolite, 9-hydroxyrisperidone, were 68% and 64% lower, respectively, in the presence of carbamazepine, when compared with patients taking risperidone alone.[5] Another study in 11 patients who had been taking risperidone for 2 to 68 weeks found that carbamazepine 200 mg twice daily for a week approximately halved the plasma levels of risperidone and its active moiety (risperidone plus 9-hydroxyrisperidone).[6] In another study in patients with acute mania, the levels of active risperidone were 40% lower in patients given risperidone with carbamazepine when compared with those given risperidone and either lithium or divalproex sodium. The efficacy of the combination of risperidone with a mood stabiliser (lithium, divalproex sodium, carbamazepine) was found to be significantly increased if patients taking carbamazepine were excluded from the analysis.[7]

Risperidone may also affect carbamazepine levels. In one study in 8 patients, risperidone 1 mg daily for 2 weeks raised carbamazepine levels by about 20%.[8]

(b) Oxcarbazepine

A study in 12 patients taking risperidone 2 to 6 mg daily found that the addition of oxcarbazepine for 5 weeks, at an initial dose of 300 mg daily, increased to 900 mg to 1.2 g after one week, had no significant effects on the pharmacokinetics of risperidone. Concurrent use was generally well tolerated.[9]

Mechanism

Risperidone is mainly metabolised by the cytochrome P450 isoenzyme CYP2D6, and it has been suggested that carbamazepine induces this route of metabolism thereby reducing risperidone levels. However, there do not appear to be any interactions with carbamazepine that occur as a result of this mechanism. Carbamazepine is a known potent inducer of CYP3A4, a more minor route of risperidone metabolism, and it seems more likely that this is the mechanism behind the interaction. The extent of the interaction appears to be related to CYP2D6 genotype (see 'Genetic factors', (p.4)), when the metabolism of risperidone by CYP3A4 becomes more important. Oxcarbazepine is not known to affect the metabolism of drugs by CYP2D6 or CYP3A4 to a clinically relevant extent.

Importance and management

An interaction between carbamazepine and risperidone appears to be established. It would seem important to monitor the levels of risperidone and 9-hydroxyrisperidone in patients given carbamazepine, being alert for the need to raise the risperidone dose, possibly by as much as two-thirds. The dose of risperidone will need to be reduced if carbamazepine is stopped. The increase in carbamazepine levels seen with risperidone is almost certainly too small to be of clinical relevance.

No special consideration or monitoring appears necessary if oxcarbazepine is given with risperidone.

1. de Leon J, Bork J. Risperidone and cytochrome P450 3A. *J Clin Psychiatry* (1997) 58, 450.
2. Takahashi H, Yoshida K, Higuchi H, Shimizu T. Development of parkinsonian symptoms after discontinuation of carbamazepine in patients concurrently treated with risperidone: two case reports. *Clin Neuropharmacol* (2001) 24, 358–60.
3. Alfaro CL, Nicolson R, Lenane M, Rapoport JL. Carbamazepine and/or fluvoxamine drug interaction with risperidone in a patient on multiple psychotropic medications. *Ann Pharmacother* (2000) 34, 122–3.
4. Spina E, Scordo MG, Avenoso A, Perucca E. Adverse drug interaction between risperidone and carbamazepine in a patient with chronic schizophrenia and deficient CYP2D6 activity. *J Clin Psychopharmacol* (2001) 21, 108–9.
5. Spina E, Avenoso A, Facciolà G, Salemi M, Scordo MG, Giacobello T, Madia AG, Perucca E. Plasma concentrations of risperidone and 9-hydroxyrisperidone: effect of comedication with carbamazepine or valproate. *Ther Drug Monit* (2000) 22, 481–5.
6. Ono S, Mihara K, Suzuki A, Kondo T, Yasui-Furukori N, Furukori H, de Vries R, Kaneko S. Significant pharmacokinetic interaction between risperidone and carbamazepine: its relationship with CYP2D6 genotypes. *Psychopharmacology (Berl)* (2002) 162, 50–54.
7. Yatham LN, Grossman F, Augustyns I, Vieta E, Ravindran A. Mood stabilisers plus risperidone or placebo in the treatment of acute mania. *Br J Psychiatry* (2003) 182, 141–7.
8. Mula M, Monaco F. Carbamazepine–risperidone interactions in patients with epilepsy. *Clin Neuropharmacol* (2002) 25, 97–100.
9. Muscatello MR, Pacetti M, Cacciola M, La Torre D, Zoccali R, D'Arrigo C, Migliardi G, Spina E. Plasma concentrations of risperidone and olanzapine during coadministration with oxcarbazepine. *Epilepsia* (2005) 46, 771–4.

Risperidone + Ginkgo (*Ginkgo biloba*)

An isolated case describes priapism in a patient taking risperidone and ginkgo.

Clinical evidence

A 26-year-old paranoid schizophrenic who had been taking risperidone 3 mg daily for the past 3 years developed priapism that had lasted for 4 hours, 2 weeks after starting to take ginkgo 160 mg daily for occasional tinnitus. The priapism required treatment, and both ginkgo and risperidone were stopped. Risperidone was then restarted and the patient reported no further episodes of priapism at follow-up 6 months later.[1]

Mechanism

Unclear. Risperidone alone does rarely cause priapism, probably because of its alpha-adrenergic properties, and ginkgo might have vascular effects that could be additive with the effects of risperidone. Ginkgo is unlikely to affect the metabolism of risperidone by inhibiting the cytochrome P450 isoenzyme CYP2D6 because it has no clinical effect on other CYP2D6 substrates.

Importance and management

Evidence for an interaction between ginkgo and risperidone appears to be limited to this isolated case. Its general relevance is therefore unclear. Bear it in mind in the event of an unexpected response to treatment.

1. Lin Y-Y, Chu S-J, Tsai S-H. Association between priapism and concurrent use of risperidone and Ginkgo biloba. *Mayo Clin Proc* (2007) 82, 1288–91.

Risperidone + Itraconazole

Itraconazole increases the plasma levels of risperidone and its active metabolite, 9-hydroxyrisperidone.

Clinical evidence

A study in 19 patients who were taking risperidone 2 to 8 mg daily found that the addition of itraconazole 200 mg daily for a week increased the plasma levels of risperidone and its active metabolite, 9-hydroxyrisperidone, by 82% and 70%, respectively. The levels returned to pre-treatment values one week after the itraconazole was stopped.[1]

Mechanism

Itraconazole is a known inhibitor of the cytochrome P450 isoenzyme CYP3A4 and it was suggested that it inhibited the metabolism of risperidone by this route, resulting in the increased levels seen.

Importance and management

Evidence appears to be limited to one study, which suggests that risperidone levels are expected to increase if itraconazole is given concurrently. Be aware of any signs of increased risperidone adverse effects (e.g. agitation, insomnia, headache), and consider reducing the dose as necessary.

1. Jung SM, Kim KA, Cho HK, Jung IG, Park PW, Byun WT, Park JY. Cytochrome P450 3A inhibitor itraconazole affects plasma concentrations of risperidone and 9-hydroxyrisperidone in schizophrenic patients. *Clin Pharmacol Ther* (2005) 78, 520–8.

Risperidone + Lamotrigine

One small study found no interaction between risperidone and lamotrigine, although a case report describes increased risperidone levels in a patient given lamotrigine, and a retrospective study suggests that lamotrigine increases the variability of risperidone levels.

Clinical evidence

An isolated case report describes markedly increased risperidone levels in a patient given increasing doses of lamotrigine. When the lamotrigine dose was increased from 175 mg daily to 200 mg daily, the risperidone level increased from 69 nanograms/mL to 263 nanograms/mL. A further increase in the lamotrigine dose to 225 mg daily, while maintaining the risperidone dose of 8 mg daily resulted in a risperidone plasma level of 412 nanograms/mL, and the patient complained of dizziness and tiredness.[1] A retrospective review of 5 patients taking risperidone and lamotrigine, for whom pharmacokinetic data were available both before and after the addition of lamotrigine, revealed a wide variation in alterations of risperidone levels, from a reduction of 41% to a rise of 74% after the addition of lamotrigine: on average there was a 7% decrease in risperidone levels.[2] A study in 10 patients taking risperidone 3 to 6 mg daily, and who were also given lamotrigine (increasing over 8 weeks to 200 mg daily) found no changes in the pharmacokinetics of risperidone.[3]

Mechanism

Risperidone is metabolised by CYP2D6, but since lamotrigine is not a known inhibitor of this enzyme, a pharmacokinetic interaction was not thought to explain the change in levels.[1]

Importance and management

The retrospective review and small study above did not find any evidence of a consistent effect of lamotrigine on risperidone pharmacokinetics. However, in view of the case report, and also the fact that some individuals in the review demonstrated large changes in risperidone levels some caution seems warranted. It would be prudent to monitor patients for an increase in adverse effects (e.g. agitation, insomnia, headache), or a lack of therapeutic effect, if lamotrigine is given with risperidone.

1. Bienentreu SD, Kronmüller K-TH. Increase in risperidone plasma level with lamotrigine. *Am J Psychiatry* (2005) 162, 811–12.
2. Castberg I, Spigset O. Risperidone and lamotrigine: no evidence of a drug interaction. *J Clin Psychiatry* (2006) 67, 1159.
3. Spina W, D'Arrigo C, Migliardi G, Santoro V, Muscatello MR, Micò U, D'Amico G, Perucca E. Effect of adjunctive lamotrigine treatment on the plasma concentrations of clozapine, risperidone and olanzapine in patients with schizophrenia or bipolar disorder. *Ther Drug Monit* (2006) 28, 599–602.

Risperidone + Levomepromazine

Levomepromazine does not appear to affect the pharmacokinetics of risperidone, but concurrent use may lead to additive adverse effects.

Clinical evidence, mechanism, importance and management

In a study, 20 patients who had been taking risperidone for at least 2 weeks were also given levomepromazine in doses of 5 to 75 mg daily. There were no changes in the pharmacokinetics of risperidone or its active metabolite, 9-hydroxyrisperidone, and there was no aggravation of extrapyramidal effects.[1]

A case report describes a woman with schizophrenia taking risperidone 8 mg daily who became agitated and restless at night 3 months after starting to take levomepromazine up to 50 mg at night. Risperidone was stopped, but after 10 days her condition had not improved, and so levomepromazine was also stopped. Within a day she began to feel less agitated. The authors suggested that her symptoms represented delayed-onset akathisia, which was attributed to additive adverse effects of both drugs.[2] However, as the patient did not take levomepromazine alone an interaction is not established in this case.

It would seem that levomepromazine may be given with risperidone without dose adjustment. Although not established, the case report serves as a reminder to consider adverse effects when prescribing two drugs with a similar adverse effect profile.

1. Yoshimura R, Shinkai K, Kakihara S, Goto M, Yamada Y, Kaji K, Ueda N, Nakamura J. Little effects of low dosage of levomepromazine on plasma risperidone levels. *Pharmacopsychiatry* (2005) 38, 98–100.
2. Shimizu E, Watanabe H, Iyo M. Delayed-onset nocturnal akathisia due to risperidone and levomepromazine: a case report. *Eur Psychiatry* (2002) 17, 294–5.

Risperidone + Melperone

Melperone appears to raise risperidone levels.

Clinical evidence

A patient taking risperidone 6 mg daily was switched from melperone 50 mg daily to pipamperone 40 mg daily. After 8 days, the patient's risperidone levels had decreased from 2.1 micrograms/L to 1 microgram/L and the 9-hydroxyrisperidone levels had increased from 21 micrograms/L to 40 micrograms/L, which was taken to suggest that melperone raises risperidone levels. This suggestion is supported by a second patient, whose dose-corrected risperidone plasma level decreased by about 69% and 9-hydroxyrisperidone plasma level increased by about 68% after the dose of risperidone was increased from 5 mg daily to 6 mg daily, and melperone was stopped. In a third patient, taking risperidone, melperone, venlafaxine and metoprolol, the dose-corrected risperidone level fell by 20% when melperone was stopped: the 9-hydroxyrisperidone level was unchanged.[1]

Mechanism

Risperidone is metabolised by the cytochrome P450 isoenzyme CYP2D6. It was suggested that melperone raises risperidone levels by inhibiting this metabolism.

Importance and management

Evidence for an interaction between risperidone and melperone appears to be limited to these three cases, and the authors suggest that further study is needed to establish their clinical relevance. Until more is known it seems prudent to be alert for risperidone adverse effects (e.g. agitation, insomnia, headache), and, as the levels of the active metabolite are reduced, it would also seem prudent to monitor efficacy if melperone is also given.

1. Köhnke MD, Lutz U, Wiatr G, Schwärzler F, Weller B, Schott K, Buchkremer G. Cytochrome P450 2D6 dependent metabolization of risperidone is inhibited by melperone. *Eur J Clin Pharmacol* (2006) 62, 333–4.

Risperidone + Phenytoin

An isolated report describes extrapyramidal symptoms in a patient taking risperidone when he was also given a single dose of phenytoin.

Clinical evidence

A 31-year-old man with schizophrenia was given risperidone and the dose was titrated up from 1 mg twice daily to 3 mg twice daily over 3 days without any adverse effects. Three days later a single 200-mg dose of phenytoin was accidentally given and 8 hours later he developed laboured breathing and severe hyperextension of the neck and oculogyric crisis. Risperidone was temporarily discontinued and he recovered after treatment with benzatropine and diazepam.[1]

Mechanism

It was suggested that risperidone levels may have been increased by competitive inhibition since both drugs are hydroxylated by cytochrome P450

isoenzymes. Further, both risperidone and phenytoin are highly protein bound and the author also suggests that phenytoin may have increased risperidone blood levels by displacing it from its binding sites.[1]

Importance and management

Evidence for an interaction between risperidone and phenytoin appears to be limited to this one case report, and its general significance is unclear. Note that, in contrast to this case report the US manufacturer of risperidone predicts that phenytoin will *reduce* risperidone levels.[2] This is in line with the way other enzyme-inducing drugs are known to interact (see 'Risperidone + Carbamazepine or Oxcarbazepine', p.904).

In the absence of further information, if phenytoin is given it would seem appropriate to monitor for risperidone adverse effects (e.g. agitation, insomnia, headache), and a lack of therapeutic effect, and adjust the dose accordingly.

1. Sanderson DR. Drug interaction between risperidone and phenytoin resulting in extrapyramidal symptoms. *J Clin Psychiatry* (1996) 57, 177.
2. Risperdal (Risperidone). Ortho-McNeil-Janssen Pharmaceuticals, Inc. US Prescribing information, July 2009.

Risperidone + Probenecid

In a study in 12 healthy subjects, probenecid 500 mg twice daily for 4 days did not affect the pharmacokinetics of a single 1-mg dose of risperidone given on day 2.[1]

1. Markowitz JS, DeVane CL, Liston HL, Bouton DW, Risch SC. The effects of probenecid on the disposition of risperidone and olanzapine in healthy volunteers. *Clin Pharmacol Ther* (2002) 71, 30–8.

Risperidone + Protease inhibitors

Neuroleptic malignant syndrome, ataxia and severe lethargy leading to coma, and extrapyramidal adverse effects have been seen in patients given risperidone with indinavir and ritonavir.

Clinical evidence

A 35-year-old man with AIDS was diagnosed with a Tourette's-like disorder and given risperidone 1 mg twice daily. After 2 weeks the risperidone was increased to 2 mg twice daily and he was also given **indinavir** 800 mg twice daily with **ritonavir** 200 mg twice daily. He discontinued the antiretrovirals after 5 days due to nausea, but started them again 1 month later when the tic disorder had improved. After one week he became short of breath and fatigued, with worsening tremor and other extrapyramidal adverse effects. The antiretrovirals were stopped and the risperidone dose increased to 3 mg twice daily. Over the next 3 days his symptoms worsened and began to interfere with daily living. Risperidone was discontinued and clonazepam started, and his symptoms resolved.[1] Another patient developed neuroleptic malignant syndrome 3 days after starting to take risperidone with **indinavir** and **ritonavir**. This patient also recovered when the risperidone was stopped.[2] A third patient taking **indinavir** and **ritonavir** was given risperidone 3 mg twice daily to treat symptoms of mania. After 2 doses he became ataxic, drowsy and disorientated, which further developed into lethargy and coma. He recovered 24 hours after stopping all medication.[3]

Mechanism

Indinavir inhibits the cytochrome P450 isoenzyme CYP3A4 and ritonavir inhibits CYP2D6 and CYP3A4, which are the main isoenzymes involved in the metabolism of risperidone. Therefore concurrent use would be expected to raise risperidone levels. The symptoms reported in the cases above may have all been due to increased risperidone levels.[1,3]

Importance and management

These appear to be the only reports of an interaction between risperidone and protease inhibitors, but they are in line with the way these drugs are generally known to interact. It is unclear if indinavir given alone would have had these effects.

If risperidone is given to any patient taking ritonavir (including ritonavir given as a pharmacokinetic enhancer) it would seem prudent to be alert for risperidone adverse effects (e.g. agitation, insomnia, headache, extrapyramidal effects). If these become troublesome consider decreasing the risperidone dose.

1. Kelly DV, Béïque LC, Bowmer MI. Extrapyramidal symptoms with ritonavir/indinavir plus risperidone. *Ann Pharmacother* (2002) 36, 827–30.
2. Lee SI, Klesmer J, Hirsch BE. Neuroleptic malignant syndrome associated with the use of risperidone, ritonavir and indinavir: a case report. *Psychosomatics* (2000) 41, 453–4.
3. Jover F, Cuadrado J-M, Andreu L, Merino J. Reversible coma caused by risperidone-ritonavir interaction. *Clin Neuropharmacol* (2002) 25, 251–3.

Risperidone + Reboxetine

Reboxetine does not appear to alter the pharmacokinetics of risperidone.

Clinical evidence, mechanism, importance and management

Reboxetine 8 mg daily was given to 7 patients with schizophrenia taking risperidone 4 to 6 mg daily for 3 weeks. Reboxetine had no significant effects on the pharmacokinetics of either risperidone or its active metabolite, 9-hydroxyrisperidone.[1] This appears to be the only study investigating the concurrent use of risperidone and reboxetine. It suggests that if both drugs are given risperidone dose adjustments are unlikely to be necessary.

1. Spina E, Avenoso A, Scordo MG, Ancione M, Madia A, Levita A. No effect of reboxetine on plasma concentrations of clozapine, risperidone, and their active metabolites. *Ther Drug Monit* (2001) 23, 675–8.

Risperidone + Rifampicin (Rifampin)

The levels of risperidone and its active metabolite are reduced by rifampicin.

Clinical evidence

In a study in 10 healthy subjects, rifampicin 600 mg daily for 5 days decreased the maximum plasma level and AUC of a single 4-mg dose of risperidone by 50% and 72%, respectively.[1] In another study, 10 healthy subjects were given rifampicin 600 mg daily for 7 days, with a single 1-mg dose of risperidone on day 6. Rifampicin reduced the maximum plasma level and AUC of risperidone by 38% and 51%, respectively and reduced the maximum plasma level and AUC of 9-hydroxyrisperidone (the active metabolite of risperidone) by 46% and 47%, respectively.[2]

Mechanism

Rifampicin is a potent inducer of the cytochrome P450 isoenzyme CYP3A4, which is partly responsible for the metabolism of risperidone. Concurrent use would therefore be expected to increase risperidone metabolism and reduce its levels. It has also been suggested that P-glycoprotein may have played a part in this interaction.[2]

Importance and management

The interaction between risperidone and rifampicin would appear to be established. Reduced levels of risperidone and its active 9-hydroxy metabolite would be expected to lead to reduced efficacy. It would therefore be prudent to monitor the outcome of concurrent use to ensure that risperidone is effective, increasing the dose if necessary.

1. Mahatthanatrakul W, Nontaput T, Ridtitid W, Wongnawa M, Sunbhanich M. Rifampin, a cytochrome P450 3A inducer, decreases plasma concentrations of antipsychotic risperidone in healthy volunteers. *J Clin Pharm Ther* (2007) 32, 161–7.
2. Kim K-A, Park P-W, Liu K-H, Kim K-B, Lee H-J, Shin J-G, Park J-Y. Effect of rifampin, an inducer of CYP3A and P-glycoprotein, on the pharmacokinetics of risperidone. J Clin Pharmacol (2008) 48, 66–72.

Risperidone + SSRIs

Fluoxetine, fluvoxamine, and paroxetine appear to raise risperidone levels. Sertraline appears to only moderately increase risperidone levels at high doses. The combination of SSRIs and

risperidone is generally useful, but has resulted in a number of adverse effects including priapism, extrapyramidal effects and serotonin syndrome.

Clinical evidence

(a) Citalopram

A study in 7 patients found that citalopram had no effect on the plasma levels of risperidone or its active metabolite, 9-hydroxyrisperidone.[1]

A case report describes a 29-year-old man with idiopathic priapism, about one 4-hour erection every 1 to 2 months, which typically woke him up, who began to experience much longer bouts of priapism lasting 6 to 8 hours when he was given risperidone 4 mg daily. Within about 4 weeks of adding citalopram 40 mg daily to a slightly reduced risperidone dose (3 mg daily), he began to have almost daily erections lasting 12 hours. Three days after his dosages were changed to risperidone 3 mg twice daily with citalopram 20 mg daily he had an episode of such persistent priapism that emergency detumescence was needed. When both drugs were stopped he improved markedly and then only had occasional 4-hour erections, as before.[2]

(b) Fluoxetine

A pharmacokinetic study in 10 patients found that fluoxetine 20 mg daily raised the levels of risperidone 2 or 3 mg twice daily from 12 nanograms/mL to 19 nanograms/mL after 3 weeks of concurrent use and to 56 nanograms/mL after 4 weeks of concurrent use. All patients experienced a rise in risperidone levels, but this varied from a twofold rise to a tenfold rise. One patient withdrew from the study because of severe akathisia and another two patients needed to be given biperiden to control parkinsonian adverse effects.[3] Similar results were found in another study.[4]

A 30-year-old woman taking valproate, clonazepam, and risperidone 3 mg daily for schizophrenia was also given fluoxetine 5 mg daily for a depressive disorder. The depression improved, but she noticed painful bilateral breast enlargement, which resolved when risperidone was stopped. Similar symptoms were noted when the risperidone was later restarted.[5]

Extrapyramidal adverse effects have developed in a number of patients taking fluoxetine with risperidone.[6-8] Other adverse effects, including urinary retention, constipation and sedation also occurred in one of these patients.[7] A patient with obsessive-compulsive disorder, who was partially successfully treated with fluoxetine 60 mg daily, saw his condition return to his pre-fluoxetine state when risperidone 3 mg daily was started. His condition gradually improved over a 3-month period after the risperidone was stopped.[9]

(c) Fluvoxamine

A 24-year-old woman taking risperidone 3 mg twice daily developed fever, limb rigidity, and confusion 3 days after starting fluvoxamine 50 mg daily. She required ventilation after her condition worsened, and she was eventually diagnosed as having either serotonin syndrome or neuroleptic malignant syndrome. Both drugs were stopped and her condition resolved. She subsequently, uneventfully took fluvoxamine 100 mg twice daily.[10]

A study in 6 patients who had been taking risperidone 3 to 6 mg daily for at least 4 weeks, with fluvoxamine 100 mg daily for a further 8 weeks, found no changes in the pharmacokinetics of risperidone or its metabolite. However, in 5 other patients included in this study, the dose of fluvoxamine was increased to 200 mg daily for weeks 5 to 8, and there was an 85% increase in plasma risperidone levels by the end of week 8. There was no change in the pharmacokinetics of the active metabolite of risperidone, 9-hydroxyrisperidone, and no adverse reactions to risperidone were noted.[11]

(d) Paroxetine

In a study, 10 patients taking risperidone 2 to 4 mg twice daily were given paroxetine 20 mg daily. After 4 weeks of concurrent use, the levels of risperidone and its active metabolite, 9-hydroxyrisperidone, had increased by 45%. Although the combination was generally well-tolerated one patient developed parkinsonian adverse effects.[12] In another study, 12 patients taking risperidone 2 mg twice daily were given paroxetine in doses increasing from 10 mg daily to 20 mg and 40 mg at 4 week intervals. The plasma levels of risperidone were increased 3.8-fold, 7.1-fold and 9.7-fold when given with paroxetine 10 mg, 20 mg and 40 mg daily, respectively. There was no change in the pharmacokinetics of the active metabolite of risperidone, 9-hydroxyrisperidone. Negative symptoms of schizophrenia were improved, but there was an increased incidence of extrapyramidal adverse effects when patients took paroxetine 20 mg or 40 mg daily.[13]

A case report describes two elderly patients taking paroxetine who developed serotonin syndrome within a couple of days of a risperidone dose increase. One patient's treatment had recently been changed from venlafaxine to paroxetine, which may have contributed to the reaction.[14] Another case report describes a 53-year-old man who developed symptoms suggestive of serotonin syndrome 10 weeks after starting to take risperidone 3 mg daily and paroxetine 20 mg daily. A deterioration in his condition occurred within 2 hours of doubling the dose of both drugs, and his symptoms resolved 2 days after stopping both drugs.[15] Another case report describes a patient taking risperidone, paroxetine and valproate semisodium, who discontinued risperidone after developing reduced facial expressions, stiffness and akathisia. In this patient the half-life of risperidone was estimated to be almost 24 hours (expected half-life only 3 hours).[16]

(e) Sertraline

A 69-year-old man taking venlafaxine for depression with psychosis started taking risperidone 0.5 mg twice daily. Five days later trazodone was started, venlafaxine was gradually stopped and sertraline 25 mg daily was started. Over the next 2 weeks the dose of risperidone was increased to 3 mg daily and the dose of sertraline was increased to 150 mg daily. The patient became tremulous with myoclonus, had cogwheel rigidity of bilateral upper extremities, and a fine tremor. He was diagnosed with serotonin syndrome: risperidone, sertraline and trazodone were stopped, and the symptoms resolved within 24 hours.[17]

A study in 11 patients taking risperidone 4 to 6 mg daily found that sertraline 50 to 100 mg daily for 8 weeks did not affect the mean pharmacokinetics of risperidone. However, in 2 patients sertraline was increased to 150 mg daily by week 8, and in these patients the risperidone levels were increased by 36% and 52%, respectively. No significant adverse effects were reported in any of the patients.[18]

Mechanism

Fluoxetine and paroxetine inhibit the cytochrome P450 isoenzyme CYP2D6 by which risperidone is metabolised. Concurrent use therefore decreases risperidone metabolism, and its levels rise. This can lead to extrapyramidal adverse effects and, it has been suggested, the increased prolactin levels and gynaecomastia seen in one patient.[5] Sertraline is thought to have a dose-dependent effect on CYP2D6 inhibition,[18] but the effects are modest, even in high dose.

Many of the other reactions (sedation, urinary retention, priapism) appear to be a result of additive adverse effects of the SSRIs and risperidone. Serotonin syndrome can result when two drugs with serotonin effects are given together, see 'Additive or synergistic interactions', (p.9).

Importance and management

The elevated risperidone levels seen with fluoxetine and paroxetine appear to be well-documented and clinically significant. Concurrent use should be well monitored and the risperidone dose reduced accordingly: a one-third reduction has been suggested with fluoxetine.[4]

The other SSRIs have less effect on CYP2D6 than fluoxetine and paroxetine and would therefore not be expected to have an effect, or only modest effects, on risperidone levels; this is borne out by the studies with citalopram (no effect), fluvoxamine (modest increase with high dose fluvoxamine) and sertraline (modest increase with high dose sertraline). It would therefore seem prudent to bear a possible interaction in mind if risperidone adverse effects (e.g. agitation, insomnia, headache) occur.

The case reports of the serotonin syndrome appear to be rare, but they should be borne in mind when prescribing SSRIs and risperidone together. See 'serotonin syndrome', (p.9), for more information about managing this adverse effect.

1. Avenoso A, Facciolà G, Scordo MG, Gitto C, Ferrante GD, Madia AG, Spina E. No effect of citalopram on plasma levels of clozapine, risperidone and their active metabolites in patients with chronic schizophrenia. *Clin Drug Invest* (1998) 16, 393–8.
2. Freudenreich O. Exacerbation of idiopathic priapism with risperidone-citalopram combination. *J Clin Psychiatry* (2002) 63, 249–50.
3. Spina E, Avenoso A, Scordo MG, Ancione M, Madia A, Gatti G, Perucca E. Inhibition of risperidone metabolism by fluoxetine in patients with schizophrenia: a clinically relevant pharmacokinetic interaction. *J Clin Psychopharmacol* (2002) 22, 419–23.
4. Bondolfi G, Eap CB, Bertschy G, Zullino D, Vermeulen A, Baumann P. The effect of fluoxetine on the pharmacokinetics and safety of risperidone in psychotic patients. *Pharmacopsychiatry* (2002) 35, 50–56.

5. Benazzi F. Gynecomastia with risperidone-fluoxetine combination. *Pharmacopsychiatry* (1999) 32, 41.
6. Daniel DG, Egan M, Hyde T. Probable neuroleptic induced tardive dyskinesia in association with combined SSRI and risperidone treatment. *Schizophr Res* (1996) 18, 149.
7. Bozikas V, Petrikis P, Karavatos A. Urinary retention caused after fluoxetine-risperidone combination. *J Psychopharmacol* (2001) 15, 142–3.
8. Dubbelman YD, Thung FH, Heeringa M. Ernstige tardieve dyskinesieën tijdens behandeling met risperidon en fluoxetine. *Ned Tijdschr Geneeskd* (1998) 142, 1508–11.
9. Andrade C. Risperidone may worsen fluoxetine-treated OCD. *J Clin Psychiatry* (1998) 59, 255–6.
10. Reeves RR, Mack JE, Bedingfield JJ. Neurotoxic syndrome associated with risperidone and fluvoxamine. *Ann Pharmacother* (2002) 36, 440–3.
11. D'Arrigo C, Migliardi G, Santoro V, Morgante L, Muscatello MR, Ancione M, Spina E. Effect of fluvoxamine on plasma risperidone concentrations in patients with schizophrenia. *Pharmacol Res* (2005) 52, 497–501.
12. Spina E, Avenoso A, Facciolà G, Scordo MG, Ancione M, Madia AG. Plasma concentrations of risperidone and 9-hydroxyrisperidone during combined treatment with paroxetine. *Ther Drug Monit* (2001) 23, 223–7.
13. Saito M, Yasui-Furukori M, Nakagami T, Furukori H, Kaneko S. Dose-dependent interaction of paroxetine with risperidone in schizophrenic patients. *J Clin Psychopharmacol* (2005) 25, 527–32.
14. Karki SD, Masood G-R. Combination risperidone and SSRI-induced serotonin syndrome. *Ann Pharmacother* (2003) 37, 388–91.
15. Hamilton S, Malone K. Serotonin syndrome during treatment with paroxetine and risperidone. *J Clin Psychopharmacol* (2000) 20, 103–5.
16. Barnhill J, Susce MT, Diaz FJ, de Leon J. Risperidone half-life in a patient taking paroxetine. *Pharmacopsychiatry* (2005) 38, 223–5.
17. Kohen I, Gordon ML, Manu P. Serotonin syndrome in elderly patients treated for psychotic depression with atypical antipsychotics and antidepressants: two case reports. *CNS Spectr* (2007) 12, 596–8.
18. Spina E, D'Arrigo C, Migliardi G, Morgante L, Zoccali R, Ancione M, Madia A. Plasma risperidone concentrations during combined treatment with sertraline. *Ther Drug Monit* (2004) 26, 386–90.

Risperidone + Tetracycline

A patient taking risperidone and sertraline experienced a worsening of his tics when tetracycline was added.

Clinical evidence, mechanism, importance and management

A 15-year-old boy taking risperidone 1.5 mg twice daily and sertraline 100 mg daily was given tetracycline 250 mg twice daily. His tics worsened, and did not respond to an increase in his sertraline dosage from 100 to 150 mg daily. After stopping the tetracycline, his tics improved within a few weeks. The exact mechanism of this interaction is unclear, but it has been suggested that the tetracycline somehow reduced the activity of the risperidone. Induction of CYP2D6 by tetracycline was thought unlikely: inactivation of the risperidone or its active metabolite was considered a possible explanation.[1] This appears to be the only reported case of this interaction and its general significance is unknown.

1. Steele M, Couturier J. A possible tetracycline-risperidone-sertraline interaction in an adolescent. *Can J Clin Pharmacol* (1999) 6, 15–17.

Risperidone + Topiramate

Topiramate does not affect the plasma levels of risperidone.

Clinical evidence, mechanism, importance and management

In a study, 9 patients taking long-term clozapine 3 to 6 mg daily were given topiramate in a dose that was increased gradually to 200 mg daily. The plasma levels of risperidone and its metabolite 9-hydroxyrisperidone were not significantly affected by topiramate and the combination was well tolerated.[1]

1. Migliardi G, D'Arrigo C, Santoro V, Bruno A, Cortese L, Campolo D, Cacciola M, Spina E. Effect of topiramate on plasma concentrations of clozapine, olanzapine, risperidone, and quetiapine in patients with psychotic disorders. *Clin Neuropharmacol* (2007) 30, 107–13.

Risperidone + Tricyclic and related antidepressants

Amitriptyline and mirtazapine do not appear to affect the pharmacokinetics of risperidone, and limited evidence suggests that risperidone does not affect the pharmacokinetics of mirtazapine. Risperidone appears to increase the plasma levels of maprotiline. Extrapyramidal reactions have been reported in one patient taking amitriptyline with risperidone.

Clinical evidence, mechanism, importance and management

(a) Amitriptyline

A study in 12 schizophrenic patients found that amitriptyline 50 to 100 mg daily had no effect on the serum levels of risperidone 3 mg twice daily.[1] However, a 26-year-old man taking amitriptyline 25 mg daily developed extrapyramidal reactions after his dosage of risperidone was increased from 2 to 4 mg daily.[2] On another occasion extrapyramidal adverse effects developed after risperidone 2 mg daily was added to treatment with amitriptyline 25 mg and fluoxetine 20 mg daily.[2] Both pharmacokinetic and pharmacodynamic reasons for this reaction have been suggested.[3] The cases illustrate that there is the potential for an adverse interaction, which should be borne in mind when prescribing both drugs.

(b) Maprotiline

A 39-year-old patient with a schizodepressive disorder taking pipamperone and lorazepam, and also taking maprotiline 175 mg daily for a severe depressive episode, had plasma levels of maprotiline of 145 nanograms/mL and 166 nanograms/mL after 4 and 6 weeks, respectively. After 8 weeks, she was given risperidone to treat acute psychotic symptoms. The dose of risperidone was titrated over 5 days up to 5 mg daily and the dose of pipamperone was increased from 40 to 80 mg at night. She had a rapid remission of the psychotic symptoms and almost complete remission of the depression, but gradually developed antimuscarinic adverse effects. Ten days after starting risperidone and with maprotiline at a slightly lower dose of 150 mg daily, maprotiline plasma levels had increased to 266 nanograms/mL. The doses of maprotiline and risperidone were reduced to 100 mg and 3 mg daily, respectively, and this reduced the severity of the adverse effects.[4]

Two other patients have been reported to have gradual increases in maprotiline levels over 6 to 7 weeks during the concurrent use of risperidone. One of the patients was also taking **nortriptyline**, but its levels were unaltered.[4]

This interaction is unconfirmed but be aware of the possibility of an interaction if maprotiline adverse effects are troublesome.

(c) Mirtazapine

A pilot study in 6 psychiatric patients taking risperidone 1 to 3 mg twice daily for 1 to 4 weeks followed by 2 to 4 weeks of combined treatment with mirtazapine 15 to 30 mg at night, found that mirtazapine did not affect the plasma levels of risperidone or its 9-hydroxy metabolite. Data from another patient suggest that giving risperidone with mirtazapine does not result in clinically relevant changes in the plasma levels of mirtazapine. Concurrent use did not appear to increase the incidence of adverse effects, but the number of patients was limited.[5] Similarly, a later study in 8 patients taking risperidone in doses ranging from 3 to 8 mg daily found no significant change in the pharmacokinetics of risperidone and its metabolite, 9-hydroxyrisperidone when they were also given mirtazapine 30 mg daily.[6]

1. Sommers DK, Snyman JR, van Wyk M, Blom MW, Huang ML, Levron JC. Lack of effect of amitriptyline on risperidone pharmacokinetics in schizophrenic patients. *Int Clin Psychopharmacol* (1997) 12, 141–5.
2. Brown ES. Extrapyramidal side effects with low-dose risperidone. *Can J Psychiatry* (1997) 42, 325–6.
3. Caley CF. Extrapyramidal reactions from concurrent SSRI and atypical antipsychotic use. *Can J Psychiatry* (1998) 43, 307–8.
4. Normann C, Lieb K, Walden J. Increased plasma concentration of maprotiline by coadministration of risperidone. *J Clin Psychopharmacol* (2002) 22, 92–4.
5. Loonen AJM, Doorschot CH, Oostelbos MCJM, Sitsen JMA. Lack of drug interactions between mirtazapine and risperidone in psychiatric patients: a pilot study. *Eur Neuropsychopharmacol* (1999) 10, 51–7.
6. Zoccali R, Muscatello MR, La Torre D, Malara G, Canale A, Crucitti D, D'Arrigo C, Spina E. Lack of a pharmacokinetic interaction between mirtazapine and the newer antipsychotics clozapine, risperidone and olanzapine in patients with chronic schizophrenia. *Pharm Res* (2003) 48, 411–14.

Risperidone + Valproate

There are case reports describing oedema in patients taking risperidone and valproate. Valproate appears not to affect the metabolism of risperidone. Studies suggest that risperidone does not alter the pharmacokinetics of valproate, although cases of increased and decreased levels have been reported.

Clinical evidence, mechanism, importance and management

A study comparing 10 patients taking **sodium valproate** and risperidone with 23 patients taking risperidone alone found no significant difference in the levels of risperidone and its metabolite, 9-hydroxyrisperidone, between the two groups, suggesting that **sodium valproate** does not affect risperidone pharmacokinetics.[1] Similarly, in a study in 12 patients with schizophrenia given **valproic acid** 400 to 800 mg daily and risperidone 2 to 6 mg daily, **valproic acid** did not affect plasma levels of risperidone or 9-hydroxyrisperidone.[2]

The effect of risperidone on valproate levels has also been studied. A study in 21 patients with bipolar disorder who were given **valproate semisodium** (**divalproex sodium**) 1 g daily with risperidone 2 mg daily for 2 days increasing to 4 mg daily for 12 days found no significant changes in the pharmacokinetics of valproate. Adverse effects were unaltered.[3] However, the valproate levels of a 10-year-old boy increased from 143 micrograms/mL to 191 micrograms/mL 5 days after he started to take risperidone (initially 2 mg daily, then later 3 mg daily). This was attributed to an interaction, the exact mechanism of which is unclear.[4,5] Conversely, a 15-year-old girl experienced a *reduction* in her valproate levels, from 80 micrograms/mL to 57 micrograms/mL when risperidone 1 mg three times daily was added to established treatment with **valproic acid**.[6] Another case report describes the development of generalised acute oedema in a schizophrenic patient when risperidone (titrated to 10 mg daily) was added to established **sodium valproate** treatment. The oedema was unresponsive to diuretics, but resolved when the risperidone dose was reduced to 2 mg. When the risperidone dose was later increased to 8 mg the oedema reappeared, so the risperidone was withdrawn.[7] A second case of oedema has been reported in a 35-year-old man who had taken **valproate semisodium** uneventfully for over 6 years. After taking risperidone for two-and-a-half weeks, significant oedema developed, which responded to treatment with hydrochlorothiazide and triamterene.[8] Note that both drugs can cause oedema alone.[9,10]

In general the data seem to suggest that no special precautions are necessary if valproate and risperidone are given together, but it is worth bearing these cases in mind in the event of oedema, or otherwise unexpected changes in valproate levels.

1. Spina E, Avenoso A, Facciolà G, Salemi M, Scordo MG, Giacobello T, Madia AG, Perucca E. Plasma concentrations of risperidone and 9-hydroxyrisperidone: effect of comedication with carbamazepine or valproate. *Ther Drug Monit* (2000) 22, 481–5.
2. Yoshimura R, Shinkai K, Ueda N, Nakamura J. Valproic acid improves psychotic agitation without influencing plasma risperidone levels in schizophrenic patients. *Pharmacopsychiatry* (2007) 40, 9–13.
3. Ravindran A, Silverstone P, Lacroix D, von Schaick E, Vermeulen A, Alexander J. Risperidone does not affect steady-state pharmacokinetics of divalproex sodium in patients with bipolar disorder. *Clin Pharmacokinet* (2004) 43, 733–40.
4. van Wattum PJ. Valproic acid and risperidone. *J Am Acad Child Adolesc Psychiatry* (2001) 40, 866–7.
5. Sund JK, Aamo T, Spigset O. Valproic acid and risperidone: a drug interaction? *J Am Acad Child Adolesc Psychiatry* (2003) 42, 1–2.
6. Bertoldo M. Valproic acid and risperidone. *J Am Acad Child Adolesc Psychiatry* (2002) 41, 632.
7. Sanders RD, Lehrer DS. Edema associated with addition of risperidone to valproate treatment. *J Clin Psychiatry* (1998) 59, 689–90.
8. Baldassano CF, Ghaemi SN. Generalized edema with risperidone: divalproex sodium treatment. *J Clin Psychiatry* (1996) 57, 422.
9. Risperdal (Risperidone). Janssen-Cilag Ltd. UK Summary of product characteristics, December 2008.
10. Depakote (Valproate semisodium). Sanofi-Aventis. UK Summary of product characteristics, November 2009.

Risperidone + Venlafaxine

No clinically relevant pharmacokinetic interaction appears to occur between risperidone and venlafaxine.

Clinical evidence, mechanism, importance and management

In a study in 30 healthy subjects, steady-state venlafaxine 75 mg every 12 hours was found to increase the AUC of a single 1-mg oral dose of risperidone by about 32%, but the pharmacokinetic profile of the risperidone plus its active metabolite (9-hydroxyrisperidone) was not significantly changed, nor were any adverse events seen.[1]

The modest effects on risperidone levels are not expected to be clinically significant, and therefore the dose of risperidone does not need adjusting if venlafaxine is given.

1. Amchin J, Zarycranski W, Taylor KP, Albano D, Klockowski PM. Effect of venlafaxine on the pharmacokinetics of risperidone. *J Clin Pharmacol* (1999) 39, 297–309.

Ritanserin + Miscellaneous

Ritanserin does not interact with alcohol, and cimetidine and ranitidine do not affect ritanserin pharmacokinetics to a clinically relevant extent.

Clinical evidence, mechanism, importance and management

A study in 20 healthy subjects given ritanserin 10 mg with and without **alcohol** 0.5 g/kg found no pharmacokinetic or pharmacodynamic interactions between these drugs.[1] **Cimetidine** 800 mg daily or **ranitidine** 300 mg daily given to 9 healthy subjects for 11 days caused only small changes in the pharmacokinetics of a single 10-mg dose of ritanserin given on day 3. These changes were attributed to altered absorption,[2] but were of little or no clinical significance.

1. Estevez F, Parrillo S, Giusti M, Monti JM. Single-dose ritanserin and alcohol in healthy volunteers: a placebo-controlled trial. *Alcohol* (1995) 12, 541–5.
2. Trenk D, Seiler K-U, Buschmann M, Szathmary S, Benn H-P, Jähnchen E. Effect of concomitantly administered cimetidine or ranitidine on the pharmacokinetics of the 5-HT_2-receptor antagonist ritanserin. *J Clin Pharmacol* (1993) 33, 330–4.

Sertindole + Miscellaneous

Erythromycin, a CYP3A4 inhibitor, increases sertindole levels, which increases the risk of QT prolongation. Other CYP3A4 inhibitors are predicted to interact similarly. Fluoxetine and paroxetine also increase sertindole levels. Carbamazepine, phenobarbital, phenytoin and rifampicin (rifampin), CYP3A4 inducers, reduce plasma sertindole levels. No clinically relevant interactions occur between sertindole and alprazolam, antacids, food or tobacco smoking.

Clinical evidence, mechanism, importance and management

(a) Antacids or Food

In a study in 16 healthy subjects, a standardised breakfast or *Maalox* [**aluminium/magnesium hydroxide**] 45 mL had no significant effect on the AUC of a single 4-mg dose of sertindole, and only minor and unimportant changes occurred in maximum serum levels.[1,2] No special precautions are needed if sertindole is given with *Maalox*, and it may be given without regard to meals.

(b) Benzodiazepines

A pharmacokinetic study in 14 healthy subjects found only minor changes in pharmacokinetics of a single 1-mg dose of **alprazolam** in the presence of sertindole 12 mg daily. The changes were considered to be clinically unimportant.[3]

(c) CYP3A4 inducers

The metabolism of sertindole is markedly increased by enzyme inducers, such as **rifampicin** (**rifampin**), **phenobarbital**, **phenytoin** and **carbamazepine**, and plasma sertindole levels may be reduced by two- to threefold. The manufacturers therefore say that the daily dose of sertindole may need to be increased towards the upper end of the maximum dose range to accommodate this interaction.[4,5]

(d) CYP3A4 inhibitors

In a study, 10 healthy subjects were given a single 4-mg dose of sertindole before and after they took **erythromycin** 250 mg every 6 hours for 10 days. The mean maximum serum levels of sertindole were increased by 15%, but this was not considered to be clinically significant. However, the incidence of adverse effects rose (diarrhoea, abdominal pain, dizziness), although no ECG changes were seen.[6,7] Nevertheless the manufacturers contraindicate **erythromycin** because raised sertindole levels may prolong the QT interval,[4] which can lead to life-threatening arrhythmias. For more information on QT interval prolongation, see 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290.

Erythromycin probably increases sertindole levels by inhibiting its metabolism by the cytochrome P450 isoenzyme CYP3A4. The manufactur-

ers of sertindole reasonably predict that other CYP3A4 inhibitors will interact similarly. They name **clarithromycin**, **indinavir**, **itraconazole**, **ketoconazole**, **diltiazem**, **verapamil**, and **cimetidine**, and contraindicate the use of these drugs with sertindole. Note that in one study **diltiazem**, **nifedipine** and **verapamil** resulted in a 20% reduction in the sertindole clearance.[5]

This list is not inclusive and other drugs may also reduce sertindole metabolism. For example, the manufacturer of **miconazole oral gel** contraindicates its use with sertindole.[8] For a list of CYP3A4 inhibitors, see 'Table 1.4', (p.6).

(e) Drugs that prolong the QT interval

In a study, 14 healthy subjects were given sertindole 20 mg daily for 5 days followed by a single 120-mg dose of **terfenadine**. The pharmacokinetics of neither drug was significantly changed, nor that of the metabolite of **terfenadine** (carboxyterfenadine), although it was concluded that sertindole may be a modest inhibitor of the first pass metabolism of **terfenadine**.[9,10] However, it was found that the combination caused an additive increase of 49 milliseconds in the QTc interval and therefore these two drugs are contraindicated by the manufacturer.[4] Other drugs may prolong the QT interval, and the manufacturers contraindicate their concurrent use. They specifically name **astemizole**, **terfenadine**, class Ia antiarrhythmics (**quinidine**), class III antiarrhythmics (**amiodarone**, **dofetilide**, **sotalol**), **erythromycin**, **gatifloxacin**, **cisapride**, **lithium**, **thioridazine**, and **moxifloxacin**.

See also 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290, for a further list of QT-prolonging drugs.

(f) SSRIs

Fluoxetine and **paroxetine** are inhibitors of the cytochrome P450 isoenzyme CYP2D6. Concurrent use results in a two- to three-fold increase in sertindole plasma levels. The manufacturers advise that low maintenance doses of sertindole may be needed and recommend close ECG monitoring when doses are adjusted.[4] An isolated case report describes a man with paranoid psychosis and unipolar depression whose condition unexpectedly seriously worsened when **paroxetine** was stopped while continuing to take sertindole.[11]

(g) Tobacco

The clearance of sertindole is increased by tobacco smoking (probably because of the induction of cytochrome P450 isoenzymes) but no sertindole dosage alteration is thought necessary.[5]

1. Granneman GR, Wozniak P, Ereshefsky L, Silber C, Mack R. Effect of food and antacid on the bioavailability of sertindole (M94–164). Poster presentation at the American College of Neuropsychopharmacology Annual Meeting, San Juan, Puerto Rico, December 1996.
2. Wong S, Linnen P, Mack R, Granneman GR. Effects of food, antacid, and dosage form on the pharmacokinetics and relative bioavailability of sertindole in healthy volunteers. *Biopharm Drug Dispos* (1997) 18, 533–41.
3. Wong SL, Locke C, Staser J, Granneman GR. Lack of multiple dosing effect of sertindole on the pharmacokinetics of alprazolam in healthy volunteers. *Psychopharmacology (Berl)* (1998) 135, 236–41.
4. Serdolect (Sertindole). Lundbeck Ltd. UK Summary of product characteristics, July 2007.
5. Granneman GR, Wozniak P, Ereshefsky L, Silber C, Mack R. Population pharmacokinetics of sertindole during long-term treatment of patients with schizophrenia. Poster presentation at the American College of Neuropsychopharmacology Annual Meeting, San Juan, Puerto Rico, December 1996.
6. Granneman GR, Wozniak P, Ereshefsky L, Silber C, Mack R. Effect of erythromycin on the pharmacokinetics of sertindole (M94–145). Poster presentation at the American College of Neuropsychopharmacology Annual Meeting, San Juan, Puerto Rico, December 1996.
7. Wong SL, Cao G, Mack RJ, Granneman GR. The effect of erythromycin on the CYP3A component of sertindole clearance in healthy volunteers. *J Clin Pharmacol* (1997) 37, 1056–61.
8. Daktarin Oral Gel (Miconazole). Janssen-Cilag Ltd. UK Summary of product characteristics, September 2008.
9. Granneman GR, Wozniak P, Ereshefsky L, Silber C, Mack R. Effect of sertindole on the pharmacokinetics of terfenadine (M94–146). Poster presentation at the American College of Neuropsychopharmacology Annual Meeting, San Juan, Puerto Rico, December 1996.
10. Wong SL, Cao G, Mack R, Granneman GR. Lack of CYP3A inhibition effects of sertindole on terfenadine in healthy volunteers. *Int J Clin Pharmacol Ther* (1998) 36, 146–51.
11. Walker-Kinnear M, McNaughton S. Paroxetine discontinuation syndrome in association with sertindole therapy. *Br J Psychiatry* (1997) 170, 389.

Sulpiride + Miscellaneous

Sucralfate and an aluminium/magnesium hydroxide antacid can reduce the absorption of sulpiride. An isolated case describes extrapyramidal adverse effects in a patient taking sulpiride and fluoxetine.

Clinical evidence, mechanism, importance and management

(a) Antacids and Sucralfate

A study in 6 healthy subjects found that the bioavailability of a single 100-mg dose of sulpiride was reduced by 40% by **sucralfate** 1 g and by 32% by 30 mL of *Simeco* (**aluminium**/**magnesium hydroxide** and **simeticone**). When either the **sucralfate** or the antacid were taken 2 hours before sulpiride the reduction in bioavailability was only about 25%, and no change in bioavailability was seen in one subject when the **sucralfate** was given 2 hours after the sulpiride.[1]

The mechanism by which antacids reduce sulpiride absorption has not been established, but it seems possible that sulpiride becomes adsorbed onto the antacid, reducing the amount available for absorption.

Information about an interaction between sulpiride and antacids appears to be limited to this one study, which did not establish the clinical relevance of the effect found. With other antacid interactions, separating the doses by as much as possible (1 to 2 hours) to avoid admixture in the gut usually minimises any effects. It may be prudent to consider separating dosing if sulpiride seems less effective in a patient taking an antacid.

(b) Fluoxetine

Parkinson-like symptoms developed in a patient taking sulpiride and maprotiline when fluoxetine was also given.[2] This isolated case of extrapyramidal adverse effects should not prevent concurrent use; however, if extrapyramidal effects become troublesome bear this interaction in mind as a possible cause.

1. Gouda MW, Hikal AH, Babhair SA, ElHofy SA, Mahrous GM. Effect of sucralfate and antacids on the bioavailability of sulpiride in humans. *Int J Pharmaceutics* (1984) 22, 257–63.
2. Touw DJ, Gernaat HBPE, van der Woude J. Parkinsonisme na toevoeging van fluoxetine aan behandeling met neuroleptica of carbamazepine. *Ned Tijdschr Geneeskd* (1992) 136, 332–4.

Tiotixene + Miscellaneous

Tiotixene levels are reduced by the enzyme-inducers carbamazepine, phenytoin, primidone and tobacco smoke. Enzyme inhibitors may reduce the clearance of tiotixene. Paroxetine does not alter tiotixene levels.

Clinical evidence, mechanism, importance and management

(a) Antiepileptics, enzyme-inducing

A retrospective study in 42 patients found that the mean clearance of tiotixene in those taking liver enzyme inducer drugs (**carbamazepine**, **phenytoin**, **primidone**) was threefold greater than in the control group. Of the group taking enzyme inducers, 5 patients had non-detectable serum tiotixene levels, and not surprisingly showed no clinical response.[1] It may be necessary to increase the tiotixene dosage if any of these antiepileptics is also given. Remember too that if the antiepileptics are withdrawn it may be necessary to reduce the tiotixene dose.

(b) Paroxetine

A study in 10 healthy subjects found that paroxetine 20 mg daily for 3 days did not significantly affect the pharmacokinetics of a single 20-mg dose of tiotixene. It was suggested that CYP2D6 is not the main isoenzyme involved in the metabolism and clearance of tiotixene.[2]

(c) Tobacco

Tobacco smoking increased the clearance of tiotixene in patients taking enzyme inhibitors or no other drugs, but not in patients taking enzyme inducers. Those who smoked were found to need on average 45% more tiotixene than the non-smokers taking no other interacting drugs.[1]

(d) Other drugs

A group of patients taking **cimetidine**, **doxepin**, **isoniazid**, **nortriptyline**, or **propranolol** had a tiotixene clearance of 9.51 L/minute, which was 71% less than that seen in patients taking tiotixene alone.[1] It was suggested that these drugs inhibited the metabolism of tiotixene, thereby reducing its clearance. It is unclear whether this reduction in clearance significantly increases tiotixene levels, and therefore the clinical relevance of this finding is unclear. However, a case report describes adverse effects in a patient

taking tiotixene and chlorpromazine with **propranolol**, see 'Beta blockers + Phenothiazines', p.1014.

1. Ereshefsky L, Saklad SR, Watanabe MD, Davis CM, Jann MW. Thiothixene pharmacokinetic interactions: a study of hepatic enzyme inducers, clearance inhibitors, and demographic variables. *J Clin Psychopharmacol* (1991) 11, 296–301.
2. Guthrie SK, Hariharan M, Kumar AA, Bader G, Tandon R. The effect of paroxetine on thiothixene pharmacokinetics. *J Clin Pharm Ther* (1997) 22, 221–6.

Trifluoperazine + Venlafaxine

An isolated case report describes neuroleptic malignant syndrome in a patient taking trifluoperazine, which developed after he took a single dose of venlafaxine. It was also suggested that the symptoms may have been due to the serotonin syndrome.
106 Clinical evidence, mechanism, importance and management

A patient who had taken trifluoperazine 1 mg three times daily for 10 years was also given venlafaxine 75 mg daily. Twelve hours after the first dose of venlafaxine he presented with profound anxiety, malaise, profuse sweating, tremor and rigidity. His blood pressure was found to fluctuate between 130/80 and 165/100 mmHg, with a pulse of 163 bpm, a temperature of 38.3°C, and a respiratory rate of 25 breaths/minute. Blood and urine tests were normal except for a high creatine phosphokinase concentration and neutrophilia. The drugs were stopped and the patient recovered after taking a single 70-mg dose of dantrolene and bromocriptine 15 mg twice daily for 48 hours.

It was suggested that the patient had developed neuroleptic malignant syndrome, which may have occurred as a result of dopamine inhibition by the two drugs.[1] It was subsequently suggested that the symptoms seen may have been due to 'serotonin syndrome', (p.9), resulting from serotonergic over-activity when the single dose of venlafaxine was added to established treatment with trifluoperazine.[2]

1. Nimmagadda SR, Ryan DH, Atkin SL. Neuroleptic malignant syndrome after venlafaxine. *Lancet* (2000) 354, 289–90.
2. Cassidy EM, O'Kearne V. Neuroleptic malignant syndrome after venlafaxine. *Lancet* (2000) 355, 2164–5.

Ziprasidone + Carbamazepine

Carbamazepine does not appear to affect the pharmacokinetics of ziprasidone.

Clinical evidence, mechanism, importance and management

In a randomised study, healthy subjects were given ziprasidone 20 mg twice daily with either placebo (10 subjects), or carbamazepine 200 mg twice daily (9 subjects) for 5 doses. It was found that carbamazepine reduced the AUC and maximum serum levels of ziprasidone by 36% and 27%, respectively.[1]

Carbamazepine, a known, potent inducer of the cytochrome P450 isoenzyme CYP3A4 probably increased the metabolism of ziprasidone by this pathway, resulting in the reduction in ziprasidone levels seen. However, this reduction is modest, and not expected to be clinically significant. Therefore no ziprasidone dose adjustment would seem to be necessary if carbamazepine is also given.

1. Miceli JJ, Anziano RJ, Robarge L, Hansen RA. Laurent A. The effect of carbamazepine on the steady-state pharmacokinetics of ziprasidone in healthy volunteers. *Br J Clin Pharmacol* (2000) 49 (Suppl 1), 65S–70S.

Ziprasidone + Ketoconazole

Ketoconazole moderately increases ziprasidone levels.

Clinical evidence, mechanism, importance and management

In a randomised, placebo-controlled study, 14 healthy subjects were given a 40-mg dose of ziprasidone before and after taking ketoconazole 400 mg daily for 6 days. It was found that ketoconazole increased the AUC and maximum serum levels of ziprasidone by 33% and 34%, respectively. This modest rise in levels probably occurs because ketoconazole inhibits the cytochrome P450 isoenzyme CYP3A4 by which ziprasidone is metabolised. However, it was concluded that the increase is not clinically relevant.[1] No ziprasidone dose adjustments would therefore seem to be needed on concurrent use.

1. Miceli JJ, Smith M, Robarge L, Morse T, Laurent A. The effects of ketoconazole on ziprasidone pharmacokinetics – a placebo-controlled crossover study in healthy volunteers. *Br J Clin Pharmacol* (2000) 49 (Suppl 1), 71S–76S.

Ziprasidone + Miscellaneous

The manufacturers warn of the possible risks of giving ziprasidone with drugs that prolong the QT interval. Ziprasidone may enhance the effects of antihypertensive drugs. Ziprasidone appears not to interact to a clinically relevant extent with an aluminium/magnesium hydroxide antacid, benzatropine, cimetidine, dextromethorphan, lorazepam, propranolol or tobacco smoking.

Clinical evidence, mechanism, importance and management

(a) Antacids or Cimetidine

A single 40-mg oral dose of ziprasidone were given to 10 healthy subjects either alone, with cimetidine 800 mg daily for 2 days, or with three 30-mL doses of ***Maalox*** **(aluminium/magnesium hydroxide)**. The only change in the pharmacokinetics of ziprasidone was a 6% increase in the AUC with cimetidine. It was concluded that no special precautions are needed if either of these drugs and ziprasidone are given concurrently.[1]

(b) Antihypertensives

The manufacturers note that because ziprasidone may cause hypotension, it may enhance the effects of certain antihypertensive drugs.[2]

(c) Dextromethorphan

In a single-dose study in 8 healthy subjects, ziprasidone 80 mg did not affect the pharmacokinetics of dextromethorphan 30 mg, taken 2 hours later. This suggests that the dose of dextromethorphan does not need to be adjusted if ziprasidone is also given. Furthermore, dextromethorphan is used as a probe substrate for the cytochrome P450 isoenzyme CYP2D6, and therefore this study also suggests that ziprasidone is unlikely to affect the pharmacokinetics of other CYP2D6 substrates.[3] For a list of CYP2D6 substrates, see 'Table 1.3', (p.6).

(d) Drugs that prolong the QT interval

Studies in healthy subjects found that ziprasidone 160 mg increased the QTc interval by about 10 milliseconds. While only a relatively moderate increase in the QT interval actually occurs with ziprasidone, because of the possibility of additive effects with some other drugs (and the attendant risk of torsade de pointes), to be on the safe side the manufacturer of ziprasidone contraindicates its use with other drugs that can prolong the QT interval.[2] For a list of QT-prolonging drugs, see 'Table 9.2', (p.290).

A case report describes a 70-year-old man who took **quetiapine** and ziprasidone and who developed cardiac arrhythmias with extrasystoles, and a prolonged QTc interval of 482 milliseconds, an increase of 65 milliseconds from his value with **quetiapine** alone. On stopping **quetiapine** and reducing the dose of ziprasidone, his QTc interval normalised.[4]

(e) Tobacco

The manufacturer of ziprasidone suggests that as ziprasidone is not metabolised by the cytochrome P450 isoenzyme CYP1A2, smoking should not affect its pharmacokinetics. This is borne out by studies in patients, which did not reveal any differences in the pharmacokinetics of ziprasidone between **tobacco smokers** and non-smokers.[2]

(f) Other drugs

The manufacturer of ziprasidone states that population pharmacokinetic analysis of schizophrenic patients who were enrolled in clinical studies showed that no significant pharmacokinetic interactions occurred with **benzatropine**, **lorazepam** or **propranolol**.[2]

1. Wilner KD, Hansen RA, Folger CJ, Geoffroy P. The pharmacokinetics of ziprasidone in healthy volunteers treated with cimetidine or antacid. *Br J Clin Pharmacol* (2000) 49 (Suppl 1), 57S–60S.
2. Geodon (Ziprasidone). Pfizer Inc. US Prescribing information, June 2009.
3. Wilner KD, Demattos SB, Anziano RJ, Apseloff G, Gerber N. Ziprasidone and the activity of cytochrome P450 2D6 in healthy extensive metabolizers. *Br J Clin Pharmacol* (2000) 49 (Suppl 1), 43S–47S.
4. Minov C. QTc-Zeitverlängerung unter ziprasidon in kombination mit quetiapin. *Psychiatr Prax* (2004) 31, S142–4.

Zopiclone + Gemfibrozil

Gemfibrozil does not increase zopiclone levels, but the levels of its two major metabolites may be slightly increased.

Clinical evidence, mechanism, importance and management

A placebo-controlled, crossover study in 10 healthy subjects found that gemfibrozil 600 mg twice daily for 3 days did not affect the pharmacokinetics of a single 7.5-mg oral dose of zopiclone. However, the AUCs of its two major metabolites, *N*-oxide zopiclone and *N*-desmethylzopiclone, were raised twofold and by 20%, respectively; these metabolites may have some, but weaker pharmacological activity than zopiclone. It appears that gemfibrozil, which is a potent CYP2C8 inhibitor, does not significantly affect the metabolism of zopiclone, but it may affect the further metabolism of its major metabolites. Although the pharmacodynamic effects of zopiclone, such as drowsiness, were not affected by gemfibrozil, it was suggested that, due to the increased levels of the metabolites, slightly enhanced effects could not be excluded.[1]

1. Tornio A, Neuvonen PJ, Backman JT. The CYP2C8 inhibitor gemfibrozil does not increase the plasma concentrations of zopiclone. *Eur J Clin Pharmacol* (2006) 62, 645–51.

Zotepine + Miscellaneous

There appears to be little or no information about adverse interactions between zotepine and other drugs, but the manufacturers warn about the concurrent use of antihypertensives, anaesthetics, antipsychotics, and drugs that prolong the QTc interval. Two cases of deep vein thrombosis have been reported in patients taking zotepine with paroxetine. Some benzodiazepines and fluoxetine may increase plasma levels of zotepine. Two cases of hypothermia have been reported in patients taking benzodiazepines, valproate and zotepine when the dose of zotepine was increased. The pharmacokinetics of zotepine appear not to be affected by tobacco smoking.

Clinical evidence, mechanism, importance and management

(a) Antihypertensives

Zotepine has alpha-adrenergic blocking properties, which may cause orthostatic hypotension, especially when treatment is first started or if the dose is increased. The manufacturers advise caution when it is given with hypotensive agents, including some **anaesthetics**, the implication being that any orthostatic hypotension may possibly be worsened. If patients feel faint and dizzy when they stand up, they should be advised to get up more slowly, and if necessary, a smaller dose should be used.[1]

(b) Antimuscarinics

Biperiden 6 mg daily for 2 weeks was found not to affect the pharmacokinetics of zotepine in a study in 21 patients.[2]

(c) Antipsychotics

The manufacturer of zotepine points out that, as with some other antipsychotics, zotepine has clear pro-convulsive effects, which may be additive with other antipsychotics, particularly if high doses of either or both drugs are used. They therefore recommend that zotepine doses above 300 mg daily or the concurrent use of high doses of other antipsychotics should be avoided.[1]

(d) Benzodiazepines

A study in 17 patients found that plasma zotepine levels were higher and its elimination half-life prolonged by **diazepam**.[3] The manufacturer reports that in a clinical interaction study, **diazepam** increased the plasma levels of zotepine by about 25%, and that norzotepine levels are also increased. They advise caution if diazepam and zotepine are given concurrently.[1]

A patient who was taking zotepine 50 mg daily, **valproate** 1 g daily and **lormetazepam** 2 mg daily, had his dose of zotepine increased gradually to 200 mg daily because of persistent auditory hallucinations. The **valproate** and **lormetazepam** doses were not altered. Four weeks later he presented with poor appetite, dizziness and a low body temperature (34.8°C). The dose of zotepine was reduced and his temperature increased to 36°C. The authors reported another case of hypothermia, in a patient taking **clonazepam**, **valproic acid** and zotepine. The patient's temperature became normal when the dose of zotepine was reduced from 200 mg to 150 mg, and fell when the dose was increased to 200 mg. It was suggested that zotepine may decrease body temperature by chronic suppression of 5-HT transmission and by increasing the rate of metabolism of dopamine and noradrenaline. Further, the cytochrome P450 isoenzyme CYP3A4-mediated metabolism of zotepine may be inhibited by benzodiazepines resulting in higher zotepine levels and a greater effect on body temperature. **Valproate** may also lower body temperature in a dose dependent manner and so it is possible that the combination of three drugs in each of the patients contributed to the observed hypothermia.[4]

(e) Desipramine

No pharmacokinetic interaction was seen when zotepine was given with desipramine.[1]

(f) Drugs that prolong the QT interval

The manufacturer of zotepine advises caution if it is given with drugs known to prolong the QTc interval because zotepine also shows a dose-related QTc interval prolongation,[1] the implication being that the effects may be additive. See also 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290.

(g) SSRIs

Two case reports have described mobile, elderly male patients who developed deep vein thrombosis when taking **paroxetine** and zotepine. In the first case the patient was taking **paroxetine** 40 mg daily, and zotepine was added to his treatment 3 weeks later, initially at a dose of 75 mg daily, then increased to 150 mg daily. After 17 days of treatment with zotepine 150 mg daily the patient developed significant swelling of the right leg, and a deep vein thrombosis was diagnosed by Doppler studies and venography. The second patient also received **paroxetine** 40 mg daily to which zotepine 150 mg daily was added, and within 3 days of starting zotepine, the patient had developed painful swelling of the right calf, dyspnoea and tachycardia. A deep vein thrombosis was confirmed. They were part of a review of 150 patients consecutively admitted to a psychiatric ward. They were the only two patients who received this combination of drugs, and the only two who developed a thromboembolism. The mechanism of this interaction is unclear.[5]

In a clinical interaction study, **fluoxetine** increased the plasma concentrations of zotepine by about 10% and approximately doubled those of norzotepine. The manufacturer advises caution if they are given concurrently.[1]

(h) Tobacco

A study in healthy subjects found that there were no significant differences in the pharmacokinetics of zotepine in smokers (8 subjects) and non-smokers (6 subjects).[3]

1. Zoleptil (Zotepine). Orion Pharma UK Ltd. UK Summary of product characteristics, April 2006.
2. Otani K, Hirano T, Kondo T, Kaneko S, Fukushima Y, Noda K, Tashiro Y. Biperiden and piroheptine do not affect the serum level of zotepine, a new antipsychotic drug. *Br J Psychiatry* (1990) 157, 128–30.
3. Tanaka O. Pharmacokinetics of zotepine and various factors affecting that of zotepine. *Nihon Shinkei Seishin Yakurigaku Zasshi* (1996) 16, 49–52.
4. Chen KC, Yang YK, Chen PS, Yeh TL, Yang MJ. Two cases of hypothermia induced by an increased dosage of zotepine in a combination therapy. *Psychiatry Clin Neurosci* (2003) 57, 369–71.
5. Pantel J, Schröder J, Eysenbach, K, Mundt Ch. Two cases of deep vein thrombosis associated with a combined paroxetine and zotepine therapy. *Pharmacopsychiatry* (1997) 30, 109–11.

21

Antivirals

This section is concerned with the drugs used to treat viral infections, including hepatitis, herpes, influenza, and HIV infection. These drugs may be grouped by the viral infections they are used to treat, and also by drug class (see 'Table 21.1', (p.914)). Where antivirals affect other drugs the interactions are generally covered elsewhere.

Antivirals active against herpes and hepatitis

Nucleoside and nucleotide analogues

The nucleoside analogues are principally eliminated unchanged by the kidneys by a process of active tubular secretion as well as glomerular filtration. The few interactions with these drugs mainly involve altered renal clearance (e.g. probenecid), but since they have a wide therapeutic range, even these interactions are of debatable clinical relevance. Cytochrome P450-mediated interactions are not important for this group of drugs. However, the possibility of effects on other transport systems cannot be ruled out at present, see 'Adefovir + Miscellaneous', p.916.

Antiretrovirals active against HIV

Treatment of HIV infection commonly requires a combination of 3 to 4 antiretrovirals, termed highly active antiretroviral therapy (HAART). In addition, patients often receive a large number of other drugs for comorbid conditions. This markedly increases the risk of drug interactions and complicates their assessment.

(a) CCR5 antagonists

CCR5 antagonists are a class of antiretrovirals referred to as entry inhibitors. Maraviroc is a substrate of CYP3A4 and because of this, CYP3A4 inducers (e.g. efavirenz) lower its levels and CYP3A4 inhibitors (e.g. protease inhibitors) increase its levels. Maraviroc is not expected to have a clinically relevant effect on most cytochrome P450 isoenzymes, although it may possibly inhibit intestinal P-glycoprotein.

(b) Fusion inhibitors

The fusion inhibitor, enfuvirtide, is a peptide. It does not cause cytochrome P450-mediated drug interactions, and is not affected by potent inducers or inhibitors of cytochrome P450 isoenzymes. However, modest interactions, the underlying mechanism of which is unknown, have been reported with some of the 'protease inhibitors', (p.918), such as ritonavir and tipranavir.

(c) Integrase inhibitors

Raltegravir, one of the first integrase inhibitors to be licensed, is metabolised by glucuronidation (primarily by UGT1A1). Hence, drugs that inhibit ('atazanavir', (p.991)) or induce ('rifampicin (rifampin)', (p.990)) this enzyme may affect the metabolism of raltegravir. Raltegravir is not a substrate for cytochrome P450 isoenzymes, and raltegravir does not appear to inhibit or induce many of the major cytochrome P450 isoenzymes, nor does it inhibit P-glycoprotein. However, it appears that drugs that affect gastric pH may also affect the levels of raltegravir, see 'Raltegravir + Miscellaneous', p.990, for further discussion.

(d) Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

The NNRTIs are extensively metabolised by the cytochrome P450 isoenzyme system, particularly by CYP3A4. They are also inducers (nevirapine, efavirenz, and to a lesser degree, etravirine) or inhibitors (delavirdine) of CYP3A4. NNRTIs would therefore be expected to interact with each other, and with the protease inhibitors, but not with NRTIs (see below). They also have the potential to interact with other drugs metabolised by CYP3A4, and are affected by CYP3A4 inhibitors and inducers. Delavirdine and efavirenz may also inhibit some other P450 isoenzymes: etravirine is also a weak inhibitor of some P450 isoenzymes. For a summary of these effects, see 'Table 21.2', (p.914).

(e) Nucleoside reverse transcriptase inhibitors (NRTIs)

NRTIs are prodrugs, which need to be activated by phosphorylation within cells to a triphosphate anabolite. Drugs may therefore interact with NRTIs by increasing or decreasing intracellular activation. NRTIs may also interact with each other by this mechanism. This interaction mechanism is studied *in vitro*, and clinical data are often not available, or the clinical relevance is unclear. Nevertheless, it is generally recommended that drugs inhibiting the intracellular activation of NRTIs are not used concurrently (e.g. 'doxorubicin and stavudine', (p.959), or 'zidovudine and stavudine', (p.950)). 'Hydroxycarbamide', (p.949), may increase the intracellular activation of NRTIs.

NRTIs are water soluble, and are mainly eliminated by the kidneys (didanosine, lamivudine, stavudine, and zalcitabine) or undergo hepatic glucuronidation (abacavir, zidovudine). The few important interactions with these drugs primarily involve altered renal clearance. For zidovudine (and possibly abacavir) some interactions are reported to occur via altered glucuronidation, but the clinical relevance of these are less clear (e.g. 'rifampicin (rifampin)', (p.942)). Cytochrome P450-mediated interactions are not important for this class of drugs.

Some of the didanosine preparations (e.g. chewable tablets) are formulated with antacid buffers that are intended to facilitate didanosine absorption by minimising acid-induced hydrolysis in the stomach. These preparations can therefore alter the absorption of other drugs that are affected by antacids (e.g. azole antifungals, quinolone antibacterials, tetracyclines). This interaction may be minimised by separating administration by at least 2 hours. Alternatively, the enteric-coated preparation of didanosine (gastro-resistant capsules) may be used.

(f) Protease inhibitors

The protease inhibitors are extensively metabolised by the cytochrome P450 isoenzyme system, particularly by CYP3A4. All of them inhibit CYP3A4, with ritonavir being the most potent inhibitor, followed by indinavir, nelfinavir, amprenavir, and saquinavir. The protease inhibitors therefore have the potential to interact with other drugs metabolised by CYP3A4, and are also affected by CYP3A4 inhibitors and inducers. Ritonavir and nelfinavir also affect some other cytochrome P450 isoenzymes, as summarised in 'Table 21.2', (p.914). Protease inhibitors therefore have the potential to interact with each other, and with NNRTIs, but are not likely to interact with NRTIs. In addition, protease inhibitors are substrates as well as inhibitors of P-glycoprotein.

The plasma level of protease inhibitors is thought to be critical in maintaining efficacy and minimising the potential for development of viral resistance. Therefore even modest reductions in levels are potentially clinically important.

Table 21.1 Classification of Antivirals

Group	*Drugs*
Antivirals for hepatitis viruses	
Nucleoside analogues	Entecavir, Lamivudine, Telbivudine
Nucleotide analogues	Adefovir, Tenofovir
Miscellaneous	Interferon alfa, Peginterferon alfa, Ribavirin
Antivirals for herpes viruses	
Guanine nucleoside analogues	Aciclovir, Famciclovir, Ganciclovir, Penciclovir, Valaciclovir, Valganciclovir
Other nucleoside analogues	Idoxuridine, Trifluridine, Vidarabine
Nucleotide analogues	Cidofovir, Fomivirsen
Miscellaneous	Foscarnet sodium, Inosine pranobex
Antivirals for HIV infection (antiretrovirals)	
CCR5 antagonists	Maraviroc
HIV-fusion inhibitors	Enfuvirtide
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	Delavirdine, Efavirenz, Etravirine, Nevirapine
Nucleoside reverse transcriptase inhibitors (NRTIs)	Abacavir, Didanosine, Emtricitabine, Lamivudine, Stavudine, Zalcitabine, Zidovudine
Nucleotide reverse transcriptase inhibitors	Tenofovir
Protease inhibitors	Amprenavir, Atazanavir, Darunavir, Fosamprenavir, Indinavir, Lopinavir, Nelfinavir, Ritonavir, Saquinavir, Tipranavir
Antivirals for influenza	
Neuraminidase inhibitors	Oseltamivir, Zanamivir
Others	Amantadine, Rimantadine

Table 21.2 Summary of the effect of the protease inhibitors and NNRTIs on cytochrome P450 isoenzymes

Antiviral	*Substrate*	*Inhibits*	*Induces*
Protease inhibitors			
Amprenavir or Fosamprenavir	CYP3A4	CYP3A4	
Atazanavir	CYP3A4	CYP3A4	
Darunavir	CYP3A4	CYP3A4	
Indinavir	CYP3A4	CYP3A4	
Lopinavir	CYP3A4	CYP3A4	
Nelfinavir	CYP3A4, CYP2C19, CYP2C9, CYP2D6	CYP3A4	
Ritonavir	CYP3A4, CYP2D6	CYP3A4, CYP2D6	CYP3A4
Saquinavir	CYP3A4	CYP3A4	
Tipranavir	CYP3A4	CYP3A4, CYP2D6	CYP3A4
NNRTIs (Non-nucleoside reverse transcriptase inhibitors)			
Delavirdine	CYP3A4, CYP2D6	CYP3A4, CYP2C9, CYP2D6, CYP2C19	
Efavirenz	CYP3A4, CYP2B6	CYP3A4, CYP2C9, CYP2C19	CYP3A4
Etravirine	CYP3A4, CYP2C9, CYP2C19	CYP2C9, CYP2C19	CYP3A4
Nevirapine	CYP3A4		CYP3A4

Antivirals active against influenza

The oral neuraminidase inhibitor oseltamivir is metabolised by esterases in the liver, and the carboxylate metabolites are then renally excreted. A clinically relevant interaction with other drugs that affect renal tubular excretion does not usually appear to occur, see 'Oseltamivir + Drugs that affect renal clearance', p.961. It is not metabolised by cytochrome P450 isoenzymes. Zanamivir, the inhaled influenza antiviral, is also not metabolised by the liver and is not protein bound, therefore it is not expected to be affected by any significant drug interactions.

1. Barry M, Mulcahy F, Merry C, Gibbons S, Back D. Pharmacokinetics and potential interactions amongst antiretroviral agents used to treat patients with HIV infection. *Clin Pharmacokinet* (1999) 36, 289–304.

2. de Maat MMR, Ekhart GC, Huitema ADR, Koks CHW, Mulder JW, Beijnen JH. Drug interactions between antiretroviral drugs and comedicated agents. *Clin Pharmacokinet* (2003) 42, 223–82.

Aciclovir and related drugs + Antacids

Valaciclovir does not interact with an aluminium/magnesium hydroxide antacid.

Clinical evidence, mechanism, importance and management

On three separate occasions, 18 healthy subjects were given a single 1-g oral dose of **valaciclovir**, either alone, 65 minutes before, or 30 minutes after they took 30 mL of *Maalox* (**aluminium**/**magnesium hydroxide**). The pharmacokinetics of aciclovir (the active metabolite of valaciclovir) remained unchanged. It was concluded that no special precautions are needed if these drugs are taken together, and the authors of the report also suggest that it is unlikely that other antacids will interact.[1]

1. de Bony F, Bidault R, Peck R, Posner J. Lack of interaction between valaciclovir, the L-valyl ester of acyclovir, and Maalox antacid. *J Antimicrob Chemother* (1996) 37, 383–7.

Aciclovir and related drugs + Cephalosporins

Retrospective data from children suggest that ceftriaxone might have increased the renal toxicity of intravenous aciclovir. Cefalexin does not appear to alter the absorption of valaciclovir to a clinically relevant extent.

Clinical evidence, mechanism, importance and management

(a) Cefalexin

In a single-dose, crossover study involving 16 healthy subjects, the concurrent use of cefalexin 500 mg and **valaciclovir** 500 mg caused only a minimal mean 7% reduction in the AUC of aciclovir (the metabolite of **valaciclovir**). However, this reduction was only seen if one subject who had an increase in aciclovir AUC was excluded from the analysis. Furthermore, there was considerable interindividual variability in the effects of cefalexin.

Both cefalexin and **valaciclovir** are substrates for human peptide transporter 1 (hPEPT1), and *in vitro* and *animal* data indicated that cefalexin might markedly reduce **valaciclovir** absorption.[1] However, the findings in this clinical study show a minimal interaction. No special precautions appear to be needed on concurrent use.

(b) Ceftriaxone

A retrospective analysis of 17 children who had received intravenous aciclovir and ceftriaxone for suspected meningo-encephalitis revealed that 12 children developed a significant increase in serum creatinine, and three of these developed acute renal failure. This rate of renal toxicity is higher than that seen with aciclovir alone, and was attributed to the concurrent use of ceftriaxone. The dose of aciclovir correlated with nephrotoxicity. The authors concluded that caution is required with the combination, and that renal function should be monitored if both drugs are needed.[2]

1. Phan DD, Chin-Hong P, Lin ET, Anderle P, Sadee W, Guglielmo BJ. Intra- and interindividual variabilities of valacyclovir oral bioavailability and effect of coadministration of an hPEPT1 inhibitor. *Antimicrob Agents Chemother* (2003) 47, 2351–3.
2. Vomiero G, Carpenter B, Robb I, Filler G. Combination of ceftriaxone and acyclovir - an underestimated nephrotoxic potential? *Pediatr Nephrol* (2002) 17, 633–7.

Aciclovir and related drugs + Cimetidine

Single-dose studies have found that cimetidine increases the AUC of aciclovir and valaciclovir. No clinically important interaction appears to occur if famciclovir is given with cimetidine.

Clinical evidence

(a) Aciclovir or Valaciclovir

Twelve healthy subjects were given a 1-g dose of valaciclovir alone or with cimetidine 800 mg, taken 10 hours and one hour earlier. The $AUC_{0\text{-}3}$ for the prodrug valaciclovir was increased by 73% by cimetidine, and the $AUC_{0\text{-}24}$ for the active metabolite of valaciclovir, aciclovir, was increased by 27%. The renal clearance of aciclovir was reduced by 22%, although the total urinary recovery of aciclovir was unchanged.[1]

(b) Famciclovir

In a study, 12 healthy subjects were given cimetidine 400 mg twice daily for 8 days with a single 500-mg dose of famciclovir, a prodrug for penciclovir, on the last day. The AUC of penciclovir was increased by about 18% by cimetidine, but there was no change in renal clearance.[2,3]

Mechanism

The increase in aciclovir AUC with cimetidine is attributable to a reduction in its renal excretion, probably due to competition for secretion by the kidney tubules.[1] When 'probenecid', (p.916), a competitor for renal tubular secretion, and cimetidine were both given the effects on aciclovir were greater than either drug alone.[1]

Importance and management

These interactions are established but, because aciclovir has such a wide therapeutic index,[4] the authors of the study suggest that its interaction with cimetidine is probably clinically unimportant.[1] It seems likely that no changes in the usual doses of aciclovir or valaciclovir will be needed in patients also taking cimetidine. However, the UK manufacturer states that caution is required with high doses of valaciclovir, and that alternatives to cimetidine could be considered in this situation.[4] No special precautions would seem necessary if cimetidine is used with famciclovir.

1. De Bony F, Tod M, Bidault R, On NT, Posner J, Rolan P. Multiple interactions of cimetidine and probenecid with valaciclovir and its metabolite acyclovir. *Antimicrob Agents Chemother* (2002) 46, 458–63.
2. Pratt SK, Fowles SE, Pierce DM, Prince WT. An investigation of the potential interaction between cimetidine and famciclovir in non-patient volunteers. *Br J Clin Pharmacol* (1991) 32, 656P–657P.
3. Daniels S, Schentag JJ. Drug interaction studies and safety of famciclovir in healthy volunteers: a review. *Antiviral Chem Chemother* (1993) 4 (Suppl 1), 57–64.
4. Valtrex (Valaciclovir). GlaxoSmithKline UK. UK Summary of product characteristics, August 2008.

Aciclovir + Cytarabine

High-dose cytarabine reduces the bioavailability of oral, but not intravenous, aciclovir.

Clinical evidence, mechanism, importance and management

In a study, 5 patients given high-dose intravenous cytarabine 1.5 g/m^2 twice daily for 6 days were given a single 800-mg dose of oral aciclovir or a single 250-mg/m^2 dose of intravenous aciclovir one or 2 days before the start of the course of cytarabine, and again on either day 14 or 15. Cytarabine did not affect the bioavailability of intravenous aciclovir. However, cytarabine reduced the maximum serum levels of oral aciclovir by 43% and the absolute bioavailability of aciclovir was reduced by 38%. The clinical importance of this reduction is not known.[1] Until more is known bear the possibility of this interaction in mind should a reduced response occur in a patient taking oral aciclovir and given a course of cytarabine.

1. Sitar DS, Aoki FY, Bow EJ. Acyclovir bioavailability in patients with acute myelogenous leukemia treated with daunorubicin and cytarabine. J Clin Pharm (2008) 48, 995–8.

Aciclovir and related drugs + Hydrochlorothiazide

Hydrochlorothiazide does not affect the pharmacokinetics or safety profile of valaciclovir.

Clinical evidence, mechanism, importance and management

A study in a group of elderly subjects (65 to 83 years old) given **valaciclovir** 500 mg or 1 g, three times daily for 8 days, found that its safety profile was unchanged in the presence of hydrochlorothiazide, and was similar to that in young healthy subjects.[1] The pharmacokinetics of the active metabolite of **valaciclovir**, aciclovir, were not significantly different.[1] There would seem to be no reason for avoiding the concurrent use of either **valaciclovir** or aciclovir and hydrochlorothiazide.

1. Wang LH, Schultz M, Weller S, Smiley ML, Blum MR. Pharmacokinetics and safety of multiple-dose valaciclovir in geriatric volunteers with and without concomitant diuretic therapy. *Antimicrob Agents Chemother* (1996) 40, 80–5.

Aciclovir and related drugs + Probenecid

Probenecid reduces the renal excretion and increases the plasma levels of aciclovir, valaciclovir, and ganciclovir. Famciclovir and valganciclovir are predicted to interact similarly.

Clinical evidence

(a) Aciclovir or Valaciclovir

Twelve healthy subjects were given valaciclovir 1 g alone, or with probenecid 1 g, taken 2 hours earlier. Probenecid increased the $AUC_{0\text{-}3}$ for the prodrug valaciclovir by 22%, and the $AUC_{0\text{-}24}$ for its active metabolite, aciclovir, by 48%. The renal clearance of aciclovir was reduced by 33%, although the total urinary recovery of aciclovir was unchanged. The authors report that both drugs were well tolerated.[1] An earlier study had found that oral probenecid 1 g caused a similar increase in the AUC of intravenous aciclovir.[2]

(b) Ganciclovir

In a pharmacokinetic study, 11 HIV-positive patients were given probenecid 500 mg every 6 hours with oral ganciclovir 1 g every 8 hours. The AUC of ganciclovir was increased by 53%, and the renal clearance was reduced by 19% (10 subjects only) in the presence of probenecid.[3]

Mechanism

The increases in the AUCs of aciclovir and ganciclovir are attributable to a reduction in their renal excretion by probenecid, probably due to competition for secretion by the kidney tubules.[1,3] The effects on aciclovir of combining probenecid and *cimetidine*, which also affects the renal excretion of aciclovir, were greater than either drug alone, consider 'Aciclovir and related drugs + Cimetidine', p.915.

Importance and management

Although the information is limited to the studies above, the modest pharmacokinetic interaction between probenecid and aciclovir, valaciclovir and ganciclovir appears to be established. However, because aciclovir has such a wide therapeutic index, a clinically important interaction is not expected and it seems unlikely that a dose adjustment of aciclovir or valaciclovir will be needed in patients taking probenecid. However, the UK manufacturer states that caution is required with high doses of valaciclovir, and that alternatives to probenecid could be considered in this situation.[4]

It may be prudent to be alert for increased ganciclovir adverse effects and toxicity (such as diarrhoea, nausea, neutropenia and thrombocytopenia) if probenecid is used concurrently. **Valganciclovir** is a prodrug of ganciclovir, and the manufacturers recommend that patients taking valganciclovir with probenecid should be closely monitored for ganciclovir toxicity.[5,6]

The manufacturers of **famciclovir** suggest that a similar interaction might also occur with probenecid, resulting in an increase in the plasma levels of penciclovir (the active metabolite of famciclovir).[7,8]

1. De Bony F, Tod M, Bidault R, On NT, Posner J, Rolan P. Multiple interactions of cimetidine and probenecid with valaciclovir and its metabolite acyclovir. *Antimicrob Agents Chemother* (2002) 46, 458–63.
2. Laskin OL, de Miranda P, King DH, Page DA, Longstreth JA, Rocco L, Lietman PS. Effects of probenecid on the pharmacokinetics and elimination of acyclovir in humans. *Antimicrob Agents Chemother* (1982) 21, 804–7.
3. Cimoch PJ, Lavelle J, Pollard R, Gaines Griffy K, Wong R, Tarnowski TL, Casserella S, Jung D. Pharmacokinetics of oral ganciclovir alone and in combination with zidovudine, didanosine, and probenecid in HIV-infected subjects. *J Acquir Immune Defic Syndr Hum Retrovirol* (1998) 17, 227–34.
4. Valtrex (Valaciclovir). GlaxoSmithKline UK. UK Summary of product characteristics, August 2008.
5. Valcyte (Valganciclovir hydrochloride). Roche Products Ltd. UK Summary of product characteristics, September 2007..
6. Valcyte (Valganciclovir hydrochloride). Roche Pharmaceuticals. US Prescribing information, August 2009
7. Famvir (Famciclovir). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, February 2009.
8. Famvir (Famciclovir). Novartis Pharmaceuticals Corp. US Prescribing information, December 2008.

Adefovir + Miscellaneous

No clinically significant interaction appears to occur between adefovir and co-trimoxazole, didanosine, ibuprofen, indinavir, lamivudine, or paracetamol. Adefovir appears to reduce delavirdine and saquinavir levels. No pharmacokinetic interaction occurs between tacrolimus and adefovir, however, additive nephrotoxicity may occur between adefovir and tacrolimus or ciclosporin. Drugs that affect renal function may theoretically reduce adefovir excretion.

Clinical evidence, mechanism, importance and management

(a) Antiretrovirals

In a population pharmacokinetic analysis, combination of **saquinavir** with adefovir appeared to result in a 49% increase in the clearance of saquinavir.[1] In a further pharmacokinetic study in 37 HIV-positive patients by the same group, **ritonavir-boosted saquinavir** was given with **delavirdine** or adefovir or both drugs, and **saquinavir** with **nelfinavir** was given with **delavirdine** or adefovir or both. The addition of adefovir to **ritonavir-boosted saquinavir** with delavirdine resulted in a 50% lower **saquinavir** concentration when compared to the regimen without adefovir. The concentration of **delavirdine** was reduced by about 50% in patients who also received adefovir. No difference in **delavirdine** concentrations occurred between the **ritonavir** and **nelfinavir**-containing regimens. The concentrations of **nelfinavir** and low-dose **ritonavir** were unchanged, and the AUC of adefovir was not significantly affected between the different treatment groups. The authors suggest that this reduction in **saquinavir** and **delavirdine** levels may possibly be due to induction of P-glycoprotein by adefovir. As this appears to have resulted in a reduced virological effect in the parent study (ACTG 359), the authors advise against the concurrent use of **delavirdine** and adefovir, and suggest that further study is needed.[2] It would be prudent to use similar caution if **ritonavir-boosted saquinavir** is given with adefovir until further information is available.

The US manufacturer reports that, in a study in 21 healthy subjects, there was no pharmacokinetic interaction between adefovir 10 mg once daily and enteric-coated **didanosine** 400 mg.[3] The concurrent use of adefovir 60 mg with **didanosine** buffered tablets increased the AUC of **didanosine** by 29%, which is not clinically relevant.[4] The manufacturers also note that, in a study in 18 subjects, there was no pharmacokinetic interaction between adefovir 10 mg once daily and **lamivudine** 100 mg daily.[3,4] See also *Lamivudine* and *Tenofovir*, below.

(b) Ciclosporin or Tacrolimus

In a study in 16 stable liver transplant patients taking tacrolimus 2 to 10 mg daily, adefovir 10 mg daily taken for 14 days had no significant effect on the pharmacokinetics of tacrolimus. Adefovir pharmacokinetics were also unaffected by tacrolimus, when compared with historical data. No significant changes in renal function were found during concurrent use in this short-term study.[5]

The UK manufacturer predicts that, as ciclosporin is metabolised by the same route as tacrolimus, a pharmacokinetic interaction between adefovir and ciclosporin is also unlikely. However, the US manufacturer states that the effect of adefovir on ciclosporin levels is unknown.[3] Both manufacturers[3,4] advise close monitoring if either tacrolimus or ciclosporin is given with adefovir as both drugs can cause nephrotoxicity, see below, *Drugs affecting renal function*.

(c) Drugs affecting renal function

The manufacturers advise caution with concurrent use of drugs that may affect renal function or cause nephrotoxicity and those that are renally excreted, as this may lead to an increase in adefovir levels. They specifically name intravenous **aminoglycosides**, **amphotericin B**, **ciclosporin**, **cidofovir**, **foscarnet**, **pentamidine**, **vancomycin**, and **tacrolimus**.[3,4] Note, however, that a study reported no pharmacokinetic interaction and no change in renal function with concurrent use of **tacrolimus** and adefovir, see above *(b) Ciclosporin or Tacrolimus*, above. The US manufacturers also list **NSAIDs**;[3] however, note that **ibuprofen** does not appear have a clinically relevant interaction with adefovir, see *Drugs undergoing, or affecting, tubular secretion*, below.

(d) Drugs undergoing, or affecting, tubular secretion

Adefovir is excreted by the kidneys, by a combination of glomerular filtration and active secretion via the renal transporter, human Organic Anion Transporter 1 (hOAT1). The potential for pharmacokinetic interactions with **cidofovir**, **co-trimoxazole**, **ibuprofen**, **lamivudine**, **paracetamol** and **tenofovir** (other drugs that also undergo, or may affect tubular secretion) has been investigated.[3,4]

1. Co-trimoxazole (Trimethoprim with Sulfamethoxazole). The manufacturers note that in a study in 18 healthy subjects, there was no pharmacokinetic interaction between adefovir 10 mg once daily and co-trimoxazole 960 mg twice daily.[3,4]

2. Ibuprofen. The concurrent use of adefovir 10 mg and ibuprofen 800 mg three times daily modestly increased the AUC and maximum level of adefovir by 23% and 33%, respectively. These changes were considered to be due to higher bioavailability rather than a reduction in renal clearance, and are not considered clinically relevant. Adefovir did not alter ibuprofen pharmacokinetics.[3,4] See also, *Drugs affecting renal function*, above.

3. Lamivudine. The manufacturers note that in a study in 18 healthy subjects, there was no pharmacokinetic interaction between adefovir 10 mg once daily and lamivudine 100 mg once daily.[3,4]

4. Paracetamol. The manufacturers note that in a study in 20 healthy subjects, there was no pharmacokinetic interaction between adefovir 10 mg once daily and paracetamol 1 g four times daily.[3,4]

5. Tenofovir. In a study in 24 healthy subjects there was no pharmacokinetic interaction between a single 10-mg dose of adefovir dipivoxil given alone and on day 7 of tenofovir disoproxil fumarate 300 mg daily for 7 days. In particular, renal clearances of both drugs were not changed on concurrent use.[6] However, the manufacturers advise against the concurrent use of adefovir with tenofovir.[3,4]

(e) Interferons

The US manufacturer reports that the pharmacokinetics of adefovir were unaffected by pegylated interferon alpha-2a. However, the results of a study to investigate the effects of a single 10-mg dose of adefovir on the pharmacokinetics of pegylated interferon alpha-2a 180 micrograms were inconclusive due to the high pharmacokinetic variability of pegylated interferon.[3] The UK manufacturer still advises caution with concurrent use, even though they state that the possibility of an interaction is small, as adefovir and pegylated interferons are excreted by different pathways.[4]

1. Fletcher CV, Jiang H, Brundage RC, Acosta EP, Haubrich R, Katzenstein D, Gulick RM. Sex-based differences in saquinavir pharmacology and virologic response in AIDS Clinical Trials Group Study 359. *J Infect Dis* (2004) 189, 1176–84.
2. Fletcher CV, Acosta EP, Cheng H, Haubrich R, Fischl M, Raasch R, Mills C, Hu XJ, Katzenstein D, Remmel RP, Gulick RM, for the ACTG 884 Protocol Team. *AIDS* (2000) 14, 2495–2501.
3. Hepsera (Adefovir dipivoxil). Gilead Sciences, Inc. US Prescribing information, October 2009.
4. Hepsera (Adefovir dipivoxil). Gilead Sciences Ltd. UK Summary of product characteristics, June 2009.
5. Terrault NA, Tran TT, Schiff E, McGuire BM, Brown RS, Tupper R, Ramanathan S, Enejosa J, Zhong L, Zong J, for the Study 531 team. Pharmacokinetics of tacrolimus co-administered with adefovir dipivoxil to liver transplant patients. Liver Int (2009) 29, 1178–83.
6. Kearney BP, Ramanathan S, Cheng AK, Ebrahimi R, Shah J. Systemic and renal pharmacokinetics of adefovir and tenofovir upon coadministration. *J Clin Pharmacol* (2005) 45, 935–40. Erratum. Ibid., 1206.

Cidofovir + Miscellaneous

Cidofovir with probenecid modestly decreased the levels of trimethoprim and sulfamethoxazole (co-trimoxazole), and caused moderate increases in didanosine levels, but did not alter fluconazole pharmacokinetics. None of these drugs altered cidofovir pharmacokinetics.

Clinical evidence

(a) Co-trimoxazole (Trimethoprim with Sulfamethoxazole)

In a study, 6 HIV-positive subjects were given co-trimoxazole 960 mg daily with a single 3-mg/kg dose of cidofovir with probenecid given on day 7. The AUC and maximum plasma concentrations of both trimethoprim and sulfamethoxazole were decreased by about 30% and renal clearance was significantly increased. The pharmacokinetics of cidofovir were not affected.[1]

(b) Didanosine

In a study, 6 HIV-positive subjects were given didanosine 100 or 200 mg twice daily for 7 days with a single 3-mg/kg dose of cidofovir with probenecid given on day 7. The AUC of didanosine was increased by 60%, but the pharmacokinetics of cidofovir were not affected.[1]

(c) Fluconazole

In a study, 6 HIV-positive subjects were given fluconazole 100 mg daily for 13 days with a single 3-mg/kg dose of cidofovir with probenecid given on day 13. The pharmacokinetics of both drugs were unaffected.[1]

Mechanism

It was suggested that cidofovir with probenecid might alter the renal elimination of these drugs.[1]

Importance and management

The modest decreases in trimethoprim and sulfamethoxazole levels, and moderate increases in didanosine levels caused by cidofovir with probenecid are considered unlikely to be clinically relevant because of the infrequent dosing schedule of cidofovir with probenecid. No dose adjustments are considered necessary.[1]

1. Luber A, Lalezari J, Rooney J, Jaffe H, Flaherty J. Drug-drug interaction study with intravenous cidofovir (CDV) and either trimethoprim/sulfamethoxazole (TMP/SMX), didanosine (DDI), or fluconazole (FLU) in HIV-infected individuals. *Intersci Conf Antimicrob Agents Chemother* (2002) 42, 27.

Cidofovir + Probenecid

Probenecid reduces the nephrotoxicity of cidofovir.

Clinical evidence, mechanism, importance and management

In a study 24 HIV-positive patients with cytomegalovirus retinitis were given either a single, oral 2-g dose of probenecid, taken one hour before intravenous cidofovir 5 mg/kg, or the standard licensed regimen of oral probenecid 2 g taken 3 hours before the same dose of cidofovir, with a 1 g dose of probenecid taken at 2 and 8 hours after cidofovir administration. No significant difference in the pharmacokinetics of cidofovir or in the adverse effects of probenecid was reported between the two regimens, and no increase in renal toxicity was seen in the patients given the lower probenecid dose.[1]

Probenecid inhibits the renal tubular secretion of cidofovir, and this reduction in the renal elimination of cidofovir reduces the incidence of nephrotoxicity.[1,2] The study[1] suggests that the reduced-dose probenecid regimen may also be beneficial and clinically important in reducing cidofovir nephrotoxicity. However, the authors recommend that further study using the single-dose regimen is needed, particularly with longer treatment courses and in patients with pre-existing renal impairment.[1]

Note that it is recommended that probenecid should always be used concurrently with cidofovir;[3,4] when using probenecid with cidofovir the interactions of probenecid should be considered.

1. Wolf DL, Rodríguez CA, Mucci M, Ingrosso A, Duncan BA, Nickens DJ. Pharmacokinetics and renal effects of cidofovir with a reduced dose of probenecid in HIV-infected patients with cytomegalovirus retinitis. *J Clin Pharmacol* (2003) 43, 43–51.
2. Cundy KC, Petty BG, Flaherty J, Fisher PE, Polis MA, Wachsman M, Lietman PS, Lalezari JP, Hitchcock MJM, Jaffe HS. Clinical pharmacokinetics of cidofovir in human immunodeficiency virus-infected patients. *Antimicrob Agents Chemother* (1995) 39, 1247–52.
3. Vistide (Cidofovir). Gilead Sciences Ltd. UK Summary of product characteristics, October 2009.
4. Vistide (Cidofovir). Gilead Sciences, Inc. US Prescribing information, September 2000.

Enfuvirtide + Cytochrome P450 substrates

Enfuvirtide does not affect the metabolism of dapsone or debrisoquine, and has no clinically significant effect on the metabolism of caffeine, chlorzoxazone, or mephenytoin.

Clinical evidence, mechanism, importance and management

A single oral dose of five drugs (**caffeine** 100 mg, **chlorzoxazone** 250 mg, **dapsone** 100 mg, **debrisoquine** 10 mg and **mephenytoin** 100 mg) was given to 12 HIV-positive subjects, before, and after they were given subcutaneous enfuvirtide 90 mg twice daily for 6 days. Enfuvirtide had no effect on the urinary **dapsone** recovery ratio (a measure of the activity of the cytochrome P450 isoenzyme CYP3A4), plasma monoacetyldapsone-to-**dapsone** ratio (a measure of *N*-acetyltransferase (NAT) activity) or urinary **debrisoquine** recovery ratio (a measure of CYP2D6 activity). Enfuvirtide had little effect (less than 30% change) on the plasma paraxanthine-to-**caffeine** ratio (a measure of CYP1A2 activity), the plasma 6-hydroxychlorzoxazone-to-**chlorzoxazone** ratio (a measure of CYP2E1 activity) and urinary recovery of 4-hydroxy**mephenytoin** (a measure of CYP2C19 activity). Subjects in this study were taking up to three NRTIs in stable doses, and were not taking any NNRTIs or protease inhibitors.[1]

This type of study is being increasingly used to assess the potential for

new drugs to cause clinically important cytochrome P450-mediated drug interactions. The results indicate that enfuvirtide is unlikely to cause clinically important changes in the pharmacokinetics of drugs metabolised by CYP3A4, NAT and CYP2D6. They also give some reassurance that drugs metabolised by CYP1A2, CYP2E1 and CYP2C19 are unlikely to be significantly affected. No substrate for CYP2C9 was included in this study, but enfuvirtide does not affect CYP2C9 *in vitro*.[1]

1. Zhang X, Lalezari JP, Badley AD, Dorr A, Kolis SJ, Kinchelow T, Patel IH. Assessment of drug-drug interaction potential of enfuvirtide in human immunodeficiency virus type 1–infected patients. *Clin Pharmacol Ther* (2004) 75, 558–68.

Enfuvirtide + Protease inhibitors

Ritonavir and ritonavir-boosted saquinavir slightly increase enfuvirtide exposure. Enfuvirtide appears to slightly increase the trough levels of ritonavir-boosted lopinavir. Enfuvirtide appears to moderately increase ritonavir-boosted tipranavir trough levels, and, although a case of hepatotoxicity has been reported, the overall incidence of hepatotoxicity does not appear to be increased with concurrent use.

Clinical evidence, mechanism, importance and management

(a) Lopinavir with ritonavir

In a sub-analysis of the RESIST study data, the mean lopinavir trough values in 60 patients taking ritonavir-boosted lopinavir with enfuvirtide were only slightly raised by 19%, when compared to 240 patients taking ritonavir-boosted lopinavir without enfuvirtide.[1] This minor increase in lopinavir levels would not be expected to be clinically relevant. Therefore, no ritonavir-boosted lopinavir dose adjustment appears to be needed when it is taken with enfuvirtide.

(b) Ritonavir and Saquinavir with ritonavir

In a study in 24 HIV-positive patients, subcutaneous enfuvirtide 90 mg twice daily was given for 7 days with either ritonavir 200 mg twice daily or ritonavir-boosted saquinavir 100 mg/1 g twice daily given for the last 4 days. Ritonavir caused a minor 24% increase in the AUC of enfuvirtide, and ritonavir-boosted saquinavir caused a 14% increase in the AUC of enfuvirtide. Such small increases in enfuvirtide exposure are not clinically relevant. Therefore, no special precautions appear to be needed during the concurrent use of either ritonavir 200 mg twice daily or ritonavir-boosted saquinavir with enfuvirtide.[2]

(c) Tipranavir with ritonavir

In a study in 55 HIV-positive patients, the mean trough level of ritonavir-boosted tipranavir was reported to be increased by about 50% in patients also given subcutaneous enfuvirtide 90 mg twice daily. Similarly, the mean trough level of ritonavir was nearly doubled in those patients given enfuvirtide. Two subjects who stopped enfuvirtide had a subsequent decrease in their tipranavir trough levels by about 25% and 50%, respectively, and a patient who started enfuvirtide while taking tipranavir had an increase in tipranavir trough levels of about 72%.[3] A patient who had been taking zidovudine 300 mg twice daily, lamivudine 150 mg twice daily and subcutaneous enfuvirtide 90 mg twice daily for 12 months, developed hepatotoxicity 2 weeks after starting ritonavir-boosted tipranavir 200/500 mg twice daily. When enfuvirtide was stopped for 6 weeks, the patient's liver enzyme levels decreased by 50%. However, when enfuvirtide was restarted, the liver enzymes began to rise again, so ritonavir-boosted tipranavir was stopped, and the increase in the liver enzymes resolved. An increase in tipranavir levels caused by enfuvirtide was thought to have led to hepatotoxicity, although no drug levels were measured.[4] The mechanism for this increase in tipranavir levels with enfuvirtide is unknown, as enfuvirtide has no significant effects on cytochrome P450 isoenzymes, the main metabolic route for both tipranavir and ritonavir. However, subsequent data from a sub-study of the RESIST study reported that despite the increases in tipranavir trough levels seen in patients given ritonavir-boosted tipranavir with enfuvirtide (a median increase in tipranavir trough levels of 31%), no additional increase in the incidence of hepatotoxicity occurred.[1]

This suggests that, in most patients, the increase in tipranavir trough levels with concurrent enfuvirtide is unlikely to lead to serious adverse effects. However, due to reports of hepatotoxicity with ritonavir-boosted tipranavir alone, routine close monitoring of liver function is recommended.

1. Raffi F, Battegay M, Rusconi S, Opravil M, Blick G, Steigbigel RT, Kraft M, Neubacher D, Sabo JP. Combined tipranavir and enfuvirtide use associated with higher plasma tipranavir concentrations but not with increased hepatotoxicity: sub-analysis from RESIST. *AIDS* (2007) 21, 1977–80.
2. Ruxrungtham K, Boyd M, Bellibas SE, Zhang X, Dorr A, Kolis S, Kinchelow T, Buss N, Patel IH. Lack of interaction between enfuvirtide and ritonavir or ritonavir-boosted saquinavir in HIV-1-infected patients. *J Clin Pharmacol* (2004) 44, 793–802.
3. González de Requena D, Calcagno A, Bonora S, Ladetto L, D'Avolio A, Sciandra M, Siccardi M, Bargiacchi O, Sinicco A, Di Perri G. Unexpected drug-drug interaction between tipranavir/ritonavir and enfuvirtide. *AIDS* (2006) 20, 1977–9.
4. Jülg B, Bogner JR, Goebel FD. Severe hepatotoxicity associated with the combination of enfuvirtide and tipranavir/ritonavir: case report. *AIDS* (2006) 20, 1563.

Enfuvirtide + Rifampicin (Rifampin)

Rifampicin does not affect the pharmacokinetics of enfuvirtide.

Clinical evidence, mechanism, importance and management

Subcutaneous enfuvirtide 90 mg twice daily for 3 days was given to 12 HIV-positive subjects before, and during the last 3 days, of a 10-day course of rifampicin 600 mg daily. The AUC of enfuvirtide and its metabolite were not significantly altered by rifampicin.[1]

Enfuvirtide is a peptide and would not be expected to be affected by enzyme inducers such as rifampicin. The findings of this study support this. Therefore no dose adjustments of enfuvirtide are required when it is given with rifampicin.

1. Boyd MA, Zhang X, Dorr A, Ruxrungtham K, Kolis S, Nieforth K, Kinchelow T, Buss N, Patel IH. Lack of enzyme-inducing effect of rifampicin on the pharmacokinetics of enfuvirtide. *J Clin Pharmacol* (2003) 43, 1382–91.

Entecavir + Miscellaneous

No pharmacokinetic interaction appears to occur between entecavir and adefovir, lamivudine or tenofovir. However, interactions with other renally excreted drugs cannot be excluded. No interactions mediated by cytochrome P450 isoenzymes are expected with entecavir.

Clinical evidence, mechanism, importance and management

(a) Renally excreted drugs

A study in 22 healthy subjects given entecavir 1 mg daily, and/or **adefovir** 10 mg daily found no pharmacokinetic interaction and concurrent use was well tolerated.[1] The manufacturers note that there was no pharmacokinetic interaction between entecavir and **lamivudine**, **adefovir** or **tenofovir** at steady state.[2,3]

As entecavir is predominantly eliminated by the kidney, the concurrent use of drugs that reduce renal function or compete for active renal tubular secretion may increase the serum concentrations of either entecavir or the concurrent drug. However, the manufacturers say that, apart from the drugs listed above, the effects of the concurrent use of entecavir with drugs that are either excreted renally or affect renal function have not been evaluated, and they therefore recommend that patients should be monitored closely for adverse reactions when entecavir is given.[2,3]

(b) Cytochrome P450-mediated interactions

The manufacturers say that entecavir is not a substrate, an inducer or an inhibitor of cytochrome P450 isoenzymes. Therefore drug interactions are unlikely to occur with entecavir by this mechanism.[2,3]

1. Bifano M, Yan J-H, Smith RA, Zhang D, Grasela DM, LaCreta F. Absence of a pharmacokinetic interaction between entecavir and adefovir.*J Clin Pharmacol* (2007) 47, 1327–34.
2. Baraclude (Entecavir). Bristol-Myers Squibb Pharmaceuticals Ltd. UK Summary of product characteristics, August 2009.
3. Baraclude (Entecavir). Bristol-Myers Squibb Company. US Prescribing information, July 2009.

Famciclovir + Miscellaneous

No clinically important pharmacokinetic interactions appear to occur when famciclovir is given with allopurinol, digoxin or theo-

phylline. Raloxifene is predicted to inhibit the metabolism of famciclovir to penciclovir.

Clinical evidence, mechanism, importance and management

When 12 healthy subjects were given famciclovir 500 mg after taking **allopurinol** 300 mg daily for 5 days there were no clinically relevant changes in the pharmacokinetics of either drug.[1] It was concluded that xanthine oxidase does not play an important role in the metabolism of famciclovir to penciclovir.[1,2]

Similarly, in studies in healthy subjects given famciclovir, **theophylline**[3] and **digoxin**[4] had no clinically significant effect on the pharmacokinetics of famciclovir. The pharmacokinetics of **theophylline** and **digoxin** were also unaffected by famciclovir.[4,5] Therefore, no dose adjustments would seem to be necessary if any of these drugs are given with famciclovir.

Famciclovir is converted to its active drug, penciclovir, by aldehyde oxidase. An *in vitro* study[6] reported that **raloxifene** is a potent aldehyde oxidase inhibitor, and the manufacturer of famciclovir predicts that raloxifene may affect the metabolic activation of famciclovir.[7] However, other *in vitro* inhibitors of aldehyde oxidase, such as cimetidine, do not appear to interact with famciclovir to a clinically relevant extent, see 'Aciclovir and related drugs + Cimetidine', p.915, and there appear to be no published reports of an interaction in clinical practice.

1. Fowles SE, Pratt SK, Laroche J, Prince WT. Lack of a pharmacokinetic interaction between oral famciclovir and allopurinol in healthy volunteers. *Eur J Clin Pharmacol* (1994) 46, 355–9.
2. Daniels S, Schentag JJ. Drug interaction studies and safety of famciclovir in healthy volunteers: a review. *Antiviral Chem Chemother* (1993) 4 (Suppl 1), 57–64.
3. Fairless AJ, Pratt SK, Pue MA, Fowles SE, Wolf D, Daniels S, Prince WT. An investigation into the potential interaction between theophylline and oral famciclovir in healthy male volunteers. *Br J Clin Pharmacol* (1992) 34, 171P–172P.
4. Pue MA, Saporito M, Laroche J, Lua S, Bygate E, Daniels S, Broom C. An investigation of the potential interaction between digoxin and oral famciclovir in healthy male volunteers. *Br J Clin Pharmacol* (1993) 36, 177P.
5. Siederer S, Scott S, Fowles S, Haveresch L, Hust R. Lack of interaction between steady-state digoxin and famciclovir. *Intersci Conf Antimicrob Agents Chemother* (1996) 36, A33.
6. Obach RS. Potent inhibition of human liver aldehyde oxidase by raloxifene. *Drug Metab Dispos* (2004) 32, 89–97.
7. Famvir (Famciclovir). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, February 2009.

Foscarnet + NRTIs

No pharmacokinetic interactions occur between foscarnet and didanosine, zalcitabine or zidovudine.

Clinical evidence, mechanism, importance and management

(a) Didanosine

In a three-phase study, 12 HIV-positive patients were given 4 doses of intravenous foscarnet 90 mg/kg, 4 doses of oral didanosine 200 mg, and 4 doses of both drugs together. Based on the data obtained from these patients (drug clearance, volume of distribution, half-life, mean residence time), no pharmacokinetic interactions were said to occur between these two drugs. This suggests that no dose adjustments will be needed during concurrent use.[1] The antiretroviral effects of foscarnet and didanosine were synergistic.[2]

(b) Stavudine

Foscarnet does not affect stavudine intracellular activation.[3]

(c) Zalcitabine

Intravenous foscarnet 90 mg/kg every 12 hours and oral zalcitabine 750 micrograms every 8 hours were given to 12 HIV-positive subjects for 2 days. There were no clinically significant alterations in the pharmacokinetics of either drug.[4] However, the manufacturers of zalcitabine[5,6] suggested that the concurrent use of zalcitabine and foscarnet should be well monitored, because foscarnet may possibly decrease the renal clearance of the zalcitabine, thereby increasing its serum levels and its toxicity, particularly peripheral neuropathy. The antiretroviral effects of foscarnet and zalcitabine were synergistic.[2]

(d) Zidovudine

The antiviral effects of foscarnet and zidovudine appear to be additive or synergistic. No significant alteration in the pharmacokinetics of either drug was seen in a 14-day study in 5 patients with AIDS given both drugs.[7] Foscarnet does not appear to affect zidovudine intracellular activation,[8] and the manufacturer notes that there was no evidence of increased myelotoxicity when foscarnet was used with zidovudine.[9] No special precautions are required on concurrent use.

1. Aweeka FT, Mathur V, Dorsey R, Jacobson MA, Martin-Munley S, Pirrung D, Franco J, Lizak P, Johnson J, Gambertoglio J. Concomitant foscarnet and didanosine; a pharmacokinetic (PK) evaluation in patients with HIV disease. American Society of Microbiology 2nd National Conference on Human Retroviruses and Related infections, Washington DC, 1995. Abstract 492.
2. Palmer S, Harmenberg J, Cox S. Synergistic inhibition of human immunodeficiency virus isolates (including 3'-azido-3'-deoxythymidine-resistant isolates) by foscarnet in combination with 2',3'-dideoxyinosine or 2',3'-dideoxycytidine. *Antimicrob Agents Chemother* (1996) 40, 1285–8.
3. Hoggard PG, Kewn S, Barry MG, Khoo SH, Back DJ. Effects of drugs on 2',3'-dideoxy-2',3'-didehydrothymidine phosphorylation in vitro. *Antimicrob Agents Chemother* (1997) 41, 1231–6.
4. Aweeka FT, Brody SR, Jacobson M, Botwin K, Martin-Munley S. Is there a pharmacokinetic interaction between foscarnet and zalcitabine during concomitant administration? *Clin Ther* (1998) 20, 232–43.
5. Hivid (Zalcitabine). Roche Products Ltd. UK Summary of product characteristics, November 2004.
6. Hivid (Zalcitabine). Roche Pharmaceuticals. US Prescribing information, September 2002.
7. Aweeka FT, Gambertoglio JG, van der Horst C, Raasch R, Jacobson MA. Pharmacokinetics of concomitantly administered foscarnet and zidovudine for treatment of human immunodeficiency virus infection (AIDS clinical trials group protocol 053). *Antimicrob Agents Chemother* (1992) 36, 1773–8.
8. Brody SR, Aweeka FT. Pharmacokinetics of intracellular zidovudine and its phosphorylated anabolites in the absence and presence of other antiviral agents using an in vitro human PBMC model. *Clin Pharmacol Ther* (1997) 61, 149.
9. Foscavir (Foscarnet trisodium hexahydrate). AstraZeneca UK Ltd. UK Summary of product characteristics, May 2007.

Foscarnet + Pentamidine

Marked hypocalcaemia, including one fatality, has been reported in four patients given foscarnet with intravenous pentamidine. Additive renal impairment may also occur on concurrent use.

Clinical evidence, mechanism, importance and management

Four patients with suspected AIDS-related cytomegaloviral chest infections developed signs of hypocalcaemia within 10 days of starting treatment with foscarnet and intravenous pentamidine (doses not stated). All 4 had paraesthesia of the hands and feet, and 3 of them had Chvostek's and Trousseau's signs (signs of tetany). The serum calcium levels of 3 of them fell but normalised when one of the drugs was stopped. The fourth patient had severe hypocalcaemia of 1.42 mmol/L and died.[1]

Both drugs have been associated with hypocalcaemia in HIV-positive patients, and in these 4 patients their effects appear to have been additive. The manufacturer of foscarnet also reports that renal impairment has also been reported on the concurrent use of intravenous pentamidine.[2] Therefore close monitoring of calcium levels and renal function is advised if foscarnet is used with parenteral pentamidine.

1. Youle MS, Clarbour J, Gazzard B, Chanas A. Severe hypocalcaemia in AIDS patients treated with foscarnet and pentamidine. *Lancet* (1988) 1, 1455–6.
2. Foscavir (Foscarnet trisodium hexahydrate). AstraZeneca UK Ltd. UK Summary of product characteristics, May 2007.

Foscarnet + Probenecid

Probenecid does not alter the pharmacokinetics of foscarnet.

Clinical evidence, mechanism, importance and management

A study in 10 HIV-positive patients found that probenecid 1 g twice daily for 3 days had no effect on the pharmacokinetics of foscarnet 90 mg/kg given intravenously over 2 hours. The authors conclude that, because of the lack of interaction with probenecid, almost all of the renal elimination of foscarnet is by glomerular filtration, with only a minimal contribution of active tubular secretion.[1] No special precautions seem to be necessary if both drugs are given.

1. Noormohamed FH, Youle MS, Higgs CJ, Gazzard BG, Lant AF. Renal excretion and pharmacokinetics of foscarnet in HIV sero-positive patients: effect of probenecid pretreatment. *Br J Clin Pharmacol* (1997) 43, 112–15.

Foscarnet + Quinolones

Two patients developed tonic-clonic seizures when they were given foscarnet with ciprofloxacin.

Clinical evidence

An HIV-positive patient taking multiple drugs (including ciprofloxacin 750 mg twice daily, clarithromycin, cimetidine, fluconazole, morphine, rifampicin (rifampin) and vancomycin) was also given intravenous foscarnet 60 mg/kg every 8 hours for a cytomegalovirus infection. He was only given half of the first dose, but 9 hours later he developed a tonic-clonic seizure. On completing the infusion of the first dose he again experienced similar seizure activity. About 45 minutes after the start of the second foscarnet dose, he had a third grand mal seizure. No further seizures occurred when the foscarnet was stopped.[1] Another HIV-positive patient was given foscarnet 60 mg/kg every 8 hours for 10 days without problem, until he started ciprofloxacin 750 mg twice daily, clofazimine, ethambutol, pyrazinamide and rifampicin for mycobacterial sepsis. Within 2 days, a few minutes after the start of the foscarnet infusion, he developed a seizure. This resolved when the foscarnet was stopped, and recurred when the foscarnet was restarted.[1]

Mechanism

Both foscarnet and ciprofloxacin have the potential to cause seizures and it seems that some enhancement of this activity occurs if they are used in combination. Subsequent study in *mice* has shown that the combination of ciprofloxacin and foscarnet does increase the likelihood of seizures, and that the interaction is likely to be due to altered GABA-receptor binding. An interaction was not found for **enoxacin** and foscarnet.[2]

Importance and management

Direct information seems to be limited to these two cases. It is impossible to know for certain if the seizures were due to the combined effects of these two drugs or not, but the evidence seems to point in that direction. The general importance of this interaction is uncertain, but it would seem prudent to monitor very closely if these drugs are used together.

1. Fan-Havard P, Sanchorawala V, Oh J, Moser EM, Smith SP. Concurrent use of foscarnet and ciprofloxacin may increase the propensity for seizures. *Ann Pharmacother* (1994) 28, 869–72.
2. Matsuo H, Ryu M, Nagata A, Uchida T, Kawakami J-I, Yamamoto K, Iga T, Sawada Y. Neurotoxicodynamics of the interaction between ciprofloxacin and foscarnet in mice. *Antimicrob Agents Chemother* (1998) 42, 691–4.

Ganciclovir or Valganciclovir + Imipenem

Based on an early possible report,[1] the manufacturer notes that generalised seizures have been reported in patients who received ganciclovir and imipenem with cilastatin. They recommend that ganciclovir and its prodrug, valganciclovir, should not be used with imipenem unless the benefits outweigh the risks.[2-4] No further reports of this interaction appear to have been published, or reported to the manufacturer.[1] Note that both ganciclovir and imipenem alone may cause seizures.

1. Roche Products Ltd. Personal communication, March 2007.
2. Cymevene IV (Ganciclovir sodium). Roche Products Ltd. UK Summary of product characteristics, February 2006.
3. Valcyte (Valganciclovir hydrochloride). Roche Products Ltd. UK Summary of product characteristics, September 2007.
4. Cytovene-IV (Ganciclovir sodium). Roche Laboratories, Inc. US Prescribing information, August 2008.

Ganciclovir + Trimethoprim

No clinically relevant pharmacokinetic interaction occurs between ganciclovir and trimethoprim. However, there may be an increased risk of myelosuppression on concurrent use.

Clinical evidence, mechanism, importance and management

In a study in 12 HIV-positive subjects, trimethoprim 200 mg daily for 7 days reduced the clearance of ganciclovir 1 g every 8 hours by 13%, and increased its half-life by 18%. The trimethoprim minimum plasma concentration was raised by 13% by ganciclovir. The combination was well tolerated and none of these changes were considered clinically significant, so no dose alteration appears necessary on concurrent use.[1] However, both ganciclovir and trimethoprim are known to be myelosuppressive,[2] and the manufacturer of ganciclovir and its prodrug, **valganciclovir**, notes that there is the possibility that the risk of this toxicity may be increased when they are used together. Therefore, they recommend that the combination should only be used if the benefits outweigh the risks of treatment.[3-5] Full blood counts should be closely monitored if concurrent use is necessary.

1. Jung D, AbdelHameed MH, Hunter J, Teitelbaum P, Dorr A, Griffy K. The pharmacokinetics and safety profile of oral ganciclovir in combination with trimethoprim in HIV- and CMV-seropositive patients. *Br J Clin Pharmacol* (1999) 47, 255–9.
2. Meynard J-L, Guiguet M, Arsac S, Frottier J, Meyohas M-C. Frequency and risk factors of infectious complications in neutropenic patients infected with HIV. *AIDS* (1997) 11, 995–8.
3. Cymevene IV (Ganciclovir sodium). Roche Products Ltd. UK Summary of product characteristics, February 2006.
4. Valcyte (Valganciclovir hydrochloride). Roche Products Ltd. UK Summary of product characteristics, September 2007.
5. Cytovene-IV (Ganciclovir sodium). Roche Laboratories, Inc. US Prescribing information, August 2008.

Idoxuridine + Miscellaneous

The topical solution of idoxuridine, *Herpid*, contains the solvent dimethyl sulfoxide as an absorption enhancer. This can increase the absorption of many substances, and therefore no other topical medications should be used concurrently on the same areas as *Herpid*.[1]

1. Herpid (Idoxuridine). Astellas Pharma Ltd. UK Summary of product characteristics, January 2008.

Influenza vaccines + Paracetamol (Acetaminophen)

Paracetamol does not affect antibody production in response to influenza vaccination, and may possibly reduce the adverse effects of influenza vaccination. The pharmacokinetics of paracetamol do not appear to be affected by influenza vaccination.

Clinical evidence, mechanism, importance and management

In a study in healthy subjects, the pharmacokinetics of a single 650-mg dose of intravenous paracetamol were unaffected when it was given 7 and 21 days after 0.5 mL of trivalent influenza vaccine given intramuscularly.[1] Paracetamol 1 g four times daily for 2 days had no effect on the production of influenza virus antibodies in a group of 39 elderly patients given an inactivated influenza virus vaccine, and paracetamol appeared to reduce the adverse effects of the vaccine (e.g. fever), although this was not statistically significant.[2]

In a placebo-controlled study, 262 healthy subjects were given a single 0.5-mL intramuscular dose of inactivated, trivalent, whole-virus influenza vaccine with paracetamol 325 mg or 650 mg given at the same time as the influenza vaccine and then every 4 hours for a total of 4 doses. The incidence of sore arm at the vaccination site was reduced by 25% and 28% in the subjects given the lower and higher dose of paracetamol, respectively. The concurrent use of paracetamol also reduced the incidence of vaccine-related nausea by 20% and 90% in those subjects given the lower and higher dose of paracetamol, respectively. However, paracetamol had no statistically significant effect on other vaccine-related adverse effects such as fever, headache and muscle pain. Paracetamol did not appear to affect the antibody response to the vaccine, as no difference in the haemagglutination inhibition antibody was reported between the placebo and paracetamol groups.[3]

From the limited data available, no special precautions appear to be necessary on the concurrent use of paracetamol and influenza vaccine.

1. Scavone JM, Blyden GT, Greenblatt DJ. Lack of effect of influenza vaccine on the pharmacokinetics of antipyrine, alprazolam, paracetamol (acetaminophen) and lorazepam. *Clin Pharmacokinet* (1989) 16, 180–5.
2. Gross PA, Levandowski RA, Russo C, Weksler M, Bonelli J, Dran S, Munk G, Deichmiller S, Hilsen R, Panush RF. Vaccine immune response and side effects with the use of acetaminophen with influenza vaccine. *Clin Diagn Lab Immunol* (1994) 1, 134–8.
3. Aoki FY, Yassi A, Cheang M, Math M, Murdzak C, Hammond GW, Sekla LH, Wright B. Effects of acetaminophen on adverse effects of influenza vaccination in health care workers. *Can Med Assoc J* (1993) 149, 1425–30.

Influenza vaccine; Live + Antivirals active against influenza

The manufacturers advise that antivirals active against influenza such as oseltamivir, rimantadine and zanamivir should not be given until 2 weeks after the administration of *live* influenza virus vaccines, and that these vaccines should not be given until 48 hours after stopping the antiviral.[1-4] This is because of the theoretical concern that these antiviral drugs will inhibit replication of live vaccine virus, and therefore reduce its effect. Note that most influenza vaccines are inactivated (split virion or surface antigen), and that these would not be expected to be affected by antivirals active against influenza.

1. FluMist (Influenza virus vaccine live, intranasal). MedImmune Vaccines, Inc. US Prescribing information, June 2009.
2. Tamiflu (Oseltamivir phosphate). Roche Pharmaceuticals. US Prescribing information, August 2008.
3. Flumadine (Rimantadine hydrochloride). Forest Pharmaceuticals, Inc. US Prescribing information, April 2007.
4. Relenza (Zanamivir). GlaxoSmithKline. US Prescribing information, September 2009.

Influenza vaccine; Live + Aspirin

The manufacturer advises that *live* influenza vaccines should not be given to children or adolescents who are given aspirin. This possible interaction is linked to the association of Reye's syndrome with aspirin and wild-type influenza infection. Concurrent use is contraindicated.[1]

1. FluMist (Influenza virus vaccine live, intranasal). MedImmune Vaccines, Inc. US Prescribing information, June 2009.

Interferons + ACE inhibitors

A case series suggests that severe granulocytopenia can develop if ACE inhibitors and interferon are given concurrently.

Clinical evidence

Patients with cryoglobulinaemia were treated with 3 million units of recombinant **interferon alfa-2a** (35 patients) or natural **interferon beta** (3 patients), usually given daily for 3 months, then on alternate days for periods of 6 to 17 months. Severe toxicity developed in 3 patients, who were the only ones amongst the group to also be taking ACE inhibitors. Granulocytopenia developed in 2 patients within a few days of starting **enalapril** 10 mg daily or **captopril** 50 mg daily, and subsided 1 to 2 weeks after both drugs were stopped. Another patient, already taking **enalapril** 5 mg daily, developed severe granulocytopenia when interferon was started, and again when re-challenged with both drugs. None of the other 35 patients receiving interferon alone developed any significant haematological problems. The reasons for this severe reaction are not understood but the authors of the report suggest that it may be an autoimmune response.[1]

A follow-up letter commenting on this report described 2 further patients with hepatitis C infection, cryoglobulinaemia and glomerulonephritis, who took **captopril** 75 mg or **enalapril** 20 mg daily for several weeks, and who had granulocytopenia within 9 days of being given 3 million units of recombinant **interferon alfa-2a**, daily or on alternate days. However, this resolved without any change in treatment. Another patient with multiple myeloma given **interferon alfa-2a** 3 million units three times weekly and long-term **benazepril** 10 mg daily had a normal granulocyte count after 3 months.[2]

Mechanism

Interferons alone are associated with myelosuppression, particularly granulocytopenia. ACE inhibitors have, rarely, caused neutropenia and agranulocytosis.

Importance and management

These two reports appear to be the only information suggesting an interaction. Regular full blood counts are generally recommended when interferons are used, and therefore, no extra precautions would appear to be required if ACE inhibitors are also given.

1. Casato M, Pucillo LP, Leoni M, di Lullo L, Gabrielli A, Sansonno D, Dammacco F, Danieli G, Bonomo L. Granulocytopenia after combined therapy with interferon and angiotensin-converting enzyme inhibitors: evidence for a synergistic hematologic toxicity. *Am J Med* (1995) 99, 386–91.
2. Jacquot C, Caudwell V, Belenfant X. Granulocytopenia after combined therapy with interferon and angiotensin-converting enzyme inhibitors: evidence for a synergistic hematologic toxicity. *Am J Med* (1996) 101, 235–6.

Interferons + Miscellaneous

Prednisone and paracetamol have disparate effects on some measures of the antiviral activity of interferon, but the clinical relevance of this is unclear. Isolated cases of acute hepatitis have been seen when interferon was given with paracetamol.

Clinical evidence, mechanism, importance and management

(a) Aspirin or Paracetamol

Single intramuscular doses of recombinant human **interferon alfa-2a** 18 million units were given to groups of 8 healthy subjects alone, or after 24 hours after starting either aspirin 650 mg every 4 hours or paracetamol 650 mg every 4 hours for a total of 8 days. Neither aspirin nor paracetamol reduced the interferon adverse effects of fever, chills, headache, or myalgia.[1] In a later similar study by the same research group, the effect of the same drugs and doses (started 3 days before the interferon) was evaluated with a lower dose of **interferon alfa-2a** (3 million units). When the data for aspirin or paracetamol (or prednisone, see below) were combined, the subjects had a 47% reduction in symptom score, when compared with control subjects not taking any of these three drugs. In this study, aspirin did not consistently alter measures of the antiviral activity of interferon, but paracetamol appeared to enhance them.[2] Taken together, the results of these two studies suggest that these drugs may reduce the flu-like adverse effects of interferon, perhaps more so at lower doses of interferon. The clinical relevance of the measures of antiviral activity of interferon is uncertain, so the disparate effects found with paracetamol are unclear.

The authors of a report describing an unusual acute form of hepatitis, occurring in 3 patients receiving **interferon alfa-2a**, vinblastine and paracetamol, suggested that this might have been due to a drug interaction.[3] Another two similar cases have been reported with **interferon alfa-2b** and paracetamol, but no liver toxicity occurred when one of these patients was given **indometacin** with interferon instead.[4] The general relevance of these isolated reports is unclear.

Note that the manufacturers of interferon alfa-2a, **interferon beta-1a** and **interferon gamma-1b** advise that paracetamol,[5,6] NSAIDs[7] or an antipyretic analgesic[8,9] may be used to manage the flu-like adverse effects of interferon treatment. The manufacturer of interferon gamma-1b also states that the potential adverse effects of anti-inflammatory drugs, such as NSAIDs, on the efficacy of interferon gamma is unknown, however they give no specific guidance on concurrent use.[5]

(b) Corticosteroids

A single intramuscular dose of recombinant human **interferon alfa-2a** 18 million units was given to 8 healthy subjects alone, or to 8 similar healthy subjects 24 hours after starting **prednisone** 40 mg daily, for a total of 8 days. **Prednisone** did not reduce the interferon adverse effects of fever, chills, headache, or myalgia, but appeared to reduce one of the two measures of interferon activity.[1] In a later similar study by the same research group, the effect of the same dose of **prednisone**, started 3 days before the interferon, was evaluated with a lower dose of **interferon alfa-2a** (3 million units). Subjects taking **prednisone** had a 43% reduction in symptom score, and also had fewer hours of fever, when compared with control subjects taking **interferon alfa-2a** alone. In this study, **prednisone** did not consistently alter measures of the antiviral activity of interferon.[2] Taken together the results of these two studies suggest **prednisone** may reduce the flu-like adverse effects of interferon, perhaps more so at lower doses of interferon.

The manufacturers of **interferon beta-1a** and **interferon beta-1b** state that although it has not been specifically studied, corticosteroids may be used with interferon beta during relapses of multiple sclerosis, and that

concurrent use for up to 28 days has not resulted in any significant interaction.[7,8] The manufacturer of **interferon gamma-1b** states that it does not affect the therapeutic efficacy of corticosteroids when used to treat osteopetrosis or chronic granulomatous disease.[5] Therefore, it would appear that concurrent use of corticosteroids with interferons for specific conditions may be beneficial.

1. Witter FR, Woods AS, Griffin MD, Smith CR, Nadler P, Lietman PS. Effects of prednisone, aspirin and acetaminophen on an *in vivo* biologic response to interferon in humans. *Clin Pharmacol Ther* (1988) 44, 239–43.
2. Hendrix CW, Petty BG, Woods A, Kuwahara SK, Witter FR, Soo W, Griffin DE, Lietman PS. Modulation of α-interferon's antiviral and clinical effects by aspirin, acetaminophen, and prednisone in healthy volunteers. *Antiviral Res* (1995) 28, 121–31.
3. Kellokumpu-Lehtinen P, Iisalo E, Nordman E. Hepatotoxicity of paracetamol in combination with interferon and vinblastine. *Lancet* (1989) 1, 1143.
4. Fabris P, Dalla Palma M, de Lalla F. Idiosyncratic acute hepatitis caused by paracetamol in two patients with melanoma treated with high-dose interferon-α. *Ann Intern Med* (2001) 134, 345.
5. Immukin (Interferon gamma-1b). Boehringer Ingelheim Ltd. UK Summary of product characteristics, September 2007.
6. Roferon (Interferon alfa-2a). Roche Products Ltd. UK Summary of product characteristics, December 2008.
7. Betaferon (Interferon beta-1b). Bayer plc. UK Summary of product characteristics, February 2009.
8. Avonex (Interferon beta-1a). Biogen Idec Ltd. UK Summary of product characteristics, June 2008.
9. Rebif (Interferon beta-1a). Merck Serono. UK Summary of product characteristics, October 2009.

Interferons + Ribavirin

There was no evidence of any changes in pharmacokinetic parameters when ribavirin and interferon alfa-2b were given together.[1] Another study using peginterferon alfa-2b also found no pharmacokinetic interactions with ribavirin.[2] The combination of interferon alfa and ribavirin has enhanced efficacy against hepatitis C.

1. Khakoo S, Glue P, Grellier L, Wells B, Bell A, Dash C, Murray-Lyon I, Lypnyj D, Flannery B, Walters K, Dusheiko GM. Ribavirin and interferon alfa-2b in chronic hepatitis C: assessment of possible pharmacokinetic and pharmacodynamic interactions. *Br J Clin Pharmacol* (1998) 46, 563–70.
2. Glue P, Rouzier-Panis R, Raffanel C, Sabo R, Gupta SK, Salfi M, Jacobs S, Clement RP. A dose-ranging study of pegylated interferon alfa-2b and ribavirin in chronic hepatitis C. The Hepatitis C Intervention Therapy Group. *Hepatology* (2000) 32, 647–53.

Maraviroc + Co-trimoxazole

Co-trimoxazole has no significant effect on the pharmacokinetics of maraviroc.

Clinical evidence

In a study, co-trimoxazole (sulfamethoxazole with trimethoprim) 960 mg twice daily had no clinically relevant effect on the pharmacokinetics of maraviroc 300 mg twice daily (a 11% increase in AUC and a 19% increase in maximum level).[1]

Mechanism

Maraviroc undergoes some degree of renal clearance (about 20% of its total clearance).[1] Co-trimoxazole affects renal tubular transport and so it was predicted that it may possibly affect maraviroc levels.[1]

Importance and management

The pharmacokinetic data suggest that no maraviroc dose adjustment is likely to be needed if it is given with co-trimoxazole.

1. Abel S, Russell D, Whitlock LA, Ridgway CE, Muirhead GJ. The effects of cotrimoxazole or tenofovir co-administration on the pharmacokinetics of maraviroc in healthy volunteers. Br J Clin Pharmacol (2008) 65 (Suppl 1), 47–53.

Maraviroc + Ketoconazole and other CYP3A4 inhibitors

Ketoconazole increases the AUC of maraviroc about fivefold. Other potent CYP3A4 inhibitors would be expected to interact similarly.

Clinical evidence

In a study in 12 healthy subjects, **ketoconazole** 400 mg daily increased the AUC and maximum level of maraviroc 100 mg twice daily fivefold and 3.4-fold, respectively. No serious adverse effects were reported.[1]

Mechanism

Maraviroc is a substrate of the cytochrome P450 isoenzyme CYP3A4 and P-glycoprotein. Ketoconazole is a potent inhibitor of CYP3A4. Therefore, the levels of maraviroc would be expected to be significantly increased if it is taken with ketoconazole. Other inhibitors of CYP3A4 would be expected to interact similarly. From *in vitro* data, the potential for maraviroc to affect the pharmacokinetics of concurrent drugs is low.[2]

Importance and management

The effects of **ketoconazole** on maraviroc metabolism are established and clinically important. Increases in maraviroc levels of this magnitude are likely to result in increased adverse effects. The manufacturers of maraviroc advise that the dose of maraviroc should be reduced to 150 mg twice daily in the presence of ketoconazole.[2,3] **Itraconazole** is predicted to interact similarly, and the same dose reduction of maraviroc is advised.[2] Other azoles also inhibit CYP3A4 (see 'azoles antifungals', (p.233)), and although not specifically mentioned by the manufacturers, some caution is probably warranted, and consideration should be given to reducing the maraviroc dose. **Fluconazole** has less of an effect on CYP3A4 than the other azoles, so no dose alteration is needed when it is taken with maraviroc, although caution is advised.[2]

The manufacturers also predict that the macrolide antibacterials **clarithromycin** and **telithromycin** will significantly increase maraviroc levels, and they recommend reducing the maraviroc dose to 150 mg twice daily.[2,3]

Consider also 'Maraviroc + Protease inhibitors', p.923, and for a list of other inhibitors of CYP3A4, which might be expected to interact similarly, although to varying extents, see 'Table 1.4', (p.6).

1. Abel S, Russell D, Taylor-Worth RJ, Ridgway CE, Muirhead GJ. Effect of CYP3A4 inhibitors on the pharmacokinetics of maraviroc in healthy volunteers. Br J Clin Pharmacol (2008) 65 (Suppl 1), 27–37.
2. Celsentri (Maraviroc). Pfizer Ltd. UK Summary of product characteristics, November 2009.
3. Selzentry (Maraviroc). Pfizer Labs. US Prescribing information, June 2009.

Maraviroc + Miscellaneous

Maraviroc has no clinically relevant effect on the pharmacokinetics of lamivudine with zidovudine or midazolam. Food may modestly reduce the absorption of maraviroc. No interaction is expected between maraviroc and enfuvirtide. Tenofovir has no significant effect on the pharmacokinetics of maraviroc. No dose adjustment of maraviroc is expected to be needed if it is taken with buprenorphine, methadone, peginterferon, ribavirin, or statins.

Clinical evidence, mechanism, importance and management

(a) Debrisoquine

In a study in 72 healthy subjects, maraviroc 25 to 300 mg twice daily had no significant effect on the metabolism of debrisoquine; however, maraviroc 600 mg daily resulted in an 3.3-fold increase in the debrisoquine metabolic ratio.[1] Debrisoquine is a probe substrate for the cytochrome P450 isoenzyme CYP2D6, and the study above indicates that maraviroc, taken at usual clinical doses, is unlikely to significantly increase the levels of drugs metabolised by CYP2D6.

(b) Enfuvirtide

The US manufacturers advise that no maraviroc dose adjustment is need if it is taken with enfuvirtide.[2]

(c) Food

The UK manufacturer reports that in healthy subjects, a high-fat breakfast reduced the AUC and maximum concentration of a single 300-mg dose of maraviroc by about 33%. However, they state that as there were no food restrictions during clinical studies of maraviroc, and this did not influence the efficacy or safety outcomes of these studies. Therefore maraviroc may be taken with or without food.[3]

(d) Midazolam

In a placebo-controlled study in 12 healthy subjects, maraviroc 300 mg twice daily for 7 days slightly increased the AUC of a single 7.5-mg dose of oral midazolam taken on day 7 by 18%. This increase is unlikely to be clinically relevant.[4] Midazolam is a probe substrate for the cytochrome P450 isoenzyme CYP3A4, and the findings suggest that maraviroc is unlikely to have an important effect on other CYP3A4 substrates.

(e) NRTIs

In a placebo-controlled, crossover study in 11 healthy subjects, maraviroc 300 mg twice daily had no clinically relevant effect on the pharmacokinetics of **zidovudine** with **lamivudine** 300/150 mg twice daily, when they were taken together for one week.[4] In a placebo-controlled, crossover study in 16 healthy subjects, the concurrent use of maraviroc 300 mg twice daily and tenofovir disoproxil fumarate 300 mg daily had no effect on the pharmacokinetics of maraviroc.[5] Therefore no dose adjustments of zidovudine with lamivudine are needed when it is taken with maraviroc 300 mg twice daily.[3] The US manufacturers state that no dose adjustment of maraviroc is needed when it is used with NRTIs.[2]

(f) Tenofovir

In a placebo-controlled, crossover study in 16 healthy subjects, the concurrent use of maraviroc 300 mg twice daily and tenofovir disoproxil fumarate 300 mg daily had no effect on the pharmacokinetics of maraviroc.[5] Maraviroc undergoes some degree of renal clearance (about 20% of total clearance) and tenofovir is predominantly excreted renally, so it was predicted that it may possibly affect maraviroc levels.[5] However, the pharmacokinetic data suggest that no maraviroc dose adjustment is likely to be needed if it is given with tenofovir.

(g) Other drugs

The manufacturer states that, although there have been no specific drug interaction studies, no dose adjustment of maraviroc 300 mg twice daily is needed if it is taken with **buprenorphine**, **methadone**, **peginterferon**, **ribavirin**, and **statins**, as an interaction would not be expected.[3]

1. Abel S, van der Ryst E, Rosario MC, Ridgway CE, Medhurst CG, Taylor-Worth RJ, Muirhead GJ. Assessment of the pharmacokinetics, safety, tolerability of maraviroc, a novel CCR5 antagonist, in healthy volunteers. Br J Clin Pharmacol (2008) 65 (Suppl 1), 5–18.
2. Selzentry (Maraviroc). Pfizer Labs. US Prescribing information, June 2009.
3. Celsentri (Maraviroc). Pfizer Ltd. UK Summary of product characteristics, November 2009.
4. Abel S, Russell D, Whitlock LA, Ridgway CE, Muirhead GJ. Effect of maraviroc on the pharmacokinetics of midazolam, lamivudine/zidovudine, and ethinyloestradiol/levonorgestrel in healthy volunteers. Br J Clin Pharmacol (2008) 65 (Suppl 1), 19–26.
5. Abel S, Russell D, Whitlock LA, Ridgway CE, Muirhead GJ. The effects of cotrimoxazole or tenofovir co-administration on the pharmacokinetics of maraviroc in healthy volunteers. Br J Clin Pharmacol (2008) 65 (Suppl 1), 47–53.

Maraviroc + NNRTIs

Efavirenz reduces the levels of maraviroc by about 50%. Nevirapine and etravirine modestly increase the levels of maraviroc; delavirdine is predicted to interact similarly. Maraviroc is predicted not to affect the pharmacokinetics of efavirenz or nevirapine.

Clinical evidence

(a) Efavirenz

In a placebo-controlled study in 12 healthy subjects, efavirenz 600 mg daily for 14 days reduced the steady-state AUC and maximum plasma level of maraviroc 100 mg twice daily by about 45% and 51%, respectively. Doubling the dose of maraviroc to 200 mg twice daily overcame this reduction in maraviroc levels, resulting in a minor 15% *increase* in AUC and a 16% *increase* in maximum level, when compared with maraviroc 100 mg twice daily alone.[1] Similarly, in another study in HIV-positive patients, the AUC of a single 300-mg dose of maraviroc was about 52% lower in two groups of 8 patients compared with patients given maraviroc alone; one group was taking efavirenz, lamivudine and zidovudine and the other was taking efavirenz, didanosine and tenofovir.[2] Note that the NRTIs zidovudine, lamivudine and tenofovir, do not have a clinically significant effect on maraviroc pharmacokinetics (see 'Maraviroc + Miscellaneous', p.922).

In a study in 12 healthy subjects, ritonavir-boosted lopinavir 100/400 mg twice daily was given with maraviroc 300 mg twice daily for 21 days, with efavirenz 600 mg daily added on day 8. Efavirenz halved the increase in the AUC of maraviroc seen with ritonavir-boosted lopinavir: on day 7 the maraviroc AUC was increased by 150% by efavirenz, lopinavir and ritonavir, compared with an increase of 300% seen with lopinavir and ritonavir.[3] Similarly, efavirenz 600 mg daily more than halved the effect of ritonavir-boosted saquinavir 100 mg/1 g twice daily on the AUC of maraviroc 100 mg twice daily: efavirenz, saquinavir an lopinavir increased the AUC of maraviroc by 400%, compared with 877% seen with saquinavir and ritonavir.[3] For further details on the effects of the protease inhibitors on the metabolism of maraviroc, see 'Maraviroc + Protease inhibitors', p.923.

(b) Etravirine

The manufacturer reports that, in a study, etravirine 200 mg twice daily reduced the AUC and maximum level of maraviroc 300 mg twice daily by 53% and 60%, respectively. Maraviroc had no clinically significant effect on the AUC, maximum or minimum level of etravirine.[3]

(c) Nevirapine

In a study in 8 HIV-positive patients taking nevirapine 200 mg twice daily with lamivudine and tenofovir, the AUC of a single 300-mg dose of maraviroc was unchanged but its maximum plasma level was about 54% *higher*, when compared with HIV-positive subjects taking maraviroc alone.[2] Note that the NRTIs lamivudine and tenofovir, do not have a clinically significant effect on maraviroc pharmacokinetics (see 'Maraviroc + Miscellaneous', p.922).

Mechanism

Maraviroc is a substrate of the cytochrome P450 isoenzyme CYP3A4, hence its levels are reduced by efavirenz, an inducer of CYP3A4. Nevirapine and etravirine are also inducers of CYP3A4; however, the study above suggests that their effects on the metabolism of maraviroc are modest.

In contrast, **delavirdine** inhibits CYP3A4, and would therefore be expected to increase maraviroc levels.

Importance and management

The pharmacokinetic interaction between maraviroc and **efavirenz** is of clinical importance. The reduction in maraviroc plasma levels could result in a decrease in therapeutic efficacy and the development of viral resistance. In one study,[1] doubling the dose of maraviroc overcame this interaction. The manufacturers therefore recommend that the dose of maraviroc should be increased to 600 mg twice daily in patients taking efavirenz and *not* taking protease inhibitors or other potent inhibitors of CYP3A4.[3,4] Note that the UK manufacturer[3] does not recommend concurrent use of maraviroc in patients taking both efavirenz and the potent CYP3A4 inducer rifampicin, see 'Maraviroc + Rifampicin (Rifampin) and other CYP3A4 inducers', p.924, for further information. **Etravirine** should be prescribed with a protease inhibitor: no dose adjustment of etravirine is required if it is taken with maraviroc and protease inhibitors.[5] For information on dosing recommendations for maraviroc when using the NNRTIs efavirenz or etravirine with maraviroc and the protease inhibitors, see 'Maraviroc + Protease inhibitors', p.923.

Nevirapine is also an inducer of CYP3A4, however it appears to have no significant effect on the AUC of maraviroc and caused only a modest *increase* in maraviroc levels. Therefore, no dose adjustment of maraviroc appears to be needed in patients taking nevirapine.[3,4]

Delavirdine *inhibits* CYP3A4 and the manufacturers predict that it will significantly increase maraviroc levels. They therefore recommend reducing the maraviroc dose to 150 mg twice daily if delavirdine is also given.[4]

Maraviroc is not expected to have an effect on efavirenz or nevirapine pharmacokinetics.[3]

1. Abel S, Jenkins TM, Whitlock LA, Ridgway E, Muirhead GJ. Effects of CYP3A4 inducers with and without CYP3A4 inhibitors on the pharmacokinetics of maraviroc in healthy volunteers. Br J Clin Pharmacol (2008) 65, (Suppl 1), 38–46.
2. Pozniak AL, Boffito M, Russell D, Ridgway CE, Muirhead GJ. A novel probe drug interaction study to investigate the effect of selected antiretroviral combinations on the pharmacokinetics of a single oral dose of maraviroc in HIV-positive subjects. Br J Clin Pharmacol (2008), 65 (Suppl 1), 54–9.
3. Celsentri (Maraviroc). Pfizer Ltd. UK Summary of product characteristics, November 2009.
4. Selzentry (Maraviroc). Pfizer Labs. US Prescribing information, June 2009.
5. Intelence (Etravirine). Janssen-Cilag Ltd. UK Summary of product characteristics, November 2009.

Maraviroc + Protease inhibitors

Atazanavir and saquinavir, and ritonavir-boosted atazanavir, darunavir and lopinavir markedly increase the AUC of maraviroc by about three- to fivefold. Ritonavir-boosted saquinavir has

an even greater effect, whereas ritonavir-boosted tipranavir has no significant effect on the pharmacokinetics of maraviroc.

Clinical evidence

(a) Atazanavir

In a study in 12 healthy subjects, atazanavir 400 mg daily increased the AUC and maximum level of maraviroc 300 mg twice daily (both drugs taken for 7 days) 3.6-fold and twofold, respectively. Atazanavir 300 mg daily with ritonavir 100 mg daily increased the AUC of maraviroc almost fivefold and increased the maximum concentration of maraviroc about 2.5-fold.[1]

(b) Darunavir

In a study in 12 subjects, darunavir 600 mg twice daily with ritonavir 100 mg twice daily increased the AUC, the maximum concentration and the minimum concentration of maraviroc 150 mg twice daily by fourfold, 2.3-fold, and eightfold, respectively.[2,3]

(c) Lopinavir

In a study in 5 HIV-positive patients taking ritonavir-boosted lopinavir 100/400 mg twice daily with stavudine and lamivudine, the AUC of a single 300-mg oral dose of maraviroc was increased 2.6-fold and the maraviroc maximum concentration was increased by nearly twofold, when compared with HIV-positive subjects taking maraviroc 300 mg daily alone.[4] In a study in 12 healthy subjects, ritonavir-boosted lopinavir 100/400 mg twice daily increased the AUC and maximum level of maraviroc 300 mg twice daily almost fourfold and twofold, respectively.[5] Adding efavirenz 600 mg daily nearly halved the effect of ritonavir-boosted lopinavir on the AUC and maximum concentration of maraviroc (to a smaller increase of 2.5-fold and 20%, respectively), and also led to an increase in adverse effects, such as dizziness.[5] Another cohort study was planned to investigate the concurrent use of ritonavir-boosted lopinavir, saquinavir and efavirenz with maraviroc; however, this was discontinued due to a high rate of gastrointestinal adverse effects with the combination of ritonavir-boosted lopinavir, saquinavir and maraviroc.[5]

(d) Saquinavir

In a study in 12 healthy subjects, saquinavir 1.2 g three times daily increased the AUC and maximum level of maraviroc 100 mg twice daily 4.2-fold and 3.3-fold, respectively.[1] In another study in healthy subjects by the same group, ritonavir-boosted saquinavir 100/400 mg twice daily for 7 days increased the AUC and maximum concentration of maraviroc 100 mg twice daily by about 9.7-fold and 4.8-fold, respectively. Adding efavirenz 600 mg daily nearly halved this effect, although the AUC and maximum concentrations of maraviroc were still raised fivefold and 2.3-fold, respectively.[5]

(e) Tipranavir

A study in 12 healthy subjects found that ritonavir-boosted tipranavir 200/500 mg twice daily had no clinically significant effect on the AUC or maximum plasma levels of maraviroc 150 mg twice daily. An initial rise in maraviroc trough plasma levels was seen on days one to 4, but this resolved thereafter.[1]

Mechanism

Maraviroc is a substrate of the cytochrome P450 isoenzyme CYP3A4 and P-glycoprotein. CYP3A4 is inhibited to various degrees by the protease inhibitors. Therefore, the levels of maraviroc would be expected to be significantly increased if it is taken with the protease inhibitors.

From *in vitro* data, the potential for maraviroc to affect the pharmacokinetics of concurrent drugs is low.[2]

Importance and management

The effect of the protease inhibitors on maraviroc metabolism is established and clinically important. Increases in maraviroc levels of this magnitude are likely to result in increased adverse effects. The manufacturers advise that the dose of maraviroc should be reduced to 150 mg twice daily when it is taken with *most* protease inhibitors. This dose reduction is also recommended when maraviroc is given with most protease inhibitors and the NNRTIs **efavirenz** or **etravirine**.[2,3] However, some protease inhibitors are excepted from this dosing recommendation. In the UK, the manufacturer recommends that when maraviroc is used with ritonavir-boosted **fosamprenavir**, the usual dose of maraviroc 300 mg twice daily should be used; this maraviroc dose should also be used if the NNRTIs efavirenz or etravirine are also added.[2] In both the UK and the US, the manufacturers recommend that when maraviroc is used with ritonavir-boosted **tipranavir**, the usual dose of maraviroc 300 mg twice daily should be used.[2,3] However while the UK manufacturer[2] recommends increasing maraviroc dose to 600 mg twice daily if the NNRTI efavirenz is also added, the US manufacturer[3] does not appear to give any specific guidance if efavirenz is also added to ritonavir-boosted tipranavir.

Note that the UK manufacturer of maraviroc states that if **rifabutin** is started in a patient taking maraviroc with protease inhibitors no further dose adjustment is needed.[2] See 'Maraviroc + Rifampicin (Rifampin) and other CYP3A4 inducers', p.924, for further information on the effect of rifabutin or rifampicin on the pharmacokinetics of maraviroc.

1. Abel S, Russell D, Taylor-Worth RJ, Ridgway CE, Muirhead GJ. Effect of CYP3A4 inhibitors on the pharmacokinetics of maraviroc in healthy volunteers. Br J Clin Pharmacol (2008) 65 (Suppl 1), 27–37.
2. Celsentri (Maraviroc). Pfizer Ltd. UK Summary of product characteristics, November 2009.
3. Selzentry (Maraviroc). Pfizer Labs. US Prescribing information, June 2009.
4. Pozniak AL, Boffito M, Russell D, Ridgway CE, Muirhead GJ. A novel probe drug interaction study to investigate the effect of selected antiretroviral combinations on the pharmacokinetics of a single oral dose of maraviroc in HIV- positive subjects. Br J Clin Pharmacol (2008), 65 (Suppl 1), 54–9.
5. Abel S, Jenkins TM, Whitlock LA, Ridgway CE, Muirhead GJ. Effects of CYP3A4 inducers with and without CYP3A4 inhibitors on the pharmacokinetics of maraviroc in healthy volunteers. Br J Clin Pharmacol (2008) 65 (Suppl 1), 38–46.

Maraviroc + Rifampicin (Rifampin) and other CYP3A4 inducers

Rifampicin reduces the plasma levels of maraviroc by about two-thirds. Other inducers of CYP3A4, such as carbamazepine, phenobarbital, phenytoin, rifabutin and St John's wort, are predicted to have a similar effect.

Clinical evidence

In a placebo-controlled study in 12 healthy subjects, **rifampicin** 600 mg daily for 14 days reduced the steady-state AUC, the maximum plasma level and the minimum plasma level of maraviroc 100 mg twice daily by about two-thirds. Doubling the dose of maraviroc to 200 mg twice daily overcame this increase in metabolism, resulting in an AUC comparable to that of maraviroc 100 mg twice daily alone. No serious adverse effects were reported.[1]

Mechanism

Maraviroc is a substrate of the cytochrome P450 isoenzyme CYP3A4, hence its levels are significantly reduced by rifampicin, a potent inducer of CYP3A4; other inducers of CYP3A4 would therefore also be expected to reduce maraviroc levels. For a list of CYP3A4 inducers, see 'Table 1.4', (p.6). Note that maraviroc is also a substrate for P-glycoprotein, and rifampicin, which also induces P-glycoprotein, may further reduces maraviroc levels by this mechanism.

Importance and management

The pharmacokinetic interaction between maraviroc and rifampicin is clinically significant as the reduction in maraviroc plasma levels could result in a decrease in therapeutic efficacy and the development of viral resistance. Therefore, the manufacturers advise that the dose of maraviroc should be increased to 600 mg twice daily in patients taking rifampicin but *not* in those also taking a potent inhibitor of CYP3A4.[2,3] For further information on the effects of CYP3A4 inhibitors, such as ketoconazole or the protease inhibitors, on maraviroc, see 'Maraviroc + Ketoconazole and other CYP3A4 inhibitors', p.922, and 'Maraviroc + Protease inhibitors', p.923.

Other inducers of CYP3A4 are also predicted to reduce maraviroc levels. The US manufacturer[3] specifically recommends a dose increase of maraviroc to 600 mg twice daily in patients taking **carbamazepine**, **phenytoin** or **phenobarbital**, known potent inducers of CYP3A4. It would seem prudent to also consider this dose increase with **primidone** (which is metabolised to phenobarbital) and **fosphenytoin** (a prodrug of phenytoin). **St John's wort** is another known inducer of CYP3A4 and is expected to significantly reduce the levels of maraviroc and potentially reduce its antiviral effects: the manufacturers advise against its concurrent use with maraviroc.[2,3] Note that The UK manufacturer of maraviroc[2] does not rec-

ommend the concurrent use of maraviroc in patients taking both rifampicin and efavirenz, which is also an enzyme inducer. For further information on the effects of efavirenz on maraviroc, see 'Maraviroc + NNRTIs', p.923.

Rifabutin is a weaker inducer of CYP3A4 than rifampicin, and its use with maraviroc does not appear to have been studied. Note that if **rifabutin** is started in a patient taking maraviroc with a protease inhibitor, (except ritonavir-boosted fosamprenavir or tipranavir), the UK manufacturer advises that the dose of maraviroc is reduced to 150 mg twice daily.[2]

For a list of CYP3A4 inducers, see 'Table 1.4', (p.6).

1. Abel S, Jenkins TM, Whitlock LA, Ridgway E, Muirhead GJ. Effects of CYP3A4 inducers with and without CYP3A4 inhibitors on the pharmacokinetics of maraviroc in healthy volunteers. Br J Clin Pharmacol (2008) 65, (Suppl 1), 38–46.
2. Celsentri (Maraviroc). Pfizer Ltd. UK Summary of product characteristics, November 2009.
3. Selzentry (Maraviroc). Pfizer Labs. US Prescribing information, June 2009.

NNRTIs + Antiepileptics; Enzyme-inducing

Carbamazepine significantly reduces the levels of delavirdine, efavirenz and nevirapine, and is predicted to reduce the levels of etravirine. Other enzyme-inducing antiepileptics (e.g. phenytoin and phenobarbital) are expected to interact similarly, and cases of antiretroviral treatment failure have been reported.
Efavirenz and nevirapine reduce carbamazepine levels.

Clinical evidence

(a) Delavirdine

The manufacturer of delavirdine reports that in 8 subjects taking delavirdine 300 to 400 mg three times daily, **carbamazepine**, **phenytoin**, and **phenobarbital** reduced the minimum level of delavirdine by 90%. No information on other pharmacokinetic parameters is available.[1]

(b) Efavirenz

In a crossover study, 26 healthy subjects took either efavirenz 600 mg daily for 35 days with **carbamazepine** titrated from 200 mg daily to 400 mg daily from days 15 to 35, or carbamazepine titrated from 200 mg to 400 mg daily for 35 days with efavirenz 600 mg daily from days 22 to 35. **Carbamazepine** significantly reduced the AUC, peak plasma levels and trough plasma levels of efavirenz by 36%, 21% and 47%, respectively. Efavirenz reduced the AUC, peak plasma levels and trough plasma levels of **carbamazepine** by 27%, 20% and 35%, respectively. However, no significant increase was seen in the pharmacokinetics of the 10,11-epoxide metabolite of carbamazepine. No significant increase in serious adverse effects was reported with either combination.[2]

A case of undetectable efavirenz levels has been reported in one HIV-positive patient taking **phenytoin** 400 mg daily with efavirenz 800 mg daily. The dose of efavirenz was increased to 600 mg twice daily but the efavirenz levels did not increase until the **phenytoin** was stopped and lamotrigine and levetiracetam were started.[3] Another case of low efavirenz levels has been reported in a patient taking **phenytoin** 300 mg twice daily. When phenytoin was changed to levetiracetam, the patient's efavirenz levels rose from 0.58 micrograms/mL to 2.5 micrograms/mL within 3 weeks.[4]

One report describes efavirenz treatment failure in a patient given **oxcarbazepine**. However, in this particular case, efavirenz levels had been checked before and during **oxcarbazepine** treatment and were unchanged, and on further questioning the patient admitted poor adherence to the HAART regimen.[5]

(c) Nevirapine

In a study, healthy subjects were given a single dose of nevirapine alone or with a single dose of **carbamazepine** 400 mg, **phenobarbital** 200 mg or **phenytoin** 184 mg, or with a 3-day or 7-day course of **phenytoin** 184 mg daily. The half-life and time to first undetectable level of nevirapine were reduced by the single dose of **carbamazepine** and the two courses of **phenytoin** but not by the single doses of **phenytoin** or **phenobarbital**. Nevirapine plasma levels 8 hours after administration of the enzyme inducers were not affected.[6]

Mechanism

The NNRTIs are all primarily metabolised by the cytochrome P450 isoenzyme CYP3A4, and so their metabolism would be expected to be increased by drugs that are potent inducers of this isoenzyme, such as carbamazepine, phenytoin and phenobarbital. Efavirenz is also an inducer of CYP3A4, and so it can increase the metabolism of carbamazepine. Nevirapine would be expected to interact similarly (see 'Table 21.2', (p.914)).

Importance and management

The manufacturer of **delavirdine** does not recommend the concurrent use of carbamazepine, phenytoin or phenobarbital as it could result in the loss of efficacy of delavirdine and lead to the development of delavirdine resistance.[1] Note that primidone is metabolised to phenobarbital, and fosphenytoin is a prodrug of phenytoin, so these drugs should probably also be avoided.

From the study and case reports, the concurrent use of carbamazepine and **efavirenz** reduce the levels of both drugs, and this may also lead to treatment failure. The manufacturers therefore recommend that an alternative to carbamazepine should be considered.[7,8] The UK manufacturer states that no data are available on the potential interactions of efavirenz with phenytoin or phenobarbital.[7] Both manufacturers say that when efavirenz is given with these drugs, there is the potential for a reduction or increase in the plasma concentrations of both the antiepileptic as well as efavirenz. They recommend periodic monitoring of the plasma levels of phenytoin (and therefore probably fosphenytoin) or phenobarbital (and therefore probably primidone) on concurrent use.[7,8] Note that efavirenz may itself cause seizures, therefore the manufacturers recommend caution in patients with a history of convulsions.[7,8]

The US manufacturer of **nevirapine** recommends caution on the concurrent use of carbamazepine.[9]

Etravirine is also metabolised by CYP3A4, the manufacturer predicts that its levels will be reduced by carbamazepine, phenytoin or phenobarbital. They therefore advise against concurrent use.[10]

A number of other antiepileptics have been suggested as alternatives to the enzyme-inducing antiepileptics in patients taking NNRTIs. These include **gabapentin**, **lamotrigine**, **levetiracetam** and **vigabatrin**.[2-4,7]

1. Rescriptor (Delavirdine mesylate). Pfizer Inc. US Prescribing information, May 2008.
2. Ji P, Damle B, Xie J, Unger SE, Grasela DM, Kaul S. Pharmacokinetic interaction between efavirenz and carbamazepine after multiple-dose administration in healthy subjects. J Clin Pharmacol (2008) 48, 948–56.
3. Spak CW, Dhanireddy S, Kosel BW. Clinical interaction between efavirenz and phenytoin. AIDS (2008) 22, 164–5.
4. Robertson SM, Penzak SR, Lane J, Pau AK, Mican JM. A potentially significant interaction between efavirenz and phenytoin: a case report and review of the literature. *Clin Infect Dis* (2005) 41, e15–e18.
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6. L'homme RFA, Dijkema T, van der Ven AJAM, Burger DM. Enzyme inducers reduce elimination half-life after a single dose of nevirapine in healthy women. *J Acquir Immune Defic Syndr* (2006) 43, 193–6.
7. Sustiva Film-coated Tablets (Efavirenz). Bristol-Myers Squibb Pharmaceuticals Ltd. UK Summary of product characteristics, June 2009.
8. Sustiva (Efavirenz). Bristol-Myers Squibb Company. US Prescribing information, September 2009.
9. Viramune (Nevirapine). Boehringer Ingelheim Pharmaceuticals, Inc. US Prescribing information, November 2008.
10. Intelence (Etravirine). Janssen-Cilag Ltd. UK Summary of product characteristics, November 2009.

NNRTIs + Azoles; Fluconazole

Fluconazole doubles nevirapine exposure. Fluconazole causes a minor rise in efavirenz steady-state levels, and does not alter delavirdine levels. Fluconazole is predicted to increase etravirine levels. Fluconazole levels are not altered by these NNRTIs.

Clinical evidence, mechanism, importance and management

(a) Delavirdine

In a study, 8 HIV-positive subjects were given delavirdine mesilate 300 mg three times daily for 30 days, with fluconazole 400 mg daily on days 16 to 30. When compared with 5 subjects given delavirdine alone, fluconazole had no significant effect on the pharmacokinetics of delavirdine. Fluconazole pharmacokinetics were not significantly affected by the concurrent use of delavirdine, when compared with previously reported data for healthy subjects, HIV-positive patients, and patients with AIDS.[1]

On the basis of these results, it would appear that no dose adjustments are needed if delavirdine and fluconazole are used together.

(b) Efavirenz

In a study, 20 healthy subjects were given fluconazole 400 mg daily for one day and then 200 mg daily for 6 days with efavirenz 400 mg daily. The pharmacokinetics of fluconazole were not affected by efavirenz, but the AUC of efavirenz was slightly raised, by 15%.[2] These effects are slight, and therefore it would appear that no dose adjustments are needed if efavirenz and fluconazole are used together.

(c) Etravirine

The manufacturers of etravirine predict that as fluconazole is an inhibitor of the cytochrome P450 isoenzyme CYP2C9, it will increase the levels of etravirine, which is partly metabolised by this route; however, this has not been specifically studied. Nevertheless, the UK manufacturer advises that no dose adjustment of etravirine is expected to be needed when it is taken with fluconazole.[3] Etravirine is not expected to affect the metabolism of fluconazole.[4]

(d) Nevirapine

In a study in 19 subjects, nevirapine 200 mg daily for 14 days and then 200 mg twice daily for 14 days did not have any clinically relevant effect on the pharmacokinetics of fluconazole 200 mg daily.[5] However, the concurrent use of fluconazole 200 mg daily[6] and nevirapine doubled the exposure to nevirapine, compared with historical control data.[5,6] In a retrospective study of patients who had received nevirapine-based HAART, there was no increase in the incidence of clinical hepatitis, elevated aminotransferases or skin rashes, when the outcomes of 225 patients not taking fluconazole, 392 patients taking fluconazole 400 mg weekly, and 69 patients taking fluconazole 200 mg daily with nevirapine were compared.[7] A retrospective study, by the same authors, in HIV-positive patients taking nevirapine-based HAART compared the trough levels of nevirapine and rate of adverse effects in patients also taking fluconazole with those not taking fluconazole. In 41 patients taking nevirapine with fluconazole 200 mg daily or 400 mg daily, the mean nevirapine trough levels were 9.8 mg/L and 12.2 mg/L, respectively, compared with a mean nevirapine trough level of 6.5 mg/L in the 81 patients not taking fluconazole. No significant increase in liver function tests occurred in the patients taking fluconazole compared with the control group, although one case of clinical hepatitis was reported with the concurrent use of fluconazole. The incidence of rash was higher in the control group compared with those patients also taking fluconazole.[8] Nevertheless, the manufacturers advise that, if fluconazole and nevirapine are used concurrently, patients should be closely monitored for nevirapine-associated adverse effects (such as rash and hepatitis).[5,6]

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2. Benedek IH, Fiske WD, White SJ, Kornhauser DM. Plasma levels of fluconazole (FL) are not altered by coadministration of DMP 266 in healthy volunteers. *Intersci Conf Antimicrob Agents Chemother* (1997) 37, 1.
3. Intelence (Etravirine). Janssen-Cilag Ltd. UK Summary of product characteristics, November 2009.
4. Intelence (Etravirine). Tibotec, Inc. US Prescribing information, November 2009.
5. Viramune (Nevirapine). Boehringer Ingelheim Pharmaceuticals, Inc. US Prescribing information, November 2008.
6. Viramune (Nevirapine anhydrate). Boehringer Ingelheim Ltd. UK Summary of product characteristics, May 2009.
7. Manosuthi W, Chumpathat N, Chaovavanich A, Sungkanuparph S. Safety and tolerability of nevirapine-based antiretroviral therapy in HIV-infected patients receiving fluconazole for cryptococcal prophylaxis: a retrospective cohort study. *BMC Infect Dis* (2005) 5, 67.
8. Manosuthi W, Athichathanabadi C, Uttayamakul S, Phoorisri T, Sungkanuparph S. Plasma nevirapine levels, adverse effects and efficacy of antiretroviral therapy among HIV-infected patients concurrently receiving nevirapine-based antiretroviral therapy and fluconazole. *BMC Infect Dis* (2007) 7, 14.

NNRTIs + Azoles; Itraconazole

Itraconazole had no effect on efavirenz levels in one study, whereas efavirenz modestly decreased itraconazole levels. Nevirapine may also decrease itraconazole levels. Etravirine is predicted to decrease itraconazole levels, and itraconazole is expected to increase etravirine levels.

Clinical evidence

(a) Efavirenz

In a study in healthy subjects, efavirenz 600 mg daily decreased the steady-state maximum plasma levels and the AUC of itraconazole 200 mg twice daily by 37% and 39%, respectively, and caused a similar decrease in the levels of the metabolite, hydroxyitraconazole. The steady-state maximum plasma levels and the AUC of efavirenz were not affected by itraconazole.[1,2]

A retrospective study identified 10 HIV-positive patients taking antiretroviral drugs, with itraconazole 200 mg or 400 mg daily for disseminated histoplasmosis. The 4 patients taking NNRTI-based regimens (efavirenz or nevirapine) had subtherapeutic itraconazole levels (less than 0.05 micrograms/mL). Two patients taking a protease inhibitor with an NNRTI had itraconazole levels between 0.5 and 0.7 micrograms/mL. Three patients had their NNRTI stopped due to subtherapeutic itraconazole levels. One patient taking a protease inhibitor with an NNRTI had a 500% increase in itraconazole levels when the NNRTI was stopped.[3]

A case of subtherapeutic itraconazole levels has been reported in an HIV-positive patient taking efavirenz, stavudine and lamivudine with disseminated histoplasmosis. The patient had been taking itraconazole 200 mg daily with some signs of clinical improvement, but itraconazole levels more than one year after the start of treatment were undetectable. The dose of itraconazole was subsequently increased to 200 mg twice daily but the levels remained undetectable and the urine levels of *Histoplasma* antigen remained raised. Stopping efavirenz and changing to a protease inhibitor-based regimen resulted in an increase in itraconazole levels and a reduction in the urine levels of *Histoplasma* antigen.[4] Note that protease inhibitors can raise itraconazole levels, see 'Protease inhibitors + Azoles; Itraconazole', p.964.

Another case of significantly reduced itraconazole levels, and an *increase* in the minimum plasma levels of its active metabolite hydroxyitraconazole, has also been reported.[5]

(b) Nevirapine

In a study in 12 healthy subjects, itraconazole 200 mg daily for 7 days had no significant effects on the pharmacokinetics of nevirapine 200 mg daily, also taken for 7 days. However, nevirapine decreased the AUC and maximum plasma concentration of itraconazole by 61% and 38%, respectively.[6]

Mechanism

The metabolism of itraconazole by the cytochrome P450 isoenzyme CYP3A4 is induced by efavirenz. Nevirapine and **etravirine** might interact similarly as they also induce CYP3A4, to varying degrees.

Importance and management

On the basis of the pharmacokinetic study, the manufacturers of **efavirenz** say that alternatives to itraconazole should be considered.[1,2] If there are no appropriate alternatives, it might be prudent to increase the dose of itraconazole, with increased monitoring for efficacy and toxicity of the combination.

As **nevirapine** also appears to reduce itraconazole levels, itraconazole efficacy should be monitored carefully; anticipate the need to increase the dose of itraconazole. No dose adjustments of efavirenz or nevirapine are needed if they are taken with itraconazole.

The manufacturers of **etravirine** predict that, as itraconazole is both an inhibitor and substrate of CYP3A4, it will increase the levels of etravirine, and etravirine will reduce itraconazole levels.[7,8] The US manufacturer advises that dose adjustments of itraconazole may be required, depending on other concurrent drugs.[8] However, the UK manufacturer advises that no dose adjustment of either itraconazole or etravirine is needed on concurrent use.[7]

1. Sustiva Film-coated Tablets (Efavirenz). Bristol-Myers Squibb Pharmaceuticals Ltd. UK Summary of product characteristics, June 2009.
2. Sustiva (Efavirenz). Bristol-Myers Squibb Company. US Prescribing information, September 2009.
3. Andrade RA, Evans RT, Hamill RJ, Zerai T, Giordano TP. Clinical evidence of an interaction between itraconazole and nonnucleoside reverse transcriptase inhibitors in HIV-infected patients with disseminated histoplasmosis. Ann Pharmacother (2009) 43, 908–13.
4. Koo HL, Hamill RJ, Andrade RA. Drug-drug interaction between itraconazole and efavirenz in a patient with AIDS and disseminated histoplasmosis. *Clin Infect Dis* (2007) 45, e77–e79.
5. Huet E, Hadji C, Hulin A, Botterel F, Bretagne S, Lévy Y. Therapeutic monitoring is necessary for the association itraconazole and efavirenz in a patient with AIDS and disseminated histoplasmosis. AIDS (2008) 22, 1885–6.

6. Jaruratanasirikul S, Sriwiriyajan S. Pharmacokinetic study of the interaction between itraconazole and nevirapine. *Eur J Clin Pharmacol* (2007) 63, 451–6.
7. Intelence (Etravirine). Janssen-Cilag Ltd. UK Summary of product characteristics, November 2009.
8. Intelence (Etravirine). Tibotec, Inc. US Prescribing information, November 2009.

NNRTIs + Azoles; Ketoconazole

Nevirapine markedly reduces the AUC of ketoconazole. Efavirenz interacts similarly, whereas delavirdine may increase ketoconazole levels. NNRTI plasma levels may be raised by ketoconazole.

Clinical evidence

(a) Delavirdine

The manufacturer notes that, in 26 patients taking ketoconazole, the minimum plasma level of delavirdine was 50% higher than population pharmacokinetic data.[1]

(b) Efavirenz

In a study in 12 HIV-positive patients, efavirenz 600 mg daily for 15 days reduced the $AUC_{0\text{-}24}$ and maximum plasma concentration of a single 400-mg dose of ketoconazole by 72% and 44%, respectively.[2]

(c) Nevirapine

The manufacturers of nevirapine quote a study in which nevirapine 200 mg twice daily was given with ketoconazole 400 mg daily. The ketoconazole AUC was markedly reduced by 72% and its maximum plasma levels were reduced by 44%.[3,4] In addition, the nevirapine plasma levels were raised by 15 to 28%, when compared with historical control data.[3]

Mechanism

Ketoconazole is likely to inhibit the metabolism of the NNRTIs by the cytochrome P450 isoenzyme CYP3A4. Efavirenz and nevirapine both induce the metabolism of ketoconazole by CYP3A4. In theory, **etravirine**, a weak CYP3A4 inducer may interact similarly, whereas delavirdine is likely to inhibit ketoconazole metabolism by CYP3A4.

Importance and management

A clinically significant interaction appears to occur between the NNRTIs and ketoconazole, which may lead to antifungal treatment failure. The manufacturers of **nevirapine** state that ketoconazole and nevirapine should not be used together, because of the likely reduced efficacy of ketoconazole.[3,4] **Efavirenz** appears to cause a similar reduction in ketoconazole levels; the possible effect of ketoconazole on efavirenz does not appear to have been studied.[5]

The manufacturers of **etravirine** state that, as ketoconazole is a potent inhibitor of CYP3A4, it would be expected to increase plasma levels of etravirine, whereas etravirine is expected to reduce plasma levels of ketoconazole.[6,7] The US manufacturer advises that dose adjustments of ketoconazole may be required, depending on other concurrent drugs.[7] However, the UK manufacturer advises that no dose adjustment of either ketoconazole or etravirine is required on concurrent use.[6]

NNRTI levels might be raised by ketoconazole, which might increase adverse effects. Cautious monitoring of both the efficacy of ketoconazole and of an increase in the adverse effects of the NNRTIs would be prudent if concurrent use is necessary.

1. Rescriptor (Delavirdine mesylate). Pfizer Inc. US Prescribing information, May 2008.
2. Sriwiriyajan S, Mahatthanatrakul W, Ridtitid W, Jaruratanasirikul S. Effect of efavirenz on the pharmacokinetics of ketoconazole in HIV-infected patients. *Eur J Clin Pharmacol* (2007) 63, 479–483.
3. Viramune (Nevirapine anhydrate). Boehringer Ingelheim Ltd. UK Summary of product characteristics, May 2009.
4. Viramune (Nevirapine). Boehringer Ingelheim Pharmaceuticals, Inc. US Prescribing information, November 2008.
5. Sustiva Film-coated Tablets (Efavirenz). Bristol-Myers Squibb Pharmaceuticals Ltd. UK Summary of product characteristics, June 2009.
6. Intelence (Etravirine). Janssen-Cilag Ltd. UK Summary of product characteristics, November 2009.
7. Intelence (Etravirine). Tibotec, Inc. US Prescribing information, November 2009.

NNRTIs + Azoles; Posaconazole

Efavirenz reduces the levels of posaconazole. No change in efavirenz levels appears to occur with posaconazole. Etravirine levels are predicted to be raised by posaconazole.

Clinical evidence, mechanism, importance and management

In a study in 10 healthy subjects, **efavirenz** 400 mg daily reduced the AUC and maximum concentration of posaconazole by 50% and 45%, respectively.[1] Posaconazole is a substrate for glucuronosyltransferases, and it is suggested that **efavirenz** induces this route of metabolism to reduce the levels of posaconazole.[1] Posaconazole is an inhibitor of the cytochrome P450 isoenzyme CYP3A4, and would therefore be expected to inhibit the metabolism of **efavirenz**. However, the same study reported that posaconazole had no significant effect on the pharmacokinetics of **efavirenz**.[1] The manufacturer of posaconazole advises avoiding concurrent use of **efavirenz** unless the benefits outweigh the risks.[2]

The levels of **etravirine** are predicted to be increased by posaconazole; however, the UK manufacturer states that no dose adjustment is needed on concurrent use.[3]

1. Moton A, Ma L, Khrisna G, Martinho M, Seiberling M, McLeod J. Pharmacokinetics (PK) of the antifungal triazole posaconazole (POS) and the NRTI efavirenz when coadministered in healthy adult volunteers. 11th European AIDS conference (EACS), Madrid, 2007. Abstract P4.3/05.
2. Noxafil (Posaconazole). Schering-Plough Ltd. UK Summary of product characteristics, November 2009.
3. Intelence (Etravirine). Janssen-Cilag Ltd. UK Summary of product characteristics, November 2009.

NNRTIs + Azoles; Voriconazole

Voriconazole modestly increases efavirenz levels, and is predicted to increase the levels of delavirdine, etravirine, and nevirapine. Efavirenz markedly decreases voriconazole levels: nevirapine is predicted to interact similarly, whereas delavirdine and etravirine are predicted to increase voriconazole levels.

Clinical evidence

In a study in 17 healthy subjects, **efavirenz** 400 mg daily decreased the steady-state maximum plasma levels and the AUC of voriconazole 200 mg twice daily by 62% and 78%, respectively. At the same time, the steady-state maximum plasma levels and the AUC of **efavirenz** were increased by 37% and 44%, respectively. No increase in adverse effects was reported with the concurrent use of efavirenz and voriconazole, compared with efavirenz alone.[1] In a dose-adjustment study in 15 healthy subjects, when compared with voriconazole 200 mg twice daily alone, the AUC and maximum plasma concentration of voriconazole 300 mg twice daily were 55% and 36% lower, respectively, when **efavirenz** 300 mg daily for 7 days was also taken. The **efavirenz** AUC was equivalent to that seen with efavirenz 600 mg daily alone. When the voriconazole dose was increased to 400 mg twice daily in 14 of the subjects, the AUC of voriconazole was just 7% lower than that seen with voriconazole 200 mg twice daily alone. The AUC of **efavirenz** was increased by 17% and the maximum plasma concentration was equivalent, when compared with efavirenz 600 mg daily alone.[2]

There is one case of a patient taking a variety of antiretrovirals and antibacterials who developed oral candidiasis while taking voriconazole 200 mg twice daily, which was attributed to an interaction with **efavirenz**. The dose of voriconazole was titrated upwards to 350 mg twice daily to achieve higher trough levels. The candidiasis was eventually found to be resistant to voriconazole, and it was suggested that this developed because of under-dosing in the presence of **efavirenz**.[3]

Mechanism

The metabolism of voriconazole by the cytochrome P450 isoenzyme CYP3A4 is induced by efavirenz and therefore concurrent use lowers voriconazole levels. Nevirapine is predicted to interact similarly, whereas delavirdine has been reported to inhibit the metabolism of voriconazole *in vitro*.[4] **Etravirine** is a weak inducer of CYP3A4, and is a weak inhibitor of CYP2C9 and CYP2C19. As voriconazole is primarily metabolised by CYP2C19 as well as CYP2C9 and CYP3A4, an increase in voriconazole

levels may be expected on concurrent use.[5,6] All of the NNRTIs are substrates of CYP3A4, which is inhibited by voriconazole, and therefore voriconazole may raise the levels of the NNRTIs.

Importance and management

On the basis of the pharmacokinetic studies the manufacturers state that **efavirenz** should not be given with voriconazole, unless the doses of both drugs are adjusted.[4,7-9] The recommendation is to double the usual dose of voriconazole to 400 mg twice daily, and to halve the usual efavirenz dose to 300 mg daily. The dose of efavirenz should be increased back to 600 mg daily when the voriconazole course is finished.[4,7-9]

Nevirapine significantly reduces the levels of other antifungals metabolised by CYP3A4, such as 'ketoconazole', (p.927), and it would be expected to have a similar effect on voriconazole metabolism, whereas **delavirdine** might increase voriconazole levels. NNRTI levels might also be raised by voriconazole, which might increase adverse effects. The manufacturers of voriconazole suggest that patients given delavirdine or nevirapine should be carefully monitored for evidence of drug toxicity and/or loss of efficacy during concurrent use.[4,7]

The manufacturers of **etravirine** state that the levels of both etravirine and voriconazole are likely to be raised on concurrent use.[5,6] The US manufacturer advises that dose adjustments of voriconazole may be required depending on other concurrent drugs.[6] However, the UK manufacturer advises that no dose adjustment of either voriconazole or etravirine are required on concurrent use.[5]

1. Liu P, Foster G, LaBadie R, Gutierrez MJ, Sharma A. Pharmacokinetic interaction between voriconazole and efavirenz at steady state in healthy male subjects. J Clin Pharmacol (2008) 48, 73–84.
2. Damle B, LaBadie R, Crownover P, Glue P. Pharmacokinetic interactions of efavirenz and voriconazole in healthy volunteers. *Br J Clin Pharmacol* (2007) 65, 523–30.
3. Gerzenshtein L, Patel SM, Scarsi KK, Postelnick MJ, Flaherty JP. Breakthrough *Candida* infections in patients receiving voriconazole. *Ann Pharmacother* (2005) 39, 1342–5.
4. VFEND (Voriconazole). Pfizer Ltd. UK Summary of product characteristics, September 2009.
5. Intelence (Etravirine). Janssen-Cilag Ltd. UK Summary of product characteristics, November 2009.
6. Intelence (Etravirine). Tibotec, Inc. US Prescribing information, November 2009.
7. VFEND (Voriconazole). Pfizer Inc. US Prescribing information, December 2009.
8. Sustiva (Efavirenz). Bristol-Myers Squibb Company. US Prescribing information, September 2009.
9. Sustiva Film-coated Tablets (Efavirenz). Bristol-Myers Squibb Pharmaceuticals Ltd. UK Summary of product characteristics, June 2009.

NNRTIs + Drugs that affect gastric pH

Antacids roughly halve the AUC of delavirdine, and the H_2-receptor antagonists or proton pump inhibitors would be expected to interact similarly. Aluminium/magnesium antacids and H_2-receptor antagonists do not appear to interact to a clinically relevant extent with efavirenz or nevirapine. Omeprazole modestly increases the AUC of etravirine whereas ranitidine slightly reduces the AUC of etravirine.

Clinical evidence, mechanism, importance and management

(a) Delavirdine

Delavirdine is poorly soluble at pHs greater than 3, so the effect of giving delavirdine 300 mg ten minutes after an **antacid** was studied in 12 healthy subjects. The AUC and maximum serum levels of delavirdine were reduced by 48% and 57%, respectively, suggesting that delavirdine should not be given with **antacids**.[1] The manufacturer recommends separating administration by at least one hour.[2] Although it has not been studied, it is predicted that other drugs that reduce gastric acidity, such as **H_2-receptor antagonists** and **proton pump inhibitors**, will also reduce the absorption of delavirdine, and their long-term use with delavirdine is not recommended.[2]

Note that **didanosine** tablets are buffered with an **antacid**, and may reduce the levels of delavirdine. See 'NNRTIs + NRTIs', p.930, for further information.

(b) Efavirenz

The manufacturer notes that **aluminium/magnesium hydroxide** antacids and **famotidine** did not have any effect on the absorption or pharmacokinetics of efavirenz.[3,4] Therefore, no efavirenz dose adjustment is necessary with these drugs.[4] Other drugs that reduce gastric acidity are not expected to affect efavirenz absorption.[3]

(c) Etravirine

In a study in 16 healthy subjects, **ranitidine** 150 mg twice daily for 7 days slightly decreased the AUC of a single 100-mg dose of etravirine by 14%.[5] In 17 healthy subjects, **omeprazole** 40 mg daily for 7 days increased the AUC of a single 100-mg dose of etravirine by 41%, when compared with the AUC in 18 healthy subjects given etravirine alone. However, no significant change in the maximum concentration of etravirine occurred with either drug.[5]

In a study in 12 healthy subjects to investigate the effect of etravirine on the cytochrome P450 isoenzyme CYP2C19, a single 40-mg dose of **omeprazole** was given on days one and 14 of a 14-day course of etravirine 200 mg twice daily. Etravirine increased the ratio of the AUC of **omeprazole** to 5-hydroxyomeprazole by 29% on day one and 3.9-fold on day 14, of etravirine use.[6]

The mechanism of this modest increase in the AUC of etravirine with **omeprazole** is unclear. Subsequent pharmacokinetic analysis by the same group suggested that inhibition of the cytochrome P450 isoenzyme CYP2C19 by **omeprazole** may be involved.[5] However, this modest increase in the AUC of etravirine is not considered clinically relevant. Similarly, the minor decrease in etravirine AUC with **ranitidine** is not clinically significant therefore no special precautions are needed with concurrent use. The moderate increase in omeprazole levels would not be expected to be clinically significant or result in adverse effects as omeprazole has a wide therapeutic margin

The manufacturers therefore recommend that no dose adjustment is needed if etravirine is taken with a **proton pump inhibitor** or an **H_2-receptor antagonist**.[7,8]

(d) Nevirapine

In a study in 24 healthy subjects it was found that 30 mL of *Maalox* (**aluminium/magnesium hydroxide**) caused some moderate changes in the pharmacokinetics of nevirapine 200 mg, but none of them was considered to be clinically relevant.[9] The manufacturer states that nevirapine has no significant effect on the pharmacokinetics of **cimetidine**, and **cimetidine** causes only a slight 7% increase in the trough levels of nevirapine.[10] Therefore, no special precautions would seem to be necessary when nevirapine is taken with an **antacid** or with **cimetidine**.

1. Cox SR, Della-Coletta AA, Turner SW, Freimuth WW. Single-dose pharmacokinetic (PK) studies with delavirdine (DLV) mesylate: dose proportionality and effects of food and antacid. *Intersci Conf Antimicrob Agents Chemother* (1994) 34, 82.
2. Rescriptor (Delavirdine mesylate). Pfizer Inc. US Prescribing information, May 2008.
3. Sustiva Film-coated Tablets (Efavirenz). Bristol-Myers Squibb Pharmaceuticals Ltd. UK Summary of product characteristics, June 2009.
4. Sustiva (Efavirenz). Bristol-Myers Squibb Company. US Prescribing information, September 2009.
5. Schöller-Gyüre M, Kakuda TN, De Smedt G, Vanaken H, Bouche M-P, Peeters M, Woodfall B, Hoetelmans RMW. A pharmacokinetic study of etravirine (TMC125) co-administered with ranitidine and omeprazole in HIV-negative volunteers. Br J Clin Pharmacol (2008) 66, 508–516.
6. Schöller-Gyüre M, Kakuda TN, Stevens T, Aharchi F, De Smedt G, Peeters M, Hoetelmans RMW. Effect of etravirine on cytochrome P450 isoenzymes assessed by the Cooperstown 5+1 cocktail. 48th Annual ICAAC/ IDSA 46th General Meeting, Washington DC, 25th-28th October 2008.
7. Intelence (Etravirine). Janssen-Cilag Ltd. UK Summary of product characteristics, November 2009.
8. Intelence (Etravirine). Tibotec, Inc. US Prescribing information, November 2009.
9. Lamson M, Cort S, Macy H, Love J, Korpalski D, Pav J, Keirns J. Effects of food or antacid on the bioavailability of nevirapine 200 mg tablets. 11th International Conference on AIDS, Vancouver, 1996. Abstract Tu.B.2323.
10. Viramune (Nevirapine anhydrate). Boehringer Ingelheim Ltd. UK Summary of product characteristics, May 2009.

NNRTIs + Food

Food modestly increases efavirenz levels, and this may increase the frequency of adverse effects. Food increases the bioavailability of etravirine. Food has no clinically relevant effect on the levels of delavirdine or nevirapine; however, orange juice may affect delavirdine absorption.

Clinical evidence, mechanism, importance and management

(a) Delavirdine

In a randomised, crossover study in 13 HIV-positive patients taking delavirdine 400 mg three times daily, there were no changes in the steady-state serum levels of delavirdine taken with food, or taken at least one hour before or 2 hours after food, for 2 weeks. Food had no significant effect on the AUC or trough plasma level of delavirdine, although the peak plasma concentration of delavirdine was reduced by 21%.[1] This differed from a

previous single-dose study, in which there was a 26% fall in the AUC of delavirdine when it was taken with food.[2] There would appear to be no need to avoid taking delavirdine with food.

Orange juice increased delavirdine absorption by 50% to 70% in subjects with gastric hypoacidity, but had less effect (0 to 30%) in those with normal gastric acidity. However, despite the use of **orange juice**, the AUC of delavirdine was still about 50% lower in patients with gastric hypoacidity than those without.[3]

Delavirdine is a weak base that is poorly soluble at neutral pH. Therefore, in subjects with gastric hypoacidity, the absorption of delavirdine is reduced, and substances that lower gastric pH increase its absorption. The manufacturer of delavirdine recommends that, in patients with achlorhydria, delavirdine should be taken with an acidic beverage such as **orange** or **cranberry juice**, although this has not been specifically investigated.[4]

(b) Efavirenz

The manufacturers of efavirenz note that a high-fat meal increased the AUC of a 600-mg efavirenz *tablet* by 28%, when compared with fasting conditions, and increased its maximum concentration by 79%.[5,6] After a similar meal, the AUC and maximum level of the *capsule* formulation was increased by 22% and 39%, respectively, and after a low-fat meal the increases were 17% and 51%, respectively.[6] The manufacturers say that these increases might increase the frequency of adverse effects and they recommend that efavirenz is taken on an empty stomach, preferably at bedtime.[5,6]

(c) Etravirine

In a randomised, crossover study in 20 healthy subjects, a single 100-mg dose of etravirine was taken on an empty stomach, with a light breakfast (a croissant), with a standard breakfast, with a high-fibre breakfast or with a high-fat breakfast. The AUC of etravirine was 51% lower when it was taken on an empty stomach, compared with a standard breakfast. The AUC of etravirine taken after a light breakfast or high-fibre breakfast was 20% and 25% lower respectively, than after a standard breakfast. A high-fat breakfast resulted in a slight 9% increase in the AUC of etravirine. As the absorption of etravirine was nearly halved when it was taken on an empty stomach, it is recommended that etravirine should be taken with food. The differences between the types of meals were not considered to be clinically relevant.[7]

(d) Nevirapine

In a study in 24 healthy subjects, a high-fat breakfast caused some moderate changes in the pharmacokinetics of nevirapine 200 mg, but the AUC was not affected and none of the changes were considered to be clinically relevant.[8] Nevirapine may therefore be taken with or without food.

1. Morse GD, Fischl MA, Shelton MJ, Cox SR, Thompson L, Della-Coletta AA, Freimuth WW. Effect of food on the steady-state pharmacokinetics of delavirdine in patients with HIV infection. *Clin Drug Invest* (2003) 23, 255–61.
2. Cox SR, Della-Coletta AA, Turner SW, Freimuth WW. Single-dose pharmacokinetic (PK) studies with delavirdine (DLV) mesylate: dose proportionality and effects of food and antacid. *Intersci Conf Antimicrob Agents Chemother* (1994) 34, 82.
3. Shelton MJ, Hewitt RG, Adams JM, Cox SR, Chambers JH, Morse GD. Delavirdine malabsorption in HIV-infected subjects with spontaneous gastric hypoacidity. *J Clin Pharmacol* (2003) 43, 171–9.
4. Rescriptor (Delavirdine mesylate). Pfizer Inc. US Prescribing information, May 2008.
5. Sustiva Film-coated Tablets (Efavirenz). Bristol-Myers Squibb Pharmaceuticals Ltd. UK Summary of product characteristics, June 2009.
6. Sustiva (Efavirenz). Bristol-Myers Squibb Company. US Prescribing information, September 2009.
7. Schöller-Gyüre M, Boffito M, Pozniak AL, Leemans R, Kakuda TN, Woodfall B, Vyncke V, Peeters M, Vandermeulen K, Hoetelmans RMW. Effects of different meal compositions and fasted state on the oral bioavailability of etravirine. Pharmacotherapy (2008) 28, 1215–22.
8. Lamson MJ, Cort S, Sabo JP, MacGregor TR, Keirns JJ, Effects of food or antacid on the bioavailability of nevirapine 200 mg in 24 healthy volunteers. *Pharm Res* (1995) 12 (9 Suppl), S-101.

NNRTIs + Macrolides

Delavirdine may increase the levels of clarithromycin, whereas efavirenz, etravirine, and nevirapine may reduce clarithromycin levels, and increase those of its hydroxy metabolite. Clarithromycin does not appear to affect the pharmacokinetics of delavirdine, efavirenz or nevirapine to a clinically relevant extent, but may modestly increase etravirine levels. There is no pharmacokinetic interaction between azithromycin and efavirenz. A case of a neuropsychiatric reaction has been attributed to the use of clarithromycin in a man taking nevirapine.

Clinical evidence

(a) Delavirdine

In a study in 7 HIV-positive patients, **clarithromycin** 500 mg twice daily for 15 days did not cause a clinically significant change in the pharmacokinetics of delavirdine 300 mg three times daily, when compared with 4 other HIV-positive patients taking only delavirdine. The combination was well tolerated and no serious adverse events occurred.[1] However, although delavirdine levels are unaffected, the manufacturer notes that the AUC of **clarithromycin** was doubled by delavirdine.[2]

(b) Efavirenz

The manufacturers note that the concurrent use of **clarithromycin** 500 mg twice daily and efavirenz 400 mg daily for 7 days reduced the AUC of **clarithromycin** by 39% and increased the AUC of its hydroxy metabolite by 34%. Moreover, 46% of subjects receiving the combination developed a rash.[3,4] Clarithromycin had a minimal effect on the pharmacokinetics of efavirenz.[4] The manufacturers also note that there was no clinically significant pharmacokinetic interaction when a single 600-mg dose of **azithromycin** was given to healthy subjects who had been taking efavirenz 400 mg daily for 7 days.[3,4]

(c) Etravirine

The manufacturer of etravirine notes that concurrent use of etravirine and **clarithromycin** 500 mg twice daily reduced the AUC, and the maximum and minimum concentrations of **clarithromycin** by 39%, 53%, and 34%, respectively. The AUC and maximum concentration of the hydroxy metabolite were increased by 21% and 33%, respectively. In addition, **clarithromycin** increased the AUC and maximum concentration of etravirine by 42% and 44%, respectively.[5]

(d) Nevirapine

In a study in 15 HIV-positive patients, nevirapine 200 mg twice daily reduced the AUC of **clarithromycin** by 30% and reduced the maximum and minimum level of **clarithromycin** by 21% and 46%, respectively. Nevirapine also increased the AUC of the hydroxy metabolite of **clarithromycin** by about 27%.[6] The manufacturers also report that the AUC of nevirapine was increased by 26% by **clarithromycin**, when compared with historical controls. The AUC of **clarithromycin** was reduced by 31% and the AUC of its hydroxy metabolite was increased by 42%.[7,8]

A man developed hyperactivity (poor concentration, anxiety, suicidal and homicidal ideation) when taking **clarithromycin** and antiretroviral drugs, including nevirapine. This was thought to be due to accumulation of the hydroxy metabolite of **clarithromycin**.[9]

Mechanism

The NNRTIs are substrates of the cytochrome P450 isoenzyme CYP3A4, which is inhibited by clarithromycin. Delavirdine is also reported to inhibit CYP3A4, whereas efavirenz and nevirapine induce CYP3A4. Etravirine is also reported to weakly induce CYP3A4.[5] Therefore alterations in the metabolism of these drugs by CYP3A4 results in the altered levels seen.

Importance and management

Delavirdine may increase levels of clarithromycin. The manufacturer of delavirdine recommends that when both drugs are given to patients with renal impairment, the dose of clarithromycin should be reduced.[2]

In contrast, nevirapine may decrease clarithromycin levels and increase the levels of the hydroxy metabolite of clarithromycin. The manufacturer of **nevirapine** suggests that no dose adjustment of clarithromycin is needed; however, they say that alternatives to clarithromycin should be considered for the treatment of *Mycobacterium avium* complex (MAC) infection, as the hydroxy metabolite is not as active against this bacterium.[7,8] The UK manufacturer also advises close monitoring of liver function tests on the concurrent use of nevirapine and clarithromycin.[7]

Efavirenz may also decrease clarithromycin levels and increase the levels of the hydroxy metabolite of clarithromycin The manufacturers of efavirenz say that the clinical significance of the changes to clarithromycin pharmacokinetics is not known, but they suggest alternatives to clarithromycin, such as azithromycin, should be considered.[3,4] They also note that, as a possible interaction with erythromycin has not been studied, dose recommendations for concurrent use with efavirenz cannot be advised.[3]

Etravirine may also decrease clarithromycin levels and increase the levels of the hydroxy metabolite of clarithromycin. The UK manufacturer of **etravirine** also advise that, as the hydroxy metabolite of clarithromycin has reduced activity against *Mycobacterium avium* complex (MAC), an alternative to clarithromycin should considered for treating MAC.[5] The

increase in etravirine levels caused by clarithromycin would not be expected to be of clinical relevance.

1. Cox SR, Borin MT, Driver MR, Levy B, Freimuth WW. Effect of clarithromycin on the steady-state pharmacokinetics of delavirdine in HIV-1 patients. American Society for Microbiology, 2nd National Conference on Human Retroviruses, 1995. Abstract 487.
2. Rescriptor (Delavirdine mesylate). Pfizer Inc. US Prescribing information, May 2008.
3. Sustiva Film-coated Tablets (Efavirenz). Bristol-Myers Squibb Pharmaceuticals Ltd. UK Summary of product characteristics, June 2009.
4. Sustiva (Efavirenz). Bristol-Myers Squibb Company. US Prescribing information, September 2009.
5. Intelence (Etravirine). Janssen-Cilag Ltd. UK Summary of product characteristics, November 2009.
6. Robinson P, Gigliotti M, Lamson M, Azzam S, MacGregor T. Effect of the reverse transcriptase inhibitor, nevirapine, on the steady-state pharmacokinetics of clarithromycin in HIV-positive patients. 6th Conference on Retroviruses and Opportunistic Infections, Chicago, 1999. Abstract 374.
7. Viramune (Nevirapine anhydrate). Boehringer Ingelheim Ltd. UK Summary of product characteristics, May 2009.
8. Viramune (Nevirapine). Boehringer Ingelheim Pharmaceuticals, Inc. US Prescribing information, November 2008.
9. Prime K, French P. Neuropsychiatric reaction induced by clarithromycin in a patient on highly active antiretroviral therapy (HAART). *Sex Transm Infect* (2001) 77, 297–8.

NNRTIs + NNRTIs

Nevirapine modestly reduces the levels of efavirenz, whereas efavirenz has no effect on nevirapine levels. Efavirenz and nevirapine may reduce the levels of etravirine.

Clinical evidence, mechanism, importance and management

In a study in HIV-positive patients taking efavirenz 600 mg daily, the addition of **nevirapine** 400 mg daily resulted in a median decrease in the AUC of **efavirenz** of 22%, and a decrease in its minimum plasma concentration of 36%. The steady-state pharmacokinetics of **nevirapine** were not altered by **efavirenz**, when compared with historical control data.[1] However, the UK manufacturer does not recommend this combination as concurrent use could lead to a higher risk of adverse effects and does not improve efficacy over either NNRTI alone.[2]

In a study in 24 healthy subjects, pre-dosing with **efavirenz** 600 mg daily (taken on days one to 14) reduced the AUC, and maximum and trough levels of **etravirine** 400 mg once daily (taken on days 15 to 28) by 32%, 22% and 42%, respectively. When **etravirine** was taken as 200 mg twice daily, the AUC, and maximum and trough levels of **etravirine** were reduced (by 26%, 19%, and 34%, respectively). The authors note that **etravirine** is metabolised by the cytochrome P450 isoenzyme CYP3A4 and its bioavailability is reduced by 40% when given with **efavirenz**, an inducer of this isoenzyme. However, the pharmacokinetic changes were not considered to be of clinical significance.[3] The UK manufacturer of **etravirine** advises that **efavirenz** and **nevirapine** may reduce the levels of **etravirine** and therefore concurrent use is not recommended because it may cause treatment failure.[4]

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NNRTIs + NRTIs

Delavirdine absorption is reduced by the buffered preparation of didanosine, but probably not the enteric-coated preparation of didanosine. Delavirdine does not affect the pharmacokinetics of zidovudine. There is no pharmacokinetic interaction between efavirenz and zidovudine or lamivudine; or between nevirapine and didanosine, lamivudine, stavudine, zalcitabine or zidovudine. No interaction is predicted to occur between etravirine and abacavir, didanosine, emtricitabine, lamivudine, stavudine or zidovudine.

Clinical evidence, mechanism, importance and management

(a) Delavirdine

A study in 34 HIV-positive patients taking **zidovudine** 200 mg three times daily found that delavirdine mesilate 400 mg to 1.2 g daily for 9 days had no clinically significant effect on the pharmacokinetics of **zidovudine**.[1]

In a steady-state study, 9 HIV-positive patients taking **didanosine** 200 mg twice daily were also given delavirdine mesilate 400 mg three times daily for 14 days. **Didanosine** caused a 37% reduction in the maximum delavirdine serum levels and a trend towards a lower AUC, but when the drugs were given one hour apart no significant effect occurred. The pharmacokinetics of **didanosine** were not significantly affected by delavirdine.[2] A single-dose study in 12 HIV-positive patients found similar results.[3] The buffered preparation of **didanosine** contains antacids to increase its absorption, and antacids decrease the absorption of delavirdine (see 'NNRTIs + Drugs that affect gastric pH', p.928). The authors of the multiple-dose study advise that as **didanosine** had no clinically significant effect on the AUC of delavirdine, there is no reason to separate the doses.[2] However, the US manufacturer of delavirdine advises that concurrent use with buffered **didanosine** may reduce the levels of both delavirdine and didanosine, and they therefore recommend separating their administration by at least one hour.[4] The enteric-coated preparation of **didanosine**, which does not contain antacids, would not be expected to reduce the absorption of delavirdine.

(b) Efavirenz

The manufacturer notes that there were no clinically significant pharmacokinetic interactions between efavirenz and **lamivudine** or **zidovudine** in HIV-positive patients.[5,6] No dose adjustments are required on concurrent use.[6] No pharmacokinetic interactions are anticipated with other NRTIs.[5,6]

(c) Etravirine

The manufacturer of etravirine states that no significant interaction occurs between etravirine and **didanosine**. Therefore, no dose adjustment is needed on concurrent use. They also state that no interaction would be expected with other NRTIs which are primarily renally excreted, such as **abacavir**, **emtricitabine**, **lamivudine**, **stavudine**, and **zidovudine**.[7]

(d) Nevirapine

The pharmacokinetics of **didanosine** and **zidovudine** with or without nevirapine were assessed in 175 HIV-positive subjects. The bioavailability of **didanosine** was not affected, but the bioavailability of **zidovudine** was decreased by about one-third by nevirapine.[8] In a steady-state study in 24 HIV-positive patients, nevirapine 200 mg every 12 hours was added to regimens of **didanosine**, **didanosine** with **zidovudine**, or **zidovudine** with **zalcitabine**, for a 4-week period. No significant changes in the pharmacokinetics of **didanosine** or **zalcitabine** were seen. However, in the group taking **didanosine** with **zidovudine** the peak **zidovudine** plasma levels and AUC were reduced by 27% and 32%, respectively by nevirapine. The **zidovudine** pharmacokinetics in the group taking **zidovudine** and **zalcitabine** were not affected by nevirapine.[9] The reasons for these changes are not clear, but the clinical consequences are thought to be small, and the safety data indicate that the concurrent use of these drugs is safe and well tolerated. In another study in 4 patients, the simultaneous administration of nevirapine with **didanosine** tablets containing antacids had no effect on nevirapine absorption.[10] In a study in 22 patients, nevirapine 200 mg once daily for 2 weeks then 200 mg twice daily had no effect on the AUC of **stavudine** 30 to 40 mg twice.[11] Nevirapine appears to have no effect on **lamivudine** clearance, based on a population pharmacokinetic study.[12]

The UK manufacturer says that no dose adjustments are needed if **didanosine**, **lamivudine**, **stavudine**, **zalcitabine** or **zidovudine** is taken with nevirapine.[13]

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NNRTIs + Protease inhibitors

In general, efavirenz and nevirapine decrease the levels of the protease inhibitors, whereas delavirdine increases them. Amprenavir and nelfinavir decrease the levels of delavirdine. Most protease inhibitors do not appear to affect the levels of efavirenz or nevirapine. There is some evidence of increased adverse effects with antiviral doses of ritonavir and efavirenz, or saquinavir and delavirdine, including raised liver enzymes.

Clinical evidence, mechanism, importance and management

(a) Delavirdine

For a summary of the studies of the pharmacokinetic interactions of delavirdine and various protease inhibitors, see 'Table 21.3', (p.932). In general, these studies show that delavirdine can markedly increase protease inhibitor exposure. In addition, **amprenavir** and **nelfinavir** have been shown to approximately halve the AUC of delavirdine.

Delavirdine and the protease inhibitors are known to be both inhibitors of, and substrates for the cytochrome P450 isoenzyme CYP3A4, see 'Table 21.2', (p.914).

It has been suggested that delavirdine could be used clinically to boost the exposure to protease inhibitors, and this has been tried in at least one study.[1] However, this combination is complicated by the reduction in delavirdine levels caused by some protease inhibitors, and the combination may not be appropriate if the antiviral effect of delavirdine is required.[2] Moreover, if the combination is used, patients should be closely monitored for toxicity as in one study of **nelfinavir** and delavirdine, 4 out of 24 subjects had to stop both drugs before completing the study because of neutropenia, which resolved over several days.[3] The UK manufacturer of **saquinavir** says that liver function should be monitored frequently if delavirdine is also given, because in a small preliminary study hepatic enzymes were raised in 13% of subjects (grade 3 or 4 in 6%) receiving the combination.[4]

(b) Efavirenz

For a summary of the studies of the pharmacokinetic interactions of efavirenz and various protease inhibitors, see 'Table 21.3', (p.932). Most of the protease inhibitors did not affect efavirenz levels, although **ritonavir** caused a 20% increase in levels. Efavirenz is an inducer of the cytochrome P450 isoenzyme CYP3A4, by which the protease inhibitors are metabolised. With the exceptions of **nelfinavir** and **ritonavir**, which showed minor to modest increases in levels, efavirenz reduces the levels of the protease inhibitors, often to levels likely to lead to reduced antiviral efficacy. Ways to overcome this include the addition of low-dose **ritonavir** to boost the levels of the protease inhibitor (recommended for **amprenavir**, **atazanavir**, **fosamprenavir**, **saquinavir**) or increasing the dose for protease inhibitors already boosted by **ritonavir** (recommended for **lopinavir**). For a summary of the manufacturers' recommended regimens for use with efavirenz 600 mg daily, see 'Table 21.4', (p.936). However, the manufacturers of efavirenz note that increased adverse effects, including dizziness, nausea, paraesthesia and elevated liver enzyme levels, occurred with the concurrent use of efavirenz and **ritonavir** 500 or 600 mg twice daily (antiretroviral dose), and the combination was not well tolerated.[5,6] They recommend monitoring liver enzyme levels with this combination.[6] The UK manufacturer says that the tolerability of low-dose **ritonavir** with efavirenz has not been assessed, and they caution that the possibility of an increase in the incidence of efavirenz-associated adverse events should be considered with any **ritonavir**-boosted regimen used with efavirenz, due to a possible interaction.[5]

With **ritonavir**-boosted **lopinavir**, although an increased dose of 133/533 mg twice daily with efavirenz or nevirapine produced similar plasma levels of lopinavir to those seen with the lower dose of 400/100 mg twice daily without an NNRTI, the proportion of patients with a suboptimal minimum lopinavir level tended to be higher in those patients receiving the NNRTI.[7] This suggests that some patients may need a further increase in lopinavir/ritonavir dose. Another study with **ritonavir**-boosted **atazanavir** also found that the increased dose of atazanavir for use with NNRTIs did not appear to overcome the inducer effect of NNRTIs (efavirenz or nevirapine) and led to a 43% lower median minimum atazanavir level, and a greater proportion of patients with suboptimal minimum levels (25% versus 7%).[8] The US guidelines recommend a dose of **atazanavir** 400 mg with **ritonavir** 100 mg if it is given with efavirenz to treatment-naive patients; concurrent use is not recommended in treatment-experienced patients. However, note that the concurrent use of an NNRTI with a protease inhibitor is not a recommended regimen when starting antiretrovirals in treatment-naive patients.[9,10]

(c) Etravirine

For a summary of the studies of the pharmacokinetic interactions of etravirine and various protease inhibitors, see 'Table 21.3', (p.932). Etravirine is a weak inducer of the cytochrome P450 isoenzyme CYP3A4, and it may also inhibit CYP2C19 and P-glycoprotein, and the manufacturers advise that it may therefore significantly affect the levels of the protease inhibitors.[11,12] Hence the concurrent use of etravirine with unboosted protease inhibitors is not recommended.[10-12] Etravirine itself is also partly metabolised by CYP3A4 and therefore some protease inhibitors can affect its levels.[11,12] For a summary of the manufacturers' recommended regimens for use with etravirine, see 'Table 21.4', (p.936). The US guidelines specifically advise against the concurrent use of etravirine with unboosted protease inhibitors or with ritonavir-boosted **atazanavir**, **fosamprenavir** or **tipranavir**.[10]

Note that the concurrent use of an NNRTI with a protease inhibitor is not a recommended regimen when starting antiretrovirals in treatment-naive patients.[9,10]

(d) Nevirapine

For a summary of the studies of the pharmacokinetic interactions of nevirapine and various protease inhibitors, see 'Table 21.3', (p.932). Most protease inhibitors do not appear to affect the levels of nevirapine, although some caused a minor to modest increase. Nevirapine is an inducer of the cytochrome P450 isoenzyme CYP3A4, and so would be expected to reduce the levels of some of the protease inhibitors (see 'Table 21.2', (p.914)), sometimes to levels that are unlikely to be effective. Low-dose **ritonavir** has been used to boost the levels of some protease inhibitors when they were given with nevirapine. For a summary of the manufacturers' recommended regimens for use with nevirapine see 'Table 21.4', (p.936). If nevirapine is used with protease inhibitors, therapy should be closely monitored. For studies suggesting that increased doses of **ritonavir**-boosted **lopinavir** and **atazanavir** may not be sufficient in all patients given NNRTIs (including nevirapine), see *Efavirenz*, above. Note that the concurrent use of an NNRTI with a protease inhibitor is not a recommended regimen when starting antiretrovirals in treatment-naive patients.[9,10]

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Table 21.3 Summary of the pharmacokinetic interactions of NNRTIs and protease inhibitors

Drug combination	*No. of healthy subjects (unless specified)*	*Change in AUC (unless specified)*		*Refs*
		NNRTI	**Protease inhibitor**	
Delavirdine studies (usually 400 mg three times daily or 600 mg twice daily)				
Amprenavir	6 HIV-positive children		3-fold increase in Cmax* 5- to 10-fold increase in Cmin*	1
Amprenavir 1200 mg Amprenavir 1200 mg twice daily alone then 600 mg twice daily in combination	12 11	21% increase 47% decrease	4-fold increase 32% increase versus twice the dose given alone	2
Amprenavir 600 mg twice daily	18	61% decrease	130% increase	3
Indinavir 800 mg alone then 600 mg in combination	14	No change	44% increase versus higher dose given alone	4, 5
Nelfinavir 750 mg three times daily	24	42% decrease	92% increase	6
Ritonavir 300 mg twice daily		No change in steady state level	No change in steady state level	4
Ritonavir 600 mg twice daily	12 HIV-positive subjects	No change*	64% increase 81% increase in Cmin	7
Ritonavir 100 mg twice daily	19	No change	80% increase	8
Saquinavir 600 mg three times daily		No change in steady state level	5-fold increase in steady state level	4
Efavirenz studies (600 mg once daily)				
Amprenavir	2 HIV-positive children		Undetectable levels in less than 4 hours†	1
Amprenavir 1200 mg twice daily	7 HIV-positive subjects		About an 80% decrease in trough levels†	9
Amprenavir 1200 mg twice daily	11 HIV-positive subjects	No change*	24% decrease 43% decrease in Cmin	10
Atazanavir 400 mg once daily			74% decrease	11
Atazanavir/Ritonavir 300/100 mg once daily			39% increase	11
Darunavir/Ritonavir 300/100 mg twice daily	12	21% increase, 15% increase in Cmax, 17% increase in Cmin	13% decrease with a 31% decrease in Cmin, 15% decrease in Cmax (darunavir)	12
Fosamprenavir/Ritonavir 1395 mg/200 mg once daily	11		31% decrease in Cmin (amprenavir)	13
Fosamprenavir/Ritonavir 700 mg/100 mg twice daily	14		Slight decrease in Cmin (amprenavir)	13
Fosamprenavir/Ritonavir 1395 mg/300 mg once daily	11		Amprenavir levels comparable to that seen with fosamprenavir/ritonavir 1395/200 mg alone	13
Indinavir 1000 mg three times daily			Decrease of about 31% versus lower dose given alone	14
Indinavir/Ritonavir 800/100 mg twice daily	14	No change*	25% decrease (indinavir) 36% decrease (ritonavir)	15
Indinavir/Ritonavir 800/100 mg twice daily	20 HIV-positive subjects	31% increase in Cmin*	Cmin halved* (indinavir)	16
Lopinavir/Ritonavir 400/100 mg twice daily	24 HIV-positive subjects		44% decrease in Cmin* (lopinavir)	17
Lopinavir/Ritonavir 533/133 mg twice daily	26 HIV-positive subjects		No significant change in Cmin versus lower dose given without efavirenz* (lopinavir)	17
Lopinavir/Ritonavir 500/125 mg twice daily			No change in steady state level (lopinavir) relative to lopinavir/ritonavir 400/100 mg twice daily	18

Continued

Table 21.3 Summary of the pharmacokinetic interactions of NNRTIs and protease inhibitors (continued)

Drug combination	*No. of healthy subjects (unless specified)*	*Change in AUC (unless specified)*		*Refs*
		NNRTI	**Protease inhibitor**	
Lopinavir/Ritonavir 300/75 mg/m^2 twice daily	15 HIV-positive children	No change*	No change*	19
Nelfinavir 750 mg three times daily		No change	20% increase (nelfinavir), 37% decrease in M8 metabolite of nelfinavir	20
Nelfinavir/Ritonavir 1875/200 mg once daily	24	No change*	30% increase (nelfinavir) 20% decrease (ritonavir)	21
Ritonavir 500 mg twice daily		21% increase	17% increase	22
Saquinavir/Ritonavir 400/400 mg twice daily	12	No change*	No change in Cmin (ritonavir) 10% decrease in Cmin (saquinavir)	23
Tipranavir/Ritonavir 500/100 mg twice daily	24/21	No change	About a 40% decrease in Cmin (tipranavir)*	24
Etravirine studies (100 mg or 200 mg twice daily)				
Atazanavir/Ritonavir 300/100 mg daily		30% increase with 30% increase in Cmax and 26% increase in Cmin	14% decrease with 38% decrease in Cmin and no change in Cmax (atazanavir)	25
Darunavir/Ritonavir 600/100 mg twice daily	23	37% decrease with 32% decrease in Cmax, 49% decrease in Cmin	No change with etravirine 100 mg, 15% increase with etravirine 200 mg, no significant change in Cmin and Cmax (darunavir)	26
Darunavir/Ritonavir 600/100 mg twice daily	10 HIV-positive subjects	No significant change	No significant change	27
Fosamprenavir/Ritonavir 700/100 mg twice daily		No change	69% increase with 77% increase in Cmin and 62% increase in Cmax (amprenavir)	25
Lopinavir/Ritonavir 400/100 mg twice daily		35% decrease with 45% decrease in Cmin and 30% decrease in Cmax	No significant change in AUC or Cmax and 20% decrease in Cmin (lopinavir)	25
Saquinavir/Ritonavir 1000/100 mg twice daily		33% decrease with 29% decrease in Cmin and 37% decrease in Cmax	No change in AUC or Cmax and 20% decrease in Cmin (saquinavir)	25
Tipranavir/Ritonavir 500/200 mg twice daily		76% decrease with 82% decrease in Cmin and 71% decrease in Cmax	18% increase with 24% increase in Cmin and 14% increase in Cmax (tipranavir)	25
Nevirapine studies (200 mg once daily increased to twice daily)				
Darunavir/Ritonavir 400/100 mg twice daily		27% increase	No change in Cmin* (darunavir)	12
Fosamprenavir 1400 mg twice daily		29% increase with 25% increase in Cmax, 34% increase in Cmin	33% decrease with 35% decrease in Cmin, 25% decrease in Cmax (amprenavir)	28
Fosamprenavir/Ritonavir 700/100 mg twice daily		14% increase with 13% increase in Cmax, 22% increase in Cmin	11% decrease with 19% decrease in Cmin (amprenavir)	28
Indinavir 800 mg three times daily	19 HIV-positive subjects	No change*	28% decrease 48% decrease in Cmin	29
Indinavir 800 mg three times daily alone or 1000 mg three times daily in combination	124 HIV-positive subjects	No change	27% decrease in Cmin versus therapy alone at lower dose	30
Indinavir/Ritonavir 800/100 mg twice daily	21 HIV-positive subjects		57% decrease in Cmin (indinavir)‡	31
Lopinavir/ritonavir 300/75 mg/m^2 twice daily	27 HIV-positive children		22% decrease, 55% decrease in Cmin (lopinavir)	32
Nelfinavir 750 mg three times daily	7 HIV-positive subjects	No change*	50% decrease possibly due to sampling before nelfinavir steady state was reached	33, 34
Nelfinavir 750 mg three times daily	23 HIV-positive positive	No change*	No change	35

Continued

Table 21.3 Summary of the pharmacokinetic interactions of NNRTIs and protease inhibitors (continued)

Drug combination	*No. of healthy subjects (unless specified)*	*Change in AUC (unless specified)*		*Refs*
		NNRTI	**Protease inhibitor**	
Nelfinavir 750 mg three times daily	13 HIV-positive subjects		No change	36
Nelfinavir 750 mg three times daily	23 HIV-positive subjects		No change; 32% decrease in Cmin 62% decrease in M8 metabolite	37, 38
Ritonavir 600 mg twice daily	18 HIV-positive subjects	No change	No change	37, 38
Saquinavir 600 mg three times daily	21 HIV-positive subjects	No change	27% decrease	39
Saquinavir/ritonavir	20 HIV-positive subjects	No change*	No change	38
Tipranavir/ritonavir 250/200 mg twice daily	26 HIV-positive subjects	No change	No data	24

*Versus historical control data
†Therapeutic levels subsequently achieved by the addition of low-dose ritonavir
‡Versus data from 139 patients not taking nevirapine
Cmax = maximum serum concentration, Cmin = minimum serum concentration

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Continued

Table 21.3 Summary of the pharmacokinetic interactions of NNRTIs and protease inhibitors (continued)

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NNRTIs + Rifabutin

Rifabutin causes a very marked fall in delavirdine plasma levels: rifabutin levels are raised when the delavirdine dose is increased to compensate for this. Rifabutin does not affect efavirenz levels, whereas efavirenz decreases rifabutin levels. There is usually no important interaction between rifabutin and nevirapine, although some patients may have a higher risk of rifabutin adverse effects. No significant pharmacokinetic interaction appears to occur between etravirine and rifabutin.

Clinical evidence

(a) Delavirdine

In a controlled study in 7 HIV-positive patients taking delavirdine mesilate 400 mg three times daily for 30 days, the addition of rifabutin 300 mg daily from days 16 to 30 caused a fivefold increase in delavirdine clearance, and an 84% fall in its steady-state plasma levels. Rifabutin pharmacokinetics were not significantly altered.[1]

In another study in 5 HIV-positive patients taking rifabutin 300 mg daily, the dose of delavirdine was titrated to achieve a trough level of at least 5 micromol/L. The delavirdine dose had to be increased from 400 mg three times daily to at least 600 mg three times daily to achieve therapeutic levels, when compared with control patients not taking rifabutin. In these control patients similar delavirdine levels were achieved with delavirdine 400 mg three times daily. Delavirdine was reported to increase the AUC and trough level of rifabutin 3.4-fold and 5.5-fold, respectively.[2]

(b) Efavirenz

In a study in healthy subjects, the concurrent use of efavirenz 600 mg daily and rifabutin 300 mg daily for 2 weeks resulted in a modest 38% decrease in the AUC of rifabutin and a 45% decrease in its minimum levels, but no change in efavirenz levels.[3] In one study, doubling the rifabutin dose from 300 mg twice weekly to 600 mg twice weekly when starting efavirenz resulted in rifabutin AUCs that were 20% higher than baseline values.[4] In an analysis, 8 of 35 patients taking efavirenz and given rifabutin 450 mg daily were found to have subtherapeutic rifabutin levels, and they were switched to isoniazid.[5]

A case report describes treatment failure in a patient with tuberculous adenitis taking an efavirenz-containing HAART regimen with rifabutin. The patient had a persistently low rifabutin level (less than 0.1 micrograms/mL) despite large increases in the dose of rifabutin up to 1350 mg daily. When efavirenz was changed to nevirapine the rifabutin levels increased to 0.6 micrograms/mL and the patient developed rifabutin-induced iritis requiring a reduction in the rifabutin dose.[6]

(c) Etravirine

The manufacturer of etravirine reports that the concurrent use of etravirine with rifabutin 300 mg daily resulted in a reduction in the AUC, peak level and trough level of etravirine of about 35%. The AUC, peak level and trough level of rifabutin were also modestly reduced by 17%, 10% and 24%, respectively.[7]

(d) Nevirapine

In one study in 19 patients, the pharmacokinetics of nevirapine were only minimally affected by rifabutin, when compared with historical data.[8] In one HIV-positive patient with low rifabutin levels changing efavirenz to nevirapine resulted in high levels of rifabutin requiring dose reduction[6] (see under *Efavirenz*, above). The manufacturer notes that the concurrent use of rifabutin with nevirapine caused a minor 9% increase in nevirapine clearance and a 17% increase in its AUC, and a 28% increase in the maximum steady-state rifabutin levels.[9,10]

Mechanism

Efavirenz is a potent inducer of the cytochrome P450 isoenzyme CYP3A4, by which rifabutin is metabolised, and therefore concurrent use reduces rifabutin levels. As rifabutin is also an inducer of CYP3A4, it may reduce the levels of the NNRTIs, which are substrates of this isoenzyme.

Importance and management

The interactions between the NNRTIs and rifabutin are clinically significant. The concurrent use of **delavirdine** and rifabutin results in a clinically significant effect on the pharmacokinetics of both drugs, which may lead to treatment failure and an increase in adverse effects, respectively. The CDC in the US and the US manufacturer recommend that rifabutin should be not used with delavirdine.[11,12]

The CDC in the US advise that patients taking **efavirenz** should have the dose of rifabutin increased to 450 mg or 600 mg (taken daily or intermittently).[11] The British HIV Association (BHIVA) also recommend increasing the rifabutin dose to 450 mg daily in patients taking efavirenz.[13] Concurrent use should be closely monitored.

No significant pharmacokinetic interaction appears to occur between **nevirapine** and rifabutin, and no change in the dose of either drug is needed on concurrent use.[11,13] However, in the UK, the use of rifabutin in patients tak-

Table 21.4 Summary of the manufacturers' dose recommendations (unless stated otherwise) for combined use of protease inhibitors and NNRTIs

	Dose of protease inhibitor to be used with standard dose of the NNRTI			
	Delavirdine 400 mg three times daily	**Efavirenz 600 mg daily**	**Etravirine 200 mg twice daily**	**Nevirapine 200 mg twice daily**
Amprenavir	Appropriate dose not established (amprenavir levels increased)	Appropriate dose not established (amprenavir levels reduced)	Avoid	Appropriate dose not established (amprenavir levels may be decreased)
Amprenavir/Nelfinavir		No dose adjustments required		
Amprenavir/Ritonavir*	Appropriate dose not established. Care (unpredictable effect)	No dose adjustments required (amprenavir 600 mg with ritonavir100 or 200 mg twice daily)	Dose reduction may be needed (UK) Avoid - appropriate dose not established (US)	
Amprenavir/Saquinavir		Avoid		
Atazanavir		Avoid	Avoid	Avoid
Atazanavir/Ritonavir*		Not recommended but increase to 400/200 mg once daily† if required (UK) 300/100 mg once daily (US)	No dose adjustments required (UK) Avoid (US)	In the absence of data, avoid
Darunavir/Ritonavir*		Care	No dose adjustments required	No dose adjustments required
Fosamprenavir	Caution (delavirdine potentially subtherapeutic)	Appropriate dose not established	Avoid	Avoid
Fosamprenavir/Ritonavir*		700/100 mg twice daily or 1400/300 mg once daily	Dose reduction required (UK) Avoid - appropriate dose not established (US)	No dose adjustments required (700/100 mg twice daily)
Indinavir	Consider reducing indinavir dose to 600 mg three times daily. Optimum dose not established	Optimum dose not known. Increasing the dose to 1 g three times daily does not compensate for induced metabolism	Avoid (indinavir levels decreased)	Consider increasing to 1 g three times daily. Optimum dose not known
Indinavir/Ritonavir*		Appropriate dose not established. 800/100 mg twice daily has been tried		
Lopinavir/Ritonavir*	Appropriate dose not established	533/133 mg twice daily† or 600/150 mg twice daily. Avoid once daily regimens	No dose adjustments required (UK) Caution – etravirine levels increased (US)	533/133 mg twice daily† or 600/150 mg (US) or 500/125 mg (UK) twice daily. Avoid once daily regimens
Nelfinavir	Appropriate dose not established	No dose adjustments required	Avoid (increase in nelfinavir levels predicted)	No dose adjustment likely (UK). Appropriate dose not established (US)
Ritonavir*	Appropriate dose not established. Ritonavir dose reductions might be appropriate	No dose adjustments required, but not well tolerated. Monitor liver function	Avoid with ritonavir 600 mg twice daily	No dose adjustments required
Saquinavir	Appropriate dose not established. Monitor liver function	Avoid	Avoid	Appropriate dose not established
Saquinavir/Ritonavir*		No dose adjustments required. Monitor liver function	No dose adjustments required	No dose adjustments required
Tipranavir/Ritonavir*		No dose adjustments required	Avoid (etravirine levels decreased)	No dose adjustments required

*The UK manufactuer of efavirenz advises caution, because the possibility of an increase in the incidence of efavirenz-associated adverse events should be considered with any ritonavir-boosted regimen used with efavirenz, due to a possible interaction. This is because the combination of efavirenz with ritonavir at antiviral doses caused increased dizziness, nausea, paraesthesia and elevated transaminase levels.
†This dose increase may not be sufficient in some patients, so some caution is required.

ing nevirapine is not recommended due to limited data.[13] The manufacturers advise that, because of the high intersubject variability, some patients may experience large increases in rifabutin exposure and may be at higher risk of adverse effects, therefore if concurrent use is appropriate, it should be well monitored and undertaken with caution.[9,10]

As there is limited clinical data regarding the use of rifabutin with **etravirine**, the CDC in the US and BHIVA in the UK advise caution on concurrent use. They state that no dose adjustment of either drug is required.[11,13] The manufacturer of etravirine also advises caution on the concurrent use of rifabutin, due to the risk of reduced levels of both drugs.[7]

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NNRTIs + Rifampicin (Rifampin)

Rifampicin causes a very marked fall in delavirdine plasma levels, and is predicted to reduce etravirine levels. Neither efavirenz nor nevirapine affect rifampicin levels, but rifampicin modestly reduces the levels of these NNRTIs.

Clinical evidence

(a) Delavirdine

A study using rifampicin in place of rifabutin found that rifampicin caused a 27-fold increase in clearance of delavirdine, and the steady-state plasma levels became almost undetectable.[1] For more information on the effects of rifabutin on delavirdine, see 'NNRTIs + Rifabutin', p.935.

(b) Efavirenz

In a prospective study in 71 HIV-positive patients taking rifampicin and given efavirenz 600 mg daily, the mean 12-hour concentrations of efavirenz at week 6 and week 12 of concurrent use were 4.27 mg/L and 3.54 mg/L, respectively, and 2 patients were reported to have subtherapeutic 12-hour efavirenz concentrations (less than 1 mg/L) at week 12. Further analysis reported that low 12-hour concentrations, indicating low exposure to efavirenz, were associated with an increased risk of treatment failure.[2]

In a cross-sectional analysis of therapeutic drug monitoring in 339 HIV-positive patients taking efavirenz, 56 patients were also taking rifampicin and of these 48 patients (86%) were taking efavirenz 800 mg daily and the rest were taking 600 mg daily. Rifampicin was found to be associated with a 35% decrease in efavirenz plasma levels. However, adjustment for factors such as higher efavirenz doses and mostly black ethnicity in patients taking rifampicin, which were associated with 52% and 59% higher efavirenz levels, respectively, reversed the rifampicin effect, resulting in 48% higher efavirenz levels.[3]

Several studies suggest that efavirenz 800 mg daily with rifampicin is approximately equivalent to efavirenz 600 mg daily alone:

- In patients with HIV and tuberculosis the concurrent use of HAART including efavirenz (600 mg once daily) with antitubercular therapy including rifampicin (480 mg to 720 mg daily) decreased the AUC of efavirenz by 22% and decreased the trough concentration by 25% (although large interpatient variability was observed). Overall the pharmacokinetics of efavirenz 800 mg daily with rifampicin were similar to those of efavirenz 600 mg daily without rifampicin. The pharmacokinetics of rifampicin were not substantially altered by efavirenz.[4]
- Similar results were found in another study in HIV-positive patients taking HAART regimens containing efavirenz with rifampicin 450 mg or 600 mg daily. The mean trough plasma level for efavirenz when it was taken with rifampicin was 1.39 micrograms/mL. Four patients were found to have efavirenz levels of less than 0.1 micrograms/mL from 7 results; however, none of these patients failed HAART therapy and their viral loads remained below 50 copies/mL.[5]
- A slight increase in efavirenz clearance was reported in another small study in 16 HIV-positive patients taking rifampicin with efavirenz 800 mg daily, but no other significant differences in the pharmacokinetic parameters of efavirenz were seen when compared with 13 patients taking efavirenz 600 mg daily without rifampicin. Peak plasma levels were not elevated with efavirenz 800 mg and no increase in adverse effects occurred, although the authors did advise caution due to large interpatient variability.[6]

Further studies indicate that other efavirenz dose adjustments may be required in some patients if rifampicin is also given:

- In a retrospective study, 10 of 20 patients taking efavirenz 600 mg daily (3 patients) or 800 mg daily (7 patients) had therapeutic efavirenz levels while taking rifampicin. One patient taking efavirenz 800 mg daily had excessively raised efavirenz levels (24.47 micrograms/mL). Five patients had further plasma levels analysed. Two patients had subtherapeutic efavirenz levels, one patient had levels at the low end of the therapeutic range, and 2 patients were found to have raised efavirenz levels, one of which had a level of 23.47 micrograms/mL and developed toxicity. One of the patients with low efavirenz levels only achieved a therapeutic range with efavirenz dose increases from 800 mg to 1.2 g daily.[7]
- In 2 HIV-positive patients, rifampicin significantly lowered the plasma levels of efavirenz, necessitating a dose increase of efavirenz. When rifampicin was stopped, the efavirenz dose needed to be reduced by up to one-third to maintain levels within the accepted range of 1 to 4 mg/L.[8]
- A similar 26% reduction in the efavirenz AUC was reported in a study in healthy subjects.[9]

A few studies suggest that efavirenz 600 mg is a suitable dose in patients also given rifampicin. These studies often include patients of low bodyweight:

- In a study in 20 HIV-positive African patients taking efavirenz 600 mg daily and given a rifampicin-containing regimen for tuberculosis, 16 patients were reported to have undetectable viral loads, and only 2 patients failed HIV treatment. Of these two patients only one had subtherapeutic efavirenz levels. Tuberculosis was successfully treated in 19 patients. A large degree of interindividual variability in efavirenz levels was reported, which was greater during rifampicin treatment compared with after rifampicin treatment; however this did not result in antiviral treatment failure.[10]
- In a study in 57 HIV-positive patients with tuberculosis taking efavirenz 600 mg daily, the effect of rifampicin 450 mg or 600 mg daily on the pharmacokinetics of efavirenz 600 mg daily was evaluated in 19 of these patients. Rifampicin decreased the AUC, peak and trough plasma levels of efavirenz by 19%, 18%, and 20%, respectively, although this was not statistically significant. Four of the 57 patients taking rifampicin were found to have subtherapeutic efavirenz levels (less than 1 microgram/mL); 2 of the patients in the control group, who were not taking rifampicin, were also found to have subtherapeutic efavirenz trough levels. In the population studied, CYP2B6 G516T polymorphism, but not rifampicin, significantly affected the pharmacokinetics of efavirenz. It was suggested that modification of efavirenz dose may not be required with concurrent rifampicin.[11]
- In a study in Thai patients taking rifampicin, median efavirenz plasma levels were comparable between those receiving 600 mg daily and 800 mg daily and similar virological outcomes were seen. However, these findings may not be applicable to other populations with bodyweights above 50 kg.[12,13]
- An efficacy study in 1074 HIV-positive patients taking efavirenz 600 mg daily with rifampicin and 961 HIV-positive patients taking efavirenz 600 mg daily without rifampicin found no difference in probability of higher viral load or virological failure in the first 2 years of therapy between the groups.[14]
- A study in 15 children found no difference in efavirenz trough plasma levels between when the patients were taking rifampicin and after stopping rifampicin, although wide interpatient variability was reported. Subtherapeutic efavirenz levels were reported during and after rifampicin treatment in 9 and 8 children, respectively.[15]

Some studies found an association between the cytochrome P450 isoenzyme CYP2B6 metaboliser status and the efavirenz dose required with the concurrent use of rifampicin:

- In a study 26 HIV-positive patients taking efavirenz 600 mg daily as part of a HAART regimen and rifampicin for tuberculosis, the AUC and maximum and trough plasma concentrations of efavirenz did not differ significantly between the patients with cytochrome P450 isoenzyme CYP2B6 extensive metaboliser status (that is, those with normal levels of this isoenzyme) and those with intermediate levels of CYP2B6, who may be expected to have slightly higher levels of efavirenz. Those pa-

tients who were poor metabolisers (those lacking or deficient in CYP2B6) had significantly higher levels of efavirenz despite rifampicin treatment.[16]

- In one analysis, 7 of 9 patients receiving rifampicin and efavirenz 800 mg daily developed significant clinical toxicity and were found to have efavirenz levels markedly higher than the therapeutic range. The individual differences in CYP2B6 expression, although this was not confirmed with genetic testing.[17]
- A case report describes significantly *raised* efavirenz levels of up to 10 mg/L, with agitation and drowsiness, in a patient taking efavirenz 600 mg daily with rifampicin. The efavirenz dose needed to be reduced to 200 mg daily. However, in this case, genetic testing found that the patient was a poor metaboliser of CYP2B6.[18]

(c) Nevirapine

The concurrent use of nevirapine and rifampicin may result in subtherapeutic levels of nevirapine and possibly treatment failure:

- In a prospective, randomised, controlled study in 71 HIV-positive patients taking rifampicin and given nevirapine 400 mg daily, by week 12, subtherapeutic 12-hour concentrations were found in 21.3% of nevirapine patients. Further analysis reported that low 12-hour concentrations, indicating low exposure to nevirapine, were associated with treatment failure.[2]
- A study in 16 HIV-positive patients taking nevirapine 200 mg twice daily, and rifampicin 450 mg or 600 mg daily found the AUC, and maximum and trough plasma concentrations of nevirapine were increased by 67%, 63%, and 37%, respectively, at least 10 days after rifampicin was stopped. Of the three patients who were reported to have a raised viral load during rifampicin treatment, only one had a subtherapeutic nevirapine trough level of 1.3 mg/L, whereas five other patients with subtherapeutic nevirapine levels (less than 3 mg/L) had viral loads less than 400 copies/mL.[19]
- In another study in 13 patients taking nevirapine 200 mg twice daily, the addition of rifampicin 450 mg or 600 mg daily caused a 46% reduction in the AUC of nevirapine, and a 53% reduction in the minimum levels, with 8 of the patients having a nevirapine trough level below the therapeutic range (3 micrograms/mL). In 7 of the patients who had a reduction in the minimum levels to less than the therapeutic range, increasing the dose of nevirapine to 300 mg twice daily for 2 weeks increased the levels to above the therapeutic range in all patients without increasing adverse effects.[20]
- In a retrospective study, 6 patients taking nevirapine 200 mg twice daily (5 patients) or 300 mg twice daily (one patient) had therapeutic nevirapine levels while taking rifampicin. In the same study, another 4 patients had subtherapeutic nevirapine levels, one patient had levels at the low end of the therapeutic range, whereas one patient was found to have raised nevirapine levels.[7]
- Another retrospective analysis of therapeutic drug monitoring of nevirapine in HIV-positive patients also reported that the concurrent use of rifampicin was associated with about a 40% reduction in nevirapine plasma concentrations.[3] An efficacy study found that the 209 HIV-positive patients taking nevirapine 200 mg daily with rifampicin had a higher risk of raised viral loads at 6 months and had a shorter time to virological failure than 1726 HIV-positive patients taking nevirapine without rifampicin. No pharmacokinetic data for nevirapine were reported in this study.[14]
- The manufacturer states that the AUC of nevirapine was reduced by 58% by rifampicin in 14 subjects, when compared with historical data. There was no change in steady-state rifampicin pharmacokinetics.[21,22]

Some studies suggest the reduction in nevirapine levels does not result in therapeutic failure:

- In a study in HIV-positive patients with tuberculosis found that rifampicin caused a 31% decrease in the AUC of nevirapine and a non-significant 21% decrease in its trough concentration.[23] The authors of this study suggested that there is probably no need to increase the nevirapine dose, since the trough levels were still sufficiently above the level needed for antiviral activity.[23] Moreover, in contrast to the studies reported above, subsequent observational data supported the continued efficacy of standard dose nevirapine when it was used with rifampicin.[24]
- Others have also reported the successful use of nevirapine with twice weekly rifampicin with little effect on trough nevirapine levels.[25]
- In yet another study, the concurrent use of rifampicin and nevirapine reduced nevirapine levels by about 18% with no reduction in virological response, although the proportion of patients with trough levels below the recommended level was much higher (29.7% versus 6.8%) at 8 weeks.[26] When these patients stopped rifampicin treatment, the nevirapine levels were reported to increase from 5.4 mg/L to 6.4 mg/L. No difference in viral load reductions and CD4+ counts were seen between the group treated with rifampicin and the control group.[27]

Mechanism

Rifampicin is a potent inducer of the cytochrome P450 isoenzyme CYP3A4, by which the NNRTIs are metabolised, therefore reducing their levels. Efavirenz is also metabolised by CYP2B6, and this isoenzyme may also be affected by rifampicin.

Importance and management

The interactions between the NNRTIs and rifampicin are clinically significant; however, there is considerable debate regarding optimum dosing of efavirenz with concurrent use of rifampicin.

It has been recommended that the combination of **delavirdine** and rifampicin should be considered as contraindicated because the effects of the interaction are so large.[1] The CDC in the US and the manufacturer recommend that rifampicin should not be used with delavirdine.[28,29]

The manufacturer of **etravirine** predicts that rifampicin will decrease the plasma concentration of etravirine. Due to the risk of therapeutic failure, they therefore contraindicate the concurrent use of etravirine and rifampicin,[30] as do the CDC in the US.[28]

Efavirenz may be taken with rifampicin, however guidance on the appropriate dose adjustments required for efavirenz are conflicting. The CDC in the US suggest that usually no dose alteration of efavirenz is needed when it is taken with rifampicin but note however, that some experts recommend increasing the efavirenz dose to 800 mg daily in patients weighing more than 60 kg.[28] The British HIV Association (BHIVA) recommend increasing the efavirenz dose to 800 mg daily in patients more than 50 kg.[31] This is supported by evidence from some studies.[12,13] The UK manufacturer recommends a dose increase to 800 mg daily regardless of weight.[32] However, one study reported increases in efavirenz levels and adverse effects with the higher dose.[12,13,17] Some patients may be lacking or deficient in CYP2B6, and as one study found, may have raised efavirenz levels despite rifampicin use.[16] In these patients it is likely that a 600 mg dose of efavirenz may be sufficient. Concurrent use should be closely monitored and the efavirenz dose adjusted accordingly.

Based on these pharmacokinetic data, the manufacturers suggests that the concurrent use of rifampicin with **nevirapine** is not recommended, and that rifabutin may be considered instead, with close monitoring of adverse effects.[21,22] In the UK, rifampicin is not recommended for use with nevirapine, but if the combination is used, standard doses and monitoring of nevirapine is advised.[31] The CDC in the US state note that no dose alteration is needed for either nevirapine or rifampicin on concurrent use.[28]

Rifabutin may be used with some NNRTIs as an alternative to rifampicin. For further information and advice on the management of drug interactions between rifabutin and the NNRTIs, see 'NNRTIs + Rifabutin', p.935.

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22. Viramune (Nevirapine). Boehringer Ingelheim Pharmaceuticals, Inc. US Prescribing information, November 2008.
23. Ribera E, Pou L, Lopez RM, Crespo M, Falco V, Ocaña I, Ruiz I, Pahissa A. Pharmacokinetic interaction between nevirapine and rifampicin in HIV-infected patients with tuberculosis. *J Acquir Immune Defic Syndr* (2001) 28, 450–3.
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29. Rescriptor (Delavirdine mesylate). Pfizer Inc. US Prescribing information, May 2008.
30. Intelence (Etravirine). Janssen-Cilag Ltd. UK Summary of product characteristics, November 2009.
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32. Sustiva Film-coated Tablets (Efavirenz). Bristol-Myers Squibb Pharmaceuticals Ltd. UK Summary of product characteristics, June 2009.

NNRTIs + St John's wort (*Hypericum perforatum*)

There is some evidence to suggest that St John's wort may decrease the levels of nevirapine. Delavirdine, efavirenz and etravirine would be expected to be similarly affected.

Clinical evidence

Nevirapine levels, obtained by routine monitoring, were noted to be lower in 5 men who were also taking St John's wort. Based on a pharmacokinetic modelling analysis, it was estimated that St John's wort increased the oral clearance of **nevirapine** by about 35%.[1]

Mechanism

This finding supports predictions based on the known metabolism of the NNRTIs by the cytochrome P450 isoenzyme CYP3A4 (see 'Table 21.2', (p.914)), of which St John's wort is a known inducer.

Importance and management

The interaction between St John's wort and nevirapine confirms advice issued by the CSM in the UK,[2] that St John's wort may decrease blood levels of the NNRTIs with possible loss of HIV suppression. Therefore concurrent use should be avoided.

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2. Committee on Safety of Medicines. Message from Professor A Breckenridge (Chairman of CSM) and Fact Sheet for Health Care Professionals, 29th February 2000.

NNRTIs + Tenofovir

In general, no pharmacokinetic interaction appears to occur between tenofovir and efavirenz, etravirine, or nevirapine, although raised efavirenz levels have been reported in some patients. Neuropsychiatric adverse effects have been reported with the concurrent use of efavirenz and tenofovir. Some clinical data have shown a high rate of treatment failure when tenofovir is given with enteric-coated didanosine and either efavirenz or nevirapine.

Clinical evidence

(a) Efavirenz

In a pharmacokinetic study in 29 subjects, there was no interaction between efavirenz 600 mg daily and tenofovir disoproxil fumarate 300 mg daily.[1,2] Also, efavirenz plasma levels did not differ between patients taking tenofovir and patients not taking tenofovir. It appeared that efavirenz did not alter tenofovir levels.[3]

Another study also reported no overall difference in efavirenz levels in 18 HIV-positive patients also taking tenofovir, when compared with 151 HIV-positive patients taking efavirenz alone. However, further analysis found that 23 patients who were poor metabolisers of the cytochrome P450 isoenzyme CYP2B6 (those lacking or deficient in CYP2B6) had higher levels of efavirenz than those who were extensive metabolisers of CYP2B6 (that is, those with normal levels of this isoenzyme). Five of the 23 were taking tenofovir with efavirenz and were found to have significantly higher levels of efavirenz than the 18 who were not taking tenofovir. In one case, the addition of tenofovir increased the AUC of efavirenz by about 66% resulting in neuropsychological adverse effects. These adverse effects resolved when the efavirenz dose was reduced to 200 mg daily.[4]

Nine cases of neuropsychiatric adverse effects, such as nightmares, insomnia, and dizziness, have been reported in HIV-positive patients taking efavirenz, in each case developing within 48 hours of starting tenofovir. These patients had previously been taking long-term efavirenz-based HAART with no reports of neurological adverse effects. In 6 of these patients, the symptoms resolved when tenofovir was stopped.[5]

Some clinical data have shown a high rate of treatment failure with a once daily combination of tenofovir disoproxil fumarate 300 mg, enteric-coated didanosine 200 or 250 mg and efavirenz 600 mg daily.[6]

(b) Etravirine

In a study, healthy subjects were given tenofovir 300 mg daily for 16 days with etravirine 200 mg or 800 mg twice daily on days one to 8 or days 9 to 16. Tenofovir modestly reduced the $AUC_{0\text{-}12}$ of etravirine by 19 to 31%. Etravirine slightly increased the AUC of tenofovir by about 15%.[7]

(c) Nevirapine

In a retrospective analysis, plasma levels of nevirapine 200 mg twice daily or 400 mg once daily did not differ between patients taking tenofovir disoproxil fumarate 300 mg daily and those not taking tenofovir. It appeared that nevirapine did not alter tenofovir levels.[3]

Some clinical data have shown a high rate of treatment failure with a once daily combination of tenofovir disoproxil fumarate 300 mg, enteric-coated didanosine 200 or 250 mg and nevirapine 400 mg daily.[6]

Mechanism

Efavirenz is metabolised by the cytochrome P450 isoenzyme CYP2B6. Patients lacking or with low levels of this isoenzyme (poor metabolisers) are known to have increased levels of efavirenz, which may increase the risk of adverse effects. However, as tenofovir is not known to have significant inhibitory effects on cytochrome P450 isoenzymes, the mechanism for the raised efavirenz levels reported with tenofovir is unclear. The au-

thors of this study note that tenofovir has been found to weakly inhibit CYP2B6 *in vitro*.[4]

Importance and management

In general, no significant pharmacokinetic interaction appears to occur between efavirenz and tenofovir. However, the study[4] suggesting that patients who are poor metabolisers of CYP2B6 may have higher levels of efavirenz when treated with tenofovir warrants further investigation. Until further information is available, it may be prudent to bear the possibility of an interaction in mind should a patient taking efavirenz develop an increase in adverse effects when tenofovir is started. Note that there are clinical data supporting the use of other tenofovir and efavirenz-based regimens.[1,2]

The modest changes in etravirine and tenofovir pharmacokinetics are not expected to be of clinical significance, so no dose adjustment is needed with concurrent use. No significant pharmacokinetic interaction appears to occur between nevirapine and tenofovir.

The combination of efavirenz or nevirapine with tenofovir and didanosine should probably not be used, and the UK manufacturer specifically advises against the use of tenofovir with didanosine,[1] see 'NRTIs + Tenofovir', p.957.

1. Viread (Tenofovir disoproxil fumarate). Gilead Sciences Ltd. UK Summary of product characteristics, July 2009.
2. Viread (Tenofovir disoproxil fumarate). Gilead Sciences, Inc. US Prescribing information, October 2009.
3. Droste JAH, Kearney BP, Hekster YA, Burger DM. Assessment of drug-drug interactions between tenofovir disoproxil fumarate and the nonnucleoside reverse transcriptase inhibitors nevirapine and efavirenz in HIV-infected patients. *J Acquir Immune Defic Syndr* (2006) 41, 37–43.
4. Rotger M, Colombo S, Furrer H, Décosterd L, Buclin T, Telenti A. Does tenofovir influence efavirenz pharmacokinetics. *Antivir Ther* (2007) 12, 115–8.
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NNRTIs + Valproate

Efavirenz levels were not altered by valproic acid in one study in HIV-positive patients, and valproic acid levels were not different to those in a control group not taking efavirenz. However, one patient had a marked decrease in valproate levels after starting efavirenz. A case of hepatotoxicity has occurred in a patient taking valproic acid with nevirapine, ritonavir and saquinavir.

Clinical evidence

In a study in 11 HIV-positive patients taking **efavirenz** 600 mg daily with various NRTIs, there was no change in the pharmacokinetics of **efavirenz** after they took valproic acid 250 mg twice daily for 7 days. Valproic acid levels achieved in these patients were not significantly different from those in 11 HIV-positive control patients mainly taking NRTIs, even when the 3 control patients taking a protease inhibitor or NNRTI (amprenavir, indinavir, or nelfinavir with nevirapine) were excluded.[1]

However, a patient with a bipolar disorder and multidrug addiction had a decrease in plasma valproic acid levels of more than 50% shortly after starting an antiretroviral regimen including **efavirenz**. Even though the valproate dose was increased to 4 g daily, it was found difficult to achieve a target plasma level of 50 mg/dL. About 3 months later, following a valproate dose reduction to 1.5 g daily due to adverse effects, his level was unaltered, at 52 mg/dL.[2]

A case of valproate-associated hepatotoxicity occurred in a 51-year-old man about 3 weeks after he started **nevirapine** 200 mg twice daily, ritonavir 400 mg twice daily, saquinavir 400 mg twice daily, and stavudine. Serum valproic acid levels remained therapeutic.[3]

Mechanism

Uncertain.

Importance and management

The findings of the study[1] suggest that valproate can be used with efavirenz-based regimens without any pharmacokinetic drug interaction. However, the case report of reduced valproic acid levels introduces a note of caution. It may be appropriate to monitor valproate levels in patients taking efavirenz. It is unclear whether the case of hepatotoxicity was a result of a drug interaction. Note that there has been some concern about using valproate in HIV infection but there seems to be no established reason to avoid or specifically promote the use of valproate in HIV-infection *per se*.

1. DiCenzo R, Peterson D, Cruttenden K, Morse G, Riggs G, Gelbard H, Schifitto G. Effects of valproic acid coadministration on plasma efavirenz and lopinavir concentrations in human immunodeficiency virus-infected adults. *Antimicrob Agents Chemother* (2004) 48, 4328–31.
2. Saraga M, Preisig M, Zullino DF. Reduced valproate plasma levels possible after introduction of efavirenz in a bipolar patient. *Bipolar Disord* (2006) 8, 415–17.
3. Cozza KL, Swanton EJ, Humphreys CW. Hepatotoxicity with combination of valproic acid, ritonavir, and nevirapine: a case report. *Psychosomatics* (2000) 41, 452–3.

NNRTIs; Delavirdine + Glutamic acid

Glutamic acid increases the absorption of delavirdine in patients with poor gastric acid production.

Clinical evidence, mechanism, importance and management

When **glutamic acid** 1.36 g three times daily was given with delavirdine 400 mg three times daily to 8 HIV-positive subjects with gastric hypoacidity, the AUC of delavirdine was increased by 50%.[1] Delavirdine is a weak base that is poorly soluble at neutral pH. Therefore, in subjects with gastric hypoacidity, the absorption of delavirdine is reduced, and substances that lower gastric pH increase its absorption. However, the clinical value of using **glutamic acid** with delavirdine to boost its absorption is unknown. The manufacturer recommends that, in patients with achlorhydria, delavirdine should be taken with an **acidic beverage** such as **orange** or **cranberry juice**.[2]

1. Morse GD, Adams JM, Shelton MJ, Hewitt RG, Cox SR, Chambers JH. Gastric acidification increases delavirdine mesylate (DLV) exposure in HIV+ subjects with gastric hypoacidity (GH). *Clin Pharmacol Ther* (1996) 59, 141.
2. Rescriptor (Delavirdine mesylate). Pfizer Inc. US Prescribing information, May 2008.

NNRTIs; Etravirine + Miscellaneous

Etravirine modestly decreases the levels of maraviroc. Etravirine is predicted to decrease the levels of some antiarrhythmics, immunosuppressants (ciclosporin, sirolimus and tacrolimus), and the phosphodiesterase-type-5 inhibitors (sildenafil, tadalafil, and vardenafil).
Etravirine has no clinically significant effect on the pharmacokinetics of digoxin and enfuvirtide. No interaction is expected to occur between etravirine and ribavirin.

Clinical evidence, mechanism, importance and management

(a) Antiarrhythmics

The manufacturers of etravirine predict that it will reduce the levels of **amiodarone**, **disopyramide**, **flecainide**, **lidocaine** (systemic use), **mexiletine**, **propafenone**, and **quinidine**. They therefore recommend caution on concurrent use and to monitor the drug levels of the affected antiarrhythmic, if this is possible.[1,2]

(b) Digoxin

The UK manufacturer reports that etravirine slightly increased the AUC and maximum concentration of digoxin by 18% and 19%, respectively.[1] This minor change in digoxin levels would not be expected to be of clinical significance, and no digoxin dose adjustment is needed on concurrent use. The US manufacturer states that, when starting digoxin in a patient taking etravirine the lowest possible dose of digoxin should be used. If etravirine is started in a patient taking digoxin, they state that no dose adjustments of either drug are necessary.[2] Both the UK and US manufacturer advises monitoring of digoxin levels on the concurrent use of etravirine.[1,2]

(c) Enfuvirtide

The UK manufacturer reports that enfuvirtide 90 mg twice daily had no significant effect on the pharmacokinetics of etravirine. The levels of enfuvirtide are not expected to be affected by etravirine. No dose adjustment is necessary on concurrent use.[1]

(d) Immunosuppressants

The manufacturers predict that etravirine will reduce the levels of **ciclosporin**, **tacrolimus** and **sirolimus**. This is because etravirine is an inducer of the isoenzyme CYP3A4, by which ciclosporin, sirolimus and tacrolimus are metabolised. They therefore recommend caution on concurrent use, and suggest monitoring the drug levels of the affected immunosuppressant to prevent a loss of therapeutic effect.[1,2]

(e) Maraviroc

The UK manufactures reports that concurrent use of etravirine with maraviroc 300 mg twice daily decreases the AUC, maximum concentration, and minimum concentration of maraviroc by 53%, 60%, and 39%, respectively. However, when etravirine was taken with maraviroc and ritonavir-boosted **darunavir** 100/600 mg twice daily, the AUC, maximum concentration and minimum concentration of maraviroc were increased 3-fold, 1.8-fold, and 5.3-fold, respectively. The pharmacokinetics of etravirine were minimally affected and no dose adjustment of etravirine appears to be needed when it is taken with maraviroc and a ritonavir-boosted protease inhibitor. For maraviroc, the manufacturer[1] advises following the dose adjustments given for concurrent use with the protease inhibitors, see 'Maraviroc + Ketoconazole and other CYP3A4 inhibitors', p.922.

(f) Phosphodiesterase type-5 inhibitors

The manufacturers report that etravirine reduces the AUC and maximum concentration of **sildenafil** by 57% and 45%, respectively. Similarly, the AUC and maximum levels of its active metabolite, *N*-desmethylsildenafil, are also reduced, by 41% and 25%, respectively.[1,2] Other phosphodiesterase inhibitors (**tadalafil** and **vardenafil**) are predicted to be similarly affected. This is because etravirine induces the isoenzyme CYP3A4, by which these phosphodiesterase inhibitors are metabolised. An initial dose adjustment of the phosphodiesterase inhibitor is not considered to be necessary on concurrent use. However, given the reductions reported with sildenafil, some patients may require a dose increase, according to clinical effect.[1,2]

(g) Ribavirin

The UK manufacturer states that although the combination has not been studied, an interaction between etravirine and ribavirin is unlikely. Therefore no dose adjustment of either drug is needed with concurrent use.[1]

1. Intelence (Etravirine). Janssen-Cilag Ltd. UK Summary of product characteristics, November 2009.
2. Intelence (Etravirine). Tibotec, Inc. US Prescribing information, November 2009.

NRTIs + Aciclovir and related drugs

The concurrent use of zidovudine and aciclovir normally appears to be uneventful, but an isolated report describes overwhelming fatigue in one patient given zidovudine and intravenous aciclovir. No interaction would be expected between zidovudine and valaciclovir. Famciclovir does not alter the pharmacokinetics of zidovudine or emtricitabine.

Clinical evidence, mechanism, importance and management

(a) Emtricitabine

In a study in 12 healthy subjects no important pharmacokinetic interaction was found between single doses of emtricitabine 200 mg and **famciclovir** 500 mg.[1]

(b) Zidovudine

1. Aciclovir or Valaciclovir. A study in 20 HIV-positive men found no pharmacokinetic interaction between zidovudine 100 mg and aciclovir 400 or 800 mg, both given every 4 hours, 5 times a day, and the combination was well tolerated over a 6-month period.[2] When 41 HIV-positive patients taking zidovudine were given aciclovir, no changes in the pharmacokinetics of the zidovudine occurred and the adverse effects were unchanged.[3] In a group of patients with AIDS taking zidovudine, some of whom were also given aciclovir, no obvious problems developed that could be attributed to the use of the aciclovir.[4]

In contrast, a man with herpes who had been treated with intravenous aciclovir 250 mg every 8 hours for 3 days, developed overwhelming fatigue and lethargy within about an hour of starting oral zidovudine 200 mg every 4 hours. This lessened slightly on changing from intravenous to oral aciclovir, which was continued for 3 days, and symptoms resolved when the aciclovir was withdrawn. The symptoms developed again when intravenous aciclovir was given as a test.[5] This isolated case of fatigue is not understood, and no other cases appear to have been reported. It is therefore unlikely to be of general relevance.

Note that as valaciclovir is a prodrug of aciclovir, no interaction would generally be expected when it is given with zidovudine.

2. Famciclovir. Minimal changes in zidovudine pharmacokinetics were seen when 12 HIV-positive patients taking zidovudine 400 mg to 1 g daily were given a single 500-mg dose of famciclovir.[6]

1. Wang LH, Blum MR, Hui J, Hulett L, Chittick GE, Rousseau F. Lack of significant pharmacokinetic interactions between emtricitabine and other nucleoside antivirals in healthy volunteers. *Intersci Conf Antimicrob Agents Chemother* (2001) 41, 18.
2. Hollander H, Lifson AR, Maha M, Blum R, Rutherfod GW, Nusinoff-Lehrman S. Phase I study of low-dose zidovudine and acyclovir in asymptomatic human immunodeficiency virus seropositive individuals. *Am J Med* (1989) 87, 628–32.
3. Tartaglione TA, Collier AC, Opheim K, Gianola FG, Benedetti J, Corey L. Pharmacokinetic evaluations of low- and high-dose zidovudine plus high-dose acyclovir in patients with symptomatic human immunodeficiency virus infection. *Antimicrob Agents Chemother* (1991) 35, 2225–31.
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5. Bach MC. Possible drug interaction during therapy with azidothymidine and acyclovir for AIDS. *N Engl J Med* (1987) 316, 547.
6. Rousseau F, Scott S, Pratt S, Fowles S, Sparrow P, Lascoux C, Lehner V, Sereni D. Safe coadministration of famciclovir and zidovudine. *Intersci Conf Antimicrob Agents Chemother* (1994) 34, 83.

NRTIs + Antacids

Aluminium/magnesium hydroxide modestly reduces the bioavailability of zalcitabine. Antacids would not be expected to have any additional pharmacokinetic effect on buffered didanosine preparations.

Clinical evidence, mechanism, importance and management

(a) Didanosine

Didanosine is acid labile, so to increase its absorption, some didanosine preparations (e.g. buffered tablets) have been formulated with antacids.[1] Additional concurrent antacids would not be expected to have any further clinically relevant effect on didanosine pharmacokinetics, although the US manufacturers of the oral powder for solution[2] suggest that additional antacids may increase the adverse effects of the components of this preparation (presumably both the antacid and didanosine components).

(b) Zalcitabine

A study in 12 HIV-positive patients given a single 1.5-g dose of zalcitabine found that 30 mL of *Maalox* [**aluminium/magnesium hydroxide**] caused a 25% reduction in the bioavailability of zalcitabine.[3] These changes are moderate and of uncertain clinical importance. The manufacturers recommended that zalcitabine should not be taken at the same time as **aluminium/magnesium**-containing antacids.[4,5]

1. Videx Tablets (Didanosine). Bristol-Myers Squibb Pharmaceuticals Ltd. UK Summary of product characteristics, August 2008.
2. Videx Pediatric Powder for Oral Solution (Didanosine). Bristol-Myers Squibb Company. US Prescribing information, June 2009.
3. Massarella JW, Holazo AA, Koss-Twardy S, Min B, Smith B, Nazareno LA. The effects of cimetidine and Maalox® on the pharmacokinetics of zalcitabine in HIV-positive patients. *Pharm Res* (1994) 11 (10 Suppl), S-415.
4. Hivid (Zalcitabine). Roche Products Ltd. UK Summary of product characteristics, November 2004.
5. Hivid (Zalcitabine). Roche Pharmaceuticals. US Prescribing information, September 2002.

NRTIs + Antiepileptics

Valproate increases the bioavailability of zidovudine, and one case of severe anaemia was attributed to the interaction. A case of liver toxicity has also been reported on the concurrent use of these

drugs. Phenytoin and phenobarbital are predicted to slightly decrease abacavir levels.

Clinical evidence

(a) Abacavir

The UK manufacturer of abacavir says that **phenobarbital** and **phenytoin** may slightly decrease abacavir concentrations by affecting glucuronyltransferases.[1] The US manufacturer however does not mention this potential interaction.[2]

(b) Zidovudine

In a study in 6 HIV-positive subjects, the AUC and mean plasma levels of zidovudine 100 mg every 8 hours were increased by 80% when they were given **valproic acid** 250 mg or 500 mg every 8 hours for 4 days. No adverse reactions, changes in hepatic or renal function, or alterations in the blood picture were reported.[3] A case report describes a patient with AIDS taking zidovudine 100 mg five times daily who had a two- to threefold increase in trough and peak serum zidovudine levels, and a 74% increase in the CSF zidovudine levels while taking **valproic acid** 500 mg three times daily.[4] In another report, a patient taking **carbamazepine**, **clobazam** and **gabapentin** was given zidovudine, **lamivudine** and **abacavir**. Nine months later, **valproic acid** 500 mg twice daily was added because of a seizure frequency of greater than one per month. At this time, his haemoglobin level was normal. About 2 months later, he was found to have severe anaemia, requiring a blood transfusion. **Stavudine** was substituted for zidovudine in his antiretroviral therapy, and 4 months later his haemoglobin was normal. The adverse haematological effects were attributed to an interaction between the **valproate** and zidovudine.[5] Another HIV-positive patient, who had been taking **valproate** for 2 years and zidovudine, developed severe encephalopathy, adult respiratory distress syndrome and liver failure (steatosis). Both valproate and zidovudine were stopped, and the patient gradually recovered.[6]

For the possible effect of zidovudine on phenytoin levels, see 'Phenytoin + Zidovudine', p.648.

Mechanism

The evidence indicates that the metabolism (glucuronidation) of zidovudine is inhibited by valproate so that its bioavailability is increased.[3,4] It was suggested that this caused the zidovudine haematological toxicity in the case reported.[5] The glucuronidation of abacavir is predicted to be increased by drugs that can induce glucuronyltransferases, such as phenobarbital and phenytoin.[1]

Importance and management

Information seems to be limited to the papers cited, but an interaction between zidovudine and valproate would appear to be established. It would therefore seem prudent to monitor for increases in zidovudine adverse effects and possible toxicity if valproate is added. The other NRTIs do not undergo significant glucuronidation (see 'Antivirals', (p.913)), and would therefore not be expected to interact with valproate.

Bear in mind the possibility of an interaction should a patient taking phenytoin or phenobarbital have a reduced response to abacavir.

For a discussion of drug-disease considerations when using valproate in HIV infection, see under Importance and management in 'Protease inhibitors + Valproate', p.988.

1. Ziagen (Abacavir sulfate). ViiV Healthcare UK Ltd. UK Summary of product characteristics, June 2009.
2. Ziagen (Abacavir sulfate). GlaxoSmithKline. US Prescribing information, December 2008.
3. Lertora JJL, Rege AB, Greenspan DL, Akula S, George WJ, Hyslop NE, Agrawal KC. Pharmacokinetic interaction between zidovudine and valproic acid in patients infected with human immunodeficiency virus. *Clin Pharmacol Ther* (1994) 56, 272–8.
4. Akula SK, Rege AB, Dreisbach AW, Dejace PMJT, Lertora JJL. Valproic acid increases cerebrospinal fluid zidovudine levels in a patient with AIDS. *Am J Med Sci* (1997) 313, 244–6.
5. Antoniou T, Gough K, Yoong D, Arbess G. Severe anemia secondary to a probable drug interaction between zidovudine and valproic acid. *Clin Infect Dis* (2004) 38, e38–40.
6. Leppik IE, Gapany S, Walczak T. An HIV-positive patient with epilepsy. *Epilepsy Behav* (2003) 4 (Suppl 1), S17–S19.

NRTIs + Antimycobacterials

Didanosine, stavudine and zalcitabine are not expected to interact with rifabutin, but rifabutin may modestly increase the clearance of zidovudine. An isolated case describes undetectable rifabutin levels in a patient taking antiretrovirals including buffered didanosine.
Rifampicin (rifampin) appears to modestly increase the clearance of zidovudine, and is predicted to interact similarly with abacavir.
Isoniazid, pyrazinamide and ethambutol appear not to interact with zidovudine.
The clearance of isoniazid is increased by zalcitabine, and there is a theoretical increased risk of peripheral neuropathy.

Clinical evidence, mechanism, importance and management

(a) Abacavir

The UK manufacturer of abacavir[1] says that potent enzyme inducers such as **rifampicin** (**rifampin**) may slightly decrease abacavir plasma concentrations due to their ability to induce glucuronyltransferases (see also *Zidovudine*, below). As yet, there appears to be no other information on this.

(b) Didanosine

In a study in 12 patients with AIDS, **rifabutin** 300 to 600 mg daily for 12 days did not significantly affect the pharmacokinetics of [buffered] didanosine 167 to 250 mg twice daily.[2] The steady-state pharmacokinetics of **rifabutin** were not affected by didanosine (buffered sachet preparation),[3] which suggests that the buffer used in the didanosine preparation had no effect on **rifabutin** absorption.[3] However, a case has been reported of a patient taking ritonavir-boosted lopinavir, efavirenz, lamivudine and buffered didanosine who had impaired **rifabutin** absorption. When **rifabutin** was taken 30 minutes after didanosine, **rifabutin** levels were undetectable, but when **rifabutin** was taken 3 hours after didanosine, **rifabutin** levels were apparent.[4]

The controlled study[3] suggests that no special precautions are necessary if both drugs are given. However, the case report[4] introduces an element of caution, especially if other drugs that may affect **rifabutin** pharmacokinetics are used. If indeed **rifabutin** absorption is affected by antacids (there appear to be no clinical data on this), then giving the drugs at least 2 hours apart, or using the enteric-coated didanosine preparation should avoid the interaction.[4]

For a discussion on the effects of antacids contained in buffered didanosine preparations on the absorption of **isoniazid**, see 'Isoniazid + Antacids', p.346.

(c) Stavudine

A study in 10 HIV-positive subjects found that **rifabutin** 300 mg daily had no significant effects on the pharmacokinetics of the stavudine 30 mg or 40 mg twice daily and the incidence of adverse effects did not increase.[5] No special precautions would seem necessary if both drugs are given.

(d) Zalcitabine

A study in 12 HIV-positive patients found that when zalcitabine 1.5 mg three times daily was given with **isoniazid** 300 mg daily the pharmacokinetics of zalcitabine remained unchanged but the clearance of **isoniazid** was approximately doubled.[6] The UK manufacturer of zalcitabine[7] recommended caution with the combination because of the possibility of an increased risk of peripheral neuropathy: the US manufacturer recommended that the combination should be avoided where possible.[8]

The UK manufacturer of **rifabutin** suggests that no significant interaction would be expected between **rifabutin** and zalcitabine.[9]

(e) Zidovudine

The pharmacokinetics of **rifabutin** are not affected by the concurrent use of zidovudine in patients with AIDS,[10] and **rifabutin** does not affect the pharmacokinetics of zidovudine in HIV-positive patients,[11] although one analysis found a trend towards increased zidovudine clearance.[12] No increase in adverse effects appears to occur when **rifabutin** is given with zidovudine.[10]

In a retrospective study of healthy subjects and HIV-positive individuals, the clearance of zidovudine was increased by 132% by **rifampicin** (**rifampin**) and by 50% by **rifabutin**, suggesting that the enzyme-inducing effects of **rifabutin** are less than those of **rifampicin**, so less significant interactions would be expected.[13]

A comparative study in HIV-positive patients given zidovudine and antimycobacterials (**isoniazid**, **rifampicin**, **pyrazinamide**, and **ethambutol** initially, then **isoniazid** and **rifampicin**) for 8 months, found no evidence of an adverse interaction. However, marked anaemia occurred in those subjects given both groups of drugs, but it was not necessary to permanently stop zidovudine in any patient. The authors therefore advised care-

ful monitoring for haematological toxicity.[14] Another study in 4 HIV-positive patients found that **rifampicin** lowered the AUC and increased the clearance of zidovudine in all patients, probably due to the enzyme-inducing activity of **rifampicin**, which increases the glucuronidation of zidovudine. When **rifampicin** was stopped in one patient, the zidovudine AUC doubled.[15] A later study of the same interaction in 8 HIV-positive men found that **rifampicin** significantly induced the glucuronidation of zidovudine and suggested that the effect wore off 14 days after stopping **rifampicin**. The authors of this study suggested that dose alterations may not be necessary on concurrent use.[16] The British HIV Association (BHIVA) advise that standard doses of zidovudine may be used.[17]

1. Ziagen (Abacavir sulfate). ViiV Healthcare UK Ltd. UK Summary of product characteristics, June 2009.
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3. Li RC, Narang PK, Sahai J, Cameron W, Bianchine JR. Rifabutin absorption in the gut unaltered by concomitant administration of didanosine in AIDS patients. *Antimicrob Agents Chemother* (1997) 41, 1566–70.
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5. Piscitelli SC, Kelly G, Walker RE, Kovacs J, Falloon J, Davey RT, Raje S, Masur H, Polis MA. A multiple drug interaction study of stavudine with agents for opportunistic infections in human immunodeficiency virus-infected patients. *Antimicrob Agents Chemother* (1999) 43, 647–50.
6. Lee BL, Täuber MG, Chambers HF, Gambertoglio J, Delahunty T. The effect of zalcitabine on the pharmacokinetics of isoniazid in HIV-infected patients. *Intersci Conf Antimicrob Agents Chemother* (1994) 34, 3.
7. Hivid (Zalcitabine). Roche Products Ltd. UK Summary of product characteristics, November 2004.
8. Hivid (Zalcitabine). Roche Pharmaceuticals. US Prescribing information, September 2002.
9. Mycobutin (Rifabutin). Pharmacia Ltd. UK Summary of product characteristics, June 2009.
10. Li RC, Nightingale S, Lewis RC, Colburn DC, Narang PK. Lack of effect of concomitant zidovudine on rifabutin kinetics in patients with AIDS-related complex. *Antimicrob Agents Chemother* (1996) 40, 1397–1402.
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12. Narang PK, Sale M. Population based assessment of rifabutin (R) effect on zidovudine (ZDV) disposition in AIDS patients. *Clin Pharmacol Ther* (1993) 53, 219.
13. Narang PK, Gupta S, Li RC, Strolin-Benedetti M, Della Bruna C, Bianchine JR. Assessing dosing implications of enzyme inducing potential: rifabutin (RIF) vs. rifampin (RFM). *Intersci Conf Antimicrob Agents Chemother* (1993) 33, 228.
14. Antoniskis D, Easley AC, Espina BM, Davidson PT, Barnes PF. Combined toxicity of zidovudine and antituberculosis chemotherapy. *Am Rev Respir Dis* (1992) 145, 430–4.
15. Burger DM, Meenhorst PL, Koks CHW, Beijnen JH. Pharmacokinetic interaction between rifampin and zidovudine. *Antimicrob Agents Chemother* (1993) 37, 1426–31.
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17. Pozniak AL, Collins S, Coyne KM, Freedman AR, Johnson MA, Lipman MCI, Lucas SB, Miller RF, Ormerod LP on behalf of the BHIVA Guidelines Writing Committee. British HIV Association guidelines for the treatment of TB/ HIV co-infection 2009. Available at: http://www.bhiva.org/documents/Guidelines/Treatment%20Guidelines/Current/TreatmentGuidelines2009.pdf (accessed 04/02/10).

NRTIs + Atovaquone

Moderate increases in the AUC of zidovudine have been seen with atovaquone. Atovaquone appears to decrease the AUC of didanosine. Didanosine and zidovudine do not affect the pharmacokinetics of atovaquone.

Clinical evidence

(a) Didanosine

The manufacturer of atovaquone notes that it decreased the AUC of didanosine by 24% in a multiple dose interaction study. There was no change in the pharmacokinetics of atovaquone.[1]

(b) Zidovudine

A study in 14 HIV-positive patients given atovaquone 750 mg every 12 hours and zidovudine 200 mg every 8 hours found that under steady-state conditions the zidovudine had no effect on the pharmacokinetics of atovaquone.[2] This confirmed the findings of a previous analysis of pharmacokinetic data from a small number of patients enrolled in clinical studies.[3] However, the AUC of zidovudine was increased by about 30%, and its clearance was reduced by 25% by the concurrent use of atovaquone.[2]

Mechanism

Atovaquone might inhibit the metabolism (glucuronidation) of zidovudine.[2]

Importance and management

The manufacturer of atovaquone notes that the decrease in **didanosine** levels is unlikely to be clinically relevant.[1]

The manufacturer of atovaquone states that the increased plasma levels of **zidovudine** likely with a 3-week course of atovaquone for acute pneumocystis pneumonia are unlikely to increase the adverse effects of zidovudine,[1] and routine dose adjustments are not required.[4] Nevertheless, the manufacturers of atovaquone and zidovudine recommend regular monitoring for zidovudine-associated adverse effects when the drugs are used together, particularly if atovaquone suspension is used, as this achieves higher atovaquone levels, which might have a greater effect.[1,5] The authors of the study with zidovudine[2] suggest that increases could possibly be important in patients also taking other drugs causing bone marrow toxicity (such as ganciclovir, see 'NRTIs + Ganciclovir or Valganciclovir', p.948, and flucytosine, see 'NRTIs; Zidovudine + Myelosuppressive drugs', p.961). If bone marrow toxicity is seen, it is suggested that the zidovudine dose may need to be reduced by a third.[2]

1. Wellvone Oral Suspension (Atovaquone). GlaxoSmithKline UK. UK Summary of product characteristics, March 2008.
2. Lee BL, Täuber MG, Sadler B, Goldstein D, Chambers HF. Atovaquone inhibits the glucuronidation and increases the plasma concentrations of zidovudine. *Clin Pharmacol Ther* (1996) 59, 14–21.
3. Sadler BM, Blum MR. Relationship between steady-state plasma concentrations of atovaquone (C_{ss}) and the use of various concomitant medications in AIDS patients with *Pneumocystis carinii* pneumonia. 9th International Conference AIDS & 4th STD World Congress, Berlin, June 6–11 1993. Abstract PO-B31-2213.
4. Retrovir (Zidovudine). GlaxoSmithKline. US Prescribing information, November 2009.
5. Retrovir (Zidovudine). ViiV Healthcare UK Ltd. UK Summary of product characteristics, December 2008.

NRTIs + Azoles

Fluconazole has no significant effect on the pharmacokinetics of didanosine or stavudine, but it may modestly increase zidovudine levels. Fluconazole levels are unaffected by these NRTIs.
Itraconazole has no affect on the pharmacokinetics of zidovudine. The levels of itraconazole from capsules are markedly reduced when buffered didanosine is given at the same time, but itraconazole tablets and ketoconazole are not affected if buffered didanosine is given 2 hours later. Enteric-coated didanosine has no clinically relevant effect on the pharmacokinetics of fluconazole, itraconazole or ketoconazole. The frequency of haematological toxicity with zidovudine does not appear to be increased by ketoconazole.

Clinical evidence

(a) Didanosine

1. Buffered preparation. A 35-year-old patient with AIDS was given **itraconazole** capsules 200 mg twice daily following an episode of cryptococcal meningitis. When he relapsed it was noted that he had been taking the **itraconazole** at the same time as his buffered didanosine. Subsequent study in this patient indicated a marked delay in **itraconazole** absorption when it was taken with didanosine. Two hours after the dose, plasma **itraconazole** concentrations of 1.6 micrograms/mL were seen without didanosine, but were undetectable with didanosine. A peak **itraconazole** level of 1.4 micrograms/mL was seen when it was given 8 hours after a dose of didanosine.[1] In a study in 6 healthy subjects when [buffered] didanosine was given with a single 200-mg oral dose of **itraconazole**, the peak levels of **itraconazole** were undetectable; in the absence of didanosine, **itraconazole** levels were 0.9 micrograms/mL.[2] A later study in 12 HIV-positive patients found that the AUC of a single 200-mg dose of **itraconazole** was not significantly different when buffered didanosine 200 mg was given 4 hours before or 2 hours after **itraconazole**.[3]

Twelve HIV-positive patients were given buffered didanosine 375 mg twice daily either alone or 2 hours after **ketoconazole** 200 mg daily, for 4 days. Didanosine maximum plasma levels were slightly reduced by 12% and no significant changes in the pharmacokinetics of **ketoconazole** were seen when dosing was separated in this way.[4]

A group of 12 HIV-positive subjects taking buffered didanosine 100 to 250 mg twice daily were also given **fluconazole** for 7 days (two 200-mg doses on the first day, followed by 200 mg daily). The pharmacokinetics of didanosine remained unchanged in the presence of **fluconazole**, and concurrent use was well tolerated. **Fluconazole** pharmacokinetics were not assessed.[5]

2. Enteric-coated preparation. Enteric-coated didanosine 400 mg had no significant effect on the pharmacokinetics of **fluconazole** 200 mg in 14 healthy subjects, and no clinically relevant effect on the pharmacokinetics of **itraconazole** 200 mg in 25 healthy subjects.[6] Similarly, in a study in 24 healthy subjects, enteric-coated didanosine 400 mg had no clinically relevant effect on the pharmacokinetics of **ketoconazole** 200 mg. Three of the subjects had increased concentrations of **ketoconazole** with didanosine, but their values for **ketoconazole** alone appeared unusually low. When their data were excluded, no effect on AUC was seen in the remaining 21 subjects.[7]

(b) Stavudine

A study in 10 HIV-positive subjects taking stavudine 40 mg twice daily, found that the addition of **fluconazole** 200 mg daily for one week had no significant effect on the pharmacokinetics of the stavudine.[8]

(c) Zidovudine

On two occasions, 12 HIV-positive men were given zidovudine 200 mg every 8 hours with and without **fluconazole** 400 mg daily for 7 days. While taking **fluconazole** the AUC of zidovudine increased by 74%, the maximum serum levels increased by 84%, the terminal half-life was increased by 128% and the clearance was reduced by 43%.[9] In contrast, another study in 10 HIV-positive patients found only a very small change in the pharmacokinetics of a single 500-mg dose of zidovudine given before and after 7 days of treatment with **fluconazole** (e.g. a 7% increase in the AUC of zidovudine). In another 10 patients, zidovudine had no effect on the pharmacokinetics of a single dose of **fluconazole**.[10]

Itraconazole 200 mg daily for 2 weeks was reported to have no effect on the pharmacokinetics of zidovudine in 7 patients, but the serum levels in 2 patients were higher.[11]

A study of zidovudine use in 282 patients with AIDS found that haematological abnormalities (anaemia, leucopenia, neutropenia) were very common, but this was not increased by the concurrent use of **ketoconazole** in some of these patients.[12]

Mechanism

Itraconazole and ketoconazole depend on stomach acidity for absorption. A raised gastric pH, caused by the antacids in the buffered didanosine formulation appears to reduce itraconazole absorption from the capsule formulation (consider, 'Azoles + Antacids', p.243). The didanosine itself appears to have no part to play in this interaction. The enteric-coated preparation of didanosine does not contain any antacids and therefore does not interact.

In vitro data suggest that the altered zidovudine pharmacokinetics may, in part, occur because fluconazole inhibits zidovudine glucuronidation.[13]

Importance and management

The most significant interaction occurs between the buffered preparation of **didanosine** and itraconazole *capsules*. Patients should avoid taking both drugs at the same time, but taking itraconazole capsules at least 2 hours before buffered didanosine appears to solve the problem. Any possible interaction with ketoconazole can similarly be avoided by giving ketoconazole at least 2 hours before a buffered didanosine preparation. Alternatively, the interaction may be avoided by using the enteric-coated preparation of didanosine or itraconazole *solution*.

There is no pharmacokinetic interaction between **stavudine** and fluconazole. No interaction would be expected with other similar NRTIs such as **lamivudine** and **zalcitabine** (see 'Antivirals', (p.913)).

There is evidence of a minor interaction between **zidovudine** and fluconazole, but this is unlikely to be clinically significant.

1. Moreno F, Hardin TC, Rinaldi MG, Graybill JR. Itraconazole-didanosine excipient interaction. *JAMA* (1993) 269, 1508.
2. May DB, Drew RH, Yedinak KC, Bartlett JA. Effect of simultaneous didanosine administration on itraconazole absorption in healthy volunteers. *Pharmacotherapy* (1994) 14, 509–13.
3. Hardin TC, Sharkey-Mathis PK, Rinaldi MG, Graybill JR. Evaluation of the pharmacokinetic interaction between itraconazole and didanosine in HIV-infected subjects. *Intersci Conf Antimicrob Agents Chemother* (1995) 35, 6.
4. Knupp CA, Brater DC, Relue J, Barbhaiya RH. Pharmacokinetics of didanosine and ketoconazole after coadministration to patients seropositive for the human immunodeficiency virus. *J Clin Pharmacol* (1993) 33, 912–17.
5. Bruzzese VL, Gillum JG, Israel DS, Johnson GL, Kaplowitz LG, Polk RE. Effect of fluconazole on pharmacokinetics of 2′,3′-dideoxyinosine in persons seropositive for human immunodeficiency virus. *Antimicrob Agents Chemother* (1995) 39, 1050–53.
6. Damle B, Hess H, Kaul S, Knupp C. Absence of clinically relevant drug interactions following simultaneous administration of didanosine-encapsulated, enteric-coated bead formulation with either itraconazole or fluconazole. *Biopharm Drug Dispos* (2002) 23, 59–66.
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13. Asgari M, Back DJ. Effect of azoles on the glucuronidation of zidovudine by human liver UDP-glucuronyltransferase. *J Infect Dis* (1995) 172, 1634–5.

NRTIs + Co-trimoxazole or Trimethoprim

Trimethoprim, both alone and as co-trimoxazole (trimethoprim with sulfamethoxazole) reduces the renal clearance of lamivudine, zalcitabine and zidovudine, and therefore raises their plasma levels. No clinically significant pharmacokinetic interaction occurs if didanosine is given with co-trimoxazole or trimethoprim.

Clinical evidence

(a) Didanosine

A study in 10 HIV-positive subjects investigated the pharmacokinetics of didanosine 200 mg, trimethoprim 200 mg and sulfamethoxazole 1 g in combination. Most pharmacokinetic parameters were unchanged. However, didanosine clearance was reduced by 35%, trimethoprim clearance was decreased by 32%, and sulfamethoxazole clearance was increased by 39%, when all three drugs were given together. When only two of the three drugs were given, trimethoprim caused a 27% decrease in the clearance of didanosine, and didanosine caused an 82% increase in the clearance of sulfamethoxazole.[1] Despite these alterations in clearance, the maximum serum concentration, AUC and half-life of each of the three drugs were minimally affected.[1]

(b) Lamivudine

A study of 14 HIV-positive patients taking co-trimoxazole 960 mg daily for 5 days found that the AUC of a single 300-mg dose of lamivudine given on day 4 was increased by 43% and the renal clearance was decreased by 35%. The pharmacokinetics of trimethoprim and sulfamethoxazole were unaffected.[2] Similarly, in a population pharmacokinetic analysis, the concurrent use of lamivudine and co-trimoxazole was associated with a 31% reduction in the apparent oral clearance of lamivudine, and an estimated 43% increase in steady-state lamivudine levels.[3] The UK manufacturer notes that the interaction is due to trimethoprim, and that sulfamethoxazole did not interact.[4]

(c) Stavudine

The UK manufacturer notes that an interaction with trimethoprim is possible, as both drugs are actively secreted by the renal tubules.[5]

(d) Zalcitabine

In a steady-state study, 8 HIV-positive patients took zalcitabine 1.5 mg three times daily with and without trimethoprim 200 mg twice daily. Trimethoprim increased the AUC and decreased the clearance of zalcitabine by about 35%.[6]

(e) Zidovudine

A study in 9 HIV-positive patients given zidovudine 3 mg/kg by infusion over one hour found that trimethoprim 150 mg or co-trimoxazole 960 mg did not affect the metabolic clearance of the zidovudine. However, the renal clearances of zidovudine were reduced by 48% by trimethoprim and by 58% by co-trimoxazole, and the renal clearances of its glucuronide metabolite were reduced by 20% and 27%, respectively.[7] Another study also found that co-trimoxazole did not alter zidovudine pharmacokinetics.[8] A further 5 HIV-positive patients had a 30% increase in the AUC of zidovudine when they were given trimethoprim (doses not stated).[9] Zidovudine renal clearance was reduced by 58% in 8 HIV-positive subjects when they were also given trimethoprim 200 mg, but the $AUC_{0\text{-}6}$ of the zidovudine glucuronide to zidovudine ratio was unchanged, suggesting that the metabolism was unaffected.[10]

Increases in the half-lives of trimethoprim, sulfamethoxazole and

N-acetyl sulfamethoxazole of 72%, 39%, and 115%, respectively, were seen when co-trimoxazole was given to 4 patients with AIDS taking zidovudine 250 mg every 8 hours for 8 days.[11]

A study of zidovudine use in 282 patients with AIDS found that haematological abnormalities (anaemia, leucopenia, neutropenia) were common. However, the frequency was not increased in the patients (number unknown) also taking co-trimoxazole.[12] However, a later study in a sub-Saharan population taking co-trimoxazole and zidovudine reported a higher than expected level of blood disorders.[13]

Mechanism

It is suggested that trimethoprim inhibits the secretion of both zidovudine and its glucuronide by the kidney tubules. It is not known why the half-life of co-trimoxazole is increased. The other NRTIs that interact are likely to do so by the same mechanism.

Importance and management

Established interactions. With the NRTIs that are actively excreted via the kidneys (e.g. **lamivudine**, **stavudine**, and **zalcitabine**), it is unlikely that dose alterations are necessary unless the patient has renal impairment. However, when both drugs are needed, patients should be closely monitored for signs of toxicity. However, the UK manufacturer of lamivudine recommends that the use of lamivudine with high-dose co-trimoxazole for the treatment of pneumocystis pneumonia and toxoplasmosis should be avoided.[4]

As renal clearance represents only 20 to 30% of the total clearance of **zidovudine**, the authors of two of these reports[7,10] suggest that this interaction is unlikely to be clinically important for zidovudine unless the glucuronidation by the liver is impaired by liver disease or by other drugs, see 'NRTIs; Zidovudine + Drugs that inhibit glucuronidation', p.960. The possible increased risk of haematological adverse effects requires confirmation. The manufacturer[14] of zidovudine advises that although limited data suggest that there is no significant increased risk of adverse effects when zidovudine is taken with *prophylactic* co-trimoxazole, in general the concurrent use of zidovudine with drugs that are known to cause myelosuppression, such as co-trimoxazole, should be closely monitored, see also 'NRTIs; Zidovudine + Myelosuppressive drugs', p.961.

Didanosine also does not appear to interact with co-trimoxazole or trimethoprim to a clinically relevant extent. Nevertheless concurrent use should be well monitored, especially because co-trimoxazole alone has been associated with a high incidence of adverse effects in patients with AIDS.[15]

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NRTIs + Cytokines

Interferon alfa does not alter the pharmacokinetics of didanosine or lamivudine to a clinically relevant extent. Interferon alfa and, particularly, interferon beta can cause an increase in the levels of zidovudine. HIV-positive patients infected with hepatitis C and given interferon alfa and ribavirin may be at special risk of NRTI-associated lactic acidosis.
Interleukin-2 does not appear to interact significantly with zidovudine.

Clinical evidence

(a) Didanosine

Interferon alfa 1 million to 15 million units daily was given to 26 HIV-positive patients taking didanosine sachets 100 to 375 mg twice daily. Interferon appeared to have no clinically significant effects on the pharmacokinetics of didanosine.[1]

(b) Lamivudine

In a study in 19 healthy subjects, a single subcutaneous injection of **interferon alfa** 10 million units had no clinically significant effects on the pharmacokinetics of lamivudine 100 mg daily for 7 days. Lamivudine did not appear to alter the pharmacokinetics of **interferon alfa**.[2]

(c) Zidovudine

In a study, patients with AIDS who had been taking zidovudine 200 mg every 4 hours for 8 weeks were also given subcutaneous **recombinant beta interferon** 45 million units daily. After 3 days and 15 days the zidovudine metabolism was reduced by 75% and 97%, respectively. By day 15, the zidovudine half-life was increased by about twofold.[3] Another study in 6 children aged 3 months to 17 years found that 5 weeks of the concurrent use of **interferon alfa** increased the AUC of zidovudine by 36%, increased its maximum serum level by 69% and reduced its clearance by 20%.[4]

A study found that a 4-week course of **interleukin-2** (0.25 million units/m^2 daily) by continuous infusion had no clinically significant effect on the pharmacokinetics of a 100-mg intravenous dose of zidovudine.[5] Another study in 8 HIV-positive men given oral zidovudine 200 mg every 4 hours found similar results.[1]

Mechanism

Interferon beta appears to inhibit the metabolism (glucuronidation) of zidovudine by the liver.

Importance and management

Information seems to be limited to these reports. The results of the first report suggest that the **zidovudine** dose may need to be reduced if interferon beta is added in order to avoid increased zidovudine toxicity. A dose reduction of two-thirds, or even more, may be necessary. More study is needed to confirm these observations. Interferon alfa appears to interact to a lesser extent. The manufacturers warn that the risk of haematological toxicity may be increased if zidovudine and interferon are used together, and that concurrent use in hepatitis C may increase the risk of NRTI-associated lactic acidosis. Patients at risk should be carefully monitored.[6,7]

No significant pharmacokinetic interaction appears to occur between interferon alfa and **didanosine** or **lamivudine**. Nevertheless, all manufacturers note that, because of the risk of NRTI-associated lactic acidosis, caution should be exercised when giving NRTIs (**abacavir**, didanosine, **emtricitabine**, lamivudine, **stavudine**, zidovudine) to any patient with hepatomegaly, hepatitis or other known risk factors for liver disease and hepatic steatosis. They also state that HIV-positive patients infected with hepatitis C and treated with interferon alfa and ribavirin may constitute a special risk. Patients at increased risk should be monitored closely.

No clinically significant interaction appears to occur between zidovudine and interleukin-2.

For the discussion of the effects of ribavirin, both alone and when used in combination with interferons, on NRTIs, see 'NRTIs + Ribavirin', p.956.

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NRTIs + Dapsone

Buffered didanosine does not alter the pharmacokinetics of dapsone, but there is some circumstantial evidence to suggest that it may reduce the prophylactic effects of dapsone in preventing pneumocystis pneumonia. Dapsone has no effect on the pharmacokinetics of zalcitabine, whereas zalcitabine causes a small rise in the levels of dapsone, and there is a theoretical increased risk of peripheral neuropathy with the combination. Dapsone appears not to affect the pharmacokinetics of zidovudine, although concurrent use may be associated with an increased risk of blood dyscrasias.

Clinical evidence, mechanism, importance and management

(a) Didanosine

An early report of the use of buffered didanosine described the development of pneumocystis pneumonia in 11 out of 28 HIV-positive patients taking dapsone prophylaxis, compared with only one of 12 patients taking aerosolised pentamidine, and none of 17 patients taking co-trimoxazole (trimethoprim with sulfamethoxazole). Of the 11 patients where prophylaxis failed, 4 died from respiratory failure.[1] The authors suggested that the most likely explanation of the high failure rate of dapsone with didanosine, was reduced dapsone absorption due to the citrate-phosphate buffer in the didanosine formulation.[1] This has led to some recommending that the drugs be taken at least 2 hours apart. However, in a controlled study in 6 HIV-positive subjects, dapsone pharmacokinetics were not altered when a dose of buffered didanosine was taken within 5 minutes.[2] Similarly, in 6 healthy subjects, dapsone pharmacokinetics were not altered by the aluminium/magnesium antacids and other excipients contained in didanosine tablets.[2] Another study in healthy subjects similarly did not find that a marked rise in gastric pH affects the absorption of dapsone, see 'Dapsone + Antacids', p.341. Furthermore, low dapsone levels have been found in patients receiving a weekly dapsone regimen who took dapsone at least 2 hours before or 6 hours after didanosine, and in patients taking zidovudine or no antiretrovirals (although this study did not look at whether dapsone levels were correlated with efficacy).[3] In a retrospective analysis, other authors found no evidence to confirm a correlation between failure of pneumocystis pneumonia prophylaxis with dapsone and use of drugs that increase gastric pH (didanosine, H_2-receptor antagonists, antacids).[4]

It has therefore been adequately demonstrated that the buffered preparation of didanosine and antacids do not affect dapsone absorption. The explanation for the apparent failure of pneumocystis pneumonia prophylaxis in the original report[1] is unresolved. Despite the use of both didanosine and dapsone in the management of HIV and opportunistic infections there do not appear to be any further reports of problems with the combination.

(b) Zalcitabine

A pharmacokinetic study in 12 HIV-positive patients who were given zalcitabine 1.5 mg three times daily and dapsone 100 mg daily, alone or together, found that dapsone did not significantly affect the pharmacokinetics of zalcitabine. However, zalcitabine decreased the clearance of dapsone by 21%, increased its maximum serum levels by 19% and increased its half-life by 34%.[5] These changes are relatively small and seem unlikely to have much clinical relevance, but until this is confirmed it would seem prudent to monitor the concurrent use of these two drugs. The UK manufacturer[6] recommended caution with the combination because of the possibility of an increased risk of peripheral neuropathy: the US manufacturer advised avoiding the combination where possible.[7]

(c) Zidovudine

In a study in 8 HIV-positive subjects, dapsone 100 mg daily had no effect on the pharmacokinetics of a single 200-mg dose of zidovudine.[8] In a further study, which considered the safety of dapsone in combination with zidovudine, dapsone was shown to increase the risk of zidovudine-related blood dyscrasias.[9] Therefore it would seem that dapsone and zidovudine can be given concurrently, but monitoring for an increase in adverse events would seem advisable.

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NRTIs + Drugs that cause pancreatitis

An isolated case of additive pancreatic toxicity has been described with zalcitabine and intravenous pentamidine, and is expected when didanosine or stavudine, and possibly lamivudine, are given with other drugs that can cause pancreatitis. An isolated case describes pancreatitis with lamivudine and azathioprine.

Clinical evidence

A single case report describes a 51-year-old woman with a kidney transplant who developed pancreatitis after starting **lamivudine**. **Azathioprine** had been discontinued only 3 days before and it is possible (although the evidence is weak) that the residual serum **azathioprine** had interacted with **lamivudine** to cause the pancreatitis.[1] Note that **lamivudine** alone may cause pancreatitis.[2,3]

Fatal fulminant pancreatitis occurred in a patient given **zalcitabine** and intravenous **pentamidine**.[4]

A case of pancreatitis has been reported in a patient taking **stavudine** 30 mg twice daily and **lamivudine** 150 mg twice daily with nevirapine 200 mg twice daily. Stavudine was stopped and the patient recovered.[5]

A retrospective, case-control study in HIV-positive patients found that use of **stavudine** was associated with an increased risk of developing acute pancreatitis (adjusted odds ratio 2.19). Further, nebulised **pentamidine** was associated with an increased risk of developing pancreatitis (adjusted odds ratio 6.27). The use of **co-trimoxazole**, **dapsone**, **didanosine**, and **hydroxycarbamide** appeared to be associated with an increased risk for developing pancreatitis, but after adjustments for factors such as race, no statistically significant increased risk was found. No increased risk of pancreatitis was found with **abacavir**.[6] However, note that the use of hydroxycarbamide, stavudine and didanosine is associated with an increased risk of pancreatitis, see 'NRTIs + Hydroxycarbamide', p.949.

Mechanism

The specific mechanism for NRTI-associated pancreatitis is not known but may be due to mitochondrial toxicity caused by inhibition of host mitochondrial DNA polymerise gamma.[6] Concurrent use of NRTIs with other drugs known to cause pancreatitis may increase the risk.

Importance and management

Of the NRTIs, didanosine, stavudine and zalcitabine have been associated with fatal pancreatitis.[4,7-11] Pancreatitis has occurred in patients taking

lamivudine.[2,3] Concurrent use of other drugs known to cause pancreatitis may possibly increase the risk of pancreatitis occurring.

The manufacturers of **didanosine** recommend that if another drug that has the potential to cause pancreatitis is required, treatment with didanosine should be stopped. However, if concurrent use is unavoidable, patients should be closely monitored.[7,8] Similarly, other authors recommend temporarily discontinuing didanosine in patients needing systemic pentamidine or sulfonamide-containing regimens.[12]

The UK manufacturer of **stavudine** recommends that patients receiving concurrent treatment with drugs known to cause pancreatitis should be carefully observed,[9] and the US manufacturer specifically recommends caution and close monitoring with the concurrent use of didanosine and stavudine,[10] see 'NRTIs + NRTIs', p.950. The manufacturers of **zalcitabine** recommended that if a drug that has the potential to cause pancreatitis is required, treatment with zalcitabine should be interrupted.[4,11] They specifically applied this to the use of pentamidine to treat pneumocystis pneumonia.[4,11]

Note that hydroxycarbamide (hydroxyurea) may increase the risk of pancreatitis with didanosine and stavudine, and the combination should probably be avoided, see 'NRTIs + Hydroxycarbamide', p.949.

The UK manufacturer states that **lamivudine** is rarely associated with pancreatitis, but recommend that treatment with lamivudine should be stopped if there is any suspicion of pancreatitis.[2] No firm conclusions can be drawn from the case discussed above. However, as other isolated reports have attributed pancreatitis to lamivudine use alone, it would be prudent to exercise caution with concurrent use of lamivudine with other drugs known to cause pancreatitis.

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NRTIs + Food

Food can reduce the extent of absorption of didanosine, possibly causing a loss in efficacy. The extent of absorption of zalcitabine and zidovudine is reduced slightly by food. Food does not affect the extent of absorption of abacavir, emtricitabine, lamivudine, and stavudine.

Clinical evidence, mechanism, importance and management

(a) Abacavir

The manufacturer of abacavir notes that food delayed the rate, but not the extent, of abacavir absorption. Therefore, abacavir can be taken with or without food.[1,2]

(b) Didanosine

1. Buffered preparations. Didanosine (as two 150-mg chewable tablets) was given to 10 HIV-positive subjects on four occasions: 30 minutes before breakfast, one hour before breakfast, one hour after breakfast, and 2 hours after breakfast. When the dose was given before breakfast the results were very similar to those obtained for subjects in the fasting state. When given after breakfast, the didanosine AUC and maximum plasma concentration were both decreased by about 50%.[3] Similar results were found in another study.[4] A further study[5] using sachets containing didanosine, sucrose and citrate-phosphate buffer, similarly found that food reduced the bioavailability of didanosine by 41% (a reduction from 29% to 17%). The reason for this effect would appear to be that food delays gastric emptying so that didanosine is exposed to prolonged contact with gastric acid, which causes decomposition (see 'Antivirals', (p.913)), with a resultant fall in bioavailability. To achieve maximum bioavailability, didanosine buffered preparations should be taken on an empty stomach at least 30 minutes before food[6,7] or 2 hours after food.[7]

2. Enteric-coated preparation. In a study in 20 healthy subjects, a high-fat meal reduced the AUC and maximum concentration of a single 400-mg dose of didanosine (from an enteric-coated bead formulation) by 19% and 46%, respectively, and increased the time to maximum concentration by 3 hours. A light meal also reduced the maximum concentration and AUC of didanosine by 22% and 27%, respectively, and delayed the time to maximum concentration by about 2.5 hours. Modest reductions in the AUC and maximum concentration were also seen when the same enteric-coated bead didanosine was taken either after fasting, one hour before and 2 hours after a light meal, or sprinkled over yoghurt or apple sauce; however, these changes were not statistically significant.[8]

Based on these results, the manufacturer recommends that didanosine gastro-resistant capsules are taken intact on an empty stomach,[9,10] at least 2 hours before or 2 hours after a meal.[9] However, a study in 668 patients found that in those patients who adhered to their HAART regimen taking enteric-coated didanosine with food did not lead to an increase in therapeutic failure.[11] An open-label study in 21 HIV-positive patients also found that taking enteric-coated didanosine with food had no effect on its virological efficacy.[12]

(c) Emtricitabine

The manufacturer says that giving emtricitabine hard capsules with a high-fat meal did not affect the AUC of emtricitabine[13,14] but slightly reduced the maximum level by 29%.[14] Similarly, giving emtricitabine oral solution with a low-fat or high-fat meal did not affect the AUC or maximum level of emtricitabine. Therefore, both these formulations of emtricitabine may be given with or without food.[13,14]

(d) Lamivudine

In a study in 24 healthy subjects, food slightly reduced the maximum concentration of lamivudine (from a combined tablet with zidovudine) by 15% when compared with fasting subjects, but did not significantly affect the extent of absorption.[15] The US manufacturer reports that, in a study in 12 HIV-positive patients, food delayed the absorption of lamivudine and decreased the maximum concentration by 40% when compared with the fasting patients. However, the AUC of lamivudine was unaffected.[16] The UK manufacturer notes that food delayed the rate and reduced the maximum plasma concentration (by about 47%), but not the extent (AUC) of lamivudine absorption.[17] Therefore, lamivudine can be taken with or without food.[16,17]

(e) Stavudine

The UK manufacturer of stavudine notes that a standardised high-fat meal delayed the absorption and reduced the maximum plasma concentration (specific details not given), but did not alter the extent of systemic exposure of stavudine, when compared with the fasting state. Nevertheless, they recommend that, for optimal absorption, stavudine should be taken on an empty stomach at least one hour before meals. However, if this is not possible, they suggest giving stavudine with a light meal; in addition, the contents of the capsule may be mixed with food.[18] The US manufacturer states that stavudine can be taken with food or on an empty stomach.[19]

(f) Zalcitabine

The manufacturers of zalcitabine[20,21] noted that food decreased the maximum plasma concentration by 39% and prolonged the time to achieve maximum concentrations from 0.8 hours to 1.6 hours, when compared with the fasting state. The extent of absorption was decreased by 14%. The UK manufacturer stated that zalcitabine could be taken with or without food.[20]

(g) Zidovudine

Zidovudine was given to 13 patients with AIDS either with breakfast or when fasting. The maximum plasma level of zidovudine was 2.8-fold greater in the fasted patients, and the AUC was reduced by 22% when zidovudine was given with food.[22] Zidovudine rate and extent of absorption was reduced in another study by a standard breakfast (14% decrease in AUC with a 200-mg dose and 33% with a 100-mg dose).[23] In a study[24] of 8 patients, a high-fat meal reduced the maximum zidovudine serum levels by about 50%. In all these cases inter-individual variation in zidovudine

absorption was high.[22-24] However, when a sustained-release formulation of zidovudine was used, the absorption was delayed, but the AUC was increased by 28% by a high-fat meal.[25] In contrast, the AUC of zidovudine was not affected by 25 g of a protein supplement.[26] In a study in 24 healthy subjects, although food reduced the maximum concentration of zidovudine (from a combined tablet with lamivudine) by 45% when compared with fasting subjects, it had no significant effect on the extent of absorption of zidovudine.[15]

Inter-individual variation in zidovudine absorption appears high and the practical consequences of the changes caused are uncertain. Some have suggested that zidovudine should be taken on an empty stomach;[23,24] the US manufacturer states that zidovudine can be taken with or without food,[27] but the UK manufacturer gives no specific recommendations regarding its administration in relation to food.[28]

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NRTIs + Ganciclovir or Valganciclovir

The concurrent use of zidovudine and ganciclovir produces a very marked increase in haematological toxicity, without any apparent increase in efficacy. Didanosine levels are raised by ganciclovir, but there is some evidence suggesting that the efficacy of ganciclovir prophylaxis is reduced. Ganciclovir does not appear to interact with stavudine, and there is no clinically important pharmacokinetic interaction between ganciclovir and zalcitabine. Valganciclovir is a prodrug of ganciclovir and expected to interact similarly.

Clinical evidence

(a) Didanosine

In a study, buffered didanosine 200 mg twice daily was given to 12 HIV-positive patients with oral ganciclovir 1 g three times daily. When didanosine was given 2 hours before ganciclovir, the maximum serum levels and AUC of didanosine were raised by about 47% and 83%, respectively, and those of ganciclovir were decreased by about 26% and 22%, respectively. When didanosine was given simultaneously with ganciclovir, the maximum serum levels and AUC of didanosine were similarly raised, by about 53% and 77%, respectively, but those of ganciclovir were unchanged. The renal clearance of didanosine was not significantly changed by ganciclovir.[1] Similar increases in didanosine levels with intravenous ganciclovir[2] and high-dose oral ganciclovir 2 g every 8 hours have also been reported.[3] However, in contrast, an earlier study found that the pharmacokinetics of didanosine (sachet preparation) were not altered by intravenous ganciclovir.[4]

Rates of dose-limiting intolerance to the combination of didanosine and ganciclovir were reported to be similar to those seen with didanosine alone in one small study (15 of 32 patients tolerated usual doses of didanosine with the ganciclovir).[5] However, analysis of the results of a large randomised study unexpectedly suggested that there was an increased risk of cytomegalovirus infection in those patients taking ganciclovir and didanosine, when compared with those not taking didanosine.[6]

There is a case report[7] of a persistently low CD4+ cell count, but with complete viral suppression, in a patient taking buffered didanosine 200 mg twice daily with valganciclovir 900 mg twice daily. When didanosine was replaced with abacavir, the CD4+ count increased from about 80 cells/m^2 to 323 cells/m^2.

(b) Stavudine

In a study of 11 HIV-positive patients, oral ganciclovir 1 g three times daily had no significant effect on the pharmacokinetics of stavudine 40 mg twice daily, nor were the pharmacokinetics of ganciclovir affected by the stavudine.[8] There were no serious or severe adverse events attributed to the combination.

(c) Zalcitabine

In a study in 10 HIV-positive patients, zalcitabine 750 micrograms every 8 hours increased the AUC of oral ganciclovir 1 g three times daily by 22%. There was no change in zalcitabine pharmacokinetics. There were no serious or severe adverse events attributed to the combination.[8]

(d) Zidovudine

The efficacy of zidovudine 100 or 200 mg every 4 hours, given alone or with intravenous ganciclovir 5 mg/kg twice daily for 14 days, then daily for 5 days of each week, was assessed in 40 patients for the treatment of cytomegalovirus (CMV). Severe haematological toxicity occurred in all of the first 10 patients given zidovudine 1.2 g daily and ganciclovir. Consequently the dose of zidovudine was reduced to 600 mg daily. Overall 82% of the 40 patients enrolled experienced profound and rapid toxicity (anaemia, neutropenia, leucopenia, gastrointestinal disturbances). Zidovudine dose reductions to 300 mg daily were needed in many patients. No change in the pharmacokinetics of zidovudine or ganciclovir was noted.[9]

Another study in 6 patients with AIDS and CMV retinitis, given zidovudine and ganciclovir, found increased bone marrow toxicity but no improved efficacy over ganciclovir alone.[10] Increased toxicity (myelotoxicity and pancytopenia) following the use of both drugs has also been reported elsewhere.[11,12]

In contrast to the first study,[9] a specific study on the pharmacokinetics of zidovudine and ganciclovir in HIV-positive subjects reported that oral ganciclovir increased the maximum levels and AUC of zidovudine by 38% and 15%, respectively, without altering renal clearance. Zidovudine did not alter ganciclovir pharmacokinetics.[1]

Mechanism

Ganciclovir inhibits purine nucleoside phosphorylase-4, the enzyme involved in the breakdown of didanosine, and this may result in an increase in its levels. Valganciclovir is rapidly metabolised to ganciclovir and would be expected to interact similarly.[7]

The toxicity resulting from the concurrent use of zidovudine and ganciclovir may be simply additive,[9] but *in vitro* studies with three human cell lines found synergistic cytotoxicity when both drugs were used.[13]

There is some *in vitro* evidence to suggest that ganciclovir antagonises the anti-HIV activity of zidovudine and didanosine.[14]

Importance and management

The interactions between ganciclovir and **didanosine** or **zidovudine** would appear to be established, but the clinical importance is uncertain. Zidovudine seems to be associated with greater toxicity than didanosine. However, there is also some evidence suggesting reduced ganciclovir efficacy in the presence of didanosine, and this requires further study. Close and careful monitoring is required if either combination is used.

Ganciclovir does not appear to alter the pharmacokinetics of **stavudine** or **zalcitabine**. Zalcitabine increased ganciclovir levels to a minor extent, although this is probably not clinically important.

As valganciclovir is a prodrug of ganciclovir, it would be prudent to use similar precaution when prescribing valganciclovir with these NRTIs.

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NRTIs + H_2-receptor antagonists

The concurrent use of buffered didanosine and ranitidine results in a minor increase in the levels of didanosine, and a minor decrease in the levels of ranitidine. Cimetidine raises zalcitabine levels. Cimetidine and ranitidine do not have a clinically significant effect on zidovudine or lamivudine levels.

Clinical evidence, mechanism, importance and management

(a) Didanosine

Didanosine 375 mg (buffered sachet preparation) was given to 12 HIV-positive patients either alone, or 2 hours after a single 150-mg dose of **ranitidine**. The didanosine AUC was increased by 14% by **ranitidine**.[1] The reason for this effect is not known but the **ranitidine** possibly enhanced the effects of the citrate-phosphate buffer with which the didanosine was formulated. The **ranitidine** AUC was reduced by 16% for reasons that are not understood, but it is possible that antacids (such as the citrate-phosphate buffer) that are formulated with didanosine reduce the absorption of **ranitidine**[1] (see 'H_2-receptor antagonists + Antacids', p.1147).

These bioavailability changes appear to be too small to matter clinically, and no particular precautions would seem necessary if the drugs are taken in this way.

(b) Lamivudine

Lamivudine is cleared predominantly from the body by the kidneys using the organic cationic transport system; however, the manufacturer states that **cimetidine** and **ranitidine**, which are partially eliminated by this mechanism, do not interact with lamivudine.[2]

(c) Zalcitabine

A study in 12 HIV-positive patients given a single 1.5-mg dose of zalcitabine found that **cimetidine** 800 mg caused a 24% reduction in the renal clearance of zalcitabine (assumed to be due to a reduction in renal tubular secretion) and a 36% increase in the AUC of zalcitabine.[3] These changes are relatively moderate but it would seem prudent to be alert for possible toxicity on concurrent use.

(d) Zidovudine

In a randomised crossover study, zidovudine 600 mg daily was given to 5 HIV-positive men and one man with AIDS. Zidovudine was given either alone, with **cimetidine** 300 mg four times daily, or with **ranitidine** 150 mg twice daily, each for 7 days. **Cimetidine** reduced the renal elimination of zidovudine by 56%, but had no effect on its AUC. It was suggested that the reduction in clearance was due to inhibition of tubular secretion. **Ranitidine** had no effect on zidovudine pharmacokinetics. No clinical toxicity occurred and the immunological parameters measured (CD4 and CD8) were not significantly altered. The authors concluded that no change in the dose of zidovudine is needed if either of these H_2-receptor antagonists is given concurrently.[4] Information about other H_2-receptor antagonists seems to be lacking.

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NRTIs + Hydroxycarbamide

Hydroxycarbamide appears to increase the antiviral activity of NRTIs, particularly didanosine. However, the concurrent use of hydroxycarbamide and didanosine may carry a higher risk of adverse effects including neuropathy and pancreatitis, especially if stavudine is also given.

Clinical evidence, mechanism, importance and management

Data from *in vitro* studies have shown that hydroxycarbamide increases the antiviral activity of NRTIs, particularly **didanosine**, possibly by increasing their intracellular activation (phosphorylation).[1,2] The combination is therefore under clinical investigation. Some randomised studies[3-5] have shown that the addition of hydroxycarbamide to reverse transcriptase inhibitors improves virologic response, whereas others have not found this.[6] One of these studies in patients taking **efavirenz** and **abacavir** found no increased rate of adverse effects in patients taking hydroxycarbamide 500 mg twice daily compared with patients not taking hydroxycarbamide, but more subjects in the hydroxycarbamide group withdrew from the study because of adverse effects 23% versus 4%). There was no increase in the incidence of blood dyscrasias with the concurrent use of hydroxycarbamide.[5]

However, a number of studies have found increased toxicity, particularly with **didanosine** and **stavudine**. One study reported that the relative risk of neuropathy when **didanosine** was given with hydroxycarbamide was 2.35, compared with **didanosine** alone, and increased to 7.8 when **stavudine** was also added.[7] Another study reported an increased incidence of neuropathy, and an increased incidence of fatigue and nausea and vomiting.[8] The risk of pancreatitis may also be increased. In one study, 3 patients randomised to receive indinavir, **didanosine**, **stavudine** and hydroxycarbamide developed pancreatitis and died, compared with no deaths in those receiving the same antivirals without hydroxycarbamide.[9] Another case of pancreatitis (non-fatal) has been reported when hydroxycarbamide was given with **stavudine**, **didanosine** and nevirapine.[10] Fatal hepatotoxicity and hepatic failure have also been reported in patients given hydroxycarbamide with **didanosine** and **stavudine**.[11,12] In response to these data, the manufacturers of **didanosine** and **stavudine** specifically

state that use of these two NRTIs with hydroxycarbamide should be avoided.[11-14] Moreover, the UK manufacturers go as far as to say that hydroxycarbamide should not be used in the treatment of HIV infection.[14]

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NRTIs + Macrolides

Clarithromycin causes some reduction in the bioavailability of zidovudine. Clarithromycin does not appear to interact with didanosine, stavudine or zalcitabine, and azithromycin does not interact with didanosine or zidovudine.

Clinical evidence

(a) Didanosine

When **azithromycin** 1.2 g daily for 14 days was given to 12 HIV-positive subjects with didanosine 200 mg twice daily there was no significant change in the pharmacokinetics of either drug.[1]

Clarithromycin 1 g twice daily for 7 days was given to 4 HIV-positive patients and 8 patients with AIDS taking oral didanosine. For the group as a whole the pharmacokinetics of didanosine remained unchanged, but there were large differences in the AUC between subjects that could have hidden an interaction.[2]

(b) Stavudine

A study in 10 HIV-positive subjects found that the addition of **clarithromycin** 500 mg twice daily to stavudine 30 or 40 mg twice daily had no significant effects on the pharmacokinetics of stavudine and the incidence of adverse effects did not increase.[3]

(c) Zalcitabine

A 7-day course of **clarithromycin** 500 mg twice daily was given to 12 HIV-positive subjects taking zalcitabine. The addition of **clarithromycin** caused no change to the pharmacokinetics of zalcitabine.[4]

(d) Zidovudine

In a study in 12 HIV-positive subjects, **azithromycin** 600 mg to 1.2 g daily for 14 days did not affect the pharmacokinetics of zidovudine 100 mg five times daily.[1] Similarly, **azithromycin** 1 g, given weekly to 9 HIV-positive subjects, caused no change in the pharmacokinetics of zidovudine 10 mg/kg daily. The **azithromycin** pharmacokinetics also remained unchanged.[5]

Fifteen HIV-positive patients were given zidovudine 100 mg every 4 hours five times a day and oral **clarithromycin** 500 mg, 1 g or 2 g every 12 hours, both together and alone. The pharmacokinetics of **clarithromycin** were not substantially changed by zidovudine, but the zidovudine levels and AUCs were reduced by 23 to 58% and 12 to 36%, respectively, by **clarithromycin**. However, these effects were not seen in all patients.[6,7] Another study similarly found that **clarithromycin** caused a moderate reduction in the AUC of oral zidovudine (by up to 27%). No changes were seen when zidovudine was given 4 or more hours after **clarithromycin**.[8] In a study in 16 patients with AIDS, zidovudine and **clarithromycin** were given 2 hours apart for 4 days. The maximum plasma levels of zidovudine rose by about 50%, but the minimum levels and the AUC over 8 hours did not change.[9]

Mechanism

Not understood but the interaction between clarithromycin and zidovudine may possibly be due to some changes in absorption.

Importance and management

The overall picture is slightly confusing, but it seems that some reductions in **zidovudine** levels are likely if clarithromycin is taken at the same time, but no important changes seem to occur if the administration of the drugs is separated. The authors of one study recommend that the clarithromycin is given at least 2 hours before or after zidovudine.[7] The UK manufacturer of zidovudine includes this recommendation,[10] but the US manufacturer does not include any information on its use with clarithromycin.[11] Azithromycin appears to be a potential non-interacting alternative.

The authors of the report on **didanosine** conclude that clarithromycin may safely be given with didanosine,[2] and it also seems likely that didanosine and azithromycin can be used safely together. Similarly, **stavudine** and **zalcitabine** may safely be used with clarithromycin.

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NRTIs + NRTIs

Some combinations of NRTIs are potentially antagonistic (stavudine with zidovudine, lamivudine with zalcitabine) and some are expected to result in additive toxicity (didanosine with stavudine or zalcitabine, and possibly stavudine with zalcitabine). Some do not appear to result in additional benefits (emtricitabine with lamivudine or zalcitabine), and some are considered inferior to other combinations (stavudine with lamivudine, zidovudine with zalcitabine or didanosine). Sole use of all triple NRTI regimens should generally be avoided.

Clinical evidence, mechanism, importance and management

A. Abacavir

(a) Lamivudine

In a study, 13 HIV-positive subjects were given a single 150-mg dose of lamivudine with abacavir 600 mg. The pharmacokinetics of abacavir were not significantly affected, but the lamivudine maximum plasma levels and AUC were decreased by 35% and 15%, respectively. These changes were considered to be consistent with a change in absorption. The extent of the

change is not thought to be clinically significant and so no dose alteration would seem necessary on concurrent use.[1] In UK and US guidelines, the combination of abacavir and lamivudine is currently a recommended dual NRTI option for use with an NNRTI or a protease inhibitor for the treatment of HIV-infection in treatment naïve patients.[2,3] The triple NRTI combination of abacavir, lamivudine and **zidovudine** is generally not recommended as it is less efficacious than other recommended regimens. US guidelines recommend that it should only be used when another NNRTI- or protease inhibitor-based regimen cannot be used.[3]

(b) Zidovudine

In a study in 13 HIV-positive patients, a single 300-mg dose of zidovudine had no significant effect on the pharmacokinetics of abacavir 600 mg. The maximum plasma level of zidovudine was decreased by 20%, but the AUC was unchanged. These results were confirmed in a steady-state study in which 79 HIV-positive subjects received 8 weeks of treatment with abacavir 600 mg to 1.8 g daily, in divided doses, and zidovudine 600 mg daily, in divided doses.[4] This change is not thought to be clinically significant, and so no dose alteration would seem necessary on the concurrent use of abacavir and zidovudine.[1] The triple NRTI combination of abacavir, **lamivudine** and zidovudine is generally not recommended as it is less efficacious than other recommended regimens. US guidelines recommend that it should only be used when another NNRTI- or protease inhibitor-based regimen cannot be used.[3]

B. Didanosine

(a) Emtricitabine

In UK and US guidelines, the combination of didanosine and emtricitabine is currently a recommended alternative dual NRTI option for use with an NNRTI or a protease inhibitor, for the treatment of HIV-infection in treatment naïve patients.[2,3]

(b) Lamivudine

The manufacturer notes that as lamivudine is cleared predominantly from the body by the kidneys using the organic cationic transport system and didanosine is not cleared in this way, an interaction between these two drugs by this mechanism is unlikely.[5] Didanosine does not affect the intracellular activation of lamivudine *in vitro*.[6] In UK and US guidelines, the combination of didanosine and lamivudine is currently a recommended alternative dual NRTI option for use with an NNRTI or a protease inhibitor, for the treatment of HIV-infection in treatment naïve patients.[2,3]

(c) Stavudine

In a study in 10 HIV-positive patients, stavudine 40 mg twice daily, taken for 9 doses, had no significant effect on the pharmacokinetics of didanosine 100 mg taken twice daily. The half-life of the stavudine increased from 1.56 hours to 1.96 hours, but the AUC was unchanged and adverse effects were minimal. The authors of the report concluded that no clinically significant pharmacokinetic interaction is likely to occur on concurrent use and that no change in acute safety and tolerance would be expected.[7] Didanosine does not interfere with the intracellular activation of stavudine *in vitro*.[8] However, both didanosine and stavudine can cause peripheral neuropathy and pancreatitis, and there is some evidence that this risk may be additive. In one early study, stavudine and didanosine were given to 13 HIV-positive subjects for 8 weeks. Neuropathy occurred in 3 patients, with only 2 restarting treatment.[9] In another study, the relative risk of neuropathy was 1.39 for stavudine alone, relative to didanosine alone, and 3.5 for the concurrent use of both drugs.[10] In 1999, the manufacturer of didanosine issued a stronger warning about the risk of pancreatitis with didanosine, and noted this risk was higher in patients also taking stavudine.[11] Concurrent use should be therefore be closely monitored. A case of symptomatic hyperlactataemia occurred in a patient after changing his antiretroviral therapy to didanosine, stavudine and nevirapine.[12] The concurrent use of stavudine and didanosine has been associated with a high incidence of toxicity, particularly peripheral neuropathy, pancreatitis, and lactic acidosis. The development of lactic acidosis has resulted in fatalities in pregnant women.[3] It has been suggested that this combination of NRTIs is associated with the greatest toxicity.[12] US guidelines say that the combination of didanosine and stavudine should not be recommended at any time, with the exception of when no other antiretroviral options are available, and only if the potential benefits outweigh the risks.[3] UK guidelines say that stavudine is not recommended for use as one of the NRTIs for initial therapy of HIV because of its toxicity.[2]

See also 'NRTIs + Drugs that cause pancreatitis', p.946.

(d) Zalcitabine

A 29-year-old man with persistent mild neuropathy due to zalcitabine developed severe neuropathy when given didanosine 3 weeks after discontinuing zalcitabine. As the didanosine neuropathy developed so rapidly it was suggested that it was caused by additive toxicity with zalcitabine.[13] Note also that both drugs are associated with pancreatitis. The US manufacturer advised against use of the combination,[14] whereas the UK manufacturers advised caution and careful monitoring if drugs that share these serious adverse effects are used concurrently.[15] See also 'NRTIs + Drugs that cause pancreatitis', p.946.

In vitro, didanosine had no significant effect on the intracellular activation of zalcitabine.[15]

(e) Zidovudine

A study in 8 HIV-positive patients found that when they were given zidovudine 250 mg with didanosine 250 mg (buffered sachet formulation), the pharmacokinetics of didanosine were unaltered but the zidovudine AUC was raised by 35%, possibly due to altered absorption.[16] Conversely, in another study zidovudine plasma levels were lower in 4 out of 5 HIV-positive patients when given didanosine (chewable tablets) and there was an average 14% reduction in the zidovudine AUC. Zidovudine clearance was increased by 29% but didanosine pharmacokinetics were unchanged.[17] A study in over 50 young subjects ranging in age from 3 months to 21 years found that, when compared with day 3 (start of concurrent use), no significant changes in AUCs occurred after 4 or 12 weeks of them taking zidovudine 60 to 180 mg/m^2 every 6 hours with didanosine 60 to 180 mg/m^2 every 12 hours (given 2 minutes after an antacid).[18] Several other studies have not found a pharmacokinetic interaction or evidence of increased toxicity when didanosine and zidovudine were used concurrently.[19-21] The UK manufacturer of didanosine states that there is no evidence that concurrent use increases the myelosuppressive effects of zidovudine.[22]

The reports are slightly contradictory, but the weight of evidence seems to be that no clinically relevant interaction occurs. UK guidelines say there are no data on the use of zidovudine with enteric-coated didanosine as part of HAART, and that the combination cannot be recommended.[2]

C. Emtricitabine

(a) Lamivudine

The manufacturer of emtricitabine states that there is no information on the concurrent use of cytidine analogues such as emtricitabine and lamivudine, and the combination should not be used.[23] The US guidelines also state that the combination of emtricitabine and lamivudine should not be offered at any time because of the similar resistance profile of the two drugs and there being no potential benefit.[3]

(b) Stavudine

In a single-dose study in 6 healthy subjects, no important pharmacokinetic interaction occurred between emtricitabine 200 mg and stavudine 40 mg.[24] UK guidelines say that stavudine is not recommended for use as one of the NRTIs for initial therapy of HIV because of its toxicity.[2]

(c) Zalcitabine

The manufacturer of emtricitabine states that there is no information on the concurrent use of cytidine analogues, such as emtricitabine and zalcitabine, and therefore, the combination should not be used.[23]

(d) Zidovudine

In a single-dose study in 6 healthy subjects, the AUC and maximum level of zidovudine 300 mg were increased by 26% and 66%, respectively, by emtricitabine 200 mg. The pharmacokinetics of emtricitabine were not altered.[24] The authors suggest that these increases in zidovudine levels are unlikely to be clinically relevant based on experience of using the two drugs together for 48 weeks in a phase III clinical study.[24] Further experience is needed.

D. Lamivudine

(a) Stavudine

Nucleoside reverse transcriptase inhibitors such as lamivudine need to be activated by phosphorylation within the cells to a triphosphate anabolite. Because stavudine does not affect this phosphorylation *in vitro*[6] it is predicted that no interaction is likely to occur by this mechanism. The manufacturer briefly states that no clinically relevant pharmacokinetic interaction was noted between stavudine 40 mg and lamivudine 150 mg in a single-dose study.[25,26] Nevertheless, current US guidelines state that the combination of stavudine and lamivudine is not a preferred or alternative dual NRTI combination for use in initial antiretroviral regimens because

of significant toxicities including lipoatrophy, peripheral neuropathy and serious, life-threatening lactic acidosis with hepatic steatosis, with or without pancreatitis, and rapidly progressive neuromuscular weakness.[3] Similarly, UK guidelines say that stavudine is not recommended for use as one of the NRTIs for initial therapy of HIV because of its toxicity.[2]

(b) Zalcitabine

The manufacturers say that lamivudine is not recommended to be used with zalcitabine, because lamivudine may inhibit the intracellular activation of zalcitabine.[14,15,27]

(c) Zidovudine

In a study, lamivudine 300 mg twice daily was given to 12 HIV-positive patients for 5 doses, with a 200-mg dose of zidovudine with the last dose. No major changes in the pharmacokinetics of the zidovudine occurred and it was concluded that dose adjustments are not needed if these two drugs are given concurrently.[28] Another study found the same results,[1] and an extensive study in over 200 patients has shown that concurrent use can be safe and effective.[29]

However, there are case reports of blood dyscrasias occurring with concurrent use. Zidovudine 500 to 600 mg daily was given with lamivudine 300 mg daily to 13 HIV-positive patients. Zidovudine or lamivudine alone had previously been given to 9 of these 13 without problem. However, when both drugs were given, blood dyscrasias occurred in all patients within 7 weeks. Significant anaemia occurred in all patients, with precipitous declines in haemoglobin levels and one patient developed leucopenia and thrombocytopenia. Both drugs were stopped, blood transfusions were given, and all patients improved or recovered. Zidovudine or lamivudine alone was later started in 8 patients and 2 patients tolerated the combination (with the zidovudine dose halved in one patient and the drugs added sequentially in the other) without further haematological problems.[30] Similar precipitous falls in haemoglobin occurred in another 2 patients when lamivudine 300 mg daily was added to their long-term zidovudine treatment. Again both recovered when the drugs were stopped and blood was given.[31] Anaemia is a common adverse effect of zidovudine, but these patients had no problems until the lamivudine was added. However, the available evidence indicates that concurrent use can be safe and effective, with the adverse interactions cited here being uncommon. It has been suggested that a complete baseline blood count should be done, both when concurrent use is started, and every month for the first 3 months of treatment.[31] The manufacturers[5,27] state that no clinically significant interaction occurs on concurrent use, and a combination product is available. In the UK and US guidelines, the combination of zidovudine and lamivudine is currently a recommended alternative dual NRTI option for use with an NNRTI or a protease inhibitor for the treatment of HIV-infection in treatment naïve patients.[2,3] The US guidelines state that the triple NRTI combination of **abacavir**, lamivudine and zidovudine is generally not recommended as it is less efficacious than other recommended regimens. They advise that it should only be used when another NNRTI- or protease inhibitor-based regimen cannot be used.[3]

E. Stavudine

(a) Zalcitabine

In vitro, stavudine had no significant effect on the intracellular activation of zalcitabine.[15,25] Both stavudine and zalcitabine have the potential to cause peripheral neuropathy and pancreatitis. The concurrent use of drugs causing these serious adverse effects should be closely monitored (see also 'NRTIs + Drugs that cause pancreatitis', p.946).

(b) Zidovudine

Nucleoside reverse transcriptase inhibitors such as stavudine need to be phosphorylated within the cells to a triphosphate anabolite before they become effective. *In vitro* studies using mononucleated blood cells found that zidovudine significantly inhibited this phosphorylation.[8] Antagonism between zidovudine and stavudine has also been seen in a clinical study.[32] Therefore, the manufacturers[25,26] and the US guidelines[3] currently do not recommend the combination. Similarly, UK guidelines say that stavudine is not recommended for use as one of the NRTIs for initial therapy of HIV because of its toxicity.[2]

F. Zalcitabine

In vitro, zalcitabine had no significant effect on the intracellular activation of **zidovudine**.[15] In a study in 56 patients with advanced HIV infection, taking zidovudine 50 to 200 mg every 8 hours and zalcitabine 5 to 10 micrograms/kg every 8 hours, neither drug affected the pharmacokinetics of the other nor was toxicity increased.[33] No special precautions would appear to be necessary. Note that zalcitabine is now rarely used and the licensed product has been withdrawn in many countries.

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NRTIs + Paracetamol (Acetaminophen)

Limited and unconfirmed evidence suggests that paracetamol possibly increases the bone marrow suppressant effects of zidovu-

dine. Single case reports describe severe liver toxicity when patients were given paracetamol with either zidovudine or didanosine.

Clinical evidence

(a) Didanosine

Increasing abdominal pain occurred in a 47-year-old HIV-positive man one month after he started didanosine (his other medications included nevirapine, hydroxycarbamide, aciclovir and lorazepam). He had been treating the pain with paracetamol, and had taken 4 g over 3 days. Severe hepatitis and pancreatitis were diagnosed, which slowly resolved over the following 3 weeks.[1]

(b) Zidovudine

An early study of zidovudine use in 282 patients with AIDS found that haematological abnormalities (anaemia, leucopenia, neutropenia) were very common and 21% needed multiple red cell transfusions. Some of the patients also received paracetamol, which increased the haematological toxicity (neutropenia) by an unstated amount.[2]

Short-term clinical studies using paracetamol 650 mg up to every 4 hours found that it had no clinically significant effects on the pharmacokinetics of zidovudine,[3-6] although in one case zidovudine clearance was slightly increased.[7] An 8-month study in a single patient suggested that long-term concurrent use did not affect the pharmacokinetics of either drug. However, in this individual, very rapid absorption and a high peak serum level of zidovudine were seen, so as a precaution the zidovudine dose was reduced from 200 mg every 4 hours to 100 mg every 6 hours.[8]

A patient taking zidovudine and co-trimoxazole took 3.3 g of paracetamol over 36 hours. Within 2 days he developed severe hepatotoxicity, and as other causes were excluded, the reaction was attributed to the paracetamol. The authors suggested that zidovudine may have augmented the paracetamol toxicity.[9] However, in a single-dose study, reduced paracetamol glucuronidation and increased formation of hepatotoxic metabolites were seen in patients with advanced HIV infection compared with healthy HIV-positive subjects and those without HIV, and this effect was independent of zidovudine use.[10] In contrast, in another study, disease state (AIDS versus healthy HIV-positive subjects) was not found to alter paracetamol metabolism, and zidovudine was found to *increase* paracetamol glucuronidation in some patients.[11]

Mechanism

Not understood. Paracetamol does not increase the serum levels of zidovudine,[3-5,7] which might have provided an explanation for the apparent increased toxicity. One *in vitro* study found that paracetamol does not affect the glucuronidation of zidovudine,[12] whereas another found that paracetamol did inhibit zidovudine glucuronidation.[13] The effect of zidovudine on paracetamol metabolism is also unclear.

Didanosine may cause pancreatitis or hepatic disease, and zidovudine may also rarely cause hepatic disease. It has been suggested that the hepatotoxicity of these drugs are augmented when they are given together.[1]

Importance and management

Paracetamol is a widely used non-prescription analgesic, and this appears to be an isolated report of potential combined toxicity with **didanosine**, although the authors suggest extreme caution when potentially hepatotoxic drugs such as paracetamol are used with didanosine.[1] Both drugs may cause hepatotoxicity alone, and didanosine itself may cause severe pancreatitis, and there is limited evidence that hepatotoxicity may increased by the concurrent use of these drugs. Consider stopping paracetamol and didanosine in any patient who develops signs or symptoms of hepatotoxicity or pancreatitis.

The short-term use of **zidovudine** and paracetamol does not appear to alter the pharmacokinetics of either drug. Whether paracetamol can increase the haematological toxicity of zidovudine and whether the drugs have combined hepatotoxicity is unclear from the available data. More study is needed.

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NRTIs + Probenecid

Probenecid reduces the loss of zalcitabine and zidovudine, increasing their levels. The concurrent use of zalcitabine and probenecid is well tolerated, but the incidence of adverse effects appears to be greatly increased with the concurrent use of probenecid and zidovudine.

Clinical evidence

(a) Zalcitabine

In a single-dose study, 12 HIV-positive or AIDS patients were given zalcitabine 1.5 mg alone or with probenecid 500 mg, given 8 and 2 hours before then 4 hours after zalcitabine. The renal clearance of the zalcitabine was decreased by 42% by probenecid, its half-life was increased by 47% and its AUC was increased by 54%.[1]

(b) Zidovudine

In 12 patients with AIDS or AIDS-related complex the concurrent use of zidovudine and probenecid 500 mg every 8 hours for 3 days increased the AUC of zidovudine by an average of 80% (range 14 to 192%).[2] Other studies in patients[3-5] and healthy subjects[6] found that probenecid roughly doubled the AUC of zidovudine when given in a variety of dosing schedules.[3,4] However, the effects on zidovudine pharmacokinetics were minimal if the two drugs were given 6 hours apart.[5] Another report describes a very high incidence of rashes in 6 out of 8 HIV-positive men given zidovudine with probenecid 500 mg every 6 hours. The rash and other symptoms (such as malaise, fever and myalgia) were sufficiently severe for the probenecid to be withdrawn in 4 patients.[7] A later study found that when using only 250 mg of probenecid every 8 hours the AUC of zidovudine was increased by 70% but the adverse effects still occurred, although the incidence was possibly somewhat lower.[8] Conversely, others reported the successful use of probenecid 500 mg three times daily with a reduced dose of zidovudine (600 mg daily) in 7 patients without any occurrence of rash.[9]

Mechanism

Experimental clinical evidence indicates that probenecid reduces the metabolism (glucuronidation) of zidovudine by liver enzymes, and inhibits the renal secretion of the zidovudine glucuronide metabolite.[2-4,6,10,11] The interaction with zalcitabine is presumably due to inhibition of zalcitabine secretion in the renal tubules.[1]

Importance and management

The concurrent use of **zidovudine** and probenecid should be well monitored to ensure that zidovudine levels do not rise excessively. Reduce the zidovudine dose as necessary. However, the apparent increase in adverse effects during concurrent use seen by one group of researchers[7,8] should be borne in mind.

Note that *cidofovir* should be given with probenecid, and if these drugs

are given to a patient taking zidovudine caution is particularly recommended.[12,13] The US manufacturer of cidofovir advises that zidovudine should be temporarily discontinued or the dose halved when cidofovir with probenecid is given.[13]

The concurrent use of **zalcitabine** and probenecid was well tolerated, and because the zalcitabine half-life is short compared to its dosing schedule significant accumulation would not be expected.

It would seem prudent to monitor for any signs of toxicity if either drug combination is used long-term. The safety of concurrent use needs further assessment.

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NRTIs + Protease inhibitors

Buffered didanosine decreases the AUC of indinavir and interacts similarly with atazanavir. Ritonavir-boosted atazanavir, lopinavir and tipranavir appear to reduce the AUC of abacavir. Ritonavir-boosted tipranavir reduces the AUC of zidovudine. The changes in pharmacokinetics seen when giving other combinations of protease inhibitors with NRTIs do not appear to be clinically significant. Protease inhibitors do not affect the intracellular activation of NRTIs.

Clinical evidence, mechanism, importance and management

The protease inhibitors **indinavir**, **ritonavir**, and **saquinavir** had no effect on intracellular activation of various NRTIs (**didanosine**, **lamivudine**, **stavudine**, **zalcitabine** and **zidovudine**).[1] No interaction would be expected by this mechanism. Other potential interactions are discussed below.

Current local and national guidelines should be consulted when choosing protease inhibitor and NRTI combinations, and they recommend the use of two NRTIs and a ritonavir-boosted protease inhibitor as an alternative to using two NRTIs and an NNRTI such as efavirenz.[2,3] See also 'NRTIs + NRTIs', p.950, for information on the choice of NRTI combinations.

(a) Abacavir

1. Amprenavir or Fosamprenavir. A phase I study in HIV-positive patients given amprenavir 900 mg twice daily with abacavir 300 mg twice daily for 3 weeks found that neither drug had any clinically significant effect on the pharmacokinetics of the other.[4] The manufacturer of amprenavir notes that its AUC, minimum levels and maximum levels were increased by 29%, 27%, and 47%, respectively, by abacavir,[5,6] without any change in abacavir pharmacokinetics, but no dose adjustments are considered necessary on concurrent use.[5] The manufacturer of fosamprenavir states that, based on data with amprenavir, no significant interaction is expected with abacavir.[7]

2. Atazanavir with Ritonavir. In a study in 24 HIV-positive patients, ritonavir-boosted atazanavir 100/300 mg daily slightly reduced the AUC of abacavir 600 mg daily by 17% but had no significant effect on the maximum or minimum plasma concentrations of abacavir. The pharmacokinetics of ritonavir-boosted atazanavir were not significantly affected by abacavir. The reduction in abacavir levels is thought to be due to induction of abacavir glucuronidation by ritonavir.[8-10]

The authors of this study state that the clinical significance of this interaction remains unclear, however, they note that even though a larger reduction in abacavir levels was seen with ritonavir-boosted **lopinavir** (see *Lopinavir with Ritonavir*, below) a regimen containing abacavir and ritonavir-boosted lopinavir with lamivudine has been shown to be effective in the management of HIV infection. The authors[10] suggest that further study is needed, and it would seem prudent to monitor concurrent use to ensure antiviral efficacy, until further data is available. Note that the concurrent use of abacavir and lamivudine with ritonavir-boosted atazanavir is one of the recommended regimens for treatment-naive patients.[2,3]

3. Darunavir with Ritonavir. The manufacturers of darunavir state that no interaction is expected between abacavir and ritonavir-boosted darunavir.[11,12]

4. Lopinavir with Ritonavir. In a study in 24 HIV-positive patients, ritonavir-boosted lopinavir 100/400 mg twice daily reduced the AUC, maximum plasma concentration and minimum plasma concentration of abacavir 600 mg daily by 31%, 34%, and 64%, respectively. The pharmacokinetics of ritonavir-boosted lopinavir were not significantly affected by abacavir.[10] The reduction in abacavir levels is thought to be due to induction of abacavir glucuronidation by ritonavir, and possibly also lopinavir.[8-10]

The authors of this study state that the clinical significance of this interaction remains unclear, however, a regimen containing abacavir, lamivudine and ritonavir-boosted lopinavir has been shown to be effective in the management of HIV infection. The authors[10] suggest that further study is needed, and it would seem prudent to monitor concurrent use to ensure antiviral efficacy, until further data is available. Note that the concurrent use of abacavir and lamivudine with ritonavir-boosted lopinavir is one of the recommended regimens for treatment-naïve patients.[2,3]

5. Tipranavir with Ritonavir. Ritonavir-boosted tipranavir given decreased the AUC of abacavir by approximately 40%. The clinical relevance of this reduction has not been established,[13,14] but it may decrease the efficacy of abacavir.[13] Therefore the UK manufacturer states that the concurrent use of ritonavir-boosted tipranavir and abacavir is not recommended unless there are no other available NRTIs suitable for patient management.[13]

(b) Didanosine

1. Amprenavir or Fosamprenavir. The AUC and the minimum level of amprenavir 600 mg twice daily were not altered to a clinically relevant extent when it was given simultaneously with, or one hour before, buffered didanosine; or simultaneously with the enteric-coated preparation of didanosine. The only notable change was a 15% decrease in the maximum levels of amprenavir when it was given with buffered didanosine, which was not considered clinically significant.[15] Nevertheless, the manufacturers of amprenavir suggested that it should be given at least one hour apart from didanosine,[5,6] and this has also be recommended for regimens containing amprenavir and ritonavir.[15] However, the manufacturer of fosamprenavir, a prodrug of amprenavir, state that, although no specific study has been done, a clinically relevant interaction due to the antacid content of didanosine would not be expected. Enteric-coated didanosine is not expected to interact with fosamprenavir.[7]

2. Atazanavir. The manufacturer of atazanavir found that buffered didanosine markedly decreased atazanavir plasma levels, with little change in didanosine levels,[16] and they recommend that administration should be separated.[16,17] Conversely, although enteric-coated didanosine did not alter atazanavir levels, simultaneous administration with food reduced didanosine levels.[16,17] Therefore, the UK manufacturer[17] recommends that ritonavir-boosted atazanavir should be taken with food, 2 hours before didanosine (both the buffered tablets and enteric-coated formulations), whereas the US manufacturer[16] advises taking atazanavir 2 hours before or one hour after didanosine. Note that 'didanosine', (p.947), is preferably taken on an empty stomach, whereas 'atazanavir', (p.971), should be taken with food.

3. Darunavir with Ritonavir. Didanosine 400 mg daily, given on an empty stomach 2 hours before ritonavir-boosted darunavir 100/600 mg twice daily, did not affect the pharmacokinetics of darunavir. Therefore, the manufacturer of darunavir advises that no dose adjustments are required when these drugs are given together.[11] However, note that 'didanosine', (p.947), is preferably taken on an empty stomach, whereas 'darunavir', (p.971), should be taken with food. Therefore, the US manufacturer advis-

es taking didanosine one hour before or 2 hours after ritonavir-boosted darunavir, which is taken with food.[12]

4. Indinavir. The concurrent use of [buffered] didanosine and indinavir reduced the AUC of indinavir by 80%, but when indinavir was given one hour before didanosine its pharmacokinetics were not significantly affected.[18] Similarly, another study found that the pharmacokinetics of indinavir 800 mg were unchanged when it was given one hour after buffered didanosine 400 mg.[19] In a single-dose study in 23 healthy subjects, an enteric-coated preparation of didanosine had no effect on the pharmacokinetics of indinavir.[20] Indinavir may require a normal acidic gastric pH for optimal absorption, whereas some didanosine preparations are formulated with buffering agents to raise gastric pH. Any increase in pH would therefore be expected to reduce indinavir absorption.[21] The manufacturers of indinavir recommend that indinavir and didanosine should be given at least one hour apart.[21,22] This recommendation does not apply to the enteric-coated preparation of didanosine.[20,21,23] Note that both 'didanosine', (p.947), and 'indinavir', (p.971), are preferably taken on an empty stomach.

5. Lopinavir with Ritonavir. The manufacturers advise that ritonavir-boosted lopinavir *tablets* may be taken at the same time as didanosine, on an empty stomach. However, didanosine must be taken one hour before or 2 hours after ritonavir-boosted lopinavir *oral solution*, which should be taken with food.[8,9]

6. Nelfinavir. The pharmacokinetics of nelfinavir were not significantly altered after concurrent use with didanosine.[24] Note that 'nelfinavir', (p.971), should preferably be taken with food, and all 'didanosine preparations', (p.947), without food. The US manufacturer states that no interaction occurred when nelfinavir was taken one hour after didanosine and therefore recommends that nelfinavir is therefore taken one hour after didanosine enteric-coated preparations.[23]

7. Ritonavir. In a study in 13 HIV-positive subjects, buffered didanosine 200 mg twice daily was given with ritonavir 600 mg twice daily. Administration of the two drugs was separated by 2.5 hours, and treatment was given for 4 days. Treatment was staggered in this way, because 'ritonavir', (p.971), should be given with food, and 'didanosine', (p.947), without food. There was little or no change in the pharmacokinetics of ritonavir, and the maximum serum levels and AUC of didanosine were reduced by 16% and 13%, respectively, which was not considered to be clinically significant. It was suggested that these changes may have been due to altered absorption in the presence of ritonavir.[25] The manufacturer of ritonavir therefore recommends that ritonavir and didanosine should be taken 2.5 hours apart and suggest that dose alterations should not be necessary.[26]

8. Saquinavir. In a study in 8 healthy subjects, a single 400-mg dose of didanosine decreased the AUC and maximum plasma concentration of saquinavir (taken as ritonavir-boosted saquinavir 100/1600 mg soft capsules) by about 30% and 25%, respectively, but did not significantly affect the minimum plasma concentration of saquinavir. The manufacturer considers these changes are of doubtful clinical significance, and state that no dose adjustment is needed on concurrent use.[27] Note also that 'saquinavir', (p.971), should preferably be taken with food, and all 'didanosine preparations', (p.947), should be taken on an empty stomach.

9. Tipranavir with Ritonavir. Ritonavir-boosted tipranavir caused a 33% reduction in the AUC of didanosine in one of three studies,[14] but the clinical relevance of this has not been established.[13,14] Consequently, the manufacturer recommends that dosing of enteric-coated didanosine and ritonavir-boosted tipranavir should be separated by at least 2 hours to avoid formulation incompatibility.[13,14]

(c) Emtricitabine

The manufacturers of **darunavir** state that no interaction is expected between emtricitabine and ritonavir-boosted darunavir.[11,12]

The manufacturer of emtricitabine also states that no clinically significant interaction occurs with the concurrent use of **indinavir**.[28]

(d) Lamivudine

Lamivudine metabolism does not involve the cytochrome P450 isoenzyme CYP3A4. Therefore it is unlikely that it will interact with drugs, such as the protease inhibitors, that are metabolised by this system.[29] No pharmacokinetic interaction appears to occur between lamivudine and **amprenavir**,[5,6] **atazanavir**,[16,17] **fosamprenavir**,[7] **indinavir**,[21,22] ritonavir-boosted **lopinavir**[8,9] and **nelfinavir**,[30,31] and no interaction is expected with ritonavir-boosted **darunavir**.[11,12] Ritonavir-boosted **tipranavir** does not appear to cause a significant change in the AUC of lamivudine.[13,14]

(e) Stavudine

The manufacturer of **atazanavir**[16,17] notes that there was no pharmacokinetic interaction with stavudine.

The manufacturers of darunavir state that no interaction is expected between stavudine and ritonavir-boosted **darunavir**.[11,12]

The AUC of stavudine was increased by 25% when stavudine 40 mg twice daily was given with **indinavir** 800 mg every 8 hours for a week, which was not considered to be clinically significant. The serum levels of **indinavir** were unchanged.[32] Similarly, in a study in 24 healthy subjects, ritonavir-boosted **indinavir** 200/800 mg twice daily increased the AUC of stavudine by 24%, but this change was not considered clinically relevant.[33] No dose adjustments are needed on concurrent use.[21]

The manufacturer of ritonavir-boosted **lopinavir** notes that no significant interaction occurs with stavudine.[8,9]

In an early pilot study, the concurrent use of **nelfinavir** and stavudine was well tolerated, and the adverse effects were similar to those seen when stavudine was given alone, although the incidence of diarrhoea did increase.[34] The manufacturer of **nelfinavir** notes that no clinically significant interactions have been seen with stavudine.[30,31]

In a study in HIV-positive children, **ritonavir** oral clearance was about 50% slower and the AUC about 2.5-fold higher in 6 children who received stavudine than in 7 who received zidovudine and lamivudine, although these differences did not reach statistical significance.[35]

Ritonavir-boosted **tipranavir** does not appear to cause a significant change in the AUC of stavudine.[13,14] Therefore, no dose adjustment is needed on concurrent use.[13]

(f) Zalcitabine

The manufacturer of zalcitabine noted that there is no pharmacokinetic interaction with **saquinavir**.[36,37] They stated that pharmacokinetic interactions with protease inhibitors would not be expected because zalcitabine is mainly excreted unchanged in the urine.[36] The manufacturers of **darunavir** similarly state that no interaction is expected between zalcitabine and ritonavir-boosted darunavir.[11,12]

(g) Zidovudine

1. Amprenavir or Fosamprenavir. The manufacturer of amprenavir noted that the AUC and maximum levels of zidovudine were increased by 31% and 40%, respectively, when given with amprenavir. However, the pharmacokinetics of amprenavir were unchanged.[5,6] The UK manufacturer of amprenavir stated that no dose adjustment of either drug is necessary when amprenavir and zidovudine are used together.[5] The manufacturer of fosamprenavir advises that, based on data with amprenavir, no significant interaction is expected with zidovudine.[7]

2. Atazanavir. The manufacturer of atazanavir notes that there was no clinically relevant pharmacokinetic interaction with zidovudine.[17]

3. Darunavir with Ritonavir. The manufacturers of darunavir state that no interaction is expected between zidovudine and ritonavir-boosted darunavir.[11,12]

4. Indinavir. A study found that when zidovudine 200 mg every 8 hours and indinavir 1 g every 8 hours were given together for a week the AUC of zidovudine was increased by 17% and the AUC of indinavir was increased by 13%.[32] In another study, the concurrent use of indinavir and zidovudine with lamivudine increased the zidovudine AUC by 39% but did not change indinavir pharmacokinetics.[22] The manufacturer of indinavir also reports that the concurrent use of zidovudine 200 mg three times daily with indinavir 1 g three times daily, both taken for 7 days, had no effect on the pharmacokinetics of indinavir and on the AUC of zidovudine, although the minimum level of zidovudine was increased by 51%.[21,22] These changes are not clinically relevant, and the UK manufacturer of indinavir states that no dose adjustment is needed with concurrent use.[21]

5. Lopinavir with Ritonavir. The manufacturer of ritonavir-boosted lopinavir notes that it induces glucuronidation and therefore has the potential to reduce zidovudine levels. However this, and its clinical relevance, have yet to be studied.[8,9]

6. Nelfinavir. The manufacturer of nelfinavir notes that clinically significant interactions have not been observed with zidovudine, and no dose adjustments are needed.[30,31]

7. Ritonavir. A crossover study in 18 HIV-positive subjects found that the pharmacokinetics of ritonavir 300 mg every 6 hours were unchanged by zidovudine 200 mg every 8 hours. However, the maximum plasma levels and AUC of zidovudine were both reduced by about 25%. The lack of change in the other pharmacokinetic parameters suggested that these

changes were not due to altered metabolism,[38] although the manufacturer of ritonavir suggests that ritonavir may have induced the glucuronidation of zidovudine.[26] Nevertheless, dose alterations are not considered necessary.[26]

8. Saquinavir. The UK manufacturer of saquinavir notes that there was no pharmacokinetic interaction with zidovudine.[27]

9. Tipranavir with Ritonavir. Ritonavir-boosted tipranavir decreased the AUC of zidovudine by about 35%, without affecting glucuronidated-zidovudine levels. The clinical relevance of this reduction has not been established,[13,14] but it may decrease the efficacy of zidovudine.[13] Therefore, the UK manufacturer states that concurrent use of ritonavir-boosted tipranavir with zidovudine is not recommended unless there are no other available NRTIs suitable for patient management.[13]

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NRTIs + Ribavirin

The use of ribavirin with the NRTIs may result in increased toxicity (lactic acidosis, blood dyscrasias and hepatotoxicity), which may be more frequent with didanosine than other NRTIs. These effects may also be exacerbated by the additional use of interferon for hepatitis C. Early *in vitro* data suggested that ribavirin may reduce the antiretroviral effects of some NRTIs but this does not appear to have been demonstrated in practice.

Clinical evidence and mechanism

(a) Abacavir

In a retrospective study in HIV-positive patients with hepatitis C, the use of abacavir was reported to increase the risk of therapeutic failure with interferon alfa and ribavirin, particularly in patients with ribavirin levels of less than 2.3 micrograms/mL.[1] Similarly, another study found abacavir reduced the response to ribavirin.[2]

(b) Didanosine

In two studies, ribavirin did not alter the pharmacokinetics of didanosine in HIV-positive adults or children.[3,4] However, *in vitro*, ribavirin increases the intracellular activation of didanosine, and the manufacturers note that this could result in increased adverse effects.[5-7] In one early study, no increase in adverse effects was seen when ribavirin 600 mg daily was given to 16 HIV-positive patients who had already been taking didanosine 125 to 200 mg twice daily for 4 weeks. Ribavirin was given 6 hours after the morning dose of didanosine. Over the 8 or 20 weeks of the study the combination was well tolerated.[3] Nevertheless, cases of mitochondrial toxicity (hepatotoxicity, pancreatitis, lactic acidaemia) have been reported when ribavirin was added to didanosine-containing antiretroviral regimens,[8-10] and fatalities have occurred.[8,11] In an analysis of data from the adverse event reporting system of the FDA in the US, 31 patients were identified who had adverse events suggestive of mitochondrial toxicity while taking ribavirin with an NRTI. Of these, nearly 90% had received didanosine, 71% stavudine, and 65% both didanosine and stavudine. Five patients died; all of who were taking didanosine, with stavudine in three of these cases. The use of ribavirin with didanosine was associated with an increased risk of mitochondrial toxicity (odds ratio 12.4) compared with patients receiving ribavirin with other NRTIs (odds ratios: didanosine with stavudine, 8; stavudine, 3.3; abacavir, 1.1; lamivudine, 0.2; zidovudine, 0.06).[11] Some other studies have shown an increased risk of mitochondrial toxicity when ribavirin was given with didanosine.[12,13]

(c) Lamivudine

In vitro, ribavirin reduced the intracellular activation and antiretroviral activity of lamivudine.[14] However, in a study in 22 HIV-positive patients with hepatitis C, ribavirin 800 mg daily had no statistically significant effect on the pharmacokinetics of lamivudine (a 27% increase in AUC), and no effect on the intracellular activation of lamivudine, when compared with 24 similar patients who received placebo.[15]

(d) Stavudine

In vitro, ribavirin reduced the intracellular activation and antiretroviral activity of stavudine.[6,16] However, in a study in 5 HIV-positive patients with hepatitis C, ribavirin 800 mg daily had no statistically significant effect on the pharmacokinetics of stavudine (a 45% increase in AUC), and no effect on intracellular activation of stavudine, when compared with similar patients who received placebo.[15] Similarly, no decrease in the antiviral activity of stavudine (as assessed by plasma HIV-RNA levels) has been seen when ribavirin was given with interferon for hepatitis C infection in patients with HIV.[17,18]

(e) Zidovudine

In vitro, ribavirin reduced the intracellular activation and antiretroviral activity of zidovudine.[6,19] However, in a study in 14 patients with hepatitis C

and HIV infections, the addition of ribavirin to treatment with zidovudine 300 mg twice daily had no significant effect on the pharmacokinetics of zidovudine.[20] Similarly, an earlier study in a study in 7 HIV-positive patients with hepatitis C, ribavirin 800 mg daily had no statistically significant effect on the pharmacokinetics of zidovudine (a 22% decrease in AUC), and no effect on the intracellular activation of zidovudine, when compared with similar patients who received placebo.[15] Moreover, in a study in 8 patients taking zidovudine, there was no significant variation in HIV viral load or CD4 counts after 3 or 6 months of ribavirin treatment, compared with baseline values.[18] One US manufacturer of ribavirin includes details of a study in which patients treated with zidovudine, interferon alfa and ribavirin had a higher incidence of severe neutropenia (15% versus 9%) and severe anaemia (5% versus 1%) than other similar patients not receiving zidovudine.[21]

Importance and management

In the UK, the manufacturers of all NRTIs state that patients co-infected with hepatitis C and treated with 'interferon alfa', (p.945), and ribavirin may be at increased risk of lactic acidosis. Patients at increased risk should be closely monitored.

The UK manufacturer of **didanosine**[5] advises that treatment with nucleoside analogues [such as didanosine] should be discontinued in the setting of symptomatic hyperlactataemia and metabolic/lactic acidosis, progressive hepatomegaly, or rapidly elevating aminotransferase levels. Others consider that didanosine should not be systematically replaced in patients requiring treatment for hepatitis C because the risk of lactic acidosis is only small.[22] Nevertheless, they suggest that if a modification of antiretroviral treatment is needed then it is best to avoid didanosine.[22] As a result of the increased risk of mitochondrial toxicity, the manufacturers say that the concurrent use of ribavirin and didanosine is not recommended,[5,6,21,23,24] and the US manufacturer of didanosine[7] and the British HIV Association (BHIVA) contraindicates concurrent use.[25]

Similarly, the British HIV Association recommends avoiding the concurrent use of **abacavir** with ribavirin for hepatitis C infection if possible, as concurrent use may reduce intracellular levels of ribavirin and possibly reduce the response to treatment.

The US manufacturer of **stavudine** states that patients also receiving 'interferon', (p.945), with or without ribavirin, should be closely monitored for treatment-associated toxicities, particularly hepatic decompensation.[26] Based on an analysis of data from the adverse event reporting system of the FDA in the US, the UK manufacturers[6,23] of ribavirin consider that concurrent use of stavudine should be avoided to limit the risk of mitochondrial toxicity. The British HIV Association (BHIVA) also recommends avoiding concurrent use, if possible.[25] However, one manufacturer of ribavirin also advises that plasma HIV-RNA levels are closely monitored in patients taking ribavirin with stavudine to ensure continued efficacy.[6]

The manufacturer of **lamivudine** advises caution if NRTIs are given to patients with risk factors for liver disease and notes that patients with hepatitis C treated with interferon and ribavirin may be a special risk category.[27]

The US manufacturer of **zidovudine** advises that patients also receiving interferon alfa, with or without ribavirin, should be closely monitored for treatment-associated toxicities, especially hepatic decompensation, neutropenia, and anaemia. They also recommend that nucleoside analogues that antagonise the antiretroviral activity of zidovudine, such as ribavirin, should be avoided.[28] The British HIV Association (BHIVA) recommends avoiding the concurrent use of ribavirin with zidovudine, if possible.[25] However, one manufacturer of ribavirin also advises that plasma HIV-RNA levels are closely monitored in patients taking ribavirin with zidovudine to ensure continued efficacy.[6] Both UK manufacturers[6,23] of ribavirin also note that patients treated with zidovudine are at increased risk of developing anaemia, and one does not recommend concurrent use.[23] They advise that an alternative choice to zidovudine should be considered in patients requiring treatment with ribavirin, particularly those with a previous history of zidovudine-induced anaemia.[23] The US manufacturer of zidovudine gives similar advice.[28]

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NRTIs + Tenofovir

Tenofovir increases the levels of didanosine: an increased risk of pancreatitis and peripheral neuropathy has been reported, and a high level of treatment failure. There is no pharmacokinetic interaction between tenofovir and abacavir, emtricitabine, lamivudine or stavudine. However, the combination of tenofovir, lamivudine and abacavir was unexpectedly associated with a high level of treatment failure. Triple-NRTI regimens involving tenofovir are not recommended, with the possible exception of tenofovir, lamivudine and zidovudine.

Clinical evidence, mechanism, importance and management

Note that tenofovir is a nucleotide (nucleoside monophosphate) analogue and is often classed as an NRTI.

(a) Abacavir

In a study in HIV-positive patients taking ritonavir-boosted lopinavir, no significant pharmacokinetic interaction was reported between tenofovir, and abacavir or lamivudine.[1] Similarly, in a study in 8 healthy subjects, no clinically relevant pharmacokinetic interaction was found between tenofo-

vir and abacavir.[2,3] However, the combination of tenofovir, lamivudine and abacavir was unexpectedly associated with a high rate of treatment failure (early virological non-response) in clinical studies.[4] Consequently, in July 2003 the manufacturer and others recommended that this triple therapy should not be used alone, and if these three drugs are used with other antiretrovirals, virological response should be closely monitored.[4] US guidelines (November 2008) for the treatment of HIV-1 infection state that triple NRTI regimens like this should not be used routinely (with two specific exceptions) because of suboptimal virological activity or lack of data.[5] Similarly, UK guidelines (2008) state that triple NRTI regimens such as tenofovir, abacavir and lamivudine should not be used because of unacceptably high rates of virological failure.[6]

(b) Didanosine

The AUC of buffered didanosine 250 mg or 400 mg was increased by 44% when it was given one hour before tenofovir.[2] Similarly the AUC of enteric-coated didanosine 400 mg was increased by 48% and 60% when didanosine was given 2 hours before or at the same time as tenofovir disoproxil fumarate 300 mg, respectively.[7] The pharmacokinetics of tenofovir were unchanged.[2,7] Another study found that the AUC of enteric-coated didanosine 250 mg (simultaneously or 2 hours apart, fasted or with food) was about equivalent to that seen with didanosine 400 mg alone when tenofovir was given.[7]

The main concern with raised didanosine levels is the increased risk of adverse effects, particularly pancreatitis and peripheral neuropathy. One retrospective analysis found that 5 of 185 patients receiving didanosine with tenofovir developed pancreatitis compared with one of 182 taking didanosine without tenofovir and none of 208 taking tenofovir without didanosine, suggesting an increased risk of pancreatitis with the combination. All 6 cases of pancreatitis were in women without renal impairment, who weighed less than 60 kg. Five had received a reduced dose of didanosine (250 mg) and one had received didanosine 400 mg. Pancreatitis developed after 12 to 24 weeks.[8] Similarly, another analysis found that the use of tenofovir with didanosine (400 mg daily or 250 mg daily if weight less than 60 kg) was associated with a higher incidence of peripheral neuropathy (12% versus 4%) and pancreatitis (4% versus 0%) than use with lower doses of didanosine (100 mg to 250 mg daily).[9] However, another analysis failed to find an enhanced risk of toxicity with the combination of didanosine and tenofovir at full dose during the first 6 months of use.[10] Tenofovir is rarely associated with acute renal failure, and in one study[11], the concurrent use of didanosine with tenofovir was found to be associated with an increased risk of developing renal impairment (odds ratio 3.1). In an analysis of 5 HIV-positive patients with acute renal failure and 22 cases reported in the literature, all of whom were taking tenofovir, 9 patients were also taking didanosine, and it was suggested that tenofovir-associated renal failure, might be due to an interaction,[12] although others contend that this does not necessarily infer an association.[13] Cases of pancreatitis[14,15] or lactic acidosis and renal failure[16-18] have been reported (the use of ritonavir may be a factor in at least one of these cases[18]).

Furthermore, a once daily combination of tenofovir disoproxil fumarate 300 mg, enteric-coated didanosine 250 mg and lamivudine 300 mg was unexpectedly associated with a high rate of treatment failure (early virological non-response) in a clinical study in treatment-naïve patients.[19] Similarly, other studies have shown a high rate of treatment failure with a once daily combination of tenofovir disoproxil fumarate 300 mg, enteric-coated didanosine 250 mg and either efavirenz or nevirapine in treatment-naïve patients with high baseline viral loads and low CD4 counts.[20] A poor immune response (lack of increase in CD4 cell counts) has also been seen with full-dose didanosine with tenofovir regimens in treatment-experienced patients.[21]

The pharmacokinetic interaction is established, and raised didanosine levels would be expected when it is given with tenofovir. The US manufacturers recommend that the dose of didanosine should be reduced to 250 mg daily when given with tenofovir in patients weighing more than 60 kg with a creatinine clearance of at least 60 mL/minute,[2,22] and 200 mg daily in patients weighing less than 60 kg and with a creatinine clearance of at least 60 mL/minute; the dose in patients with a creatinine clearance of less than 60 mL/minute has not been established.[22] However, the UK manufacturer of tenofovir notes that reducing the didanosine dose to 250 mg has been associated with a high rate of virological failure.[23] Nevertheless, because of the high rates of treatment failure seen with didanosine in combination with tenofovir and an NNRTI or lamivudine, and the potential for tenofovir to potentiate didanosine-related toxicity, the EMEA,[24] the MHRA in the UK[25] and UK guidelines[6] now recommend that didanosine should not be used with tenofovir in any antiretroviral combination. Similarly, the 2008 US guidelines also say that didanosine should not be used with tenofovir as part of initial therapy because of a high rate of early virological failure, rapid selection of resistant mutations, and the potential for immunological non-response/CD4 decline.[5] If the combination is considered necessary, the dose should be adjusted as recommended and the patient should be carefully monitored for didanosine-related adverse effects (e.g. pancreatitis, peripheral neuropathy) and for antiviral efficacy.

(c) Emtricitabine

In a study in 16 healthy subjects, no pharmacokinetic interaction was reported between tenofovir disoproxil fumarate 300 mg daily and emtricitabine 200 mg daily, both for 7 days.[26] The 2008 UK and US guidelines for treatment of HIV infections recommend the combination of tenofovir and emtricitabine with either an NNRTI or a protease inhibitor.[5,6] Tenofovir and emtricitabine are available in a fixed dose combination product.

(d) Lamivudine

In a study in HIV-positive patients, no significant pharmacokinetic interaction was reported between tenofovir and abacavir or lamivudine.[1] The manufacturer also briefly notes that there was no pharmacokinetic interaction between tenofovir and lamivudine.[23] The 2008 UK guidelines for treatment of HIV infections recommend the combination of tenofovir and lamivudine with either an NNRTI or a protease inhibitor.[6]

However, for studies showing a high rate of virological failure with the combination of tenofovir, lamivudine and one other NRTI, see *Abacavir*, and *Didanosine*, above. UK and US guidelines say to avoid sole use of all regimens of tenofovir plus two NRTIs (triple-NRTI regimens), with the possible exception of tenofovir plus lamivudine and zidovudine when a protease inhibitor or NNRTI-based regimen cannot be used.[5,6]

(e) Stavudine

There is information to suggest that tenofovir disoproxil fumarate 300 mg does not alter levels of stavudine 100 mg.[27]

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NRTIs; Didanosine + Allopurinol

Allopurinol markedly raises didanosine levels.

Clinical evidence, mechanism, importance and management

In a study, buffered didanosine 400 mg was given to 14 healthy subjects, with and without allopurinol 300 mg daily for 7 days. Allopurinol significantly increased didanosine absorption, shown by a twofold increase in the AUC of didanosine and a 69% rise in its maximum serum levels.[1] Similar findings were seen in HIV-positive subjects.[2] Moreover, the addition of allopurinol 300 mg daily allowed the dose of didanosine to be halved from 400 mg daily to 200 mg daily in 4 patients taking buffered didanosine, hydroxycarbamide and chloroquine. Didanosine plasma levels and antiviral efficacy were unchanged when compared with pre-treatment levels in patients taking didanosine 400 mg daily without allopurinol.[3] The US manufacturer notes that, in subjects with renal impairment, allopurinol 300 mg increased the AUC and maximum plasma concentration of a single 200-mg dose of didanosine 3.1-fold and 2.3-fold, respectively.[4] The manufacturer notes that allopurinol may increase the exposure to didanosine by inhibiting xanthine oxidase, an enzyme involved in didanosine metabolism.[5] This interaction has been studied for its therapeutic benefit.[3] However, if the dose of didanosine is not reduced, there is the potential for an increase in didanosine adverse effects. The manufacturers state that concurrent use of allopurinol with didanosine is contraindicated,[4,5] and that patients requiring allopurinol should be changed from didanosine to an alternative antiretroviral regimen.[5]

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NRTIs; Didanosine + Loperamide or Metoclopramide

Loperamide and metoclopramide do not appear to alter the pharmacokinetics of didanosine.

Clinical evidence, mechanism, importance and management

In a study in 6 men and 6 women who were HIV-positive, the pharmacokinetics of oral buffered didanosine 300 mg were not altered to a clinically relevant extent by 4 mg of loperamide, given 19, 13, 7 and one hour before the didanosine. The rate of didanosine absorption was slightly decreased but the extent of absorption was unchanged. Similarly, the pharmacokinetics of oral buffered didanosine 300 mg were found to be unaffected by 10 mg of intravenous metoclopramide.[1] It appears that neither delaying nor accelerating gastrointestinal transit time appreciably alters the pharmacokinetics of didanosine, which is acid labile. On the basis of this study the authors conclude that neither the dose nor the frequency of didanosine administration need to be altered if either loperamide or metoclopramide is given concurrently.[1]

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NRTIs; Stavudine + Doxorubicin

***In vitro* evidence suggests that doxorubicin may inhibit the activation of stavudine.**

Clinical evidence, mechanism, importance and management

Nucleoside reverse transcriptase inhibitors such as stavudine need to be phosphorylated within cells before they become effective. *In vitro* studies using mononucleated blood cells found that doxorubicin may interfere with stavudine phosphorylation at clinically relevant concentrations.[1] The clinical importance of this interaction awaits assessment. However, caution is recommended on concurrent use.

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NRTIs; Zidovudine + Aspirin or NSAIDs

***In vitro* evidence suggests that indometacin and naproxen inhibit the glucuronidation of zidovudine. However, in subsequent clinical studies, indometacin and naproxen did not affect zidovudine pharmacokinetics. The concurrent use of ibuprofen and zidovudine appears to increase the risk of bleeding in patients with haemophilia.**

Clinical evidence, mechanism, importance and management

An *in vitro* study using human liver microsomes found that **indometacin** and **naproxen** inhibited the glucuronidation of zidovudine by 50% or more, and aspirin also had some inhibitory effect.[1] This suggested that these drugs might possibly increase the effects and the toxicity of zidovudine. However, clinical studies have found no changes in the pharmacokinetics of zidovudine given with **indometacin** 25 mg twice daily for 3 days[2] or **naproxen** 500 mg to 1 g daily for 3 or 4 days.[2,3] Many drugs that were reported to inhibit the glucuronidation of zidovudine *in vitro* appear to have only modest effects on zidovudine levels in clinical studies, which are unlikely to be clinically important in most patients (see 'NRTIs; Zidovudine + Drugs that inhibit glucuronidation', p.960). No clinically relevant pharmacokinetic interaction appears to occur between zidovudine and NSAIDs. However, in 2007, the MHRA in the UK issued minimum requirements to manufacturers regarding the content of licensed product characteristics for systemic NSAIDs. This included a statement that the concurrent use of NSAIDs increased the risk of haematological toxicity with zidovudine, and that there is evidence of an increased risk of haemarthroses and haematoma in HIV-positive patients with haemophilia taking zidovudine and ibuprofen.[4,5] This appears to be based on data from a study in 10 HIV-positive patients with haemophilia taking zidovudine 100 or 200 mg five times daily, which found a reduction in platelet adhesion and an increase in bleeding times in those patients given **ibuprofen** 400 mg four times daily for at least 2 weeks. Three patients had an excess bleeding tendency on concurrent use, although this did not correlate with platelet function defects. Neither the clearance of zidovudine or **ibuprofen** was affected by concurrent use.[6] A patient with AIDS and haemophilia taking **ibuprofen** had a fourfold increase in spontaneous haemorrhages of the joints after starting zidovudine. This eventually resolved when zidovudine was stopped and restarted at a reduced dose of zidovudine 100 mg three times daily with once-daily **ibuprofen**.[7] Another case has also been reported of a prolonged bleeding time with bleeding from a venous ulcer in a patient taking zidovudine who self-medicated with **ibuprofen** 800 mg tablets. His bleeding time had returned to normal 4 weeks after stopping **ibuprofen**.[8] An earlier study of zidovudine use in 282 patients with AIDS

found that haematological abnormalities were not increased by the concurrent use of aspirin in 47 patients.[9]

Although there is limited published evidence, the increased risk of bleeding reported in HIV-positive patients with haemophilia taking **ibuprofen** with zidovudine appears to be of clinical significance, and these patients require close monitoring if they are also prescribed NSAIDs. Whether this increased risk is restricted to those patients with haemophilia is unclear.

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4. Medicines and Healthcare products Regulatory Authority (MHRA). Minimum clinical particulars: non-selective POM NSAIDs for systemic administration (excludes aspirin/salicylic acid derivatives).
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5. Medicines and Healthcare products Regulatory Authority (MHRA). Minimum clinical particulars: P and GSL ibuprofen for systemic administration (Guidance for MA holders).
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7. Ragni MV, Tama G, Lewis JH, Ho M. Increased frequency of haemarthroses in haemophilic patient treated with zidovudine. *Lancet* (1992) 40, 176–82.
8. Pieper B, Smitherman HC. Altered bleeding time associated with ibuprofen and zidovudine use. *Nurse Pract* (1998) 23, 74–5.
9. Richman DD, Fischl MA, Grieco MH, Gottlieb MS, Volberding PA, Laskin OL, Leedom JM, Groopman JE, Mildvan D, Hirsch MS, Jackson GG, Durack DT, Nusinoff-Lehrman S and the AZT Collaborative Working Group. The toxicity of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex. A double-blind, placebo-controlled trial. *N Engl J Med* (1987) 317, 192–7.

NRTIs; Zidovudine + Benzodiazepines

Oxazepam causes a modest increase in the bioavailability of zidovudine, and concurrent use can increase the incidence of headaches. Lorazepam is predicted to interact similarly.

Clinical evidence, mechanism, importance and management

A pharmacokinetic study in 6 HIV-positive patients found that **oxazepam** did not significantly affect the bioavailability of zidovudine. All of the patients were sleepy and fatigued while taking **oxazepam** (as expected), but 5 of the 6 complained of headaches while taking both drugs, compared with only one of 6 while taking zidovudine alone and none while taking **oxazepam** alone. The authors of the report suggest that if headaches occur during concurrent use, the benzodiazepine should be stopped.[1] A previous *in vitro* study using human liver microsomes confirmed that **oxazepam** inhibits the metabolism of zidovudine to its glucuronide, and **lorazepam** behaves in the same way.[2] The same precautions suggested for **oxazepam** would therefore also appear to apply to **lorazepam**.

1. Mole L, Israelski D, Bubp J, O'Hanley P, Merigan T, Blaschke T. Pharmacokinetics of zidovudine alone and in combination with oxazepam in the HIV infected patient. *J Acquir Immune Defic Syndr* (1993) 6, 56–60.
2. Unadkat JD, Chien J. Lorazepam and oxazepam inhibit the metabolism of zidovudine (ZDV or azidothymidine) in an *in vitro* human liver microsomal system. *Pharm Res* (1988) 5 (Suppl), S177.

NRTIs; Zidovudine + Drugs that inhibit glucuronidation

***In vitro* evidence suggests that chloramphenicol inhibits the glucuronidation of zidovudine. Dipyridamole does not appear to alter the pharmacokinetics of zidovudine.**

Clinical evidence and mechanism

(a) Chloramphenicol

An *in vitro* study using human liver microsomes found that chloramphenicol inhibited the glucuronidation of zidovudine by 50% or more, suggesting that the effects and toxicity of zidovudine may be increased.[1] The effect of concurrent use in patients awaits assessment.

(b) Dipyridamole

Theoretically, dipyridamole and zidovudine might inhibit the metabolism of each other by competing for glucuronidation, the major clearance mechanism for both drugs. However, a study in 11 asymptomatic HIV-positive patients found that dipyridamole 75 to 100 mg every 4 hours for 5 days caused no significant changes in the pharmacokinetics of zidovudine 500 mg daily, but the dipyridamole adverse effects (headaches, nausea) when taking the higher dose were found to be intolerable.[2]

Importance and management

Many drugs that have been reported to inhibit the glucuronidation of zidovudine *in vitro* (such as naproxen and indometacin, see 'NRTIs; Zidovudine + Aspirin or NSAIDs', p.959) appear to have only modest or no significant effects on zidovudine pharmacokinetics in *clinical* studies. In general, these minor pharmacokinetic interactions are unlikely to be of clinically importance in most patients. No significant interaction appears to occur between dipyridamole and zidovudine, and therefore no special precautions appear to be necessary.

Based on data from studies with other drugs that affect the glucuronidation of zidovudine and the lack of a reported clinical interaction, it seems unlikely that a clinically relevant pharmacokinetic interaction will occur between chloramphenicol and zidovudine. However bear the possibility in mind should a patient develop zidovudine adverse effects, particularly as both drugs can cause haematological toxicity.

1. Sim SM, Back DJ, Breckenridge AM. The effect of various drugs on the glucuronidation of zidovudine (azidothymidine; AZT) by human liver microsomes. *Br J Clin Pharmacol* (1991) 32, 17–21.
2. Hendrix CW, Flexner C, Szebeni J, Kuwahara S, Pennypacker S, Weinstein JN, Lietman PS. Effect of dipyridamole on zidovudine pharmacokinetics and short-term tolerance in asymptomatic human immunodeficiency virus-infected subjects. *Antimicrob Agents Chemother* (1994) 38, 1036–40.

NRTIs; Zidovudine + Lithium

Lithium can apparently oppose the neutropenic effects of zidovudine in some patients.

Clinical evidence, mechanism, importance and management

A study in 5 patients with AIDS found that serum lithium carbonate levels of 0.6 to 1.2 mmol/L increased their neutrophil counts sufficiently to allow the re-introduction of zidovudine, which had previously been withdrawn due to neutropenia. Withdrawal of the lithium resulted in a rapid fall in neutrophil levels in 2 patients.[1] Improvement in neutropenia occurred in another patient with AIDS taking zidovudine 1.2 g daily when lithium carbonate 300 mg three times daily was also given.[2] Lithium has been found to induce granulopoiesis, and these reports suggest that no adverse reaction appears to occur in patients taking zidovudine and lithium, and that there may be some advantages to their use. However, lithium has a narrow therapeutic range and its toxic symptoms might be difficult to distinguish from any neurological complications caused by the disease. The addition of lithium could also increase the risk of interactions with other drugs.[3,4] A study of 3 further patients found a lack of a beneficial effect with lithium in 2 of the patients and only a short-term improvement in the neutrophil count in the third. In addition, one patient experienced severe diarrhoea necessitating discontinuation of the lithium.[5]

1. Roberts DE, Berman SM, Nakasato S, Wyle FA, Wishnow RM, Segal GP. Effect of lithium carbonate on zidovudine-associated neutropenia in the acquired immunodeficiency syndrome. *Am J Med* (1988) 85, 428–31.
2. Herbert V, Hirschman S, Jacobson J. Lithium for zidovudine-induced neutropenia in AIDS. *JAMA* (1988) 260, 3588.
3. Nathwani D, Green ST. Lithium for zidovudine-induced neutropenia in AIDS. *JAMA* (1989) 262, 775–6.
4. Klutman NE. Lithium carbonate therapy for zidovudine-associated neutropenia in patients with acquired immunodeficiency syndrome. *Am J Med* (1989) 87, 362–3.
5. Worthington M. Lack of effect of lithium carbonate on zidovudine-associated neutropenia in patients with AIDS. *J Infect Dis* (1990) 162, 777–8.

NRTIs; Zidovudine + Megestrol

Megestrol acetate does not affect the pharmacokinetics of zidovudine.

Clinical evidence, mechanism, importance and management

In a study in 12 asymptomatic HIV-positive patients, megestrol acetate 800 mg daily for 13 days had no effect on the steady-state pharmacokinetics of zidovudine or its glucuronide metabolite.[1] As megestrol does not appear to affect the metabolism of zidovudine, no dose adjustment of zidovudine appears to be necessary on concurrent use.

1. Van Harken DR, Pei JC, Wagner J, Pike IM. Pharmacokinetic interaction of megestrol acetate with zidovudine in human immunodeficiency virus-infected patients. *Antimicrob Agents Chemother* (1997) 41, 2480–3.

NRTIs; Zidovudine + Myelosuppressive drugs

There have been reports of serious myelotoxicity when zidovudine was given with vancomycin or cytotoxic antineoplastics, and, on theoretical grounds, any drug causing bone marrow suppression might be additive with the effects of zidovudine. Moderate pharmacokinetic changes have been seen when zidovudine was given with chemotherapy regimens used for Kaposi's sarcoma, Hodgkin's disease, and non-Hodgkin's lymphoma.

Clinical evidence and mechanism

(a) Antineoplastics

In one preliminary report, the addition of **vinblastine** to zidovudine resulted in severe bone marrow depression.[1] Similarly, 9 of 21 patients could not tolerate zidovudine while receiving a chemotherapy regimen (**cyclophosphamide**, **doxorubicin**, **teniposide**, **prednisone**, **vincristine** and **bleomycin**) because of haematological toxicity.[2] However, a small retrospective case review in patients with Kaposi's sarcoma who were given **vincristine** 2 mg and **bleomycin** 30 mg or **vinblastine** 2.5 mg to 5 mg (every 3 to 4 weeks) found no significant increased risk of relapse or effect on survival in those also taking zidovudine. Of the patients taking zidovudine, 11 (24%) developed anaemia. Peripheral neuropathy was reported in 13 (28%) of all patients treated.[3] Similarly, another group have reported that the concurrent use of zidovudine 400 mg to 1 g daily with **vincristine** 2 mg and **bleomycin** 30 units (both given once every 2 weeks) in 19 HIV-positive patients with Kaposi's sarcoma was well-tolerated. Neutropenia occurred in 4 patients (21%) and neuropathy occurred in one patient (5%).[4] The pharmacokinetic interaction of chemotherapy with zidovudine was assessed in HIV-positive patients being treated for Kaposi's sarcoma, non-Hodgkin's lymphoma or Hodgkin's disease. The antineoplastics used were **bleomycin**, **cyclophosphamide**, **doxorubicin**, **epirubicin**, **etoposide**, **vinblastine**, **vincristine**, **vindesine** and **vinorelbine**. Zidovudine metabolism was unchanged, but a 43% decrease was noted in the maximum plasma levels of zidovudine and the time to peak level was prolonged by 51%, which was independent of the chemotherapy given.[5] The authors concluded that dose changes of zidovudine were not needed with the antineoplastics used, based on these pharmacokinetic changes alone, as the zidovudine AUC remained unchanged and maximum plasma levels have not been shown to clearly correlate with its activity.[5] Thus it appears that any interaction is likely to be attributable to additive myelosuppressive effects.

(b) Vancomycin

A report describes marked neutropenia in 4 HIV-positive patients receiving zidovudine when they were given vancomycin (which can also, rarely, have neutropenic effects).[6]

Importance and management

On theoretical grounds any drug causing bone marrow suppression might be additive with the effects of zidovudine. The manufacturers recommend that extra care be taken in monitoring haematological parameters if concurrent treatment with any myelosuppressive drug and zidovudine is required.[7,8] The UK manufacturer specifically mention systemic **pentamidine**, '**dapsone**', (p.946), '**pyrimethamine**', (p.269), '**co-trimoxazole**', (p.944), **amphotericin** (myelotoxicity and nephrotoxicity seen in a study in *dogs*[9]), **flucytosine**, '**ganciclovir**', (p.948), '**interferon**', (p.945), **vinblastine**, and **doxorubicin**,[7] whereas the US manufacturer advises caution with '**ganciclovir**', (p.948), '**interferon alfa**', (p.945), and '**ribavirin**', (p.956).[8] However, the UK manufacturer[7] also states that limited clinical data do not indicate a significantly increased risk of adverse reactions to zidovudine if it is given with prophylactic doses of '**co-trimoxazole**', (p.944), aerosolised **pentamidine**, pyrimethamine, and '**aciclovir**', (p.941).

Note that the UK manufacturer[7] also states that the use of **vincristine** with zidovudine may lead to additive myelosuppression, although vincristine is much less commonly associated with blood dyscrasias and anaemia than vinblastine.

1. Gharakhanian S, De Sahb R, Vaseghi M, Cardon B, Rozenbaum W. Evaluation of the association of zidovudine and vinblastine in treatment of AIDS-related Kaposi's sarcoma. 5th International Conference on AIDS, Montreal, 1989. Abstract MBP368.
2. Tirelli U, Errante D, Oksenhendler E, Spina M, Vaccher E, Serraino D, Gastaldi R, Repetto L, Rizzardini G, Carbone A, et al. French-Italian Cooperative Study Group. Prospective study with combined low-dose chemotherapy and zidovudine in 37 patients with poor-prognosis AIDS-related non-Hodgkin's lymphoma. *Ann Oncol* (1992) 3, 843–7.
3. Gompels MM, Hill A, Jenkins P, Peters B, Tomlinson D, Harris JRW, Stewart S, Pinching AJ. Kaposi's sarcoma in HIV infection treated with vincristine and bleomycin. *AIDS* (1992) 6, 1175–80.
4. Lipman MCI, Swaden LS, Sabin CA, Collis C, Johnson MA. Kaposi's sarcoma in HIV infection treated with vincristine and bleomycin. *AIDS* (1993) 7, 592–3.
5. Toffoli G, Errante D, Corona G, Vaccher E, Bertola A, Robieux I, Aita P, Sorio R, Tirelli U, Boiocchi M. Interactions of antineoplastic chemotherapy with zidovudine pharmacokinetics in patients with HIV-related neoplasms. *Chemotherapy* (1999) 45, 418–28.
6. Kitchen LW, Clark RA, Hanna BJ, Pollock B, Valainis GT. Vancomycin and neutropenia in AZT-treated AIDS patients with staphylococcal infections. *J Acquir Immune Defic Syndr* (1990) 3, 925–6.
7. Retrovir (Zidovudine). ViiV Healthcare UK Ltd. UK Summary of product characteristics, December 2008.
8. Retrovir (Zidovudine). GlaxoSmithKline. US Prescribing information, November 2009.
9. Abelcet (Amphotericin B lipid complex). Cephalon Ltd. UK Summary of product characteristics, November 2007.

NRTIs; Zidovudine + Nimodipine

***Animal* studies suggest that nimodipine may increase the bioavailability of zidovudine.**

Clinical evidence, mechanism, importance and management

Studies in *animals* have shown that the AUC of zidovudine is increased and its volume of distribution and clearance rate decreased when it is given with nimodipine.[1] The clinical relevance of the interaction is not known, but as the adverse effects of zidovudine are dose related, the manufacturer of nimodipine suggests that this interaction should be considered in patients given both drugs.[2]

1. Gallo JM, Swagler AR, Mehta M, Qian M. Pharmacokinetic evaluation of drug interactions with anti-human immunodeficiency virus drugs. VI. Effect of the calcium channel blocker nimodipine on zidovudine kinetics in monkeys. *J Pharmacol Exp Ther* (1993) 264, 315–20.
2. Nimotop Tablets (Nimodipine). Bayer plc. UK Summary of product characteristics, May 2008.

Oseltamivir + Drugs that affect renal clearance

Probenecid inhibits the renal secretion of the active metabolite of oseltamivir and markedly raises its plasma levels. No pharmacokinetic interaction occurs between amoxicillin and oseltamivir, and cimetidine does not appear to alter oseltamivir pharmacokinetics.

Clinical evidence

(a) Amoxicillin

In a study in healthy subjects, oseltamivir 75 mg twice daily for 4.5 days had no effect on the pharmacokinetics of a single 500-mg dose of amoxicillin given with the last dose of oseltamivir. Similarly, amoxicillin had no effect on the pharmacokinetics of the active metabolite of oseltamivir.[1]

(b) Cimetidine

In a crossover study[1] in 18 healthy subjects, cimetidine 400 mg every 6 hours for 4 days had no effect on the pharmacokinetics of a single 150-mg dose of oseltamivir given on day 2.

(c) Probenecid

In a crossover study in 18 healthy subjects, probenecid 500 mg every 6 hours for 4 days approximately halved the renal clearance of the active metabolite of oseltamivir, and increased its AUC about 2.5-fold when a single 150-mg dose of oseltamivir was given on day 2. Population pharmacokinetic data have been used to assess the possibility of using a lower dose of oseltamivir in combination with probenecid. Oseltamivir 45 mg twice daily, but not oseltamivir 30 mg twice daily, with probenecid 500 mg every 6 hours resulted in the same plasma levels of active metabolite as oseltamivir 75 mg twice daily alone.[2]

Mechanism

Probenecid appears to completely inhibit the renal tubular secretion of the active metabolite of oseltamivir via the anionic renal transporter process. Oseltamivir does not alter amoxicillin pharmacokinetics, suggesting minimal potential to inhibit the renal anionic transport process.[1] Cimetidine, which inhibits the renal tubular secretion of drugs via the cationic secretion transport process, had no effect on oseltamivir.

Importance and management

Probenecid markedly increased the AUC of the active metabolite of oseltamivir, but because of the large safety margin of oseltamivir, this increase is not considered to be clinically relevant.[1,3,4] Although one study found that a reduced dose of oseltamivir with probenecid produced therapeutic oseltamivir metabolite levels, it was suggested that the use of the combination may compromise tolerability, increase the potential for interactions, and the increased dosing requirements of the oseltamivir with probenecid regimen may reduce compliance.[2]

Oseltamivir did not alter **amoxicillin** pharmacokinetics, and is therefore unlikely to interact with other renally secreted organic acids. Other drugs that are involved in the active anionic tubular secretion mechanism are also unlikely to interact. **Cimetidine** does not interact with oseltamivir, and other drugs that are inhibitors of the renal cationic secretion transport process are unlikely to interact.[1]

Although the UK manufacturer states that clinically important drug interactions involving competition for renal tubular secretion are unlikely, they recommend care should be taken when giving oseltamivir to patients taking other similarly excreted drugs with a narrow therapeutic margin, and they give **chlorpropamide**, **methotrexate**, and **phenylbutazone** as examples.[3]

1. Hill G, Cihlar T, Oo C, Ho ES, Prior K, Wiltshire H, Barrett J, Liu B, Ward P. The anti-influenza drug oseltamivir exhibits low potential to induce pharmacokinetic drug interactions via renal secretion–correlation of in vivo and in vitro studies. *Drug Metab Dispos* (2002) 30, 13–19.
2. Rayner GR, Chanu P, Gieschke R, Boak LM, Jonsson EN. Population pharmacokinetics of oseltamivir when coadministered with probenecid. J Clin Pharm (2008) 48 (8) 935-47
3. Tamiflu (Oseltamivir phosphate). Roche Products Ltd. UK Summary of product characteristics, October 2009.
4. Tamiflu (Oseltamivir phosphate). Roche Pharmaceuticals. US Prescribing information, August 2008.

Oseltamivir and Zanamivir + Miscellaneous

Antacids do not affect the pharmacokinetics of oseltamivir, and there is no pharmacokinetic interaction between amantadine, aspirin or paracetamol (acetaminophen) and oseltamivir. Aspirin and a variety of other drugs used for influenza management do not affect the antiviral activity of zanamivir *in vitro*.

Clinical evidence, mechanism, importance and management

(a) Oseltamivir

1. Amantadine. In a crossover study, 17 healthy subjects were given oseltamivir 75 mg twice daily alone or with amantadine 100 mg twice daily for 5 days. Amantadine did not significantly affect the pharmacokinetics of oseltamivir or its active metabolite, oseltamivir carboxylate, and the pharmacokinetics of amantadine were not significantly affected by oseltamivir.[1] Therefore, no dose adjustment of either drug appears to be necessary on concurrent use.

2. Antacids. In a single-dose study, the pharmacokinetics of oseltamivir 150 mg and its active carboxylate metabolite were not affected by antacids. The antacids used were an **aluminium/magnesium hydroxide** suspension (*Maalox*) and **calcium carbonate** tablet (*Titralac*).[2] No dose adjustment of oseltamivir appears to be necessary on concurrent use.

3. Aspirin. A pharmacokinetic interaction between oseltamivir and aspirin was predicted to occur, because both drugs are hydrolysed by esterases and secreted by anionic tubular secretion.[3] However, in a study in 12 healthy subjects given a single 900-mg dose of aspirin before, during and/or after oseltamivir 75 mg twice daily for 9 doses, no pharmacokinetic interaction occurred between aspirin and oseltamivir.[3] Therefore, no dose adjustment of either drug appears to be necessary on concurrent use.

4. Paracetamol (Acetaminophen). The manufacturer notes that no pharmacokinetic interaction occurs between paracetamol and oseltamivir.[4,5] Therefore, no dose adjustment of either drug appears to be necessary with concurrent use.

(b) Zanamivir

The *in vitro* antiviral potency of zanamivir was not affected by **aspirin**, **paracetamol**, **ibuprofen**, **phenylephrine**, **oxymetazoline**, **promethazine**, or **co-amoxiclav** (amoxicillin with clavulanic acid).[6] Zanamivir is used as an inhalation, and has a low systemic bioavailability, so interactions would not generally be expected.

1. Morrison D, Roy S, Rayner C, Amer A, Howard D, Smith JR, Evans TG . A randomized, crossover study to evaluate the pharmacokinetics of amantadine and oseltamivir administered alone and in combination. *PLoS One* (2007) 2, e1305.
2. Snell P, Oo C, Dorr A, Barrett J. Lack of pharmacokinetic interaction between the oral anti-influenza neuraminidase inhibitor prodrug oseltamivir and antacids. *Br J Clin Pharmacol* (2002) 54, 372–7.
3. Oo C, Barrett J, Dorr A, Liu B, Ward P. Lack of pharmacokinetic interaction between the oral anti-influenza prodrug oseltamivir and aspirin. *Antimicrob Agents Chemother* (2002) 46, 1993–5.
4. Tamiflu (Oseltamivir phosphate). Roche Products Ltd. UK Summary of product characteristics, October 2009.
5. Tamiflu (Oseltamivir phosphate). Roche Pharmaceuticals. US Prescribing information, August 2008.
6. Daniel MJ, Barnett JM, Pearson BA. The low potential for drug interactions with zanamivir. *Clin Pharmacokinet* (1999) 36 (Suppl 1), 41–50.

Protease inhibitors + Aciclovir and related drugs

No significant pharmacokinetic interaction occurs between valaciclovir or aciclovir and tipranavir or ritonavir.

Clinical evidence, mechanism, importance and management

In a study, 26 healthy subjects were given ritonavir-boosted tipranavir 200/500 mg twice daily, with a single 500-mg dose of **valaciclovir**, a prodrug of aciclovir. Steady-state ritonavir-boosted tipranavir increased the AUC and trough level of aciclovir by 7% and 19%, respectively, and decreased its peak concentration by 5%. **Valaciclovir** had no significant effects on the pharmacokinetics of tipranavir, although the AUC, maximum concentration and minimum concentration of ritonavir were slightly reduced by 14%, 19% and 6%, respectively. The most common adverse effects were gastrointestinal disorders, although 3 subjects stopped taking ritonavir-boosted tipranavir as a result of increases in liver enzymes.[1]

The slight increase in aciclovir levels are not of significance as aciclovir has a wide therapeutic margin. The slight reduction in ritonavir levels is also not considered clinically significant. No dose adjustment is therefore needed when **valaciclovir**, and therefore probably aciclovir, are given with tipranavir or ritonavir.

1. Sabo JP, Cong XJ, Haas D, Eskoetter H, Kraft M, Mauss S. Lack of a pharmacokinetic effect between steady-state tipranavir/ritonavir (TPV/r) and single-dose valacyclovir in healthy volunteers. 48th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, October 2008. Abstract A-967.

Protease inhibitors + Antiepileptics; Miscellaneous

Stiripentol did not alter single-dose saquinavir pharmacokinetics in a controlled study. In one case report, ritonavir did not alter zonisamide levels. Ritonavir is predicted to increase ethosuximide levels.

Clinical evidence, mechanism, importance and management

(a) Ethosuximide

The US manufacturer advises that **ritonavir** may increase the levels of ethosuximide, and that a dose reduction of ethosuximide may be needed with concurrent use and monitoring is advised.[1] However, the UK manufacturer[2] does not mention this interaction, and there appear to be no published clinical data regarding this.

(b) Stiripentol

In a crossover study in 12 healthy subjects,[3] stiripentol 1 g twice daily for 8 days had no effect on the pharmacokinetics of a single 400-mg dose of **saquinavir** given on day 8. No dose adjustment of unboosted saquinavir [now not recommended] appears to be needed with the concurrent use of

stiripentol. However, the effects of using ritonavir-boosted saquinavir with stiripentol have not been reported. Further study is needed.

(c) Zonisamide

A 20-year-old HIV-positive man with epilepsy, who had his seizures controlled with carbamazepine 350 mg twice daily and zonisamide 140 mg twice daily, was admitted to hospital for review of his antiretrovirals. He started taking **ritonavir**, and after the first 200-mg dose his zonisamide levels remained unchanged.[4] However, his levels of carbamazepine were almost doubled.

1. Norvir (Ritonavir). Abbott Laboratories. US Prescribing information, November 2009.
2. Norvir Soft Capsules (Ritonavir). Abbott Laboratories Ltd. UK Summary of product characteristics, October 2009.
3. Cazali N, Tran A, Treluyer JM, Rey E, d'Athis P, Vincent J, Pons G. Inhibitory effect of stiripentol on carbamazepine and saquinavir metabolism in human. *Br J Clin Pharmacol* (2003) 56, 526–36.
4. Kato Y, Fujii T, Mizoguchi N, Takata N, Ueda K, Feldman MD, Kayser SR. Potential interaction between ritonavir and carbamazepine. *Pharmacotherapy* (2000) 20, 851–4.

Protease inhibitors + Atovaquone

Atovaquone modestly reduces the minimum level of indinavir. Ritonavir alone, or used as a pharmacological booster for other protease inhibitors, is predicted to decrease atovaquone levels.

Clinical evidence, mechanism, importance and management

(a) Indinavir

Preliminary results from a study in healthy subjects suggest that the concurrent use of atovaquone 750 mg twice daily and indinavir 800 mg three times daily results in a minor 5% decrease in the AUC of indinavir, and a 13% increase in the AUC of atovaquone.[1] The UK manufacturer of atovaquone notes that concurrent use decreased the minimum level and AUC of indinavir by 23% and 9%, respectively. They recommend that caution should be exercised on concurrent use because of the potential risk of indinavir treatment failure.[2] However, note that the effect on indinavir was small and it is often used with other antiretrovirals, which might modify the interaction by affecting indinavir levels. The UK manufacturer of indinavir states that as **ritonavir** is predicted to affect atovaquone glucuronidation, caution and careful monitoring is needed when ritonavir-boosted indinavir is taken with atovaquone.[3] See also *Ritonavir*, below.

(b) Ritonavir

The manufacturer of ritonavir predicts that it will decrease the plasma levels of atovaquone,[4,5] by inducing atovaquone glucuronidation.[5] They say that the clinical significance of this prediction is unknown, but that an increase in the atovaquone dose might be needed.[4] However, the manufacturer of atovaquone[2] states that there are no data regarding an interaction between atovaquone and protease inhibitors other than indinavir (see above). Careful monitoring of serum levels and/or therapeutic effects is recommended when atovaquone is given with ritonavir, either as a pharmacokinetic enhancer or as an antiretroviral.[5] This predicted interaction would therefore apply to ritonavir-boosted **lopinavir**[6] and any other ritonavir-boosted protease inhibitor. However, there does not appear to be any data to confirm that the interaction occurs or is clinically relevant.

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3. Crixivan (Indinavir sulphate). Merck Sharp & Dohme Ltd. UK Summary of product characteristics, October 2008.
4. Norvir (Ritonavir). Abbott Laboratories. US Prescribing information, November 2009.
5. Norvir Soft Capsules (Ritonavir). Abbott Laboratories Ltd. UK Summary of product characteristics, October 2009.
6. Kaletra (Lopinavir with Ritonavir). Abbott Laboratories. US Prescribing information, April 2009.

Protease inhibitors + Azoles; Fluconazole

Fluconazole may modestly increase the levels of amprenavir, saquinavir and tipranavir, but does not significantly affect atazanavir, indinavir, lopinavir, nelfinavir, or ritonavir levels.

Clinical evidence

A study in 9 HIV-positive patients taking **amprenavir** 600 mg to 750 mg, **lopinavir** 400 mg to 533 mg and **ritonavir** 100 mg to 233 mg, all twice daily, found that the addition of fluconazole 100 mg daily increased the trough plasma levels of **amprenavir**, **lopinavir** and **ritonavir** by 66%, 18%, and 35%, respectively.[1]

The manufacturer of **atazanavir** reports that fluconazole 200 mg daily had no significant effect on the pharmacokinetics of ritonavir-boosted atazanavir 100/300 mg daily. Fluconazole concentrations were unaffected by ritonavir-boosted **atazanavir**.[2]

A study in 8 healthy subjects found that fluconazole 400 mg on day one, followed by 200 mg daily for 4 days did not alter any of the pharmacokinetic parameters of **ritonavir** 200 mg every 6 hours by more than 15%.[3] Similarly, fluconazole had no effect on the pharmacokinetics of **ritonavir** in 3 HIV-positive subjects.[4]

The pharmacokinetics of both **indinavir** 1 g every 8 hours and fluconazole 400 mg daily were not significantly affected by concurrent use in 11 HIV-positive patients.[5] Another study also found no significant interaction between **indinavir** and fluconazole.[6]

A population pharmacokinetic analysis estimated that fluconazole decreased **nelfinavir** clearance by 26 to 30%, but this was not considered clinically significant.[7] The effects of concurrent ritonavir on the interaction of fluconazole with nelfinavir in 3 patients has been reported. In one patient taking **nelfinavir** 1.25 g twice daily with ritonavir-boosted **lopinavir** 133.3/533.3 mg twice daily, the addition of fluconazole 100 mg twice daily for 4 weeks significantly increased the AUC, maximum plasma concentration and trough plasma concentration of **nelfinavir** by 2.44-fold, 2,12-fold, and 2.6-fold, respectively. The levels of the M8 metabolite of nelfinavir were barely detected in the presence of fluconazole. In two other patients taking **nelfinavir** 1.25 g twice daily with stavudine 40 mg twice daily and either efavirenz 800 mg daily or abacavir 300 mg twice daily, the same fluconazole course had no significant effect on the pharmacokinetics of **nelfinavir** or its metabolite.[8]

In a study in 5 HIV-positive subjects, fluconazole 400 mg on day 2, followed by 200 mg daily for 6 days increased the median AUC of **saquinavir** by 50%, and the maximum level by 56%.[4]

In a study in 20 healthy subjects, fluconazole 100 mg daily increased the AUC, maximum plasma levels and minimum plasma levels of ritonavir-boosted **tipranavir** 200/500 mg twice daily by 50%, 32%, and 69%, respectively. Fluconazole levels were not affected.[9]

Mechanism

Fluconazole is a moderate inhibitor of the cytochrome P450 isoenzyme CYP3A4 by which the protease inhibitors are metabolised.[3,5] Fluconazole also inhibits CYP2C9 and CYP2C19; one study[1] suggested that in the presence of ritonavir (an inhibitor of CYP3A4) fluconazole will have a more significant inhibitory effect on CYP2C9 than CYP3A4. This is supported by the study of the effects of fluconazole on nelfinavir pharmacokinetics in the absence or presence of ritonavir which suggested that the effect of fluconazole on CYP2C19 may be increased by ritonavir.[8]

Importance and management

Fluconazole appears to have no clinically significant effects on the pharmacokinetics of atazanavir, indinavir, and ritonavir. The small to modest changes in the pharmacokinetics of saquinavir seen with fluconazole are unlikely to be of clinical significance. Similarly, the modest effects of fluconazole on nelfinavir pharmacokinetics found in the population analysis are not expected to be of clinical relevance.[10] However, the case of significantly raised nelfinavir levels suggests that in some cases a clinically relevant interaction may occur in patients taking also taking ritonavir. Bear the potential for an interaction in mind should a patient develop raised nelfinavir levels and/or adverse effects.

Because fluconazole causes a more significant increase in tipranavir levels, the manufacturer of tipranavir states that fluconazole, in doses of greater than 200 mg daily, is not recommended. No dose adjustments are recommended for lower doses of fluconazole.[11,12]

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11. Aptivus (Tipranavir). Boehringer Ingelheim Pharmaceuticals, Inc. US Prescribing information, June 2009.
12. Aptivus Soft Capsules (Tipranavir). Boehringer Ingelheim Ltd. UK Summary of product characteristics, June 2009.

Protease inhibitors + Azoles; Itraconazole

Itraconazole increases the levels of fosamprenavir, indinavir, ritonavir-boosted lopinavir, and saquinavir, and may theoretically increase the levels of other protease inhibitors. Similarly, some protease inhibitors may also increase itraconazole levels, and cases of raised itraconazole levels and adverse effects have been reported. No significant interaction is predicted to occur between itraconazole and nelfinavir.

Clinical evidence

Two patients taking **indinavir**, and another taking **ritonavir**-boosted **saquinavir**, who were also given itraconazole, developed eczematous eruptions and raised serum transaminases. These effects may be seen with protease inhibitors alone, and were attributed to raised levels of both medications, arising from concurrent use. The patient taking **ritonavir**-boosted **saquinavir** had a very prolonged itraconazole half-life.[1] In another patient, the itraconazole dose was halved when ritonavir-boosted **lopinavir** was started, and after 5 weeks of concurrent use the itraconazole half-life had increased about tenfold, although no signs of itraconazole toxicity were seen.[2] In a study in 17 HIV-positive patients, itraconazole caused a median fivefold increase in the AUC of **saquinavir**, and it was considered that itraconazole may be an alternative to **ritonavir** for boosting **saquinavir** levels;[3] another study has investigated this potential use.[4] The UK manufacturer says that giving **indinavir** 600 mg every 8 hours with itraconazole 200 mg twice daily produces an AUC similar to that achieved when **indinavir** 800 mg every 8 hours is given alone.[5] The manufacturers report that in a study in 12 subjects, itraconazole 200 mg twice daily for 7 days increased the trough level of **indinavir** 600 mg three times daily for 7 days by 49%.[5,6]

Mechanism

Itraconazole is a known substrate and potent inhibitor of the cytochrome P450 isoenzyme CYP3A4, and the protease inhibitors also inhibit and share this pathway of metabolism. Thus enzyme inhibition and competition for metabolism results in raised serum levels of both drugs.

Importance and management

Information about the interactions of protease inhibitors with itraconazole is limited. The UK manufacturer of itraconazole states that protease inhibitors (such as **indinavir**, **ritonavir**, and **saquinavir**) should be used with caution with itraconazole. They advise close monitoring of concurrent use and note that a dose reduction of the protease inhibitor may be required.[7] The US manufacturer specifically states that the levels of indinavir, ritonavir, and saquinavir may be increased by itraconazole, and also note that indinavir and ritonavir may increase itraconazole levels.[8] On the basis of the available data, it is possible that itraconazole has greater effects than ketoconazole on protease inhibitor levels, consider 'Protease inhibitors + Azoles; Ketoconazole', p.964. The manufacturers of indinavir advise reducing the indinavir dose to 600 mg every 8 hours if it is to be given with itraconazole.[5,6] As both indinavir and ritonavir can inhibit CYP3A4, and as the use of ritonavir-boosted indinavir with itraconazole has not been specifically studied, the manufacturers advise close monitoring for itraconazole adverse effects.[5] The UK manufacturer of saquinavir recommends monitoring for saquinavir toxicity if itraconazole is used but states that no data are available for ritonavir-boosted saquinavir.[9]

Some protease inhibitors, especially ritonavir and possibly indinavir, may increase itraconazole levels and most manufacturers say that doses of itraconazole greater than 200 mg a day are not recommended. The US manufacturers[10] of **fosamprenavir** recommend increased monitoring for adverse effects and state that the dose of itraconazole may need to be reduced if it is greater than 400 mg daily. However, both manufacturers advise against the use of itraconazole doses greater than 200 mg daily when fosamprenavir is taken with ritonavir.[10,11]

The US manufacturer[12] of **nelfinavir** suggests that, based on the known pharmacokinetics of both nelfinavir and itraconazole, no significant interaction is likely to occur; the modest changes in nelfinavir pharmacokinetics seen with ketoconazole, another potent inhibitor of CYP3A4, support this prediction. Consider also 'Protease inhibitors + Azoles; Ketoconazole', p.964.

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6. Crixivan (Indinavir sulfate). Merck & Co., Inc. US Prescribing information, October 2009.
7. Sporanox Capsules (Itraconazole). Janssen-Cilag Ltd. UK Summary of product characteristics, October 2009.
8. Sporanox Capsules (Itraconazole). Janssen. US Prescribing information, March 2009.
9. Invirase Hard Capsules (Saquinavir mesilate). Roche Products Ltd. UK Summary of product characteristics, January 2009.
10. Lexiva (Fosamprenavir calcium). GlaxoSmithKline. US Prescribing information, September 2009.
11. Telzir (Fosamprenavir calcium). ViiV Healthcare UK Ltd. UK Summary of product characteristics, May 2009.
12. Viracept (Nelfinavir mesylate). Agouron Pharmaceuticals, Inc. US Prescribing information, September 2008.

Protease inhibitors + Azoles; Ketoconazole

Most protease inhibitors increase the levels of ketoconazole. Ketoconazole may increase the levels of the protease inhibitors.

Clinical evidence

(a) Amprenavir or Fosamprenavir

In a single-dose study, amprenavir 1.2 g caused a modest 44% increase in the AUC of ketoconazole 400 mg. The AUC of amprenavir was also increased by 32%.[1] In a study in 15 healthy subjects, ritonavir-boosted fosamprenavir 100/700 mg twice daily taken for 10 days increased the AUC and maximum plasma concentration of ketoconazole 200 mg daily (taken from days 6 to 10) 2.69-fold and by 25%, respectively. However, in this study, the pharmacokinetics of amprenavir were unaffected by ketoconazole, and the AUC and maximum plasma concentration of ritonavir were slightly increased by 13% and 17%, respectively.[2]

(b) Atazanavir

The pharmacokinetics of atazanavir 400 mg daily were not affected by the concurrent use of ketoconazole 200 mg daily for 7 days.[3]

(c) Darunavir

In a study in healthy subjects, ketoconazole 200 mg twice daily for 13 doses increased the $AUC_{0\text{-}12}$, maximum plasma level and minimum plasma level of darunavir by 155%, 78%, and 179%, respectively. However, when ritonavir 100 mg twice daily was added to darunavir 400 mg twice daily, the same dose of ketoconazole had a much less pronounced effect on darunavir levels: the $AUC_{0\text{-}12}$, maximum plasma level and minimum plasma level of darunavir were increased by 42%, 21%, and 73%, respectively. Darunavir alone had no significant effect on the pharmacokinetics of ketoconazole; however, ritonavir-boosted darunavir increased the $AUC_{0\text{-}12}$, maximum plasma level and minimum plasma level of ketoconazole 3.1-fold, 2.1-fold, and 9.7-fold, respectively. Ketoconazole had no signif-

icant effects on the pharmacokinetics of ritonavir. The incidence of adverse effects was similar for all the treatment regimens.[4]

(d) Indinavir

In a study in 10 healthy subjects, ketoconazole 400 mg daily for 4 doses increased the AUC of a single 400-mg dose of indinavir by 62%. The maximum concentration was increased by 14%, which is not clinically significant.[5]

(e) Lopinavir

A single 200-mg dose of ketoconazole had no effect on the pharmacokinetics of lopinavir (taken as ritonavir-boosted lopinavir 100/400 mg twice daily). However, the AUC of ketoconazole was increased threefold by ritonavir-boosted lopinavir.[6] In contrast, in an HIV-positive patient, ketoconazole 200 mg daily for 14 days was associated with a 68% increase in trough lopinavir levels and a 33% increase in ritonavir levels.[7]

(f) Nelfinavir

In a study in healthy subjects, ketoconazole increased the AUC of nelfinavir by 35%. Nelfinavir had no significant effect on the pharmacokinetics of ketoconazole. The doses and duration of treatment with ketoconazole and nelfinavir were not reported.[8]

(g) Ritonavir

The manufacturers report that, in a study in 12 subjects, ritonavir 500 mg twice daily for 10 days increased the AUC of ketoconazole 200 mg daily for 7 days 3.4-fold and increased the maximum plasma level by 60%.[9,10] The pharmacokinetics of ritonavir were minimally affected.[10]

(h) Saquinavir

In one early clinical study, patients who received ketoconazole with saquinavir had a greater drop in viral load after 3 months than those not receiving ketoconazole.[11] However, in one pharmacokinetic study in 7 HIV-positive patients, ketoconazole 200 mg daily for 7 days then 400 mg daily for 7 days had no consistent effect on saquinavir peak and trough plasma levels, although inter-individual variability was great. Saquinavir (as hard gelatin capsules[12]) was given at the low dose of 600 mg three times daily.[13] Conversely, when saquinavir (soft gel capsule) 1.2 g three times daily was given to 12 healthy subjects with ketoconazole 400 mg daily for 7 days, the saquinavir AUC and maximum plasma levels were raised by 190% and 171%, respectively.[12] A similar study in 22 HIV-positive patients, using ketoconazole 200 mg daily, found that the saquinavir AUC and maximum plasma levels were raised by 69% and 36%, respectively.[12]

In 12 HIV-positive patients, ketoconazole 200 mg or 400 mg increased the AUC of saquinavir and ritonavir in combination (both 400 mg twice daily) by 37% and 29%, respectively. The distribution of ritonavir was also affected, with disproportionate rises seen in CSF concentrations. All these changes appeared to be unrelated to the dose of ketoconazole used.[14]

The peak plasma level of ketoconazole 400 mg daily was similar to that usually seen with ketoconazole 800 mg alone when ritonavir-boosted saquinavir were given.[14] Moreover, in this study, dose escalation to higher doses of ketoconazole was discontinued as the first patient given ketoconazole 600 mg daily stopped treatment early because of adverse gastrointestinal effects.[14] However, saquinavir alone did not affect ketoconazole pharmacokinetics.[12] A further study in 25 stable HIV-positive patients investigated the potential for using ketoconazole rather than ritonavir as a pharmacological booster for saquinavir. Patients were given ritonavir-boosted saquinavir 100/2000 mg daily for at least 4 weeks before ritonavir was changed to ketoconazole 400 mg daily for 2 weeks. The AUC, maximum plasma level and minimum plasma level of saquinavir were 80%, 69%, and 67% lower, respectively, in the ketoconazole-boosted regimen than in the ritonavir-boosted regimen. Thirteen patients given ketoconazole compared with 2 patients given ritonavir had saquinavir levels below the minimum recommended level. A positive correlation between the AUC of ketoconazole and saquinavir was noted.[15] In another study in 32 healthy subjects, ketoconazole 200 mg daily had no significant effect on the pharmacokinetics of ritonavir-boosted saquinavir 100/1000 mg twice daily. However, the $AUC_{0\text{-}12}$ and maximum plasma concentration of ketoconazole were increased by 168% and 45%, respectively. No significant increase in adverse effects was reported.[16]

Mechanism

Ketoconazole is a known substrate and inhibitor of the cytochrome P450 isoenzyme CYP3A4, and the protease inhibitors also inhibit and share this pathway of metabolism.[1,12,14] Thus enzyme inhibition, and competition for metabolism results in raised serum levels of both drugs. Ketoconazole may also inhibit the P-glycoprotein transport of saquinavir and ritonavir, causing a decrease in their clearance, and raising serum levels.[12,14] Inhibition of P-glycoprotein may reduce the transport of protease inhibitors out of the CSF, so increasing CSF levels.[14]

Importance and management

The magnitude of the changes in the pharmacokinetics of the protease inhibitors seen with ketoconazole are unlikely to warrant dose changes of the protease inhibitors or cause significant increase in their adverse effects, although the manufacturer of ketoconazole advises that a protease inhibitor dose reduction may be needed.

The manufacturers of **indinavir** recommend considering reducing the dose of indinavir to 600 mg every 8 hours in the presence of ketoconazole.[17,18]

The significant increase seen with unboosted **darunavir** is unlikely to be of significance in clinical practice, as it is usually combined with low-dose ritonavir, and the interaction between ritonavir-boosted darunavir and ketoconazole is modest in comparison.

The data on the effect of protease inhibitors on ketoconazole are more limited. A marked effect was seen for ritonavir alone, and for ritonavir-boosted **darunavir**, **fosamprenavir**, **lopinavir**, **saquinavir**, and theoretically **tipranavir**. This may increase the adverse effects of ketoconazole. Most protease inhibitor manufacturers say that ketoconazole in doses of greater than 200 mg daily is not recommended. The US manufacturer of **fosamprenavir** states that if unboosted fosamprenavir is given with a dose of ketoconazole greater than 400 mg daily, the ketoconazole dose may need to be reduced: increased monitoring for ketoconazole adverse effects is advised.[19] However, both the UK and US manufacturers advise against the use of ketoconazole doses greater than 200 mg daily when fosamprenavir is taken with ritonavir.[19,20] Similarly, the UK manufacturers of ketoconazole and **ritonavir** say that, due to an increase in gastrointestinal and hepatic adverse effects, a dose reduction of ketoconazole should be considered when it is given with ritonavir (either at full dose or when it is used to boost the effects of other protease inhibitors).[9,21]

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17. Crixivan (Indinavir sulfate). Merck & Co., Inc. US Prescribing information, October 2009.
18. Crixivan (Indinavir sulphate). Merck Sharp & Dohme Ltd. UK Summary of product characteristics, October 2008.
19. Lexiva (Fosamprenavir calcium). GlaxoSmithKline. US Prescribing information, September 2009.

20. Telzir (Fosamprenavir calcium). ViiV Healthcare UK Ltd. UK Summary of product characteristics, May 2009.
21. Nizoral Tablets (Ketoconazole). Janssen-Cilag Ltd. UK Summary of product characteristics, October 2008.

Protease inhibitors + Azoles; Miscellaneous

Systemic clotrimazole is predicted to increase the levels of darunavir, and miconazole is predicted to increase the levels of the protease inhibitors, such as saquinavir. An interaction between the protease inhibitors and topical or intravaginal azoles is unlikely.

Clinical evidence, mechanism, importance and management

The extent of absorption from many topical or intravaginal azole antifungals is low, and therefore the likelihood of an interaction with the protease inhibitors is small, see 'Azoles; Topical + Miscellaneous', p.251. More specific information on individual azoles that are most commonly used topically is given below

(a) Clotrimazole

The UK manufacturer of **darunavir** reports that the concurrent use of systemic clotrimazole increased the AUC of **darunavir** (from ritonavir-boosted darunavir) by a mean of 33% (using a population pharmacokinetic model). They suggest that clotrimazole may inhibit **darunavir** metabolism by the cytochrome P450 isoenzyme CYP3A4, and therefore advise close monitoring when clotrimazole is taken with ritonavir-boosted darunavir.[1] However, this modest increase in darunavir levels is unlikely to be of clinical significance and there appears to be no published data to support the suggestion that clotrimazole has a clinically relevant effect on darunavir levels. The US manufacturers give no specific advice regarding this interaction.[2]

(b) Miconazole

The UK manufacturer of miconazole oral gel states that it may inhibit the metabolism of drugs by CYP3A4 and they specifically name **saquinavir**.[3] However, the UK manufacturer of **saquinavir** states that an interaction between ritonavir-boosted **saquinavir** and miconazole has not been studied.[4] The US manufacturers make no specific comment regarding the possibility of an interaction between miconazole and saquinavir.[5] Note that a large proportion of miconazole oral gel (both prescription and non-prescription doses) may be swallowed and therefore adequate systemic absorption may occur to produce an interaction.

1. Prezista (Darunavir ethanolate). Janssen-Cilag Ltd. UK Summary of product characteristics, October 2009.
2. Prezista (Darunavir ethanolate). Tibotec, Inc. US Prescribing information, June 2009.
3. Daktarin Oral Gel (Miconazole). Janssen-Cilag Ltd. UK Summary of product characteristics, September 2008.
4. Invirase Film-coated Tablets (Saquinavir mesilate). Roche Products Ltd. UK Summary of product characteristics, January 2009.
5. Invirase (Saquinavir mesylate). Roche Laboratories Inc. US Prescribing information, July 2007.

Protease inhibitors + Azoles; Posaconazole

Posaconazole appears to increase the AUC of both atazanavir and ritonavir-boosted atazanavir. Other protease inhibitors are predicted to be similarly affected.

Clinical evidence, mechanism, importance and management

In a study in healthy subjects, oral posaconazole 400 mg twice daily given with **atazanavir** 300 mg daily for 7 days, increased the maximum serum levels and AUC of **atazanavir** about 2.6-fold and 3.7-fold, respectively. When the study was repeated with **ritonavir**-boosted **atazanavir** 100/300 mg daily, the maximum serum levels and AUC of **atazanavir** were increased by about 50%, and 2.5-fold, respectively, and plasma bilirubin levels were increased.

These effects probably occur because posaconazole, a potent inhibitor of the cytochrome P450 isoenzyme CYP3A4, decreases the metabolism of **atazanavir** by this isoenzyme, leading to an increase in both its levels and adverse effects. The manufacturer of posaconazole recommends that patients should be carefully monitored for **atazanavir** adverse effects and toxicity during concurrent use.[1] Other protease inhibitors are predicted to interact similarly, and the same precautions are advisable.

1. Noxafil (Posaconazole). Schering-Plough Ltd. UK Summary of product characteristics, November 2009.

Protease inhibitors + Azoles; Voriconazole

The current use of protease inhibitors and voriconazole is predicted to interfere with the metabolism of both drugs. Ritonavir appears to decrease voriconazole levels in most patients, although some individuals may conversely have increased voriconazole levels. No interaction appears to occur between indinavir and voriconazole.

Clinical evidence

(a) Indinavir

The manufacturers note that *in vitro* studies suggest that the metabolism of protease inhibitors may be inhibited by voriconazole, and the metabolism of voriconazole may be inhibited by protease inhibitors.[1,2] However, in a study in 18 healthy subjects, the pharmacokinetics of both indinavir 800 mg three times daily and voriconazole 200 mg twice daily were unaffected by at least one week of concurrent use.[3]

(b) Ritonavir

In a study in 29 healthy subjects, ritonavir 400 mg twice daily for 10 days decreased the mean steady-state maximum plasma levels and $AUC_{0\text{-}12}$ of oral voriconazole (400 mg twice daily for one day, then 200 mg twice daily for 9 days) by 68% and 83%, respectively, although one subject had a 2.5-fold *increase* in the steady-state maximum levels and $AUC_{0\text{-}12}$ of voriconazole. Large intersubject variability in ritonavir levels were reported with some subjects having a 50% decrease and others a twofold increase during voriconazole exposure. Overall these changes were not considered statistically significant. Low-dose ritonavir (100 mg daily) decreased the mean $AUC_{0\text{-}12}$ and the maximum plasma concentration of voriconazole by 39% and 24%, respectively. However 4 subjects had increases in voriconazole exposure, which was modest in 3 of them (increases of between 10% and 42%) but in one subject threefold increases occurred.[4]

In contrast, a study in 20 healthy subjects also found that ritonavir 300 mg twice daily for 2 days significantly reduced the oral clearance of a single 400-mg dose of voriconazole, given with the first dose of ritonavir. This effect was much greater in those patients who were poor metabolisers of CYP2C19 (those lacking or deficient in this isoenzyme) than those who had normal levels of CYP2C19 (i.e. extensive metabolisers).[5]

Mechanism

Voriconazole is an inhibitor of the cytochrome P450 isoenzyme CYP3A4: protease inhibitors are also metabolised by this route, and can, to varying degrees, also inhibit this isoenzyme. Voriconazole is primarily metabolised by CYP2C9 and CYP2C19, with some minor involvement from CYP3A4. Ritonavir is known to induce the CYP2C9 and CYP2C19 isoenzymes, leading to a reduction in voriconazole levels.[4] Some individuals may have low levels or lack the isoenzyme CYP2C19 (poor metabolisers), an isoenzyme subject to 'genetic polymorphism', (p.4), and other routes of metabolism may take precedence. In this case, CYP3A4 may have developed a more prominent role in voriconazole metabolism. As ritonavir has an overall inhibitory effect on CYP3A4, it is possible that the individuals with significantly raised voriconazole levels were poor metabolisers of CYP2C19. However the authors do note that these subjects were not phenotyped.[4]

Importance and management

Based on the evidence of significantly reduced voriconazole levels and the possible risk of voriconazole treatment failure, the manufacturers say that the concurrent use of **ritonavir** (at doses of 400 mg and above twice daily) is contraindicated.[1,6] The manufacturers also recommend that when ritonavir is used as a pharmacokinetic enhancer (usually 100 mg twice daily) voriconazole should only be given if the benefits outweigh the risks.[1,2,6] Conversely, it should be borne in mind that voriconazole levels may be *increased* by ritonavir in some individuals should voriconazole adverse effects develop.

Most protease inhibitors are given with ritonavir as a pharmacokinetic

enhancer; however, caution is also warranted if they are given alone, as all protease inhibitors can inhibit CYP3A4 to some extent and may therefore also increase voriconazole levels. Voriconazole may also affect protease inhibitor levels, but other than ritonavir and **indinavir**, which are not significantly affected, this does not appear to have been studied. Be aware that some increase in their levels is theoretically possible if voriconazole is given. The manufacturer of voriconazole suggests that patients should be carefully monitored for evidence of drug toxicity and/or loss of efficacy during concurrent use of other HIV-protease inhibitors (**amprenavir**, **nelfinavir** and **saquinavir** are specifically mentioned).[1]

1. VFEND (Voriconazole). Pfizer Ltd. UK Summary of product characteristics, September 2009.
2. VFEND (Voriconazole). Pfizer Inc. US Prescribing information, December 2009.
3. Purkins L, Wood N, Kleinermans D, Love ER. No clinically significant pharmacokinetic interactions between voriconazole and indinavir in healthy volunteers. *Br J Clin Pharmacol* (2003) 56 (Suppl 1), 62–8.
4. Liu P, Foster G, Gandelman K, LaBadie RR, Allison MJ, Gutierrez MJ, Sharma A. Steady-state pharmacokinetic and safety profiles of voriconazole and ritonavir in healthy male subjects. *Antimicrob Agents Chemother* (2007) 51, 3617–26.
5. Mikus G, Schöwel V, Drzewinska M, Rengelshausen J, Ding R, Riedel K-D, Burhenne J, Weiss J, Thomsen T, Haefeli WE. Potent cytochrome P450 2C19 genotype–related interaction between ritonavir and the cytochrome P450 3A4 inhibitor ritonavir. *Clin Pharmacol Ther* (2006) 80, 126–35.
6. Norvir Soft Capsules (Ritonavir). Abbott Laboratories Ltd. UK Summary of product characteristics, October 2009.

Protease inhibitors + Barbiturates

Phenobarbital and other barbiturates are predicted to increase the metabolism of the protease inhibitors, thereby reducing their levels and possibly resulting in failure of the antiretrovirals. However, one case suggested that this may not have occurred with primidone and ritonavir with saquinavir. Another case reported unchanged phenobarbital levels when a patient was changed from indinavir to ritonavir and saquinavir.

Clinical evidence, mechanism, importance and management

The manufacturers of many of the protease inhibitors predict that their levels may be reduced by **phenobarbital**, due to induction of the cytochrome P450 isoenzyme CYP3A4 by which they are metabolised. The UK manufacturer of **darunavir** notes that when it is boosted with ritonavir, concurrent phenobarbital is not recommended as it may significantly reduce darunavir levels.[1] In contrast, the US manufacturer of **darunavir** notes that its levels are not affected by **phenobarbital**, although **phenobarbital** levels may be decreased by **ritonavir**-boosted **darunavir**.[2]

There do not appear to be any controlled studies to demonstrate the extent of the pharmacokinetic interaction between **phenobarbital** and different protease inhibitors. Data from one case report of carbamazepine toxicity with ritonavir-boosted saquinavir provides indirect evidence to suggest that the interaction with **primidone** is not clinically important. In this report, a patient taking an antiretroviral regimen including **ritonavir** and **saquinavir** had his antiepileptic medication changed from carbamazepine to **primidone** 500 mg daily, due to raised carbamazepine levels and toxicity. The authors noted that during follow-up (duration not stated), viral load was still undetectable and seizures remained under control.[3] **Primidone** is metabolised to **phenobarbital**, and might have been expected to cause antiretroviral therapy failure. Alternatively, the effect of **ritonavir**, which is a potent inhibitor of CYP3A4, may have been sufficient to offset any increased clearance associated with **phenobarbital**.

Another patient taking **phenobarbital**, phenytoin and carbamazepine was found to have unchanged phenobarbital levels 2 days after switching from an antiretroviral regimen including **indinavir** to one containing **ritonavir** 300 mg twice daily and **saquinavir**. His plasma levels of carbamazepine had doubled, and there was a 33% drop in the levels of phenytoin.[4] For further discussion about the interaction of carbamazepine or phenytoin with the protease inhibitors, see 'Protease inhibitors + Carbamazepine', p.967, and 'Protease inhibitors + Phenytoin', p.977.

The combination of protease inhibitors and barbiturates should be used with caution, with increased monitoring of antiviral efficacy.

1. Prezista (Darunavir ethanolate). Janssen-Cilag Ltd. UK Summary of product characteristics, October 2009.
2. Prezista (Darunavir ethanolate). Tibotec, Inc. US Prescribing information, June 2009.
3. Berbel Garcia A, Latorre Ibarra A, Porta Etessam J, Martinez Salio A, Perez Martinez DA, Saiz Diaz R, Toledo Heras M. Protease inhibitor-induced carbamazepine toxicity. *Clin Neuropharmacol* (2000) 23, 216–18.
4. Mateu-de Antonio J, Grau S, Gimeno-Bayón J-L, Carmona A. Ritonavir-induced carbamazepine toxicity. *Ann Pharmacother* (2001) 35, 125–6.

Protease inhibitors + Cannabinoids

The short-term use of cannabis cigarettes or dronabinol (Δ^9-tetrahydrocannabinol) did not appear to adversely affect indinavir or nelfinavir levels or viral loads in HIV-positive patients.

Clinical evidence

In 9 HIV-positive patients on a stable regimen containing **indinavir** (mostly 800 mg every 8 hours), smoking a **cannabis cigarette** (3.95% tetrahydrocannabinol) three times daily before meals for 14 days resulted in a median 14% decrease in AUC and maximum level and a 34% decrease in minimum indinavir level. However, only the change in maximum level was statistically significant.[1] Similarly, **dronabinol** (Δ^9-tetrahydrocannabinol) 2.5 mg three times daily for 14 days had no significant effect on **indinavir** pharmacokinetics.[1]

In another 11 patients on a stable regimen containing **nelfinavir** 750 mg three times daily, there was a non-significant 10% decrease in the AUC, a 17% decrease in maximum level, and a 12% decrease in minimum nelfinavir level after 14 days of **cannabis cigarettes.**[1] Similarly, **dronabinol** 2.5 mg three times daily for 14 days had no significant effect on **nelfinavir** pharmacokinetics.[1]

There was no adverse effect on viral load or CD4 count in the patients receiving cannabis cigarettes or dronabinol.[2]

Mechanism

Unknown.

Importance and management

Short-term use of cannabis cigarettes or dronabinol does not appear to have any important effect on levels of indinavir or nelfinavir, nor on markers of HIV infection.

1. Kosel BW, Aweeka FT, Benowitz NL, Shade SB, Hilton JF, Lizak PS, Abrams DI. The effects of cannabinoids on the pharmacokinetics of indinavir and nelfinavir. *AIDS* (2002) 16, 543–50.
2. Abrams DI, Hilton JF, Leiser RJ, Shade SB, Elbeik TA, Aweeka FT, Benowitz NL, Bredt BM, Kosel B, Aberg JA, Deeks SG, Mitchell TF, Mulligan K, Bacchetti P, McCune JM, Schambelan M. Short-term effects of cannabinoids in patients with HIV-1 infection: a randomized, placebo-controlled clinical trial. *Ann Intern Med* (2003) 139, 258–66.

Protease inhibitors + Carbamazepine

Case reports suggest that ritonavir markedly increases carbamazepine levels and toxicity. Cases have also been reported with ritonavir-boosted lopinavir, and nelfinavir. Ritonavir-boosted darunavir also appears to increase the levels of carbamazepine. Carbamazepine reduces indinavir levels and efficacy, reduces tipranavir levels, and would also be expected to decrease the levels of other protease inhibitors.

Clinical evidence

(a) Darunavir

The manufacturer reports that ritonavir-boosted darunavir 100/600 mg twice daily increased the $AUC_{0\text{-}12}$ and trough level of carbamazepine 200 mg twice daily by 45% and 54%, respectively. The $AUC_{0\text{-}12}$ of ritonavir was reduced by 49%. The pharmacokinetics of darunavir were unaffected by carbamazepine.[1]

(b) Indinavir

A report describes a 48-year-old man whose antiretrovirals (indinavir 800 mg every 8 hours, lamivudine 150 mg twice daily and zidovudine 200 mg three times daily) became ineffective after a 10-week course of carbamazepine for postherpetic neuralgia. Over this time indinavir levels were up to 16 times lower than those measured in the absence of carbamazepine.[2] In two further cases, patients taking carbamazepine had partial failure of indinavir-containing antiretroviral regimens, which prompted a change in their therapy to include ritonavir rather than indinavir.[3,4]

In 3 of the case reports described under *Ritonavir*, below, in which ritonavir increased carbamazepine levels,[3-5] patients had previously received indinavir (800 mg three times daily[3,5]) and carbamazepine (600 mg daily[3,4] or 400 mg three times daily[5]) without experiencing carbamazepine

toxicity (therapeutic carbamazepine levels were reported in 2 of the cases[3,4]). This suggests that indinavir does not increase carbamazepine levels. However, in the case described above,[2] carbamazepine levels reached the therapeutic range for epilepsy even though the dose of carbamazepine was only 200 mg daily, suggesting indinavir may increase carbamazepine levels in some patients.

(c) Lopinavir

An HIV-positive patient who had a serum carbamazepine level of 10.3 mg/L while taking carbamazepine 400 mg three times daily reported feeling very drowsy within 9 days of starting to take tenofovir, lamivudine and ritonavir-boosted lopinavir 100/400 mg twice daily. His carbamazepine serum level was found to have increased by 46%, to 15 mg/L. The carbamazepine dose was reduced to 400 mg twice daily, and 2 days later the carbamazepine level was 7.4 mg/L.[6]

(d) Nelfinavir

An HIV-positive patient who had a serum carbamazepine level of 9.8 mg/L while taking carbamazepine 400 mg three times daily started feeling more tired and unsteady on his feet 3 days after starting to take tenofovir, lamivudine and nelfinavir 1.25 g twice daily. His carbamazepine level was found to have increased by 53%, to 15 mg/L. The carbamazepine dose was reduced to 400 mg twice daily, and 2 days later the carbamazepine level was 9.3 mg/L.[6]

(e) Ritonavir

An 20-year-old HIV-positive man with epilepsy, whose seizures had been controlled with carbamazepine 350 mg twice daily and zonisamide 140 mg twice daily, was admitted to hospital for review of his antiretrovirals. He started taking ritonavir 200 mg three times daily, but after the first dose of ritonavir his serum carbamazepine levels rose from 9.5 mg/L to 17.8 mg/L. This was accompanied by intractable vomiting and vertigo, so after 2 days the ritonavir was stopped. Symptoms resolved over the next few days. Subsequently ritonavir 200 mg daily was started, with the same effect, so the carbamazepine dose was reduced by two-thirds, which resulted in carbamazepine levels of 6.2 micrograms/mL. Levels of ritonavir were not measured.[7] Three other cases also document two- to threefold rises in carbamazepine levels with associated toxicity caused by the addition of ritonavir 300 mg, 400 mg or 600 mg twice daily and **saquinavir** 400 mg twice daily.[3-5] In one case, an increase in carbamazepine levels was not expected as the effects of '**efavirenz**', (p.925), an inducer of CYP3A4, which can reduce carbamazepine levels, were expected to balance the inhibitory effects of ritonavir and saquinavir. However, the patient needed a carbamazepine dose reduction from 600 mg daily to 100 mg daily to keep the levels within the therapeutic range, before ritonavir was discontinued.[4]

(f) Tipranavir

Carbamazepine 200 mg twice daily reduces the minimum levels of tipranavir (dose not stated) by 61%, when compared with historical controls. This may result in reduced tipranavir effectiveness. The minimum levels of carbamazepine and its active metabolite were increased by 23%, which is not expected to be clinically significant.[8] In a multiple dose study, 17 subjects were given carbamazepine 200 mg twice daily for 43 doses and ritonavir-boosted tipranavir 200/500 mg [twice daily] for 15 doses. The minimum levels of carbamazepine were increased by 35% and the AUC was increased by 26%. A similar study, in which carbamazepine was given at a dose of 100 mg twice daily, found no clinically significant interaction.[9]

Mechanism

Ritonavir is a potent inhibitor of the cytochrome P450 isoenzyme CYP3A4 and consequently markedly increases the levels of carbamazepine, which is metabolised by this isoenzyme. Other protease inhibitors would be expected to interact similarly, although to a lesser degree (see also 'Antivirals', (p.913)). Moreover, carbamazepine is an inducer of CYP3A4, and therefore can increase the metabolism of protease inhibitors causing the levels to become subtherapeutic. The use of ritonavir-boosted protease inhibitors could theoretically offset this effect, but it may lead to increased carbamazepine toxicity.

Importance and management

Although the evidence is limited, these interactions seem to be established. It would therefore appear that the use of carbamazepine with protease inhibitors should be avoided where possible (mainly because of the risk of antiviral treatment failure). If both must be used then extremely close monitoring of both antiviral efficacy and carbamazepine levels/toxicity is warranted. Symptoms of carbamazepine toxicity include nausea, vomiting, ataxia and drowsiness.

The UK manufacturer of darunavir suggests that the dose of carbamazepine may need to be reduced by 25 to 50%, according to clinical effect, if it is given with ritonavir-boosted darunavir; no dose adjustment of ritonavir-boosted darunavir is required.[1] The US manufacturer advises that no initial dose adjustment of carbamazepine is needed but that the dose should then be adjusted according to clinical response and carbamazepine levels.[10] The authors of one report suggest that amitriptyline or gabapentin would be possible alternatives for carbamazepine used for pain, or valproic acid or lamotrigine for carbamazepine used for seizures.[2] However, note that ritonavir is predicted to increase the levels of amitriptyline, so caution is needed on concurrent use, see 'Tricyclic and related antidepressants + Protease inhibitors', p.1511. Furthermore, reduced lamotrigine and valproate levels have also been reported with ritonavir-boosted protease inhibitors, see 'Protease inhibitors + Lamotrigine', p.974, and 'Protease inhibitors + Valproate', p.988.

1. Prezista (Darunavir ethanolate). Janssen-Cilag Ltd. UK Summary of product characteristics, October 2009.
2. Hugen PWH, Burger DM, Brinkman K, ter Hofstede HJM, Schuurman R, Koopmans PP, Hekster YA. Carbamazepine-indinavir interaction causes antiretroviral therapy failure. *Ann Pharmacother* (2000) 34, 465–70.
3. Berbel Garcia A, Latorre Ibarra A, Porta Etessam J, Martinez Salio A, Perez Martinez DA, Saiz Diaz R, Toledo Heras M. Protease inhibitor-induced carbamazepine toxicity. *Clin Neuropharmacol* (2000) 23, 216–18.
4. Burman W, Orr L. Carbamazepine toxicity after starting combination antiretroviral therapy including ritonavir and efavirenz. *AIDS* (2000) 14, 2793–4.
5. Mateu-de Antonio J, Grau S, Gimeno-Bayón J-L, Carmona A. Ritonavir-induced carbamazepine toxicity. *Ann Pharmacother* (2001) 35, 125–6.
6. Bates DE, Herman RJ. Carbamazepine toxicity induced by lopinavir/ritonavir and nelfinavir. *Ann Pharmacother* (2006) 40, 1190–5.
7. Kato Y, Fujii T, Mizoguchi N, Takata N, Ueda K, Feldman MD, Kayser SR. Potential interaction between ritonavir and carbamazepine. *Pharmacotherapy* (2000) 20, 851–4.
8. Aptivus Soft Capsules (Tipranavir). Boehringer Ingelheim Ltd. UK Summary of product characteristics, June 2009.
9. Aptivus (Tipranavir). Boehringer Ingelheim Pharmaceuticals, Inc. US Prescribing information, June 2009.
10. Prezista (Darunavir ethanolate). Tibotec, Inc. US Prescribing information, June 2009.

Protease inhibitors + Cat's claw (*Uncaria tomentosa*)

An isolated case report describes raised atazanavir, ritonavir and saquinavir levels following the use of cat's claw.

Clinical evidence

An HIV-positive woman awaiting liver transplantation, taking **atazanavir** 300 mg daily, **ritonavir** 100 mg daily and **saquinavir** 1 g daily, in combination with abacavir 600 mg daily and lamivudine 300 mg daily, was found to have an increased trough level of all three protease inhibitors. **Atazanavir** trough levels were 1.22 micrograms/mL (expected range of 0.15 to 0.18 micrograms/mL), **ritonavir** trough levels were 6.13 micrograms/mL (expected level of 2.1 micrograms/mL), and **saquinavir** trough levels were 3.4 micrograms/mL (expected range 0.1 to 0.25 micrograms/mL). On further questioning, the patient reported no change in her compliance with the medication but reported that she been taking a herbal supplement containing cat's claw for the previous 2 months. No evidence of protease inhibitor related toxicity was found and the patient reported no adverse effects. The supplement was stopped and by day 15 the levels of all three drugs had returned to within normal limits.[1]

Mechanism

In vitro studies suggested that cat's claw may inhibit the cytochrome P450 isoenzyme CYP3A4, the main isoenzyme responsible for the metabolism of atazanavir, ritonavir and saquinavir; however, the results of this study are questionable.

Importance and management

Evidence appears to be limited to one case report from which it is difficult to draw general conclusions. What it illustrates is that more research is needed into the use of cat's claw with protease inhibitors. Patients taking drugs for serious conditions such as HIV-infection should carefully con-

sider the risks and benefits of adding herbal medicines to their existing regimen, where the outcome of concurrent use is unknown.

1. López Galera RM, Ribera Pascuet E, Esteban Mur JI, Montoro Ronsano JB, Juárez Giménez. Interaction between cat's claw and protease inhibitors atazanavir, ritonavir and saquinavir. Eur J Clin Pharmacol (2008) 64, 1235–6.

Protease inhibitors + Co-trimoxazole

Minor pharmacokinetic changes have been seen when co-trimoxazole is given with the protease inhibitors.

Clinical evidence, mechanism, importance and management

A study in 12 healthy subjects given **indinavir** 400 mg every 6 hours with co-trimoxazole 960 mg every 12 hours found that there was no change in the AUC of **indinavir**, but a small 17% decrease in **indinavir** trough levels occurred. In addition, there was an 18% increase in the AUC of **trimethoprim**, and a 5% increase in the AUC of **sulfamethoxazole**. None of these changes were considered to be clinically important.[1] A retrospective cohort study in 781 patients taking **indinavir** reported that the concurrent use of prophylactic co-trimoxazole in 362 patients was not associated with an increased risk of developing **indinavir**-related renal toxicity.[2]

In a study in 15 healthy subjects, **ritonavir** 500 mg twice daily caused a 20% increase in the AUC of **trimethoprim** and a 20% decrease in the AUC of **sulfamethoxazole** from a single 960-mg dose of co-trimoxazole. These changes were considered too small to be of clinical relevance.[3] The pharmacokinetics of **ritonavir** were not assessed.

The combination of **saquinavir** 600 mg three times daily and co-trimoxazole 960 mg three times weekly caused no changes in the pharmacokinetics of **saquinavir**.[4]

There would seem to be no reason for avoiding the use of co-trimoxazole with any of the protease inhibitors.

1. Sturgill MG, Seibold JR, Boruchoff SE, Yeh KC, Haddix H, Deutsch P. Trimethoprim/sulfamethoxazole does not affect the steady-state disposition of indinavir. *J Clin Pharmacol* (1999) 39, 1077–84.
2. Herman JS, Ives NJ, Nelson M, Gazzard BG, Easterbrook PJ. Incidence and risk factors for the development of indinavir-associated renal complications. *J Antimicrob Chemother* (2001) 48, 355–60.
3. Bertz RJ, Cao G, Cavanaugh JH, Hsu A, Granneman GR, Leonard JM. Effect of ritonavir on the pharmacokinetics of trimethoprim/sulfamethoxazole. 11th International Conference on AIDS, Vancouver, 1996. Abstract Mo.B.1197.
4. Maserati R, Villani P, Cocchi L, Regazzi MB. Co-trimoxazole administered for *Pneumocystis carinii* pneumonia prophylaxis does not interfere with saquinavir pharmacokinetics. *AIDS* (1998) 12, 815–6.

Protease inhibitors + Drugs that affect gastric pH

Proton pump inhibitors and H_2-receptor antagonists significantly reduce atazanavir levels. Other drugs that increase gastric pH are also predicted to reduce the plasma levels of atazanavir. Fosamprenavir may be similarly affected (moderate effects seen with ranitidine), although antacids and esomeprazole had little effect in one study. Omeprazole decreases indinavir levels and an antacid modestly decreased tipranavir levels. Neither ranitidine nor omeprazole had any effect on the levels of ritonavir-boosted darunavir or lopinavir. In contrast, cimetidine, ranitidine and omeprazole have been shown to increase saquinavir levels.

Clinical evidence

(a) Atazanavir

1. H_2-receptor antagonists. In a study in 40 healthy subjects, **famotidine** 40 mg daily, as either a single dose or in two divided doses, for 7 days minimally reduced the AUC and maximum level of ritonavir-boosted atazanavir 100/300 mg by 4 to 12% and reduced the minimum concentration by about 20%. No significant difference in this effect was seen when **famotidine** was taken at the same time as atazanavir or when it was taken 2 or 12 hours later. When ritonavir-boosted atazanavir was given 2 hours before the morning dose of **famotidine** 40 mg twice daily, the atazanavir AUC, maximum levels and minimum levels were reduced by 21%, 26%, and 28% respectively.[1] The manufacturers report that, in another study in healthy subjects, **famotidine** 40 mg twice daily reduced the atazanavir AUC, maximum levels and minimum levels by 18%, 14%, and 28%, respectively, when given simultaneously with ritonavir-boosted atazanavir 100/300 mg once daily.[2,3] A greater effect (41% reduction in AUC) was seen when the drugs were given without ritonavir.[3] In a randomised study in healthy subjects, **ranitidine** 150 mg one hour before breakfast reduced the atazanavir AUC, maximum level and minimum level by 48%, 52%, and 43%, respectively, when ritonavir-boosted atazanavir 100/300 mg daily was taken 30 minutes after breakfast.[4]

2. Proton pump inhibitors. In a study in 19 healthy subjects, the addition of **omeprazole** 20 mg daily for 7 days reduced the AUC and minimum plasma concentration of ritonavir-boosted atazanavir 100/300 mg daily by 27%, and reduced the maximum concentration by 33%. A large degree of interindividual variability was reported and in 4 subjects, the reduction in AUC and minimum plasma levels was greater than 50%. No significant increase in adverse effects occurred with omeprazole.[5]

In another study in healthy subjects, a higher dose of **omeprazole** 40 mg daily for 10 days significantly reduced the AUC, maximum concentration and minimum concentration of ritonavir-boosted atazanavir 100/300 mg daily by 76%, 72%, and 79%, respectively. Giving the protease inhibitors with cola or increasing the atazanavir dose by 100 mg daily only slightly improved these values.[6] Similar results were found in another study in healthy subjects,[4] and an even greater effect (94% reduction in AUC) was seen when atazanavir 400 mg alone was given with omeprazole 40 mg,[3] and the same effect was seen with **lansoprazole** 60 mg.[7] In one study, ritonavir levels were not affected by **omeprazole**.[4]

Atazanavir trough levels were significantly lower in patients taking proton pump inhibitors than in those taking H_2-receptor antagonists in another study.[8] A 65-year-old HIV-positive man had a marked reduction in atazanavir trough levels and AUC in a 12-hour study while receiving **esomeprazole** and ritonavir-boosted atazanavir.[9] However, 9 of 12 subjects had a successful virological outcome while taking atazanavir with or without ritonavir together with a proton pump inhibitor (**esomeprazole**, **lansoprazole**, **omeprazole**, **pantoprazole**, **rabeprazole**) in a retrospective analysis of concurrent use.[10] Another retrospective analysis also found no difference in virological outcome in 10 patients taking ritonavir-boosted atazanavir with proton pump inhibitors (**rabeprazole**, **omeprazole**) and 66 patients not taking proton pump inhibitors.[11] In a retrospective review, 10 patients were found to be taking atazanavir with a proton pump inhibitor (**esomeprazole**, **lansoprazole**, **omeprazole** or **pantoprazole**). Only 2 patients did not maintain adequate viral suppression. Omeprazole was stopped in one of these patients; however, this did not result in an improvement in viral load.[12] Another study in HIV-positive patients reported that the concurrent use of omeprazole 20 mg or 40 mg daily or rabeprazole 20 mg daily had no significant effect on the pharmacokinetics of ritonavir-boosted atazanavir.[13] Similarly, in one patient taking ritonavir-boosted atazanavir 100/300 mg daily, tenofovir and lamivudine, and **lansoprazole** 30 mg twice daily, the AUC, maximum level and minimum level of atazanavir were higher than those seen historically with ritonavir-boosted atazanavir and tenofovir.[14] Another two patients maintained virological suppression when **omeprazole** 20 mg to 40 mg daily was taken with ritonavir-boosted atazanavir 150 mg twice daily and 300 mg daily, respectively.[15,16]

(b) Darunavir

In a crossover study in 16 healthy subjects, **omeprazole** 20 mg daily and **ranitidine** 150 mg twice daily had no significant effect on the AUC or minimum level of darunavir after ritonavir-boosted darunavir 100/400 mg was given twice daily for 5 days.[17]

(c) Fosamprenavir

In a crossover study in healthy subjects, the AUC of amprenavir (derived from a single 1.4-g dose of fosamprenavir) was decreased by 18% and the maximum plasma level was decreased by 35%, but the minimum level was not significantly altered by the concurrent use of 30 mL of an **aluminium**/**magnesium hydroxide antacid** *(Maalox TC)*.[18] In the same study, **ranitidine** 300 mg, given one hour before fosamprenavir 1.4 g, decreased the AUC of amprenavir by 30% and decreased its maximum level by 51% without altering the minimum level.[18]

In contrast, in studies in healthy subjects, **esomeprazole** 20 mg daily had no effect on the steady-state pharmacokinetics of amprenavir after either fosamprenavir 1.4 g twice daily or ritonavir-boosted fosamprenavir 100/700 mg twice daily. However, fosamprenavir 1.4 g twice daily increased the **esomeprazole** AUC by 55%. In this study, the daily dose of **esomeprazole** was given simultaneously with the first dose of protease inhibitor.[19] Another study in healthy subjects given ritonavir-boosted fosamprenavir 100/1400 mg daily for 7 days found that **omeprazole**

20 mg in the evening had no significant effect on the pharmacokinetics of amprenavir.[5] Similarly, no pharmacokinetic interaction was apparent in an 8-hour study in a 65-year-old HIV-positive patient who was given ritonavir-boosted fosamprenavir with **esomeprazole**.[9]

(d) Indinavir

The manufacturer notes that, in a study in 12 healthy subjects, **cimetidine** 600 mg twice daily for 6 days had no clinically significant effect on the pharmacokinetics of a single 400-mg dose of indinavir.[20]

In a study in 8 healthy subjects given **omeprazole** 40 mg daily with a single 800-mg dose of indinavir, half of the subjects had a clinically significant decrease in the plasma levels of indinavir; no significant pharmacokinetic changes occurred in the others.[21] In a review by the same authors, 4 of 9 patients taking **omeprazole** with indinavir had lower plasma levels of indinavir than expected. In 2 patients, increasing the indinavir dose from 800 mg to 1 g, three times daily, resulted in acceptable plasma levels.[22] In a later randomised controlled study in 14 healthy subjects, **omeprazole** 40 mg daily for 7 days reduced the AUC of a single 800-mg dose of indinavir by 47%. However, the addition of ritonavir 200 mg to indinavir negated the effect of **omeprazole**.[23]

Note that 'buffered didanosine', (p.954), has also been shown to reduce indinavir levels.

(e) Lopinavir

In a randomised study in healthy subjects, **omeprazole** 40 mg daily or **ranitidine** 150 mg one hour before breakfast had no effect on the relative bioavailability of either lopinavir or ritonavir when ritonavir-boosted lopinavir 200/800 mg daily was taken 30 minutes after breakfast, or when ritonavir-boosted lopinavir 100/400 mg twice daily (30 minutes after a meal, as tablets) was given 1.5 hours after the acid-reducing drug.[4]

In a clinical study of ritonavir-boosted lopinavir daily (8 study patients, 86 control patients) or twice daily (7 study patients, 45 control patients) given with tenofovir and emtricitabine, the trough levels of lopinavir were assessed at 4, 8, 16, 24 and 48 weeks: patients taking acid-reducing drugs (**proton pump inhibitors** 67%, **H_2-receptor antagonists** or **antacids**) were then compared with control patients not using acid-reducing drugs. There was no significant difference in trough lopinavir levels between the patients taking acid-reducing drugs and the controls, except that at 24 weeks the trough level of lopinavir was 50% higher, and at 48 weeks it was 73% higher, in users of acid-reducing drugs taking ritonavir-boosted lopinavir daily. No difference was seen in the group taking ritonavir-boosted lopinavir twice daily.[24]

(f) Nelfinavir

In a study, 19 healthy subjects were given **omeprazole** 40 mg daily for 4 days with 1.25 g nelfinavir twice daily for 7 doses. **Omeprazole** reduced the AUC and maximum plasma concentration of nelfinavir by almost 40%, although in 3 patients the AUC of nelfinavir was actually *increased* by **omeprazole**. The pharmacokinetics of the active metabolite of nelfinavir, M8, were also affected, with a reduction in AUC and maximum plasma concentration of 92% and 89%, respectively. Four subjects had undetectable nelfinavir metabolite levels.[25]

(g) Saquinavir

When **cimetidine** 400 mg twice daily was given with saquinavir, the AUC of saquinavir 1.2 g twice daily was 120% greater when compared with saquinavir 1.2 g three times daily alone.[26] In a study in 12 healthy subjects, the AUC of saquinavir given with food was 67% higher when it was given after two 150-mg doses of **ranitidine** given 12 hours apart, and one hour before the saquinavir.[27]

In a study in 18 healthy subjects, **omeprazole** 40 mg daily increased the AUC of saquinavir by 82% when ritonavir-boosted saquinavir 100/1000 mg was given twice daily.[28] In another study in 12 HIV-positive patients taking ritonavir-boosted saquinavir 100/1000 mg twice daily, **omeprazole** 40 mg taken for one week at the same time as saquinavir, significantly increased the AUC, maximum plasma concentration and minimum plasma concentration of saquinavir by 54%, 55% and 73%, respectively. Taking **omeprazole** 2 hours before ritonavir-boosted saquinavir resulted in slightly larger increases of 67%, 65%, and 97%, in the AUC, maximum plasma concentration and minimum plasma concentration of saquinavir, respectively. The pharmacokinetics of ritonavir were not affected by **omeprazole**. Increases in saquinavir bioavailability did not result in an increase in adverse effects.[29]

(h) Tipranavir

In a single-dose study in healthy subjects, 20 mL of an **aluminium**/**magnesium hydroxide** antacid *(Maalox Plus)* decreased the AUC, minimum level and maximum level of tipranavir by 25 to 29%, after ritonavir-boosted tipranavir 500/200 mg was taken at the same time as the antacid.[30-32]

The manufacturer notes that when **omeprazole** 40 mg daily was given with ritonavir-boosted tipranavir there were no changes in the pharmacokinetics of either protease inhibitor, but the AUC and maximum plasma concentration of **omeprazole** were reduced by 71% and 73%, respectively.[32] Similar effects were found with **esomeprazole**.[32]

Mechanism

The UK manufacturer of indinavir states that a normal (acidic) gastric pH may be necessary for optimum absorption of indinavir.[33] Any drug that increases the gastric pH could therefore potentially reduce absorption. Altered gastric pH may also account for the interaction with atazanavir[34] and nelfinavir.[25] In addition, omeprazole may inhibit the metabolism of nelfinavir to its M8 metabolite by the cytochrome P450 isoenzyme CYP2C19.[25] Cimetidine probably boosts saquinavir levels by inhibiting its first-pass metabolism.[26] It is not understood why ranitidine and omeprazole increase saquinavir levels.

Importance and management

Atazanavir

Proton pump inhibitors. The marked pharmacokinetic interaction of omeprazole with atazanavir (with or without ritonavir) is established; lansoprazole appears to act similarly. Based on the available data, advice in Europe[34] and the US[35] is that atazanavir or ritonavir-boosted atazanavir should not be given with omeprazole or other proton pump inhibitors. However, the UK manufacturer[2] advises that if the concurrent use of a proton pump inhibitor is necessary, the dose of ritonavir-boosted atazanavir should be increased to 400 mg daily and both the UK and US manufacturers advise that a maximum dose of 20 mg of omeprazole (or the equivalent in other proton pump inhibitors) should be used.[2,3] The US manufacturers limit this advice to treatment-naive patients, and advise that the dose of the proton pump inhibitor should be taken 12 hours before atazanavir.[3]

H_2-receptor antagonists. Modest effects were seen with atazanavir and the simultaneous use of famotidine, whereas ranitidine taken 1.5 hours before ritonavir-boosted atazanavir had a more marked effect. The manufacturers state that **ritonavir-boosted atazanavir** 100/300 mg (with food) should be given with or 10 hours after famotidine 20 mg twice daily (or the comparable dose of another H_2-receptor antagonist).[2,3] In the US, famotidine up to 40 g twice daily may be given to treatment-naive patients, with the same dose, and dose interval as the lower famotidine dose.[3] In the UK, if famotidine 40 mg twice daily or more is required, then the manufacturers suggest considering increasing the dose of ritonavir-boosted atazanavir to 100/400 mg.[2]

In the presence of **tenofovir** the UK manufacturer suggests that concurrent use of ritonavir-boosted atazanavir with an H_2-receptor antagonist should be avoided unless the combination is considered essential. If the combination is given, both the US and UK manufacturers advise that the dose of atazanavir may be increased to 400 mg, but this has not been fully evaluated.[2,3] The US manufacturer limits this advice to treatment-experienced patients, and suggests no dose alteration for treatment-naive patients.

For **unboosted atazanavir**, in treatment-naive patients, the US manufacturer recommends a dose of 400 mg daily with food, which should be given 2 hours before or 10 hours after the H_2-receptor antagonist. The dose of famotidine (or equivalent) should not exceed 20 mg in any single dose or 40 mg in a day.[3]

Buffered medicinal products. The manufacturers recommend atazanavir should be given 2 hours before or one hour after buffered medicinal products.[2,3] This would include didanosine buffered tablets (see 'NRTIs + Protease inhibitors', p.954).

Other protease inhibitors

Based on the limited data with other protease inhibitors, the manufacturers of **amprenavir** recommended that it should not be given within one hour of antacids.[36,37] However, the decrease in amprenavir levels seen when **fosamprenavir** is given with an antacid are not considered clinically relevant, and no fosamprenavir dose adjustments are considered to be necessary.[38] Greater decreases were seen with ranitidine, although the minimum

levels were unchanged. The UK manufacturer[38] states that no fosamprenavir dose adjustment is needed with ranitidine or other H_2-receptor antagonists, whereas the US manufacturer[39] says the combination should be used with caution as fosamprenavir may become less effective. However, no interaction occurred with esomeprazole, and this, or other proton pump inhibitors may be given at the same time as fosamprenavir.[38,39]

The interaction between omeprazole and **indinavir** would appear to be established. Omeprazole should probably not be used with indinavir unless ritonavir is used to boost the indinavir levels.[23] This would be likely apply to other proton pump inhibitors used with indinavir as well. No significant interaction occurs between **indinavir** and cimetidine, and based on this result, the other H_2-receptor antagonists would not be expected to interact.

The reduction in the levels of **nelfinavir** and its active metabolite may lead to loss of virological activity, and therefore the UK manufacturer contraindicates the concurrent use of omeprazole and recommends caution if other proton pump inhibitors are used with nelfinavir.[40] The manufacturer of esomeprazole similarly contraindicates concurrent use with nelfinavir.[41] However the US manufacturer recommends that no proton pump inhibitors should be given with nelfinavir.[42]

Cimetidine very markedly increases **saquinavir** levels, and further study is required to discover whether this is clinically useful.[26] Ranitidine causes a fairly marked increase in saquinavir levels, although this is probably not clinically relevant. If omeprazole or other proton pump inhibitors are taken with ritonavir-boosted saquinavir, the manufacturer of saquinavir recommends monitoring for potential saquinavir toxicity.[43] Separating the dose of omeprazole from saquinavir does not appear to minimise the interaction.

Antacids modestly decreased **tipranavir** levels, and administration should be separated by at least 2 hours.[32] The use of tipranavir with omeprazole or esomeprazole is not recommended,[32] but if both drugs are given consider increasing the dose of the proton pump inhibitor,[31,32] according to response.

Omeprazole and ranitidine do not appear to alter the pharmacokinetics of ritonavir-boosted **darunavir** or **lopinavir**.

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Protease inhibitors + Food

Food increases the bioavailability of atazanavir, darunavir, ritonavir-boosted lopinavir soft capsules and solution, nelfinavir and saquinavir (all formulations), but decreases that of indinavir. A high-fat meal increases the bioavailability of tipranavir, but food also improves its tolerability. Food only minimally affects the bioavailability of amprenavir, fosamprenavir, ritonavir-boosted lopinavir tablets and ritonavir. Mixing ritonavir with enteral feeds does not affect the pharmacokinetics of ritonavir.

Clinical evidence, mechanism, importance and management

(a) Absorption decreased

A single 600-mg dose of **indinavir** was given to 7 HIV-positive subjects immediately after various types of meal. The protein, carbohydrate, fat and high-viscosity meals reduced the AUC of **indinavir** by 68%, 45%, 34% and 30%, respectively. The fat meal was associated with the largest inter-subject variation in bioavailability. The effect of the protein meal was attributed to the fact that it raised gastric pH and therefore impaired the absorption of **indinavir** (a weak base). The impairment of **indinavir** absorption caused by the other meals, which did not alter gastric pH, may have been due to delayed gastric emptying.[1] A similar study comparing a full breakfast with light breakfasts (toast or cereal) on indinavir absorption found that the full breakfast reduced the absorption of **indinavir** by 78% and reduced its maximum serum levels by 86%, while the light breakfasts had no significant effect.[2] The manufacturers[3,4] advise that **indinavir** is taken one hour before or 2 hours after meals, or with low-fat light meals only, although the UK manufacturers also state that when indinavir is tak-

en with ritonavir it may be taken with or without food.[3] The US manufacturer gives examples of a light meal, such as dry toast with jam, juice, and coffee with skimmed milk and sugar; or corn flakes, skimmed milk and sugar.[4]

(b) Absorption increased

1. Atazanavir. The manufacturers of atazanavir report that a light meal increased the AUC and maximum concentration of a single 300-mg dose of ritonavir-boosted atazanavir by 33% and 40%, respectively, compared with the fasting state, whereas a high-fat meal did not significantly increase the absorption of atazanavir.[5,6] The US manufacturer also notes that a light meal increased the AUC and maximum concentration of atazanavir 400 mg by 70% and 57%, respectively.[6] Administration with a light meal or a high-fat meal also decreased the wide variation in plasma levels. The manufacturers therefore recommend that atazanavir should be taken with food to enhance bioavailability and minimise variability.[5,6]

2. Darunavir. In a study in 22 healthy subjects, the relative bioavailability of ritonavir-boosted darunavir was found to be 30% lower when it is taken on an empty stomach, compared with intake immediately after food. In this study, no significant difference in the affects of food on darunavir were seen between the different meals tested (a high-fat breakfast, a standard breakfast, a protein-rich drink, or a croissant and coffee). Taking darunavir with food did not affect interindividual variability in darunavir absorption.[7] Therefore, the manufacturers advise that ritonavir-boosted darunavir tablets should be taken with food.[8,9]

3. Lopinavir. A moderate-fat meal increased the AUC and maximum level of lopinavir capsules by 48% and 23%, respectively, and a high-fat meal increased the AUC and maximum level of lopinavir capsules by 96% and 43%, respectively. The corresponding increases for lopinavir solution were 80% and 54% for the moderate-fat meal, and 130% and 56% for the high-fat meal.[10] The manufacturers of ritonavir-boosted lopinavir *soft capsules* and *oral solution* say that it should be taken with food.[10,11]
No clinically significant difference was seen in the bioavailability of ritonavir-boosted lopinavir *tablets* between fasting and fed subjects, therefore the manufacturers say that it can be taken with or without food.[11,12]

4. Nelfinavir. When nelfinavir 400 mg or 800 mg was given to 12 healthy subjects in the fasted state, the AUC was only 27% to 50% of that observed when nelfinavir was taken with a meal.[13] The US manufacturer reports that in two studies in healthy subjects, food significantly increased the exposure to a 1.25-g dose of nelfinavir two- to threefold when compared with the fasting state, with the highest increase in the AUC and maximum concentration of nelfinavir occurring with the high-calorie, high-fat meal (1000 kcal and 50% fat).[14] A small study in healthy subjects also found a similar effect.[15] The UK manufacturer reports that this effect appears to be less in multiple-dose studies where a high-fat meal (800 kcal and 50% fat) increased the AUC and maximum concentration by a modest 20% compared with a lighter meal (250 kcal and 33% fat).[16] Another study in 24 healthy subjects found that the AUC of nelfinavir 1.25 g taken twice daily for 17 days, was only reduced by 13% when it was taken with a light breakfast (250 kcal and 13 g fat) compared with a standard breakfast (800 kcal and 35 g fat).[17] As food significantly increases the absorption of nelfinavir the manufacturers recommend that it should be taken with food.[14,18]

5. Saquinavir. The manufacturer of saquinavir hard capsules and tablets notes that, in a crossover study in 22 HIV-positive patients taking ritonavir-boosted saquinavir 100/1000 mg twice daily and receiving three consecutive doses under fasting conditions or after a high-fat, high-calorie meal, the AUC, maximum and minimum levels of saquinavir under fasting conditions were about 70% lower than with a high-fat meal. There were no clinically significant differences in the pharmacokinetic profile of ritonavir in fasting and fed conditions but the ritonavir minimum level was about 30% lower in the fasting state, when compared with its administration with a meal.[16,19] Ritonavir-boosted saquinavir should be given with, or up to 2 hours after, a meal.[16,19,20]

6. Tipranavir. The US manufacturer states that, in a study, the pharmacokinetics of tipranavir were unaffected when it was taken with food (500 to 682 kcal, 23 to 25% of the calories from fat), compared with fasting conditions. They therefore state that tipranavir can be taken with or without food.[21] The UK manufacturer states that food improves the tolerability of ritonavir-boosted tipranavir, and recommends that it should be taken with food.[22]

(c) Absorption minimally affected

1. Amprenavir. The manufacturers reported that food resulted in a 25% reduction in the AUC of amprenavir, but no change in its steady-state trough level. Consequently, the manufacturers stated it can be taken with or without food,[23,24] but the US manufacturer said that it should not be taken with a high-fat meal.[24]

2. Fosamprenavir. In a study in 24 healthy subjects, food had no clinically significant effects on the bioavailability of a 1.73 g dose of fosamprenavir from a tablet formulation.[25] Fosamprenavir *tablets* may be taken without regard to food intake.[26,27]
A high-fat meal modestly reduced the AUC and maximum concentration of a 1.73-g dose of fosamprenavir *suspension* by 20% and 41%, respectively.[25] The manufacturers advise that adults should take the oral *suspension* without food and on an empty stomach. However, they advise that in order to improve palatability and ensure compliance, children may take the *suspension* with food.[27,28]

3. Ritonavir. The US manufacturer notes that a meal increased the absorption of ritonavir capsules by 13%, when compared with the fasting state, whereas the absorption of the oral solution was decreased by 7%.[29] See also *Lopinavir* and *Saquinavir*, above. Although these changes are modest, the manufacturers state that ritonavir capsules and solution are preferably taken with food.[29-31]
There is also some evidence that mixing ritonavir with **enteral feeds** does not affect ritonavir pharmacokinetics. A 600-mg dose of ritonavir oral solution was mixed with 240 mL of **enteral feeds** (either *Advera* or *Ensure*), **chocolate milk** or water within one hour of dosing. When given up to 15 minutes after a low-fat meal, the pharmacokinetics of ritonavir in either of the **enteral feeds** or the **milk** were almost identical to those when ritonavir was given in water.[32]

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27. Lexiva (Fosamprenavir calcium). GlaxoSmithKline. US Prescribing information, September 2009.

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30. Norvir Oral Solution (Ritonavir). Abbott Laboratories Ltd. UK Summary of product characteristics, October 2009.
31. Norvir Soft Capsules (Ritonavir). Abbott Laboratories Ltd. UK Summary of product characteristics, October 2009.
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Protease inhibitors + Garlic

A garlic supplement reduced the plasma levels of saquinavir by 50% in one study, but had little effect in another. Another garlic supplement did not significantly affect the pharmacokinetics of a single dose of ritonavir.

Clinical evidence

In a study in 9 healthy subjects garlic reduced the AUC, and maximum and minimum plasma levels of **saquinavir** by about 50%. The garlic was taken in the form of a dietary supplement (*GarliPure, Maximum Allicin Formula* caplets) twice daily for 20 days. **Saquinavir** 1.2 g three times daily was given for 4-day periods before, during, and after the garlic supplement. Fourteen days after the garlic supplement was stopped the **saquinavir** pharmacokinetics had still not returned to baseline values. Of the 9 subjects, 6 had a substantial drop in the AUC of **saquinavir** while taking garlic, then a rise when garlic was stopped. The remaining 3 had no change in the AUC of **saquinavir** while taking garlic, but had a drop when garlic was stopped.[1] However, in another study, garlic extract (*Garlipure*) 1.2 g daily for 3 weeks had no significant effect on the pharmacokinetics of a single 1.2-g dose of **saquinavir** (a slight decrease in AUC in 7 subjects and a slight increase in 3).[2]

In a study in 10 healthy subjects the use of a garlic extract (10 mg, equivalent to 1 g of fresh garlic) twice daily for 4 days did not significantly affect the pharmacokinetics of a single 400-mg dose of **ritonavir**. There was a non-significant 17% decrease in the AUC of **ritonavir**. The garlic was given in the form of capsules (*Natural Source Odourless Garlic Life Brand*).[3] Gastrointestinal toxicity was noted in 2 patients taking garlic or garlic supplements when they started to take **ritonavir**-containing regimens.[4]

Mechanism

The mechanism of this interaction is uncertain, but it is thought that garlic reduced the bioavailability of saquinavir by increasing its metabolism in the intestine.[1] Why there was a disparity in the effect of garlic on saquinavir between patients is unclear.

Allicin is thought to have inhibited the activity of P-glycoprotein *in vitro*, which caused the build-up of ritonavir within the cell.[5]

Importance and management

Although information is limited, a reduction in saquinavir plasma levels of the magnitude seen in the first study could diminish its antiviral efficacy. All garlic supplements should probably be avoided in those taking saquinavir as the sole protease inhibitor, but note that this is no longer generally recommended. The effect of garlic on saquinavir levels in the presence of ritonavir (as a pharmacokinetic enhancer) does not appear to have been studied. The pharmacokinetic effect on single-dose ritonavir was not clinically important, but this requires confirmation in a multiple-dose study.

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Protease inhibitors + Ginkgo (*Ginkgo biloba*)

Ginkgo does not appear to affect the pharmacokinetics of ritonavir-boosted lopinavir.

Clinical evidence

In a study in 14 healthy subjects, ginkgo 120 mg twice daily for 2 weeks had no significant effect on the pharmacokinetics of ritonavir-boosted **lopinavir** 100/400 mg twice daily (given for 2 weeks alone before adding the ginkgo). The ginkgo extract was assayed and contained 29% flavonol glycosides and 5% terpene lactones.[1]

Mechanism

The authors suggest that without ritonavir, the levels of lopinavir would have been reduced by ginkgo because they also found that ginkgo modestly reduced the levels of midazolam, probably by inducing the cytochrome P450 isoenzyme CYP3A4. As ritonavir is an inhibitor of CYP3A4, they suggest that it attenuates the action of ginkgo on lopinavir metabolism. However, note that all protease inhibitors are inhibitors of CYP3A4 to varying extents, and note also that in other studies with midazolam, ginkgo had no effect on midazolam levels, or even caused a minor increase in levels, which suggests that ginkgo does not have a clinically relevant effect on CYP3A4 activity.

Importance and management

The study here shows that ginkgo does not alter the pharmacokinetics of ritonavir-boosted lopinavir, and no special precautions are required on concurrent use. This would apply to all other ritonavir-boosted protease inhibitors. As regards protease inhibitors that are not boosted by ritonavir, the authors of this study recommend avoiding ginkgo.[1] This seems an over-cautious approach, given that the sum of studies available show that ginkgo does not have a clinically relevant effect on the probe CYP3A4 substrate midazolam.

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Protease inhibitors + Grapefruit and other fruit juices

Grapefruit juice does not have any clinically significant effects on the pharmacokinetics of either amprenavir or indinavir, but may double the AUC of saquinavir. Seville orange juice did not alter indinavir pharmacokinetics in one study.

Clinical evidence, mechanism, importance and management

(a) Amprenavir and Fosamprenavir

In a study in 12 healthy subjects, 200 mL of grapefruit juice (given on two occasions) slightly delayed the rate but not the extent of absorption of a single 1.2-g dose of amprenavir and modestly reduced the maximum plasma concentration of by 22%. These effects were not clinically significant. No adverse effects were reported in this study.[1] The manufacturer of fosamprenavir notes that taking amprenavir with grapefruit juice was not associated with clinically significant changes in plasma amprenavir pharmacokinetics.[2] Note that fosamprenavir is metabolised to amprenavir in the gut. No special precautions appear to be necessary with concurrent use.

(b) Indinavir

In a single-dose study in 10 healthy subjects, grapefruit juice (8 oz, about 200 mL) reduced the AUC of indinavir 400 mg by 27%, although this was not considered clinically significant.[3] In another study in 13 healthy subjects, grapefruit juice or **Seville orange juice** (both about 200 mL) had no effect on the pharmacokinetics of indinavir. In this study indinavir 800 mg was given every 8 hours for 4 doses; with water, grapefruit juice, or Seville orange juice given with the last 2 doses.[4] Similarly, in 14 HIV-positive subjects, grapefruit juice (180 mL of double strength) had no effect on the steady-state pharmacokinetics of indinavir (a non-significant 5% increase in AUC was seen and a slight delay in the rate of absorption).[5]

(c) Saquinavir

In a study of the effects of the concurrent use of grapefruit juice 400 mL and saquinavir (*Invirase*; hard capsules) 600 mg, grapefruit juice was found to increase the AUC of saquinavir by 50%, possibly by affecting the cytochrome P450 isoenzyme CYP3A4 in the intestine.[6] The manufacturer notes that the increase was 100% when double-strength grapefruit juice was used.[7] They say that these increases are unlikely to be clinically relevant, and no saquinavir dose adjustment is necessary, although they note that ritonavir-boosted saquinavir has not been specifically studied.[7]

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Protease inhibitors + Lamotrigine

Ritonavir-boosted atazanavir and lopinavir appear to reduce lamotrigine plasma levels, whereas the protease inhibitor levels do not appear to be altered. An increased dose of lamotrigine was required in a patient who was also taking ritonavir-boosted saquinavir. Atazanavir alone does not appear to have any significant effect on the pharmacokinetics of lamotrigine.

Clinical evidence

(a) Atazanavir

In a study, 17 healthy subjects were given a single 100-mg dose of lamotrigine alone, after 6 days of atazanavir 400 mg daily, and after 10 days of ritonavir-boosted atazanavir 100 mg/300 mg daily. Atazanavir alone had no significant effect on the pharmacokinetics of lamotrigine. However ritonavir-boosted atazanavir reduced the AUC and maximum plasma concentration of lamotrigine by 32% and 6%, respectively. Formation of lamotrigine-2N-glucuronide was also increased by ritonavir-boosted atazanavir.[1]

(b) Lopinavir

In a study in 18 healthy subjects taking lamotrigine 100 mg twice daily, ritonavir-boosted lopinavir 100/400 mg twice daily for 10 days decreased the steady-state minimum plasma level of lamotrigine by 55%, decreased the AUC of lamotrigine by 46%, and increased its clearance by 85%. Doubling the dose of lamotrigine to 200 mg twice daily increased the AUC to a similar level to that seen with the lower dose without ritonavir-boosted lopinavir. Pharmacokinetic parameters for lopinavir and ritonavir were similar to those in historical controls.[2] The authors of a review describe a patient taking lamotrigine 25 mg twice daily who had a favourable decline in viral load 2 months after starting to take ritonavir-boosted lopinavir, lamivudine and stavudine. There was no toxicity and no recurrence of seizures.[3]

(c) Saquinavir and Ritonavir

A 30-year-old woman taking nevirapine, saquinavir 1.2 g daily, and ritonavir 600 mg daily with an undetectable viral load had her epilepsy medication changed from gabapentin and lorazepam to lamotrigine and phenytoin because of an increased frequency and severity of seizures. The lamotrigine dose was eventually increased to 1.8 g daily to achieve serum levels of 5 to 8 mg/L. The ritonavir dose was doubled and the saquinavir dose increased to 2 g daily to compensate for the enzyme-inducing effects of phenytoin (consider also 'Protease inhibitors + Phenytoin', p.977). The patient's viral load remained undetectable, and her seizures decreased over the next 6 months, but she died suddenly of unexplained causes following a tonic-clonic seizure (autopsy not performed).[4]

Mechanism

Ritonavir decreases lamotrigine levels by induction of glucuronidation,[5] although an effect of lopinavir cannot be ruled out.[2] Atazanavir is known to inhibit glucuronidation by UGT1A1, and would therefore have been expected to have a significant effect on lamotrigine pharmacokinetics; however. this was not seen in the study above.

Importance and management

The pharmacokinetic interaction between lamotrigine and ritonavir would appear to be established; however, as the relationship between lamotrigine levels and efficacy is not clear, the clinical relevance of the decrease is uncertain.[2] Lamotrigine efficacy should be monitored in patients taking ritonavir or any ritonavir-boosted antiretroviral regimen. Anticipate the need to increase the lamotrigine dose.

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Protease inhibitors + Macrolides

Nelfinavir approximately doubles the levels of azithromycin. Single doses of azithromycin have no effect on the levels of indinavir and nelfinavir. Atazanavir, darunavir, ritonavir and tipranavir increase clarithromycin levels, whereas amprenavir, indinavir and saquinavir do not have a clinically significant effect on clarithromycin pharmacokinetics. Clarithromycin has no important effect on the pharmacokinetics of amprenavir, atazanavir, darunavir, indinavir or ritonavir, but it increases tipranavir levels, and may markedly raise saquinavir levels (from soft capsules). Erythromycin may also increase the levels of saquinavir from soft capsules. Additive QT prolongation is predicted to occur if ritonavir-boosted lopinavir is taken with clarithromycin or erythromycin.

Clinical evidence

(a) Azithromycin

1. Indinavir. A single 1.2-g dose of azithromycin had no effect on the pharmacokinetics of indinavir in healthy subjects who had taken indinavir 800 mg three times daily for 5 days. The pharmacokinetics of azithromycin were not assessed[1]

2. Nelfinavir. A single 1.2-g dose of azithromycin was given to 12 healthy subjects who had taken nelfinavir 750 mg every 8 hours for 8 days. The pharmacokinetics of nelfinavir were minimally affected, but the AUC and maximum serum levels of azithromycin were about doubled.[2]

(b) Clarithromycin

1. Amprenavir. In a study in 12 healthy adults, amprenavir 1.2 g twice daily was given with clarithromycin 500 mg twice daily, for 4 days. The AUC and maximum serum levels of amprenavir were slightly increased, by 18% and 15%, respectively, whereas the pharmacokinetics of clarithromycin were not significantly altered. None of these changes were considered to be clinically significant.[3]

2. Atazanavir. The concurrent use of atazanavir 400 mg daily and clarithromycin 500 mg twice daily for 4 days increased the AUC of clarithromycin by 94%, and reduced the AUC of the metabolite 14-hydroxyclarithromycin by 70%. In addition, there was a minor 28% increase in the AUC of atazanavir.[4]

3. Darunavir. In a study, 17 healthy subjects were given ritonavir-boosted darunavir 100/400 mg twice daily, clarithromycin 500 mg twice daily or both drugs together, all for 13 doses. Clarithromycin had no significant effect on the pharmacokinetics of darunavir: the maximum plasma concentration and AUC of darunavir were reduced by 17% and 13%, respectively, and the minimum plasma concentration was unchanged.

However, the AUC, peak plasma levels and trough plasma levels of clarithromycin were increased by 57%, 26% and 174%, respectively. The metabolite, 14-hydroxyclarithromycin, was not detectable.[5]

4. Indinavir. In 11 healthy subjects clarithromycin 500 mg every 12 hours, given with indinavir 800 mg every 8 hours, caused no clinically important alterations in the pharmacokinetics of indinavir: the only significant change was a 52% increase in the trough level. The AUC of clarithromycin was increased by about 50%, and that of 14-hydroxyclarithromycin reduced by about 50%, but neither of these changes were considered clinically important because of the wide safety margin of clarithromycin.[6]

5. Lopinavir. A case of rhabdomyolysis has been reported in an HIV-positive patient taking clarithromycin, ritonavir-boosted lopinavir, and atorvastatin, see 'Statins + Macrolides', p.1337.

6. Ritonavir. When ritonavir 200 mg every 8 hours was given with clarithromycin 500 mg every 12 hours there were only minimal changes in ritonavir pharmacokinetics (13% increase in AUC and 15% increase in maximum plasma level). However, the AUC of clarithromycin increased by 77% with an almost total inhibition of 14-hydroxyclarithromycin formation (99.7% decrease in AUC).[7]

7. Saquinavir. In a study in healthy subjects the concurrent use of saquinavir soft capsules *(Fortovase)* [no longer available] 1.2 g three times daily and clarithromycin 500 mg twice daily increased the AUC and maximum serum levels of saquinavir by 177% and 187%, respectively. The AUC and maximum serum levels of clarithromycin were about 40% higher than when it was given alone.[8,9] The manufacturer notes that there are no data on the interaction using ritonavir-boosted saquinavir hard capsules or tablets (*Invirase*).[8,9]

8. Tipranavir. In a study in 21 healthy subjects, clarithromycin 500 mg twice daily was taken for 13 days with ritonavir-boosted tipranavir 200/500 mg twice daily from day 6 to 13. Ritonavir-boosted tipranavir increased the minimum plasma level of clarithromycin by 68%, although the AUC and maximum concentration were minimally affected. The $AUC_{0\text{-}12}$ and maximum plasma concentration of the 14-hydroxy metabolite of clarithromycin were also reduced by 97%, and its minimum level reduced by 95%. No increase in adverse effects was reported, although one subject taking ritonavir-boosted tipranavir and clarithromycin had a significant grade 3 increase in ALT. Clarithromycin increased the AUC, maximum and minimum concentration of tipranavir by 66%, 40%, and 100%, respectively.[10]

(c) Erythromycin

The concurrent use of saquinavir soft capsules (*Fortovase*) [no longer available] 1.2 g three times daily and erythromycin 250 mg four times daily doubled the AUC and maximum serum levels of saquinavir in HIV-infected subjects.[11] The manufacturers note that there are no data on the interaction using ritonavir-boosted saquinavir hard capsules or tablets (*Invirase*).[8,9]

Mechanism

Ritonavir is a potent inhibitor of the cytochrome P450 isoenzyme CYP3A4 and consequently markedly inhibits the 14-hydroxylation of clarithromycin by this isoenzyme. Other protease inhibitors would be expected to interact similarly, although to a lesser degree (see also 'Antivirals', (p.913)). The effect of ritonavir-boosted darunavir on clarithromycin may also possibly be due to P-glycoprotein inhibition.[12] Clarithromycin is a moderate inhibitor of CYP3A4, but generally has only a small effect on the protease inhibitors, except for saquinavir. The effect of clarithromycin on saquinavir, and nelfinavir on azithromycin may involve inhibition of P-glycoprotein.[2,3]

Importance and management

The interaction of amprenavir or indinavir with **clarithromycin** does not appear to be clinically significant. Similarly, although large increases in saquinavir levels have been seen, the manufacturers say that for short courses no dose adjustment is needed.[8,9] However, with ritonavir, because the hepatic metabolism of clarithromycin is so strongly inhibited it becomes more dependent on renal clearance, therefore the interaction may be significant in patients with renal failure.[7] The manufacturers of ritonavir and clarithromycin suggest that no dose reductions should be needed in those with normal renal function, but they recommend a 50% reduction in the dose of clarithromycin for those with a creatinine clearance of 30 to 60 mL/minute and a 75% reduction for clearances of less than 30 mL/minute.[13-16] Some advise avoiding clarithromycin in doses exceeding 1 g daily.[13,14] Similar clarithromycin dose reductions in renal impairment are recommended for ritonavir-boosted darunavir,[17] fosamprenavir,[18] and ritonavir-boosted tipranavir.[19,20] The UK manufacturer of tipranavir also advises that patients taking a dose of clarithromycin of more than 500 mg twice daily should be monitored for clarithromycin adverse effects. They also note that the low levels of 14-hydroxyclarithromycin due to the interaction with ritonavir-boosted tipranavir may be of clinical relevance in the treatment of *Haemophilus influenzae*.[20] Although there are no formal studies or specific dose recommendations for other ritonavir-boosted protease inhibitors (lopinavir and saquinavir), similar precautions would seem prudent. Atazanavir also reduces the conversion of clarithromycin to its 14-hydroxy metabolite, and it is usually given with ritonavir. The US manufacturer of atazanavir suggest that if the combination is used the clarithromycin dose should be reduced by 50%, as clarithromycin may prolong the QT interval. As the levels of 14-hydroxyclarithromycin are also significantly reduced, they advise that for most infections an alternative to clarithromycin should be considered with the exception of *Mycobacterium avium* complex infections, where this metabolite is inactive.[21] However, the UK manufacturer cautions that reducing the dose of clarithromycin to avoid high levels of the parent drug may result in subtherapeutic levels of the 14-hydroxy metabolite, which is active against *Haemophilus influenzae*.[22] The US manufacturer states that the concurrent use of ritonavir-boosted atazanavir with clarithromycin has not been studied.[21]

The increase in **azithromycin** levels with nelfinavir is likely to be of clinical significance,[2] and, although the outcome is presumed to be positive, this has yet to be assessed in practice. If concurrent use is necessary, monitor for azithromycin adverse effects (e.g. hepatic adverse effects, hearing impairment).[23] The manufacturers of ritonavir-boosted lopinavir do not expect a clinically significant interaction with azithromycin.[24,25]

Despite the increases in saquinavir levels, the UK manufacturer says that no dose adjustment is needed when saquinavir is given with **erythromycin**.[8] The UK manufacturer of ritonavir suggests that because erythromycin levels may rise, due to inhibition of its metabolism by ritonavir, care should be taken if both drugs are given.[13] It would seem prudent to monitor for erythromycin adverse effects. A similar warning has been issued by the UK manufacturer of fosamprenavir about the use of erythromycin.[18] The US manufacturer of atazanavir does not expect a clinically significant interaction with erythromycin.[21]

Note that clarithromycin and erythromycin have been associated with QT prolongation, and rises in their levels may increase this risk. The US manufacturer[25] of ritonavir-boosted lopinavir states that a clinically significant interaction with erythromycin is not expected. However, the UK manufacturer states that both **erythromycin** and **clarithromycin** can prolong the QT interval and that cardiac adverse effects have also been reported with ritonavir-boosted lopinavir. As ritonavir-boosted lopinavir may also increase the levels of these macrolides, they advise caution with concurrent use.[24] For more information about the risks of QT prolongation, see 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290.

The UK manufacturer of **telithromycin** predicts that the protease inhibitors will increase its levels and, as telithromycin has been reported to cause QT prolongation, they advise caution on concurrent use, and contraindicate concurrent use in patients with severe renal or hepatic impairment.[26]

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9. Invirase (Saquinavir mesylate). Roche Laboratories Inc. US Prescribing information, July 2007.

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12. Prezista (Darunavir ethanolate). Janssen-Cilag Ltd. UK Summary of product characteristics, October 2009.
13. Norvir Soft Capsules (Ritonavir). Abbott Laboratories Ltd. UK Summary of product characteristics, October 2009.
14. Klaricid (Clarithromycin). Abbott Laboratories Ltd. UK Summary of product characteristics, September 2006.
15. Norvir (Ritonavir). Abbott Laboratories. US Prescribing information, November 2009.
16. Biaxin (Clarithromycin). Abbott Laboratories. US Prescribing information, August 2009.
17. Prezista (Darunavir ethanolate). Tibotec, Inc. US Prescribing information, June 2009.
18. Telzir (Fosamprenavir calcium). ViiV Healthcare UK Ltd. UK Summary of product characteristics, May 2009.
19. Aptivus (Tipranavir). Boehringer Ingelheim Pharmaceuticals, Inc. US Prescribing information, June 2009.
20. Aptivus Soft Capsules (Tipranavir). Boehringer Ingelheim Ltd. UK Summary of product characteristics, June 2009.
21. Reyataz (Atazanavir sulfate). Bristol-Myers Squibb. US Prescribing information, November 2009.
22. Reyataz (Atazanavir sulfate). Bristol-Myers Squibb Pharmaceuticals Ltd. UK Summary of product characteristics, July 2009.
23. Viracept (Nelfinavir mesylate). Agouron Pharmaceuticals, Inc. US Prescribing information, September 2008.
24. Kaletra Tablets (Lopinavir with Ritonavir). Abbott Laboratories Ltd. UK Summary of product characteristics, November 2009.
25. Kaletra (Lopinavir with Ritonavir). Abbott Laboratories. US Prescribing information, April 2009.
26. Ketek (Telithromycin). Sanofi-Aventis. UK Summary of product characteristics, June 2009.

Protease inhibitors + Mefloquine

No pharmacokinetic interaction appears to occur between mefloquine and indinavir or nelfinavir. Ritonavir does not appear to alter mefloquine pharmacokinetics, but mefloquine may modestly decrease steady-state ritonavir levels.

Clinical evidence

Two HIV-positive patients receiving HAART, one taking **indinavir** 800 mg three times daily, the other taking **nelfinavir** 1.25 g twice daily were given mefloquine 250 mg weekly, before a trip to Africa. Mefloquine therapeutic levels were achieved, and its half-life was similar to that found in healthy subjects. In addition, no consistent changes in the plasma levels of the protease inhibitors were found.[1]

In 12 healthy subjects **ritonavir** 200 mg twice daily for one week had no significant effect on the pharmacokinetics of mefloquine.[2] Conversely, mefloquine (250 mg daily for 3 days, then 250 mg weekly) significantly reduced the steady-state AUC, maximum plasma levels and minimum plasma levels of **ritonavir** 200 mg twice daily by 31%, 36%, and 43%, respectively, but had no effect on the pharmacokinetics of single-dose **ritonavir**.[2]

Mechanism

Despite being inhibitors of the cytochrome P450 isoenzyme CYP3A4, the protease inhibitors do not appear to alter mefloquine pharmacokinetics.[1,2] It was suggested that the decrease in ritonavir levels was due to decreased absorption, perhaps due to mefloquine-induced inhibition of bile acid production or induction of P-glycoprotein.[2]

Importance and management

The limited evidence suggests that protease inhibitors do not affect mefloquine pharmacokinetics. The data on the effect of mefloquine on ritonavir are less clear. Until further evidence is available, if concurrent use is necessary, it may be prudent to closely monitor ritonavir levels/efficacy.

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Protease inhibitors + Minocycline

Minocycline appears to reduce the levels of ritonavir-boosted atazanavir, but does not appear to significantly affect the levels of ritonavir.

Clinical evidence, mechanism, importance and management

In a study, 12 HIV-positive subjects who had been taking **ritonavir-boosted atazanavir** 100/300 mg daily for at least 4 weeks as part of a HAART regimen were given minocycline 100 mg twice daily for 14 days. Minocycline reduced the AUC, maximum concentration and minimum concentration of **atazanavir** by 33%, 25%, and 50%, respectively. The addition of valproic acid 250 mg twice daily for a further 14 days did not significantly change the outcome of the interaction. Minocycline had no statistically significant effect on the pharmacokinetics of **ritonavir** in the subset of 9 subjects analysed (10% and 5% reduction in the AUC and maximum concentration respectively, with a 23% increase in the minimum concentration).[1]

The possible mechanism and clinical significance of this interaction are unclear. Note that this was a small study and patients were allowed to continue their regular medication during the study, which may have influenced the outcome. However, the possibility of a clinically relevant interaction cannot be excluded. The authors suggest that further study is needed to establish the pharmacokinetic interaction, as well as its likely treatment outcomes. They also advise that although no significant interaction was seen with **ritonavir**, an interaction cannot be excluded due to the small sample size.[1]

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Protease inhibitors + Miscellaneous

Indinavir levels are raised by interleukin-2, but not affected by influenza vaccination. Nelfinavir does not appear to interact with pancreatic enzyme supplements. In one case report, the combination of ritonavir and saquinavir with fusidic acid raised the plasma levels of all three drugs.

Clinical evidence, mechanism, importance and management

(a) Fusidic acid

A 32-year-old HIV-positive man was admitted with suspected fusidic acid toxicity after taking fusidic acid 500 mg three times daily for one week, with his usual treatment of **ritonavir** 400 mg twice daily, **saquinavir** 400 mg twice daily and stavudine 40 mg twice daily. His plasma fusidic acid level was found to be twice the expected level, and his **ritonavir** and **saquinavir** levels were also elevated. He improved spontaneously, but 4 days later he returned with jaundice, nausea and vomiting. All medications were stopped, but after 6 days his fusidic acid level was still 30% greater than expected, his **saquinavir** level was 16.3 micrograms/mL (reference range 1 to 4 micrograms/mL) and his **ritonavir** level was 43.4 micrograms/mL (reference range 4 to 12 micrograms/mL). He was later able to restart his antiretrovirals without problem. It is possible that there was mutual inhibition of drug metabolism. The authors recommend avoiding this drug combination.[1] This appears to be the only published report, and further study is needed to confirm this interaction. However, bear this case in mind should a patient taking fusidic acid with antiretrovirals developing fusidic acid toxicity.

(b) Influenza vaccine

In a study, influenza whole virus vaccine was given to 9 patients taking **indinavir** containing HAART. No significant changes were found in **indinavir** pharmacokinetics.[2] Therefore, no special precautions appear to be necessary on concurrent use.

(c) Interleukins

In a pharmacokinetic study in 9 HIV-positive patients, the subjects continued taking their usual antiretrovirals and were given a 4-week course of **indinavir** 800 mg three times daily followed by infusions of 3 to 12 million units of interleukin-2, daily for 5 days. The AUC of **indinavir** increased in 8 of the 9 subjects (average increase 88%). During this time interleukin-6 was also elevated, so it was thought that the increased **indinavir** concentrations were due to the inhibitory effects of interleukin-6 on the cytochrome P450 isoenzyme CYP3A4. Increased **indinavir** trough

levels were also seen in a further 8 patients not participating in the pharmacokinetic study.[3]

(d) Pancreatic enzymes

In a study in 9 HIV-positive subjects, the concurrent use of pancreatic enzymes (pancrelipase 20,000 USP units, amylase 65,000 USP units and protease 65,000 USP units) and **nelfinavir** 1.25 g twice daily for 14 days resulted in no significant changes in the pharmacokinetics of **nelfinavir**.[4]

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Protease inhibitors + Phenytoin

Nelfinavir, and ritonavir-boosted fosamprenavir and lopinavir appear to modestly reduce phenytoin levels. In case reports, ritonavir has decreased, increased or not altered phenytoin levels. Phenytoin decreased lopinavir levels, and possibly also indinavir and ritonavir levels, had only had a minor effect on the levels of amprenavir (given as ritonavir-boosted fosamprenavir), but did not alter nelfinavir levels. Phenytoin is predicted to reduce the levels of atazanavir, darunavir, saquinavir, and tipranavir.

Clinical evidence

(a) Fosamprenavir

In a randomised crossover study, healthy subjects were given ritonavir-boosted fosamprenavir 100/700 mg daily with phenytoin 300 mg daily for 10 days. The AUC and maximum plasma concentration of amprenavir were increased by 20% and 7%, respectively, and the AUC and maximum plasma concentration of phenytoin were decreased by 22% and 20%, respectively.[1]

(b) Indinavir

A 39-year-old HIV-positive man, taking phenytoin 300 mg daily, started to take indinavir 800 mg three times daily. When the phenytoin dose was reduced to 200 mg daily, the viral load dropped by almost half and his CD4 count doubled.[2]

(c) Lopinavir

In studies in healthy subjects, the concurrent use of phenytoin 300 mg daily and ritonavir-boosted lopinavir 100/400 mg twice daily resulted in a 30% decrease in the AUC of lopinavir and a 23% decrease in the AUC of phenytoin.[3]

(d) Nelfinavir

An HIV-positive man taking phenytoin and phenobarbital for epilepsy had been taking nelfinavir 750 mg three times daily and stavudine 30 mg twice daily for nearly 3 months when he had a tonic-clonic seizure. After starting nelfinavir and stavudine, serum phenytoin levels were found to have dropped from around 10 mg/L to around 5 mg/L.[4] Similarly, in healthy subjects, nelfinavir 1.25 g twice daily for 7 days decreased the AUC of phenytoin by about 30% and the maximum serum level by 21%, whereas the nelfinavir levels were not altered.[5]

(e) Ritonavir

A case report describes the intentional use of ritonavir 600 mg twice daily to boost phenytoin levels in a 14-year-old boy who had been having seizures for 28 days, despite the use of several antiepileptics. Phenytoin at 20 mg/kg daily had originally failed to produce satisfactory plasma levels, although it did reduce the rate of seizures. After starting ritonavir his seizures were controlled and the phenytoin level became therapeutic. Seizures started again after the ritonavir was stopped.[6] Conversely, an HIV-positive patient taking carbamazepine and phenytoin had little change in his phenytoin levels, which remained at around 15 mg/L, 2 months after switching from an antiretroviral regimen including **indinavir** to one containing ritonavir 600 mg twice daily and **saquinavir**.[7] Another patient taking phenobarbital, phenytoin and carbamazepine had a 33% drop in his phenytoin level 2 days after switching from an antiretroviral regimen including **indinavir** to one containing ritonavir 300 mg twice daily and **saquinavir**. The level of carbamazepine had doubled, and the level of phenobarbital was unchanged.[8]

A 30-year-old woman taking nevirapine, **saquinavir** 1.2 g daily and ritonavir 600 mg daily with undetectable viral load had her epilepsy medication changed from gabapentin and lorazepam to lamotrigine and phenytoin because of increased frequency and severity of seizures. She required phenytoin 8 mg/kg daily to maintain therapeutic serum levels. The ritonavir dose was doubled and the saquinavir dose increased to 2 g daily to compensate for the enzyme-inducing effects of phenytoin. The patient's viral load remained undetectable, and her seizures decreased over the next 6 months but she died suddenly of unexplained causes following a tonic-clonic seizure (autopsy not performed).[9]

Mechanism

Phenytoin is an inducer of the cytochrome P450 isoenzyme CYP3A4, and would be expected to increase the metabolism of the protease inhibitors, although nelfinavir levels were not altered, possibly because it is a substrate for several other isoenzymes.

Phenytoin is principally metabolised by CYP2C9 and CYP2C19, and would therefore, not be expected to be substantially affected by most protease inhibitors. However, both increases and modest decreases in phenytoin levels have been seen.

Importance and management

Although information is limited, some of these interactions are expected. Phenytoin may decrease the plasma levels of indinavir, lopinavir, and possibly ritonavir. The manufacturers of **saquinavir**[10,11] and **tipranavir**[12,13] also predict that their levels may be reduced by phenytoin, although they note that the effect on ritonavir-boosted saquinavir has not been assessed.[10,11]

The UK manufacturer of **darunavir** states that phenytoin may significantly decrease darunavir levels and advises against concurrent use,[14] whereas the US manufacturer notes that darunavir levels are not affected by phenytoin.[15] The manufacturers of **atazanavir** also predict that its levels may be reduced by inducers of CYP3A4.[16,17] The UK manufacturer specifically advises against the concurrent use of ritonavir-boosted **atazanavir** with drugs that induce CYP3A4 [not named].[16]

Phenytoin appears not to alter nelfinavir levels, and have only a minor, probably clinically unimportant effect on the levels of amprenavir (given as ritonavir-boosted fosamprenavir).

In addition, protease inhibitors appear to alter phenytoin levels. Therefore an alternative antiepileptic, such as sodium valproate, which does not affect cytochrome P450 isoenzymes, may be more appropriate in patients taking protease inhibitors. See 'Protease inhibitors + Valproate', p.988, for further comment on the use of valproate with protease inhibitors. However, if there is no option but to use phenytoin, close monitoring of antiviral efficacy and phenytoin levels is essential.

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Protease inhibitors + Protease inhibitors

Various dual combinations of protease inhibitors have been tried, or are used, to boost the levels and consequently the efficacy of one of the protease inhibitors. Ritonavir is the most potent at boosting levels of the other protease inhibitors. Some protease inhibitor combinations may result in additive toxicity (indinavir and ritonavir or atazanavir).

Clinical evidence

A. Amprenavir or Fosamprenavir

(a) Atazanavir

The concurrent use of fosamprenavir 1.4 g daily with atazanavir 400 mg daily decreases the AUC and minimum level of atazanavir by 33% and 57%, respectively, and increases the AUC and minimum concentration of amprenavir by 78% and 283%, respectively. The use of ritonavir-boosted fosamprenavir 100/700 mg twice daily with atazanavir 300 mg daily reduces the AUC and maximum concentration of atazanavir by 22% and 24%, respectively, with no effect on the pharmacokinetics of amprenavir.[1] The US manufacturer states that the appropriate dose for concurrent use has not been established.[2] The US guidelines say there is insufficient data to make a dose recommendation with concurrent use.[1]

- The appropriate dose of fosamprenavir with atazanavir is not established.[1,2]

(b) Indinavir

The manufacturer of indinavir reports that indinavir 1.2 g twice daily increased the AUC of amprenavir 1.2 g twice daily by 90%. The pharmacokinetics of indinavir were unaffected. They state that there are no data on the concurrent use of ritonavir-boosted indinavir with amprenavir.[3] Similarly, the manufacturers of fosamprenavir state that there are no interaction studies on the concurrent use of indinavir with ritonavir-boosted fosamprenavir.[4] The steady-state AUC of amprenavir was 33% higher when amprenavir 750 or 800 mg three times daily was given with indinavir 800 mg three times daily. In this study, the AUC of indinavir was 38% lower than historical control data.[5] Similarly, in a model-based pharmacokinetic analysis of data from a clinical study, amprenavir intrinsic clearance was reduced by 54% by indinavir.[6] This agrees with *in vitro* data.[7] It was suggested[5] that the effect of amprenavir on indinavir was due to the lipid-like formulation of amprenavir reducing the absorption of indinavir (analogous to 'food', (p.971)). The changes in amprenavir levels were not considered to be clinically relevant.[5]

- The appropriate dose of amprenavir or fosamprenavir with indinavir is not established.[1-3] No drug interaction studies have been performed with ritonavir-boosted fosamprenavir.[4]

(c) Lopinavir

Preliminary data suggest that giving amprenavir 600 mg twice daily with ritonavir-boosted lopinavir 100/400 mg twice daily resulted in amprenavir trough plasma levels that were lower than with ritonavir-boosted amprenavir at the same doses. Similarly the lopinavir levels were lower than those without amprenavir.[8] Others have reported similar findings,[9] and increasing the dose of ritonavir did not prevent a decrease in amprenavir levels with lopinavir.[10] Similar findings were also reported for fosamprenavir with ritonavir-boosted lopinavir,[11] and further study showed that separation of doses reduced the effect of amprenavir on ritonavir-boosted lopinavir levels, but increased the effect on amprenavir levels.[12] However, the manufacturer of ritonavir-boosted lopinavir reports that concurrent use of ritonavir-boosted lopinavir/ritonavir 100/400 mg twice daily with amprenavir 750 mg twice daily for 10 days resulted in an increase in the amprenavir AUC, maximum level and minimum level of 72%, 12% and 457%, respectively, when compared with amprenavir 1200 mg twice daily alone.[13]

The manufacturer of fosamprenavir notes that giving ritonavir-boosted lopinavir 100/400 mg with ritonavir-boosted fosamprenavir 100/700 mg, both twice daily for 2 weeks, increased the AUC and minimum level of lopinavir by 37% and 52%, respectively, whereas the AUC and minimum level of amprenavir were decreased by 63% and 65%, respectively.[2] In addition, they say that the rate of adverse effects, in particular gastrointestinal adverse effects and increases in triglyceride levels, was higher with this combination.[2,4]

- The US manufacturer of ritonavir-boosted lopinavir advises against the concurrent use of once daily ritonavir-boosted lopinavir with fosamprenavir,[13] whereas the UK manufacturer of ritonavir-boosted lopinavir advises against the concurrent use of fosamprenavir.[14]
- An optimum dose for the concurrent use of ritonavir-boosted fosamprenavir with lopinavir has not been established.[2,13] Avoid once daily regimens.[13]
- The US guidelines[1] and the UK manufacturer[14] advise against the concurrent use of ritonavir-boosted lopinavir with fosamprenavir. However, the US manufacturer of lopinavir recommends a dose increase of ritonavir-boosted lopinavir *tablets* to 125/500 mg twice daily may be needed if amprenavir or fosamprenavir is given. The manufacturer recommends a dose increase of ritonavir-boosted lopinavir *oral solution* to 133/533 mg twice daily (dose rounded to 6.5 mL) if fosamprenavir is given; once daily regimens should be avoided.[13]

(d) Nelfinavir

The trough concentration of amprenavir 750 or 800 mg three times daily was increased by 189% by nelfinavir 750 mg three times daily, but the AUC and maximum level of amprenavir were not significantly altered. In this study, the pharmacokinetics of nelfinavir were not altered, when compared with historical control data.[5] In a model-based pharmacokinetic analysis of data from a clinical study, amprenavir intrinsic clearance was reduced by about 40% by nelfinavir,[6] which agrees with *in vitro* data.[7] The increase in amprenavir trough concentration could result in improved antiviral efficacy, but further study is needed.[5]

- The manufacturer of amprenavir recommended that no dose adjustment of either drug is needed when amprenavir is given with nelfinavir.[15]
- The appropriate dose of fosamprenavir with nelfinavir is not established.[1,2] No drug interaction studies have been performed with fosamprenavir.[4]

(e) Ritonavir

The AUC, minimum levels, and maximum levels of amprenavir 1.2 g twice daily were increased by 131%, 484%, and 33%, respectively, by ritonavir 200 mg twice daily.[16] This agrees with *in vitro* data.[7] The manufacturer recommends that doses of both protease inhibitors be reduced when they are used together.[16,17] Based on modelling of pharmacokinetic data, a dose of amprenavir 600 mg with ritonavir 100 mg, both twice daily, has been suggested.[18] This combination has shown good clinical efficacy in at least one study,[19] and resulted in satisfactory amprenavir levels when efavirenz was also used[20] (see also 'NNRTIs + Protease inhibitors', p.931). Amprenavir levels with ritonavir-boosted fosamprenavir 100/700 mg twice daily were similar to those achieved with ritonavir-boosted amprenavir 100/600 mg twice daily.[21] The manufacturers advise that ritonavir oral solution should not be given with amprenavir oral solution to children due to the risk of toxicity from excipients in the two formulations.[22]

- Ritonavir may be given as a pharmacokinetic booster with fosamprenavir in the following doses, depending on the patients previous antiretroviral treatment: ritonavir 100 mg or 200 mg daily with fosamprenavir 1400 mg daily, or ritonavir 100 mg twice daily with fosamprenavir 700 mg twice daily.[1,2,4]

(f) Saquinavir

The steady-state AUC of amprenavir was reduced by 32% when amprenavir 750 or 800 mg three times daily was given with saquinavir (soft gel capsule) 800 mg three times daily, and the maximum plasma level was reduced by 37%. In this study, the pharmacokinetics of saquinavir were not changed when compared with historical control data.[5] In a model-based pharmacokinetic analysis of data from a clinical study, amprenavir intrinsic clearance was not altered by saquinavir,[6] which confirms *in vitro* data.[7] It was suggested that, as amprenavir was given with 'food', (p.971), in the first study, this may have accounted for the reduced amprenavir levels.[5]

- No dose adjustment of amprenavir or ritonavir-boosted saquinavir is needed when they are given together.[23]
- Appropriate dose of fosamprenavir with saquinavir not established.[1,2] No drug interaction studies have been performed with saquinavir and fosamprenavir.[4]

(g) Tipranavir

In a clinical study of dual-boosted protease inhibitors in multiple-treatment experienced HIV-positive adults there was a 55% reduction in minimum amprenavir levels when ritonavir-boosted tipranavir 200/500 mg twice daily was added to ritonavir-boosted amprenavir 100/600 mg twice daily.[24,25] Therefore the use of ritonavir-boosted tipranavir with ritonavir-boosted amprenavir or fosamprenavir is not recommended, as the clinical relevance of the reduction in amprenavir levels has not been established.[1] If the combination is nevertheless considered necessary, close monitoring of the plasma levels of the protease inhibitors is strongly encouraged.[24,25]

- Concurrent use is not recommended.[1,24,25]

B. Atazanavir

(a) Darunavir

The manufacturer notes that giving atazanavir 300 mg daily with ritonavir-boosted darunavir 100/400 mg twice daily did not significantly alter the AUC and minimum level of darunavir. In addition, the AUC and minimum level of atazanavir were not significantly changed, when compared with ritonavir-boosted atazanavir 100/300 mg daily alone, although the minimum level of atazanavir was increased by 52%.[26,27]

- No dose adjustment of either drug is needed.[1,26,27]

(b) Indinavir

There are no pharmacokinetic data on the use of atazanavir with indinavir, but it is predicted that there may be an additive risk of unconjugated hyperbilirubinaemia.

- Concurrent use is not recommended.[1,28,29]

(c) Ritonavir

In a study in 61 HIV-positive patients, the addition of ritonavir 100 mg to atazanavir 300 mg increased the AUC of atazanavir about 3.5-fold, and increased its trough plasma level about eightfold, when compared with atazanavir 400 mg alone.[28] The manufacturer of atazanavir recommends that a dose of atazanavir 300 mg daily is given with ritonavir 100 mg daily.[28,29]

- Ritonavir is recommended as a pharmacokinetic booster with atazanavir.[28,29]

(d) Saquinavir

In a study in 7 subjects, the addition of atazanavir 400 mg daily to saquinavir soft capsules 1.2 g daily increased the AUC of saquinavir about 5.5-fold, and increased its trough plasma level about sevenfold.[29] In another study in 18 HIV-positive patients, atazanavir 300 mg daily increased the AUC and maximum concentration of ritonavir-boosted saquinavir 100/1600 mg daily by 60% and 42%, respectively.[23,30] The AUC and maximum concentration of ritonavir was also increased by 41% and 34%, respectively, with no change in atazanavir pharmacokinetics. The manufacturer notes that there is no clinical data available for the concurrent use of atazanavir with ritonavir-boosted saquinavir 100/1000 mg twice daily.[23,30] However, the US manufacturer of atazanavir notes that a regimen including this combination, as well as tenofovir, did not provide adequate efficacy.[29]

- Not an effective combination. The appropriate dose of atazanavir with ritonavir-boosted or unboosted saquinavir not established.[1,29]

(e) Tipranavir

The manufacturer notes that, in a study in healthy subjects, the concurrent use of atazanavir 300 mg daily with ritonavir-boosted tipranavir 100/500 mg twice daily increased tipranavir exposure (minimum plasma level increased by 75%) and ritonavir exposure (AUC increased by 51%) while markedly reducing atazanavir exposure (AUC reduced by 68%, and minimum level reduced by 81%).

- Concurrent use is not recommended.[24,25]

C. Darunavir

(a) Indinavir

The manufacturers note that, in a study in 9 subjects, giving indinavir 800 mg twice daily with ritonavir-boosted darunavir 100/400 mg twice daily increased the AUC and minimum level of darunavir by 24% and 44%, respectively. In addition, the AUC and minimum level of indinavir were increased by 23% and 125%, respectively, when compared with ritonavir-boosted indinavir 100/800 mg twice daily alone.[26,27] The US manufacturer[27] states that the appropriate dose of indinavir with ritonavir-boosted darunavir has not been established; however, the UK manufacturer[26] suggests that the dose of indinavir may need reducing from 800 mg twice daily to 600 mg twice daily if adverse effects occur.

- No dose adjustment is usually needed. Decreasing the dose of indinavir to 600 mg twice daily may be necessary if the combination is poorly tolerated.[26]

(b) Lopinavir

The manufacturers note that, in a study in 14 subjects, giving ritonavir-boosted lopinavir 100/400 mg with ritonavir-boosted darunavir 100/1200 mg, both twice daily, decreased the AUC and minimum level of darunavir by 38% and 51%, respectively. When ritonavir-boosted lopinavir 133.3/533 mg was given with unboosted darunavir 1200 mg, both twice daily, the AUC and minimum level of darunavir were decreased by 41% and 55%, respectively. The pharmacokinetics of lopinavir were unaffected in both studies.[26,27] The manufacturers and the US guidelines state that the appropriate doses for concurrent use have not been established.

- The manufacturers contraindicate concurrent use.[1,26,27]

(c) Saquinavir

The manufacturer notes that giving saquinavir hard capsules 1 g twice daily with ritonavir-boosted darunavir 100/400 mg twice daily decreased the AUC and minimum level of darunavir by 26% and 42%, respectively. The levels of saquinavir were not changed, when compared with using ritonavir-boosted saquinavir 100/1000 mg twice daily alone.[26,27] The US manufacturer and US guidelines state that the appropriate doses for concurrent use have not been established.[1,27]

- Concurrent use is not recommended.[1,26,27]

(d) Other protease inhibitors

The combination of darunavir with other protease inhibitors, other than atazanavir, indinavir, ritonavir-boosted lopinavir and saquinavir, or with ritonavir as a pharmacological booster, has not been studied. Therefore, the manufacturer does not recommended concurrent use.[26,27]

D. Indinavir

(a) Lopinavir

In a study in 13 subjects, indinavir 600 mg twice daily for 10 days with ritonavir-boosted lopinavir 100/400 mg twice daily produced a similar indinavir AUC, a 3.5-fold higher indinavir minimum level and 29% lower indinavir maximum level when compared with indinavir 800 mg three times daily alone.[13,14] Based on historical comparisons, lopinavir levels were similar to those seen without indinavir.[14]

- Reduce the dose to indinavir 600 mg twice daily if a ritonavir-boosted lopinavir twice daily dosing regimen is given.[1,13] Ritonavir-boosted lopinavir given once daily has not been studied with indinavir.[13]

(b) Nelfinavir

The concurrent use of indinavir 1.2 g every 12 hours with nelfinavir 1.25 g every 12 hours produced plasma levels that were equivalent to the standard dose of indinavir 800 mg every 8 hours in HIV-positive subjects. This suggests that nelfinavir only modestly inhibits indinavir metabolism. In this multiple-dose study, indinavir did not affect the pharmacokinetics of nelfinavir.[31] In contrast, a single 750-mg dose of nelfinavir, given after indinavir 800 mg every 8 hours for 7 days to 6 subjects resulted in an 83% increase in the AUC of nelfinavir and a 31% increase in its maximum concentration. In addition, giving a single 800-mg dose of indinavir after nelfinavir 750 mg three times daily for 7 days to 6 subjects resulted in a 51% increase in the indinavir plasma AUC, but no significant effect on the maximum or minimum concentration of indinavir.[15,32] The US guidelines note that there is limited data for giving indinavir 1.2 g twice daily with nelfinavir 1.25 g twice daily.[1]

- The appropriate dose of indinavir with nelfinavir has not been established.[32,33]

(c) Ritonavir

The effects of a range of doses of ritonavir (200, 300, or 400 mg every 12 hours) on indinavir pharmacokinetics were assessed in 39 healthy subjects. The AUC of indinavir 400 or 600 mg was increased two- to fivefold by ritonavir. It is suggested that the combination of indinavir 400 mg every 12 hours with ritonavir 400 mg every 12 hours will result in an AUC of indinavir roughly equivalent to that of indinavir 800 mg every 8 hours, without any effect on the pharmacokinetics of ritonavir.[34] In another similar study, when compared with historical data for indinavir 800 mg every 8 hours, the AUC of indinavir was at least 1.4-fold, 2.3-fold, and 3.3-fold

higher when ritonavir-boosted indinavir was given in twice daily doses of 400/400 mg, 100/800 mg, and 200/800 mg, respectively. The regimens also produced markedly higher trough indinavir levels. The 100/800 mg regimen was the best tolerated.[35] In another study, indinavir 800 mg twice daily for 14 days increased the AUC, maximum concentration and minimum concentration of ritonavir 100 mg twice daily, also taken for 14 days, by 72%, 61% and 62%, respectively. Increasing the dose of ritonavir to 200 mg twice daily had a lesser effect on the maximum concentration (increase of 19%) and had a similar effect on the AUC, increasing it by 96%. However, this produced a more significant increase in the trough level of ritonavir, of 4.7-fold.[33] The US manufacturer states that the appropriate doses for concurrent use have not been established.[33]

- If ritonavir is given as a pharmacokinetic booster, the manufacturers recommended dose is ritonavir-boosted indinavir 100/400 mg twice daily.[3] The US guidelines advise giving indinavir 800 mg with ritonavir 100 or 200 mg, both twice daily, or indinavir 400 mg with ritonavir 400 mg twice daily.[1]
- Caution is needed when indinavir is used at a dose of 800 mg twice daily with ritonavir, because of the possibility of an increased risk of nephrolithiasis. Appropriate hydration is strongly recommended.[3,33]
- The US guidelines state that concurrent use is not recommended as part of initial therapy because of the risk of nephrolithiasis.[1]

(d) Saquinavir

In a single-dose study in 6 subjects, the concurrent use of indinavir and saquinavir 600 mg (hard capsule), or 800 mg or 1.2 g (soft capsule), increased the AUC of saquinavir 6-fold, 7.2-fold and 4.6-fold, respectively. Large increases in both the minimum and maximum concentrations of saquinavir were also reported.[3,33] Concurrent use with ritonavir-boosted saquinavir has not been studied.[30]

- The appropriate dose of indinavir with saquinavir is not established.[1,3,33]

(e) Tipranavir

The concurrent use of tipranavir with indinavir is not recommended as there is insufficient data and doses are not established.[1]

E. Lopinavir

(a) Nelfinavir

The US manufacturer notes that, in a study in 13 subjects, the concurrent use of nelfinavir 1 g twice daily with ritonavir-boosted lopinavir 100/400 mg twice daily resulted in similar nelfinavir pharmacokinetics to nelfinavir 1.25 g twice daily alone, but with markedly increased levels of the M8 metabolite of nelfinavir. Lopinavir levels were modestly reduced (27% decrease in the AUC and 38% decrease in the minimum level).[13] The US guidelines state that there are no dosing recommendations.[1]

- A dose increase of ritonavir-boosted lopinavir *oral solution* to 133/533 mg twice daily or ritonavir-boosted lopinavir *tablets* to 125/500 mg twice daily may be needed. In children, the dose of ritonavir-boosted lopinavir should be increased to 75/300 mg/m^2. Avoid once daily regimens.[13,14]

(b) Ritonavir

Ritonavir is used to increase the plasma levels of lopinavir. The marketed combination is lopinavir 400 mg twice daily with ritonavir 100 mg twice daily.[13,14] When an additional 100 mg of ritonavir twice daily was added to this combination, the AUC of lopinavir was increased by 33% and its trough concentration was increased by 64%.[14]

- The use of lopinavir with ritonavir as a pharmacokinetic enhancer is established. The dose of additional ritonavir is not established, and is generally not recommended.[1]

(c) Saquinavir

Saquinavir 800 mg twice daily given with ritonavir-boosted lopinavir produced a 9.6-fold increase in saquinavir AUC relative to saquinavir 1.2 g three times daily given alone. When compared with ritonavir-boosted saquinavir 100/1000 mg twice daily, the increase in saquinavir AUC was about 30%, and was similar to that reported after ritonavir-boosted saquinavir 400/400 mg twice daily alone. When saquinavir 1.2 g twice daily was given with ritonavir-boosted lopinavir, no further increase in concentrations was noted. Lopinavir levels did not appear to be affected by saquinavir, based on historical comparison with ritonavir-boosted lopinavir alone.[14]

- In the US, the manufacturer recommends that saquinavir 1 g twice daily be used with ritonavir-boosted lopinavir 100/400 mg twice daily.[1,13]

(d) Tipranavir

In a clinical study of dual-boosted protease inhibitors in multiple-treatment experienced HIV-positive adults there was a 70% reduction in minimum lopinavir levels when ritonavir-boosted tipranavir 200/500 mg twice daily was added to ritonavir-boosted lopinavir 100/400 mg twice daily.[24,25] The clinical relevance of the reduction in lopinavir levels has not been established.

- Concurrent use is not recommended.[1,24,25] Appropriate doses are not established.[1]

F. Nelfinavir

(a) Ritonavir

Single-dose data indicate that ritonavir increases the AUC of nelfinavir by 1.8- to 2.5-fold, whereas the AUC of ritonavir is unchanged.[36] In a multiple-dose study in healthy subjects, ritonavir 100 or 200 mg twice daily increased the steady-state AUC of nelfinavir 1.25 g twice daily by 20% and 39%, after morning and evening doses, respectively. The AUC of the M8 metabolite of nelfinavir was increased by 74% and 86%, respectively. There was no difference in the effect of the two doses of ritonavir on nelfinavir AUC.[37]

- The appropriate dose of nelfinavir with ritonavir is not established.[1,32]

(b) Saquinavir

A single 1.2-g dose of saquinavir (soft gel capsules), given after 3 days of nelfinavir 750 mg every 8 hours had no effect on the pharmacokinetics of nelfinavir, but the nelfinavir caused a fourfold increase in the AUC of saquinavir.[38] Similar two- to twelvefold increases have been found in other studies in HIV-positive subjects.[39-42] A study in which 157 patients received 12 weeks of saquinavir with nelfinavir (doses unstated) found that concurrent use was well tolerated.[43] The US manufacturer states that saquinavir 1.2 g with nelfinavir 1.25 g, both taken twice daily, gives adequate plasma concentrations of both drugs.[30]

- No dose adjustment is needed for ritonavir-boosted saquinavir 100/1200 mg with nelfinavir 1.25 g taken twice daily.[23]

G. Ritonavir

(a) Saquinavir

A study in 6 patients with advanced HIV infection found that while taking saquinavir 600 mg three times daily the addition of ritonavir 300 mg twice daily increased the maximum saquinavir plasma levels 33-fold, and increased the AUC 58-fold at steady state.[44] A pilot study in HIV-positive patients given both drugs together (saquinavir 800 mg daily, ritonavir 400 to 600 mg daily) found that the ritonavir serum levels were unaffected. However, the saquinavir levels were substantially higher than those achieved with saquinavir alone in daily doses of 3.6 to 7.2 g.[45] A study in 57 healthy subjects covering a range of ritonavir and saquinavir *(Invirase)* doses (200 to 600 mg) found that saquinavir did not affect ritonavir pharmacokinetics, but ritonavir increased the AUC of saquinavir 50 to 132-fold. The authors suggested that giving both drugs in a dose of 400 mg every 12 hours might be optimal.[46] Subsequent study has revealed that the effect of ritonavir on saquinavir is not related to the ritonavir dose in the range of 100 to 400 mg twice daily,[47-49] and that the use of a combination with a higher dose of saquinavir and a lower dose of ritonavir may be preferable, as the lower doses of ritonavir are associated with fewer adverse effects.[49] A dose of saquinavir 1 g twice daily with ritonavir 100 mg twice daily is recommended by the manufacturers of saquinavir.[23,30] The UK manufacturer of ritonavir also states that doses of ritonavir higher than 100 mg twice daily should not be used in combination with saquinavir.[50] The manufacturers of ritonavir note that higher doses of ritonavir have been associated with an increased incidence of adverse events, including a significant increase in total triglycerides and cholesterol.[50,51] The concurrent use of saquinavir and ritonavir has led to severe adverse events, mainly diabetic ketoacidosis and liver disorders, especially in patients with pre-existing liver disease.[50]

- When ritonavir is given as a pharmacokinetic booster, the recommended dose is saquinavir 1000 mg with ritonavir 100 mg twice daily.[1,23,30,50,51] Higher ritonavir doses are associated with increased adverse effects and should not be used.[50]

H. Saquinavir

(a) Tipranavir

In a clinical study of dual-boosted protease inhibitors in multiple-treatment experienced HIV-positive adults there was a marked, approximately

80%, reduction in minimum saquinavir levels when ritonavir-boosted tipranavir 200/500 mg twice daily was added to ritonavir-boosted saquinavir 100/600 mg twice daily.[24,25] The clinical relevance of the reduction in saquinavir levels has not been established.

- Concurrent use is not recommended.[1,24,25] Appropriate doses are not established.[1] However, the combination is given, close monitoring the plasma levels of the protease inhibitors is strongly encouraged.[25]

Mechanism

Protease inhibitors are inhibitors and substrates of the cytochrome P450 isoenzyme CYP3A4, with ritonavir being the most potent inhibitor and saquinavir one of the least (see 'Antivirals', (p.913)). They probably interact by inhibiting each other's gut (pre-absorption) and hepatic (post-absorption) metabolism, so resulting in increased absorption and decreased elimination.[46,52] A mechanism involving inhibition of P-glycoprotein may also be involved.[52]

Importance and management

Ritonavir inhibits the metabolism of amprenavir (and amprenavir derived from fosamprenavir), atazanavir, darunavir, indinavir, lopinavir, nelfinavir, tipranavir, and particularly saquinavir. Low-dose ritonavir is therefore used in combination with other protease inhibitors to boost their levels, and allow a reduction in the protease inhibitor dose and the frequency of dosing. The US guidelines state that ritonavir-boosted atazanavir, darunavir, fosamprenavir or lopinavir are the protease inhibitors preferred as alternative options to efavirenz for use with dual NRTIs for the treatment of HIV-infection in treatment naïve patients. Ritonavir-boosted saquinavir is considered inferior to these.[1] The 2009 UK guidelines recommend dual NRTIs with a boosted protease inhibitor as an alternative option to dual NRTIs with efavirenz. The preferred ritonavir-boosted protease inhibitors are atazanavir, fosamprenavir, lopinavir and saquinavir: unboosted atazanavir may be used as an alternative regimen for patients with cardiovascular risk factors (dyslipidaemia).[53] The US guidelines state that indinavir should be avoided as initial therapy because of a high incidence of nephrolithiasis, and that atazanavir with indinavir should never be used because of potential additive hyperbilirubinaemia. They also state that darunavir, saquinavir and tipranavir must not be used without low-dose ritonavir.[1] There appears to be no clinically important pharmacokinetic interactions between amprenavir with indinavir, nelfinavir, or saquinavir, between atazanavir with darunavir and ritonavir, and probably also indinavir with nelfinavir. Various dual ritonavir-boosted protease inhibitor combinations act to lower the levels of one of the protease inhibitors and should therefore probably be avoided. When considering appropriate protease inhibitor combinations, in addition to pharmacokinetic interactions, cross resistance patterns and adverse effects should also be considered. Current local and national guidelines should be consulted when choosing protease inhibitor combinations.

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Protease inhibitors + Rifampicin (Rifampin)

Rifampicin markedly reduces the bioavailability of amprenavir, atazanavir, indinavir, indinavir, ritonavir-boosted lopinavir, nelfinavir and both saquinavir and ritonavir-boosted saquinavir, but only modestly reduces the bioavailability of ritonavir. It is also predicted to reduce the levels of ritonavir-boosted darunavir and tipranavir. Some protease inhibitors increase the levels of rifampicin.

Clinical evidence

(a) Amprenavir or Fosamprenavir

When 11 healthy subjects were given amprenavir 1.2 g twice daily with rifampicin 600 mg daily for 4 days the pharmacokinetics of rifampicin were not affected, but the AUC of amprenavir was reduced by 82%. The maximum plasma level of amprenavir was also reduced by 70%, from 9.2 to 2.78 micrograms/mL, and its minimum level was reduced by 94%, from 0.32 to 0.02 micrograms/mL.[1]

It is expected that the concurrent use of fosamprenavir or ritonavir-boosted fosamprenavir with rifampicin will also result in large decreases in the plasma concentrations of the metabolite, amprenavir.[2,3]

(b) Atazanavir

In a study, 52 healthy subjects were given atazanavir 400 mg daily for 6 days, followed by ritonavir-boosted atazanavir 100/300 mg daily for 10 days. They were then given rifampicin 600 mg daily for the next 10 days with either the same dose of ritonavir-boosted atazanavir or with of ritonavir-boosted atazanavir in higher doses of either 200/300 mg daily or 200/400 mg daily. The addition of rifampicin to ritonavir-boosted atazanavir 100/300 mg daily reduced the AUC, maximum plasma concentration and minimum plasma concentration of atazanavir by 72%, 49% and 97%, respectively. However, increasing the ritonavir dose by just 100 mg daily resulted in smaller although still clinically significant reduction in the AUC, maximum concentration and minimum concentration of atazanavir (53%, 35% and 93%, respectively). Similarly, increasing both the atazanavir and ritonavir doses by 100 mg again slightly reduced the effects of rifampicin; however, the AUC and minimum plasma level of atazanavir were still reduced, by 46% and 92%, respectively. The AUC and maximum plasma levels of rifampicin were increased by ritonavir-boosted atazanavir by 49 to 64% and 32 to 36%, respectively, with the effects slightly increasing with the increase in atazanavir and ritonavir doses, as before.[4]

In another study in 10 healthy subjects, the effects of rifampicin 600 mg daily on the pharmacokinetics of atazanavir 300 mg or 400 mg twice daily for between 8 and 11 days were investigated. Rifampicin reduced the mean AUC of atazanavir 300 mg by 79% and that of atazanavir 400 mg by 59%. The mean maximum and minimum plasma concentrations of atazanavir were reduced by 63% and 94% and 40% and 87% for atazanavir 300 mg and 400 mg twice daily, respectively. No significant increases in rifampicin exposure were reported.[5] A small study in 3 HIV-positive patients also reported subtherapeutic levels of atazanavir (given as ritonavir-boosted atazanavir 100/300 mg daily) with rifampicin 600 mg daily , and the study was stopped prematurely.[6] None of these studies reported significant increase in adverse effects with the concurrent use of atazanavir or ritonavir-boosted atazanavir and rifampicin.[4-6] However, a subsequent pharmacokinetic study in 15 healthy subjects who received rifampicin 600 mg daily with ritonavir-boosted atazanavir 100/300 mg daily was stopped prematurely due to nausea and vomiting, and significant increases in hepatic transaminases.[7]

(c) Indinavir

A study in 11 patients with AIDS given indinavir 800 mg every 8 hours and rifampicin 600 mg daily for 14 days found that the AUC of rifampicin was increased by 73%.[8] In a similar study looking at the effects of rifampicin on indinavir, the indinavir AUC and maximum serum levels were decreased by 92% and 86%, respectively.[9] In another study, in 6 HIV-positive patients taking ritonavir-boosted indinavir 100/800 mg twice daily, rifampicin 300 mg daily for 4 days decreased the median indinavir plasma levels (measured 12 hours after the last dose) by 87% and the median ritonavir levels by 94%.[10]

(d) Lopinavir

In a study in healthy subjects, rifampicin 600 mg daily for 10 days decreased the AUC of lopinavir (given as ritonavir-boosted lopinavir 100/400 mg twice daily) by 75%.[11] In another study, a dose titration of ritonavir-boosted lopinavir was carried out in healthy subjects to try to overcome the interaction with rifampicin.[12] In 10 evaluable subjects, rifampicin 600 mg daily with ritonavir-boosted lopinavir 200/800 mg twice daily decreased the minimum lopinavir level by 57% without affecting the maximum level, when compared with ritonavir-boosted lopinavir 100/400 mg twice daily without rifampicin. In another 9 evaluable subjects, rifampicin 600 mg daily with ritonavir-boosted lopinavir 400/400 mg twice daily did not alter the maximum or minimum level of lopinavir, but markedly *increased* ritonavir levels, when compared with ritonavir-boosted lopinavir 100/400 mg twice daily without rifampicin. Of 29 subjects who received the adjusted doses of ritonavir-boosted lopinavir with rifampicin, 9 subjects had grade 2 to 3 elevations in liver enzymes, and this was more common in the 400/400 mg group than the 200/800 mg group.[12] In a subsequent study, healthy subjects were given rifampicin 600 mg daily for 5 days and then also given ritonavir-boosted lopinavir at standard doses. However, on day 8, the study was stopped prematurely due to a high incidence of adverse effects, including nausea, vomiting and hepatotoxicity.[13]

A study in children investigated the difference between a control group taking ritonavir-boosted lopinavir in the standard ratio of 1:4 and a group taking rifampicin with ritonavir-boosted lopinavir in a ratio of 1:1. The AUC, maximum plasma concentration and minimum plasma concentration of lopinavir were 31%, 26% and 15% lower in the rifampicin group, when compared with the control group. However the minimum levels in 13 of the 15 children were still above the minimum recommended levels of lopinavir (greater than 1 mg/L).[14]

(e) Nelfinavir

Rifampicin 600 mg daily for 7 days decreased the AUC of nelfinavir 750 mg every 8 hours for 6 days by 82%.[15] A 7-month-old infant with HIV and tuberculosis was given a rifampicin-based antimycobacterial regimen with nelfinavir-based HAART. Nelfinavir plasma levels were found to be very low, so ritonavir was added. This improved nelfinavir levels, and also greatly increased those of the principal active metabolite of nelfinavir. The regimen was well tolerated and had a good clinical response.[16]

(f) Ritonavir

When ritonavir 500 mg every 12 hours was given with rifampicin 300 mg or 600 mg daily for 10 days, the AUC of ritonavir was 35% lower and the maximum level 25% lower than in subjects receiving ritonavir alone.[17]

(g) Saquinavir

In a pharmacokinetic study in HIV-positive patients, the concurrent use of rifampicin and isoniazid reduced the AUC, maximum serum concentration and minimum serum concentration of saquinavir by 40%, 35%, and 49%, respectively. Similarly, the AUC, maximum serum concentration and minimum serum concentration of ritonavir were also reduced, by 43%, 50%, and 64%, respectively. The ritonavir trough level was undetectable in most of the patients. Ritonavir-boosted saquinavir had no significant effect on the pharmacokinetics of rifampicin or isoniazid.[18] Rifampicin 600 mg daily decreased the AUC of saquinavir (soft capsules, *Fortovase*) 1.2 g three times daily by 70%.[19] It was suggested that the combination of ritonavir and saquinavir (both 400 mg twice daily) could cancel out the effects of rifampicin on saquinavir, so therapeutic levels of all three drugs could be achieved. This assumption has been confirmed in HIV-positive patients.[20,21] Five of 20 patients originally given the combination developed hepatotoxicity, 2 of whom had co-morbidities.[21] However, in a further study in healthy subjects, severe hepatotoxicity with transaminase elevations about 20 times the upper limit of normal occurred in 11 of 17 subjects after they took ritonavir-boosted saquinavir 100/1000 mg twice daily with rifampicin 600 mg daily for one to 5 days.[22]

Mechanism

Rifampicin is a potent inducer of the cytochrome P450 isoenzyme CYP3A4, by which the protease inhibitors are at least partially metabolised, and therefore it markedly reduces protease inhibitor levels.

The mechanism for the increase in rifampicin levels seen with ritonavir-boosted atazanavir is unknown. As rifampicin and its metabolite are not substrates for CYP3A4, which atazanavir inhibits, and atazanavir is only a weak inhibitor of P-glycoprotein, the authors of one study suggest that other mechanisms, such as competition for biliary excretion or other transport systems may be involved.[4]

Importance and management

Rifampicin markedly reduces the levels of many of the protease inhibitors, and its use with unboosted protease inhibitors should be avoided, because of the risk of reduced antiviral efficacy and emergence of resistant viral strains. There are limited data to suggest that ritonavir as the sole protease inhibitor, or ritonavir used as a pharmacokinetic enhancer with other protease inhibitors such as saquinavir, can be used with rifampicin.[23] However, further study has shown a high incidence of hepatotoxicity with ritonavir-boosted saquinavir 100/1000 mg twice daily and rifampicin, and therefore the manufacturers of both ritonavir and saquinavir contraindicate the concurrent use of rifampicin.[17,24-26] The manufacturers of atazanavir, **darunavir**, fosamprenavir, indinavir, nelfinavir, **tipranavir**, and ritonavir-boosted lopinavir also contraindicate the concurrent use of rifampicin.[2,3,27-37]

UK guidelines from 2009 state that, until more data are available, ritonavir-boosted protease inhibitors should not be used with rifampicin. They recommend that rifampicin should be switched to rifabutin for use with protease inhibitors, or that the protease inhibitor should be changed to an alternative antiretroviral if this is possible.[38] Similarly, the US guidelines state that all unboosted protease inhibitors should not be given with rifampicin or **rifapentine**, and that rifabutin should be used instead.[39] They also advise against the use of higher doses of ritonavir with lopinavir or saquinavir due to the high rate of hepatic adverse effects. The UK manufacturer of ritonavir-boosted lopinavir and also notes that high rates of hepatic adverse effects have been reported when a dose of ritonavir-boosted lopinavir 400/400 mg twice daily was used to overcome the inductive effects of rifampicin. They advise that if use of this regimen is unavoidable, the dose of lopinavir should be only be increased after rifampicin has been started and patients should be very closely monitored for adverse effects and efficacy.[40]

Both the UK and US guidelines[23,38,39] state that rifampicin may only be used with full-dose ritonavir (600 mg to 1.2 g daily) and advise caution on concurrent use; the UK guidelines note that this combination is poorly tolerated.[38]

'Table 21.5', (p.984), summarises the clinical recommendations for the concurrent use of protease inhibitors and rifampicin.

For further guidance on the use of rifabutin with the protease inhibitors, see 'Protease inhibitors + Rifabutin', p.983.

1. Polk RE, Brophy DF, Israel DS, Patron R, Sadler BM, Chittick GE, Symonds WT, Lou Y, Kristoff D, Stein DS. Pharmacokinetic interaction between amprenavir and rifabutin or rifampin in healthy males. *Antimicrob Agents Chemother* (2001) 45, 502–508.
2. Telzir (Fosamprenavir calcium). ViiV Healthcare UK Ltd. UK Summary of product characteristics, May 2009.
3. Lexiva (Fosamprenavir calcium). GlaxoSmithKline. US Prescribing information, September 2009.
4. Burger DM, Agarwala S, Child M, Been-Tiktak A, Wang Y, Bertz R. Effect of rifampin on steady-state pharmacokinetics of atazanavir with ritonavir in healthy volunteers. *Antimicrob Agents Chemother* (2006) 50, 3336–42.
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17. Norvir (Ritonavir). Abbott Laboratories. US Prescribing information, November 2009.
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24. Invirase Hard Capsules (Saquinavir mesilate). Roche Products Ltd. UK Summary of product characteristics, January 2009.
25. Invirase (Saquinavir mesylate). Roche Laboratories Inc. US Prescribing information, July 2007.
26. Norvir Soft Capsules (Ritonavir). Abbott Laboratories Ltd. UK Summary of product characteristics, October 2009.
27. Reyataz (Atazanavir sulfate). Bristol-Myers Squibb Pharmaceuticals Ltd. UK Summary of product characteristics, July 2009.
28. Reyataz (Atazanavir sulfate). Bristol-Myers Squibb. US Prescribing information, November 2009.
29. Prezista (Darunavir ethanolate). Janssen-Cilag Ltd. UK Summary of product characteristics, October 2009.
30. Prezista (Darunavir ethanolate). Tibotec, Inc. US Prescribing information, June 2009.
31. Viracept (Nelfinavir mesilate). Roche Products Ltd. UK Summary of product characteristics, July 2008.
32. Viracept (Nelfinavir mesylate). Agouron Pharmaceuticals, Inc. US Prescribing information, September 2008.
33. Aptivus Soft Capsules (Tipranavir). Boehringer Ingelheim Ltd. UK Summary of product characteristics, June 2009.
34. Aptivus (Tipranavir). Boehringer Ingelheim Pharmaceuticals, Inc. US Prescribing information, June 2009.
35. Crixivan (Indinavir sulphate). Merck Sharp & Dohme Ltd. UK Summary of product characteristics, October 2008.
36. Crixivan (Indinavir sulfate). Merck & Co., Inc. US Prescribing information, October 2009.
37. Kaletra (Lopinavir with Ritonavir). Abbott Laboratories. US Prescribing information, April 2009.
38. Pozniak AL, Collins S, Coyne KM, Freedman AR, Johnson MA, Lipman MCI, Lucas SB, Miller RF, Ormerod LP, on behalf of the BHIVA Guidelines Writing Committee. British HIV Association guidelines for treatment of TB/HIV co-infection, 2009. Available at: http://www.bhiva.org/documents/Guidelines/Treatment%20Guidelines/Current/TreatmentGuidelines2009.pdf (05/02/10).
39. US Department of Health and Human Services; Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. November 3, 2008. Available at: http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf (accessed 29/01/10).
40. Kaletra Tablets (Lopinavir with Ritonavir). Abbott Laboratories Ltd. UK Summary of product characteristics, November 2009.

Protease inhibitors + Rifabutin

Rifabutin bioavailability is significantly increased by the protease inhibitors, in particular ritonavir, with an increased risk of toxicity. Rifabutin modestly decreases the bioavailability of indinavir, nelfinavir, and particularly saquinavir (with an increased risk of therapeutic failure), and appears to increase ritonavir-boosted darunavir, but has no significant effect on amprenavir, atazanavir, and ritonavir-boosted fosamprenavir or ritonavir-boosted tipranavir.

Clinical evidence

(a) Amprenavir or Fosamprenavir

When amprenavir 1.2 g twice daily was given with rifabutin 300 mg daily to 11 healthy subjects for 10 days there was an almost threefold increase in the AUC of rifabutin, but the pharmacokinetics of amprenavir were not significantly altered. The combination was poorly tolerated, with 5 of 11 subjects stopping treatment between days one and 9 due to adverse events.[1] When reduced doses of rifabutin (150 mg every other day) were given with ritonavir-boosted fosamprenavir 100/700 mg twice daily for 2 weeks to healthy subjects the rifabutin $AUC_{0\text{-}48}$ was unchanged and the maximum level was decreased by 14%, when compared with rifabutin 300 mg daily given alone. However, the $AUC_{0\text{-}48}$ and maximum level of the 25-*O*-desacetylrifabutin metabolite were increased by 11-fold and nearly sixfold,

Table 21.5 Summary of the recommendations for the use of protease inhibitors with rifamycins

Protease inhibitor	*Rifabutin*	*Rifampicin (Rifampin)*	*Refs*
Protease inhibitors			
Amprenavir	Rifabutin dose reduced to 150 mg daily or every other day. Amprenavir dose unchanged.	Not recommended (amprenavir levels markedly reduced).	1
Atazanavir	Rifabutin dose reduced to 150 mg daily.	Not recommended (atazanavir levels markedly reduced).	1
Fosamprenavir	Rifabutin dose reduced to 150 mg daily or 300 mg three times per week. Fosamprenavir dose unchanged.	Not recommended (amprenavir levels markedly reduced).	1-4
Indinavir	Rifabutin dose reduced to 150 mg daily or 300 mg three times per week. Indinavir dose increased to 1 g every 8 hours. Not recommended in UK Guidelines or by UK manufacturer.	Not recommended (indinavir levels markedly reduced, rifampicin levels raised).	1, 2, 4-7
Nelfinavir	Rifabutin dose reduced to 150 mg once daily or 300 mg three times per week. Nelfinavir dose unchanged (1.25 g twice daily preferred).	Not recommended (nelfinavir levels markedly reduced).	1, 2, 4, 8, 9
Ritonavir	Rifabutin dose reduced to 150 mg every other day or three times per week. Further dose reductions may be necessary.* Ritonavir dose unchanged.	May be used at usual doses, although limited data (ritonavir levels reduced). May lead to loss of virologic response.	2, 10
Saquinavir	Not recommended (saquinavir levels reduced).	Not recommended (saquinavir levels markedly reduced).	1, 2
Ritonavir-boosted protease inhibitors			
Atazanavir	Rifabutin dose reduced by up to 75% (150 mg every other day or three times per week). Ritonavir-boosted atazanavir dose unchanged.	Not recommended (atazanavir levels markedly reduced).	2, 11, 12
Darunavir	Rifabutin dose reduced to 150 mg every other day. Ritonavir-boosted darunavir dose unchanged.	Not recommended (darunavir levels predicted to be markedly reduced).	13, 14
Fosamprenavir	Rifabutin dose reduced by at least 75% (150 mg every other day or three times per week). Ritonavir-boosted fosamprenavir dose unchanged.	Not recommended (amprenavir levels predicted to be markedly reduced).	1, 3, 4, 15
Indinavir	Rifabutin dose reduced to 150 mg every other day or three times per week. Ritonavir-boosted indinavir dose unchanged. Not recommended in UK guidelines or by UK manufacturer	Not recommended (indinavir levels markedly reduced).	1, 2, 4, 16
Lopinavir	Rifabutin dose reduced to 150 mg every other day or three times per week. Ritonavir-boosted lopinavir dose unchanged.	Not recommended (lopinavir levels markedly reduced). However, adjusted doses of ritonavir-boosted lopinavir (200/800 mg or 400/400 mg twice daily) may overcome the pharmacokinetic interaction, but have a high incidence of elevated liver enzymes, and so if used, close monitoring is needed.	1, 2, 4, 17-19
Saquinavir	Rifabutin dose reduced to 150 mg every other day or three times per week. Appropriate ritonavir-boosted saquinavir dose not established. Consider usual dose (100/1000 mg twice daily).	Rifampicin dose unchanged. Ritonavir-boosted saquinavir 400/400 mg twice daily. Note that a regimen of 100/1000 mg twice daily with rifampicin was associated with severe hepatotoxicity, and the combination is contraindicated.	1, 2, 4, 20, 21
Tipranavir	Rifabutin dose reduced to 150 mg every other day or three times per week. Further dose reductions may be necessary. Ritonavir-boosted tipranavir dose unchanged.	Not recommended (tipranavir levels predicted to be markedly reduced).	1, 4, 22, 23

*Formerly considered contraindicated (rifabutin levels markedly increased with risk of toxicity)

1. Pozniak AL, Collins S, Coyne KM, Freedman AR, Johnson MA, Lipman MCI, Lucas SB, Miller RF, Ormerod LP, on behalf of the BHIVA Guidelines Writing Committee. British HIV Association guidelines for treatment of TB/HIV co-infection, 2009. Available at: http://www.bhiva.org/files/file1031760.pdf (03/06/2009).
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4. US Department of Health and Human Services; Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. November 3 2008. http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf (accessed 02/07/2009).
5. Jaruratanasirikul S, Sriwiriyajan S. Pharmacokinetics of rifampicin administered alone and with indinavir. *J Antimicrob Chemother* (1999) 44 (Suppl A), 58.
6. Crixivan (Indinavir sulfate). Merck Sharp & Dohme Ltd. UK Summary of product characteristics, October 2008.
7. Crixivan (Indinavir sulfate). Merck & Co., Inc. US Prescribing information, October 2009.
8. Viracept (Nelfinavir mesilate). Roche Products Ltd. UK Summary of product characteristics, July 2008.
9. Viracept (Nelfinavir mesilate). Agouron Pharmaceuticals, Inc. US Prescribing information, September 2008.
10. Norvir Soft Capsules (Ritonavir). Abbott Laboratories. US Prescribing information, November 2009.
11. Reyataz (Atazanavir sulfate). Bristol-Myers Squibb Pharmaceuticals Ltd. UK Summary of product characteristics, July 2009.

Continued

Table 21.5 Summary of the recommendations for the use of protease inhibitors with rifamycins (continued)

12. Reyataz (Atazanavir sulfate). Bristol-Myers Squibb. US Prescribing information, November 2009.
13. Prezista (Darunavir ethanolate). Janssen-Cilag Ltd. UK Summary of product characteristics, June 2009.
14. Prezista (Darunavir ethanolate). Tibotec, Inc. US Prescribing information, June 2009.
15. Telzir (Fosamprenavir calcium). GlaxoSmithKline UK. UK Summary of product characteristics, May 2009.
16. Justesen US, Andersen ÅB, Klitgaard NA, Brøsen K, Gerstoft J, Pedersen C. Pharmacokinetic interaction between rifampin and the combination of indinavir and low-dose ritonavir in HIV-infected patients. *Clin Infect Dis* (2004) 38, 426-9.
17. Kaletra (Lopinavir/ritonavir). Abbott Laboratories Ltd. UK Summary of product characteristics, December 2009.
18. Kaletra Tablets (Lopinavir/ritonavir). Abbott Laboratories. US Prescribing information, April 2009.
19. la Porte CJL, Colbers EPH, Bertz R, Voncken DS, Wikstrom K, Boeree MJ, Koopmans PP, Hekster YA, Burger DM. Pharmacokinetics of adjusted-dose lopinavir-ritonavir combined with rifampin in healthy volunteers. *Antimicrob Agents Chemother* (2004) 48, 1553–60.
20. Invirase (Saquinavir mesilate). Roche Products Ltd. UK Summary of product characteristics, January 2009.
21. Invirase (Saquinavir mesilate). Roche Pharmaceuticals. US Prescribing information, July 2007.
22. Aptivus (Tipranavir). Boehringer Ingelheim Ltd. UK Summary of product characteristics, June 2009.
23. Aptivus (Tipranavir). Boehringer Ingelheim. US Prescribing information, June 2009.

respectively, which could potentially lead to an increase of rifabutin-related adverse effects such as uveitis. The AUC, maximum plasma concentration and minimum plasma concentration of amprenavir were modestly increased by 36%, 35% and 17%, respectively, compared with historical data.[2] No additional increase in significant adverse effects was reported on concurrent use.[2]

(b) Atazanavir

The manufacturers report that in a study in 7 subjects, atazanavir 400 mg daily given with rifabutin 150 mg daily for 14 days did not have any important effect on the pharmacokinetics of atazanavir. However, in 3 subjects, the AUC and minimum level of rifabutin 150 mg were 2.1-fold and 3.4-fold higher, respectively, than historical data for a standard 300-mg dose of rifabutin when given with atazanavir 600 mg daily. The AUC and minimum levels of the rifabutin 25-*O*-desacetyl metabolite were significantly increased, by 22-fold and 75-fold, respectively.[3,4]

(c) Darunavir

In a study in healthy subjects, either ritonavir-boosted darunavir 100/600 mg twice daily, rifabutin 150 mg on alternate days, or both drugs were taken for 13 days. The AUC of rifabutin was not significantly changed compared with rifabutin 300 mg daily alone. However, the AUC and minimum plasma level of its 25-*O*-desacetyl metabolite was increased almost 10-fold and 27-fold, respectively. Rifabutin increased the AUC of both darunavir and ritonavir by 57% and 66%, respectively. In addition, rifabutin increased the AUC and minimum plasma level of darunavir by 57% and 75%, respectively. A higher rate of adverse effects (headache, diarrhoea, back pain, dizziness and vomiting) was reported with concurrent use.[5]

(d) Indinavir

When 10 healthy subjects were given rifabutin 300 mg daily with indinavir 800 mg every 8 hours to for 10 days, the indinavir maximum serum levels and AUC were reduced by about one-third, whereas the rifabutin maximum serum levels and AUC were increased two- to three-fold.[6] When the same dose of indinavir (800 mg every 8 hours) was given with half the dose of rifabutin (150 mg daily), the AUC of indinavir was similarly reduced (by 32%), but the increase in the AUC of rifabutin was less (54% increase).[6] In a further study, the pharmacokinetics of indinavir 1 g every 8 hours (increased dose) and rifabutin 150 mg daily (reduced dose) were investigated in healthy and HIV-positive subjects. The AUC of indinavir was the same with this increased dose as with indinavir 800 mg every 8 hours alone. However, despite halving the rifabutin dose, the AUC was still up to 70% higher than with the 300-mg dose alone.[7] When the combination was used in practice, there were no treatment failures in 25 patients taking rifabutin and HAART (containing indinavir and/or nelfinavir). Rifabutin was given as 300 mg twice weekly and the indinavir dose was increased from 800 mg to 1.2 g every 8 hours to achieve satisfactory levels.[8]

(e) Lopinavir

When healthy subjects were given ritonavir-boosted lopinavir 100/400 mg twice daily with rifabutin 150 or 300 mg daily for 10 days the AUC of rifabutin was increased threefold and the AUC of lopinavir was increased by 17%.[9] A case of rifabutin-induced uveitis has been reported in an HIV-positive patient taking rifabutin 300 mg daily and also taking ritonavir-boosted lopinavir 100/400 mg twice daily.[10]

(f) Nelfinavir

When rifabutin 300 mg daily for 8 days was given with nelfinavir 750 mg every 8 hours for 7 to 8 days, the nelfinavir AUC and minimum concentration were reduced by 32% and 53%, respectively. Nelfinavir increased the rifabutin AUC, maximum concentration and minimum concentration by 207%, 146%, and 305%, respectively.[11,12] When the same dose of nelfinavir was given with half the dose of rifabutin (150 mg daily) for 8 days, the nelfinavir AUC was reduced by a similar amount (23%), although the minimum concentration was only reduced by 25%. The rifabutin AUC and minimum concentration were increased by nelfinavir but by a lower amount (83% and 177%, respectively), and the maximum concentration of rifabutin was minimally affected.[12,13] A study in 7 HIV-positive patients taking rifabutin 300 mg twice weekly with nelfinavir 1.25 g twice daily reported a small increase of 22% in the AUC of rifabutin and a larger increase of 246% in the AUC of its 25-*O*-desacetyl metabolite. The pharmacokinetics of nelfinavir and its M8 metabolite were unaffected. However, the sample size in this study was too small to establish or exclude statistical significance.[14]

(g) Ritonavir

In a study in 5 healthy subjects when ritonavir 500 mg twice daily was given with rifabutin 150 mg daily for 8 days, the maximum serum level of rifabutin was increased threefold and the AUC was increased fourfold. The AUC of the rifabutin active metabolite, 25-*O*-desacetylrifabutin, was increased 35-fold. Seven subjects had to be withdrawn due to adverse effects, primarily leucopenia.[15] Retrospective analysis of regimens containing ritonavir found that the concurrent use of rifabutin was associated with a higher incidence of rifabutin-related adverse effects including arthralgia, joint stiffness, uveitis and leucopenia.[16]

(h) Saquinavir

In 12 HIV-positive subjects, the AUC of saquinavir 600 mg three times daily was reduced by about 40% by rifabutin 300 mg daily.[17] Similarly, in 14 HIV-positive patients, the AUC of saquinavir (soft capsules) 1.2 g three times daily was decreased by 47% by rifabutin 300 mg daily. In addition, the rifabutin AUC was increased by 44% by saquinavir.[18] However, the concurrent use of ritonavir and saquinavir (hard capsules), both 400 mg twice daily, with intermittent rifabutin dosing (300 mg weekly or 150 mg every 3 days) for 8 weeks was reported to be safe and manageable. Rifabutin did not significantly alter the protease inhibitor levels, and the rifabutin pharmacokinetics were similar to those usually seen with rifabutin 300 mg daily alone.[19]

A case of anterior uveitis has been reported in an HIV-positive patient taking ritonavir-boosted saquinavir 200/1000 mg daily and rifabutin 300 mg daily. The patient was also taking abacavir, lamivudine, tenofovir, atovaquone, omeprazole, isoniazid and pyridoxine. Rifabutin was stopped, and the patient's vision improved when treated with topical prednisolone.[20]

(i) Tipranavir

In a study in 20 healthy subjects, a single 150-mg dose of rifabutin was taken on day 8 of a 13-day course of ritonavir-boosted tipranavir 200/500 mg twice daily. The single dose of rifabutin had no significant effect on the pharmacokinetics of tipranavir. However, ritonavir-boosted tipranavir significantly increased the AUC, maximum serum concentration and minimum serum concentration of rifabutin 2.9-fold, 1.7-fold and

2.14-fold, respectively. In addition, the AUC, maximum concentration and minimum concentration of 25-*O*-desacetylrifabutin were increased 20.7-fold, 3.2-fold and 7.8-fold, respectively. The effects of the single dose of rifabutin on the pharmacokinetics of ritonavir were not reported.[21]

Mechanism

The protease inhibitors are metabolised by the cytochrome P450 isoenzyme CYP3A4, and as rifabutin is a weak inducer of this isoenzyme, it may reduce the levels of the protease inhibitors.

Rifabutin itself is partially metabolised by CYP3A4 whereas 25-*O*-desacetyl rifabutin is completely metabolised by CYP3A4. Therefore inhibition of CYP3A4 by the protease inhibitors, and in particular ritonavir, can increase the levels of rifabutin and greatly increase the levels of its 25-*O*-des-acetyl metabolite.[21]

Importance and management

Established interactions of clinical importance. The protease inhibitors increase the levels of rifabutin and its active 25-*O*-desacetyl metabolite, with a consequent increase in adverse effects unless the rifabutin dose is reduced. **Ritonavir** is the most potent protease inhibitor in this regard, and the combination has been considered contraindicated. However, rifampicin is contraindicated for use with the protease inhibitors (see 'Protease inhibitors + Rifampicin (Rifampin)', p.982), and both the CDC in the US and the British HIV Association (BHIVA) advise that rifabutin is used instead of rifampicin, but only if the dose of rifabutin is markedly reduced.[22-24]

For patients taking **ritonavir-boosted protease inhibitors**, the US guidelines recommend that the dose of rifabutin is reduced to 150 mg every other day or three times per week whereas the British HIV Association (BHIVA) just recommend using a rifabutin dose of 150 mg three times weekly.[22-24] The BHIVA in the UK also advise against using rifabutin with unboosted indinavir or saquinavir, and they suggest that the dose of rifabutin is reduced to 150 mg daily with other unboosted protease inhibitors.[23] 'Table 21.5', (p.984), summarises the clinical recommendations for the concurrent use of protease inhibitors and rifabutin.

In addition, rifabutin decreases the levels of some protease inhibitors, particularly **saquinavir**, increasing the risk of HIV treatment failure. Rifabutin should not be used when saquinavir is the sole protease inhibitor (no longer recommended). However, there is some evidence that rifabutin can be used with ritonavir-boosted saquinavir. In this case the manufacturer recommends that patients should be closely monitored for hepatic adverse effects.[25]

The US manufacturer of **indinavir** advises that the dose of indinavir is increased to 1 g every 8 hours and the dose of rifabutin halved if both drugs are given,[26] whereas the UK manufacturer does not recommend concurrent use and suggests an alternative HIV regimen is considered.[27]

Therapy should be closely monitored to minimise the occurrence of rifabutin-related adverse effects, in particular uveitis and blood dyscrasias. Patients should also be closely monitored for adherence to the protease inhibitor regimen, as non-compliance could lead to subtherapeutic rifabutin levels and tuberculosis treatment failure. Note that, in one analysis, the use of rifabutin 150 mg twice weekly with low-dose ritonavir and a second protease inhibitor was associated with low rifabutin levels.[28] Further rifamycin-resistant *Mycobacterium tuberculosis* may occur in HIV-positive patients resulting in relapse.[29]

1. Polk RE, Brophy DF, Israel DS, Patron R, Sadler BM, Chittick GE, Symonds WT, Lou Y, Kristoff D, Stein DS. Pharmacokinetic interaction between amprenavir and rifabutin or rifampin in healthy males. *Antimicrob Agents Chemother* (2001) 45, 502–508.
2. Ford SL, Chen Y-C, Lou Y, Borland J, Min SS, Yuen GJ, Shelton MJ. Pharmacokinetic interaction between fosamprenavir-ritonavir and rifabutin in healthy subjects. Antimicrob Agents Chemother (2008) 52, 534–8.
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Protease inhibitors + St John's wort (*Hypericum perforatum*)

St John's wort causes a marked reduction in the serum levels of indinavir, which may result in HIV treatment failure. Other protease inhibitors, whether used alone or boosted by ritonavir, are predicted to interact similarly.

Clinical evidence

In a single-drug pharmacokinetic study, 8 healthy subjects were given three 800-mg doses of **indinavir** on day 1 of to achieve steady-state serum levels, and then an 800-mg dose on day 2. For the next 14 days they were given St John's wort extract 300 mg three times daily. Starting on day 16, the indinavir dosing was repeated. It was found that St John's wort reduced the mean AUC of **indinavir** by 54% and decreased the 8-hour **indinavir** trough serum level by 81%.[1]

Mechanism

Not fully understood, but it seems highly likely that the St John's wort induces the activity of the cytochrome P450 isoenzyme CYP3A4, thereby increasing the metabolism of indinavir and therefore reducing its levels.

Importance and management

Direct information seems to be limited to this study, but the interaction would appear to be established. Such a large reduction in the serum levels

of indinavir is likely to result in treatment failures and the development of viral resistance. Therefore St John's wort should be avoided. There seems to be no direct information about other protease inhibitors, but since they are also metabolised by CYP3A4 it is reasonable to expect that they will be similarly affected by St John's wort. The FDA in the US has suggested that concurrent use of St John's wort and protease inhibitors is not recommended.[2] Similarly, the CSM in the UK has advised that patients taking protease inhibitors should avoid St John's wort and that anyone already taking both should stop the St John's wort and have their HIV RNA viral load measured.[3] The levels of the protease inhibitors are likely to increase as the induction effects of St John's wort diminish, usually over one to two weeks.[4] Therefore the dose of the protease inhibitor will probably need adjusting. The US and UK manufacturers of all protease inhibitors (**amprenavir**, **atazanavir**, **darunavir**, **fosamprenavir**, **lopinavir/ritonavir**, **nelfinavir**, **ritonavir**, **saquinavir**, **tipranavir**) either contraindicate or advise against the use of St John's wort.

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Protease inhibitors + Tenofovir

Ritonavir-boosted atazanavir, darunavir and lopinavir modestly increase the levels of tenofovir, and there is at least one case report of nephrotoxicity with the combination of tenofovir, didanosine, and ritonavir-boosted lopinavir. Ritonavir-boosted saquinavir, tipranavir, and probably also fosamprenavir, have little effect on tenofovir levels. Tenofovir modestly decreases atazanavir levels. Tenofovir has no important effect on ritonavir-boosted darunavir, lopinavir, and tipranavir levels, and modestly increased those of ritonavir-boosted saquinavir in one of two studies. No pharmacokinetic interaction occurs between tenofovir and indinavir or nelfinavir.

Clinical evidence

(a) Atazanavir

In a study in 33 subjects, tenofovir disoproxil fumarate 300 mg daily decreased the AUC and trough level of unboosted atazanavir 400 mg daily, taken for 14 days, by 25% and 40%, respectively. Atazanavir increased the AUC and trough level of tenofovir by 24% and 22%, respectively.[1-3] Similar results were seen when administration was separated by 12 hours.[2]

When atazanavir 300 mg daily was given with ritonavir 100 mg daily (as a pharmacokinetic booster) to 10 subjects for 42 days, the addition of tenofovir disoproxil fumarate 300 mg daily reduced the AUC of atazanavir by a similar amount (25%), but had less of an effect on the trough level (23% reduction), when compared with ritonavir-boosted atazanavir alone.[4] Similarly, in two studies in HIV-positive patients, the pharmacokinetics of ritonavir-boosted atazanavir did not differ significantly between patients taking tenofovir and those not taking tenofovir.[5,6] Other studies have suggested that the concurrent use of ritonavir-boosted atazanavir increases the AUC of tenofovir by 37% and increases its minimum level by 29%.[1,2,7]

(b) Darunavir

In a study in 12 healthy subjects, the concurrent use of ritonavir-boosted darunavir 100/300 mg twice daily with tenofovir disoproxil fumarate 300 mg daily for 14 days modestly increased the tenofovir AUC and minimum level by 22% and 37%, respectively. The pharmacokinetics of darunavir were not significantly changed (minimum level increased by 24% and AUC increased by 21%). Tenofovir had no significant effect on the pharmacokinetics of ritonavir. No significant increase in adverse effects was reported with concurrent use.[8]

(c) Fosamprenavir

The US manufacturer notes that, in a phase III clinical study in 45 subjects, amprenavir trough plasma levels (derived from fosamprenavir) were similar in subjects receiving tenofovir 300 mg daily with ritonavir-boosted fosamprenavir 100/700 mg twice daily for 4 to 48 weeks to those in subjects not receiving tenofovir.[9] Similarly, in a pharmacokinetic study in 30 healthy subjects given ritonavir-boosted fosamprenavir 100/1400 mg daily or 200/1400 mg daily for 28 days, tenofovir disoproxil fumarate 300 mg daily (taken on days 15 to 28) had no significant effect on the pharmacokinetics of amprenavir.[10]

An observational cohort study[11] in 445 HIV-positive patients taking tenofovir reported that the concurrent use of amprenavir was associated with an increased risk of tenofovir-induced renal failure (odds ratio 3.6), whereas another cohort study of 1428 HIV-positive patients including 105 patients taking tenofovir and fosamprenavir found no statistically significant decline in renal function with concurrent use and the use of ritonavir-boosted protease inhibitors did not increase the risk of renal adverse effects.[12]

(d) Indinavir

The manufacturer of tenofovir notes that, in a study in 13 subjects, there was no clinically significant pharmacokinetic interaction between tenofovir disoproxil fumarate 300 mg daily and indinavir 800 mg three times daily, taken for 7 days.[3,7]

(e) Lopinavir

In a study in 24 healthy subjects, the concurrent use of ritonavir-boosted lopinavir 100/400 mg twice daily with tenofovir 300 mg daily for 14 days, resulted in a 32% increase in the AUC and a 51% increase in the trough level of tenofovir, but no change in the clearance of tenofovir. The pharmacokinetics of lopinavir and ritonavir were unaffected by tenofovir. No serious adverse effects were reported in this short-term study, and no subjects had changes in creatinine clearance or developed renal failure.[13] Another study in 30 HIV-positive patients found that ritonavir-boosted lopinavir reduced tenofovir clearance by 18%.[14]

A study in 20 HIV-positive subjects found that concurrent use of tenofovir reduced the AUC and maximum concentration of lopinavir by 26% and 28%, respectively. The AUC and maximum concentration of ritonavir were also similarly affected by tenofovir, with a reduction of 37% and 45%, respectively. However, the minimum concentrations of either drug were not significantly reduced by tenofovir.[15] There is one case report of Fanconi syndrome with nephrogenic diabetes insipidus, which developed in a patient taking ritonavir-boosted lopinavir 200/800 mg daily, tenofovir disoproxil fumarate 300 mg daily, didanosine and lamivudine (for an interaction between tenofovir and didanosine, see 'NRTIs + Tenofovir', p.957). The tenofovir level was 3.7-fold higher than expected and the didanosine level was eightfold higher than it had been before tenofovir was started. Lopinavir levels were unchanged.[16]

(f) Nelfinavir

In a study in 29 healthy subjects, there was no significant pharmacokinetic interaction between tenofovir disoproxil fumarate 300 mg daily and unboosted nelfinavir 1.25 g twice daily, taken for 14 days. No serious adverse effects were reported with concurrent use in this study.[7,17]

(g) Saquinavir

In a study in 35 healthy subjects, tenofovir disoproxil fumarate 300 mg daily modestly increased the AUC and minimum level of saquinavir by 29% and 47%, respectively, after administration of ritonavir-boosted saquinavir 100/1000 mg twice daily taken for 14 days. The minimum level of ritonavir was also increased by 23%. The only change in tenofovir pharmacokinetics was a slight mean 23% increase in minimum level.[18] In another study,[19] in 18 HIV-positive patients taking ritonavir-boosted saquinavir 100/1000 mg twice daily and tenofovir disoproxil fumarate 300 mg daily, the AUC and maximum values of saquinavir were just 1% and 7% lower, respectively, than those seen with ritonavir-boosted saquinavir alone.

(h) Tipranavir

In a study in 22 subjects, ritonavir-boosted tipranavir 100/500 mg twice daily had no effect on the AUC and minimum level of a single 300-mg dose of tenofovir disoproxil fumarate, but it decreased the tenofovir maximum level by 23%. The tipranavir AUC and minimum level were decreased by 18% and 21%, respectively. With an increased dose of ritonavir-boosted tipranavir 200/750 mg twice daily, taken for 23 doses, the maximum level of tenofovir was reduced by 38% with no significant change in AUC and a slight 14% increase in the minimum level, and the decreases in tipranavir AUC and minimum levels were less (decreases of 9% in the AUC and 12% in the minimum level).[20]

Mechanism

It has been suggested that ritonavir increases tenofovir levels via its effect on drug transporter proteins, such as P-glycoprotein in the renal tubuli.[16,21] However, an *in vitro* study found that most protease inhibitors have low or minimal effects on the renal excretion of tenofovir. They suggest instead that an interaction may occur in the intestine, as tenofovir and most protease inhibitors are substrates for intestinal P-glycoprotein.[22] Another *in vitro* study reported that the overall increase in tenofovir levels by some protease inhibitors was due to a combination of different mechanisms including inhibition of tenofovir hydrolysis in intestinal tissue, inhibition of P-glycoprotein-mediated tenofovir efflux and induction of P-glycoprotein expression by the protease inhibitors.[23]

Importance and management

The modest increase in tenofovir levels with ritonavir-boosted **atazanavir**, **darunavir** and **lopinavir** is of uncertain clinical relevance. However, it has been suggested that higher tenofovir levels could potentiate tenofovir-associated adverse events, including renal disorders.[1,2,7,24] For this reason, the UK manufacturer of tenofovir says that renal function should be closely monitored when these three ritonavir-boosted protease inhibitors are given with tenofovir. Particular care should be taken with patients who have underlying systemic or renal disease, or with patients taking nephrotoxic drugs.[3,7] The manufacturers of atazanavir, darunavir and ritonavir-boosted lopinavir also recommend close monitoring of renal function,[1,21,25] and this seems a prudent precaution. The US manufacturer recommends a dose of ritonavir-boosted atazanavir of 100/300 mg daily when it is given with tenofovir.[2] The US manufacturers of atazanavir and tenofovir state that unboosted atazanavir should not be given[2,3] with tenofovir because of the potential for reduced efficacy and development of resistance.

The decrease in atazanavir levels with tenofovir is not of clinical importance if ritonavir is also used, and this combination has been used successfully as part of antiretroviral therapy in clinical studies.[1,7]

The increase in ritonavir-boosted **saquinavir** levels are not likely to be clinically relevant, and the UK manufacturer of saquinavir states that no saquinavir dose adjustment is needed with concurrent use.[26]

The slight interaction between tenofovir and ritonavir-boosted **tipranavir** is unlikely to be clinically relevant. The UK manufacturer of tipranavir states that no tenofovir dose adjustment is needed on concurrent use.[27]

There is no clinically relevant interaction between **nelfinavir** or **indinavir** and tenofovir.

The 2009 UK guidelines give tenofovir as one of the preferred drugs as part of a dual NRTI regimen, to be used with ritonavir-boosted atazanavir, fosamprenavir, lopinavir or saquinavir, for the treatment of HIV infection in treatment naïve patients.[28] The US guidelines also give similar recommendations.[29] When considering appropriate antiretroviral combinations, in addition to pharmacokinetic interactions, cross resistance patterns and adverse effects should be considered. Current local and national guidelines should be consulted when choosing antiretroviral regimens.

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Protease inhibitors + Valproate

Lopinavir levels appeared to be raised by valproic acid in one study in HIV-positive patients, whereas valproic acid levels were not significantly different to those in a control group not taking ritonavir-boosted lopinavir. However, in one case, starting an antiretroviral regimen including ritonavir-boosted lopinavir decrease the valproic acid level, which resulted in an exacerbation of mania. A case of hepatotoxicity has occurred in a patient taking valproic acid with nevirapine and ritonavir-boosted saquinavir.

Clinical evidence

(a) Lopinavir

In a study in 8 HIV-positive patients taking ritonavir-boosted lopinavir 100/400 mg twice daily with various NRTIs, the median AUC of lopinavir increased by 75% without any change in the estimated half-life after they took valproic acid 250 mg twice daily for 7 days. Although the maximum and minimum lopinavir levels were also higher, the difference was not statistically significant. Ritonavir levels were not assessed. Valproic acid levels achieved in the patients taking ritonavir-boosted lopinavir were not significantly different from those in 11 HIV-positive control patients mainly taking NRTIs, even when the 3 patients taking a protease inhibitor or NNRTI (amprenavir, indinavir, or nelfinavir with nevirapine) were excluded.[1] However, one report describes a decrease in valproate levels in a 30-year-old man after he started taking ritonavir-boosted lopinavir.[2] This patient, who had been taking valproic acid 375 mg daily as divalproex sodium for 7 months after an episode of mania, had a subtherapeutic valproic acid level of 197 micromol/L. The dose was increased to 250 mg three times daily and after 25 days his trough valproic acid level had increased to 495 micromol/L. He was then started on an antiretroviral regimen of lamivudine, zidovudine, ritonavir-boosted lopinavir and paroxetine for depression. Four days later he was hypomanic and the paroxetine was replaced with sertraline, which the patient discontinued. Twenty-one days later he had become increasingly manic, and the valproic acid level was

found to be 238 micromol/L, about 50% lower than the previous level. An increase in the valproic acid dose to 1.5 g daily was eventually required to achieve a therapeutic level of 392 micromol/L.

(b) Saquinavir

A case of valproate-associated hepatotoxicity occurred in a 51-year-old man about 3 weeks after he started taking nevirapine 200 mg twice daily, saquinavir 400 mg twice daily, ritonavir 400 mg twice daily, and stavudine. Serum valproic acid levels remained therapeutic.[3]

Mechanism

Ritonavir, and possibly lopinavir, might decrease the plasma levels of valproic acid by induction of glucuronidation. See also 'Protease inhibitors + Lamotrigine', p.974, which is similarly affected.

Importance and management

It has been predicted that ritonavir might reduce valproate levels,[4,5] but the case report[2] appears to be the first clinical evidence of this occurring. Other evidence from the earlier study[1] suggested valproate levels were not affected to a statistically significant extent by ritonavir, although there was a downward trend in valproic acid levels. However, the authors subsequently noted that this study used a low-dose of valproate and that a more clinically significant interaction may occur with higher doses of valproate.[6] In addition, this study unexpectedly found that lopinavir levels appeared to be higher in patients taking valproic acid, although the increase is probably not clinically relevant.[1] If possible, monitor valproate levels when any antiretroviral regimen that includes ritonavir is used. Further study is needed. Note that there has been some concern about using valproate in HIV infection but there seems to be no established reason to avoid or specifically promote the use of valproate in HIV-infection *per se*.

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Protease inhibitors; Fosamprenavir + Miscellaneous

Fosamprenavir is a prodrug of amprenavir, and is rapidly and almost completely hydrolysed to amprenavir and inorganic phosphate primarily in the lining of the gut.[1,2] The interactions of fosamprenavir are therefore primarily those of amprenavir.

1. Telzir (Fosamprenavir calcium). ViiV Healthcare UK Ltd. UK Summary of product characteristics, May 2009.
2. Lexiva (Fosamprenavir calcium). GlaxoSmithKline. US Prescribing information, September 2009.

Protease inhibitors; Indinavir + Ascorbic acid (Vitamin C)

Ascorbic acid (vitamin C) 1 g daily caused a minor decrease in indinavir levels in healthy subjects.

Clinical evidence, mechanism, importance and management

In a study[1] in healthy subjects, high-dose vitamin C 1 g daily for 7 days caused a 14% reduction in the AUC of indinavir 800 mg taken every 8 hours (4 doses beginning on day 6) and a 20% reduction in its maximum plasma level. However, whether this is a real effect needs further study as a similar reduction in plasma levels after a similar indinavir regimen was thought to be a time-dependent effect, see 'Protease inhibitors; Indinavir + Milk thistle', p.989. No recommendations can therefore be made based on this isolated report.

1. Slain D, Amsden JR, Khakoo RA, Fisher MA, Lalka D, Hobbs GR. Effect of high-dose vitamin C on the steady-state pharmacokinetics of the protease inhibitor indinavir in healthy volunteers. *Pharmacotherapy* (2005) 25, 165–70.

Protease inhibitors; Indinavir + Goldenseal (*Hydrastis*)

Goldenseal root had no effect on the pharmacokinetics of a single dose of indinavir in one study.

Clinical evidence

In a study in 10 healthy subjects, the peak plasma level and oral clearance of indinavir after a single 800-mg dose was not changed by goldenseal root (*Nature's Way*) 1.14 g twice daily for 2 weeks. In addition, there was no change in the indinavir half-life. Eight of the subjects had less than a 20% change in oral clearance, but one subject had a 46% increase and one a 46% decrease.[1]

Mechanism

Goldenseal (*Hydrastis canadensis*) was found to be an inhibitor of cytochrome P450 isoenzyme CYP3A4 *in vitro*.[2] This was confirmed in a clinical study using oral midazolam as a probe substrate for CYP3A4, which found a decrease of about 40% in the metabolism of midazolam to hydroxymidazolam.[3] Goldenseal root might therefore be expected to inhibit the metabolism of indinavir.

Importance and management

This study suggests that goldenseal root has no effect on indinavir levels, and may be taken without any undue concern in patients on this protease inhibitor. However, confirmation may be required in light of the midazolam probe study and the two subjects who experienced a relatively greater change in indinavir oral clearance. Further study is needed before firm clinical recommendations can be made

1. Sandhu RS, Prescilla RP, Simonelli TM, Edwards DJ. Influence of goldenseal root on the pharmacokinetics of indinavir. *J Clin Pharmacol* (2003) 43, 1283–8.
2. Budzinski JW, Foster BC, Vandenhoek S, Arnason JT. An in vitro evaluation of human cytochrome P450 3A4 inhibition by selected commercial herbal extracts and tinctures. *Phytomedicine* (2000) 7, 273–82.
3. Gurley BJ, Gardner SF, Hubbard MA, Williams DK, Gentry WB, Khan IA, Shah A. In vivo effects of goldenseal, kava kava, black cohosh, and valerian on human cytochrome P450 1A2, 2D6, 2E1, and 3A4/5 phenotypes. *Clin Pharmacol Ther* (2005) 77, 415–26.

Protease inhibitors; Indinavir + Milk thistle

Although some studies have found that milk thistle slightly lowers indinavir levels, it appears that this is a time-dependent effect rather than a drug interaction, as it also occurred in a control group in one study. The balance of evidence suggests that no important pharmacokinetic interaction occurs.

Clinical evidence

Milk thistle (*Silybum marianum*) 175 mg three times daily (*Thisilyn; Nature's Way,* standardised for 80% silymarin content) for 3 weeks caused a 9% reduction in the AUC of indinavir and a 25% reduction its trough plasma level after four doses of indinavir 800 mg every 8 hours, but only the value for the trough level reached statistical significance.[1] The authors suggested that the effect on the trough level could represent a time-dependent effect of indinavir pharmacokinetics, as the plasma levels without milk thistle were found to be similarly lowered after a washout phase.[1] In another similar study, in 10 healthy subjects, milk thistle standardised for silymarin 160 mg (*General Nutrition Corp.*) three times daily for 13 days and then with indinavir 800 mg every 8 hours for 4 doses did not cause any statistically significant changes in the indinavir pharmacokinetics (6% reduction in AUC and 32% reduction in minimum level).[2] In yet another similar study, in 8 healthy subjects, milk thistle extract 456 mg, standardised for silymarins (*Kare and Hope Ltd*) three times daily for 28 days had no effect on the pharmacokinetics of indinavir 800 mg every 8 hours for four doses when compared with 6 subjects in a control group

not receiving milk thistle extract. Both the control and indinavir group had a lower indinavir AUC after the second and third time of administration compared with the first, and this decline was greater in the control group.[3] A meta-analysis of these 3 studies showed no effect of milk thistle on indinavir levels.[3]

Mechanism

Based on *animal* data, milk thistle might be expected to increase indinavir levels by inhibiting its metabolism,[1] or to have effects via P-glycoprotein.[2]

Importance and management

The available data suggest that milk thistle extract does not have an effect on the pharmacokinetics of indinavir, although it is not totally conclusive. The reduction in indinavir levels appears to be just a time-dependent effect rather than an effect of the milk thistle, and further study is needed with longer exposure to indinavir than just four doses. Evidence appears to be too slim to prohibit concurrent use, but until more is known it may be prudent to give milk thistle cautiously to patients taking indinavir.

1. Piscitelli SC, Formentini E, Burstein AH, Alfaro R, Jagannatha S, Falloon J. Effect of milk thistle on the pharmacokinetics of indinavir in healthy volunteers. *Pharmacotherapy* (2002) 22, 551–6.
2. DiCenzo R, Shelton M, Jordan K, Koval C, Forrest A, Reichman R, Morse G. Coadministration of milk thistle and indinavir in healthy subjects. *Pharmacotherapy* (2003) 23, 866–70.
3. Mills E, Wilson K, Clarke M, Foster B, Walker S, Rachlis B, DeGroot N, Montori VM, Gold W, Phillips E, Myers S, Gallicano K. Milk thistle and indinavir: a randomized controlled pharmacokinetics study and meta-analysis. *Eur J Clin Pharmacol* (2005) 61, 1–7.

Protease inhibitors; Indinavir + Venlafaxine

In a single-dose study, venlafaxine lowered indinavir levels.

Clinical evidence, mechanism, importance and management

In a study, 9 healthy subjects were given a single dose of indinavir before and after 10 days of venlafaxine 150 mg daily in divided doses. Indinavir did not affect the pharmacokinetics of venlafaxine, but venlafaxine reduced the AUC and maximum plasma levels of indinavir by 28% and 36%, respectively. This is possibly enough to reduce the efficacy of indinavir.[1] The reason for this effect is not clear. More study is needed to establish the effects of multiple doses. Until more is known it would seem prudent to monitor closely to ensure that the antiviral effects of indinavir are not compromised.

1. Levin GM, Nelson LA, DeVane CL, Preston SL, Eisele G, Carson SW. A pharmacokinetic drug-drug interaction study of venlafaxine and indinavir. *Psychopharmacol Bull* (2001) 35, 62–71.

Protease inhibitors; Nelfinavir + Calcium compounds

Calcium supplements do not affect the levels of nelfinavir.

Clinical evidence, mechanism, importance and management

Calcium supplements had no effect on plasma levels of nelfinavir or its M8 metabolite in 15 patients receiving nelfinavir 1.25 g twice daily as part of a HAART regimen. Calcium was given as calcium carbonate 1.35 g twice daily to 9 patients, and calcium gluconate/calcium carbonate 2.95 g/300 mg twice daily to 6 patients, both for 14 days. The plasma levels of nelfinavir were measured before a dose and 3 hours after a dose.[1] Similar results were reported in another study.[2] No nelfinavir dose adjustments appear necessary if calcium supplements are given.

1. Jensen-Fangel S, Justesen US, Black FT, Pedersen C, Obel N. The use of calcium carbonate in nelfinavir-associated diarrhoea in HIV-1-infected patients. *HIV Med* (2003) 4, 48–52.
2. Kopp Hutzler B, Perez-Rodriguez E, Norton S, Hsyu PH. Pharmacokinetics (PK) interactions between nelfinavir (NFV) and calcium supplements (P277). *AIDS* (2000) 14 (Suppl 4), S96.

Raltegravir + Miscellaneous

Rifampicin (rifampin) reduces raltegravir levels. Drugs that affect gastric pH, such as omeprazole, may increase raltegravir levels. Raltegravir does not significantly affect the pharmacokinetics of combined hormonal contraceptives, lamotrigine, and midazolam. Reduced plasma levels of both raltegravir and maraviroc may occur on their concurrent use.

Clinical evidence, mechanism, importance and management

(a) Drugs that affect gastric pH

In a study in 14 healthy subjects, **omeprazole** 20 mg daily for 5 days increased the AUC and maximum plasma levels of raltegravir 3.1-fold and 4.1-fold, respectively. However, HIV-positive patients may have an increased baseline gastric pH and the effect of drugs such as **omeprazole** on raltegravir may be less in patients than in healthy subjects.[1] The UK manufacturer advises that as the effects of raised gastric pH on raltegravir are unclear, raltegravir should not be used with drugs that increase gastric pH (they name **proton pump inhibitors** and **H_2-receptor antagonists**) unless this is unavoidable.[2] In contrast, the US manufacturer states that, although drugs that increase gastric pH may be expected to increase raltegravir levels, the use of raltegravir with **proton pump inhibitors** and **H_2-receptor antagonists** in phase III studies did not result in significant adverse outcomes. Therefore no raltegravir dose adjustment is required.[3]

(b) Hormonal contraceptives

The manufacturers[2,3] report that, in drug interaction studies, raltegravir 400 mg twice daily had no clinically significant effects on the pharmacokinetics of hormonal contraceptives (**ethinylestradiol** and **norelgestromin** are specifically mentioned).[2] No dose adjustment is needed with concurrent use.[2] However, note that whatever other methods of contraception are being used, barrier methods are always advisable to reduce the risk of HIV transmission.

(c) Lamotrigine

In a study in 24 healthy subjects, raltegravir 400 mg twice daily for 5 days had no significant effects on the pharmacokinetics of a single 100-mg dose of lamotrigine given on day 4. Therefore, raltegravir appears not to affect the glucuronidation of lamotrigine. No serious adverse effects were reported.[4] From this study, it appears that no lamotrigine dose adjustments are usually needed in patients also taking raltegravir.

(d) Maraviroc

In a study in 17 healthy subjects, the pharmacokinetics of raltegravir and maraviroc were analysed when taken separately (raltegravir 400 mg twice daily for 3 days and maraviroc 300 mg twice daily for 5 days) or taken together for 3 days. Raltegravir reduced the AUC and maximum plasma concentration of maraviroc by 14% and 21%, respectively. Similarly, maraviroc reduced the AUC, the maximum plasma concentration and the trough plasma concentration of raltegravir by 37%, 30%, and 28%, respectively. The average plasma concentration of maraviroc did not fall below the predicted therapeutic levels of greater than 100 nanograms/mL. The reductions in raltegravir and maraviroc levels are unlikely to be clinically significant and no dose adjustment of either drug appears to be needed on concurrent use.[5]

(e) Midazolam

A study[6] in 10 healthy subjects found that raltegravir 400 mg twice daily for 14 days had no significant effects on a single 2-mg dose of oral midazolam taken on day 14. Midazolam is used as a probe substrate for the cytochrome P450 isoenzyme CYP3A4. This suggests that raltegravir is unlikely to affect the metabolism of other substrates of CYP3A4.

(f) Rifampicin (Rifampin)

In a study in 9 healthy subjects, rifampicin 600 mg daily for 15 days reduced the AUC, the peak plasma levels and the trough plasma levels of a single 400-mg dose of raltegravir given on day 14 by 40%, 38% and 61%, respectively. In a subsequent study, 17 healthy subjects were given an increased dose of raltegravir 800 mg twice daily (to try to overcome the effects of rifampicin) with rifampicin 600 mg daily for 14 days. The AUC and maximum concentration of raltegravir were *increased* by 27% and 62%, respectively. However, doubling the raltegravir dose still resulted in a decrease in the trough level of raltegravir by 53%, when compared with raltegravir alone. No significant increase in adverse effects was reported on concurrent use, and all adverse effects reported were transient.[7]

Raltegravir is primarily metabolised by glucuronyltransferases (UGT1A1), which may be induced by rifampicin. The clinical significance of this is unknown, but the UK manufacturer suggests that a doubling of the raltegravir dose may be considered if the concurrent use of rifampicin cannot be avoided;[2] this dose is also recommended by the US

manufacturers.[3] Although evidence from the second study suggests that this may overcome the reduction in the AUC, the likely clinical significance of the low raltegravir trough level (despite the increase in raltegravir dose) is as yet unclear and should be borne in mind.[7]

(g) Other drugs

The UK manufacturer also advises that no dose adjustment of raltegravir is needed with **glucocorticoids**, **phenytoin**, **phenobarbital**, **rifabutin**, and **St John's wort**). These are said to be less potent inducers of glucuronyltransferases than rifampicin (see under *Rifampicin*, above).[2]

1. Iwamoto M, Wenning LA, Nguyen B-Y, Teppler H, Moreau AR, Rhodes RR, Hanley WD, Jin B, Harvey CM, Breidinger SA, Azrolan N, Farmer HF, Isaacs RD, Chodakewitz JA, Stone JA, Wagner JA. Effects of omeprazole on plasma levels of raltegravir. Clin Infect Dis (2009) 48, 489–92.
2. Isentress (Raltegravir potassium). Merck Sharp & Dohme Ltd. UK Summary of product characteristics, September 2009.
3. Isentress (Raltegravir potassium). Merck & Co. US Prescribing information, October 2009.
4. Van Luin M, Colbers A, Van Ewijk-Beneken Kolmer E, Verway-Van Wissen C, Van Der Kolk M, Da Silva H, Koopmans P, Burger D. Raltegravir has no influence on UGT1A4/2B7 when using lamotrigine as a phenotypic probe. 16th Conference on retroviruses and Opportunistic Infections, Montréal, 2009. Poster 693.
5. Andrews E, Glue P, Fang J, Crownover P, Tressler R, Damle B. A pharmacokinetic study to evaluate an interaction between maraviroc and raltegravir in healthy adults. 48th Annual ICAAC/IDSA 46th Annual Meeting, Washington DC, 2009. Poster H-4055.
6. Iwamoto M, Kassahun K, Troyer MD, Hanley WD, Lu P, Rhoton A, Petry AS, Ghosh K, Mangin E, DeNoia EP, Wenning LA, Stone JA, Gottesdiener KM, Wagner JA. Lack of a pharmacokinetic effect of raltegravir on midazolam: in vitro/ in vivo correlation. J Clin Pharmacol (2008) 48, 209–14.
7. Wenning LA, Hanley WD, Brainard DM, Petry AS, Ghosh K, Jin B, Mangin E, Marbury TC, Berg JK, Chodakewitz JA, Stone JA, Gottesdiener KM, Wagner JA, Iwamoto M. Effect of rifampin, a potent inducer of drug metabolizing enzymes, on the pharmacokinetics of raltegravir. Antimicrobial Agents Chemother (2009) 53, 2852–6.

Raltegravir + NNRTIs

Efavirenz and etravirine modestly reduce the AUC of raltegravir. Nevirapine is predicted to interact similarly. However, four cases of significantly reduced raltegravir levels have been reported in patients taking antiretroviral drugs including etravirine.

Clinical evidence, mechanism, importance and management

(a) Efavirenz

In a study in 9 healthy subjects, efavirenz 600 mg daily for 14 days modestly reduced the AUC and maximum plasma levels of a single 400-mg dose of raltegravir (taken on day 12) by 36%.[1]

Raltegravir is metabolised by glucuronosyltransferases (primarily UGT1A1). Efavirenz is thought to induce UGT1A1 thereby modestly reducing raltegravir levels.[1,2]

The reduction in raltegravir levels is not expected to be clinically relevant, and the UK manufacturer advises that no dose adjustments are required on the concurrent use of efavirenz.[2] However, note that the US manufacturer makes no recommendation and advises that the clinical relevance of this reduction has not been directly studied.[3]

(b) Etravirine

In a study in 19 healthy subjects, etravirine 200 mg twice daily for 12 days was taken with raltegravir 400 mg twice daily from day 8 to day 12. Etravirine modestly reduced the trough levels of raltegravir by 34%; however, this was not statistically significant. No change in etravirine pharmacokinetics was reported with raltegravir and no serious adverse effects were reported.[4]

A patient taking enfuvirtide, ritonavir-boosted darunavir and raltegravir was found to have subtherapeutic trough plasma levels of raltegravir one month after enfuvirtide was replaced with etravirine. Three other cases of reduced raltegravir trough plasma levels have also been reported in patients taking antiretroviral drugs including etravirine.[5]

No raltegravir dose adjustment is likely to be needed if it is taken with etravirine.[2,4] However, the US manufacturer advises that this reduction in raltegravir has not been directly assessed.[3] Given the isolated case reports of reduced raltegravir levels in patients also taking etravirine, until further information is available, it may be prudent to consider the potential for an interaction during concurrent use.

(c) Nevirapine

The UK manufacturer predicts that nevirapine will induce the glucuronidation of raltegravir (primarily by UGT1A1). However, they advise that no dose adjustment is needed on concurrent use.[2]

1. Iwamoto M, Wenning LA, Petry AS, Laethem M, De Smet M, Kost JT, Breidinger SA, Mangin E, Azrolan N, Greenberg HE, Haazen W, Stone JA, Gottesdiener KM. Minimal effects of ritonavir and efavirenz on the pharmacokinetics of raltegravir. Antimicrobial Agents Chemother (2008) 52 4338–43.
2. Isentress (Raltegravir potassium). Merck Sharp & Dohme Ltd. UK Summary of product characteristics, September 2009.
3. Isentress (Raltegravir potassium). Merck & Co. US Prescribing information, October 2009.
4. Anderson MS, Kakuda TN, Hanley W, Miller J, Kost JT, Stoltz R, Wenning LA, Stone JA, Hoetelmans RMW, Wagner JA, Iwamoto M. Minimal pharmacokinetic interaction between human immunodeficiency virus nonnucleoside reverse transcriptase inhibitor etravirine and the integrase inhibitor raltegravir in healthy subjects. Antimicrobial Agents Chemother (2008) 52, 4228–32.
5. Ménard A, Solas C, Mokthari S, Bregigeon S, Drogoul M-P, Tamalet C, Lacarelle B, Martin IP. Etravirine–raltegravir, a marked interaction in HIV-1-infected patients: about four cases. AIDS (2009) 27, 869–71.

Raltegravir + NRTIs

No clinically significant interaction occurs between raltegravir and lamivudine or tenofovir.

Clinical evidence, mechanism, importance and management

In a study, 9 healthy subjects were given **tenofovir** 300 mg daily with raltegravir 400 mg twice daily for 4 days. The AUC_{0-12} and maximum plasma concentration of raltegravir were increased by 49% and 64%, respectively, and a minor reduction in the AUC_{0-24} and maximum plasma concentration of **tenofovir** was also reported. In a subsequent study by the same authors, 25 HIV-positive patients taking **tenofovir** 300 mg daily and **lamivudine** 300 mg daily were given raltegravir 100 mg to 600 mg twice daily. The raltegravir AUC_{0-12} and maximum concentration were increased by 41% and 33%, respectively.[1] No serious adverse effects were reported on the concurrent use of **tenofovir** and raltegravir. The mechanism for this interaction is unknown. However, the modest increases in raltegravir levels and minor reduction in **tenofovir** levels seen in these studies are not expected to be of clinical relevance. The manufacturer of raltegravir recommends that no dose adjustment of either raltegravir or **tenofovir** is needed.[2]

The US manufacturer also reports that, in drug interaction studies, the pharmacokinetics of **lamivudine** were not affected to a clinically significant extent by raltegravir.[3] There appears to be no information about other NRTIs and raltegravir.

1. Wenning LA, Friedman EJ, Kost JT, Breidinger SA, Stek JE, Lasseter KC, Gottesdiener KM, Chen J, Teppler H, Wagner JA, Stone JA, Iwamoto M. Lack of a significant drug interaction between raltegravir and tenofovir. Antimicrob Agents Chemother (2008) 52, 3253–8.
2. Isentress (Raltegravir potassium). Merck Sharp & Dohme Ltd. UK Summary of product characteristics, September 2009.
3. Isentress (Raltegravir potassium). Merck & Co. US Prescribing information, October 2009.

Raltegravir + Protease inhibitors

Atazanavir may modestly increase the levels of raltegravir. Indinavir and saquinavir are predicted to increase raltegravir levels, but to a lesser extent than atazanavir. Low-dose ritonavir and ritonavir-boosted tipranavir appear to have no clinically relevant effect on the pharmacokinetics of raltegravir.

Clinical evidence

(a) Atazanavir

In a study in 19 healthy subjects, raltegravir 400 mg twice daily was taken with atazanavir 300 mg twice daily for 14 days. The concurrent use of atazanavir and raltegravir resulted in a decrease in the AUC and maximum concentration of atazanavir by 17% and 11%, respectively, and an increase in the AUC and maximum concentration of raltegravir by 54% and 39%, respectively. The incidence of adverse effects was not increased with concurrent use.[1] In another study in 12 healthy subjects, atazanavir 400 mg daily for 9 days increased the AUC and maximum concentration of a single 100-mg dose of raltegravir (taken on day 7) by 72% and 53%, respectively.[2] In another study by the same authors in 10 healthy subjects, raltegravir 400 mg twice daily was taken alone or with ritonavir-boosted atazanavir 300 mg daily for 10 days. Ritonavir-boosted atazanavir increased the AUC of raltegravir by 41%; a slight increase of 24% in the maximum concentration was also reported; however, this was not statistically significant. Atazanavir levels were not assessed in this study. No serious adverse effects or clinically relevant ECG changes were reported.[2] A

case series in 3 HIV-positive patients taking unboosted atazanavir 300 mg twice daily with raltegravir 400 mg twice daily reported no increase in adverse effects with this combination and no loss of therapeutic efficacy. Three other patients taking the same regimen but with additional antiretrovirals (one taking lamivudine, another patient taking abacavir with **saquinavir**, and another patient taking lamivudine and tenofovir) similarly had viral loads less than 50 copies/mL and no increase in adverse effects.[3]

(b) Darunavir

In a small study in 18 healthy subjects, only 6 subjects finished the course of ritonavir-boosted darunavir 100/600 mg twice daily with raltegravir 400 mg twice daily for 12 days. Eight cases of a rash occurred; seven were mild to moderate in nature; however, one case progressed to a severe maculopapular rash. As insufficient subjects completed the study, no clear interpretations can be made from the data. However, the data from the remaining 6 subjects suggested that ritonavir-boosted darunavir reduced the AUC and maximum concentration of raltegravir by 29% and 33%, respectively, when compared with raltegravir taken alone for 4 days. No difference was found with ritonavir-boosted darunavir pharmacokinetics when compared with historical data in healthy subjects.[4]

(c) Ritonavir

In a study in 10 healthy subjects, ritonavir 100 mg twice daily was taken for 16 days with a single 400-mg dose of raltegravir taken on day 14. The AUC and maximum plasma concentration of raltegravir were reduced by 16% and 24%, respectively, but this was not statistically significant.[5]

(d) Tipranavir

In a study, 15 healthy subjects were given ritonavir-boosted tipranavir 200/500 mg twice daily for 11 days with raltegravir 400 mg twice daily from day 8 to day 11. Ritonavir-boosted tipranavir reduced the trough plasma level of raltegravir by 55%; the AUC and peak plasma levels of raltegravir were also reduced by 24% and 18%, respectively, but this was not statistically significant.[6]

Mechanism

The main route of metabolism for raltegravir is by glucuronosyltransferases (primarily UGT1A1), and atazanavir is a known inhibitor of this pathway.[7,8] The manufacturers also suggest that less potent inhibitors of UGT1A1, such as indinavir and saquinavir, may interact to a lesser extent than atazanavir. The US manufacturer of ritonavir reports that it may induce glucuronyltransferases.[9]

Importance and management

Although only a modest pharmacokinetic interaction appears to occur between raltegravir and ritonavir-boosted **darunavir**, the high incidence of rash reported in the study above suggests a note of caution is warranted on concurrent use.

The interaction between **atazanavir** and raltegravir appears to be established. However the modest increases reported are not expected to be clinically concurrent use of atazanavir and raltegravir appear to support this. The manufacturers therefore advise that no dose adjustment is needed when raltegravir is given with atazanavir alone or with ritonavir-boosted atazanavir. They also suggest that no dose adjustment is likely to be needed for less potent inhibitors of UGT1A1 such as **indinavir** and **saquinavir**.[7,8]

Although ritonavir may be predicted to have some effect on the pharmacokinetics of raltegravir, as it is a known inducer of glucuronyltransferases, the limited data above suggests that the impact of low doses of **ritonavir**, such as those used for pharmacological boosting of other protease inhibitors, on the pharmacokinetics of raltegravir is unlikely to be clinically significant. No dose adjustment appears to be needed with low-dose ritonavir specifically; however, until further data is available, it may be prudent to monitor concurrent use in patients taking higher doses of ritonavir. Further study is needed.

As the efficacy of raltegravir was not affected by ritonavir-boosted **tipranavir**, the manufacturers advise that no dose adjustment is needed.[7,8]

1. Zhu L, Mahnke L, Butterton J, Perrson A, Stonier M, Comisar W, Paneblianco D, Breidinger S, Zhang J, Bertz R. Pharmacokinetics and safety of twice-daily atazanavir (300 mg) and raltegravir (400 mg) in healthy subjects. 16th Conference on retroviruses and Opportunistic Infections, Montréal, 2009. Abstract 696.
2. Iwamoto M, Wenning LA, Mistry GC, Petry AS, Liou SY, Ghosh K, Breidinger S, Azrolan N, Gutierrez MJ, Bridson WE, Stone JA, Gottesdiener KM, Wagner JA. Atazanavir modestly increases plasma levels of raltegravir, Clin Infect Dis (2008) 47, 137–40.
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5. Iwamoto M, Wenning LA, Petry AS, Laethem M, De Smet M, Kost JT, Breidinger SA, Mangin E, Azrolan N, Greenberg HE, Haazen W, Stone JA, Gottesdiener KM. Minimal effects of ritonavir and efavirenz on the pharmacokinetics of raltegravir. Antimicrob Agents Chemother (2008) 52 4338–43.
6. Hanley WD, Wenning LA, Moreau A, Kost JT, Mangin E, Shamp T, Stone JA, Gottesdiener KM, Wagner JA, Iwamoto M. Effect of tipranavir-ritonavir on pharmacokinetics of raltegravir. Antimicrob Agents Chemother (2009) 53, 2752–5.
7. Isentress (Raltegravir potassium). Merck & Co. US Prescribing information, October 2009.
8. Isentress (Raltegravir potassium). Merck Sharp & Dohme Ltd. UK Summary of product characteristics, September 2009.
9. Norvir (Ritonavir). Abbott Laboratories. US Prescribing information, November 2009.

Ribavirin + Antacids

The manufacturers of ribavirin note that there was a minor 14% decrease in the AUC of ribavirin 600 mg when it was given with an antacid containing aluminium, magnesium, and simeticone,[1-3] but this is not considered clinically relevant.[1,2] No ribavirin dose adjustment is needed on concurrent use.

1. Copegus (Ribavirin). Roche Products Ltd. UK Summary of product characteristics, November 2009.
2. Rebetol (Ribavirin). Schering-Plough Ltd. UK Summary of product characteristics, April 2009.
3. Rebetol (Ribavirin). Schering Corporation. US Prescribing information, November 2009.

Rimantadine + Aspirin or Paracetamol (Acetaminophen)

Both aspirin and paracetamol slightly reduce the levels of rimantadine, but this is unlikely to be clinically relevant.

Clinical evidence, mechanism, importance and management

(a) Aspirin

In a study in healthy subjects, rimantadine 100 mg twice daily was given for 13 days. On day 11, aspirin 650 mg four times daily was started and continued for 8 days. The peak plasma levels and AUC of rimantadine were reduced by about 10% in the presence of aspirin.[1] This reduction is unlikely to be clinically relevant.

(b) Paracetamol

In a study in healthy subjects, rimantadine 100 mg twice daily was given for 13 days. On day 11, paracetamol 650 mg four times daily was started and continued for 8 days. The peak plasma levels and AUC of rimantadine were reduced by about 11% in the presence of paracetamol.[1] This reduction is unlikely to be clinically relevant.

1. Flumadine (Rimantadine hydrochloride). Forest Pharmaceuticals, Inc. US Prescribing information, April 2007.

Rimantadine + Cimetidine

Cimetidine causes a small but probably clinically unimportant rise in the plasma levels of rimantadine.

Clinical evidence, mechanism, importance and management

In 23 healthy subjects the AUC of a single 100-mg dose of rimantadine was increased by 20% and the apparent total clearance reduced by 18% when it was taken one hour after the first dose of cimetidine 300 mg four times daily for 6 days. The authors of the study suggest that these changes are likely to have little, if any, clinical consequences.[1] The effects of multiple-dose concurrent use are not known.

1. Holazo AA, Choma N, Brown SY, Lee LF, Wills RJ. Effect of cimetidine on the disposition of rimantadine in healthy subjects. *Antimicrob Agents Chemother* (1989) 33, 820–3.

Rimantadine + Food

In a study in 12 healthy subjects, the rate and extent of absorption of a single 100-mg dose of rimantadine was not altered by the absence or presence of food.[1] Therefore rimantadine may be taken without regard to food.

1. Wills RJ, Rodriguez LC, Choma N, Oakes M. Influence of a meal on the bioavailability of rimantadine HCl. *J Clin Pharmacol* (1987) 27, 821–3.

Telbivudine + Miscellaneous

Drugs affecting renal function may alter the plasma concentration of telbivudine. It is unknown whether the risk of myopathy with telbivudine is increased by the concurrent use of other drugs that can cause myopathy. Peginterferon-alfa 2a does not alter telbivudine pharmacokinetics; however, the incidence of neuropathy with telbivudine may be increased. Food does not affect telbivudine pharmacokinetics. No pharmacokinetic interaction appears to occur between telbivudine and adefovir, ciclosporin, lamivudine, or tenofovir. No cytochrome P450-mediated interactions are expected to occur with telbivudine.

Clinical evidence, mechanism, importance and management

(a) Adefovir

In a study in healthy subjects the concurrent use of telbivudine 600 mg daily and adefovir 10 mg daily for 7 days did not alter the pharmacokinetics of either drug, when compared with their use alone.[1] No dose adjustment of either drug appears to be needed on concurrent use.

(b) Ciclosporin

The manufacturers of telbivudine note that no pharmacokinetic interaction occurs between ciclosporin and telbivudine.[2,3] However, there is a possibility that additive myopathy may occur, see under *Drugs causing myopathy*, below.

(c) Cytochrome P450-mediated interactions

The manufacturers note that telbivudine is not metabolised by cytochrome P450 and is principally excreted unchanged by the kidneys. It is therefore unlikely to be affected by drugs that induce or inhibit cytochrome P450 isoenzymes.[2,3] Furthermore, *in vitro* studies suggest that telbivudine does not inhibit or induce cytochrome P450 isoenzymes, and is therefore unlikely to interact with drugs that are substrates for these isoenzymes.[2,3]

(d) Drugs affecting renal function

The manufacturers note that telbivudine is eliminated primarily by renal excretion.[2,3] Therefore, the concurrent use of drugs that affect renal function (the manufacturers name **aminoglycosides**, **loop diuretics**, **platinum compounds**, **vancomycin**, **amphotericin B**,[3] and **ciclosporin** and **tacrolimus**[2]) may affect the plasma concentrations of telbivudine. Caution is advised[3] and it would be sensible to closely monitor renal function during concurrent use.

(e) Drugs causing myopathy

The manufacturers of telbivudine note that it is unknown whether the risk of myopathy during treatment is increased by the concurrent use of other drugs associated with myopathy (such as **statins**, **fibrates**, and **ciclosporin**).[2,3] The US manufacturer also lists **corticosteroids**, **chloroquine**, **hydroxychloroquine**, **penicillamine**, **zidovudine**, **erythromycin**, **nicotinic acid**, and certain **azoles**.[2] Monitor concurrent use closely. Patients should be told to report any signs of myopathy and possible rhabdomyolysis (i.e. otherwise unexplained muscle pain, tenderness or weakness or dark coloured urine).[2,3] If myopathy does occur, telbivudine should be stopped.[3]

(f) Food

In a study in healthy subjects, when a single 600-mg dose of telbivudine was given immediately after a high-fat/high-calorie meal there was no effect on the pharmacokinetics of telbivudine, when compared with the fasting state.[4] Telbivudine may be taken with or without food.

(g) Interferons

The manufacturers note that peginterferon-alfa 2a did not alter the pharmacokinetics of telbivudine, although no conclusion can be made about the effect of telbivudine on peginterferon-alfa 2a because of high interindividual variability in its levels.[2,3] However, telbivudine causes neuropathy, and the incidence and possibly severity of this appears to be increased by peginterferon-alfa 2a. The MHRA and CHM in the UK therefore advise that the combination cannot be recommended. If both drugs are given, patients should be closely monitored for peripheral neuropathy. If peripheral neuropathy develops, telbivudine and peginterferon should be stopped.[5] The UK manufacturers advise that the increased risk of neuropathy cannot be excluded if telbivudine is used with other interferon alfa products.[3]

(h) Lamivudine

In a study in healthy subjects, when telbivudine 200 mg daily and lamivudine 100 mg daily were given concurrently for 7 days the pharmacokinetics of both drugs were unchanged.[1] No dose adjustment of either drug appears to be needed if they are used together.

(i) Tenofovir

The manufacturers note that there was no pharmacokinetic interaction between tenofovir disoproxil fumarate and telbivudine.[2,3] Therefore, no dose adjustment of either drug appears to be needed if they are used together.

1. Zhou X-J, Fielman BA, Lloyd DM, Chao GC, Brown NA. Pharmacokinetics of telbivudine in healthy subjects and absence of drug interaction with lamivudine or adefovir dipivoxil. *Antimicrob Agents Chemother* (2006) 50, 2309–15.
2. Tyzeka (Telbivudine). Novartis Pharmaceuticals Corporation. US Prescribing information, April 2009.
3. Sebivo (Telbivudine). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, October 2009.
4. Zhou X-J, Lloyd DM, Chao GC, Brown NA. Absence of food effect on the pharmacokinetics of telbivudine following oral administration in healthy subjects. *J Clin Pharmacol* (2006) 46, 275–81.
5. Medicines Healthcare Products Regulatory Agency and the Commission on Human Medicines. Telbivudine: risk of peripheral neuropathy with pegylated interferon. Drug Safety Update (2008) 1 (Issue 8), 4. Available at: http://www.mhra.gov.uk/Publications/Safetyguidance/DrugSafetyUpdate/CON014099 (accessed 29/01/10).

Tenofovir + Miscellaneous

Tenofovir absorption is increased by high-fat food. Cases of additive nephrotoxicity have been reported with tenofovir and NSAIDs or vancomycin, and the concurrent use of drugs that may cause renal toxicity is not recommended. Tenofovir does not appear to alter the pharmacokinetics of ribavirin, and there was no clinically significant pharmacokinetic interaction with rifampicin (rifampin) or tacrolimus.

Clinical evidence, mechanism, importance and management

(a) Cidofovir

Tenofovir is actively secreted by human organic anion transporter 1 (hOAT1) in the kidneys. Therefore, the manufacturers suggest that if it is given with other drugs that are also secreted by this renal transporter, such as cidofovir, increased levels of tenofovir or the other drug could result. In the UK, they specifically recommend that tenofovir and cidofovir are not given together, unless clearly necessary, when renal function should be monitored weekly.[1]

(b) Food

Administration of tenofovir with a high-fat meal increased its AUC by about 40%, and its maximum level by about 14%, when compared with the fasted state, whereas administration with a light meal had no effect.[1,2] The UK manufacturer recommends that tenofovir is taken with food,[1] whereas the US manufacturer states that it can be taken without regard to food.[2]

(c) NSAIDs

A case of acute tubular necrosis has been reported in an HIV-positive patient taking tenofovir 300 mg daily, ritonavir-boosted lopinavir 33/133 mg daily and lamivudine 300 mg daily when **diclofenac** was started 5 days earlier for limb pain. The patient had been stable on tenofovir for several years with no adverse effects on renal function, and the authors suggests that **diclofenac** affected the renal clearance of tenofovir leading to nephrotoxicity.[3] There is another report of three cases of renal failure with tenofovir. In all cases, the patients had multiple risk factors for developing

renal failure secondary to tenofovir; however, the addition of an NSAID (**indometacin** suppositories in one case, **naproxen** in the other two) lead to the development of acute renal failure. In one of these cases the patient died and another developed end stage renal failure requiring regular dialysis.[4] Ten cases[5] of nephrotoxicity with tenofovir (including 2 of the 3 cases noted above[4] as well as details of a patient who had recently started taking valdecoxib) have been reported to Health Canada between March 2003 and December 2005. Another report describes a possible exacerbation of tenofovir-induced renal failure by NSAIDs: **diclofenac** in one case, and **ibuprofen** and **rofecoxib** in the other.[6]

Tenofovir has the potential to cause nephrotoxicity, and renal function should be routinely monitored during use.[1] NSAIDs reduce renal blood flow and may also cause renal failure. From the cases reported above, it seems that NSAIDs may precipitate renal failure in patients taking tenofovir, particularly these with pre-existing risk factors or mild renal impairment. The manufacturers do not recommend the concurrent use of tenofovir with other drugs that cause renal failure. They also recommend avoiding the use of tenofovir in patients who have recently taken a nephrotoxic drug.[1,2] If concurrent use is unavoidable, they advise increasing the monitoring of renal function to weekly.[1]

(d) Other nephrotoxic drugs

Two cases of acute renal failure, which developed after intravenous **vancomycin** was given, have been reported in patients previously stable on tenofovir for 6 to 10 months.[7] Tenofovir has the potential to cause nephrotoxicity, and the manufacturer recommends monthly monitoring of renal function. Although the concurrent use of other nephrotoxic drugs has not been studied, the manufacturer suggests that renal function should be monitored more frequently (weekly) if concurrent use is unavoidable. The UK manufacturer specifically names **aminoglycosides**, **amphotericin B**, **cidofovir** (see above), **foscarnet**, **ganciclovir**, **interleukin-2**, **pentamidine** and **vancomycin**.[1] The US manufacturer specifically names **cidofovir**, **aciclovir**, **valaciclovir**, **ganciclovir**, and **valganciclovir**.[2] **NSAIDs** may also cause renal failure and cases of nephrotoxicity with tenofovir have been reported, see under *NSAIDs*, above.

(e) Ribavirin

Tenofovir disoproxil fumarate 300 mg daily did not alter the pharmacokinetics of a single 600-mg dose of ribavirin in 22 subjects, and the pharmacokinetics of tenofovir did not appear to be changed by ribavirin when compared with historical data.[8] Note that, there is evidence that HIV-positive patients co-infected with hepatitis C and treated with interferon alfa and ribavirin may be at increased risk of lactic acidosis and hepatic decompensation when receiving any 'NRTI', (p.956), including tenofovir, and increased monitoring is recommended.[1]

(f) Rifampicin (Rifampin)

In a study in 23 subjects, when rifampicin 600 mg daily was given with tenofovir disoproxil fumarate 300 mg daily, the pharmacokinetics of both drugs were not significantly changed (tenofovir compared with historical data). One subject who was withdrawn from the study had raised liver enzyme values.[9] The UK manufacturer notes that no clinically significant interaction occurs between rifampicin and tenofovir. Therefore no special precautions appear to be necessary on concurrent use.[1]

(g) Tacrolimus

In a study in healthy subjects taking a combination of **emtricitabine** 200 mg daily and tenofovir 300 mg daily alone or with tacrolimus 100 micrograms/kg daily, no clinically significant change in the pharmacokinetics of all three drugs was reported.[10] However, both tacrolimus and tenofovir have the potential to cause nephrotoxicity. The manufacturer of tenofovir recommends that renal function should be monitored more frequently (weekly) if concurrent use of other nephrotoxic drugs, such as tacrolimus, is unavoidable.[1]

1. Viread (Tenofovir disoproxil fumarate). Gilead Sciences Ltd. UK Summary of product characteristics, July 2009.
2. Viread (Tenofovir disoproxil fumarate). Gilead Sciences, Inc. US Prescribing information, October 2009.
3. Morelle J, Labriola L, Lambert M, Cosyns J-P, Jouret F, Jadoul M. Tenofovir-related acute kidney injury and proximal tubule dysfunction precipitated by diclofenac: a case of drug-drug interaction. Clin Nephrol (2009) 71, 567–70.
4. Marcotte S, Talbot A, Trottier B. Acute renal failure in four HIV-infected patients: potential association with tenofovir and nonsteroidal anti-inflammatory drugs. Can J Infect Dis Med Microbiol (2008) 19, 75–6.
5. McMorran M. Tenofovir (Viread) and NSAIDs: acute renal failure. *Can Adverse React News* (2006) 16, 1–2.
6. Parsonage MJ, Wilkins EGL, Snowden N, Issa BG, Savage MW. The development of hypophosphataemic osteomalacia with myopathy in two patients with HIV infection receiving tenofovir therapy. *HIV Med* (2005) 6, 341–6.
7. Psevdos G, Gonzalez E, Sharp V. Acute renal failure in patients with AIDS on tenofovir while receiving prolonged vancomycin course for osteomyelitis. AIDS Read (2009) 19, 235–8.
8. Ramanathan S, Cheng A, Mittan A, Ebrahimi R, Kearney BP. Absence of clinically relevant pharmacokinetic interaction between ribavirin and tenofovir in healthy subjects. *J Clin Pharmacol* (2006) 46, 559–66.
9. Droste JAH, Verweij-van Wissen CPWGM, Kearney BP, Buffels R, vanHorssen PJ, Hekster YA, Burger DM. Pharmacokinetic study of tenofovir disoproxil fumarate combined with rifampin in healthy volunteers. *Antimicrob Agents Chemother* (2005) 49, 680–4.
10. Chittick GE, Zong J, Begley JA, Alianti JR, Sorbel JJ, Blum MR. Pharmacokinetics of emtricitabine/tenofovir disoproxil fumarate and tacrolimus at steady state when administered alone or in combination. Int J Clin Pharmacol Ther (2008) 46, 627–36.

Vidarabine + Allopurinol

There is some evidence to suggest that if allopurinol and vidarabine (adenine arabinoside) are given together the toxicity of vidarabine may be increased.

Clinical evidence

Two patients with chronic lymphocytic leukaemia taking allopurinol 300 mg daily developed severe neurotoxicity (coarse rhythmic tremors of the extremities and facial muscles, and impaired mentation) 4 days after vidarabine was added for the treatment of viral infections.[1] A retrospective search to find other patients who had taken both drugs for 4 days revealed a total of 17 patients, 5 of whom had experienced adverse reactions including tremors, nausea, pain, itching and anaemia.[1] Another possible case report describes neurological toxicity in a patient taking both drugs.[2]

Mechanism

Uncertain. One suggestion is that the allopurinol causes hypoxanthine arabinoside, the major metabolite of vidarabine, to accumulate by inhibiting xanthine oxidase. A study with *rat* liver cytosol found that allopurinol greatly increased the half-life of this metabolite.[3]

Importance and management

Information seems to be limited to these reports, and so the general clinical importance of this possible interaction is uncertain, but it would be prudent to exercise particular care if these drugs are used together.

1. Friedman HM, Grasela T. Adenine arabinoside and allopurinol – possible adverse drug interaction. *N Engl J Med* (1981) 304, 423.
2. Collignon PJ, Sorrell TC. Neurological toxicity associated with vidarabine (adenine arabinoside) therapy. *Aust N Z J Med* (1983) 13, 627–9.
3. Drach JC, Rentea RG, Cowen ME. The metabolic degradation of 9-β-D-arabinofuranosyladenine (ara-A) *in vitro*. *Fedn Proc* (1973) 32, 777.

22

Beta blockers

The adrenoceptors of the sympathetic nervous system are of two main types, namely alpha and beta. Drugs that block the beta adrenoceptors (better known as the beta blockers) are therapeutically exploited to reduce, for example, the normal sympathetic stimulation of the heart. The activity of the heart in response to stress and exercise is reduced, its consumption of oxygen is diminished, and in this way exercise-induced angina can be managed. Beta blockers given orally can also be used in the management of cardiac arrhythmias, hypertension, myocardial infarction, and heart failure. They may also be used for some symptoms of anxiety and for migraine prophylaxis. Some beta blockers are used in the form of eye drops for glaucoma and ocular hypertension.

Not all beta receptors are identical but can be further subdivided into two groups, $beta_1$ and $beta_2$. The former are found in the heart and the latter in the bronchi. Since one of the unwanted adverse effects of generalised beta blockade can be the loss of the normal noradrenaline-stimulated bronchodilation (leading to bronchospasm), cardioselective $beta_1$-blocking drugs (e.g. atenolol, metoprolol) were developed, which have less effect on $beta_2$ receptors. However, it should be emphasised that the selectivity is not absolute because bronchospasm can still occur with these drugs, particularly at high doses. 'Table 22.1', (below) includes an indication of the cardioselectivity of commonly used systemic beta blockers. Some beta blockers also have $alpha_1$-blocking activity, which causes vasodilatation, and this is also indicated in 'Table 22.1', (below). Some beta blockers, such as celiprolol and nebivolol, also have vasodilator activity but produce this by mechanisms other than blocking $alpha_1$ receptors. Other beta blockers also possess intrinsic sympathomimetic activity in that they can *activate* beta receptors and are therefore partial agonists. Sotalol has additional class III antiarrhythmic activity, and therefore it has a range of interactions not shared by most other beta blockers.

Beta blockers may be lipophilic drugs (such as metoprolol) or hydrophilic (such as atenolol). The lipophilic beta blockers are more likely to be involved in pharmacokinetic interactions than the hydrophilic drugs. Many of the lipophilic beta blockers are principally metabolised by the cytochrome P450 isoenzyme CYP2D6 (see 'Table 22.1', (below)), and drugs that are inhibitors or inducers of this isoenzyme (see 'Table 1.3', (p.6)) increase or decrease their levels. Propranolol is also metabolised in part by CYP1A2 (see 'Beta blockers + SSRIs', p.1019).

Beta blockers may also be involved in pharmacodynamic interactions with other drugs that are based on enhancement or antagonism of pharmacological effects (such as additive blood pressure reduction).

This section is generally concerned with those drugs that affect the activity of the beta blockers. Where the beta blocker is the affecting drug, the interaction is dealt with elsewhere.

Table 22.1 The actions and metabolism of widely used systemic beta blockers

Drug	*$Beta_1$-receptor selectivity*	*Alpha-blocking activity?*	*ISA**	*Lipophilicity*	*Bioavailability*	*First pass metabolism*	*Metabolism*
Acebutolol	Selective	No	Yes (weak)	Hydrophilic	50 to 70%	30 to 50%	Rapidly metabolised to an active metabolite after which about 50% is excreted by the liver and 50% excreted in the urine.
Atenolol	Selective	No	No	Hydrophilic	40 to 50%	Less than 10%	Largely excreted unchanged in the urine.
Bisoprolol	Selective	No	No	Intermediate	88%	Less than 10%	50% hepatic metabolism and 50% excreted unchanged in the urine.
Carvedilol	Non-selective	Yes ($alpha_1$)	No	Lipophilic	25 to 35%	60 to 80%	Primarily metabolised by CYP2D6, although other isoenzymes do contribute.
Celiprolol	Selective	Yes (weak $alpha_2$)	Yes	Hydrophilic	30 to 70%	Little	Mostly excreted unchanged (only 1-3% metabolised) with 50% excreted in the bile and 50% excreted in the urine.
Esmolol	Selective	No	No	Relatively hydrophilic	N/A	Extensive	Rapidly hydrolysed in red blood cells (half-life 9 minutes).
Labetalol	Non-selective	Yes (postsynaptic $alpha_2$)	No	Moderately lipophilic	25 to 40%	Extensive	Conjugated in the liver.
Metoprolol	Selective	No	No	Lipophilic	50%	About 40 to 60%	Metabolised by CYP2D6.
Nadolol	Non-selective	No	No	Hydrophilic	20 to 40%	Little	Largely excreted unchanged in the urine.
Nebivolol	Selective	No	No		12 to 96%	Extensive	Metabolised by CYP2D6.
Oxprenolol	Non-selective	No	Yes	Lipophilic	19 to 74%	25 to 80%	Extensively metabolised by the liver.
Pindolol	Non-selective	No	Yes	Moderately lipophilic	90 to 100%	Little	30 to 40% excreted unchanged in the urine, rest excreted by liver and kidney as inactive metabolites.
Propranolol	Non-selective	No	No	Lipophilic	30 to 70%	Up to 95%	Mainly metabolised by CYP2D6 with some contribution by CYP1A2.
Sotalol	Non-selective	No	No	Hydrophilic	75 to 90%	None	Largely excreted unchanged in the urine.
Timolol	Non-selective	No	No	Lipophilic	61%	About 50 to 70%	Mostly metabolised by the liver, with some involvement from CYP2D6. 20% excreted unchanged. Timolol and metabolites renally excreted.

*Intrinsic sympathomimetic activity (partial agonists)

Beta blockers + 5-Alpha reductase inhibitors

Finasteride and dutasteride do not appear to interact with beta blockers.

Clinical evidence, mechanism, importance and management

In a study in healthy subjects, **finasteride** 5 mg daily for 10 days caused no change in the pharmacokinetics or pharmacodynamics of a single 80-mg dose of **propranolol**.[1] Further, the manufacturers say that **finasteride** was used with beta blockers in clinical studies without any evidence of an interaction.[2,3] Similarly, **dutasteride** does not appear to interact with beta blockers.[4]

1. Gregoire S, Williams R, Gormely G, Lin E. Effect of finasteride (Mk-906), a new potent 5 alpha reductase inhibitor on the disposition of D and L-propranolol. *J Clin Pharmacol* (1990) 30, 847.
2. Proscar (Finasteride). Merck Sharp & Dohme Ltd. UK Summary of product characteristics, March 2008.
3. Proscar (Finasteride). Merck & Co., Inc. US Prescribing information, March 2007.
4. GlaxoSmithKline, Personal communication, August 2003.

Beta blockers + Antacids or Kaolin-pectin

Some antacids and kaolin-pectin may cause a modest reduction in the absorption of atenolol, indenolol, propranolol, or sotalol, and possibly a slight increase in the absorption of metoprolol.

Clinical evidence

(a) Atenolol

In a study in 6 healthy subjects, **aluminium hydroxide** 5.6 g reduced the plasma levels of a single 100-mg dose of atenolol by 20%, which had no effect on the atenolol-induced reduction in exercising heart rate. Similarly, **aluminium hydroxide** had no significant effect on atenolol pharmacokinetics when both drugs were given together for 6 days.[1] Another study in 6 healthy subjects found that 30 mL of *Novalucol forte* (an **aluminium/magnesium-containing antacid**) reduced the peak plasma level and AUC of a single 100-mg dose of atenolol by 37% and 33%, respectively, which was considered to be of possible significance in some patients.[2]

In a study in 6 healthy subjects a single 500-mg dose of **calcium** (as the lactate, gluconate and carbonate) caused a 51% reduction in the peak plasma level of a single 100-mg dose of atenolol. **Calcium** also reduced the AUC of atenolol by 32%, and increased the elimination half-life from 6.2 to 11 hours. The effect of atenolol on heart rate was decreased by 12%. However, these changes were no longer statistically significant after 6 days of concurrent use, except for a 21% reduction in peak plasma atenolol levels, which would not be expected to be clinically relevant. In a further 6 hypertensive subjects, neither **calcium** 500 mg daily nor **aluminium hydroxide** 5.6 g daily had any influence on the blood pressure lowering effect of atenolol 100 mg daily, given for 4 weeks.[1]

(b) Indenolol

A study in *rats* found that when indenolol was given with either *Simeco* (**aluminium/magnesium hydroxide** with **simeticone**) or *Kaopectate* (**kaolin-pectin**), the $AUC_{0\text{-}6}$ was reduced by 15% and 30%, respectively.[3]

(c) Metoprolol

In 6 healthy subjects, 30 mL of *Novalucol forte* (an **aluminium/magnesium-containing antacid**) increased the peak plasma level and AUC of a single 100-mg dose of metoprolol by 25% and 11%, respectively.[2]

(d) Propranolol

In a study in 6 healthy subjects, **aluminium hydroxide gel** 30 mL did not affect either the plasma level of a single 40-mg dose of propranolol, or the reduction in exercise heart rate in response to propranolol.[4] In contrast, a study in 5 healthy subjects found that 30 mL of an **aluminium hydroxide gel** reduced the levels and AUC of a single 80-mg dose of propranolol by almost 60%.[5] *In vitro* and *animal* data suggest that **bismuth subsalicylate**, **kaolin-pectin** and **magnesium trisilicate** can also reduce the absorption of propranolol.[6,7]

(e) Sotalol

A study in 5 healthy subjects found that single doses of **aluminium hydroxide** suspension (*Neutragel*) or **calcium carbonate** suspension, given after an overnight fast, had negligible effects on the pharmacokinetics of a single 160-mg dose of sotalol.[8] However, a single dose of **magnesium hydroxide** slightly reduced the AUC of sotalol by 16%.[8] A further study in 6 healthy subjects found that when 20 mL of *Maalox* (**aluminium/magnesium hydroxide**) was given at the same time as 160 mg of sotalol, the maximum plasma level of the sotalol was reduced by 26% and its AUC was reduced by 21%. Changes in heart rates reflected these pharmacokinetic changes.[9] No interaction occurred when *Maalox* was given 2 hours after sotalol.[9]

Mechanism

Uncertain. The reduction in absorption could possibly be related to a delay in gastric emptying caused by the antacid, delayed dissolution due to an increase in gastric pH, or to the formation of a complex of the two drugs in the gut, which reduces absorption. However, one *in vitro* study indicated that sotalol was only subject to minor absorption or complexation interactions.[9] Another study found that 35 to 40% of sotalol was bound by magnesium hydroxide, but this may be reversible under physiological conditions and therefore unlikely to be relevant during long-term clinical use.[8]

Importance and management

Evidence for an interaction between antacids and beta blockers is generally limited, and largely confined to *animal* or single-dose studies, which may not reflect the situation with multiple dosing. Indeed, one study with atenolol and aluminium hydroxide found a modest pharmacokinetic interaction with single doses, but no interaction after 6 days of concurrent use. Some changes in beta blocker absorption may possibly occur but no study seems to have shown that there is a significant effect on the therapeutic effectiveness of the beta blockers with multiple dosing. However, it may be prudent to consider an interaction if the effects of beta blockers are reduced, especially during the initial stages of concurrent use. Separating the dosages by 2 hours was shown to avoid the interaction in one study with sotalol,[9] and this would seem a simple way of avoiding problems should they occur.

1. Kirch W, Schäfer-Korting M, Axthelm T, Köhler H, Mutschler E. Interaction of atenolol with furosemide and calcium and aluminium salts. *Clin Pharmacol Ther* (1981) 30, 429–35.
2. Regårdh CG, Lundborg P, Persson BA. The effect of antacid, metoclopramide and propantheline on the bioavailability of metoprolol and atenolol. *Biopharm Drug Dispos* (1981) 2, 79–87.
3. Tariq M, Babhair SA. Effect of antacid and antidiarrhoeal drugs on the bioavailability of indenolol. *IRCS Med Sci* (1984) 12, 87–8.
4. Hong CY, Hu SC, Lin SJ, Chiang BN. Lack of influence of aluminium hydroxide on the bioavailability and beta-adrenoceptor blocking activity of propranolol. *Int J Clin Pharmacol Ther Toxicol* (1985) 23, 244–6.
5. Dobbs JH, Skoutakis VA, Acchardio SR, Dobbs BR. Effects of aluminium hydroxide on the absorption of propranolol. *Curr Ther Res* (1977) 21, 887–92.
6. Moustafa MA, Gouda MW, Tariq M. Decreased bioavailability of propranolol due to interactions with adsorbent antacids and antidiarrhoeal mixtures. *Int J Pharmaceutics* (1986) 30, 225–8.
7. McElnay JC, D'Arcy PF, Leonard JK. The effect of activated dimethicone, other antacid constituents, and kaolin on the absorption of propranolol. *Experientia* (1982) 38, 605–7.
8. Kahela P, Anttila M, Sundqvist H. Antacids and sotalol absorption. *Acta Pharmacol Toxicol (Copenh)* (1981) 49, 181–3.
9. Läer S, Neumann J, Scholz H. Interaction between sotalol and an antacid preparation. *Br J Clin Pharmacol* (1997) 43, 269–72.

Beta blockers + Anticholinesterases

A small number of reports describe marked bradycardia and hypotension during the recovery period from anaesthesia and neuromuscular blockade, when patients taking beta blockers were given anticholinesterase drugs. However, normally no adverse reaction seems to occur. Note that oral and topical beta blockers given alone have caused myasthenic symptoms and myasthenia gravis in some patients.

Clinical evidence

(a) Anticholinesterase effects

Three patients developed myasthenic symptoms when given beta blockers (two taking **propranolol** and one taking **oxprenolol**). Two of them were effectively treated with **pyridostigmine**.[1] Another patient developed fulminant myasthenia gravis within 2 weeks of starting to take **acebutolol**.[2]

Similarly, in a patient with myasthenia gravis, the use of **timolol** eye drops was associated with a deterioration in muscle strength,[3] and in another patient, a serious deterioration in myasthenia.[4] These would appear to be drug-disease effects.

In a study in 10 myasthenic patients with mild to moderate symptoms, intravenous **propranolol** 100 micrograms/kg did not result in a worsening of neuromuscular transmission (assessed by muscle function tests and repetitive nerve stimulation), even though 8 of those with mild symptoms had reduced their **pyridostigmine** dose during the study to allow the effects of the additional drug to be more readily seen.[5]

(b) Bradycardia

1. Neostigmine. A study in 10 patients with severe hypertension due to renal ischaemia who were treated with **propranolol** 10 to 36 mg/kg daily (or equivalent doses of **oxprenolol** or **labetalol**) found that during surgery neostigmine consistently reduced heart rates to below 45 bpm despite atropinisation.[6] A patient taking **nadolol** 40 mg daily, recovering from surgery during which suxamethonium (succinylcholine) and pancuronium had been given, developed prolonged bradycardia of 32 to 36 bpm and hypotension (systolic blood pressure 60 to 70 mmHg) when neostigmine and atropine were given to reverse the neuromuscular blockade. Isoprenaline and phenylephrine infusions were required to maintain a systolic blood pressure of 90 mmHg, and were gradually reduced over 3 days. **Propranolol** was substituted for **nadolol**, and about 10 weeks later the patient underwent general anaesthesia again (this time without a neuromuscular blocker/neostigmine) and she recovered uneventfully.[7] Prolonged bradycardia and hypotension, requiring isoprenaline then adrenaline (epinephrine), were seen in an elderly woman taking **atenolol** 50 mg daily and nitrates when she was given neostigmine and atropine for the reversal of muscle relaxation at the end of general anaesthesia.[8] Another report similarly describes bradycardia in a patient taking **propranolol** when intravenous neostigmine was used to reverse pancuronium-induced blockade. This responded to atropine.[9]

2. Physostigmine. A patient taking **propranolol** 20 mg twice daily, recovering from surgery during which alcuronium had been used, received glycopyrronium and **neostigmine** without any change in heart rate. However, one hour later he developed severe bradycardia (a fall from 65 to 40 bpm) and hypotension (systolic blood pressure 70 mmHg) when given intravenous physostigmine 2 mg over 5 minutes, for extreme drowsiness attributed to the premedication. His symptoms responded to glycopyrronium.[10]

3. Pyridostigmine. A study in 8 hypertensive patients taking long-term **atenolol** or **propranolol** found no significant changes in heart rate and no serious adverse reactions when they were given low-dose oral pyridostigmine 30 mg three times daily for 2 days.[11]

Mechanism

It would appear that the bradycardic effects of the beta blockers and the acetylcholine-like effects of these anticholinesterase drugs can be additive. These were inadequately controlled by the use of atropine in some of the instances cited. The myasthenic symptoms may be due to beta blockers exerting a depressant effect on the neuromuscular junction.[2,3]

Importance and management

The information available indicates that marked adverse reactions between beta blockers and anticholinesterases after surgery are uncommon, but be aware of the possibility of an interaction if a patient becomes bradycardic or hypotensive shortly after surgery.

Limited information suggests that beta blockers given orally or topically could, in some cases, oppose the efficacy of anticholinesterases in the treatment of myasthenia gravis. However, one study suggests that not all patients are affected. Strictly speaking this is a drug-disease rather than a drug-drug interaction.

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Beta blockers + Anticholinesterases; Centrally acting

The concurrent use of centrally-acting anticholinesterases and beta blockers may increase the risk of bradycardia.

Clinical evidence, mechanism, importance and management

An analysis of the French Pharmacovigilance Database for adverse drug reactions involving a centrally-acting anticholinesterase (**donepezil**, **galantamine** and **rivastigmine**), up to March 2006, found 83 potential drug interactions between anticholinesterases and beta blockers. Of these, 33 were thought to have caused adverse drug reactions, including syncope, bradycardia, arrhythmia or cardiac arrest. The concurrent use of a centrally-acting anticholinesterase drug and a drug with bradycardic effects resulted in 5 fatalities; however, it is unclear if any of these cases involved a beta blocker.[1]

It would appear that the effects of these centrally-acting anticholinesterases on heart rate can be additive with those of the beta blockers, sometimes resulting in a dramatic slowing of the heart. Be alert for bradycardia if a beta blocker is given with **donepezil**, **galantamine** or **rivastigmine**. The effects of **tacrine** do not appear to have been studied, but it would be expected to interact similarly.

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Beta blockers + Aspirin or NSAIDs

There is evidence that most NSAIDs can increase blood pressure in patients taking antihypertensives, although some studies have not found the increase to be clinically relevant. Similarly, multiple-dose aspirin, both in high and low dose, did not reduce the efficacy of antihypertensives including beta blockers in three studies. However, various small studies, have found some evidence of reduced beta blocker effects, either for hypertension or heart failure, in patients given NSAIDs including indometacin, piroxicam, ibuprofen and naproxen, or aspirin. Isolated case reports also describe hypertension in patients taking a beta blocker and an NSAID.

Celecoxib may decrease the metabolism of metoprolol, but in general the NSAIDs do not significantly affect the pharmacokinetics of the beta blockers.

Clinical evidence

Various large epidemiological studies and meta-analyses of clinical studies have been conducted to assess the effect of NSAIDs on blood pressure in patients taking **antihypertensives**, and the findings of these are summarised in 'Table 23.2', (p.1027). In these studies, NSAIDs were not always associated with an increase in blood pressure, and the maximum increase was 6.2 mmHg. The effect has been shown for both COX-2 inhibitors and non-selective NSAIDs. In two meta-analyses,[1,2] the effects were evaluated by NSAID. The confidence intervals for all the NSAIDs overlapped, showing that there was no statistically significant difference between the NSAIDs, with the exception of the comparison between **indometacin** and **sulindac** in one analysis.[1] Nevertheless, an attempt was made at ranking the NSAIDs based on the means. In one analysis,[1] the effect was greatest for **piroxicam**, **indometacin**, and **ibuprofen**, intermediate for **naproxen**, and least for **sulindac** and **flurbiprofen**. In the other meta-analysis,[2] the effect was greatest for **indometacin** and **naproxen**, intermediate for **piroxicam**, and least for **ibuprofen** and **sulindac**. An attempt was also made to evaluate the effect by **antihypertensive** in one analysis.[1] The

mean effect was greatest for beta blockers, intermediate for vasodilators (includes ACE inhibitors and calcium-channel blockers), and least for diuretics. However, the differences between the groups were not significant.

The findings of individual clinical and pharmacological studies that have studied the effects of aspirin or specific NSAIDs on beta blockers are outlined in the subsections below.

(a) Aspirin and other salicylates

A small study in patients taking various antihypertensives (including beta blockers and diuretics) found that aspirin, in both low doses (650 mg daily) and high doses (3.9 g daily) for 3 or 4 weeks, did not cause clinically significant increases in blood pressure.[3] Similarly, a study in 11 patients taking a number of antihypertensives (which included a few patients taking **propranolol** or **pindolol**) found that aspirin 650 mg three times daily for 7 days did not affect the control of blood pressure.[4] In contrast, another study found that 5 g of aspirin given over 24 hours prevented the antihypertensive effects of a single 1-mg intravenous dose of **pindolol**, and a single 1- to 1.5-g dose of aspirin reduced the antihypertensive effect of a single 5-mg intravenous dose of **propranolol**.[5] Aspirin was reported not to affect the control of hypertension by **metipranolol**.[6] A retrospective study of patients with heart failure taking **carvedilol** found that aspirin did not significantly affect systolic blood pressure or heart rate but did observe that left ventricular ejection fraction improved less in those patients taking aspirin in addition to **carvedilol** The effect appeared to be dose-related.[7]

A single-dose study in 6 healthy subjects found that aspirin 500 mg did not affect the pharmacokinetics of **atenolol**.[8] Another study in 6 healthy subjects found that aspirin did not affect the pharmacokinetics of **metoprolol**, but the maximum plasma levels of aspirin were increased by **metoprolol**, although this was not considered to be clinically relevant.[9]

Sodium salicylate did not affect either the pharmacokinetics of **alprenolol** or its effects on heart rate and blood pressure during exercise in a single-dose study in healthy subjects.[10] **Imidazole salicylate** did not affect the blood pressure control of patients treated with **atenolol**.[11]

(b) Celecoxib

In a randomised, crossover study in 12 healthy subjects, celecoxib 200 mg twice daily for 7 days increased the AUC of a single 50-mg dose of **metoprolol** by 64%.[12]

(c) Diclofenac

A study in 16 patients taking **atenolol**, **metoprolol**, **propranolol** or **pindolol** and/or a diuretic found that diclofenac 50 mg three times daily had no effect on the control of blood pressure.[13]

(d) Flurbiprofen

A study in 10 patients with hypertension found that flurbiprofen 100 mg daily for 7 days did not affect the pharmacokinetics of single-doses of either **propranolol** 80 mg or **atenolol** 100 mg. However, the hypotensive effects of **propranolol** were reduced by the flurbiprofen, whereas those of **atenolol** were not affected.[14]

(e) Ibuprofen

In a randomised study in 6 hypertensive patients treated with thiazides and beta blockers, ibuprofen 400 mg every 8 hours caused significant increases in blood pressure (mean increases of about 5 to 7 mmHg)[15] The antihypertensive effect of **pindolol** was antagonised by ibuprofen in one patient.[16] However, in one randomised controlled study, ibuprofen 400 mg four times daily had no effect on the control of blood pressure in patients taking **propranolol**.[17]

(f) Indometacin

A study found that when indometacin 25 mg three times daily was given to hypertensive patients taking thiazides with or without beta blockers, their blood pressure increased by 8 to 10 mmHg.[3] The diastolic blood pressures of 7 hypertensive patients treated with **pindolol** 15 mg daily or **propranolol** 80 to 160 mg daily rose from 82 to 96 mmHg when they were given indometacin 100 mg daily over a 10-day period. Changes in systolic pressures were not statistically significant.[18]

In another study, indometacin 50 mg twice daily raised the blood pressure of patients taking **propranolol** 60 to 320 mg daily by 14/5 mmHg when lying and 16/9 mmHg when standing.[19] This interaction has also been seen in other studies in patients taking **atenolol**,[11,20,21] **labetalol**,[22] **metipranolol**,[6] **oxprenolol**,[23,24] and **propranolol**.[4,25] Two women with pre-eclampsia taking **propranolol** or **pindolol** became markedly hypertensive (rises in blood pressure from 135/85 to 240/140 mmHg, and from 130/70 to 230/130 mmHg, respectively) within 4 to 5 days of being given indometacin to inhibit premature contractions.[26]

(g) Naproxen

A study in hypertensive patients taking **timolol** and hydrochlorothiazide with amiloride found that naproxen 250 mg twice daily caused a 4 mmHg rise in diastolic blood pressure, but did not significantly increase systolic blood pressure.[27] Similarly, in another study, naproxen 500 mg twice daily caused an average 4 mmHg rise in systolic blood pressure in patients taking **atenolol**, but did not significantly increase diastolic blood pressure.[28] In contrast, another study found that naproxen caused no changes in hypertension controlled with **propranolol**,[29] and a study in patients taking antihypertensives [drugs not specified] found that naproxen did not cause clinically significant increases in blood pressure.[3] A case report describes one patient taking **propranolol** who had a marked rise in blood pressure when given naproxen.[30]

(h) Oxaprozin

A study in 32 hypertensive arthritic patients found that oxaprozin 1.2 g daily for 4 weeks did not affect the antihypertensive effects of **metoprolol** 100 mg twice daily, although at 2 weeks there was a significant increase in systolic blood pressure.[31]

(i) Parecoxib

In a randomised, crossover study, 15 healthy subjects were given a single 50-mg dose of **metoprolol** after taking valdecoxib (the main metabolite of parecoxib) 20 mg daily for 7 days. The AUC and maximum levels of **metoprolol**, and its effect of on heart rate were unchanged by the NSAID.[32]

(j) Piroxicam

A double-blind study found that about one-quarter of the patients given piroxicam 20 mg daily and **propranolol** 80 to 160 mg daily developed diastolic pressure rises of 10 mmHg or more when lying or standing.[33,34] Increases in both systolic and diastolic pressures (8.1/5.2 mmHg lying and 8.5/8.9 mmHg standing) were seen in another study in 3 patients.[35] In contrast, patients taking **propranolol** and piroxicam 20 mg daily had blood pressure rises of 5.8/2.4 mmHg when lying and 3.5/0.5 mmHg when standing, after 2 weeks, but these increases were not statistically significant.[36] Blood pressure showed a trend towards higher levels in another study in 20 patients given **timolol** and piroxicam 20 mg daily.[27]

A study in 6 healthy subjects given **atenolol** 100 mg daily and piroxicam 20 mg daily for 7 days found no pharmacokinetic interaction. An associated study in another 6 healthy subjects given **metoprolol** 100 mg twice daily and piroxicam 20 mg daily for 7 days found that **metoprolol** levels were increased by piroxicam, but not to a statistically significant extent.[37]

(k) Sulindac

Sulindac 200 mg twice daily had little or no effect on the control of hypertension in patients taking hydrochlorothiazide with amiloride and **atenolol**, **metoprolol**, **propranolol** or **pindolol**.[13] In another study, diastolic blood pressure was slightly and significantly lower when sulindac was given with **timolol**.[27] No statistically significant rises in blood pressure occurred in other studies in patients taking **propranolol**[29,33-35] or **atenolol**[21,28] or unspecified antihypertensives[3] given sulindac 200 mg twice daily. In contrast, another study claimed that patients given **propranolol** with sulindac 200 mg twice daily had blood pressure rises of 10.3/4.8 mmHg when standing and 2.4/7.1 mmHg when lying, after 2 weeks, but only the increase in standing systolic blood pressure statistically significant.[36] Similarly, a crossover study in 26 hypertensive patients taking **labetalol** found that sulindac 200 mg twice daily for 7 days raised the mean systolic blood pressure by 6 mmHg when sitting, and by 9 to 14 mmHg when standing, which was considered potentially clinically significant. Diastolic pressures were not affected.[22]

(l) Tenoxicam

In one study, the control of hypertension in 16 patients taking **atenolol** was not affected by tenoxicam 40 mg daily.[38]

Mechanism

Indometacin alone can raise blood pressure (13 hypertensive patients given indometacin 150 mg daily for 3 days had a mean systolic blood pressure rise from 118 mmHg to 131 mmHg).[39] One suggested reason is that indometacin inhibits the synthesis and release of two prostaglandins (PGA and PGE), which have a potent dilating effect on peripheral arterioles throughout the body. In their absence the blood pressure rises. Thus the hypotensive actions of the beta blockers are opposed by the hypertensive actions of indometacin. This mechanism has been questioned and it is possible that other physiological and pharmacological mechanisms have a

part to play.[3,40,41] One study found that although indometacin caused increases in blood pressure in treated hypertensive patients, other inhibitors of prostaglandin synthesis (aspirin, naproxen and sulindac) did not.[3] Further, all four drugs caused similar reductions in plasma renin activity and aldosterone concentration, which suggests that the effect of indometacin on blood pressure may not be dependent on such changes.[3]

Celecoxib inhibits the metabolism of metoprolol by the cytochrome P450 isoenzyme CYP2D6.[12]

Importance and management

Overall, the evidence suggests that some patients taking beta blockers can have a rise in blood pressure when given an NSAID, but this may not always be clinically relevant. Some consider that the use of NSAIDs should be kept to a minimum in patients taking antihypertensives.[42] The effects may be greater in the elderly and in those with blood pressures that are relatively high, as well as in those with high salt intake.[42] However, others consider that the clinical importance of an interaction between NSAIDs and antihypertensives is less than has previously been suggested.[43] While their findings do not rule out a 2/1 mmHg increase in blood pressure with NSAIDs in treated hypertensives, they suggest that if patients in primary care have inadequate control of blood pressure, other reasons (such as 'white-coat hypertension', poor adherence to treatment, or disease progression) may be more likely than any effect of concurrent NSAIDs.[43] There is insufficient data at present to clearly differentiate between NSAIDs, although there is some evidence that the effects of indometacin are greatest and those of sulindac least.

For the effects of NSAIDs on other antihypertensive drug classes see 'ACE inhibitors', (p.32), 'calcium-channel blockers', (p.1027) and 'thiazide diuretics', (p.1138).

A few multiple-dose studies have not found **aspirin** to alter the antihypertensive effect of beta blockers, even in high doses, but one single-dose high-dose study reported an interaction. Another study suggested that aspirin might attenuate the benefit of carvedilol in heart failure, but the evidence is currently too slim to warrant a change in practice.

Although **celecoxib** increased the levels of metoprolol, increases in plasma metoprolol levels of this size are unlikely to be clinically relevant in most patients. Those most at risk would be patients with heart failure, in whom the use of NSAIDs should generally be avoided.

Parecoxib (which is rapidly hydrolysed to valdecoxib) at low daily doses does not appear to interact with metoprolol. Nevertheless, the authors of the study suggest that the possibility of an interaction with higher doses cannot been excluded,[32] and the manufacturers of parecoxib suggest that caution is warranted.[44] However, the lack of interaction with low-dose parecoxib would seem to imply that higher doses would only have a moderate effect, if any, on metoprolol metabolism. Furthermore, metoprolol is generally considered to have a wide therapeutic index and therefore a very large rise in levels would be necessary for the interaction to become clinically relevant. The exception may be heart failure, where the beta blockers are considered to be narrow therapeutic index, but it should be noted that NSAIDs should generally be avoided in those with heart failure.

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Beta blockers + Barbiturates

The plasma levels and the effects of beta blockers that are mainly metabolised by the liver (e.g. alprenolol, metoprolol, timolol) are reduced by the barbiturates. Alprenolol concentrations are halved by pentobarbital, but metoprolol is less affected.

Clinical evidence

(a) Pentobarbital

In a study in 6 hypertensive patients, pentobarbital 100 mg daily for 10 days at bedtime reduced the plasma levels of **alprenolol** 400 mg twice daily by 59%. On day 11, the mean pulse rate at rest had risen from 70 to 74 bpm and blood pressure had risen from 134/89 to 145/97 mmHg. The changes were seen within 4 to 5 days of starting the barbiturate, and decreased within 8 to 9 days of stopping it.[1] These results are similar to

those found in previous studies by the same research group using pentobarbital 100 mg daily in healthy subjects.[2,3] In one of these studies, pentobarbital reduced the plasma levels of a single 200-mg dose of **alprenolol** by 38%, 90 minutes after the **alprenolol** was given, and reduced its AUC by 43%. The elimination half-life of **alprenolol** was unchanged. There was also a 20% reduction in the effects of the beta blocker on heart rate during exercise.[3] In the other study, the AUC of oral **alprenolol** was reduced by about 80% by pentobarbital, but that of intravenous **alprenolol** was unaffected.[2]

Another study in 8 healthy subjects found that pentobarbital 100 mg daily for 10 days reduced the AUC of **metoprolol** 100 mg by 32% (range 2 to 46%).[4]

(b) Phenobarbital

In a study in 12 healthy subjects phenobarbital 100 mg daily for 7 days reduced the AUC of **timolol** by 24%, but this was not statistically significant.[5]

Mechanism

Barbiturates are potent liver enzyme inducers that can increase the metabolism and clearance of other drugs from the body. Beta blockers that are removed from the body principally by liver metabolism (e.g. alprenolol, metoprolol, timolol) can therefore possibly be cleared more quickly in the presence of a barbiturate.

Importance and management

The interaction between alprenolol and pentobarbital is well documented and likely to be of modest clinical importance when the beta blocker is being used to treat hypertension, and possibly angina. Monitor the effects of alprenolol and increase the dose as necessary. Where possible it may be preferable to replace the barbiturate with a non-interacting alternative, such as one of the 'benzodiazepines', (p.843), which only have minor effects on the beta blockers. Alternatively, consider using a different beta blocker. Those that are not hepatically metabolised (see 'Table 22.1', (p.995)) would not be expected to interact, but note that this does not appear to have been studied.

A reduced response is possible if any of the beta blockers that are extensively metabolised (see 'Table 22.1', (p.995)) are given with pentobarbital, but the effects on the AUC of metoprolol appear to be smaller than the effects on alprenolol. Detailed information about the clinical importance of this interaction is largely lacking, but seems likely to be minor. However, if a problem does occur consider the alternative measures suggested for alprenolol, above.

Evidence is largely lacking, but all barbiturates would be expected to interact similarly, although the extent of the interaction may vary. For example, the interaction between phenobarbital and timolol was not statistically significant, and a clinically relevant effect is unlikely.

1. Seideman P, Borg K-O, Haglund K, von Bahr C. Decreased plasma concentrations and clinical effects of alprenolol during combined treatment with pentobarbitone in hypertension. *Br J Clin Pharmacol* (1987) 23, 267–71.
2. Alvan G, Piafsky K, Lind M, von Bahr C. Effect of pentobarbital on the disposition of alprenolol. *Clin Pharmacol Ther* (1977) 22, 316–21.
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Beta blockers + Bile-acid binding resins

Although both colestyramine and colestipol can moderately reduce the absorption of propranolol, this does not seem to reduce its effects. Colesevelam does not appear to affect the absorption of metoprolol.

Clinical evidence

(a) Colesevelam

A single-dose study in 33 healthy subjects found that colesevelam 4.5 g did not cause a clinically relevant alteration in the plasma levels of sustained-release **metoprolol** 100 mg.[1]

(b) Colestipol

When 6 healthy subjects took a single 120-mg dose of **propranolol** with a 10-g dose of colestipol the peak plasma **propranolol** levels were *raised* by 30%. However, if an additional 10 g dose of colestipol was taken 12 hours before the **propranolol** the peak plasma levels were decreased by 36% and the AUC was reduced by about 30%. No changes in blood pressure or pulse rates were seen.[2]

(c) Colestyramine

When 6 healthy subjects took a single 120-mg dose of **propranolol** with an 8-g dose of colestyramine the peak **propranolol** plasma levels were reduced by almost 25% and the AUC was reduced by 13%. An additional dose of colestyramine 12 hours before the **propranolol** reduced the AUC by 43%. However, no changes in blood pressure or pulse rate were seen.[2] Preliminary results of another study found that colestyramine (single unstated dose) caused no significant changes in the blood levels of **propranolol** in 5 patients with type II hyperlipidaemia taking **propranolol** 40 mg four times daily.[3]

Mechanism

Uncertain. It seems probable that both colestyramine and colestipol can, to some extent, bind to propranolol in the gut, thereby modestly reducing its absorption.

Importance and management

Information is limited. Even though both colestyramine and colestipol can modestly reduce the absorption of a single dose of propranolol, no changes in its effects were reported,[2] suggesting that the interaction is of minimal clinical importance. There is therefore no obvious reason for avoiding concurrent use. However, note that it is usually recommended that other drugs are given 1 hour before or 4 to 6 hours after colestyramine, and 1 hour before or 4 hours after colestipol.

1. Donovan JM, Stypinski D, Stiles MR, Olson TA, Burke SK. Drug interactions with colesevelam hydrochloride, a novel, potent lipid-lowering agent. *Cardiovasc Drugs Ther* (2000) 14, 681–90.
2. Hibbard DM, Peters JR, Hunninghake DB. Effects of cholestyramine and colestipol on the plasma concentrations of propranolol. *Br J Clin Pharmacol* (1984) 18, 337–42.
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Beta blockers + Bupropion

A patient taking metoprolol developed bradycardia and hypotension when bupropion was also given.

Clinical evidence, mechanism, importance and management

A 50-year-old man taking **metoprolol** 75 mg twice daily and diltiazem 240 mg twice daily for hypertension developed fatigue 12 days after starting to take bupropion 150 mg twice daily. He was found to have a pulse rate of 43 bpm, a blood pressure of 102/65 mmHg, and signs of mild heart failure. He recovered within 24 hours of stopping all three drugs.[1] It was suggested that these effects had occurred as a result of raised **metoprolol** levels, which had occurred because bupropion inhibited the metabolism of **metoprolol** by the cytochrome P450 isoenzyme CYP2D6.

The manufacturers of bupropion have predicted this interaction and recommend that if **metoprolol** is added to treatment with bupropion, doses at the lower end of the range should be used. If bupropion is added to existing treatment, decreased dosages of **metoprolol** should be considered.[2,3] These precautions seem prudent, especially in patients with heart failure, where raised beta blocker levels seem most likely to cause an adverse effect.

It seems likely that this interaction could occur with any of the beta blockers metabolised by CYP2D6 (see 'Table 22.1', (p.995), for a list).

1. McCollum DL, Greene JL, McGuire DK. Severe sinus bradycardia after initiation of bupropion therapy: a probable drug-drug interaction with metoprolol. *Cardiovasc Drugs Ther* (2004) 18, 329–30.
2. Zyban (Bupropion hydrochloride). GlaxoSmithKline UK. UK Summary of product characteristics, January 2009.
3. Zyban (Bupropion hydrochloride). GlaxoSmithKline. US Prescribing information, July 2009.

Beta blockers + Calcium-channel blockers; Dihydropyridines

The use of beta blockers with felodipine, isradipine, lacidipine, nicardipine, nimodipine and nisoldipine normally appears to be useful and safe. However, severe hypotension and heart failure have occurred rarely when a beta blocker was given with nifedipine or nisoldipine. Changes in the pharmacokinetics of the beta blockers and calcium-channel blockers may also occur on concurrent use, but they do not appear to be clinically important.

Clinical evidence

(a) Felodipine

A double-blind, crossover study in 8 healthy subjects found that over a 5-day period, **metoprolol** 100 mg twice daily did not affect the pharmacokinetics of felodipine 10 mg twice daily. However, the bioavailability and peak plasma levels of **metoprolol** were modestly increased by 31% and 38%, respectively.[1] Another study in 10 healthy subjects given felodipine 10 mg with either **metoprolol** 100 mg, **pindolol** 5 mg, **propranolol** 80 mg, or **timolol** 10 mg found no changes in heart rate, PR interval or blood pressure that might be considered to be harmful to patients with hypertension or angina. However, 7 of the 10 subjects reported some increase in adverse effects.[2]

(b) Isradipine

A preliminary report of a study in 24 healthy subjects found that **propranolol** 40 mg twice daily given with isradipine 5 mg twice daily caused some modest changes in the pharmacokinetics of both drugs (peak **propranolol** plasma levels increased by 17%, peak isradipine plasma levels reduced by 18%), but the AUCs were not significantly altered.[3] An earlier preliminary report by the same research group in 17 subjects found an increase in the **propranolol** AUC of 28%, a reduction in the isradipine AUC of 22%, and a 59% increase in the peak **propranolol** levels.[4]

(c) Lacidipine

Twelve patients with mild to moderate hypertension not satisfactorily controlled by **atenolol** alone were given lacidipine 4 mg daily with or without **atenolol** 100 mg daily for 14 days. There was no evidence of a significant change in drug levels, but there was a significant additive reduction in blood pressure during concurrent use, when compared with the reductions observed with either drug alone.[5]

Single-dose studies in 24 healthy subjects found that **propranolol** 160 mg reduced the peak plasma levels and AUC of lacidipine 4 mg by 38% and 42%, respectively, while the peak plasma levels and AUC of the **propranolol** were increased by 35% and 26%, respectively. There was a modest additive reduction of 4 to 6 mmHg in blood pressure, and the combination reduced the heart rate, but not to an extent greater than **propranolol** alone. No significant adverse effects were seen.[6] A further preliminary report of a study by the same authors, in which 12 hypertensive patients were given **propranolol** 160 mg twice daily and lacidipine 4 mg daily for 2 weeks, found a non-significant 30% increase in systemic availability of lacidipine, and no change in **propranolol** pharmacokinetics. In addition, no clinically significant alterations in ECG recordings, blood pressure, or pulse rate were seen.[7]

(d) Lercanidipine

The manufacturer notes that when lercanidipine was given with **metoprolol**, the bioavailability of lercanidipine was reduced by 50% while the bioavailability of **metoprolol** was unchanged. They suggest that any beta blocker may alter lercanidipine bioavailability.[8]

(e) Nicardipine

In a single-dose study in healthy subjects, nicardipine 30 mg did not affect the pharmacokinetics or pharmacodynamics of **atenolol** 100 mg.[9]

In another study, 14 healthy subjects were given nicardipine 50 mg every 12 hours and **metoprolol** 100 mg every 12 hours, both together and alone, for 11 doses. **Metoprolol** plasma levels were raised by 28% by the nicardipine in the 7 subjects who were of the extensive CYP2D6 metaboliser phenotype (that is, those with normal levels of this isoenzyme), but had no significant effect in the poor metabolisers (those lacking or deficient in CYP2D6). The extent of the beta-blockade was unchanged in all of them.[10]

Preliminary analysis of another study in healthy subjects found that the pharmacokinetics of both **propranolol** 80 mg twice daily and nicardipine 30 mg three times daily were unaffected when they were given together for 6 days.[11] However, two single-dose studies found that nicardipine 30 mg increased the AUC and peak plasma levels of **propranolol** 80 mg by 47% and 80%, respectively,[12] and raised the AUC and peak plasma levels of sustained-release **propranolol** 80 mg to a lesser extent (17% and 22%, respectively).[13] A related single-dose study found that in elderly healthy subjects nicardipine 30 mg increased the maximum plasma levels and AUC of **propranolol** 40 mg by about 100% and 80%, respectively. Nicardipine caused a further decrease in blood pressure, and attenuated the reduction in heart rate seen with **propranolol** alone.[14]

A study in 8 healthy subjects found that the increase in heart rate during exercise associated with a single 40-mg dose of nicardipine was reduced by one drop of **timolol** 0.5% put into each eye. Systolic blood pressure was also reduced during concurrent use, but nicardipine did not cause any further reduction in intraocular pressure than **timolol** alone.[15]

(f) Nifedipine

Nifedipine 10 mg three times daily did not alter the pharmacokinetics of **atenolol** 100 mg daily,[16,17] **betaxolol**,[18] **metoprolol** 100 mg twice daily[16,17] or **propranolol** 80 mg twice daily.[16] A single-dose study also found no pharmacokinetic interaction between nifedipine and **atenolol**.[19] However, a multiple-dose study found that nifedipine 10 mg three times daily increased the peak plasma level and AUC of **propranolol** 80 mg twice daily by 56% and 23%, respectively.[18] Another study found that the absorption of a single-dose of **propranolol** appeared to be faster, leading to higher initial concentrations, when it was given after nifedipine.[20]

Regardless of the pharmacokinetic changes, none of these studies in healthy subjects found any adverse haemodynamic effects as a result of giving nifedipine with any of these beta blockers.[16,18,19] Similarly, in studies in patients with normal left ventricular function there was no evidence of adverse haemodynamic effects when nifedipine (single-dose sublingual[21,22] or intravenously,[23] or daily dose orally[23]) was given with **atenolol**,[23] **celiprolol**[22] or **propranolol**.[21,24] However, there are a few earlier isolated case reports of hypotension and heart failure with the combination:

- Two patients with angina taking **alprenolol** or **propranolol** developed heart failure when they were given nifedipine 10 mg three times daily. The signs of heart failure disappeared when the nifedipine was withdrawn.[25]
- One out of 15 patients with hypertension and exertional angina progressively developed hypotension (90/60 mmHg) when given nifedipine 10 mg twice daily with **atenolol** 50 mg daily and a diuretic for one month.[26]
- A patient with angina taking **propranolol** 160 mg four times daily developed severe and prolonged hypotension (blood pressure initially not recordable, then 60 mmHg systolic) 18 days after nifedipine 10 mg three times daily was substituted for 'isosorbide', and this may have been a factor that led to fatal myocardial infarction.[27]
- Heart failure developed in a patient with angina taking **atenolol** (and various other drugs) when nifedipine 20 mg three times daily was given.[28]

A further report describes a patient who developed hypotension and severe bradycardia on two occasions after being given her usual antihypertensive medication of **labetalol** and extended-release nifedipine crushed and given via a nasogastric tube. Crushing the nifedipine tablet altered its release characteristics so that the total dose was released quickly resulting in profound hypotension. The **labetalol** produced additional hypotensive effects and prevented a compensatory increase in heart rate.[29]

(g) Nimodipine

In a preliminary report of a study in 12 healthy subjects, nimodipine 30 mg three times daily for 4 days had no significant effect on the changes in heart rate, blood pressure or cardiac output seen with either **propranolol** 40 mg or **atenolol** 25 mg three times daily. The pharmacokinetics of the beta blockers were also unaltered.[30]

(h) Nisoldipine

A single 20-mg dose of nisoldipine increased the steady-state AUC and peak plasma level of **propranolol** 160 mg daily by 35% and 55%, respectively. After concurrent use for 7 days, the AUC of **propranolol** was increased by 60% and the peak plasma level was increased by 55%. The combination enhanced blood pressure reduction to a small extent, but nisoldipine did not significantly reduce the effect of **propranolol** on heart rate.[31] Similarly, another study found that a single 20-mg dose of nisol-

dipine increased the AUC and peak plasma level of a single 40-mg dose of **propranolol** by 43% and 68%, respectively, and that the AUC and peak plasma level of nisoldipine increased by 30% and 57%, respectively. In this study, nisoldipine was reported to enhance beta-blockade.[32] However, the same research group later found that the steady-state pharmacokinetics of **propranolol** 80 mg twice daily and nisoldipine 10 mg twice daily were not affected by concurrent use for 7 days, but nisoldipine attenuated the decrease in forearm blood flow seen with propranolol.[33] The manufacturer of nisoldipine notes that severe hypotension can occur when it is given at the same time as beta blockers, and that, in isolated cases, signs of heart failure can also occur.[34]

Mechanism

Not understood. Where pharmacokinetic changes are seen, a possible reason is that the metabolism of the beta blockers is altered by changes in blood flow through the liver. The pharmacodynamic changes with nifedipine may be explained by the fact that nifedipine reduces the contractility of the heart muscle. This is counteracted by a sympathetic reflex increase in heart rate due to nifedipine-induced peripheral vasodilation, so that the ventricular output stays the same or is even improved. The presence of a beta blocker may oppose this to some extent by slowing the heart rate, which allows the negative inotropic effects of nifedipine to go unchecked.

The manufacturers of lercanidipine suggest that the reduction in lercanidipine bioavailability may be due to reduced hepatic blood flow caused by beta-adrenoceptor blockade.[8]

Importance and management

The concurrent use of beta blockers and the dihydropyridine calcium-channel blockers is common, and normally valuable. However, isolated cases of severe hypotension and heart failure have been seen in a few patients taking beta blockers and nifedipine or nisoldipine. It has been suggested that those likely to be most at risk are patients with impaired left ventricular function[35] (which is a caution for the use of nifedipine anyway) and/or those taking beta blockers in high dosage. Bear this in mind. It should also be noted that the topical use of beta blockers (such as timolol eye drops) may reduce heart rate and blood pressure. It may also be worth noting that all but one of the cases of an adverse reaction with a beta blocker and nifedipine occurred with 'short-acting' formulations, which are now considered unsuitable for long-term management of angina or hypertension, since they are associated with larger variations in blood pressure and heart rate. The remaining case was associated with the incorrect use of an extended-release nifedipine preparation.

Changes in the pharmacokinetics of the beta blockers and calcium-channel blockers may also occur, but these do not appear to be clinically important.

The manufacturer of lercanidipine suggests that, as a reduction in lercanidipine bioavailability may occur with any beta blocker, some adjustment of the lercanidipine dose may be needed.[8]

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Beta blockers + Calcium-channel blockers; Diltiazem

The cardiac depressant effects of diltiazem and beta blockers are additive, and although concurrent use can be beneficial, close monitoring is recommended. A number of patients, (usually those with pre-existing ventricular failure or conduction abnormalities) have developed serious and potentially life-threatening bradycardia. Diltiazem increases the serum levels of propranolol and metoprolol, but not those of atenolol.

Clinical evidence

(a) Cardiac depressant effects

Ten patients were admitted to an intensive coronary care unit during one year with severe bradycardia (heart rates of 24 to 44 bpm) after taking diltiazem 90 to 360 mg daily with **propranolol** 30 to 120 mg daily, **atenolol** 50 to 100 mg daily, or **pindolol** 90 mg daily. All were relatively elderly and presented with lethargy, dizziness, syncope, chest pain, and in one case pulmonary oedema. The ECG abnormalities were localised in the sinus node, the primary rhythm disorders being junctional escape rhythms, sinus bradycardia and sinus pause. These resolved within 24 hours of withdrawing the drugs, although a temporary pacemaker was needed in 4 patients.[1]

In an analysis of drug use in cases listed in a post-mortem toxicology database in Finland for the period 2000 to 2006, drug combinations possessing potentially severe interactions were found in 267 cases (0.71% of cases). Combinations of beta blockers with verapamil or diltiazem accounted for 22 possible pharmacodynamic interactions. In one case, a 63-year-old man who died in a car accident was found to have slightly elevated levels of **bisoprolol** (0.13 mg/L) and therapeutic levels of diltiazem. It was speculated that the combination may have led to bradyar-

rhythmias or other adverse cardiac effects, which may have contributed to the fatality.[2]

Symptomatic and severe bradyarrhythmias of this kind have been described in case reports in 16 other patients taking diltiazem with **atenolol**,[3] **carteolol**,[4] **metoprolol**,[3,5,6] **nadolol**,[7] **pindolol**,[8] **propranolol**,[3,5,7,9] or **sotalol**.[4,8] AV block with unusual ECG changes (T-wave inversion and ST-segment depression) was found in a 16-year-old girl following an overdose of diltiazem and **propranolol**.[10] In a later prospective study of hospital admissions due to cardiovascular adverse drug reactions, bradycardia, hypotension, syncope and worsening heart failure were noted in 21 patients taking beta blockers with diltiazem. The beta blockers involved were **propranolol** (13 patients), **atenolol** (5), **metoprolol** (2) and **oxprenolol** (1).[11] Similarly severe sinus bradycardia occurred in 8 of 59 patients in three early clinical studies of the combination of diltiazem and **propranolol**.[12-14] One patient developed congestive heart failure.[14] In contrast, four other similar clinical studies did not report any adverse effects,[15-18] and in a single-dose study, one drop of **timolol** 0.5% eye drops did not cause an additional reduction in heart rate when it was given to healthy subjects with a 60-mg dose of diltiazem.[19]

(b) Pharmacokinetics

In healthy subjects, diltiazem increased the AUC of **propranolol** and **metoprolol** by 48% and 33%, respectively, and increased the maximum serum levels of these beta blockers by 45% and 71%, respectively. The pharmacokinetics of **atenolol** were not significantly affected by diltiazem.[20] Another study found that diltiazem caused a 24 to 27% reduction in **propranolol** clearance.[21]

Mechanism

The bradycardic effects of the beta blockers can be additive with the delay in conduction through the atrioventricular node caused by diltiazem.[8] This advantageously increases the antianginal effects in most patients, but in a few these effects may exacerbate existing cardiac abnormalities. Diltiazem apparently also inhibits the metabolism of propranolol and metoprolol, but the exact mechanism for this is not clear.[20]

Importance and management

The concurrent use of a beta blocker and diltiazem is unquestionably valuable and uneventful in many patients, but severe adverse effects can develop. This is well established. On the basis of 6 reports, the incidence of symptomatic bradyarrhythmia was estimated to be about 10 to 15%.[1] It can occur with different beta blockers, even with very low doses, and at any time from within a few hours of starting treatment to 2 years of concurrent use.[1] The main risk factors seem to be ventricular dysfunction, or sinoatrial or AV nodal conduction abnormalities,[1] which are usually contraindications to the use of diltiazem. Patients with normal ventricular function and no evidence of conduction abnormalities are usually not at risk. Concurrent use should be well monitored for evidence of adverse effects. Changes in the pharmacokinetics of the beta blockers may also occur, but these changes are probably not clinically important.

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Beta blockers + Calcium-channel blockers; Verapamil

The cardiac depressant effects of verapamil and beta blockers are additive, and although concurrent use can be beneficial, serious cardiodepression (bradycardia, asystole, sinus arrest) sometimes occurs. It has been suggested that the combination should only be given to those who can initially be closely supervised. An adverse interaction can also occur with beta blockers given as eye drops.

Clinical evidence

(a) Pharmacodynamic interactions

In an analysis of drug use in cases listed in a post-mortem toxicology database in Finland, for the period 2000 to 2006, drug combinations possessing potentially severe interactions were found in 267 cases (0.71% of cases). Combinations of beta blockers with verapamil or diltiazem accounted for 22 possible pharmacodynamic interactions.[1]

1. Intravenous use. Ventricular asystole developed in a 70-year-old man and a 6-month-old baby when intravenous verapamil was given after the unsuccessful use of intravenous **practolol** to treat supraventricular tachycardia.[2] In a later study, the combination of intravenous verapamil and intravenous **practolol** produced a marked reduction in cardiac contractility, which was more evident when **practolol** was given first.[3]

2. Oral use. In one series, 34 out of 42 patients taking verapamil 360 mg daily with beta blockers (daily dose: **atenolol** 100 mg (34 patients), **atenolol** 50 mg (2), **propranolol** 160 mg (4), **pindolol** 20 mg (1), or **metoprolol** 100 mg (1)) experienced a reduction in anginal episodes over a mean period of 6.5 months while taking both drugs. However, 12 patients needed a reduced dosage or withdrawal of one or both drugs. One had non-specific symptoms (drugs withdrawn), 2 had bradyarrhythmias (drugs withdrawn) and 6 experienced dyspnoea (3 withdrawals and 3 dosage reductions), which were presumed to be secondary to left ventricular failure. Other complications were tiredness (2 patients) and postural hypotension (1 patient), which were dealt with by reducing the dosage.[4] In another study in 15 patients with angina who were taking **atenolol** with verapamil, 4 patients experienced profound lethargy, one had left ventricular failure and 4 had bradyarrhythmias.[5]

Other case reports and studies describe heart failure,[6,7] dyspnoea,[6,8,9] sinus arrest,[10,11] heart block,[10,12-14] hypotension,[6,7,9,11,14-17] and bradycardia[5,6,9,11,12,15-19] in patients taking verapamil with **alprenolol**,[10] **atenolol**,[7,10,11,13] **metoprolol**,[6,12,14,16] **propranolol**[8,9,15,17-19] or **pindolol**.[6] A number of reports noted that patients experiencing this interaction had reasonable left ventricular function.[6,11,13] Heart block and hypotension or cardiogenic shock has also been reported after verapamil was given with **atenolol**[20] or **propranolol**[21] in overdose.

3. Ocular use. In two cases, bradycardia occurred in patients taking verapamil and using **timolol** eye drops.[22,23] Another case has been reported, but this was complicated by the presence of 'flecainide', (p.1006).

(b) Pharmacokinetic interactions

1. Atenolol. In one study in a single patient, the pharmacokinetics of atenolol were not altered by verapamil.[24] A study in 15 patients found that the plasma levels of verapamil and atenolol varied greatly during individual and concurrent use but mean concentrations were not significantly

changed.[5] In another study, in 10 patients, the mean AUC of atenolol was not significantly increased by verapamil, but individual patients had atenolol AUC increases of up to 112%.[25]

2. Metoprolol. In a study in 10 patients, verapamil raised the metoprolol AUC by 33% and the peak plasma levels by 41%. The minimum pulse rate and systolic blood pressure (1 to 3 hours post dose) were also lower in those taking the combination than with metoprolol alone.[16] Similarly, in a single-dose study in 9 healthy subjects, the AUC and maximum plasma level of metoprolol were increased by 35% and 64%, respectively, and the AUC and half-life of verapamil were increased by 57% and 29%, respectively, when both drugs were given together.[26]

3. Propranolol. In healthy subjects, verapamil reduced the clearance of propranolol by 26 to 32% and increased its AUC by 46 to 58% after 6 days of concurrent use.[27] Similarly, in 5 patients, verapamil increased the peak plasma levels of propranolol by 94%, and increased its AUC by 66%.[19] Propranolol did not affect the pharmacokinetics of verapamil.[19] However, in another study in healthy subjects, no pharmacokinetic interaction was noted when propranolol and verapamil were taken together for 6 days.[28]

4. Talinolol. In a randomised, crossover study in 9 healthy subjects, a single 120-mg dose of *(R)*-verapamil reduced the bioavailability of a single 50-mg dose of talinolol by 25%.[29]

Mechanism

Both the beta blockers and verapamil have negative inotropic effects on the heart, which can be additive.[28] Given together they can cause marked bradycardia and may even depress the contraction of the ventricle completely. Verapamil can also raise the serum levels of beta blockers that are extensively metabolised in the liver (e.g. metoprolol, propranolol), probably by inhibiting their metabolism,[30] although the exact mechanism for this is unclear. It is thought that verapamil affects talinolol bioavailability by modulating intestinal P-glycoprotein.[29,31]

Importance and management

Well documented and well established interactions. Although concurrent use can be uneventful and successful, the reports cited here amply demonstrate that it may not always be safe. The difficulty is identifying the patients most at risk. In the UK, the BNF says that oral concurrent use should only be considered if myocardial function is well preserved, and that verapamil should not be injected in patients recently given beta blockers because of the risk of hypotension and asystole. They also note that, although 30 minutes has been suggested as a sufficient interval before giving a beta blocker when a verapamil injection has been given first, the safety of this has not been established.[32] The manufacturers of verapamil contraindicate its intravenous use in those receiving intravenous beta blockers.[33]

It has been advised that the initiation of treatment should be restricted to hospital practice, where the dose of each drug can be carefully titrated and the patient closely supervised, particularly during the first few days when adverse effects are most likely to develop.[4,5,19] Some have suggested that beta blockers that are extensively metabolised (e.g. metoprolol, propranolol) may possibly carry some additional risk because verapamil raises their serum levels.[24] However, others contend that, since the interaction occurs with atenolol (which is largely excreted unchanged in the urine), the pharmacodynamic effects are more important than any pharmacokinetic changes.[5,11,19] Note that the latter argument is probably valid, as changes of this size, or even more, in the AUC of beta blockers have proved not to be clinically important, even in those patients likely to be sensitive to the effects of the beta blockers, such as those with heart failure.

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Beta blockers + Chloroquine or Hydroxychloroquine

Hydroxychloroquine and possibly chloroquine may increase the blood levels of metoprolol and probably other similarly metabolised beta blockers.

Clinical evidence, mechanism, importance and management

In a study in 7 healthy subjects, hydroxychloroquine 400 mg daily for 8 days increased the AUC and peak plasma levels of a single 100-mg dose of **metoprolol** by 65% and 72%, respectively.[1] The subjects in this study were of the extensive CYP2D6 metaboliser phenotype, meaning that they had normal levels of this isoenzyme. Hydroxychloroquine may inhibit the metabolism of **metoprolol** by the cytochrome P450 isoenzyme CYP2D6. The clinical significance of this interaction is unknown, but normally the beta blockers are considered to have a wide therapeutic range, and so raises in levels are generally well tolerated. Patients with heart failure are usually more at risk, because drugs such as metoprolol lose their selectivity at higher levels, but even in this patient group the rise in levels seems unlikely to be generally important. There appears to be no information about oth-

er beta blockers, but all those metabolised by CYP2D6 would be expected to be affected to some extent. See 'Table 22.1', (p.995), for a list.

In vitro study suggests that **chloroquine** may interact with **metoprolol** in the same way as hydroxychloroquine.[2] More study is needed to establish the clinical relevance of any interaction.

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Beta blockers + Dextropropoxyphene (Propoxyphene)

A single-dose study has shown that the bioavailability of metoprolol is markedly increased by dextropropoxyphene and a case report is in line with these findings. The bioavailability of propranolol is also increased by dextropropoxyphene, but to a lesser extent.

Clinical evidence

A 48-year-old man taking **metoprolol** 100 mg daily developed dizziness and sweating 3 hours after taking dextropropoxyphene 200 mg and paracetamol (acetaminophen) 1.3 g. He was found to have a heart rate of 30 to 40 bpm and a blood pressure of 98/65 mmHg, which returned to normal over the following 8 hours. Assessment of blood samples showed that his normal **metoprolol** level was 89 nanograms/mL, but that this had risen to 160 nanograms/mL in the presence of dextropropoxyphene.[1]

Preliminary results of a study in healthy subjects suggest that after taking dextropropoxyphene (dose not stated) for a day the bioavailability of a single 100-mg oral dose of **metoprolol** was increased by almost 260% and the total body clearance was reduced by 18%. The bioavailability of a single 40-mg oral dose of **propranolol** was increased by about 70% by dextropropoxyphene.[2]

Mechanism

Dextropropoxyphene inhibits the metabolism of metoprolol and propranolol by the cytochrome P450 isoenzyme CYP2D6, which results in increased levels and therefore increased effects. Propranolol is probably affected to a lesser extent as it is also metabolised by CYP1A2.

Importance and management

Evidence is limited, but an interaction seems established. It seems likely that this interaction could occur with any of the beta blockers metabolised by CYP2D6 (see 'Table 22.1', (p.995)). Therefore it would be prudent to be alert for evidence of an increased response to the beta blocker but so far there seems to be very little evidence to suggest that concurrent use causes problems. Patients with heart failure are usually more at risk, because drugs such as metoprolol lose their selectivity at higher levels, and therefore some monitoring (e.g. shortness of breath, bradycardia, hypotension) may be prudent. No interaction would be expected with those beta blockers that are largely excreted unchanged in the urine (see 'Table 22.1', (p.995)).

1. Marraffa JM, Lang L, Ong G, Lehmann DF. Profound metoprolol-induced bradycardia precipitated by acetaminophen-propoxyphene. *Clin Pharmacol Ther* (2006) 79, 282–6.
2. Lundborg P, Regård CG. The effect of propoxyphene pretreatment on the disposition of metoprolol and propranolol. *Clin Pharmacol Ther* (1981) 29, 263–4.

Beta blockers + Diphenhydramine

Diphenhydramine moderately inhibits the metabolism of metoprolol.

Clinical evidence

In a placebo-controlled study in 16 healthy male subjects, a single 100-mg dose of **metoprolol** was given on day 3 of a 5-day course of diphenhydramine 50 mg three times daily. Diphenhydramine decreased the clearance of **metoprolol** by 46% and increased its AUC by 61% in the 10 subjects who were of the extensive CYP2D6 metaboliser phenotype (meaning those that had normal levels of this isoenzyme), but had no significant effect in the 6 poor metabolisers (that is, those lacking or deficient in CYP2D6). However, the **metoprolol** AUC in the extensive metabolisers taking diphenhydramine was still only about one-third of that in the poor metabolisers taking placebo, suggesting a limited effect. The effect of **metoprolol** on heart rate and systolic blood pressure during exercise was also increased by diphenhydramine in extensive metabolisers. However, as before, it was not as great as the effect of **metoprolol** alone in poor metabolisers.[1] The same group of researchers repeated this study in 20 healthy women and found broadly similar results.[2]

Mechanism

Diphenhydramine modestly inhibits the cytochrome P450 isoenzyme CYP2D6, which is responsible, in part, for the metabolism of metoprolol and some other beta blockers. CYP2D6 shows polymorphism, with some individuals lacking significant CYP2D6 activity (poor metabolisers), in whom diphenhydramine would have little or no effect. See 'Genetic factors', (p.4), for more information on genetic polymorphism.

Importance and management

Information appears to be limited to these studies. Increases in plasma metoprolol levels of this size are unlikely to be clinically relevant. Patients with heart failure are usually more at risk, because drugs such as metoprolol lose their selectivity at higher levels, but even in this patient group the rise in levels seems unlikely to be generally important. Indeed, despite the likely widespread use of extensively metabolised beta blockers (see 'Table 22.1', (p.995)) and diphenhydramine, no problems seem to have been reported.

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Beta blockers + Dronedarone

Dronedarone increases the AUC of metoprolol in most patients. The increase in the negative inotropic effects are modest at the recommended therapeutic dose of dronedarone. Theoretically, additive bradycardia may occur if dronedarone is taken with a beta blocker.

Clinical evidence

In a study, 44 healthy subjects (39 extensive and 5 poor CYP2D6 metabolisers; that is, 39 subjects with normal levels of CYP2D6 and 5 subjects lacking or deficient in CYP2D6) were given **metoprolol** 200 mg daily for 13 days with dronedarone 800 mg, 1.2 g or 1.6 g daily from day 5. Dronedarone increased the AUC of **metoprolol** in a dose-dependent manner in the 39 subjects who were extensive metabolisers by 1.63-fold, 2.08-fold and 2.53-fold, respectively, without affecting **metoprolol** plasma levels. Concurrent use resulted in an additive dose-dependent negative inotropic effect.[1]

Mechanism

Dronedarone is structurally related to amiodarone, which is known to inhibit the cytochrome P450 isoenzyme CYP2D6, by which metoprolol is metabolised (see 'Amiodarone + Beta blockers', p.276). This study also shows that dronedarone inhibits CYP2D6, effectively making extensive metabolisers into poor metabolisers. For more information on metaboliser status, see 'Genetic factors', (p.4).

Importance and management

A pharmacokinetic interaction between dronedarone and metoprolol is established, but its clinical relevance is uncertain. The negative inotropic effect of metoprolol was almost doubled by the addition of dronedarone 1.6 g daily, but at the anticipated therapeutic dose of 800 mg the effects were modest. Other beta blockers that are metabolised by CYP2D6 (see

'Table 22.1', (p.995)) would be expected to interact similarly. Note that as dronedarone may cause bradycardia, and this would be expected to be additive with the effects of beta blockers, caution should be used with concurrent use.

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Beta blockers + Fish oils

The hypotensive effect of propranolol may be enhanced by fish oil.

Clinical evidence, mechanism, importance and management

In a study, 36 patients with mild hypertension were given either **propranolol** 80 mg daily or fish oil 9 g daily (as capsules and equivalent to **eicosapentaenoic acid** 1.8 g and **docosahexaenoic acid** 1.1 g daily) for 36 weeks, followed by placebo for 4 weeks. A further group of 16 patients were given **propranolol** 80 mg daily for 12 weeks, **propranolol** plus fish oil 9 g daily for 12 weeks, **propranolol** plus fish oil placebo for 12 weeks, and finally **propranolol** placebo for 4 weeks. Fish oil alone decreased blood pressure to a similar extent to **propranolol**, and decreases in blood pressure with the combination were greater than with either **propranolol** or fish oil alone.[1]

A further similar study in 14 patients taking a beta blocker found that when they were also given 4 capsules of *Omacor* (equivalent to **eicosapentaenoic acid** 1.9 g and **docosahexaenoic acid** 1.5 g) daily for 6 weeks their blood pressure decreased by a further 3.3/1.9 mmHg.[2]

The mechanism is uncertain, but as fish oil seems to have a hypotensive effect of its own, it may enhance the hypotensive effect of any beta blocker. However, the effects are modest and so an adverse hypotensive response seems unlikely.

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Beta blockers + Flecainide

The combined use of flecainide and beta blockers may have additive cardiac depressant effects. An isolated case of bradycardia and fatal AV block has been reported during the use of flecainide with sotalol, and bradycardia has been reported in a patient taking flecainide who was given timolol eye drops.

Clinical evidence, mechanism, importance and management

A study on cardiac function and drug clearance in 10 healthy subjects found that when **propranolol** 80 mg three times daily was given with flecainide 200 mg twice daily for 4 days the AUCs of both drugs were increased by 20 to 30%, and they had some additive negative inotropic effects.[1] A report describes a patient taking flecainide 100 mg twice daily who developed bradycardia and fatal atrioventricular conduction block 3 hours after taking a second dose of **sotalol** 40 mg.[2] Another report describes a patient with chronic atrial fibrillation that had been stable for 5 years during treatment with flecainide and verapamil. Within 3 days of starting **timolol** 0.1% eye drops twice daily, she developed bradycardia with a heart rate of 35 to 40 bpm. The eye drops were stopped and 16 hours after the last dose, her heart rate had increased to 90 to 100 bpm.[3] Careful monitoring has therefore been recommended if beta blockers are added to flecainide. Note that serious cardiac depression has been seen following the use of flecainide with other drugs that have negative inotropic effects such as 'verapamil', (p.294).

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Beta blockers + Food

Food can increase, decrease or not affect the bioavailability of beta blockers.

Clinical evidence

Food increased the AUC of **propranolol** by 50 to 80%,[1-3] and increased the AUC of both **metoprolol**[1] and **labetalol**[4] by about 40%. In contrast, food did not affect the extent of absorption of a sustained-release formulation of **propranolol**,[2] and had very little effect on the absorption of **oxprenolol**[5,6] and **pindolol**.[7] In another study, food reduced the AUC of **atenolol** by about 20%.[8]

Mechanism

Food probably increases the bioavailability of propranolol, metoprolol and labetalol by changing the extent of their first pass metabolism through the liver.[2-4] It has been suggested that changes in propranolol disposition with a high protein meal may be partly due to a transient increase in hepatic blood flow[9-11] and rate of gastrointestinal absorption, which are subject to high intraindividual variation.[11] One study found that changes in hepatic blood flow, similar to those occurring with food consumption, had little effect on propranolol bioavailability.[12] A later study suggested that atenolol (and possibly other hydrophilic beta blockers, see 'Table 22.1', (p.995)) become tightly associated with bile acid micelles, preventing their absorption.[13]

Importance and management

None of the changes in beta blocker bioavailability associated with food have been shown to be of clinical importance, nor is it clear whether it matters if patients take these drugs in a regular pattern in relation to meals. Beta blocker serum levels vary widely between patients (a 20-fold difference in propranolol AUC has been noted),[1] and individualising the dose is therefore more of an issue than food intake.

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Beta blockers + Grapefruit and other fruit juices

The bioavailability of celiprolol is markedly reduced by both grapefruit juice and orange juice, the bioavailability of atenolol is moderately reduced by orange juice, and the bioavailability of

talinolol is reduced by grapefruit juice. Acebutolol does not appear to interact with grapefruit juice to a clinically relevant extent.

Clinical evidence, mechanism, importance and management

(a) Acebutolol

In a randomised, crossover study, 10 healthy subjects were given 200-mL of normal-strength grapefruit juice three times a day for 4 days (total of 11 drinks), with a single 400-mg dose of acebutolol on the morning of day 3. Grapefruit juice decreased the maximum plasma levels and AUC of acebutolol by a modest 19% and 6%, respectively. No significant changes in the heart rate or blood pressure were seen.[1]

(b) Atenolol

In a randomised, crossover study, 10 healthy subjects were given 200 mL of **orange juice** (from concentrate) three times daily with a single 50-mg dose of atenolol on the third day. **Orange juice** reduced the AUC and maximum plasma levels of atenolol by 40% and 49%, respectively, and also attenuated the atenolol-induced reduction in heart rate. However, the effect of atenolol on blood pressure was unchanged.[2] This suggests that orange juice could make atenolol less effective when it is used for rate control, but the clinical significance of this effect is unclear.

(c) Celiprolol

In a randomised, crossover study, 12 healthy subjects were given grapefruit juice 200 mL three times daily for 2 days. On the third day celiprolol 100 mg was given with the second of four 200 mL volumes of grapefruit juice, and on day 4 two further 200 mL volumes of grapefruit juice were given. The AUC and peak plasma levels of celiprolol were reduced by about 87% and 95%, respectively, and the half-life of celiprolol was slightly prolonged. However, grapefruit juice did not affect the changes in blood pressure or heart rate caused by celiprolol.[3] In a similar study in 10 healthy subjects, 200 mL of normal-strength **orange juice**, given two to four times daily for 4 days, with a single 100-mg dose of celiprolol on day 3. **Orange juice** reduced the AUC and peak plasma levels of celiprolol by 83% and 89%, respectively. The half-life of celiprolol was prolonged from 4.6 to 10.8 hours and the renal excretion of celiprolol was reduced by 77%. However, the effects of celiprolol on blood pressure or heart rate were not altered by the **orange juice**.[4]

The mechanism of this effect is not known, but suggestions include an effect on intraduodenal pH and the lipid solubility of celiprolol, or the formation of a complex between celiprolol and an ingredient of grapefruit or **orange juice** that interfered with celiprolol absorption. Alternatively, inhibition of uptake transporter proteins in the intestine may have reduced absorption.[3,4]

Although the clinical relevance of these effects has not been fully assessed, the studies suggest that the effects of celiprolol on blood pressure and heart rate are not affected. Nevertheless the marked reduction in celiprolol bioavailability in the presence of grapefruit or **orange juice** suggests this interaction may be of clinical significance in some patients.[3,4]

(d) Talinolol

Grapefruit juice 300 mL decreased the AUC of a single 50-mg dose of talinolol by 44%, decreased the maximum serum level by 42%, and increased the oral clearance by 62%. Similar results were seen after repeated administration of grapefruit juice over 6 days. However, the haemodynamic effects of talinolol were not altered.[5] Because P-glycoprotein levels did not appear to be affected by grapefruit juice, it was suggested that constituents in the juice might inhibit an uptake process other than P-glycoprotein. [Note that, in contrast, a study in *animals* found that the bioavailability of talinolol was increased by grapefruit juice.[6]] The decreases in talinolol levels are unlikely to be clinically relevant.

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Beta blockers + H_2-receptor antagonists; Cimetidine

No clinically significant interaction appears to occur between the beta blockers and cimetidine, although the blood levels of some extensively metabolised beta blockers (e.g. metoprolol, propranolol) can be doubled. Isolated case reports describe bradycardia with atenolol, an irregular heart beat with metoprolol, and hypotension with labetalol, in patients also taking cimetidine.

Clinical evidence

(a) Acebutolol

A study *in animals* found that the pharmacokinetics of acebutolol were not affected by cimetidine, which suggests that a clinical interaction is unlikely.[1]

(b) Atenolol

A report briefly mentions a patient taking a beta blocker for angina who developed profound sinus bradycardia (36 bpm) and hypotension when cimetidine was also given.[2] The beta blocker was not specified, but it was identified as atenolol elsewhere.[3] Three well controlled studies in healthy subjects and patients found that cimetidine did not significantly alter the blood levels of atenolol, nor did it alter the effect of atenolol on heart rate.[4-9] Atenolol did not affect cimetidine pharmacokinetics.[6]

(c) Betaxolol

The plasma levels and pharmacokinetics of betaxolol were unaffected by cimetidine in one study.[10]

(d) Bisoprolol

A study in 6 healthy subjects found that the maximum plasma level, AUC and clearance of bisoprolol were not significantly affected by cimetidine,[11,12] although an analysis of the results by other authors suggested that cimetidine may cause a significant reduction in the renal clearance of bisoprolol.[13]

(e) Carvedilol

The plasma levels and pharmacokinetics of carvedilol were unaffected by cimetidine in one study.[14]

(f) Labetalol

The AUC and bioavailability of a single 200-mg oral dose of labetalol was increased by 66% and 56%, respectively, in 6 healthy subjects who took cimetidine 400 mg four times daily for 4 days.[15] One subject developed postural hypotension (70/40 mmHg), felt light-headed and almost fainted on standing.[15] Conversely, the AUC of intravenous labetalol was unaffected by cimetidine.[15]

(g) Metoprolol

A study in 6 healthy subjects given metoprolol 100 mg twice daily for a week found that cimetidine 1 g daily in divided doses increased the peak plasma levels of metoprolol by 70% and the AUC by 61%, but this did not increase the effect of metoprolol on the heart rate during exercise.[4-6] Metoprolol did not affect cimetidine pharmacokinetics.[6]

Three other studies confirmed that cimetidine increased metoprolol plasma levels after single or multiple doses, but none of the studies found that this interaction resulted in an increase in the effect of metoprolol on heart rate during exercise.[16-19] An isolated case describes one patient who complained of a "very irregular heart beat" while taking both drugs, which was much less marked when he took the two drugs separated by as much time as possible.[20] In contrast, two other studies found that cimetidine did not affect the plasma levels of a single 100-mg dose of metoprolol.[7,8]

(h) Nadolol

A review cites a study in which the plasma levels and pharmacokinetics of nadolol were not affected by cimetidine, and the effects of the beta blocker on heart rate and blood pressure were unchanged.[21]

(i) Nebivolol

In one study, cimetidine 400 mg twice daily increased the AUC and peak plasma levels of a single 5-mg dose of nebivolol by 48% and 23%, respectively, but did not alter the effect of nebivolol on blood pressure or heart rate.[22]

(j) Penbutolol

The plasma levels and pharmacokinetics of penbutolol[9,23] were not affected by cimetidine, and the effects of the beta blocker on heart rate and blood pressure were unchanged.[23]

(k) Pindolol

Cimetidine 1 g daily in divided doses increased the AUC and peak plasma levels of pindolol 10 mg twice daily by 30% and 33%, respectively, although these changes were not statistically significant.[9] In another study, cimetidine 400 mg twice daily increased the AUC of pindolol by about 40% and decreased its renal clearance by about 35%.[24]

(l) Propranolol

In a study, 12 healthy subjects were given cimetidine 300 mg four times daily for a week with propranolol 80 mg every 12 hours from day 3 onwards. The mean steady-state blood levels and the AUC of propranolol were raised by 47%, and the half-life was prolonged by 17%, but cimetidine did not alter the effect of propranolol on heart rate.[25] A number of other single-dose and steady-state studies confirm that cimetidine causes rises of 35 to 136% in the plasma levels, AUC and clearance of propranolol,[4-6,10,21,26-32] but this does not appear to increase the effect of the beta blocker on blood pressure,[21,27,29] or on heart rate, either at rest or during exercise.[4,21,27-29]

In contrast, one study found a further reduction in heart rate when cimetidine was given with propranolol.[33] In another study, the increase in the steady-state AUC of propranolol tended to be higher when cimetidine was given simultaneously with propranolol than when they were given separated by 10 hours (41% versus 26%), but the difference was not significant.[34] A letter describes one patient who had a three- to fourfold increase in the serum levels and AUC of a single 80-mg dose of propranolol after taking cimetidine 1 g daily for 6 weeks.[2]

In one study propranolol did not affect cimetidine pharmacokinetics.[6]

(m) Timolol

A double-blind study in 12 healthy subjects found that cimetidine 400 mg twice daily for 3 days did not modify the effect of a single drop of timolol 0.5%, put into each eye, on heart rate or intraocular pressure, to either a statistically or clinically relevant extent.[35]

Mechanism

The plasma levels of beta blockers extensively metabolised in the liver by the cytochrome P450 isoenzyme CYP2D6 (e.g. metoprolol, nebivolol and propranolol) are increased because cimetidine reduces their metabolism by inhibiting the activity of the liver enzymes. However, this does not seem to be a complete explanation as cimetidine does not affect carvedilol, which is metabolised by CYP2D6, but does affect labetalol, which is not metabolised by CYP2D6.[15] Pindolol is partly excreted by an active renal tubular secretion mechanism, and cimetidine increases pindolol levels by inhibiting this mechanism.[24] Cimetidine may reduce the renal clearance of bisoprolol by a similar mechanism.[12] Therefore a renal mechanism may play a part. However, those beta blockers that are largely excreted unchanged in the urine (e.g. atenolol, nadolol) are not affected by cimetidine.[8,21]

Importance and management

These are well studied and established interactions, but despite the considerable rises in plasma levels that can occur when some beta blockers are given with cimetidine, the effects are not normally clinically important; cases describing clinically relevant effects (hypotension, bradycardia) appear rare. Normally the beta blockers are considered to have a wide therapeutic range, and so raises in levels are generally well tolerated. Patients with heart failure are usually more at risk, because drugs such as metoprolol lose their selectivity at higher levels, but even in this patient group the rise in levels seems unlikely to be generally important. However, it has been suggested that any patient with impaired liver function who are given cimetidine with beta blockers that are extensively metabolised in the liver (see 'Table 22.1', (p.995)) might possibly develop grossly elevated plasma levels, which could cause adverse effects. It would seem prudent to either monitor this type of patient (for effects such as hypotension, bradycardia, shortness of breath) or to use a non-interacting H_2-receptor antagonist, such as 'ranitidine', (p.1009).

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Beta blockers + H2-receptor antagonists; Famotidine

Famotidine does not appear to interact with the beta blockers.

Clinical evidence, mechanism, importance and management

A survey of 15 patients taking beta blockers (**acebutolol**, **atenolol**, **betaxolol**, **nadolol**, **pindolol**, **propranolol** or **sotalol**) for 6 to 8 weeks found no evidence of changes in antihypertensive effects or bradycardia while they were taking famotidine 40 mg daily.[1] No interaction would be expected, and no special precautions would seem necessary if famotidine is taken with these or any other beta blocker.

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Beta blockers + H_2-receptor antagonists; Nizatidine

An isolated report suggests that the reduction in heart rate caused by atenolol is increased by nizatidine.

Clinical evidence, mechanism, importance and management

After taking **atenolol** 100 mg daily for 7 days the mean resting heart rate of 12 healthy subjects fell from about 64 to 53 bpm three hours after dosing. A further fall of 6 bpm occurred when they were also given nizatidine 300 mg daily for 7 days. Nizatidine alone caused a fall in heart rate of about 8 bpm.[1]

However, up to the end of 2007, the manufacturers have had only 4 reports of bradycardia with nizatidine, by which time it had been used in more than 100 million patients, and the Adverse Drug Reactions On-line Information Tracking system (ADROIT) of the MHRA in the UK includes only one case of sinus bradycardia associated with nizatidine since its launch. Further, the manufacturers note there are no interaction reports of nizatidine with other drugs that have a bradycardic potential.[2] Therefore, a clinically significant interaction between beta blockers and nizatidine seems unlikely.

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Beta blockers + H_2-receptor antagonists; Ranitidine

Ranitidine does not alter either the steady-state plasma levels or the therapeutic effects of atenolol, nebivolol, propranolol or tertatolol. Some studies have shown moderate rises in metoprolol levels in those also given ranitidine.

Clinical evidence

In a study in 12 healthy subjects the plasma levels of **metoprolol** 100 mg twice daily were unaffected by ranitidine 300 mg daily for 7 days.[1] Two other studies also suggest that ranitidine did not significantly affect the plasma levels of **metoprolol**,[2-5] although these studies did find increases of up to 38% in the AUC of single intravenous or oral doses of **metoprolol**.[2-5] Another study found that ranitidine increased the AUC and plasma levels of **metoprolol** 100 mg twice daily by 55% and 34%, respectively.[6-8] All of these studies found that ranitidine did not alter the effect of **metoprolol** on heart rate during exercise.[1,2,5,6]

In a study in 5 healthy subjects, ranitidine 300 mg daily for 6 days did not affect the steady-state plasma levels of **propranolol** 160 mg daily nor did it alter the effect of **propranolol** on heart rate or blood pressure.[9] Similarly no changes in plasma **propranolol** levels were seen in other multiple-dose[10] or single-dose studies.[11-14]

In other studies, ranitidine 150 mg twice daily did not significantly alter the pharmacokinetic or pharmacodynamic effects of a single 5-mg dose of **nebivolol**,[15] a single 5-mg dose of **tertatolol**,[16] or **atenolol** 100 mg daily for 7 days.[6,8]

Mechanism

The rises in metoprolol serum levels caused by ranitidine in the two single-dose metoprolol studies are not understood, nor is it clear why one of four studies found an increase after multiple doses.

Importance and management

The possible effects of ranitidine on the plasma levels and effects of propranolol and metoprolol have been well studied. Although some studies have shown moderate rises in metoprolol levels, particularly after single-doses, the majority of the data from multiple-dose studies suggest that an interaction does not generally occur.

Less is known about atenolol, nebivolol and tertatolol, although no clinically relevant interactions have been seen. There is nothing to suggest that the concurrent use of ranitidine and any beta blocker should be avoided.

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Beta blockers + Haloperidol

Carteolol may increase serum haloperidol levels. An isolated case report describes severe hypotension and cardiopulmonary arrest in a woman shortly after she was given haloperidol and propranolol. Plasma levels of haloperidol in three patients were not significantly changed by propranolol. The concurrent use of sotalol and haloperidol should generally be avoided because of the possible increased risk of QT prolongation.

Clinical evidence, mechanism, importance and management

(a) Carteolol

In a single-dose study in 8 healthy subjects, oral carteolol 10 mg increased the peak plasma level and AUC of haloperidol by about 25% and 40%, respectively and decreased its clearance by 33%, possibly by altering hepatic blood flow. The pharmacokinetics of carteolol were unaffected by haloperidol. Two patients experienced sleepiness with concurrent use, but this was mild and resolved within 24 hours.[1] These increases in haloperidol levels are modest, and therefore no particular precautions seem necessary if carteolol is also given.

(b) Propranolol

A middle-aged woman with schizophrenia and hypertension experienced three episodes of severe hypotension within 30 to 120 minutes of being given propranolol 40 to 80 mg and haloperidol 10 mg.[2] On two of the occasions she had a cardiopulmonary arrest. She fainted each time, became cyanotic, had no palpable pulses and had severe hypotension, but rapidly responded to cardiopulmonary resuscitation. She suffered no adverse consequences.[2] The reasons for the severe hypotension are not understood, although both drugs alone can cause hypotension.

A study found that the steady-state plasma levels of haloperidol 6 to 15 mg daily were not significantly changed in 3 patients by long-acting propranolol (given in incremental doses up to 480 mg daily).[3]

There seems to be only one case of an interaction between haloperidol and propranolol on record. Bearing in mind the widespread use of these drugs, this interaction would appear to be rare. There would seem to be little reason for avoiding concurrent use.

(c) Sotalol

Both haloperidol and sotalol can prolong the QT interval and should therefore not generally be used together, see ‘Drugs that prolong the QT interval + Other drugs that prolong the QT interval’, p.290.

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Beta blockers + Hormonal contraceptives

The plasma levels of metoprolol are increased in women taking combined hormonal contraceptives, but the clinical importance of this is probably very small. Acebutolol, oxprenolol and propranolol pharmacokinetics are minimally affected by hormonal contraceptive use.

Clinical evidence

The peak plasma levels and the AUC of a single 100-mg dose of **metoprolol** were 36% and 70% higher, respectively, in 12 women taking low-dose combined oral contraceptives, when compared with a similar group not taking contraceptives. The elimination half-life of **metoprolol** was unaffected.[1] In a further study by the same research group, the AUC of **metoprolol** was 71% higher, the AUC of **oxprenolol** was 26% higher, the AUC of **propranolol** was 42% higher, and the AUC of **acebutolol** was marginally lower in women taking combined hormonal contraceptives, when compared with those not taking contraceptives. However only the **metoprolol** difference was statistically significant.[2] In another study in 8 women, the total clearance of a single 80-mg dose of **propranolol** was increased (although not significantly) by **ethinylestradiol** 50 micrograms daily, and an even smaller increase was seen when they were taking a combined hormonal contraceptive containing **ethinylestradiol** and **norethisterone**.[3]

Mechanism

The reason for the changes appears to be that ethinylestradiol alters the metabolism of these beta blockers. In the case of propranolol its conjugation and oxidation are increased by the ethinylestradiol.[3]

Importance and management

The increases in plasma levels of propranolol, oxprenolol and acebutolol are almost certainly too small to matter, but with metoprolol the changes are somewhat larger. Even so, changes of this size caused by the interactions of other drugs with beta blockers are not usually clinically relevant. No special precautions are generally necessary if any of these beta blockers are given to women taking combined oral contraceptives containing ethinylestradiol, (or those taking ethinylestradiol alone for other indications). Patients with heart failure are usually more at risk, because drugs such as metoprolol lose their selectivity at higher levels, but even in this patient group the rise in levels seems unlikely to be generally important. There appears to be no information about other beta blockers, but all those metabolised by CYP2D6 would be expected to be affected to some extent. See 'Table 22.1', (p.995), for a list.

If beta blockers are being used to treat hypertension, it is of note that combined hormonal contraceptives may cause increases in blood pressure (but consider also 'Antihypertensives + Hormonal contraceptives or HRT', p.1050). Stopping combined hormonal contraceptives has been suggested as an effective antihypertensive intervention in women with hypertension.[4] Also be aware that some of the indications for beta blockers, including hypertension and migraine are cautions for, or preclude the use of, combined hormonal contraceptives.

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Beta blockers + Hydralazine

The plasma levels of propranolol and other extensively metabolised beta blockers (such as metoprolol and oxprenolol) are increased by hydralazine, but no increase in adverse effects appears to have been reported.

Clinical evidence

In a study in 5 healthy subjects, single 25- and 50-mg doses of hydralazine increased the AUC of a single 40-mg dose of **propranolol** by 60% and 110%, respectively, and raised the peak plasma levels by 144 and 240%, respectively,[1] Similarly, in another single-dose study, hydralazine increased the AUC of **propranolol** by 62 to 77%.[2] However, a further single-dose study using sustained-release **propranolol** found that hydralazine had no effect on **propranolol** pharmacokinetics.[3]

In other studies hydralazine increased the AUC of sustained-release **oxprenolol** by 41% at steady-state;[4] whereas **oxprenolol** was found not to have a significant effect on the pharmacokinetics of hydralazine.[4]

Further studies have found that hydralazine increases the AUC of **metoprolol** by 30% after a single dose,[5] and by 38% at steady-state,[6] whereas hydralazine did not affect the AUC of **acebutolol** or **nadolol** in single-dose studies.[5]

Mechanism

Uncertain. Hydralazine appears to increase the bioavailability of those beta blockers that undergo high hepatic extraction and not those that are largely excreted unchanged in the urine. Hepatic extraction is discussed in more detail under 'Changes in first-pass metabolism', (p.4), and 'Table 22.1', (p.995), lists the metabolic routes of the commonly used systemic beta blockers. It has been suggested that hydralazine may alter hepatic blood flow or inhibit hepatic enzymes,[1,5,6] although other mechanisms may also be involved.[3,7,8]

Importance and management

Moderately well documented and established interactions, but the increased beta blocker plasma levels appear to cause no adverse clinical effect. Concurrent use is usually valuable in the treatment of hypertension, and it has been suggested that the addition of beta blockers may provide additional benefit in patients taking hydralazine and isosorbide dinitrate for heart failure.[9]

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Beta blockers + Imatinib

The plasma levels of metoprolol are slightly increased by imatinib.

Clinical evidence

In a pharmacokinetic study in 20 Chinese patients, a single 100-mg dose of **metoprolol** was given alone and then on day 7 of a 9-day course of imatinib 400 mg twice daily. The AUC and maximum plasma levels of **metoprolol** were increased by about 20%, with an increase in AUC of 24% in 13 patients that were CYP2D6 extensive metabolisers (that is, those with normal levels of this isoenzyme) and by 17% in 7 patients that were said to be CYP2D6 intermediate metabolisers (those with lower levels of this isoenzyme). There were no clinically significant changes in laboratory parameters, vital signs or ECG recordings.[1]

Mechanism

The manufacturer notes that *in vitro*, imatinib inhibits the cytochrome P450 isoenzyme CYP2D6,[2] by which metoprolol is extensively metabolised. The study shows that clinically imatinib is only a weak CYP2D6 inhibitor.

Importance and management

The increase in metoprolol levels seen here is not clinically important, and no interaction would be expected. Nevertheless, the manufacturer of imatinib recommends that clinical monitoring should be considered in patients taking metoprolol when given imatinib, because they consider metoprolol to be a drug with a narrow therapeutic index.[2] However, metoprolol is only usually classified as such in patients with heart failure, and even then, increases of this magnitude are not considered clinically relevant. Therefore this advice seems over cautious. There appears to be no information about other beta blockers, but all those metabolised by CYP2D6 would be expected to be affected by imatinib to some extent. See 'Table 22.1', (p.995), for a list.

In addition, on the basis of this study, the manufacturer says that dose adjustments are not likely to be necessary when imatinib is given with any CYP2D6 substrates. However, they do recommend caution with those that have a narrow therapeutic index,[2] although this seems over cautious.

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Beta blockers + Inotropes and Vasopressors

Effects on blood pressure and heart rate: the hypertensive effects of adrenaline (epinephrine) can be markedly increased in patients taking non-selective beta blockers such as propranolol. A severe and potentially life-threatening hypertensive reaction and/or marked bradycardia can develop. Cardioselective beta blockers such as atenolol and metoprolol interact minimally. Dobutamine would be expected to interact similarly, but some studies and case reports suggest that paradoxical effects may occur. The pressor effects of noradrenaline appear to be diminished by the beta blockers. An isolated report describes a fatal hypertensive reaction in a patient given propranolol and phenylephrine, but concurrent use normally seems to be uneventful.
Anaphylaxis: some evidence suggests that anaphylactic shock in patients taking beta blockers may be resistant to treatment with adrenaline (epinephrine).

Clinical evidence

A. Effects on blood pressure and heart rate

(a) Adrenaline (Epinephrine)

1. Non-selective beta blockers. An early study in 10 healthy subjects found that intravenous adrenaline (epinephrine) 5 micrograms/minute increased heart rates and caused minimal changes in blood pressure. However, after pretreatment with intravenous **propranolol** 10 mg, the same dose of adrenaline caused a *fall* in heart rate of 12 bpm and an increase in arterial pressure of 20/10 mmHg.[1] One case report describes 6 patients taking **propranolol** 20 to 80 mg daily, undergoing plastic surgery, who experienced marked hypertensive reactions (blood pressures in the range of 190/110 to 260/150 mmHg) and bradycardia when their eyelids and/or faces were infiltrated with 8 to 40 mL of local anaesthetic solutions of lidocaine containing 1:100 000 or 1:200 000 (10 or 5 micrograms/mL) of adrenaline. Cardiac arrest occurred in one patient.[2]
Similar marked increases in blood pressure, associated with marked bradycardia, have been described in other studies and case reports involving the use of adrenaline and **propranolol**.[3-11]
After pretreatment with a single 5-mg dose of **pindolol**, only small reductions in blood pressure (4 mmHg) and heart rate (about 5 bpm) were seen with the intra-oral injection of 3.6 mL of lidocaine 2% containing 1:80 000 adrenaline (45 micrograms of adrenaline) in healthy subjects.[12]
In 24 healthy subjects given either **nadolol**, atenolol or placebo for 1 week followed by an infusion of adrenaline, mean arterial pressure and calf vascular resistance rose markedly in the **nadolol**-treated group. Marked bradycardia also occurred in those given **nadolol** and adrenaline.[13]

2. Selective beta blockers. A study in which adrenaline (epinephrine) was given to patients taking **metoprolol**, found only a small rise in blood pressure.[4] This was confirmed in another study in which patients given identical infusions of adrenaline developed a hypertensive/bradycardic reaction while taking propranolol but not while taking **metoprolol**.[5] In 24 healthy subjects given either nadolol, **atenolol** or placebo for 1 week followed by an infusion of adrenaline, mean arterial pressure and calf vascular resistance was not affected in the **atenolol** group.[13]

3. Beta blockers with alpha-blocking activity. In 6 healthy subjects, giving adrenaline after intravenous **labetalol** 1 mg/kg, resulted in a 13 to 21 mmHg increase in mean arterial pressure and a 23 to 29 bpm reduction in heart rate, when compared with adrenaline alone.[14]

(b) Dobutamine

A 54-year-old man with severe heart failure was given **carvedilol** 3.125 to 6.25 mg twice daily. His symptoms worsened and he was admitted for treatment with intravenous dobutamine; the **carvedilol** was discontinued and other medications apart from furosemide were withheld short-term. Dobutamine was started at 1 microgram/kg per minute and gradually increased to 5 micrograms/kg per minute. However, with each 1 microgram/kg increment the systolic blood pressure *dropped* to about 70 mmHg for 5 to 10 minutes and then quickly returned to the baseline level of 80 to 84 mmHg. When the dose of dobutamine reached 5 micrograms/kg per minute, his systolic blood pressure dropped to 56 mmHg and the dobutamine was discontinued. The blood pressure returned to normal over the next 30 minutes. Two months later when the patient was no longer taking **carvedilol** he was again given intravenous dobutamine and his systolic blood pressure increased, as would be expected.[15]

(c) Isoprenaline (Isoproterenol)

In a study in patients with asthma, oral doses of the non-selective beta blockers **propranolol** 100 mg, **oxprenolol** 100 mg, **pindolol** 5 mg and **timolol** 10 mg blocked the bronchodilator response to inhaled isoprenaline 1.5 mg, but the selective beta blockers **metoprolol** 100 mg, **acebutolol** 300 mg and **atenolol** 100 mg did not interfere with bronchodilatation.[16]
In a placebo-controlled study in healthy subjects, isoprenaline 0.03 micrograms/kg per minute was infused over 5 minutes, 30 minutes before single oral doses of either **metoprolol** 40 mg or 80 mg or **propranolol** 40 mg were given. Isoprenaline 0.09 micrograms/kg per minute [for 5 minutes] was then given at intervals of 30 minutes starting 60 minutes after administration of the beta blocker. Isoprenaline increased heart rate by a mean of 32 bpm. Although the dose of isoprenaline was increased threefold after administration of the beta blockers, the effect of isoprenaline after **propranolol** was very small and consistently more reduced by **propranolol** than by **metoprolol**.[17] Another study in patients with hypertension found that the blood pressure and cardiac responses to isoprenaline were attenuated or inhibited by both intravenous **propranolol** and **pindolol**.[18] In a study in 6 healthy subjects, intravenous **labetalol** 1.5 mg/kg antagonised the increases in heart rate and diastolic pressure due to isoprenaline.[19] A further study in 12 healthy subjects found that a single 40-mg dose of **nadolol** attenuated isoprenaline-evoked venodilatation in the dorsal hand vein; **bisoprolol** 5 mg had no effect on the response to isoprenaline.[20]

(d) Noradrenaline (Norepinephrine)

A study in patients with hypertension found that the initial increase in heart rate due to noradrenaline was attenuated by intravenous **propranolol** 670 micrograms/kg and abolished by intravenous **pindolol** 35 micrograms/kg and the fall in systolic pressure was abolished by beta blockade. After the initial response, noradrenaline produced a fall in heart rate and rise in systolic pressure which was not affected by **propranolol** but virtually abolished by **pindolol**.[18] In another study in healthy subjects, the increase in blood pressure due to noradrenaline was antagonised by intravenous **labetalol** 1.5 mg/kg.[19] In studies in 12 healthy subjects, single doses of **bisoprolol** 5 mg or 10 mg were found to decrease the venoconstriction in the dorsal hand vein associated with infusion of noradrenaline; **nadolol** 40 mg had no effect on the response to noradrenaline.[21,22]

(e) Phenylephrine

A woman taking **propranolol** 40 mg four times daily for hypertension was given phenylephrine hydrochloride 10% solution, one drop in each eye, during an ophthalmic examination. About 45 minutes later she complained of a sudden and sharp bi-temporal pain and shortly afterwards became unconscious. She later died of an intracerebral haemorrhage due to the rupture of a berry aneurysm. She had received a similar dose of phenylephrine on a previous occasion in the absence of **propranolol** without any problems.[23]

However, no change in blood pressure was seen in a study in both normotensive subjects and patients taking **metoprolol** who were given 0.5 to 4-mg intranasal doses of phenylephrine every hour, to a total of 7.5 to 15 mg (4 to 30 times the usual dose).[24] Similarly, in a placebo-controlled study in 12 hypertensive patients, **propranolol** and **metoprolol** did not significantly alter the dose of intravenous phenylephrine required to cause a 25 mmHg increase in systolic blood pressure.[25] In a study in 12 healthy subjects, single doses of **bisoprolol** 5 mg or 10 mg were found to decrease the venoconstriction in the dorsal hand vein associated with infusion of phenylephrine.[21]

B. Anaphylaxis: resistance to treatment

A patient taking **propranolol** who suffered an anaphylactic reaction after receiving an allergy injection for desensitisation did not respond to adrenaline (epinephrine) and required intubation.[26] Anaphylactic shock, refractory to adrenaline, occurred in a penicillin-allergic patient taking **acebutolol** after she accidentally took amoxicillin.[27] Resistance to adrenaline treatment for anaphylaxis occurred in another patient using **timolol** eye drops.[28] It has also been proposed that the incidence and severity of anaphylactic reactions may be increased in those taking beta blockers,[29,30] one idea being that the adrenoceptors concerned with suppressing the release of the mediators of anaphylaxis may be blocked by either $beta_1$ or $beta_2$ antagonists.[29] However, one study failed to find any evidence to support an increased incidence of systemic reactions in patients taking beta blockers receiving allergen immunotherapy.[31] See also 'X-ray contrast media', (p.1021), and 'penicillins', (p.1014), for other anaphylactic reactions potentially exacerbated by beta blockers.

A beta-agonist bronchodilator, for example isoprenaline (isoproterenol) or salbutamol (albuterol) may be effective in patients taking beta blockers with anaphylaxis resistant to adrenaline,[29] and glucagon was effective in treating a severe anaphylactoid reaction in one patient taking a beta blocker.[30] Severe hypertension, sometimes with bradycardia, has been described following the use of adrenaline to treat allergic reactions, including presumed anaphylaxis, in patients taking **propranolol**.[6-8] These are discussed under *Effects on blood pressure and heart rate,* above.

Mechanism

Adrenaline (**epinephrine**) stimulates alpha- and beta-receptors of the cardiovascular system, the former results in vasoconstriction (mainly $alpha_1$) and the latter in both vasodilatation (mainly $beta_2$), and stimulation of the heart (mainly $beta_1$). The net result is usually a modest increase in heart rate and a small rise in blood pressure. However, if the beta-receptors are blocked by a non-selective beta blocker, such as propranolol or nadolol (see 'Table 22.1', (p.995) for a list), the unopposed alpha vasoconstriction causes a marked rise in blood pressure, followed by reflex bradycardia. Cardioselective beta blockers such as atenolol and metoprolol, which are more selective for $beta_1$ receptors, do not prevent the vasodilator action of adrenaline at $beta_2$ receptors to the same extent, and therefore the effect of any interaction is relatively small. Consequently, adrenaline has been used to assess the degree of beta blockade produced by propranolol and other beta blockers.[13,32]

Noradrenaline (**norepinephrine**) stimulates alpha receptors (although to a lesser extent than adrenaline) and $beta_1$ receptors but has minimal effects on $beta_2$ receptors. The precise mechanism for the effects of the beta blockers on the pressor effects of noradrenaline are unclear, but as beta blockers lower blood pressure and noradrenaline raises blood pressure a reduction in the response to noradrenaline is not unexpected.

Isoprenaline (**isoproterenol**) acts almost exclusively on beta-receptors and the increase in heart rate is due to stimulation of the heart ($beta_1$), increase in sympathetic nerve activity secondary to peripheral vasodilatation ($beta_2$), and direct effect on the heart ($beta_2$). Nadolol, pindolol and propranolol exert their effects by blockade at both $beta_1$ and $beta_2$ receptors while bisoprolol and metoprolol, which are selective for $beta_1$ receptors, exert less effect on the isoprenaline-induced effects on heart rate or venodilatation. Labetalol is also a non-selective beta blocker (and alpha blocker) and also antagonises the effects of isoprenaline.

Phenylephrine is largely an alpha stimulator, therefore beta blockers should have a minimal effect on its action.

Dobutamine is a $beta_1$, $beta_2$ and $alpha_1$ adrenergic agonist and carvedilol is a non-selective beta blocker, but at low doses it is primarily a selective $beta_1$ adrenergic antagonist and it is also an $alpha_1$ antagonist. It was proposed that the drop in blood pressure was caused by vasodilation due to vascular $beta_2$ receptor activation, which was not blocked by low doses of carvedilol.[15]

Importance and management

The interaction between propranolol and **adrenaline** (**epinephrine**) is established. It may be serious and potentially life-threatening, depending on the dosage of adrenaline used. Marked and serious blood pressure rises and severe bradycardia have occurred in patients given 300 micrograms of adrenaline (0.3 mL of 1:1000) subcutaneously[6-8] or 40 to 400 micrograms by infiltration of the skin and eyelids during plastic surgery.[2] Adrenaline 15 micrograms given intravenously can cause an almost 40% fall in heart rate.[9] Patients taking non-selective beta blockers such as propranolol (see 'Table 22.1', (p.995) for a list) should only be given adrenaline in very reduced dosages because of the marked bradycardia and hypertension that can occur. Acute hypertensive episodes have been controlled with chlorpromazine or phentolamine (both of which are alpha blockers). Hydralazine,[2,10] nifedipine[7] and aminophylline[10] have also been used. Reflex bradycardia may be managed with atropine and the pre-emptive use of glycopyrrolate has also been suggested.[10] A less marked effect is likely with the cardioselective beta blockers,[4] such as atenolol and metoprolol (see 'Table 22.1', (p.995) for a list). Local anaesthetics used in dental surgery usually contain very low concentrations of adrenaline (e.g. 5 to 20 micrograms/mL, i.e. 1:200 000 to 1:50 000) and only small volumes are usually given, so that an undesirable interaction is unlikely.

Similar effects to those seen with adrenaline (hypotension and reflex bradycardia) are also theoretically possible if **dobutamine**, which also causes alpha- and beta-receptor stimulation, is given with a beta blocker (see adrenaline under *Mechanism*, above), but the case report describing *hypotension* suggests that the effects may not always be predictable.

In general, the beta blockers appear to attenuate the rise in blood pressure caused by **noradrenaline** (**norepinephrine**); beta blockers are often omitted in patients requiring inotropic support with noradrenaline for this reason. Some sources suggest that noradrenaline will interact with beta blockers in the same way as adrenaline, but there does not seem to be any evidence supporting this prediction. Furthermore, it should be noted that the beta effects of noradrenaline are not the same as those of adrenaline (see *Mechanism*, above).

No interaction between **phenylephrine** and the beta blockers would be expected, and apart from the single unexplained case cited above, the literature appears to support this. Concurrent use normally appears to be clinically unimportant, particularly bearing in mind the widespread use of beta blockers and the ready availability of phenylephrine in the form of non-prescription cough-and-cold remedies and nasal decongestants.

Similarly, an interaction resulting in hypertension and reflex bradycardia would not be expected if **isoprenaline** (**isoproterenol**) is given with a beta blocker, and the studies support this theory. However, the studies do suggest that the bronchodilator effects of isoprenaline may be antagonised by non-selective beta blockers.

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Beta blockers + Itraconazole

Itraconazole markedly increases the bioavailability of celiprolol and only slightly affects the pharmacokinetics of atenolol, without affecting heart rate or blood pressure.

Clinical evidence, mechanism, importance and management

(a) Atenolol

In a study in 10 healthy subjects itraconazole 200 mg twice daily for 5 doses had only minor effects on the pharmacokinetics of a single 50-mg dose of atenolol and no effects on heart rate or blood pressure were seen.[1]

(b) Celiprolol

In a study in 12 healthy subjects, itraconazole 200 mg twice daily for 5 doses increased the AUC of a single 100-mg dose of celiprolol by 80%, without increasing its half-life. However, itraconazole did not increase the effect of celiprolol on heart rate or blood pressure.[2]

It was suggested that itraconazole probably increases the absorption of celiprolol by inhibiting P-glycoprotein in the intestinal wall.[2] Although the increase in plasma levels was marked, it was suggested that it is unlikely to be clinically relevant because celiprolol has a wide therapeutic range.[2]

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Beta blockers + Macrolides

The serum levels of talinolol and possibly nadolol are increased by erythromycin, and telithromycin may increase the bioavailability of metoprolol. A study suggests that telithromycin does not adversely affect sotalol-induced QT prolongation, whereas the combined use of sotalol and intravenous erythromycin should generally be avoided because of the possible additive effects on QT interval prolongation.

Clinical evidence, mechanism, importance and management

(a) Metoprolol

The peak plasma level and AUC of metoprolol are reported to be increased by about 38% by **telithromycin**, but the elimination half-life is not affected. The manufacturer of **telithromycin** considers the increased exposure to metoprolol may be of clinical importance in patients with heart failure, and that in such patients, caution is suggested.[1] However, other interactions suggest that the levels of metoprolol may need to be almost doubled before this interaction becomes clinically relevant, even in patients with heart failure.

(b) Nadolol

A study, in which 7 healthy subjects were given a single 80-mg dose of nadolol after **erythromycin** 500 mg plus neomycin 500 mg every 6 hours for 2 days, suggested an increase in the rate of beta blocker absorption (reduced time to maximum plasma level, but no effect on AUC). A decrease in the elimination half-life was also seen.[2] More study is needed to determine the clinical significance of these findings, but any effect seems likely to be small.

(c) Sotalol

Sotalol prolongs the QT interval and should generally not be given with other drugs that do the same, such as intravenous **erythromycin**, because of the increased risk of torsade de pointes arrhythmia (see also 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290). **Telithromycin** does not appear to be associated with QT prolongation and a study in 24 healthy women found that a single 800-mg dose of **telithromycin** had no adverse effect on the QT-prolongation induced by a 160-mg dose of sotalol. **Telithromycin** slightly reduced the AUC and maximum serum levels of sotalol, which was attributed to a decrease in its absorption,[3] but this is expected to be of little clinical significance.

(d) Talinolol

A single-dose study in 8 healthy subjects found that the AUC and serum levels of talinolol 50 mg were increased by 51% and 26%, respectively, by **erythromycin** 2 g. It was suggested that the increased bioavailability of talinolol was due to increased intestinal absorption caused by the inhibition of P-glycoprotein by **erythromycin**.[4]

The clinical relevance of these effects is unclear, but until more is known it may be prudent to monitor the outcome of concurrent use to ensure the beta blocker effects are not excessive.

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Beta blockers + Metoclopramide

A patient with scleroderma suffered a fatal cardiac arrest after receiving intravenous labetalol and intravenous metoclopramide postoperatively. Metoclopramide increased the rate of absorption of a conventional formulation of propranolol, but did not affect a sustained-release preparation.

Clinical evidence, mechanism, importance and management

(a) Labetalol

A 38-year-old patient with scleroderma, hypertension (for which she was taking lisinopril) and gangrene of her left index finger underwent minor hand surgery. While in postoperative care her blood pressure rose to 153/120 mmHg and she was given intravenous labetalol 10 mg. About 15 minutes later she experienced nausea and vomiting, and so she was given intravenous metoclopramide 10 mg. About 5 minutes later her heart rate decreased to 38 bpm and she became unresponsive with no palpable

pulse: an ECG showed junctional bradycardia. She was initially resuscitated but died about 13 hours later after a further episode of bradycardia, despite full supportive treatment. It was noted that the bradycardia did not respond well to atropine, and there was persistent hypotension, despite escalating vasopressor use.

Scleroderma and lisinopril may have contributed to the failure to resuscitate the patient; however, bradycardia or heart block and hypotension may occur with intravenous metoclopramide. In this patient the use of labetalol may have exacerbated the effects of metoclopramide by causing reductions in ventricular contractility due to its beta-adrenergic effects and limiting vasoconstrictive compensatory mechanisms due to alpha-adrenergic effects.[1] However, it has subsequently been suggested that this reaction may have been due to local anaesthetic toxicity rather than a drug interaction,[2] although this was disputed by the original authors.[3]

A study in 11 untreated hypertensive patients found that intravenous metoclopramide (7.5 micrograms/kg per minute for 30 minutes) caused a slight decrease in the responsiveness to labetalol 400 to 600 mg daily. However, as metoclopramide only attenuated the systolic blood pressure response to labetalol by 3 mmHg this effect seems unlikely to be clinically significant in most patients.[4]

(b) Propranolol

In a study in 12 healthy subjects metoclopramide syrup 20 mg, given 30 minutes before sustained-release propranolol 160 mg, had no effect on the pharmacokinetics of propranolol.[5] In contrast, an earlier brief report found that the rate of absorption of a conventional formulation of propranolol 80 mg was increased by intravenous metoclopramide 10 mg in 4 healthy subjects. In the first 2 hours after dosing, propranolol levels were increased by 1.3 to 2.5-fold.[6] However, these changes are unlikely to be clinically relevant.

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Beta blockers + Morphine

Morphine may moderately raise the serum levels of esmolol in some patients. The fatal doses of morphine and propranolol are markedly reduced by concurrent use in *animals*, but the clinical relevance of this in man is uncertain.

Clinical evidence, mechanism, importance and management

In a study in 10 healthy men a 3-mg injection of morphine sulfate increased the steady-state levels of a 300 microgram/kg per minute infusion of **esmolol**, given over 4 hours. However, the increases were only statistically significant in 2 of the subjects (increase of 46%), and were considered to be of no clinical importance. The pharmacokinetics of morphine were unchanged.[1]

Studies in *animals* have shown that the median fatal dose of **propranolol** was reduced two- to sevenfold by morphine in *mice*[2] and the median lethal dose of morphine was reduced fifteen- to sixteenfold by **propranolol** in *rats*.[3] The same interaction has also been seen in *dogs*.[3] There do not appear to be any published reports of synergistic toxicity involving morphine and **propranolol**, so the clinical relevance of this is uncertain.

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3. Davis WM, Hatoum NS. Possible toxic interaction of propranolol and narcotic analgesics. *Drug Intell Clin Pharm* (1981) 15, 290–1.

Beta blockers + Penicillins

Plasma atenolol levels are halved by 1-g doses of ampicillin, but no important interaction occurs if atenolol is given with ampicillin 250 mg every 6 hours. One brief report suggests that anaphylactic reactions to penicillins may be more severe in patients taking beta blockers.

Clinical evidence

In a single-dose study in 6 healthy subjects, **ampicillin** 1 g reduced the AUC of **atenolol** 100 mg by 40%, and decreased its bioavailability from 60% to 36%.[1] Similarly, when **atenolol** 100 mg was given with **ampicillin** 1 g daily for 6 days, the mean steady-state plasma atenolol level was reduced by 52% (from 199 to 95 nanograms/mL), and the AUC was reduced by 52%. The blood pressure lowering effect of **atenolol** at rest was not affected, but after exercise a small rise in systolic pressure of up to 17 mmHg occurred, whereas diastolic pressure was unchanged. The effects of **atenolol** on reducing heart rate during exercise were diminished from 24% to 11% at 12 hours.[1]

A further single-dose study found that when **atenolol** 50 mg was given with oral **ampicillin** 1 g the AUC of **atenolol** was reduced by 52%, whereas when **ampicillin** 250 mg four times daily was given for 24 hours, the AUC was only reduced by 18%.[2]

A brief report describes 2 patients, one taking **nadolol** and one taking **propranolol**, who developed fatal anaphylactic shock after taking **phenoxymethylpenicillin**. The authors suggested that, as fatal reactions to penicillins are rare, the reaction had been exacerbated by the presence of a non-selective beta blocker.[3] For a report of anaphylaxis associated with **amoxicillin**, refractory to adrenaline treatment, in a patient taking **acebutolol**, see 'Beta blockers + Inotropes and Vasopressors', p.1011.

Mechanism

Uncertain. Ampicillin, in large doses, apparently affects the absorption of atenolol.

Importance and management

Information about interactions between penicillins and beta blockers is limited, but the absorption interaction between 1 g dose of ampicillin and atenolol appears to be established. The clinical importance awaits full evaluation but the modest effects on blood pressure and heart rate[1] suggest that it is of limited importance. Information about other beta blockers and penicillins is lacking. Information on potentiation of anaphylaxis is too limited to make comment, but note that some evidence suggests that anaphylactic shock in patients taking beta blockers may be resistant to treatment with adrenaline (epinephrine), see 'Beta blockers + Inotropes and Vasopressors', p.1011.

1. Schäfer-Korting M, Kirch W, Axthelm T, Köhler H, Mutschler E. Atenolol interaction with aspirin, allopurinol, and ampicillin. *Clin Pharmacol Ther* (1983) 33, 283–8.
2. McLean AJ, Tonkin A, McCarthy P, Harrison P. Dose-dependence of atenolol-ampicillin interaction. *Br J Clin Pharmacol* (1984) 18, 969–71.
3. Berkelman RL, Finton RJ, Elsea WR. Beta-adrenergic antagonists and fatal anaphylactic reactions to oral penicillins. *Ann Intern Med* (1986) 104, 134.

Beta blockers + Phenothiazines

The concurrent use of chlorpromazine with propranolol can result in a marked rise in the plasma levels of both drugs. A similar interaction appears to occur between thioridazine and pindolol. Propranolol markedly increases plasma thioridazine levels. Both beta blockers and phenothiazines can cause hypotension, and these effects could be additive: a handful of case reports suggest that this could occasionally be serious. The concurrent use of sotalol and phenothiazines that prolong the QT interval should generally be avoided.

Clinical evidence

(a) Chlorpromazine

In 4 healthy subjects and one hypertensive patient the mean steady-state levels of **propranolol** 80 mg every 8 hours were raised by 70% (from 41.5 nanograms/mL to 70.2 nanograms/mL) when they were given chlorpromazine 50 mg every 8 hours.[1] The increase was considerable in some subjects but barely detectable in others. A sixth subject taking **propranolol** promptly fainted when getting out of bed after the first dose of chlorpromazine. He was found to have a pulse rate of 35 to 40 bpm and a

blood pressure of 70/0 mmHg. He rapidly recovered, achieving a pulse rate of 85 bpm and a blood pressure of 120/70 mmHg when given atropine 3 mg. However, it is unclear whether the adverse effect was due to chlorpromazine alone, or to an interaction with **propranolol**.[1]

Propranolol (mean daily dose 8.1 mg/kg) increased the serum chlorpromazine levels of 7 schizophrenics by about 100 to 500%, and raised the plasma levels of the active metabolites of chlorpromazine by about 50 to 100%.[2] The same or similar work by the same authors is described elsewhere.[3] One of the patients was withdrawn from the study because he suffered a cardiovascular collapse while taking both drugs.[3] It has been suggested that the value of **propranolol** in the treatment of schizophrenia probably results from the rise in serum chlorpromazine levels.[3]

A report briefly mentions a diabetic girl who had an episode of minor hypotension with chlorpromazine that appeared to have been exacerbated by **sotalol**.[4] A schizophrenic patient taking chlorpromazine and **tiotixene** experienced delirium, grand mal seizures and skin photosensitivity, attributed to a rise in the serum levels of the antipsychotic drugs caused by increasing doses of **propranolol** (up to a total of 1.2 g daily).[5]

(b) Thioridazine

Serum **pindolol** levels were 2.5-fold higher in 7 patients taking thioridazine than in 17 patients taking haloperidol, phenytoin, and/or phenobarbital.[6] Furthermore, **pindolol** 40 mg daily increased serum thioridazine levels by about 50% in 8 patients.[6]

Two patients, who were stable taking thioridazine 600 or 800 mg daily, had three- and fivefold rises in plasma levels, respectively, when given **propranolol**, in increasing doses up to a total of 800 mg daily, over 26 to 40 days. No signs or symptoms of thioridazine toxicity were seen even though plasma levels had risen into the toxic range.[7] Similarly, in another study thioridazine levels rose by about 55 to 370% in 5 patients taking **propranolol** 320 to 520 mg daily.[8]

Mechanism

Pharmacokinetic evidence[1] and *animal* studies[9] suggest that propranolol and chlorpromazine mutually inhibit the liver metabolism of the other drug so that both accumulate within the body. The mechanism of the interaction between propranolol and thioridazine is probably similar. Thioridazine is an inhibitor of cytochrome P450 isoenzyme CYP2D6 and may inhibit the metabolism of propranolol and metoprolol, which are substrates for this isoenzyme. Both beta blockers and phenothiazines can cause hypotension, and these effects could be additive.

Importance and management

The interaction between propranolol and chlorpromazine appears to be established although information is limited. Concurrent use should be well monitored and the dosages reduced if necessary. The same precautions apply with propranolol and thioridazine.[7] The manufacturer of **metoprolol** advises caution with the concurrent use of thioridazine.[10] Normally the beta blockers are considered to have a wide therapeutic range, and so increases in levels are generally well tolerated. Patients with heart failure are usually more at risk, because drugs such as metoprolol lose their selectivity at higher levels, and therefore, until the magnitude of any interaction is known, some monitoring (e.g. for shortness of breath, bradycardia, hypotension) may be prudent.

There seems to be no information about any interaction between other beta blockers and phenothiazines, but if the mechanism of interaction suggested above is true, it seems possible that other beta blockers that are mainly cleared from the body by liver metabolism might interact similarly with chlorpromazine, whereas those mainly cleared unchanged in the urine are less likely to have a pharmacokinetic interaction, although additive hypotensive effects would still be expected. See 'Table 22.1', (p.995), for information on the metabolism of the commonly used systemic beta blockers.

Note that **sotalol** and some phenothiazines, including chlorpromazine and thioridazine prolong the QT interval (see 'Table 9.2', (p.290) for a more extensive list). Combined use should therefore generally be avoided, because of the increased risk of torsade de pointes. See also 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290.

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2. Peet M, Middlemiss DN, Yates RA. Pharmacokinetic interaction between propranolol and chlorpromazine in schizophrenic patients. *Lancet* (1980) ii, 978.
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4. Baker L, Barcai A, Kaye R, Haque N. Beta adrenergic blockade and juvenile diabetes: acute studies and long-term therapeutic trial. *J Pediatr* (1969) 75, 19–29.
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7. Silver JM, Yudofsky SC, Kogan M, Katz BL. Elevation of thioridazine plasma levels by propranolol. *Am J Psychiatry* (1986) 143, 1290–2.
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9. Shand DG, Oates JA. Metabolism of propranolol by rat liver microsomes and its inhibition by phenothiazine and tricyclic antidepressant drugs. *Biochem Pharmacol* (1971) 20, 1720–3.
10. Lopresor (Metoprolol tartrate). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, July 2008.

Beta blockers + Phenylpropanolamine

A small rise in blood pressure may occur in patients taking beta blockers who take single doses of phenylpropanolamine, but there only appears to be one case report (in a patient taking oxprenolol with methyldopa and phenylpropanolamine) that describes an adverse effect from this interaction. Propranolol attenuates the blood pressure rise seen with phenylpropanolamine.

Clinical evidence, mechanism, importance and management

(a) Effect on beta blockers

A study in 13 patients taking various antihypertensives, including 5 taking unnamed beta blockers, found that a single dose of *Dimetapp Extentabs* (phenylpropanolamine 75 mg with brompheniramine 12 mg) caused a blood pressure rise of 1.7/0.9 mmHg over a 4-hour period, which was not statistically or clinically significant.[1] Another study in 7 stabilised hypertensive patients taking beta blockers (**atenolol** 5 patients, **metoprolol** 1, **propranolol** 1) found that a single 25-mg dose of rapid-release phenylpropanolamine (*Super Odrinex*) increased the mean peak blood pressures by about 8/5 mmHg over a 6-hour period.[2] These rises in blood pressure after single doses are small and relatively short-lived, and probably of little clinical importance. A later multiple dose study in the same subjects (only 5 of whom completed the study), taking the same beta blockers, found that on day 1 phenylpropanolamine increased diastolic blood pressure by 9 to 16 mmHg, and on day 7 by up to 14 mmHg. The day 1 and day 7 results were not statistically different, which suggests that the increase in blood pressure is not enhanced by multiple dosing.[3] Note that a marked rise in blood pressure was seen in one patient taking methyldopa and oxprenolol when phenylpropanolamine was also given, see 'Methyldopa + Nasal decongestants', p.1070.

(b) Effect on phenylpropanolamine

In a placebo-controlled study in 6 healthy subjects, **propranolol** given either orally as a pretreatment or intravenously after phenylpropanolamine, was found to antagonise the rise in blood pressure induced by the phenylpropanolamine. Oral phenylpropanolamine 75 mg alone increased blood pressure from 116/63 to 148/83 mmHg; pretreatment with oral **propranolol** 80 mg every 6 hours reduced the baseline blood pressure to 107/62 mmHg and the increase with phenylpropanolamine was lower, reaching only 119/72 mmHg. Intravenous **propranolol** 0.3 mg/kg given after the phenylpropanolamine decreased blood pressure from 144/87 to 121/84 mmHg.[4]

1. Petrulis AS, Imperiale TF, Speroff T. The acute effect of phenylpropanolamine and brompheniramine on blood pressure in controlled hypertension. *J Gen Intern Med* (1991) 6, 503–6.
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3. O'Connell MB, Gross CR. The effect of multiple doses of phenylpropanolamine on the blood pressure of patients whose hypertension was controlled with β blockers. *Pharmacotherapy* (1991) 11, 376–81.
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Beta blockers + Pilocarpine

The concurrent use of pilocarpine and beta blockers is said to be associated with a risk of conduction disorders.

Clinical evidence, mechanism, importance and management

The manufacturer of *oral* pilocarpine notes that it should be given with caution to patients taking beta blockers because of the possibility of con-

duction disorders.[1] Although palpitations are said to be common with the use of oral pilocarpine there appears to be no published reports to suggest that the concurrent use of a beta blocker presents an additional risk.

Adverse effects from pilocarpine *eye drops* appear rare but cases of cardiac decompensation have been reported, although these followed the use of excessive doses of pilocarpine before surgery.[2]

1. Salagen (Pilocarpine hydrochloride). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, September 2007.
2. Everitt DE, Avorn J. Systemic effects of medications used to treat glaucoma. *Ann Intern Med* (1990) 112, 120–25.

Beta blockers + Policosanol

Policosanol appears to increase the blood pressure-lowering effects of beta blockers.

Clinical evidence

In a randomised study in patients aged 60 to 80 years taking beta blockers, the addition of policosanol 5 mg tablets daily (titrated to a dose of 2 to 4 tablets) found that the average blood pressure was reduced from about 141/83 mmHg to 131/81 mmHg after one year, and to 126/79 mmHg after 3 years. The efficacy of policosanol was not reduced and adverse effects were actually slightly lower in the policosanol group.[1]

Mechanism

Policosanol is thought to reduce vascular resistance.

Importance and management

Policosanol increased the blood pressure-lowering effects of beta blockers and the clinical study suggests that the effect is gradual and beneficial. Furthermore, adverse effects related to hypotension were not reported. It therefore appears that, as with other conventional antihypertensives, policosanol may increase the effects of the beta blockers and so some caution is warranted, but no adverse effects such as first-dose hypotension would be expected.

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Beta blockers + Potassium-depleting drugs

The use of potassium-depleting diuretics can precipitate the development of potentially life-threatening torsade de pointes arrhythmias in patients taking sotalol, unless potassium levels are maintained. This would also be expected with other potassium-depleting drugs such as corticosteroids, possibly some laxatives, and intravenous amphotericin.
Chlortalidone and hydrochlorothiazide may reduce the bioavailability of celiprolol, but the evidence for this is sparse.

Clinical evidence

(a) Pharmacokinetic effects

A study in 12 healthy subjects found that when **sotalol** 160 mg was given with **hydrochlorothiazide** 25 mg the pharmacokinetics of both drugs were unchanged.[1]

The manufacturers of **celiprolol** suggest that **chlortalidone** and **hydrochlorothiazide** reduce its bioavailability.[2] This appears to be based on an *in vitro* study,[3] which found that **chlortalidone** and **hydrochlorothiazide** blocked the active transport of **celiprolol** across the intestinal epithelium. The authors of this study also cite a single-dose study that found that **chlortalidone** decreased the bioavailability of **celiprolol**, but details are not given.

(b) QT-prolongation

A 4-year study in cardiac clinics in South Africa identified 13 patients who developed syncope and a prolonged QT interval while taking **sotalol** 80 to 480 mg daily. Twelve patients were taking a combined preparation (*Sotazide*) containing **sotalol** 160 mg and **hydrochlorothiazide** 25 mg. Eleven patients were being treated for hypertension, one for ventricular asystoles, and one for both. Polymorphous ventricular tachycardia was seen in 12 of the patients, and torsade de pointes were seen in 10 of these 12. Arrhythmias occurred within 72 hours of starting **sotalol** in 6 patients, and at varying intervals from 10 days to 3 years in the other 6 patients. Definite hypokalaemia (defined by the study as serum potassium of less than 3.5 mmol/L) was detected in 8 of the 13 patients. Four of the patients were also taking other drugs known to prolong the QT interval, namely disopyramide and tricyclic antidepressants. The problems resolved in all of the cases within 12 hours of stopping the **sotalol** and giving potassium supplements when indicated.[4] A further case of torsade de pointes has also been reported in a patient who developed hypokalaemia while taking **sotalol** and **hydrochlorothiazide**.[5]

Mechanism

Potassium-depleting drugs may cause hypokalaemia, which increases the potential for torsade de pointes arrhythmia with any drug that prolongs the QT interval, including sotalol.

Importance and management

The interaction between potassium-depleting diuretics such as hydrochlorothiazide and sotalol that results in QT prolongation is established, clinically important and potentially life threatening.

Torsade de pointes may occur in patients taking sotalol alone and who appear to have no predisposing factors.[6] One study found that there is an increased risk of proarrhythmia as the dose of sotalol is increased, with an abrupt change occurring at doses greater than 320 mg daily.[7] According to the manufacturer, the incidence of severe proarrhythmias, including torsade de pointes, in clinical study patients taking sotalol was less than 2% for doses up to 320 mg daily, but more than doubled at higher doses.[8] However, torsade de pointes can occur even with small doses of sotalol if potassium depletion is present or allowed to develop.[8,9] It is clearly very important therefore to ensure that potassium levels are maintained if potassium-depleting drugs are given with sotalol. A list of potassium-depleting diuretics is given in 'Table 26.1', (p.1121). Other drugs that may cause potassium depletion include **corticosteroids** and intravenous **amphotericin**. It has also been suggested that stimulant **laxatives**, may cause potassium depletion, but note that this generally tends to occur with abuse, or long-term use.

The interactions of chlortalidone and hydrochlorothiazide with celiprolol are poorly documented and their clinical significance is unclear, although it would be expected to be limited.

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Beta blockers + Propafenone

Plasma metoprolol and propranolol levels can be markedly raised (two to fivefold) by propafenone. This has led to toxicity in some cases.

Clinical evidence

(a) Metoprolol

Four patients with ventricular arrhythmias taking metoprolol 150 to 200 mg daily had a two to fivefold rise in their steady-state metoprolol plasma levels when they were given propafenone 150 mg three times daily. One of them developed distressing nightmares, and another had acute

left ventricular failure with pulmonary oedema and haemoptysis, which resolved when the metoprolol dosage was reduced or stopped. In four other patients taking metoprolol 50 mg three times daily and propafenone 150 mg three times daily, it was found that stopping metoprolol did not affect propafenone plasma levels.[1] Single-dose studies in healthy subjects found a twofold decrease in the clearance of metoprolol and a further 20% reduction in exercise-induced tachycardia at 90 minutes when propafenone was also given.[1]

A patient developed neurotoxicity (including vivid nightmares, fatigue, headache) when given metoprolol 100 mg daily in divided doses, which worsened while it was being withdrawn and replaced by propafenone 300 mg daily. The symptoms disappeared when both drugs were stopped.[2]

(b) Propranolol

In a study in 12 healthy subjects propafenone 225 mg every 8 hours more than doubled the steady-state plasma levels of propranolol 50 mg every 8 hours. However, the beta-blocking effects were only modestly increased and the propafenone pharmacokinetics remained unchanged.[3]

Mechanism

It is suggested that propafenone reduces the metabolism of metoprolol and propranolol by the liver, thereby reducing their clearance and raising serum levels.[1,3]

Importance and management

Information is limited but the interaction would seem to be established. Concurrent use need not be avoided but anticipate the need to reduce the dosage of metoprolol and propranolol. Monitor closely because some patients may experience adverse effects. If the suggested mechanism of interaction is correct it is possible (but not confirmed) that other beta blockers that undergo liver metabolism will interact similarly but not those largely excreted unchanged in the urine. See 'Table 22.1', (p.995) for the metabolism of some commonly used beta blockers. Also note that propafenone and the beta blockers have negative inotropic effects, which could be additive and result in unwanted cardiodepression.

1. Wagner F, Kalusche D, Trenk D, Jähnchen E, Roskamm H. Drug interaction between propafenone and metoprolol. *Br J Clin Pharmacol* (1987) 24, 213–20.
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Beta blockers + Protease inhibitors

Ritonavir (including ritonavir used in low dose as a pharmacokinetic enhancer) may increase plasma levels of metoprolol and propranolol. Tipranavir (with ritonavir) is predicted to increase metoprolol levels.

Clinical evidence, mechanism, importance and management

(a) Metoprolol

Metoprolol is metabolised by the cytochrome P450 isoenzyme CYP2D6, and because of this the manufacturer advises caution when it is given with a potent inhibitor of CYP2D6, such as **ritonavir**, as this may result in raised metoprolol plasma levels.[1] Some CYP2D6 inhibitors can raise metoprolol levels to the point where the beta blocker loses its selectivity, and this is of importance in patients being treated with metoprolol for heart failure. If both drugs are given, it may be prudent to monitor for symptoms such as shortness of breath, hypotension and bradycardia, and reduce the dose of metoprolol or withdraw the beta blocker as appropriate. However, the manufacturers of **tipranavir** note that **tipranavir** with **ritonavir** may raise metoprolol levels, and contraindicate the combination when metoprolol is used for heart failure.[2]

(b) Propranolol

As propranolol is metabolised by CYP2D6 the US manufacturers[3] suggest that inhibitors of this isoenzyme may inhibit propranolol metabolism. Some CYP2D6 inhibitors have been seen to interact (such as 'quinidine', (p.1017)), but the pharmacokinetic effects are modest in many cases, probably because propranolol is also metabolised by CYP1A2. However, **ritonavir** also inhibits CYP1A2, and therefore a larger rise in propranolol levels than that seen with other CYP2D6 inhibitors could occur. It would therefore seem prudent to monitor for decreases in blood pressure and heart rate if **ritonavir** is given with propranolol.

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2. Aptivus Soft Capsules (Tipranavir). Boehringer Ingelheim Ltd. UK Summary of product characteristics, June 2009.
3. Inderal LA (Propranolol hydrochloride). Wyeth Pharmaceuticals Inc. US Prescribing information, November 2007.

Beta blockers + Proton pump inhibitors

Omeprazole does not affect the pharmacokinetics of metoprolol or propranolol, and lansoprazole does not affect the pharmacokinetics of propranolol.

Clinical evidence, mechanism, importance and management

In a study in 8 healthy subjects, **omeprazole** 20 mg daily for 8 days had no effect on the steady-state plasma levels of **propranolol** 80 mg twice daily, and no effect on resting and exercising heart rates or blood pressure.[1] Another study found that **omeprazole** 40 mg daily for 8 days had no effect on the steady-state plasma levels of **metoprolol** 100 mg daily.[2]

A double-blind crossover study in 18 healthy subjects found that **lansoprazole** 60 mg daily for 7 days did not significantly affect the pharmacokinetics of a single 80-mg dose of **propranolol**.[3]

Metoprolol and **propranolol** are mainly metabolised by cytochrome P450 isoenzyme CYP2D6 and so would not be expected to interact with **lansoprazole** and **omeprazole**, which are inhibitors of and substrates for CYP2C19. No dosage adjustments would therefore seem necessary if these proton pump inhibitors are given with **propranolol** or **metoprolol**.

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Beta blockers + Quinidine

An isolated report describes a patient taking quinidine who developed marked bradycardia when using timolol eye drops. Other case reports describe orthostatic hypotension when quinidine was given with atenolol, propranolol or unnamed beta blockers. Quinidine can raise plasma metoprolol, propranolol, and timolol levels.

Both sotalol and quinidine can prolong the QT interval, which may increase the risk of torsade de pointes arrhythmia if they are used together.

Clinical evidence

(a) Atenolol

Orthostatic hypotension occurred in a 56-year-old woman taking isosorbide dinitrate, diltiazem and quinidine sulfate 300 mg four times daily, 3 days after she started taking atenolol 50 mg daily. This resolved within 2 days of stopping the atenolol. Before starting the quinidine, she had previously taken atenolol and the other drugs without problems.[1]

(b) Metoprolol

A metabolic study in 5 healthy subjects who had normal levels of CYP2D6 (extensive metabolisers) found that a single 50-mg dose of quinidine markedly inhibited the metabolism of a single 100-mg dose of metoprolol, which effectively made the subjects poor metabolisers (i.e. those that are deficient or lacking CYP2D6). The plasma levels of metoprolol were approximately tripled. Quinidine had no effect on metoprolol pharmacokinetics in 5 poor metabolisers.[2] Similar results have been found when quinidine 50 mg daily was given with metoprolol 100 mg twice daily for 7 days,[3] and when a 20-mg dose of metoprolol was given intravenously following either a single 50-mg dose of quinidine or quinidine slow-release tablets 250 mg twice daily for 3 days.[4] The effect on heart-rate reduction was small given the increase in metoprolol levels.[3]

(c) Propranolol

A single-dose pharmacokinetic study found that quinidine 200 mg doubled the AUC and the peak plasma levels of a 20-mg dose of propranolol. Maximum heart rates during exercise were suppressed by 45% more than propranolol alone.[5] Other studies have also found that quinidine increases the AUC of propranolol two- to threefold,[6,7] and this has resulted in increased beta-blockade.[7]

In 7 patients, propranolol 40 to 400 mg daily increased the peak plasma levels of a single 200-mg dose of quinidine by more than 50% and decreased its clearance by almost 40%, when compared with 8 control patients not taking propranolol. However, the quinidine elimination half-life was unchanged.[8] In contrast, two other studies did not find any interaction between propranolol and quinidine.[9,10]

A man taking propranolol 40 mg four times daily developed orthostatic hypotension, with symptoms of dizziness and faintness on standing, when he took quinidine 200 mg four times daily. This resolved when quinidine was withdrawn.[11] The same authors subsequently briefly reported another two cases of orthostatic hypotension when quinidine was given with **unnamed beta blockers**.[12]

(d) Sotalol

Although one study reports the safe concurrent use of sotalol and quinidine,[13] both drugs can prolong the QT interval, which may increase the risk of torsade de pointes arrhythmia if they are used together. See 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290, for a general review of QT-prolongation and drug interactions.

(e) Timolol

An elderly man taking quinidine sulfate 500 mg three times daily for premature atrial beats was hospitalised with dizziness 12 weeks after starting to use timolol 0.5% eye drops for open-angle glaucoma. He was found to have a sinus bradycardia of 36 bpm. The symptoms abated when the drugs were withdrawn and normal sinus rhythm returned after 24 hours. The same symptoms developed within 30 hours of re-starting both drugs, but disappeared when the quinidine was withdrawn.[14]

In a later study in healthy subjects, a single 50-mg oral dose of quinidine was given 30 minutes before 2 drops of timolol 0.5% ophthalmic solution, put into each *nostril*. In 13 patients with normal levels of CYP2D6 (extensive metabolisers), quinidine caused a further decrease in heart rate and increase in plasma timolol levels, when compared with timolol alone. Giving quinidine with timolol in these extensive metabolisers gave results similar to giving timolol alone in 5 poor metabolisers of CYP2D6 (i.e. those that are deficient or lacking CYP2D6).[15] In another study, quinidine augmented the plasma levels and cardiac effects of intravenous timolol.[16]

Mechanism

Quinidine appears to increase metoprolol, propranolol and timolol plasma levels by inhibiting the cytochrome P450 isoenzyme CYP2D6, thereby reducing their clearance.[2,7,15] As CYP2D6 shows polymorphism, these interactions would be most apparent in patients with normal CYP2D6 activity (extensive metabolisers), effectively making them poor metabolisers. See 'Genetic factors', (p.4), for further information on genetic polymorphism.

Importance and management

The pharmacokinetic interaction between quinidine and metoprolol, propranolol and timolol would seem to be established, but it is of uncertain clinical importance. Normally the beta blockers are considered to have a wide therapeutic range, and so raises in levels are generally well tolerated. Patients with heart failure are usually more at risk, because drugs such as metoprolol lose their selectivity at higher levels, and therefore some monitoring in this patient group (e.g. for shortness of breath, bradycardia, hypotension) may be prudent. There appears to be no information about other beta blockers, but all those metabolised by CYP2D6 would be expected to be affected to some extent. See 'Table 22.1', (p.995), for a list.

Only one isolated case of possible excessive beta-blockade has been reported (with quinidine and timolol eye drops). Concurrent use need not be avoided (and may be beneficial in the treatment of atrial fibrillation), but some care is warranted as both quinidine and the beta blockers have negative inotropic effects, which could be additive and result in unwanted cardiodepression. The general relevance of the isolated reports of orthostatic hypotension with atenolol or propranolol and quinidine is uncertain.

Both quinidine and sotalol prolong the QT interval. The general consensus is that the combination of two drugs that prolong the QT interval should usually be avoided, or only used with great caution. See 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290, for more information about the concurrent use of QT prolonging drugs.

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Beta blockers + Quinolones

Ciprofloxacin reduces the clearance of metoprolol. The concurrent use of sotalol and quinolones that prolong the QT interval should generally be avoided.

Clinical evidence, mechanism, importance and management

(a) Ciprofloxacin

Preliminary evidence from 7 healthy subjects given a single 100-mg dose of **metoprolol** suggested that pretreatment with 5 doses of ciprofloxacin 500 mg, given every 12 hours, increased the AUC of *(+)*-metoprolol by 54% and reduced its clearance by 39%. The AUC of *(–)*-metoprolol was increased by 29% and its clearance reduced by 12%.[1] It has been suggested that this interaction may occur because ciprofloxacin inhibits the activity of the cytochrome P450 isoenzymes concerned with the metabolism and clearance of **metoprolol**. However, this is questionable as **metoprolol** is metabolised, predominantly, by the cytochrome P450 isoenzyme CYP2D6 while ciprofloxacin inhibits CYP1A2. Changes of this size, or even more, in the AUC of beta blockers are not usually considered to be clinically relevant because the beta blockers have a wide therapeutic margin. Patients with heart failure are usually more at risk, because drugs such as metoprolol lose their selectivity at higher levels, but even in this patient group the rise in levels seems unlikely to be generally important.

(b) Quinolones that prolong the QT interval

In an analysis of cases of torsade de pointes associated with fluoroquinolones on the FDA Adverse Events Reporting System database, two cases of torsade de pointes were noted in patients taking a fluoroquinolone with **sotalol** (there were 37 cases identified, and 19 occurred in patients also taking other drugs known to prolong the QT interval).[2] **Sotalol** has class III antiarrhythmic effects and prolongs the QT interval, and this could be additive with the effects of quinolones that prolong the QT interval (e.g. **gatifloxacin**, **moxifloxacin**, **sparfloxacin**, see 'Table 9.2', (p.290)).The concurrent use of **sotalol** and these quinolones should generally be avoided (see 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290).

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Beta blockers + Rifampicin (Rifampin)

Rifampicin increases the clearance of bisoprolol, carvedilol, celiprolol, metoprolol, tertatolol and talinolol, and reduces their plasma levels. The extent to which this reduces the effects of these beta blockers is uncertain, but it is probably small. Similar effects have been seen when atenolol is given with rifampicin, but a case report suggests that occasionally the effects may be of clinical relevance. The effects of rifampicin on propranolol appear more pronounced, but evidence regarding the clinical relevance of this appears to be lacking.

Clinical evidence

(a) Atenolol

A case report describes a man taking atenolol for angina whose exercise threshold before developing angina symptoms appreciably worsened when he was given rifampicin. Rifampicin was stopped, and after a week **rifabutin** was started. **Rifabutin** did not cause any change in his baseline exercise tolerance.[1] In a randomised, placebo-controlled, crossover study, 9 healthy subjects were given rifampicin 600 mg daily for 5 days, with a single 100-mg dose of atenolol on day 6. Although some pharmacokinetic changes were seen they were variable between subjects and in most cases slight. Heart rate and blood pressure were on average slightly higher in the presence of rifampicin (3.5 bpm and 4.3/3.9 mmHg, respectively), suggesting a modest reduction in the effects of atenolol, which was expected to be of only minor clinical relevance.[2]

(b) Bisoprolol

The AUC of bisoprolol 10 mg daily was reduced by 34% in healthy subjects given rifampicin 600 mg daily.[3]

(c) Carvedilol

Rifampicin 600 mg daily for 12 days caused a 60% decrease in the maximum serum levels and the AUC of carvedilol.[4]

(d) Celiprolol

In a study in healthy subjects, rifampicin 600 mg daily reduced the AUC of a single 200-mg dose of celiprolol by 55%.[5]

(e) Metoprolol

In a study in healthy subjects, rifampicin 600 mg daily reduced the AUC of a single 100-mg dose of metoprolol by 33%.[6]

(f) Propranolol

In a study in 6 healthy subjects, rifampicin 600 mg daily for 3 weeks increased the oral clearance of propranolol almost threefold. Increasing the rifampicin dosage to 900 or 1200 mg daily did not further increase the clearance. Four weeks after withdrawing the rifampicin the blood levels of propranolol had returned to normal.[7] In a similar study the oral clearance of propranolol was increased by about fourfold by rifampicin 600 mg daily for 3 weeks in both poor and extensive metabolisers of propranolol.[8]

(g) Talinolol

In a study in 8 healthy subjects, rifampicin 600 mg daily decreased the AUC of a single-dose of talinolol 30 mg intravenously or 100 mg orally by 21% and 35%, respectively.[9]

(h) Tertatolol

Rifampicin 600 mg daily for a week increased the clearance of tertatolol almost threefold and reduced the half-life from 9 hours to 3.4 hours. A slight reduction in the effects of tertatolol on blood pressure was seen and heart rates were raised from 68 to 74 bpm.[10]

Mechanism

Rifampicin is a potent liver-enzyme inducer that increases the metabolism and clearance of extensively metabolised beta blockers such as propranolol and metoprolol. Rifampicin may also interact by mechanisms other than enzyme induction. Rifampicin increases duodenal P-glycoprotein expression, so increased clearance of talinolol (which is not hepatically metabolised) may be due to induction of P-glycoprotein, which increases the excretion of talinolol.[9] The effects on atenolol, which is not extensively metabolised, are also possibly due to induction of P-glycoprotein,[2] although this needs confirmation.

Importance and management

The interactions between rifampicin and the beta blockers are established. Their clinical importance is uncertain but probably small.[10] Nevertheless, they cannot be completely dismissed as the case report with atenolol shows. Consider increasing the dosage of the beta blocker if there is any evidence that the therapeutic response is inadequate. Any beta blockers that undergoes extensive liver metabolism would be expected to be affected by the enzyme-inducing effects of rifampicin (see 'Table 22.1', (p.995)). Those beta blockers mainly lost unchanged in the urine would not be expected to be affected, but it appears that an interaction may occur with beta blockers that are substrates for P-glycoprotein, such as talinolol.

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Beta blockers + SSRIs

Fluoxetine can increase serum pindolol and carvedilol levels. Isolated reports describe lethargy and bradycardia in patients taking metoprolol with fluoxetine, and propranolol with fluoxetine or fluvoxamine. Paroxetine may increase levels of metoprolol resulting in increased beta-blocking effects, and this has led to AV block in one case. Citalopram and escitalopram may also increase metoprolol levels. Sertraline does not alter the beta-blocking effects of atenolol, and fluvoxamine does not alter the pharmacokinetics of atenolol, although slight bradycardia and hypotension were reported.

Clinical evidence

(a) Citalopram

The UK manufacturers of citalopram say that no pharmacodynamic interactions have been noted in clinical studies in which citalopram was given with beta blockers.[1] However, the US manufacturers say that although the concurrent use of **metoprolol** and citalopram has no clinically significant effect on heart rate and blood pressure, the plasma levels of **metoprolol** are increased twofold, which may decrease its cardioselectivity.[2]

(b) Escitalopram

The manufacturers say that escitalopram causes a 50% increase in the plasma levels of **metoprolol** and an 82% increase in its AUC. They note that, although the concurrent use of **metoprolol** and escitalopram has no clinically significant effect on heart rate and blood pressure, this increase in plasma levels may decrease the cardioselectivity of **metoprolol**.[3]

(c) Fluoxetine

Metoprolol 100 mg daily improved the angina of a man who had undergone a coronary artery bypass 4 years earlier. A month later he was given fluoxetine 20 mg daily for depression. Within 2 days he complained of profound lethargy, and his resting heart rate was found to have fallen from 64 to 36 bpm. The fluoxetine was withdrawn, and within 5 days his heart

rate returned to 64 bpm. The **metoprolol** was replaced by **sotalol** 80 mg twice daily and fluoxetine reintroduced without problems.[4]

A patient taking **propranolol** 40 mg twice daily developed bradycardia of 30 bpm, heart block and syncope 2 weeks after starting fluoxetine 20 mg daily. This patient possibly also had some pre-existing conduction disease contributing to the effect.[5]

When 9 healthy subjects were given **pindolol** 5 mg every 6 hours with fluoxetine (20 mg daily for 3 days and then 60 mg daily for another 7 days), the **pindolol** AUC rose by about 75% and its clearance fell by about 45%, when compared with a single 5-mg dose of **pindolol**. Only mild to moderate alterations in pulse rate and blood pressure were seen.[6] Some studies including a high proportion of patients with first-episode depression have suggested that the antidepressant response to fluoxetine is accelerated by **pindolol**[7] while other studies in patients with predominantly chronic or recurrent depression did not find an enhanced response.[8] A crossover study in 10 patients with heart failure, taking **carvedilol** 25 to 50 mg twice daily, found that the addition of fluoxetine 20 mg daily for 28 days increased the AUC of ***(R)*-carvedilol** by 77%, and decreased the clearance of both enantiomers by 44 to 56%. However, these pharmacokinetic changes were of little clinical significance, and there were no changes in blood pressure, heart rate, and heart rate variability.[9]

(d) Fluvoxamine

A 79-year-old man who had taken **propranolol** for prophylaxis of migraine for several years developed fatigue and lightheadedness within a few days of starting fluvoxamine. He was admitted to hospital with syncope and bradycardia of 38 bpm but recovered after both drugs were discontinued.[10] Fluvoxamine 100 mg daily raised the plasma levels of **propranolol** 160 mg daily fivefold in healthy subjects, but the bradycardic effects were only slightly increased (by 3 bpm). The diastolic pressure following exercise was only slightly reduced but the general hypotensive effects remained unaltered.[11] Fluvoxamine did not change the plasma levels of **atenolol** 100 mg daily, but the heart-slowing effects were slightly increased and the hypotensive effects were slightly decreased.[11]

(e) Paroxetine

A patient taking paroxetine 20 mg daily developed presyncope and complete AV block 15 days after starting **metoprolol** 50 mg daily. Both drugs were stopped and the AV block resolved over 5 days. **Metoprolol** was then reinstated for 5 days without any sign of bradyarrhythmia. Two weeks after replacing **metoprolol** with amlodipine and aspirin, paroxetine was reintroduced at 10 mg daily and gradually increased to 20 mg daily without any signs of bradyarrhythmia.[12] A study in 8 healthy subjects found that paroxetine 20 mg daily for 6 days increased the AUCs of ***(R)*-** and ***(S)*-metoprolol** by eightfold and fivefold, respectively, after a single 100-mg dose of **metoprolol**. The maximum plasma concentration and elimination half-life were increased about twofold. The beta-blocking effects of **metoprolol** were more sustained and the reduction in exercise systolic pressure was more pronounced when paroxetine was also taken, when compared with **metoprolol** alone.[13]

(f) Sertraline

In a single-dose study in 10 healthy subjects, the beta-blocking effects of **atenolol** 50 mg were unchanged by sertraline 100 mg given 5 hours before the **atenolol**.[14,15]

Mechanism

Fluoxetine and paroxetine inhibit the cytochrome P450 isoenzyme CYP2D6 thus inhibiting the metabolism of some beta blockers (e.g. propranolol, metoprolol, carvedilol) so that they accumulate, the result being that their effects, such as bradycardia, may be increased.[4] Citalopram and escitalopram may also inhibit CYP2D6. *In vitro* studies with human liver microsomes found that fluoxetine and paroxetine are potent inhibitors of metoprolol metabolism whereas fluvoxamine, sertraline and citalopram have less of an effect.[16] However, fluvoxamine also potently inhibits the metabolism of propranolol by CYP1A2.[10,17] Beta blockers that are not extensively metabolised, such as atenolol and sotalol, would not be expected to be affected.

Pindolol may augment the antidepressant effect of fluoxetine by its antagonistic effects at 5-HT_{1A} receptors.[7,8,18]

Importance and management

Pharmacokinetic interactions have been found between fluoxetine, fluvoxamine or paroxetine and some beta blockers, but despite marked pharmacokinetic changes, the clinical effects are not generally significant. However, be aware that there are a few isolated reports of AV block with metoprolol and paroxetine and severe bradycardia with beta blockers and fluoxetine, or fluvoxamine. If problems arise, the interaction can apparently be avoided by giving a beta blocker (such as atenolol), which is not extensively metabolised. Alternatively, sertraline and citalopram seem to be less likely than the other SSRIs to interact with extensively metabolised beta blockers.[16] However, because metoprolol is considered to have a narrow therapeutic index in the treatment of heart failure, the UK manufacturers of escitalopram say that caution and possible dosage adjustments are warranted on concurrent use.[19] Similarly the manufacturers of paroxetine suggest that concurrent use should be avoided if metoprolol is being used for heart failure.[20] Remember that fluoxetine and particularly its metabolite have long half-lives so that this interaction may possibly still occur for some days after the fluoxetine has been stopped.

There appears to be no information about other beta blockers, but all those metabolised by CYP2D6 would be expected to be affected by paroxetine and fluoxetine to some extent. See 'Table 22.1', (p.995), for a list. Note that one of the manufacturers of **timolol**[21] predict this interaction with all SSRIs; however, most are less potent inhibitors of CYP2D6 than fluoxetine and paroxetine and therefore less likely to interact to a clinically relevant extent.

The combination of pindolol with fluoxetine may be advantageous in the treatment of depression in some patients.[7,8]

1. Cipramil Tablets (Citalopram hydrobromide). Lundbeck Ltd. UK Summary of product characteristics, September 2009.
2. Celexa (Citalopram hydrobromide). Forest Pharmaceuticals, Inc. US Prescribing information, January 2009.
3. Lexapro (Escitalopram oxalate). Forest Pharmaceuticals Inc. US Prescribing information, March 2009.
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9. Graff DW, Williamson KM, Pieper JA, Carson SW, Adams KF, Cascio WE, Patterson JH. Effect of fluoxetine on carvedilol pharmacokinetics, CYP2D6 activity, and autonomic balance in heart failure patients. *J Clin Pharmacol* (2001) 41, 97–106.
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16. Belpaire FM, Wijnant P, Temmerman A, Rasmussen BB, Brøsen K. The oxidative metabolism of metoprolol in human liver microsomes: inhibition by the selective serotonin reuptake inhibitors. *Eur J Clin Pharmacol* (1998) 54, 261–4.
17. Brøsen K, Skelbo E, Rasmussen BB, Poulsen HE, Loft S. Fluvoxamine is a potent inhibitor of cytochrome P4501A2. *Biochem Pharmacol* (1993) 45, 1211–14.
18. Dawson LA, Nguyen HQ, Smith DI, Schechter LE. Effects of chronic fluoxetine treatment in the presence and absence of (+/-)pindolol: a microdialysis study. *Br J Pharmacol* (2000) 130, 797–804.
19. Cipralex (Escitalopram oxalate). Lundbeck Ltd. UK Summary of product characteristics, October 2008.
20. Seroxat (Paroxetine hydrochloride hemihydrate). GlaxoSmithKline UK. UK Summary of product characteristics, May 2009.
21. Cosopt Opthalmic Solution (Dorzolamide hydrochloride with Timolol maleate). Merck Sharp & Dohme Ltd. UK Summary of product characteristics, June 2009.

Beta blockers + Sulfinpyrazone

The antihypertensive effects of oxprenolol can be reduced or abolished by sulfinpyrazone. The pharmacokinetics of metoprolol are not affected by sulfinpyrazone.

Clinical evidence

Oxprenolol 80 mg twice daily was given to 10 hypertensive subjects for 15 days, which reduced their mean supine blood pressure from 161/101 mmHg to 149/96 mmHg, and their heart rate from 72 bpm to 66 bpm. When they were additionally given sulfinpyrazone 400 mg twice

daily for 15 days, their mean blood pressure rose to about the former level. The reduction in mean heart rate remained unaffected. Sulfinpyrazone attenuated the reduction in cardiac workload seen with **oxprenolol** alone by about half.[1]

A study in 9 healthy subjects found that sulfinpyrazone 400 mg twice daily did not affect the pharmacokinetics of **metoprolol** 100 mg twice daily. No adverse effects were noted in healthy subjects during concurrent use.[2]

Mechanism

Not understood. One idea is that the sulfinpyrazone inhibits the production of vasodilatory (antihypertensive) prostaglandins by the kidney. This would oppose the actions of the oxprenolol. However, if this was the case, an interaction with metoprolol would also be expected, but this does not seem to be the case.

Importance and management

Information seems to be limited. If sulfinpyrazone is given to patients taking oxprenolol for hypertension, the effects should be monitored. It seems possible that this interaction could be accommodated by raising the dosage of the oxprenolol but this needs confirmation. The effect of this interaction on cardiac workload appears to be less important, but it would still be prudent to monitor concurrent use if oxprenolol is used for angina. Metoprolol may be a suitable alternative to oxprenolol as it does not appear to interact with sulfinpyrazone. There appears to be no information regarding other beta blockers.

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2. Cortellaro M, Boschetti C, Antoniazzi V, Polli EE, de Gaetano G, De Blasi A, Gerna M, Pezzi L, Garattini S. A pharmacokinetic and platelet function study of the combined administration of metoprolol and sulfinpyrazone to healthy volunteers. *Thromb Res* (1984) 34, 65–74.

Beta blockers + Tobacco or Nicotine ± Caffeine

Tobacco smoking can reduce the beneficial effects of beta blockers on heart rate and blood pressure. Some increase in the dosage of the beta blocker may be necessary. Drinking coffee may have a similar but smaller effect, probably due to the caffeine content. Nicotine attenuates the effects of tobacco withdrawal, and this effect may be enhanced by some beta blockers.

Clinical evidence

(a) Caffeine

In a placebo-controlled study in 12 healthy subjects, taking **propranolol** 240 mg or **metoprolol** 300 mg, two 150-mL cups of caffeine-containing coffee (made from 24 g of coffee) increased the mean blood pressure by 7%/22% with **propranolol** and 7%/19% with **metoprolol**. The increase with placebo was similar, at 4%/16% mmHg. The beta blockers and placebo were given in divided doses over 15 hours before the test.[1]

(b) Nicotine

A placebo-controlled, single-dose study in smokers given **carvedilol** 25 or 50 mg 140 minutes before a 4-mg nicotine lozenge found that **carvedilol** attenuated nicotine-induced increases in heart rate and blood pressure and also attenuated the self-reported 'bad effects' of nicotine but did not affect tobacco withdrawal symptoms.[2] Another similar study in 9 smokers found that a single 200-mg dose of **labetalol** attenuated the effects of a 15-mg/kg intravenous injection of nicotine on heart rate, whereas a single 100-mg dose of **labetalol** had no effect. Both doses of **labetalol** had no effect on the increase in blood pressure caused by nicotine. **Labetalol** 200 mg in conjunction with nicotine caused a greater attenuation in the symptoms of tobacco withdrawal than **labetalol** 100 mg.[3]

(c) Tobacco smoking

A placebo-controlled study in 10 smokers with angina pectoris, taking **propranolol** 240 mg daily or **atenolol** 100 mg daily, found that smoking reduced their plasma **propranolol** levels by 25%, when compared with a non-smoking phase. Plasma **atenolol** levels were not significantly altered. Both of the beta blockers reduced heart rate at rest and during exercise, but the reductions were less when subjects smoked (effects attenuated by 8 to 14%).[4]

Other studies found that serum **propranolol** levels in smokers were about half those in non-smokers.[5,6]

In another study, smoking caused an increase in blood pressure and heart rate in patients with angina and these effects were still evident, to a reduced extent, during **propranolol** treatment. In addition smoking abolished the beneficial effects of **propranolol** on ST-segment depression.[7]

(d) Tobacco smoking and caffeine

Eight patients with mild hypertension taking **propranolol** 80 mg twice daily, **oxprenolol** 80 mg twice daily or **atenolol** 100 mg daily over a 6-week period had their blood pressure monitored after smoking 2 tipped cigarettes and drinking coffee, containing 200 mg of caffeine. Their mean blood pressure rises over the following 2 hours were 8.5/8 mmHg in those taking **propranolol**, 12.1/9.1 mmHg in those taking **oxprenolol** and 5.2/4.4 mmHg in those taking **atenolol**.[8]

Mechanism

Smoking tobacco increases heart rate, blood pressure and the severity of myocardial ischaemia, probably as a direct effect of the nicotine and due to the reduced oxygen-carrying capacity of the blood.[4,7] These actions oppose and may even totally abolish the beneficial actions of the beta blockers. In addition, smoking stimulates the liver enzymes concerned with the metabolism of some beta blockers (e.g. propranolol) so that their serum levels are reduced. In contrast, the use of a beta blocker appears to enhance the beneficial effects of nicotine on tobacco withdrawal symptoms.

Caffeine causes the release of catecholamines, such as adrenaline, into the blood, which could account for the increases in heart rate and blood pressure that were seen in one study.[8] The blood pressure rise may be exaggerated in the presence of non-selective beta blockers, which block vasodilatation leaving the alpha (vasoconstrictor) effects of adrenaline unopposed. This will also oppose the actions of the beta blockers.

Importance and management

Evidence for an interaction between tobacco smoking and/or coffee intake and beta blockers is generally sparse. Smoking tobacco and (to a very much lesser extent) drinking coffee may oppose the effects of the beta blockers in the treatment of angina or hypertension, but the extent of any effect appears relatively modest. However, patients should be encouraged to stop smoking because, quite apart from its other toxic effects, it aggravates myocardial ischaemia, increases heart rate and can impair blood pressure control. If patients continue to smoke, it may be necessary to raise the dosages of the beta blockers. The effects of the caffeine are quite small and there seems to be no strong reason to forbid the intake of beverages containing caffeine (e.g. tea, coffee, cola), but the excessive consumption of large amounts may not be a good idea, particularly in those who also smoke.

Evidence for an interaction between nicotine replacement therapy and beta blockers is also sparse; however, the concurrent use of nicotine and a beta blocker may actually be beneficial in minimising the effects of tobacco withdrawal. This requires further study.

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2. Sofuoglu M, Mouratidis M, Yoo S, Kosten T. Adrenergic blocker carvedilol attenuates the cardiovascular and aversive effects of nicotine in abstinent smokers. *Behav Pharmacol* (2006) 17, 731–5.
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4. Fox K, Deanfield J, Krikler S, Ribeiro P, Wright C. The interaction of cigarette smoking and β-adrenoceptor blockade. *Br J Clin Pharmacol* (1984) 17, 92S–93S.
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6. Gardner SK, Cady WJ, Ong YS. Effect of smoking on the elimination of propranolol hydrochloride. *Int J Clin Pharmacol Ther Toxicol* (1980) 18, 421–4.
7. Fox K, Jonathan A, Williams H, Selwyn A. Interaction between cigarettes and propranolol in treatment of angina pectoris. *BMJ* (1980) 281, 191–3.
8. Freestone S, Ramsey LE. Effect of β-blockade on the pressor response to coffee plus smoking in patients with mild hypertension. *Drugs* (1983) 25 (Suppl 2), 141–5.

Beta blockers + X-ray contrast media

There is some evidence to suggest that use of a beta blocker is a risk factor for anaphylactoid reactions to X-ray contrast media. Severe hypotension has been seen in two patients taking beta blockers who were given sodium meglumine amidotrizoate and in a further patient taking atenolol who was given iohexol.

Clinical evidence

A case-control study of anaphylactoid reactions to X-ray contrast media found that the risk of bronchospasm during intravenous contrast media procedures was associated with beta blocker use and also with asthma, while the risk of major and life-threatening anaphylactoid reactions were associated with cardiovascular disorders. The use of a beta blocker also increased the risk of hospitalisation in those patients who had a severe anaphylactoid reaction.[1]

Two patients, one taking **nadolol** and the other **propranolol**, developed severe hypotensive reactions when given **sodium meglumine amidotrizoate** as a contrast agent for X-ray urography. Both patients developed slowly progressive erythema on the face and arms followed by tachycardia and a weak pulse. Each was successfully treated with subcutaneous adrenaline (epinephrine) and hydrocortisone.[2]

Another patient who had developed a transient rash during cardiac catheterisation 6 years earlier, and who was subsequently given **atenolol**, developed generalised urticaria and severe hypotension immediately after an injection of **iohexol** for coronary angiography. The hypotension was refractory to aggressive standard treatment with adrenaline, atropine, and dopamine and the patient remained in shock (BP 60/34 mmHg). Noradrenaline (norepinephrine) infusion produced a modest improvement (BP 80/40 mmHg), but significant improvement in blood pressure occurred only after intravenous injections of glucagon 1 mg.[3]

See also, *Anaphylaxis* under 'Beta blockers + Inotropes and Vasopressors', p.1011.

Mechanism

Iodinated contrast media are associated with hypersensitivity reactions due to the release of histamine. It is suggested that beta blockers compromise the ability of the body to cope with the effects of histamine release.[2]

Importance and management

Limited documentation. Withdrawal of the beta blocker 2 to 3 days before use of contrast media has been suggested,[2] but because of the potential for beta blocker withdrawal syndromes this must be considered on an individual risk/benefit basis.[1] Pretreatment with an antihistamine such as diphenhydramine and a corticosteroid such as prednisone may reduce the risk of reactions.[3-5] Ephedrine and cimetidine have also been tried, but their use is controversial.[5] Use of low osmolality, non-ionic contrast media may reduce the risk of adverse reactions, including anaphylaxis.[1,5,6] However, even mild reactions to contrast media may sensitise the patient and a serious anaphylactoid reaction may occur on further exposure, despite pretreatment and the use of low osmolality contrast media.[3] Pre-testing with a small amount of the contrast media has been shown to be a poor predictor of a reaction.[5]

When anaphylactic reactions do occur in patients taking beta blockers, it may be preferable to use a beta-agonist bronchodilator such as isoprenaline, rather than adrenaline (epinephrine).[2] Glucagon, which has inotropic and chronotropic actions that are only minimally antagonised by beta blockers, may also be effective in reversing anaphylactoid shock in patients taking beta blockers.[3]

1. Lang DM, Alpern MB, Visintainer PF, Smith ST. Elevated risk of anaphylactoid reaction from radiographic contrast media is associated with both β-blocker exposure and cardiovascular disorders. *Arch Intern Med* (1993) 153, 2033–40.
2. Hamilton G. Severe adverse reactions to urography in patients taking beta-adrenergic blocking agents. *Can Med Assoc J* (1985) 133, 122.
3. Javeed N, Javeed H, Javeed S, Moussa G, Wong P, Rezai F. Refractory anaphylactoid shock potentiated by beta-blockers. *Cathet Cardiovasc Diagn* (1996) 39, 383–4.
4. Greenberger PA, Patterson R, Tapio CM. Prophylaxis against repeated radiocontrast media reactions in 857 cases. *Arch Intern Med* (1985) 145, 2197–2200.
5. Wittbrodt ET, Spinler SA. Prevention of anaphylactoid reactions in high-risk patients receiving radiographic contrast media. *Ann Pharmacother* (1994) 28, 236–41.
6. Greenberger PA, Patterson R. The prevention of immediate generalized reactions to radiocontrast media in high-risk patients. *J Allergy Clin Immunol* (1991) 87, 867–72.

Beta blockers; Atenolol + Allopurinol

In a study in 6 healthy subjects, allopurinol 300 mg daily for 6 days did not affect the steady-state pharmacokinetics of atenolol 100 mg daily.[1] No special precautions would therefore appear to be necessary on concurrent use.

1. Schäfer-Korting M, Kirch W, Axthelm T, Köhler H, Mutschler E. Atenolol interaction with aspirin, allopurinol, and ampicillin. *Clin Pharmacol Ther* (1983) 33, 283–8.

Beta blockers; Metoprolol + Acetylcholine

An isolated case describes bronchospasm, which developed when a patient taking metoprolol was given intra-ocular acetylcholine.

Clinical evidence, mechanism, importance and management

An elderly patient with a history of hypertension, obstructive pulmonary disease and stable angina, taking several drugs including metoprolol, experienced severe bronchospasm and pulmonary oedema immediately following the intra-ocular injection of acetylcholine chloride during cataract surgery. Her blood pressure rapidly increased, and she became tachycardic. She had also received phenylephrine eye drops before surgery. The patient may have been more sensitive to the pulmonary effects of acetylcholine, such as bronchospasm, because of pre-existing disease and the presence of metoprolol.[1] It was suggested that phenylephrine may also have been involved, but cases of an interaction between phenylephrine and beta blockers are rare, see 'Beta blockers + Inotropes and Vasopressors', p.1011.

The general clinical relevance of this single case is uncertain but it seems likely to be small.

1. Rasch D, Holt J, Wilson M, Smith RB. Bronchospasm following intraocular injection of acetylcholine in a patient taking metoprolol. *Anesthesiology* (1983) 59, 583–5.

Beta blockers; Metoprolol + Sevelamer

In a study in 31 healthy subjects the concurrent use of a single 2.418-g dose of sevelamer did not alter the AUC of a single 100-mg dose of metoprolol.[1] No particular precautions therefore seem necessary on concurrent use.

1. Burke SK, Amin NS, Incerti C, Plone MA, Lee JW. Sevelamer hydrochloride (Renagel®), a phosphate-binding polymer, does not alter the pharmacokinetics of two commonly used antihypertensives in healthy volunteers. *J Clin Pharmacol* (2001) 41, 199–205.

Beta blockers; Nebivolol + Spironolactone

The concurrent use of spironolactone and nebivolol does not appear to affect the pharmacokinetics of either drug.

Clinical evidence, mechanism, importance and management

A randomised study in 36 healthy subjects given nebivolol 10 mg daily with spironolactone 25 mg daily found no clinically significant changes in the pharmacokinetics of spironolactone and its metabolites canrenone and 7α-thiomethyl spirolactone. Further, spironolactone is reported not to affect the pharmacokinetics of nebivolol.[1] No particular precautions therefore seem necessary on concurrent use, although note that both drugs can lower blood pressure, and this should be borne in mind if they are both given.

1. Morton TL, Tu HC, Lui S, Chervenick SW, Rackley RJ, Huang MY. Lack of pharmacokinetic interaction between nebivolol and spironolactone. *Clin Pharmacol Ther* (2005) 77, P46.

Beta blockers; Propranolol + Ascorbic acid (Vitamin C)

Ascorbic acid reduces the bioavailability of propranolol but the extent of the reduction is too small to be of clinical significance.

Clinical evidence, mechanism, importance and management

A study in 5 healthy subjects given a single 80-mg dose of propranolol found that a single 2-g dose of ascorbic acid reduced the maximum plasma levels of propranolol by 28%, reduced the AUC by 37% and reduced the recovery of propranolol metabolites in the urine by 66%. The reduction in

heart rate in response to propranolol was also very slightly diminished. The reason for this interaction appears to be that ascorbic acid reduces both the absorption and the metabolic conjugation of propranolol.[1] However, none of the changes seen would appear to be of clinical relevance.

1. Gonzalez JP, Valdivieso A, Calvo R, Rodríguez-Sasiaín JM, Jimenez R, Aguirre C, du Souich P. Influence of vitamin C on the absorption and first pass metabolism of propranolol. *Eur J Clin Pharmacol* (1995) 48, 295–7.

Beta blockers; Propranolol + Dextromoramide

An isolated report describes two patients who developed marked bradycardia and severe hypotension when they were given propranolol and dextromoramide following the induction of anaesthesia.

Clinical evidence, mechanism, importance and management

Two women about to undergo a partial thyroidectomy were given propranolol 30 mg and dextromoramide 1.25 or 4 mg by injection during the pre-operative period, after which anaesthesia was induced with a barbiturate. Each woman developed marked bradycardia and severe hypotension, which responded rapidly to intravenous atropine.[1] The authors of the report attributed this effect to the use of dextromoramide and propranolol; however, the reasons for this response are not established (e.g. the induction of anaesthesia may have played a part) and therefore the general significance of this interaction (if such it is) is unclear.

1. Cabanne F, Wilkening M, Caillard B, Foissac JC, Aupecle P. Interférences médicamenteuses induites par l'association propranolol-dextromoramide. *Anesth Analg Reanim* (1973) 30, 369–75.

Beta blockers; Propranolol + Miscellaneous

The manufacturers predict that propranolol levels will be raised by inhibitors and substrates of CYP1A2 (such as ciprofloxacin) and inhibitors and substrates of CYP2C19 (such as fluconazole and tolbutamide).

Clinical evidence, mechanism, importance and management

(a) CYP1A2 substrates or inhibitors

As propranolol is partly metabolised by CYP1A2 the US manufacturer[1] predicts that its levels may be raised by substrates or inhibitors of this isoenzyme.

However, data for 'imipramine', (p.1500), 'isoniazid', (p.348), and 'theophylline', (p.1433), (substrates of CYP1A2) suggest that in fact propranolol raises the levels of these drugs.

Inhibitors of CYP1A2 raise propranolol levels (as seen with 'fluvoxamine', (p.1019)) and therefore an interaction with **ciprofloxacin** (as predicted by the manufacturer) seems possible. However, note that propranolol levels fluctuate greatly between individuals, and propranolol is not exclusively metabolised by CYP1A2, and so any interaction seems likely to produce only moderate clinical effects.

(b) CYP2C19 substrates or inhibitors

The US manufacturer[1] suggests that raised propranolol levels may occur with **fluconazole** or **tolbutamide**, which are an inhibitor and a substrate of CYP2C19, respectively. However, CYP2C19 only plays a small part in propranolol metabolism. Further, the manufacturer also notes that omeprazole and lansoprazole (both inhibitors and substrates for CYP2C19) do not interact with propranolol (see 'Beta blockers + Proton pump inhibitors', p.1017), and so a clinically significant interaction involving CYP2C19 seems unlikely.

1. Inderal LA (Propranolol hydrochloride). Wyeth Pharmaceuticals Inc. US Prescribing information, November 2007.

Beta blockers; Propranolol + Misoprostol

Misoprostol does not significantly alter the pharmacokinetics of propranolol.

Clinical evidence, mechanism, importance and management

In 12 healthy subjects, misoprostol 400 micrograms twice daily raised the AUC of propranolol 80 mg twice daily by about 20 to 40%, and this remained raised 7 days after misoprostol was discontinued.[1] However, as these findings were unexpected, the authors conducted a randomised, crossover, placebo-controlled study and ensured that propranolol was at steady state before assessing the effect of misoprostol. No significant effects on the pharmacokinetics of propranolol were found.[2] No dosage adjustment of propranolol would therefore seem necessary if misoprostol is given.

1. Bennett PN, Fenn GC, Notarianni LJ. Potential drug interactions with misoprostol: effects on the pharmacokinetics of antipyrine and propranolol. *Postgrad Med J* (1988) 64 (Suppl 1), 21–4.
2. Bennett PN, Fenn GC, Notarianni LJ, Lee CE. Misoprostol does not alter the pharmacokinetics of propranolol. *Postgrad Med J* (1991) 67, 455–7.

Beta blockers; Propranolol + Nefazodone

Nefazodone does not significantly affect the pharmacokinetics of propranolol.

Clinical evidence, mechanism, importance and management

A study in 18 healthy subjects found that nefazodone 200 mg every 12 hours reduced the AUC of propranolol 40 mg every 12 hours by 14% and decreased its maximum plasma levels by 29%, but no clinically significant changes in the response to propranolol or relevant adverse effects were seen. The pharmacokinetics of nefazodone were also largely unchanged.[1] No special precautions would therefore seem to be necessary if both drugs are given.

1. Salazar DE, Marathe PH, Fulmor IE, Lee JS, Raymond RH, Uderman HD. Pharmacokinetic and pharmacodynamic evaluation during coadministration of nefazodone and propranolol in healthy men. *J Clin Pharmacol* (1995) 35, 1109–18.

Beta blockers; Propranolol + Sucrose polyesters

One study suggests that sucrose polyesters (e.g. *Olestra*) do not interact with propranolol.

Clinical evidence, mechanism, importance and management

Eight healthy subjects were given sucrose polyester 18 g and a single unstated dose of propranolol. Sucrose polyester had no effect on the pharmacokinetics of propranolol.[1] Sucrose polyesters, are non-absorbable, non-calorific fat replacements. It has been concluded that sucrose polyesters are unlikely to reduce the absorption of oral drugs in general.[2]

1. Roberts RJ, Leff RD. Influence of absorbable and nonabsorbable lipids and lipidlike substances on drug bioavailability. *Clin Pharmacol Ther* (1989) 45, 299–304.
2. Goldman P. Olestra: assessing its potential to interact with drugs in the gastrointestinal tract. *Clin Pharmacol Ther* (1997) 61, 613–18.

Beta blockers; Sotalol + Paracetamol (Acetaminophen)

One isolated report suggests that paracetamol may enhance the effects of sotalol on heart rate.

Clinical evidence, mechanism, importance and management

A brief report describes 9 patients with hypertension who were given a single 240-mg dose of sotalol daily for 2 weeks. Sotalol alone reduced the heart rate by 10 bpm by day 10; however, 5 of the patients also given paracetamol 2 g daily in three divided doses on days 8 to 10 (for headache), and in these patients there was an average reduction in heart rate of

18 bpm.[1] This appears to be an old and isolated report and therefore the clinical relevance of any interaction seems likely to be small.

1. Tongia SK. Paracetamol augments the sotalol-induced bradycardia in man. *Indian J Physiol Pharmacol* (1982) 26, 97–8.

Beta blockers; Sotalol + Terfenadine

Episodes of torsade de pointes arrhythmia developed in a woman taking sotalol when terfenadine was added.

Clinical evidence, mechanism, importance and management

A 71-year-old woman with a history of atrial fibrillation was successfully treated with sotalol 80 mg twice daily. She started to take terfenadine 60 mg twice daily, and 8 days later developed repeated self-limiting episodes of torsade de pointes arrhythmia. On one occasion she required resuscitation. Both drugs were stopped and no further episodes of arrhythmia occurred 72 hours after temporary pacing was discontinued.[1]

It seems likely that what happened resulted from the additive effects of both drugs on the QT interval, which can lead to the development of torsade de pointes. This case confirms a previous mention of the possibility of this interaction.[2]

Although this seems to be the first report of this interaction, it is consistent with the known pharmacology of both drugs. Torsade de pointes is potentially life threatening, so the concurrent use of these two drugs should generally be avoided. See 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290, for a further discussion on the concurrent use of drugs that prolong the QT interval.

1. Feroze H, Suri R, Silverman DI. Torsades de pointes from terfenadine and sotalol given in combination. *Pacing Clin Electrophysiol* (1996) 19, 1519–21.
2. Woosley RL, Chen Y, Freiman JP, Gillis RA. Mechanism of the cardiotoxic actions of terfenadine. *JAMA* (1993) 269, 1532–6.

Beta blockers; Talinolol + Carbamazepine

Carbamazepine may modestly reduce the absorption of talinolol.

Clinical evidence, mechanism, importance and management

A study in 7 healthy subjects found that the concurrent use of **carbamazepine** 600 mg daily and **talinolol** 100 mg daily for 18 days decreased the AUC of **talinolol** by about 15%. These changes were thought to be due to changes in the intestinal transport of **talinolol**, caused by **carbamazepine**-induced changes in the expression of the drug transporter protein MRP2. However, AUC changes of this magnitude are not of clinical relevance, and therefore no dosage alterations would be expected to be needed on concurrent use.[1]

1. Giessmann T, May K, Modess C, Wegner D, Hecker U, Zschiesche M, Dazert P, Grube M, Schroeder E, Warzok R, Cascorbi I, Kroemer HK, Siegmund W. Carbamazepine regulates intestinal P-glycoprotein and multidrug resistance protein MRP2 and influences disposition of talinolol in humans. *Clin Pharmacol Ther* (2004) 76, 192–200.

Beta blockers; Talinolol + St John's wort (*Hypericum perforatum*)

St John's wort modestly decreases the plasma levels of talinolol.

Clinical evidence

In a randomised study, a single oral dose of talinolol 50 mg was given to 9 healthy subjects after 12-days of St John's wort (Jarsin, Lichtwer Pharma) 900 mg daily. St John's wort was found to reduce the AUC and oral bioavailability of talinolol by about 31% and 25%, respectively. The non-renal clearance of a single dose of talinolol 30 mg given as a 30 minute infusion was increased by about 26%. Other pharmacokinetic parameters of both oral and intravenous talinolol were not significantly affected.[1]

Mechanism

Talinolol is a known substrate for P-glycoprotein. This study found that the levels of intestinal P-glycoprotein in the duodenal biopsy samples of 9 subjects were raised by St John's wort, leading to a reduction in the absorption of talinolol.

Importance and management

Information appears to be limited to this study but it is in line with the known effects of St John's wort on substrates of P-glycoprotein, such as digoxin (consider also 'Digoxin + St John's wort (*Hypericum perforatum*)', p.1115). The modest decrease in talinolol levels suggests that, in most patients, this interaction is unlikely to be clinically significant. Nevertheless, consider this interaction if blood pressure is difficult to control.

1. Schwarz UI, Hanso H, Oertel R, Miehlke S, Kuhlisch E, Glaeser H, Hitzl M, Dresser GK, Kim RB, Kirch W. Induction of intestinal P-glycoprotein by St John's wort reduces the oral bioavailability of talinolol. *Clin Pharmacol Ther* (2007) 81, 669–78.

Beta blockers; Talinolol + Sulfasalazine

Sulfasalazine markedly reduces the absorption of talinolol.

Clinical evidence

In a study in 8 healthy subjects the AUC of talinolol 50 mg was reduced by 91% by sulfasalazine 4 g. The maximum serum levels were also markedly reduced, from 112 nanograms/mL to 23 nanograms/mL in 3 subjects, and to undetectable levels in the other 5 subjects.[1]

Mechanism

Not known. It is suggested that talinolol is adsorbed onto the sulfasalazine, thereby preventing its absorption.[1]

Importance and management

Information is limited to this study, but it would appear to be an established and probably clinically important interaction. The efficacy of the talinolol would be expected to be markedly reduced, but this does not appear to have been studied. If the mechanism suggested by the authors is true, their advice to separate the dosages by 2 to 3 hours should minimise this interaction.[1] Nevertheless, it would still be prudent to monitor the outcome of concurrent use (e.g. blood pressure). More study is needed to confirm the clinical effects of the interaction, how effective separating the doses is, and whether other beta blockers behave similarly.

1. Terhaag B, Palm U, Sahre H, Richter K, Oertel R. Interaction of talinolol and sulfasalazine in the human gastrointestinal tract. *Eur J Clin Pharmacol* (1992) 42, 461–2.

Beta blockers; Talinolol + Surfactant excipients

The surfactant excipient d-α-Tocopheryl polyethylene glycol 1000 succinate (TPGS) increases the bioavailability of talinolol, whereas another surfactant poloxamer 188 has no effect.

Clinical evidence, mechanism, importance and management

A study in 9 healthy subjects given talinolol 50 mg via nasogastric tube, either alone, with **d-α-tocopheryl polyethylene glycol 1000 succinate** (**TPGS**; 0.04%), or with **poloxamer 188** (0.8%), found that **TPGS** increased the peak plasma level and AUC of talinolol by 100% and 39%, respectively, probably by inhibition of intestinal P-glycoprotein. **Poloxamer 188** did not significantly affect the pharmacokinetics of talinolol.[1] No relevant changes in heart rate or blood pressure were noted with either surfactant, and the increase in talinolol levels caused by **TPGS** was only modest. Therefore a clinically relevant interaction seems unlikely.

1. Bogman K, Zysset Y, Degen L, Hopfgartner G, Gutmann H, Alsenz J, Drewe J. P–glycoprotein and surfactants: effect on intestinal talinolol absorption. *Clin Pharmacol Ther* (2005) 77, 24–32.

23

Calcium-channel blockers

This section is primarily concerned with those interactions where the activity of the calcium-channel blockers is changed by the presence of another drug. Where the calcium-channel blocker is the affecting drug, the relevant monograph is usually categorised under the heading of the affected drug.

Calcium-channel blockers in current clinical usage affect the slow L-type channel. They are usually classified by their chemical structure, which determines their selectivity for vascular smooth muscle over myocardium, and hence their potential to slow the heart rate (negative inotropic activity) see 'Table 23.1', (below). Interactions due to additive inotropic effects will therefore apply only to the benzothiazepine (diltiazem) and phenylalkylamine-type (verapamil) calcium-channel blockers, and usually not to the dihydropyridine-type (e.g. nifedipine) calcium-channel blockers. All three types of calcium-channel blocker will have additive hypotensive effects with other drugs with blood-pressure lowering activity.

Calcium-channel blockers also undergo interactions due to altered metabolism. Both verapamil and diltiazem are principally metabolised by the cytochrome P450 isoenzyme CYP3A4, and also inhibit this enzyme (see 'Table 1.4', (p.6)). They are therefore affected by drugs that induce or inhibit CYP3A4, and also themselves interact with drugs metabolised by CYP3A4.

Many of the dihydropyridine-type calcium-channel blockers are also metabolised by CYP3A4, and are affected by inducers or inhibitors of this isoenzyme to varying degrees. However, they do not generally inhibit CYP3A4, or other isoenzymes to a clinically relevant extent. The exception is perhaps nicardipine, which may cause a clinically relevant inhibition of CYP3A4.

Mibefradil is a calcium-channel blocker that acts on the fast T-type calcium channel. It was withdrawn soon after it was launched because of identification of an increasing number of serious drug interactions caused by its inhibitory effects on CYP3A4 and CYP2D6. It was thought that the practical problems of implementing all the warnings relating to these interactions were too difficult and risky.

Table 23.1 Classification of calcium-channel blockers that act on slow L-type channels

Class	*Rate limiting?*	*Effect on AV or SA node*	*Examples*
Dihydropyridine	No	Little or none	Amlodipine, Barnidipine, Benidipine, Felodipine, Isradipine, Lacidipine, Lercanidipine, Manidipine, Nicardipine, Nifedipine, Nilvadipine, Nimodipine,† Nisoldipine, Nitrendipine
Benzothiazepine	Yes	Depression (negative inotropic activity)	Diltiazem
Phenylalkylamine	Yes	Depression (negative inotropic activity)	Gallopamil, Verapamil

†Nimodipine crosses the blood-brain barrier and therefore affects cerebral blood vessels, and is used for cerebral ischaemia.

Calcium-channel blockers + Aliskiren

Verapamil is predicted to raise aliskiren levels. The concurrent use of aliskiren and amlodipine does not result in any clinically significant pharmacokinetic changes. The use of aliskiren with calcium-channel blockers is expected to result in additive blood pressure lowering effects.

Clinical evidence, mechanism, importance and management

(a) Amlodipine

In a study, 18 healthy subjects were given amlodipine 10 mg daily and aliskiren 300 mg daily, either alone, or together for 2 weeks. Amlodipine increased the AUC of aliskiren by 29%, but there was no significant change in the maximum plasma level of aliskiren, although the time to maximum plasma concentration increased from 1 to 3 hours. The pharmacokinetics of amlodipine were not affected by aliskiren.[1] The UK manufacturers note that, in patients who did not adequately respond to amlodipine 5 mg, the addition of aliskiren 150 mg resulted in a lowering of the blood pressure similar to that achieved by giving amlodipine 10 mg.[2]

A change in the AUC of aliskiren of 29% would not be expected to be clinically relevant, and therefore the dose of aliskiren does not need to be adjusted in amlodipine is also given. However, as expected, the concurrent use of amlodipine with aliskiren results in additive effects on blood pressure: other calcium-channel blockers seem likely to interact in the same way.

(b) Verapamil

Aliskiren is a substrate of the transporter protein, P-glycoprotein. Potent inhibitors of P-glycoprotein have increased the exposure to aliskiren by up to fivefold. The UK manufacturers therefore contraindicate the use of any potent P-glycoprotein inhibitors, and specifically name verapamil.[2]

1. Vaidyanathan S, Valencia J, Kemp C, Zhao C, Yeh C-M, Bizot M-N, Denouel J, Dieterich HA, Dole WP. Lack of pharmacokinetic interactions of aliskiren, a novel direct renin inhibitor for the treatment of hypertension, with the antihypertensives amlodipine, valsartan, hydrochlorothiazide (HCTZ) and ramipril in healthy volunteers. *Int J Clin Pract* (2006) 60, 1343–56.
2. Rasilez (Aliskiren hemifumarate). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, April 2009.

Calcium-channel blockers + Antihistamines

An isolated report describes increased adverse effects in two patients when terfenadine was given with nifedipine or verapamil. The manufacturers of lercanidipine advise caution with the concurrent use of astemizole and terfenadine. Verapamil markedly increased the AUC of a single dose of fexofenadine in one study, but another study found a much more modest effect. However, even a marked increase may not be clinically important. Diltiazem does not appear to affect the pharmacokinetics of fexofenadine. In one study no pharmacodynamic interaction occurred between diltiazem and mizolastine, and mizolastine did not alter diltiazem pharmacokinetics. Nifedipine is predicted to increase the levels of mizolastine.

Clinical evidence, mechanism, importance and management

(a) Fexofenadine

In a study in 12 healthy subjects **verapamil** 240 mg daily for 6 days increased the AUC of a single 120-mg dose of fexofenadine 2.5-fold and increased its maximum level 2.9-fold. There was marked interindividual variation in these effects.[1] Another study showed a smaller 30% increase in maximum level of fexofenadine when a single 60-mg dose was given to subjects who had taken **verapamil** 240 mg daily for 10 days. However, after 38 days of **verapamil**, the maximum level and clearance of fexofenadine was not significantly changed.[2] Fexofenadine is not metabolised by cytochrome P450, and it was suggested that **verapamil** may have increased fexofenadine bioavailability by inhibiting P-glycoprotein or OATPs, which are drug transporters.[1]

In another study, pretreatment with slow-release **diltiazem** did not affect the pharmacokinetics of fexofenadine.[3]

Note that fexofenadine has a relatively wide therapeutic range and marked increases in fexofenadine levels with 'erythromycin', (p.671) and 'ketoconazole', (p.665) did not increase adverse effects and were not associated with any prolongation of the QT interval. This suggests that a clinically relevant interaction between **verapamil** and fexofenadine is not expected, but some caution may be warranted until further experience is gained.

(b) Mizolastine

A double-blind, crossover study in 12 healthy subjects taking **diltiazem** 60 mg three times daily found that the concurrent use of mizolastine 10 mg daily for 5 days did not alter ECGs or blood pressures. No significant increases in adverse effects were seen and the pharmacokinetics of **diltiazem** remained unchanged. However, mizolastine pharmacokinetics were not assessed.[4] Some manufacturers of **nifedipine**[5] and mizolastine[6] suggest that concurrent use may raise mizolastine levels by inhibition of the cytochrome P450 isoenzyme CYP3A4, and caution is therefore advised,[6] presumably because mizolastine has a weak potential to prolong the QT interval. If caution is required with **nifedipine**, then this should be extended to both **diltiazem** and **verapamil**, since these are both moderate inhibitors of CYP3A4. Further study is needed. However, note that nifedipine is not usually known to interact by inhibiting CYP3A4.

(c) Terfenadine and Astemizole

An isolated report describes severe angina in a patient taking **nifedipine** 10 mg three times daily when she took terfenadine 60 mg for seasonal allergy. A second patient taking **verapamil** 80 mg three times daily also experienced adverse effects (including severe headache and confusion) after taking a single 60-mg dose of terfenadine.[7] **Verapamil**, **diltiazem**, and to a lesser extent **nicardipine** are inhibitors of CYP3A4, but there appear to be no other reports of interactions with terfenadine or astemizole (both substrates of CYP3A4). Of all the calcium-channel blockers, only the UK manufacturer of **lercanidipine** advises caution during the concurrent use of terfenadine and astemizole;[8] however, lercanidipine does not appear to inhibit CYP3A4, and therefore an interaction, at least by this mechanism, seems unlikely.

1. Yasui-Furukori N, Uno T, Sugawara K, Tateishi T. Different effects of three transporting inhibitors, verapamil, cimetidine, and probenecid, on fexofenadine pharmacokinetics. *Clin Pharmacol Ther* (2005) 77, 17–23.
2. Lemma GL, Hamman MA, Hall SD, Wang Z. The effect of verapamil administration on the pharmacokinetics of fexofenadine. *Clin Pharmacol Ther* (2003), 73, P16.
3. Shimizu M, Uno T, Sugawara K, Tateishi T. Effects of itraconazole and diltiazem on the pharmacokinetics of fexofenadine, a substrate of P-glycoprotein. *Br J Clin Pharmacol* (2006) 61, 538–44.
4. Miget N, Herrmann WM, Bergougnan L, Dubruc C, Weber F, Rosenzweig P. Lack of interaction between mizolastine and diltiazem in healthy volunteers. *Methods Find Exp Clin Pharmacol* (1996) 18 (Suppl B), 204.
5. Coracten SR (Nifedipine). UCB Pharma Ltd. UK Summary of product characteristics, June 2005.
6. Mizollen (Mizolastine). Sanofi-Aventis. UK Summary of product characteristics, March 2009.
7. Falkenberg HM. Possible interaction report. *Can Pharm J* (1988) 121, 294.
8. Zanidip (Lercanidipine hydrochloride). Recordati Pharmaceuticals Ltd. UK Summary of product characteristics, October 2004.

Calcium-channel blockers + Aprepitant

The concurrent use of aprepitant and diltiazem increases the levels of both drugs. Fosaprepitant moderately raises diltiazem levels. It seems likely that verapamil will interact with both drugs in the same way as diltiazem.

Clinical evidence

The US manufacturer notes that the use of aprepitant 230 mg daily with **diltiazem** 120 mg three times daily for 5 days increased the AUC of aprepitant twofold and increased the AUC of **diltiazem** by 70% in patients with hypertension. Nevertheless, aprepitant did not alter the effects of **diltiazem** on heart rate or blood pressure.[1] The UK manufacture of fosaprepitant notes that when subjects with mild to moderate hypertension were given a 100-mg infusion of fosaprepitant with **diltiazem** 120 mg three times daily, the AUC of **diltiazem** was increased by 40%, and the AUC of **fosaprepitant** was increased by 50%. A small but clinically meaningful decrease in blood pressure occurred, but the heart rate and PR interval were not affected to a clinically relevant extent.[2]

Mechanism

Both aprepitant, its prodrug fosaprepitant, and diltiazem are substrates and inhibitors of the cytochrome P450 isoenzyme CYP3A4. Concurrent use therefore inhibits the metabolism of the other drug. The effects on fosaprepitant may be smaller because it is given intravenously.

Importance and management

Evidence appears to be limited to these two, apparently unpublished studies by the manufacturers, but the findings are in line with the known effects of the drugs. The manufacturer of aprepitant[1] recommends caution if moderate inhibitors of CYP3A4 are also given, and this would be expected to include diltiazem. Although the effects of diltiazem were not increased in the study with aprepitant, the smaller rise that occurred with fosaprepitant did have some clinically relevant effects on blood pressure, and it may therefore be prudent to be aware of a potential decrease in blood pressure if either of these antiemetics is given to a patient taking diltiazem.

It may be prudent to consider giving the lower dose of aprepitant, where possible, as a twofold increase in its levels is likely to be clinically significant. Be alert for adverse effects such as hiccups, fatigue, constipation, and headache. Furthermore, the CYP3A4 inhibitory effects are dose-dependent and using a smaller dose may minimise the effects on diltiazem. The rise in fosaprepitant levels is not expected to be clinically significant.

Evidence about other calcium-channel blockers is lacking, but note that **verapamil** is also a moderate CYP3A4 inhibitor, and therefore would be expected to interact similarly.

1. Emend (Aprepitant). Merck & Co., Inc. US Prescribing information, July 2009.
2. IVEMEND (Fosaprepitant dimeglumine). Merck Sharp & Dohme Ltd. UK Summary of product characteristics, August 2009.

Calcium-channel blockers + Aspirin or NSAIDs

There is evidence that most NSAIDs can increase blood pressure in patients taking antihypertensives, although some studies have not found the increase to be clinically relevant. Some small pharmacokinetic interactions may occur, but they do not appear to be clinically relevant.

Some small studies suggest that low-dose aspirin does not alter the antihypertensive effect of felodipine, isradipine, nifedipine or nitrendipine, and long-term aspirin did not alter the cardiovascular benefits of nitrendipine.

Two reports describe abnormal bruising and prolonged bleeding times in two patients and one healthy subject taking verapamil with aspirin. There are conflicting reports as to whether or not gastrointestinal bleeding is increased by giving NSAIDs with calcium-channel blockers.

One report suggests that calcium-channel blockers, particularly nifedipine, may increase the risk of acute renal failure associated with NSAIDs.

Table 23.2 Summary of epidemiological studies and meta-analyses of the effect of NSAIDs on blood pressure in patients taking antihypertensive drugs

Study type	*Patients*	*Antihypertensives*	*NSAIDs*	*Findings*	*Refs*
Case-control (2005)	184 cases 762 controls (UK primary care)	Not stated. Median of two different drugs	Ibuprofen (78 cases) Diclofenac (60) Other (25)	BP control in treated hypertensives was not affected by use of NSAIDs. No evidence that either systolic BP or diastolic BP differed according to type of NSAID.	1
Retrospective analysis (2004)	8538 patients with rheumatic disease and hypertension	Not stated	NSAID (1164 patients) Celecoxib (654) Rofecoxib (417)	NSAID or celecoxib use was not associated with difficulty in controlling blood pressure, but rofecoxib use was (odds ratio 1.38).	2
Meta-analysis (1994)	50 randomised controlled studies in 771 patients or healthy subjects	Beta blockers (15) Vasodilators (18) Diuretics (12)	Indometacin (33 studies) Sulindac (7) Ibuprofen (5) Piroxicam (4) Flurbiprofen (4)	NSAIDs elevated mean supine BP by 5 mmHg. NSAIDs antagonised all antihypertensives, but only the effect on beta blockers was statistically significant (6.2 mmHg). Among the NSAIDs, only the effect of piroxicam was statistically significant, with piroxicam, indometacin and ibuprofen causing the greatest increase, and sulindac and flurbiprofen the least.	3
Case-control (1993)	133 cases 133 controls	Hydrochlorothiazide, furosemide, methyldopa, propranolol	Ibuprofen (30% of cases) Indometacin (22%) Naproxen (18%) Sulindac (13%)	Systolic BP was about 5 mmHg higher (not statistically significant) in those taking NSAIDs, but diastolic BP did not differ. Findings the same if indometacin users removed.	4
Cross-sectional cohort (1993)	2800 elderly patients (12% taking both an NSAID and antihypertensives)	Not stated	Not stated	NSAID use was associated with a 29% increased risk of hypertension in those taking antihypertensives, but not in those not taking antihypertensives.	5
Meta-analysis (1993)	54 studies with 108 NSAID treatment arms in 1213 hypertensive patients	Not stated	Indometacin (600 patients) Naproxen (72) Piroxicam (51) Ibuprofen (55) Sulindac (277)	Increase in mean arterial pressure with indometacin 3.6 mmHg, naproxen 3.7 mmHg, piroxicam 0.5 mmHg, decrease in mean arterial pressure with ibuprofen 0.8 mmHg, sulindac 0.16 mmHg. The difference between indometacin and sulindac was statistically significant.	6

1. Sheridan R, Montgomery AA, Fahey T. NSAID use and BP in treated hypertensives: a retrospective controlled observational study. *J Hum Hypertens* (2005) 19, 445–50.
2. Wolfe F, Zhao S, Pettitt D. Blood pressure destabilization and edema among 8538 users of celecoxib, rofecoxib, and nonselective nonsteroidal antiinflammatory drugs (NSAID) and nonusers of NSAID receiving ordinary clinical care. *J Rheumatol* (2004) 31, 1143–51.
3. Johnson AG, Nguyen TV, Day RO. Do nonsteroidal anti-inflammatory drugs affect blood pressure? A meta-analysis. *Ann Intern Med* (1994) 121, 289–300.
4. Chrischilles EA, Wallace RB. Nonsteroidal anti-inflammatory drugs and blood pressure in an elderly population. *J Gerontol* (1993) 48, M91–M96.
5. Johnson AG, Simons LA, Simons J, Friedlander Y, McCallum J. Non-steroidal anti-inflammatory drugs and hypertension in the elderly: a community-based cross-sectional study. *Br J Clin Pharmacol* (1993) 35, 455–9.
6. Pope JE, Anderson JJ, Felson DT. A meta-analysis of the effects of nonsteroidal anti-inflammatory drugs on blood pressure. *Arch Intern Med* (1993) 153, 477–84.

Clinical evidence

A. Antagonism of antihypertensive effects

Various large epidemiological studies and meta-analyses of clinical studies have been conducted to assess the effect of NSAIDs on blood pressure in patients taking antihypertensives, and the findings of these are summarised in 'Table 23.2', (p.1027). In these studies, NSAIDs were not always associated with an increase in blood pressure, and the maximum increase was 6.2 mmHg. The effect has been shown for both COX-2 inhibitors and non-selective NSAIDs. In two meta-analyses,[1,2] the effects were evaluated by NSAID. The confidence intervals for all the NSAIDs overlapped, showing that there was no statistically significant difference between the NSAIDs, with the exception of the comparison between **indometacin** and **sulindac** in one analysis.[2] Nevertheless, an attempt was made at ranking the NSAIDs based on the means. In one analysis,[1] the effect was greatest for **piroxicam**, **indometacin**, and **ibuprofen**, intermediate for **naproxen**, and least for **sulindac** and **flurbiprofen**. In the other meta-analysis,[2] the effect was greatest for **indometacin** and **naproxen**, intermediate for **piroxicam**, and least for **ibuprofen** and **sulindac**. An attempt was also made to evaluate the effect by antihypertensive in one analysis.[1] The mean effect was greatest for beta blockers, intermediate for vasodilators (includes ACE inhibitors and calcium-channel blockers), and least for diuretics. However, the differences between the groups were not significant.

The findings of individual clinical and pharmacological studies that have studied the effects of aspirin or specific NSAIDs on specific calcium-channel blockers are outlined in the subsections below.

(a) Aspirin

1. Felodipine. In the Hypertension Optimal Treatment (HOT) study, 18 790 treated hypertensive patients, about 82% of whom were taking a calcium-channel blocker, usually felodipine alone or in combination, were also given either aspirin 75 mg daily or placebo for an average of 3.8 years. It was found that long-term, low-dose aspirin does not interfere with the blood pressure lowering effects of the antihypertensive drugs studied.[3]

2. Isradipine. A study in 20 patients with essential hypertension, who had been taking isradipine 2.5 mg daily for 8 weeks found that the addition of aspirin 100 mg daily for a further 8 weeks did not affect the antihypertensive efficacy of the calcium-channel blocker.[4]

3. Nifedipine. In a small study in 18 patients, low-dose aspirin 100 mg daily for 2 weeks did not alter the blood pressure lowering effect of nifedipine 30 to 60 mg daily, given as a modified-release preparation.[5]

4. Nitrendipine. A study in 19 patients with essential hypertension, who had taken nitrendipine 10 mg daily for 8 weeks found that the addition of aspirin 100 mg daily for a further 8 weeks did not affect the antihypertensive efficacy of the calcium-channel blocker.[4] A post-hoc analysis of the Syst-Eur study of nitrendipine-based antihypertensive treatment found no difference in cardiovascular outcome between 861 patients who were also taking long-term aspirin (700 patients) and/or other NSAIDs (161 patients) and 2882 patients who had never taken aspirin or NSAIDs. Patients in this study were randomised to receive nitrendipine, which could be combined or replaced by enalapril, hydrochlorothiazide, or both.[6]

5. Unnamed calcium-channel blockers. In a randomised study, the use of low-dose aspirin 100 mg daily for 3 months did not alter blood pressure control in patients taking calcium-channel blockers or ACE inhibitors, when compared with placebo.[7]

(b) Diclofenac

A study in elderly women with hypertension found that diclofenac 25 mg three times daily for one week had no effect on the control of their blood pressure with **nifedipine**.[8] In 18 healthy subjects, the AUC of **isradipine** 5 mg twice daily for a week was not affected by a single 50-mg dose of diclofenac, but the maximum plasma levels were raised by a modest 20%. Platelet aggregation was unaffected and the pharmacokinetics of the diclofenac were unchanged.[9] Hypertensive subjects taking slow-release **verapamil** 240 mg daily had a 26% reduction in the AUC of **verapamil** when they took diclofenac 75 mg twice daily.[10]

(c) Ibuprofen

A study in 12 patients with mild or moderate essential hypertension controlled with **amlodipine** 10 mg daily, found that ibuprofen 400 mg three times daily for 3 days increased the mean blood pressure by 7.8/3.9 mmHg.[11] However, 53 hypertensive patients had no changes in their blood pressure control with **verapamil** 240 or 480 mg daily when they also took ibuprofen 400 mg three times daily for 3 weeks.[12]

(d) Indometacin

In a study in 10 patients with mild to moderate essential hypertension indometacin 100 mg daily for a week did not significantly affect the hypotensive effects of **nifedipine** 20 mg twice daily.[13] In contrast, in another study, indometacin 100 mg in divided doses over 24 hours was found to raise the mean arterial pressure by 17 to 20 mmHg in 5 out of 8 hypertensive patients taking **nifedipine** 15 to 40 mg daily.[14]

Five other studies, two in healthy subjects[15,16] and 3 in patients with hypertension[17-19] found that indometacin did not alter the blood pressure lowering effects of **amlodipine**,[19] **felodipine**,[15,17] **nicardipine**[16] or **verapamil**.[18] Similarly, in 24 healthy elderly subjects, the haemodynamic effects of **nimodipine** 30 mg three times daily were not affected to a clinically relevant extent by indometacin 25 mg twice daily in, although the AUC of **nimodipine** and its maximum plasma levels were slightly increased.[20] However, in 15 patients taking **nitrendipine** 5 to 20 mg twice daily, indometacin 25 mg three times daily raised systolic and diastolic blood pressure by a mean of 4 mmHg.[21]

(e) Naproxen

A placebo-controlled study in 100 patients taking **nicardipine** 30 mg three times daily found that naproxen 375 mg twice daily caused no clinically relevant changes in the control of their blood pressure.[22] In another study, 55 hypertensive patients had no changes in their blood pressure control with **verapamil** 240 to 480 mg daily when they were given naproxen 250 mg twice daily for 3 weeks.[12] Similarly, naproxen 375 mg twice daily had no effect on the pharmacokinetics of **verapamil** in hypertensive subjects.[10]

(f) Piroxicam

A study in hypertensive patients given up to 440 mg of **verapamil** daily found that piroxicam 20 mg daily for 4 weeks did not significantly alter the antihypertensive effects of **verapamil**.[23]

(g) Sulindac

A study in elderly women with hypertension found that sulindac 100 mg three times daily for one week had no effect on the control of their blood pressure with **nifedipine**.[8]

A study in hypertensive patients given up to 440 mg of **verapamil** daily found that sulindac 200 mg twice daily for 4 weeks did not significantly alter the antihypertensive effects of **verapamil**.[23]

B. Antiplatelet effects and gastrointestinal bleeding

Abnormal bruising and prolonged bleeding times occurred in a woman taking **verapamil** 80 mg three times daily when she took **aspirin** 650 mg several times a week for headaches. The bruising ceased when the **verapamil** was stopped. Her normal bleeding time of 1 minute rose to 4.5 minutes while she was taking **verapamil**, and to 9 minutes while she was taking **verapamil** and **aspirin**. A healthy subject taking the same doses of **verapamil** and **aspirin** noticed the appearance of new petechiae and her bleeding time rose from 4.5 minutes to more than 15 minutes in the presence of both drugs.[24] An 85-year-old man taking enteric-coated **aspirin** 325 mg daily developed widespread and serious ecchymoses of his arms and legs and a retroperitoneal bleed about 3 weeks after starting to take **verapamil** 240 mg daily.[25]

A prospective cohort study[26] in 1636 elderly hypertensive patients, and a case-control study,[27] found that calcium-channel blockers were associated with an increased risk of gastrointestinal bleeding, when compared with beta blockers. In one of the studies, **verapamil** was associated with the highest rate of bleeding, followed by **diltiazem** and **nifedipine**.[26] However, two other studies indicated that gastrointestinal bleeding was not increased by calcium-channel blockers.[28,29] Furthermore, a post-hoc analysis of the Syst-Eur data found that there was no interaction between chronic NSAID intake (81% **aspirin**) and antihypertensive use (based on **nitrendipine**) in terms of the incidence of gastrointestinal bleeding. In fact, the results suggested that chronic NSAID use tended to be associated with a *lower* incidence of bleeding in patients taking **nitrendipine**-based therapy than those receiving placebo.[6]

C. Effects on renal function

A case-control study using the UK General Practice Research Database found that current NSAID use increased the risk of acute renal failure (relative risk 3.2 compared with non-NSAID use) and this risk was further increased by the concurrent use of a calcium-channel blocker (relative risk 7.8); **nifedipine** appeared to be most likely to interact.[30]

Mechanism

A. Antagonism of antihypertensive effects

There is some evidence that NSAIDs may increase blood pressure in patients taking antihypertensives. Possible explanations for this include inhibition of vasodilator and natriuretic prostaglandins in the kidney and/or a decrease in vascular or endothelial prostaglandin synthesis, resulting in salt retention and vasoconstriction.[31] In contrast, low-dose aspirin appears not to affect the blood pressure lowering effects of calcium-channel blocker-based antihypertensive therapy.[3]

B. Antiplatelet effects and gastrointestinal bleeding

The prolonged bleeding times noted with verapamil[24] may occur as a result of inhibition of platelet aggregation, because calcium-channel blockers interfere with the movement of calcium ions through cell membranes, which can affect platelet function. This appears to be additive with the effects of other antiplatelet drugs. It was suggested that vasodilation produced by calcium-channel blockers in conjunction with inhibition of platelet aggregation may increase the risk of bleeding, or at least prevent the normal vasoconstrictive response to bleeding,[26] although a protective effect of beta blockers rather than an adverse effect of calcium-channel blockers may also be the reason.[28]

C. Effects on renal function

It has been suggested that the increased adverse renal effects seen when NSAIDs are given with nifedipine may be due to nifedipine-induced potential afterload reduction (renal hypoperfusion) secondary to an excess decrease in blood pressure, particularly among the elderly. However, the use of cardiac medications might also be markers of underlying conditions such as cardiovascular disease, low circulating plasma volume and/or already compromised renal function.[30]

Importance and management

Although several studies exist, the evidence for an interaction between the calcium-channel blockers and NSAIDs or aspirin is still somewhat inconclusive. Some consider that the use of NSAIDs should be kept to a minimum in patients taking antihypertensives. The effects may be greater in the elderly and in those with relatively high blood pressure, as well as in those with a high salt intake.[32] However, others consider that the clinical importance of an interaction between NSAIDs and antihypertensives is less than has previously been suggested.[33] While their findings do not rule out a 2/1 mmHg increase in blood pressure with NSAIDs in treated hypertensives, they suggest that if patients in primary care have inadequate control of blood pressure, other reasons may be more likely than any effect of concurrent NSAIDs (e.g. poor compliance or 'white-coat' hypertension).[33] There is insufficient data at present to clearly differentiate between NSAIDs. However, there is some limited evidence to suggest that the interaction of NSAIDs with calcium-channel blockers is less than that with ACE inhibitors.[5,17,19] For the effects of NSAIDs on other antihypertensive drugs, see 'ACE inhibitors', (p.32), 'beta blockers', (p.997) and 'thiazide diuretics', (p.1138).

The risk of renal failure with NSAIDs appears to be increased in patients taking calcium-channel blockers, particularly nifedipine, but it is not clear whether this is due to the drugs or the disease state. A low circulating plasma volume can increase the risk of adverse renal effects and so caution has been suggested in the elderly, especially in patients with hypertension and/or heart failure.[30]

Clinically significant interactions between NSAIDs and calcium-channel blockers that result in bleeding appear to be rare.

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Calcium-channel blockers + Azoles

Itraconazole can markedly raise the serum levels of felodipine, which increases its adverse effects, in particular ankle and leg oedema. A few case reports suggest that isradipine and nifedipine can interact similarly with itraconazole, and that fluconazole can also interact with nifedipine. Ketoconazole can markedly raise the plasma levels of lercanidipine and nisoldipine. Caution is warranted with calcium-channel blockers when azole antifungals, particularly itraconazole and ketoconazole, are used.

Clinical evidence

(a) Felodipine

In a placebo-controlled study in 9 healthy subjects, **itraconazole** 200 mg daily for 4 days, increased the AUC of a single 5-mg dose of felodipine sixfold, and its maximum plasma levels were increased eightfold. The effects of the felodipine on blood pressure and heart rate were also increased.[1]

A 52-year-old woman, who had been taking felodipine 10 mg daily for hypertension for a year, without problems, developed ankle and leg swell-

ing within 7 days of starting **itraconazole** 100 mg daily for tinea pedis. The oedema disappeared within 2 to 4 days of stopping the **itraconazole**.[2] Virtually the same reaction occurred in another woman taking both drugs. Later tests found that her AUC_{0-6} of a single 5-mg dose of felodipine was increased at least fourfold (possibly up to tenfold) while taking **itraconazole**, and ankle swelling was noted.[2]

(b) Isradipine

Ankle swelling was noted in a patient taking isradipine 5 mg daily when **itraconazole** 200 mg twice daily was also taken.[2]

(c) Lercanidipine

The manufacturer of lercanidipine notes that an interaction study found that **ketoconazole** increased the AUC of *S*-lercanidipine and its peak plasma levels 15-fold and eightfold, respectively.[3]

(d) Nifedipine

A report describes massive pitting oedema in the legs and ankles of a patient taking nifedipine when **itraconazole** 100 mg twice daily was also taken.[4] Another patient similarly had ankle oedema and markedly raised serum nifedipine levels (trough levels raised almost fivefold) while taking **itraconazole**.[5] A patient with malignant phaeochromocytoma, whose persistent hypertension was controlled with nifedipine, had a rise in blood pressure when **fluconazole** 200 mg daily was *stopped*. His blood pressure fell again when the **fluconazole** was restarted. A later study found that his maximum nifedipine plasma levels and AUC_{0-5} were raised about threefold by **fluconazole**.[6]

(e) Nisoldipine

A study in 7 healthy subjects found that **ketoconazole** 200 mg daily for 5 days increased the AUC and peak plasma levels of a single 5-mg dose of nisoldipine 24-fold and 11-fold, respectively. The levels of nisoldipine metabolite were similarly increased.[7]

Mechanism

Ankle swelling due to precapillary vasodilatation is a relatively common adverse effect of the dihydropyridine calcium-channel blockers, and this effect appears to be dose-related. Calcium-channel blockers are metabolised in the gut wall and liver by the cytochrome P450 CYP3A subfamily of isoenzymes, which are inhibited by itraconazole, ketoconazole and to a lesser extent by fluconazole. Therefore in the presence of these antifungals the levels of the calcium-channel blockers are raised and their adverse effects increased.

Importance and management

The interaction between felodipine and itraconazole would appear to be established and clinically important. It also seems that isradipine, lercanidipine, nifedipine and nisoldipine can interact similarly with itraconazole, ketoconazole, and possibly fluconazole. It is likely that all calcium-channel blockers will behave in the same way, although probably to a greater or lesser extent. Note that fluconazole is only likely to interact in doses of greater than 200 mg daily (see under 'azole antifungals', (p.233)).

Other azoles such as **posaconazole**, which is a potent inhibitor of CYP3A4, and **voriconazole** would be expected to interact similarly. Note that, at the maximum doses **miconazole** oral gel is sufficiently absorbed to potentially have systemic effects, and may therefore also interact. If any of these azoles is given to a patient on established treatment with a calcium-channel blocker be alert for the need to lower the dosage of the calcium-channel blocker. It would seem prudent to monitor for adverse effects, such as hypotension, headache, flushing, and oedema. However, note that the UK manufacturer of lercanidipine[3] specifically contraindicates the concurrent use of itraconazole or ketoconazole.

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Calcium-channel blockers + Bile-acid binding resins

Colesevelam slightly reduces the bioavailability of verapamil, and colestipol slightly reduces the bioavailability of diltiazem.

Clinical evidence, mechanism, importance and management

(a) Colesevelam

A study in 31 healthy subjects found that a single 4.5-g dose of colesevelam reduced the peak plasma levels and AUC of a single 240-mg dose of **verapamil** by about 33% and about 15%, respectively. These changes were not considered to be clinically significant.[1]

(b) Colestipol

A study in 12 healthy subjects found that colestipol reduced the AUC and peak plasma levels of a single 120-mg dose of sustained-release **diltiazem** by 22% and 36%, respectively, and those of a single 120-mg dose of immediate-release **diltiazem** by 27% and 33%, respectively. In a further study sustained-release **diltiazem** 120 mg was given alone, 1 hour before or 4 hours after multiple doses of colestipol. The AUC of **diltiazem** was decreased by 17% when it was taken 1 hour before colestipol and by 22% when taken 4 hours after colestipol. This suggests that the effects of colestipol on **diltiazem** bioavailability are not reduced by separating their administration. However, these small reductions in the AUC of **diltiazem** are unlikely to result in a reduction in its efficacy. Nevertheless, the authors advise caution if these drugs are used concurrently.[2]

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Calcium-channel blockers + Calcium-channel blockers

Plasma levels of both nifedipine and diltiazem are increased by concurrent use and blood pressure is reduced accordingly. Verapamil is predicted to interact similarly with nifedipine. Amlodipine levels are raised by diltiazem (and therefore possibly verapamil). There are isolated reports of intestinal occlusion attributed to the concurrent use of nifedipine and diltiazem. Note that if nimodipine is used with another calcium-channel blocker, the hypotensive effect may be increased and careful monitoring is recommended.

Clinical evidence

Pretreatment of 6 healthy subjects with **diltiazem** 30 or 90 mg three times daily for 3 days was found to increase the AUC of a single 20-mg dose of **nifedipine** two- and threefold, respectively.[1] Similar and related results are reported elsewhere.[2,3] In another study it was found that **nifedipine** 10 mg three times daily for 3 days increased the maximum plasma levels of a single 60-mg dose of **diltiazem** by 54% and increased its AUC by 49%.[4]

One of the manufacturers of **amlodipine** briefly mentions that, in elderly patients, **diltiazem** increases the levels of **amlodipine** by 50%, and this is accompanied by an increase in its effects.[5]

A patient taking **nifedipine** 20 mg twice daily developed abdominal distension and vomiting, 2 days after starting to take **diltiazem** 100 mg twice daily. Both calcium-channel blockers were stopped and abdominal X-ray suggested paralytic ileus, which resolved, but then recurred when both drugs were restarted.[6] Another report describes a patient taking diltiazem, who developed complete or partial intestinal occlusion on three occasions, each time when **nifedipine** was added.[7]

Mechanism

The increase in nifedipine and diltiazem levels is thought to occur as a result of a reduction in the metabolism of both drugs in the liver.[4] It has been suggested that an increased relaxant effect on smooth muscle resulted in

intestinal occlusion,[7] and this may related to increased the increased nifedipine levels.[6]

Importance and management

Established interactions but of uncertain clinical importance. Some manufacturers of nifedipine advise caution when it is used with diltiazem because of possible increases in nifedipine levels.[8,9] They say a reduction in the dose of nifedipine should be considered.[9] **Verapamil** is likely to interact similarly with nifedipine,[9] as it has similar effects to diltiazem on hepatic metabolism. Some caution may also be prudent if diltiazem or, in theory, verapamil are given with amlodipine. Consider increasing blood pressure monitoring.

Information about the use of combinations of other calcium-channel blockers appears to be lacking. However, the manufacturers of **nimodipine**[10,11] warn that the blood pressure lowering effect of other calcium-channel blockers could be enhanced by the addition of nimodipine: the UK manufacturer[10] advises careful monitoring of the patient.

Note that the clinical use of two calcium-channel blockers is rarely justified and consideration should be given to stopping one or other of the drugs, as appropriate.

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Calcium-channel blockers + Calcium compounds

An isolated report describes antagonism of the antiarrhythmic effects of oral verapamil due to the use of oral calcium. Note that intravenous calcium compounds are sometimes given before intravenous verapamil, where the hypotensive effects of verapamil would be detrimental, and calcium has been used to reverse the effects of calcium-channel blocker overdose.

Clinical evidence, mechanism, importance and management

An elderly woman with atrial fibrillation, successfully treated for over a year with **verapamil**, developed atrial fibrillation within a week of starting to take an oral calcium compound 1.2 g with calciferol (vitamin D) 3000 units daily for diffuse osteoporosis. Her serum calcium levels had risen from 2.45 to 2.7 mmol/L. Normal sinus rhythm was restored by giving 500 mL of sodium chloride 0.9% and repeated doses of furosemide 20 mg and **verapamil** 5 mg by intravenous injection.[1]

Verapamil acts by inhibiting the passage of calcium ions into cardiac muscle cells and it would appear that in this case the increased concentration of calcium ions outside the cells opposed the effects of the **verapamil**.

The general importance of this isolated case is uncertain, but bear it in mind in the event of an unexpected reduction in **verapamil** effects.

Note that intravenous calcium compounds are sometimes given before intravenous verapamil in the treatment of ventricular arrhythmias to prevent verapamil-induced hypotension in situations where this could be detrimental. This is said not to affect the antiarrhythmic efficacy.[2] Calcium, usually in the form of intravenous calcium gluconate, is used as an antidote in cases of overdose of calcium-channel blockers.

There therefore seems no reason to avoid the use of calcium in patients taking calcium-channel blockers, but, if the effects of the calcium-channel blocker are diminished, it may be prudent to consider monitoring serum calcium levels.

1. Bar-Or D, Yoel G. Calcium and calciferol antagonise effect of verapamil in atrial fibrillation. *BMJ* (1981) 282, 1585–6.
2. Moser LR, Smythe MA, Tisdale JE. The use of calcium salts in the prevention and management of verapamil-induced hypotension. *Ann Pharmacother* (2000) 34, 622–9.

Calcium-channel blockers + Clonidine

Two hypertensive patients taking verapamil developed complete heart block after they also started to take clonidine. The hypotensive effects of nifedipine and clonidine were additive in hypertensive patients. Transdermal clonidine has been successfully used with nifedipine or diltiazem in small studies.

Clinical evidence

(a) Diltiazem

In a clinical study, transdermal clonidine decreased blood pressure in 58 of 60 patients with hypertension inadequately controlled by sustained-release diltiazem 90 mg twice daily. The addition of clonidine did not cause a significant decrease in heart rate.[1]

(b) Nifedipine

In a study in 12 patients, sustained-release clonidine 250 micrograms daily for 2 weeks increased the hypotensive effects of nifedipine 20 mg twice daily by about 5 mmHg (mean blood pressure reduction). Clonidine did not alter the slight heart rate increase seen with nifedipine.[2] In a clinical study, in 39 patients with hypertension inadequately controlled by nifedipine GITS (gastrointestinal therapeutic system) 30 to 60 mg daily, transdermal clonidine successfully decreased blood pressure in all 35 patients who completed a titration phase and then an 8-week maintenance phase.[3]

(c) Verapamil

A 54-year-old woman with refractory hypertension (blood pressure 240/140 mmHg) and hyperaldosteronism, was given verapamil 160 mg three times daily and spironolactone 100 mg daily for 10 days, and had a reduction in her blood pressure to 180/100 mmHg. Clonidine 150 micrograms twice daily was then added, and after the second dose she became confused and her blood pressure was found to have fallen to 90/70 mmHg, with a heart rate of 50 bpm. She had developed complete AV block, which resolved when all the drugs were stopped. A 65-year-old woman with persistent hypertension did not have a satisfactory reduction in blood pressure with extended-release verapamil 240 mg daily (blood pressure 165/100 mmHg). Clonidine 150 micrograms twice daily was then added, and the next day a routine ECG showed that she had a nodal rhythm of 80 bpm, which developed into complete AV block. Her blood pressure had fallen to 130/80 mmHg.[4]

Mechanism

Not fully understood. Verapamil very occasionally causes AV node disturbances, but both of these patients had normal sinus rhythm before the clonidine was added. Clonidine alone has been associated with AV node dysfunction in hypertensive patients. It would seem, therefore, that these effects were additive in these two patients.[4]

Importance and management

Information about the interaction between verapamil and clonidine seems to be limited to the one report.[4] Its authors say that a review of the literature from 1966 to 1992 revealed no reports of any adverse interactions between these drugs. Nonetheless, they suggest that it would now be prudent to give these two drugs together with caution and good monitoring in any patient, even in those without sinus or AV node dysfunction.

There was no adverse effect on heart rate in one study in patients taking diltiazem and using transdermal clonidine and the additive blood pressure lowering effect seen with nifedipine is what would be expected with the use of clonidine and any calcium-channel blocker. One US manufacturer of clonidine warns about the potential for additive effects such as bradycardia and AV block if calcium-channel blockers are also given;[5] however, this seems most likely to be a problem with diltiazem or verapamil,

rather than the dihydropyridine-type calcium-channel blockers (see 'Table 23.1', (p.1025)).

1. Lueg MC, Herron J, Zellner S. Transdermal clonidine as an adjunct to sustained-release diltiazem in the treatment of mild-to-moderate hypertension. *Clin Ther* (1991) 13, 471–81.
2. Salvetti A, Pedrinelli R, Magagna A, Stornello M, Scapellato L. Calcium antagonists: interactions in hypertension. *Am J Nephrol* (1986) 6 (Suppl 1), 95–9.
3. Houston MC, Hays L. Transdermal clonidine as an adjunct to nifedipine-GITS therapy in patients with mild-to-moderate hypertension. *Am Heart J* (1993) 126, 918–23.
4. Jaffe R, Livshits T, Bursztyn M. Adverse interaction between clonidine and verapamil. *Ann Pharmacother* (1994) 28, 881–3.
5. Catapres Tablets (Clonidine hydrochloride). Boehringer Ingelheim Pharmaceuticals, Inc. US Prescribing information, January 2010.

Calcium-channel blockers + Dantrolene

An isolated report describes acute hyperkalaemia and cardiovascular collapse when intravenous dantrolene was given to a patient taking verapamil. Another case describes severe hyperkalaemia in a patient taking diltiazem when intravenous dantrolene was given. *Animal* studies have found similar effects with the combination of dantrolene and verapamil or diltiazem. Nifedipine and amlodipine do not appear to interact.

Clinical evidence, mechanism, importance and management

(a) Diltiazem

A case report describes a 42-year-old patient who developed severe hyperkalaemia after being given an intravenous infusion of dantrolene sodium 200 mg, before the induction of anaesthesia for coronary artery bypass grafting. Preoperatively, the patient was taking metoprolol twice daily and diltiazem 30 mg every 6 hours.[1] One *animal* study also suggests that diltiazem may sometimes interact with dantrolene to produce hyperkalaemia and cardiovascular collapse.[2] Note that, in the UK the use of diltiazem with dantrolene infusion is generally contraindicated because the combination of a calcium-channel blocker and dantrolene is said to be potentially dangerous.

(b) Verapamil

A case report describes a 60-year-old man with insulin-dependent diabetes undergoing a right hemicolectomy. Due to inoperable coronary artery disease, which was causing angina pain, he was taking verapamil 80 mg three times daily. On the morning of surgery he was given verapamil 80 mg with his pre-operative sedation and then, 2 hours later at the start of surgery, he was given intravenous dantrolene 220 mg over 30 minutes, because he was known to have previously had malignant hypertension. After surgery, when he was in intensive care, it was found that his potassium had risen from 4.6 mmol/L before surgery to 6.1 mmol/L at the end of surgery (about 90 minutes after the dantrolene infusion). He was given 10 units of insulin, but an hour later his potassium was 7.1 mmol/L. He was given more insulin, but then developed metabolic acidosis and some cardiac depression, which resolved when he was given bicarbonate and hetastarch 5%. He received three further doses of dantrolene without incident.[3]

The authors of the report attributed the effects seen to an interaction between verapamil and dantrolene. They note that hyperkalaemia has been seen following dantrolene infusions, but the case they cite in support of this suggestion actually describes hyperkalaemia in response to *suxamethonium*. Furthermore, the UK and US manufacturers of dantrolene do not include hyperkalaemia as an adverse effect.[4,5] Nevertheless, the overall picture is that hyperkalaemia, of whatever cause, can apparently increase the myocardial depression caused by verapamil.[6,7] This case seems to be the only report of an interaction between verapamil, and several factors do not make this a clear-cut case of an interaction. However, hyperkalaemia and cardiovascular collapse have been seen in *pigs* and *dogs* given dantrolene and verapamil,[8-10] and so an interaction cannot be completely ruled out. The manufacturers of dantrolene recommend that the combination of intravenous dantrolene sodium and calcium-channel blockers, such as verapamil, is not used during the management of malignant hyperthermia crisis,[4,5] and one manufacturer of verapamil contraindicates intravenous dantrolene.[11]

(c) Miscellaneous

Studies suggest that **amlodipine**[6] and **nifedipine**[2] do not interact with dantrolene and they may therefore be safer alternatives to diltiazem or verapamil. In the case above with verapamil[3] the patient later underwent further surgery while taking **nifedipine**, without any significant adverse effect (although the potassium was moderately raised at 5.4 mmol/L).

1. Yoganathan T, Casthely PA, Lamprou M. Dantrolene-induced hyperkalemia in a patient treated with diltiazem and metoprolol. *J Cardiothorac Anesth* (1988) 2, 363–4.
2. Saltzman LS, Kates RA, Norfleet EA, Corke BC, Heath KS. Hemodynamic interactions of diltiazem-dantrolene and nifedipine and nifedipine-dantrolene. *Anesthesiology* (1984) 61, A11.
3. Rubin AS, Zablocki AD. Hyperkalemia, verapamil, and dantrolene. *Anesthesiology* (1987) 66, 246–9.
4. Dantrium Intravenous (Dantrolene sodium). SpePharm UK Ltd. UK Summary of product characteristics, July 2008.
5. Dantrium Intravenous (Dantrolene sodium). Procter & Gamble Pharmaceuticals. US Prescribing information, October 2007.
6. Freysz M, Timour Q, Bernaud C, Bertrix L, Faucon G. Cardiac implications of amlodipine-dantrolene combinations. *Can J Anaesth* (1996) 43, 50–5.
7. Jolly SR, Keaton N, Movahed A, Rose GC, Reeves WC. Effect of hyperkalemia on experimental myocardial depression by verapamil. *Am Heart J* (1991) 121, 517–23.
8. Lynch C, Durbin CG, Fisher NA, Veselis RA, Althaus JS. Effects of dantrolene and verapamil on atrioventricular conduction and cardiovascular performance in dogs. *Anesth Analg* (1986) 65, 252–8.
9. San Juan AC, Port JD, Wong KC. Hyperkalemia after dantrolene administration in dogs. *Anesth Analg* (1986) 65, S131.
10. Saltzman LS, Kates RA, Corke BC, Norfleet EA, Heath KR. Hyperkalemia and cardiovascular collapse after verapamil and dantrolene administration in swine. *Anesth Analg* (1984) 63, 473–8.
11. Univer (Verapamil hydrochloride). Cephalon Ltd. UK Summary of product characteristics, September 2008.

Calcium-channel blockers + Diuretics

No pharmacokinetic interaction appears to occur between hydrochlorothiazide and diltiazem or isradipine. Similarly, spironolactone does not alter the pharmacokinetics of felodipine. Combinations of diuretics and calcium-channel blockers are used clinically for their additive antihypertensive effects.

Clinical evidence, mechanism, importance and management

A study in 21 healthy subjects given **diltiazem** 60 mg four times daily (for 21 doses) and **hydrochlorothiazide** 25 mg twice daily (for 11 doses), either alone or in combination, found that at steady-state there was no clinically significant pharmacokinetic interaction between the two drugs.[1] **Diltiazem** and **verapamil** increase the levels of **eplerenone**, and dosage adjustments are recommended, see 'Potassium-sparing diuretics; Eplerenone + CYP3A4 inhibitors', p.1135.

The pharmacokinetics of **isradipine** and **hydrochlorothiazide** are not affected by concurrent use,[2,3] and **spironolactone** 50 mg was found not to affect either the pharmacokinetics or the clinical effects of **felodipine**.[4]

Amlodipine was found to be effective (13/11 mmHg fall in blood pressure) with an acceptable safety profile when added to **hydrochlorothiazide** in patients with inadequately controlled hypertension.[5] The manufacturers say that **amlodipine** has been safely given with **thiazides** and no dosage adjustment of **amlodipine** is required.[6,7]

Additive antihypertensive effects are expected when diuretics such as **hydrochlorothiazide** are used in combination with calcium-channel blockers, and such combinations are used clinically.

1. Weir SJ, Dimmitt DC, Lanman RC, Morrill MB, Geising DH. Steady-state pharmacokinetics of diltiazem and hydrochlorothiazide administered alone and in combination. *Biopharm Drug Dispos* (1998) 19, 365–71.
2. Prescal (Isradipine). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, June 2007.
3. Dynacirc CR (Isradipine). Reliant Pharmaceuticals, Inc. US prescribing information, August 2005.
4. Janzon K, Edgar B, Lundborg P, Regårdh CG. The influence of cimetidine and spironolactone on the pharmacokinetics and haemodynamic effects of felodipine in healthy subjects. *Acta Pharmacol Toxicol (Copenh)* (1986) 59 (Suppl 4), 98.
5. Glasser SP, Chrysant SG, Graves J, Rofman B, Koehn DK. Safety and efficacy of amlodipine added to hydrochlorothiazide therapy in essential hypertension. *Am J Hypertens* (1989) 2, 154–7.
6. Istin (Amlodipine besilate). Pfizer Ltd. UK Summary of product characteristics, July 2007.
7. Norvasc (Amlodipine besylate). Pfizer Inc. US Prescribing information, August 2006.

Calcium-channel blockers + Food

Some modified-release preparations of felodipine, nifedipine, and nisoldipine show markedly increased levels when given with food, particularly high-fat food. The bioavailability of lercanidipine is markedly increased and the absorption of manidipine is improved by food. Food modestly decreases the rate and extent of absorption of nimodipine capsules and food also modestly decreases the peak level of nicardipine. Food does not appear to

have a clinically significant effect on the absorption of amlodipine, diltiazem, isradipine, or verapamil.

Clinical evidence

(a) Amlodipine

There was no difference in rate or extent of absorption of amlodipine capsules between the fed and fasted state in a study in healthy subjects.[1] Similarly, another study in healthy subjects found that a high-fat meal had no effect on the bioavailability of amlodipine.[2]

(b) Diltiazem

The rate and extent of absorption of both a slow-release and a conventional tablet of diltiazem were unaffected by food in healthy subjects.[3] Similarly, in a study in healthy subjects, the pharmacokinetic parameters of another sustained-release formulation of diltiazem (*Mono-Tildiem LP*) showed only minor changes when given with food.[4]

(c) Felodipine

The manufacturer of one prolonged-release tablet of felodipine (*Vascalpha*) notes that taking it with a high-fat meal markedly increased the maximum level (2- to 2.5-fold) without altering the extent of absorption.[5]

(d) Isradipine

Compared with the fasted state, the pharmacokinetic parameters of isradipine differed by less than 20% when modified-release and standard-release formulations of isradipine were given with a light meal.[6]

(e) Lercanidipine

The manufacturer notes that the oral bioavailability of lercanidipine is increased fourfold when it is taken up to 2 hours after a high-fat meal.[7]

(f) Manidipine

In a study in 12 healthy subjects, the bioavailability of single 20-mg dose of manidipine was increased by 42% when given after a standard breakfast rather than in the fasting state. Peak plasma levels were increased by about 25% by food (not statistically significant), and the rate of absorption was unaffected.[8]

(g) Nicardipine

Nicardipine peak plasma levels are reduced by 30% when given with a high-fat meal.[9] When a sustained-release preparation of nicardipine (*Cardene SR*) was given with a high-fat breakfast, the mean maximum plasma concentration was 45% lower, the AUC was 25% lower and trough levels were 75% higher, compared with the fasting state.[10]

(h) Nifedipine

Some single-dose studies suggested that food might delay the absorption of nifedipine[11] and reduce its peak levels,[12,13] but a multiple dose study found that food did not have an important effect on the steady-state levels of nifedipine in a 'biphasic' formulation.[14] A further single-dose study in healthy subjects found that the bioavailability of two modified-release preparations of nifedipine (*Adalat OROS* or *Nifedicron*) were not significantly different when they were given in the fasting state, although the maximum plasma levels were 31 micrograms/L and 53 micrograms/L, respectively. The bioavailability and maximum plasma level (38 micrograms/L) of *Adalat OROS* were similar when given after a high-fat or in the fasting state. However, the maximum plasma level of *Nifedicron* increased 2.4-fold to 128 micrograms/L after a high-fat breakfast. Although the bioavailability of *Nifedicron* was only modestly increased by food, the increase in plasma levels indicates a loss of modified-release characteristics and suggests that the effect of food on nifedipine may depend on the product formulation.[15] Similar results were found in another study.[16] The manufacturer of another modified-release preparation of nifedipine (*Adalat CC*) also notes that administration immediately after a high-fat meal increased the peak plasma level by 60% without altering the AUC.[17]

(i) Nimodipine

The US manufacturer notes that taking nimodipine capsules after a standard breakfast reduced the AUC by 38% and the peak level by 68%, when compared with the fasted state in healthy subjects.[18]

(j) Nisoldipine

The manufacturer of an extended-release nisoldipine preparation (*Sular*) notes that food with a high fat content markedly increases the maximum plasma level (by up to 300%), but decreases total exposure by 25%. They note that this appears to be specific to the controlled-release preparation, as food had a lesser effect on the immediate-release tablet.[19]

(k) Verapamil

The absorption of verapamil from a multiparticulate sustained-release preparation was not affected when it was given with food.[20]

Mechanism

The increase in bioavailability of manidipine in the presence of food may be because it is lipophilic and solubilised by food and bile secretions.[8] Other lipophilic dihydropyridine calcium-channel blockers include lercanidipine,[21] felodipine and nisoldipine.[8] Food may alter the release characteristics of modified-release preparations of drugs, increasing the rate of absorption of the drug, and thereby potentially increasing effects.

Importance and management

Some modified-release preparations of felodipine, nifedipine and nisoldipine have shown markedly increased peak levels when given with meals, particularly if they are high in fat content. Because of this increase, the manufacturers of *Vascalpha* (felodipine),[5] *Adalat CC* (nifedipine)[17] and *Sular* (nisoldipine)[19] recommend that they are taken on an empty stomach[5,17] or with a light meal,[5] avoiding high-fat meals.[5,19] Note that these precautions do not apply to all preparations of these calcium-channel blockers (e.g. *Plendil* (felodipine) can be taken irrespective of meals), so the manufacturer's literature needs to be consulted.

Food markedly increases the bioavailability of lercanidipine, and it should therefore be taken at least 15 minutes before meals.[7] However, food modestly increases the extent of absorption of manidipine, and it has been recommended that manidipine should be given with food.[8]

In contrast, food modestly decreases the absorption of nimodipine *capsules*, and the US manufacturer says they should preferably be taken not less than one hour before, or 2 hours after, meals.[18] Food also modestly decreases the peak level of nicardipine, and the manufacturers of the sustained release preparation suggest that taking *Cardene SR* with a meal reduces the fluctuation in plasma levels.[10,22]

Food had no clinically significant effect on the absorption of amlodipine, diltiazem, isradipine, or verapamil from the preparations studied (see *Clinical evidence*, above).

1. Faulkner JK, Hayden ML, Chasseaud LF, Taylor T. Absorption of amlodipine unaffected by food. Solid dose equivalent to solution dose. *Arzneimittelforschung* (1989) 39, 799–801.
2. Chung M, Calcagni A, Glue P, Bramson C. Effect of food on the bioavailability of amlodipine besylate/atorvastatin calcium combination tablet. *J Clin Pharmacol* (2006) 46, 1212–16.
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4. Bianchetti G, Bagheri H, Houin G, Dubruc C, Thénot JP. Pharmacokinetic and bioavailability of diltiazem sustained-release: influence of food and time of administration. *Fundam Clin Pharmacol* (1995) 9, 197–201.
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6. Holmes DG, Kutz K. Bioequivalence of a slow-release and a non-retard formulation of isradipine. *Am J Hypertens* (1993) 6 (3 Pt 2), 70S–73S.
7. Zanidip (Lercanidipine hydrochloride). Recordati Pharmaceuticals Ltd. UK Summary of product characteristics, October 2004.
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9. Cardene (Nicardipine hydrochloride). Astellas Pharma Ltd. UK Summary of product characteristics, November 2005.
10. Cardene SR (Nicardipine hydrochloride). PDL BioPharma, Inc. US Prescribing information, January 2007.
11. Ochs HR, Rämsch K-D, Verburg-Ochs B, Greenblatt DJ, Gerloff J. Nifedipine: kinetics and dynamics after single oral doses. *Klin Wochenschr* (1984) 62, 427–9.
12. Reitberg DP, Love SJ, Quercia GT, Zinny MA. Effect of food on nifedipine pharmacokinetics. *Clin Pharmacol Ther* (1987) 42, 72–5.
13. Challenor VF, Waller DG, Gruchy BS, Renwick AG, George CF. Food and nifedipine pharmacokinetics. *Br J Clin Pharmacol* (1987) 23, 248–9.
14. Rimoy GH, Idle JR, Bhaskar NK, Rubin PC. The influence of food on the pharmacokinetics of 'biphasic' nifedipine at steady state in normal subjects. *Br J Clin Pharmacol* (1989) 28, 612–15.
15. Schug BS, Brendel E, Wonnemann M, Wolf D, Wargenau M, Dingler A, Blume HH. Dosage form-related food interaction observed in a marketed once-daily nifedipine formulation after a high-fat American breakfast. *Eur J Clin Pharmacol* (2002) 58, 119–25.
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17. Adalat CC (Nifedipine). Bayer HealthCare. US Prescribing information, October 2004.
18. Nimotop Capsules (Nimodipine). Bayer HealthCare Pharmaceuticals. US Prescribing information, February 2008.
19. Sular (Nisoldipine). Sciele Pharma, Inc. US Prescribing information, January 2008.
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22. Cardene SR (Nicardipine hydrochloride). Astellas Pharma Ltd. UK Summary of product characteristics, June 2006.

Calcium-channel blockers + Grapefruit juice

Grapefruit juice very markedly increases the bioavailability of felodipine, manidipine and nisoldipine and alters their haemodynamic effects. The bioavailability of nicardipine, nifedipine, nimodipine, nitrendipine or verapamil are also increased, but the haemodynamic effects appear to be less, whereas the bioavailability of amlodipine and diltiazem are only minimally affected. An isolated report describes peripheral oedema and weight gain in a black man taking nifedipine when also drinking grapefruit juice, and case reports suggest that amlodipine may occasionally interact with grapefruit juice.

Clinical evidence

(a) Grapefruit juice

There are several studies on the effects of grapefruit juice on calcium-channel blockers. These are summarised in 'Table 23.3', (p.1035). In addition, an isolated report describes a 54-year-old black African man taking **nifedipine** retard 60 mg daily, lisinopril 5 mg daily and aspirin 75 mg who presented with peripheral oedema, weight gain, and apparently improved blood pressure control of a period of about 6 months. Over this time he had been drinking about 400 mL of freshly squeezed grapefruit juice every morning as part of a diet regimen. He was advised to stop drinking grapefruit juice, and 2 weeks later the oedema had disappeared, he had lost 2 kg in weight, and his blood pressure was slightly higher (140/85 mmHg) than when he presented (130/80 mmHg).[1] Other cases have been reported with amlodipine. In 2002 the Adverse Drug Reactions Advisory Committee (ADRAC) in Australia reported that they had received three case reports describing an interaction between amlodipine and grapefruit juice. No details were given.[2]

(b) Whole grapefruit

Some studies have found that grapefruit pulp (equivalent to one fruit), grapefruit segments (including seed but devoid of vascular layer), or grapefruit segment-free extract (extract of peel and pith) may increase the AUCs of **nifedipine**, **nisoldipine** and **felodipine** by 30%, 30%, and threefold, respectively.[3,4]

Mechanism

Complex. It has been suggested that the increases in bioavailability are due to components of the fruit juice particularly furanocoumarins including bergamottin (also found in Seville (or bitter) oranges and lime juice) and 6',7'-dihydroxybergamottin;[5-10] other components including flavonoids such as naringin[11-13] (but not quercetin[14]) or sesquiterpenoids[15] might also be involved, but appear to have a more minor role. These components inhibit the activity of the cytochrome P450 isoenzymes CYP3A subfamily in the intestinal wall so that the first-pass metabolism of these calcium-channel blockers is reduced, thereby increasing their bioavailability and therefore their effects. Grapefruit juice has little effect on hepatic CYP3A4 and this is borne out by the fact that it interacts with oral but not intravenous preparations. Therefore, the sensitivity of the interaction with grapefruit juice may be related to the oral bioavailability of the calcium-channel blocker.[16,17] Thus, amlodipine and diltiazem with high bioavailability are least affected, nifedipine is intermediate; and felodipine[16] and nisoldipine,[17] which have lower bioavailability, are most sensitive to the activity of grapefruit juice. The exception is verapamil, which has low bioavailability and appears to be only modestly affected by grapefruit juice, but this is possibly because cytochrome P450 isoenzymes other than CYP3A4 are involved in its metabolism.[16] The plasma protein binding[17] or lipophilicity[18] of the calcium-channel blocker may also contribute to the strength of the interaction, as drugs with a higher plasma protein binding ratio such as manidipine[17] or highly lipophilic drugs such as **lercanidipine**[18] are predicted to interact with grapefruit juice to a greater extent than nifedipine.

The authors of the case report,[1] suggested that black Africans may be more susceptible to any interaction, as they already have reduced systemic clearance of nifedipine, when compared with Caucasians. However, the magnitude of the interaction shows wide variation among individuals, which is presumably related to CYP3A4 levels in the intestinal epithelium, and therefore it might be anticipated that the higher the CYP3A4 levels, the greater the interaction.

Furanocoumarins and possibly other components of grapefruit juice may also increase the levels of calcium-channel blockers by inhibition of intestinal P-glycoprotein efflux transport.[5,6,16]

Importance and management

These are established interactions and several manufacturers of felodipine[19-21] suggest that it should not be taken with grapefruit juice. Similar advice is given for most other calcium-channel blockers. However, the UK manufacturer of lercanidipine[22] contraindicates its use with grapefruit juice and one manufacturer of verapamil[23] also contraindicate grapefruit juice, although other manufacturers suggest that this interaction appears to be of little clinical relevance[24] in the majority of patients. It is noteworthy that only one probable case report of the interaction appears to have been published.

Generally speaking, the studies suggest that the concurrent use of grapefruit juice and most calcium channel-blockers other than felodipine, and possibly manidipine or nisoldipine, need not be avoided. However, it would be worth checking the diet of any patient who complains of increased or excessive adverse effects with any calcium-channel blocker (e.g. hypotension, headache, flushing, oedema). Any problems can be solved either by avoiding grapefruit juice, or, where possible, by swapping the calcium-channel blocker for one less likely to interact (although note that cases have been reported with amlodipine, which is generally considered as unlikely to interact). Note that some studies suggest that the effects of grapefruit juice can persist for several days, and this should be taken into account when adjusting treatment.

It has also been suggested that **whole grapefruit** or products made from **grapefruit peel** such as marmalade should also be avoided in patients taking felodipine.[4]

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Table 23.3 Summary of pharmacokinetic studies involving calcium-channel blockers and grapefruit juice*

Calcium-channel blocker	*Pharmacokinetic effects*	*Pharmacodynamic effects*	*Refs*
Amlodipine	AUC increased by 7 to 16%, which would not be expected to be clinically significant.	No clinically relevant changes in healthy subjects.	1-3
Diltiazem	AUC increased by10 to 20%, which would not be expected to be clinically significant.	No clinically relevant changes in healthy subjects.	4, 5
Felodipine	AUC increased 2- to 3-fold in healthy subjects. Marked and variable increases in felodipine bioavailability. Effects of grapefruit juice may continue for at least 24 hours after intake. Extended-release tablets less affected; AUC increased by 60 to 100%. IV felodipine not affected.	Decreased blood pressure and increased heart rate seen. Adverse effects (headache; facial flushing; lightheadedness) also increased.	6-17
Manidipine	AUC increased 2.3- to 3-fold.	Adverse effects (headache; flushing; palpitations) more frequent.	18
Nicardipine	AUC increased by 40 to 80%. IV nicardipine not affected.	No clinically relevant effects in healthy subjects, apart from an increase in heart rate.	19
Nifedipine	AUC increased by 10 to 100%. Effects of GFJ may last at least 3 days after intake. IV nifedipine not affected.	One patient experienced a drop in blood pressure.	6, 20-25
Nimodipine	AUC increased by 50%. Effects of grapefruit juice may last at least 4 days after intake.	Heart rate increased in healthy subjects.	26
Nisoldipine	AUC increased 2- to 4-fold. Effects of GFJ may last 3 days after intake.	Some studies suggest blood pressure decreased and heart rate slightly increased in healthy subjects, whereas others suggest no clinically relevant effects occur.	27, 28
Nitrendipine	AUC increased 2.3-fold.	No clinically relevant changes in healthy subjects.	29
Verapamil	No clinically relevant effects with a single drink of grapefruit juice, but AUC increased by 30 to 50% with multiple doses. Pharmacokinetic effect showed considerable intersubject variation.	Effects generally not clinically significant in healthy subjects, but the PR interval was prolonged in 2 subjects; this was considered to be of borderline significance (increases to above 350 milliseconds in 2 subjects, usual maximal PR intervals of 200 to 260 milliseconds).	30-32

*The usual volume of grapefruit juice used in the studies was 200 to 250 mL

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Continued

Table 23.3 Summary of pharmacokinetic studies involving calcium-channel blockers and grapefruit juice* (continued)

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Calcium-channel blockers + H_2-receptor antagonists

The plasma levels of diltiazem, felodipine, isradipine, lacidipine, nifedipine, nimodipine, nisoldipine, and nitrendipine are increased by cimetidine. High doses of cimetidine may increase the bioavailability of lercanidipine. The manufacturers of nicardipine advise caution with cimetidine, although studies suggest no clinically important interactions occur. Cimetidine does not interact with amlodipine, and it is uncertain whether cimetidine interacts significantly with verapamil. Ranitidine appears to interact only minimally with calcium-channel blockers, if at all. There is no pharmacokinetic interaction between famotidine and nifedipine.

Clinical evidence

(a) Amlodipine

A crossover study in 12 healthy subjects found that **cimetidine** 400 mg twice daily for 14 days had no effect on the pharmacokinetics of amlodipine 10 mg.[1]

(b) Diltiazem

In a single-dose study, **cimetidine** increased the AUC of diltiazem by 25 to 50% and increased its serum levels by 40%.[2] In a study in 6 healthy subjects, **cimetidine** 300 mg before meals and at bedtime for a week increased the AUC of a single 60-mg oral dose of diltiazem by 50% and increased its peak plasma levels by 57%. In the same study, **ranitidine** 150 mg twice daily for a week had no significant effect on the AUC of diltiazem.[3] No adverse interaction was seen in 22 patients given calcium-channel blockers, including diltiazem, with oral **famotidine** for 6 to 8 weeks.[4]

(c) Felodipine

In a study in 12 subjects, **cimetidine** 1 g daily increased the AUC of felodipine 10 mg by 56%, and raised its peak serum level by 54%. There was a short lasting effect on heart rate but the clinical effects were minimal.[5]

(d) Isradipine

The manufacturer of isradipine[6] notes that **cimetidine** increases the bioavailability of isradipine by about 50%.

(e) Lacidipine

In a study in healthy subjects a single 800-mg dose of **cimetidine** increased the maximum plasma level of a single 4-mg dose of lacidipine by 59% and increased its AUC by 74%. Pulse rate and blood pressure were unaffected.[7]

(f) Lercanidipine

The manufacturers of lercanidipine state that **cimetidine** 800 mg daily causes no significant alteration in the plasma levels of lercanidipine;[8,9] the AUC and maximum plasma concentration were increased by a mean of 11%,[9] which would not be expected to be clinically relevant. However, they suggest that the bioavailability of lercanidipine and its hypotensive effects may be increased by higher doses of **cimetidine**.[8,9]

(g) Nicardipine

In a study in 12 healthy subjects, intravenous **cimetidine** 300 mg every 6 hours for 48 hours did not alter the pharmacokinetics or pharmacodynamics of a 12-hour intravenous infusion of nicardipine 24 mg.[10] In a review of patients prescribed H_2-receptor antagonists, no adverse interaction was seen in 22 patients given calcium-channel blockers, including nicardipine, with **famotidine** for 6 to 8 weeks.[4]

(h) Nifedipine

In a pharmacokinetic study, **cimetidine** 1 g daily for a week increased the AUC of nifedipine 40 mg daily by about 60% and increased the maximum plasma levels by about 90%. **Ranitidine** 150 mg twice daily for a week caused an insignificant rise of about 25% in maximum nifedipine plasma levels and AUC.[11] Seven hypertensive patients had a fall in mean blood pressure from 127 mmHg to 109 mmHg after taking nifedipine 40 mg daily for 4 weeks, and a further fall to 95 mmHg after they also took **cimetidine** 1 g daily for 3 weeks. When they took **ranitidine** 300 mg instead of **cimetidine**, blood pressure was not significantly affected.[11,12] Other studies clearly confirm that **cimetidine** causes a very significant rise in plasma nifedipine levels and an increase in its effects, whereas **ranitidine** interacts only minimally.[13-19] Overall, cimetidine appears to increase the AUC of nifedipine by about 1.5- to 2-fold and the maximum plasma concentration by about 1.6- to 2-fold.[20]

A study found no pharmacokinetic interaction between nifedipine and **famotidine**, but **famotidine** reversed the effects of nifedipine on systolic time intervals and significantly reduced the stroke volume and cardiac output.[21,22] In a review of patients prescribed H_2-receptor antagonists, no adverse interaction was seen in 22 patients given calcium-channel blockers, including nifedipine, with **famotidine** for 6 to 8 weeks.[4]

(i) Nimodipine

In a study in 8 healthy subjects, **cimetidine** 1 g daily for 7 days increased the bioavailability of nimodipine 30 mg three times daily by 75%, but the haemodynamic effects were unchanged. **Ranitidine** did not interact.[23]

(j) Nisoldipine

A study in 8 healthy subjects found that taking **cimetidine** 1 g in divided doses on the day before the study and then three 200 mg doses every 4 hours on the study day, increased the bioavailability of a single 10-mg dose of nisoldipine by about 50%, but the haemodynamic effects of the nisoldipine were unaltered.[24] The manufacturer reports that **cimetidine** 400 mg twice daily increases the AUC and maximum plasma concentration of nisoldipine by 30 to 45%, whereas **ranitidine** does not interact.[25]

(k) Nitrendipine

In a study, 9 healthy subjects were given **cimetidine** 800 mg before a single 20-mg dose of nitrendipine, and **cimetidine** 400 mg in divided doses after the nitrendipine. **Cimetidine** increased the bioavailability of nitrendipine by 154% but its haemodynamic effects were unchanged.[26] Another study found that the AUC of oral nitrendipine 20 mg daily for 1 week was increased by about 50% by ranitidine and its clearance was decreased, but there were no changes in the haemodynamic measurements (systolic time intervals, impedance cardiography).[27,28] A further study found that **ranitidine** increases the AUC of nitrendipine by 89%, but no adverse effects were noted as a result of this increase.[29]

(l) Verapamil

A study in 8 healthy subjects found that **cimetidine** 300 mg every 6 hours for 8 days did not affect the pharmacokinetics of a single 10-mg intravenous dose of verapamil, but the bioavailability of a 120-mg oral dose of verapamil was increased from 26% to 49%. There was, however, no significant change in oral clearance and the changes in the PR interval caused by the verapamil were unaltered in the presence of **cimetidine**.[30]

Another study found that **cimetidine** 300 mg four times daily for 5 days reduced the clearance of a single intravenous dose of verapamil by 21% and increased its elimination half-life by 50%.[31] A further study found that **cimetidine** 400 mg twice daily for a week increased the bioavailability of verapamil from 35% to 42% and its apparent oral clearance was reduced by almost 30%.[32] Yet another study found that **cimetidine** increased the bioavailability of both enantiomers of verapamil and increased the effect of verapamil on atrioventricular conduction.[33] In contrast, other studies have found that the pharmacokinetics[34,35] and pharmacodynamics[34] of verapamil were unaffected by **cimetidine**.

Mechanism

It is believed that cimetidine increases the bioavailability of nifedipine and other interacting calcium-channel blockers by inhibiting their oxidative metabolism by the liver. It has been proposed that ranitidine may increase the bioavailability of nifedipine by lowering gastric acidity.[15]

Importance and management

The interaction of cimetidine with nifedipine is established. Concurrent use need not be avoided but the increase in the calcium-channel blocker effects should be taken into account and blood pressure monitored. If necessary, a dosage reduction should be considered; a reduction of 40 to 50% has been suggested.[36,37] Cimetidine also increases the bioavailability of diltiazem, felodipine, isradipine, lacidipine, nimodipine and nitrendipine, although the haemodynamic changes usually appear minimal. Nevertheless, the dose of these calcium-channel blockers may possibly need to be reduced; it has been suggested that the dosage of diltiazem should be reduced by 30 to 50%,[36,37] and the dosage of isradipine should be reduced by 50%.[6]

The interaction between verapamil and cimetidine is not well established, but, until more is known, it may be prudent to monitor concurrent use for verapamil adverse effects. It has been suggested that the verapamil dose may need to be reduced by 50%.[37] Similarly, high doses of cimetidine may increase the hypotensive effects of lercanidipine and caution is advised.[8,9] One study indicated no interaction between nicardipine and cimetidine, but the manufacturers note that cimetidine increases nicardipine plasma levels and careful monitoring is recommended.[38,39] Amlodipine and cimetidine do not interact and one study suggests that cimetidine does not alter the clinical effects of nisoldipine.

Ranitidine does not interact significantly with diltiazem, nifedipine, nimodipine or nisoldipine, and famotidine does not interact with nifedipine. Ranitidine may therefore be a suitable non-interacting alternative to cimetidine with these and probably other calcium-channel blockers. Note that the nitrendipine AUC was increased by 50% and 89% by ranitidine, although this was not considered clinically relevant.

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Calcium-channel blockers + Hormonal contraceptives

A 21-day course of combined hormonal contraceptives appeared to have little effect on the AUC of nifedipine, but the AUC of its metabolite was reduced. Diltiazem may slightly raise estradiol levels.

Clinical evidence

(a) Combined hormonal contraceptives

A study in 23 healthy women investigated the influence of oral contraceptives on the pharmacokinetics of a single 10-mg dose of **nifedipine**. The intake of oral contraceptives containing **dienogest** 2 mg with **ethinylestradiol** 30 micrograms or **levonorgestrel** 125 micrograms with **ethinylestradiol** 30 micrograms for 21 days did not influence the AUC of **nifedipine**, but the $AUC_{0–24}$ of its main metabolite, dehydronifedipine, was reduced by about 25%.

(b) Estradiol

A study in 5 healthy postmenopausal women given **diltiazem** 30 mg twice daily for 4 days with a single 2-mg oral dose of estradiol on day 2, found that there was a slight but non-significant increase in the maximum levels of estrone.[1]

Mechanism

The reduction in dehydronifedipine levels suggests that the formation rate of the metabolite was reduced, probably because the contraceptive reduced the metabolism of nifedipine to dehydronifedipine by the cytochrome P450 isoenzyme CYP3A4.[2]

Diltiazem is a moderate inhibitor of the cytochrome P450 isoenzyme CYP3A4 and would be expected to decrease the metabolism of estradiol.

Importance and management

The effects of combined hormonal contraceptives on nifedipine appear minimal, but a multiple-dose study would be needed to confirm the expected lack of a clinically relevant interaction. The current data suggests that the efficacy of nifedipine would not be expected to be reduced by a pharmacokinetic mechanism; however, for further comments on the effect of hormonal contraceptives on blood pressure, see 'Antihypertensives + Hormonal contraceptives or HRT', p.1050.

The increase in oestrogen levels caused by diltiazem is small and unlikely to cause any clinically significant adverse effects. However, the dose of diltiazem given in the study was much lower than commonly prescribed doses, the number of patients involved in the study was small, and therefore these results may not accurately reflect the effect of concurrent use..The available data is insufficient to warrant any change in practice, but more study is needed to confirm the absence of a clinically relevant interaction.

1. Annas A, Carlström K, Alván G, AL-Shurbaji A. The effect of ketoconazole and diltiazem on oestrogen metabolism in postmenopausal women after single dose oestradiol treatment. *Br J Clin Pharmacol* (2003) 56, 334–6.
2. Balogh A, Gessinger S, Svarovsky U, Hippius M, Mellinger U, Klinger G, Hoffmann A, Oettel M. Can oral contraceptive steroids influence the elimination of nifedipine and its primary pyridine metabolite in humans? *Eur J Clin Pharmacol* (1998) 54, 729–34.

Calcium-channel blockers + Imatinib

A man taking nifedipine developed a gallstone after starting imatinib. Imatinib is predicted to increase levels of dihydropyridine-type calcium-channel blockers.

Clinical evidence, mechanism, importance and management

A patient taking **nifedipine** developed nausea, vomiting and abdominal pain 8 weeks after starting to take imatinib 400 mg [daily]. Ultrasound showed a thickened gallbladder wall, dilatation of the principal bile ducts and a gallstone. He had not previously had any gall bladder disease. Imatinib was stopped until the abdominal pain was resolved and then restarted at half the initial dose.[1]

Imatinib is known to be an inhibitor of cytochrome P450 isoenzyme CYP3A4, by which nifedipine is metabolised. It was suggested that imatinib may have inhibited the metabolism of **nifedipine**, leading to an increase in its effects on lipids, leading to an increase in biliary secretion and gallstone development.[1] However, gallstones would not usually be considered a sign of raised nifedipine levels.

The reason for the case report of gallstones is unclear. The manufacturers suggest that the levels of the **dihydropyridine-type calcium-channel blockers** may be increased by imatinib.[2,3] This seems reasonable, as imatinib raises the levels of the CYP3A4 substrate simvastatin, see 'Statins + Imatinib', p.1337. It would therefore seem prudent to monitor the concurrent use of these calcium-channel blockers and imatinib for an increase in calcium-channel blocker adverse effects, such as hypotension, headache, flushing, and oedema.

1. Breccia M, D'Andrea M, Alimena G. Can nifedipine and estrogen interaction with imatinib be responsible for gallbladder stone development? *Eur J Haematol* (2005) 75, 89–90.
2. Glivec (Imatinib mesilate). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, April 2009.
3. Gleevec (Imatinib mesylate). Novartis Pharmaceuticals Corporation. US Prescribing information, May 2009.

Calcium-channel blockers + Macrolides

Erythromycin markedly increases the bioavailability of felodipine. Isolated reports describe increased felodipine or verapamil effects and toxicity in patients also given erythromycin. There are also a few reports of verapamil or nifedipine toxicity with clarithromycin, and two with verapamil and erythromycin (prolonged QT interval) or telithromycin. A retrospective analysis revealed 3 cases of sudden cardiac death in patients taking erythromycin with diltiazem or verapamil, which represented about a fivefold increase in risk. No increased risk was seen with nifedipine and erythromycin.

Clinical evidence

(a) Diltiazem

A patient who had marked hypotension and bradycardia when **erythromycin** was added to verapamil and propranolol (see *Verapamil*, below) had previously taken **erythromycin** with diltiazem and a beta blocker without any reported adverse effects.[1]

In a retrospective cohort study, there was one sudden cardiac death in 106 person-years among patients taking diltiazem with **erythromycin**. When combined with the two deaths with concurrent verapamil and **erythromycin**, this represented about a fivefold increase in risk of sudden death when compared with those who were not taking CYP3A4 inhibitors (defined as ketoconazole, itraconazole, fluconazole, diltiazem, verapamil or troleandomycin) or **erythromycin**.[2]

(b) Felodipine

In a pharmacokinetic study, 12 healthy subjects were given felodipine 10 mg before and after taking **erythromycin** 250 mg four times daily for a day.[3] The felodipine AUC was increased almost threefold by the **erythromycin**, the maximum plasma levels were more than doubled and the half-life prolonged from 6.9 to 11.1 hours.[3]

A hypertensive woman taking felodipine 10 mg daily developed tachycardia, flushing and massive ankle oedema within 2 to 3 days of starting to take **erythromycin** 250 mg twice daily. Her blood pressure had fallen from 120/90 to 110/70 mmHg. She fully recovered within a few days of stopping the **erythromycin**.[4]

(c) Nifedipine

1. Clarithromycin. A 77-year-old man with slight renal impairment, taking sustained-release nifedipine 60 mg twice daily, captopril, and doxazosin, had persistent systolic hypertension (170 to 180 mmHg). Two days after starting to take clarithromycin 500 mg twice daily for breathing difficulty and cough, his blood pressure was 140/70 mmHg at a routine appointment, and the doxazosin dose was halved and valsartan substituted for captopril. Later that day, he was admitted with hypotension (80/40 mmHg) and bradycardia (40 bpm). Clarithromycin was replaced with erythromycin and the antihypertensives stopped. After 3 days his

blood pressure was stabilised with nifedipine 60 mg daily and furosemide, and the clarithromycin was restarted. Septic shock was ruled out as a cause of the hypotension.[5]

2. Erythromycin. In a retrospective cohort study, there were no sudden deaths from cardiac causes in 114 person-years of the use of oral erythromycin with calcium-channel blockers that do not inhibit CYP3A4 to a clinically relevant extent (mostly nifedipine).[2] This was in contrast to the increased risk of sudden death with erythromycin and diltiazem (see above) or verapamil (see below).

(d) Verapamil

1. Clarithromycin. A 53-year-old woman on haemodialysis 3 times a week, and a range of medicines including digoxin, was given clarithromycin 250 mg and verapamil 120 mg both twice daily because of an acute exacerbation of chronic obstructive pulmonary disease and a recurrence of atrial fibrillation. After 24 hours she experienced dizziness and episodes of fainting. A day later her supine blood pressure was 89/39 mmHg and her pulse rate 50 bpm. Verapamil was stopped and she recovered within 2 days, after which verapamil was re-started at a dose of 40 mg before each dialysis session. The authors suggest that, although an interaction between digoxin and verapamil cannot be ruled out, the digoxin levels were very low before verapamil was started, and they therefore believe that the effects seen cannot entirely have been due to raised digoxin levels.[6] Another report[1] describes a 77-year-old woman with hypertension, taking propranolol and verapamil, who developed marked bradycardia (37 to 50 bpm), within 4 days of starting a course of clarithromycin 500 mg twice daily. The problem was solved by temporarily reducing the dose of verapamil from 80 mg twice daily to 40 mg twice daily and halving the dose of propranolol until the clarithromycin course had been finished. Essentially the same thing happened 2 years later when erythromycin was added (see below).

2. Erythromycin. A 79-year-old woman taking verapamil 240 mg twice daily and ramipril was admitted to hospital with extreme fatigue and dizziness one week after starting a course of erythromycin 2 g daily for a respiratory tract infection. Her blood pressure was 80/60 mmHg and her respiratory rate was 18 breaths per minute. ECG showed complete AV block, escape rhythm of 50 bpm, pattern of left bundle-branch block and QTc interval prolongation (583 milliseconds compared with 436 milliseconds 20 days before admission). Verapamil and erythromycin were stopped and intravenous fluids, dopamine and calcium were given. Her blood pressure increased to 110/70 mmHg and after 4 days the QTc interval prolongation had resolved and her heart rate was 76 bpm.[7] Another patient taking verapamil and propranolol developed marked bradycardia and hypotension 2 days after starting to take erythromycin 333 mg three times daily.[1]

In a retrospective cohort study, there were two sudden cardiac deaths in 78 person-years among patients taking verapamil with erythromycin. When combined with the one death with current diltiazem and erythromycin, this represented about a fivefold increase in risk of sudden death when compared with those who used were not taking CYP3A4 inhibitors (defined as ketoconazole, itraconazole, fluconazole, diltiazem, verapamil or troleandomycin) or erythromycin.[2]

3. Telithromycin. A 76-year-old woman taking verapamil 180 mg daily experienced shortness of breath and weakness 2 days after starting telithromycin 800 mg daily for a sinus infection. She was found to have marked hypotension (systolic BP 50 to 60 mmHg) and bradycardia (30 bpm). She required a transvenous pacemaker for 3 days and pressor drugs.[8]

Mechanism

Calcium-channel blockers are metabolised in the gut wall and liver by the cytochrome P450 CYP3A subfamily of isoenzymes, which are inhibited by erythromycin, clarithromycin, and telithromycin, so that in their presence a normal oral dose becomes in effect an overdose with its attendant adverse effects.[1,3,4,8] Verapamil, erythromycin[7] and possibly clarithromycin are also P-glycoprotein inhibitors, which may contribute to the pharmacokinetic interaction by reducing the elimination of the calcium-channel blocker,[6] or by increasing macrolide absorption.[7]

Erythromycin has been associated with prolongation of the QT interval; an effect that is likely to be increased by drugs that increase erythromycin levels such as diltiazem and verapamil.[2]

Importance and management

Information seems to be limited but the interaction would appear to be established and clinically important, although its incidence is probably low. Anticipate the need to reduce the felodipine or verapamil dosage if erythromycin or clarithromycin, or possibly also telithromycin, is added. Nifedipine may also interact. Other reports suggests that the cardiac toxicity of erythromycin may be increased by verapamil,[2,7] and diltiazem,[2] and the authors of one of these reports consider that erythromycin should not be used with CYP3A4 inhibitors (that is diltiazem and verapamil).[2] There seem to be no reports of interactions between any of the other calcium-channel blockers and macrolides. However, because of the theoretical possibility of an interaction, many of the manufacturers of calcium-channel blockers warn of the possibility of increased plasma levels with macrolides such as erythromycin, clarithromycin, or telithromycin, and suggesting monitoring the outcome of concurrent use (e.g. for hypotension, headache, flushing, and oedema), reducing the calcium-channel blocker dose where necessary. However, the UK manufacturer of **lercanidipine** contraindicates the concurrent use of erythromycin.[9] Note that some macrolides such as **azithromycin** appear to have little or no effect on the CYP3A subfamily and so would be less likely to interact.

1. Steenbergen JA, Stauffer VL. Potential macrolide interaction with verapamil. *Ann Pharmacother* (1998) 32, 387–8.
2. Ray WA, Murray KT, Meredith S, Narasimhulu SS, Hall K, Stein CM. Oral erythromycin and the risk of sudden death from cardiac causes. *N Engl J Med* (2004) 351, 1089–96.
3. Bailey DG, Bend JR, Arnold JMO, Tran LT, Spence JD. Erythromycin-felodipine interaction: magnitude, mechanism, and comparison with grapefruit juice. *Clin Pharmacol Ther* (1996) 60, 25–33.
4. Liedholm H, Nordin G. Erythromycin–felodipine interaction. *DICP Ann Pharmacother* (1991) 25, 1007–8.
5. Gerónimo-Pardo M, Cuartero-del-Pozo AB, Jiménez-Vizuete JM, Cortiñas-Sáez M, Peyró-García R. Clarithromycin-nifedipine interaction as possible cause of vasodilatory shock. *Ann Pharmacother* (2005) 39, 538–42.
6. Kaeser YA, Brunner F, Drewe J, Haefeli WE. Severe hypotension and bradycardia associated with verapamil and clarithromycin. *Am J Health-Syst Pharm* (1998) 55, 2417–18.
7. Goldschmidt N, Azaz-Livshits T, Gotsman I, Nir-Paz R, Ben-Yehuda A, Muszkat M. Compound cardiac toxicity of oral erythromycin and verapamil. *Ann Pharmacother* (2001) 35, 1396–9.
8. Reed M, Wall GC, Shah NP, Heun JM, Hicklin GA. Verapamil toxicity resulting from a probable interaction with telithromycin. *Ann Pharmacother* (2005) 39, 357–60.
9. Zanidip (Lercanidipine hydrochloride). Recordati Pharmaceuticals Ltd. UK Summary of product characteristics, October 2004.

Calcium-channel blockers + Magnesium compounds

Pregnant women have developed bilateral hand contractures or muscular weakness and then paralysis, after receiving magnesium sulfate either alone or with nifedipine. Profound hypotension occurred in two women when nifedipine was added to magnesium sulfate and methyldopa. However, a retrospective study did not find these effects.

Clinical evidence

(a) Hypotension

Two women with pre-eclampsia, unsuccessfully treated with methyldopa and magnesium sulfate, experienced severe hypotension when a single 10-mg oral dose of **nifedipine** was added.[1] In contrast, a study in 10 women with severe pre-eclampsia receiving magnesium sulfate found that oral **nifedipine** 10 mg followed by 20 mg every 20 minutes, caused a steady decrease in mean arterial pressure and severe hypotension was not observed.[2] Moreover, in a retrospective study, the incidence of hypotension in 162 women given **nifedipine** and magnesium sulfate was lower than in 183 receiving magnesium sulfate and no antihypertensive (41.4% versus 53%).[3] For further details of this study, see (b) below.

(b) Neuromuscular blockade and hypocalcaemia

A report describes symptomatic hypocalcaemia (serum calcium levels 1.35 mmol/L) in a woman at 33 weeks gestation after she received magnesium sulfate and **nifedipine**.[4] However, this report also describes this effect in a patient taking magnesium sulfate alone. Both women experienced bilateral hand contractures and were successfully treated with calcium gluconate.[4]

A pregnant woman at 32 weeks gestation was effectively treated for premature uterine contractions with **nifedipine**, 60 mg orally over 3 hours, and later 20 mg every 8 hours. When contractions began again 12 hours later she was given magnesium sulfate 500 mg intravenously. She devel-

oped jerky movements of the extremities, complained of difficulty in swallowing, paradoxical respirations and an inability to lift her head from the pillow. The magnesium was stopped and the muscle weakness disappeared over the next 25 minutes.[5]

A woman at 28 weeks gestation with mild pre-eclampsia was given an infusion of magnesium sulfate 2 g/hour. Her plasma magnesium levels were found to be 2.75 mmol/L. No untoward reactions developed when she took a 20-mg dose of **nifedipine**, but 30 minutes after taking a second dose [by implication 3 to 4 hours later] she complained of flushing and sweating and had difficulty in lifting her head and limbs. Shortly afterwards almost complete muscular paralysis developed. The magnesium sulfate was stopped and a dramatic improvement followed within 15 minutes of a 1-g intravenous injection of calcium gluconate.[6]

In contrast, a retrospective analysis found no increased risk of serious magnesium-related maternal adverse effects in 162 women with pre-eclampsia who were also given **nifedipine** compared with 32 women receiving another antihypertensive or 183 who received no antihypertensive. The women receiving **nifedipine** had more severe pre-eclampsia and a longer magnesium sulfate infusion. However, the incidence of neuromuscular weakness was about 53% in these women, compared with 53% in those receiving another antihypertensive and 45% in those receiving no antihypertensive. These differences were not statistically significant. Moreover, the incidence of maternal hypotension was lower in those receiving **nifedipine** than in those receiving no antihypertensive (see (a) above).[3]

Mechanism

The probable reason for neuromuscular effects is that both drugs can seriously reduce the amount of calcium ions needed for normal muscular contraction. Nifedipine inhibits the inflow of extracellular calcium across cell membranes. Magnesium probably acts in the same way, and also reduces intracellular calcium by activating adenyl cyclase and increasing cyclic adenosine monophosphate (cAMP). In addition magnesium stimulates calcium-dependent ATPase, which promotes calcium uptake by the sarcoplasmic reticulum. The result is muscular paralysis, which is reversed by giving large amounts of calcium. Magnesium sulfate is also known to have neuromuscular blocking activity. Both drugs can also cause hypotension, which could be additive.

Importance and management

Direct information about the neuromuscular effects and hypotensive effects of the combination of nifedipine and magnesium seems to be limited. Although a few cases of possible additive effects have been reported, one large retrospective study did not find an increase in risk of neuromuscular effects or of hypotension with combined use. Nevertheless, one manufacturer of nifedipine advises particular caution when it is used in combination with intravenous magnesium sulfate in pregnant women, and recommends careful monitoring of blood pressure.[7] The same interaction would be expected to occur with other calcium-channel blockers, but this does not appear to have been studied.

1. Waisman GD, Mayorga LM, Cámera MI, Vignolo CA, Martinotti A. Magnesium plus nifedipine: potentiation of hypotensive effect in preeclampsia? *Am J Obstet Gynecol* (1988) 159, 308–9.
2. Scardo JA, Vermillion ST, Hogg BB, Newman RB. Hemodynamic effects of oral nifedipine in preeclamptic hypertensive emergencies. *Am J Obstet Gynecol* (1996) 175, 336–8.
3. Magee LA, Miremadi S, Li J, Cheng C, Ensom MHH, Carleton B, Coté A-M, von Dadelszen P. Therapy with both magnesium sulfate and nifedipine does not increase the risk of serious magnesium-related maternal side effects in women with preeclampsia. *Am J Obstet Gynecol* (2005) 193, 153–63.
4. Koontz SL, Friedman SA, Schwartz ML. Symptomatic hypocalcemia after tocolytic therapy with magnesium sulfate and nifedipine. *Am J Obstet Gynecol* (2004) 190, 1773–6.
5. Snyder SW, Cardwell MS. Neuromuscular blockade with magnesium sulfate and nifedipine. *Am J Obstet Gynecol* (1989) 161, 35–6.
6. Ben-Ami M, Giladi Y, Shalev E. The combination of magnesium sulphate and nifedipine: a cause of neuromuscular blockade. *Br J Obstet Gynaecol* (1994) 101, 262–3.
7. Adalat Retard (Nifedipine). Bayer plc. UK Summary of product characteristics, May 2008.

Calcium-channel blockers + Melatonin

Melatonin may have some modest effects on blood pressure in patients taking nifedipine.

Clinical evidence

Forty-seven subjects with mild to moderate hypertension well-controlled with **nifedipine** GITS 30 mg or 60 mg daily for the past 3 months were given melatonin immediate-release capsules 5 mg each evening for 4 weeks. At the end of the 4 weeks, there was a modest increase in mean 24-hour systolic and diastolic blood pressure of 6.5 mmHg and 4.9 mmHg, respectively, and an increase in heart rate of 3.9 bpm. However, there was no difference in single-time point 'clinic' blood pressure (136/85 mmHg versus 138/87 mmHg) and heart rate. While taking melatonin, there was a greater incidence of drowsiness, during the morning, and weakness. One subject dropped out of the study complaining of marked weakness.[1]

Mechanism

Unknown. Melatonin has been reported to possess blood pressure-lowering properties when used alone and was expected to have additive effects with nifedipine.[1]

Importance and management

The chronic use of melatonin appears to modestly impair the hypotensive effects of nifedipine and increase the blood pressure and heart rates of patients. However, this was only detected on 24-hour blood pressure monitoring, and was not apparent with single-measures of blood pressure at the clinic. Therefore, given that the overall change was small, the clinical relevance of the effect is probably minor. Nevertheless, it is not clear just why this change occurred, and until more is known, it may be prudent to consider the use of melatonin if blood pressure is hard to control in any patient taking a calcium-channel blocker.

1. Lusardi P, Piazza E, Fogari R. Cardiovascular effects of melatonin in hypertensive patients well controlled by nifedipine: a 24-hour study. *Br J Clin Pharmacol* (2000) 49, 423–7.

Calcium-channel blockers + Nitrates

As may be expected, enhanced hypotensive effects can occur when calcium-channel blockers are given with nitrates. Some manufacturers of amlodipine,[1,2] diltiazem,[3] nifedipine[4] and verapamil[5] suggest that the concurrent use of long-acting nitrates and/or sublingual glyceryl trinitrate may be safely undertaken. However, one manufacturer of diltiazem suggests caution in those also taking nitrates, as increased hypotensive effects and faintness, due to additive vasodilating effects, may occur. They recommend that the dosage of any concurrent nitrate should be increased gradually.[6]

1. Istin (Amlodipine besilate). Pfizer Ltd. UK Summary of product characteristics, July 2007.
2. Norvasc (Amlodipine besylate). Pfizer Inc. US Prescribing information, August 2006.
3. Cardizem LA (Diltiazem hydrochloride). Abbott Laboratories. US Prescribing information, September 2007.
4. Procardia (Nifedipine). Pfizer Inc. US Prescribing information, March 2006.
5. Calan (Verapamil hydrochloride). Pfizer Inc. US Prescribing information, May 2006.
6. Tildiem Retard (Diltiazem hydrochloride). Sanofi-Aventis. UK Summary of product characteristics, March 2007.

Calcium-channel blockers + NNRTIs

Efavirenz decreases the bioavailability of diltiazem, whereas diltiazem has no clinically significant effect on efavirenz pharmacokinetics. Potentially, other calcium-channel blockers might be expected to interact similarly with efavirenz. Delavirdine is predicted to inhibit the metabolism of the calcium-channel blockers.

Clinical evidence, mechanism, importance and management

(a) Delavirdine

The manufacturer of delavirdine warns that it may inhibit the metabolism of calcium-channel blockers (they name **amlodipine**, **diltiazem**, **felodipine**, **isradipine**, **nifedipine**, **nicardipine**, **nimodipine**, **nisoldipine** and **verapamil**), resulting in increased concentrations of the calcium-channel blocker. Caution is warranted and clinical monitoring of patients is recommended.[1] It would seem prudent to monitor blood pressure closely if delavirdine is given to a patient taking a calcium-channel blocker, decreasing the dose of the calcium-channel blocker if necessary. If a calcium-channel blocker is to be started in a patient taking efavirenz it would seem prudent to start with the lowest possible dose and titrate carefully,

according to response. Note that this interaction probably occurs because delavirdine is an inhibitor of the cytochrome P450 isoenzyme CYP3A4, by which the calcium-channel blockers are metabolised. Therefore if dose titration of the calcium-channel blocker proves difficult it may be prudent, where possible, to try an alternative class of drugs. Note that ACE inhibitors, angiotensin II receptor antagonists and beta blockers are not known to be affected by CYP3A4.

(b) Efavirenz

In a study in healthy subjects, efavirenz 600 mg daily decreased the steady-state AUC and maximum plasma level of **diltiazem** by 69% and 60%, respectively. Levels of diltiazem metabolites were also reduced. The pharmacokinetics of efavirenz were not altered to a clinically relevant extent.[2,3] The manufacturer of efavirenz suggests that the dose of **diltiazem** may need to be adjusted [increased], depending on clinical response.[2,3]

No data are available on the potential interaction of efavirenz with other calcium-channel blockers. However, efavirenz is known to induce CYP3A4, the main route of metabolism of many of the calcium-channel blockers, and therefore efavirenz may be expected to reduce their levels. The manufacturers suggest that any dose adjustments should be guided by clinical response (e.g. blood pressure).[2,3] Note that ACE inhibitors, angiotensin II receptor antagonists and beta blockers are not known to be affected by CYP3A4, and therefore they may provide a suitable alternative in some patients..

1. Rescriptor (Delavirdine mesylate). Pfizer Inc. US Prescribing information, May 2008.
2. Sustiva Film-coated Tablets (Efavirenz). Bristol-Myers Squibb Pharmaceuticals Ltd. UK Summary of product characteristics, June 2009.
3. Sustiva (Efavirenz). Bristol-Myers Squibb Company. US Prescribing information, September 2009.

Calcium-channel blockers + Phenobarbital

Phenobarbital greatly reduces the levels and/or increases the clearance of felodipine (one case), nifedipine, nimodipine, and verapamil. Primidone is expected to interact similarly. Other calcium-channel blockers are expected to be similarly affected by both phenobarbital and primidone.

Clinical evidence

(a) Felodipine

Felodipine levels were studied in 10 patients with epilepsy. After taking felodipine 10 mg daily for 4 days the peak levels of felodipine were found to be 1.6 nanomol/L which was much lower than that in 12 control subjects not taking antiepileptic drugs (level 8.9 nanomol/L). Of the 10 patients, one was taking phenobarbital.[1]

(b) Nifedipine

In a pharmacokinetic study in 15 healthy subjects the clearance of a single 20-mg dose of nifedipine was increased almost threefold after they took phenobarbital 100 mg daily for 2 weeks. The nifedipine AUC was reduced by about 60%.[2]

(c) Nimodipine

A study in 8 epileptic patients receiving long-term antiepileptic treatment (including 4 who were taking phenobarbital and 2 who were taking phenobarbital with carbamazepine) found that the AUC of a single 60-mg oral dose of nimodipine was reduced by about 85%, when compared with a group of healthy subjects.[3]

(d) Verapamil

A study in 7 healthy subjects found that phenobarbital 100 mg daily for 3 weeks increased the clearance of verapamil 80 mg every 6 hours fourfold and reduced the bioavailability fivefold.[4]

Mechanism

Phenobarbital is an enzyme inducer that can increase the metabolism of calcium-channel blockers by the cytochrome P450 isoenzyme CYP3A4 in the liver. This results in lower plasma levels of the calcium-channel blocker.

Importance and management

Phenobarbital markedly reduces nifedipine, nimodipine and verapamil levels, and probably has a similar effect on felodipine levels. A considerable increase in the dosage of these calcium-channel blockers will probably be needed in patients taking phenobarbital. The UK manufacturers of nimodipine and **isradipine** contraindicate[5] or recommend avoidance of concurrent use,[6] and the US manufacturer of felodipine suggests that, since a clinically significant interaction may be anticipated, an alternative antihypertensive should be considered in patients receiving phenobarbital long-term.[7] Note that ACE inhibitors and angiotensin II receptor antagonists are not known to be affected by CYP3A4, and therefore may provide a suitable alternative to a calcium-channel blocker in some patients.

As **primidone** is metabolised to phenobarbital, it seems likely that it may interact similarly. There is no direct information of interactions with other calcium-channel blockers, but as they are metabolised, to a greater of lesser extent, in the same way they would generally be expected to interact similarly with both phenobarbital and primidone.

1. Capewell S, Freestone S, Critchley JAJH, Pottage A, Prescott LF. Reduced felodipine bioavailability in patients taking anticonvulsants. *Lancet* (1988) ii, 480–2.
2. Schellens JHM, van der Wart JHF, Brugman M, Breimer DD. Influence of enzyme induction and inhibition on the oxidation of nifedipine, sparteine, mephenytoin and antipyrine in humans as assessed by a "cocktail" study design. *J Pharmacol Exp Ther* (1989) 249, 638–45.
3. Tartara A, Galimberti CA, Manni R, Parietti L, Zucca C, Baasch H, Caresia L, Mück W, Barzaghi N, Gatti G, Perucca E. Differential effects of valproic acid and enzyme-inducing anticonvulsants on nimodipine pharmacokinetics in epileptic patients. *Br J Clin Pharmacol* (1991) 32, 335–40.
4. Rutledge DR, Pieper JA, Mirvis DM. Effects of chronic phenobarbital on verapamil disposition in humans. *J Pharmacol Exp Ther* (1988) 246, 7–13.
5. Nimotop Tablets (Nimodipine). Bayer plc. UK Summary of product characteristics, May 2008.
6. Prescal (Isradipine). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, June 2007.
7. Plendil (Felodipine). AstraZeneca. US Prescribing information, November 2003.

Calcium-channel blockers + Phenothiazines

The hypotensive adverse effects of the phenothiazines are expected to be additive with the known blood pressure lowering effects of the calcium-channel blockers.

Clinical evidence, mechanism, importance and management

An isolated report describes a patient taking chlorpromazine, who was given **nifedipine** the day before surgery, and then developed marked hypotension during surgery, which was eventually controlled with noradrenaline (norepinephrine).[1] It was suggested that the hypotension was due to an interaction between **nifedipine** and chlorpromazine. Although in general the hypotensive adverse effects of phenothiazines would be expected to be additive with the blood pressure lowering effects of the calcium-channel blockers there are many other factors that mean that the hypotensive effects seen in the case cannot be directly attributed to an interaction. For example, the dose of nifedipine given was not stated, the patient was additionally taking cimetidine, which can increase the bioavailability of nifedipine, see 'Calcium-channel blockers + H_2-receptor antagonists', p.1036, and, furthermore, the concurrent use of antihypertensives and general anaesthetics can also result in enhanced hypotension, for example, see 'Anaesthetics, general + ACE inhibitors or Angiotensin II receptor antagonists', p.102. Nevertheless, because of the known effects of both groups of drugs, some caution seems prudent on their concurrent use. Warn patients to take time in getting up to minimise orthostatic hypotension.

1. Stuart-Taylor ME, Crosse MM. A plea for noradrenaline. *Anaesthesia* (1989) 44, 916–17.

Calcium-channel blockers + Protease inhibitors

A patient taking nifedipine experienced hypotension, oedema and acute renal failure when lopinavir/ritonavir also given. Symptomatic orthostasis occurred in another patient taking nifedipine with nelfinavir and then ritonavir and indinavir. A further patient had similar symptoms when nelfinavir was given with felodipine. Atazanavir markedly increased diltiazem bioavailability with an increase in cardiac effects in a study in healthy subjects. Similarly, ritonavir/indinavir caused a modest to marked increase in diltiazem and amlodipine levels. Based on this evidence, protease inhibitors, especially ritonavir are predicted to raise the levels of all calcium-channel blockers.

Clinical evidence

(a) Amlodipine

In a study in 18 healthy subjects, **indinavir** 800 mg twice daily and **ritonavir** 100 mg twice daily given with amlodipine 5 mg daily for 7 days, increased the median AUC of amlodipine by 90%. Amlodipine had no effect on the steady-state AUCs of the protease inhibitors.[1] For mention of a patient who tolerated amlodipine and **lopinavir** with **ritonavir** after serious adverse effects had occurred with nifedipine and these protease inhibitors, see below.

(b) Diltiazem

1. Atazanavir. A study in healthy subjects found that atazanavir 400 mg daily given with diltiazem 180 mg daily resulted in a two- to threefold increase in the bioavailability of diltiazem and its metabolite desacetyldiltiazem. The pharmacokinetics of atazanavir were not affected by diltiazem. There was an increase in the maximum PR interval with combined use compared to that found with atazanavir alone.[2,3]

2. Indinavir with Ritonavir. In a study in 13 healthy subjects indinavir 800 mg twice daily and ritonavir 100 mg twice daily, given with diltiazem 120 mg daily for 7 days, modestly increased the median AUC of diltiazem by 27%, which was not statistically significant. However, two of the subjects had a fourfold increase in the AUC of diltiazem, and the desacetyl-diltiazem AUC was doubled. Diltiazem had no effect on the steady-state AUCs of the protease inhibitors.[1]

(c) Felodipine

A woman taking metoprolol 50 mg daily and felodipine 5 mg daily for hypertension developed bilateral leg oedema, orthostatic hypotension, and other symptoms including dizziness and fatigue, 3 days after starting HAART following a needle-stick injury. The antiretrovirals included zidovudine, lamivudine, and **nelfinavir** 2 g daily. Antihypertensive treatment was stopped and the adverse effects abated within 3 days. The patient was then successfully switched to a diuretic-based regimen without recurrence of oedema.[4]

(d) Nifedipine

A 51-year-old HIV-positive man with coronary artery disease, hypertension and osteoarthritis, and taking atenolol, also started taking extended-release nifedipine 60 mg daily. When his blood pressure control improved he was given zidovudine 300 mg, lamivudine 150 mg, and **nelfinavir** 1.25 g all twice daily. Within 3 days of starting the antiretrovirals he experienced dizziness, weakness and hypotension and developed complete heart block with a junctional escape rhythm. His ECG returned to normal within 24 hours of stopping the antiretrovirals, but he developed orthostatic symptoms within 2 days of restarting **nelfinavir**. He later tolerated a regimen consisting of stavudine, didanosine and efavirenz without any episodes of dizziness, hypotension or bradycardia. However, when he was given zidovudine, abacavir, **ritonavir**, and **indinavir**, he experienced hypotension, decreased heart rate, weakness and fatigue. His symptoms were controlled by modifying his antihypertensives, including discontinuation of atenolol and reduction of the dose of nifedipine to 30 mg daily.[5]

Another case report describes a patient taking antihypertensive drugs including nifedipine 30 mg twice daily, who developed malaise, severe hypotension, oliguria and progressive generalised oedema on the second day of taking **lopinavir** with **ritonavir**. He had previously developed hypotension and progressive renal failure when receiving nifedipine and HAART (including **lopinavir** with **ritonavir**). All antihypertensive and antiretroviral drugs were discontinued and the patient improved, but the same symptoms recurred after the nifedipine and then **lopinavir** and **ritonavir** were reintroduced. All drugs were stopped, then HAART (including **lopinavir** with **ritonavir**) was reintroduced again and **amlodipine** 15 mg daily was substituted for nifedipine. This regimen was well tolerated.[6]

Mechanism

Protease inhibitors, particularly ritonavir (see 'Antivirals', (p.913)), are potent inhibitors of the cytochrome P450 isoenzyme CYP3A4, by which the calcium-channel blockers are extensively metabolised. It appears that some protease inhibitors can cause a clinically relevant increase in calcium-channel blocker levels. Verapamil, diltiazem and possibly nicardipine can also inhibit CYP3A4, and might therefore theoretically reduce the metabolism of the protease inhibitors. However, the effect might depend on which is the more potent inhibitor, since, in the studies above, diltiazem did not affect atazanavir, indinavir or ritonavir levels.

Importance and management

Although information is limited, the pharmacokinetic interactions between some protease inhibitors and calcium-channel blockers are predictable, and potentially serious. To date, clinically relevant increases in calcium-channel blocker levels or effects have been shown for amlodipine with indinavir and ritonavir (in combination), diltiazem with atazanavir and lopinavir with ritonavir, felodipine with nelfinavir, nifedipine with nelfinavir, indinavir with ritonavir and lopinavir with ritonavir (in combination). Caution would be required with any of these combinations, anticipating the need to use lower doses of the calcium-channel blocker.

All protease inhibitors can inhibit CYP3A4 to a greater or lesser extent. Many are given with ritonavir as a pharmacokinetic enhancer, and this lower dose is also expected to interact.[7,8] Further, all calcium-channel blockers are metabolised, to a greater or lesser extent, by CYP3A4. Consequently, any combination of calcium-channel blocker and protease inhibitor has the potential to interact, although the severity of the interaction is likely to vary between individual pairs of drugs. Therefore it would be prudent to monitor patients for calcium-channel blocker adverse effects (e.g. hypotension, headache, flushing, and oedema), and consider reducing the dose of the calcium-channel blocker as necessary. Particular caution may be warranted with **verapamil** because adverse cardiac effects (conduction disorders) are more commonly associated with this particular calcium-channel blocker.

Note that the UK manufacturer of **lercanidipine**[9] contraindicates the concurrent use of ritonavir or other strong inhibitors of CYP3A4, which would be expected to include most, if not all protease inhibitors. The manufacturers of **atazanavir** specifically recommend that, if diltiazem is also given, its initial dose should be reduced by 50% with subsequent dose titration and ECG monitoring.[2,3]

It has been suggested that other antihypertensive drugs such as ACE inhibitors and diuretics, which are primarily eliminated renally, could be considered as alternatives to calcium-channel blockers:[10] this seems prudent advice.

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7. Norvir Soft Capsules (Ritonavir). Abbott Laboratories Ltd. UK Summary of product characteristics, October 2009.
8. Norvir (Ritonavir). Abbott Laboratories. US Prescribing information, November 2009.
9. Zanidip (Lercanidipine hydrochloride). Recordati Pharmaceuticals Ltd. UK Summary of product characteristics, October 2004.
10. Vourvahis M, Kashuba AD. Mechanisms of pharmacokinetic and pharmacodynamic drug interactions associated with ritonavir-enhanced tipranavir. *Pharmacotherapy* (2007) 27, 888–909.

Calcium-channel blockers + Quinupristin/Dalfopristin

Quinupristin/dalfopristin modestly increased the AUC of nifedipine. Other calcium-channel blockers are predicted to be similarly affected.

Clinical evidence, mechanism, importance and management

The manufacturer notes that the AUC of repeated-dose **nifedipine** was increased by 40% by quinupristin/dalfopristin, and the maximum level was increased by 20%.[1] This is probably because quinupristin/dalfopristin inhibits the metabolism of **nifedipine** by the cytochrome P450 isoenzyme CYP3A4.[2] Although the clinical relevance of these increases have not been assessed, an increase in the AUC of nifedipine of 40% is fairly modest. The manufacturers of **nifedipine** advise blood pressure monitoring and, if necessary, a reduction of the **nifedipine** dosage during concurrent use.[1,3] It is predicted that other calcium-channel blockers[2] will also have their levels raised by quinupristin/dalfopristin, and this seem likely, as all calcium-channel blockers are metabolised, at least in part, by CYP3A4; however, the extent of the interaction is likely to vary between drugs. It may therefore be prudent to be alert for an increase in their effects (e.g. a

drop in blood pressure, headache, flushing, peripheral oedema) and reduce the dose if problems occur.

1. Adalat CC (Nifedipine). Bayer HealthCare. US Prescribing information, October 2004.
2. Rubinstein E, Prokocimer P, Talbot GH. Safety and tolerability of quinupristin/dalfopristin: administration guidelines. *J Antimicrob Chemother* (1999) 44 (Suppl A), 37–46.
3. Adalat Retard (Nifedipine). Bayer plc. UK Summary of product characteristics, May 2008.

Calcium-channel blockers + Rifampicin (Rifampin)

Rifampicin markedly reduces the plasma levels of diltiazem, nifedipine, nilvadipine, verapamil and possibly reduces those of barnidipine, isradipine, lercanidipine, manidipine, nicardipine, nimodipine, and nisoldipine. Rifapentine and rifabutin would also be expected to reduce the levels of the calcium-channel blockers.

Clinical evidence

(a) Barnidipine and Manidipine

A brief report states that elderly patients with hypertension well-controlled with calcium-channel blockers including barnidipine or manidipine had blood pressure rises when rifampicin was added. Increased dosages or additional antihypertensives were needed to control the blood pressures, and reduced doses were required when the rifampicin was withdrawn.[1]

(b) Diltiazem

A study in 12 subjects found that the peak plasma level following a single 120-mg oral dose of diltiazem alone was 186 nanograms/mL, but after taking rifampicin 600 mg daily for 8 days maximum plasma diltiazem levels were less than 8 nanograms/mL.[2] One patient with angina controlled with diltiazem 120 mg daily began to feel chest pain at rest one month after starting rifampicin and isoniazid.[3]

(c) Nifedipine

A woman with hypertension well controlled with nifedipine 40 mg twice daily, had a blood pressure rise from under 160/90 mmHg to 200/110 mmHg within 2 weeks of starting to take antitubercular treatment, which included rifampicin 450 mg daily. When the rifampicin was stopped and then restarted, the blood pressure fell and then rose again. The peak nifedipine plasma levels and the AUC fell by about 60% in the presence of rifampicin.[4] Another patient had anginal attacks refractory to nifedipine while taking rifampicin, but which were controlled by nifedipine when the rifampicin was stopped. Restarting rifampicin reduced nifedipine levels (peak plasma levels and AUCs roughly halved) and increased the number of anginal attacks.[3] Yet another patient taking nifedipine had a loss of blood pressure control when given rifampicin.[5]

Six healthy subjects were given nifedipine 20 micrograms/kg intravenously and nifedipine 20 mg orally on separate days before and after taking rifampicin 600 mg daily for 7 days. The pharmacokinetics of intravenous nifedipine were not significantly changed by the rifampicin, but the oral clearance increased from 1.5 L/minute to 20.9 L/minute and the bioavailability fell from about 41% to 5%.[6] A pharmacokinetic study in 6 healthy subjects found that when a single 10-mg oral dose of nifedipine was taken 8 hours after a single 1.2-g dose of rifampicin, the bioavailability of nifedipine was reduced to 36%, its half-life was more than halved, and its clearance increased threefold.[7]

(d) Nilvadipine

A study in 5 healthy normotensive subjects found that rifampicin 450 mg daily for 6 days reduced the peak plasma level and AUC of a single 4-mg dose of nilvadipine by about 20-fold and 30-fold, respectively. The hypotensive effect and reflex tachycardia associated with nilvadipine alone in these subjects was also abolished by rifampicin.[8]

(e) Nisoldipine

There is some evidence to suggest that nisoldipine is ineffective in reducing blood pressure in the presence of rifampicin.[1,4]

(f) Verapamil

The observation that a patient whose raised blood pressure was not reduced by verapamil while receiving antitubercular drugs, prompted a study in 4 other patients.[9] No verapamil could be detected in the plasma of 3 patients who took a single 40-mg dose of verapamil with rifampicin 450 to 600 mg daily, isoniazid 5 mg/kg daily, and ethambutol 15 mg/kg daily. A maximum verapamil level of 20 nanograms/mL was found in the fourth patient. Six other subjects not taking antitubercular drugs had a mean maximum verapamil plasma concentration of 35 nanograms/mL.[9] Similar results have been reported by the same authors in another study.[10]

Supraventricular tachycardia was inadequately controlled in a patient taking rifampicin 600 mg daily and isoniazid 300 mg daily, despite a verapamil dose of 480 mg every 6 hours. Substitution of the rifampicin by ethambutol resulted in a fourfold rise in serum verapamil levels.[11] A later study in 6 healthy subjects found that after taking rifampicin 600 mg daily for 2 weeks the oral bioavailability of verapamil was reduced from 26% to 2%, and the effects of verapamil on the ECG were abolished.[12] Yet another study in elderly patients similarly found that rifampicin 600 mg daily markedly increased the clearance of verapamil 120 mg twice daily. The effects of verapamil on AV conduction were almost abolished.[13]

Mechanism

Rifampicin reduces the effectiveness of nifedipine and verapamil to a greater extent after oral than after intravenous use. The evidence suggests that rifampicin increases the cytochrome P450 isoenzyme CYP3A4-mediated metabolism of calcium-channel blockers in the gastrointestinal wall,[6,13,14] thereby reducing their oral bioavailability. **Rifabutin** and **rifapentine** are also inducers of CYP3A4, although to a lesser extent than rifampicin, and would therefore also be expected to reduce the levels of the calcium-channel blockers.

Importance and management

The interactions between diltiazem, nifedipine, or verapamil, and rifampicin are established and of clinical importance. There is some evidence that barnidipine, manidipine, nilvadipine, and nisoldipine interact with rifampicin and the manufacturers of a number of other calcium-channel blockers (e.g. **lercanidipine**[15] and **nicardipine**[16]) warn of similar interactions. Monitor the effects closely if rifampicin is given with any calcium-channel blocker, being alert for the need to make a marked increase in their dosage. However, note that some manufacturers of nifedipine,[17] and **nimodipine**[18] contraindicate their use with rifampicin and some manufacturers of diltiazem[19] and **isradipine**[20] suggest avoiding concurrent use. **Rifabutin** and **rifapentine** would also be expected to reduce levels of calcium-channel blockers, although perhaps to a lesser extent than rifampicin. However, there does not appear to be any data to prove this. Note that, with some of the reduction in levels seen, it seems unlikely that blood pressure control will be possible with calcium-channel blockers in patients taking rifampicin. Therefore other drugs such as beta blockers or ACE inhibitors may be required, where appropriate. However, note that these classes of drugs are not entirely free of interactions with rifampicin, although the effects seem less marked than with some of the calcium-channel blockers. See also 'Beta blockers + Rifampicin (Rifampin)', p.1019, and 'ACE inhibitors + Rifampicin (Rifampin)', p.37.

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8. Saima S, Furuie K, Yoshimoto H, Fukuda J, Hayashi T, Echizen H. The effects of rifampicin on the pharmacokinetics and pharmacodynamics of orally administered nilvadipine to healthy subjects. *Br J Clin Pharmacol* (2002) 53, 203–6.
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16. Cardene (Nicardipine hydrochloride). Astellas Pharma Ltd. UK Summary of product characteristics, November 2005.
17. Adalat Retard (Nifedipine). Bayer plc. UK Summary of product characteristics, May 2008.
18. Nimotop Tablets (Nimodipine). Bayer plc. UK Summary of product characteristics, May 2008.
19. Cardizem LA (Diltiazem hydrochloride). Abbott Laboratories. US Prescribing information, September 2007.
20. Prescal (Isradipine). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, June 2007.

Calcium-channel blockers + SSRIs

Two patients taking verapamil and two taking nifedipine developed increased adverse effects (oedema, headaches, nausea, flushing, orthostatic hypotension) when they also took fluoxetine. Fluoxetine appears to increase nimodipine levels, whereas nimodipine may decrease fluoxetine levels. Fluoxetine does not appear to alter lercanidipine pharmacokinetics.

Clinical evidence

(a) Lercanidipine

The manufacturer notes that a study in elderly subjects found that **fluoxetine** had no clinically relevant effects on the pharmacokinetics of lercanidipine. No other details were given.[1]

(b) Nifedipine

A patient taking nifedipine 60 mg daily developed nausea and flushing after also starting to take **fluoxetine** 20 mg every other day. The adverse effects gradually disappeared over the next 2 to 3 weeks when the nifedipine dosage was halved.[2] An 80-year-old woman taking nifedipine developed tachycardia, hypotension and profound weakness 10 days after starting to take **fluoxetine** 20 mg daily. On admission to hospital 8 days later she was unable to stand, her standing blood pressure was 90/50 mmHg and her heart rate was 120 bpm. She fully recovered within a week of stopping the fluoxetine.[3]

(c) Nimodipine

The manufacturer notes that, in elderly patients, nimodipine 30 mg twice daily given with **fluoxetine** 20 mg daily resulted in an increase in plasma levels of nimodipine, a reduction in plasma levels of fluoxetine, and a trend towards increased levels of the metabolite norfluoxetine,[4] but no specific values were given.

(d) Verapamil

A woman taking verapamil 240 mg daily developed oedema of the feet and ankles, and neck vein distension within 6 weeks of starting to take **fluoxetine** 20 mg every other day. The oedema resolved within 2 to 3 weeks of reducing the verapamil dosage to 120 mg daily.[2] Another patient taking verapamil 240 mg daily for the prophylaxis of migraine developed morning headaches (believed by the patient not to be migraine) about one week after his **fluoxetine** dosage was increased from 20 to 40 mg daily. The headaches stopped when the verapamil dosage was reduced and then stopped.[2]

Mechanism

The calcium-channel blockers are metabolised by the cytochrome P450 isoenzyme CYP3A4, which can be inhibited by fluoxetine. This results in a marked reduction in the metabolism and clearance of the calcium-channel blockers. The reactions reported appear to be the exaggeration of the adverse effects of these calcium-channel blockers, possibly due to an increase in their levels.

Importance and management

Although a pharmacokinetic interaction might be predicted, information on an important clinical interaction appears to be limited to these reports. This suggests that adverse interactions occur only rarely. Bear the possibility of a pharmacokinetic interaction in mind if a patient shows an exaggerated response to a calcium-channel blocker after starting fluoxetine, being alert for the need to reduce the drug dosages (note that reducing the fluoxetine dose resolved the interaction in some of the cases described above). The clinical significance of the interaction between nimodipine and fluoxetine is not known,[4] and without knowing the extent of the interaction making clinical recommendations is difficult; however, until more is known it may be prudent to monitor for an increase in adverse effects with nimodipine, such as hypotension, and a reduction in the response to fluoxetine when both drugs are given.

Information about other calcium-channel blockers with fluoxetine, or other SSRIs, appears to be lacking.

1. Zanidip (Lercanidipine hydrochloride). Recordati Pharmaceuticals Ltd. UK Summary of product characteristics, October 2004.
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3. Azaz-Livshits TLT, Danenberg HD. Tachycardia, orthostatic hypotension and profound weakness due to concomitant use of fluoxetine and nifedipine. *Pharmacopsychiatry* (1997) 30, 274–5.
4. Nimotop Tablets (Nimodipine). Bayer plc. UK Summary of product characteristics, May 2008.

Calcium-channel blockers + St John's wort (*Hypericum perforatum*)

St John's wort significantly reduces the bioavailability of nifedipine and verapamil. Other calcium-channel blockers would be expected to interact similarly.

Clinical evidence

(a) Nifedipine

In a study in 10 healthy subjects, St John's wort 900 mg daily for 14 days decreased the maximum levels and AUC of a single 10-mg oral dose of nifedipine by about 38% and 45%, respectively. The maximum levels and AUC of the active metabolite of nifedipine, dehydronifedipine, were raised by about 45% and 26%, respectively. The St John's wort preparation used was standardised to contain hypericin 0.3% and hyperforin 5%.[1]

(b) Verapamil

In a study in 8 healthy subjects, verapamil 24 mg was given as a jejunal perfusion over 100 minutes both before and after they took St John's wort tablets *(Movina;* containing 3 to 6% hyperforin) 300 mg three times daily for 14 days. St John's wort did not affect jejunal permeability or the absorption of either *R*- or *S*-verapamil. The AUCs of *R*- and *S*-verapamil were decreased by 78% and 80%, respectively, and the peak plasma levels were decreased by 76% and 78%, respectively. The terminal half-life was not changed significantly. The AUC for *R*-verapamil was sixfold higher than that of *S*-verapamil, and St John's wort did not change this ratio.[2]

Mechanism

It appears that St John's wort decreased the bioavailability of both nifedipine and verapamil by inducing their metabolism by the cytochrome P450 isoenzyme CYP3A4 in the gut. An effect on P-glycoprotein-mediated transport is not likely, as intestinal permeability was not significantly altered.[2]

Importance and management

The general importance of this interaction is unclear, as neither study reported on the clinical outcome of these reductions in calcium-channel blocker levels. Patients taking St John's wort with nifedipine or verapamil should have their blood pressure and heart rate monitored to ensure they are still effective, and the dose should be adjusted if needed. There appears to be no information about other calcium-channel blockers, but as they are all metabolised by CYP3A4, to a greater or lesser extent, it would seem prudent to monitor concurrent use carefully. If an interaction occurs it may be prudent to use an alternative class of drugs (ACE inhibitors, angiotensin II receptor antagonists and beta blockers are not known to be affected by CYP3A4), or advise against the use of St John's wort.

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Calcium-channel blockers + Valproate

Nimodipine and possibly nifedipine levels are raised by valproate.

Clinical evidence, mechanism, importance and management

In a pharmacokinetic study, 8 patients with epilepsy who had been taking valproate alone for at least 4 months were given a single 60-mg dose of **nimodipine**. The AUC of **nimodipine** was about 50% higher, when compared with that found in a control group not taking valproate.[1] The **nimodipine** dosage may need to be reduced if it is given with valproate.

One manufacturer of **nifedipine** suggests that there is a theoretical possibility that levels of **nifedipine** may be increased in the presence of valproate,[2] and advises that blood pressure should be monitored and, if necessary, a reduction in the dose of **nifedipine** should be considered.[2] Note that they suggest that this may occur because valproate inhibits the cytochrome P450 isoenzyme CYP3A4, by which **nifedipine** is metabolised; however, clinically relevant examples of valproate interacting by this mechanism are largely lacking.

1. Tartara A, Galimberti CA, Manni R, Parietti L, Zucca C, Baasch H, Caresia L, Mück W, Barzaghi N, Gatti G, Perucca E. Differential effects of valproic acid and enzyme-inducing anticonvulsants on nimodipine pharmacokinetics in epileptic patients. *Br J Clin Pharmacol* (1991) 32, 335–40.

2. Adalat Retard (Nifedipine). Bayer plc. UK Summary of product characteristics, May 2008.

Calcium-channel blockers + X-ray contrast media

The hypotensive effects of an intravenous bolus of an ionic X-ray contrast medium can be increased by the presence of calcium-channel blockers. No interaction or only a small interaction appears to occur with non-ionic contrast media.

Clinical evidence, mechanism, importance and management

It is well recognised that ionic x-ray contrast media used for ventriculography reduce the systemic blood pressure due to peripheral vasodilation. They also have a direct depressant effect on the heart muscle. A comparative study of the haemodynamic response of 65 patients found that the hypotensive effect of a bolus dose of an ionic agent (0.5 mL/kg of **meglumine amidotrizoate** and **sodium amidotrizoate** with edetate sodium or disodium) was increased by the concurrent use of **nifedipine** or **diltiazem**. Haemodynamic effects occurred earlier (3.1 seconds compared with 12.9 seconds), were more profound (a fall in systolic pressure of 48.4 mmHg compared with 36.9 mmHg) and more prolonged (62 seconds compared with 36 seconds).[1] A similar interaction was seen in *dogs* given **verapamil**.[2] No interaction or only a minimal interaction was seen in the patients and *dogs* when non-ionic contrast media (**iopamidol** or **iohexol**) were used instead.[1,2] The clinical relevance of these findings is uncertain. Note that calcium-channel blockers have been tried to prevent the nephrotoxicity of contrast media.

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Calcium-channel blockers; Amlodipine + Chloroquine

A case report attributes an acute hypotensive episode to the use of amlodipine with chloroquine.

Clinical evidence, mechanism, importance and management

A case report describes a 48-year-old hypertensive man, who had been taking amlodipine 5 mg daily for 3 months with optimal blood pressure control. Because he had self-diagnosed malaria, he took chloroquine base 600 mg: two hours later he fainted and had a systolic blood pressure of 80 mmHg, and an unrecordable diastolic blood pressure. He was given supportive fluids and recovered over the following 2 hours. The severe adverse reaction was attributed to acute synergistic hypotensive, venodilator and cardiac effects of the two drugs.[1] However, any interaction remains unproven, as there was no re-challenge, and it seems reasonable that the faint may simply have been as a result of the fever from which he was suffering. Furthermore, the authors note that concurrent use of these two drugs would be expected to be quite frequent, and this appears to be the only case reported. No special precautions are therefore considered warranted based on this isolated case report.

1. Ajayi AAL, Adigun AQ. Syncope following oral chloroquine administration in a hypertensive patient controlled on amlodipine. *Br J Clin Pharmacol* (2002) 53, 404–5.

Calcium-channel blockers; Nifedipine + Co-trimoxazole

Adverse effects (leg cramps, facial flushing) have been reported in one patient taking nifedipine when co-trimoxazole was also taken. One study found that co-trimoxazole had no effect on the pharmacokinetics and hypotensive action of a single dose of nifedipine.

Clinical evidence, mechanism, importance and management

The observation of a patient taking nifedipine who developed leg cramps and facial flushing (possibly as a result of raised plasma nifedipine levels) when given co-trimoxazole, prompted further study of this possible interaction in 9 healthy subjects. After taking co-trimoxazole 960 mg twice daily for 3 days the pharmacokinetics and hypotensive effects of a single 20-mg dose of nifedipine were found to be unchanged.[1] No special precautions would therefore normally seem to be necessary on concurrent use.

1. Edwards C, Monkman S, Cholerton S, Rawlins MD, Idle JR, Ferner RE. Lack of effect of co-trimoxazole on the pharmacokinetics and pharmacodynamics of nifedipine. *Br J Clin Pharmacol* (1990) 30, 889–91.

Calcium-channel blockers; Nifedipine + Ginkgo (*Ginkgo biloba*)

Ginkgo may increase the levels and some of the effects of nifedipine.

Clinical evidence

In the preliminary report of a clinical study, 22 healthy subjects were given ginkgo 120 mg daily for 18 days before a single 10-mg oral dose of nifedipine. Ginkgo increased the levels of nifedipine by about 50%.[1]

In another study, a single 240-mg dose of ginkgo extract did not significantly affect the pharmacokinetics of a single 10-mg oral dose of nifedipine when they were given at the same time to 8 healthy subjects. However, the maximum level tended to increase (30% increase), and two subjects experienced a doubling of nifedipine maximum serum levels. In addition, the incidence and severity of headaches, hot flushes and dizziness tended to be higher with the combination when compared with nifedipine alone. Subjects also experienced increased heart rate with the combination although the decrease in blood pressure was unaffected.[2] The ginkgo extract used in this study contained 24% flavonoids and 6% terpene lactones.

Mechanism

Ginkgo may inhibit the cytochrome P450 isoenzyme CYP3A4, which would reduce the metabolism of nifedipine, a CYP3A4 substrate, and increase its levels. Note that simultaneous administration of single doses is probably insufficient to completely evaluate CYP3A4 inhibition. Note also that clinically relevant CYP3A4 inhibition has not been seen with ginkgo and the conventional CYP3A4 probe substrates such as midazolam.

Importance and management

Limited clinical data suggest that ginkgo may raise the levels of nifedipine and increase its effects. Until more is known, some caution might be warranted when they are used together. Monitor for signs of nifedipine

adverse effects such as headaches, hot flushes, dizziness and palpitations. If they become apparent, advise the patient to stop taking ginkgo.

1. Smith M, Lin KM, Zheng YP. An open trial of nifedipine-herb interactions: nifedipine with St. John's wort, ginseng or Ginko [sic] biloba. *Clin Pharmacol Ther* (2001) 69, P86.
2. Yoshioka M, Ohnishi N, Koishi T, Obata Y, Nakagawa M, Matsumoto T, Tagagi K, Takara K, Ohkuni T, Yokoyama T, Kuroda K. Studies on interactions between functional foods or dietary supplements and medicines. IV. Effects of Ginkgo biloba leaf extract on the pharmacokinetics and pharmacodynamics of nifedipine in healthy volunteers. *Biol Pharm Bull* (2004) 27, 2006–9.

Calcium-channel blockers; Nifedipine + Terbinafine

A study in 12 healthy subjects found that terbinafine 250 mg did not alter the pharmacokinetics of nifedipine 30 mg (as *Procardia XL*).[1]

1. Cramer JA, Robbins B, Barbeito R, Bedman TC, Dreisbach A, Meligeni JA. Lamisil®: interaction study with a sustained release nifedipine formulation. *Pharm Res* (1996) 13 (9 Suppl), S436.

Calcium-channel blockers; Nifedipine + Vancomycin

An isolated case report suggests that the hypotensive effects of the rapid infusion of vancomycin may occur more readily in those who are already vasodilated with nifedipine, but it seems likely that the effects seen were solely due to the vancomycin.

Clinical evidence, mechanism, importance and management

A man with severe systemic sclerosis was hospitalised for Raynaud's phenomenon and dental extraction. After he started taking nifedipine 40 mg daily, he was given intravenous vancomycin 1 g in 200 mL of dextrose 5% over 30 minutes. After 20 minutes he experienced a severe headache and was found to have a marked macular erythema on the upper trunk, head, neck and arms. His blood pressure fell to 100/60 mmHg and his pulse rate was 90 bpm. He recovered spontaneously.[1] The authors of the report acknowledge the possibility of 'red-man syndrome' caused by the vancomycin, and suggest that it may occur more readily in those already vasodilated with nifedipine. However, given that this is an isolated report, and the vancomycin was given over 3 times faster than the recommended rate, it seems likely that this is purely an adverse effect of vancomycin.

1. Daly BM, Sharkey I. Nifedipine and vancomycin-associated red man syndrome. *Drug Intell Clin Pharm* (1986) 20, 986.

Calcium-channel blockers; Nitrendipine + Bile acids

Chenodeoxycholic acid and ursodeoxycholic acid reduce the AUC of nitrendipine.

Clinical evidence, mechanism, importance and management

In a single-dose study, 6 healthy subjects were given nitrendipine 10 mg with or without either **chenodeoxycholic acid** 200 mg or 600 mg, or **ursodeoxycholic acid** 50 mg. **Chenodeoxycholic acid** 200 mg decreased the peak plasma level and AUC of nitrendipine by about 20%, whereas **chenodeoxycholic acid** 600 mg had a greater effect, reducing the peak plasma level and AUC of nitrendipine by 54% and 68%, respectively. **Ursodeoxycholic acid** reduced the peak plasma level and AUC of nitrendipine by 54% and 75%, respectively. The reduction in the AUC of nitrendipine was possibly due to the effects of the bile acids on tablet disintegration or more probably on drug solubilisation.[1] The clinical importance of the interaction is not known, but the extent of the reduction in the AUC of nitrendipine suggests that its effects may be diminished. It may therefore be prudent to consider monitoring the outcome of concurrent use, increasing the dose of nitrendipine as necessary.

1. Sasaki M, Maeda A, Sakamoto K-I, Fujimura A. Effect of bile acids on absorption of nitrendipine in healthy subjects. *Br J Clin Pharmacol* (2001) 52, 699–701.

Calcium-channel blockers; Verapamil + Ceftriaxone and Clindamycin

An isolated report describes the development of complete heart block in a man taking verapamil, which was attributed to the use of intravenous ceftriaxone and clindamycin. However, the validity of this interaction has been questioned.

Clinical evidence, mechanism, importance and management

A 59-year-old man who had been taking sustained-release verapamil 240 mg twice daily for 2 years and phenytoin 300 mg daily for several years, developed complete heart block an hour after being given intravenous ceftriaxone 1 g and clindamycin 900 mg for bilateral pneumonia. He needed cardiopulmonary resuscitation and the insertion of a temporary pacemaker, but spontaneously recovered normal sinus rhythm after 16 hours, and subsequently made a full recovery. The reasons for this serious reaction are not known, but the authors of the report postulate that these two antibacterials precipitated acute verapamil toxicity, possibly by displacing it from its plasma protein binding sites. Although both antibacterials are highly protein-bound (93% or more),[1] they are acidic and do not bind to the same sites as the verapamil (a base), so that this mechanism of interaction seems very unlikely. This seems to be the first and only report of this reaction, and the suggestion by the authors that it was due to a drug interaction has been seriously questioned.[2] There seems to be no other evidence that either of these antibacterials interact with verapamil, either given orally or intravenously. The current evidence is insufficient to suggest that extra caution is warranted if these drugs are given concurrently.

1. Kishore K, Raina A, Misra V, Jonas E. Acute verapamil toxicity in a patient with chronic toxicity: possible interaction with ceftriaxone and clindamycin. *Ann Pharmacother* (1993) 27, 877–80.
2. Horn JR, Hansten PD. Comment: pitfalls in reporting drug interactions. *Ann Pharmacother* (1993) 27, 1545–6.

Calcium-channel blockers; Verapamil + Sulfinpyrazone

The clearance of verapamil is markedly increased by sulfinpyrazone.

Clinical evidence, mechanism, importance and management

A study in 8 healthy subjects found that sulfinpyrazone 800 mg daily for a week, increased the clearance of a single oral dose of verapamil by about threefold, possibly due to an increase in its liver metabolism.[1] The clinical importance of this effect is uncertain, but be alert for reduced verapamil effects. It seems probable that the dosage of verapamil may need to be increased, or an alternative drug considered.

1. Wing LMH, Miners JO, Lillywhite KJ. Verapamil disposition—effects of sulphinpyrazone and cimetidine. *Br J Clin Pharmacol* (1985) 19, 385–91.

24

Cardiovascular drugs, miscellaneous

The drugs dealt with in this section include the centrally acting drugs (e.g. clonidine, methyldopa), inotropes and vasopressors (e.g. adrenaline, phenylephrine), adrenergic neurone blockers (e.g. guanethidine), some vasodilator antihypertensives (e.g. hydralazine, diazoxide), nitrates (e.g. glyceryl trinitrate), potassium channel activators (e.g. nicorandil), peripheral vasodilators (e.g. pentoxifylline), calcium sensitisers (e.g. levosimendan), endothelin receptor antagonists (e.g. ambrisentan, bosentan and sitaxentan), direct renin inhibitors (e.g. aliskiren) and other drugs used in the management of angina (e.g. ivabradine and ranolazine).

(a) Miscellaneous antihypertensives

The combination of two antihypertensive drugs often results in an increased antihypertensive action. Likewise the combination of drugs that may have hypotension as an adverse effect, can lead to an unexpected increase in hypotension. Examples of this type of interaction are discussed in the monograph 'Antihypertensives + Other drugs that affect blood pressure', p.1051. Some drugs are known to antagonise the effect of antihypertensives, and these are also generally discussed in this monograph.

(b) Sympathomimetics

Many of the inotropes and vasopressors have actions on the sympathetic nervous system. Noradrenaline (norepinephrine) is the principal neurotransmitter involved in the final link between nerve endings of the sympathetic nervous system and the adrenergic receptors of the organs or tissues innervated. The effects of stimulating this system can be reproduced or mimicked by exogenous noradrenaline and by a number of other drugs that also stimulate these receptors. The drugs that behave in this way are described as 'sympathomimetics' and act either directly, like noradrenaline, on the adrenergic receptors, or indirectly by releasing stored noradrenaline from the nerve endings. Some drugs do both. This is very simply illustrated in 'Figure 24.1', (below).

The adrenergic receptors of the sympathetic system are not identical but can be subdivided into two main types, namely alpha and beta receptors, which can then be further subdivided. The sympathomimetics are categorised in 'Table 24.1', (p.1048), and a brief summary of the principal effects of stimulation of these receptors is listed below:

- Alpha$_1$ (vasoconstriction, increased blood pressure and sometimes reflex bradycardia; contraction of smooth muscle; mydriasis in the eye)
- Alpha$_2$ (role in feedback inhibition of neurotransmitter release; inhibition of insulin release)
- Beta$_1$ (increased rate and force of contraction or the heart)
- Beta$_2$ (vasodilatation and bronchodilation; uterine relaxation and decreased gastrointestinal motility; release of insulin)

A third distinct group of receptors, which occur primarily within the CNS and may be affected by some sympathomimetics, are the dopamine receptors.

It is therefore possible to broadly categorise the sympathomimetics into groups according to their activity.

Given these wide ranging actions on a number of different receptors the group 'sympathomimetics' is clearly a very diverse collection of drugs with a wide range of uses. One should not, therefore, extrapolate the interactions seen with one drug to any other without fully taking into account their differences. For this reason, where possible, this term has been avoided and drugs have been grouped by therapeutic use. This section is generally concerned with the interactions of sympathomimetics that have predominately cardiovascular actions (mainly through stimulation of alpha$_1$ and/or beta$_1$ receptors). Those used as decongestants (through stimulation of alpha receptors with or without beta activity) are mainly discussed in 'Miscellaneous', (p.1546), but some of these drugs are also given intravenously for their pressor actions, in which case their interactions are discussed here. Interactions involving beta agonists, such as salbutamol, which selectively stimulate the beta$_2$ receptors in bronchi causing bronchodilation, are mainly covered in 'Respiratory drugs', (p.1413) and interactions involving dopaminergics, such as levodopa, are dealt with in 'Antiparkinsonian and related drugs', (p.784).

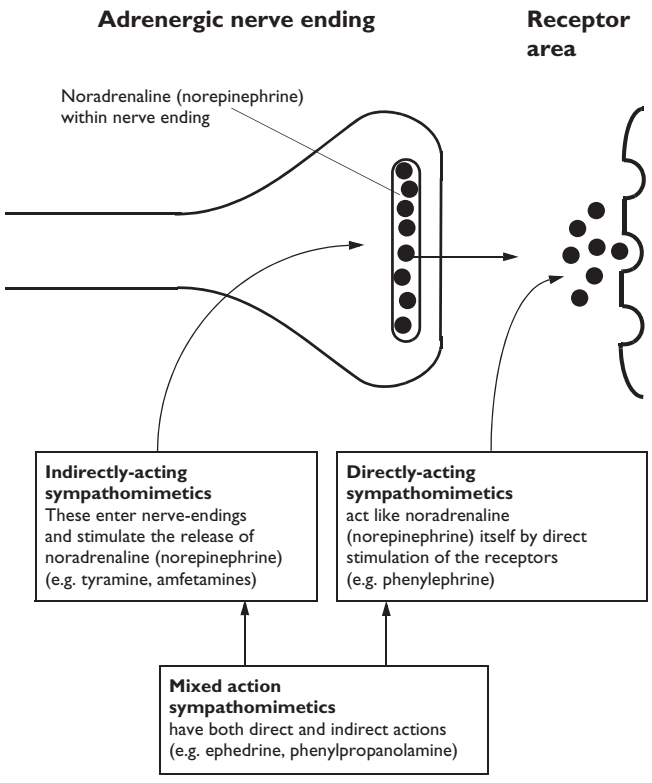

Fig. 24.1 A very simple illustration of the modes of action of indirectly-acting, directly-acting and mixed action sympathomimetics at adrenergic neurones.

Table 24.1 A categorisation of some sympathomimetic drugs

Drug	*Receptors stimulated*
Direct stimulators of alpha and beta receptors	
Adrenaline (Epinephrine)	Beta more marked than alpha
Mainly direct stimulators of alpha receptors	
Phenylephrine	Predominantly alpha
Metaraminol	Predominantly alpha
Methoxamine	Predominantly alpha
Noradrenaline (Norepinephrine)	Predominantly alpha
Mainly direct stimulators of beta-1 receptors	
Dobutamine	Predominantly beta-1, some beta-2 and alpha
Dopamine	Predominantly beta-1, some alpha
Direct stimulators of beta-1 and beta-2 receptors (beta-agonist bronchodilators)	
Bambuterol	Predominantly beta-2
Fenoterol	Predominantly beta-2
Formoterol	Predominantly beta-2
Isoetharine	Predominantly beta-2
Isoprenaline (Isoproterenol)	Beta-1 and beta-2
Orciprenaline	Predominantly beta-2
Pirbuterol	Predominantly beta-2
Reproterol	Predominantly beta-2
Rimiterol	Predominantly beta-2
Ritodrine	Predominantly beta-2
Salbutamol (Albuterol)	Predominantly beta-2
Salmeterol	Predominantly beta-2
Terbutaline	Predominantly beta-2
Tulobuterol	Predominantly beta-2
Direct and indirect stimulators of alpha and beta receptors	
Ephedrine	Alpha and beta
Etefedrine	Alpha and beta
Phenylpropanolamine	Alpha and beta
Pseudoephedrine	Alpha and beta
Mainly indirect stimulators of alpha and beta receptors	
Amfetamine (Amphetamine)	Alpha and beta – also central stimulant
Mephentermine	Alpha and beta – also central stimulant
Methylphenidate	Alpha and beta – also central stimulant
Tyramine	Alpha and beta

Aliskiren + Miscellaneous

A number of studies found that there were no clinically significant pharmacokinetic interactions between aliskiren and allopurinol, atenolol, cimetidine, digoxin, fenofibrate, irbesartan, isosorbide mononitrate, lovastatin, ramipril or valsartan. There was no pharmacokinetic interaction between aliskiren and celecoxib, but the concurrent use of aliskiren with NSAIDs in patients with renal impairment such as the elderly, may result in further deterioration in renal function and even renal failure.

Clinical evidence, mechanism, importance and management

(a) Allopurinol

In a study in 20 healthy subjects given aliskiren 300 mg daily, allopurinol 300 mg daily for 5 days did not affect the AUC or peak plasma levels of aliskiren, although there was wide variability in plasma levels.[1]

(b) Angiotensin II receptor antagonists

A study in 18 healthy subjects given aliskiren 300 mg daily for 11 days with **valsartan** 320 mg daily for the last 4 days found that the AUC of aliskiren was reduced by 26% and the AUC of **valsartan** was decreased by 14%.[2] The US manufacturer states that multiple dosing with **irbesartan** reduces the peak levels of aliskiren by up to 50%.[3] However, in a study in healthy subjects and patients with renal impairment, **irbesartan** 300 mg daily for 7 days had no effect on the pharmacokinetics of steady-state aliskiren 300 mg daily and concurrent use was well tolerated.[4]

(c) Cimetidine

In a study in 22 healthy subjects given aliskiren 300 mg daily for 7 days, followed by aliskiren with cimetidine 800 mg daily for a further 5 days, cimetidine increased the peak plasma levels and AUC of aliskiren by 25% and 20%, respectively.[1] Another study in 12 healthy subjects given cimetidine 800 mg daily for 5 days, the AUC, peak plasma level and half-life of a single 150-mg dose of aliskiren given on day 3 were increased by 17%, 19%, and 15%, respectively.[5] These modest pharmacokinetic changes would not be expected to be clinically relevant.

(d) Digoxin

In a study, 19 healthy subjects were given aliskiren 300 mg daily for 7 days, then after a washout period, digoxin 250 micrograms daily for 9 days, with aliskiren 300 mg daily added for a further 7 days. Digoxin had no significant effect on the pharmacokinetics of aliskiren. The AUC of digoxin was reduced by 15%, but peak digoxin levels were unaffected by aliskiren.[6] This modest change in digoxin levels would not be expected to be clinically relevant.

(e) Food

The AUC and peak plasma levels of aliskiren are reduced by about 70% and 85%, respectively when it is taken with a high-fat meal.[3,7] The UK manufacturer recommends taking aliskiren with a light meal, preferably at the same time each day.[7] Due to lack of data, a possible interaction between aliskiren and **grapefruit juice** cannot be excluded. Therefore, the UK manufacturer advises that grapefruit juice should not be taken with aliskiren.[7]

(f) Isosorbide mononitrate

In a study, 18 healthy subjects were given isosorbide mononitrate alone for 3 days, then after a washout period, aliskiren 300 mg daily for 7 days, then aliskiren was given with isosorbide mononitrate 40 mg daily for a further 3 days. There was no clinically significant pharmacokinetic interaction but dizziness and low blood pressure were more frequent during concurrent use than with either drug alone.[8] It may be prudent to be alert for these effects if both drugs are given, and adjust the doses accordingly.

(g) NSAIDs

In a study, aliskiren 300 mg daily was given to 22 healthy subjects for 7 days alone, and then with **celecoxib** 200 mg twice daily for a further 4.5 days. **Celecoxib** caused a slight (14%) reduction in the aliskiren AUC and there was wide variability in peak plasma levels. Dizziness was more frequently reported during concurrent use than with either drug alone.[1] In a single-dose study, **celecoxib** 200 mg caused a slight increase (about 9%) in the AUC of aliskiren and increased peak plasma levels by 36%.[5] Although there is not a significant pharmacokinetic interaction between aliskiren and celecoxib, NSAIDs may reduce the antihypertensive effect of aliskiren through their action on the renin-angiotensin system. Furthermore, in dehydrated or elderly patients with some renal impairment, the concurrent aliskiren and NSAIDs may result in further deterioration of renal function and possible renal failure. The UK manufacturer recommends caution, especially in the elderly.[7]

(h) Other drugs

Single-dose studies found no pharmacokinetic interactions between aliskiren 150 mg and either **lovastatin** 40 mg or **atenolol** 100 mg.[5] In a study in 21 healthy subjects, there was no pharmacokinetic interaction between aliskiren 300 mg daily and **fenofibrate** 200 mg daily.[9]

Peak plasma levels of aliskiren were increased by about 30% and the AUC was increased by about 15% when it was given with **ramipril** in an initial dose of 2.5 mg titrated to 10 mg daily. The AUC of **ramipril** was increased by 22% during the use of aliskiren.[2] These pharmacokinetic changes would not be expected to be clinically relevant, although additive blood pressure lowering effects may occur.

1. Ayalasomayajula S, Tchaloyan S, Yeh C-M, Bizot M-N, Dieterich HA, Howard D, Dole WP. A study of the pharmacokinetic interactions of the direct renin inhibitor aliskiren with allopurinol, celecoxib and cimetidine in healthy subjects. Curr Med Res Opin (2008) 24, 717–26.
2. Vaidyanathan S, Valencia J, Kemp C, Zhao C, Yeh C-M, Bizot M-N, Denouel J, Dieterich A, Dole WP. Lack of pharmacokinetic interactions of aliskiren, a novel direct renin inhibitor for the treatment of hypertension, with the antihypertensives amlodipine, valsartan, hydrochlorothiazide (HCTZ) and ramipril in healthy volunteers. *Int J Clin Pract* (2006) 60, 1343–56.
3. Tekturna (Aliskiren hemifumarate). Novartis. US Prescribing information, December 2007.
4. Vaidyanathan S, Bigler H, Yeh CM, Bizot M-N, Dieterich HA, Howard D, Dole WP. Pharmacokinetics of the oral direct renin inhibitor aliskiren alone and in combination with irbesartan in renal impairment. *Clin Pharmacokinet* (2007) 46, 661–75.
5. Dieterle W, Corynen S, Vaidyanathan S, Mann J. Pharmacokinetic interactions of the oral renin inhibitor aliskiren with lovastatin, atenolol, celecoxib and cimetidine. *Int J Clin Pharmacol Ther* (2005) 43, 527–35.
6. Vaidyanathan S, Camenisch G, Schuetz H, Reynolds C, Yeh C-M, Bizot M-N, Dieterich HA, Howard D, Dole WP. Pharmacokinetics of the oral direct renin inhibitor aliskiren in combination with digoxin, atorvastatin, and ketoconazole in healthy subjects: the role of P-glycoprotein in the disposition of aliskiren. J Clin Pharmacol (2008) 48, 1323–8.
7. Rasilez (Aliskiren hemifumarate). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, April 2009.
8. Vaidyanathan S, Bartlett M, Dieterich HA, Yeh C-M, Antunes A, Howard D, Dole WP. Pharmacokinetic interaction of the direct renin inhibitor aliskiren with furosemide and extended-release isosorbide-5-mononitrate in healthy subjects. Cardiovasc Ther (2008) 26, 238–46.
9. Vaidyanathan S, Maboudian M, Warren V, Yeh C-M, Dieterich HA, Howard D, Dole WP. A study of the pharmacokinetic interactions of the direct renin inhibitor aliskiren with metformin, pioglitazone and fenofibrate in healthy subjects. Curr Med Res Opin (2008) 24, 2313–26.

Aliskiren + P-glycoprotein inducers and inhibitors

Atorvastatin, ciclosporin and ketoconazole increase aliskiren levels, probably by inhibiting P-glycoprotein. Other P-glycoprotein inhibitors are predicted to interact similarly, and P-glycoprotein inducers (e.g. rifampicin) are predicted to lower aliskiren levels.

Clinical evidence

(a) Atorvastatin

In a study, 20 healthy subjects were given aliskiren 300 mg daily for 11 days, with atorvastatin 80 mg daily for the last 4 days. Atorvastatin increased the AUC and peak plasma levels of aliskiren by 47% and 50%, respectively, and reduced its clearance by 34%. Peak levels of atorvastatin were reduced by 23% during the concurrent use of aliskiren, but there were no clinically significant effects on the AUC of atorvastatin and its metabolites.[1]

(b) Ciclosporin

A study in healthy subjects found that ciclosporin, in doses of 200 mg or 600 mg, increased the peak levels and AUC of a single 75-mg dose of aliskiren by about 2.5-fold and 5-fold, respectively. It was suggested that these increases may be higher with larger doses of aliskiren.[2,3]

(c) Ketoconazole

In a study, 20 healthy subjects were given aliskiren 300 mg daily for 11 days, with the concurrent use of ketoconazole 200 mg twice daily for the last 4 days. Ketoconazole increased the AUC, peak plasma levels and minimum plasma levels of aliskiren by 76%, 81% and 64%, respectively. The clearance of aliskiren was reduced by 43%.[1] Ketoconazole is therefore predicted to effectively double the dose of aliskiren, and doses of this order (up to 600 mg of aliskiren daily) have been found to be well-tolerat-

ed.[2] A daily dose of ketoconazole 400 mg is predicted to increase blood levels further.[3]

Mechanism

P-glycoprotein is reported to be the major efflux system involved in the intestinal absorption and biliary excretion of aliskiren. The potential for interactions mediated by P-glycoprotein probably depends on the degree of inhibition of the transporter. Therefore moderate and potent inhibitors of P-glycoprotein such as ketoconazole and ciclosporin cause significant increases in aliskiren levels.

Importance and management

Evidence for an interaction between aliskiren and atorvastatin, ciclosporin or ketoconazole is limited, but in line with the way these drugs are known to interact. Moderate and potent inhibitors of P-glycoprotein cause significant increases in the plasma levels of aliskiren and it is suggested that they may have greater effects on tissue levels. The manufacturers of aliskiren therefore contraindicate its use with potent inhibitors of P-glycoprotein such as ciclosporin and **quinidine**.[2,3]

The UK manufacturer advises caution if aliskiren is given with ketoconazole or other moderate inhibitors of P-glycoprotein. They specifically name **amiodarone**, **clarithromycin**, **erythromycin**, **itraconazole**, and **telithromycin**.[2] The effect of atorvastatin is more modest, but until more is known, some caution is probably advisable if it is given with aliskiren. If any of these drugs are given with aliskiren it may be prudent to be alert for aliskiren adverse effects such as diarrhoea, dyspepsia and hypotension. Adjust the aliskiren dose as necessary.

The effect of aliskiren on atorvastatin is not expected to be clinically relevant. Studies with P-glycoprotein *inducers* do not appear to have been undertaken, but based on the known effects of the P-glycoprotein inhibitors, it is logical to expect that they may decrease aliskiren levels. The UK manufacturers specifically name **rifampicin** and **St John's wort**.[2] It may therefore be prudent to monitor concurrent use for aliskiren efficacy.

1. Vaidyanathan S, Camenisch G, Schuetz H, Reynolds C, Yeh C-M, Bizot M-N, Dieterich HA, Howard D, Dole WP. Pharmacokinetics of the oral direct renin inhibitor aliskiren in combination with digoxin, atorvastatin, and ketoconazole in healthy subjects: the role of P-glycoprotein in the disposition of aliskiren. J Clin Pharmacol (2008) 48, 1323–38.
2. Rasilez (Aliskiren hemifumarate). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, April 2009.
3. Tekturna (Aliskiren hemifumarate). Novartis. US Prescribing information, December 2007.

Antihypertensives + Hormonal contraceptives or HRT

Oral combined hormonal contraceptives are associated with increased blood pressure and may antagonise the efficacy of antihypertensive drugs. However, the effects are far greater with the high-dose contraceptives that were used historically, and the risks appear to be smaller with the newer low-dose contraceptives. The risks with progestogen-only contraceptives seem to be negligible.
Drospirenone HRT appears to further decrease blood pressure when given with enalapril or hydrochlorothiazide.

Clinical evidence, mechanism, importance and management

(a) Hormonal contraceptives

Early after the introduction of the oral **combined hormonal contraceptives** it was realised that they can cause increases in blood pressure and clinical hypertension.[1,2] One study[3] from the 1970s, in 83 women, found that the average rise in blood pressure was 9.2/5 mmHg, and that it was about twice as likely to occur as in those not taking a contraceptive. Another study from the 1980s found that women taking an oral combined hormonal contraceptive containing **levonorgestrel** 250 micrograms and **ethinylestradiol** 50 micrograms had higher blood pressures (systolic and diastolic blood pressures were 3.6 to 5 mmHg and 1.9 to 2.7 mmHg higher, respectively) than a similar group of women using non-hormonal contraception.[4] Additionally, cases were noted where antihypertensives (at that time, commonly **guanethidine** and/or **methyldopa**) were not that effective in women with hypertension taking oral **combined hormonal contraceptives**.[2,5] Although modern oral **combined hormonal contraceptives** are lower dose, they are still associated with a small increased risk of elevated blood pressure.[6,7] A UK study found that oral **combined hormonal contraceptives** were associated with a 2.6/1.8 mmHg rise in blood pressure, whereas oral **progestogen-only contraceptives** did not affect blood pressure.[6] A review of four studies also found no significant association between high blood pressure and the use of oral **progestogen-only hormonal contraceptives** during follow-up periods of 2 to 3 years.[8] A study in women who had been using depot **medroxyprogesterone** for 10 years, found that it did not raise blood pressure.[9]

This is only a very brief review of this subject, but the risks of hypertension with **combined hormonal contraceptives** appear to be modest. Nevertheless, it is generally advised that **combined hormonal contraceptives** are not used in women with hypertension, and they should be avoided in women with other risk factors for cardiovascular disease. Where considered appropriate, oral **combined hormonal contraceptives** may be used in women with treated hypertension, if blood pressure control is good. However, **progestogen-only contraceptives** are usually the preferred hormonal method of contraception in women with hypertension.[10] Although **drospirenone** HRT has been shown to lower blood pressure (see *Drospirenone HRT*, below), there appear to be no data on blood pressure in women taking the drospirenone-containing **combined hormonal contraceptives**.

(b) Menopausal HRT

In general, use of menopausal HRT has been found to have little effect on blood pressure in hypertensive women.[11]

Drospirenone HRT. In a study in 24 postmenopausal women with hypertension taking **enalapril** 10 mg twice daily, the use of **enalapril** with drospirenone 3 mg with **estradiol** 1 mg (12 women) produced a significant *decrease* in blood pressure of 9/5 mmHg after 14 days of treatment, when compared with the placebo group (12 patients).[12] In another study, 34 hypertensive postmenopausal women taking **hydrochlorothiazide** 25 mg daily were given either drospirenone 3 mg with **estradiol** 1 mg or placebo. Mean systolic and diastolic blood pressures were *reduced* significantly (by 7.2 mmHg and 4.5 mmHg, respectively) when compared with the placebo group, and drospirenone with **estradiol** also counteracted the **hydrochlorothiazide**-induced potassium loss. Drospirenone with **estradiol** did not affect the pharmacokinetics of **hydrochlorothiazide**.[13]
Note that drospirenone is an analogue of spironolactone, and shares its aldosterone antagonist effects, thereby lowering blood pressure and having some potassium-sparing effects.
Bear in mind the possibility that drospirenone HRT might further decrease blood pressure in women taking antihypertensives. However, hypertension has also been reported as an adverse effect.[14,15] It would be prudent to monitor blood pressure on starting concurrent use.
Note also that drospirenone has some potassium-sparing effects, which attenuated the effect of **hydrochlorothiazide** in the study cited, and might be additive with the effect of ACE inhibitors and angiotensin II receptor antagonists, see 'Drospirenone-containing contraceptives or HRT + Potassium-sparing drugs', p.1197.

1. Wallace MR. Oral contraceptives and severe hypertension. *Aust N Z J Med* (1971) 1, 49–52.
2. Woods JW. Oral contraceptives and hypertension. *Lancet* (1967) iii, 653–4.
3. Weir RJ, Briggs E, Mack A, Naismith L, Taylor L, Wilson E. Blood pressure in women taking oral contraceptives. *BMJ* (1974) 1, 533–5.
4. WHO Task Force on Oral Contraceptives.The WHO multicentre trial of the vasopressor effects of combined oral contraceptives: 1. comparison with IUD. *Contraception* (1989) 40, 129–45.
5. Clezy TM. Oral contraceptives and hypertension: the effect of guanethidine. *Med J Aust* (1970) 1, 638–40.
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7. Khaw K-T, Peart WS. Blood pressure and contraceptive use. *BMJ* (1982) 285, 403–7.
8. Hussain SF. Progestogen-only pills and high blood pressure: is there an association? A literature review. *Contraception* (2004) 69, 89–97.
9. Taneepanichskul S, Reinprayoon D, Jaisamrarn U. Effect of DMPA on weight and blood pressure in long-term acceptors. *Contraception* (1999) 59, 301–3.
10. Williams B, Poulter NR, Brown MJ, Davis M, McInnes GT, Potter JF, Sever PS, McG Thom S. British Hypertension Society Guidelines. Guidelines for management of the fourth working party of the British Hypertension Society, 2004–BHS IV. *J Hum Hypertens* (2004) 18, 139–85.
11. Sweetman SC, ed. Martindale: The complete drug reference. 36th ed. London: Pharmaceutical Press; 2009. p. 2073.
12. Preston RA, Alonso A, Panzitta D, Zhang P, Karara AH. Additive effect of drospirenone/17-β-estradiol in hypertensive postmenopausal women receiving enalapril. *Am J Hypertens* (2002) 15, 816–22.
13. Karara AH, Hanes V, Alonso A, Ni P, Poola N, Silang R, Blode H, Preston RA. Pharmacokinetics and pharmacodynamics of drospirenone-estradiol combination hormone therapy product coadministered with hydrochlorothiazide in hypertensive postmenopausal women. *J Clin Pharmacol* (2007) 47, 1292–302.
14. Angeliq (Drospirenone/Estradiol). Bayer plc. UK Summary of product characteristics, May 2008.
15. Angeliq (Drospirenone/Estradiol). Bayer HealthCare Pharmaceuticals, Inc. US Prescribing information, March 2008.

Antihypertensives + Other drugs that affect blood pressure

The blood pressure lowering effect of the antihypertensives can be enhanced by other antihypertensives, as would be expected. Although first-dose hypotension (dizziness, lightheadedness, fainting) can occur with some combinations, the additive effects are usually clinically useful. Perhaps of more concern is the use of antihypertensives with drugs that lower blood pressure as an adverse effect, where the effects may not be anticipated. Some drugs antagonise the blood pressure-lowering effects of the antihypertensives and should therefore be used with caution.

Clinical evidence, mechanism, importance and management

(a) Antihypertensive drugs

Enhanced hypotensive effects should be expected when using two antihypertensives together and it is widely acknowledged that most people require more than one antihypertensive to control blood pressure.[1,2] In the US, more than two-thirds of patients receive two or more antihypertensives in order to reach the desired target blood pressure. Not only does this improve blood pressure control, but adverse effects can also be reduced as lower doses of each drug can be used.[3]

Therefore many antihypertensive combinations produce additive hypotensive effects that are exploited clinically. Calcium-channel blockers and diuretics (see 'Calcium-channel blockers + Diuretics', p.1032) are often used together for additional blood pressure lowering in patients with hypertension. However, the side effects of the drug combinations may also be additive, and although there are only a few reports describing these additive interactions, they are highly probable, and caution is advised when using two antihypertensives together. The most common symptoms seen in hypotensive patients are dizziness, fatigue, headache, nausea, confusion, general weakness, lightheadedness, faintness and possible loss of consciousness.

Investigation of whether the effects of two antihypertensives is additive, greater than additive or less than additive is difficult to assess.[2] However, in some cases combining two or more antihypertensives has led to severe, first-dose hypotension, see 'Alpha blockers + ACE inhibitors or Angiotensin II receptor antagonists', p.93. Further, life-threatening bradycardia, asystole and sinus arrest can occur when antihypertensives that cause cardiodepression are given together (see 'Beta blockers + Calcium-channel blockers; Diltiazem', p.1002).

In contrast, a sharp and serious rise in blood pressure (rebound hypertension) can occur following the sudden withdrawal of clonidine, and this can be exacerbated in the presence of a beta blocker (see 'Clonidine and related drugs + Beta blockers', p.1053). In some cases fatalities have occurred. 'Table 24.2', (p.1052) lists antihypertensive combinations that have been implicated in adverse events.

(b) Drugs with significant hypotensive adverse effects

Caution must also be used when combining two or more drugs that, although not primarily indicated for hypertension, may have blood pressure lowering adverse effects. In fact, it is these drugs, rather than drugs commonly given for their blood pressure lowering effects that may cause more of a problem, as the effects are less likely to be deliberately sought. These drugs are listed in 'Table 24.3', (p.1052) with cross-references to the individual monographs that discuss the reports of adverse effects from these combinations.

(c) Drugs that antagonise hypotensive effects

When using antihypertensive drugs it is important to consider the implications of using drugs that antagonise their effects. The NSAIDs are the prime example of this. In the US, NSAIDs and steroids are reported to be the most common classes of drugs that raise blood pressure. Calcineurin inhibitors (ciclosporin and tacrolimus) and epoetins are reported to raise blood pressure in most patients.[4] Similarly, **danazol** is reported oppose the action of antihypertensives, possibly by increasing fluid retention.[5] Drugs that are thought to antagonise the effects of antihypertensives are listed in 'Table 24.4', (p.1052), with cross-references to the individual monographs that discuss the reports of adverse effects from these combinations.

1. Williams B, Poulter NR, Brown MJ, Davis M, McInnes GT, Potter JF, Sever PS, McG Thom S. British Hypertension Society. Guidelines for management of hypertension: report of the fourth working party of the British Hypertension Society, 2004-BHS IV. *J Hum Hypertens* (2004) 18, 139–185.
2. McInnes GT. Antihypertensive drugs in combination: additive or greater than additive? *J Hum Hypertens* (2007) 21, 914–6.
3. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jones DW, Materson BJ, Oparil S, Wright JT, Roccella EJ and the National High Blood Pressure Education Program Co-ordinating Committee. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of Blood Pressure. *Hypertension* (2003) 42, 1206–52.
4. Elliott WJ. Drug interactions and drugs that affect blood pressure. *J Clin Hypertens* (2006) 8, 731–7.
5. Danol (Danazol). Sanofi-Aventis. UK Summary of product characteristics, July 2007.

Antihypertensives + Phenylpropanolamine

A single dose of a sustained-release preparation of phenylpropanolamine and brompheniramine was found to cause a minor and clinically insignificant rise in the blood pressures of patients taking various antihypertensives.

Clinical evidence, mechanism, importance and management

A randomised, double-blind, crossover study in 13 patients with hypertension controlled with unnamed **diuretics** (7), **ACE inhibitors** (6), **beta blockers** (5), **calcium-channel blockers** (1) and a **centrally acting alpha-agonist** (1) found that a single dose of *Dimetapp Extentabs* (phenylpropanolamine 75 mg with brompheniramine 12 mg) caused only a minor rise in blood pressure of 1.7/0.9 mmHg over 4 hours.[1] This sustained-release preparation in this dose has therefore no clinically important effect on blood pressure, but (as the authors point out), these results do not necessarily apply to different doses and immediate-release preparations. A marked rise in blood pressure was seen in one patient taking **methyldopa** and **oxprenolol** when given phenylpropanolamine, see 'Methyldopa + Nasal decongestants', p.1070. Consider also 'Beta blockers + Phenylpropanolamine', p.1015.

1. Petrulis AS, Imperiale TF, Speroff T. The acute effect of phenylpropanolamine and brompheniramine on blood pressure in controlled hypertension. *J Gen Intern Med* (1991) 6, 503–6.

Clonidine + Antipsychotics

The hypotensive adverse effects of the phenothiazines, and possibly haloperidol may be additive with the antihypertensive effects of clonidine. Patients may feel faint and dizzy if they stand up quickly.

Clinical evidence

One report describes a patient who experienced dizziness and hypotension (systolic blood pressure 76 mmHg) about an hour after being given **chlorpromazine** 100 mg, clonidine 100 micrograms and furosemide 40 mg. Another patient also experienced hypotension 2 hours after being given clonidine 100 micrograms and a 1-mg intramuscular dose of **haloperidol**.[1]

There is also an isolated and unexplained case of a patient with psychosis taking **fluphenazine decanoate** who began to exhibit delirium, agitation, disorientation, short-term memory loss, confusion and clouded consciousness within 10 days of starting to take clonidine 200 micrograms daily. These symptoms disappeared when the clonidine was stopped and returned when it was re-started. Previous use of **haloperidol** with clonidine had been uneventful.[2]

Mechanism

Simple addition of the hypotensive effects of both drugs seems to be the explanation for the increased hypotension and orthostasis. However, note that in contrast to the case report above, *animal* studies have shown that chlorpromazine *reduces* the antihypertensive effect of clonidine.[3]

Importance and management

The increased hypotension and orthostasis that can occur if phenothiazines are used with antihypertensive drugs such as clonidine is established. Note that, of the phenothiazines, **levomepromazine** is particularly associated with postural hypotension. One report suggests that haloperidol may interact similarly. Monitor, particularly during the initial stages of concurrent use, and warn patients that if they feel faint and dizzy they should lie down, and that they should remain lying down until symptoms abate completely. Dose adjustment may be necessary.

Table 24.2 Antihypertensive + Antihypertensive drug interactions

Drugs	*Additive antihypertensive interactions*
ACE inhibitors	ACE inhibitors + Beta blockers ACE inhibitors + Calcium-channel blockers ACE inhibitors + Clonidine ACE inhibitors + Diuretics; Loop, Thiazide and related Alpha blockers + ACE inhibitors or Angiotensin II receptor antagonists
Adrenergic neurone blockers (e.g. guanethidine)	Minoxidil + Miscellaneous
Alpha blockers	Alpha blockers + ACE inhibitors or Angiotensin II receptor antagonists Alpha blockers + Beta blockers Alpha blockers + Calcium-channel blockers Alpha blockers + Diuretics
Angiotensin II receptor antagonists	Angiotensin II receptor antagonists + Beta blockers Angiotensin II receptor antagonists + Calcium-channel blockers Angiotensin II receptor antagonists + Diuretics; Loop, Thiazide and related
Beta blockers	ACE inhibitors + Beta blockers Alpha blockers + Beta blockers Angiotensin II receptor antagonists + Beta blockers Beta blockers + Calcium-channel blockers; Dihydropyridines Beta blockers + Calcium-channel blockers; Diltiazem Beta blockers + Calcium-channel blockers; Verapamil Beta blockers + Hydralazine Clonidine and related drugs + Beta blockers Ketanserin + Beta blockers
Calcium-channel blockers	ACE inhibitors Alpha blockers + Calcium-channel blockers Angiotensin II receptor antagonists + Calcium-channel blockers Beta blockers + Calcium-channel blockers; Dihydropyridines Beta blockers + Calcium-channel blockers; Diltiazem Beta blockers + Calcium-channel blockers; Verapamil Calcium-channel blockers + Calcium-channel blockers Calcium-channel blockers + Diuretics Calcium-channel blockers + Nitrates Glyceryl trinitrate (Nitroglycerin) + Nifedipine
Centrally acting antihypertensives (e.g. clonidine, moxonidine)	ACE inhibitors + Clonidine Clonidine + Beta blockers Moxonidine + Hydrochlorothiazide
Diazoxide	Diazoxide + Hydralazine
Diuretics	ACE inhibitors + Diuretics; Loop, Thiazide and related Alpha blockers + Diuretics Angiotensin II receptor antagonists + Diuretics; Loop, Thiazide and related Calcium-channel blockers + Diuretics
Nicorandil	Nicorandil + Miscellaneous
Nitrates	Calcium-channel blockers + Nitrates Glyceryl trinitrate (Nitroglycerin) + Nifedipine Sodium nitroprusside + Miscellaneous
Rauwolfia alkaloids	—
Vasodilators (e.g. hydralazine)	Beta blockers + Hydralazine Diazoxide + Hydralazine Minoxidil + Miscellaneous Nicorandil + Miscellaneous

Table 24.3 Antihypertensive drug interactions involving drugs with significant hypotensive properties or adverse effects

Drugs	*Additive antihypertensive interactions*
Alcohol	Alcohol + Antihypertensives
Anaesthetics	Anaesthetics, general + ACE inhibitors or Angiotensin II receptor antagonists Anaesthetics, general + Beta blockers Anaesthetics, general + MAOIs and related drugs Anaesthetics, local + Antihypertensives
Antipsychotics	ACE inhibitors + Antipsychotics Beta blockers + Haloperidol Clonidine + Antipsychotics Clozapine + Antihypertensives Guanethidine + Antipsychotics Methyldopa + Haloperidol
Dopamine agonists (e.g. apomorphine, bromocriptine etc.)	Apomorphine + Miscellaneous Bromocriptine and other dopamine agonists + ACE inhibitors
Levodopa	Guanethidine + Levodopa Levodopa + Methyldopa
Moxisylyte	Moxisylyte + Miscellaneous
Phosphodiesterase type-5 inhibitors	Phosphodiesterase type-5 inhibitors + Alpha blockers Phosphodiesterase type-5 inhibitors + Antihypertensives Phosphodiesterase type-5 inhibitors + Nitrates
Procarbazine	Procarbazine + Miscellaneous
Tizanidine	Tizanidine + Antihypertensives
Other drugs suggested to cause hypotension but where no reports of adverse interaction found	Aldesleukin Alprostadil MAOIs

Table 24.4 Antihypertensive drugs and drugs antagonising their effect

Drugs	*Antagonising antihypertensive interactions*
Amfetamines	Guanethidine + Amfetamines and related drugs
High-dose aspirin	ACE inhibitors + Aspirin
Carbenoxolone	Carbenoxolone + Antihypertensives
Hormonal contraceptives	Antihypertensives + Hormonal contraceptives or HRT
Epoetin	ACE inhibitors and Angiotensin II receptor antagonists + Epoetins
NSAIDs	ACE inhibitors + NSAIDs Alpha blockers + Aspirin or NSAIDs Angiotensin II receptor antagonists + Aspirin or NSAIDs Beta blockers + Aspirin or NSAIDs Calcium-channel blockers + Aspirin or NSAIDs Guanethidine + NSAIDs Hydralazine + NSAIDs Thiazide diuretics + NSAIDs
Phenylpropanolamine	Antihypertensives + Phenylpropanolamine Beta blockers + Phenylpropanolamine
Other drugs suggested to antagonise the effects of antihypertensives	Corticosteroids

The manufacturers of clonidine note that a reduced antihypertensive effect may occur with antipsychotics with alpha-blocking properties (e.g. chlorpromazine),.[4] but the only evidence for this appears to come from *animal* data. However, it has been suggested that the tricyclics may interact by a similar mechanism, see 'Clonidine and related drugs + Tricyclic and related antidepressants', p.1054.

1. Fruncillo RJ, Gibbons WJ, Vlasses PH, Ferguson RK. Severe hypotension associated with concurrent clonidine and antipsychotic medication. *Am J Psychiatry* (1985) 142, 274.
2. Allen RM, Flemenbaum A. Delirium associated with combined fluphenazine-clonidine therapy. *J Clin Psychiatry* (1979) 40, 236–7.
3. van Zwieten PA. The interaction between clonidine and various neuroleptic agents and some benzodiazepine tranquillizers. *J Pharm Pharmacol* (1977) 29, 229–34.
4. Catapres Tablets (Clonidine hydrochloride). Boehringer Ingelheim Ltd. UK Summary of product characteristics, July 2009.

Clonidine and related drugs + Beta blockers

The use of clonidine with beta blockers can be therapeutically valuable, but a sharp and serious rise in blood pressure (rebound hypertension) can follow the sudden withdrawal of clonidine, which may be worsened by the presence of a beta blocker. Moxonidine is predicted to interact similarly. Isolated cases of marked bradycardia and hypotension have been seen in patients given clonidine with esmolol. There are also two reports describing paradoxical hypertension when clonidine was given with a beta blocker.

Clinical evidence

(a) Antagonism of the hypotensive effects

In a study in 10 patients, the concurrent use of **sotalol** 160 mg daily and clonidine 450 micrograms daily caused a marked rise in blood pressure in 6 of the 10 patients, compared with either clonidine alone (3 patients) or **sotalol** alone (3 patients). Of the 4 patients who did not have a marked rise in blood pressure, 2 patients had blood pressures that were lower than with either drug alone, and 2 patients had no appreciable change in blood pressure.[1] Two cases of hypertension involving clonidine with **propranolol** have also been described,[2] and in some studies the concurrent use of clonidine and **nadolol**[3] or **propranolol**[4] has been no more effective than either drug alone.

(b) Bradycardia and hypotension

A man anaesthetised with thiopental and diamorphine, with oxygen, nitrous oxide, enflurane and atracurium, was given clonidine 50 micrograms to control hypertension. After 15 minutes he became tachycardic with a heart rate of up to 170 bpm. **Esmolol** 75 mg was given by slow infusion, whereupon his heart rate fell to 20 bpm. He responded to atropine 1.2 mg, adrenaline (epinephrine) 1 mg and calcium chloride 10 mL with a stable heart rate of 110 bpm.[5] In a clinical study, 32 patients were given **esmolol** during surgery: one patient developed marked hypotension and bradycardia, which responded to ephedrine 10 mg. It was noted that this patient had been receiving clonidine.[6] A subset of 5 patients involved in a study investigating the use of clonidine with **propranolol** and minoxidil had a reduction in blood pressure when clonidine (200 to 400 micrograms daily) was added. After the discontinuation of **propranolol**, blood pressure returned to that seen before clonidine was added, indicating that **propranolol** and clonidine have additive hypotensive actions.[7] Similarly, **atenolol** and clonidine have been found to have additive hypotensive effects.[3,4]

(c) Peripheral vascular disorders

The manufacturer of clonidine notes that the concurrent use of a beta blocker may possibly potentiate peripheral vascular disorders.[8] This is based on the known pharmacology of the drugs,[9] and no specific cases appear to have been reported.

(d) Rebound hypertension

A woman with a blood pressure of 180/140 mmHg was taking clonidine and **timolol**. When the clonidine was stopped in error, she developed a violent throbbing headache and became progressively confused, ataxic and semicomatose, and had a grand mal convulsion. Her blood pressure was found to have risen to over 300/185 mmHg.[10]

A number of other reports describe similar cases of hypertensive rebound (a sudden and serious rise in blood pressure) within 24 to 72 hours of stopping the clonidine, apparently worsened by the presence of **propranolol**.[11-15] The symptoms resemble those of phaeochromocytoma, and include tremor, apprehension, flushing, nausea, vomiting, severe headache, and a serious rise in blood pressure. One patient died from a cerebellar haemorrhage.[14]

Mechanism

The normal additive hypotensive effects of these drugs result from their actions at different but complementary sites in the cardiovascular system. Just why antagonism sometimes occurs is unexplained. The hypertensive rebound following clonidine withdrawal is thought to be due to an increase in the levels of circulating catecholamines. With the beta (vasodilator) effects blocked by a beta blocker, the alpha (vasoconstrictor) effects of the catecholamines are unopposed and the hypertension is further exaggerated.

Importance and management

The interaction whereby the beta blockers seriously worsen the rebound hypertension following clonidine withdrawal is well established. This adverse effect can be controlled by stopping the beta blocker several days before starting a gradual withdrawal of clonidine.[16] A successful alternative is to replace the clonidine and the beta blocker with labetalol,[17] which is both an alpha and a beta blocker: The blood catecholamine levels still rise markedly (20-fold) and the patient may experience tremor, nausea, apprehension and palpitations, but no serious blood pressure rise or headaches appear to occur.[17] The dose of labetalol will need to be titrated to effect, with regular checks on the blood pressure over 2 to 3 days. If a hypertensive episode develops, it can be managed with an alpha-blocking drug such as phentolamine.[11] Diazoxide is also said to be effective.[10,14] Reintroduction of oral or intravenous clonidine should also stabilise the situation. It is clearly important to emphasise to patients taking clonidine and beta blockers that they should not stop taking these drugs without seeking medical advice.

Clonidine and atenolol (a cardio-selective beta blocker) have additive hypotensive effects and smaller doses of clonidine can be given, which decreases its troublesome adverse effects (sedation and dry mouth). In contrast, limited evidence suggests that if clonidine is given with propranolol or nadolol (non-selective beta blockers) the blood pressure reductions were the same as with either drug alone, although this has not been confirmed in other studies. The weight of evidence suggests that paradoxical hypertension is rare.[1,2]

There appears to be no evidence regarding this interaction with **moxonidine**, which is related to clonidine. Moxonidine is reported to have less affinity for central alpha-receptors than clonidine and therefore would be expected to present less of a risk. Furthermore, no such rebound hypertension has been seen when moxonidine is withdrawn. However, to be on the safe side the manufacturers advise that any beta blocker should be stopped first, followed by the moxonidine a few days later.[18,19]

1. Saarimaa H. Combination of clonidine and sotalol in hypertension. *BMJ* (1976) i, 810.
2. Warren SE, Ebert E, Swerdlin A-H, Steinberg SM, Stone R. Clonidine and propranolol paradoxical hypertension. *Arch Intern Med* (1979) 139, 253.
3. Fogari R, Corradi L. Interaction of clonidine and beta blocking agents in the treatment of essential hypertension. In 'Low dose oral and transdermal therapy of hypertension' (Proceedings of Conference 1984), edited by Weber MA, Drayer JIM, Kolloch R. Springer-Verlag, 1985, p. 118–21.
4. Lilja M, Jounela AJ, Juustila H, Mattila MJ. Interaction of clonidine and β-blockers. *Acta Med Scand* (1980) 207, 173–6.
5. Perks D, Fisher GC. Esmolol and clonidine — a possible interaction. *Anaesthesia* (1992) 47, 533–4.
6. Kanitz DD, Ebert TJ, Kampine JP. Intraoperative use of bolus doses of esmolol to treat tachycardia. *J Clin Anesth* (1990) 2, 238–42.
7. Pettinger WA, Mitchell HC, Güllner H-G. Clonidine and the vasodilating beta blocker antihypertensive drug interaction. *Clin Pharmacol Ther* (1977) 22, 164–71.
8. Catapres Tablets (Clonidine hydrochloride). Boehringer Ingelheim Ltd. UK Summary of product characteristics, July 2009.
9. Boehringer Ingelheim. Personal communication, 29 March 2005.
10. Bailey RR, Neale TJ. Rapid clonidine withdrawal with blood pressure overshoot exaggerated by beta-blockade. *BMJ* (1976) i, 942–3.
11. Bruce DL, Croley TF, Lee JS. Preoperative clonidine withdrawal syndrome. *Anesthesiology* (1979) 51, 90–2.
12. Cairns SA, Marshall AJ. Clonidine withdrawal. *Lancet* (1976) i, 368.
13. Strauss FG, Franklin SS, Lewin AJ, Maxwell MH. Withdrawal of antihypertensive therapy. Hypertensive crisis in renovascular hypertension. *JAMA* (1977) 238, 1734–6.
14. Vernon C, Sakula A. Fatal rebound hypertension after abrupt withdrawal of clonidine and propranolol. *Br J Clin Pract* (1979) 33, 112,121.
15. Reid JL, Wing LMH, Dargie HJ, Hamilton CA, Davies DS, Dollery CT. Clonidine withdrawal in hypertension. Changes in blood pressure and plasma and urinary noradrenaline. *Lancet* (1977) i, 1171–4.
16. Harris AL. Clonidine withdrawal and blockade. *Lancet* (1976) i, 596.
17. Rosenthal T, Rabinowitz B, Boichis H, Elazar E, Brauner A, Neufeld HN. Use of labetalol in hypertensive patients during discontinuation of clonidine therapy. *Eur J Clin Pharmacol* (1981) 20, 237–40.

18. Physiotens (Moxonidine). Solvay Healthcare Ltd. UK Summary of product characteristics, June 2009.
19. Solvay Healthcare. Personal communication, September 1996.

Clonidine + Bupropion

In a study in 8 healthy subjects, bupropion 100 mg three times daily for 9 days did not reduce the hypotensive effect of a single 300-microgram dose of oral clonidine.[1]

1. Cubeddu LX, Cloutier G, Gross K, Grippo R, Tanner L, Lerea L, Shakarjian M, Knowlton G, Harden TK, Arendshorst W and Rogers JF. Bupropion does not antagonize cardiovascular actions of clonidine in normal subjects and spontaneously hypertensive rats. *Clin Pharmacol Ther* (1984) 35, 576–84.

Clonidine and related drugs + CNS depressants

Increased sedation may occur if alcohol or other CNS depressants are taken with clonidine, moxonidine, guanfacine or guanabenz.

Clinical evidence, mechanism, importance and management

Sedation is a common adverse effect of clonidine and other central alpha-adrenoceptor agonists such as **moxonidine**, **guanfacine** and **guanabenz**, particularly during the initial stages of treatment.[1-4] However, the effects of this in the presence of other CNS depressants does not appear to have been widely studied.

In one study with **moxonidine**, the cognitive function of 24 healthy subjects was not impaired by moxonidine 400 micrograms daily, but the presence of moxonidine was found to increase the cognitive impairment caused by **lorazepam** 1 mg daily.[1] For this reason the manufacturer warns that the sedative effects of the benzodiazepines may possibly be enhanced by moxonidine,[2] and this also seems possible with the related drugs **clonidine**, **guanfacine** and **guanabenz**. Patients starting treatment with these drugs should be warned that their tolerance to **alcohol** and other CNS depressant drugs may be diminished. Patients who are affected should not drive or operate machinery.

1. Catapres Tablets (Clonidine hydrochloride). Boehringer Ingelheim Ltd. UK Summary of product characteristics, July 2009.
2. Guanfacine hydrochloride. Watson Laboratories, Inc. US Prescribing information, October 2007.
3. Catapres Tablets (Clonidine hydrochloride). Boehringer Ingelheim Pharmaceuticals, Inc. US Prescribing information, January 2010.
4. Physiotens (Moxonidine). Solvay Healthcare Ltd. UK Summary of product characteristics, June 2009.

Clonidine + Hormonal contraceptives

The sedative effects of intravenous clonidine were increased in one study by an oral combined hormonal contraceptive.

Clinical evidence, mechanism, importance and management

A study[1] in a group of 10 women found that the sedative effects of a single 1.3-microgram/kg dose of intravenous clonidine were increased by an oral combined hormonal contraceptive (**ethinylestradiol** 30 micrograms with **levonorgestrel** 150 or 250 micrograms). The clinical importance of this is uncertain. Consider also 'Antihypertensives + Hormonal contraceptives or HRT', p.1050.

1. Chalmers JS, Fulli-Lemaire I, Cowen PJ. Effects of the contraceptive pill on sedative responses to clonidine and apomorphine in normal women. *Psychol Med* (1985) 15, 363–7.

Clonidine + Naloxone

Naloxone does not appear to alter the blood pressure lowering effects of clonidine, or its effects on heart rate.

Clinical evidence, mechanism, importance and management

A study in *animals* suggesting naloxone blocked the antihypertensive effects of clonidine prompted a placebo-controlled study in 6 patients with hypertension. Each patient received a single oral dose of clonidine 300 micrograms during an infusion of either naloxone 6 micrograms/kg per hour or placebo for 8 hours. Supine and standing blood pressure and heart rate were monitored. Naloxone was not found to affect the hypotensive or bradycardic effect of clonidine.[1]

1. Rogers JF, Cubeddu LX. Naloxone does not antagonize the antihypertensive effect of clonidine in essential hypertension. *Clin Pharmacol Ther* (1983) 34, 68–73.

Clonidine + Prazosin

There is some evidence to suggest that prazosin can reduce the antihypertensive effects of clonidine, whereas some other evidence suggests that this does not occur.

Clinical evidence, mechanism, importance and management

In 18 patients with essential hypertension, the hypotensive effect of a 150-microgram intravenous dose of clonidine was reduced by 47% by prazosin (mean dose 11 mg three times daily for 4 days).[1] A later crossover study by the same research group in 17 patients with essential hypertension (mean blood pressures 170/103 mmHg) found that clonidine 300 micrograms daily for 4 days reduced the mean blood pressure by 38/18 mmHg and prazosin 6 mg daily for 3 days reduced the mean blood pressure by 10/4 mmHg. However, when prazosin and clonidine were given together the mean blood pressure was only reduced to a similar extent as prazosin alone (12/6 mmHg).[2] Similarly, some earlier studies had suggested that the concurrent use of clonidine and prazosin produced only a modest,[3] or no additive antihypertensive effect.[4] Conversely, other studies using the combination have not reported a reduced antihypertensive effect.[5,6] In the presence of prazosin the rebound hypertension following clonidine withdrawal was said to be moderate (a rise from 145/85 mmHg to 169/104 mmHg).[6]

Clonidine is an $alpha_2$ agonist, whereas prazosin is an $alpha_1$ blocker. Consequently, it has been postulated that the drugs may be partially antagonistic when given together, and the authors of the first study cite a number of *animal* studies to support this.[1] Although not conclusive, it seems possible that concurrent use may not always be favourable. Therefore it would seem prudent to monitor the effects of concurrent use on blood pressure.

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2. Farsang C, Varga K, Kapocsi J. Prazosin-clonidine and prazosin-guanfacine interactions in hypertension. *Pharmacol Res Commun* (1988) 20 (Suppl 1), 85–6.
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Clonidine + Rifampicin (Rifampin)

Rifampicin does not interact with clonidine.

Clinical evidence, mechanism, importance and management

In 6 subjects taking clonidine 200 micrograms twice daily the use of rifampicin 600 mg twice daily for 7 days did not affect the elimination kinetics of clonidine, or its effects on pulse rate or blood pressure.[1] No special precautions would seem necessary on concurrent use.

1. Affrime MB, Lowenthal DT, Rufo M. Failure of rifampin to induce the metabolism of clonidine in normal volunteers. *Drug Intell Clin Pharm* (1981) 15, 964–6.

Clonidine and related drugs + Tricyclic and related antidepressants

The tricyclic antidepressants reduce or abolish the antihypertensive effects of clonidine and a case report describes a hypertensive crisis as a result of this interaction. Moxonidine is expected to interact similarly. The tetracyclics, maprotiline and mianserin do

not appear to alter the antihypertensive effects of clonidine, although a case report describes a hypertensive crisis in a patient taking the related drug mirtazapine with clonidine.

Clinical evidence

(a) Tetracyclic and related antidepressants

In a study in 8 healthy subjects, **maprotiline** 100 mg in four divided doses over 22 hours did not alter the effect of a single 300-microgram dose of clonidine on blood pressure or heart rate.[1] **Mianserin** 20 mg three times daily for 2 weeks had no effect on the control of blood pressure in 5 patients receiving clonidine.[2,3] Similarly, in healthy subjects, **mianserin** pretreatment did not significantly alter the hypotensive action of a single 300-microgram dose of clonidine.[2,4] In contrast, an isolated report describes hypertensive urgency in a man with end-stage renal disease taking clonidine, metoprolol and losartan when **mirtazapine** (a **mianserin** analogue) was added for depression.[5]

(b) Trazodone

A 12-year-old boy taking clonidine 100 micrograms three times daily and dexamfetamine 15 mg twice daily was given trazodone 50 mg at bedtime. After a few weeks his trazodone dose was increased to 100 mg at bedtime. Within 45 minutes of taking his first increased dose he had a hypotensive episode with bradycardia and sedation. The trazodone dose was reduced back to 50 mg, but the drug was discontinued 2 weeks later because of low blood pressure.[6]

(c) Tricyclic antidepressants

Desipramine 75 mg daily for 2 weeks caused the lying and standing blood pressures of 4 out of 5 hypertensive patients taking clonidine 600 to 1800 micrograms daily (with chlortalidone or hydrochlorothiazide) to rise by 22/15 mmHg and 12/10 mmHg respectively.[7] This interaction has been seen in other patients taking **clomipramine**, **desipramine** and **imipramine**.[8-11] In one study, the antihypertensive effects of a single intravenous dose of clonidine were reduced by about 50% in 6 patients given **desipramine** for 3 weeks.[12] Similarly, in 8 healthy subjects, the blood pressure lowering effect of a single 300-microgram dose of clonidine was reduced by 40 to 50% when it was given on day 9 of treatment with **imipramine** 25 mg three times daily.[13] An elderly woman taking clonidine 200 micrograms daily developed severe frontal headache, dizziness, chest and neck pain and tachycardia of 120 bpm with hypertension (230/124 to 130 mmHg) on the second day of taking **imipramine** 50 mg for incontinence.[14]

A case report describes a 73-year-old woman, who developed rebound hypertension and tachycardia on the withdrawal of clonidine. This may have been made worse by the presence of **amitriptyline**.[15]

A man with severe pain, well controlled with **amitriptyline**, sodium valproate and intrathecal boluses of diamorphine, experienced severe pain within 5 minutes of an intrathecal test dose of clonidine 75 micrograms. It was considered that an interaction between the tricyclic and the clonidine may have been responsible.[16]

Mechanism

Not understood. One idea is that the tricyclics desensitise or block central alpha$_2$-receptors.[17] This would explain the interaction with mirtazapine (a mianserin analogue), which also has alpha-blocking properties.[5] However, mianserin (also an alpha blocker) did not interact.[2] Another idea is that tricyclics block noradrenaline uptake. However, maprotiline, which also blocks noradrenaline uptake, did not interact.[1] Trazodone, which also has alpha-blocking properties was predicted to inhibit the effect of clonidine based on a study in *animals* where it antagonised the hypotensive effect of clonidine when given centrally (note this effect was not seen when it was given intravenously).[18] The case of hypotension described could be explained by the hypotensive effect of trazodone alone, but may have been compounded by the hypotensive effect of clonidine.

Importance and management

The interaction between clonidine and the tricyclics is established and clinically important. The incidence is uncertain but an interaction is not seen in all patients.[7] Avoid concurrent use unless the effects can be monitored. Increasing the dose of clonidine may possibly be effective. The clonidine dose was apparently successfully titrated in 10 out of 11 hypertensive patients already taking amitriptyline or imipramine.[19] Only clomipramine, desipramine and imipramine have been implicated so far, but other tricyclics would be expected to behave similarly (amitriptyline, **nortriptyline** and **protriptyline** have been shown to interact in *animals*[20]). The tetracyclic antidepressants maprotiline and mianserin do not generally appear to interact with clonidine. The isolated case of hypotension with trazodone and the isolated case of severe pain with amitriptyline and clonidine are of unknown general importance.

There appears to be no evidence regarding an interaction between **moxonidine** and the tricyclics. The manufacturer of moxonidine advises avoiding tricyclic antidepressants, because of the lack of clinical experience of concurrent use.[21] Presumably, this is because moxonidine is related to clonidine. It may therefore be prudent to follow the same precautions described for clonidine.

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4. Elliott HL, McLean K, Sumner DJ, Reid JL. Pharmacodynamic studies on mianserin and its interaction with clonidine. *Eur J Clin Pharmacol* (1981) 21, 97–102.
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9. Andrejak M, Fournier A, Hardin J-M, Coevoet B, Lambrey G, De Fremont J-F, Quichaud J. Suppression de l'effet antihypertenseur de la clonidine par la prise simultanée d'un antidépresseur tricyclique. *Nouv Presse Med* (1977) 6, 2603.
10. Lacomblez L, Warot D, Bouche P, Derouesné C. Suppression de l'effet antihypertenseur de la clonidine par la clomipramine. *Rev Med Interne* (1988) 9, 291–3.
11. Manchon ND, Bercoff E, Lemarchand P, Chassagne P, Senant J, Bourreille J. Fréquence et gravité des interactions médicamenteuses dans une population âgée: étude prospective concernant 639 malades. *Rev Med Interne* (1989) 10, 521–5.
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13. Cubeddu LX, Cloutier G, Gross K, Grippo PA-CR, Tanner L, Lerea L, Shakarjian M, Knowlton G, Harden TK, Arendshorst W, Rogers JF. Bupropion does not antagonize cardiovascular actions of clonidine in normal subjects and spontaneously hypertensive rats. *Clin Pharmacol Ther* (1984) 35, 576–84.
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15. Stiff JL, Harris DB. Clonidine withdrawal complicated by amitriptyline therapy. *Anesthesiology* (1983) 59, 73–4.
16. Hardy PAJ, Wells JCD. Pain after spinal intrathecal clonidine. An adverse interaction with tricyclic antidepressants? *Anaesthesia* (1988) 43, 1026–7.
17. van Spanning HW, van Zwieten PA. The interference of tricyclic antidepressants with the central hypotensive effect of clonidine. *Eur J Pharmacol* (1973) 24, 402–4.
18. van Zwieten PA. Inhibition of the central hypotensive effect of clonidine by trazodone, a novel antidepressant. *Pharmacology* (1977) 15, 331–6.
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20. van Zwieten PA. Interaction between centrally active hypotensive drugs and tricyclic antidepressants. *Arch Int Pharmacodyn Ther* (1975) 214, 12–30.
21. Physiotens (Moxonidine). Solvay Healthcare Ltd. UK Summary of product characteristics, June 2009.

Diazoxide + Hydralazine

Severe hypotension, in some cases fatal, has followed the use of high doses of intravenous diazoxide, given before or after hydralazine.

Clinical evidence

A previously normotensive 25-year-old woman had a blood pressure of 250/150 mmHg during the 34th week of pregnancy, which did not respond to intravenous magnesium sulfate 4 g. Her blood pressure fell transiently to 170/120 mmHg when she was given hydralazine 15 mg intravenously. One hour later intravenous diazoxide 5 mg/kg resulted in a blood pressure fall to 60/0 mmHg. Despite large doses of noradrenaline (norepinephrine), the hypotension persisted and the woman died.[1]

Other cases of severe hypotension in patients given high doses of intravenous diazoxide and intravenous or oral hydralazine are described in this[1] and other studies and reports.[2-4] In some instances the patients had also received other antihypertensives such as methyldopa[1] or reserpine.[1,4] At least three of the cases had a fatal outcome.[4]

Mechanism

Not fully understood. The (vasodilatory) hypotensive effects of the two drugs are additive and it would seem that in some instances the normal compensatory responses of the cardiovascular system to maintain an ade-

quate blood pressure reach their limit. This can occur with intravenous diazoxide alone.[2]

Importance and management

The concurrent use of intravenous diazoxide and hydralazine should be undertaken extremely cautiously with thorough monitoring. Note that the doses of diazoxide used in the above reports were frequently higher than those currently recommended for hypertensive crises.[5] In addition, there are now many more options available for the treatment of very severe hypertension, and the BNF in the UK considers intravenous diazoxide to be one of the less suitable choices.[5] Moreover, diazoxide was frequently associated with clinically important hypotension when used in pregnancy, and is not considered a good choice in this situation.[6]

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2. Kumar GK, Dastoor FC, Robayo JR, Razzaque MA. Side effects of diazoxide. *JAMA* (1976) 235, 275–6.
3. Tansey WA, Williams EG, Landesman RH and Schwarz MJ. Diazoxide. *JAMA* (1973) 225, 749.
4. Davey M, Moodley J, Soutter P. Adverse effects of a combination of diazoxide and hydrallazine therapy. *S Afr Med J* (1981) 59, 496–7.
5. British National Formulary. 58th ed. London: BMJ Publishing Group Ltd and RPS Publishing; 2009. p. 96.
6. Duley L, Henderson-Smart DJ, Meher S. Drugs for treatment of very high blood pressure during pregnancy. Available in the Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 12/09/06).

Diazoxide + Other drugs with hyperglycaemic activity

The risk of hyperglycaemia is increased if diazoxide is given with other drugs with hyperglycaemic activity (e.g. the thiazides, chlorpromazine, corticosteroids, combined hormonal contraceptives).

Clinical evidence, mechanism, importance and management

An isolated report[1] describes a child receiving long-term treatment for hypoglycaemia with diazoxide 8 mg/kg daily in divided doses and **bendroflumethiazide** 1.25 mg daily, who developed a diabetic pre-coma and severe hyperglycaemia after taking a single 30-mg dose of **chlorpromazine**. The reason for this reaction is not understood but one idea is that all three drugs had additive hyperglycaemic effects. Enhanced hyperglycaemia has been seen in other patients given diazoxide with **trichlormethiazide**.[2] Caution is clearly needed to ensure that the hyperglycaemic effects do not become excessive. The manufacturers of diazoxide also mention that the risk of hyperglycaemia may be increased by **corticosteroids** or oestrogen-progestogen combinations (e.g. **combined hormonal contraceptives**).[3]

1. Aynsley-Green A, Illig R. Enhancement by chlorpromazine of hyperglycaemic action of diazoxide. *Lancet* (1975) ii, 658–9.
2. Seltzer HS, Allen EW. Hyperglycemia and inhibition of insulin secretion during administration of diazoxide and trichlormethiazide in man. *Diabetes* (1969) 18, 19–28.
3. Eudemine Tablets (Diazoxide). UCB Pharma Ltd. UK Summary of product characteristics, March 2009.

Endothelin receptor antagonists + Ketoconazole and other CYP3A4 inhibitors

Ketoconazole increases bosentan levels by twofold: fluconazole is predicted to have a greater effect. Ketoconazole modestly increases ambrisentan levels. Fluconazole and ketoconazole do not interact with sitaxentan.

Clinical evidence, mechanism, importance and management

(a) Ambrisentan

A study in 16 healthy subjects found that **ketoconazole** 400 mg daily for 4 days increased the AUC and maximum concentration of a single 10-mg dose of ambrisentan by 35% and 20%, respectively. These modest increases are not expected to be clinically relevant, therefore no ambrisentan dose adjustment is required if **ketoconazole** is also given.[1] It seems unlikely that other azoles will interact with ambrisentan, but this does not appear to have been studied.

(b) Bosentan

In a randomised crossover study, 10 healthy subjects were given bosentan 62.5 mg twice daily for 11 doses, either alone, or with **ketoconazole** 200 mg daily. The maximum plasma level of bosentan was increased 2.1-fold, and the AUC was increased 2.3-fold (range 1.4- to 4-fold) by **ketoconazole**. This interaction probably occurs because bosentan is metabolised by the cytochrome P450 isoenzyme CYP3A4, of which ketoconazole is a known, potent inhibitor.[2]

Other potent CYP3A4 inhibitors (e.g. **itraconazole**) are expected to interact similarly to **ketoconazole**.[3] However, because **fluconazole** (a moderate inhibitor of CYP3A4) also inhibits CYP2C9, another enzyme involved in the metabolism of bosentan, it is anticipated that it could cause even larger increases in bosentan levels.

The clinical significance of raised the bosentan levels is unclear. Bosentan has been tolerated in single-doses of up to 2.4 g in healthy subjects, although elevations in liver transaminases have been seen during long-term, high-dose treatment.[2] Even so, the manufacturers do not recommend the combination of **fluconazole** with bosentan because of the risk of liver toxicity.[3] Similarly using **ketoconazole** or **itraconazole** in combination with a CYP2C9 inhibitor (the manufacturers name **voriconazole**) and bosentan is also not recommended.[3] Other drugs that inhibit CYP2C9 are listed in 'Table 1.3', (p.6).

Until more is known, it may be prudent to carefully monitor liver function when the combination is used. The manufacturers suggest that no adjustment of the bosentan dose is likely to be required when it is used with **ketoconazole**.[3]

(c) Sitaxentan

The concurrent use of **fluconazole** and sitaxentan did not affect the pharmacokinetics of either drug. Similarly, the concurrent use of **ketoconazole** and sitaxentan did not affect the pharmacokinetics of either drug.[4] No dose adjustment therefore seems necessary on concurrent use.

1. Richards DB, Walker GA, Mandagere A, Magee MH, Henderson LS. Effect of ketoconazole on the pharmacokinetic profile of ambrisentan. J Clin Pharmacol (2009) 49, 719–24.
2. van Giersbergen PLM, Halabi A, Dingemanse J. Single- and multiple-dose pharmacokinetics of bosentan and its interaction with ketoconazole. *Br J Clin Pharmacol* (2002) 53, 589–95.
3. Tracleer (Bosentan monohydrate). Actelion Pharmaceuticals UK Ltd. UK Summary of product characteristics, July 2009.
4. Thelin (Sitaxentan sodium). Encysive (UK) Ltd. UK Summary of product characteristics, April 2009.

Endothelin receptor antagonists + Miscellaneous

The pharmacokinetics of bosentan were not significantly altered when it was taken with losartan or nimodipine. Sitaxentan does not affect nifedipine pharmacokinetics. Omeprazole does not alter the pharmacokinetics of ambrisentan, and sitaxentan does not alter the pharmacokinetics of omeprazole.

Clinical evidence, mechanism, importance and management

(a) Losartan

A study in healthy subjects found that the pharmacokinetics of **bosentan** 125 mg twice daily were unaffected by the concurrent use of losartan 100 mg once daily for 9 doses.[1]

(b) CYP2C19 substrates

1. Ambrisentan. Ambrisentan is metabolised, in part, by the cytochrome P450 isoenzyme CYP2C19, and therefore caution is advised if potent CYP2C19 inhibitors are also given, presumably because of the possibility that ambrisentan levels may be raised. However, the US manufacturer notes that concurrent use with **omeprazole** (a CYP2C19 substrate and inhibitor) does not have clinically significant effects on ambrisentan pharmacokinetics,[2] and therefore a clinically relevant interaction seems unlikely.

2. Sitaxentan. The manufacturers of sitaxentan note that it is an inhibitor of the cytochrome P450 isoenzyme CYP2C19, and it may therefore decrease the levels of other drugs metabolised by this isoenzyme.[3] However, in one

study, **omeprazole** (a CYP2C19 substrate and inhibitor) was found to increase the AUC of sitaxentan by 30%, which is not considered to be clinically significant.[3]

(c) Nifedipine

Sitaxentan does not alter the clearance of nifedipine (given as three 10 mg doses).[3,4] The manufacturer states that, because the dose of nifedipine was small, a significant effect with larger doses cannot be ruled out.[3] However, note that **sitaxentan** did not affect the pharmacokinetics of other CYP3A4 substrates such as sildenafil (see 'Phosphodiesterase type-5 inhibitors + Endothelin receptor antagonists', p.1535) to a clinically significant extent, and so an interaction at any nifedipine dose seems unlikely.

(d) Nimodipine

In a study of 6 patients with subarachnoid haemorrhage, the pharmacokinetics of a single 500-mg intravenous dose of **bosentan** were not affected by the concurrent use of nimodipine (dose not specified).[5]

1. van Giersbergen PLM, Clozel M, Bodin F. A drug interaction study between bosentan and ketoconazole and losartan. *Clin Pharmacol Ther* (2001) 69, P67
2. Letairis (Ambrisentan). Gilead Sciences, Inc. US Prescribing information, August 2009.
3. Thelin (Sitaxentan sodium). Encysive (UK) Ltd. UK Summary of product characteristics, April 2009.
4. Thelin. European Public Assessment Report: Scientific Discussion. Available at: http://www.emea.europa.eu/humandocs/PDFs/EPAR/thelin/H-679-en6.pdf (accessed 01/02/10).
5. Dingemanse J, van Giersbergen PLM. Clinical pharmacology of bosentan, a dual endothelin receptor antagonist. *Clin Pharmacokinet* (2004) 43, 1089–1115.

Endothelin receptor antagonists + Rifampicin (Rifampin)

Rifampicin may cause transient increases in trough levels of bosentan, but at steady-state plasma levels of bosentan are decreased. Rifampicin may affect the pharmacokinetics of ambrisentan.

Clinical evidence, mechanism, importance and management

(a) Ambrisentan

The drug interactions of ambrisentan have not been studied in detail *in vivo*, and are largely based on *in vitro* predictions. Ambrisentan is a substrate of a number of drug transporters. Therefore the US manufacturer advises caution in patients also taking drugs that affect transporter proteins, such as **rifampicin**, which is known to induce multiple hepatic enzymes and P-glycoprotein.[1] Until more is known, monitor the outcome of concurrent use closely.

(b) Bosentan

In a crossover study in 9 healthy subjects, bosentan 125 mg twice daily was given for 6 and a half days, either alone or with rifampicin 600 mg daily (which was given with the evening dose of bosentan for 6 days). Rifampicin decreased the AUC and peak plasma levels of bosentan by 58% and 53%, respectively. Trough levels of bosentan were increased up to 15-fold on day 2 of concurrent use, but fell with subsequent treatment and by day 4 were lower than those with bosentan alone. The initial increase in bosentan levels was possibly due to the inhibition, by rifampicin, of the hepatic uptake of bosentan by organic ion-transporting polypeptides (OATP1B1 and OATP1B3).[2,3] The decrease in bosentan levels at steady-state were probably due to its increased metabolism in the presence of rifampicin, due to induction of the cytochrome P450 isoenzymes CYP3A4 and CYP2C9. The continued decrease in bosentan levels to below those of bosentan alone may be explained by autoinduction of its own metabolism.[2] The UK manufacturer warns that the risk of liver dysfunction with bosentan may be increased when it is given with inhibitors of the bile salt export pump such as rifampicin, and therefore suggest that concurrent use is not recommended.[4]

1. Letairis (Ambrisentan). Gilead Sciences, Inc. US Prescribing information, August 2009.
2. van Giersbergen PLM, Treiber A, Schneiter R, Dietrich H, Dingemanse J. Inhibitory and inductive effects of rifampin on the pharmacokinetics of bosentan in healthy subjects. *Clin Pharmacol Ther* (2007) 81, 414–9.
3. Treiber A, Schneiter R, Häusler S, Stieger B. Bosentan is a substrate of human OATP1B1 and OATP1B3: inhibition of hepatic uptake as the common mechanism of its interactions with cyclosporin A, rifampicin, and sildenafil. *Drug Metab Dispos* (2007) 35, 1400–7.
4. Tracleer (Bosentan monohydrate). Actelion Pharmaceuticals UK Ltd. UK Summary of product characteristics, July 2009.

Endothelin receptor antagonists; Bosentan + Food

In a study in 16 healthy subjects the pharmacokinetics of bosentan were not significantly changed by the presence of food. Bosentan may therefore be given without regard to meal times.[1]

1. Dingemanse J, Bodin F, Weidekamm E, Kutz K, van Giersbergen P. Influence of food intake and formulation on the pharmacokinetics and metabolism of bosentan, a dual endothelin receptor antagonist. *J Clin Pharmacol* (2002) 42, 283–9.

Glyceryl trinitrate (Nitroglycerin) + Antimuscarinics

Dry mouth associated with the use of antimuscarinic drugs may reduce the dissolution and thus, the effectiveness of sublingual glyceryl trinitrate tablets.

Clinical evidence, mechanism, importance and management

There is a report of a patient taking **imipramine** who found that the effects of glyceryl trinitrate sublingual tablets for the relief of angina were delayed. The patient had a dry mouth associated with the antimuscarinic adverse effects of **imipramine** and the problem was resolved when imipramine was discontinued.[1] Another brief report notes that the dissolution of glyceryl trinitrate sublingual tablets following **atropine** may take over 5 minutes.[2] Drugs with antimuscarinic effects, such as the **tricyclic antidepressants** and **disopyramide**, depress salivation and many patients complain of having a dry mouth. In a study in patients with angina of effort, both the sublingual and oral spray formulations were equally effective if the oral mucosa was moist (7 patients), but the oral spray was found to be better than sublingual tablets in patients with dry mouth (10 patients).[3] Sublingual glyceryl trinitrate tablets will dissolve less readily under the tongue in patients with dry mouth, thereby reducing glyceryl trinitrate absorption and effects. 'Table 18.1', (p.784), and 'Table 18.2', (p.786) list drugs that have antimuscarinic effects. A possible alternative is to use a glyceryl trinitrate spray in patients who suffer from dry mouth.

1. Robbins LJ. Dry mouth and delayed dissolution of sublingual nitroglycerin. *N Engl J Med* (1983) 309, 985.
2. Kimchi A. Dry mouth and delayed dissolution of nitroglycerin. *N Engl J Med* (1984) 310, 1122–3.
3. Sato H, Koretsune Y, Taniguchi T, Fukui S, Shimazu T, Sugii M, Matsuyama T, Karita M, Hori M. Studies on the response of nitroglycerin oral spray compared with sublingual tablets for angina pectoris patients with dry mouth. A multicenter trial. *Arzneimittelforschung* (1997) 47, 128–31.

Glyceryl trinitrate (Nitroglycerin) + Aspirin

Some limited evidence suggests that analgesic doses of aspirin can increase the levels of glyceryl trinitrate given sublingually, possibly resulting in an increase in its adverse effects such as hypotension and headache. Paradoxically, long-term aspirin use appears to reduce the effects of intravenous glyceryl trinitrate used for vasodilatation in patients following coronary artery bypass surgery.

Clinical evidence

(a) Intravenous effects reduced

A study in patients following coronary artery bypass surgery found that those who had been taking aspirin 150 or 300 mg daily (33 patients) for at least 3 months, needed more glyceryl trinitrate to control blood pressure during the recovery period than those who had not taken aspirin (33 patients). To achieve the blood pressure criteria required, the aspirin-group needed an 8.2 micrograms/minute infusion of glyceryl trinitrate. The dose remained relatively high at 3.3 micrograms/minute even after 8 hours, whereas the non-aspirin group needed only 5.5 micrograms/minute, which was reduced to 1.9 micrograms/minute after 8 hours.[1]

(b) Sublingual effects increased

When aspirin 1 g was given to 7 healthy subjects followed one hour later by 800 micrograms of glyceryl trinitrate sublingual spray, the mean plasma glyceryl trinitrate levels 30 minutes after administration were

increased by 54% (from 0.24 to 0.37 nanograms/mL). The haemodynamic effects of the glyceryl trinitrate (including heart rate and reduced diastolic blood pressure) were enhanced. Some changes were seen when aspirin 500 mg was given every 2 days (described as an anti-aggregant dose) but the effects were not statistically significant.[2,3]

(c) Sublingual effects unchanged

A study in 40 healthy subjects who were given 650 mg aspirin or placebo, followed after one to 2 hours by sublingual glyceryl trinitrate 432 micrograms found no significant alterations in the peak haemodynamic response or in the area under the time-pressure and time-pulse curves. There was a transient pressor response, which occurred one minute after glyceryl trinitrate was given: this was blunted by aspirin. Taken alone, this change was significant, but when the overall pattern of changes during the 30 minute study was considered, the differences were not significant.[4]

Mechanism

Not understood. Prostaglandin-synthetase inhibitors such as aspirin can, to some extent, suppress the vasodilator effects of glyceryl trinitrate by blocking prostaglandin release. However, it seems that a much greater pharmacodynamic interaction also occurs, in which aspirin reduces the flow of blood through the liver, so that the metabolism of the glyceryl trinitrate is reduced, thus increasing its levels, and therefore its effects.

Importance and management

A confusing and unexplained situation. It seems possible that patients taking sublingual glyceryl trinitrate may experience an exaggeration of its adverse effects such as hypotension and headaches if they are taking analgesic doses of aspirin. Also be aware that long-term aspirin use may reduce the vasodilatory effects of intravenous glyceryl trinitrate. The antiplatelet effects of aspirin and glyceryl trinitrate appear to be additive.[5]

1. Key BJ, Keen M, Wilkes MP. Reduced responsiveness to nitro-vasodilators following prolonged low dose aspirin administration in man. *Br J Clin Pharmacol* (1992) 34, 453P–454P.
2. Weber S, Rey E, Pipeau C, Lutfalla G, Richard M-O, Daoud-El-Assaf H, Olive G, Degeorges M. Influence of aspirin on the hemodynamic effects of sublingual nitroglycerin. *J Cardiovasc Pharmacol* (1983) 5, 874–7.
3. Rey E, El-Assaf HD, Richard MO, Weber S, Bourdon A, Picard G, Olive G. Pharmacological interaction between nitroglycerin and aspirin after acute and chronic aspirin treatment of healthy subjects. *Eur J Clin Pharmacol* (1983) 25, 779–82.
4. Levin RI, Feit F. The effect of aspirin on the hemodynamic response to nitroglycerin. *Am Heart J* (1988) 116, 77–84.
5. Karlberg K-E, Ahlner J, Henriksson P, Torfgård K, Sylvén C. Effects of nitroglycerin on platelet aggregation beyond the effects of acetylsalicylic acid in healthy subjects. *Am J Cardiol* (1993) 71, 361–4.

Glyceryl trinitrate (Nitroglycerin) + Nifedipine

The effect of sublingual glyceryl trinitrate was not altered by pretreatment with nifedipine in two studies. Nifedipine and intravenous glyceryl trinitrate had additive vasodilator effects in one study, but the preliminary results of another study found that nifedipine may increase glyceryl trinitrate requirements.

Clinical evidence, mechanism, importance and management

(a) Sublingual glyceryl trinitrate

In 9 patients with stable chronic angina, there was no significant haemodynamic interaction between sublingual glyceryl trinitrate and a single 20-mg dose of nifedipine, or nifedipine 20 mg three times daily for 5 days.[1] In another study in healthy subjects, the venodilatory effect of sublingual glyceryl trinitrate was not altered by pretreatment with nifedipine 10 mg.[2] No special precautions are required during concurrent use.

(b) Intravenous glyceryl trinitrate

In 7 patients with severe congestive heart failure, a single 10-mg dose of oral nifedipine increased stroke volume, with a peak effect at 30 minutes. The addition of intravenous glyceryl trinitrate at 2 hours further increased stroke volume and increased the cardiac index.[3] Therefore the addition of glyceryl trinitrate enhanced the vasodilator action of nifedipine. Conversely, in the preliminary findings of a comparative study of 3 groups of patients undergoing coronary bypass graft surgery, those taking nifedipine 20 mg twice daily needed initial doses of intravenous glyceryl trinitrate (to reduce cardiac workload, maintain graft patency and control blood pressure) that were about 40% higher than those in the other two groups; one taking nifedipine 10 mg twice daily for hypertension, and the other a control group of normotensive patients. Moreover, these higher doses had little effect on the initial mean systolic blood pressure of half of the group taking nifedipine 20 mg twice daily, and they needed an additional infusion of nitroprusside.[4] It was suggested that as glyceryl trinitrate is converted to nitric oxide to elicit its vasodilator effect, it is possible that the nifedipine inhibits the enzymic production of the nitrous oxide. This appears to be the only study to suggest a negative interaction, and the clinical relevance of its findings is unclear. Note that this study was non-randomised, and there may have been other important differences between the patients in each group that would account for the effects seen.

1. Boje KM, Fung H-L, Yoshitomi K, Parker JO. Haemodynamic effects of combined oral nifedipine and sublingual nitroglycerin in patients with chronic stable angina. *Eur J Clin Pharmacol* (1987) 33, 349–54.
2. Gascho JA, Apollo WP. Effects of nifedipine on the venodilatory response to nitroglycerin. *Am J Cardiol* (1990) 65, 99–102.
3. Kubo SH, Fox SC, Prida XE, Cody RJ. Combined hemodynamic effects of nifedipine and nitroglycerin in congestive heart failure. *Am Heart J* (1985) 110, 1032–4.
4. Key BJ, Wilkes MP, Keen M. Reduced responsiveness to glyceryl trinitrate following antihypertensive treatment with nifedipine in man. *Br J Clin Pharmacol* (1993) 36, 499P.

Guanethidine + Amfetamines and related drugs

The antihypertensive effects of guanethidine can be reduced or abolished by drugs including dexamfetamine, ephedrine, metamfetamine and methylphenidate. The blood pressure may even rise higher than before treatment with the antihypertensive.

Clinical evidence

When 16 hypertensive patients taking guanethidine 25 to 35 mg daily were given single-doses of **dexamfetamine** 10 mg orally, **ephedrine** 90 mg orally, **metamfetamine** 30 mg intramuscularly or **methylphenidate** 20 mg orally, the hypotensive effects of the guanethidine were completely abolished, and in some instances the blood pressures rose higher than before treatment with the guanethidine.[1] Another report describes the same interaction between guanethidine and **dexamfetamine**.[2]

Mechanism

These drugs are all indirectly-acting sympathomimetic amines, which not only prevent guanethidine-like drugs from entering the adrenergic neurones of the sympathetic nervous system, but also displace the antihypertensive drug already there.[3] As a result the blood pressure lowering effects are lost. In addition these amines release noradrenaline (norepinephrine) from the neurones, which raises the blood pressure. Thus the antihypertensive effects are not only opposed, but the pressure may even be raised higher than before treatment.[3-8]

Importance and management

Well documented, well established, and clinically important interactions. Other drugs, such as **phenylpropanolamine**, which is also an indirectly-acting sympathomimetic, are likely to interact similarly. Patients taking guanethidine should avoid indirectly-acting sympathomimetics, see 'Table 24.1', (p.1048), for a list. Warn them against the temptation to use proprietary non-prescription nasal decongestants containing any of these amines to relieve the nasal stuffiness commonly associated with the use of guanethidine and related drugs. The same precautions apply to the sympathomimetics used as appetite suppressants (although note that the use of these drugs for this indication is not generally recommended). However, one brief report stated that **diethylpropion** has been used with guanethidine without any adverse events.[9] Note that the antihypertensive use of guanethidine and related adrenergic neurone blockers has largely been superseded by other antihypertensive drug classes.

Guanethidine increases the hypertensive effects of the *directly*-acting sympathomimetics used as inotropes and vasopressors, see 'Inotropes and Vasopressors + Guanethidine', p.1064.

1. Gulati OD, Dave BT, Gokhale SD, Shah KM. Antagonism of adrenergic neuron blockade in hypertensive subjects. *Clin Pharmacol Ther* (1966) 7, 510–4.
2. Ober KF, Wang RIH. Drug interactions with guanethidine. *Clin Pharmacol Ther* (1973) 14, 190–5.
3. Flegin OT, Morgan DH, Oates JA, Shand DG. The mechanism of the reversal of the effect of guanethidine by amphetamines in cat and man. *Br J Pharmacol* (1970) 39, 253P–254P.
4. Day MD, Rand MJ. Antagonism of guanethidine and bretylium by various agents. *Lancet* (1962) 2, 1282–3.
5. Day MD, Rand MJ. Evidence for a competitive antagonism of guanethidine by dexamphetamine. *Br J Pharmacol* (1963) 20, 17–28.

6. Day MD. Effect of sympathomimetic amines on the blocking action of guanethidine, bretylium and xylocholine. *Br J Pharmacol* (1962) 18, 421–39.
7. Starke K. Interactions of guanethidine and indirectly-acting sympathomimetic amines. *Arch Int Pharmacodyn Ther* (1972) 195, 309–14.
8. Boura ALA, Green AF. Comparison of bretylium and guanethidine: tolerance and effects on adrenergic nerve function and responses to sympathomimetic amines. *Br J Pharmacol* (1962) 19, 13–41.
9. Seedat YK, Reddy J. Diethylpropion hydrochloride (Tenuate Dospan) in the treatment of obese hypertensive patients. *S Afr Med J* (1974) 48, 569.

Guanethidine + Antipsychotics

Large doses of chlorpromazine may reduce or even abolish the antihypertensive effects of guanethidine, although in some patients the inherent hypotensive effects of the chlorpromazine may possibly predominate. Case reports suggest that haloperidol and tiotixene may interact similarly. Molindone is reported not to interact with guanethidine, and a single-dose of prochlorperazine did not interact with guanethidine.

Clinical evidence

Two severely hypertensive patients, with stable blood pressure while taking guanethidine 80 mg daily, were given **chlorpromazine** 200 to 300 mg daily. The diastolic blood pressure of one patient rose over 10 days from 94 mmHg to 112 mmHg and continued to rise to 116 mmHg, even when the **chlorpromazine** was withdrawn. Similarly, the diastolic pressure of the other patient rose from 105 mmHg to 127 mmHg, and then to 150 mmHg, even after the **chlorpromazine** had been withdrawn.[1] Other reports also describe marked rises in blood pressure in patients taking guanethidine with **chlorpromazine** 100 to 400 mg daily.[2-4]

Three hypertensive patients taking guanethidine 60 to 150 mg daily had an increase in their blood pressure when **haloperidol** 6 to 9 mg daily was added. The blood pressure rose from 132/95 mmHg to 149/99 mmHg in the first patient; from 125/84 mmHg to 148/100 mmHg in the second patient; and from 138/91 mmHg to 154/100 mmHg in the third patient. **Tiotixene** 60 mg daily was later given to one of the patients and the blood pressure rose from 126/87 mmHg to 156/110 mmHg.[2] These results have been reported elsewhere.[3,4]

However, a single 25-mg dose of **prochlorperazine** did not significantly antagonise the effect of guanethidine 15 to 20 mg daily in 5 patients.[5] In another study in 7 patients taking guanethidine 50 to 95 mg daily, the addition of **molindone** 30 to 120 mg daily had no effect on blood pressure.[6]

Mechanism

Chlorpromazine prevents the entry of guanethidine into the adrenergic neurones of the sympathetic nervous system resulting in a loss of its blood pressure-lowering effects. The other interacting antipsychotics probably have similar effects. This is essentially the same mechanism of interaction as that seen with the tricyclic antidepressants (consider also 'Guanethidine + Tricyclic and related antidepressants', p.1060).

Importance and management

Direct information is limited but the interaction between guanethidine and chlorpromazine is established and can be clinically important. It may take several days to develop. Not all patients may react to the same extent.[2,7] Monitor concurrent use and raise the guanethidine dose if necessary. It is uncertain how much chlorpromazine is needed before a significant effect occurs, but the smallest dose of chlorpromazine used in the studies was 100 mg with 90 mg guanethidine, which raised the blood pressure by 40/23 mmHg.[2] The inherent hypotensive effects of the chlorpromazine may possibly reduce the effects of this interaction. Other antipsychotics (particularly the phenothiazines) might be expected to interact similarly and this has been seen with tiotixene and haloperidol. The effects should be monitored. However, molindone is reported not to interact, and a single-dose of prochlorperazine did not interact. Note that the antihypertensive use of guanethidine and related adrenergic neurone blockers has largely been superseded by other antihypertensive drug classes.

1. Fann WE, Janowsky DS, Davis JM, Oates JA. Chlorpromazine reversal of the antihypertensive action of guanethidine. *Lancet* (1971) ii, 436–7.
2. Janowsky DS, El-Yousef MK, Davis JM, Fann WE, Oates JA. Guanethidine antagonism by antipsychotic drugs. *J Tenn Med Assoc* (1972) 65, 620–2.
3. Janowsky DS, El-Yousef MK, Davis JM, Fann WE. Antagonism of guanethidine by chlorpromazine. *Am J Psychiatry* (1973) 130, 808–12.
4. Davis JM. Psychopharmacology in the aged. Use of psychotropic drugs in geriatric patients. *J Geriatr Psychiatry* (1974) 7, 145–59.
5. Ober KF, Wang RIH. Drug interactions with guanethidine. *Clin Pharmacol Ther* (1973) 14, 190–5.
6. Simpson LL. Combined use of molindone and guanethidine in patients with schizophrenia and hypertension. *Am J Psychiatry* (1979) 136, 1410–14.
7. Tuck D, Hamberger B and Sjoqvist F. Drug interactions: effect of chlorpromazine on the uptake of monoamines into adrenergic neurones in man. *Lancet* (1972) ii, 492.

Guanethidine + Levodopa

Levodopa appeared to enhance the antihypertensive effects of guanethidine in two patients.

Clinical evidence, mechanism, importance and management

A brief report describes a patient taking guanethidine and a diuretic who, when given levodopa (dose not stated), required a reduction in his daily dose of guanethidine, from 60 to 20 mg. Another patient similarly treated was able to discontinue the diuretic.[1] The suggested reason is that the hypotensive adverse effects of the levodopa are additive with the effects of the guanethidine. Direct information seems to be limited to this report but it would be wise to confirm that excessive hypotension does not develop if levodopa is added to treatment with guanethidine. Note that the antihypertensive use of guanethidine and related adrenergic neurone blockers has largely been superseded by other antihypertensive drug classes, but note that any antihypertensive may interact in this way, see 'Antihypertensives + Other drugs that affect blood pressure', p.1051.

1. Hunter KR, Stern GM, Laurence DR. Use of levodopa with other drugs. *Lancet* (1970) ii, 1283–5.

Guanethidine + MAOIs

The antihypertensive effects of guanethidine can be reduced by nialamide, and probably therefore by other non-selective MAOIs.

Clinical evidence, mechanism, importance and management

Four out of 5 hypertensive patients taking guanethidine 25 to 35 mg daily had a rise in blood pressure from 140/85 mmHg to 165/100 mmHg six hours after being given a single 50-mg dose of **nialamide**.[1] The reason for this effect is not understood but one idea is that the MAOIs possibly oppose the guanethidine-induced loss of noradrenaline from sympathetic neurones. In *animal* studies, effective antagonism of guanethidine was shown by those MAOIs that also possess sympathomimetic effects (**phenelzine** and **tranylcypromine**), but not by **iproniazid** or **nialamide**,[2] and the antagonism was weaker than that seen with some other sympathomimetics.[3]

Direct clinical information seems to be limited to the single dose study,[1] but it would be prudent to monitor the effects if any non-selective MAOI is given to patients taking any guanethidine-like drug. The manufacturers of guanethidine actually contraindicate the use of MAOIs because of the possibility of the release of large quantities of catecholamines and the risk of hypertensive crisis. They recommend that at least 14 days should elapse between stopping an MAOI and starting guanethidine.[4] Note that the antihypertensive use of guanethidine and related adrenergic neurone blockers has largely been superseded by other antihypertensive drug classes.

1. Gulati OD, Dave BT, Gokhale SD, Shah KM. Antagonism of adrenergic neuron blockade in hypertensive subjects. *Clin Pharmacol Ther* (1966) 7, 510–4.
2. Day MD. Effect of sympathomimetic amines on the blocking action of guanethidine, bretylium and xylocholine. *Br J Pharmacol* (1962) 18, 421–39.
3. Day MD, Rand MJ. Antagonism of guanethidine and bretylium by various agents. *Lancet* (1962) 2, 1282–3.
4. Ismelin Ampoules (Guanethidine monosulphate). Amdipharm. UK Summary of product characteristics, April 2005.

Guanethidine + NSAIDs

Phenylbutazone and kebuzone reduce the antihypertensive effects of guanethidine.

Clinical evidence, mechanism, importance and management

When 20 patients taking guanethidine 75 mg daily were given **phenylbutazone** or **kebuzone** 750 mg daily the mean systolic blood pressure rose by 20 mmHg (from 169 mmHg to 189 mmHg).[1] This rise represents about

a 35% reduction in the antihypertensive effect of guanethidine. The mechanism of this interaction is uncertain but it is probably due to salt and water retention caused by these pyrazolone compounds. Direct evidence seems to be limited to this report. Patients taking guanethidine should be monitored if **phenylbutazone** or **kebuzone** is given concurrently. There does not appear to be any information on guanethidine and other NSAIDs, but indometacin, in particular, is well known to reduce the efficacy of other classes of antihypertensives, see for example 'ACE inhibitors + NSAIDs', p.32. Some caution may therefore be warranted with other NSAIDs.

1. Polak F. Die hemmende Wirkung von Phenylbutazon auf die durch einige Antihypertonika hervorgerufene Blutdrucksenkung bei Hypertonikern. *Z Gesamte Inn Med* (1967) 22, 375–6.

Guanethidine + Tricyclic and related antidepressants

The antihypertensive effects of guanethidine are reduced or abolished by amitriptyline, desipramine, imipramine, nortriptyline and protriptyline. Doxepin in doses of 300 mg or more daily interacts similarly, but in smaller doses appears not to do so, although one case is reported with doxepin 100 mg daily. A few case reports suggest that maprotiline and mianserin do not interact with guanethidine.

Clinical evidence

(a) Tricyclic antidepressants

Five hypertensive patients taking guanethidine sulfate 50 to 150 mg daily had a mean arterial blood pressure rise of 27 mmHg when they were also given **desipramine** 50 or 75 mg daily or **protriptyline** 20 mg daily for one to 9 days. The full antihypertensive effects of the guanethidine were not re-established until 5 days after the antidepressants were withdrawn.[1]

The same interaction has been described in other reports, with guanethidine and **desipramine**,[2,3] **imipramine**,[4] **amitriptyline**,[5-7] **protriptyline**[3] or **nortriptyline**.[8] The interaction may take several days to develop fully and can last an average of 5 days after discontinuation of the tricyclic.[2] Some studies, and clinical experience suggests that **doxepin** does not begin to interact until doses of about 200 to 250 mg daily are used, then at 300 mg or more daily it interacts to the same extent as other tricyclics.[9-13] However, in one case excessive hypertension occurred in a man taking guanethidine and **doxepin** 100 mg daily.[14]

(b) Tetracyclic antidepressants

Maprotiline 25 mg three times daily caused no appreciable change in blood pressure in 2 patients taking guanethidine.[7] Similarly, in a study in 2 patients, **mianserin** 20 mg three times daily for 2 days did not alter the antihypertensive efficacy of guanethidine.[15]

Mechanism

The guanethidine-like drugs exert their hypotensive actions by entering the adrenergic nerve endings associated with blood vessels using the noradrenaline uptake mechanism. The tricyclics successfully compete for the same mechanism so that the antihypertensives are unable to reach their site of action, and as a result, the blood pressure rises once again.[16] The differences in the rate of development, duration and extent of the interactions reflect the pharmacokinetic differences between the various tricyclics, as well as individual differences between patients.

Importance and management

A very well documented and well established interaction of clinical importance. Not every combination of guanethidine and tricyclic antidepressant has been studied but all are expected to interact similarly, to a greater or lesser extent. Concurrent use should be avoided unless the effects are very closely monitored and the interaction balanced by raising the dose of the antihypertensive. Note that the antihypertensive use of guanethidine and related adrenergic neurone blockers has largely been superseded by other antihypertensive drug classes.

1. Mitchell JR, Arias L, Oates JA. Antagonism of the antihypertensive actions of guanethidine sulfate by desipramine hydrochloride. *JAMA* (1967) 202, 973–6.
2. Oates JA, Mitchell JR, Feagin OT, Kaufmann JS, Shand DG. Distribution of guanidinium antihypertensives-mechanism of their selective action. *Ann N Y Acad Sci* (1971) 179, 302–9.
3. Mitchell JR, Cavanaugh JH, Arias L, Oates JA. Guanethidine and related agents. III. Antagonism by drugs which inhibit the norepinephrine pump in man. *J Clin Invest* (1970) 49, 1596–1604.
4. Leishman AWD, Matthews HL, Smith AJ. Antagonism of guanethidine by imipramine. *Lancet* (1963) i, 112.
5. Meyer JF, McAllister CK, Goldberg LI. Insidious and prolonged antagonism of guanethidine by amitriptyline. *JAMA* (1970) 213, 1487–8.
6. Ober KF, Wang RIH. Drug interactions with guanethidine. *Clin Pharmacol Ther* (1973) 14, 190–5.
7. Smith AJ, Bant WP. Interactions between post-ganglionic sympathetic blocking drugs and anti-depressants. *J Int Med Res* (1975) 3 (Suppl 2), 55–60.
8. McQueen EG. New Zealand Committee on Adverse Reactions: Ninth Annual Report 1974. *N Z Med J* (1974) 80, 305–11.
9. Oates JA, Fann WE, Cavanaugh JH. Effect of doxepin on the norepinephrine pump. A preliminary report. *Psychosomatics* (1969) 10 (Suppl), 12–13.
10. Fann WE, Cavanaugh JH, Kaufmann JS, Griffith JD, Davis JM, Janowsky DS, Oates JA. Doxepin: effects on transport of biogenic amines in man. *Psychopharmacologia* (1971) 22, 111–25.
11. Gerson IM, Friedman R, Unterberger H. Non-antagonism of antiadrenergic agents by dibenzoxepine (preliminary report). *Dis Nerv Syst* (1970) 31, 780–2.
12. Ayd FJ. Long-term administration of doxepin (Sinequan). *Dis Nerv Syst* (1971) 32, 617–22.
13. Ayd FJ. Doxepin with other drugs. *South Med J* (1973) 66, 465–71.
14. Poe TE, Edwards JL, Taylor RB. Hypertensive crisis possibly due to drug interaction. *Postgrad Med* (1979) 66, 235–7.
15. Burgess CD, Turner P, Wadsworth J. Cardiovascular responses to mianserin hydrochloride: a comparison with tricyclic antidepressant drugs. *Br J Clin Pharmacol* (1978) 5, 21S–28S.
16. Cairncross KD. On the peripheral pharmacology of amitriptyline. *Arch Int Pharmacodyn Ther* (1965) 154, 438–48.

Guanfacine + Phenobarbital or Phenytoin

In two patients, the concurrent use of phenobarbital or phenytoin increased the metabolism of guanfacine.

Clinical evidence, mechanism, importance and management

When a hypertensive patient with chronic renal failure who was taking guanfacine 4 mg daily, was given phenobarbital 10 mg daily the antihypertensive effects of guanfacine were noted to be reduced and its dose was progressively raised over about 18 months to 12 mg daily. Phenobarbital was eventually stopped. Single measurements of the pharmacokinetics of guanfacine, both when the patient was taking phenobarbital, and 2 months after cessation of phenobarbital, found that the half-life of guanfacine increased fourfold when the phenobarbital was stopped.[1] The manufacturer also reports a similar case with phenytoin and guanfacine.[2] Phenobarbital and phenytoin probably induce the metabolism of guanfacine. Patients taking these drugs are likely to need more frequent doses of guanfacine. Primidone is metabolised to **phenobarbital**, and **fosphenytoin** is a prodrug of phenytoin. These drugs may therefore be expected to interact similarly.

1. Kiechel JR, Lavene D, Guerret M, Comoy E, Godin M, Fillastre JP. Pharmacokinetic aspects of guanfacine withdrawal syndrome in a hypertensive patient with chronic renal failure. *Eur J Clin Pharmacol* (1983) 25, 463–6.
2. Guanfacine hydrochloride. Watson Laboratories, Inc. US Prescribing information, October 2007.

Guanfacine + Tricyclic antidepressants

A single case report describes a reduced antihypertensive response to guanfacine in a patient given amitriptyline and later imipramine. The sedative effects of guanfacine and tricyclics are predicted to be additive.

Clinical evidence

A 38-year-old woman with stable hypertension, taking guanfacine 2 mg daily, had a rise in her mean blood pressure from 138/89 mmHg to 150/100 mmHg while taking **amitriptyline** 75 mg daily for 14 days. The patient's blood pressure fell again when the **amitriptyline** was stopped. A month later her blood pressure rose to 142/98 mmHg after she had taken **imipramine** 50 mg daily for 2 days, and fell again when it was stopped.[1]

Mechanism

Uncertain. A possible reason is that, like clonidine (another alpha-2 agonist), the uptake of guanfacine into neurones within the brain is blocked by tricyclic antidepressants, thereby reducing its effects.

Importance and management

Direct information is limited to this report, but it is supported by *animal* studies[2] and consistent with the way another alpha-2 agonist interacts with tricyclic antidepressants (see 'Clonidine and related drugs + Tricyclic and

related antidepressants', p.1054). Be alert for this interaction in any patient given guanfacine and any tricyclic antidepressant. **Guanabenz** is another alpha-2 agonist that might interact similarly, but as yet there is no direct clinical evidence that it does so. Note that the sedative effects of guanfacine or guanabenz and tricyclics would be predicted to be additive.

1. Buckley M, Feeley J. Antagonism of antihypertensive effect of guanfacine by tricyclic antidepressants. *Lancet* (1991) 337, 1173–4.
2. Ohkubo K, Suzuki K, Oguma T, Otorii T. Central hypotensive effects of guanfacine in anaesthetised rabbits. *Nippon Yakurigaku Zasshi* (1982) 79, 263–74.

Hydralazine + Adrenaline (Epinephrine)

The manufacturers note that patients taking hydralazine who develop hypotension while undergoing surgery should *not* be treated with adrenaline (epinephrine).[1] This is because hydralazine frequently causes tachycardia,[2] and adrenaline would enhance this.[1]

1. Apresoline (Hydralazine hydrochloride). Amdipharm. UK Summary of product characteristics, November 2007.
2. Lin M-S, McNay JL, Shepherd AMM, Musgrave GE, Keeton TK. Increased plasma norepinephrine accompanies persistent tachycardia after hydralazine. *Hypertension* (1983) 5, 257–63.

Hydralazine + Food

The effect of food on hydralazine absorption is uncertain: food increased the AUC of hydralazine in two studies, had no effect in one study, and decreased it in three others. In other studies, a bolus dose of enteral feed decreased the AUC of hydralazine, but an enteral feed infusion had no effect.

Clinical evidence, mechanism, importance and management

Food *enhanced* the bioavailability of a single 50-mg dose of hydralazine in healthy subjects by two- to threefold in one study.[1] Similar findings were reported by the same research group with conventional hydralazine tablets, but not slow-release tablets.[2] In contrast, others found that food had no effect on the AUC of hydralazine in healthy subjects.[3] Furthermore, other studies have found that food decreases the AUC of hydralazine by 46% when it is given as oral solution,[4] by 44% after conventional tablets,[5] and by 29% (not statistically significant) after a slow-release preparation.[5] A reduction in the antihypertensive effect of hydralazine was noted in the first of these studies,[4] but no significant alteration in antihypertensive effect was seen in the second.[5] Similarly, another study reported a decrease in the AUC of hydralazine of 55% when it was given with a meal, and 62% when it was given with a bolus dose of **enteral feed**, but no significant change when it was given during an **enteral feed infusion**.[6]

The widely different findings of these studies may be related to the problems in analysing hydralazine and its metabolites, all of which are unstable. All these studies were single-dose, and no studies have adequately assessed the possible clinical importance of any pharmacokinetic changes in long-term clinical use. Note that the bioavailability of hydralazine varies widely between individuals depending on their acetylator status. No recommendations can be made as to whether or not hydralazine should be taken at a set time in relation to meals.

1. Melander A, Danielson K, Hanson A, Rudell B, Schersten B, Thulin T, Wåhlin E. Enhancement of hydralazine bioavailability by food. *Clin Pharmacol Ther* (1977) 22, 104–7.
2. Liedholm H, Wåhlin-Boll E, Hanson A, Melander A. Influence of food on the bioavailability of 'real' and 'apparent' hydralazine from conventional and slow-release preparations. *Drug Nutr Interact* (1982) 1, 293–302.
3. Walden RJ, Hernadez R, Witts D, Graham BR, Prichard BN. Effect of food on the absorption of hydralazine in man. *Eur J Clin Pharmacol* (1981) 20, 53–8.
4. Shepherd AM, Irvine NA, Ludden TM. Effect of food on blood hydralazine levels and response in hypertension. *Clin Pharmacol Ther* (1984) 36, 14–18.
5. Jackson SHD, Shepherd AMM, Ludden TM, Jamieson MJ, Woodworth J, Rogers D, Ludden LK, Muir KT. Effect of food on oral bioavailability of apresoline and controlled release hydralazine in hypertensive patients. *J Cardiovasc Pharmacol* (1990) 16, 624–8.
6. Semple HA, Koo W, Tam YK, Ngo LY, Coutts RT. Interactions between hydralazine and oral nutrients in humans. *Ther Drug Monit* (1991) 13, 304–8.

Hydralazine + NSAIDs

Oral indometacin abolished the hypotensive effects of intravenous hydralazine in one study, but no effect was found in another. In patients with pulmonary hypertension, intravenous indometacin reduced the effects of intravenous hydralazine, and in patients with hypertension, intravenous diclofenac reduced the effects of intravenous dihydralazine.

Clinical evidence, mechanism, importance and management

In 9 healthy subjects, oral **indometacin** 50 mg every 6 hours for four doses abolished the hypotensive response to intravenous hydralazine 150 micrograms/kg, and the subjects only responded when given another dose of hydralazine 30 minutes later.[1] A study in 7 patients with pulmonary hypertension given **indometacin** 50 mg and hydralazine 350 micrograms/kg, both intravenously, either alone, or concurrently, also found that the effects of hydralazine (reduction in systemic arterial pressure, heart rate, cardiac index) were reduced by **indometacin**.[2] In contrast, another study in 9 healthy subjects[3] found that oral **indometacin** 25 mg four times daily for 2.5 days did not affect the hypotensive response to a single 200-microgram/kg intravenous dose of hydralazine.

Thus it is not clear if **indometacin** interacts with intravenous hydralazine, and it is uncertain if an interaction occurs when hydralazine is given orally.

On the other hand, a single-dose study in 4 hypertensive subjects found that the actions of intravenous **dihydralazine** (effects on blood pressure, urinary excretion, heart rate and sodium clearance) were reduced by intravenous **diclofenac**.[4]

NSAIDs can cause increases in blood pressure due to their effects on sodium and water retention. Various NSAIDs have been reported to reduce the efficacy of other antihypertensive drug classes, for example see 'ACE inhibitors + NSAIDs', p.32. It would therefore be prudent to monitor concurrent use of hydralazine and any NSAID.

1. Cinquegrani MP, Liang C-S. Indomethacin attenuates the hypotensive action of hydralazine. *Clin Pharmacol Ther* (1986) 39, 564–70.
2. Adnot S, Defouilloy C, Brun-Buisson C, Piquet J, De Cremoux H, Lemaire F. Effects of indomethacin on pulmonary hemodynamics and gas exchange in patients with pulmonary artery hypertension, interference with hydralazine. *Am Rev Respir Dis* (1987) 136, 1343–9.
3. Jackson SHD, Pickles H. Indomethacin does not attenuate the effects of hydralazine in normal subjects. *Eur J Clin Pharmacol* (1983) 25, 303–5.
4. Reimann IW, Ratge D, Wisser H, Fröhlich JC. Are prostaglandins involved in the antihypertensive effect of dihydralazine? *Clin Sci* (1981) 61, 319S–321S.

Inotropes and Vasopressors + Amfetamines

The manufacturers of amfetamine and dexamfetamine state that amfetamines enhance the adrenergic effects of noradrenaline (norepinephrine).[1,2] This may result in increased vasoconstriction, and could enhance the pressor effects of noradrenaline (norepinephrine). Other inotropes and vasopressors with adrenergic actions may be similarly affected, but this does not appear to be specifically mentioned. Consider 'Table 24.1', (p.1048), for a list of these drugs.

1. Adderall XR (Mixed salts of amphetamine and dextroamphetamine). Shire US Inc. US Prescribing information, March 2009.
2. Dexedrine (Dextroamphetamine sulfate). GlaxoSmithKline. US Prescribing information, July 2008.

Inotropes and Vasopressors + Antimuscarinics

The hypertensive and other serious adverse effects of intravenous phenylephrine and phenylephrine absorbed from *eye drops* can be markedly increased by intravenous or intramuscular atropine.

Clinical evidence

A brief report describes 7 cases of pseudo-phaeochromocytoma, with severe rises in blood pressure and tachycardia, which occurred in young adults and children when they underwent eye operations and were given phenylephrine 10% eye drops and atropine. Only two of them had any pre-existing cardiovascular illness (moderate hypertension). All were under general anaesthesia with propofol, phenoperidine and vecuronium, and premedicated with intramuscular **atropine**, and some were later given more intravenous **atropine** to control the bradycardia that occurred as a result of stretching the oculomotor muscles. The total atropine doses were less than 10 micrograms/kg in adults and 20 micrograms/kg in children. At least 0.4 mL of phenylephrine 10% was used. In three cases left ven-

tricular failure and pulmonary oedema occurred, which needed monitoring in intensive care.[1] The authors say that no further cardiovascular adverse events were observed during similar procedures when steps were taken to reduce the amount of phenylephrine used and absorbed (see *Importance and Management*, below). Before this case report was made, a number of cases of cardiovascular adverse effects (severe hypertension, cardiac arrhythmias, myocardial infarction) had been reported for phenylephrine eye drops (usually 10%), or subconjunctival injection, and many of these patients had also received antimuscarinics (**atropine**, **cyclopentolate**, **homatropine**, **hyoscine**, **tropicamide**),[2-6] although the contribution, if any, of these antimuscarinics to the adverse effects is unknown.

In a study, 6 healthy subjects were given an intravenous phenylephrine infusion at incremental rates before and after being given three intravenous doses of **atropine**, 20, 10, and 10 micrograms/kg at 90, 120 and 150 minutes, respectively. It was found that phenylephrine 420 nanograms/kg per minute raised the diastolic and systolic blood pressures by 4 mmHg before using atropine, and 17 mmHg after atropine was given. For safety reasons the increases in blood pressure were limited to 30 mmHg above the baseline.[7]

Mechanism

Phenylephrine causes vasoconstriction, which can raise the blood pressure. Normally this would be limited by a baroreflex mediated by the vagus nerve, but if this cholinergic mechanism is blocked by atropine or other antimuscarinics, the rise in blood pressure is largely uncontrolled. Severe hypertension may occur, and other adverse cardiac events such as acute cardiac failure may follow.

Importance and management

A surprisingly large amount of phenylephrine can be absorbed from eye drops, and the potential cardiovascular adverse effects of this are well documented. The reports cited here suggest that these risks are clearly increased by the systemic use of atropine. The authors of one of the reports[1] found that the systemic absorption of phenylephrine can be reduced by using lower concentrations of phenylephrine, swabbing to minimise the amount that drains into the nasolachrymal duct to the nasal mucosa where rapid absorption occurs, and reducing the drop size by using a thin-walled cannula. Others have demonstrated that a cannula reduced the dose of phenylephrine given by two-thirds without loss of efficacy.[8] Other suggestions for reducing systemic absorption of phenylephrine are punctal plugging, nasolachrymal duct compression, and lid closure after instillation of the eye drop.[8] Note that phenylephrine eye drops are contraindicated in those with cardiovascular disease.[9] Note also that topical phenylephrine is commonly used with a topical antimuscarinic to enhance mydriasis.

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Inotropes and Vasopressors + Calcium compounds

Calcium chloride infusions reduce the cardiotonic effects of adrenaline (epinephrine) and dobutamine, but not those of amrinone.

Clinical evidence, mechanism, importance and management

In a double-blind, randomised, crossover study in 12 patients following coronary artery bypass grafting, calcium chloride (10 mg/kg bolus followed by a 2 mg/kg per hour infusion) was found to attenuate the effects of **adrenaline** (**epinephrine**) 10 and 30 nanograms/kg per minute, given for 8 minutes each. **Adrenaline** alone produced a significant increase in the cardiac index, but following the calcium infusion **adrenaline** had no significant effect and the maximal **adrenaline**-induced increase in cardiac index was reduced by 70%. **Adrenaline** 30 nanograms/kg per minute alone increased mean arterial blood pressure from 87 mmHg to 95 mmHg; calcium chloride also raised blood pressure from 85 mmHg to 93 mmHg. After calcium was given, **adrenaline** had no further significant effect on blood pressure.[1]

Some of these workers also studied the mode of action of **dobutamine** in 22 patients recovering from coronary artery bypass surgery.[2] It was found that an infusion of calcium chloride (1 mg/kg per minute initially, then 0.25 mg/kg per minute) attenuated the increase in cardiac output produced by an infusion of **dobutamine** 2.5 to 5 micrograms/kg per minute by 30%. In a group of 24 similar patients the cardiotonic actions of **amrinone** (a phosphodiesterase inhibitor) were unaffected by the calcium infusion.[2]

Just how the calcium alters the effects of **adrenaline** and **dobutamine** is not known, but as they are both beta-receptor agonists a reasonable suggestion is that calcium interferes with the signal transduction through the beta-adrenergic receptor complex. The clinical importance of these findings is uncertain.

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Inotropes and Vasopressors + Cimetidine

An exaggerated hypertensive response to dobutamine occurred during anaesthetic induction in a patient taking cimetidine. Another case report describes supraventricular tachycardia, which occurred when a patient receiving dobutamine and dopamine was given cimetidine.

Clinical evidence, mechanism, importance and management

A patient about to undergo coronary artery bypass grafting was anaesthetised with midazolam, fentanyl, vecuronium and oxygen. When a 5 micrograms/kg per minute infusion of **dobutamine** was given the patient developed unexpectedly marked hypertension of 210/100 mmHg. The infusion was stopped and over the next 15 minutes the blood pressure fell to 90/50 mmHg. A new infusion had the same hypertensive effect, and the patient's blood pressure was subsequently controlled at 120/80 mmHg with **dobutamine** 1 microgram/kg per minute.[1] The authors of the report suggest that this exaggerated response to **dobutamine** may have been due to cimetidine 1 g daily, which the patient was also taking. They postulate that the cimetidine may possibly have inhibited the metabolism and clearance of the **dobutamine** by the liver, thereby increasing its effects.[1]

A post-operative patient receiving **dopamine** and **dobutamine** infusions developed a supraventricular tachycardia 30 seconds after an intravenous injection of cimetidine. Similar episodes of tachycardia occurred on rechallenge with both drugs, but not when each drug was given separately.[2]

These are isolated cases and the general importance is not known but it seems likely to be small.

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Inotropes and Vasopressors + Clonidine

Studies suggest that pretreatment with clonidine decreases the blood pressure response to small doses of dopamine; does not affect the blood pressure response to noradrenaline (norepinephrine); and can increase the blood pressure responses to

dobutamine, ephedrine, isoprenaline (isoproterenol) and phenylephrine.

Clinical evidence

In a study in 70 patients undergoing elective surgery, 35 patients were given clonidine 5 micrograms/kg 90 minutes before the induction of anaesthesia and 35 patients were used as a control group. While under anaesthesia, and when haemodynamically stable for at least 10 minutes, all patients were given a 10-minute infusion of **dopamine** 3 or 5 micrograms/kg per minute or **dobutamine** 0.5, 1, or 3 micrograms/kg per minute.[1] Clonidine attenuated the response to the 5 micrograms/kg per minute dose of **dopamine** (blood pressure rise 19/10 mmHg in the control group but only 4/0 mmHg in the clonidine group). However, **dopamine** 3 micrograms/kg per minute did not significantly affect blood pressure in either the control group or the clonidine group. Conversely, clonidine enhanced the response to **dobutamine** at all 3 doses. The study had to be stopped after 2 minutes in the clonidine group receiving the highest dose of **dobutamine** as the rise in blood pressure exceed the study limits (rise 45/24 mmHg compared with 16/7 mmHg in the control group).[1] In a study of the same design, 20 clonidine-treated patients and 20 controls were given a bolus infusion of **phenylephrine** 3 micrograms/kg or **isoprenaline** (**isoproterenol**) 0.02 micrograms/kg. Those who received clonidine had a greater and more prolonged increase in arterial pressure and heart rate with **phenylephrine** (10 minutes compared with 2 to 3 minutes) and increase in heart rate (but not arterial pressure) with **isoprenaline** (**isoproterenol**).[2]

In another similar study, 77 patients (38 premedicated with clonidine 5 micrograms/kg and famotidine 20 mg, 90 minutes before anaesthetic induction, and a control group of 39 given only famotidine) were given **noradrenaline** (**norepinephrine**) 0.5 micrograms/kg or **phenylephrine** 2 micrograms/kg. It was found that the overall response to **noradrenaline** (**norepinephrine**) was not significantly affected by clonidine, although 2 to 4 minutes after administration the mean arterial blood pressure was raised in the clonidine group. The blood pressure rise in response to **phenylephrine** was found to be augmented. There were no significant differences between the groups in terms of the incidence of hypertension, arrhythmias or bradycardia.[3] Similar results have been reported with **phenylephrine** in other studies (see below). The same group of workers repeated this study using two doses of **ephedrine** 100 micrograms/kg as the vasopressor. Clonidine prolonged the response to **ephedrine** by 2 minutes and increased the rise in blood pressure (rise in mean blood pressure in response to **ephedrine** at 3 minutes of 12.7 mmHg with clonidine, compared with 6.6 mmHg without clonidine). The rise in blood pressure was greater in both groups after a second dose of **ephedrine** was given but the effect in the clonidine group was still greater (rise in mean blood pressure in response to **ephedrine** at 4 minutes of 15 mmHg with clonidine compared with 9.4 mmHg without clonidine).[4]

Additional effects on blood pressure were found in another group of patients who were anaesthetised with enflurane and nitrous oxide/oxygen, and given intravenous **ephedrine** 100 micrograms/kg after pretreatment with clonidine (about 5 micrograms/kg).[5] A study in patients anaesthetised with propofol found premedication with clonidine enhanced the pressor and tachycardic effects of **ephedrine**, especially in elderly patients (over 60 years old) given standard dose of propofol (1 mg/kg at induction followed by 6 mg/kg per hour as maintenance).[6] In another study, 21 patients were premedicated with oral clonidine (about 5 micrograms/kg) and famotidine 20 mg, 90 minutes before spinal anaesthesia with tetracaine and a further 20 patients were given famotidine alone as premedication. All patients were given intravenous **ephedrine** 200 micrograms/kg when their systolic pressure decreased to below 100 mmHg or to less than 80% of pre-anaesthetic value. Premedication with clonidine enhanced the pressor response of **ephedrine** and its duration.[7]

Further study, using enflurane and nitrous oxide/oxygen for anaesthesia, found that the mean maximum blood pressure increased in a group of patients premedicated with clonidine and given intravenous **phenylephrine** 2 micrograms/kg by 26% and 32%, for awake and anaesthetised subjects, respectively. This was greater than the blood pressure rises seen in a group not given clonidine, which were 13% and 18%, for awake and anaesthetised subjects, respectively.[8] In a placebo-controlled study, patients with hypertension were given intravenous **phenylephrine** in increasing bolus doses or 30 to 300 micrograms on the day before surgery, before induction of anaesthesia and one and 3 hours postoperatively. Oral clonidine 6 micrograms/kg, was given 2 hours before surgery and a further dose of 3 micrograms/kg intravenously during the last hour of surgery. The pressor response calculated for a dose of **phenylephrine** 1.5 micrograms/kg was 42 mmHg in patients given clonidine before surgery compared with 27 mmHg for those given placebo. The postoperative pressor response to **phenylephrine** was 37 mmHg and 26 mmHg for the clonidine and placebo groups, respectively.[9]

Mechanism

Not understood. Clonidine is an alpha$_2$ agonist, which blocks the release of noradrenaline (norepinephrine) from the nerve endings, and most suggested mechanisms consider noradrenaline release to be involved in some way.

Importance and management

An interaction is established, although the exact outcome of the concurrent use of clonidine and these sympathomimetic vasopressors is not clear. It has been suggested that the effects may be different at different doses of dopamine.[8] The authors of the one report,[3] studying phenylephrine and noradrenaline (norepinephrine) with clonidine, suggested that the increase in pressor response was unlikely to be clinically significant.

Be aware that dobutamine, ephedrine, and phenylephrine may have a greater than expected effect if clonidine has been taken. Some of these drugs may also be used as nasal decongestants (e.g. ephedrine, and phenylephrine). The outcome of the concurrent use of clonidine in these circumstances is unclear, but a rise in blood pressure seems possible. However, note that these products are usually cautioned in patients with hypertension.

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Inotropes and Vasopressors + Ergometrine (Ergonovine)

An isolated report attributes the development of gangrene and subsequently fatal septicaemia to the use of dopamine following the use of ergometrine. A similar case has been reported with ergometrine and noradrenaline (norepinephrine).

Clinical evidence, mechanism, importance and management

One patient developed gangrene of the hands and feet after being given an infusion of **dopamine** (10 micrograms/kg per minute, later doubled) started approximately 2 hours after the use of ergometrine (two 400-microgram doses).[1] This would seem to have resulted from the additive peripheral vasoconstrictor effects of both drugs, which reduced the circulation to such an extent that gangrene and then fatal septicaemia developed. Note that gangrene has been reported with the use of both drugs alone, and it is recommended that peripheral tissue perfusion should be monitored in elderly patients or patients with a history of peripheral vascular disease receiving **dopamine**.[2] This would also seem to be a prudent precaution in those who have previously received ergometrine.

A similar case report describes a pregnant woman (24-weeks gestation) with severe burns who received ergometrine to treat post-partum bleeding after spontaneous abortion and **noradrenaline** (**norepinephrine**) to treat hypotensive septic shock. The combination of these two vasoconstrictors is thought to have contributed to ischaemia of the fingers, resulting in loss of some digits.[3]

In the rare circumstances when it may be necessary to use both of these drugs, close attention should be paid to peripheral tissue perfusion.

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Inotropes and Vasopressors + Guanethidine

The increase in blood pressure in response to noradrenaline (norepinephrine), phenylephrine, and metaraminol can be enhanced in the presence of guanethidine. These drugs can also be used as eye drops, and in this situation their mydriatic effects are similarly enhanced and prolonged by guanethidine.

Clinical evidence

(a) Blood pressure response

A study in 6 normotensive subjects given guanethidine 200 mg on the first day of the study and 100 mg daily for the next 2 days, found that their mean arterial blood pressure in response to a range of doses of **noradrenaline** (**norepinephrine**), was increased by 6 to 18% (a 6 to 20 mmHg increase). Moreover, cardiac arrhythmias appeared at lower doses of **noradrenaline** and with greater frequency than in the absence of guanethidine, and were more serious in nature.[1]

In another report, a patient taking guanethidine 20 mg daily was given intramuscular **metaraminol** 10 mg, which rapidly caused the blood pressure to rise to 220/130 mmHg accompanied by severe headache and extreme angina.[2] An increase in blood pressure from 165/90 mmHg to 170/110 mmHg was also seen in a patient taking guanethidine who, before surgery, was given **phenylephrine** eye drops.[3]

(b) Mydriatic response

The mydriasis due to **phenylephrine** given as a 10% eye drop solution was prolonged for up to 10 hours in a patient taking guanethidine for hypertension.[4] This enhanced mydriatic response has been described in another study using guanethidine eye drops with **adrenaline** (**epinephrine**), **phenylephrine** or **methoxamine** eye drops.[5]

Mechanism

By preventing the release of noradrenaline from adrenergic neurones, guanethidine and other adrenergic neurone blockers cause a temporary drug-induced sympathectomy, which is also accompanied by hypersensitivity of the receptors. This results in the increased response to the stimulation of the receptors by directly-acting sympathomimetics such as noradrenaline (norepinephrine) and phenylephrine.

Importance and management

An established, well-documented and potentially serious interaction. As the increase in blood pressure can be grossly exaggerated, doses of inotropes or vasopressors with directly-acting sympathomimetic actions (alpha-agonists) should be reduced appropriately. In addition it should be remembered that the incidence and severity of cardiac arrhythmias is increased.[1] Considerable care is required. Direct evidence seems to be limited to noradrenaline (norepinephrine), phenylephrine, metaraminol, and methoxamine. **Dopamine** also possesses direct sympathomimetic activity and may be expected to interact similarly. If as a result of this interaction the blood pressure becomes grossly elevated, it can be controlled by giving an alpha-adrenergic blocker such as phentolamine.[6] Phenylephrine, which is used as a vasopressor, is also contained in a number of non-prescription cough and cold preparations, which may contain 12 mg in a dose. A single dose of this size is only likely to cause a moderate blood pressure rise. However, this requires confirmation, particularly as the non-prescription products may be taken up to four times daily for up to 7 days, and higher doses may be available in some countries.

An exaggerated pressor response is clearly much more potentially serious than enhanced and prolonged mydriasis, but the latter is also possible and undesirable. The same precautions apply with the use of smaller amounts of these drugs.

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Inotropes and Vasopressors + Lithium

The pressor effects of noradrenaline (norepinephrine) and phenylephrine are slightly reduced by lithium carbonate.

Clinical evidence, mechanism, importance and management

A study in 8 patients with manic depression found that after taking lithium carbonate for 7 to 10 days (serum level range 0.72 to 1.62 mmol/L) the dose of a **noradrenaline** (**norepinephrine**) infusion had to be increased by 1.8 micrograms in 7 patients to maintain a blood pressure increase of 25 mmHg. This equated to a 22% reduction in the pressor effect of **noradrenaline**.[1] Another study in 17 depressed patients with serum lithium levels in the range 0.8 to 1.2 mmol/L found that 12% more **noradrenaline** and 31% more **phenylephrine** were needed to raise the blood pressure by 30 mmHg.[2] The reasons for this interaction are not known. Results from an *animal* study suggest that lithium may increase the inactivation of **noradrenaline** and decrease the **noradrenaline** available for adrenergic receptors.[3]

These decreases in the pressor response to **noradrenaline** and to **phenylephrine** in the presence of lithium carbonate are both relatively small and it seems unlikely that they will present any problems in practice.

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Inotropes and Vasopressors + Reserpine

The effects of adrenaline (epinephrine), noradrenaline (norepinephrine) and other related drugs are slightly increased in the presence of reserpine.

Clinical evidence

In 11 patients taking reserpine, pretreatment with **phenylephrine** 10% eye drops caused a blood pressure increase of 30/12 mmHg, whereas no significant increase in blood pressure occurred in 176 patients who were given **phenylephrine** eye drops and who were not taking reserpine.[1] After 7 healthy subjects took reserpine 0.25 to 1 mg daily for 2 weeks the increase in the blood pressure in response to **noradrenaline** (**norepinephrine**) was increased by 20 to 40%.[2] A man taking reserpine who became hypotensive while undergoing surgery did not respond to an intravenous injection of **ephedrine**, but did so after 30 minutes treatment with **noradrenaline**, presumably because the stores of **noradrenaline** at adrenergic neurones had become replenished.[3] The mydriatic effects of **ephedrine** have also been found to be antagonised by pretreatment with reserpine.[4] However, in contrast, one report claimed that **ephedrine** 25 mg given orally or intramuscularly, once or twice daily, proved to be an effective treatment for reserpine-induced hypotension and bradycardia in patients with schizophrenia.[5]

Studies in *dogs* have demonstrated that **adrenaline** (**epinephrine**), **noradrenaline** and **phenylephrine** (all sympathomimetics with direct actions) remain effective vasopressors after treatment with reserpine, and their actions are enhanced to some extent.[6-8] **Metaraminol** has also been successfully used to raise blood pressure in reserpine-treated patients.[9]

Mechanism

The rauwolfia alkaloids (e.g. reserpine) cause adrenergic neurones to lose their stores of noradrenaline (norepinephrine), so that they can no longer stimulate adrenergic receptors and transmission ceases. Indirectly-acting sympathomimetics, which work by stimulating the release of stored noradrenaline, may therefore be expected to become ineffective. In contrast, the effects of directly-acting sympathomimetics should remain unchanged. However, their effects may be enhanced (as described above) because when the receptors are deprived of stimulation by noradrenaline for any length of time they can become supersensitive. Drugs with mixed direct and indirect actions, such as ephedrine, should fall somewhere between the two, although the reports cited seem to indicate that ephedrine has predominantly indirect activity.[3,4]

Importance and management

These are established interactions, but the paucity of clinical information suggests that in practice they do not present many problems, perhaps because the effects of these vasopressors are so closely monitored, and titrated to effect. If a pressor drug is required, a directly-acting drug such as noradrenaline (norepinephrine) or phenylephrine may be expected to be effective. The receptors may show some supersensitivity so that a dose reduction may be required. 'Table 24.1', (p.1048) gives a classification of the sympathomimetics.

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Inotropes and Vasopressors; Dobutamine + Dipyridamole

The addition of dipyridamole to dobutamine for echocardiography can cause potentially hazardous hypotension.

Clinical evidence, mechanism, importance and management

Ten patients with a low probability of coronary artery disease underwent dobutamine echocardiography. Five were given dobutamine alone, while the other 5 were given a low intravenous dose of dipyridamole with the maximum dose of dobutamine, to see whether the sensitivity of the test could be improved. Four of the patients given both drugs experienced severe hypotension while no hypotension was seen in the control group. The conclusion was reached that this combination of drugs can be hazardous and should not be used in patients suspected of coronary heart disease.[1] Note that, although both of these drugs are commonly used in stress echocardiography, they are not given together.

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Inotropes and Vasopressors; Dopamine + Phenytoin

Some limited evidence suggests that patients needing dopamine to support their blood pressure can become severely hypotensive if they are also given intravenous phenytoin.

Clinical evidence, mechanism, importance and management

Five critically ill patients treated with a number of different drugs, were given dopamine to maintain an adequate blood pressure. When seizures developed they were given intravenous phenytoin at an infusion rate of 5 to 25 mg/minute. Their previously stable blood pressures then fell rapidly, one patient became bradycardic, and 2 patients died from cardiac arrest. A similar reaction was found in *dogs* made hypovolaemic and hypotensive by bleeding, and then given dopamine followed by a phenytoin infusion.[1] However, another study in *dogs* was unable to find evidence of this serious adverse interaction,[2] and no evidence of marked hypotension occurred when a patient with cardiogenic shock was given a phenytoin infusion while receiving dopamine and dobutamine.[3]

The documentation of this adverse interaction therefore appears to be limited to this single report. However, intravenous phenytoin is known to cause hypotension if it is given rapidly, particularly in gravely ill patients. Blood pressure is doubtless being monitored in patients receiving dopamine, and should be monitored when phenytoin is given intravenously. However, more frequent monitoring may be necessary initially, as any interaction appears to develop rapidly.

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3. Torres E, Garcia B, Sosa P, Alba D. No interaction between dopamine and phenytoin. *Ann Pharmacother* (1995) 29, 1300–1.

Inotropes and Vasopressors; Dopamine + Selegiline

A case report describes a hypertensive reaction attributed to the concurrent use of dopamine and selegiline.

Clinical evidence, mechanism, importance and management

A 75-year-old man, who was taking selegiline 5 mg twice daily for Parkinson's disease, was given intravenous dopamine 3.5 micrograms/kg per minute because of a decline in blood pressure and urine output following a serious road traffic accident. Twenty minutes after the infusion was started his blood pressure had hardly changed, but 30 minutes later it had risen from 108/33 mmHg to 228/50 mmHg. The dopamine infusion was discontinued and the blood pressure decreased to 121/40 mmHg over the next 30 minutes. The dopamine infusion was reinstituted twice more at lower doses (1.03 and 0.9 micrograms/kg per minute), but each time similar reactions occurred. The exaggerated vasopressor response was thought to be due to inhibition of dopamine metabolism by selegiline.[1]

The authors of the report[1] and the manufacturers of selegiline recommend that dopamine should be used cautiously,[2] and only after careful risk-benefit assessment,[3] in patients who are currently taking selegiline or who have taken selegiline in the 2 weeks before dopamine is required. In addition, the manufacturers of dopamine warn that in patients who have received MAOIs within the previous 2 to 3 weeks, the initial dose of dopamine should be no greater than 10% of the usual dose.[4]

1. Rose LM, Ohlinger MJ, Mauro VF. A hypertensive reaction induced by concurrent use of selegiline and dopamine. *Ann Pharmacother* (2000) 34, 1020– 4.
2. Eldepryl (Selegiline hydrochloride). Orion Pharma (UK) Ltd. UK Summary of product characteristics, June 2009.
3. Zelapar (Selegiline hydrochloride). Cephalon Ltd. UK Summary of product characteristics, September 2008.
4. Dopamine Sterile Concentrate (Dopamine hydrochloride). Hospira UK Ltd. UK Summary of product characteristics, April 2003.

Inotropes and Vasopressors; Dopamine + Tolazoline

Acute and eventually fatal hypotension occurred in a patient given dopamine and tolazoline.

Clinical evidence

A patient receiving ventilatory support following surgery was given **dopamine** on the third postoperative day. Pulmonary arterial pressure had been steadily rising since the surgery, so on day 4 he was given a slow 2-mg/kg bolus injection of tolazoline. Systemic arterial pressure immedi-

ately fell to 50/30 mmHg so the **dopamine** infusion was increased but, contrary to the expected effect, the arterial pressure then fell even further to 38/15 mmHg. The **dopamine** was stopped and ephedrine, methoxamine and fresh frozen plasma were given. Two hours later his blood pressure was 70/40 mmHg. Two further attempts were made to give **dopamine**, but the arterial pressure fell to 40/15 mmHg on the first occasion, and to 38/20 mmHg on the second, which resulted in a fatal cardiac arrest.[1]

Mechanism

The interaction between dopamine and tolazoline is not fully understood. Dopamine has both alpha (vasoconstrictor) and beta (vasodilator) activity. With the alpha effects on the systemic circulation competitively blocked by the tolazoline, its vasodilatory actions would predominate, resulting in paradoxical hypotension.

Importance and management

Information on the interaction between dopamine and tolazoline is limited but this interaction would appear to be established. The authors of this report warn that an infusion of dopamine should not be considered for several hours after even a small single dose of tolazoline has been given. They point out that impaired renal function often accompanies severe respiratory failure, which may significantly prolong the effects of tolazoline.

1. Carlon GC. Fatal association of tolazoline and dopamine. *Chest* (1979) 76, 336.

Ivabradine + CYP3A4 inducers

The manufacturers advise that patients taking CYP3A4 inducers (they specifically name barbiturates, phenytoin, and rifampicin (rifampin)) may need dose increases of ivabradine.[1] This would seem prudent as St John's wort, a known CYP3A4 inducer, reduces ivabradine levels, see 'Ivabradine + St John's wort (*Hypericum perforatum*)', p.1066. See also 'Table 1.4', (p.6), for a list of known CYP3A4 inducers. Monitor the concurrent use of these drugs for ivabradine efficacy and adjust the dose as necessary. Remember to re-adjust the dose of ivabradine if concurrent use of these drugs is stopped.

1. Procoralan (Ivabradine hydrochloride). Servier Laboratories Ltd. UK Summary of product characteristics, October 2009.

Ivabradine + CYP3A4 inhibitors

Ivabradine is metabolised by CYP3A4 and its levels may therefore be increased significantly in the presence of inhibitors of this isoenzyme, such as some azoles, diltiazem, grapefruit juice, some macrolides, nefazodone, protease inhibitors, or verapamil.

Clinical evidence

A study found that **ketoconazole** 200 mg daily or **josamycin** 1 g twice daily increased ivabradine plasma levels by seven- to eightfold. Studies in healthy subjects and patients given **diltiazem** or **verapamil** have resulted in an increase in the AUC of ivabradine of two to threefold, and an additional heart rate reduction of 5 bpm.[1]

Mechanism

Ivabradine is a substrate of the cytochrome P450 isoenzyme CYP3A4, and its metabolism is reduced by inhibitors of CYP3A4, resulting in increased plasma levels and increased therapeutic effects.[1]

Importance and management

The manufacturer contraindicates the use of potent inhibitors of CYP3A4 with ivabradine, (they specifically mention **clarithromycin**, **oral erythromycin**, **itraconazole**, josamycin, ketoconazole, **nefazodone**, **nelfinavir**, **ritonavir**, and **telithromycin**).The manufacturer suggests that if moderate inhibitors of CYP3A4 are given (they name **fluconazole**), ivabradine may be used, but at a lower starting dose of 2.5 mg twice daily, with consideration of heart rate monitoring.[1] Diltiazem and verapamil are also moderate inhibitors of CYP3A4, but their use is not recommended because of their effects on heart rate. Note that clinically relevant inhibitors of CYP3A4 are listed in 'Table 1.4', (p.6). The manufacturers of ivabradine[1] also state that **grapefruit juice** (an inhibitor of CYP3A4 in the intestine) increases the exposure to ivabradine twofold, and they therefore recommend that the intake of grapefruit juice by patients also taking ivabradine is restricted. Note that this increase is similar to that seen with moderate inhibitors of CYP3A4, for which an ivabradine dose reduction has been suggested.

1. Procoralan (Ivabradine hydrochloride). Servier Laboratories Ltd. UK Summary of product characteristics, October 2009.

Ivabradine + Drugs that prolong the QT interval

The manufacturers advise that ivabradine should not be taken with drugs that prolong the QT interval, but also advise that if concurrent use with such drugs appears necessary, close cardiac monitoring is needed. Bradycardia is a pharmacological effect of ivabradine, and QT prolongation may be exacerbated by heart rate reductions.[1] For a list of drugs known to affect the QT interval see 'Table 9.2', (p.290).

1. Procoralan (Ivabradine hydrochloride). Servier Laboratories Ltd. UK Summary of product characteristics, October 2009.

Ivabradine + St John's wort (*Hypericum perforatum*)

The metabolism of ivabradine is increased by St John's wort.

Clinical evidence

Twelve healthy subjects were given a single oral dose of ivabradine 10 mg 24 hours before St John's wort (*Jarsin* tablets) 300 mg three times daily was given for 14 days. On day 16, they were given a further dose of ivabradine 10 mg with a single 300-mg dose of St John's wort. The maximum levels and AUC of ivabradine were reduced by more than half by St John's wort. The maximum levels and AUC of its active metabolite were reduced by 25% and 32%, respectively. No adverse effects were reported, and the heart rate and blood pressure remained unchanged.[1] Similar findings are also reported by the manufacturers of ivabradine.[2]

Mechanism

St John's wort is a known inducer of the cytochrome P450 isoenzyme CYP3A4, by which ivabradine is metabolised. Concurrent use therefore increases the metabolism of ivabradine, which results in a reduction in its plasma levels, and a potential reduction in effects.

Importance and management

Evidence is limited to the study above, and despite the lack of change in pharmacodynamic effects seen in this study, the pharmacokinetic changes may be large enough to affect individual patients. Monitor concurrent use for ivabradine efficacy and adjust the dose as necessary. Remember to re-adjust the dose of ivabradine if the concurrent use of these drugs is stopped. The UK manufacturer suggests that the use of St John's wort should be restricted in patients taking ivabradine.[2]

1. Portolés A, Terleira A, Calvo A, Martínez I, Resplandy G. Effects of Hypericum perforatum on ivabradine pharmacokinetics in healthy volunteers: an open-label, pharmacokinetic interaction clinical trial. *J Clin Pharmacol* (2006) 46, 1188–94.
2. Procoralan (Ivabradine hydrochloride). Servier Laboratories Ltd. UK Summary of product characteristics, October 2009.

Ivabradine + Miscellaneous

The manufacturers say that in specific drug-drug interaction studies, ivabradine was also found not to interact with sildenafil, statins (simvastatin), dihydropyridine calcium-channel blockers (amlodipine, lacidipine), digoxin and warfarin. During clinical studies, ivabradine was taken with ACE inhibitors, angiotensin II

receptor antagonists, diuretics, short and long acting nitrates, statins, fibrates, proton pump inhibitors, oral antidiabetics, aspirin and other antiplatelet drugs, and there was no evidence of safety concerns.[1] A specific drug interaction study in 12 healthy subjects found that omeprazole 40 mg daily or lansoprazole 60 mg daily for 5 days did not significantly affect the pharmacokinetics of a single 10-mg dose of ivabradine.[2]

1. Procoralan (Ivabradine hydrochloride). Servier Laboratories Ltd. UK Summary of product characteristics, October 2009.
2. Portolés A, Calvo A, Terleira A, Laredo L, Resplandy G, Gorostiaga C, Moreno A. Lack of pharmacokinetic interaction between omeprazole or lansoprazole and ivabradine in healthy volunteers: an open-label, randomized, crossover, pharmacokinetic interaction clinical trial. *J Clin Pharmacol* (2006) 46, 1195–203.

Ketanserin + Beta blockers

There is no pharmacokinetic interaction between ketanserin and propranolol, but additive hypotensive effects may occur. Very marked acute hypotension has been seen in two patients taking atenolol when they were first given ketanserin.

Clinical evidence, mechanism, importance and management

A study in 6 patients and 2 healthy subjects given ketanserin 40 mg twice daily for 3 weeks found that **propranolol** 80 mg twice daily for 6 days did not significantly alter the steady-state plasma levels of ketanserin.[1] Another study in healthy subjects, using single doses of both drugs, found that neither drug affected the pharmacokinetics of the other.[2] In a third study, **propranolol** 80 mg twice daily had no effect on the pharmacokinetics of a single 10-mg intravenous dose of ketanserin. However, ketanserin 40 mg twice daily modestly decreased the clearance of a single 160-mg dose of **propranolol** by 29% and increased its maximum serum level by 38%, although neither of these changes were statistically significant.[3] The hypotensive effects of ketanserin were slightly increased by **propranolol** in the first study,[1] and additive hypotensive effects were seen in another study in patients with essential hypertension.[4]

Acute hypotension is reported to have occurred in 2 patients taking **atenolol** within an hour of taking a 40-mg oral dose of ketanserin. One of them briefly lost consciousness.[5]

The concurrent use of ketanserin and beta blockers can be valuable and uneventful, but a few patients may experience marked hypotensive effects when first given ketanserin. Patients should be warned.

1. Trenk D, Lühr A, Radkow N, Jähnchen E. Lack of effect of propranolol on the steady-state plasma levels of ketanserin. *Arzneimittelforschung* (1985) 35, 1286–8.
2. Williams FM, Leeser JE, Rawlins MD. Pharmacodynamics and pharmacokinetics of single doses of ketanserin and propranolol alone and in combination in healthy volunteers. *Br J Clin Pharmacol* (1986) 22, 301–8.
3. Ochs HR, Greenblatt DJ, Höller M, Labedzky L. The interactions of propranolol and ketanserin. *Clin Pharmacol Ther* (1987) 41, 55–60.
4. Hedner T, Persson B. Antihypertensive properties of ketanserin in combination with β-adrenergic blocking agents. *J Cardiovasc Pharmacol* (1985) 7 (Suppl 7), S161–S163.
5. Waller PC, Cameron HA, Ramsey LE. Profound hypotension after the first dose of ketanserin. *Postgrad Med J* (1987) 63, 305–7.

Ketanserin + Diuretics

Sudden deaths, probably from cardiac arrhythmias, were markedly increased in patients taking potassium-depleting diuretics and high doses of ketanserin. No interaction occurred with low doses of ketanserin in those with normal potassium levels. Potassium-sparing diuretics do not interact in this way.

Clinical evidence

A large multi-national study[1] in 3899 patients found that a harmful and potentially fatal interaction could occur in those given ketanserin 40 mg three times daily and **potassium-depleting diuretics**. Of 249 patients taking both drugs, 35 patients (14%) died (16 suddenly) compared with only 15 patients (6%, with 5 sudden deaths) of 260 patients taking a placebo and **potassium-depleting diuretics**. No significant increase in the number of deaths occurred in those taking ketanserin and **potassium-sparing diuretics**. A further analysis of the results found that in patients given ketanserin, the relative mortality was 87% for those not taking diuretics, 76% for those taking **potassium-sparing diuretics** and 313% for those taking **potassium-depleting diuretics**.[2]

It was found that the corrected QT interval was prolonged as follows: ketanserin alone 18 milliseconds, ketanserin with **potassium-sparing diuretics** 24 milliseconds, ketanserin with **potassium-depleting diuretics** 30 milliseconds. Preliminary results of a later study in 33 patients using a smaller dose of ketanserin (20 mg twice daily) with **potassium-depleting diuretics** (**furosemide**, **thiazides**) found no evidence of a prolonged QTc interval in patients with normal potassium levels.[3] The pharmacokinetics of a single 20-mg dose of ketanserin were not altered by single 25-mg doses of **hydrochlorothiazide**.[4]

Mechanism

Potassium-depleting diuretics may cause hypokalaemia, which increases the risk of QT-prolongation and torsade de pointes, which can result in sudden death. Ketanserin also prolongs the QT interval in a dose-related way, and its effects would be expected to be additive with that of diuretic-induced hypokalaemia. See also 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290.

Importance and management

The use of potassium-depleting diuretics (see 'Table 26.1', (p.1121)) with ketanserin 40 mg three times daily should be avoided. Lower doses of ketanserin (20 mg twice daily) have less effect on the QT interval, and can probably be used cautiously with potassium-depleting diuretics, as long as serum potassium levels are maintained. Potassium-sparing diuretics do not interact.

1. Prevention of Atherosclerotic Complications with Ketanserin Trial Group. Prevention of atherosclerotic complications: controlled trial of ketanserin. *BMJ* (1989) 298, 424–30.
2. Verstraete M. The PACK trial: morbidity and mortality effects of ketanserin. *Vasc Med* (1996) 1 135–40.
3. Van Gool R, Symoens J. Ketanserin in combination with diuretics: effect on QTc-interval. *Eur Heart J* (1990) 11 (Suppl), 57.
4. Botha JH, McFadyen ML, Leary WPP, Janssens M. No effect of single-dose hydrochlorothiazide on the pharmacokinetics of single-dose ketanserin. *Curr Ther Res* (1991) 49, 225–30.

Ketanserin + Miscellaneous

Ketanserin should not be given with certain antiarrhythmics, naftidrofuryl, or tricyclic antidepressants because of the risk of potentially fatal cardiac arrhythmias. Drowsiness and dizziness are common adverse effects, which may possibly be additive with the effects of other CNS depressants.

Clinical evidence, mechanism, importance and management

Ketanserin has weak class III antiarrhythmic activity and can prolong the QT_c interval. For safety reasons it has therefore been advised that it should be avoided in patients with existing QT_c prolongation, atrioventricular or sinoauricular block of higher degree, or severe bradycardia of less than 50 bpm.[1] For the same reason the concurrent use of drugs that affect repolarisation (**class Ia**, **class Ic** and **class III arrhythmics**) or drugs that cause conduction disturbances (**naftidrofuryl**, **tricyclic antidepressants**) should be avoided.[1] See also 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290, and 'Ketanserin + Diuretics', above.

Dizziness and drowsiness are common adverse effects of ketanserin and therefore it seems likely that these will be additive with other **CNS depressants** and **alcohol**, which may possibly make driving more hazardous, but this needs confirmation.

1. Distler A. Clinical aspects during therapy with the serotonin antagonist ketanserin. *Clin Physiol Biochem* (1990) 8 (Suppl 3), 64–80.

Ketanserin + Nifedipine

Two patients experienced an increase in cardiac arrhythmias when they were given ketanserin with nifedipine.

Clinical evidence, mechanism, importance and management

A study in 20 subjects aged 60 years or more, with normal or slightly raised blood pressures, found that the concurrent use of ketanserin and

nifedipine for a week did not, on average, affect their blood pressures, heart rates, or QT intervals, but two of the subjects monitored over 24 hours had a marked increase in the frequency of ectopic beats, couplets and ventricular tachycardia.[1] The reasons are not understood. The authors of this study say that their findings do not exclude the possibility that the concurrent use of these two drugs might therefore increase arrhythmia in some elderly patients.[1] Concurrent use should be monitored.

1. Alberio L, Beretta-Piccoli C, Tanzi F, Koch P, Zehender M. Kardiale Interaktionen zwischen Ketanserin und dem Calcium-Antagonisten Nifedipin. *Schweiz Med Wochenschr* (1992) 122, 1723–7.

Levosimendan + ACE inhibitors

The haemodynamic effects of levosimendan were not significantly altered by captopril in one study.

Clinical evidence, mechanism, importance and management

Captopril, in doses of up to 50 mg twice daily, did not change the haemodynamic effects of a single 1-mg or 2-mg intravenous dose of levosimendan in 24 patients with heart failure. No additional decrease in blood pressure was observed.[1] No special precautions appear to be required if levosimendan is given to patients taking captopril. Other ACE inhibitors do not appear to have been studied, but they would be expected to behave in the same way as captopril.

1. Antila S, Eha J, Heinpalu M, Lehtonen L, Loogna I, Mesikepp A, Planken U, Sandell E-P. Haemodynamic interactions of a new calcium sensitizing drug levosimendan and captopril. *Eur J Clin Pharmacol* (1996) 49, 451–8.

Levosimendan + Beta blockers

The haemodynamic effects of levosimendan were not significantly altered by carvedilol or other unnamed beta blockers.

Clinical evidence, mechanism, importance and management

In 12 healthy subjects, carvedilol 25 mg twice daily for 7 to 9 days did not alter the effects of a single 2-mg intravenous dose of levosimendan on cardiac contractility. In addition, the heart rate and diastolic blood pressure responses were not altered, but the systolic blood pressure response was blunted.[1] In a study to compare levosimendan with dobutamine in patients with severe, low-output heart failure, 33 of the 102 patients receiving levosimendan were also given unnamed beta blockers. The use of a beta blocker was found not to reduce the haemodynamic effects of levosimendan. The authors say this suggests that there may be a place for levosimendan in the management of exacerbations of heart failure not controlled by beta blockers.[2] In another study in elderly patients with acute decompensated systolic heart failure, beta blockers did not reduce the beneficial haemodynamic effects of levosimendan.[3]

1. Lehtonen L, Sundberg S. The contractility enhancing effect of the calcium sensitiser levosimendan is not attenuated by carvedilol in healthy subjects. *Eur J Clin Pharmacol* (2002) 58, 449–52.
2. Follath F, Cleland JGF, Just H, Papp JGY, Scholz H, Peuhkurinen K, Harjola VP, MItrovic V, Abdalla M, Sandell E-P, Lehtonen L, for the Steering Committee and Investigators of the Levosimendan Infusion versus Dobutamine (LIDO) Study. Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study): a randomised double-blind trial. *Lancet* (2002) 360, 196–202.
3. Kirlidis TT, Skoularigis J, Tsaknakis KT, Karayiannis G, Tsaknakis TK, Triposkiadis F. The influence of β-blockade on the hemodynamic effects of levosimendan in elderly (≥ 70 years) patients with acutely decompensated heart failure. Int J Pharmacol Ther (2009) 47, 454–9.

Levosimendan + CYP3A4 inhibitors

Itraconazole does not alter the pharmacokinetics of levosimendan and therefore interactions with other CYP3A4 inhibitors are unlikely.

Clinical evidence, mechanism, importance and management

A study in 12 healthy subjects found that the pharmacokinetics of a single 2-mg oral dose of levosimendan were unchanged by **itraconazole** 200 mg daily for 5 days, and there was no change in heart rates or ECGs (including the QTc interval). It was concluded that because **itraconazole**, a potent inhibitor of the cytochrome P450 isoenzyme CYP3A4, does not interact significantly with levosimendan, interactions with other CYP3A4 inhibitors, by this mechanism, are unlikely.[1] For a list of CYP3A4 inhibitors, see 'Table 1.4', (p.6).

1. Antila S, Honkanen T, Lehtonen L, Neuvonen PJ. The CYP3A4 inhibitor itraconazole does not affect the pharmacokinetics of a new calcium-sensitizing drug levosimendan. *Int J Clin Pharmacol Ther* (1998) 36, 446–9.

Levosimendan + Felodipine

The haemodynamic effects of levosimendan were not significantly altered by felodipine.

Clinical evidence, mechanism, importance and management

A study of the use of oral levosimendan 500 micrograms four times daily and felodipine 5 mg daily in 24 men with coronary heart disease found that concurrent use was well tolerated. Felodipine did not antagonise the positive inotropic effects of levosimendan and had no effect on exercise capacity. Both drugs increased heart rate during exercise, and there was a slight additional effect with concurrent use (5 to 8 bpm for levosimendan alone versus 6 to 10 bpm for the combination).[1] There would appear to be no reason for avoiding concurrent use.

1. Pöder P, Eha J, Antila S, Heinpalu M, Planken Ü, Loogna I, Mesikepp A, Akkila J, Lehtonen L. Pharmacodynamic interactions of levosimendan and felodipine in patients with coronary heart disease. *Cardiovasc Drugs Ther* (2003) 17, 451–8.

Levosimendan + Nitrates

Orthostatic hypotension occurred when levosimendan was given with isosorbide mononitrate.

Clinical evidence, mechanism, importance and management

In 12 healthy subjects at rest, giving an infusion of levosimendan (12 micrograms/kg over 10 minutes, then 0.2 micrograms/kg per minute for 110 minutes) with a single 20-mg oral dose of **isosorbide mononitrate** had no additional effects on haemodynamic parameters (heart rate, blood pressure, leg blood flow, cardiac output) to the use of levosimendan alone. However, during an orthostatic test, the circulatory response of the combination was significantly potentiated, and three subjects were unable to remain standing for the stipulated time.[1] Care is therefore required when levosimendan and **isosorbide mononitrate**, or similar drugs, are used concurrently. Whether a similar effect occurs with oral levosimendan is unclear, but as with other drugs that cause postural hypotension, patients should be warned.

1. Sundberg S, Lehtonen L. Haemodynamic interactions between the novel calcium sensitiser levosimendan and isosorbide-5-mononitrate in healthy subjects. *Eur J Clin Pharmacol* (2000) 55, 793–9.

Methyldopa + Barbiturates

Methyldopa levels are not altered by the use of phenobarbital.

Clinical evidence, mechanism, importance and management

Indirect evidence from one study in hypertensive patients suggested that phenobarbital could reduce methyldopa levels,[1] but later work, which directly measured the plasma levels of methyldopa, did not find any evidence of a pharmacokinetic interaction.[2,3]

1. Káldor A, Juvancz P, Demeczky M, Sebestyen, Palotas J. Enhancement of methyldopa metabolism with barbiturate. *BMJ* (1971) 3, 518–19.
2. Kristensen M, Jørgensen M, Hansen T. Plasma concentration of alfamethyldopa and its main metabolite, methyldopa-O-sulphate, during long term treatment with alfamethyldopa with special reference to possible interaction with other drugs given simultaneously. *Clin Pharmacol Ther* (1973) 14, 139–40.
3. Kristensen M, Jørgensen M, Hansen T. Barbiturates and methyldopa metabolism. *BMJ* (1973) 1, 49.

Methyldopa + Bile-acid binding resins

Colestyramine and colestipol are reported to have no important effect on the absorption of methyldopa.[1]

1. Hunninghake DB, King S. Effect of cholestyramine and colestipol on the absorption of methyldopa and hydrochlorothiazide. *Pharmacologist* (1978) 20, 220.

Methyldopa + Cephalosporins

Pustular eruptions developed in two women taking methyldopa and cefradine or cefazolin. The use of methyldopa may have been coincidental.

Clinical evidence, mechanism, importance and management

A 74-year-old black woman taking methyldopa and insulin developed pruritus on her arms and legs within 2 hours of starting to take **cefradine** 250 mg every 6 hours. **Cefradine** was stopped after 7 doses. Over the next 2 days, fever and a widespread pustular eruption developed.[1] Another 65-year-old black woman taking methyldopa and furosemide experienced severe pruritus within 8 hours of starting to receive intravenous **cefazolin sodium** 1 g every 12 hours. Over the next 2 days superficial and coalescing pustules appeared on her trunk, arms and legs.[2] The authors of the first report attributed the reaction to **cefradine**.[1] The authors of the second report note that the concurrent use of methyldopa may or may not have been a contributing factor in both reports.[2] There seem to be no other reports of this reaction.

1. Kalb RE, Grossman ME. Pustular eruption following administration of cephradine. *Cutis* (1986) 38, 58–60.
2. Stough D, Guin JD, Baker GF, Haynie L. Pustular eruptions following administration of cefazolin: a possible interaction with methyldopa. *J Am Acad Dermatol* (1987) 16, 1051–2.

Methyldopa + Disulfiram

An isolated report describes a patient with hypertension, which was unresponsive to methyldopa in the presence of disulfiram.

Clinical evidence, mechanism, importance and management

An alcoholic patient taking disulfiram did not respond to moderate to high doses of intravenous methyldopa, given to control his hypertension, but responded to oral low-dose clonidine. The suggested reason for this lack of response to methyldopa is that disulfiram blocks the activity of dopamine beta-hydroxylase, the enzyme responsible for the conversion of the methyldopa to its active form.[1] The general importance of this apparent interaction is uncertain.

1. McCord RW, LaCorte WS. Hypertension refractory to methyldopa in a disulfiram-treated patient. *Clin Res* (1984) 32, 923A.

Methyldopa + Haloperidol

Two cases of marked CNS adverse effects have been attributed to the use of methyldopa and haloperidol. Another patient taking both drugs became irritable and aggressive. In a small pilot study, the concurrent use of methyldopa and haloperidol lowered blood pressure, and symptomatic hypotension occurred in one patient. The combination also caused marked sedation.

Clinical evidence

Two patients who had been taking methyldopa 1 to 1.5 g daily for hypertension, without problems, developed a dementia syndrome (cognitive disabilities, loss of memory, disorientation, etc.) within 3 days of starting to take haloperidol 6 to 8 mg daily for anxiety. The symptoms totally cleared within 72 hours of stopping the haloperidol.[1] Another patient taking haloperidol for schizophrenia, and methyldopa for hypertension, became very irritable and aggressive. When the methyldopa was replaced with hydrochlorothiazide, the patient's behaviour improved dramatically.[2]

In a pilot study of the therapeutic potential of using haloperidol 10 mg daily with methyldopa 500 mg daily for 4 weeks, in the treatment of schizophrenia, the supine diastolic blood pressure decreased significantly from 65 mmHg to 59.5 mmHg. Six of the 10 patients complained of dizziness, and one patient needed a reduction in the drug doses because of transient hypotension. Somnolence occurred in 8 of the 10 patients.[3]

Mechanism

The hypotensive effects of methyldopa and haloperidol might be expected to be additive. The CNS effects are not understood, although methyldopa can cause sedation, depression and dementia, and haloperidol can cause drowsiness, dizziness and depression.

Importance and management

Concurrent use need not be avoided, but it would be prudent to be on the alert for excessive sedation, excessive reductions in blood pressure or the development of other unexpected CNS adverse effects, particularly in the initial stages of concurrent use.

1. Thornton WE. Dementia induced by methyldopa with haloperidol. *N Engl J Med* (1976) 294, 1222.
2. Nadel I, Wallach M. Drug interaction between haloperidol and methyldopa. *Br J Psychiatry* (1979) 135, 484.
3. Chouinard G, Pinard G, Serrano M, Tetreault L. Potentiation of haloperidol by α-methyldopa in the treatment of schizophrenic patients. *Curr Ther Res* (1973) 15, 473–83.

Methyldopa + Iron compounds

The antihypertensive effects of methyldopa can be reduced by ferrous sulfate. Ferrous gluconate appears to interact similarly. Ferric chloride may also interact but iron complexes such as iron polymaltose are predicted not to interact with methyldopa.

Clinical evidence

Ferrous sulfate 325 mg three times daily was given to 5 hypertensive patients who had been taking methyldopa 250 mg to 1.5 g daily for more than a year. After 2 weeks the blood pressures of all of them had risen, and the systolic pressures of 3 of them had risen by more than 15 mmHg. Four had diastolic blood pressure rises, two of them exceeding 10 mmHg.[1] The renal excretion of unmetabolised methyldopa was reduced by 88% and 79% when methyldopa was given with **ferrous sulfate** and **ferrous gluconate**, respectively.[1] A further study found that if the **ferrous sulfate** was given 2 hours before, one hour before or with the methyldopa, its bioavailability was reduced by 42%, 55%, and 83%, respectively.[2] An *in vitro* study suggests that ferric chloride but not iron polymaltose would interact with methyldopa.[3]

Mechanism

The increase in the metabolic sulfonation of the methyldopa seems to have a part to play in the interaction. However, it appears that methyldopa chelates or complexes with the iron in the gut, reducing its absorption by about 50%.[1,4,5] It has been suggested that if iron is in the form of a complex such as iron polymaltose, it will not form complexes with methyldopa.[3]

Importance and management

Information is limited, but an interaction between methyldopa and iron compounds appears to be established and clinically important. Monitor the effects of concurrent use and increase the methyldopa dose as necessary. Separating the doses by up to 2 hours apparently only partially reduces the effects of this interaction. Ferrous gluconate appears to interact like ferrous sulfate, and all iron salts would be expected to interact similarly, but iron in the form of complexes with carbohydrates such as iron polymaltose is predicted not to interact.

1. Campbell N, Paddock V, Sundaram R. Alteration of methyldopa absorption, metabolism, and blood pressure control caused by ferrous sulfate and ferrous gluconate. *Clin Pharmacol Ther* (1988) 43, 381–6.
2. Campbell NRC, Hasinoff BB. Iron supplements: a common cause of drug interactions. *Br J Clin Pharmacol* (1991) 31, 251–55.
3. Burckhardt-Herold S, Klotz J, Funk F, Büchi R, Petrig-Schaffland J, Geisser P. Interactions between iron(III)-hydroxide polymaltose complex and commonly used drugs: simulations and *in vitro* studies. *Arzneimittelforschung* (2007) 57, 360–9.

4. Campbell NRC, Campbell RRA, Hasinoff BB. Ferrous sulfate reduces methyldopa absorption: methyldopa: iron complex formation as a likely mechanism. *Clin Invest Med* (1990) 13, 329–32.

5. Greene RJ, Hall AD, Hider RC. The interaction of orally administered iron with levodopa and methyldopa therapy. *J Pharm Pharmacol* (1990) 42, 502–4.

Methyldopa + Nasal decongestants

Phenylpropanolamine and related drugs might be expected to cause a blood pressure rise in patients taking methyldopa, and an isolated case report describes such a reaction. The mydriatic effects of ephedrine are reported to be reduced by methyldopa.

Clinical evidence, mechanism, importance and management

A man with renal hypertension, whose blood pressure was well controlled with methyldopa 250 mg twice daily and oxprenolol 160 mg three times daily, had a rise in blood pressure from under 140/80 mmHg to 200/150 mmHg within 2 days of starting to take two tablets of *Triogesic* (**phenylpropanolamine** 12.5 mg and paracetamol 500 mg) three times daily. His blood pressure fell when the *Triogesic* was withdrawn.[1]

The reason for this is uncertain. One suggestion is that the methyldopa causes the replacement of noradrenaline at adrenergic nerve endings by methylnoradrenaline, which has weaker pressor (alpha) activity but greater vasodilator (beta) activity. With the vasodilator activity blocked by the oxprenolol, the vasoconstrictor (pressor) activity of the **phenylpropanolamine** would be unopposed and exaggerated. Alternatively it could have been that he was unusually sensitive to the pressor effects of **phenylpropanolamine**.

In a study in 5 hypertensive patients taking methyldopa 2 to 3 g daily, the rise in blood pressure in response to **tyramine** was doubled.[2] In another study the pressor effect of **tyramine** was 50/16 mmHg, compared with 18/10 mmHg before methyldopa was given.[3]

Despite the information derived from the studies with tyramine and the single report cited, there seems to be nothing else in the literature to suggest that phenylpropanolamine and other indirectly-acting sympathomimetics normally cause an adverse reaction with methyldopa. One report briefly mentions that the antihypertensive effects of various drugs, including methyldopa, were not affected by **diethylpropion**.[4] In contrast, one report suggests that methyldopa may reduce the effects of other related drugs. In 9 patients with untreated hypertension, the normal mydriatic effects of **ephedrine** were reduced by 54% after they started treatment with methyldopa 500 mg to 1.5 g daily.[5] The clinical relevance of this finding is unclear.

1. McLaren EH. Severe hypertension produced by interaction of phenylpropanolamine with methyldopa and oxprenolol. *BMJ* (1976) 3, 283–4.

2. Pettinger W, Horwitz D, Spector S, Sjoerdsma A. Enhancement by methyldopa of tyramine sensitivity in man. *Nature* (1963) 200, 1107–8.

3. Dollery CT, Harington M, Hodge JV. Haemodynamic studies with methyldopa: effect on cardiac output and response to pressor amines. *Br Heart J* (1963) 25, 670–6.

4. Seedat YK, Reddy J. Diethylpropion hydrochloride (Tenuate, Dospan) in the treatment of obese hypertensive patients. *S Afr Med J* (1974) 48, 569.

5. Sneddon JM, Turner P. Ephedrine mydriasis in hypertension and the response to treatment. *Clin Pharmacol Ther* (1969) 10, 64–71.

Methyldopa + Oxazepam

A single, unsubstantiated case report suggests that blood pressure control with methyldopa may possibly be made more difficult in the presence of oxazepam.

Clinical evidence, mechanism, importance and management

A 54-year-old woman with insomnia and essential hypertension had unexplained variability in blood pressure while taking methyldopa 750 mg three times daily and a thiazide diuretic. Within a week of stopping oxazepam 60 mg at night, she developed grand mal convulsions and hypertension (190/90 mmHg standing, 240/140 mmHg lying). Her hypertension was then successfully controlled by switching to atenolol and prazosin. The authors of this report suggest that short-acting benzodiazepines such as oxazepam can cause transient hypotension after a dose, but that *hyper*tension may occur on withdrawal. These effects may complicate the management of hypertension.[1] The general importance of this possible interaction is not established, but it seems likely to be limited.

1. Stokes GS. Can short-acting benzodiazepines exacerbate essential hypertension? *Cardiovasc Rev Rep* (1989) 10, 60–1.

Methyldopa + Phenothiazines

The hypotensive adverse effects of chlorpromazine and other phenothiazines may be additive with the antihypertensive effects of methyldopa. Patients may feel faint and dizzy if they stand up quickly. An isolated report describes paradoxical hypertension in a patient given methyldopa and trifluoperazine.

Clinical evidence

In one study, 8 normotensive patients given methyldopa 500 mg to 1 g daily with **chlorpromazine** 200 to 400 mg daily for schizophrenia experienced orthostatic dizziness and had reductions in their standing systolic blood pressure.[1] In contrast, an isolated report describes a paradoxical *rise* in blood pressure in a patient with systemic lupus erythematosus and renal failure when methyldopa and **trifluoperazine** were given. When the **trifluoperazine** was stopped, the blood pressure fell.[2]

Mechanism

Simple addition of the hypotensive effects of both drugs seems to be the explanation for the increased hypotension and orthostasis. The suggested explanation for the hypertensive interaction with methyldopa and trifluoperazine is that the phenothiazine blocked the reuptake of the 'false transmitter' (alpha-methyl noradrenaline) that is produced when methyldopa is given.[2]

Importance and management

The increased hypotension and orthostasis that can occur if chlorpromazine or other phenothiazines are used with antihypertensive drugs such as methyldopa is established. Note that, of the phenothiazines, **levomepromazine** is particularly associated with postural hypotension. Warn patients that they may feel faint and dizzy particularly during the initial stages of concurrent use, and that if this occurs they should lie down, and that they should remain lying down until symptoms abate completely. Dose adjustments may be necessary.

1. Chouinard G, Pinard G, Prenoveau Y, Tetreault L. Alpha methyldopa-chlorpromazine interaction in schizophrenic patients. *Curr Ther Res* (1973) 15, 60–72.

2. Westhervelt FB, Atuk NO. Methyldopa-induced hypertension. *JAMA* (1974) 227, 557.

Methyldopa + Phenoxybenzamine

An isolated case report describes a patient who had undergone bilateral lumbar sympathectomy who developed total urinary incontinence when taking methyldopa and phenoxybenzamine.

Clinical evidence, mechanism, importance and management

A woman who had previously had bilateral lumbar sympathectomy for Raynaud's disease developed total urinary incontinence when given methyldopa 500 mg to 1.5 g daily in divided doses with phenoxybenzamine 12.5 mg daily, but not when she was taking either drug alone. This would seem to be the outcome of the additive effects of the sympathectomy and the two drugs on the sympathetic control of the bladder sphincters.[1] Stress incontinence has previously been described with these drugs alone, and therefore the general importance of this interaction is probably small.

1. Fernandez PG, Sahni S, Galway BA, Granter S, McDonald J. Urinary incontinence due to interaction of phenoxybenzamine and α-methyldopa. *Can Med Assoc J* (1981) 124, 174.

Methyldopa + Tricyclic and related antidepressants

The antihypertensive effects of methyldopa are not normally adversely affected by desipramine, but an isolated report describes hypertension, tachycardia, tremor and agitation in a man taking

methyldopa and amitriptyline. The tetracyclic mianserin does not appear to interact with methyldopa to a clinically significant extent.

Clinical evidence

A man with hypertension, taking methyldopa 250 mg three times daily and a thiazide diuretic, experienced tremor, agitation, tachycardia (148 bpm) and hypertension (a rise from under 150/90 mmHg to 170/110 mmHg) within 10 days of starting to take **amitriptyline** 25 mg three times daily. A week after stopping all treatment his pulse rate was 100 bpm and his blood pressure 160/90 mmHg.[1] In contrast, a double-blind, crossover study in 5 subjects (one with mild hypertension) found that **desipramine** 25 mg three times daily for 3 days had no significant effect on the hypotensive effects of a single 750-mg dose of methyldopa.[2] Another study in 3 hypertensive patients taking methyldopa 2.5 to 3 g daily found that **desipramine** 75 mg daily for 5 to 6 days did not antagonise the action of methyldopa. In fact, the blood pressure fell slightly.[3] **Mianserin** 20 mg three times daily for 2 weeks had no effect on the control of blood pressure in 6 patients receiving methyldopa, although 2 patients developed symptomatic hypotension after the first dose of **mianserin**.[4,5]

Mechanism

Not understood. Antagonism of the antihypertensive actions of methyldopa by tricyclic antidepressants is seen in *animals* and it seems to occur within the brain.[6,7]

Importance and management

Normally no adverse interaction occurs. However, in view of the case report consider an interaction as a possible cause if a patient taking a tricyclic antidepressant appears unresponsive to methyldopa. Note that methyldopa sometimes induces depression, and so it should generally be avoided in depressed patients.

1. White AG. Methyldopa and amitriptyline. *Lancet* (1965) ii, 441.
2. Reid JL, Porsius AJ, Zamboulis C, Polak G, Hamilton CA, Dean CR. The effects of desmethylimipramine on the pharmacological actions of alpha methyldopa in man. *Eur J Clin Pharmacol* (1979) 16, 75–80.
3. Mitchell JR, Cavanaugh JH, Arias L, Oates JA. Guanethidine and related agents. III. Antagonism by drugs which inhibit the norepinephrine pump in man. *J Clin Invest* (1970) 49, 1596–1604.
4. Elliott HL, Whiting B, Reid JL. Assessment of the interaction between mianserin and centrally-acting antihypertensive drugs. *Br J Clin Pharmacol* (1983) 15, 323S–328S.
5. Elliott HL, McLean K, Sumner DJ, Reid JL. Absence of an effect of mianserin on the actions of clonidine or methyldopa in hypertensive patients. *Eur J Clin Pharmacol* (1983) 24, 15–19.
6. van Spanning HW, van Zwieten PA. The interaction between alpha-methyl-dopa and tricyclic antidepressants. *Int J Clin Pharmacol Biopharm* (1975) 11, 65–7.
7. van Zwieten PA. Interaction between centrally acting hypotensive drugs and tricyclic antidepressants. *Arch Int Pharmacodyn Ther* (1975) 214, 12–30.

Minoxidil + Glibenclamide (Glyburide)

There is some evidence that a 5-mg dose of glibenclamide, but not a 2.5-mg dose, may reduce the hypotensive effect of minoxidil.

Clinical evidence, mechanism, importance and management

A single-dose study in 9 healthy subjects found that glibenclamide 2.5 mg did not alter the hypotensive effect of oral minoxidil 5 mg. However, in a further 4 subjects a 5-mg dose of glibenclamide appeared to cause some loss in the hypotensive effect of minoxidil, but this was not statistically significant. The authors therefore suggested that this interaction may be dose-related. The suggested reason for these effects is that these two drugs have opposing effects on the potassium channels of the smooth muscle of blood vessels.[1] In this study, subjects were pre-treated with propranolol to prevent reflex tachycardia when given minoxidil, which is how minoxidil is used clinically.[1] What is not yet clear is whether any interaction occurs between minoxidil and glibenclamide in a clinical setting.

1. Stein CM, Brown N, Carlson MG, Campbell P, Wood AJJ. Coadministration of glyburide and minoxidil, drugs with opposing effects on potassium channels. *Clin Pharmacol Ther* (1997) 61, 662–8.

Minoxidil + Miscellaneous

The manufacturer notes that excessive blood pressure reductions may occur if minoxidil is used in patients taking guanethidine, because of the adrenergic blocking effects of guanethidine.[1,2] If excessive hypotension occurs with minoxidil, this should *not* be treated with adrenaline (epinephrine) or noradrenaline (norepinephrine), because this may result in excessive tachycardia.[1]

1. Loniten Tablets (Minoxidil). Pharmacia Ltd. UK Summary of product characteristics, January 2008.
2. Minoxidil. Watson Pharmaceuticals, Inc. US Prescribing information, October 2002.

Minoxidil; Topical + Miscellaneous

The absorption of topical minoxidil is increased by topical tretinoin and also possibly by topical corticosteroids, dithranol and soft paraffin. Increased minoxidil absorption could possibly potentiate the hypotensive effects of vasodilators.

Clinical evidence, mechanism, importance and management

A study in 19 healthy subjects found that the absorption of topical minoxidil was increased by almost threefold by the use of topical **tretinoin** 0.05% applied one hour before the minoxidil.[1] In another study, in 29 male patients, the use of topical minoxidil 5% with **tretinoin** 0.01% daily in 15 patients was found to be as effective and safe as the use of minoxidil 5% alone twice daily in the other 14 patients for the treatment of male pattern baldness.[2]

The manufacturer notes that *topical* drugs that alter the stratum corneum barrier, such as **corticosteroids**, **tretinoin**, **dithranol**, or **white** or **yellow soft paraffin**, could result in increased absorption of minoxidil if both drugs are applied concurrently. They suggest that, theoretically, one possible effect of minoxidil absorption would be potentiation of orthostatic hypotension caused by **vasodilators**.[3] The exact drugs are not stated but this caution would be expected to cover drugs such as the **nitrates** and **hydralazine**.

1. Ferry JJ, Forbes KK, VanderLugt JT, Szpunar GJ. Influence of tretinoin on the percutaneous absorption of minoxidil from an aqueous topical solution. *Clin Pharmacol Ther* (1990) 47, 439–46.
2. Shin HS, Won CH, Lee SH, Kwon OS, Kim KH, Eun HC. Efficacy of 5% minoxidil versus combined 5% minoxidil and 0.01% tretinoin for male pattern hair loss: a randomized, double-blind, comparative clinical trial. *Am J Clin Dermatol* (2007) 8, 285–90.
3. Regaine for Men Gel (Minoxidil). McNeil Ltd. UK Summary of product characteristics, April 2008.

Moxisylyte + Miscellaneous

There is a theoretical possibility of increased blood pressure lowering effects if moxisylyte is used with antihypertensives or tricyclic antidepressants.

Clinical evidence, mechanism, importance and management

Moxisylyte is an alpha-1, and to a lesser extent, an alpha-2 blocker, which may be used orally as a peripheral vasodilator in Raynaud's syndrome. The manufacturer suggests that if moxisylyte is used by patients taking **antihypertensives**, it may theoretically potentiate the antihypertensive effect of these drugs, although at the recommended doses this has not been reported.[1]

The manufacturer also says that **tricyclic antidepressants** might increase any hypotensive effect of moxisylyte.[1]

For further commentary on the use of two or more drugs with antihypertensive effects, see 'Antihypertensives + Other drugs that affect blood pressure', p.1051.

1. Opilon (Moxisylyte hydrochloride). Archimedes Pharma UK Ltd. UK Summary of product characteristics, October 2008.

Moxonidine + Hydrochlorothiazide

No clinically significant pharmacokinetic interaction occurs between moxonidine and hydrochlorothiazide; however, the blood pressure lowering effects of the combination is greater than that seen with either drug alone.

Clinical evidence, mechanism, importance and management

In a study in 18 healthy subjects, no clinically relevant pharmacokinetic interaction was seen at steady state between moxonidine 200 micrograms twice daily and hydrochlorothiazide 25 mg twice daily.[1] A double-blind, placebo-controlled study found that when moxonidine 400 micrograms daily was given with hydrochlorothiazide 25 mg daily an increased blood pressure lowering effect was seen, compared with either drug alone. A mean reduction of 27/16 mmHg was noted with the combination, compared with 13/9 mmHg, 20/12 mmHg, and 22/13 mmHg for placebo, moxonidine and hydrochlorothiazide, respectively.[2] No particular precautions seem necessary on concurrent use, unless the combined effect on blood pressure is greater than desired.

1. Weimann H-J, Pabst G, Weber W. Lack of pharmacokinetic interaction between moxonidine and hydrochlorothiazide. *Eur J Clin Pharmacol* (1992) 43, 209–10.
2. Frei M, Küster L, Gardosch von Krosigk PP, Koch HF, Küppers H. Moxonidine and hydrochlorothiazide in combination: a synergistic antihypertensive effect. *J Cardiovasc Pharmacol* (1994) 24, (Suppl 1), S25–S28.

Moxonidine + Miscellaneous

No clinically significant pharmacokinetic interactions occur with moxonidine and digoxin, glibenclamide (glyburide), moclobemide, or quinidine.

Clinical evidence, mechanism, importance and management

(a) Digoxin

In 15 healthy subjects, no clinically relevant pharmacokinetic interaction was seen at steady state between moxonidine 200 micrograms twice daily and digoxin 200 micrograms daily.[1]

(b) Glibenclamide (Glyburide)

In 18 healthy subjects, glibenclamide 2.5 mg daily had no effect on the steady-state pharmacokinetics of moxonidine 200 micrograms twice daily. There was a minor 12% decrease in the AUC of glibenclamide, and a 14% increase in its clearance, but these changes are unlikely to be of any clinical relevance.[2]

(c) Moclobemide

A study found no pharmacokinetic interaction occurred when healthy subjects were given moxonidine 400 micrograms daily and a single 300-mg dose of moclobemide. Moxonidine alone or with moclobemide did not significantly affect cognitive function.[3]

(d) Quinidine

In a single-dose study in 6 healthy subjects, quinidine sulfate 400 mg, given one hour before moxonidine 200 micrograms, caused a minor 11% increase in the AUC of moxonidine and decreased its clearance by 10%. These small changes are unlikely to be of any clinical relevance.[4]

1. Pabst G, Weimann H-J, Weber W. Lack of pharmacokinetic interactions between moxonidine and digoxin. *Clin Pharmacokinet* (1992) 23, 477–81.
2. Müller M, Weimann H-J, Eden G, Weber W, Michaelis K, Dilger C, Achtert G. Steady state investigation of possible pharmacokinetic interactions of moxonidine and glibenclamide. *Eur J Drug Metab Pharmacokinet* (1993) 18, 277–83.
3. Wesnes K, Simpson PM, Jansson B, Grahnén A, Wemann H-J, Küppers H. Moxonidine and cognitive function: interactions with moclobemide and lorazepam. *Eur J Clin Pharmacol* (1997) 52, 351–8.
4. Wise SD, Chan C, Schaefer HG, He MM, Pouliquen IJ, Mitchell MI. Quinidine does not affect the renal clearance of moxonidine. *Br J Clin Pharmacol* (2002) 54, 251–4.

Nicorandil + Miscellaneous

Neither cimetidine nor rifampicin had any clinically relevant effect on the pharmacokinetics of nicorandil. Nicorandil did not alter the anticoagulant effects of acenocoumarol. Although *animal* studies suggest antagonism of effects, a study in patients found no pharmacodynamic interaction between nicorandil and glibenclamide. Nicorandil may potentiate the hypotensive effects of other vasodilators, tricyclic antidepressants and alcohol. Gastrointestinal perforations have been reported during the concurrent use of nicorandil and corticosteroids.

Clinical evidence, mechanism, importance and management

(a) Acenocoumarol

Nicorandil 10 mg twice daily for 4 days then 20 mg twice daily for 7 days did not alter the INR in 11 patients stabilised on acenocoumarol.[1]

(b) Cimetidine

Cimetidine 400 mg twice daily for 7 days had no effect on the pharmacokinetics of nicorandil 20 mg twice daily for 7 days, except that the nicorandil AUC showed a minor 10% increase, which is not clinically important.[1]

(c) Corticosteroids

Gastrointestinal perforations have been reported in patients given nicorandil and corticosteroids. Therefore, the manufacturer advises caution if concurrent use is considered.[2]

(d) Glibenclamide

Studies in *animals* have indicated that there may be antagonism between nicorandil and glibenclamide. However, in a study, 8 patients with diabetes and angina taking glibenclamide, and 11 similar patients not receiving glibenclamide, were given nicorandil 15 mg daily for more than 8 weeks. In contrast to the findings in the *animal* studies, glibenclamide did not cause inhibition of the anti-anginal effects of nicorandil, nor was there any disturbance of diabetic control.[3]

(e) Miscellaneous drugs

Combined data from clinical studies in 1 152 patients taking nicorandil found no evidence of increased adverse effects or an increased number of withdrawals in patients taking unnamed **beta blockers** (210 patients), **calcium-channel blockers** (117 patients), **long-acting nitrates** (130 patients), **diltiazem** (91 patients), **verapamil** (9 patients), **amiodarone** (23 patients) or **molsidomine** (30 patients). It has also been reported that unnamed **antihypertensives**, **antidiabetic** or **lipid-regulating drugs** do not appear to interact adversely with nicorandil.[4] No adverse ECG effects have been seen (including QT or ST segment modifications) with nicorandil.[4] However, the manufacturers suggest that nicorandil may possibly potentiate the blood pressure-lowering effects of other **vasodilators**, **tricyclic antidepressants** or **alcohol**.[2] For further discussion on additive blood pressure lowering effects, consider also 'Antihypertensives + Other drugs that affect blood pressure', p.1051. For mention that phosphodiesterase inhibitors (e.g. **sildenafil**, **tadalafil**, **vardenafil**) should not be used with nicorandil, see 'Phosphodiesterase type-5 inhibitors + Nitrates', p.1537.

(f) Rifampicin

Rifampicin 600 mg daily for 5 days had no effect on the pharmacokinetics of nicorandil 20 mg twice daily for 5 days, except for a minor 17% decrease in the elimination half-life, which is not clinically important.[1]

1. Frydman A. Pharmacokinetic profile of nicorandil in humans: an overview. *J Cardiovasc Pharmacol* (1992) 20 (Suppl 3), S34–S44.
2. Ikorel (Nicorandil). Sanofi-Aventis. UK Summary of product characteristics, February 2009.
3. Hata N, Takano M, Kunimi T, Kishida H, Takano T. Lack of antagonism between nicorandil and sulfonylurea in stable angina pectoris. *Int J Clin Pharmacol Res* (2001) 21, 59–63.
4. Witchitz S, Darmon J-Y. Nicorandil safety in the long-term treatment of coronary heart disease. *Cardiovasc Drugs Ther* (1995) 9, 237–43.

Pentoxifylline + Cimetidine

Cimetidine increases pentoxifylline levels to a moderate extent, which may increase the incidence of adverse effects.

Clinical evidence, mechanism, importance and management

A study in 10 healthy subjects found that the mean steady-state plasma levels of controlled-release pentoxifylline 400 mg every 8 hours were raised by about 27% when cimetidine 300 mg four times daily for 7 days was added.[1] Adverse effects such as headache, nausea, and vomiting were said to be more common and bothersome while taking the cimetidine.[1]

The reason for this interaction is not known. However, cimetidine is known to inhibit the metabolism of theophylline (see 'Theophylline + H_2-receptor antagonists', p.1440, to which pentoxifylline is structurally related.

The findings of this study suggest that this interaction may be clinically relevant. If cimetidine is required in a patient taking pentoxifylline, mon-

itor for adverse effects, and decrease the pentoxifylline dose if problems occur.

1. Mauro VF, Mauro LS, Hageman JH. Alteration of pentoxifylline pharmacokinetics by cimetidine. *J Clin Pharmacol* (1988) 28, 649–54.

Pentoxifylline + Ciprofloxacin

Evidence from one study suggests that ciprofloxacin increases the levels of pentoxifylline, and may increase the incidence of adverse effects. In some clinical studies ciprofloxacin has been used to boost the levels of pentoxifylline.

Clinical evidence

Because patients taking pentoxifylline and ciprofloxacin often complained of headache, the possibility of a pharmacokinetic interaction was studied in 6 healthy subjects. The study found that ciprofloxacin 500 mg daily for 3 days increased the peak serum levels of a single 400-mg dose of pentoxifylline by almost 60% (from 114.5 to 179.5 nanograms/mL), and increased the AUC by 15%. All 6 subjects complained of a frontal headache.[1]

Mechanism

The evidence suggests that ciprofloxacin inhibits the metabolism of the pentoxifylline (a xanthine derivative) by the liver. Studies in *animals* found that ciprofloxacin inhibited the cytochrome P450 isoenzyme CYP1A2 which is involved in the metabolism of pentoxifylline.[2]

Importance and management

Information on this interaction and its clinical relevance is limited. The author of the pharmacokinetic study suggests that, if the drugs need to be used together, the dose of pentoxifylline should be halved.[1] In the absence of other information, if a short-course of ciprofloxacin is required in a patient taking pentoxifylline, this may be a sensible precaution. Alternatively, because the increase in AUC was minor, it may be sufficient to recommend a reduction in pentoxifylline dose only in those who experience adverse effects (e.g. nausea, headache). Note that ciprofloxacin has been used to boost pentoxifylline levels in studies investigating the possible therapeutic value of the ability of pentoxifylline to inhibit various cytokines. For example, ciprofloxacin 500 mg twice daily was used with pentoxifylline 800 mg three times daily for up to one year in patients with myelodysplastic syndrome.[3]

1. Cleary JD. Ciprofloxacin (CIPRO) and pentoxifylline (PTF): a clinically significant drug interaction. *Pharmacotherapy* (1992) 12, 259–60.
2. Peterson TC, Peterson MR, Wornell PA, Blanchard MG, Gonzalez FJ. Role of CYP1A2 and CYP2E1 in the pentoxifylline ciprofloxacin drug interaction. *Biochem Pharmacol* (2004) 68, 395–402.
3. Raza A, Qawi H, Lisak L, Andric T, Dar S, Andrews C, Venugopal P, Gezer S, Gregory S, Loew J, Robin E, Rifkin S, Hsu W-T, Huang R-W. Patients with myelodysplastic syndromes benefit from palliative therapy with amifostine, pentoxifylline, and ciprofloxacin with or without dexamethasone. *Blood* (2000) 95, 1580–87.

Perhexiline + SSRIs

Case reports describe an increase in perhexiline levels resulting in toxicity when citalopram, fluoxetine or paroxetine were given.

Clinical evidence, mechanism, importance and management

An 86-year-old woman taking perhexiline was admitted to hospital because of ataxia, falls, lethargy, nausea, and an inability to cope at home. She had started to take **paroxetine** 20 mg daily 5 weeks earlier. Her serum perhexiline levels were 2.02 mg/L (reference range 0.15 to 0.6 mg/L).[1] Perhexiline toxicity was also seen in two other elderly women, following the use of **paroxetine** in one case, and **fluoxetine** in the other. The perhexiline serum levels fell when both drugs were stopped, but in one case the fall was very slow.[2] Another case report describes toxicity and raised perhexiline levels in an elderly man shortly after he started taking **citalopram**.[3]

The reason for the rise in perhexiline levels is not known, but it seems likely that these SSRIs can inhibit its metabolism, probably by the cytochrome P450 isoenzyme CYP2D6, although note that citalopram is usually considered to be a weak inhibitor of this isoenzyme. The general importance of these interactions is not known, but it would seem prudent to monitor the outcome of concurrent use for perhexiline toxicity and consider monitoring perhexiline levels where possible. The perhexiline dose may need to be reduced. More study is needed.

1. Alderman CP. Perhexiline-paroxetine interaction. *Aust J Hosp Pharm* (1998) 28, 254–5.
2. Alderman CP, Hundertmark JD, Soetratma TW. Interaction of serotonin re-uptake inhibitors with perhexiline. *Aust N Z J Psychiatry* (1997) 31, 601–3.
3. Nyfort-Hansen K. Perhexiline toxicity related to citalopram use. *Med J Aust* (2002) 176, 560–61.

Ranolazine + Azoles

Ketoconazole raises ranolazine levels. Other azoles are expected to interact similarly.

Clinical evidence

In a double-blind, randomised study, healthy subjects were given slow-release ranolazine 375 mg twice daily for 9 days, with ketoconazole 200 mg twice daily on days 5 to 9. The same study was repeated with ranolazine 1 g twice daily. It was found that ketoconazole increased the AUC, levels (mean, peak and trough) and half-life of ranolazine by 2.5- to 4.5-fold. The most common adverse events were headaches, dizziness and nausea. In some patients the higher dose of ranolazine with ketoconazole resulted in intolerable adverse effects.[1]

Mechanism

Ranolazine is a substrate of cytochrome P450 isoenzyme CYP3A4, of which ketoconazole is a potent inhibitor. Concurrent use therefore raises ranolazine levels. All azoles are, to a greater or lesser extent, inhibitors of this isoenzyme and may therefore interact similarly.

Importance and management

Information regarding an interaction between ranolazine and ketoconazole appears to be limited to this study, but what is known is in line with the known effects of these drugs, and is therefore established. The dose-related adverse effects of ranolazine such as nausea and dizziness are increased by ketoconazole. Further, increases in plasma levels of ranolazine may cause significant QT prolongation and the possible risk of arrhythmias (see also, 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290).

The manufacturers of ranolazine contraindicate its use with ketoconazole and other potent CYP3A4 inhibitors. Others they specifically name include **itraconazole**, **posaconazole**, and **voriconazole**.[2,3]

Fluconazole is only a moderate inhibitor of CYP3A4, and therefore the US manufacturer recommends that the dose of ranolazine should be limited to 500 mg twice daily,[2] whereas the UK manufacturer recommends careful dose titration of ranolazine. There appear to be no recommendations about **miconazole**; however, a large proportion of miconazole oral gel (both prescription and non-prescription doses) may be swallowed and therefore adequate systemic absorption may occur to produce an interaction. It would therefore seem prudent to monitor concurrent use closely. For systemic miconazole, similar precautions to those recommended for fluconazole would seem prudent.

1. Jerling M, Huan B-L, Leung K, Chu N, Abdallah H, Hussein Z. Studies to investigate the pharmacokinetic interactions between ranolazine and ketoconazole, diltiazem or simvastatin during combined administration in healthy subjects. J Clin Pharmacol. (2005) 45, 422–33.
2. Ranexa (Ranolazine). CV Therapeutics, Inc. US Prescribing Information, March 2009.
3. Ranexa (Ranolazine). A Menarini Pharma UK SRL. UK Summary of product characteristics, August 2009.

Ranolazine + Calcium-channel blockers

Diltiazem and verapamil raise ranolazine levels, which increases the risk of ranolazine adverse effects. However, concurrent use may be beneficial.

Clinical evidence

(a) Diltiazem

In a placebo-controlled study in 12 healthy subjects, diltiazem 60 mg three times daily was given to 12 healthy subjects for 7 days with ranolazine 240 mg three times daily on days 4 to 7. Ranolazine did not alter the pharmacokinetics of diltiazem, but diltiazem increased the AUC and maximum plasma level of ranolazine by 85% and twofold, respectively. A further study using modified-release diltiazem 180 mg, 240 mg, and 360 mg daily, and a slow-release preparation of ranolazine 1 g twice daily, resulted in increases in the AUC of ranolazine of 52%, 93%, and 139%, respectively.[1] However, a clinical study in patients with angina who were taking diltiazem 180 mg daily, with amlodipine or atenolol, and were given ranolazine or placebo, found that ranolazine 750 mg or 1000 mg twice daily provided additional anti-anginal efficacy with minimal haemodynamic effects.[2]

(b) Verapamil

The plasma levels of ranolazine are reported to be increased twofold by the concurrent use of verapamil 120 mg three times daily.[3]

Mechanism

Ranolazine is a substrate of cytochrome P450 isoenzyme CYP3A4. Diltiazem and verapamil are moderate inhibitors of this isoenzyme, and therefore increase ranolazine levels. Ranolazine is also a substrate of P-glycoprotein and therefore verapamil, which also inhibits P-glycoprotein, may increase its levels by this mechanism as well.

Importance and management

Information regarding an interaction between ranolazine and diltiazem or verapamil is limited, but what is known is in line with the known effects of these drugs, and is therefore established. The dose-related adverse effects of ranolazine such as nausea and dizziness may be increased by concurrent use of drugs that increase its plasma levels. Further, increases in plasma levels of ranolazine may cause significant QT prolongation and the possible risk of arrhythmias (see also, 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290).

The US manufacturer recommends that the dose of ranolazine should be limited to 500 mg twice daily when given to patients also taking moderate CYP3A4 inhibitors including diltiazem, verapamil.[3] The UK manufacturer recommends careful dose titration of ranolazine in patients taking diltiazem, and suggests that lower ranolazine doses may be needed in the presence of verapamil.[4]

There appears to be no information about the use of ranolazine with other calcium-channel blockers, but as these drugs are not inhibitors of CYP3A4 or P-glycoprotein, a pharmacokinetic interaction would not be expected.

1. Jerling M, Huan B-L, Leung K, Chu N, Abdallah H, Hussein Z. Studies to investigate the pharmacokinetic interactions between ranolazine and ketoconazole, diltiazem or simvastatin during combined administration in healthy subjects. J Clin Pharmacol. (2005) 45, 422–33.
2. Chaitman BR, Pepine CJ, Parker JO, Skopal J, Chumakova G, Kuch J, Wang W, Skettino SL, Wolff AA, for the Combination Assessment of Ranolazine In Stable Angina (CARISA) investigators. Effects of ranolazine with atenolol, amlodipine, or diltiazem on exercise tolerance and angina frequency in patients with severe chronic angina: a randomized controlled trial. *JAMA* (2004) 291, 309–16.
3. Ranexa (Ranolazine). CV Therapeutics, Inc. US Prescribing Information, March 2009.
4. Ranexa (Ranolazine). A Menarini Pharma UK SRL. UK Summary of product characteristics, August 2009.

Ranolazine + CYP2D6 inhibitors or substrates

Paroxetine does not affect ranolazine levels to a clinically significant extent. Although drugs such as the tricyclics are predicted to affect the pharmacokinetics of ranolazine, this seems unlikely.

Clinical evidence, mechanism, importance and management

(a) CYP2D6 inhibitors

Paroxetine has been reported to increase the average steady-state plasma concentrations of ranolazine 1 g twice daily by 20%.[1,2] Ranolazine is partially metabolised by the cytochrome P450 isoenzyme CYP2D6, which **paroxetine** inhibits. Therefore, the UK manufacturer predicts that a potent inhibitor of CYP2D6, like **paroxetine**, could increase the AUC of ranolazine 500 mg twice daily (therapeutic dose) by about 62%.[1] However, as CYP2D6 is not the main route of metabolism, only very modest effects are seen, and no dose adjustment is necessary.[1,2]

(b) CYP2D6 substrates

Ranolazine is partially metabolised by cytochrome P450 isoenzyme CYP2D6. Although there are no studies on the concurrent use of CYP2D6 substrates with ranolazine, the manufacturers predict that levels of drugs metabolised by CYP2D6, such as **tricyclic antidepressants** and **antipsychotics**, may be increased and that lower doses of these drugs may be required.[1,2] However, as CYP2D6 inhibitors do not appear to have a clinically relevant effect on ranolazine, an interaction seems highly unlikely.

1. Ranexa (Ranolazine). A Menarini Pharma UK SRL. UK Summary of product characteristics, August 2009.
2. Ranexa (Ranolazine). CV Therapeutics, Inc. US Prescribing Information, March 2009.

Ranolazine + CYP3A4 inducers

Rifampicin (a CYP3A4 and P-glycoprotein inducer) markedly reduces ranolazine levels. Other CYP3A4 inducers are predicted to interact similarly.

Clinical evidence, mechanism, importance and management

Rifampicin 600 mg daily is reported to decrease the steady-state plasma levels of ranolazine 1 g twice daily by about 95%. This is due to the induction of the metabolism of ranolazine by cytochrome P450 isoenzyme CYP3A4 and possibly also by P-glycoprotein. Such a marked reduction in levels would be expected to abolish the effects of ranolazine and the manufacturers of ranolazine therefore contraindicate concurrent use.[1,2] The manufacturers recommend avoiding the concurrent use of ranolazine with other CYP3A4 inducers, including **carbamazepine**, **phenobarbital**, **phenytoin**, **rifabutin**, **rifapentine** and **St John's wort**.[1,2] In the absence of any information on the magnitude of the effect of these CYP3A4 inducers on ranolazine levels, this seems prudent.

1. Ranexa (Ranolazine). CV Therapeutics, Inc. US Prescribing Information, March 2009.
2. Ranexa (Ranolazine). A Menarini Pharma UK SRL. UK Summary of product characteristics, August 2009.

Ranolazine + Miscellaneous

Ranolazine may increase levels of ciclosporin and digoxin. Ciclosporin may also increase ranolazine levels. In theory ranolazine may increase the levels of bupropion, efavirenz and cyclophosphamide. The concurrent use of ranolazine and moderate or potent inhibitors of CYP3A4, will result in increased levels of ranolazine, and can predispose the patient to adverse effects including QT interval prolongation. Cimetidine does not interact with ranolazine to a clinically significant extent. Ranolazine may increase the levels of simvastatin.

Clinical evidence, mechanism, importance and management

(a) Ciclosporin

Ranolazine inhibits P-glycoprotein and has been shown to raise digoxin levels (see *Digoxin*, below). However, ranolazine is also a substrate of P-glycoprotein and plasma levels of ranolazine are increased by inhibitors of P-glycoprotein, such as ciclosporin. The manufacturers of ranolazine therefore advise caution if it is given to patients taking ciclosporin, which is also a P-glycoprotein inhibitor [and substrate].[1,2] The dose of ranolazine should be titrated according to clinical response and down-titration may be required.[1,2] Until more is known it may also be prudent to be alert for any changes in ciclosporin levels.

(b) Cimetidine

The manufacturers report that in healthy subjects cimetidine 400 mg three times daily does not increase levels of ranolazine.[1]

(c) CYP2B6 substrates

Although the potential for ranolazine to inhibit the cytochrome P450 isoenzyme CYP2B6 has not been evaluated, the UK manufacturer advises caution if it is given with CYP2B6 substrates and they give as examples

bupropion, **efavirenz** and **cyclophosphamide**.[2] The clinical relevance of any interaction is unknown.

(d) Digoxin

A study in healthy subjects given ranolazine 1 g twice daily and digoxin 125 micrograms found that ranolazine increased the plasma levels of digoxin by about 50%. Plasma levels of ranolazine were not significantly affected by digoxin.[1,2] Ranolazine probably raises digoxin levels by inhibiting P-glycoprotein. Digoxin levels should be monitored if ranolazine is started or stopped, and the digoxin dose may have to be adjusted.[1,2]

(e) Other drugs

Ranolazine is a substrate of the cytochrome P450 isoenzyme CYP3A4 and inhibitors of CYP3A4 increase plasma levels of ranolazine. Potent inhibitors of CYP3A4 such as ketoconazole (see 'Ranolazine + Azoles', p.1073) cause a three to fourfold increase in ranolazine levels and moderate inhibitors such as diltiazem (see 'Ranolazine + Calcium-channel blockers', p.1073) may increase levels about twofold. The dose-related adverse effects of ranolazine such as nausea and dizziness may be increased by concurrent use of drugs that increase its plasma levels. Further, increases in plasma levels of ranolazine may cause significant QT prolongation and the possible risk of arrhythmias (see also, 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290).

The manufacturers of ranolazine contraindicate its use with potent CYP3A4 inhibitors. They include **clarithromycin**, **nefazodone** and the **protease inhibitors** (the US manufacturer[1] names **indinavir**, **nelfinavir**, **ritonavir** and **saquinavir**). The UK manufacturer[2] also names **telithromycin**.

The US manufacturer recommends that the dose of ranolazine should be limited to 500 mg twice daily when given to patients taking moderate CYP3A4 inhibitors including **aprepitant** and **erythromycin**.[1] The UK manufacturer recommends careful dose titration of ranolazine in patients taking moderately potent CYP3A4 inhibitors, and name **erythromycin**.

While the UK manufacturers of ranolazine consider **grapefruit juice** to be a potent inhibitor of CYP3A4 and therefore contraindicate its use with ranolazine, the US manufacturer includes **grapefruit juice** and **grapefruit-containing products** as moderate inhibitors and recommends limiting the dose of ranolazine to 500 mg twice daily during concurrent use.[1]

Ranolazine is also a substrate of P-glycoprotein and therefore ritonavir, which inhibits P-glycoprotein may also increase ranolazine levels by this mechanism (see *Digoxin*, above).

1. Ranexa (Ranolazine). CV Therapeutics, Inc. US Prescribing Information, March 2009.
2. Ranexa (Ranolazine). A Menarini Pharma UK SRL. UK Summary of product characteristics, August 2009.

Sodium nitroprusside + Miscellaneous

Smaller doses of sodium nitroprusside might be required in patients receiving antihypertensive drugs. Clonidine does not affect the response to nitroprusside. There is a risk of severe hypotension if phosphodiesterase inhibitors (e.g. sildenafil, tadalafil and vardenafil) are used with sodium nitroprusside.

Clinical evidence, mechanism, importance and management

(a) Antihypertensives

The manufacturer notes that smaller doses of sodium nitroprusside might be required in patients receiving antihypertensive drugs. In any event the required dose varies considerably between patients and so should be titrated to effect.[1]

In a placebo-controlled study, patients with hypertension were given intravenous sodium nitroprusside in increasing bolus doses of 30 to 300 micrograms on the day before surgery, before induction of anaesthesia and one and 3 hours postoperatively. Oral **clonidine** 6 micrograms/kg, was given 2 hours before surgery with a further dose of 3 micrograms/kg intravenously over the last hour of surgery. **Clonidine** did not affect the perioperative response to nitroprusside.[2]

When nitroprusside is used for controlled hypotension during anaesthesia, the hypotensive effect of other drugs, particularly anaesthetics, should be remembered.[1] The manufacturer specifically names **halothane** and **enflurane**. Consider also 'Antihypertensives + Other drugs that affect blood pressure', p.1051.

(b) Phosphodiesterase type-5 inhibitors

The use of phosphodiesterase inhibitors (e.g. **sildenafil**, **tadalafil** and **vardenafil**) with sodium nitroprusside is contraindicated by the manufacturers, due to the risk of severe hypotension. See also 'Phosphodiesterase type-5 inhibitors + Nitrates', p.1537. A case report describes the therapeutic use of **sildenafil** to enhance the hypotensive effect of sodium nitroprusside and other antihypertensives in a patient with a hypertensive crisis.[3]

1. Sodium Nitroprusside. Mayne Pharma plc. UK Summary of product characteristics, May 2005.
2. Parlow JL, Sagnard P, Begou G, Viale J-P, Quinin L. The effects of clonidine on sensitivity to phenylephrine and nitroprusside in patients with essential hypertension recovering from surgery. *Anesth Analg* (1999) 88, 1239–43.
3. Bahadur MM, Aggarwal VD, Mali M, Thamba A. Novel therapeutic option in hypertensive crisis: sildenafil augments nitroprusside-induced hypotension. *Nephrol Dial Transplant* (2005) 20, 1254–6.

Tirilazad + Miscellaneous

Phenobarbital and phenytoin reduce the levels of tirilazad mesilate whereas ketoconazole increases them. Finasteride inhibits the metabolism of tirilazad mesilate to its active metabolite. No pharmacokinetic interaction appears to occur between cimetidine or nimodipine and tirilazad mesilate.

Clinical evidence, mechanism, importance and management

(a) Cimetidine

A study in 16 healthy men found that cimetidine 300 mg every 6 hours for 4 days had no effect on the pharmacokinetics of a single 2-mg/kg dose of tirilazad mesilate, given by infusion over 10 minutes on day 2, nor on U-89678, its active metabolite.[1] No special precautions would seem necessary if cimetidine is given with tirilazad mesilate.

(b) Finasteride

In a study, 8 healthy men were given finasteride 5 mg daily for 10 days, with tirilazad mesilate 10 mg/kg orally or 2 mg/kg intravenously on day 7. Finasteride increased the AUCs of intravenous and oral tirilazad by 21% and 29%, respectively. Oral finasteride reduced the AUCs of the active metabolite (U-89678) by 92% when tirilazad was given intravenously and by 75% when tirilazad was given orally. Although the metabolism of tirilazad to U-89678 was inhibited there was only a moderate effect on the overall clearance of tirilazad and the interaction was considered unlikely to be of clinical significance.[2]

(c) Ketoconazole

Tirilazad mesilate, 10 mg/kg orally or 2 mg/kg intravenously, was given to 12 healthy subjects (both men and women), either alone or on day 4 of a 7-day regimen of ketoconazole 200 mg daily. The ketoconazole more than doubled the absolute bioavailability of the oral tirilazad mesilate (from 8.7% to 20.9%), apparently because its metabolism by the cytochrome P450 isoenzyme CYP3A in the gut wall and during the first pass through the liver was inhibited.[3] The clinical importance of this interaction awaits assessment.

(d) Nimodipine

In a single-dose study in 12 healthy men, there was no pharmacokinetic or pharmacodynamic interaction between intravenous tirilazad mesilate 2 mg/kg and oral nimodipine 60 mg.[4] No special precautions would seem necessary if nimodipine is given with tirilazad mesilate

(e) Phenobarbital

The pharmacokinetics of tirilazad mesilate (1.5 mg/kg as 10 minute intravenous infusions every 6 hours for 29 doses) were studied in 15 healthy subjects before and after they took phenobarbital 100 mg daily for 8 days. Phenobarbital increased the clearance of tirilazad by 25% in the male subjects and 29% in the female, and the AUC of the active metabolite of tirilazad (U-89678) was reduced by 51% in the males and 69% in the females. This was thought to occur because phenobarbital acts as an enzyme inducer, which increases the metabolism of the tirilazad.[5] The clinical importance of these pharmacokinetic changes awaits assessment, but be alert for evidence of reduced effects if both drugs are given. It is doubtful if the full enzyme-inducing effects of the phenobarbital would have been reached in this study after only one week, so anticipate a greater effect if it is given for a longer period. Note that **primidone** is metabolised to phenobarbital, and therefore it may be expected to interact similarly.

(f) Phenytoin

In a study in 12 healthy subjects, phenytoin 200 mg every 8 hours for 11 doses then 100 mg every 8 hours for 5 doses, reduced the $AUC_{0\text{-}6}$ of tirilazad mesilate by 35%. The AUC of the active metabolite, U-89678, was reduced by 87%.[6] Another report by the same group of workers[7] found that phenytoin every 8 hours for 7 days (9 doses of 200 mg followed by 13 doses of 100 mg) reduced the clearance of tirilazad by 92% and of U-89678 by 93%. In another report the authors noted that phenytoin increased the metabolism of tirilazad and its metabolite in men and women to similar extents.[8] The clinical importance of these reductions is still to be assessed, but be alert for any evidence of reduced tirilazad effects if both drugs are given. Note that **fosphenytoin** is a prodrug of phenytoin, and may therefore be expected to interact similarly.

1. Fleishaker JC, Hulst LK, Peters GR. Lack of pharmacokinetic interaction between cimetidine and tirilazad mesylate. *Pharm Res* (1994) 11, 341–4.
2. Fleishaker JC, Pearson PG, Wienkers LC, Pearson LK, Moore TA, Peters GR. Biotransformation of tirilazad in human: 4. effect of finasteride on tirilazad clearance and reduced metabolite formation. J Pharmacol Exp Ther. (1998) 287, 591–7.
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4. Fleishaker JC, Hulst LK, Peters GR. Lack of a pharmacokinetic/pharmacodynamic interaction between nimodipine and tirilazad mesylate in healthy volunteers. *J Clin Pharmacol* (1994) 34, 837–41.
5. Fleishaker JC, Pearson LK, Peters GR. Gender does not affect the degree of induction of tirilazad clearance by phenobarbital. *Eur J Clin Pharmacol* (1996) 50, 139–45.
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7. Fleishaker JC, Pearson LK, Peters GR. Induction of tirilazad clearance by phenytoin. *Biopharm Drug Dispos* (1998) 19, 91–6.
8. Fleishaker JC, Pearson LK, Peters GR. Effect of gender on the degree of induction of tirilazad clearance by phenytoin. *Clin Pharmacol Ther* (1996) 59, 168.

Tolazoline + H_2-receptor antagonists

Cimetidine and ranitidine can reduce or abolish the effects of tolazoline used as a pulmonary vasodilator in children.

Clinical evidence

A newborn infant with persistent foetal circulation was given a continuous infusion of tolazoline to reduce pulmonary hypertension. The oxygenation improved but gastrointestinal bleeding occurred. When **cimetidine** was given, the condition of the child deteriorated with a decrease in oxygen saturation and arterial pO_2 values.[1] A second case report describes a similar outcome in a 2-day-old neonate, who had an initial improvement with tolazoline alone, but then developed worsening hypoxaemia when cimetidine was given.[2]

These reports are similar to another, in which the tolazoline-induced reduction in pulmonary arterial pressure in a child was reversed when **cimetidine** was given, for acute gastrointestinal haemorrhage.[3] Another study in 12 children found that intravenous **ranitidine** 3 mg/kg abolished the tolazoline-induced reduction in pulmonary and systemic vascular.[4]

Mechanism

Tolazoline dilates the pulmonary vascular system by stimulating both H_1- and H_2-receptors. Cimetidine and ranitidine block H_2-receptors so that at least part of the effects of tolazoline are abolished. It has been suggested that this interaction is confined to children.[3]

Importance and management

An established interaction. Cimetidine and ranitidine are not suitable drugs for prophylaxis of the gastrointestinal adverse effects of tolazoline in children. Other H_2-receptor antagonists would be expected to behave similarly.

1. Roll C, Hanssler L. Interaktion von Tolazolin und Cimetidin bei persistierender fetaler Zirkulation des Neugeborenen. *Monatsschr Kinderheilkd* (1993) 141, 297–9.
2. Huang C-B, Huang S-C. Caution with use of cimetidine in tolazoline induced upper gastrointestinal bleeding. Changgeng Yi Xue Za Zhi. (1996) 19, 268–71.
3. Jones ODH, Shore DF, Rigby ML, Leijala M, Scallan J, Shinebourne EA, Lincoln JCR. The use of tolazoline hydrochloride as a pulmonary vasodilator in potentially fatal episodes of pulmonary vasoconstriction after cardiac surgery in children. *Circulation* (1981) 64 (Suppl II), II-134–II-139.
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25

Digitalis glycosides

Plant extracts containing cardiac glycosides have been in use for thousands of years. The ancient Egyptians were familiar with squill (a source of **proscillaridin**), as were the Romans who used it as a heart tonic and diuretic. The foxglove was mentioned in the writings of Welsh physicians in the thirteenth century and features in 'An Account of the Foxglove and some of its Medical Uses', published by William Withering in 1785, in which he described its application in the treatment of 'dropsy' or the oedema that results from heart failure.

The most commonly used cardiac glycosides are those obtained from the members of the foxglove family, *Digitalis purpurea* and *Digitalis lanata*. The leaves of *D. lanata* are the source of a number of purified glycosides including **digoxin**, **digitoxin**, **acetyldigoxin**, **acetyldigitoxin**, **lanatoside C**, **deslanoside**, of gitalin (an amorphous mixture largely composed of digitoxin and digoxin), and of powdered whole leaf **digitalis lanata leaf**. *D. purpurea* is the source of **digitoxin**, **digitalis leaf**, and the standardised preparation **digitalin**. **Metildigoxin** is a semi-synthetic digitalis glycoside. Occasionally ouabain or strophanthin-K (also of plant origin) are used for particular situations, while for a number of years the Russians have exploited cardiac glycosides from lily of the valley (**convallaria**). Bufalin is a related cardioactive compound obtained from toads, and is found in a number of Chinese medicines.

Digitalisation

The cardiac glycosides have two main actions and two main applications. They reduce conductivity within the atrioventricular (AV) node, hence are used for treating supraventricular tachycardias (especially atrial fibrillation), and they have a positive inotropic effect (i.e. increase the force of contraction), and hence may be used for congestive heart failure.

Because the most commonly used glycosides are derived from digitalis, the achievement of the desired therapeutic serum concentration of any cardiac glycoside is usually referred to as digitalisation. Treatment may be started with a large loading dose so that the therapeutic concentrations are achieved reasonably quickly, but once these have been reached the amount is reduced to a maintenance dose. This has to be done carefully because there is a relatively narrow gap between therapeutic and toxic serum concentrations. Normal therapeutic levels are about one-third of those that are fatal, and serious toxic arrhythmias begin at about two-thirds of the fatal levels. The therapeutic range for digoxin levels is 0.8 to 2 nanograms/mL (or 1.02 to 2.56 nanomol/L). To convert nanograms/mL to nanomol/L multiply by 1.28, or to convert nanomol/L to nanograms/mL multiply by 0.781. Note that micrograms/L is the same as nanograms/mL.

If a patient is over-digitalised, signs of toxicity will occur, which may include loss of appetite, nausea and vomiting, and bradycardia. These symptoms are often used as clinical indicators of toxicity and a pulse rate of less than 60 bpm is usually considered to be an indication of over-treatment. Note that paroxysmal atrial tachycardia with AV block and junctional tachycardia can also occur as a result of digitalis toxicity. Other symptoms include visual disturbances, headache, drowsiness and occasionally diarrhoea. Death may result from cardiac arrhythmias. Patients given digitalis for cardiac arrhythmias can therefore demonstrate arrhythmias when they are both under- as well as over-digitalised.

Interactions of the cardiac glycosides

The pharmacological actions of these glycosides are very similar, but their rates and degree of absorption, metabolism and clearance are different. For example, digoxin is mainly renally cleared whereas digitoxin undergoes a degree of metabolism by the liver. It is therefore most important not to extrapolate a pharmacokinetic interaction seen with one glycoside and apply it uncritically to any other. Because the therapeutic ratio of the cardiac glycosides is low, a quite small change in serum levels may lead to inadequate digitalisation or to toxicity. For this reason interactions that have a relatively modest effect on serum levels may sometimes have serious consequences.

Many interactions between digoxin and other drugs are mediated by P-glycoprotein. Drugs that inhibit the activity of P-glycoprotein in the renal tubules may reduce the elimination of digoxin in the urine and this may result in toxic serum levels. Further, the induction or inhibition of P-glycoprotein in the gut may affect the oral absorption of digoxin. See also 'Drug transporter proteins', (p.8).

Digoxin and related drugs + ACE inhibitors

Most ACE inhibitors do not interact with digoxin to a clinically relevant extent. Some studies have found that serum digoxin levels rise by about 20% or more if captopril is used, but others have found no significant changes. It has been suggested that any interaction is likely to occur only in those patients who have pre-existing renal impairment. Digitoxin and captopril appear not to interact.

Clinical evidence

(a) Digitoxin and Captopril

A study in 12 healthy subjects given digitoxin 70 micrograms daily for up to 58 days found no evidence that the addition of captopril 25 mg daily had a relevant effect on the pharmacokinetics of digitoxin, or its effects on the heart.[1]

(b) Digoxin and Captopril

The serum digoxin levels of 16 patients with severe chronic congestive heart failure rose by 21% (from 1.1 to 1.3 nanograms/mL), while taking captopril (average dose 93.7 mg daily). Serum digoxin levels were above the therapeutic range at 2 nanograms/mL on 3 out of 63 occasions, but no toxicity was seen. All patients had impaired renal function and were being treated with diuretics.[2,3] Another study[4] found a rise of about 30% in serum digoxin levels in patients with congestive heart failure (NYHA class II) given captopril and a further study[5] found an approximate 60% rise in peak serum digoxin levels in patients with congestive heart failure (NYHA class IV) given captopril. Conversely, another study in 31 patients with stable congestive heart failure, given captopril 25 mg three times daily, found no significant changes in serum digoxin levels over a 6-month period.[6] Two other studies in healthy subjects[7] and patients with congestive heart failure[8] also found no evidence of an interaction.

(c) Digoxin and Other ACE inhibitors

In general no significant interactions have been seen between ACE inhibitors and digoxin.

- **Cilazapril** 5 mg for 14 days did not alter the trough plasma digoxin levels in healthy subjects.[9]
- **Enalapril** 20 mg daily for 30 days had no significant effect on the pharmacokinetics of digoxin 250 micrograms daily in 7 patients with congestive heart failure.[10]
- **Imidapril** 10 mg daily had no effect on the serum digoxin levels of 12 healthy subjects, but slight reductions in levels of the active form imidaprilat and in ACE inhibition of about 15% were seen, which were of uncertain clinical relevance.[11]
- **Lisinopril** 5 mg daily for 4 weeks had no significant effect on the serum digoxin levels of 9 patients.[12] This confirms the findings of a single-dose study.[13]
- **Moexipril** has been reported, by the manufacturer, to have had no important pharmacokinetic interaction with digoxin in healthy subjects.[14] The manufacturer also has clinical studies that show no evidence of clinically important adverse interactions when moexipril was used with digoxin.[15]
- **Perindopril** 2 to 4 mg daily for a month had no effect on the steady-state serum digoxin levels of 10 patients with mild chronic heart failure.[16]
- **Quinapril** is also reported not to alter the steady-state levels of digoxin in healthy subjects,[17] and patients with congestive heart failure.[18]
- **Ramipril** 5 mg daily for 14 days had no effect on the serum digoxin levels of 12 healthy subjects.[19]
- **Spirapril** 12 to 48 mg daily did not significantly affect the pharmacokinetics nor the steady-state serum levels of digoxin in 15 healthy subjects taking digoxin 250 micrograms twice daily.[20]
- **Trandolapril** has been shown to have no significant pharmacokinetic interaction with digoxin in healthy subjects.[21] The manufacturers also note that, in patients with left ventricular dysfunction after myocardial infarction, no clinical interactions have been found between trandolapril and digoxin.[22,23]

Mechanism

Not fully understood. It has been suggested that an interaction is only likely to occur in those who have renal impairment because the glomerular filtration rate of these patients may be maintained by the vasoconstrictor action of angiotensin II on the post-glomerular blood vessels, which would be impaired by ACE inhibition. As a result some of the loss of digoxin through the tubules is reduced.[7]

Importance and management

The overall picture is that no clinically important adverse interaction occurs between digoxin and ACE inhibitors in patients with normal renal function, and that serum digoxin monitoring is only needed in those who have a high risk of reversible ACE inhibitor-induced renal failure (e.g. patients with congestive heart failure during chronic diuretic treatment, with bilateral renal artery stenosis or unilateral renal artery stenosis in a solitary kidney);[7] however, note these latter two conditions are contraindications to the use of ACE inhibitors. The critical factor does not seem to be the particular ACE inhibitor used but the existence of abnormal renal function or conditions that increase the risk of renal impairment. This needs confirmation.

No interaction apparently occurs between digitoxin and captopril in healthy subjects, but this ideally needs confirmation in patients.

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14. Perdix (Moexipril hydrochloride). UCB Pharma Ltd. UK Summary of product characteristics, April 2009.
15. Perdix (Moexipril). Schwarz Pharma. Product Monograph. Data on file, September 1995.
16. Vandenburg MJ, Stephens JD, Resplandy G, Dews IM, Robinson J, Desche P. Digoxin pharmacokinetics and perindopril in heart failure patients. *J Clin Pharmacol* (1993) 33, 146–9.
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21. New horizons in antihypertensive therapy. Gopten® Trandolapril. Knoll AG, 1992.
22. Gopten (Trandolapril). Abbott Laboratories Ltd. UK Summary of product characteristics, July 2009.
23. Mavik (Trandolapril). Abbott Laboratories. US Prescribing information, April 2009.

Digoxin + Acipimox

One study suggests that acipimox does not interact with digoxin.

Clinical evidence, mechanism, importance and management

In 6 elderly patients acipimox 250 mg three times daily for a week was found to have no significant effect on plasma digoxin levels, clinical con-

dition, ECGs, plasma urea or electrolyte levels.[1] No special precautions would seem necessary during concurrent use.

1. Chijioke PC, Pearson RM, Benedetti S. Lack of acipimox-digoxin interaction in patient volunteers. *Hum Exp Toxicol* (1992) 11, 357–9.

Digoxin + Allopurinol

Allopurinol does not appear to affect digoxin levels.

Clinical evidence, mechanism, importance and management

No significant changes in the serum digoxin levels of 5 healthy subjects occurred over a 7-day period while they were taking allopurinol 300 mg daily.[1] No digoxin dose adjustments would appear to be necessary on concurrent use.

1. Havelund T, Abildtrup N, Birkebaek N, Breddam E, Rosager AM. Allopurinols effekt på koncentrationen af digoksin i serum. *Ugeskr Laeger* (1984) 146, 1209–11.

Digoxin + Alpha blockers

A rapid and marked rise in serum digoxin levels occurred in one study when prazosin was also given, whereas a decrease in digoxin levels was reported in another study with prazosin. Alfuzosin, doxazosin, tamsulosin and terazosin appear not to interact with digoxin.

Clinical evidence, mechanism, importance and management

(a) Alfuzosin

The manufacturers of alfuzosin report that no pharmacodynamic or pharmacokinetic interaction was observed in healthy subjects given alfuzosin 10 mg [daily] with digoxin 250 micrograms daily for 7 days.[1,2]

(b) Doxazosin

Doxazosin is highly bound to plasma proteins (98%), but the manufacturer notes that *in vitro* data in human plasma indicated that doxazosin did not affect the protein binding of digoxin.[3,4] Although there appears to be no clinical evidence of an interaction between digoxin and doxazosin, an *in vitro* study found that doxazosin inhibited the P-glycoprotein-mediated transcellular transport of digoxin, suggesting that an interaction is possible, as digoxin renal transport may be inhibited.[5] More study is needed.

(c) Prazosin

In 20 patients prazosin 2.5 mg twice daily increased the mean steady-state plasma digoxin level by 43% (from 0.94 to 1.34 nanograms/mL) after one day, and by 60% (from 0.94 to 1.51 nanograms/mL) after 3 days, although the individual response varied from an increase to a decrease, or no effect. Three days after the prazosin was stopped, by which time it would be totally cleared from the body, the serum digoxin concentrations had fallen to their previous levels.[6] Another study found that prazosin shortened the half-life of digoxin, decreased serum levels and increased its clearance, but did not affect digoxin bioavailability.[7]

The reason for this response is not understood. There do not appear to be any other reports in the literature, and the manufacturer notes that, in clinical experience, prazosin has been given with digoxin (and **digitalis**) without any adverse drug interaction.[8] However, bear this interaction in mind in case of an unexpected response to treatment.

(d) Tamsulosin

A placebo-controlled study in 10 healthy subjects found that tamsulosin 800 micrograms daily had no effect on the pharmacokinetics of a single 500-microgram intravenous dose of digoxin. The most frequently reported adverse effect was dizziness and the safety profile was considered acceptable.[9] The manufacturers note that dose adjustments are not necessary when tamsulosin is given with digoxin.[10]

(e) Terazosin

The manufacturer of terazosin states that terazosin has been given with cardiac glycosides without evidence of an interaction.[11]

1. Xatral (Alfuzosin hydrochloride). Sanofi-Aventis. UK Summary of product characteristics, February 2009.
2. Uroxatral (Alfuzosin hydrochloride extended-release tablets). Sanofi-Aventis US LLC. US Prescribing information, June 2009.
3. Cardura (Doxazosin mesilate). Pfizer Ltd. UK Summary of product characteristics, August 2009.
4. Cardura (Doxazosin mesylate). Pfizer Inc. US Prescribing information, July 2009.
5. Takara K, Kakumoto M, Tanigawara Y, Funakoshi J, Sakaeda T, Okumura K. Interaction of digoxin with antihypertensive drugs *via* MDR1. *Life Sci* (2002) 70, 1491–1500.
6. Çopur S, Tokgözoğlu L, Oto A, Oram E, Uğurlu Ş. Effects of oral prazosin on total plasma digoxin levels. *Fundam Clin Pharmacol* (1988) 2, 13–17.
7. Halawa B, Mazurek W. Interakcja digoksyny z dihydralazyną I prazosyną. Pol Tyg Lek 1986) 41, 1521–3.
8. Hypovase (Prazosin hydrochloride). Pfizer Ltd. UK Summary of product characteristics, August 2007.
9. Miyazawa Y, Starkey LP, Forrest A, Schentag JJ, Kamimura H, Swarz H, Ito Y. Effects of the concomitant administration of tamsulosin (0.8 mg) on the pharmacokinetic and safety profile of intravenous digoxin (Lanoxin®) in normal healthy subjects: a placebo-controlled evaluation. *J Clin Pharm Ther* (2002) 27, 13–19.
10. Flomax (Tamsulosin hydrochloride). Astellas Pharma Inc. US Prescribing information, December 2009.
11. Hytrin (Terazosin monohydrochloride dihydrate). Amdipharm. UK Summary of product characteristics, June 2009.

Digoxin + Alpha-glucosidase inhibitors

Some but not all studies have found that digoxin levels can be markedly reduced by acarbose. Miglitol modestly reduced digoxin levels in healthy subjects, but no change was seen in diabetic patients. Voglibose does not appear to interact adversely with digoxin.

Clinical evidence, mechanism, importance and management

(a) Acarbose

A woman taking digoxin 250 micrograms daily, insulin, nifedipine, isosorbide dinitrate, clorazepate and nabumetone had subtherapeutic plasma digoxin levels of 0.48 to 0.64 nanograms/mL while taking acarbose, even when her digoxin dose was increased by adding 125 micrograms on 2 days of the week. Later, in the absence of acarbose and with the original digoxin dose, her plasma levels were 1.9 nanograms/mL.[1,2] Similarly, two other patients had markedly reduced plasma digoxin levels while taking acarbose. When the acarbose was stopped, the plasma digoxin levels rose from 0.23 nanograms/mL to 1.6 nanograms/mL and from 0.56 nanograms/mL to 1.9 nanograms/mL, respectively.[3] Another patient with heart failure and type 2 diabetes taking digoxin and voglibose, was found to have subtherapeutic levels of digoxin when his treatment was changed from voglibose (see below) to acarbose. The serum levels unexpectedly remained subtherapeutic for at least a month when treatment was switched back to voglibose.[4]

A pharmacokinetic study in 7 healthy subjects, using either a 200-mg dose of acarbose or pretreatment with acarbose 100 mg doses three times daily, similarly found that the serum levels and AUC of a single 500-microgram dose of digoxin were reduced. Maximum digoxin serum levels were reduced by about 30 to 40% and the AUC was reduced by about 40%.[5] The reasons for this interaction are not understood but a reduction in the absorption of the digoxin from the gut has been suggested.[5] These reports contrast with other studies that found no significant interaction between single-dose digoxin and acarbose in healthy subjects.[6,7] Just why there is an inconsistency between these reports is not understood but it would clearly be prudent to consider monitoring digoxin levels if both drugs are used, being alert for any evidence of reduced levels.

(b) Miglitol

The manufacturer of miglitol notes that in a study in healthy subjects, miglitol 50 mg or 100 mg three times daily reduced the average plasma concentrations of digoxin by 19% and 28%, respectively. However, in diabetic patients plasma digoxin levels were not altered by the concurrent use of miglitol 100 mg three times daily for 14 days.[8] The effects in healthy subjects are modest, and the lack of effect in patients suggests that no interaction is likely, but this needs confirmation.

(c) Voglibose

A randomised, crossover study in 8 healthy subjects taking digoxin 250 micrograms daily after breakfast for 8 days found that voglibose 200 micrograms three times daily had no effect on the pharmacokinetics of the digoxin.[9] No dose adjustment of digoxin therefore seems necessary if voglibose is given.

1. Serrano JS, Jiménez CM, Serrano MI, Balboa B. A possible interaction of potential clinical interest between digoxin and acarbose. *Clin Pharmacol Ther* (1996) 60, 589–92.
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5. Miura T, Ueno K, Tanaka K, Sugiura Y, Mizutani M, Takatsu F, Takano Y, Shibakawa M. Impairment of absorption of digoxin by acarbose. *J Clin Pharmacol* (1998) 38, 654–7.
6. Cohen E, Almog S, Staruvin D, Garty M. Do therapeutic doses of acarbose alter the pharmacokinetics of digoxin? *Isr Med Assoc J* (2002) 4, 772–5.
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8. Glyset (Miglitol). Pfizer Inc. US prescribing information, September 2009.
9. Kusumoto M, Ueno K, Fujimura Y, Kameda T, Mashimo K, Takeda K, Tatami R, Shibakawa M. Lack of kinetic interaction between digoxin and voglibose. *Eur J Clin Pharmacol* (1999) 55, 79–80.

Digoxin + 5-Alpha reductase inhibitors

Dutasteride and finasteride do not appear to affect the pharmacokinetics of digoxin.

Clinical evidence, mechanism, importance and management

A placebo-controlled study in 20 healthy subjects taking digoxin found that its steady-state pharmacokinetics were unchanged by **dutasteride** 500 micrograms daily for 3 weeks.[1] Similarly, in a randomised study, 17 healthy subjects were given a single 400-microgram dose of digoxin while taking **finasteride** 5 mg daily for 10 days. Finasteride had no significant effect on the single-dose pharmacokinetics of digoxin.[2] No digoxin dose adjustment would be expected to be necessary on concurrent use of either of these 5-alpha reductase inhibitors.

1. Avodart (Dutasteride). GlaxoSmithKline. US Prescribing information, June 2008.
2. Gregoire S, Williams R, Gormley G, Lin E. Effect of finasteride (MK-906) on the disposition of digoxin. *J Clin Pharmacol* (1990) 30, 847.

Digoxin and related drugs + Aminoglutethimide

The clearance of digitoxin is markedly increased by aminoglutethimide and a reduction in its effects would be expected.

Clinical evidence, mechanism, importance and management

The clearance of digitoxin was increased by a mean of 109% in 5 patients who took aminoglutethimide (250 mg four times a day in 4 patients, and 125 mg twice daily in one patient).[1,2] The likely reason for this effect is that aminoglutethimide increases the metabolism of digitoxin by the liver.

This increase in clearance would be expected to be clinically important, but this does not appear to have been assessed. Check that patients do not become under-digitalised during concurrent use. No interaction would be expected with digoxin because it is largely excreted unchanged in the urine and therefore metabolism by the liver has little part to play in its clearance.

1. Lønning PE, Kvinnsland S and Bakke OM. Effect of aminoglutethimide on antipyrine, theophylline and digitoxin disposition in breast cancer. *Clin Pharmacol Ther* (1984) 36, 796–802.
2. Lønning PE. Aminoglutethimide enzyme induction: pharmacological and endocrinological implications. *Cancer Chemother Pharmacol* (1990) 26, 241–4.

Digoxin + Aminoglycosides

Digoxin levels can be reduced by oral neomycin and increased by intramuscular gentamicin.

Clinical evidence

(a) Gentamicin

In a study in 12 patients with congestive heart failure taking digoxin 250 micrograms daily, the addition of gentamicin 80 mg intramuscularly twice daily for 7 days was found to increase serum digoxin levels by 129%. In a further 12 patients with congestive heart failure and diabetes, the same dose of gentamicin increased digoxin levels more than twofold, to 2 nanograms/mL. However, no symptoms of digoxin toxicity were seen. It should be noted that serum creatinine levels were higher in both groups than those in healthy controls even before receiving gentamicin, and were further increased after gentamicin.[1]

An earlier study similarly found that gentamicin prolonged the half-life of digoxin and increased its serum levels by 47% (from 1.9 to 2.8 nanograms/mL).[2]

(b) Neomycin

Neomycin 1 to 3 g orally was found to delay and reduce the absorption of a single 500-microgram dose of digoxin in healthy subjects.[3] The AUC of digoxin was reduced by 41 to 51%. Absorption was affected even when neomycin was given 3 to 6 hours before digoxin. In a steady-state study, neomycin 2 g given with digoxin 250 to 500 micrograms daily reduced the serum level of digoxin by 8 to 49% (mean 28%).[3]

Mechanism

Gentamicin impairs renal function, so decreasing digoxin clearance.[2] Higher digoxin levels and serum creatinine levels in diabetic compared with non-diabetic patients may be due to differences in renal function,[1] with concurrent gentamicin causing a further impairment of renal function and even higher digoxin levels. The reduction in digoxin toxicity is not fully understood but changes in ionic transport may be involved. The inhibition by gentamicin of Na^+/K^+ ATPase, which acts as a specific receptor for digoxin, may also be a factor.[1]

Neomycin can cause a general but reversible malabsorption syndrome, which affects the absorption of several drugs. The extent of this is probably offset in some patients, because the neomycin also reduces the breakdown of digoxin by the bacteria in the gut.[4]

Importance and management

Information is limited, but patients should be monitored for increased digoxin effects if gentamicin is given, especially those with diabetes or any other patient with renal impairment. Initially, checking pulse rate is probably adequate. There seems to be no information about other parenteral aminoglycosides.

Patients should be monitored for reduced digoxin effects if neomycin is given and suitable dose adjustments made if necessary. Separating administration of the two drugs does not prevent this interaction. Other aminoglycosides that can be given orally such as **kanamycin** and **paromomycin** might possibly interact similarly to neomycin, but this requires confirmation.

1. Alkadi HO, Nooman MA, Raja'a YA. Effect of gentamicin on serum digoxin level in patients with congestive heart failure. *Pharm World Sci* (2004) 26, 107–9.
2. Halawa B. Interakcje digoksyny z cefradina (Sefril), tetracyklina (Tetracyclinum), gentamycyna (Gentamycin) i wankomycyna (Vancocin). *Pol Tyg Lek* (1984) 39, 1717–20.
3. Lindenbaum J, Maulitz RM, Butler VP. Inhibition of digoxin absorption by neomycin. *Gastroenterology* (1976) 71, 399–404.
4. Lindenbaum J, Tse-Eng D, Butler VP, Rund DG. Urinary excretion of reduced metabolites of digoxin. *Am J Med* (1981) 71, 67–74.

Digoxin + 5-Aminosalicylates

Digoxin levels can be reduced by sulfasalazine. The manufacturers of balsalazide suggest that it may interact similarly.

Clinical evidence, mechanism, importance and management

The observation that a patient taking **sulfasalazine** 8 g daily had low serum digoxin levels, prompted a crossover study in 10 healthy subjects. In this study a single 500-microgram dose of digoxin syrup was given alone, and the subjects had taken **sulfasalazine** 2 to 6 g daily for 6 days. Digoxin absorption was reduced, ranging from 0 to 50% depending on the dose of **sulfasalazine** used.[1] Serum digoxin levels were reduced accordingly.[1] The reasons for this effect are not understood. This seems to be the only report of this interaction. Concurrent use need not be avoided, but it would be prudent to check for under-digitalisation, initially by checking symptoms and pulse rate, and then taking digoxin levels if an interaction is suspected. In the initial patient, separating the doses did not appear to prevent this interaction.[1]

Although no interaction involving digoxin and **balsalazide** has been reported, based on the information with sulfasalazine, the manufacturer of **balsalazide** recommend that plasma levels of digoxin should be monitored in digitalised patients starting **balsalazide**.[2]

1. Juhl RP, Summers RW, Guillory JK, Blaug SM, Cheng FH, Brown DD. Effect of sulfasalazine on digoxin bioavailability. *Clin Pharmacol Ther* (1976) 20, 387–94.
2. Colazide (Balsalazide). Almirall Ltd. UK Summary of product characteristics, September 2005.

Digoxin + Aminosalicylic acid

Aminosalicylic acid causes a small reduction in digoxin levels in healthy subjects.

Clinical evidence, mechanism, importance and management

In a study in 10 healthy subjects, the bioavailability of a single 750-microgram dose of digoxin, using urinary excretion as a measure, was reduced by 20% by aminosalicylic acid 2 g four times daily for 2 weeks.[1] This seems to be just another aspect of the general malabsorption caused by aminosalicylic acid. The importance of this interaction in patients is not known, but it would be expected to be small.

1. Brown DD, Juhl RP, Warner SL. Decreased bioavailability of digoxin due to hypocholesterolemic interventions. *Circulation* (1978) 58, 164–72.

Digoxin and related drugs + Amiodarone

Digoxin levels can be approximately doubled by amiodarone. Some individuals may show even greater increases. The same interaction also appears to occur with digitoxin.

Clinical evidence

(a) Acetyldigoxin

Torsade de pointes developed in one patient 3 days after the amiodarone dose was increased to 600 mg daily, and beta-acetyldigoxin 100 micrograms and bisoprolol 1.25 mg daily were added, for persistent atrial fibrillation. Serum levels of digoxin and amiodarone were normal. Withdrawal of all medications and treatment with intravenous magnesium resolved the arrhythmias.[1]

(b) Digitoxin

Two elderly patients (aged 77 years and 78 years) taking digitoxin 100 micrograms daily were given loading doses of amiodarone followed by maintenance doses of 200 to 400 mg daily. Within 2 months in one case, and within 4 months in the other, they were hospitalised because of bradycardia, dyspnoea, nausea and malaise. One of them had total AV block (38 bpm). The serum digitoxin levels of both of them were found to be elevated (54 nanograms/mL and 45 nanograms/mL, respectively) well above the therapeutic range of 9 to 30 nanograms/mL. Serum amiodarone and desethylamiodarone levels were normal. Both patients recovered when the digitoxin was stopped.[2]

(c) Digoxin

The observation that patients taking digoxin developed digoxin toxicity when given amiodarone[3] prompted a study of this interaction. Seven patients receiving digoxin had a mean rise in their plasma digoxin levels of 69% (from 1.17 to 1.98 nanograms/mL), when they were given amiodarone 200 mg three times daily. Two other patients similarly treated also developed this interaction.[3]

Numerous studies in patients have confirmed this interaction with reported increases in serum digoxin levels of 75% to 158%.[4-8] The occasional patient may show three- to fourfold increases, whereas others may show little or no change.[6,9] Children seem particularly sensitive, with threefold, and even as much as ninefold rises reported.[10] Other reports confirm that the digoxin levels are markedly increased or roughly doubled, and toxicity can occur.[9,11-20] In contrast, one group of workers state that they observed no change in serum digoxin levels in 5 patients given amiodarone.[21,22] There is also a case report of a 31-year-old man with dilated cardiomyopathy who had his dose of digoxin reduced from 250 to 125 micrograms daily, four days before starting an oral loading-dose regimen of amiodarone 600 mg daily. Before starting amiodarone, his digoxin levels were 1.27 nanograms/mL, and these increased to 1.79 nanograms/mL 10 hours post-dose on day 2, and 2.93 nanograms/mL 8.4 hours post-dose on day 3. Digoxin was stopped and 15.5 hours later the level was 1.8 nanograms/mL. However, on day 4, 9.25 hours after amiodarone was given, the digoxin level had increased to 2.52 nanograms/mL. Twice daily monitoring of digoxin over the next 3 days found that levels rose and fell, with the highest levels occurring between 8 and 10 hours after amiodarone administration. The patient did not develop any signs of digoxin toxicity.[23]

There is also some evidence that, in the treatment of resistant atrial tachyarrhythmias, the risk of arrhythmias may be increased by the concurrent use of digoxin and amiodarone,[19,24] and another study found that concurrent use had an unfavourable effect on survival in patients with atrial fibrillation and sinus rhythm.[25]

A review of prescribing in an Australian hospital revealed 42 patients who had taken amiodarone with digoxin (both long-term (16), either drug recently started (21), or both drugs recently started (5)). Of 31 patients who had digoxin levels monitored, 12 required a change in dose of the digoxin, and in 3, digoxin was stopped.[26] It is unclear whether this was purely on the basis of serum levels, or whether patients experienced adverse effects.

Mechanism

Not fully understood. Amiodarone reduces both the renal and non-renal excretion of digoxin.[27] *In vitro* studies have found that amiodarone (and possibly desethylamiodarone) inhibits P-glycoprotein-mediated transcellular transport of digoxin. This suggests that any interaction may occur, at least in part, by inhibiting digoxin renal tubular secretion.[28,29]

Another possible mechanism that has been suggested involves changes in thyroid function. Serum digoxin levels have been found to be lower in hyperthyroidism and higher in hypothyroidism, when compared to those found when thyroid function is normal. It has been suggested that amiodarone-induced hypothyroidism may precipitate digoxin toxicity.[30]

Protein-binding displacement has also been suggested as a possible mechanism.[31,32] and the lack of digoxin toxicity in some studies where high plasma digoxin levels were reported is thought to be due to redistribution of digoxin from tissue-binding sites to plasma in the presence of amiodarone.[23,31,32]

Another study in healthy subjects found that amiodarone increased the plasma levels and the AUC of digoxin given orally but had no effect on digoxin given intravenously. It was suggested that amiodarone may increase the bioavailability of orally digoxin, by prolonging intestinal transit time which may enhance absorption.[4]

It is thought that amiodarone can also inhibit the metabolism of digitoxin by the liver, which would explain why its serum levels are increased.[2]

Importance and management

The pharmacokinetic interaction between **digoxin** and amiodarone is well documented, well established and of considerable clinical importance. It occurs in most patients. It is clearly evident after a few days and develops over the course of one to 4 weeks.[7] If no account is taken of this interaction the patient may develop digitalis toxicity. Reduce the digoxin dose by between one-third to one-half when amiodarone is added,[3-5,14] with further adjustment of the dosage after a week or two, and possibly a month or more,[14] depending on digoxin levels. Particular care is needed in children, who may have much larger rises in digoxin levels than adults. Amiodarone has a long half-life so that the effects of this interaction will persist for several weeks after its withdrawal.[18] A synergistic effect on heart rate and atrioventricular conduction is also possible, which may result in the development of new arrhythmias. Also note that some authors suggest that concurrent use may possibly worsen the prognosis in some patients.[24,25]

Far less is known about the interaction between **digitoxin** and amiodarone but the limited evidence available suggests that all of the precautions appropriate for digoxin should be used for digitoxin as well. Note that the interaction may possibly take months to develop.

1. Schrickel J, Bielik H, Yang A, Schwab JO, Shlevkov N, Schimpf R, Lüderitz B, Lewalter T. Amiodarone-associated 'torsade de pointes'. *Z Kardiol* (2003) 92, 889–92.
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6. Oetgen WJ, Sobol SM, Tri TB, Heydorn WH, Rakita L. Amiodarone-digoxin interaction. Clinical and experimental observations. *Chest* (1984) 86, 75–9.
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12. McQueen EG. New Zealand Committee on Adverse Drug Reactions. 17th Annual Report 1982. *N Z Med J* (1983) 96, 95–9.
13. McGovern B, Garan H, Kelly E, Ruskin JN. Adverse reactions during treatment with amiodarone hydrochloride. *BMJ* (1983) 287, 175–80.
14. Marcus FI, Fenster PE. Drug therapy. Digoxin interactions with other cardiac drugs. *J Cardiovasc Med* (1983) 8, 25–8.
15. Strocchi E, Malini PL, Graziani A, Ambrosioni E, Magnani B. L'interazione tra digossina ed amiodarone. *G Ital Cardiol* (1984) 14, 12–15.
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Digoxin + Angiotensin II receptor antagonists

Candesartan, eprosartan, irbesartan, losartan, olmesartan, and valsartan do not appear to affect the pharmacokinetics of digoxin, but telmisartan may cause a rise in serum digoxin levels.

Clinical evidence

(a) Candesartan

In a study in 12 healthy subjects there was no pharmacokinetic interaction between candesartan 16 mg daily and digoxin, given as a loading dose of 750 micrograms then 250 micrograms daily.[1]

(b) Eprosartan

A study in 12 healthy men given a single 600-microgram dose of digoxin found that eprosartan 200 mg every 12 hours for 4 days had no significant effect on the pharmacokinetics of digoxin.[2]

(c) Irbesartan

A study in 10 healthy subjects taking digoxin for 2 weeks found no changes in the AUC or maximum serum levels of digoxin, when, during the second week, they also took irbesartan 150 mg daily.[3]

(d) Losartan

In 13 healthy subjects the pharmacokinetics of a single 500-microgram oral or intravenous dose of digoxin were not affected by losartan 50 mg daily for a week.[4]

(e) Olmesartan

In a study in 24 healthy subjects given digoxin 375 micrograms daily after a loading dose of 1.125 mg on day one and olmesartan medoxomil 20 mg daily for 7 days there were no clinically significant pharmacokinetic interactions.[5]

(f) Telmisartan

A study in 12 healthy subjects given a 500-microgram loading dose of digoxin followed by 250 micrograms daily found that the maximum serum concentration, the trough serum concentration and the AUC were increased by 50%, 13%, and 22%, respectively, when telmisartan 120 mg daily was given for 7 days.[6] No clinically relevant changes in vital signs or ECGs were noted.

(g) Valsartan

In a study in 12 healthy subjects there was no adverse interaction between a single 160-mg dose of valsartan and digoxin 250 micrograms.[7]

Mechanism

It has been suggested that telmisartan may have caused digoxin to be more rapidly absorbed.[6] An *in vitro* study found that candesartan and losartan do not appear to inhibit P-glycoprotein-mediated transcellular transport. Therefore interactions resulting in reduced digoxin renal excretion are unlikely.[8]

Importance and management

No special precautions seem to be necessary when digoxin is used with candesartan, eprosartan, irbesartan, losartan, or valsartan. However, note that information for eprosartan, losartan, and valsartan is from single-dose studies, although the authors of the eprosartan study consider that a clinically relevant interaction with multiple doses of digoxin is unlikely.[2] The small increase in trough serum digoxin level with telmisartan suggests that the dose of digoxin need not automatically be reduced when telmisartan is started, but consideration should be given to monitoring digoxin effects (e.g. monitor for bradycardia) and take digoxin levels if necessary.

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Digoxin and related drugs + Antacids

Although some studies suggest that antacids can reduce the bioavailability of digoxin and digitoxin, there is other evidence suggesting that no clinically relevant interactions occur.

Clinical evidence

(a) Digoxin

1. Evidence of an interaction. A study in 10 healthy subjects given digoxin 750 micrograms with 60 mL of either 4% **aluminium hydroxide gel**, 8% **magnesium hydroxide gel** or **magnesium trisilicate** found that the cumulative 6-day urinary excretion of digoxin, expressed as a percentage of the original dose, was 40% for control; 31% for **aluminium hydroxide**; 27% for **magnesium hydroxide**; and 29% for **magnesium trisilicate**.[1] Other studies describe reductions in digoxin absorption of 11% with **aluminium hydroxide**, 15% with **bismuth carbonate** and **light magnesium carbonate**, and 99.5% with **magnesium trisilicate**.[2]
When digoxin was given with 30 mL of an **aluminium/magnesium hydroxide** antacid and mexiletine, the digoxin AUC was approximately halved. As mexiletine (see 'Digoxin + Mexiletine', p.1106) does not appear to interact with digoxin the interaction was attributed to the antacid.[3]

2. Evidence of no interaction. A study in 4 patients taking long-term digoxin 250 to 500 micrograms daily, found that the concurrent use of either 10 mL of **aluminium hydroxide mixture BP** or **magnesium trisilicate mixture BP**, three times daily, did not reduce the bioavailability of the digoxin and none of the patients had any reduction in the control of their symptoms.[4] Other bioavailability studies have not found a significant interaction between digoxin capsules and **aluminium/magnesium hydroxide**.[5]

(b) Other cardiac glycosides

In vitro studies with **digitoxin** suggest that it might possibly be absorbed by various antacids,[6] but **lanatoside C** probably does not interact.[7] A study in 10 patients with heart failure found that their steady-state serum **digitoxin** levels were slightly, but not significantly raised by 11% (from 13.6 to 15.1 nanograms/mL) while taking 20 mL of **aluminium/magnesium hydroxide** gel three or four times daily, separated from the **digitoxin** dosage by at least one to 2 hours.[8] Bioavailability studies have not found a significant interaction between **beta-acetyldigoxin** and **aluminium/magnesium hydroxide**.[9]

Mechanism

Not established. One suggestion is that the digoxin can become adsorbed onto the antacids and therefore unavailable for absorption.[1,6] This is probably also true for digitoxin. However, some results are not consistent with this idea.

Importance and management

The interactions between digoxin or digitoxin and antacids are only moderately well documented, and the evidence is inconsistent. Nevertheless, the findings of most studies is of a modest interaction, at worst, and no clearly clinically relevant interactions have been reported. Separating the doses by one to 2 hours to minimise admixture is effective with many other drugs that interact with antacids in this way, and seems to work with digitoxin. However, unless further information becomes available it seems unlikely that separating administration is necessary, although it may be worth bearing in mind if, on rare occasions, a patient experiences an interaction.

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Digoxin and related drugs + Anticholinesterases; Centrally acting

There is no pharmacokinetic interaction between digoxin and tacrine or donepezil. The bradycardic effects of centrally-acting anticholinesterases and digoxin may possibly be additive.

Clinical evidence

(a) Donepezil

A single-dose study in 12 healthy subjects found that the pharmacokinetics of donepezil 5 mg and digoxin 250 micrograms were not affected by concurrent use and no clinically relevant changes in cardiac conduction parameters occurred.[1] In a study in patients with Alzheimer's disease who were given donepezil for 12 weeks, the risk of bradycardia was not significantly increased by the concurrent use of digoxin.[2]

(b) Galantamine

In a study in healthy subjects, galantamine 24 mg daily had no effect on the pharmacokinetics of digoxin 375 micrograms daily. However, one subject was hospitalised for second-and third-degree heart block and bradycardia.[3]

(c) Rivastigmine

The manufacturers of rivastigmine[4,5] say that the combination has no pharmacokinetic interaction, nor does it appear to interfere with cardiac conduction.[4]

(d) Tacrine

In one study in healthy subjects given a single 500-microgram dose of digoxin, the pharmacokinetics of the digoxin were unchanged by tacrine 20 mg every 6 hours.[6]

Mechanism

No pharmacokinetic interaction appears to occur. Both the centrally-acting anticholinesterases and digoxin (and indeed other **digitalis glycosides**) can slow the heart rate, and the bradycardia seen in the isolated case may have simply been due to the additive effects of both drugs.

Importance and management

No pharmacokinetic interaction appears to occur between any of the centrally-acting anticholinesterases and digoxin, and therefore no dose adjustments are needed on a pharmacokinetic basis. However, the digitalis glycosides are known to slow the heart rate, and in clinical studies, bradycardia was reported in 2 to 3% of patients taking galantamine compared with less than 1% of those given placebo.[3] Therefore the UK manufacturers of galantamine[7] caution about the possibility of a pharmacodynamic interaction that may result in bradycardia. This seems logical. Nevertheless, few cases appear to have been reported. The manufacturer of tacrine suggests that patients with conduction abnormalities or bradyarrhythmias, may be at particular risk of an interaction.[8] Therefore it may be prudent to be alert for bradycardia if any of these centrally-acting anticholinesterases are given with a digitalis glycoside.

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8. Cognex (Tacrine hydrochloride). Sciele Pharma, Inc. US Prescribing information, June 2006.

Digoxin and related drugs + Antiepileptics; Miscellaneous

There is little evidence to suggest that carbamazepine interacts with digoxin, and topiramate causes only a small reduction in digoxin serum levels. Levetiracetam and tiagabine do not appear to interact with digoxin.

Clinical evidence, mechanism, importance and management

(a) Carbamazepine

In an early clinical study, bradycardia seen in 3 patients taking **digitalis** and carbamazepine was tentatively attributed to their concurrent use.[1]There appear to be no other reports to confirm or refute this.

(b) Levetiracetam

In a placebo-controlled study, 11 healthy subjects were given an initial loading dose of digoxin 500 micrograms followed by 250 micrograms daily with levetiracetam 1 g twice daily for one week. Levetiracetam did not significantly affect the pharmacokinetics or pharmacodynamics of digoxin, and the pharmacokinetics of levetiracetam were not significantly altered by digoxin.[2] No additional precautions seem necessary on concurrent use.

(c) Tiagabine

In a crossover study, 13 healthy subjects were given a loading dose of digoxin 500 micrograms twice daily for one day then 250 micrograms daily for 8 days, either alone or with tiagabine 4 mg three times daily for 9 days. It was found that the pharmacokinetics of digoxin were not significantly altered by tiagabine.[3]

(d) Topiramate

In a study in 12 healthy subjects, topiramate 100 mg twice daily for 9 days caused a small reduction in serum digoxin levels. The maximum serum levels and the AUC were reduced by 16% and 12%, respectively, and the oral digoxin clearance was increased by 13%.[4-6] The manufacturers suggest good monitoring of digoxin if topiramate is added or withdrawn,[5] but changes in the pharmacokinetics of digoxin of this magnitude seem unlikely to be clinically relevant in most patients.

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4. Liao S, Palmer M. Digoxin and topiramate drug interaction study in male volunteers. *Pharm Res* (1993) 10 (10 Suppl), S405.
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Digoxin and related drugs + Antiepileptics; Phenytoin

Phenytoin reduces the levels of digoxin and digitoxin. Cases of bradycardia have been seen in digitalised patients given phenytoin. Phenytoin was formerly used for the treatment of digitalis-induced cardiac arrhythmias, but sudden cardiac arrest has been reported.

Clinical evidence

(a) Acetyldigoxin

A study in 6 healthy subjects given beta-acetyldigoxin 400 micrograms daily found that the half-life of digoxin was reduced by 30% (from 33.9 to 23.7 hours) and the AUC was reduced by 23% after they took phenytoin 200 mg twice daily for a week. Total digoxin clearance increased by 27%.[1]

(b) Digitoxin

The plasma digitoxin levels of a man were reduced on three occasions when he was given phenytoin. On the third occasion, while taking digitoxin 200 micrograms daily, the addition of phenytoin 900 mg daily caused a 60% fall in digitoxin levels (from 25 to 10 nanograms/mL) over 7 to 10 days.[2]

(c) Digoxin

A patient with Down's syndrome and mitral valve insufficiency taking digoxin 250 micrograms daily developed bradycardia of 34 bpm and complete heart block when his phenytoin dose was increased from 200 to 300 mg daily.[3]

(d) Unnamed digitalis glycosides

A patient with suspected digitalis-induced cardiac arrhythmias developed bradycardia, then became asystolic and died, following an intravenous injection of phenytoin.[4] The discussion of this case briefly mentions a further 6 fatalities in patients similarly treated.[4]

Mechanism

Phenytoin has a stabilising effect on the myocardial cells so that the toxic threshold of digoxin at which arrhythmias occur is raised. However, the bradycardic effects of the digitalis glycoside are not opposed and the lethal dose is unaltered, so that the cardiac arrest reported would appear to be the result of excessive bradycardia. It seems possible that the fall in plasma digitoxin levels may be due to a phenytoin-induced increase in the metabolism of the digitoxin by the liver.[5]

Importance and management

Phenytoin was formerly used for treating digitalis-induced arrhythmias, but this use now appears to be obsolete. Intravenous phenytoin should not be used in patients with a high degree of heart block or marked bradycardia because of the risk that cardiac arrest may occur. Information about the effects of phenytoin on digitalis glycoside levels seems to be confined to these single reports, but it may be prudent to check that patients who are taking digitoxin (and possibly digoxin), and are subsequently given phenytoin, do not become under-digitalised.

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2. Solomon HM, Reich S, Spirt N, Abrams WB. Interactions between digitoxin and other drugs *in vitro* and *in vivo*. *Ann N Y Acad Sci* (1971) 179, 362–9.
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Digoxin and related drugs + Antineoplastics; Cytotoxic

Treatment with radiation and/or antineoplastic cytotoxics can damage the lining of the intestine so that digoxin (given as tablets) is much less readily absorbed. This appears to be resolved by giving the digoxin in liquid or liquid-in-capsule form, or by substituting digitoxin.

Clinical evidence

A study in 13 patients with various forms of neoplastic disease found that radiation therapy and/or various high-dose cytotoxic regimens (including **carmustine**, **cyclophosphamide**, **melphalan**, **cytarabine** and **methotrexate**) reduced the absorption of digoxin from tablets (*Lanoxin*) by almost 46%, but the reduction was not significant (15%) when the digoxin was given as capsules (*Lanoxicaps*).[1]

Other studies confirm that a 50% reduction in serum digoxin levels (using **beta-acetyldigoxin**) occurred in patients given **cyclophosphamide**, **vincristine**, **procarbazine** and prednisone (COPP); **cyclophosphamide**, **vincristine** and prednisone (COP); **cyclophosphamide**, **vincristine**, **cytarabine** and prednisone (COAP); and **doxorubicin**, **bleomycin** and prednisone (ABP). These effects disappeared about a week after cytotoxic therapy finished.[2] Radiation has a smaller effect.[3] **Digitoxin** absorption does not seem to be affected by antineoplastics.[4]

Mechanism

The reduced absorption is thought to result from damage to the intestinal epithelium caused by the antineoplastic cytotoxics.[5]

Importance and management

The interaction appears to be established. Patients taking digoxin and receiving treatment with these antineoplastic cytotoxics (cyclophosphamide and vincristine appear to be the most frequently implicated) should be monitored for signs of under-digitalisation. The problem appears to be overcome by replacing digoxin tablets with digoxin in liquid form or in solution inside a capsule. The effects of the interaction are short-lived so that a downward readjustment may be necessary about a week after treatment is withdrawn. An alternative is to use digitoxin, which does not appear to be affected.

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Digoxin + Aprepitant

Aprepitant does not affect the pharmacokinetics of digoxin.

Clinical evidence, mechanism, importance and management

A placebo-controlled, randomised, study in 11 healthy subjects found that the pharmacokinetics of digoxin 250 micrograms daily were not affected by aprepitant (125 mg given on day 7 and 80 mg given daily on days 8 to 11).

In vitro evidence indicates that aprepitant is a substrate and weak inhibitor of P-glycoprotein. However, at the doses used for the prevention of chemotherapy-induced nausea and vomiting, it appears unlikely to interact with P-glycoprotein substrates such as digoxin.[1] **Fosaprepitant** is a prodrug of aprepitant, and it would therefore be expected to behave in the same way.

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Digoxin + Argatroban

No significant pharmacokinetic interaction occurs between digoxin and argatroban.

Clinical evidence, mechanism, importance and management

A placebo-controlled, crossover study in 12 healthy subjects found that the pharmacokinetics of steady-state digoxin 375 micrograms daily were not affected by an infusion of argatroban 2 micrograms/kg per minute for 120 hours. Steady-state argatroban levels were obtained within 3 hours and maintained throughout the infusion. Dose adjustments should not be necessary during concurrent use.[1]

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Digoxin + Aspirin

Aspirin, in analgesic doses, may cause a moderate rise in digoxin levels.

Clinical evidence, mechanism, importance and management

Although aspirin can double the serum concentrations of digoxin in *dogs*, a study in 8 healthy subjects found no interaction, even when high doses of aspirin (975 mg three times daily) were given.[1] However, in another study in 9 healthy subjects given aspirin 1.5 g daily for 10 days, the serum levels of digoxin were increased by 31%.[2] A further study found a 49% increase in digoxin levels when it was given with aspirin 1.5 g daily.[3] Bearing in mind that both drugs have been in use for a very considerable number of years, the lack of reports in the literature describing problems suggests that no clinically important interaction normally occurs.

1. Fenster PE, Comess KA, Hanson CD and Finley PR. Kinetics of digoxin-aspirin combination. *Clin Pharmacol Ther* (1982) 32, 428–30.
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Digoxin + Azoles; Itraconazole

Itraconazole causes a marked increase in digoxin levels. Toxicity may occur unless the digoxin dose is suitably reduced. Theoretically, itraconazole might also oppose the positive inotropic effects of digoxin.

Clinical evidence

In a placebo-controlled, crossover study, 10 healthy subjects taking digoxin 250 micrograms daily were given itraconazole 200 mg daily for 10 days. The serum digoxin levels increased by about 80% (from 1 to 1.8 nanograms/mL). New steady-state digoxin levels were not fully achieved during the 10-day period with itraconazole, so greater rises might occur on longer-term use.[1] A study in 3 patients with congestive heart failure taking digoxin found that itraconazole decreased digoxin clearance by 50% and increased digoxin levels: ECG changes (premature ventricular contractions, AV block and ST depression) occurred.[2]

A 68-year-old man taking digoxin 250 micrograms twice daily and ibuprofen developed nausea and fatigue (interpreted later as digoxin toxicity) after starting to take itraconazole 400 mg daily for an infected elbow. The symptoms disappeared when both itraconazole and ibuprofen were stopped, but returned when itraconazole was restarted. After 7 days his heart rate had fallen, from 60 bpm to 40 bpm, and his digoxin level had doubled (from 1.6 to 3.2 nanograms/mL). He was later satisfactorily restabilised on a quarter of the digoxin dose while taking the same dose of itraconazole.[3] Several other patients developed digoxin toxicity (a sixfold increase in serum digoxin level in one case) within 3 to 13 days of starting to take itraconazole,[4-10] and after 4 weeks in one case.[11] A possible case of digoxin toxicity has also occurred with itraconazole pulse therapy.[12] Two cases of digoxin toxicity have been reported when itraconazole was given to renal transplant patients, but other factors may have contributed to the high levels of digoxin in these 2 patients.[13]

Mechanism

Itraconazole inhibits P-glycoprotein, which transports digoxin out of kidney tubule cells into the urine,[14-17] and therefore digoxin urinary clearance is reduced and serum levels are increased.[5,10]

Importance and management

An established and clinically important pharmacokinetic interaction. Monitor the effects of digoxin (e.g. bradycardia, nausea, vomiting) if itraconazole is started, anticipating the need to reduce the digoxin dose. Halving the dose was suggested in one study.[2] Two of the patients cited above were restabilised with a quarter of the digoxin dose[3,4] and another with about one-third of the original digoxin dose[5] while taking itraconazole. More recent findings suggest that itraconazole may possess significant negative inotropic properties, and the CSM in the UK suggests that it should be used with caution in patients at risk of heart failure.[18] This suggests that itraconazole might oppose the pharmacological effects of digoxin.

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Digoxin + Azoles; Posaconazole

Posaconazole may increase digoxin levels.

Clinical evidence, mechanism, importance and management

The US manufacturers of posaconazole caution that increased plasma concentrations of digoxin have been found in patients taking digoxin and posaconazole, and advises monitoring during concurrent use.[1] Although the UK manufacturers of posaconazole do not mention a specific interaction between the two drugs, they do advise that digoxin levels should be monitored when initiating or discontinuing posaconazole, in the light of

the rise in digoxin levels seen when it has been given with other azoles.[2] See 'Digoxin + Azoles; Itraconazole', p.1085.

1. Noxafil (Posaconazole). Schering-Plough. US Prescribing information. February 2009.
2. Noxafil (Posaconazole). Schering-Plough Ltd. UK Summary of product characteristics, November 2009.

Digoxin + Azoles; Voriconazole

Voriconazole did not affect the steady-state pharmacokinetics of digoxin in a study in healthy patients. Another study briefly mentions increased digoxin levels in two patients receiving voriconazole.

Clinical evidence, mechanism, importance and management

A placebo-controlled study in healthy subjects given a digoxin loading dose over 2 days, then digoxin 250 micrograms daily for 20 days, found that voriconazole 200 mg twice daily for the last 12 days had no significant effect on the steady-state pharmacokinetics of digoxin.[1] Unlike itraconazole (see 'Digoxin + Azoles; Itraconazole', p.1085), voriconazole appears not to alter the P-glycoprotein-mediated transport of digoxin.

However, a clinical study in severely ill patients with invasive mycosis briefly mentions that 2 patients receiving voriconazole developed high trough digoxin levels, which required the digoxin to be withdrawn. One patient was symptomatic with an arrhythmia and ECG changes.[2] These cases appear to be the only ones reported, nevertheless, they introduce a note of caution, and it may be prudent to consider an interaction as a possible cause, if bradycardia or other digoxin adverse effects develop in a patient given voriconazole.

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Digoxin and related drugs + Barbiturates

Digitoxin levels can be halved by phenobarbital and its effects may be expected to be reduced accordingly. However, another study found that phenobarbital did not affect digitoxin, digoxin or acetyldigitoxin pharmacokinetics.

Clinical evidence

Phenobarbital 60 mg three times daily for 12 weeks, halved the steady-state plasma levels of **digitoxin** 100 micrograms daily.[1] In associated studies the half-life of **digitoxin** decreased from 7.8 days to 4.5 days during the use of **phenobarbital**.[1] In another study[2] the rate of conversion of **digitoxin** to digoxin increased from 4% to 27% in one patient who took **phenobarbital** 96 mg daily for 13 days.

In contrast, a study in groups of 10 healthy subjects given either **digitoxin** 400 micrograms, digoxin 1 mg or **acetyldigitoxin** 800 micrograms daily did not find any changes in the serum concentrations of any of these digitalis glycosides when **phenobarbital** 100 mg was given three times daily for 7 to 9 days.[3]

Mechanism

Phenobarbital and other barbiturates are well-known potent liver enzyme inducers which, it would seem, can increase the metabolism and conversion of digitoxin to digoxin.[1,2] The lack of interaction in one study may possibly have been because the barbiturate was taken for a relatively short time.[3]

Importance and management

An established interaction, although its clinical importance is somewhat uncertain because there seem to be few reports of the effects of using digitoxin with phenobarbital, or of problems in practice. Nevertheless, patients taking both drugs should be monitored for possible underdigitalisation and the dose of digitoxin increased if necessary. Other barbiturates would be expected to behave like phenobarbital. It seems unlikely that digoxin will be affected by the barbiturates because it is largely excreted unchanged in the urine.

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Digoxin and related drugs + Benzodiazepines and related drugs

Digoxin toxicity occurred in two elderly patients, and rises in digoxin levels have been seen in others, when they were given alprazolam. A reduction in the urinary clearance of digoxin has been described during the use of diazepam. No pharmacokinetic interaction seems to occur with digoxin and eszopiclone, zaleplon, or zolpidem.

Clinical evidence

(a) Benzodiazepines

1. Alprazolam. An elderly woman taking digoxin, maprotiline, isosorbide dinitrate, furosemide and potassium chloride had signs of digoxin toxicity during the second week of taking alprazolam 1 mg daily. Her serum digoxin levels were later found to have risen almost 300% (from 1.6 to 4.3 nanograms/mL), and her apparent digoxin clearance had fallen by about 60%.[1] A later study in 12 patients confirmed that digoxin levels can be significantly raised by alprazolam, particularly in those over 65 years old. One elderly man developed clinical digoxin toxicity.[2] In contrast, a study in 8 healthy subjects found no changes in the clearance of digoxin after they took alprazolam 1.5 mg daily.[3]

2. Diazepam. The observation that 3 patients developed raised digoxin levels while also taking diazepam prompted a further study in 7 healthy subjects.[4] After taking diazepam 5 mg with a single 500-microgram dose of digoxin, and diazepam 5 mg every 12 hours thereafter, all of them had a substantial reduction in the urinary excretion of digoxin and 5 of them had a moderate increase in the digoxin half-life. No further details were given.[4]

3. Metaclazepam. No statistically significant interaction was seen in 9 patients taking **beta-acetyldigoxin** when they were given metaclazepam.[5]

(b) Non-benzodiazepine hypnotics

1. Eszopiclone. In a study in 12 healthy subjects, a 3-mg single dose of eszopiclone did not alter the pharmacokinetics of digoxin, given for 7 days.[6]

2. Zaleplon. Zaleplon 10 mg daily, given to 20 healthy subjects for 5 days, had no significant effects on the steady-state pharmacokinetics of digoxin 375 micrograms daily. There were no significant differences in QTc or PR intervals.[7]

3. Zolpidem. No significant pharmacokinetic interaction occurs between zolpidem and digoxin.[8]

Mechanism

Uncertain. It has been suggested that diazepam and some other benzodiazepines may possibly alter the extent of the protein binding of digoxin within the plasma, which may have some influence on the renal tubular excretion.[4] However, see comments on protein binding interactions in 'Drug distribution interactions', (p.3). The reason for the interaction between digoxin and alprazolam is not understood.

Importance and management

Information on the interaction between digoxin and alprazolam is limited, but it may be prudent to monitor the effects of digoxin (e.g. bradycardia) in any patient if alprazolam is added, and reduce the digoxin dose as necessary. What is known suggests that an adverse interaction is more likely in the elderly. Other benzodiazepines and digoxin have been used for a considerable time but there seem to be no other reports of adverse interactions. The newer non-benzodiazepine hypnotics, eszopiclone, zaleplon and zolpidem do not appear to affect the pharmacokinetics of digoxin.

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Digoxin and related drugs + Beta-agonist bronchodilators

Oral salbutamol (albuterol) causes a small reduction in digoxin levels. Beta agonists can cause hypokalaemia, which could lead to the development of digitalis toxicity.

Clinical evidence, mechanism, importance and management

A study in 10 healthy subjects who had taken digoxin 500 micrograms daily for 10 days[1] found that, 3 hours after taking oral **salbutamol** (albuterol) 3 to 4 mg, their serum digoxin levels had fallen by 0.23 nanograms/mL and their serum potassium levels had fallen by 0.58 mmol/L. A follow-up study suggested that the digoxin distribution to skeletal muscle may have been increased.[2]

Note that all $beta_2$ agonists can cause a fall in serum potassium, which could possibly affect the response of patients to digoxin of other **digitalis glycosides**. The clinical importance of these changes is uncertain but concurrent use should be monitored. Consider monitoring potassium levels if the effects of digoxin seem excessive.

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Digoxin and related drugs + Beta blockers

In general there appears to be no pharmacokinetic interaction between digoxin and beta blockers, although talinolol and carvedilol appear to increase the bioavailability of digoxin. Pharmacodynamic interactions, resulting in additive bradycardia, are possible. A few cases of excessive bradycardia have been reported when propranolol was used to control digitalis-induced arrhythmias.

Clinical evidence

(a) Carvedilol

A 12-year-old boy with dilated cardiomyopathy taking digoxin 250 micrograms in the morning and 125 micrograms in the evening was subsequently given carvedilol 70 micrograms/kg twice daily. Several days later he lost his appetite and started vomiting, and his digoxin serum level was found to have increased from 1.6 to 2.3 nanograms/mL up to 4.2 nanograms/mL. Digoxin was stopped and subsequently restarted at half the original dose.[1] In one study, 8 children aged 2 weeks to 8 years were given digoxin for ventricular failure secondary to congenital heart disease. When they were also given carvedilol 0.06 to 1.06 mg/kg daily the clearance of digoxin was approximately halved and 2 children developed digoxin toxicity.[1]

A single-dose study in healthy adults given carvedilol 25 mg found that the maximum plasma levels of a 500-microgram dose of digoxin were increased by 0.97 nanograms/mL (60%) and the AUC was increased by about 20%, but the clinical effects of these changes were considered likely to be small.[2] No significant pharmacokinetic interaction was found in other single-dose studies in adults given carvedilol and **digitoxin**,[3] or carvedilol and intravenous digoxin.[2]

In a multiple-dose study in adult patients with hypertension, carvedilol raised the maximum serum levels and AUC of digoxin 250 micrograms daily by 32% and 14%, respectively, after 2 weeks of concurrent use. Again, these changes were considered unlikely to be clinically significant.[4] In another study in 12 male and 12 female patients taking digoxin 62.5 to 250 micrograms daily for heart failure, the addition of carvedilol 6.25 mg twice daily for 7 days increased the maximum concentration and the AUC_{0-16} of digoxin by 37% and 56%, respectively, in the men, but no significant changes to the pharmacokinetics of digoxin were noted in the women.[5]

(b) Esmolol

A single dose of intravenous esmolol did not affect the pharmacokinetics of multiple-dose digoxin, except that a small increase was seen in the AUC_{0-6} of digoxin.[6]

(c) Propranolol

Two cases, where propranolol 10 mg orally was used to treat arrhythmias associated with digoxin toxicity, are reported.[7] The first patient (who had heart failure) became bradycardic, asystolic and then died, while the second patient became bradycardic (30 bpm) but recovered after being given atropine. A further fatality was reported when intravenous propranolol was used.[8]

(d) Sotalol

In a placebo-controlled study of the use of sotalol in digitalised patients with chronic atrial fibrillation, 2 of 24 sotalol recipients were withdrawn due to bradycardia compared with none of 10 given placebo. However, the combination was still considered valuable.[9] In this study, the pharmacokinetics of multiple-dose digoxin were unaffected by sotalol 80 to 320 mg daily.[9]

(e) Talinolol

In healthy subjects talinolol 100 mg orally substantially increased the bioavailability of a single 500-microgram dose of digoxin. The AUC_{0-72} and the maximum serum levels of digoxin were increased by 23% and 45%, respectively.[10] Conversely, intravenous talinolol 30 mg had no effect on digoxin pharmacokinetics.[10]

(f) Timolol

There is a report of marked bradycardia of 35 to 50 bpm in a 91-year-old patient taking **digoxin** and using timolol 0.25% eye drops.[11] Bradycardia persisted on withdrawal of **digoxin**, and improved only after discontinuation of the timolol as well.

(g) Miscellaneous

The pharmacokinetics of multiple-dose digoxin have been shown to be unaffected by **acebutolol**,[12] **atenolol**,[13] **bevantolol** 200 mg daily,[14] **bisoprolol** 10 mg daily,[15] or **nebivolol** 10 mg daily.[16]

In a prospective analysis of adverse drug reactions leading to hospital admission over a 4-year period, 83 patients were identified who had been admitted with bradycardia. Of these, 62 were taking **digitalis glycosides**, and 14 were also taking a beta blocker.[17] Increased bradycardia may occur on the concurrent use of a digitalis glycoside and a beta blockers, but reports of this becoming a problem seem rare (although see *Propranolol*, *Sotalol*, and *Timolol*, above).

In healthy subjects, the pharmacodynamics of digoxin were unaffected by **bevantolol**,[14] and **esmolol**,[6] with no significant changes in heart rate or blood pressure occurring. A study in healthy subjects found that **atenolol** did not affect digoxin-induced inotropism.[13]

Mechanism

In most cases where the situation has had an adverse outcome the interaction seems to be due to the additive effects of the digitalis glycoside and the beta blocker on the slowing of the heart.

It has been suggested that the pharmacokinetic interaction with talinolol is due to competition with digoxin for *intestinal* P-glycoprotein, although this needs confirmation.[10] It would seem possible that this mechanism also accounts for the interaction between digoxin and carvedilol, and an *in vitro* study found that carvedilol (but not atenolol or metoprolol) inhibits P-glycoprotein-mediated transcellular transport of digoxin,[18] which may mean *renal* tubular secretion of digoxin is inhibited. It is conceivable that P-glycoprotein inhibition by carvedilol enhances the intestinal absorption of digoxin and also decreases its renal excretion. This may explain why the interaction is possibly more significant in children, as they have a higher renal clearance rate of digoxin than adults.[1] Women have lower P-glycoprotein activity in the gut than men, which may account for the gender differences seen with the interaction of carvedilol and digoxin.[5]

Importance and management

On the whole, the concurrent use of a digitalis glycoside and a beta blocker appears to be beneficial, but the potential for additive bradycardia should be borne in mind. However, any adverse effect appears rare with digoxin, and there appear to be no reports of additive bradycardia with beta blockers and digitoxin, although this is perhaps due to a lack of reporting, as this is an expected effect of concurrent use. In addition, it may be prudent to monitor digoxin levels with talinolol, and also with carvedilol, particularly in children. It has been suggested that the dose of digoxin should be reduced by at least 25% in children given carvedilol, with further adjustments as required.[1]

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Digoxin and related drugs + Beta-lactam antibacterials

No interaction normally occurs between digoxin and amoxicillin, cefazolin, cefuroxime, flucloxacillin, phenoxymethylpenicillin or ticarcillin with clavulanic acid. No pharmacokinetic interaction occurs between ampicillin and digitoxin. In contrast, one early study found that cefradine increased digoxin levels.

Clinical evidence

In 6 healthy subjects, **ampicillin** 500 mg four times daily for 5 days had no significant effect on the pharmacokinetics of a single 1-mg dose of **digitoxin**.[1] No significant changes in digoxin serum concentrations were found in 16 elderly patients given **amoxicillin** (2 patients also took erythromycin and one **flucloxacillin**), and 2 patients who took **flucloxacillin** and **phenoxymethylpenicillin**. However, a few patients complained of some 'toxic' symptoms (nausea, vomiting, anorexia, headache, fatigue, blurred vision, confusion), which the authors of the report attributed to the underlying illness or the antibacterials rather than to an interaction.[2] In a study in 15 healthy subjects, **ticarcillin/clavulanic acid** 1 g/200 mg intramuscularly every 12 hours for one week did not affect the pharmacokinetics of digoxin.[3] In another study, there was no reduction in the excretion of digoxin metabolites from the gut in 3 patients taking **cefazolin**, and a reduction occurred in only 1 of 10 patients taking penicillins (**ampicillin** 6, **oxacillin** 3, **penicillin** 1).[4]

A case-control study using data from healthcare databases in Ontario from 1994 to 2000 identified 1051 patients who had been admitted to hospital with digoxin toxicity. Of these, 5 patients (0.5%) had been exposed to **cefuroxime** in the preceding 3 weeks when compared with 0.3% of controls, suggesting that digoxin toxicity was not significantly related to **cefuroxime** exposure.[5]

In an early study, **cefradine** prolonged the half-life of digoxin and increased its serum levels from 1.8 nanograms/mL to 2.6 nanograms/mL. This effect was considered to occur as a result of reduced renal clearance.[6]

Mechanism

Up to 10% of patients receiving oral digoxin excrete it in substantial amounts in the faeces and urine as inactive metabolites (digoxin reduction products or DRPs). This metabolism seems to be due to gut flora,[7] in particular *Eubacterium lentum*, which is anaerobic and Gram positive. It was suggested that inhibition of digoxin metabolism by gut flora was responsible for any interaction, but doubt has been thrown on this theory, (see *Mechanism* under 'Digoxin and related drugs + Macrolides', p.1103).

Importance and management

The silence of the literature on adverse interactions between digoxin and beta-lactam antibacterials, and the limited evidence for a plausible mechanism suggest that interactions are unlikely.

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Digoxin and related drugs + Bufalin

Bufalin can interfere with the assay of cardiac glycosides.

Clinical evidence, mechanism, importance and management

Bufalin, a cardioactive substance of amphibian origin, and Chinese medicines such as Chan Su, Lu-Shen-Wan and Kyushin that contain bufalin, can interfere with some immunoassay methods of **digitoxin** and digoxin, particularly the fluorescence polarisation immunoassay.[1-4] The digoxin-like immunoreactivity of Kyushin was found to be equivalent to varying amounts of digoxin because of differences in the cross-reactivity of the antibody used in different immunoassays.[3] A chemiluminescent assay for **digitoxin**[2,5] and digoxin[2] did not cross-react with bufalin.

Bufalin and an extract of Chan Su displaced **digitoxin** from protein-binding sites *in vitro*.[5] Whether this would result in elevated free **digitoxin** levels and toxicity *in vivo* is not known. However, this is probably unlikely, since *in vivo* the free drug would be available for metabolism (see 'protein-binding interactions', (p.3)).

Another possibility, given the similarities between bufalin and digitalis glycosides, is that toxicity could result from additive cardiac effects. Cases of cardiotoxicity following the ingestion of bufalin (or toads) alone have been reported. In one case, the symptoms seen were very similar to those of digoxin toxicity, with nausea, vomiting, blurred vision, mental confusion, cardiopulmonary arrest and severe bradyarrhythmia. Assay for digoxin was positive (2.1 nanograms/mL) when measured by the fluorescence energy transfer immunoassay. The patient had ingested a bowl of toad soup (Bufo melanosticus Schneider) shortly before his symptoms developed.[6]

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Digoxin and related drugs + Calcium-channel blockers; Dihydropyridines

The concurrent use of digoxin and calcium-channel blockers can be valuable. Felodipine, lacidipine, nicardipine and nisoldipine cause small increases in digoxin levels, while amlodipine, isradipine and nimodipine appear not to interact. The situation with nitrendipine is uncertain but it possibly causes only a small rise in digoxin levels.

Clinical evidence

(a) Amlodipine

In a study in 21 healthy subjects, amlodipine 5 mg daily had no significant effect on the serum levels or renal clearance of digoxin 375 micrograms daily.[1]

(b) Felodipine

Felodipine 10 mg twice daily for 8 weeks raised the serum digoxin levels in 11 patients by 15%, which was not clinically significant.[2] In another study, 14 patients were given felodipine 10 mg daily for a week. Plain tablets raised the steady-state digoxin serum levels by 11%, but extended-release tablets had no significant effect.[3] A third study found that, when taking felodipine, peak plasma digoxin levels were transiently raised by about 40% one hour after intake, but that digoxin AUCs were not significantly increased.[4]

(c) Isradipine

Isradipine (given as 2.5 mg every 12 hours for 2 days, 5 mg every 12 hours for 2 days and then 5 mg three times daily for 10 days) did not interact significantly with a single 1-mg intravenous dose of digoxin given to 24 healthy subjects.[5] A similar study by the same group found that the same dosage regimen of isradipine given with oral digoxin 250 micrograms twice daily caused a small increase in peak serum digoxin levels but no changes in its steady-state levels or AUC.[6]

(d) Lacidipine

In 12 healthy subjects, a single 4-mg oral dose of lacidipine did not affect the AUC or minimum serum levels of digoxin 250 micrograms daily for 7 days, but the maximum serum levels of digoxin were increased by 34%. These changes were not considered to be clinically significant.[7]

(e) Lercanidipine

The maximum serum levels of digoxin rose by 33% in healthy subjects also given lercanidipine. However, there was no evidence of a pharmacokinetic interaction in patients given **metildigoxin** with lercanidipine.[8]

(f) Nicardipine

In 10 patients given nicardipine 20 mg three times daily for 14 days the plasma levels of digoxin 130 to 250 micrograms daily were increased by 15%, but this was not statistically significant.[9] Another 20 patients with congestive heart failure also had no significant changes in steady-state serum digoxin levels while taking nicardipine 30 mg three times daily for 5 days.[10] Yet another study in 9 patients confirmed the absence of an interaction.[11]

(g) Nifedipine

For the interaction between digoxin or digitoxin and nifedipine, see 'Digoxin and related drugs + Calcium-channel blockers; Nifedipine', p.1090.

(h) Nimodipine

In a study in 12 healthy subjects, nimodipine 30 mg twice daily caused no change in the pharmacokinetics or haemodynamic effects of **beta-acetyldigoxin**.[12]

(i) Nisoldipine

In 10 patients with heart failure nisoldipine 20 mg daily increased the plasma trough digoxin levels by about 15%.[13,14] In 8 healthy subjects, nisoldipine 10 mg twice daily caused no changes in the pharmacokinetics or haemodynamic effects of digoxin.[12]

(j) Nitrendipine

A study in 8 healthy subjects who had been taking digoxin 250 micrograms twice daily for 2 weeks, found that nitrendipine 10 mg daily caused a slight but insignificant rise in plasma digoxin levels. Nitrendipine 20 mg daily increased the AUC of digoxin by 15%, its maximum plasma levels rose from 1.34 nanograms/mL to 2.1 nanograms/mL, and its clearance fell by 13%. One subject dropped out of the study because of dizziness, nausea and vomiting, palpitations, insomnia and nervousness.[15,16]

Another study found that plasma digoxin levels were approximately doubled when nitrendipine was given,[17] but other studies in healthy subjects and patients found that nitrendipine 20 mg twice daily caused no changes in the pharmacokinetics or haemodynamic effects of digoxin,[12,18] or **beta-acetyldigoxin**.[19]

Mechanism

Where an interaction occurs it is probably due to changes in the renal excretion of the digoxin. An *in vitro* study found that several calcium-channel blockers including nicardipine, and to a lesser extent nisoldipine (as well as barnidipine, manidipine, nilvadipine, and verapamil) inhibited the P-glycoprotein-mediated transcellular transport of digoxin. This suggests that any interaction may occur, at least in part, by affecting digoxin renal tubular excretion. Nitrendipine only weakly inhibited the transcellular transport of digoxin.[20]

Importance and management

The extent of the information varies from drug to drug, but the concurrent use of digoxin and calcium-channel blockers can be therapeutically valuable. Monitor the effects of digoxin (e.g. bradycardia) in patients given digoxin and lercanidipine, and consider measuring levels if the effects of digoxin seem excessive. Reduce the digoxin dose as necessary. The other calcium-channel blockers listed here either cause only minimal increases in digoxin levels, which are unlikely to be clinically important in most patients, or do not interact at all. The situation with nitrendipine needs clarification.

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Digoxin and related drugs + Calcium-channel blockers; Diltiazem

Digoxin levels are reported to be unchanged by diltiazem in a number of studies but others describe increases ranging from 20 to 85%. Serum digitoxin levels have also been reported to rise in some patients, but only by about 20%. There is a risk of additive bradycardia when digitalis glycosides are given with diltiazem.

Clinical evidence

(a) Digitoxin

Five out of 10 patients taking digitoxin had a 6 to 31% (mean 21%) rise in plasma digitoxin levels while taking diltiazem 180 mg daily for 4 to 6 weeks.[1]

(b) Digoxin

Diltiazem 30 or 60 mg four times daily had no significant effect on the serum levels of digoxin 250 micrograms daily in 9 patients with cardiac diseases.[2] Two similar studies in 12 patients[3] and 8 healthy subjects,[4] taking digoxin with diltiazem 120 to 360 mg daily confirmed the absence of an interaction. Two further studies in healthy subjects,[5,6] found that diltiazem 120 mg daily did not affect the pharmacokinetics of a single 1-mg intravenous dose of digoxin. In contrast, a study in 17 Japanese patients (some with rheumatic valvular disease) taking either digoxin or **metildigoxin** found that diltiazem 60 mg three times daily for 2 weeks increased their serum digoxin levels measured at 24 hours by 36% and 51%, respectively.[7] Another study in 8 patients with chronic heart failure secondary to ischaemic disease, taking digoxin 250 micrograms daily, found that diltiazem 60 mg three times daily increased the digoxin AUC and mean steady-state serum levels by about 50%, its peak serum level by 37% and elimination half-life by 29%, but there was no evidence of any haemodynamic changes.[8]

Other studies in Western patients[9,10] and healthy subjects[11-14] have found rises of 20 to 85% in plasma digoxin levels during diltiazem use. In one case report a 143% increase was seen.[15] The authors of two of these studies noted that the effect was highly individual with some subjects having no increase and some a large increase.[10,12] There is also a case report of raised serum digoxin levels and toxicity in a man taking digoxin when given diltiazem with or without nifedipine.[16]

In addition to these pharmacokinetic changes, a pharmacodynamic interaction has also been seen. A study in patients without sinoatrial (SA) or atrioventricular (AV) node dysfunction, found that intravenous diltiazem alone depressed SA and AV node function and slightly shortened atrial refractoriness. These effects were amplified by subsequent administration of intravenous digoxin 0.018 mg/kg. However, concurrent use did not cause any notable adverse effects in this group of patients.[17] A study identified 62 patients who had been admitted to hospital with bradycardia over a 4-year period, 18 of whom had been taking digoxin and a non-dihydropyridine calcium-channel blocker, and 12 patients who had been taking digoxin, a beta blocker and a non-dihydropyridine calcium-channel blocker. However, the specific calcium-channel blockers were not named.[18]

Mechanism

Not understood. In those individuals showing a pharmacokinetic interaction, falls in total digoxin clearance of about 25% have been described.[8,10,11,19,20] Although several calcium-channel blockers may inhibit the P-glycoprotein-mediated renal clearance of digoxin, the results of an *in vitro* study[21] suggest that this may not occur with diltiazem. A synergistic effect on heart rate and atrioventricular conduction is also possible.

Importance and management

A thoroughly investigated and well documented pharmacokinetic interaction but there is no clear explanation for the inconsistent results. All patients taking digoxin given diltiazem should be well monitored for signs of over-digitalisation (e.g. bradycardia) with digoxin levels measured as necessary. Dose reductions may be necessary. Those most at risk are patients with digoxin levels near the top end of the range. Similar precautions would appear to be necessary with digitoxin, although the documentation of this interaction is very limited and the expected rise in levels only small.

The potential for additive bradycardia and heart block should be borne in mind when using diltiazem with any digitalis glycoside.

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Digoxin and related drugs + Calcium-channel blockers; Nifedipine

Serum digoxin levels are normally unchanged or increased only to a small extent by nifedipine. However, one unexplained and conflicting study indicated that a 45% rise could occur. Digitoxin appears not to interact.

Clinical evidence

(a) Digitoxin

A study in 18 subjects showed that nifedipine 40 to 60 mg daily had no significant effect on their steady-state plasma digitoxin levels over a 6-week period.[1] This study has also been published elsewhere.[2]

(b) Digoxin

1. Serum digoxin levels unchanged. Studies in 25 patients[3-5] and 28 healthy subjects[6-8] found that serum digoxin levels were not significantly altered by nifedipine 30 to 60 mg daily. Similarly no significant changes in the pharmacokinetics of a single intravenous dose of digoxin were found in 6 patients[9] or 16 healthy subjects[10,11] taking nifedipine 40 to 90 mg daily. Furthermore, no changes in the pharmacokinetics of nifedipine were seen.[10]

2. Serum digoxin levels increased. in 12 healthy subjects nifedipine 30 mg increased the plasma levels of digoxin 375 micrograms daily by 45% (from 0.505 to 0.734 nanograms/mL) over 14 days.[12] In a study in 7 healthy subjects, nifedipine 15 to 60 mg daily increased the levels of digoxin 250 micrograms twice daily by a modest 15%.[13] These studies have been reported elsewhere.[14,15]

Nifedipine 20 mg twice daily increased the steady-state serum digoxin levels of 9 patients by 15% (from 0.87 to 1.04 nanograms/mL).[16] A 61% increase in serum digoxin levels was found in a study involving nifedipine in daily doses of 30 mg.[17]

In a study in 10 patients with congestive heart failure given **metildigoxin**

200 micrograms daily for 9 days, the concurrent use of nifedipine 60 mg for a further 7 days, increased levels of digoxin by about 25%. In another 10 patients given both nifedipine 60 mg and verapamil 320 mg daily for 7 days, digoxin levels were increased by about 66%.[18]

Mechanism

Not understood. Changes and lack of changes in both the renal and non-renal excretion of digoxin have been reported. A retrospective analysis of pharmacokinetic data suggests that clearance of digoxin may be reduced by 10% in patients also taking nifedipine.[19] Although several calcium-channel blockers may inhibit the P-glycoprotein mediated renal clearance of digoxin, the results of an *in vitro* study[20] suggest that this may not occur with nifedipine.

Importance and management

The pharmacokinetic interaction between digoxin and nifedipine is well documented but the findings are inconsistent. The weight of evidence appears to be that serum digoxin levels are normally unchanged or only modestly increased by nifedipine. Concurrent use appears normally to be safe and effective.[21] One report suggests that nifedipine has some attenuating effect on the digoxin-induced inotropism.[22] Another points out that under some circumstances (renal impairment or pre-existing digoxin overdosing) some risk of an undesirable interaction still exists.[13] If undesirable bradycardia occurs in a patient taking digoxin and nifedipine consider measuring digoxin levels, and adjust the dose accordingly. Nifedipine does not appear to interact with digitoxin to a clinically significantly extent.

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Digoxin and related drugs + Calcium-channel blockers; Verapamil

Serum digoxin levels are increased by about 40% by verapamil 160 mg daily, and by about 70% by verapamil 240 mg daily. Digoxin toxicity may develop, and deaths have occurred. Verapamil causes a rise of about 35% in digitoxin levels. There is a risk of additive bradycardia and conduction disturbances when cardiac glycosides are given with verapamil. Gallopamil, a drug chemically related to verapamil, does not appear to affect digoxin levels to a clinically relevant extent.

Clinical evidence

(a) Digitoxin

Eight out of 10 patients had a mean 35% rise (range 14 to 97%) in plasma digitoxin levels over a 4 to 6 week period while taking verapamil 240 mg daily, in three divided doses. In 2 patients (and 3 other healthy subjects given a single dose of digitoxin) the pharmacokinetics of digitoxin were not affected by verapamil.[1,2]

(b) Digoxin

After 2 weeks of treatment with verapamil 240 mg daily, in three divided doses, the mean serum digoxin levels of 49 patients with chronic atrial fibrillation had risen by 72%. The rise was seen in most patients, and it occurred largely within the first 7 days. A rise of about 40% has been seen with verapamil 160 mg daily.[3,4]

Reports in a total of 21 healthy subjects,[5,6] and 54 patients[7-9] describe rises in serum digoxin levels of 22 to 147% when verapamil 240 to 360 mg daily was added to digoxin. Similar rises are reported elsewhere.[4,10-12]

A rise in digoxin levels of about 50% was seen in chronic haemodialysis patients given verapamil 120 to 240 mg daily.[13] Nine healthy subjects had a 53% rise in their digoxin levels while taking verapamil 240 mg three times daily for 2 weeks.[5] Toxicity[14] and a fatality[15] occurred in patients whose digoxin levels became markedly increased by verapamil. Both asystole and sinus arrest have been described.[16,17] A single-dose study indicated that cirrhosis magnifies the extent of this interaction.[18]

In a study in 10 patients with congestive heart failure given **metildigoxin** 200 micrograms daily for 9 days, the concurrent use of verapamil 320 mg for a further 7 days, increased levels of digoxin by about 35%. In another 10 patients given both verapamil 320 mg and nifedipine 60 mg daily for 7 days, digoxin levels were increased by about 66%.[19]

A study identified 62 patients who had been admitted to hospital with bradycardia over a 4-year period, 18 of whom had been taking a combination of digoxin and a non-dihydropyridine calcium-channel blocker, and 12 patients who had been taking digoxin, a beta blocker and a non-dihydropyridine calcium-channel blocker. However, the specific calcium-channel blockers were not named.[20]

In 12 healthy subjects, **gallopamil** (a calcium-channel blocker that is chemically related to verapamil), in a dose of 50 mg three times daily for 2 weeks, raised the serum levels of digoxin 375 micrograms daily by 16% (from 0.58 to 0.67 nanograms/mL).[21] This change would not be expected to be clinically relevant.

Mechanism

The rise in serum digoxin levels with verapamil is due to reductions in renal and especially extra-renal (biliary) clearance; a diminution in the volume of distribution also takes place.[4,9,10,22] It has been suggested that P-glycoprotein may be involved.[23] An *in vitro* study found that verapamil can inhibit the P-glycoprotein-mediated transcellular transport of digoxin,[24] which suggests that any interaction may occur, at least in part, by inhibiting the renal tubular excretion of digoxin. Impaired extra-renal excretion is suggested as the reason for the rise in serum digitoxin levels.[1]

The increased plasma levels of digoxin caused by verapamil are reported to increase both inotropism[25] and toxic effects.[26] Verapamil may enhance the digoxin-induced elevation of intracellular sodium, which may increase the risk of arrhythmias.[26,27] A synergistic effect on heart rate and atrioventricular conduction is also possible.

Importance and management

The pharmacokinetic interaction between digoxin and verapamil is well documented, well established and occurs in most patients.[10,28] Serum digoxin levels should be well monitored and downward dose adjustments made to avoid digoxin toxicity (deaths have occurred[15]). An initial 30 to 50% dose reduction has been recommended.[29-31] The interaction develops within 2 to 7 days, approaching or reaching a maximum within 14 days or so.[3,8] The magnitude of the rise in serum digoxin is dose-dependent[32] with a significant increase if the verapamil dose is increased from 160 to 240 mg daily,[3] but with no further significant increase if the dose is raised any higher.[6] The mean rise with verapamil 160 mg daily is about 40%, and

with 240 mg or more is about 60 to 80%, but the response is variable. Some patients may have rises of up to 150% while others have only a modest increase. One study found that although the rise in serum digoxin levels was 60% within a week, this had lessened to about 30% five weeks later.[10] Large interpatient variability in the reduction in digoxin clearance has been reported.[31] Initial individual digoxin dose titration, regular monitoring and dose adjustments would seem to be necessary. Note that the potential for additive bradycardia and heart block should also be borne in mind.

The documentation of the digitoxin and verapamil interaction is limited, but the interaction appears to be established. Downward dose adjustments may be necessary, particularly in some patients.[1]

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Digoxin + Chloroquine or Hydroxychloroquine

The levels of digoxin were found to be increased by over 70% in two elderly patients when they were given hydroxychloroquine. A similar increase has been seen with chloroquine in *dogs*.

Clinical evidence, mechanism, importance and management

Two women aged 65 years and 68 years who had been taking digoxin 250 micrograms daily for 2 to 3 years for arrhythmias were given hydroxychloroquine 250 mg twice daily for rheumatoid arthritis. When the hydroxychloroquine was withdrawn the plasma digoxin levels of both women fell by 70 to 75% (from 2.3 to 0.5 nanograms/mL and from 2.4 to 0.7 nanograms/mL, respectively). Neither patient had any evidence of toxicity during concurrent use, and one of them claimed that the regularity of her heart rhythm had been improved.[1] The reason for this apparent interaction is not understood and its general significance is uncertain.

No interaction between digoxin and chloroquine has been described clinically, but increases in peak serum digoxin levels of about 77% have been seen in *dogs*.[2]

1. Leden I. Digoxin-hydroxychloroquine interaction? *Acta Med Scand* (1982) 211, 411–12.
2. McElnay JC, Sidahmed AM, D'Arcy PF and McQuade RD. Chloroquine-digoxin interaction. *Int J Pharmaceutics* (1985) 26, 267–74.

Digoxin + Cibenzoline (Cifenline)

Cibenzoline does not appear to affect plasma digoxin levels.

Clinical evidence, mechanism, importance and management

A study in 12 healthy subjects taking digoxin 250 to 375 micrograms daily found that cibenzoline 160 mg twice daily for 7 days had no effect on the pharmacokinetics of digoxin.[1] A study in 22 patients taking digoxin 250 micrograms daily found that the addition of cibenzoline 65 or 130 mg twice daily for 4 weeks did not affect the plasma levels of digoxin. Concurrent use was well-tolerated in 16 of 21 patients available for evaluation and no significant changes in vital signs occurred during the study period.[2] An *in vitro* study found that cibenzoline only slightly inhibited the P-glycoprotein-mediated transcellular transport of digoxin and therefore inhibition of the renal tubular secretion of digoxin is unlikely.[3] There appears to be no pharmacokinetic reason to adjust the dose of digoxin in patients given cibenzoline.

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2. Garnier LF, Bine-Scheck F, Pruvost P, Wanszelbaum H, Arnaud R. Association de la cibenzoline et de la digoxine administrées par voie orale chez des patients ayant une arythmie supraventriculaire. *Ann Cardiol Angeiol (Paris)* (1992) 41, 411–17.
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Digoxin + Ciclosporin

Ciclosporin causes a marked rise in digoxin levels in some patients.

Clinical evidence

Digoxin toxicity developed in 4 patients when they were given ciclosporin before a heart transplant. In the two cases described in detail, ciclosporin 10 mg/kg daily was given to patients taking digoxin 375 micrograms daily. Fourfold rises in digoxin levels, from 1.2 nanograms/mL to 4.5 nanograms/mL and from 2 nanograms/mL to 8.3 nanograms/mL, were seen within 2 to 3 days. This was accompanied by rises in serum creatinine levels from 110 micromol/L to 120 micromol/L and from 84 micromol/L to 181 micromol/L, respectively, which were considered insufficient to explain the rise in digoxin levels. As a consequence of these findings, the same authors conducted a study in 4 patients given ciclosporin and digoxin. Two patients developed acute renal failure. In the other 2 patients, the volume of distribution of digoxin was decreased by 69% and 72%, while the clearance was reduced by 47% and 58%, respectively.[1] In a further 7 patients, digoxin pharmacokinetics were assessed before heart transplant, then after transplantation during the use of maintenance ciclosporin.[2] The total body clearance of digoxin remained unchanged, which appeared to be at odds with the earlier results.[1] It was suggested that haemodynamic improvements brought about by a successful heart transplant may have counterbalanced any inhibitory effect ciclosporin had on renal clearance.[2]

Mechanism

Not fully understood. The authors of the studies concluded that ciclosporin has no specific inhibitory effect on the renal elimination of digoxin, but that it causes a non-specific reduction in renal function after acute use, which reduces digoxin elimination.[2] Conversely, another study in *animals* suggested that ciclosporin can reduce the secretion of digoxin by the kidney tubular cells by inhibiting P-glycoprotein.[3]

Importance and management

Information seems limited to the studies cited. Nevertheless, the effects of concurrent use should be monitored very closely, and the digoxin dose should be adjusted as necessary.

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3. Okamura N, Hirai M, Tanigawara Y, Tanaka K, Yasuhura M, Ueda K, Komano T, Hori R. Digoxin-cyclosporin A interaction: modulation of the multidrug transporter P-glycoprotein in the kidney. *J Pharmacol Exp Ther* (1993) 266, 1614–9.

Digoxin + Colesevelam

The absorption of a single dose of digoxin is not affected by colesevelam.

Clinical evidence, mechanism, importance and management

A single-dose study in which 26 healthy subjects were given digoxin 250 micrograms with or without colesevelam 4.5 g, followed by a standard meal, found that colesevelam did not significantly affect the absorption of digoxin.[1]

1. Donovan JM, Stypinski D, Stiles MR, Olson TA, Burke SK. Drug interactions with colesevelam hydrochloride, a novel, potent lipid-lowering agent. *Cardiovasc Drugs Ther* (2000) 14, 681–90.

Digoxin and related drugs + Colestipol

Colestipol appears not to interfere with the absorption of either digoxin or digitoxin if it is given at least 1.5 hours after the digitalis glycoside.

Clinical evidence

(a) Digitoxin

Four patients with digitoxin toxicity were given colestipol 10 g at once and 5 g every 6 to 8 hours thereafter to reduce their digitoxin serum levels. The average digitoxin half-life fell to 2.75 days compared with an untreated control patient in whom the digitoxin half-life was 9.3 days.

A comparative study in 11 patients with plasma digitoxin levels greater than 40 nanograms/mL found that when the digitoxin was stopped and colestipol 5 g four times daily was given before meals, the digitoxin half-life (6.3 days) was unaffected, when compared with 11 other patients not given colestipol (6.8 days).[1] For another study in which the levels of digitoxin were not affected by colestipol, see under *Digoxin*, below.

(b) Digoxin

In a patient with digoxin toxicity who was given colestipol in an attempt to reduce digoxin levels, the digoxin half-life was 16 hours compared with 1.8 to 2 days in two other control patients.[2] A digoxin elimination half-life of 55 hours was reported in a second patient with digoxin toxicity who was given colestipol, and this compared with a predicted time of at least 85 hours for digoxin alone.[3] Other reports also found colestipol reduced the half-life of digoxin in patients with digoxin toxicity.[4,5] In contrast, a study in healthy subjects found that colestipol 10 g given immediately after a single 250-microgram dose of digoxin did not reduce the absorption of digoxin.[6] Furthermore, 10 patients receiving long-term treatment with either digoxin 125 to 250 micrograms daily or **digitoxin** 100 to 200 micrograms daily were given colestipol 15 g daily or a placebo, taken 1.5 hour after the digitalis. Their serum digitalis levels were not significantly altered over a 1-year period by the colestipol.[7]

Mechanism

Colestipol is an ion-exchange resin, which can bind to digoxin and digitoxin.[2] In cases of toxicity, colestipol may possibly reduce serum digitalis levels because under these circumstances the excretion of digitalis in the bile increases and more becomes available for binding in the gut.[7]

Importance and management

This interaction is not well established. Giving either digoxin or digitoxin 1.5 hours before colestipol appears to avoid any possible interaction in the gut.[7] Note that it is usually recommended that other drugs are given one hour before or 4 hours after colestipol.

1. van Bever RJ, Duchateau AMJA, Pluym BFM, Merkus FWHM. The effect of colestipol on digitoxin plasma levels. *Arzneimittelforschung* (1976) 26, 1891–3.
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4. Hamburger S, Covinsky JO, Styczynski M, Uhrig L. Acute digoxin overdosage: potential role of colestipol therapy. *J Kans Med Soc* (1980) 81, 464.
5. Kilgore TL, Lehmann CR. Treatment of digoxin intoxication with colestipol. *South Med J* (1982) 75, 1259–60.
6. Neuvonen PJ, Kivistö K, Hirvisalo EL. Effects of resins and activated charcoal on the absorption of digoxin, carbamazepine and frusemide. *Br J Clin Pharmacol* (1988) 25, 229–33.
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Digoxin and related drugs + Colestyramine

The levels of both digoxin and digitoxin can be reduced by colestyramine.

Clinical evidence

A study in 12 healthy subjects given digoxin 750 micrograms found that the cumulative 6-day recovery of digoxin from the urine was reduced by almost 20% (from 40.5 to 33.1%) when colestyramine 4 g was given.[1] Two patients with congestive heart failure and toxic serum levels of digoxin of 3 nanograms/mL and 4 nanograms/mL were given colestyramine 4 g every 4 hours for 4 doses. The levels of digoxin fell to therapeutic levels within 13 to 24 hours.[2]

Other reports describe a fall in serum digoxin levels during the concurrent use of colestyramine[3-6] and an increase in the loss of digoxin and its metabolites in the faeces during long-term use.[7] Another study found that giving digoxin as a solution in a capsule reduced the effects of this interaction.[5]

Some studies have found that colestyramine reduces the half-life of **digitoxin** by 35 to 40%.[8,9] There are reports of colestyramine successfully being used in patients with **digitoxin** toxicity to increase its elimination.[10-12] However, not all studies and cases have found pronounced interactions with digoxin and **digitoxin**. In one case report of **digitoxin** overdose, the effects of colestyramine on digitoxin appeared to be delayed for 48 hours and the reduction in half-life of digitoxin from 7.4 days to 6 days was less pronounced than noted in other studies.[13] Furthermore, a study in 10 patients receiving long-term treatment with either digoxin 125 to 250 micrograms daily or **digitoxin** 100 to 200 micrograms daily were given colestyramine 12 g daily or a placebo taken 1.5 hour after the digitalis. Their plasma digitalis levels were not significantly altered by the colestyramine over a 1-year period.[14] In another study, the half-life of **digitoxin** is reported to have remained unchanged when colestyramine was given,[15] and one study suggested that **metildigoxin** may be minimally affected by colestyramine.[16]

Mechanism

Not totally understood. Colestyramine appears to bind with digitoxin in the gut, thereby reducing its bioavailability and interfering with enterohepatic recirculation so that its half-life is shortened. Digoxin may interact similarly.[2]

Importance and management

The overall picture is far from clear. Some interaction between colestyramine and digoxin or digitoxin seems possible but the extent to which it impairs the treatment of patients receiving these drugs is uncertain. Be alert for any evidence of under-digitalisation if digoxin or, more particularly, digitoxin is given with colestyramine. The studies suggest that coles-

tyramine should not be given less than 1.5 to 2 hours after the digitalis glycoside to minimise the possibility of an interaction.[14] Note that the standard recommendation is to give other drugs one hour before or 4 to 6 hours after colestyramine.

1. Brown DD, Juhl RP, Warner SL. Decreased bioavailability of digoxin produced by dietary fiber and cholestyramine. *Am J Cardiol* (1977) 39, 297.
2. Roberge RJ, Sorensen T. Congestive heart failure and toxic digoxin levels: role of cholestyramine. *Vet Hum Toxicol* (2000) 42, 172–3.
3. Smith TW. New approaches to the management of digitalis intoxication, In 'Symposium on Digitalis'. *Gyldenkal Norsk Forlag* (1977) 39, 312.
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5. Brown DD, Schmid J, Long RA, Hull JH. A steady-state evaluation of the effects of propantheline bromide and cholestyramine on the bioavailability of digoxin when administered as tablets or capsules. *J Clin Pharmacol* (1985) 25, 360–4.
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7. Hall WH, Shappell SD, Doherty JE. Effect of cholestyramine on digoxin absorption and excretion in man. *Am J Cardiol* (1977) 39, 213–16.
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9. Carruthers SG, Dujovne CA. Cholestyramine and spironolactone and their combination in digitoxin elimination. *Clin Pharmacol Ther* (1980) 27, 184–7.
10. Gilfrich HJ, Kasper W, Meinertz T, Okonek S, Bork R. Treatment of massive digitoxin overdose by charcoal haemoperfusion and cholestyramine. *Lancet* (1978) I, 505.
11. Pieroni RE, Fisher JG. Use of cholestyramine resin in digitoxin toxicity. *JAMA* (1981) 245, 1939–40.
12. Hantson P, Vandenplas O, Mahieu P, Wallemacq P, Hassoun A. Repeated doses of activated charcoal and cholestyramine for digitoxin overdose: pharmacokinetic data and urinary elimination. *J Toxicol Clin Exp* (1991) 11, 401–5.
13. Baciewicz AM, Isaacson ML, Lipscomb GL. Cholestyramine resin in the treatment of digitoxin toxicity. *Drug Intell Clin Pharm* (1983) 17, 57–9.
14. Bazzano G, Bazzano GS. Effects of digitalis binding resins on cardiac glycoside plasma levels. *Clin Res* (1972) 20, 24.
15. Pabst J, Leopold G, Schad W, Meub R. Bioavailability of digitoxin during chronic administration and influence of food and cholestyramine on the bioavailability after a single dose. *Naunyn Schmiedebergs Arch Pharmacol* (1979) 307, R70.
16. Hahn K-J, Weber E. Effect of cholestyramine on absorption of drugs. In: Blondheim SH, Alkan WJ, Brunner D (eds). Frontiers of Internal Medicine, 12th International Congress of Internal Medicine, Tel Aviv, Israel, September 1974. Basel: Karger; 1975 p. 409–11.

Digoxin + Danaparoid

No clinically significant interaction appears to occur between digoxin and danaparoid.

Clinical evidence, mechanism, importance and management

In a study, 6 healthy subjects were given digoxin 250 micrograms daily for 8 days, with a single 3250 anti-Xa-unit-bolus dose of danaparoid during day 7. The AUC of digoxin was slightly decreased by danaparoid, although this did not appear to be clinically significant. Digoxin did not alter the effects of danaparoid on clotting tests (including aPTT).[1]

1. de Boer A, Stiekema JCJ, Danhof M, Moolenaar AJ, Breimer DD. Interaction of ORG 10172, a low molecular weight heparinoid, and digoxin in healthy volunteers. *Eur J Clin Pharmacol* (1991) 41, 245–50.

Digoxin and related drugs + Danshen (*Salvia miltiorrhiza*)

Danshen can falsify the results of serum immunoassay methods for digoxin.

Clinical evidence, mechanism, importance and management

Danshen can falsify some laboratory measurements of digoxin because it contains digoxin-like immunoreactive components. A study found that a fluorescent polarization immunoassay method (Abbott Laboratories) for digoxin gave falsely high readings in the presence of danshen, whereas a microparticle enzyme immunoassay (Abbott Laboratories) gave falsely low readings. These, or similar findings have been reported elsewhere.[1] These false readings could be eliminated by monitoring the free (i.e. unbound) digoxin concentrations[2] or by choosing assay systems that are unaffected by the presence of danshen (said to be the Roche and Beckman systems[3] or an enzyme linked chemiluminescent immunosorbent digoxin assay by Bayer HealthCare[1,4]). Similarly, when assaying serum from patients taking digoxin, to which a variety of danshen extracts were added, the use of a fluorescent polarization immunoassay gave variable results, whereas the results were more consistent with a chemiluminescent assay, the EMIT 2000 digoxin assay and the Randox digoxin assay.[5] It would therefore seem prudent, wherever possible, to use a chemiluminescent assay for digoxin in patients also taking danshen.

1. Dasgupta A, Actor JK, Olsen M, Wells A, Datta P. In vivo digoxin-like immunoreactivity in mice and interference of Chinese medicine Danshen in serum digoxin measurement: elimination of interference by using a chemiluminescent assay. *Clin Chim Acta* (2002) 317, 231–4.
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3. Chow L, Johnson M, Wells A, Dasgupta A. Effect of the traditional Chinese medicines Chan Su, Lu-Shen-Wan, Dan Shen, and Asian ginseng on serum digoxin measurement by Tina-quant (Roche) and Synchron LX System (Beckman) digoxin immunoassays. *J Clin Lab Anal* (2003) 17, 22–7.
4. Dasgupta A, Kang E, Olsen M, Actor JK, Datta P. New enzyme-linked chemiluminescent immunosorbent digoxin assay is free from interference of Chinese medicine DanShen. *Ther Drug Monit* (2006) 28, 775–8.
5. Datta P, Dasgupta A. Effect of Chinese medicines Chan Su and Danshen on EMIT 2000 and Randox digoxin immunoassays: wide variation in digoxin-like immunoreactivity and magnitude of interference in digoxin measurement by different brands of the same product. *Ther Drug Monit* (2002) 24, 637–44.

Digoxin + Darifenacin or Solifenacin

Darifenacin increased digoxin exposure by a modest 16% in one study. Solifenacin does not appear to alter the pharmacokinetics of digoxin.

Clinical evidence, mechanism, importance and management

(a) Darifenacin

The manufacturers note that the concurrent use of digoxin 250 micrograms and darifenacin 30 mg daily (twice the recommended dose) increased steady-state digoxin levels and AUC by a modest 20% and 16%, respectively.[1,2] The increase in digoxin exposure could be due to competition between digoxin and darifenacin for P-glycoprotein.[2] This small increase would generally not be expected to be clinically relevant but the manufacturers advise monitoring digoxin[1,2] with the UK manufacturer specifying monitoring when starting or ending darifenacin treatment or when changing darifenacin dose.[2]

(b) Solifenacin

In a crossover study in 24 healthy subjects, solifenacin 10 mg daily for 10 days had no effect on the pharmacokinetics of digoxin 125 micrograms daily.[3]

This study suggests that no pharmacokinetic interaction occurs, and that no digoxin dose adjustment would be expected to be needed on concurrent use.

1. Enablex (Darifenacin hydrobromide). Novartis. US Prescribing information, June 2008.
2. Emselex (Darifenacin hydrobromide). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, September 2009.
3. Smulders RA, Kuipers ME, Krauwinkel WJJ. Multiple doses of the antimuscarinic agent solifenacin do not affect the pharmacodynamics or pharmacokinetics of warfarin or the steady-state pharmacokinetics of digoxin in healthy subjects. *Br J Clin Pharmacol* (2006) 62, 210–17.

Digoxin + Dexmedetomidine

An isolated report describes bradycardia when an infant receiving digoxin was given dexmedetomidine.

Clinical evidence, mechanism, importance and management

A 5-week-old infant with an atrioventricular septal defect, taking digoxin 10 micrograms twice daily and furosemide for mild congestive heart failure, developed respiratory failure requiring intubation and mechanical ventilation. She was given dexmedetomidine for sedation and received a loading dose of 0.5 micrograms/kg over 15 minutes, followed by an infusion of 0.44 micrograms/kg per hour. During the loading dose period her heart rate decreased from 133 bpm to 116 bpm. Throughout the next 13 hours the rate continued to decrease to about 90 bpm, with episodes of sinus bradycardia (heart rate around 50 bpm). Within one hour of discontinuing dexmedetomidine, the heart rate increased to its baseline value and no further episodes of bradycardia were observed. The reasons for the interaction are not known, but the authors of the report suggested that caution is warranted if dexmedetomidine is used for sedation in patients receiving digoxin.[1]

1. Berkenbosch JW, Tobias JD. Development of bradycardia during sedation with dexmedetomidine in an infant concurrently receiving digoxin. *Pediatr Crit Care Med* (2003) 4, 203–5.

Digoxin + Dietary fibre or Laxatives

Bisacodyl reduces digoxin levels. Large amounts of dietary fibre, guar gum and bulk-forming laxatives containing ispaghula or psyllium appear to have no significant effect on the absorption of digoxin. Single-dose studies show that macrogol 4000, a laxative polymer, reduces digoxin levels.

Clinical evidence

(a) Bisacodyl

Bisacodyl reduced the mean serum digoxin levels of 11 healthy subjects by about 12%. When the bisacodyl was taken 2 hours before the digoxin, serum digoxin levels were slightly raised, but not to a statistically significant extent.[1] Another study in 10 patients taking **alpha-acetyldigoxin** found that bisacodyl 30 mg daily reduced plasma digoxin levels from a peak of just over 1.6 nanograms/mL, to a low of about 1.25 nanograms/mL.[2]

(b) Fibre

The serum digoxin levels of 12 patients taking digoxin 125 to 250 micrograms daily 15 to 30 minutes before breakfast were unchanged over a 10-day period when they were given a diet supplemented each day with 22 g of dietary fibre. The fibre was given in this way to simulate the conditions that might be encountered clinically (for example to reduce the symptoms of diverticular disease).[3]

Wheat bran 7.5 g twice daily caused a small 10% reduction in the plasma digoxin levels of 14 geriatric patients after 2 weeks, but there was no significant change after 4 weeks.[4] Bran fibre 11 g caused a 6 to 7% reduction in the absorption and the steady-state serum levels of digoxin in 16 healthy subjects.[5] The cumulative urinary recovery of a single oral dose of digoxin in healthy subjects was reduced almost 20% by 5 g of fibre, whereas 0.75 g of fibre had no effect.[6]

(c) Guar gum

In 10 healthy subjects *Guarem* (95% guar gum) 5 g reduced the peak serum levels of a single 500-microgram oral dose of digoxin by 21% and the AUC_{0-6} was reduced by 16%, but the amount excreted in the urine over 24 hours was only minimally reduced.[7] Guar gum 18 g with a test meal did not affect steady-state plasma digoxin levels in 11 healthy subjects given digoxin 1 mg on day one, 750 micrograms on day 2, and then 500 micrograms daily for 3 days.[8]

(d) Ispaghula

An ispaghula preparation (*Vi-Siblin S*) was found to have no significant effect on the serum digoxin levels of 16 geriatric patients.[4] The same lack of effect was seen in another study in 15 patients given 3.6 g of a psyllium preparation (*Metamucil*) three times daily.[9]

(e) Macrogol 4000

A randomised, crossover study in 18 healthy subjects found that 20 g of macrogol 4000 daily over an 8-day period reduced the maximum serum levels of a single 500-microgram dose of digoxin by 40%, and reduced its AUC by 30%. Heart rate and the PR interval were unchanged.[10] More study is needed to assess the effects of this interaction on steady-state digoxin levels.

Mechanism

Not established. Digoxin can bind to some extent to fibre within the gut.[11] However, *in vitro* studies (with bran, carrageenan, pectin, sodium pectinate, xylan and carboxymethylcellulose) have shown that most of the binding is reversible.[12]

Importance and management

Information seems to be limited to these reports. The reduction in serum digoxin levels caused by bisacodyl is small, and not expected to be of clinical importance, and apparently preventable by giving the bisacodyl 2 hours before the digoxin. Neither dietary fibre (bran), guar gum nor the two bulk-forming laxatives (*Vi-Siblin* and *Metamucil*) have a clinically important effect on serum digoxin levels. No special precautions would appear to be necessary. The importance of the interaction between digoxin and macrogol 4000 awaits further assessment, but on the available evidence it would be prudent to be alert for the need to increase the digoxin dose.

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Digoxin and related drugs + Digoxin-like herbal medicines

Many herbal remedies contain digitalis glycosides, which could in theory have additive effects with digoxin or related digitalis glycosides, or interfere with their assays. However, there appear to be few such interactions reported.

Clinical evidence, mechanism, importance and management

(a) Additive effects possible

A 26-year-old woman developed severe and unexplained chest pain, and was later noted to have a heart rate of 39 bpm and a blood pressure of 59/36 mmHg, but these rose to normal with conservative management. She was found to have a digoxin level of 0.9 nanograms/mL and was diagnosed as having digoxin toxicity, despite not taking any prescribed digoxin. The digoxin-like digitalis glycosides were thought to have come from an unnamed herbal remedy for stress, which contained **black cohosh root** (*Cimicifuga racemosa*), **cayenne pepper fruit** (*Capsicum annuum*), **hops flowers** (*Humulus lupulus*), **skullcap herb** (*Scutellaria lateriflora*), **valerian root** (*Valeriana officinalis*) and **wood betony herb** (*Pedicularis canadensis*).[1] All of these had previously been shown to contain small amounts of digoxin-like compounds, which were only partially detected by digoxin antibody immunoassays.[1,2] In this previous *in vitro* study, 46 commercially packaged herb teas and 78 teas prepared from herbs were assayed for digoxin-like factors by their cross-reactivity with digoxin antibody or inhibition of ouabain binding, and these values were used to give approximate equivalent daily doses of digoxin. Three packaged teas (***Breathe Easy***, **blackcurrant**, and **jasmine**) and 3 herbs (**pleurisy root**, **chaparral**, **peppermint**) were found to contain greater than 30 micrograms of digoxin equivalents per cup and were postulated to provide a therapeutic daily dose of digoxin if 5 cups a day were drunk.[2] However, note that some common teas sampled in this study (e.g. English Breakfast, Earl Grey) contained over 20 micrograms of digoxin equivalents per cup, and tea drinking has not been associated with adverse cardiovascular risk.[3] Therefore the interpretation of the findings of this study is unclear.

Theoretical interactions with herbal remedies are not always translated into practice, and there do not appear to be any cases of herbals interacting with digoxin because of their cardiac glycoside content.

(b) Effects on digoxin or digitoxin assays

A 68-year-old woman who was given a loading dose of digitoxin 750 micrograms then 100 micrograms on the second day was found to have markedly elevated levels of digitoxin (greater than 100 nanograms/mL), but no clinical signs of toxicity. Two days before admission she had ingested 90 drops of **Uzara**, a preparation from *Xysmalobium undulatum*, which contains weak digitalis glycosides. Later investigations in 4 healthy subjects given 30 drops of **Uzara** confirmed that assays for **digitoxin** (CEDIA digitoxin test, Roche Diagnostics, Ger-

many) and digoxin (Tina-quant digoxin test, Roche Diagnostics, Germany) were markedly elevated by **Uzara** to levels well above usual therapeutic concentrations, but that there were no clinically relevant changes in heart rate and blood pressure.[4]

In an *in vitro* study, **plantain** (*Plantago major*) extract from capsules, liquid extract, or dry leaf did not affect the results of digoxin assays when using fluorescence polarization immunoassay or microparticle enzyme immunoassay.[5] Note that contamination of **plantain** with *Digitalis lanata* has been reported.[6]

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Digoxin + Dihydroergocryptine

Dihydroergocryptine does not appear to affect the pharmacokinetics of digoxin.

Clinical evidence, mechanism, importance and management

In a randomised study in 12 healthy subjects, dihydroergocryptine 20 mg did not affect the pharmacokinetics of a single 500-microgram dose of digoxin. No clinically significant changes were seen in the ability of the heart to initiate and conduct impulses, or repolarise. The slight drop in blood pressure during the first 2 to 4 hours after digoxin was more pronounced in the presence of dihydroergocryptine, but there was no evidence of impaired orthostatic blood pressure control.[1] No special precautions would seem necessary during concurrent use.

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Digoxin + Dipeptidylpeptidase-4 inhibitors

There appears to be no pharmacokinetic interaction between digoxin and saxagliptin or vildagliptin. Sitagliptin very slightly raised digoxin levels, but this is not likely to be clinically relevant.

Clinical evidence

(a) Saxagliptin

In a study in 14 healthy subjects, there was no change in the pharmacokinetics of digoxin or saxagliptin when digoxin (loading dose over 2 days then 250 micrograms daily for 5 days) was given with saxagliptin 10 mg daily, when compared with either drug alone.[1]

(b) Sitagliptin

The manufacturers describe a study in which digoxin 250 micrograms daily was given with sitagliptin 100 mg daily for 10 days. The AUC and maximum plasma levels of digoxin were increased by 11% and 18%, respectively.[2,3]

(c) Vildagliptin

In a study, 18 healthy subjects were given either vildagliptin 100 mg daily for 7 days or digoxin 500 micrograms on the first day then 250 micrograms for 6 days then both drugs together. No changes in the pharmacokinetics of either drug occurred.[4]

Mechanism

Sitagliptin may be a weak inhibitor of P-glycoprotein, thereby slightly raising digoxin levels.

Importance and management

The small rise in digoxin exposure with sitagliptin is unlikely to be clinically relevant, and no digoxin dose adjustment is needed when sitagliptin is started. However, the manufacturer recommends that patients at risk of digoxin toxicity should be monitored for this when sitagliptin is used,[2,3] which is a cautious approach.

Saxagliptin and vildagliptin do not alter digoxin levels, and no dose adjustment is required on concurrent use.

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Digoxin + Dipyridamole

Dipyridamole may cause a minor increase in the absorption of digoxin.

Clinical evidence, mechanism, importance and management

A study in 12 healthy subjects found that dipyridamole 150 mg twice daily for 5 doses increased the AUC_{0-4} and the AUC_{0-24} of a single 500-microgram oral dose of digoxin by 20% and 13%, respectively. This was attributed to an increase in digoxin absorption possibly mediated by intestinal P-glycoprotein inhibition.[1] *In vitro* studies[1,2] found that dipyridamole inhibits the P-glycoprotein-mediated transport of digoxin, but in one study this was only at higher levels than those achieved clinically.[2] Therefore these minor changes are not fully explained. Nevertheless, the changes in digoxin pharmacokinetics in the presence of dipyridamole are small and unlikely to be of clinical significance.

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Digoxin and related drugs + Disopyramide or Procainamide

Neither disopyramide nor procainamide normally cause a significant change in digoxin levels. A single report describes toxicity in a patient taking digitoxin and disopyramide.

Clinical evidence, mechanism, importance and management

(a) Disopyramide

A number of studies have clearly shown that disopyramide causes only a very small increase or no increase at all in the serum levels of digoxin.[1-6] A small but insignificant reduction in heart rate has been seen,[7] but the weight of evidence suggests that no adverse interaction occurs if digoxin and disopyramide are used together. However, a very brief report describes toxicity and serious arrhythmia in one patient given **digitoxin** and disopyramide.[8]

(b) Procainamide

A study in patients who had been taking digoxin for at least 7 days found that procainamide did not affect their serum digoxin levels.[2]

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Digoxin and related drugs + Diuretics; Potassium-depleting

The potassium loss caused by potassium-depleting diuretics increases the toxicity of the digitalis glycosides.

Clinical evidence

A comparative study[1] of the medical records of 418 patients taking digitalis over the period 1950 to 1952, and of 679 patients over the period 1964 to 1966, found that the incidence of digitalis toxicity had more than doubled. Of the earlier group 8.6% developed toxicity (58% taking diuretics, mainly of the **organomercurial type**) compared with 17.2% of the latter group (81% taking diuretics, mainly **chlorothiazides**, **furosemide**, **etacrynic acid**, **chlortalidone**). It was concluded that the increased toxicity was related to the increased usage of potassium-depleting diuretics.

A retrospective study of over 400 patients taking digoxin found that almost one in five had some toxic reactions attributable to the use of the digoxin. Of these, 16% had demonstrable hypokalaemia (defined as serum potassium less than 3.5 mmol/L). Almost half of the patients who had toxicity were taking potassium-depleting diuretics, notably **hydrochlorothiazide** or **furosemide**.[2] Similar results were found in other studies in a considerable number of patients.[3-9]

In contrast, a retrospective study of patients who developed digitalis toxicity showed that the likelihood of its development in those with potassium levels below 3.5 mmol/L was no greater than those with normal potassium levels.[10] Two other studies in a total of almost 200 patients did not detect any association between the development of digitalis toxicity and the use of diuretics or changes in potassium levels.[11,12]

A pharmacokinetic study in 6 patients found that single 50-mg and 100-mg doses of **cicletanine** had no effect on the plasma levels of digoxin 125 to 250 micrograms daily.[13] In addition there is also some evidence that **furosemide** may raise serum digoxin levels,[14] although two other studies found no evidence that **furosemide** affects the urinary excretion of digoxin.[15,16]

Mechanism

Not fully understood. The cardiac glycosides inhibit sodium-potassium ATP-ase, which is concerned with the transport of sodium and potassium ions across the membranes of the myocardial cells. This is associated with an increase in the availability of calcium ions concerned with the contraction of the cells. Potassium loss caused by these diuretics exacerbates the potassium loss from the myocardial cells, thereby increasing the activity and the toxicity of the digitalis. Some loss of magnesium may also have a part to play. The mechanism of this interaction is still being debated.

Importance and management

A direct link between the use of these potassium-depleting diuretics and the development of digitalis toxicity is not established beyond doubt, but concurrent use can result in digitalis toxicity. It is therefore important that potassium levels remain within the accepted normal range during the use of a digitalis glycoside. Potassium levels should be routinely monitored when diuretics are given and it may be prudent to recheck levels if patients develop symptoms of digitalis toxicity. See 'Table 26.1', (p.1121) for a list of potassium-depleting diuretics.

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Digoxin and related drugs + Diuretics; Potassium-sparing

Digoxin levels may be increased by 25% by spironolactone, but because spironolactone or its metabolite, canrenone, can interfere with some digoxin assay methods, the evaluation of this interaction is difficult. Eplerenone may also cause a minor increase in digoxin levels. Amiloride has little effect on digoxin levels in healthy subjects, but it may reduce its inotropic effects, and in patients with renal impairment it possibly raises digoxin levels.
The effects of digitoxin are reported to be both increased and decreased by spironolactone.

Clinical evidence

(a) Digitoxin

A study in 6 healthy subjects who had been taking digitoxin 100 or 150 micrograms daily for 30 days found that **spironolactone** 300 mg daily increased the digitoxin half-life by one-third (from 142 to 192 hours).[1]

In contrast, other studies have found that the digitoxin half-life was reduced (from 256 to 205 hours) by **spironolactone**.[2]

(b) Digoxin

1. Amiloride. In 6 healthy subjects amiloride 5 mg twice daily for 8 days almost doubled the renal clearance of digoxin (from 1.3 to 2.4 mL/kg per minute), but reduced the extra-renal clearance (from 2.1 to 0.1 mL/kg per minute). The balance of the two effects was to cause a small fall in total clearance and a small rise in plasma digoxin levels.[3] The positive inotropic effects of digoxin were reduced, but whether this is clinically important is uncertain. In contrast, a later study in 8 healthy subjects found that a single 75-mg [sic] oral dose of amiloride given 3 hours before an infusion of digoxin did not reduce the inotropic effects of digoxin.[4]

2. Eplerenone. In one study, the steady-state AUC of digoxin 200 micrograms daily increased by 16% (90% confidence interval: 4% to 30%) when it was given with eplerenone.[5,6]

3. Spironolactone. The plasma digoxin levels of 9 patients were increased by about 20% (from 0.8 to 1 nanograms/mL) when they were given spironolactone 100 mg daily. One patient had a three to fourfold rise in digoxin levels.[7]

The clearance of a single 750-microgram intravenous dose of digoxin was reduced by about 25% in 4 patients and 4 healthy subjects following 5 days of treatment with spironolactone 100 mg twice daily.[8] A marked fall in serum digoxin levels occurred in an elderly patient when spironolactone was withdrawn,[9] but the accuracy of the assay method used is uncertain (see *Importance and management* below). One study found that no clinically important reduction in digoxin clearance occurred when *Aldactazide* (spironolactone-hydrochlorothiazide) was also given.[10]

Mechanism

Not fully understood. Spironolactone inhibits the excretion of digoxin by the kidney (by 13%) but does not affect its biliary clearance.[11] *Animal* studies have suggested that spironolactone may induce P-glycoprotein expression, resulting in reduced intestinal absorption of substrates such as digoxin.[12] Spironolactone probably also causes a reduction in the volume of distribution of digoxin.

It has been suggested that amiloride may have increased the production of aldosterone, which suppressed the positive inotropic effects of digoxin.[3] Studies in patients with congestive heart failure are needed.

Importance and management

The pharmacokinetic interaction between digoxin and **spironolactone** appears to be established. What is known suggests that a rise in digoxin levels of up to 25% is likely to occur, although much greater increases can apparently occur in some patients.[7] Monitor concurrent use carefully for signs of over-digitalisation. Note that spironolactone or its metabolite, canrenone, can interfere with some digoxin assay methods.[13] In one report, radioimmunoassay (RIA) and affinity-column-mediated immunoassay (ACMIA) were particularly affected by spironolactone and its metabolites.[14] Conversely, falsely low digoxin readings with the AxSym MEIA assay method led to digoxin overdose and toxicity in one patient.[15] This means that monitoring is difficult unless the digoxin assay method is known to be reliable. Measurement of free digoxin levels or use of a chemiluminescent assay (CLIA) or turbidometric immunoassay for digoxin has been reported to mostly eliminate interference from spironolactone, potassium canrenoate and canrenone.[16,17]

Eplerenone also appears to cause a small increase in digoxin levels. The UK manufacturers recommend that caution is warranted when digoxin is dosed near the upper limit of therapeutic range.[5] However, the US manufacturer states that the pharmacokinetic interaction is not clinically significant.[18]

The situation with digitoxin and spironolactone is confusing because the reports are contradictory and the outcome uncertain. Concurrent use should be well monitored.

Patients with poor renal function would be expected to have a rise in digoxin levels when given **amiloride** (due to the increased reliance on renal clearance) but the clinical importance of this awaits confirmation.

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Digoxin + Dofetilide

Dofetilide does not affect the pharmacokinetics of digoxin.

Clinical evidence, mechanism, importance and management

In a placebo-controlled study in 13 subjects, dofetilide 250 micrograms twice daily for 5 days had no effect on the steady-state pharmacokinetics of digoxin, given at a dose of 250 micrograms daily after a loading dose.[1]

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Digoxin and related drugs + Drugs that affect calcium

The effects of digitalis glycosides might be increased by rises in blood calcium levels, and the use of intravenous calcium may result in the development of potentially life-threatening digitalis-induced arrhythmias. The use of digitalis glycosides in the presence of hypercalcaemia due to vitamin D administration could result in arrhythmias. Teriparatide appears not to affect the calcium-mediated effects of digoxin.

Clinical evidence

(a) Calcium

Two patients developed cardiac arrhythmias and died after being given digitalis intramuscularly and either **calcium chloride** or **calcium gluconate** intravenously. No absolutely certain causative relationship was established.[1]

There is some evidence that increases or decreases in blood **calcium** levels can increase or decrease, respectively, the effects of digitalis. A patient with congestive heart failure and atrial fibrillation was resistant to the actions of digoxin (serum levels of 1.5 to 3 nanograms/mL) until his serum **calcium** levels were raised from 1.68 mmol/L to about 2.13 mmol/L by oral **calcium and vitamin D**.[2]

(b) Teriparatide

A placebo-controlled study in 15 healthy subjects given digoxin 500 micrograms daily, adjusted to maintain steady-state serum levels in the range 1 to 2 nanograms/mL, found that a single 20-microgram subcutaneous dose of teriparatide on day 15 or 16 did not alter the calcium-mediated effects of digoxin (systolic time interval), or heart rate. Serum calcium increased slightly, with a maximum increase of 0.05 mmol/L.[3]

Mechanism

The actions of the cardiac glycosides (even now not fully understood) are closely tied up with movement of calcium ions into heart muscle cells. Increased concentrations of calcium outside these cells increase the inflow of calcium and this enhances the activity of the glycosides. This can lead to effective over-digitalisation and even potentially life-threatening arrhythmias. Conversely, a drop in calcium levels can attenuate the activity of the glycosides: **disodium edetate**,[4-6] which lowers blood calcium levels, has been used successfully in the treatment of digitalis toxicity, although less toxic drugs are generally preferred.

Importance and management

The report of deaths associated with digitalis and calcium compounds (published in 1936) seems to be the only direct clinical evidence of a serious adverse interaction, although there is plenty of less direct evidence that an interaction is possible. Intravenous calcium should be avoided in patients receiving cardiac glycosides. If that is not possible, it has been suggested[7] that it should be given slowly or only in small amounts in order to avoid transient serum calcium levels higher than 7.5 mmol/L, but it seems likely that very large doses of calcium would be required to reach this level, even transiently.

Hypercalcaemia is one of the most common adverse effects of **alfacalcidol** and **paricalcitol**, and is reported to be a common adverse effect of **calcitriol** and **ergocalciferol** usually occurring with excessive doses. Although calcium levels should be monitored in patients taking these drugs, it is particularly important to ensure that this is done in patients also taking cardiac glycosides.

The very slight increases in calcium observed with teriparatide were considered insufficient to increase cardiac sensitivity to digoxin.[3] Nevertheless, the manufacturer of teriparatide still advises caution in patients taking digitalis, because of the possibility for transiently raised calcium levels.[8,9]

1. Bower JO, Mengle HAK. The additive effects of calcium and digitalis. A warning with a report of two deaths. *JAMA* (1936) 106, 1151.
2. Chopra D, Janson P, Sawin CT. Insensitivity to digoxin associated with hypocalcaemia. *N Engl J Med* (1977) 296, 917–18.
3. Benson CT, Voelker JR. Teriparatide has no effect on the calcium-mediated pharmacodynamics of digoxin. *Clin Pharmacol Ther* (2003) 73, 87–94.
4. Jick S, Karsh R. The effect of calcium chelation on cardiac arrhythmias and conduction disturbances. *Am J Cardiol* (1959) 4, 287–93.

5. Szekely P, Wynne NA. Effects of calcium chelation on digitalis-induced cardiac arrhythmias. *Br Heart J* (1963) 25, 589–94.
6. Rosenbaum JL, Mason D, Seven MJ. The effect of disodium EDTA on digitalis intoxication. *Am J Med Sci* (1960) 240, 111–18.
7. Nola GT, Pope S, Harrison DC. Assessment of the synergistic relationship between serum calcium and digitalis. *Am Heart J* (1970) 79, 499–507.
8. Forsteo (Teriparatide). Eli Lilly and Company Ltd. UK Summary of product characteristics, August 2009.
9. Forteo (Teriparatide). Eli Lilly and Company. US Prescribing information, July 2009.

Digoxin and related drugs + Drugs that lower potassium levels

A number of drugs, including amphotericin B, carbenoxolone, and the corticosteroids, cause potassium loss, which could lead to the development of digitalis toxicity.

Clinical evidence, mechanism, importance and management

Among the well-recognised adverse effects of **amphotericin B** is hypokalaemia, which can be severe. Although there seem to be no reports of adverse interactions, it would be logical to expect that digitalis toxicity could develop in patients given both drugs if the potassium levels fall. Amiloride has been successfully used to counteract the potassium loss caused by **amphotericin B**.[1]

The adverse effects of **carbenoxolone** include an increase in blood pressure (both systolic and diastolic), fluid retention and reduced serum potassium levels. The incidence of these adverse effects is said in some reports to be as high as 50%; others quote lower figures. Hypertension and fluid retention occur early in **carbenoxolone** treatment, whereas the hypokalaemia develops later and may occur in the absence of the other two adverse effects.[2-5] **Carbenoxolone** is therefore unsuitable for patients with congestive heart failure, or those taking digitalis glycosides, unless measures to avoid hypokalaemia are taken.

Systemic corticosteroids can increase the loss of potassium, particularly those that are naturally occurring (**cortisone**, **deoxycortone**, **hydrocortisone**) whereas the synthetic derivatives (**betamethasone**, **dexamethasone, methylprednisolone**, **prednisolone**, **prednisone**, **triamcinolone**) have much less mineralocorticoid activity. There is therefore the possibility of potassium depletion, particularly when corticosteroids are used long-term, which may increase the risk of digitalis toxicity. These corticosteroids also cause sodium and water retention, resulting in oedema and hypertension, which can lead to cardiac failure in some individuals.

It is therefore important to monitor the use of digoxin and any of these drugs well. Potassium levels should be routinely monitored in any patient taking **amphotericin B**, but it is particularly important in those taking digoxin. With other drugs where potassium monitoring is not routine, it would seem prudent to watch for signs of digoxin adverse effects (e.g. bradycardia) and consider measuring potassium levels if these develop. No problems of this kind would be expected with corticosteroids used topically or by inhalation, because the amounts absorbed are likely to be relatively small.

For reports of digoxin toxicity or increased sensitivity to digoxin associated with other drugs that cause hypokalaemia, see 'Digoxin and related drugs + Diuretics; Potassium-depleting', p.1097, and 'Digoxin and related drugs + Beta-agonist bronchodilators', p.1087.

1. Smith SR, Galloway MJ, Reilly JT, Davies JM. Amiloride prevents amphotericin B related hypokalaemia in neutropenic patients. *J Clin Pathol* (1988) 41, 494–7.
2. Geismar P, Mosbech J, Myren J. A double-blind study of the effect of carbenoxolone sodium in the treatment of gastric ulcer. *Scand J Gastroenterol* (1973) 8, 251–6.
3. Turpie AGG, Thomson TJ. Carbenoxolone sodium in the treatment of gastric ulcer with special reference to side-effects. *Gut* (1965) 6, 591–4.
4. Langman MJS, Knapp DR, Wakley EJ. Treatment of chronic gastric ulcer with carbenoxolone and gefarnate: a comparative trial. *BMJ* (1973) 3, 84–6.
5. Davies GJ, Rhodes J, Calcraft BJ. Complications of carbenoxolone therapy. *BMJ* (1974) 3, 400–402.

Digoxin and related drugs + Edrophonium

Excessive bradycardia and AV-block may occur if patients taking digitalis glycosides are given edrophonium.

Clinical evidence, mechanism, importance and management

The rapid intravenous injection of edrophonium 10 mg has been used in the differentiation of cardiac arrhythmias, but in one study, 4 of 10 digitalised patients given edrophonium developed atrial tachycardia with AV block. The effect was transient; recovery of baseline ECGs occurred 15 to 20 minutes after administration.[1] Nevertheless, the authors recommended that edrophonium should not be given to patients with atrial flutter or tachycardia who are taking **digitalis glycosides**. This recommendation is reinforced by the case of an elderly woman[2] who developed bradycardia, AV block and asystole following concurrent use. She recovered after being given atropine 1 mg.

1. Reddy RCV, Gould L, Gomprecht RF. Use of edrophonium (Tensilon) in the evaluation of cardiac arrhythmias. *Am Heart J* (1971) 82, 742–9.
2. Gould L, Zahir M, Gomprecht RF. Cardiac arrest during edrophonium administration. *Am Heart J* (1971) 81, 437–8.

Digoxin + Endothelin receptor antagonists

Bosentan does not appear to affect the pharmacokinetics of digoxin.

Clinical evidence, mechanism, importance and management

(a) Ambrisentan

A study in 15 healthy subjects found that multiple doses of ambrisentan 10 mg daily (duration not stated) slightly increased the trough concentration and AUC of a single dose of digoxin (dose not stated), and modestly increased the maximum concentration digoxin, by 29%. These changes are not expected to be clinically relevant and therefore no digoxin dose adjustments are needed if ambrisentan is also given.[1]

(b) Bosentan

In a study in 18 healthy subjects, bosentan 500 mg twice daily for a week did not significantly affect the steady-state peak or trough levels of digoxin 375 micrograms daily. There was a small reduction of about 12% in the AUC of digoxin, which may have been due to induction of P-glycoprotein by bosentan. There were no changes in ECG recordings and vital signs. The results suggest that bosentan does not interact with digoxin to a clinically relevant extent and that concurrent use need not be avoided. However, the authors of the report note that further studies over the longer term, and in patients with renal impairment, may be necessary to confirm this.[2]

(c) Sitaxentan

The manufacturers of sitaxentan note that it does not alter the pharmacokinetics of digoxin.[3]

1. Volibris (Ambrisentan). GlaxoSmithKline UK. UK Summary of product characteristics, August 2009.
2. Weber C, Banken L, Birnboeck H, Nave S, Schulz R. The effect of bosentan on the pharmacokinetics of digoxin in healthy male subjects. *Br J Clin Pharmacol* (1999) 47, 701–6.
3. Thelin (Sitaxentan sodium). Encysive (UK) Ltd. UK Summary of product characteristics, April 2009.

Digoxin and related drugs + Enoximone

Studies in patients receiving long-term treatment with digoxin or digitoxin found that *oral* enoximone 100 mg three times daily for a week had no significant effect on the plasma levels of either of these digitalis glycosides.[1,2] Cardiac function was improved. There dose adjustments of these cardiac glycosides would not be expected to be necessary if enoximone is also given.

1. Glauner T, Hertrich F, Winkelmann B, Dieterich HA, Trenk D, Jähnchen E. Lack of effect of enoximone on steady-state plasma concentrations of digoxin and digitoxin. *Eur Heart J* (1988) 9 (Suppl 1), 151.
2. Trenk D, Hertrich F, Winkelmann B, Glauner T, Dieterich HA, Jähnchen E. Lack of effect of enoximone on the pharmacokinetics of digoxin in patients with congestive heart failure. *J Clin Pharmacol* (1990) 30, 235–40.

Digoxin + Etanercept

No clinically significant interaction appears to occur between digoxin and etanercept.

Clinical evidence, mechanism, importance and management

A study in 12 healthy subjects given an oral loading dose of digoxin 500 micrograms twice daily on day one, followed by 250 micrograms daily, found that subcutaneous etanercept 25 mg twice weekly did not significantly affect the pharmacokinetics of digoxin. The maximum serum levels and AUC of etanercept were 4% and 13% lower, respectively, during concurrent use but this was not considered to be clinically significant. The combination was well tolerated and there were no changes in ECG parameters.[1] No special precautions therefore seem necessary if both drugs are given.

1. Zhou H, Parks V, Patat A, Le Coz F, Simcoe D, Korth-Bradley J. Absence of a clinically relevant interaction between etanercept and digoxin. *J Clin Pharmacol* (2004) 44, 1244–51.

Digoxin + Exenatide

Exenatide delays the time to peak plasma digoxin levels.

Clinical evidence, mechanism, importance and management

In a pharmacokinetic study, 21 healthy subjects were given an oral loading dose of digoxin 500 micrograms twice daily on day one, then 250 micrograms daily for 11 days, with subcutaneous exenatide 10 micrograms twice daily on days 8 to 12. The median time to maximum plasma concentration of digoxin was increased from 1.5 hours to 4 hours, and there was a reduction of 17% in its maximum levels. There was no change in AUC and trough digoxin levels, and the renal clearance of digoxin was not altered. It is thought that the changes in digoxin pharmacokinetics occurred as a result of altered gastric emptying caused by exenatide.[1] Evidence for an interaction between digoxin and exenatide appears to be limited to this study, which suggests that the changes in digoxin pharmacokinetics are small, and unlikely to be clinically relevant. No digoxin dose adjustment is likely to be required on concurrent use.

1. Kothare AP, Soon DKW, Linnebjerg H, Park S, Chan C, Yeo A, Lim M, Mace KF, Wise SD. Effect of Exenatide on the steady-state pharmacokinetics of digoxin. *J Clin Pharmacol* (2005) 45, 1032–7.

Digoxin + Ezetimibe

Ezetimibe does not affect the pharmacokinetics of digoxin.

Clinical evidence, mechanism, importance and management

In a study in 12 healthy subjects, ezetimibe 10 mg daily for 7 days did not alter the pharmacokinetics of a single 500-microgram dose of digoxin. In addition, ezetimibe did not alter the ECG effects of digoxin.[1] No digoxin dose adjustment would be expected to be necessary if ezetimibe is also given.

1. Kosoglou T, Statkevick P, Johnson-Levonas AO, Paolini JF, Bergman AJ, Alton KB. Ezetimibe. A review of its metabolism, pharmacokinetics and drug interactions. *Clin Pharmacokinet* (2005) 44, 467–94.

Digoxin + Fenoldopam

Oral fenoldopam appears to cause a small reduction in plasma digoxin levels in most patients, but more marked changes may occur in a few individuals.

Clinical evidence, mechanism, importance and management

Ten patients with congestive heart failure receiving digoxin long-term (doses not stated) were additionally given *oral* fenoldopam 100 mg three times daily for 9 days. The mean AUC and steady-state plasma levels of digoxin were reduced by about 20%. In two patients, the steady-state plasma levels of digoxin fell by 48% (from 1.36 to 0.71 nanograms/mL), and by 68% (from 1.93 to 0.61 nanograms/mL), respectively. In a further patient, digoxin levels rose by 45% (from 1.03 to 1.49 nanograms/mL).[1] Most patients appear not to show marked changes in plasma digoxin levels, but a few individuals may possibly need some dose adjustment. Monitor concurrent use for both efficacy and digoxin adverse effects.

1. Strocchi E, Tartagni F, Malini PL, Valtancoli G, Ambrosioni E, Pasinelli F, Riva E, Fuccella LM. Interaction study of fenoldopam-digoxin in congestive heart failure. *Eur J Clin Pharmacol* (1989) 37, 395–7.

Digoxin + Flecainide

Digoxin levels are unaltered or only modestly increased by the use of flecainide.

Clinical evidence

The plasma digoxin levels of 10 patients with congestive heart failure were unchanged when they took flecainide 100 to 200 mg twice daily for 7 days. A similar lack of interaction was also seen in 4 patients who took both drugs over a 4-week period.[1]

In contrast, a study in 15 healthy subjects found that flecainide 200 mg twice daily increased the trough and peak plasma levels of digoxin 250 micrograms by 24% and 13%, respectively.[2] The changes observed in vital signs were not clinically significant. Based on the results of a single-dose study the steady-state digoxin levels were predicted to rise by about 15% during the use of flecainide 200 mg twice daily.[3]

Mechanism

Uncertain. It is suggested that any changes may be due to alterations in the volume of distribution.[3]

Importance and management

Documentation is limited but what is known suggests that either no interaction occurs, or any changes are small and unlikely to be clinically relevant in most patients. However, the UK manufacturers of flecainide recommend that digoxin plasma levels should be measured not less than 6 hours after any digoxin dose, before or after the administration of flecainide.[4] The US manufacturers suggest close monitoring of cardiac function on concurrent use.[5] The authors of one of the reports[2] suggest that patients with high drug levels, atrioventricular nodal dysfunction, or both, should be monitored during concurrent treatment.

1. McQuinn RL, Kvam DC, Parrish SL, Fox TL, Miller AM, Franciosa JA. Digoxin levels in patients with congestive heart failure are not altered by flecainide. *Clin Pharmacol Ther* (1988) 43, 150.
2. Weeks CE, Conard GJ, Kvam DC, Fox JM, Chang SF, Paone RP, Lewis GP. The effect of flecainide acetate, a new antiarrhythmic, on plasma digoxin levels. *J Clin Pharmacol* (1986) 26, 27–31.
3. Tjandramaga TB, Verbesselt R, Van Hecken A, Mullie A, De Schepper PJ. Oral digoxin pharmacokinetics during multiple-dose flecainide treatment. *Arch Int Pharmacodyn Ther* (1982) 260, 302–3.
4. Tambocor (Flecainide acetate). Meda Pharmaceuticals. UK Summary of product characteristics, October 2007.
5. Tambocor (Flecainide acetate). Graceway Pharmaceuticals LLC. US Prescribing information, April 2007.

Digoxin + Fondaparinux

No clinically significant interaction appears to occur between digoxin and fondaparinux.

Clinical evidence, mechanism, importance and management

A phase I randomised study in 24 healthy subjects found that the pharmacokinetics of oral digoxin 250 micrograms twice daily for one day then 250 micrograms daily for 6 days was unaffected by subcutaneous fondaparinux 10 mg daily. The pharmacokinetics of fondaparinux were not affected by digoxin. The combination was well tolerated and no clinically significant changes in vital signs and ECGs were observed.[1] No additional precautions therefore seem necessary on concurrent use.

1. Mant T, Fournié P, Ollier C, Donat F, Necciari J. Absence of interaction of fondaparinux sodium with digoxin in healthy volunteers. *Clin Pharmacokinet* (2002), 41 (Suppl 2), 39–45.

Digoxin + Ginkgo (*Ginkgo biloba*)

Ginkgo does not appear to affect the pharmacokinetics of digoxin.

Clinical evidence

A study in 8 healthy subjects found that ginkgo biloba leaf extract 80 mg three times daily had no significant effects on the pharmacokinetics of a single 500-microgram dose of digoxin.[1]

Mechanism

Digoxin is a P-glycoprotein substrate and *in vitro* studies[2] suggest that ginkgo may inhibit the activity of this drug transporter protein, which could lead to increased digoxin levels. However, this effect was not seen clinically.

Importance and management

The clinical study suggests that ginkgo is unlikely to alter digoxin levels in clinical use. Therefore no dose adjustment would be expected to be necessary if patients taking digoxin also wish to take ginkgo.

1. Mauro VF, Mauro LS, Kleshinski JF, Khuder SA, Wang Y, Erhardt PW. Impact of Ginkgo biloba on the pharmacokinetics of digoxin. *Am J Ther* (2003) 10, 247–51.
2. Hellum BH, Nilsen OG. *In vitro* inhibition of CYP3A4 metabolism and P-glycoprotein-mediated transport by trade herbal products. Basic Clin Pharmacol Toxicol (2008) 102, 466–75.

Digoxin + Ginseng

***Panax ginseng* (Asian ginseng), *Panax quinquefolius* (American ginseng) and *Eleutherococcus senticosus* (Siberian ginseng) may interfere with the results of digoxin assays.**

Clinical evidence, mechanism, importance and management

A 74-year-old man who had been taking digoxin for many years (serum levels normally in the range 0.9 to 2.2 nanograms/mL) was found, during a routine check, to have digoxin levels of 5.2 nanograms/mL, but without evidence of toxicity, bradycardia or any other ECG changes.[1] The levels remained high even when the digoxin was stopped. It turned out he had also been taking ***Eleutherococcus senticosus* (Siberian ginseng)** capsules. When the ginseng was stopped, the digoxin levels returned to the usual range, and digoxin was resumed. Later rechallenge with the ginseng caused a rise in his serum digoxin levels. No digoxin or digitoxin contamination was found in the capsules, and the authors of the report also rejected the idea that the eleutherosides (chemically related to cardiac glycosides) in ginseng might have been converted *in vivo* into digoxin, or that the renal elimination of digoxin might have been impaired, as the patient showed no signs of toxicity.

***Panax ginseng* (Asian ginseng)**, ***Panax quinquefolius* (American ginseng)** and ***Eleutherococcus senticosus* (Siberian ginseng)** have been found to interfere with some digoxin assays including fluorescence polarisation immunoassay (FPIA, Abbott Laboratories)[2-4] and microparticle enzyme immunoassay (MEIA, Abbott Laboratories).[2,3] The more specific monoclonal antibody-based **digoxin** immunoassay, Tina-quant (Roche), was unaffected by all the ginsengs,[3,4] and the Beckman (Synchron LX system) monoclonal assay was unaffected by ***Panax ginseng* (Asian ginseng)**.[4] It therefore seems possible that the ginsengs affected the accuracy of the digoxin assays so that they gave false results.

The interference in the digoxin measurements described in the assays was not as high as that reported in the elderly patient and there is some doubt as to whether the herbal medicine taken by the patient was actually *Eleutherococcus senticosus* (Siberian ginseng).[3,5] So, whether this is clinically important, and measurement of serum digoxin levels is actually affected, is uncertain. Nevertheless it may be sensible to ask about ginseng use when interpreting unexpected digoxin levels and consider using a more specific monoclonal immunoassay.

1. McRae S. Elevated serum digoxin levels in a patient taking digoxin and Siberian ginseng. *Can Med Assoc J* (1996) 155, 293–5.
2. Dasgupta A, Wu S, Actor J, Olsen M, Wells A, Datta P. Effect of Asian and Siberian ginseng on serum digoxin measurement by five digoxin immunoassays. Significant variation in digoxin-like immunoreactivity among commercial ginsengs. *Am J Clin Pathol* (2003) 119, 298–303.
3. Dasgupta A, Reyes MA. Effect of Brazilian, Indian, Siberian, Asian, and North American ginseng on serum digoxin measurement by immunoassays and binding of digoxin-like immunoreactive components of ginseng with Fab fragment of antidigoxin antibody (Digibind). *Am J Clin Pathol* (2005) 124, 229–36.
4. Chow L, Johnson M, Wells A, Dasgupta A. Effect of the traditional Chinese medicines Chan Su, Lu-Shen-Wan, Dan Shen, and Asian ginseng on serum digoxin measurement by Tina-quant (Roche) and Synchron LX System (Beckman) digoxin immunoassays. *J Clin Lab Anal* (2003) 17, 22–7.
5. Awang DVC. Siberian ginseng toxicity may be case of mistaken identity. *CMAJ* (1996) 155, 1237.

Digoxin + Grapefruit juice

Digoxin levels are generally unaltered or only modestly increased by grapefruit juice, but in some individuals significant changes may occur.

Clinical evidence

A crossover study in 12 healthy subjects found that when they were given either grapefruit juice 220 mL or water, 30 minutes before and 3.5, 7.5, and 11.5 hours after a single 500-microgram dose of digoxin (taken with 50 mL of grapefruit juice or water respectively), the digoxin AUC_{0-4} and AUC_{0-24} were increased by about 10%. The maximum plasma levels and renal clearance of digoxin were not significantly affected. However, in 2 subjects taking grapefruit juice, the ECGs recorded 90 minutes after digoxin was taken revealed an asymptomatic first-degree atrioventricular block. Digoxin levels in these subjects had increased by 50% to 2.4 nanograms/mL and 2.8 nanograms/mL, respectively.[1] Another study found that grapefruit juice decreased the rate but not the extent of absorption of digoxin and had no effect on its AUC or renal clearance, but there was significant inter-individual variability.[2]

Mechanism

The modest increases in digoxin levels may be due to increased intestinal absorption of digoxin, possibly due to inhibition of P-glycoprotein-mediated digoxin transport by grapefruit juice, although this mechanism has been questioned.[1] *In vitro*, pomelo (*Citrus grandis*) and grapefruit juices inhibited the transport of digoxin by P-glycoprotein.[3]

Importance and management

Although grapefruit juice appears to have little effect on the bioavailability of digoxin, it is possible that in some individuals the interaction could be of clinical significance.[2] Therefore, if a patient taking digoxin unexpectedly develops bradycardia or other adverse effects it may be prudent to ask about grapefruit juice intake, and consider this as a possible cause. More study is needed to identify which patients may be at risk of a clinically relevant interaction.

1. Becquemont L, Verstuyft C, Kerb R, Brinkmann U, Lebot M, Jaillon P, Funck-Brentano C. Effect of grapefruit juice on digoxin pharmacokinetics in humans. *Clin Pharmacol Ther* (2001) 70, 311–6.
2. Parker RB, Yates CR, Soberman JE, Laizure SC. Effects of grapefruit juice on intestinal P-glycoprotein: evaluation using digoxin in humans. *Pharmacotherapy* (2003) 23, 979–87.
3. Xu J, Go ML, Lim L-Y. Modulation of digoxin transport across Caco-2 cell monolayers by citrus fruit juices: lime, lemon, grapefruit and pummelo. *Pharm Res* (2003) 20, 169–76.

Digoxin + Guanadrel

Guanadrel did not affect the pharmacokinetics of a single dose of digoxin in one study.

Clinical evidence, mechanism, importance and management

In 13 healthy subjects, guanadrel 10 mg orally every 12 hours for 8 days did not affect the pharmacokinetics of a single intravenous dose of digoxin given on day 5. One subject experienced a 10-minute episode of asymptomatic second-degree heart block (Wenckebach) 3 hours after the dose of digoxin, but the reason for this effect was not clear.[1] There seem to be no reports of adverse interactions between digoxin and guanadrel.

1. Wright CE, Andreadis NA. Digoxin pharmacokinetics when administered concurrently with guanadrel sulfate. *Drug Intell Clin Pharm* (1986) 20, 465.

Digoxin and related drugs + H_2-receptor antagonists

Small changes in digoxin levels, both rises and falls, have been seen in patients also given cimetidine. Ranitidine does not appear to interact with metildigoxin.

Clinical evidence, mechanism, importance and management

In a study in 11 patients with congestive heart failure, **cimetidine** 300 mg every 6 or 12 hours reduced the steady-state serum digoxin levels by 25% (from 2 to 1.5 nanograms/mL), but none of them had any ECG changes or signs that their condition had worsened.[1] In four other patients with stable congestive heart failure, there was no significant changes in the pharmacokinetics of digoxin 125 to 250 micrograms daily when they were given **cimetidine** 300 mg every 6 hours.[2] Three single-dose studies in a total of 19 healthy subjects, and 6 patients with duodenal ulcers[3] found that **cimetidine** 600 mg to 1.2 g daily had no significant effect on the absorption[4] or the pharmacokinetics[3,5] of digoxin. Another study found a small increase in digoxin levels in healthy subjects, but only a small statistically insignificant rise in the steady-state levels of 11 patients given **cimetidine** 400 mg four times daily.[6] Six patients with chronic congestive heart failure given **metildigoxin** had no changes in their serum digoxin levels when they were given **ranitidine** 150 mg twice daily for a week.[7]

No interaction of clinical importance with either of these H_2-receptor antagonists has been established and no special precautions would seem to be necessary if they are given with digoxin.

1. Fraley DS, Britton HL, Schwinghammer TL, Kalla R. Effect of cimetidine on steady-state serum digoxin concentrations. *Clin Pharm* (1983) 2, 163–5.
2. Mouser B, Nykamp D, Murphy JE, Krissman PH. Effect of cimetidine on oral digoxin absorption. *DICP Ann Pharmacother* (1990) 24, 286–8.
3. Garty M, Perry G, Shmueli H, Ilfeld D, Boner G, Pitlik S, Rosenfeld J. Effect of cimetidine on digoxin disposition in peptic ulcer patients. *Eur J Clin Pharmacol* (1986) 30, 489–91.
4. Jordaens L, Hoegaerts J, Belpaire F. Non-interaction of cimetidine with digoxin absorption. *Acta Clin Belg* (1981) 36, 109–10.
5. Ochs HR, Gugler R, Guthoff T, Greenblatt DJ. Effect of cimetidine on digoxin kinetics and creatinine clearance. *Am Heart J* (1984) 107, 170–2.
6. Crome P, Curl B, Holt D, Volans GN, Bennett PN, Cole DS. Digoxin and cimetidine: investigation of the potential for a drug interaction. *Hum Toxicol* (1985) 4, 391–9.
7. Enomoto N, Kurasawa T, Ichikawa M, Shimuzu T, Matsuyama T, Sakai K, Shimamura K, Oda M. Lack of interaction of β-methyldigoxin with ranitidine in patients with chronic congestive heart failure. *Eur J Clin Pharmacol* (1992) 43, 205–6.

Digoxin and related drugs + HRT

Post hoc analysis of one study found an increased rate of cardiovascular adverse events in women taking HRT who were also taking digitalis.

Clinical evidence, mechanism, importance and management

Retrospective analysis of data from a large randomised, placebo-controlled study of HRT (conjugated estrogens/medroxyprogesterone 0.625/2.5 mg daily) in women with coronary heart disease was conducted to see if there were any subgroups of patients who responded differently. Use of digitalis was associated with a fivefold excess rate of cardiovascular events in the first year, when women receiving HRT, were compared with the control group. A lower 1.5-fold excess rate was seen over the whole duration of the study (average 4.1 years). Possible mechanisms could be a drug-drug interaction or a drug-disease effect (HRT with congestive heart failure).[1]

However, it is impossible to say whether this represents a true effect, because the number of positive sub-group analyses in this study was the same as the number predicted by chance alone. Confirmatory evidence is required.[1] See also 'Digoxin and related drugs + Medroxyprogesterone or Megestrol', p.1105 for a report suggesting high-dose medroxyprogesterone does not have a clinically relevant effect on digitoxin levels.

1. Furberg CD, Vittinghoff E, Davidson M, Herrington DM, Simon JA, Wenger NK, Hulley S. Subgroup interactions in the Heart and Estrogen/Progestin replacement study. Lessons learned. *Circulation* (2002) 105, 917–22.

Digoxin + Kaolin-pectin

Digoxin levels can be reduced by kaolin-pectin.

Clinical evidence

The concurrent use of kaolin-pectin suspension and digoxin reduced the peak plasma digoxin levels of 7 patients by 36%, while the $AUC_{0\text{-}24}$ was reduced by 15%. Conversely, when two doses of kaolin-pectin were taken, the first 2 hours before digoxin and the other 2 hours after digoxin, no significant changes were seen.[1]

Two single-dose studies have found 42% and 62% reductions in the bioavailability of digoxin caused by kaolin-pectin.[2,3] Another study found an interaction with digoxin tablets but not with digoxin capsules.[4]

Mechanism

Not understood. The digoxin may possibly become adsorbed onto the kaolin so that less is available for absorption. Another possibility is that the kaolin reduces the motility of the gut, which normally increases mixing and brings the digoxin into contact with the absorbing surface.

Importance and management

Evidence from this studies is somewhat conflicting; however, steady-state studies reflect the every-day situation much more closely than single-dose studies, and the one cited above[1] indicates that the total reduction in digoxin absorption is small (15%). This is unlikely to be of clinical importance. However, if an interaction does occur the effects can seemingly be minimised by separating the doses by 2 hours.

1. Albert KS, Elliott WJ, Abbott RD, Gilbertson TJ, Data JL. Influence of kaolin-pectin suspension on steady-state plasma digoxin levels. *J Clin Pharmacol* (1981) 21, 449–55.
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Digoxin + Kava

A standardised kava extract did not alter the pharmacokinetics of digoxin.

Clinical evidence, mechanism, importance and management

A study in 20 healthy subjects given a single 500-microgram dose of digoxin before and on the last day of treatment with a standardised kava rhizome (*Piper methysticum*) extract 1227 mg three times daily for 14 days, found no changes in the pharmacokinetics of digoxin. The product used was standardised for kavalactone content.[1]

It was suggested that kava may alter digoxin pharmacokinetics by affecting P-glycoprotein, since kavalactones are modulators of P-glycoprotein *in vitro*. However, the clinical study showed that kava does not cause clinically relevant changes in digoxin pharmacokinetics. Therefore no changes in digoxin levels would be anticipated on concurrent use, the caveat being that, as with all herbal medicines, these results may not be applicable to all kava products.[1]

1. Gurley BJ, Swain A, Barone GW, Williams DK, Breen P, Yates CR, Stuart LB, Hubbard MA, Tong Y, Cheboyina S. Effect of goldenseal (*Hydrastis canadensis*) and kava kava (*Piper methysticum*) supplementation on digoxin pharmacokinetics in humans. *Drug Metab Dispos* (2007) 35, 240–5.

Digoxin and related drugs + Ketanserin

Ketanserin does not appear to affect the pharmacokinetics of either digoxin or digitoxin.

Clinical evidence, mechanism, importance and management

In a study in healthy subjects, ketanserin 40 mg twice daily did not cause any significant changes in the pharmacokinetics of single doses of either digoxin 1.25 mg or **digitoxin** 1 mg, and it was concluded that ketanserin is unlikely to alter serum concentrations of either of these drugs during clinical use.[1]

1. Ochs HR, Verburg-Ochs B, Höller M, Greenblatt DJ. Effect of ketanserin on the kinetics of digoxin and digitoxin. *J Cardiovasc Pharmacol* (1985) 7, 205–7.

Digoxin + Lanthanum

Lanthanum did not significantly affect the pharmacokinetics of digoxin in a single-dose study.

Clinical evidence, mechanism, importance and management

In a crossover study, 14 healthy subjects were given lanthanum 1 g for 3 doses on one day, followed by a fourth dose the next day. A single 500-microgram dose of digoxin was given 30 minutes after the fourth dose of lanthanum. The digoxin half-life was increased during concurrent use from 11.4 hours to 14.8 hours but this was not considered to be clinically significant. Other pharmacokinetic parameters were not affected.[1] Ideally further multiple-dose studies in patients are needed to confirm this lack of interaction, but the available evidence suggests that a clinically relevant interaction is unlikely.

1. Fiddler G. Fosrenol™ (lanthanum carbonate) does not affect the pharmacokinetics of concomitant treatment with digoxin. *J Am Soc Nephrol* (2002) 13, 749A.

Digoxin + Liquorice

An isolated case of digoxin toxicity has been reported in an elderly patient attributed to the use of a herbal laxative containing kanzo (liquorice).

Clinical evidence

An 84-year-old man taking digoxin 125 micrograms daily and furosemide complained of loss of appetite, fatigue and oedema of the lower extremities 5 days after starting to take a Chinese herbal laxative containing liquorice (kanzo) 400 mg and rhubarb (daio) 1.6 g three times daily. He was found to have a raised digoxin level of 2.9 nanograms/mL (previous level 1 nanogram/mL) with a pulse rate of 30 bpm, and a slightly low potassium level (2.9 mmol/L).[1]

Mechanism

The reason for the increase in digoxin levels is unclear. Digoxin inhibits the sodium-potassium ATP-ase pump, which is concerned with the transport of sodium and potassium ions across the membranes of the myocardial cells. Potassium loss caused by a combination of the liquorice, rhubarb and diuretics exacerbated the potassium loss from the myocardial cells, thereby enhancing the bradycardia, already caused by an elevated digoxin level. Hypokalaemia also promotes the binding of digoxin to myocardial cells. The patients pre-existing cardiovascular disease may have also predisposed the patient to enhanced digoxin effects.

Importance and management

Evidence appears to be limited to one case. It is likely that the effects of the elevated digoxin levels were exacerbated by the hypokalaemia possibly caused by the herbal laxative. The theoretical basis for an interaction between liquorice and digoxin is well established, but there are few actual cases. Any herbal preparation that can reduce potassium levels would be expected to increase the risk of digoxin toxicity. This is likely to be additive with other concurrent medications a patient may also be taking that can cause hypokalaemia, such as loop diuretics. It would be prudent to exercise caution in patients who are taking digitalis glycosides and who regularly use/abuse laxatives including liquorice and/or anthraquinone-containing substances such as rhubarb. However, note that if these laxatives are used as recommended (at a dose producing a comfortable soft-formed motion), then this interaction is probably unlikely to be important.

1. Harada T, Ohtaki E, Misu K, Sumiyoshi T, Hosoda S. Congestive heart failure caused by digitalis toxicity in an elderly man taking a licorice-containing Chinese herbal laxative. *Cardiology* (2002) 98, 218.

Digoxin + Lithium

No pharmacokinetic interaction occurs between digoxin and lithium but the addition of digoxin to lithium possibly has a detrimental short-term effect on the control of mania. An isolated report describes severe bradycardia in one patient given both drugs.

Clinical evidence, mechanism, importance and management

A study in 6 healthy subjects taking lithium carbonate in doses to achieve mean steady-state serum levels of 0.76 mmol/L (range 0.4 to 1 mmol/L) found that the pharmacokinetics of a 750-microgram intravenous dose of digoxin were unchanged by lithium, and that there were no significant effects on sodium pump activity or electrolyte concentrations.[1] However an experimental 7-day study in patients with manic-depressive psychoses found that there was a greater improvement in those given lithium with placebo than those given lithium with digoxin. This may be a reflection of changes in Na-K ATP-ase.[2] An isolated report describes tremor, confusion and severe nodal bradycardia in a patient given both drugs. The bradycardia worsened (30 bpm) even after both drugs were stopped.[3] The clinical significance of all of these findings is uncertain. Note that one UK manufacturer of digoxin[4] lists lithium as a drug that may increase sensitivity to digoxin because it may cause hypokalaemia or intracellular potassium deficiency, but note that hypokalaemia does not appear to be a commonly accepted adverse effect of lithium.

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Digoxin and related drugs + Macrolides

Clarithromycin markedly increases digoxin levels, and numerous cases of digoxin toxicity have been reported. Increases in digoxin levels also occur with telithromycin. Cases of rapid and marked two to fourfold increase in digoxin levels have also been reported for azithromycin, erythromycin, josamycin and roxithromycin. A similar case has been seen with digitoxin and azithromycin.

Clinical evidence

A. Digitoxin

A man with congestive heart failure taking digitoxin 70 micrograms daily for 5 days of each week, with enalapril and furosemide, was admitted to hospital with nausea and bradycardia of 26 bpm 4 days after starting a 3-day course of **azithromycin** (dose not stated). His serum digitoxin levels were found to be raised from his usual baseline range of 9.9 to 19 nanograms/mL up to 34 nanograms/mL. His renal function was normal. Another patient receiving intravenous digitoxin 250 micrograms daily had a marked rise from his steady-state digitoxin range of 11 to 15 nanograms/mL after being given **azithromycin** 500 mg daily for 3 days. The digitoxin was withdrawn one day later, but the levels climbed to a peak of 32 nanograms/mL after a further 3 days, and remained in the toxic range for a further 3 days.[1]

B. Digoxin

(a) Azithromycin

A 31-month-old boy with Down's syndrome and tetralogy of Fallot (a congenital heart defect resulting in reduced blood flow to the lungs) was discharged from hospital after repair of his heart defect. He was taking digoxin 60 micrograms twice daily, furosemide, and potassium chloride. Eight days later, when readmitted with symptoms of heart failure, intermittent fever and wheezing, he was given azithromycin (10 mg/kg on day one, then 5 mg/kg daily for 4 days). Three days later his steady-state serum digoxin levels had risen from 1.79 nanograms/mL to 2.37 nanograms/mL and he experienced anorexia, nausea, and second degree atrioventricular block. All the symptoms resolved when the digoxin was withdrawn. Digoxin was restarted at 50 micrograms twice daily after the azithromycin course was completed and steady-state digoxin levels of 1.42 nanograms/mL were noted.[2]

The manufacturers of azithromycin said that, as of October 2000, there were 230 cases of the concurrent use of azithromycin and digoxin on their database. Of these, 78 cases had adverse events indicating possible digoxin toxicity. However on review, 21 cases were clearly excluded. Of the remaining cases, only 13 provided digoxin levels, and of these, high serum digoxin concentrations were reported in 6, but generally insufficient data made interpretation difficult.[3] The manufacturers concluded that the possibility that a patient may experience an increase in digoxin levels while taking azithromycin cannot be entirely excluded.[3]

(b) Clarithromycin

A woman receiving warfarin, heparin, carbamazepine and digoxin was admitted to hospital with syncope, vomiting and an irregular heart rhythm shortly after starting clarithromycin 1 g daily. Her serum digoxin levels were found to be raised. The clarithromycin was decreased, the carbamazepine and digoxin stopped, and she was treated with digoxin-specific antibody fragments (*Digibind*) and intravenous fluids. Her serum digoxin levels fell again and the digitalis toxicity disappeared.[4]

In 1995, the manufacturers of clarithromycin had a few other cases on their records of raised digoxin levels in patients following treatment with clarithromycin[4] and there are many other case reports of this interaction in the literature,[5-19] including a case series of 6 patients with end stage renal disease.[20]

A subsequent randomised, placebo-controlled study in 12 healthy subjects confirmed that clarithromycin 250 mg twice daily for 3 days increased the AUC of a single 750-microgram oral dose of digoxin by 70%. The non-glomerular renal clearance of digoxin was reduced by 40%.[21] Intravenous digoxin was much less affected.[21,22] In two further studies clarithromycin 500 mg twice daily for 7 days increased the AUC of digoxin by 57% and 35%.[23,24] Note that these studies were designed to investigate the interaction of other drugs, and clarithromycin was being used as a positive control.

Two studies that prospectively measured digoxin levels in patients before and during the use of clarithromycin found an important increase in all patients: in one study digoxin levels were increased by 70%,[25] and in the other, digoxin levels were increased from a range of 1 to 1.6 nanograms/mL up to 2.3 to greater than 4 nanograms/mL.[26] In one of these studies, there was a significant correlation between the dose of clarithromycin and the increase in digoxin serum levels.[25]

A case-control study using data from healthcare databases in Ontario from 1994 to 2000 identified 1 051 patients who had been admitted to hospital with digoxin toxicity. Of these, 55 patients (5.2%) had been exposed to clarithromycin in the preceding 3 weeks, when compared with just 0.5% of controls, which represented about a tenfold increase in risk.[27]

(c) Erythromycin

An elderly woman with a prosthetic heart valve and left ventricular dysfunction, taking warfarin, furosemide, hydralazine, isosorbide dinitrate and digoxin, was given erythromycin. She took only four 250-mg doses. Four days later her serum digoxin levels were found to have risen to 2.6 nanograms/mL from a normal steady-state range of 1.4 to 1.7 nanograms/mL, and she had evidence of digitalis toxicity.[28] Another four similar cases have also been reported.[29-31]

A study in a man who was resistant to digoxin found that erythromycin 1 g daily increased the AUC of digoxin by 300%.[32] A neonate given oral digoxin 5 micrograms/kg daily developed digoxin toxicity 2 days after erythromycin (10 mg three times daily, then 17 mg three times daily) was given. Digoxin levels rose from 1.8 nanograms/mL to 16 nanograms/mL.[33]

(d) Josamycin

A case report describes a premature neonate receiving digoxin who had a 50% increase in digoxin levels (from 2 to 2.95 nanograms/mL), resulting in bradycardia, and sinoatrial block after being given josamycin for 4 days. This was treated with antidigitalis Fab fragments.[34]

(e) Rokitamycin

In a study in 10 subjects rokitamycin did not affect serum digoxin levels.[35]

(f) Roxithromycin

A 76-year-old woman taking digoxin and a number of other drugs (enalapril, isosorbide mononitrate, furosemide, diltiazem, glyceryl trinitrate, slow-release potassium, prednisolone, omeprazole, calcitriol) developed signs of digoxin toxicity (nausea, vomiting, first degree heart block) within 4 days of starting to take roxithromycin 150 mg twice daily. Her serum digoxin levels were raised about fourfold.[36]

(g) Telithromycin

A study in 26 healthy subjects given digoxin 500 micrograms twice daily on the first day followed by 250 micrograms twice daily found that telithromycin 800 mg daily increased the digoxin AUC by 37% and increased its maximum blood levels by 74%. Trough plasma levels were increased by 21% and remained within the therapeutic range. No signs of digoxin toxicity were observed on ECGs.[37]

A 58-year-old woman taking digoxin 250 micrograms daily developed syncope and malaise after a 5-day course of telithromycin 800 mg daily. Her digoxin levels were 55% higher than her normal baseline level, and there were ECG changes.[38]

Mechanism

It was originally thought that the interaction between the macrolides and digoxin was due to the effect of the antibacterials on gut flora. Up to 10% of patients receiving oral digoxin excrete it in substantial amounts in the faeces and urine as inactive metabolites (digoxin reduction products or DRPs). This metabolism seems to be the responsibility of the gut flora,[29] in particular *Eubacterium lentum*, which is anaerobic and Gram positive.[31,39] In the presence of antibacterials that inhibit this organism, much more digoxin becomes available for absorption, which results in a marked rise in serum levels. At the same time the inactive metabolites derived from the gut disappear.[29,40] However, it is worth noting that most classes of antibacterials do not appear to interact with digoxin despite inhibiting *E. lentum in vitro*,[39] see 'Digoxin and related drugs + Beta-lactam antibacterials', p.1088. In addition, more recent data showing that digoxin levels are affected by clarithromycin in all, or the majority, of patients or subjects throw doubt on this theory.

A more plausible explanation for the interaction between digoxin and clarithromycin, and probably also erythromycin, is that the antibacterials inhibit the intestinal[22,41] or renal[14,25] P-glycoprotein transport of digoxin, which would increase the oral bioavailability and reduce the non-glomerular renal clearance respectively. Both mechanisms may be important.[21] Further, the increased gastric emptying due to erythromycin may also increase the bioavailability of digoxin[42] or digitoxin.[39]

Importance and management

The pharmacokinetic interaction between oral digoxin and clarithromycin is established, and likely to occur in the majority of patients. Digoxin toxicity has been commonly reported. Monitor all patients well for signs of increased digoxin effects when clarithromycin is first given, reducing the digoxin dose as necessary. Telithromycin appears to interact similarly to clarithromycin, and similar advice applies.

Information about azithromycin and erythromycin is limited to a relatively small number of patients, and there is only one report of an interaction between digoxin and josamycin or digoxin and roxithromycin. Until more is known, it would be prudent to monitor all patients well for signs of increased digoxin effects when any of these macrolide antibacterials is first given, reducing the digoxin dose as necessary. In addition, remember that azithromycin has a long serum half-life (60 hours), which means that it can continue to interact for several days after it has been withdrawn. Rokitamycin appears not to interact.

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Digoxin and related drugs + Medroxyprogesterone or Megestrol

Doses of medroxyprogesterone acetate or megestrol used for malignant disease do not appear to interact with digitoxin to a clinically relevant extent.

Clinical evidence, mechanism, importance and management

Steady-state **digitoxin** levels were monitored in 3 patients before and after 5 weeks of treatment with oral medroxyprogesterone acetate 500 mg twice daily or megestrol 160 mg daily. Only small and clinically irrelevant changes in **digitoxin** levels and clearance were seen.[1]

For the possible effect of HRT including medroxyprogesterone on digitalis glycosides (unnamed), see 'Digoxin and related drugs + HRT', p.1102.

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Digoxin + Methyldopa

Methyldopa does not appear to affect digoxin levels, but marked bradycardia has been seen in two elderly women given both drugs.

Clinical evidence

In 8 healthy subjects, methyldopa 250 mg daily had no effect on the steady-state serum levels of digoxin 250 micrograms daily.[1] However, a case report describes two elderly women with hypertension and left ventricular failure, who developed marked bradycardia when they were given digoxin with methyldopa 750 mg or 3.75 g daily but not when they were given digoxin alone. Average heart rates were 50 bpm and 48 bpm, respectively, while minimum heart rates were 32 bpm and 38 bpm, respectively. They were subsequently discharged taking digoxin and hydralazine with heart rates within the normal range.[2]

Mechanism

Uncertain. Both digoxin and methyldopa[3] can cause some bradycardia, but these effects seem to have been more than simply the sum of the individual drug effects on the autonomic nervous system.[2]

Importance and management

Information is limited but it would seem that concurrent use need not be avoided, but be aware that on rare occasions undesirable bradycardia has occurred.

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Digoxin + Metoclopramide

Digoxin levels may be reduced by about one-third if metoclopramide is given with slowly dissolving forms of digoxin. No interaction is likely with digoxin in liquid form or in fast-dissolving preparations.

Clinical evidence

A study in 11 patients taking slowly dissolving digoxin tablets (*Orion*) found that metoclopramide 10 mg three times a day for 10 days reduced the serum digoxin levels by 36% (from 0.72 to 0.46 nanograms/mL).[1] The digoxin concentrations rose to their former levels when the metoclopramide was withdrawn.

Another study in healthy subjects found metoclopramide 10 mg three times daily caused a 19% reduction in the AUC of digoxin and a 27% reduction in peak serum digoxin levels (digoxin formulation not stated).[2] Yet another study in healthy subjects clearly showed that metoclopramide decreased the absorption of digoxin from tablets (*Lanoxin*) but not capsules (*Lanoxicaps*).[3]

Mechanism

It would seem[4-6] that the metoclopramide increases the motility of the gut to such an extent that full dissolution and absorption of some digoxin formulations does not occur.

Importance and management

Information about an interaction between digoxin and metoclopramide is very limited, but the interaction seems to be established. It is not likely to occur with solid form, fast-dissolving digoxin preparations (e.g. liquid-filled capsules) or digoxin in liquid form, but only with those preparations which are slowly dissolving (i.e. some tablet formulations). A reduction in digoxin levels of one-third could result in under-digitalisation. Be aware of this interaction if both drugs are given.

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Digoxin + Mexiletine

Digoxin levels are not significantly altered by mexiletine.

Clinical evidence, mechanism, importance and management

In 10 healthy subjects, mexiletine 200 mg every 8 hours for 4 days slightly reduced the serum levels of digoxin 250 micrograms daily from 0.32 nanograms/mL to 0.27 nanograms/mL.[1] Two other studies in a total of 17 patients[2,3] confirmed that mexiletine does not significantly affect serum digoxin levels.

1. Saris SD, Lowenthal DT, Affrime MB. Steady-state digoxin concentration during oral mexiletine administration. *Curr Ther Res* (1983) 34, 662–66.
2. Leahey EB, Reiffel JA, Giardina E-GV, Bigger T. The effect of quinidine and other oral antiarrhythmic drugs on serum digoxin. *Ann Intern Med* (1980) 92, 605–8.
3. Day T, Hunt D. Interaction between mexiletine and digoxin. *Med J Aust* (1983) 2, 630.

Digoxin + Mizolastine

Mizolastine can cause a small but clinically irrelevant rise in digoxin levels.

Clinical evidence, mechanism, importance and management

A placebo-controlled, crossover study in 12 healthy subjects found that mizolastine 10 mg daily for a week caused a 17% increase in the maximum plasma levels of digoxin 250 micrograms daily. The digoxin AUC and half-life were unchanged and the haemodynamic parameters measured (blood pressure, ECG) were unaltered.[1] No special precautions would seem necessary during concurrent use.

1. Chaufour S, Le Coz F, Denolle T, Dubruc C, Cimarosti I, Deschamps C, Ulliac N, Delhotal-Landes B, Rosenweig P. Lack of effect of mizolastine on the safety and pharmacokinetics of digoxin administered orally in repeated doses to healthy volunteers. *Int J Clin Pharmacol Ther* (1998) 36, 286–91.

Digoxin and related drugs + Moclobemide

Moclobemide had no clinically relevant effect on the pharmacokinetics of beta-acetyldigoxin.

Clinical evidence, mechanism, importance and management

A study in 14 patients with decompensated heart failure, given an individualised dose of **beta-acetyldigoxin** for 2 weeks, found that moclobemide 100 mg three times daily given for 8 days caused a non-significant 14% reduction (from 0.99 to 0.85 nanograms/mL) in plasma **beta-acetyldigoxin** levels. No adverse effects attributable to an interaction were seen.[1] No special precautions appear to be required during the concurrent use of **acetyldigoxin** and moclobemide.

1. Amrein R, Güntert TW, Dingemanse J, Lorscheid T, Stabl M, Schmid-Burgk W. Interactions of moclobemide with concomitantly administered medication: evidence from pharmacological and clinical studies. *Psychopharmacology (Berl)* (1992) 106, S24–S31.

Digoxin + Montelukast

Montelukast does not affect the pharmacokinetics of digoxin.

Clinical evidence, mechanism, importance and management

In a randomised study in 11 healthy subjects, montelukast 10 mg was given for 12 days with a single 500-microgram dose of digoxin on day 7. It was found that the pharmacokinetic profile of the digoxin was unchanged by montelukast.[1] No digoxin dose adjustments are needed if montelukast is used concurrently.

1. Depre M, Van Hecken A, Verbesselt R, Wynants K, De Lelepeire I, Freeman A, Holland S, Shahane A, Gertz B, De Schepper PJ. Effect of multiple doses of montelukast, a CysLT1 receptor agonist, on digoxin pharmacokinetics in healthy volunteers. *J Clin Pharmacol* (1999) 39, 941–4.

Digoxin + Moracizine

Moracizine does not significantly increase digoxin levels in patients with normal renal function. However, some adverse conduction effects have been seen.

Clinical evidence

Thirteen patients taking digoxin 125 to 250 micrograms daily had a non-significant rise in their serum digoxin levels of 10 to 15% when they were given moracizine 10 mg/kg daily in three divided doses for 2 weeks. Further, 9 patients who took digoxin and moracizine for one to 6 months had no significant changes in their serum digoxin levels.[1]

In a single-dose study in 9 healthy subjects, and in a study in patients receiving maintenance treatment with digoxin over a 13-day period, the pharmacokinetics of intravenous and oral digoxin were not affected by moracizine.[2,3] However, cardiac arrhythmias (AV junctional rhythm and heart block) were seen, which resolved when the moracizine was stopped.[3]

Mechanism

Not established. There does not appear to be a pharmacokinetic interaction between moracizine and digoxin. Concurrent use can cause a significant increase in the PR interval and QRS duration, which can result in AV block.[4]

Importance and management

Although no clinically important changes in digoxin levels appear to occur during the concurrent use of moracizine, the occurrence of arrhythmias in a few patients indicates that good monitoring is advisable. It has been pointed out that the additive effects of both drugs on intranodal and intraventricular conduction may be excessive in some patients with heart disease.[4] More study is needed.

1. Kennedy HL, Sprague MK, Redd RM, Wiens RD, Blum RI, Buckingham TA. Serum digoxin concentrations during ethmozine antiarrhythmic therapy. *Am Heart J* (1986) 111, 667–72.
2. MacFarland RT, Moeller VR, Pieniaszek HJ, Whitney CC, Marcus FI. Assessment of the potential pharmacokinetic interaction between digoxin and ethmozine. *J Clin Pharmacol* (1985) 25, 138–43.
3. Antman EM, Arnold JMO, Friedman PL, White H, Bosak M, Smith TW. Drug interactions with cardiac glycosides: evaluation of a possible digoxin-ethmozine pharmacokinetic interaction. *J Cardiovasc Pharmacol* (1987) 9, 622–7.
4. Siddoway LA, Schwartz SL, Barbey JT, Woosley RL. Clinical pharmacokinetics of moricizine. *Am J Cardiol* (1990) 65, 21D–25D.

Digoxin + Nateglinide or Repaglinide

The pharmacokinetics of nateglinide and digoxin are not altered by concurrent use. Repaglinide does not affect the pharmacokinetics of digoxin.

Clinical evidence, mechanism, importance and management

(a) Nateglinide

A crossover study in 12 healthy subjects found that when a single 1-mg dose of digoxin was given with the first dose of nateglinide 120 mg three times daily for 2 days, there were no changes in the pharmacokinetics of either drug.[1]

(b) Repaglinide

A crossover, multiple-dose study in 14 healthy subjects found that repaglinide 2 mg three times daily before meals had no effect on the pharmacokinetics of digoxin 250 micrograms daily. Concurrent use was well tolerated.[2]

1. Zhou H, Walter YH, Smith H, Devineni D, McLeod JF. Nateglinide, a new mealtime glucose regulator. Lack of pharmacokinetic interaction with digoxin in healthy volunteers. *Clin Drug Invest* (2000) 19, 465–71.
2. Hatorp V, Thomsen MS. Drug interaction studies with repaglinide: repaglinide on digoxin or theophylline pharmacokinetics and cimetidine on repaglinide pharmacokinetics. *J Clin Pharmacol* (2000) 40, 184–92.

Digoxin + Nefazodone

Nefazodone causes a moderate increase in digoxin levels. Digoxin does not appear to affect the pharmacokinetics of nefazodone.

Clinical evidence, mechanism, importance and management

In a study, 18 healthy subjects were given digoxin 200 micrograms daily for 8 days, then nefazodone 200 mg twice daily for 8 days, and then both drugs together for 8 days. Nefazodone increased the AUC of digoxin by 15%, and increased the peak and trough plasma levels of digoxin by 29% and 27%, respectively. However, no clinically significant changes in ECG measurements occurred (PR, QRS and QT intervals), nor was the heart rate or any other vital sign altered. The pharmacokinetics of the nefazodone were unchanged.[1]

Evidence appears to be limited to this study, but as it was well conducted, an interaction is probably established. The increase in the AUC of digoxin is modest, and would not generally be expected to be clinically significant. This is supported by the finding of no change in adverse effects. No particular precautions would seem necessary on concurrent use.

1. Dockens RC, Greene DS, Barbhaiya RH. Assessment of pharmacokinetic and pharmacodynamic drug interactions between nefazodone and digoxin in healthy male volunteers. *J Clin Pharmacol* (1996) 36, 160–7.

Digoxin and related drugs + Neuromuscular blockers

Serious cardiac arrhythmias can develop in patients receiving digitalis glycosides who are given suxamethonium (succinylcholine) or pancuronium.

Clinical evidence

Eight out of 17 digitalised patients (anaesthetised with thiamylal and then maintained with nitrous oxide and oxygen) developed serious ventricular arrhythmias following the intravenous injection of **suxamethonium** (**succinylcholine**) 40 to 100 mg. Four out of the 8 patients reverted to their previous rhythm when they were given tubocurarine 15 to 30 mg, with one patient returning to a regular nodal rhythm from ventricular tachycardia.[1]

Of the other 9 patients, 3 had immediate and definite ST-T wave changes, and the remaining 6 had no demonstrable changes.[1] There are other reports of this interaction,[2-4] including one that describes sinus tachycardia and atrial flutter in 6 out of 18 patients taking digoxin after they were given **pancuronium**.[4]

Mechanism

Not understood. One possibility is that the suxamethonium (succinylcholine) may cause the rapid removal of potassium from the myocardial cells. Another idea is that it affects catecholamine-releasing cholinergic receptors.

Importance and management

Information regarding an interaction between the digitalis glycosides and the neuromuscular blockers is limited but the interaction with suxamethonium (succinylcholine) appears to be established. Suxamethonium should be used with great caution in patients taking digitalis glycosides. Similarly, caution would seem appropriate with pancuronium.

1. Dowdy EG, Fabian LW. Ventricular arrhythmias induced by succinylcholine in digitalized patients: A preliminary report. *Anesth Analg* (1963) 42, 501–13.
2. Pérez HR. Cardiac arrhythmia after succinylcholine. *Anesth Analg* (1970) 49, 33–8.
3. Smith RB, Petrusack J. Succinylcholine, digitalis, and hypercalcaemia: a case report. *Anesth Analg* (1972) 51, 202–5.
4. Bartolone RS, Rao TLK. Dysrhythmias following muscle relaxant administration in patients receiving digitalis. *Anesthesiology* (1983) 58, 567–9.

Digoxin and related drugs + NSAIDs

Indometacin can cause potentially toxic rises in digoxin levels particularly in neonates, while azapropazone, diclofenac, fenbufen and tiaprofenic acid raise levels to a lesser degree. Two studies found that ibuprofen raised serum digoxin levels, whereas another found no evidence of an interaction. Isoxicam, ketoprofen, lornoxicam, meloxicam, nimesulide, piroxicam, and rofecoxib do not appear to interact significantly with digoxin. In contrast, phenylbutazone appears to lower plasma digitalis glycoside levels.

Clinical evidence

A. Digitoxin

(a) Azapropazone

In 8 patients with arthritis, azapropazone 900 mg daily did not significantly alter the AUC of a single 500-microgram intravenous dose of digitoxin, but its mean half-life was increased by about 10%. Two of the patients had individual half-life increases of almost one-third.[1]

(b) Diclofenac

Digitoxin 100 micrograms had no effect on the plasma levels of diclofenac 50 mg twice daily in 8 subjects; digitoxin levels were not reported.[2]

(c) Phenylbutazone

In 6 patients, phenylbutazone 200 or 400 mg daily halved the plasma levels of digitoxin 100 micrograms daily, on two separate occasions. Digitoxin levels returned to their former values within roughly the same period of time after phenylbutazone was withdrawn.[3] A similar response has been described elsewhere in one patient.[4]

B. Digoxin

(a) Diclofenac

A study in 7 healthy subjects found that diclofenac 100 mg daily for 10 days increased the serum levels of digoxin by 29%.[5] Another study in 6 healthy subjects similarly found that diclofenac 50 mg three times daily raised the serum digoxin levels by about one-third.[6]

(b) Etoricoxib

A study in healthy subjects given digoxin found that the addition of etoricoxib 120 mg daily for 10 days did not alter the steady-state AUC of digoxin or its renal elimination, but the maximum serum digoxin levels were increased by about 33%.[7]

(c) Fenbufen

Fenbufen 900 mg daily was found to cause an insignificant rise in the serum levels of digoxin.[8]

(d) Ibuprofen

The serum digoxin levels of 12 patients were reported to have risen by about 60% after they were given at least 1.6 g of ibuprofen daily for a week. However, after a month the digoxin levels had returned to their former amount.[9] These findings may be unreliable because half of the patients were not satisfactorily compliant with treatment. Another study found that ibuprofen 1.2 g daily for 10 days raised the serum digoxin levels of 9 healthy subjects by 25%.[5] Yet another study found that ibuprofen 600 mg three times daily for 10 days had no effect on steady-state serum digoxin levels of 8 patients.[10]

(e) Indometacin

1. Neonates. A study in 11 premature neonates (gestational age 25 to 33 weeks) given digoxin found that when they were given indometacin (mean total dose of 320 micrograms/kg over 12 to 24 hours) for patent ductus arteriosus, their mean serum digoxin levels rose on average by 40%. The digoxin was stopped in 5 of them because serum levels were potentially toxic.[11] This confirms the observation of digitalis toxicity in 3 similarly treated premature neonates,[12] and of toxic serum digoxin levels in another neonate.[13] A further report describes very high digoxin levels (8.2 nanograms/mL) without symptoms of toxicity in a full-term neonate given indometacin.[14]

2. Adults. Indometacin 50 mg three times daily for 10 days increased steady-state digoxin levels of 10 patients by about 40% (from 0.57 to 0.8 nanograms/mL), with a range of 0 to 100%.[10] Indometacin 150 mg daily for 10 days increased the serum digoxin levels of 9 healthy subjects by 25%.[5] In yet another study, a 60% increase in digoxin levels was seen with indometacin 150 mg daily.[15] This contrasts with the results of single-dose studies in two groups of 6 healthy adult subjects[16,17] who were given a 4-hour infusion of digoxin. Both studies suggested that no interaction occurs with indometacin.

(f) Isoxicam

Isoxicam 200 mg daily did not affect the steady-state plasma levels of 12 healthy subjects taking **beta-acetyldigoxin**.[18] This confirms the findings of a previous study.[19]

(g) Ketoprofen

Ketoprofen 50 mg four times daily for 4 days had no effect on the serum digoxin levels of 12 patients.[20]

(h) Lornoxicam

In 12 healthy subjects, the concurrent use of lornoxicam 4 mg twice daily for 14 days and digoxin 250 micrograms daily had only a small effect on the pharmacokinetics of each drug. The apparent clearance of the digoxin was decreased by 14% while the maximum serum level of the lornoxicam was decreased by 21% and its elimination half-life increased by 36%.[21]

(i) Meloxicam

In 12 healthy subjects meloxicam 15 mg daily for 8 days had no effect on the pharmacokinetics of digoxin (given as **beta-acetyldigoxin**).[22]

(j) Nimesulide

Nimesulide 100 mg twice daily for 7 days had little effect on the pharmacokinetics of digoxin 250 micrograms daily in 9 patients with mild heart failure. No major change in their clinical condition occurred.[23]

(k) Phenylbutazone

Six healthy subjects had an a decrease of about 20% in their serum digoxin levels while taking phenylbutazone 200 mg three times daily for 4 days.[6] In contrast, one study found no alteration in the levels of digoxin when it was given with phenylbutazone 600 mg daily.[15]

(l) Piroxicam

In 10 patients taking digoxin for mild heart failure, piroxicam 10 or 20 mg daily for 15 days had no effect on the steady-state digoxin levels, nor were consistent effects seen on the pharmacokinetics of digoxin.[24] Piroxicam 20 mg daily for 10 days was found to have no effect on serum digoxin levels in 6 healthy subjects.[5]

(m) Rofecoxib

Rofecoxib 75 mg daily did not cause any significant changes in the plasma pharmacokinetics or renal elimination of a single 500-microgram dose of digoxin elixir.[25]

(n) Tiaprofenic acid

Tiaprofenic acid 200 mg three times daily for 10 days caused a non-significant 15% rise (from 0.97 to 1.12 nanograms/mL), in the serum digoxin levels of 12 healthy subjects.[26]

Mechanism

The reasons for the altered digoxin pharmacokinetics in some of the studies are not clear. However, in the studies in neonates, the elevated digoxin levels were clearly related to an indometacin-induced deterioration in renal function.[11,13,14] It should be noted that all NSAIDs have the potential to cause renal impairment.

It is suggested that phenylbutazone lowers digitoxin levels by increasing its rate of metabolism by the liver.[3]

Importance and management

The interaction between digoxin and **indometacin** seems established in neonates, but documentation is limited. It has been suggested that the digoxin dose should be halved if indometacin is given to premature or full-term infants and the serum digoxin levels and urinary output monitored. Also be alert for moderate increases in serum digoxin levels in adults if indometacin is given. In adults it may be sufficient to monitor pulse rate (for bradycardia) and take digoxin levels if an interaction is suspected.

The interaction between digoxin and **diclofenac** is less well established and its clinical importance is somewhat uncertain as the rises in digoxin levels were mostly modest. It would be prudent to monitor concurrent use (e.g. for bradycardia) and monitor digoxin levels as necessary. Adjust the digoxin dose accordingly.

The importance of the interaction with azapropazone, etoricoxib, fenbufen and tiaprofenic acid is not known. In most cases changes to doses are unlikely to be necessary, but remain aware of the potential for an interaction. No special precautions would appear to be necessary with isoxicam, ketoprofen, meloxicam, piroxicam, and rofecoxib. More study is needed in most cases, but especially with ibuprofen, where the evidence is conflicting (although note that the one study reporting a significant interaction was poor).

The interaction with **phenylbutazone** and digitoxin appears to be in direct contrast to that with the other NSAIDs, but documentation is limited. However, phenylbutazone has, unlike many of the other NSAIDs, been found to have clinically relevant effects on hepatic enzymes. The dose of digitoxin may possibly need to be increased to avoid under-digitalisation if phenylbutazone is added to established treatment. Monitor concurrent use well.

1. Faust-Tinnefeldt G, Gilfrich HJ. Digitoxin-Kinetik unter antirheumatischer Therapie mit Azapropazon. *Arzneimittelforschung* (1977) 27, 2009–11.
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3. Wirth KE. Arzneimittelinteraktionen bei der Anwendung herzwirksamer Glykoside. *Med Welt* (1981) 32, 234–8.
4. Solomon HM, Reich S, Spirt N, Abrams WB. Interactions between digitoxin and other drugs *in vitro* and *in vivo*. *Ann N Y Acad Sci* (1971) 179, 362–9.
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6. Rau R, Georgiopoulos G, Neumann P, Gross D. Die Beeinflussung des Digoxinblutspiegels durch Antirheumatika. *Akt Rheum* (1980) 5, 349–58.
7. Arcoxia (Etoricoxib). Merck Sharp & Dohme Ltd. UK Summary of product characteristics, September 2009.
8. Dunky A, Eberi R. Anti-inflammatory effects of a new anti-rheumatic drug fenbufen in rheumatoid arthritis. XIV Int Congr Rheumatology, San Francisco, 1977. Abstract No 379.
9. Quattrocchi FP, Robinson JD, Curry RW, Grieco ML, Schulman SG. The effect of ibuprofen on serum digoxin concentrations. *Drug Intell Clin Pharm* (1983) 17, 286–8.
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11. Koren G, Zarfin Y, Perlman M, MacLeod SM. Effects of indomethacin on digoxin pharmacokinetics in preterm infants. *Pediatr Pharmacol* (1984) 4, 25–30.
12. Mayes LC, Boerth RC. Digoxin-indomethacin interaction. *Pediatr Res* (1980) 14, 469.
13. Schimmel MS, Inwood RL, Eidelman AI, Eylath U. Toxic digitalis levels associated with indomethacin therapy in a neonate. *Clin Pediatr (Phila)* (1980) 19, 768–9.
14. Haig GM, Brookfield EG. Increase in serum digoxin concentrations after indomethacin therapy in a full-term neonate. *Pharmacotherapy* (1992) 12, 334–6.
15. Halawa B, Mazurek W. Interakcja digoksyny i niektórych niesteroidowych leków przeciwzapalnych, kwasu acetylosalicylowego i nifedipiny. *Pol Tyg Lek* (1982) 37, 1475–6.
16. Finch MB, Johnston GD, Kelly JG, McDevitt DG. Pharmacokinetics of digoxin alone and in the presence of indomethacin therapy. *Br J Clin Pharmacol* (1984) 17, 353–5.
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23. Baggio E, Maraffi F, Montalto C, Nava ML, Torti L, Casciarri I. A clinical assessment of the potential for pharmacological interaction between nimesulide and digoxin in patients with heart failure. *Drugs* (1993) 46 (Suppl 1), 91–4.
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Digoxin + Orlistat

Orlistat does not appear to affect the pharmacokinetics of digoxin.

Clinical evidence, mechanism, importance and management

In 12 healthy subjects, orlistat 120 mg three times daily for 6 days was found to have no effect on the pharmacokinetics of a single 400-microgram oral dose of digoxin (in soft gelatin capsules).[1] This suggests that an approximate 30% reduction in dietary fat absorption induced by orlistat should not change the efficacy of digoxin and that no special precautions will be needed in patients who are given both drugs.

1. Melia AT, Zhi J, Koss-Twardy SG, Min BH, Smith BL, Freundlich NL, Arora S, Passe SM. The influence of reduced dietary fat absorption induced by orlistat on the pharmacokinetics of digoxin in healthy volunteers. *J Clin Pharmacol* (1995) 35, 840–3.

Digoxin + Penicillamine

Digoxin levels can be reduced by penicillamine.

Clinical evidence

In 10 patients, penicillamine 1 g daily taken 2 hours after an oral dose of digoxin, reduced the serum digoxin levels measured 2, 4 and 6 hours later, by 13%, 20% and 39%, respectively. In 10 other patients similarly treated but given digoxin intravenously, the serum digoxin levels measured 4 and 6 hours later were reduced by 23% and 64%, respectively.[1] The same authors have also reported this interaction in children.[2]

Information seems to be limited to the reports cited, and the reason for its occurrence is unknown. Patients taking digoxin should be checked for signs of under-digitalisation if penicillamine is added.

1. Moezzi B, Fatourechi V, Khozain R, Eslami B. The effect of penicillamine on serum digoxin levels. *Jpn Heart J* (1978) 19, 366–70.
2. Moezzi B, Khozein R, Pooymehr F, Shakibi JG. Reversal of digoxin-induced changes in erythrocyte electrolyte concentrations by penicillamine in children. *Jpn Heart J* (1980) 21, 335–9.

Digoxin and related drugs + Pinaverium

Digoxin levels are not affected by pinaverium in patients taking either beta-acetyldigoxin or metildigoxin.

Clinical evidence, mechanism, importance and management

A study in 25 patients, taking either **beta-acetyldigoxin** or **metildigoxin** for congestive heart failure, found that pinaverium 50 mg three times daily for 12 days had no significant effect on their plasma digoxin levels.[1] Two other studies in patients taking either digoxin 125 to 250 micrograms daily or **digitoxin** 100 micrograms, daily or every other day, found that pinaverium bromide 50 mg three times daily did not affect cardiac glycoside blood levels.[2] No dose adjustments of the digitalis glycoside seem necessary on concurrent use.

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Digoxin and related drugs + Pioglitazone or Rosiglitazone

Pioglitazone and rosiglitazone do not affect the pharmacokinetics of digoxin, but they may adversely affect cardiac function in patients with cardiac failure.

Clinical evidence

(a) Pioglitazone

In healthy subjects, pioglitazone 45 mg daily did not alter the steady-state pharmacokinetics of digoxin 250 micrograms daily.[1,2]

(b) Rosiglitazone

A study in healthy subjects found that rosiglitazone 8 mg daily for 14 days had no effect on the steady-state pharmacokinetics of digoxin 375 micrograms daily. Concurrent use was safe and well tolerated (aside from one patient who withdrew because of a rash).[3]

Mechanism

Pioglitazone and rosiglitazone can cause fluid retention, which may cause or exacerbate heart failure.

Importance and management

No pharmacokinetic interaction occurs. However, the US manufacturers advise caution with the use of pioglitazone or rosiglitazone in those with a history of heart failure because it may cause fluid retention, which could lead to a deterioration in cardiac function.[1,4] They state that starting these drugs in those with severe heart failure (NYHA class III or IV) is contraindicated, whereas the UK manufacturers contraindicate use in heart failure (NYHA class I to IV).[5,6] If digoxin or any other **digitalis glycoside** is being used to treat cardiac failure, the use of pioglitazone or rosiglitazone would not therefore be recommended. This is not a drug-drug interaction but a drug-disease interaction.

1. Actos (Pioglitazone hydrochloride). Takeda Pharmaceutical Company Ltd. US Prescribing information, August 2008.
2. Kortboyer JM, Eckland DJA. Pioglitazone has low potential for drug interactions. *Diabetologia* (1999) 42 (Suppl 1), A228.
3. Di Cicco RA, Miller AK, Patterson S, Freed MI. Rosiglitazone does not affect the steady-state pharmacokinetics of digoxin. *J Clin Pharmacol* (2000) 40, 1516–21.
4. Avandia (Rosiglitazone maleate). GlaxoSmithKline. US Prescribing information, February 2009.
5. Actos (Pioglitazone hydrochloride). Takeda UK Ltd. UK Summary of product characteristics, February 2009.
6. Avandia (Rosiglitazone maleate). GlaxoSmithKline UK. UK Summary of product characteristics, May 2009.

Digoxin + Probenecid

Probenecid has no clinically significant effect on digoxin levels.

Clinical evidence, mechanism, importance and management

A study in 2 healthy subjects taking digoxin 250 micrograms daily found that after taking *ColBenemid* (probenecid 500 mg with colchicine 500 micrograms) twice daily for 3 days, their plasma digoxin levels were slightly but not significantly raised (from 0.67 to 0.7 nanograms/mL, and from 0.6 to 0.67 nanograms/mL, respectively).[1] Another study in 6 healthy subjects found that probenecid 2 g daily for 8 days had no significant effect on the pharmacokinetics of digoxin.[2] No special precautions would seem necessary during concurrent use.

1. Jaillon P, Weissenburger J, Cheymol G, Graves P, Marcus F. Les effets du probénécide sur la concentration plasmatique à l'équilibre de digoxine. *Therapie* (1980) 35, 655–6.
2. Hedman A, Angelin B, Arvidsson A, Dahlqvist R. No effect of probenecid on the renal and biliary clearances of digoxin in man. *Br J Clin Pharmacol* (1991) 32, 63–7.

Digoxin + Propafenone

Propafenone can increase digoxin levels by 30 to 90%, or even more in children.

Clinical evidence

In 5 patients, propafenone (increasing over 6 days to 300 mg every 8 hours) increased the mean steady-state serum levels of digoxin 125 to 250 micrograms daily by 83%. Three patients continued to take both drugs for 6 months, at which point the digoxin levels were 63% higher. No digitalis toxicity was seen.[1] In another study, propafenone 600 mg daily in divided doses increased the steady-state serum digoxin levels of 10 patients by 90% (from 0.97 to 1.54 nanograms/mL), and two of them developed symptoms of toxicity (nausea, vomiting).[2] An even greater increase was seen in 3 children, who had rises in their serum digoxin levels of 112 to 254% over 3 to 24 days when given propafenone 250 to 500 mg/m^2 daily.[3] The mean AUC of digoxin increased by 14% in 27 patients receiving propafenone 10 mg/kg daily in divided doses. However, there was great inter-individual variability, with 22 patients having an increase in AUC, and 5 a decrease in AUC. One patient experienced digoxin toxicity resulting in fatal ventricular fibrillation.[4]

Propafenone 450 mg daily increased the mean steady-state plasma digoxin levels of 12 healthy subjects by about 35% (from 0.58 to 0.78 nanograms/mL), and the cardiac effects were increased accordingly.[5] In a study in 6 subjects[6] given a single 1-mg intravenous dose of digoxin, propafenone 150 or 300 mg every 8 hours increased the AUC of digoxin by 28% and decreased the total clearance of digoxin by 22%. A similar study with oral digoxin found a 25% increase in the AUC of digoxin when healthy subjects were given propafenone.[7]

Mechanism

Not understood. One suggestion is that propafenone increases the bioavailability of the digoxin.[7] Another is that the volume of distribution and non-renal clearance of digoxin are changed by the propafenone.[6] Conversely, others reported that propafenone decreased the renal clearance of digoxin.[2,5] There is certainly some *in vitro* evidence that propafenone and its metabolite inhibit P-glycoprotein, which is concerned with digoxin secretion by the renal tubular cells.[8,9]

Importance and management

A very well established interaction of clinical importance. Monitor the effects of concurrent use and reduce the digoxin dose appropriately in order to avoid toxicity. Most patients appear to be affected and dose reductions in the range 15 to 70% were found necessary in one of the studies cited.[2] The data available suggest that the extent of the rise may possibly depend on the propafenone serum concentration rather than on its dose.[6,10]

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Digoxin + Propantheline

Digoxin levels may be increased by at least one-third if propantheline is given with slow-dissolving forms of digoxin tablets. No clinically significant interaction is likely with digoxin given as a liquid or in soft-gelatin capsules or in the form of fast-dissolving tablets.

Clinical evidence

The serum digoxin levels of 9 out of 13 patients rose by 30% (from 1.02 to 1.33 nanograms/mL), when they took a slow-dissolving formulation of digoxin tablets (*Orion*) with propantheline 15 mg three times daily for 10 days. The serum levels stayed the same in 3 patients and fell slightly in one. An associated study in 4 healthy subjects given digoxin in liquid form found that serum digoxin levels were unaffected by propantheline.[1]

Another study by the same workers found that propantheline increased the digoxin serum levels of a slow-dissolving tablet formulation (*Orion*) by 40%, but had no effect on serum digoxin levels with a fast-dissolving tablet formulation (*Lanoxin*).[2] In a further study, propantheline increased the AUC of digoxin from *Lanoxin* tablets by 24%, compared with a non-significant increase of 13% with digoxin in the form of a solution in a capsule (*Lanoxicaps*).[3]

Mechanism

Propantheline is an antimuscarinic, which reduces gut motility. This allows the slow-dissolving formulations of digoxin more time to pass into solution so that more is available for absorption.

Importance and management

The interaction between digoxin and propantheline appears to be established, but it is only of importance if slow-dissolving digoxin formulations are used. No interaction is likely with liquid or liquid-filled capsule forms of digoxin. With slow-dissolving forms of digoxin tablets it may be necessary to reduce the digoxin dose.

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Digoxin + Prostaglandins

Iloprost does not significantly alter digoxin pharmacokinetics. In one study epoprostenol caused a small decrease in digoxin clearance in the short-term.

Clinical evidence, mechanism, importance and management

In a study, 12 patients taking digoxin 250 micrograms daily were given a 6-hour intravenous infusion of **iloprost** 2 nanograms/kg per minute over a period of 20 days. The mean time to maximum digoxin levels was delayed by an hour, but overall the pharmacokinetics of the digoxin were unchanged.[1,2] No special precautions would seem to be necessary on concurrent use.

In 14 patients with congestive heart failure, the clearance of digoxin was reduced by an estimated 15% by **epoprostenol** given for 3 days, but this effect was no longer apparent by the end of 12 weeks of concurrent use. The clinical relevance of this awaits evaluation but it seems unlikely to be important. However, the authors of the report suggest that the possible short-term changes in patients with high trough-plasma digoxin levels and those prone to digoxin toxicity should be borne in mind when using the combination.[3]

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Digoxin + Protease inhibitors

A woman had elevated digoxin levels and signs of toxicity after she was given ritonavir. Pharmacokinetic studies have shown that ritonavir and ritonavir-boosted saquinavir cause modest to marked increases in single-dose digoxin levels.

Clinical evidence

(a) Ritonavir

A 61-year-old HIV-positive woman taking lamivudine, indinavir, stavudine, pentamidine, with warfarin and digoxin 250 micrograms daily for atrial fibrillation, presented with increasing nausea and vomiting 3 days after starting to take ritonavir 200 mg twice daily. Digoxin levels about 5 hours and 27 hours after her last dose were 5.6 nanograms/mL and 2.1 nanograms/mL, respectively.[1]

A study in 12 healthy subjects found that ritonavir 300 mg twice daily for 11 days significantly increased the AUC and volume of distribution of a single 500-microgram intravenous dose of digoxin by 86% and 77%, respectively. Non-renal and renal digoxin clearance were decreased by 48% and 35%, respectively, and its half-life increased by 156%.[2] Another study found that ritonavir 200 mg twice daily for 15 days increased the AUC of a single 400-microgram oral dose of digoxin by 22%, with 9 of 12 subjects having an increase. Non-renal clearance, but not renal clearance, was reduced.[3]

(b) Saquinavir

In a crossover study in 16 healthy subjects, ritonavir-boosted saquinavir 100/1000 mg twice daily for 16 days increased the AUC and maximum levels of a single 500-microgram dose of digoxin by 49% and 27%, respectively.[4,5]

Mechanism

Raised digoxin levels are possibly due to inhibition of the P-glycoprotein-mediated renal transport of digoxin by ritonavir and saquinavir.[1-4]

Importance and management

A pharmacokinetic interaction between ritonavir and digoxin would appear to be established, although its extent is uncertain. The study with intravenous digoxin found a marked effect, whereas the study with oral digoxin found a much smaller effect. Nevertheless, given the case report

and the study with ritonavir-boosted saquinavir, it would seem prudent to closely monitor patients taking digoxin when ritonavir and/or saquinavir[4-6] is started or stopped, being alert for the need to adjust the digoxin dose. There do not appear to be any reports or studies of the interaction of digoxin with other protease inhibitors; however, most protease inhibitors are inhibitors and/or substrates for P-glycoprotein, so it would seem likely that they may all interact to a greater or lesser extent.

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Digoxin and related drugs + Proton pump inhibitors

A small rise in digoxin levels may occur with lansoprazole, omeprazole, pantoprazole or rabeprazole, but this is not thought to be clinically significant. One case of digoxin toxicity has been reported with omeprazole.

Clinical evidence

(a) Omeprazole

In a study in healthy subjects, omeprazole 20 mg daily for 11 days caused only minor changes in the disposition of a single 1-mg oral dose of digoxin. On average the AUC was increased by 10%.[1] However, a 65-year-old woman had signs of digoxin toxicity 3 months after starting to take omeprazole 20 mg daily. She was found to have a digoxin level of 3.9 nanograms/mL (previous level 1.1 nanograms/mL) and ECG changes, which resolved after the administration of digoxin immune Fab. No changes in renal function were noted in this patient.[2]

(b) Pantoprazole

Beta-acetyldigoxin 200 micrograms twice daily was given to 18 healthy subjects, with and without pantoprazole 40 mg daily, for 5 days. The pantoprazole caused a 10% rise in the digoxin AUC and a 9% rise in the maximum digoxin serum levels, but both were considered to be clinically irrelevant. No changes in the digoxin-induced height reduction in the T-wave on the ECG occurred.[3]

(c) Rabeprazole

A preliminary report, giving few details, states that rabeprazole increased the minimum levels of digoxin by about 20%, and also increased its AUC and maximum level.[4] A study in 47 patients regularly taking digoxin and either **lansoprazole** or omeprazole found that changing the proton pump inhibitor to an equivalent dose of rabeprazole did not significantly change the mean serum digoxin level, although 12 of the patients had increases of more than 15%.[5] The US manufacturer of rabeprazole states it increases the AUC and maximum level of digoxin by 19%, and 29%, respectively.[6] However, these changes are thought to be within the normal variations of digoxin levels and so are not considered clinically significant.[7]

Mechanism

The increase in digoxin levels with omeprazole may be the result of higher gastric pH which results in less digoxin hydrolysis and an increase in digoxin absorption.[8] The manufacturers of lansoprazole predict that it may have similar effects.[9] Non-selective digoxin assay methods may not detect an interaction, whereas selective HPLC assay methods and ECG studies provide evidence that the bioavailability of digoxin may be increased by omeprazole.[8] An *in vitro* study found that omeprazole, pantoprazole and lansoprazole inhibit the P-glycoprotein-mediated intestinal transport of digoxin.[10]

Importance and management

Although some studies suggest small changes in digoxin pharmacokinetics may occur these changes are usually small and unlikely to be clinically significant. No special precautions would therefore seem to be necessary if proton pump inhibitors and digoxin are given concurrently. However, the UK manufacturer of lansoprazole recommends that plasma levels of digoxin should be monitored and dose adjustments made if necessary when starting or stopping lansoprazole.[11]

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Digoxin and related drugs + Quinidine

In most patients the serum levels of digoxin are approximately doubled within five days of starting quinidine. Digitoxin levels are also increased but to a lesser extent and the interaction takes a longer period of time to develop.

Clinical evidence

(a) Digitoxin

Quinidine 750 mg daily increased the steady-state plasma digitoxin levels of 8 healthy subjects by 45% (from 13.6 to 19.7 nanograms/mL), over 32 days.[1] Another study found a 31% increase in serum digitoxin levels over 10 days,[2] whereas yet another found a 115% increase in plasma levels after 70 days of treatment with 360 mg quinidine three times daily.[3] A study in 5 healthy subjects found that quinidine reduced the total body clearance of digitoxin by 63%, resulting in raised serum digitoxin levels.[4]

(b) Digoxin

The observation that quinidine appeared to increase serum digoxin levels prompted a retrospective study of patient records, which revealed that 25 out of 27 patients taking digoxin had a rise in their serum digoxin levels from 1.4 nanograms/mL to 3.2 nanograms/mL when given quinidine. Of the patients who had a rise,16 developed typical signs of digoxin toxicity (nausea, vomiting, anorexia), which resolved in 10 of them when the digoxin dose was reduced or withdrawn, and in 5 when the quinidine was withdrawn.[5]

This is one of the first reports published in 1978 (two other groups independently reported it at a similar time[6,7]) that clearly describes this interaction, although hints of its existence can be found in papers published over the previous 50 years. Since then large numbers of research reports, both retrospective and prospective, and case studies have confirmed and established the incidence and magnitude of this interaction. It occurs in over 90% of patients and, on average, there is a 100% increase in serum digoxin levels, although there are pronounced inter-individual differences and the increase is somewhat dependent on the quinidine dose. There are numerous reports and reviews of this interaction, only a selection of which are listed here. Two reviews published in 1982 and 1983 contain valuable bibliographies.[8,9]

Mechanism

Quinidine reduces the renal excretion of digoxin by 40 to 50%, and it also appears to have some effects on non-renal clearance, which includes a reduction in digoxin excretion in the bile.[10] There is also evidence that

increases in the rate and extent of absorption of digoxin from the gut occur.[11] More recent studies show that the mechanism behind these effects on absorption and renal excretion is likely to be P-glycoprotein inhibition by quinidine.[12-14] Digoxin also appears to cause a small reduction in the renal clearance of quinidine.[15] Quinidine appears to increase digitoxin serum levels by reducing its non-renal clearance.

Importance and management

The interaction between digoxin and quinidine is very well-documented, well-established and of definite clinical importance. As serum digoxin levels are usually roughly doubled (up to fivefold increases have been seen[8]) and over 90% of patients are affected, digitalis toxicity will develop unless the dose of digoxin is reduced (approximately halved).[5,8,16,17] A suggested rule-of-thumb is that if serum digoxin levels are no greater than 0.9 nanograms/mL and potassium levels are within the reference range then the addition of quinidine is unlikely to cause toxic digoxin levels, whereas with levels of 1 nanogram/mL or more, toxic concentrations may develop.[18] Monitor the effects and readjust the dose as necessary. Significant effects occur within a day of taking the quinidine and reach a maximum after about 3 to 6 days (quicker or slower in some patients), but digoxin levels will only stabilise when the quinidine has reached steady-state and that depends on whether a loading dose of quinidine is given. The effects are to some extent dose-related but the correlation is not good: less than 400 to 500 mg of quinidine daily has minimal effects, and increasing doses up to 1.2 g has greater effects.[16,19] About 5 days are needed after withdrawing the quinidine before serum digoxin levels fall to their former levels. It has been recommended that patients with chronic renal failure should have their digoxin dose reduced by as much as two-thirds.[20-22] An appropriate upward readjustment will be necessary if the quinidine is subsequently withdrawn.

Far less is known about the interaction between digitoxin and quinidine but similar precautions should be taken. It develops much more slowly.

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Digoxin + Quinine

The digoxin levels of some but not all patients may rise by more than 60% if they are given quinine, and there is a report of digoxin toxicity in an elderly patient during concurrent use.

Clinical evidence

After taking quinine 300 mg four times daily for a day the steady-state digoxin levels of 4 subjects taking digoxin 250 micrograms daily rose by 63%, from 0.49 to 0.8 nanograms/mL. After taking the quinine for a further 3 days the digoxin levels rose a further 11% (to 0.86 nanograms/mL). Digoxin renal clearance fell by 20%.[1]

Quinine sulfate 250 mg daily for 7 days increased the mean serum digoxin levels of 7 healthy subjects by 25%, from 0.64 to 0.8 nanograms/mL. When quinine sulfate 250 mg was given three times daily there was a further 8% rise. Considerable individual differences were seen; one subject had a 92% rise.[2] In contrast, 17 patients given quinine 750 mg daily had only a small and statistically insignificant rise in mean serum digoxin levels, from 0.8 to 0.91 nanograms/mL. Serum levels were virtually unaltered in 11 patients, decreased in two and markedly increased (amount not stated) in four.[3] Another study found that quinine reduced the total clearance of digoxin by 26%.[4]

An 76-year-old man with hypertension and atrial fibrillation taking digoxin 500 micrograms daily and quinine sulfate 750 mg daily as well as aspirin, candesartan and amlodipine was admitted after an episode of fainting, and an ECG detected AV block, a prolonged QTc interval of 570 milliseconds and torsade de pointes. Digoxin levels were found to be 5 nanograms/mL. The authors attributed the effect to digoxin toxicity caused by the presence of quinine.[5]

Mechanism

Not fully understood. A reduction in non-renal clearance is apparently largely responsible for the rise in serum digoxin levels with quinine.[2,4,6] This is possibly due to changes in digoxin metabolism or in its biliary excretion.[4,6]

Importance and management

An established interaction of clinical importance but only moderately documented. Monitor the effects of concurrent use (e.g. for bradycardia) and reduce the digoxin dose where necessary. Some patients may have a substantial increase in serum digoxin levels whereas others will have only a small or moderate rise. There appears to be only one case report of digoxin toxicity arising from this interaction.

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Digoxin and related drugs + Quinolones

Levofloxacin, gemifloxacin, moxifloxacin and sparfloxacin do not affect the pharmacokinetics of digoxin. Similarly moxifloxacin does not interact with beta-acetyldigoxin. Gatifloxacin may cause small increases in digoxin levels, which are probably not clinically significant. The effects of garenoxacin are unclear.

Clinical evidence

(a) Garenoxacin

In a study designed to look at the effects of garenoxacin on gut flora, 16 healthy subjects were given digoxin 250 micrograms every 6 hours on day one, then 250 micrograms daily to day 14, with garenoxacin 600 mg daily on days 8 to 14. Garenoxacin did not decrease (but may actually increase) the numbers of *E. lentum* in faeces (see 'Digoxin and related drugs + Macrolides', p.1103, for an explanation of the possible significance of these findings). Thus an interaction due to the effect of garenoxacin on intestinal microflora is unlikely.[1]

(b) Gatifloxacin

The vital signs of 12 healthy subjects given gatifloxacin 400 mg daily for 7 days while taking digoxin 250 micrograms daily were not altered. The

AUC and steady-state levels of digoxin were increased by 19% and 12% respectively. Dose adjustments were not considered necessary.[2]

(c) Gemifloxacin

No clinically relevant pharmacokinetic changes were seen in a study in 14 healthy elderly subjects given gemifloxacin 320 mg daily for 7 days while taking digoxin (*Lenoxin*) 250 micrograms daily. No clinically important changes in vital signs or ECGs were found.[3]

(d) Levofloxacin

The pharmacokinetics of a single 400-microgram dose of digoxin (*Lanoxicaps*) were unchanged when 12 healthy subjects were given levofloxacin 500 mg twice daily for 6 days.[4]

(e) Moxifloxacin

In 14 healthy subjects, moxifloxacin 400 mg daily for 14 days did not cause any clinically relevant changes in the steady-state pharmacokinetics of digoxin 250 micrograms daily.[5] No pharmacokinetic changes were seen in another study in 12 healthy subjects given a single 600-microgram dose of **beta-acetyldigoxin** with moxifloxacin 400 mg daily for 2 days.[6]

(f) Sparfloxacin

In 24 healthy subjects, sparfloxacin, 400 mg as a loading dose, followed by 200 mg daily for 9 days did not affect the pharmacokinetics of digoxin (*Lanoxicaps*) 300 micrograms daily.[7]

Mechanism

Up to 10% of patients receiving oral digoxin excrete it in substantial amounts in the faeces and urine as inactive metabolites (digoxin reduction products or DRPs). This metabolism seems to be due to gut flora,[8] in particular *Eubacterium lentum*, which is anaerobic and Gram positive. However, there is some doubt about this as a probable mechanism and, despite *in vitro* susceptibility of *E. lentum* to a range of antibacterials including some quinolones there is currently no information to suggest that quinolones inhibit the gut flora-mediated metabolism of digoxin.[9] For further information on the possible significance of *E. lentum*, see *Mechanism* under 'Digoxin and related drugs + Macrolides', p.1103.

Importance and management

There appears to be no clinically significant interaction between digoxin and quinolones. Information about other digitalis glycosides and quinolones generally seems to be lacking. Bearing in mind their extensive use, this silence in the literature would suggest that no problems normally arise.

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Digoxin and related drugs + Rauwolfia alkaloids

The concurrent use of digitalis glycosides and rauwolfia alkaloids is usually uneventful, but the incidence of arrhythmias appears to be increased, particularly in those with atrial fibrillation. Excessive bradycardia and syncope have also been described.

Clinical evidence

Three patients taking digoxin and either **reserpine** or whole root ***Rauwolfia serpentina*** developed arrhythmias, namely atrial tachycardia with 4:1 Wenckebach irregular block, ventricular bigeminy and tachycardia, and atrial fibrillation. A large number of other patients received both drugs without problems.[1]

The incidence of premature ventricular systoles was roughly doubled in patients taking digoxin and **rauwolfia** compared with a similar group taking **rauwolfia** alone.[2] **Reserpine** reduced the tolerated dose of **acetylstrophanthidin** in 15 patients with congestive heart failure; 8 out of 9 patients with atrial fibrillation developed ECG abnormalities, including complete heart block and ventricular ectopics, during acute digitalisation following **reserpine** use, compared with only one of 9 patients not taking **reserpine**.[3]

A case report describes a man taking digoxin 250 micrograms and 375 micrograms on alternate days and **reserpine** 25 micrograms daily, who developed sinus bradycardia and carotid sinus supersensitivity. He was hospitalised because of syncope, which resolved when the **reserpine** was withdrawn.[4]

Mechanism

Not understood. A possible explanation is that because the rauwolfia alkaloids deplete the neurotransmitter from the sympathetic nerve supply to the heart, the parasympathetic vagal supply (i.e. heart slowing) has full rein. Digitalis also reduces heart rate which in the presence of the rauwolfia becomes excessive. In this situation the rate could become so slow that ectopic foci, which would normally be swamped by a faster, more normal beat, begin to fire, leading to the development of arrhythmias. Syncope could also result from the combination of bradycardia and the hypotensive effects of reserpine.

Importance and management

Although the evidence suggests that not all patients taking digitalis glycosides and a rauwolfia alkaloid develop an interaction, some caution is advisable. One group of authors, despite having described the adverse reactions cited above,[1] conclude that time has proven the safety of the combination. However, they warn that arrhythmias must be anticipated. Particular risk of arrhythmias seems to occur in patients with atrial fibrillation, and in digitalised patients given reserpine parenterally, because of the sudden release of catecholamines that takes place.[4]

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Digoxin and related drugs + Rifampicin (Rifampin)

Digitoxin levels can be halved by rifampicin. Digoxin levels are modestly reduced by rifampicin.

Clinical evidence

(a) Digitoxin

A comparative study in 21 patients with tuberculosis and 19 healthy subjects taking digitoxin 100 micrograms daily found that the serum digitoxin levels of the patients taking rifampicin were about half of the levels in healthy subjects not taking rifampicin (18.4 nanograms/mL compared with 39.1 nanograms/mL).[1] The half-life of digitoxin was reduced from 8.2 days to 4.5 days by the rifampicin. There are case reports confirming that rifampicin can markedly reduce serum digitoxin levels.[2,3]

(b) Digoxin

A woman, hospitalised for endocarditis, taking digoxin 250 to 375 micrograms daily, furosemide, aspirin, isosorbide dinitrate and potassium chloride, had a marked fall of about 80% in her serum digoxin level when she was given rifampicin 600 mg daily. The serum digoxin returned to its former level over the 2 weeks following rifampicin withdrawal.[4] She had only moderate renal impairment (serum creatinine 221 micromol/L).

Another report describes 2 patients undergoing renal dialysis whose digoxin dose needed to be doubled while they were taking rifampicin, and similarly reduced when the rifampicin was withdrawn.[5] This confirms an earlier report.[6]

A study in 8 healthy subjects found that the AUC and maximum plasma levels of a single 1-mg oral dose of digoxin were reduced by 30% and 52%, respectively, by rifampicin 600 mg daily for 10 days.[7] In two further studies rifampicin 300 mg twice daily for 7 days reduced the AUC of a single oral dose of digoxin by 16%, and reduced its maximum levels by about 25%.[8,9] Note that these studies were designed to investigate the interaction of other drugs, and rifampicin was being used as a positive control.

A 15% reduction in the AUC and maximum plasma levels of digoxin was seen when a single 1-mg intravenous dose of digoxin was given after pre-treatment with rifampicin 600 mg daily for 10 days.[7] Similarly, a study in 8 healthy subjects who were given a single 1-mg intravenous dose of digoxin after 14 days of treatment with rifampicin 600 mg daily found an increased excretion of digoxin into the bile, and a 27% reduction in the AUC of digoxin.[10]

There is a report of rifampicin 600 mg daily being used to increase the metabolism of digoxin (as well as propafenone and warfarin) in a case of a multiple drug overdose in a 16-year-old girl. Two hours after plasma exchange, the serum digoxin level was 3.45 nanograms/mL and this had fallen by 50% 26 hours after starting rifampicin. The usual digoxin half-life is reported to be 36 to 48 hours.[11]

Mechanism

The interaction between digitoxin and rifampicin is almost certainly due to the increase in digitoxin metabolism caused by rifampicin, which is a potent enzyme inducer.[1] Digoxin is largely excreted unchanged in the urine and the interaction with rifampicin appears to be mainly due to induction of P-glycoprotein, resulting in reduced digoxin absorption from the intestine,[7,10] and increased biliary excretion.[10]

Importance and management

The interaction between digitoxin and rifampicin is established and clinically important. Under-digitalisation may occur unless the digitoxin dose is increased appropriately. Good monitoring is obviously advisable.

The pharmacokinetic interaction with digoxin is also established, but rifampicin causes only a minor to modest reduction in digoxin levels, and the few case reports suggest that these changes are generally not clinically relevant. However, it would be prudent to monitor the concurrent use of these drugs, being alert for the need to increase the digoxin dose. It may be that renal impairment increases the extent of this interaction, as several of the cases cited involved patients with some degree of renal impairment.

There does not seem to be any information regarding the other rifamycins, **rifabutin** (a weak enzyme inducer) and **rifapentine** (a moderate enzyme inducer). However, the UK manufacturers and the CSM in the UK warn that rifabutin may possibly reduce the effects of a number of drugs, including digitalis (but not digoxin).[12,13]

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Digoxin + Ropinirole

Ropinirole does not affect the pharmacokinetics of digoxin to a clinically significant extent.

Clinical evidence, mechanism, importance and management

In a placebo-controlled study, 10 patients with Parkinson's disease were given ropinirole (initially 250 micrograms increasing to 2 mg three times daily) in addition to their usual treatment with digoxin 125 or 250 micrograms daily. Although ropinirole decreased the AUC of digoxin by 10%, and decreased its maximum plasma concentration by 25%, the digoxin minimum plasma concentration was not significantly altered. The authors therefore reasonably concluded that no digoxin dose adjustment would be needed on concurrent use.[1]

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Digoxin + Sevelamer

The pharmacokinetics of a single dose of digoxin were not affected by sevelamer in one study.

Clinical evidence, mechanism, importance and management

In a randomised study a single 1-mg oral dose of digoxin was given with or without sevelamer 2.4 g followed by a standard breakfast. Five further doses of sevelamer were given immediately before subsequent meals over the following 2 days. During this time, the pharmacokinetic profile of digoxin was not altered.[1]

Sevelamer is a non-absorbed phosphate-binding polymer with bile-acid binding properties, but it appears that it does not bind with digoxin. Ideally this finding requires confirmation in long-term studies, but the available evidence suggests that a clinically significant interaction with sevelamer is unlikely.

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Digoxin + SSRIs

Citalopram, fluvoxamine, paroxetine, and sertraline appear not to affect the pharmacokinetics of digoxin. However, one case-control study found a small increased risk of digoxin toxicity after starting sertraline, paroxetine, fluoxetine or fluvoxamine, and two isolated reports describe increased serum digoxin levels attributed to the use of fluoxetine or paroxetine.

Clinical evidence

In a case-control study in 3 144 patients who had been admitted to hospital with digoxin toxicity, patients were significantly more likely than controls to have received a new prescription for **sertraline**, **fluoxetine**, **fluvoxamine**, or **paroxetine** in the 30 days before admission (adjusted odds ratios, 2.8 to 3). This was after adjusting for renal impairment and other interacting drugs. Nevertheless, this increased risk was not statistically significantly different to that in patients taking tricyclics (1.5) or benzodiazepines (2.1), which the authors considered have no known basis for an interaction.[1] Consider also 'Digoxin and related drugs + Benzodiazepines and related drugs', p.1086). In addition, the risk was small compared with the 12-fold increased risk found by the same authors in a similar study of clarithromycin (see 'Digoxin and related drugs + Macrolides', p.1103. Furthermore, there is little evidence of an interaction in other studies, although isolated case reports do describe toxicity. These are discussed in the individual sections below.

(a) Citalopram

A study in 11 healthy subjects found that citalopram 40 mg daily for 28 days did not have any significant effect on the pharmacokinetics of a single 1-mg dose of digoxin taken on day 21. No clinically significant ECG changes were observed.[2]

(b) Fluoxetine

An isolated report describes a 93-year-old woman with congestive heart failure who developed increased serum digoxin levels on two occasions when **fluoxetine** was added.[3]

(c) Fluvoxamine

After taking fluvoxamine 100 mg daily for 15 days, the pharmacokinetics of a single 1.25-mg intravenous dose of digoxin were unchanged in 8 healthy subjects.[4]

(d) Paroxetine

A study in healthy subjects found that paroxetine 30 mg daily had no effect on the pharmacokinetics of digoxin 250 micrograms daily. The pharmacokinetics of paroxetine were unaffected by digoxin.[5] A case report describes digoxin toxicity in a 68-year-old woman with atrial fibrillation and depression, which was attributed to the addition of paroxetine 20 mg daily. Her digoxin levels reached 5.2 nanograms/mL.[6]

(e) Sertraline

A placebo-controlled study in 19 healthy subjects found that sertraline, in an initial dose of 50 mg daily titrated to 200 mg daily, had no effect on the steady-state pharmacokinetics of digoxin, except for a decrease in time to maximum plasma levels.[7]

Mechanism

It has been suggested that paroxetine might inhibit P-glycoprotein leading to reduced renal excretion of digoxin.[6] This suggestion has been criticised by other authors who propose that the increase in levels seen in the case with paroxetine may be due to hospital-induced compliance or renal impairment.[8,9] Moreover, the case-control study found no evidence of a significantly different risk of digoxin toxicity between those SSRIs with greater P-glycoprotein inhibitory activity (sertraline and paroxetine) than those with less P-glycoprotein inhibitory activity (fluoxetine, fluvoxamine).[1]

Importance and management

The pharmacokinetic studies show that, in general, it is unlikely that SSRIs will affect the steady-state serum levels of digoxin. The excess risk seen in the case-control study was considered to be small and related to detection bias or confounding by indication,[1] although the findings do introduce a note of caution. Nevertheless, the fact that there are only isolated case reports of a possible interaction with digoxin for such a widely used class of drugs suggests that problems are rarely encountered. No special precautions would seem to be necessary.

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Digoxin + St John's wort (*Hypericum perforatum*)

Digoxin toxicity occurred in a patient taking digoxin when he stopped taking St John's wort. There is good evidence that some preparations of St John's wort can reduce the levels of digoxin by about one-quarter to one-third.

Clinical evidence

An 80-year-old man taking long-term digoxin and St John's wort herbal tea (2 litres daily) developed symptoms of digoxin toxicity (nodal bradycardia of 36 bpm and bigeminy) when he stopped taking the herbal tea.[1]

In a study 13 healthy subjects were given digoxin for 5 days until steady-state had been achieved, and then St John's wort extract (*LI 160*, Lichtwer Pharma) 300 mg three times daily for a further 10 days. The AUC and trough level of digoxin decreased by 28% and 37%, respectively. When compared with a parallel group of 12 subjects taking digoxin and placebo, the St John's wort group had 26% lower maximum plasma digoxin levels, 33% lower trough digoxin levels and a 25% lower AUC.[2]

In another study, 8 healthy subjects pretreated with St John's wort 300 mg three times daily for 14 days were given a single 500-microgram dose of digoxin. St John's wort decreased the AUC_{0-7} of digoxin by 18%.[3]

Another study in 18 healthy subjects found that St John's wort 300 mg three times daily (Nature's Way, containing a daily dose of 24 mg of hyperforin) for 14 days reduced the maximum levels and AUC_{0-24} of a single 250-microgram dose of digoxin by 36% and 23%, respectively. These findings were comparable to rifampicin (an established P-glycoprotein inducer) 600 mg daily for 7 days. No significant adverse effects were reported.[4]

In a further randomised placebo-controlled study, 93 healthy subjects were given digoxin alone for 7 days and then with one of ten St John's wort preparations for 14 days. The extract used in the earlier study (*LI 160*, *Jarsin 300*, Lichtwer Pharma) 300 mg three time daily similarly reduced the digoxin AUC, peak and trough plasma levels by 25%, 37%, and 19%, respectively. Comparable results were found with hypericum powder containing similar amounts of hyperforin (about 21 mg daily), while hypericum powder with half the hyperforin content (about 10 mg daily) reduced the AUC, peak and trough plasma levels by about 18%, 21%, and 13%, respectively. Some St John's wort products, including tea, juice, oil extract, and powder with low-dose hyperforin (all 5 mg daily or less), did not significantly affect the pharmacokinetics of digoxin.[5] Similarly, a further study in 28 healthy subjects found no statistically significant change in digoxin pharmacokinetics when another low-hyperforin (about 3.5 mg daily) St John's wort extract (*Esbericum*) 120 mg was given twice daily for 11 days to patients who had received a digoxin loading dose of 750 micrograms daily for 2 days before starting St John's wort, and then received digoxin 250 micrograms daily each day during the study.[6]

Mechanism

St John's wort, and specifically hyperforin, a major active constituent, has been shown to increase the activity of the P-glycoprotein drug transporter protein in the intestines, which reduces the absorption of digoxin.[2,4,7,8]

Importance and management

An interaction between St John's wort and digoxin would appear to be established. The extent of the interaction may depend on the St John's wort preparation involved and dose used and seems to be correlated with the dose of hyperforin.[4-6,8] Reductions in serum digoxin levels of the size seen with *LI 160* could diminish the control of arrhythmias or heart failure. Digoxin serum levels should therefore be well monitored if St John's wort is either started or stopped and appropriate dose adjustments made if necessary. The recommendation of the CSM in the UK is that St John's wort should not be used by patients taking digoxin.[9]

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Digoxin + Statins

Atorvastatin, fluvastatin and simvastatin cause small increases in the plasma levels of digoxin. Pravastatin and rosuvastatin appear to have no effect on digoxin pharmacokinetics.

Clinical evidence

(a) Atorvastatin

Digoxin 250 micrograms daily was given to 24 healthy subjects for 10 days, with atorvastatin 10 or 80 mg daily for a further 10 days. The mean steady-state plasma digoxin levels were unaffected by atorvastatin 10 mg, but atorvastatin 80 mg caused a 20% rise in maximum digoxin levels and a 15% rise in its AUC.[1]

(b) Fluvastatin

In a crossover study in 18 patients, fluvastatin 40 mg caused no significant changes in the pharmacokinetics of digoxin 100 to 375 micrograms daily.[2] Another similar study in patients found changes of up to 15% in maximum plasma digoxin levels and clearance.[3]

(c) Pravastatin

In 18 healthy subjects, pravastatin 20 mg daily for 9 days had no significant effect on the steady-state serum levels of digoxin 200 micrograms daily.[4]

(d) Rosuvastatin

In a randomised study, 18 healthy subjects were given rosuvastatin 40 mg daily or placebo for 12 days, with a single 500-microgram dose of digoxin on day 8. The absorption, renal excretion, AUC and maximum serum levels of digoxin were unaffected by rosuvastatin.[5]

(e) Simvastatin

Plasma digoxin levels can be slightly raised, by about 0.3 nanograms/mL, by simvastatin.[6]

Mechanism

The small changes seen in digoxin levels are probably due to the inhibitory effects of these statins on P-glycoprotein. Pravastatin does not appear to inhibit P-glycoprotein.[7]

Importance and management

The small changes seen in the digoxin levels with the statins seem unlikely to be clinically relevant in most patients.

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Digoxin + Sucralfate

Sucralfate caused only a small reduction in the absorption of digoxin in one study, but an isolated report describes a marked reduction in one patient.

Clinical evidence

In a study in 12 healthy subjects, sucralfate 1 g four times daily for 2 days had no effect on most of the pharmacokinetic parameters of a single 750-microgram dose of digoxin; however, the AUC of digoxin was reduced by 19% and the amount of digoxin eliminated in the urine was reduced by 12%. Digoxin was also absorbed faster.[1] No interaction occurred when the digoxin was given 2 hours before the sucralfate.[1]

An elderly patient was admitted to hospital with pressure-like chest pain, shortness of breath and generalised fatigue. She was taking several drugs including digoxin 125 micrograms daily and sucralfate 2 g twice daily, but her digoxin levels were found to be subtherapeutic (about 0.1 nanogram/mL), even though the doses of digoxin and sucralfate were separated by 2 hours. She was given intravenous digoxin 250 micrograms for an episode of atrial flutter on the day of admission, with a further dose the next day. Sucralfate was discontinued on day 4 as she had not had any recent gastrointestinal symptoms and, on day 5 digoxin levels were within the therapeutic range (0.9 nanograms/mL). She continued to take oral digoxin 125 micrograms daily without sucralfate and levels remained at about the therapeutic range in the 2-week period after hospitalisation.[2]

Mechanism

Uncertain. One possibility is that the digoxin and sucralfate bind together in the gut, which reduces the digoxin absorption.

Importance and management

Information appears to be limited to the reports cited. The reduction in digoxin levels reported in the study is small and therefore normally unlikely to be clinically relevant, but the unexplained and isolated case suggests that clinicians should at least be aware of the possibility of an interaction.

1. Giesing DH, Lanman RC, Dimmitt DC, Runser DJ. Lack of effect of sucralfate on digoxin pharmacokinetics. *Gastroenterology* (1983) 84,1165.
2. Rey AM, Gums JG. Altered absorption of digoxin, sustained-release quinidine, and warfarin with sucralfate administration. *Ann Pharmacother* (1991) 25, 745–6.

Digoxin + Surfactant excipients

Non-ionic surfactants used as pharmaceutical excipients such as polyoxyl castor oil (*Cremophor*) may slightly enhance the absorption of digoxin.

Clinical evidence, mechanism, importance and management

A placebo-controlled study in 12 healthy subjects found that **polyoxyl castor oil** (***Cremophor RH40***) 600 mg three times daily increased the AUC_{0-5} and peak plasma levels of a single 500-microgram oral dose of digoxin by about 22%. The absorption of digoxin was delayed. The pharmacodynamic effects of digoxin were not affected by ***Cremophor***. It was suggested that ***Cremophor*** increases digoxin plasma levels by inhibiting intestinal P-glycoprotein, or that the ***Cremophor*** prolongs the dissolution of digoxin tablets resulting in delayed absorption from the intestines.[1] Whatever the reason, the effects found were modest, an their clinical relevance is not established.

1. Tayrouz Y, Ding R, Burhenne J, Riedel K-D, Weiss J, Hoppe-Tichy T, Haefeli WE, Mikus G. Pharmacokinetic and pharmaceutic interaction between digoxin and Cremophor RH40. *Clin Pharmacol Ther* (2003) 73, 397–405.

Digoxin + Tegaserod

Tegaserod slightly reduces the AUC of digoxin.

Clinical evidence, mechanism, importance and management

A study in 12 healthy subjects given tegaserod 6 mg twice daily for 5 days found that the time to peak levels of a single 1-mg dose of digoxin, given on day 4, was reduced by 30 minutes, and the mean AUC and maximum plasma concentrations were slightly reduced by 12% and 15%, respectively.[1] These small changes are unlikely to be clinically relevant. Note that the manufacturer discontinued the marketing of tegaserod in the US be-

cause of a finding of an excess risk of serious cardiovascular ischaemic events.[2]

1. Zhou H, Horowitz A, Ledford PC, Hubert M, Appel-Dingemanse S, Osborne S, McLeod JF. The effects of tegaserod (HTF 919) on the pharmacokinetics and pharmacodynamics of digoxin in healthy subjects. *J Clin Pharmacol* (2001) 41, 1131–9.
2. Dear Dr Letter. Novartis Pharmaceuticals Corp. March 30, 2007. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm108879.htm (accessed 04/02/10).

Digoxin + Tetracycline

Limited early evidence suggested that tetracycline may cause a rise in digoxin levels.

Clinical evidence

A patient taking digoxin tablets 500 micrograms daily was given tetracycline 500 mg every 6 hours for 5 days. His urinary excretion of digoxin metabolites fell sharply within 2 days, and his steady-state serum digoxin levels rose by 43%.[1] Another subject had a marked fall in the excretion of digoxin metabolites from the gut after taking tetracycline.[2] In a study, tetracycline prolonged the half-life of digoxin and increased its serum levels by about 70% (from 1.7 to 2.9 nanograms/mL).[3]

Mechanism

Uncertain. Up to 10% of patients taking oral digoxin excrete it in substantial amounts in the faeces and urine as inactive metabolites (digoxin reduction products or DRPs). This metabolism seems to be performed by the gut flora,[1] in particular *Eubacterium lentum*, which is anaerobic and Gram positive.[2,4] In the presence of some antibacterials, such as tetracycline, which can inhibit this organism, more digoxin becomes available for absorption, which results in a rise in serum levels. At the same time the inactive metabolites derived from the gut disappear.[2] However, this is not necessarily the full explanation, see also 'Digoxin and related drugs + Macrolides', p.1103.

Importance and management

The interaction between digoxin and tetracycline is not well established, the evidence is very limited, and its general clinical importance is uncertain. Bear this interaction in mind in case of an unexpected response to digoxin.

1. Lindenbaum J, Rund DG, Butler VP, Tse-Eng D, Saha JR. Inactivation of digoxin by the gut flora: reversal by antibiotic therapy. *N Engl J Med* (1981) 305, 789–94.
2. Dobkin JF, Saha JR, Butler VP, Lindenbaum J. Effects of antibiotic therapy on digoxin metabolism. *Clin Res* (1982) 30, 517A.
3. Halawa B. Interakcje digoksyny z cefradina (Sefril), tetracyklina (Tetracyclinum), gentamycyna (Gentamycin) i wankomycyna (Vancocin). *Pol Tyg Lek* (1984) 39, 1717–20.
4. Ten Eick AP, Reed MD. Hidden dangers of coadministration of antibiotics and digoxin in children: focus on azithromycin. *Curr Ther Res* (2000) 61, 148–60.

Digoxin and related drugs + Thyroid hormones and Antithyroid drugs

Thyrotoxic patients are relatively resistant to the effects of digitalis glycosides and may need reduced doses of these drugs as treatment with antithyroid drugs (carbimazole, thiamazole) progresses, whereas patients with hypothyroidism may need increased doses of digitalis glycosides as treatment with thyroid hormones progresses. Carbimazole has been shown to reduce levels of digoxin in healthy subjects.

Clinical evidence

(a) Carbimazole

The observation of relatively low plasma digoxin levels in a patient taking carbimazole prompted a further study in 10 healthy subjects. In 9 out of the 10 subjects, steady-state peak serum digoxin levels were reduced by 23% (from 1.72 to 1.33 nanograms/mL) by a single 60-mg dose of carbimazole, but in the other subject the serum digoxin levels were increased. Other pharmacokinetic parameters were unaffected.

Carbimazole abolished the systolic blood pressure decrease seen in the first 3 hours with digoxin, and also reduced the duration of the digoxin-induced diastolic blood pressure fall from 12 hours to 6 hours. The changes in heart rates, cardiac output and stroke volumes were not statistically significant, but inter-individual differences were large.[1-3]

(b) Thiamazole

A study in 12 patients with hyperthyroidism found that normalisation of serum T3 and thyroxine by thiamazole treatment did not produce significant changes in the pharmacokinetics of digoxin.[4]

Mechanism

One explanation for the changed response to digitalis with carbimazole is that there is a direct and altered response of the heart due to the raised or lowered thyroid hormone levels. Another is that changes in glomerular filtration rate associated with hypo- or hyperthyroidism result in increased or decreased serum digoxin, respectively.[5] Why carbimazole *reduced* serum digoxin levels in healthy subjects (normal thyroid status) is not known.

Importance and management

Evidence for an interaction between thyroid hormones or antithyroid drugs and digitalis glycosides is limited, but given the evidence here, and the way thyroid hormones or antithyroid drugs are known to affect other drugs, and interaction certainly seems possible. As thyroid status is returned to normal by the use of antithyroid drugs or thyroid hormones the dose of the digitalis glycosides may need to be adjusted appropriately. Hyperthyroid patients may need to have their digitalis dose gradually reduced as treatment proceeds (because initially they are relatively resistant to the effects of digitalis and start off needing higher doses). They are also relatively insensitive to the chronotropic effects of digitalis.[6,7] Hypothyroid patients on the other hand may need a gradually increasing dose (because initially they are relatively sensitive to digitalis).[5,6] In either of these situations it would be prudent to monitor serum digoxin levels and glomerular filtration rate as treatment continues. The modest reduction in digoxin levels caused by carbimazole in healthy subjects does not fit with the need to decrease digoxin doses when antithyroid drugs are used in patients. However, the situation in healthy subjects may not accurately reflect that in subjects with thyroid disease.

1. Petereit G, Ramesh Rao B, Siepmann M, Kirch W. Influence of carbimazole on the steady state serum levels and haemodynamic effects of digoxin in healthy subjects. *Eur J Clin Pharmacol* (1995) 49, A159.
2. Rao BR, Petereit G, Ebert U, Siepmann M, Kirch W. Influence of carbimazole on the steady state serum levels and haemodynamic effects of digoxin in healthy subjects. *Therapie* (1995) 50 (Suppl), 406.
3. Rao R, Petereit G, Ebert U, Kirch W. Influence of carbimazole on serum levels and haemodynamic effects of digoxin. *Clin Drug Invest* (1997) 13, 350–4.
4. Gasińska T, Izbicka M, Dec R. Digoxin pharmacokinetics in hyperthyroid patients treated with methimazole. *J Endocrinol* (1997) 152 (Suppl), P285.
5. Croxson MS, Ibbertson HK. Serum digoxin in patients with thyroid disease. *BMJ* (1975) 3, 566–8.
6. Lawrence JR, Sumner DJ, Kalk WJ, Ratcliffe WA, Whiting B, Gray K, Lindsay M. Digoxin kinetics in patients with thyroid dysfunction. *Clin Pharmacol Ther* (1977) 22, 7–13.
7. Huffman DH, Klaassen CD, Hartman CR. Digoxin in hyperthyroidism. *Clin Pharmacol Ther* (1977) 22, 533–8.

Digoxin + Ticlopidine

In 15 subjects ticlopidine 250 mg twice daily for 10 days reduced the peak serum levels and AUC of digoxin by about 10%.[1] This reduction is small and unlikely to be of clinical importance.

1. Vargas R, Reitman M, Teitelbaum P, Ryan JR, McMahon FG, Jain AK, Ryan M, Regel G. Study of the effect of ticlopidine on digoxin blood levels. *Clin Pharmacol Ther* (1988) 43, 176.

Digoxin + Tiludronate

Tiludronate does not appear to affect the pharmacokinetics of digoxin.

Clinical evidence, mechanism, importance and management

A study in 12 healthy subjects found that tiludronate, 600 mg daily for 2 days then 400 mg daily for the next 10 days, caused no significant changes in the pharmacokinetics of digoxin 250 micrograms daily.[1] No digoxin dose adjustments would appear to be needed on concurrent use.

1. Sanofi Winthrop. Data on file, June 1996.

Digoxin + Tolvaptan

Tolvaptan may modestly increase the levels of digoxin.

Clinical evidence, mechanism, importance and management

In a study in 14 healthy subjects, tolvaptan 60 mg daily for 5 days increased the steady-state AUC and maximum plasma concentration of digoxin by about 30% and 20%, respectively. There was no change in heart rate, blood pressure, ventricular rate or QTc interval, and no change in tolvaptan pharmacokinetics, when compared with a single dose given alone.[1] Digoxin is a substrate of the drug transporter protein P-glycoprotein, which is inhibited by tolvaptan.[2] Therefore concurrent use results in the modestly increased digoxin exposure seen in the study; however, this modest increase is probably of little clinical importance in most patients. The UK manufacturer advises that patients receiving both digoxin and tolvaptan should be monitored for excessive digoxin effects,[3] (e.g. bradycardia) which would seem prudent, particularly for those patients with digoxin levels already at the high end of the therapeutic range.

1. Shoaf SE, Wang Z, Mallikaarjun S, Bricmont P, Bramer SL. Lack of clinically significant interaction between steady state tolvaptan and digoxin in healthy volunteers. *Clin Pharmacol Ther* (2004) 75, P37.
2. Samsca (Tolvaptan). Otsuka America Pharmaceutical Inc. US Prescribing information, May 2009.
3. Samsca (Tolvaptan). Otsuka Pharmaceuticals (UK) Ltd. UK Summary of product characteristics, August 2009.

Digoxin + Tramadol

Some UK manufacturers state that digoxin toxicity has occurred rarely during the concurrent use of digoxin and tramadol.[1,2] There appear to be no published reports of an interaction, and in the absence of any more information, it is difficult to judge the general relevance of these cases.

1. Zamadol (Tramadol hydrochloride). Meda Pharmaceuticals. UK Summary of product characteristics, August 2009.
2. Dromadol (Tramadol hydrochloride). Napp Pharmaceuticals Ltd. UK Summary of product characteristics, April 2008.

Digoxin + Trapidil

Trapidil does not alter digoxin levels, but may oppose some of its effects.

Clinical evidence, mechanism, importance and management

In 10 healthy subjects, trapidil 400 mg daily for 8 days had no effect on the steady-state serum levels of digoxin 375 micrograms daily. It was noted that the positive chronotropic effect of trapidil opposed the negative chronotropic effect of digoxin, which should be remembered when using both drugs, but overall no adverse effects that would prevent concurrent use were noted.[1]

1. Sziegoleit W, Weiss M, Fahr A, Scharfe S. Trapidil does not affect serum levels and cardiotonic action of digoxin in healthy humans. *Jpn Circ J* (1987) 51, 1305–9.

Digoxin + Trazodone

A rise in digoxin levels, accompanied by toxicity in one instance, has been seen when two patients taking digoxin were given trazodone.

Clinical evidence, mechanism, importance and management

An elderly woman taking digoxin 125 micrograms daily (and also taking quinidine, clonidine and triamterene with hydrochlorothiazide) complained of nausea and vomiting within about 2 weeks of starting to take trazodone (initially 50 mg, increasing to 300 mg daily over 11 days). Her serum digoxin levels had risen more than threefold (from 0.8 to 2.8 nanograms/mL). The digoxin was stopped and then restarted at half the original dose, which maintained therapeutic levels.[1] The patient had poor renal function, but this did not change significantly during this incident. Another case report also describes raised digoxin levels, apparently caused by trazodone.[2]

Direct information seems to be limited to these two reports, which is insufficient evidence to make any general recommendations; however, if a patient taking digoxin develops otherwise unexplained adverse effects, it may be prudent to consider trazodone as a possible cause.

1. Rauch PK, Jenike MA. Digoxin toxicity possibly precipitated by trazodone. *Psychosomatics* (1984) 25, 334–5.
2. Knapp JE. Mead Johnson Pharmaceutical Newsletter, 1983.

Digoxin + Trimethoprim

Digoxin levels can be modestly increased by about 22% by trimethoprim, although some individuals may show a much greater rise.

Clinical evidence

(a) Elderly patients

After taking trimethoprim 200 mg twice daily for 14 days the mean serum digoxin levels in 9 elderly patients (aged 62 to 92 years) had risen by an average of 22% (from 0.9 to 1.2 nanograms/mL). One patient had a 75% rise. A 34% increase in mean serum creatinine was also seen. When the trimethoprim was withdrawn, the serum digoxin levels returned to their previous value.[1,2]

(b) Young healthy adult subjects

Trimethoprim 200 mg twice daily for 10 days did not affect the total body clearance of a single 1-mg intravenous dose of digoxin in 6 young healthy subjects (aged 24 to 31 years). Renal clearance was reduced, but this was compensated for by an increase in extra-renal clearance.[2]

Mechanism

It is suggested that trimethoprim reduces the renal excretion of digoxin.[1,2] The paradoxical finding between the elderly patients and the young healthy subjects may be the age difference, probably as the elderly patients may not be able to accommodate an increase in extra-renal digoxin clearance.

Importance and management

Information seems to be limited to the information cited. Although the serum digoxin rise in the elderly was modest, it would seem prudent to monitor the effects because some individuals can apparently experience a marked rise. Reduce the digoxin dose if necessary. Trimethoprim is contained in **co-trimoxazole** but it is not known whether prophylactic doses of co-trimoxazole (160 mg trimethoprim a day, from 960 mg co-trimoxazole) will interact to a clinically significant extent. An interaction would seem likely with high-dose co-trimoxazole regimens and care with any co-trimoxazole regimen is needed in the elderly.

1. Kastrup J, Bartram R, Petersen P, Hansen JM. Trimetoprims indvirkning på serum-digoksin og serum-kreatinin. *Ugeskr Laeger* (1983) 145, 2286–8.
2. Petersen P, Kastrup J, Bartram R, Hansen JM. Digoxin-trimethoprim interaction. *Acta Med Scand* (1985) 217, 423–7.

Digoxin + Trimetazidine

Trimetazidine does not appear to affect the pharmacokinetics of digoxin.

Clinical evidence, mechanism, importance and management

In 13 healthy subjects, trimetazidine 20 mg twice daily for at least 14 days did not affect the pharmacokinetics of a single 500-microgram dose of digoxin.[1] These results suggest that the dose of digoxin is unlikely to need adjusting in patients who are also given trimetazidine.

1. Edeki TI, Johnston A, Campbell DB, Ings RMJ, Brownsill R, Genissel P, Turner P. An examination of the possible pharmacokinetic interaction of trimetazidine with theophylline, digoxin and antipyrine. *Br J Clin Pharmacol* (1989) 26, 657P.

Digoxin + Trospium

In a study in 40 healthy subjects, trospium 20 mg twice daily for 12 days did not affect the pharmacokinetics of a single 500-microgram dose of digoxin elixir given on day 7.[1]

1. Sandage B, Sabounjian L, Shipley J, Profy A, Lasseter K, Fox L, Harnett M. Predictive power of an in vitro system to assess drug interactions of an antimuscarinic medication: a comparison of in vitro and in vivo drug-drug interaction studies of trospium chloride with digoxin. *J Clin Pharmacol* (2006) 46, 776–84.

Digoxin + Urapidil

Urapidil does not appear to affect the pharmacokinetics of digoxin.

Clinical evidence, mechanism, importance and management

In 12 healthy subjects, urapidil 60 mg twice daily on days 5 to 8 had no significant effects on the serum levels of digoxin 250 micrograms twice daily on day one, then 250 micrograms daily on days 2 to 8. Blood pressures and pulse rates were not significantly changed.[1] No special precautions seem necessary if both drugs are given.

1. Solleder P, Haerlin R, Wurst W, Klingmann I, Mosberg H. Effect of urapidil on steady-state serum digoxin concentration in healthy subjects. *Eur J Clin Pharmacol* (1989) 37, 193–4.

Digoxin + Ursodeoxycholic acid (Ursodiol)

Ursodeoxycholic acid modestly reduces the exposure to digoxin.

Clinical evidence, mechanism, importance and management

In a study in 8 healthy subjects, ursodeoxycholic acid 13 mg/kg daily for 19 days decreased the oral absorption and the AUC_{0-4} of a single 500-microgram dose of digoxin given on day 15 by 9% and 17%, respectively. The pharmacokinetics of a single intravenous dose of digoxin were not affected by ursodeoxycholic acid. It was suggested that the reduction in the absorption of oral digoxin may have occurred because ursodeoxycholic acid may induce P-glycoprotein, which is involved in the transport of digoxin.[1] Evidence for an interaction between digoxin and ursodeoxycholic acid appears to be limited to the study cited, but an interaction would appear to be established. However, the changes seen were small, and seem unlikely to be clinically relevant. Therefore, based on this study, no adjustment would seem to be necessary in the dose of digoxin, if ursodeoxycholic acid is also given.

1. Becquemont L, Glaeser H, Drescher S, Hitzl M, Simon N, Murdter TE, Heinkele G, Hofmann U, Schaefer C, Burk O, Verstuyft C, Eichelbaum M, Fromm MF. Effects of ursodeoxycholic acid on P-glycoprotein and cytochrome P450 3A4–dependent pharmacokinetics in humans. *Clin Pharmacol Ther* (2006) 79, 449–60.

Digoxin + Valaciclovir

Valaciclovir appears not to interact with digoxin.

Clinical evidence, mechanism, importance and management

In a randomised study, 12 healthy subjects were given 1 g of oral valaciclovir alone, two 750-microgram doses of digoxin alone, valaciclovir 1 g after the second of two 750-microgram doses of digoxin given 12 hours apart, and finally valaciclovir 1 g three times daily for 8 days starting 12 hours before the first digoxin dose.[1] It was found that no clinically significant changes occurred in the pharmacokinetics of either drug and no ECG changes were seen. It was therefore concluded that no dose adjustments of either drug are needed if they are given concurrently.[1] Valaciclovir is a prodrug of **aciclovir**, it therefore also seems unlikely that an interaction will occur between **aciclovir** and digoxin.

1. Soul-Lawton JH, Weatherley BC, Posner J, Layton G, Peck RW. Lack of interaction between valaciclovir, the L-valyl ester of aciclovir and digoxin. *Br J Clin Pharmacol* (1998) 45, 87–9.

Digoxin + Valspodar

Valspodar increases the AUC of digoxin two to threefold.

Clinical evidence, mechanism, importance and management

In a study, 12 healthy subjects were given digoxin 1 mg on day one, followed by 125 micrograms daily for the next 10 days. Starting on day 7 they were also given a single 400-mg dose of valspodar, followed by valspodar 200 mg twice daily for the next 4 days. The steady-state digoxin AUC was increased by 76% after the first dose of valspodar, and by the end of valspodar dosing it had increased by 211%. This was apparently due to a 73% reduction in digoxin renal clearance and a 58% reduction in non-renal clearance, probably because of reduced tubular secretion, reduced biliary elimination, and increased intestinal absorption caused by P-glycoprotein inhibition. No symptoms of digitalis toxicity were seen and there were no changes in vital signs or ECG parameters.[1]

Information seems to be limited to this study in healthy subjects but it suggests that the digoxin dose should be reduced if valspodar is given. An initial 50% reduction has been suggested.

1. Kovarik JM, Rigaudy L, Guerret M, Gerbeau C, Rost K-L. Longitudinal assessment of a P-glycoprotein-mediated drug interaction of valspodar on digoxin. *Clin Pharmacol Ther* (1999) 66, 391–400.

Digoxin + Vancomycin

In one early study, vancomycin prolonged the half-life of digoxin and increased its serum levels from 1.6 nanograms/mL to 3 nanograms/mL. It was suggested that this effect might be as a result of reduced renal clearance.[1] This appears to be the only evidence of a possible interaction, and as such, no general recommendations can be made.

1. Halawa B. Interakcje digoksyny z cefradina (Sefril), tetracylina (Tetracyclinum), gentamycyna (Gentamycin) i wankomycyna (Vancocin). *Pol Tyg Lek* (1984) 39, 1717–20.

Digoxin + Vardenafil

Vardenafil does not appear to interact with digoxin.

Clinical evidence, mechanism, importance and management

In a placebo-controlled study, 19 healthy subjects were given digoxin 375 micrograms daily for 28 days, with vardenafil 20 mg daily on alternate days from day 16 to day 28. The pharmacokinetics of digoxin were not significantly changed by vardenafil, and there was no alteration in vital signs, ECG readings and laboratory parameters (not stated). The incidence of mild to moderate headache rose slightly from 7 out of 19 with placebo to 13 out of 19 with digoxin.[1] There would appear to be no reason to monitor digoxin levels in patients given vardenafil.

1. Rohde G, Bauer R-J, Unger S, Ahr G, Wensing G. Vardenafil, a new selective PDE5 inhibitor, produces no interaction with digoxin. *Pharmacotherapy* (2001) 21, 1254.

Digoxin + Vasodilators

Dihydralazine, and sodium nitroprusside or hydralazine infusions, can reduce digoxin levels Isosorbide dinitrate did not alter digoxin pharmacokinetics in one study.

Clinical evidence, mechanism, importance and management

(a) Hydralazine or Sodium nitroprusside

An experimental study in 8 patients with congestive heart failure found that when they were given either sodium nitroprusside by infusion (7 to 425 micrograms/minute) or hydralazine by intravenous injection (5 mg every 10 to 20 minutes to a total dose of 10 to 60 mg) the total renal digoxin clearance was increased by about 50% by both drugs and the serum digoxin levels were decreased by 20% by the nitroprusside and 11% by the hydralazine.[1] Another study found that **dihydralazine** shortened the half-

life of digoxin and reduced its serum levels, but did not affect digoxin bioavailability.[2]

It is not known whether these changes would be sustained during long-term concurrent use, but the changes in the levels seen were relatively modest. A clinically important interaction seems unlikely, but ideally longer-term studies are needed to confirm this.

(b) Isosorbide dinitrate

In a crossover study in 8 patients with chronic heart failure, given digoxin 250 micrograms daily for 20 days with isosorbide dinitrate 10 mg three times daily for the last 10 days, there was no change in the mean steady-state concentration, AUC or half-life of digoxin.[3]

1. Cogan JJ, Humphreys MH, Carlson CJ, Benowitz NL, Rapaport E. Acute vasodilator therapy increases renal clearance of digoxin in patients with congestive heart failure. *Circulation* (1981) 64, 973–6.
2. Halawa B, Mazurek W. Interakcja digoksyny z dihydralazyną I prazosyną. *Pol Tyg Lek* (1986) 41, 1521–3.
3. Mahgoub AA, El-Medany AH, Abdulatif AS. A comparison between the effects of diltiazem and isosorbide dinitrate on digoxin pharmacodynamics and kinetics in the treatment of patients with chronic ischemic heart failure. *Saudi Med J* (2002) 23, 725–31.

Digoxin + Vitamin E substances

Alpha tocoferil acetate had no effect on digoxin pharmacokinetics, but vitamin E formulations with polyethylene glycol might.

Clinical evidence, mechanism, importance and management

In a study in healthy subjects, **alpha tocoferil acetate** 400 units twice daily for 15 days did not affect the pharmacokinetics of a single 500-microgram dose of digoxin given on day 15. This was in contrast to a formulation of vitamin E containing polyethylene glycol (**alpha tocoferil acid succinate**), which altered digoxin pharmacokinetics (amount not stated) without altering its ECG effects.

It was suggested that the effect of polyethylene glycol on digoxin was via P-glycoprotein inhibition,[1] see also 'Digoxin + Surfactant excipients', p.1116.

1. Chan L, Humma LM, Schriever CA, Fahsingbauer BS, Dominguez CP, Baum CL. Vitamin E formulation affects digoxin absorption by inhibiting P-glycoprotein (P-GP) in humans. *Clin Pharmacol Ther* (2004) 75, P95.

Digoxin + Zileuton

Zileuton does not appear to affect the pharmacokinetics of digoxin.

Clinical evidence, mechanism, importance and management

In a placebo-controlled study, 12 healthy subjects were given zileuton 600 mg every 6 hours for 13 days, with digoxin 250 micrograms daily from days 1 to 11. Zileuton had no effect on the steady-state pharmacokinetics of digoxin, although the time to reach maximum plasma levels was reduced from 1.43 hours to 0.95 hours. Concurrent use was well tolerated.[1] This evidence suggests that no digoxin dose adjustment is necessary if zileuton is also given.

1. Awni WM, Hussein Z, Cavanaugh JH, Granneman GR, Dube LM. Assessment of the pharmacokinetic interaction between zileuton and digoxin in humans. *Clin Pharmacokinet* (1995) 29 (Suppl 2), 92–7.

26

Diuretics

The majority of the interactions of the diuretics appear to be pharmacodynamic in nature, that is, they appear to be due to the combined effects of the diuretic and the other interacting drug. Obvious examples of this would be hypotension caused by the use of a loop diuretic and a beta blocker, or hyperkalaemia caused by the use of an ACE inhibitor and a potassium-sparing diuretic. Some commonly accepted interactions appear to be sparsely documented, most probably because they are perceived to be a predictable effect of using two drugs with similar actions together. 'Table 26.1', (below) lists the major diuretic drug groups classified by their effect on potassium. Carbonic anhydrase inhibitors are included under potassium-depleting diuretics, but note that hypokalaemia caused by this type of drug is said to be transient and rarely clinically significant.

Eplerenone, a selective aldosterone antagonist similar to spironolactone, is metabolised by the cytochrome P450 isoenzyme CYP3A4 and is therefore affected by other drugs that are inhibitors or inducers of this enzyme.

The interactions covered in this section are mainly those in which the diuretic is affected. There are many other interactions throughout the publication where diuretics affect the actions of other drugs.

Table 26.1 Diuretics

Group	*Drugs*
Potassium-depleting diuretics	
Carbonic anhydrase inhibitors*	Acetazolamide, Diclofenamide (Dichlorphenamide)
Loop diuretics	Bumetanide, Etacrynic acid, Furosemide, Piretanide, Torasemide
Thiazides and related diuretics	Altizide, Bemetizide, Bendroflumethiazide, Benzthiazide, Butizide, Chlorothiazide, Chlortalidone, Clopamide, Cyclopenthiazide, Cyclothiazide, Epitizide, Hydrochlorothiazide, Hydroflumethiazide, Indapamide, Mefruside, Methyclothiazide, Metipamide, Metolazone, Teclothiazide, Trichlormethiazide, Xipamide
Potassium-sparing diuretics	
Aldosterone inhibitors	Eplerenone, Potassium canrenoate, Spironolactone
Other	Amiloride, Triamterene

*Note that hypokalaemia caused by this type of drug is said to be transient and rarely clinically significant

Acetazolamide + NSAIDs

A woman developed acute renal failure following retinal surgery, after the postoperative use of a total of 2 g of acetazolamide, 80 g of mannitol and 700 mg of ketoprofen over a 2-day period.[1] There appear to be no other similar case reports, and therefore the significance of this case is unclear. However, note that other interactions have been reported with related drugs. For instance, 'loop diuretics', (p.1125), are known to increase the risk of NSAID-induced acute renal failure, and a severe toxic reaction has been reported in patients receiving concurrent high-dose aspirin and acetazolamide, see 'Aspirin or other Salicylates + Carbonic anhydrase inhibitors', p.151.

1. Truc C, Rigal E, Pernot A, Vaudelin G, Boulétreau P. Anti-inflammatoires non stéroïdiens et diurétiques: une association à risque néphrotoxique. *Ann Fr Anesth Reanim* (2000) 19, 675–7.

Acetazolamide + Sodium bicarbonate

Acetazolamide is associated with the development of renal calculi (usually calcium phosphate) and it has been claimed that sodium bicarbonate, even on alternate days, potentiates the risk of calculus formation.[1] There seem to be no case reports describing an adverse interaction, and so the general significance of this suggested interaction is unclear.

1. Rubenstein MA, Bucy JG. Acetazolamide-induced renal calculi. *J Urol (Baltimore)* (1975) 114, 610–12.

Acetazolamide + Timolol

The use of acetazolamide tablets with timolol eye drops resulted in severe mixed acidosis in a patient with chronic obstructive pulmonary disease.

Clinical evidence, mechanism, importance and management

An elderly man with severe chronic obstructive pulmonary disease was given oral acetazolamide 750 mg daily and timolol maleate 0.5% eye drops, one drop in each eye twice daily, as premedication to reduce ocular hypertension before surgery for glaucoma. Five days later he developed progressively worsening dyspnoea and he was found to have a severe, mixed acidosis.[1] This seems to have been caused by the additive effects of acetazolamide, which blocked the excretion of hydrogen ions in the kidney, and the bronchoconstrictor effects of the timolol, which was absorbed in sufficient amounts to exacerbate the airway obstruction in this patient, and thereby reduced the respiration. This isolated case emphasises the potential risks of using beta blockers, even as non-systemic preparations, such as eye drops, in patients with obstructive pulmonary disease. The manufacturers of acetazolamide note that it should be used with caution in those with pulmonary obstruction or emphysema because of the increased risk of acidosis.[2,3] This is, in part, a drug-disease interaction.

1. Boada JE, Estopa R, Izquierdo J, Dorca J, Manresa F. Severe mixed acidosis by combined therapy with acetazolamide and timolol eyedrops. *Eur J Respir Dis* (1986) 68, 226–8.
2. Diamox (Acetazolamide). Wyeth Pharmaceuticals. UK Summary of product characteristics, February 2004.
3. Acetazolamide Tablets. Taro Pharmaceuticals USA Inc. US Prescribing information, March 2005.

Diuretics + Aliskiren

Aliskiren reduces the plasma levels of furosemide, but does not appear to affect the pharmacokinetics of hydrochlorothiazide. Aliskiren may cause hypotension in patients receiving high doses of diuretics and may possibly increase serum potassium levels in patients receiving potassium-sparing diuretics.

Clinical evidence, mechanism, importance and management

The AUC and maximum plasma level of **furosemide** were reduced by about 30% and 50%, respectively, by the concurrent use of aliskiren.[1,2] The manufacturers therefore say that the effects of **furosemide** may be reduced when aliskiren is started.[2]

In a study in healthy subjects aliskiren 300 mg daily did not significantly affect the pharmacokinetics of **hydrochlorothiazide** 25 mg daily. The AUC of aliskiren was not affected by **hydrochlorothiazide**, its steady state maximum plasma level was reduced by 22%; however, this was not considered to be clinically relevant. There was an increased incidence of dizziness in subjects receiving aliskiren and **hydrochlorothiazide**, when compared with either drug alone, but this might be expected with two effective antihypertensive drugs given to normotensive healthy subjects.[3] Studies in patients with mild-to-moderate hypertension, showed no difference in the rate of dizziness or the incidence of adverse effects with the combination of aliskiren and **hydrochlorothiazide**, when compared with monotherapy.[3,4]

The manufacturers of aliskiren note that in patients with marked volume- and/or salt-depletion, for example those receiving high doses of diuretics, symptomatic hypotension could occur after initiation of treatment with aliskiren. Close medical supervision is required in such patients.[1,2] Based on experience with the use of other substances that affect the renin-angiotensin system, the concurrent use of **potassium-sparing diuretics** and aliskiren may lead to increases in serum potassium and caution is advisable.[1]

1. Rasilez (Aliskiren hemifumarate). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, April 2009.
2. Tekturna (Aliskiren hemifumarate). Novartis. US Prescribing information, December 2007.
3. Vaidyanathan S, Valencia J, Kemp C, Zhao C, Yeh C-M, Bizot M-N, Denouel J, Dieterich HA, Dole WP. Lack of pharmacokinetic interactions of aliskiren, a novel direct renin inhibitor for the treatment of hypertension, with the antihypertensives amlodipine, valsartan, hydrochlorothiazide (HCTZ) and ramipril in healthy volunteers. *Int J Clin Pract* (2006) 60, 1343–56.
4. Villamil A, Chrysant SG, Calhoun D, Schober B, Hsu H, Matrisciano-Dimichino L, Zhang J. Renin inhibition with aliskiren provides additive antihypertensive efficacy when used in combination with hydrochlorothiazide. *J Hypertens* (2007) 25, 217–26.

Diuretics + Liquorice

A case report describes hypokalaemia in a patient who took hydrochlorothiazide and liquorice. This interaction seems possible with liquorice and any potassium-depleting diuretic (i.e. thiazides or loop diuretics).

Clinical evidence, mechanism, importance and management

A 41-year-old woman who presented with hypertension was unsuccessfully treated with atenolol and candesartan. After the addition of **hydrochlorothiazide**, she developed hypokalaemia with muscle cramps and weakness, which persisted for more than 4 weeks after the hydrochlorothiazide was discontinued. The patient had denied eating liquorice sweets, but was found to have been drinking at least 3 litres of liquorice tea daily.[1] Liquorice has mineralocorticoid-like actions, which may lower potassium levels. This effect may be additive with the effects of the potassium-depleting diuretics, which may result in clinically significant hypokalaemia. Evidence is extremely sparse. Consider this interaction in a case of otherwise unexplained hypokalaemia.

1. Brouwers AJBW, van der Meulen J. 'Drophypertensie'; ook door zoethoutthee. *Ned Tijdschr Geneeskd* (2001) 145, 744–7.

Eplerenone + Miscellaneous

Corticosteroids or tetracosactide may potentially reduce the antihypertensive effect of eplerenone, whereas alpha blockers, antipsychotics, amifostine, baclofen, and tricyclic antidepressants may increase its antihypertensive effects. Antacids, cisapride, and midazolam had no effect on eplerenone pharmacokinetics. Eplerenone had no important effect on cisapride, midazolam, warfarin or contraceptive steroid pharmacokinetics.

Clinical evidence, mechanism, importance and management

(a) Antacids

The manufacturer notes that **aluminium**/**magnesium**-containing antacids had no effect on the pharmacokinetics of eplerenone.[1]

(b) Cisapride

A pharmacokinetic study found no interaction between cisapride (a cytochrome P450 isoenzyme CYP3A4 substrate) and eplerenone.[1,2]

(c) Combined hormonal contraceptives

Eplerenone 100 mg daily was given to 24 healthy subjects on days 1 to 11 of a 28-day cycle of a combined hormonal contraceptive (**ethinylestradiol**/**norethisterone** 35 micrograms/1 mg). There was no change in the **ethinylestradiol** AUC, but there was a small 17% increase in the **norethisterone** AUC, which is unlikely to be clinically relevant.[3]

For comment that drospirenone may increase the risk of hyperkalaemia if given with eplerenone or other potassium-sparing diuretics, see 'Drospirenone-containing contraceptives or HRT + Potassium-sparing drugs', p.1197.

(d) Corticosteroids or Tetracosactide (Cosyntropin)

Corticosteroids or tetracosactide can cause fluid and sodium retention and coadministration with eplerenone may potentially reduce the antihypertensive effect.[2]

(e) Drugs that may cause postural hypotension

The manufacturer suggests that there is a risk of increased hypotensive effects and/or postural hypotension if eplerenone is given with **alpha blockers** (e.g. **alfuzosin**, **prazosin**), **tricyclic antidepressants**, **antipsychotics**, **amifostine** and **baclofen**.[2] Increased monitoring would seem prudent.

(f) Midazolam

A pharmacokinetic study has shown no pharmacokinetic interaction between midazolam (a cytochrome P450 isoenzyme CYP3A4 substrate) and eplerenone.[1,2]

(g) Warfarin

Eplerenone did not alter the pharmacokinetics of warfarin to a clinically significant extent.[1,2] However, in the UK the manufacturer still recommends caution when the warfarin dose is near the upper limit of the therapeutic range.[2]

1. Inspra (Eplerenone). Pfizer Inc. US Prescribing information, April 2008.
2. Inspra (Eplerenone). Pfizer Ltd. UK Summary of product characteristics, October 2009.
3. Cook CS, Berry LM, Burton E. Prediction of *in vivo* drug interactions with eplerenone in man from *in vitro* metabolic inhibition data. *Xenobiotica* (2004) 34, 215–28.

Loop diuretics + Aspirin or other Salicylates

Aspirin may reduce the diuretic effect of bumetanide, furosemide, or piretanide, and the venodilation produced by furosemide. The combination of aspirin and furosemide may increase the risk of acute renal failure and salicylate toxicity. The risk of ototoxicity with high doses of salicylates may theoretically be increased by loop diuretics.

Clinical evidence

(a) Bumetanide

In 8 healthy subjects aspirin 640 mg four times daily reduced the 24-hour urinary output in response to bumetanide 1 mg by 18%.[1]

(b) Furosemide

A study in 11 patients with chronic heart failure found that both aspirin 75 mg daily and aspirin 300 mg daily for 14 days reduced the venodilatory effects produced by a single 20-mg intravenous dose of furosemide (as measured by the forearm venous capacitance).[2] Six patients with cirrhosis and ascites had a reduced diuretic response to intravenous furosemide 40 mg given after a single intravenous dose of **lysine aspirin** 450 mg.[3] A further study in 6 patients found that the combination of furosemide and aspirin temporarily reduced creatinine clearance in patients with chronic renal insufficiency.[4]

Studies in healthy subjects similarly found that intravenous aspirin or **lysine aspirin** blunted the diuresis[5,6] and sodium excretion[6] caused by intravenous furosemide, and appeared to increase potassium excretion;[6] the reduced diuretic effect seemed to correlate with an inhibition of proximal tubular secretion.[5] A similar reduction in sodium excretion was found in a study where healthy subjects were given aspirin and furosemide orally.[7]

In contrast, another study in healthy subjects found that oral aspirin 4 g daily did not influence the effects of oral furosemide 40 mg on renal sodium excretion or urinary creatinine excretion.[8]

A study in healthy subjects found that when aspirin 600 mg and furosemide 40 mg were given at the same time there was a significant reduction in the total excretion of salicylates, but when the drugs were given 30 minutes apart the total amount of salicylate excreted increased slightly.[7]

(c) Piretanide

A study in 4 healthy subjects found that intravenous **lysine aspirin** 1 g decreased the diuresis and sodium excretion caused by intravenous piretanide 12 mg.[6]

Mechanism

Uncertain. Aspirin may compete with furosemide for a common secretory mechanism in the proximal tubule.[5,7] In addition, aspirin may also inhibit renal prostaglandins, which appear to mediate the increased renal blood flow induced by loop diuretics in cirrhotics with ascites.[3] Consider also 'Loop diuretics + NSAIDs', p.1125.

Importance and management

The clinical significance of these interactions is unclear. The UK manufacturer of furosemide warns that aspirin may attenuate the action of furosemide and may cause acute renal failure in cases of pre-existing hypovolaemia or dehydration.[9] Note that the European Society of Cardiology (ESC) and American College of Cardiology/American Heart Association (ACC/AHA) heart failure guidelines say that the prophylactic use of aspirin in patients with heart failure has not been proven and there are concerns that it may attenuate the haemodynamic and survival benefits of other drugs. However, antiplatelet drugs are recommended in patients with underlying ischaemic heart disease,[10,11] but aspirin should be avoided in patients with recurrent hospital admissions for worsening heart failure.[10]

The manufacturers also warn that salicylate toxicity may occur if furosemide is given concurrently in patients receiving high doses of salicylates, as in rheumatic disease, because of competitive renal excretory sites.[4,9] High doses of salicylates can be ototoxic, particularly if the patient is dehydrated, and the risk of ototoxicity may theoretically be increased if salicylates are given with other ototoxic drugs, including loop diuretics such as bumetanide, **etacrynic acid** or furosemide.[12,13]

1. Kaufman J, Hamburger R, Matheson J, Flamenbaum W. Bumetanide-induced diuresis and natriuresis: effect of prostaglandin synthetase inhibition. *J Clin Pharmacol* (1981) 21, 663–7.
2. Jhund PS, Davie AP, McMurray JJV. Aspirin inhibits the acute venodilator response to furosemide in patients with chronic heart failure. *J Am Coll Cardiol* (2001) 37, 1234–8.
3. Planas R, Arroyo V, Rimola A, Pérez-Ayuso RM, Rodés J. Acetylsalicylic acid suppresses the renal hemodynamic effect and reduces the diuretic action of furosemide in cirrhosis with ascites. *Gastroenterology* (1983) 84, 247–52.
4. Lasix (Furosemide). Sanofi-Aventis. US Prescribing information, August 2007.
5. Bartoli E, Arras S, Faedda R, Soggia G, Satta A, Olmeo NA. Blunting of furosemide diuresis by aspirin in man. *J Clin Pharmacol* (1980) 20, 452–8.
6. Valette H, Apoil E. Interaction between salicylate and two loop diuretics. *Br J Clin Pharmacol* (1979) 8, 592–4.
7. Oyekan AO, Laniyonu AA, Ashorobi RB. Interaction between frusemide and aspirin. *Gen Pharmacol* (1984) 15, 163–6.
8. Berg KJ. Acute effects of acetylsalicylic acid on renal function in normal man. *Eur J Clin Pharmacol* (1977) 11, 117–23.
9. Lasix (Furosemide). Sanofi-Aventis. UK Summary of product characteristics, November 2006.
10. Swedberg K, Cleland J, Dargie H, Drexler H, Follath F, Komajda M, Tavazzi L, Smiseth OA, Gavazzi A, Haverich A, Hoes A, Jaarsma T, Korewicki J, Lévy S, Linde C, Lopez-Sendon J-L, Nieminen MS, Piérard L, Remme WJ; The Task Force for the diagnosis and treatment of CHF of the European Society of Cardiology. Guidelines for the diagnosis and treatment of chronic heart failure (update 2005). *Eur Heart J* (2005) 26, 1115–40. Available at: http://eurheartj.oxfordjournals.org/cgi/content/full/26/11/1115 (accessed 05/02/10).
11. Hunt SA. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). *J Am Coll Cardiol* (2005) 46, e1–e82. Available at: http://content.onlinejacc.org/cgi/reprint/46/6/e1.pdf (accessed 01/02/10).
12. Yorgason JG, Fayad JN, Kalinec F. Understanding drug ototoxicity: molecular insights for prevention and clinical management. *Expert Opin Drug Safety* (2006) 5, 383–99.
13. Lheureux Ph, Penaloza A. Les vertiges d'origine ototoxique. Ototoxicity-related dysequilibrium. *Rev Med Brux* (2002) 23, A356–A362.

Loop diuretics + Epoprostenol

In a study modelling data from 23 patients with heart failure, an infusion of epoprostenol did not significantly alter the pharmacokinetics of furosemide.[1] Note that the combination of loop diuretics with epoprostenol may lead to an enhanced hypotensive effect.

1. Carlton LD, Patterson JH, Mattson CN, Schmith VD. The effects of epoprostenol on drug disposition II: a pilot study of the pharmacokinetics of furosemide with and without epoprostenol in patients with congestive heart failure. *J Clin Pharmacol* (1996) 36, 257–64.

Loop diuretics + Food

Some studies suggest that food modestly reduces the bioavailability and diuretic effects of furosemide, whereas others suggest that no significant effect occurs. Food does not appear to affect bumetanide or torasemide bioavailability.

Clinical evidence

(a) Solutions or standard tablets

Ten healthy subjects were given **furosemide** 40 mg with and without a standard breakfast. Food reduced the peak plasma levels and bioavailability of **furosemide**, by 55% and about 30%, respectively.[1] The results were almost identical when 5 of the subjects were given a heavy meal.[1] Furthermore, the diuresis over 10 hours was reduced by 21% (from 2072 to 1640 mL) and the diuresis over 24 hours was reduced by 15% (from 2668 to 2270 mL) when **furosemide** was taken with breakfast.[1]

A study in 10 patients with chronic respiratory failure also found that food decreased **furosemide** absorption and bioavailability; the mean 24-hour urinary recovery of unchanged drug was 11.5 mg and 9.41 mg, when the **furosemide** was given before and after food, respectively. In addition, when the data from these patients was compared with that from 11 healthy fasted subjects, the **furosemide** bioavailability was found to be lower, possibly due to enhanced glucuronidation and incomplete drug absorption. The diuretic effect was also lower in patients than healthy subjects; however, when **furosemide** was taken after food there was no significant change in the resulting diuresis, when compared with the fasting state.[2]

A comparative study in healthy subjects found that the absorption of both **bumetanide** 2 mg (9 subjects) and **furosemide** 40 mg (8 subjects), given as *solutions*, was delayed, and peak plasma levels were reduced, by a standard breakfast.[3] However, although food reduced the oral bioavailability of **furosemide** by about one-third, from 76% to 43%, the bioavailability of **bumetanide** was not significantly reduced (75% with food and 84% fasting). Food delayed the absorption but did not significantly alter the bioavailability of **furosemide** as tablets or solutions in two other studies.[4,5] In one of these studies, there was no difference in diuresis between fed and fasting subjects.[5]

A study in 14 healthy subjects given oral **torasemide** 10 mg found that administration with food decreased the absorption rate of **torasemide**, but did not affect the extent of absorption, when compared with the fasting state.[6]

(b) Sustained-release tablets

In a single-dose, crossover study in 28 subjects given two different controlled-release formulations of **furosemide** 60 mg, the absorption of one preparation (*Furix Retard*) was reduced by about 32% when it was given with breakfast, but the extent of absorption of the other formulation (*Lasix Retard*) was *increased* by about 18%. In the fasting phase of the study, *Furix Retard* had a higher extent and rate of absorption than *Lasix Retard*. However, the differences in diuresis and total natriuresis between the formulations, and between the fed and fasted state, were minor.[7] Another study suggested that **furosemide** extended-release tablets, which use an erosional matrix designed to retain the preparation in the stomach and deliver **furosemide** to the duodenum and upper jejunum over 6 hours, should be given in the fed state to ensure that the formulation remains in the stomach for long enough for absorption of **furosemide** to occur.[8]

Mechanism

Not understood.

Importance and management

Information about the effect of food on **furosemide** absorption is somewhat contradictory. Of the five studies using solutions or standard tablets, three found that the bioavailability of furosemide was modestly reduced by food (by about 30%) and the other two found no effect. Similarly, one study found a reduction in diuresis, whereas two others found no clinically relevant decrease in diuresis. It would also seem that the absorption of controlled-release formulations of furosemide may be modestly affected by food, but this may lead to increased absorption depending on the preparation.[7] The authors of this study noted that the amount of furosemide absorbed did not correlate with the extent of diuresis, and concluded that the urinary excretion profile of furosemide may be more important for producing diuresis than the amount of furosemide absorbed. Food does not appear to affect the bioavailability of **bumetanide** given as solution or **torasemide** tablets.

It would seem that furosemide, bumetanide and torasemide can be given to most patients without regard to meal times, although in some patients, such as those with heart failure or renal failure, reduced furosemide absorption may decrease urinary excretion of the drug and the diuretic threshold may not be achieved. In such patients giving furosemide without food might maximize the chance of achieving a diuretic response.[9]

1. Beermann B, Midskov C. Reduced bioavailability and effect of furosemide given with food. *Eur J Clin Pharmacol* (1986) 29, 725–7.
2. Ogata H, Kawatsu Y, Maruyama Y, Machida K, Haga T. Bioavailability and diuretic effect of furosemide during long-term treatment of chronic respiratory failure. *Eur J Clin Pharmacol* (1985) 28, 53–9.
3. McCrindle JL, Li Kam Wa TC, Barron W, Prescott LF. Effect of food on the absorption of frusemide and bumetanide in man. *Br J Clin Pharmacol* (1996) 42, 743–6.
4. Hammarlund MM, Paalzow LK, Odlind B. Pharmacokinetics of furosemide in man after intravenous and oral administration. Application of moment analysis. *Eur J Clin Pharmacol* (1984) 26, 197–207.
5. Kelly MR, Cutler RE, Forrey AW, Kimpel BM. Pharmacokinetics of orally administered furosemide. *Clin Pharmacol Ther* (1974) 15, 178–86.
6. Kramer WG. Effect of food on the pharmacokinetics and pharmacodynamics of torsemide. *Am J Ther* (1995) 2, 499–503.
7. Paintaud G, Alván G, Eckernäs S-Å, Wakelkamp M, Grahnén A. The influence of food intake on the effect of two controlled release formulations of furosemide. *Biopharm Drug Dispos* (1995) 16, 221–32.
8. Berner B, Cowles VE. Case studies in swelling polymeric gastric retentive tablets. *Expert Opin Drug Deliv* (2006) 3, 541–8.
9. Bard RL, Bleske BE, Nicklas JM. Food: an unrecognized source of loop diuretic resistance. *Pharmacotherapy* (2004) 24, 630–7.

Loop diuretics + H_2-receptor antagonists

Ranitidine and cimetidine may cause a moderate increase in the bioavailability of furosemide, but with no associated increase in diuretic effect. Cimetidine appears not to interact with torasemide.

Clinical evidence, mechanism, importance and management

(a) Furosemide

In a study in 6 healthy subjects, a single 400-mg dose of **cimetidine** increased the mean AUC of furosemide by one-third, although there was wide interpatient variation. However, there were no changes in the diuretic effects of furosemide or in the pharmacokinetics of cimetidine, and an associated study using multiple doses of **cimetidine** over 5 days found no pharmacokinetic or pharmacodynamic interaction.[1] A similar study in patients with hepatic cirrhosis also found that **cimetidine** does not interact with furosemide.[2]

Eighteen healthy subjects were given oral furosemide 40 mg one hour after intravenous **ranitidine** 50 mg or saline. The **ranitidine** increased the AUC of furosemide by 28% and increased the maximum serum levels by 37%.[3] The effects of furosemide could possibly be slightly increased by **ranitidine**, but the clinical importance of this is probably small. No special precautions seem necessary.

(b) Torasemide

In 11 healthy subjects **cimetidine** 300 mg four times daily for 3 days was found to have no effect on the pharmacokinetics of a single 10-mg oral dose of torasemide, nor were there any changes in the volume of urine or the excretion of sodium, potassium or chloride.[4]

1. Rogers HJ, Morrison P, House FR, Bradbrook ID. Effect of cimetidine on the absorption and efficacy of orally administered furosemide. *Int J Clin Pharmacol Ther Toxicol* (1982) 20, 8–11.
2. Sanchis Closa A, Lambert C, du Souich P. Lack of effect of cimetidine on furosemide kinetics and dynamics in patients with hepatic cirrhosis. *Int J Clin Pharmacol Ther Toxicol* (1993) 31, 461–6.

3. Müller FO, De Vaal AC, Hundt KL, Luus HG. Intravenous ranitidine enhances furosemide bioavailability. *Klin Pharmakol Akt* (1993) 4, 26.
4. Kramer WG. Lack of effect of cimetidine on torsemide pharmacokinetics and pharmacodynamics in healthy subjects. *Int Congr Ser* (1993), 361–4.

Loop diuretics + NSAIDs

The antihypertensive and diuretic effects of the loop diuretics appear to be reduced by NSAIDs, including coxibs, although the extent of this interaction largely depends on individual NSAIDs. Diuretics increase the risk of NSAID-induced acute renal failure. The concurrent use of NSAIDs with loop diuretics may exacerbate congestive heart failure and increase the risk of hospitalisation. Some NSAIDs may theoretically increase the risk of ototoxicity associated with loop diuretics.

Clinical evidence

Various large epidemiological studies and meta-analyses of clinical studies have been conducted to assess the effect of NSAIDs on blood pressure in patients taking **antihypertensives**, and the findings of these are summarised in 'Table 23.2', (p.1027). In these studies, NSAIDs were not always associated with an increase in blood pressure, and the maximum increase was 6.2 mmHg. The effect has been shown for both coxibs and non-selective NSAIDs. In two meta-analyses,[1,2] the effects were evaluated by NSAID. The confidence intervals for all the NSAIDs overlapped, showing that there was no statistically significant difference between the NSAIDs, with the exception of the comparison between **indometacin** and **sulindac** in one analysis.[2] Nevertheless, an attempt was made at ranking the NSAIDs based on the means. In one analysis,[1] the effect was greatest for **piroxicam**, **indometacin**, and **ibuprofen**, intermediate for **naproxen**, and least for **sulindac** and **flurbiprofen**. In the other meta-analysis,[2] the effect was greatest for **indometacin** and **naproxen**, intermediate for **piroxicam**, and least for **ibuprofen** and **sulindac**. An attempt was also made to evaluate the effect by **antihypertensive** in one analysis.[1] The mean effect was greatest for beta blockers, intermediate for vasodilators (includes ACE inhibitors and calcium-channel blockers), and least for **diuretics**. However, the differences between the groups were not significant.

A case-control study using the UK General Practice Research Database found that current NSAID use increased the risk of acute renal failure (relative risk 3.2 compared with no NSAID use) and this risk was further increased with concurrent **diuretic** use (relative risk 11.6).[3] Note that the risk of renal complications appear to be similar with coxibs as with non-specific NSAIDs.[4]

Individual clinical reports and clinical or pharmacological studies of the effects of specific NSAIDs on diuretics are outlined in the subsections below and in 'Table 26.2', (p.1126).

A. Bumetanide

(a) Celecoxib and other Coxibs

A patient taking celecoxib with bumetanide developed a moderately raised serum creatinine. Another patient taking an ACE inhibitor, spironolactone and bumetanide developed a severely raised serum creatinine, hyperkalaemia, and worsening of congestive heart failure shortly after starting celecoxib.[5] A similar case occurred in another patient taking bumetanide about 8 days after **rofecoxib** was started.[5]

(b) Indometacin

In two studies, a single 100-mg dose of indometacin was found to reduce the bumetanide-induced output of urine, sodium and chloride (but not potassium) by about 25%.[6-8] There are other reports confirming this interaction between bumetanide and indometacin, including a clinical study,[9] and a report of a patient who developed heart failure as a result of this interaction.[10]

(c) Sulindac

A study in 8 healthy subjects found that a single 300-mg dose of sulindac did not significantly reduce the diuretic response (measured by urinary volume, and urinary excretion of sodium, potassium, and chloride) to a single 1-mg dose of bumetanide.[11] However, another study in 9 healthy subjects found that pretreatment with sulindac 200 mg twice daily for 5 days reduced the diuretic effect of a single 1-mg dose of bumetanide (mean urine flow rate after 2 hours reduced by 21% and cumulative sodium excretion at 3 hours reduced by 22%).[12]

(d) Tolfenamic acid

A study in 8 healthy subjects found that tolfenamic acid 300 mg reduced the diuretic response (measured by urinary volume, and urinary excretion of sodium, potassium, and chloride) to a single 1-mg dose of bumetanide by 34% at 2 hours.[11]

B. Furosemide

A comparison of four NSAIDs with different chemical structures and different potencies for inhibiting urinary prostaglandin E_2 synthesis found that **flurbiprofen**, **indometacin**, **piroxicam** and **sulindac** were equipotent in reducing furosemide-stimulated sodium excretion and creatinine clearance.[13]

(a) Azapropazone

Ten healthy subjects had no change in their urinary excretion in response to furosemide 40 mg daily when they were also given azapropazone 600 mg twice daily. The furosemide did not antagonise the uricosuric effects of the azapropazone.[14]

(b) Celecoxib and other Coxibs

In a placebo-controlled study, 7 patients with cirrhosis and ascites were given a single 40-mg intravenous dose of furosemide before and after receiving celecoxib 200 mg twice daily for 5 doses. It was found that this short-term use of celecoxib did not reduce the natriuretic or diuretic effects of furosemide.[15]

Two patients with a history of chronic heart failure, taking furosemide 40 or 80 mg daily, developed acute renal failure when they started to take celecoxib 100 or 200 mg twice daily. Neither patient showed any sign of decompensated heart failure on admission (which can in itself cause renal failure) and both recovered on stopping the celecoxib and furosemide combination. One patient was also taking enalapril, and this was restarted with the furosemide without any changes in renal function.[16] The same authors also described two other patients taking furosemide who developed renal failure when they started to take **rofecoxib**.[16] Other cases have occurred in patients taking furosemide, often with ACE inhibitors, after they started **rofecoxib**.[5]

(c) Diclofenac

A study in patients with heart failure and cirrhosis found that diclofenac 150 mg daily reduced the furosemide-induced excretion of sodium by 38%, but the excretion of potassium was unaltered.[17]

(d) Diflunisal

A study in 12 healthy subjects found that diflunisal 500 mg twice daily reduced sodium excretion in response to furosemide by 59%, but potassium excretion remained unchanged.[18] In patients with heart failure and cirrhosis taking furosemide, diflunisal 500 to 700 mg daily decreased the sodium excretion by 36% and the potassium excretion by 47%.[17] However, another study in healthy subjects found no interaction between diflunisal and furosemide.[19]

(e) Flupirtine

A study in healthy subjects found that a single 200-mg dose of flupirtine did not affect the overall furosemide diuresis, but the diuretic effect was slightly delayed.[20]

(f) Flurbiprofen

A study in 7 healthy subjects found that the increase in renal osmolal clearance of a standard water load in response to furosemide 40 mg orally or 20 mg intravenously fell from 105% to 19% and from 140% to 70%, respectively, after flurbiprofen 100 mg was given.[21] A single-dose study in 10 healthy subjects found that flurbiprofen 100 mg reduced the urinary volume, and urinary excretion of sodium and potassium, in response to oral furosemide 80 mg by 10%, 9%, and 12%, respectively.[22,23]

(g) Ibuprofen

An elderly man with heart failure taking digoxin, isosorbide dinitrate and furosemide 80 mg daily, developed symptomatic congestive heart failure with ascites when given ibuprofen 400 mg three times daily. His serum urea and creatinine levels rose and no diuresis occurred, even when the furosemide dosage was doubled. Two days after withdrawing the ibuprofen, brisk diuresis took place, renal function returned to normal, and his condition improved steadily.[24] Another elderly patient similarly had a poor response to furosemide (also hydrochlorothiazide and later to metolazone as well) until she stopped taking ibuprofen 600 mg four times daily and at least two **aspirin** daily (for headache).[25] This was due to hyponatraemic hypovolaemia brought on by the drug combination.

Table 26.2 Summary of the interactions of diuretics and NSAIDs

NSAID	*Excretion of sodium*	*Excretion of potassium*	*Diuresis*	*Blood pressure*	*Other effects*
Bumetanide					
Celecoxib					Increased serum creatinine
Indometacin	Reduced by 25%		Reduced by 25%		Development of congestive heart failure in one case
Rofecoxib					Increased serum creatinine Worsening congestive heart failure
Sulindac	Reduced by 22%		Reduced by 21%		
Tolfenamic acid			Reduced by 34%		
Furosemide					
Azapropazone			Non-significant effect		
Celecoxib	Non-significant effect		Non-significant effect		Increased serum creatinine Acute renal failure developed in 2 cases
Diclofenac	Decreased by 38%		Non-significant effect		
Diflunisal	Decreased by 36 to 59%	No significant effect in healthy subjects Decreased by 47% in patients			
Flupirtine			Delayed		
Flurbiprofen	Decreased by 9%	Decreased by 12%	Decreased by 10%		
Ibuprofen			Decreased		Development of congestive heart failure in one case Decreased GFR
Indometacin	Decreased by 64 to 82%	Decreased by 49%	Decreased by 41 to 69%	Mean blood pressure increased by 13 mmHg	
Ketoprofen			Decreased		
Ketorolac	Decreased by 26%		Decreased by about 20%		
Lornoxicam	Decreased		Decreased		
Meloxicam			Non-significant effect		
Metamizole (Dipyrone)			Non-significant effect		
Mofebutazone	Non-significant effect	Non-significant effect	Non-significant effect		
Naproxen	Decreased		Decreased by 50%		GFR decreased
Nimesulide	Decreased		Slight decrease		
Piroxicam	Decreased		Decreased		
Rofecoxib					Development of acute renal failure
Sulindac	Decreased by 38 to 52%	Decreased by 8%	Decreased by 25 to 38%		
Tenoxicam	Non-significant effect			Non-significant effect	
Piretanide					
Indometacin	Decreased by 35%				
Naproxen		Decreased by 14%	Non-significant effect		
Piroxicam	Decreased				
Sulindac	Decreased at 0 to 4 hours, increased at 4 to 8 hours				
Torasemide					
Indometacin	Decreased				

Continued

Table 26.2 Summary of the interactions of diuretics and NSAIDs (continued)

NSAID	*Excretion of sodium*	*Excretion of potassium*	*Diuresis*	*Blood pressure*	*Other effects*
Altizide					
Rofecoxib					Congestive heart failure with weight gain occurred in one case
Bemetizide					
Indometacin	Decreased by 47%				
Bendroflumethiazide					
Ibuprofen				Small increase	Weight gain in 2 patients but overall the effect was non-significant
Indometacin				Increase of 16/9 mmHg	Weight gain
Sulindac				Decreased	
Chlortalidone					
Ibuprofen					Diabetic nephropathy reported in one case
Hydrochlorothiazide					
Diclofenac	Decreased	Non-significant effect		Non-significant effect	Weight gain
Ibuprofen				Small increase (systolic)	Weight gain
Indometacin		Increased		Transient increase of 6/3 mmHg Increase of 16/9 mmHg seen when amiloride also taken	Weight gain
Kebuzone				18 mmHg increase (systolic)	
Naproxen			Non-significant effect		Hyponatraemia reported in a patient also taking amiloride
Phenylbutazone				18 mmHg increase (systolic)	
Piroxicam				Slight increase (patients also taking amiloride)	
Rofecoxib	Decreased	Non-significant effect			
Sulindac	Decreased by 29% over 0 to 4 hours		Usually non-significant but a decrease of 35% over 0 to 4 hours has been reported	Non-significant effect Non-significant effect, or *enhanced* hypotensive effects reported when amiloride also taken	Acute renal failure reported in one case
Methyclothiazide					
Indometacin					Acute renal failure reported in one case
Metolazone					
Indometacin	Decreased by 34%	Decreased by 30%			
Sulindac	Decreased by 19%	Decreased by 16%			
Amiloride					
Indometacin					Case of hyperkalaemia in a patient also taking hydrochlorothiazide
Spironolactone					
Indometacin	Decreased by 54%				
Mefenamic acid			Decreased		
Triamterene					
Diclofenac					Acute renal failure reported in one case (trichlormethiazide also taken)

Continued

Table 26.2 Summary of the interactions of diuretics and NSAIDs (continued)

NSAID	*Excretion of sodium*	*Excretion of potassium*	*Diuresis*	*Blood pressure*	*Other effects*
Ibuprofen				Non-significant (hydrochlorothiazide also taken)	Acute renal failure reported in two cases and increased serum creatinine reported in one case (trichlormethiazide also taken in all cases)
Indometacin					Acute renal failure reported in six cases (hydrochlorothiazide also taken in one case) and increased serum creatinine reported in two cases

In a small, placebo-controlled, crossover study in 8 healthy subjects, ibuprofen 400 mg and 800 mg three times daily for 3 days significantly reduced the glomerular filtration rate and the diuresis produced by a single 20-mg intravenous dose of furosemide, but did not alter sodium excretion.[26]

Loop diuretics such as furosemide have been reported to occasionally cause hearing loss and NSAIDs including ibuprofen have also been reported to have ototoxic effects, which could theoretically be additive.[27]

(h) Indometacin

A study in 4 healthy subjects and 6 patients with essential hypertension found that furosemide 80 mg three times daily reduced the mean blood pressure by 13 mmHg, but when indometacin 50 mg four times daily was also given the blood pressures returned to virtually pretreatment levels. Moreover, the normal urinary sodium loss induced by the furosemide was significantly reduced.[28]

A study in healthy subjects and patients with congestive heart failure found that indometacin 100 mg reduced the furosemide-induced urinary output by 53% and also reduced the excretion of sodium, potassium, and chloride by 64%, 49%, and 62%, respectively, in the patients with congestive heart failure. The drug interaction was much less pronounced in the healthy subjects.[29] A study in 14 patients with ascites secondary to liver cirrhosis found that indometacin 50 mg every 6 hours for 2 doses significantly reduced the urinary volume and the natriuretic response to furosemide, by 69% and 82%, respectively, but produced only a small, non-significant reduction in creatinine clearance.[30] Another study found that indometacin reduced the urinary output in response to furosemide by 28% in healthy subjects and by 41% in elderly patients (three with mild-to-moderate heart failure).[31] There are other case reports and studies confirming the interaction between furosemide and indometacin.[26,32-38]

(i) Ketoprofen

A study in 12 healthy subjects given furosemide 40 mg daily found that ketoprofen 100 mg twice daily reduced the 6-hour urine output by 67 mL, and the 24-hour urine output by 651 mL on the first day of treatment. However no significant differences were seen after 5 days of treatment.[39]

(j) Ketorolac

Twelve healthy subjects were given oral ketorolac 30 mg four times daily, and then a single 30-mg intramuscular dose of ketorolac 30 minutes before a 40-mg intravenous dose of furosemide. No precise figures are given, but the maximum serum level of the furosemide, its diuretic effect, and the electrolyte loss were said to be significantly reduced by the ketorolac.[40] Another study in healthy elderly subjects found that when they were given oral ketorolac 120 mg, then, on the following day, intramuscular ketorolac 30 mg, followed 30 minutes later by furosemide 40 mg, the urinary output fell by 16% and the sodium output fell by 26% over the next 8 hours, when compared with furosemide alone.[41]

(k) Lornoxicam

A study in 12 healthy subjects found that lornoxicam 4 mg significantly antagonised the diuretic and natriuretic effects of furosemide, but this was not quantified.[42]

(l) Meloxicam

In a study in 12 healthy subjects meloxicam 15 mg daily for 3 days had no significant effect on the pharmacokinetics of furosemide 40 mg. The furosemide-induced diuresis was unchanged, and although the cumulative urinary electrolyte excretion was somewhat lower, this was not considered to be clinically significant.[43] A similar study in patients with heart failure taking an ACE inhibitor also found no clinically significant pharmacokinetic or pharmacodynamic interaction between furosemide and meloxicam.[44]

(m) Metamizole sodium (Dipyrone)

A study in 9 healthy subjects found that metamizole sodium 3 g daily for 3 days, reduced the clearance of intravenous furosemide 20 mg from 175 to 141 mL/minute but the diuretic effects of the furosemide were unchanged.[45]

(n) Mofebutazone

A study in 10 healthy subjects found that mofebutazone 600 mg had no effect on the diuretic effects of furosemide 40 mg. The urinary volume and excretion of sodium, potassium and chloride were unchanged.[46]

(o) Naproxen

Two elderly women with congestive heart failure did not respond to treatment with furosemide and digoxin until the naproxen they were taking was withdrawn.[24] A single-dose study in patients with heart failure found that the volume of urine excreted in response to furosemide was reduced about 50% by naproxen.[31] In a placebo-controlled study, 6 patients with cirrhosis and ascites were given a single 40-mg intravenous dose of furosemide before and after naproxen 500 mg twice daily for 5 doses. It was found that this short-term use of naproxen reduced the glomerular filtration rate and the natriuretic and diuretic effects of furosemide.[15]

Loop diuretics such as furosemide have been reported to occasionally cause hearing loss and NSAIDs including naproxen have also been reported to have ototoxic effects, which could theoretically be additive.[27,47]

(p) Nimesulide

A study in 8 healthy subjects found that nimesulide 200 mg twice daily attenuated the effects of furosemide 40 mg twice daily. Subjects who had initially lost weight when taking furosemide regained weight, diuresis was slightly reduced, cumulative sodium excretion was decreased and the glomerular filtration rate was transiently reduced.[48]

(q) Piroxicam

A 96-year-old woman with congestive heart failure did not adequately respond to furosemide until the dosage of piroxicam she was taking was reduced from 20 to 10 mg daily.[49]

In one study in 9 hypertensive patients with a creatinine clearance of less than 60 mL/minute, who were taking furosemide, piroxicam 20 mg daily for 3 days produced a significant reduction in the natriuretic and kaliuretic effects of an additional single 40-mg dose of furosemide. However, in 13 other patients, with a creatinine clearance of greater than 60 mL/minute, who were taking a thiazide diuretic, piroxicam did not alter the effects of a single 40-mg dose of furosemide. In a third group of 8 healthy subjects, the same dose of piroxicam reduced the natriuretic effects, but not the kaliuretic effects, of a single 40-mg dose of furosemide.[50]

(r) Sulindac

A study in 5 healthy subjects found that pretreatment with two 150-mg oral doses of sulindac reduced the urinary volume and urinary sodium following an intravenous dose of furosemide 80 mg by 25% and 38%, respectively. In patients with cirrhosis and ascites, two doses of sulindac 150 mg reduced the urinary volume, urinary sodium, and urinary potassium following an 80-mg intravenous dose of furosemide by 38%, 52%, and 8%, respectively.[51] In another placebo-controlled study in 15 healthy

women, sulindac 200 mg twice daily for 5 days produced a similar but slightly smaller reduction in the natriuretic effect of a single 40-mg intravenous dose of furosemide, than indometacin.[37]

(s) Tenoxicam

A study in 12 patients found that tenoxicam 20 to 40 mg daily had no significant effect on the urinary excretion of sodium or chloride due to furosemide 40 mg daily, and blood pressure, heart rate and body-weight also were not affected.[52]

C. Piretanide

(a) Indometacin

A comparative study[53] into the pharmacological mechanisms underlying the way that drugs interfere with the actions of loop diuretics found that indometacin 50 mg three times daily for 2 days reduced the peak fractional and cumulative excretion of sodium in response to a single 6-mg dose of piretanide. The clinical importance of this change was not studied.

(b) Naproxen

Pretreatment of healthy subjects with naproxen 500 mg decreased the fractional potassium clearance produced by piretanide 6 mg by 14%, but no attenuation of the diuretic response was seen. Estimation of piretanide urinary clearance was not possible as naproxen interfered with the analysis.[54]

(c) Piroxicam

A comparative study into the pharmacological mechanisms underlying the way that drugs interfere with the actions of loop diuretics found that piroxicam 20 mg twice daily for 2 days did not significantly affect the peak fractional excretion of sodium in response to a single 6-mg dose of piretanide, but the cumulative excretion of sodium over 5 and 24 hours was reduced.[53]

(d) Sulindac

Pretreatment of healthy subjects with sulindac 200 mg decreased the fractional urinary flow rate produced by piretanide 6 mg by 15% and attenuated the natriuretic effect of piretanide over 0 to 4 hours. However, natriuresis was increased over the 4 to 8-hour period of the study.[54]

D. Torasemide

A study in healthy subjects suggested that indometacin did not affect the diuretic and natriuretic effects of torasemide,[55] but on the basis of a later study, the same workers suggested that pathological factors in patients may allow an interaction similar to that between furosemide and indometacin to occur. Indometacin was found to reduce the natriuretic actions of torasemide when the subjects were given a low sodium diet, but did not affect the natriuretic actions when they received a normal diet. The sodium balance, therefore, appeared to be a determinant of the interaction between NSAIDs and loop diuretics.[56]

Mechanism

Uncertain and complex. It is likely that a number of different mechanisms come into play. NSAIDs cause fluid and salt retention, which would be expected to antagonise the effects produced by diuretics. The sodium retentive properties of NSAIDs appear to be most noticeable in patients who already have a predisposition to sodium retention, such as those with heart disease, liver disease etc.[57,58] A reduction in glomerular filtration rate is sometimes observed with NSAIDs and this may reduce the natriuretic efficacy of loop diuretics particularly in states of renal underperfusion such as congestive heart failure, volume depletion, and liver cirrhosis.[59]

One probable mechanism involves the synthesis of renal prostaglandins, particularly prostaglandin E_2 and prostacyclin, which inhibit the reabsorption of sodium and help to maintain renal blood flow and glomerular filtration rates in the face of disease or circulatory stress, such as occurs when the loop diuretics cause sodium excretion.[60] If this synthesis is blocked by NSAIDs, then renal blood flow, natriuresis and diuresis will be reduced.[59,61]

NSAIDs can also decrease renin release, leading to reduced aldosterone secretion, which results in reduced potassium secretion in the distal nephron. Patients with renal impairment or patients who are receiving other drugs that decrease potassium secretion, for example 'ACE inhibitors', (p.32), are at increased risk of hyperkalaemia.[58] It appears that coxibs also affect renal prostaglandins and renin release and are likely to interact similarly to non-selective NSAIDs.[58,62]

In addition, NSAIDs may alter the access of some diuretics to their tubular site of action by competing for transport in the proximal tubule.[59,63]

Importance and management

NSAIDs, including coxibs, can cause renal impairment, particularly in patients with hypovolaemia or dehydration and in whom prostaglandins are playing an important role in maintaining renal function. Such patients include those taking diuretics, the elderly and those with concurrent conditions such as congestive heart failure and ascites. Hence the combination of diuretics and NSAIDs may increase the nephrotoxicity of NSAIDs.[36,64-68]

Loop diuretics such as **etacrynic acid**,[69] furosemide,[27] or piretanide[70] can exhibit ototoxic properties particularly if given in high doses and in renal impairment.[27] The risk of ototoxicity may theoretically be increased if these diuretics are given with other ototoxic drugs such as some NSAIDs, including ibuprofen and naproxen.[27,47]

The antihypertensive and diuretic effects of the loop diuretics are reduced by NSAIDs. This interaction is very well documented between furosemide and indometacin, and of clinical importance, whereas less is known about the interactions with other NSAIDs. Nevertheless, the interaction should be anticipated with all of them. The use of an alternative non-NSAID analgesic should always be considered, if possible. However, in cases where concurrent use cannot be avoided, the loop diuretic dosage may need to be raised (according to clinical response), but the effects on renal function and electrolytes, as well as efficacy, should be closely monitored. Patients at greatest risk of an adverse interaction include the elderly and patients with cirrhosis, cardiac failure and/or renal impairment, and NSAIDs should usually be used with caution in these patient groups regardless of the concurrent use of diuretics. Note that a retrospective analysis of records of patients taking diuretics (thiazides, loop and/or potassium-sparing) with NSAIDs found a twofold increase in the risk of hospitalisation for congestive heart failure on concurrent use. The most common NSAIDs taken by this cohort of patients were diclofenac, ibuprofen, indometacin and naproxen.[57] Furthermore, the European Society of Cardiology (ESC) Task Force and the joint American College of Cardiology/American Heart Association both recommend avoiding NSAID use, if possible, in patients with congestive heart failure.[71,72]

Much less is known about the interactions of NSAIDs with **bumetanide**, and even less about **piretanide**, **torasemide**, and **etacrynic acid**, but the evidence suggests that they probably interact in the same way as furosemide. It would therefore seem prudent to be alert for a potential reduction in effect if an NSAID is given.

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70. Trialix (Piretanide/Ramipril). Sanofi-Aventis. Irish Summary of product characteristics, January 2007.
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Loop diuretics + Probenecid

Probenecid decreases the renal clearance of furosemide and bumetanide, but it appears not to significantly alter their overall diuretic effect. Probenecid reduces the natriuretic effect of piretanide, although the clinical relevance of this is uncertain.

Clinical evidence

(a) Bumetanide

Probenecid 1 g did not affect the natriuretic or diuretic response of 8 healthy subjects to 500 micrograms or 1 mg of intravenous bumetanide.[1] Another study reported a fall in natriuresis and a reduction in the clearance of bumetanide when probenecid was given, but this was of minimal clinical importance.[2]

(b) Furosemide

The concurrent use of furosemide and probenecid has been closely studied to determine the renal pharmacological mechanisms of loop diuretics. One study in patients given furosemide 40 mg daily found that the addition of probenecid 500 mg twice daily for 3 days reduced their urinary excretion of sodium by about 36% (from 56.3 to 35.9 mmol daily).[3] Other studies have found that probenecid causes a fall,[4] a rise,[5] and no change[6,7] in diuresis in response to furosemide, and causes a reduction of 35 to 80% in the renal clearance of furosemide.[4,6-9] One study found that probenecid 1 g increased the half-life of furosemide by 70% and decreased its oral clearance by 65%.[8] Similar results were found in another study.[10]

(c) Piretanide

A comparative study[11] into the pharmacological mechanisms underlying the way drugs interfere with the actions of loop diuretics found that probenecid 1 g reduced the peak fractional excretion of sodium produced by a 6-mg dose of oral piretanide by 65%. Another study confirmed that probenecid reduces the natriuretic effects of piretanide.[12] The clinical importance of these changes was not studied.

Mechanism

Loop diuretics are secreted from the blood into the urine through the organic acid transport pathway. Other organic acids such as probenecid can alter loop diuretic secretion by competing for transport in the proximal tubule.[13]

Importance and management

Probenecid appears to reduce the renal clearance of furosemide and bumetanide, but the effect on diuresis does not usually appear to be clinically significant. Nevertheless, one manufacturer of furosemide warns that probenecid may reduce its effects.[14] Probenecid does reduce the natriuretic effects of piretanide, and although the clinical effects of this have not been studied, it may be prudent to be alert for a decreased response to piretanide if probenecid is also given. There appears to be no direct evidence regarding **torasemide**, but one manufacturer[15] warns that its effects may be reduced by probenecid. It may be prudent to be alert for this if both drugs are given.

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5. Brater DC. Effects of probenecid on furosemide response. *Clin Pharmacol Ther* (1978) 24, 548–54.
6. Homeida M, Roberts C, Branch RA. Influence of probenecid and spironolactone on furosemide kinetics and dynamics in man. *Clin Pharmacol Ther* (1977) 22, 402–9.
7. Smith DE, Gee WL, Brater DC, Lin ET, Benet LZ. Preliminary evaluation of furosemide-probenecid interaction in humans. *J Pharm Sci* (1980) 69, 571–5.
8. Vree TB, van den Biggelaar-Martea M, Verwey-van Wissen CPWGM. Probenecid inhibits the renal clearance of frusemide and its acyl glucuronide. *Br J Clin Pharmacol* (1995) 39, 692–5.
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12. Noormohamed FH, Lant AF. Analysis of the natriuretic action of a loop diuretic, piretanide, in man. *Br J Clin Pharmacol* (1991) 31, 463–9.
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14. Lasix (Furosemide). Sanofi-Aventis. UK Summary of product characteristics, November 2006.
15. Torem (Torasemide). Meda Pharmaceuticals. UK Summary of product characteristics, September 2009.

Loop diuretics; Furosemide + Bile-acid binding resins

Colestyramine and colestipol markedly reduce the absorption and diuretic effects of furosemide.

Clinical evidence

In 6 healthy subjects **colestyramine** 8 g reduced the absorption of a single 40-mg dose of furosemide by 95%. The 4-hour diuretic response was reduced by 77% (urinary output reduced from 1510 to 350 mL). Similarly, **colestipol** 10 g reduced the absorption of furosemide by 80% and reduced the 4-hour diuretic response by 58% (urinary output reduced from 1510 to 630 mL).[1]

Mechanism

Both colestyramine and colestipol are anionic exchange resins, which can bind with furosemide in the gut, thereby reducing its absorption and its effects.

Importance and management

An established interaction, although direct evidence seems to be limited to this study. The absorption of furosemide is relatively rapid; therefore giving it 2 to 3 hours before either the colestyramine or colestipol should be an effective way of overcoming this interaction. This needs confirmation. Note that it is normally recommended that other drugs are given 1 hour before or 4 to 6 hours after colestyramine and 1 hour before or 4 hours after colestipol.

1. Neuvonen PJ, Kivistö K, Hirvisalo EL. Effects of resins and activated charcoal on the absorption of digoxin, carbamazepine and frusemide. *Br J Clin Pharmacol* (1988) 25, 229–33.

Loop diuretics; Furosemide + Cloral hydrate and related drugs

Intravenous furosemide, given after cloral hydrate, occasionally causes sweating, hot flushes, a variable blood pressure, and tachycardia. Dichloralphenazone and cloral betaine may interact similarly.

Clinical evidence

Six patients in a coronary care unit, given an intravenous bolus of 40 to 120 mg of furosemide and who had received cloral hydrate during the previous 24 hours, developed sweating, hot flushes, variable blood pressure, and tachycardia. The reaction was immediate and lasted for about 15 minutes. No special treatment was given. Furosemide had caused no problems when given before the cloral hydrate was started.[1]

A retrospective study of hospital records revealed that, out of 43 patients who had received both cloral hydrate and furosemide, one patient developed this reaction and 2 others may have done so.[2] The interaction has also been described in an 8-year-old boy.[3]

Mechanism

Not understood. One suggestion is that furosemide displaces trichloroacetic acid (the metabolite of cloral hydrate) from its protein binding sites, which in its turn displaces levothyroxine or alters the serum pH so that the levels of free levothyroxine rise leading to a hypermetabolic state.[1]

Importance and management

An established interaction, but information is limited to three reports. The incidence is uncertain but probably low. Concurrent use need not be avoided, but it would be prudent to give intravenous furosemide cautiously if cloral hydrate has been given recently. It seems possible that drugs that release cloral hydrate when metabolised (e.g. **dichloralphenazone**, **cloral betaine**) might interact similarly. There is no evidence that furosemide given orally or cloral hydrate given to patients already taking furosemide causes this reaction.[2]

1. Malach M, Berman N. Furosemide and chloral hydrate. Adverse drug interaction. *JAMA* (1975) 232, 638–9.
2. Pevonka MP, Yost RL, Marks RG, Howell WS, Stewart RB. Interaction of chloral hydrate and furosemide. A controlled retrospective study. *Drug Intell Clin Pharm* (1977) 11, 332–5.
3. Dean RP, Rudinsky BF, Kelleher MD. Interaction of chloral hydrate and intravenous furosemide in a child. *Clin Pharm* (1991) 10, 385–7.

Loop diuretics; Furosemide + Germanium

An isolated case report describes a man who became resistant to furosemide after he took germanium.

Clinical evidence, mechanism, importance and management

A 63-year-old man was hospitalised for hypertension and oedema 10 days after adding ginseng containing germanium to his usual treatment with cyclophosphamide and furosemide. He gained almost 13 kg in weight. After treatment with intravenous furosemide he was discharged and again took ginseng with germanium. This time he gained 12 kg in weight over 14 days, despite an increase in the dose of furosemide from 80 mg twice daily to 240 mg twice daily. The weight gain and oedema again resolved when the ginseng and germanium was withdrawn and intravenous furosemide was given. The authors suggest that germanium was responsible for this interaction.[1]

This is an isolated report, and its general significance is unclear. However, note that it has been said that the use of germanium should be discouraged due to its potential to cause renal toxicity.[2]

1. Becker BN, Greene J, Evanson J, Chidsey G, Stone WJ. Ginseng-induced diuretic resistance. *JAMA* (1996) 276, 606–7.
2. Sweetman SC, ed. Martindale: The complete drug reference. 36th ed. London: Pharmaceutical Press; 2009. p. 2311.

Loop diuretics; Furosemide + Paracetamol (Acetaminophen)

In 10 healthy women paracetamol 1 g four times daily for 2 days was found to have no effect on the diuresis or natriuresis in response to 20 mg of intravenous furosemide.[1]

1. Martin U, Prescott LF. The interaction of paracetamol with frusemide. *Br J Clin Pharmacol* (1994) 37, 464–7.

Loop diuretics; Furosemide + Phenytoin

The diuretic effects of furosemide can be reduced by as much as 50% by phenytoin.

Clinical evidence

A group of epileptic patients were noted to have higher than expected dependent oedema, with an apparently reduced response to diuretics: this prompted further study. In 30 patients taking **phenytoin** 200 to 400 mg

daily with phenobarbital 60 to 180 mg daily the maximal diuresis in response to furosemide 20 or 40 mg occurred after 3 to 4 hours instead of the usual 2 hours. The total diuresis was reduced by 32% for the 20-mg dose, 49% for the 40-mg dose and 50% when intravenous furosemide 20 mg was given. Some of the patients were also taking carbamazepine, pheneturide, ethosuximide, diazepam or chlordiazepoxide.[1]

Another study in 5 healthy subjects given **phenytoin** 100 mg three times daily for 10 days found that the maximum serum levels of furosemide 20 mg, given orally or intravenously, were reduced by 50%.[2]

Mechanism

Not understood. One suggestion is that the phenytoin causes changes in the jejunal sodium pump activity, which reduces the absorption of the furosemide,[2] but this is not the whole story because an interaction also occurs when furosemide is given intravenously.[1] Other suggestions, based on *in vitro* or *animal* evidence, are that the phenytoin generates a 'liquid membrane,' which blocks the transport of the furosemide to its active site,[3] or that phenytoin antagonises the diuretic effect of furosemide by interfering with the renal tubular sodium pump mechanism.[4]

Importance and management

Information is limited but the interaction is established. A reduced diuretic response should be expected in the presence of phenytoin. A dosage increase may be needed.

1. Ahmad S. Renal insensitivity to frusemide caused by chronic anticonvulsant therapy. *BMJ* (1974) 3, 657–9.
2. Fine A, Henderson IS, Morgan DR, Tilstone WJ. Malabsorption of frusemide caused by phenytoin. *BMJ* (1977) 2, 1061–2.
3. Srivastava RC, Bhise SB, Sood R, Rao MNA. On the reduced furosemide response in the presence of diphenylhydantoin. *Colloids and Surfaces* (1986) 19, 83–8.
4. Tongia SK. Antagonism of frusemide diuresis by diphenylhydantoin sodium. *Indian J Med Res* (1981) 74, 572–4.

Loop diuretics; Furosemide + Sevelamer

Sevelamer abolished the diuretic effect of furosemide in a haemodialysis patient.

Clinical evidence, mechanism, importance and management

A haemodialysis patient taking furosemide 250 mg twice daily found that her urine output reduced from 950 mL/day to zero when she started taking sevelamer 800 mg at breakfast and lunchtime, and 1.6 g with dinner. Urine output returned to the previous level within 24 hours of stopping the sevelamer. This effect also occurred on rechallenge. The dose times were adjusted so that she took furosemide 500 mg in the morning and sevelamer 1.6 g at lunch and dinner, and her urine output was unaffected and remained stable.[1]

The authors suggest that furosemide became bound to sevelamer in the gut, and this prevented its absorption.

This appears to be the only case report of an interaction between these drugs so far; however, it is worth bearing this case in mind should a similar situation arise in other patients. Note that the manufacturers of sevelamer[2,3] suggest that, when giving any other oral drug for which a reduction in the bioavailability could have a clinically significant effect on safety or efficacy, the drug should be given at least 1 hour before or 3 hours after sevelamer.

1. Fleuren HWHA, Kho Y, Schuurmans MMJ, Vollaard EJ. Drug interaction between sevelamer and furosemide. *Nephrol Dial Transplant* (2005) 20, 2288–9.
2. Renagel (Sevelamer). Genzyme Therapeutics. UK Summary of product characteristics, July 2009.
3. Renagel (Sevelamer hydrochloride). Genzyme. US Prescribing information, November 2007.

Loop diuretics; Furosemide + Sucralfate

The manufacturer notes that when sucralfate was given with furosemide the absorption of furosemide from the intestine was decreased and therefore its effects were reduced.[1] They advise that oral furosemide and sucralfate must not be taken within 2 hours of each other.[1,2] However, a study in *animals* had shown that the amount of furosemide excreted in the urine was not affected by concurrent oral administration of sucralfate, and the excretion of sodium and potassium in response to furosemide was not altered.[3]

1. Lasix (Furosemide). Sanofi-Aventis. UK Summary of product characteristics, November 2006.
2. Lasix (Furosemide). Sanofi-Aventis. US Prescribing information, August 2007.
3. Hikal AH, Walker LA, Ramachandran T. *In vitro* and *in vivo* interactions of furosemide and sucralfate. *Pharm Res* (1987) 4, 171–2.

Potassium-sparing diuretics + H_2-receptor antagonists

Although the H_2-receptor antagonists appear to cause minor changes in the pharmacokinetics of amiloride and triamterene, none of these have been shown to be of clinical significance.

Clinical evidence, mechanism, importance and management

(a) Amiloride

A study in 8 healthy subjects given amiloride 5 mg daily found that **cimetidine** 400 mg twice daily for 12 days reduced the renal clearance of amiloride by 17% and reduced its urinary excretion from 65% to 53%. Amiloride also reduced the excretion of **cimetidine** from 43% to 32%, and the AUC was reduced by 14%.[1] No changes in the diuretic effects (urinary volume, sodium or potassium excretion) occurred. It seems that each drug reduces the gastrointestinal absorption of the other drug by as yet unidentified mechanisms. The overall plasma levels of the amiloride remain unchanged because the reduced absorption is offset by a reduction in its renal excretion. These mutual interactions do not seem to be clinically significant.

(b) Triamterene

A study in 6 healthy subjects given triamterene 100 mg daily for 4 days found that **cimetidine** 400 mg twice daily increased the AUC of triamterene by 22%, reduced its metabolism (hydroxylation) by 32%, and reduced its renal clearance by 28%. There also appeared to be a reduction in the absorption of triamterene. However, the loss of sodium in the urine was not significantly changed, and the potassium-sparing effects of triamterene were not altered.[2] Because the diuretic effects of triamterene are minimally changed, this interaction is unlikely to be clinically important.[2]

In 8 healthy subjects, **ranitidine** 150 mg twice daily for 4 days roughly halved the absorption (as measured by renal clearance) of triamterene 100 mg daily. Its metabolism was also reduced, with the total effect being a 21% reduction in the AUC. As a result of the reduced plasma triamterene levels, the urinary sodium loss was reduced to some extent but potassium excretion remained unchanged.[3] Overall the diuretic effects of triamterene were only mildly affected. Another study found that a 22% reduction in the AUC of triamterene is unlikely to result in a significant change in its diuretic effects.[2] No clinically significant interaction is therefore anticipated.

1. Somogyi AA, Hovens CM, Muirhead MR, Bochner F. Renal tubular secretion of amiloride and its inhibition by cimetidine in humans and in an animal model. *Drug Metab Dispos* (1989) 17, 190–6.
2. Muirhead MR, Somogyi AA, Rolan PE, Bochner F. Effect of cimetidine on renal and hepatic drug elimination: studies with triamterene. *Clin Pharmacol Ther* (1986) 40, 400–7.
3. Muirhead M, Bochner F, Somogyi A. Pharmacokinetic drug interactions between triamterene and ranitidine in humans: alterations in renal and hepatic clearances and gastrointestinal absorption. *J Pharmacol Exp Ther* (1988) 244, 734–9.

Potassium-sparing diuretics + NSAIDs

The concurrent use of triamterene (with or without a thiazide) and an NSAID has, in several cases, rapidly led to acute renal failure. NSAIDs may possibly antagonise the antihypertensive and/or diuretic effects of potassium-sparing diuretics and may also increase the risk of hyperkalaemia. There may be an increased risk of gastrointestinal events with spironolactone and NSAIDs.

Clinical evidence

A retrospective analysis of records of patients taking diuretics (thiazides, loop and/or potassium-sparing) and NSAIDs found a twofold increase in the risk of hospitalisation for congestive heart failure on concurrent use,

although the relative risk (1.4) with potassium-sparing diuretics was less than that when combined with a thiazide (2.9). The most common NSAIDs taken by this cohort of patients were **diclofenac**, **ibuprofen**, **indometacin** and **naproxen**.[1] The combination of NSAIDs, for example indometacin, with potassium-sparing diuretics has been associated with severe hyperkalaemia, particularly in patients with impaired renal function.[2-5] NSAIDs can reduce the diuretic, natriuretic and antihypertensive effects of diuretics in some patients.[2-5] Various large epidemiological studies and meta-analyses of clinical studies have been conducted to assess the effect of NSAIDs on blood pressure in patients treated with antihypertensives, including diuretics, and the findings of these are summarised in 'Table 23.2', (p.1027). Individual clinical reports and clinical or pharmacological studies of the effects of specific NSAIDs on diuretics are outlined in the subsections below and in 'Table 26.2', (p.1126).

A. Amiloride

A 78-year-old woman, who had been receiving **indometacin** 100 mg twice daily as suppositories and furosemide 40 mg every other day, experienced progressive weakness after furosemide was discontinued and amiloride/hydrochlorothiazide 5/50 mg daily was prescribed. She was found to have severe hyperkalaemia (serum potassium 6.8 mmol/L), which resolved after the drugs were discontinued. On rechallenge neither **indometacin** nor amiloride/hydrochlorothiazide, given alone, significantly changed her serum potassium levels, but giving indometacin with amiloride subsequently resulted in hyperkalaemia.[6] For further mention of interactions between amiloride/hydrochlorothiazide and indometacin or other NSAIDs, see 'Thiazide diuretics + NSAIDs', p.1138.

B. Spironolactone

(a) Indometacin

A study in healthy subjects found that indometacin 150 mg daily reduced the natriuretic effect of spironolactone 300 mg daily by 54%.[7]

(b) Mefenamic acid

The UK manufacturer of spironolactone reports that mefenamic acid has been shown to attenuate the diuretic effect of spironolactone.[8]

(c) Rofecoxib

For a report of heart failure in an elderly woman taking spironolactone, altizide and other drugs, when rofecoxib was added to her treatment, see 'Thiazide diuretics + NSAIDs', p.1138.

(d) Unspecified NSAIDs

A retrospective, population based case-control study suggested that the current use of spironolactone was associated with a 2.7-fold increased risk of a gastrointestinal event. This association was stronger as the dosage increased and was more pronounced when spironolactone was combined with ulcerogenic drugs including NSAIDs. Increasing the dosage of other diuretics including **amiloride** or loop diuretics was not associated with upper gastrointestinal bleeding.[9] The study has been criticised because of, among other things, the use of unmatched controls,[10,11] although another retrospective study found that, with long-term treatment, spironolactone was associated with gastritis in 2% of patients.[12] The manufacturer also mentions gastric bleeding, ulceration and gastritis as adverse reactions that have been reported with spironolactone.[2]

C. Triamterene

(a) Diclofenac

A patient receiving triamterene 100 mg and **trichlormethiazide** 2 mg daily was given intramuscular diclofenac 75 mg before admission to hospital with breast pain. On admission serum creatinine was 91 micromol/L and after 2 days it had increased to 248 micromol/L, but it returned to normal over 2 weeks. The subsequent use of oral diclofenac produced no adverse effects. The observed deterioration in renal function was attributed to an interaction between triamterene and diclofenac.[13]

(b) Diflunisal

Diflunisal had no effects on the pharmacokinetics of triamterene in healthy subjects, but the plasma AUC of an active metabolite, *p*-hydroxytriamterene was increased by more than fourfold.[14]

(c) Ibuprofen

A 37-year-old black man who had regularly taken ibuprofen 800 mg one to three times daily and hydrochlorothiazide/triamterene 50/75 mg daily, developed acute renal failure after strenuous exercise. A renal biopsy showed acute tubular necrosis. The patient had taken the ibuprofen and diuretics 2 hours before exercise and it was suggested that peak anti-prostaglandin effects of the ibuprofen probably coincided with maximal exercise-induced renal vasoconstriction. Other factors such as diuretic use, hypertension and hypertensive nephrosclerosis may also have predisposed the patient to ischaemic tubular damage.[15] See also *Indometacin*, below.

(d) Indometacin

A study in 4 healthy subjects found that indometacin 150 mg daily given with triamterene 200 mg daily over a 3-day period reduced the creatinine clearance in 2 subjects by 62% and 72%, respectively. Renal function returned to normal after a month. Indometacin alone caused an average 10% fall in creatinine clearance, but triamterene alone caused no consistent change in renal function. No adverse reactions were seen in 18 other subjects treated in the same way with indometacin and furosemide, hydrochlorothiazide or spironolactone.[16,17]

A patient with systemic lupus erythematosus and membranous glomerulopathy who was taking triamterene/hydrochlorothiazide 50/25 mg daily developed raised serum creatinine after taking **ibuprofen** 600 mg daily for 35 days. One day after changing to a high dose of indometacin (50 mg three times daily by mouth and 100 mg at night as a suppository) the patient developed acute renal failure with oliguria and slight hypertension.[18] Five patients are reported to have rapidly developed acute renal failure after receiving indometacin and triamterene, either concurrently or sequentially.[19-22]

Mechanism

Uncertain. One suggestion is that triamterene causes renal ischaemia, for which the kidney compensates by increasing prostaglandin production, thereby preserving renal blood flow. Indometacin opposes this by inhibiting prostaglandin synthesis, so that the damaging effects of triamterene on the kidney continue unchecked. Increases in pharmacologically active metabolites of triamterene may occur due to competition for renal excretory pathways but the clinical significance of this is uncertain. As renal production of prostaglandins helps to maintain renal blood flow and renal vasodilatation during volume depletion, other NSAIDs might also be expected to affect this compensatory mechanism when diuretics are used.

Prostaglandins may also contribute to the natriuretic effects of spironolactone. The NSAIDs may reduce the diuretic effects of spironolactone by blocking prostaglandin synthesis.

Importance and management

Information is limited to these reports, but the increased risk of renal impairment with indometacin and triamterene is established, although the incidence is uncertain. Since acute renal failure can apparently develop unpredictably and very rapidly it would seem prudent to use triamterene and indometacin cautiously, or avoid the combination altogether. The manufacturer of triamterene[23] and the authors of the report with diclofenac[13] suggest caution with the use of any NSAID with triamterene. Strenuous exercise can reduce renal blood flow, and the author of the case report with ibuprofen notes that although renal failure secondary to this is rare, patients taking medication that reduces renal blood flow are more at risk of this complication.[15] The manufacturers of amiloride[4] and **eplerenone**[24] also warn about the possibility of acute renal failure in patients also taking NSAIDs and recommend that these patients should be adequately hydrated and have their renal function monitored.[24]

The European Society of Cardiology (ESC) Task Force and the joint American College of Cardiology/American Heart Association guidelines on the management of chronic heart failure both recommend that NSAIDs, including coxibs, should be avoided, if possible, with aldosterone antagonists (such as **eplerenone** or spironolactone), as this increases the risk of developing hyperkalaemia and renal failure.[25,26]

1. Heerdink ER, Leufkens HG, Herings RMC, Ottervanger JP, Stricker BHC, Bakker A. NSAIDs associated with increased risk of congestive heart failure in elderly patients taking diuretics. *Arch Intern Med* (1998) 158, 1108–12.
2. Aldactone (Spironolactone). G.D. Searle LLC. US Prescribing information, July 2003.
3. Inspra (Eplerenone). Pfizer Inc. US Prescribing information, April 2008.
4. Amilamont (Amiloride hydrochloride). Rosemont Pharmaceuticals Ltd. UK Summary of product characteristics, August 2009.
5. Midamor (Amiloride hydrochloride). Merck & Co., Inc. US Prescribing information, November 2002.
6. Mor R, Pitlik S, Rosenfeld JB. Indomethacin- and moduretic®-induced hyperkalemia. *Isr J Med Sci* (1983) 19, 535–7.
7. Hofmann LM, Garcia HA. Interaction of spironolactone and indomethacin at the renal level. *Proc Soc Exp Biol Med* (1972) 141, 353–5.
8. Aldactone (Spironolactone). Pharmacia Ltd. UK Summary of product characteristics, May 2007.
9. Verhamme K, Mosis G, Dieleman J, Stricker B, Sturkenboom M. Spironolactone and risk of upper gastrointestinal events: population based case-control study. *BMJ* (2006) 333, 330–3.

10. Campbell E, Shonde A, Foley S. Spironolactone and risk of upper gastrointestinal events: spironolactone may not be guilty. *BMJ* (2006) 333, 500.
11. Dawwas MF. Spironolactone and risk of upper gastrointestinal events: association is unproved. *BMJ* (2006) 333, 501.
12. Williams EM, Katholi RE, Karambelas MR. Use and side-effect profile of spironolactone in a private cardiologist's practice. *Clin Cardiol* (2006) 29, 149–53.
13. Härkönen M, Ekblom-Kullberg S. Reversible deterioration of renal function after diclofenac in patient receiving triamterene. *BMJ* (1986) 293, 698–9.
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22. Mathews A, Bailie GR. Acute renal failure and hyperkalemia associated with triamterene and indomethacin. *Vet Hum Toxicol* (1986) 28, 224–5.
23. Dyrenium (Triamterene). WellSpring Pharmaceutical Corporation. US Prescribing information, October 2005.
24. Inspra (Eplerenone). Pfizer Ltd. UK Summary of product characteristics, October 2009.
25. Hunt SA. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult. A report of the American College of Cardiology; American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). *J Am Coll Cardiol* (2005) 46, e1–e82. Available at: http://content.onlinejacc.org/cgi/reprint/46/6/e1.pdf (accessed 01/02/10).
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Potassium-sparing diuretics + Potassium compounds

The concurrent use of spironolactone or triamterene and potassium supplements can result in severe and even life-threatening hyperkalaemia. Amiloride and eplerenone are expected to interact similarly. Potassium-containing salt substitutes can be as hazardous as potassium supplements.

Clinical evidence

In a retrospective analysis of hospitalised patients who had received **spironolactone**, hyperkalaemia had developed in 5.7% of patients taking **spironolactone** alone and in 15.4% of those also taking a **potassium chloride** supplement. The incidence was 42% in those with severe azotaemia (a high blood level of urea or nitrogen compounds) given **spironolactone** and **potassium chloride**.[1] A retrospective survey of another group of 25 patients taking **spironolactone** and oral **potassium chloride** supplements found that half of them had developed hyperkalaemia.[2]

A patient developed severe hyperkalaemia and cardiotoxicity as a result of taking **spironolactone** and a **potassium supplement**.[3] Three patients taking furosemide and **spironolactone** became hyperkalaemic[4,5] because they took **potassium-containing salt substitutes** (*No Salt* in one case[4]): two developed cardiac arrhythmias.[5] In another case, the pacemaker of a patient failed because of hyperkalaemia caused by the concurrent use of **triamterene** with hydrochlorothiazide (*Dyazide*) and **potassium chloride** (*Slow-K*).[6]

Mechanism

The effects of the potassium-sparing diuretics and potassium compounds are additive, which can result in hyperkalaemia.

Importance and management

The interaction with spironolactone is established and of clinical importance. A case has also been reported with triamterene, and **amiloride** and **eplerenone** would be expected to behave similarly. Avoid potassium compounds in patients taking potassium-sparing diuretics except in cases of marked potassium depletion, where the effects can be closely monitored. Warn patients about the risks of salt substitutes containing potassium, which may increase the potassium intake by 50 to 60 mmol daily.[5] The signs and symptoms of hyperkalaemia include muscular weakness, fatigue, paraesthesia, flaccid paralysis of the extremities, bradycardia, shock and ECG abnormalities, which may develop slowly and insidiously. Note that the manufacturers of eplerenone contraindicate the concurrent use of potassium supplements,[7,8] but in the US, this contraindication is only in patients given eplerenone for hypertension.

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3. Kalbian VV. Iatrogenic hyperkalemic paralysis with electrocardiographic changes. *South Med J* (1974) 67, 342–5.
4. McCaughan D. Hazards of non-prescription potassium supplements. *Lancet* (1984) i, 513–14.
5. Yap V, Patel A, Thomsen J. Hyperkalemia with cardiac arrhythmia. Induction by salt substitutes, spironolactone, and azotemia. *JAMA* (1976) 236, 2775–6.
6. O'Reilly MV, Murnaghan DP, Williams MB. Transvenous pacemaker failure induced by hyperkalemia. *JAMA* (1974) 228, 336–7.
7. Inspra (Eplerenone). Pfizer Ltd. UK Summary of product characteristics, October 2009.
8. Inspra (Eplerenone). Pfizer Inc. US Prescribing information, April 2008.

Potassium-sparing diuretics + Total parenteral nutrition

Metabolic acidosis developed in two patients receiving total parenteral nutrition associated with the concurrent use of triamterene or amiloride. The cases were complicated by a number of pathological and other factors, but it was suggested that the major reason for the acidosis was because the diuretics prevented the kidneys from responding normally to the acid load. The authors of the report advise caution during concurrent use.[1]

1. Kushner RF, Sitrin MD. Metabolic acidosis. Development in two patients receiving a potassium-sparing diuretic and total parenteral nutrition. *Arch Intern Med* (1986) 146, 343–5.

Potassium-sparing/Thiazide diuretics + Trimethoprim

Excessively low sodium levels have been seen in a few patients taking hydrochlorothiazide with amiloride or triamterene when they were given trimethoprim or co-trimoxazole. Trimethoprim may cause hyperkalaemia and this may be additive with the effects of potassium-sparing diuretics, including the aldosterone antagonists.

Clinical evidence

A 75-year-old woman with multiple medical conditions taking methyldopa, levothyroxine and **co-amilozide** (**hydrochlorothiazide** with **amiloride**) developed nausea and anorexia, and was found to have hyponatraemia (sodium 107 mmol/L), within 4 days of starting to take trimethoprim 200 mg twice daily. The problem resolved when the diuretics and trimethoprim were stopped. When rechallenged 4 months later with trimethoprim, hyponatraemia did not occur, but it developed rapidly when **co-amilozide** was also restarted.[1] The authors of this report have seen several other patients who developed hyponatraemia within 4 to 12 days of starting trimethoprim or co-trimoxazole, all of whom were elderly and all but one of whom were taking a diuretic [unnamed].[1]

Another report describes hyponatraemia in two other patients after co-trimoxazole was added to treatment with **co-amilozide** or **co-triamterzide** (**hydrochlorothiazide** with **triamterene**).[2]

Mechanism

Not established. Thiazide diuretics combined with potassium-sparing diuretics are said to be particularly liable to cause hyponatraemia.[3] Trimethoprim can also cause hyponatraemia and/or hyperkalaemia,[4,5] by blocking amiloride-sensitive sodium channels in the collecting duct (this produces a similar effect to that of a potassium-sparing diuretic). It seems likely that these adverse effects can be additive with the effects of other drugs.

Importance and management

Information is very limited but it would seem prudent to be on the alert for any signs of hyponatraemia (nausea, anorexia, etc.) in any patient taking potassium-sparing diuretics with thiazides and trimethoprim. Although there appears to have been no specific case reports of hyperkalaemia in patients taking trimethoprim with potassium-sparing diuretics (including the **aldosterone antagonists** eplerenone and spironolactone), in theory the risk of hyperkalaemia would be increased by concurrent use. It may therefore be prudent to also monitor potassium levels.

1. Eastell R, Edmonds CJ. Hyponatraemia associated with trimethoprim and a diuretic. *BMJ* (1984) 289, 1658–9.
2. Hart TL, Johnston LJ, Edmonds MW, Brownscombe L. Hyponatremia secondary to thiazide-trimethoprim interaction. *Can J Hosp Pharm* (1989) 42, 243–6.
3. Hornick P. Severe hyponatraemia in elderly patients: cause for concern. *Ann R Coll Surg Engl* (1996) 78, 230–1.
4. Perazella MA. Trimethoprim-induced hyperkalaemia. Clinical data, mechanism, prevention and management. *Drug Safety* (2000) 22, 227–36.
5. Mori H, Kuroda Y, Imamura S, Toyoda A, Yoshida I, Kawakami M, Tabei K. Hyponatremia and/or hyperkalemia in patients treated with the standard dose of trimethoprim-sulfamethoxazole. *Intern Med* (2003) 42, 665–9.

Potassium-sparing diuretics; Eplerenone + CYP3A4 inducers

St John's wort slightly decreases the AUC of eplerenone. The manufacturers of eplerenone recommend the avoidance of St John's wort and other stronger inducers of CYP3A4, such as rifampicin (rifampin), because of the possible risk of decreased eplerenone efficacy.

Clinical evidence, mechanism, importance and management

St John's wort (*Hypericum perforatum*) caused a small 30% decrease in the AUC of a single 100-mg dose of eplerenone.[1,2] Eplerenone is metabolised by the cytochrome P450 isoenzyme CYP3A4, and therefore inducers of this isoenzyme, such as **St John's wort**, would be expected to decrease its levels. In the UK, the manufacturer predicts that a more pronounced decrease in the AUC of eplerenone might occur with stronger CYP3A4 inducers, such as **rifampicin** (**rifampin**).[1] Because of the possibility of decreased efficacy, they do not recommend the concurrent use of potent CYP3A4 inducers with eplerenone, and they specifically name **carbamazepine**, **phenytoin**, **phenobarbital**, **rifampicin**, and **St John's wort**.[1] However, it is unlikely that the decrease seen with **St John's wort** is clinically relevant. Further study of the other potential interactions is needed to demonstrate their clinical significance.

1. Inspra (Eplerenone). Pfizer Ltd. UK Summary of product characteristics, October 2009.
2. Inspra (Eplerenone). Pfizer Inc. US Prescribing information, April 2008.

Potassium-sparing diuretics; Eplerenone + CYP3A4 inhibitors

Ketoconazole markedly increases the bioavailability of eplerenone. The manufacturers of eplerenone contraindicate the concurrent use of ketoconazole, and other potent inhibitors of CYP3A4. Mild to moderate inhibitors of CYP3A4 (including diltiazem, fluconazole, saquinavir and verapamil) increase the AUC of eplerenone by up to almost threefold. Grapefruit juice had a small but unimportant effect on the AUC of eplerenone.

Clinical evidence

(a) Azoles

Ketoconazole 200 mg twice daily for 7 days increased the AUC of a single 100-mg dose of eplerenone 5.4-fold in 18 healthy subjects.[1,2] The manufacturers predict that **itraconazole** will have a similar effect to **ketoconazole**.[1,3] **Fluconazole** 200 mg daily for 7 days increased the AUC of eplerenone 2.2-fold in 18 healthy subjects.[2]

(b) Calcium-channel blockers

In 24 healthy subjects the steady-state AUC of eplerenone 100 mg daily was increased by about twofold by **verapamil** 240 mg daily for 7 days.[2] **Diltiazem** has caused similar increases in the AUC of eplerenone.[3]

(c) Grapefruit juice

Grapefruit juice caused only a small 25% increase in the AUC of eplerenone 100 mg.[1]

(d) Macrolides

In 24 healthy subjects **erythromycin** 500 mg twice daily increased the steady-state AUC of eplerenone 100 mg daily by 2.9-fold.[2] The manufacturers predict that **clarithromycin**,[1,3] **telithromycin**,[3] and **troleandomycin**[1] will have a greater effect. Eplerenone reduced the AUC of **erythromycin** by 14%, which was not considered clinically relevant.[2]

(e) Protease inhibitors

In 24 healthy subjects **saquinavir** 1.2 g three times daily increased the steady-state AUC of eplerenone 100 mg daily by 2.1-fold.[2] The manufacturers predict that **ritonavir** and **nelfinavir** will have a greater effect.[1,3] Eplerenone reduced the maximum level of **saquinavir** by 30%, and the AUC by 21%,[2] but the clinical relevance of this has not been assessed.

Mechanism

Eplerenone metabolism is primarily mediated by the cytochrome P450 isoenzyme CYP3A4, and therefore inhibitors of this isoenzyme will increase its bioavailability.

Importance and management

These pharmacokinetic interactions are established. Although the clinical relevance has not been assessed, it is known that the risk of hyperkalaemia with eplerenone is related to its dose.[3] Because the increase in the AUC of eplerenone with ketoconazole is so great, the manufacturers contraindicate this combination.[1,3] They also contraindicate the concurrent use of other potent inhibitors of CYP3A4, and they list clarithromycin, itraconazole, **nefazodone**, nelfinavir, ritonavir,[1,3] telithromycin[3] and troleandomycin.[1]

In the UK, the manufacturer recommends that the dose of eplerenone should not exceed 25 mg daily in patients taking mild to moderate CYP3A4 inhibitors such as **amiodarone**, diltiazem, erythromycin, fluconazole, saquinavir and verapamil.[3] In the US, the manufacturer recommends that the starting dose of eplerenone for hypertension should be reduced to 25 mg daily for patients taking these drugs.[1] This seems a sensible precaution. However, note that erythromycin sometimes appears to be as potent an inhibitor of CYP3A4 as clarithromycin (and certainly seems to be more potent than the other moderate CYP3A4 inhibitors listed above),[2] and so additional caution (e.g. increased monitoring of potassium levels) is probably warranted with this combination.

1. Inspra (Eplerenone). Pfizer Inc. US Prescribing information, April 2008.
2. Cook CS, Berry LM, Burton E. Prediction of *in vivo* drug interactions with eplerenone in man from *in vitro* metabolic inhibition data. *Xenobiotica* (2004) 34, 215–28.
3. Inspra (Eplerenone). Pfizer Ltd. UK Summary of product characteristics, October 2009.

Potassium-sparing diuretics; Spironolactone + Aspirin

Although aspirin reduces the spironolactone-induced loss of sodium in the urine it does not appear to alter the antihypertensive effects of spironolactone.

Clinical evidence

(a) Effects on blood pressure

Five patients with low-renin essential hypertension, well-controlled for 4 months or more with spironolactone 100 to 300 mg daily, took part in a crossover study. Aspirin 2.4 to 4.8 g daily given over 6-week periods had no effect on blood pressure, serum electrolytes, body-weight, blood-urea-nitrogen or plasma renin activity.[1]

(b) Effects on natriuresis

A study in 10 healthy subjects given single 25-, 50- and 100-mg doses of spironolactone, found that a single 600-mg dose of aspirin reduced the urinary excretion of sodium in response to spironolactone.[2] In a further study in 7 of these subjects, the effectiveness of the spironolactone was reduced by 70%, and the overnight sodium excretion was reduced by one-third when they were given spironolactone 25 mg four times daily for one week followed by a single 600-mg dose of aspirin.[2] Reductions in sodium ex-

cretion are described in other studies of this interaction.[3,4] In one of these, the sodium excretion brought about by spironolactone was completely abolished when aspirin was given 90 minutes after the spironolactone, but when the drugs were given in the reverse order the inhibition of sodium excretion, which was caused by aspirin, was not completely reversed by spironolactone.[4]

In another study in 7 patients with ascites due to liver cirrhosis, pretreatment with two doses of aspirin 900 mg reduced the natriuretic effect of spironolactone 300 mg daily by 33%. However, there was no significant change in urinary output.[5]

(c) Gynaecomastia

For mention of an isolated report of gynaecomastia occurring in a patient taking spironolactone when a compound analgesic preparation containing aspirin was added to his treatment, see 'Potassium-sparing diuretics; Spironolactone + Dextropropoxyphene (Propoxyphene)', below.

Mechanism

Uncertain. There is evidence that the active secretion of canrenone (the active metabolite of spironolactone) is blocked by aspirin, but the significance of this is not entirely clear.[3]

Importance and management

An adequately but not extensively documented interaction. Despite the results of the studies showing a reduced natriuretic effect, the small study in hypertensive patients shows that the effects of spironolactone on reducing blood pressure might not be affected by anti-inflammatory doses of aspirin. In general, concurrent use need not be avoided, but if the diuretic response to spironolactone is less than expected consider this interaction as a cause.

None of these studies looked at the effects of low-dose aspirin on spironolactone. Nevertheless, it is likely that the proven protective cardiovascular benefits of low-dose aspirin in patients with hypertension and/or coronary artery disease would usually outweigh the possible reduction in the efficacy of spironolactone. However, note that the European Society of Cardiology (ESC) and American College of Cardiology/American Heart Association (ACC/AHA) heart failure guidelines say that the prophylactic use of aspirin in patients with heart failure has not been proven unless the patient has underlying ischaemic heart disease[6,7] and should be avoided in patients with recurrent hospital admissions for worsening heart failure.[7] Consider also 'Potassium-sparing diuretics + NSAIDs', p.1132, for a discussion of the interactions of spironolactone with NSAIDs.

1. Hollifield JW. Failure of aspirin to antagonize the antihypertensive effect of spironolactone in low-renin hypertension. *South Med J* (1976) 69, 1034–6.
2. Tweeddale MG, Ogilvie RI. Antagonism of spironolactone-induced natriuresis by aspirin in man. *N Engl J Med* (1973) 289, 198–200.
3. Ramsay LE, Harrison IR, Shelton JR, Vose CW. Influence of acetylsalicylic acid on the renal handling of a spironolactone metabolite in healthy subjects. *Eur J Clin Pharmacol* (1976) 10, 43–8.
4. Elliott HC. Reduced adrenocortical steroid excretion rates in man following aspirin administration. *Metabolism* (1962) 11, 1015–18.
5. Mirouze D, Zipser RD, Reynolds TB. Effect of inhibitors of prostaglandin synthesis on induced diuresis in cirrhosis. *Hepatology* (1983) 3, 50–5.
6. Hunt SA. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult. A report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). *J Am Coll Cardiol* (2005) 46, e1–e82. Available at: http://content.onlinejacc.org/cgi/reprint/46/6/e1.pdf (accessed 01/02/10).
7. Swedberg K, Cleland J, Dargie H, Drexler H, Follath F, Komajda M, Tavazzi L, Smiseth OA, Gavazzi A, Haverich A, Hoes A, Jaarsma T, Korewicki J, Lévy S, Linde C, Lopez-Sendon JL, Nieminen MS, Piérard L, Remme WJ; Task Force for the diagnosis and treatment of CHF of the European Society of Cardiology. Guidelines for the diagnosis and treatment of chronic heart failure (update 2005). *Eur Heart J* (2005) 26, 1115–40. Available at: http://eurheartj.oxfordjournals.org/cgi/content/full/26/11/1115 (accessed 05/02/10).

Potassium-sparing diuretics; Spironolactone + Colestyramine

A few case reports have described hyperchloraemic metabolic acidosis, which was associated with the use of colestyramine and spironolactone.

Clinical evidence

Four case reports describe the development of hyperchloraemic metabolic acidosis in patients with liver cirrhosis taking colestyramine (up to about 25 g daily), who were also taking spironolactone 75 mg or 100 mg daily.[1-4] One patient developed significant hyperkalaemia (potassium 8 mmol/L),[4] and 2 patients developed mild renal impairment.[1,3] One patient had recently recovered from a respiratory tract infection, which the authors suggested may have contributed to the acidosis.[1] Acidosis resolved when the colestyramine was stopped.

Mechanism

Bicarbonate has been shown to compete *in vitro* with bile acids for binding sites on the colestyramine resin.[1,3] The chloride ions in the colestyramine resin may cause an anion exchange of not only the bile salts, as is the intention, but also bicarbonate in the small bowel. This removal of bicarbonate from the body can predispose to the development of a hyperchloraemic metabolic acidosis and hyperkalaemia. This might be exacerbated by the bicarbonate-losing and hyperkalaemic effects of spironolactone.[1-4]

Importance and management

In healthy subjects with normal renal function, acidosis does not usually occur, as the kidneys can correct it by increasing the excretion of chloride and production of bicarbonate.[1-4] However, in patients with renal impairment, volume depletion (e.g. secondary to diuretics) or concurrent conditions that predispose to acidosis (such as a respiratory tract infection), this interaction may be significant. It has been suggested that electrolytes should be closely monitored when patients who are at risk of an interaction are taking colestyramine and spironolactone,[1] although note that the interaction appears to be rare.

1. Eaves ER, Korman MG. Cholestyramine induced hyperchloremic metabolic acidosis. *Aust N Z J Med* (1984) 14, 670–2.
2. Clouston WM, Lloyd HM. Cholestyramine induced hyperchloremic metabolic acidosis. *Aust N Z J Med* (1985) 15, 271.
3. Scheel PJ, Whelton A, Rossiter K, Watson A. Cholestyramine-induced hyperchloremic metabolic acidosis. *J Clin Pharmacol* (1992) 32, 536–8.
4. Zapater P, Alba D. Acidosis and extreme hyperkalemia associated with cholestyramine and spironolactone. *Ann Pharmacother* (1995) 29, 199–200.

Potassium-sparing diuretics; Spironolactone + Dextropropoxyphene (Propoxyphene)

A single case report describes the development of gynaecomastia and a rash when a man taking spironolactone was given a compound analgesic preparation containing dextropropoxyphene.

Clinical evidence, mechanism, importance and management

A patient who had been taking spironolactone uneventfully for 4 years developed swollen, tender breasts and a rash on his chest and neck a fortnight after starting to take *Darvon Compound* (dextropropoxyphene, **aspirin**, **phenacetin** and **caffeine**). The problem disappeared when both drugs were withdrawn but the rash reappeared when the *Darvon Compound* alone was given and disappeared when it was withdrawn. No problems occurred when the spironolactone was given alone, but both the rash and the gynaecomastia recurred when the *Darvon Compound* was again added.[1] The reasons for this reaction are not understood. Gynaecomastia is a known adverse effect of spironolactone (incidence 1.2%), but the authors considered it unlikely that it should spontaneously develop after so many years of treatment. Consequently they attribute the reaction to an interaction with *Darvon Compound*, but say they cannot be sure which of the components is responsible. This is an isolated case, and would therefore not be expected to be of general relevance.

1. Licata AA, Bartter FC. Spironolactone-induced gynaecomastia related to allergic reaction to 'Darvon Compound'. *Lancet* (1976) ii, 905.

Potassium-sparing diuretics; Spironolactone + Food

Food may increase the plasma levels of spironolactone, but this did not alter its antihypertensive efficacy in one long-term study.

Clinical evidence, mechanism, importance and management

In a study in healthy subjects food increased the AUC of canrenone (the major active metabolite of spironolactone) by about 30% after a single 100-mg dose of spironolactone, when compared with the fasted state.[1] However, a 60-day study by the same research group later found that the steady-state canrenone levels did not differ when spironolactone 100 mg daily was taken at least 30 minutes before eating, compared with immediately after eating. Furthermore, in a crossover study in 10 hypertensive patients, the antihypertensive efficacy of spironolactone was not altered by food. It was suggested that the difference is due to a more specific drug assay in the second study.[2] Other authors have also found that, in healthy subjects, food increased the AUC of a single dose of spironolactone by 71%, and also increased the AUC of three of its metabolites (including canrenone) by 32%, but they did not assess whether this altered the hypotensive effect.[3] It appears from the long-term study, that food does not alter the antihypertensive efficacy of spironolactone. It has been recommended that spironolactone be taken with food to try and reduce the gastric irritant effects of the drug.[2]

1. Melander A, Danielson K, Scherstén B, Thulin T, Wåhlin E. Enhancement by food of canrenone bioavailability from spironolactone. *Clin Pharmacol Ther* (1977) 22, 100–3.
2. Thulin T, Wåhlin-Boll E, Liedholm H, Lindholm L, Melander A. Influence of food intake on antihypertensive drugs: spironolactone. *Drug Nutr Interact* (1983) 2, 169–73.
3. Overdiek HWPM, Merkus FWHM. Influence of food on the bioavailability of spironolactone. *Clin Pharmacol Ther* (1986) 40, 531–6.

Thiazide diuretics + Bile-acid binding resins

The absorption of hydrochlorothiazide can be reduced by more than one-third if colestipol is given concurrently. Chlorothiazide appears to interact similarly. Colestyramine also reduces the absorption of hydrochlorothiazide by more than two-thirds.

Clinical evidence

In 6 healthy subjects the plasma levels of **hydrochlorothiazide** were reduced by about two-thirds by **colestyramine** 8 g, taken 2 minutes before and 6 and 12 hours after a single 75-mg oral dose of **hydrochlorothiazide**. Total urinary excretion of **hydrochlorothiazide** fell by 83%. In a parallel study with **colestipol** 10 g, the blood levels of **hydrochlorothiazide** fell by about 14% and the total urinary excretion fell by 31%.[1] A further study found that giving the **colestyramine** 4 hours after the **hydrochlorothiazide** reduced the effects of the interaction but **hydrochlorothiazide** absorption was still reduced by one-third.[2] In another study **colestipol**, given simultaneously or one hour after **chlorothiazide**, reduced the urinary excretion of **chlorothiazide** by 58% and 54%, respectively.[3]

Mechanism

Hydrochlorothiazide becomes bound to these non-absorbable anionic exchange resins within the gut, and less is available for absorption.

Importance and management

Established interactions of clinical importance. The best dosing schedule would appear to be to give hydrochlorothiazide 4 hours before colestyramine to minimise mixing in the gut. Even so, a one-third reduction in hydrochlorothiazide absorption occurs[2] and the possibility of this interaction should be considered in patients taking colestyramine or colestipol who have a reduced response to this diuretic. The optimum time-interval with colestipol has not been investigated but it would be reasonable to take similar precautions. Note that it is normally recommended that other drugs are given 1 hour before or 4 to 6 hours after colestyramine and 1 hour before or 4 hours after colestipol.

1. Hunninghake DB, King S, La Croix K. The effect of cholestyramine and colestipol on the absorption of hydrochlorothiazide. *Int J Clin Pharmacol Ther Toxicol* (1982) 20, 151–4.
2. Hunninghake DB, Hibbard DM. Influence of time intervals for cholestyramine dosing on the absorption of hydrochlorothiazide. *Clin Pharmacol Ther* (1986) 39, 329–34.
3. Kauffman RE, Azarnoff DL. Effect of colestipol on gastrointestinal absorption of chlorothiazide in man. *Clin Pharmacol Ther* (1973) 14, 886–90.

Thiazide diuretics + Calcium and/or Vitamin D

Hypercalcaemia and possibly metabolic alkalosis can develop in patients who are given fairly high doses of vitamin D and/or moderately large amounts of calcium if they are also given a thiazide diuretic, which can reduce the urinary excretion of calcium. The oral vitamin D analogue, paricalcitol, is predicted to interact similarly. One case of hypercalcaemia has been reported in a patient using a high-strength topical tacalcitol with a thiazide diuretic.

Clinical evidence

(a) Calcium and vitamin D

An elderly woman taking **hydrochlorothiazide** 25 mg and triamterene 50 mg daily became confused, disorientated and dehydrated 6 months after starting to take vitamin D_2 50 000 units and calcium 1.5 g daily (as calcium carbonate) for osteoporosis. Her serum calcium level had risen to about 3.5 mmol/L (normal range about 2 to 2.6 mmol/L).[1]

A young woman with osteoporosis taking 3 mg of vitamin D_2 and calcium 2 g daily (as lactate) became hypercalcaemic 3 days after starting to take **chlorothiazide** 500 mg every 6 hours.[2]

(b) Calcium carbonate

A 47-year-old man was admitted to hospital complaining of dizziness and general weakness, which had begun 2 months previously. He was taking **chlorothiazide** 500 mg daily for hypertension, 'thyroid' 120 mg daily for hypothyroidism and calcium carbonate 7.5 to 10 g daily for heartburn. On examination he was found to have metabolic alkalosis with respiratory compensation, a total serum calcium concentration of 3.4 mmol/L (range given as 2.15 to 2.6 mmol/L) and an abnormal ECG. He was diagnosed as having the milk-alkali syndrome. Recovery was rapid when the thiazide and calcium carbonate were withdrawn and a sodium chloride infusion, furosemide and oral phosphates were given.[3]

An elderly woman with normal renal function taking **hydrochlorothiazide** 50 mg daily developed hypercalcaemia about 3 weeks after increasing her dose of calcium carbonate from 2.5 g daily to 7.5 g daily.[4] Another case describes hypercalcaemic alkalosis in an 87-year-old woman who had been prescribed **hydrochlorothiazide** with amiloride, but was also regularly self-medicating with a calcium-containing antacid (calcium/magnesium carbonate).[5]

In all three cases the thiazide diuretic was thought to be implicated as the levels of calcium ingestion, although moderately high, were in the region of the normally recommended doses.

(c) Oral vitamin D

In a group of 12 patients treated for hypoparathyroidism with vitamin D (**dihydrotachysterol** or **ergocalciferol**), 5 patients became hypercalcaemic when they took **bendroflumethiazide** or **methyclothiazide**.[6] A significant rise in plasma calcium levels occurred in 7 patients given vitamin D and **methyclothiazide** or **chlorothiazide**, and hypercalcaemia developed in 3 of them.[7] A study in 12 children taking **calcitriol** (31 nanograms/kg daily) found that the addition of **hydrochlorothiazide** (1 to 2 micrograms/kg daily) reduced the urinary excretion of calcium caused by the calcitriol.[8] Another study in 7 patients with vitamin D-induced calciuria found that the addition of **hydrochlorothiazide** and amiloride reduced the urinary excretion of calcium due to the **calcitriol** to a greater extent than **hydrochlorothiazide** alone. Moreover, the addition of amiloride helped to prevent adverse effects associated with the use of **hydrochlorothiazide**, such as hypokalaemia and alkalosis.[9]

(d) Topical vitamin D analogues

A case of asymptomatic hypercalcaemia has been reported in a patient taking **trichlormethiazide** 6 mg daily and using 10 g of a high-strength topical **tacalcitol** ointment (20 micrograms/g) daily for psoriasis as part of a clinical study. His calcium level reached a peak of 3.55 mmol/L 28 days after starting the tacalcitol ointment and it fell back to within the normal range within 7 days of stopping the ointment.[10]

Mechanism

The thiazide diuretics can cause calcium retention by reducing its urinary excretion. This, added to the increased intake of calcium, resulted in excessive calcium levels. Alkalosis (the milk-alkali syndrome, associated with hypercalcaemia, alkalosis, and renal impairment) may also occur in some individuals because the thiazide limits the excretion of bicarbonate. Note that loop diuretics such as furosemide increase the urinary excretion of calcium.

Importance and management

An established interaction. The incidence is unknown but the reports cited[6,7] suggest that it can be considerable if the intake of vitamin D and calcium are high. Concurrent use need not be avoided; thiazides have been used clinically to aid in the treatment of hypocalcaemia, by reducing urinary calcium excretion,[11] and to reduce vitamin-D induced hypercalciuria,[8,9] but the serum calcium levels should be regularly monitored to ensure that they do not become excessive. Patients should be warned about the ingestion of very large amounts of calcium carbonate (readily available without prescription) if they are taking thiazide diuretics. The manufacturer of **paricalcitol** suggests that a similar interaction is possible;[12] however, calcium levels should be routinely monitored in patients taking this drug, and so further precautions are unlikely to be necessary in those taking thiazides.

The case of hypercalcaemia with the use of a topical vitamin D analogue is rare and the strength of the preparation of tacalcitol used was fivefold higher than the current licensed preparation of 4 micrograms/g (*Curatoderm*). However, severe hypercalcaemia may develop when ointments containing **tacalcitol**, **calcipotriol** or **maxacalcitol** are abundantly applied to patients with psoriasis since the drugs can be easily absorbed through the skin lesions,[13] and it would seem reasonable to assume that this effect may be exacerbated by the concurrent use of thiazides. It may therefore be worth bearing this interaction in mind if a topical vitamin D analogue and a thiazide are given.

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Thiazide diuretics + NSAIDs

There is evidence that most NSAIDs can increase blood pressure in patients taking antihypertensives, including diuretics, although some studies have not found the increase to be clinically relevant. The concurrent use of NSAIDs with thiazide diuretics may exacerbate congestive heart failure and increase the risk of hospitalisation. Diuretics may increase the risk of NSAID-induced acute renal failure.

Clinical evidence

Various large epidemiological studies and meta-analyses of clinical studies have been conducted to assess the effect of NSAIDs on blood pressure in patients taking **antihypertensives**, and the findings of these are summarised in 'Table 23.2', (p.1027). In these studies, NSAIDs were not always associated with an increase in blood pressure, and the maximum increase was 6.2 mmHg. The effect has been shown for both coxibs and non-selective NSAIDs. In two meta-analyses,[1,2] the effects were evaluated by NSAID. The confidence intervals for all the NSAIDs overlapped, showing that there was no statistically significant difference between the NSAIDs, with the exception of the comparison between **indometacin** and **sulindac** in one analysis.[2] Nevertheless, an attempt was made at ranking the NSAIDs based on the means. In one analysis,[1] the effect was greatest for **piroxicam**, **indometacin**, and **ibuprofen**, intermediate for **naproxen**, and least for **sulindac** and **flurbiprofen**. In the other meta-analysis,[2] the effect was greatest for **indometacin** and **naproxen**, intermediate for **piroxicam**, and least for **ibuprofen** and **sulindac**. An attempt was also made to evaluate the effect by **antihypertensive** in one analysis.[1] The mean effect was greatest for beta blockers, intermediate for vasodilators (includes ACE inhibitors and calcium-channel blockers), and least for **diuretics**. However, the differences between the groups were not significant.

A retrospective analysis of records of patients taking **diuretics** (thiazides, loop and/or potassium-sparing) with NSAIDs found a twofold increase in the risk of hospitalisation for congestive heart failure on concurrent use. The most common NSAIDs taken by this cohort of patients were **diclofenac**, **ibuprofen**, **indometacin** and **naproxen**. The **diuretics** most often used were thiazides combined with potassium-sparing drugs and this therapy showed a significantly higher risk than the other diuretic therapies.[3]

A case-control study using the UK General Practice Research Database found that current NSAID use increased the risk of acute renal failure (relative risk 3.2 compared with no NSAID use) and this risk was further increased with concurrent **diuretic** use (relative risk 11.6).[4] Note that the risk of renal complications appear to be similar with coxibs as with non-specific NSAIDs.[5]

Individual clinical reports and clinical or pharmacological studies of the effects of specific NSAIDs on diuretics are outlined in the subsections below and in 'Table 26.2', (p.1126).

A. Altizide

An 80-year-old woman who had been successfully treated with altizide, **spironolactone**, bisoprolol and aspirin for 5 years experienced symptoms of progressive breathlessness, weight gain and nocturnal orthopnoea about 4 days after starting to take **rofecoxib** for arthritis. About 10 days later, she was admitted to hospital with heart failure and started to recover over the next 2 to 5 days following discontinuation of the **rofecoxib** and replacement of the beta blocker and diuretics with furosemide.[5] Note that rofecoxib has generally been withdrawn because of reports of cardiovascular adverse effects.

B. Bemetizide

In a study in healthy subjects **indometacin** 100 mg was found to reduce the urinary excretion of sodium and chloride caused by bemetizide by 47% and 44%, respectively.[6]

C. Bendroflumethiazide

(a) Ibuprofen

In a randomised, placebo-controlled study, 7 hypertensive patients taking bendroflumethiazide 5 to 10 mg daily were also given ibuprofen 400 mg four times daily for 2 weeks. Although some small increases in blood pressure occurred, the diastolic blood pressure of all patients remained below 90 mmHg throughout the ibuprofen phase. Overall no statistically significant weight gain was noted, although 2 patients gained more than 2 kg.[7]

(b) Indometacin

A controlled study in 7 hypertensive patients taking bendroflumethiazide 5 to 10 mg daily found that indometacin 100 mg daily for 3 weeks raised their blood pressure by 13/9 mmHg when lying and by 16/9 mmHg when standing. Body-weight increased by 1.1 kg.[8] Indometacin also attenuated the hypotensive effect of bendroflumethiazide in another study.[9]

(c) Sulindac

A brief report suggested that sulindac *enhanced* the hypotensive effects of bendroflumethiazide in 5 hypertensive patients.[9]

D. Chlortalidone

A 61-year-old man with a history of mild diabetes and hypertension who was taking chlortalidone 25 mg daily developed diabetic nephropathy after starting **ibuprofen**.[10]

E. Hydrochlorothiazide

(a) Coxibs

A study in healthy subjects found that a single 25-mg oral dose of **rofecoxib** reduced the natriuretic effect of hydrochlorothiazide 25 mg, but potassium excretion was unaltered.[11]

(b) Diclofenac

Diclofenac 25 mg three times daily was given to 8 patients with essential hypertension who were taking hydrochlorothiazide. Blood pressure was not significantly altered after the addition of diclofenac, but a weight gain of about 1 to 2 kg was noted, which was thought to have been caused by

the sodium retaining effects of diclofenac.[12] In another study in hypertensive black women, diclofenac 75 mg twice daily for one month did not alter the antihypertensive effect of the combination of hydrochlorothiazide 25 mg daily and lisinopril 10 to 40 mg daily.[13] A further study, in healthy subjects, found that diclofenac 50 mg reduced the natriuretic effect of hydrochlorothiazide, but potassium excretion was unchanged.[11]

(c) Diflunisal

Diflunisal 375 mg twice daily caused the plasma levels of hydrochlorothiazide to rise by 25 to 30%, but this does not appear to be clinically significant.[14] Diflunisal also has uricosuric activity, which may counteract the uric acid retention that occurs with hydrochlorothiazide.

(d) Ibuprofen

In two studies in patients taking hydrochlorothiazide, ibuprofen 400 or 600 mg three times daily for 4 weeks caused a small rise in systolic but not in diastolic blood pressure.[12,15] However, a weight gain of about 1 to 2 kg was noted in one of the studies.[12] Another study found that ibuprofen 400 mg three times daily had no effect on blood pressure controlled by **triamterene** with hydrochlorothiazide, although one patient had a marked reduction in renal function.[16] Ibuprofen 800 mg four times daily for a week had little effect on blood pressure controlled with hydrochlorothiazide in yet another study.[17] In two further studies, ibuprofen 800 mg three times daily for one month did not alter the antihypertensive effect of the combinations of hydrochlorothiazide 25 mg daily with fosinopril 10 to 40 mg daily[18] or lisinopril 10 to 40 mg daily.[13]

An 88-year-old patient taking multiple drugs developed severe hyponatraemia when hydrochlorothiazide was combined with **furosemide** and ibuprofen. The authors comment that the use of thiazides is sometimes overlooked when other drugs that may affect serum sodium, such as NSAIDs, are prescribed.[19]

For a report of acute renal failure after strenuous exercise in a patient taking ibuprofen and hydrochlorothiazide with triamterene, see 'Potassium-sparing diuretics + NSAIDs', p.1132.

(e) Indometacin

A controlled study in 7 patients with hypertension taking **amiloride** 5 to 10 mg with hydrochlorothiazide 50 to 100 mg, found that indometacin 100 mg daily for 3 weeks raised their blood pressure by 13/9 mmHg when lying and by 16/9 mmHg when standing. Body-weight increased by 1.1 kg.[8] A later study in patients taking hydrochlorothiazide found a 6/3 mmHg blood pressure rise after they took indometacin for 2 weeks, but this had gone after 4 weeks.[20] A blood pressure rise of only 5/1 mmHg was seen in another study in hypertensive patients taking hydrochlorothiazide with indometacin 100 mg daily.[21] Indometacin also attenuated the hypotensive effect of hydrochlorothiazide (given with **amiloride**) in another study.[9]

In other studies indometacin had no effect on blood pressure in healthy subjects,[22] no effect on the sodium excretion caused by hydrochlorothiazide,[23] and did not affect the pharmacokinetics of hydrochlorothiazide.[22,23] However, in one of these studies indometacin did attenuate the hydrochlorothiazide-induced decreases in body-weight and plasma potassium levels.[22]

For a report of hyperkalaemia in a patient taking indometacin and hydrochlorothiazide with amiloride and a report of acute renal failure in a patient taking indometacin and hydrochlorothiazide with triamterene, see 'Potassium-sparing diuretics + NSAIDs', p.1132.

(f) Kebuzone

A mean systolic blood pressure rise of 18 mmHg (from 171 to 189 mmHg) occurred in 15 patients taking hydrochlorothiazide 50 mg daily, when they were given kebuzone 750 mg daily. This rise represents about a 35% reduction in the antihypertensive effect of hydrochlorothiazide.[24]

(g) Naproxen

One study found that naproxen had no clinically relevant interaction with hydrochlorothiazide alone.[20] Naproxen had a similar lack of influence on the diuretic response to hydrochlorothiazide in another study in healthy subjects.[25] In a further study, in hypertensive patients, naproxen attenuated the antihypertensive efficacy of hydrochlorothiazide taken with **amiloride** and timolol, but how much of the attenuation was due to an interaction with the diuretic was unclear.[26]

A case report describes severe hyponatraemia resulting from the use of hydrochlorothiazide/**amiloride** and naproxen.[27]

(h) Phenylbutazone

A mean systolic blood pressure rise of 18 mmHg (from 171 to 189 mmHg) occurred in 15 patients taking hydrochlorothiazide 50 mg daily, when they were given phenylbutazone 750 mg daily. This rise represents about a 35% reduction in the antihypertensive effect of hydrochlorothiazide.[24]

(i) Piroxicam

One study found that piroxicam attenuated the antihypertensive efficacy of hydrochlorothiazide taken with **amiloride** and timolol, but how much of the attenuation is due to an interaction with the diuretic is unclear.[26]

(j) Sulindac

One study in healthy subjects found that pretreatment with sulindac 200 mg decreased the fractional urinary flow rate, produced by hydrochlorothiazide 100 mg alone, by 35% and attenuated the natriuretic effect of hydrochlorothiazide, over 0 to 4 hours, by 29%. However, beyond 4 hours, sulindac pretreatment did not affect these renal responses to hydrochlorothiazide.[25] Sulindac does not usually appear to reduce either the hypotensive or diuretic effects of hydrochlorothiazide,[12,20,21] and may even slightly *enhance* the antihypertensive effects of hydrochlorothiazide/**amiloride** with[26] or without,[9] timolol. Another study found that sulindac did not alter the antihypertensive efficacy of hydrochlorothiazide/**amiloride** given with beta blockers.[28] Similarly, sulindac 200 mg twice daily for one month did not alter the antihypertensive effect of the combinations of hydrochlorothiazide 25 mg daily with fosinopril 10 to 40 mg daily,[18] or lisinopril 10 to 40 mg daily.[13]

An 81-year-old woman who was taking hydrochlorothiazide, digoxin, methyldopa and potassium was admitted to hospital with pseudogout and was prescribed sulindac 400 mg followed by 200 mg twice daily for 2 days. She received 800 mg of sulindac within the first 22 hours and developed renal impairment over the next 4 days. The sulindac was discontinued and her renal function improved.[10]

F. Methyclothiazide

A 68-year-old woman with long-standing hypertension and diabetes who was receiving methyclothiazide, insulin, quinidine and nitrates was admitted to hospital with pericarditis. Renal impairment developed within 4 days of starting **indometacin** 25 mg three times daily and improved on discontinuation of the indometacin.[10]

G. Metolazone

(a) Indometacin

Indometacin was found to reduce the urinary sodium excretion in response to metolazone by 34% in 6 healthy subjects.[29] The excretion of total potassium fell by 30%.

(b) Sulindac

Sulindac was found to reduce the urinary sodium excretion in response to metolazone by 19% in 6 healthy subjects.[29] The excretion of total potassium fell by 16%.

H. Trichlormethiazide

For a report of raised serum creatinine levels when a patient receiving triamterene and trichlormethiazide was given diclofenac, see 'Potassium-sparing diuretics + NSAIDs', p.1132.

I. Unspecified

In a randomised study, **ibuprofen** 400 mg every 8 hours caused a mean increase in blood pressure of about 5 to 7 mmHg in 12 hypertensive patients taking thiazides with beta blockers or centrally-acting antihypertensives.[30]

Mechanism

Not understood. NSAIDs, including coxibs, can affect renal function and cause salt and water retention, which antagonises the effects of diuretics.[31] Prostaglandins have a role to play in renal function and drugs such as the NSAIDs, which inhibit prostaglandin synthesis, would therefore be expected to have some effect on the actions of diuretics, whose venodilatory effects also depend on the activity of the prostaglandins. See 'Loop diuretics + NSAIDs', p.1125.

The attenuation of the antihypertensive effect of thiazides by NSAIDs has not been uniformly observed; for example sulindac has been found to enhance the antihypertensive effect in some, but not all, studies, and ibuprofen and indometacin have been found to have variable effects.[32] It has been suggested that, in some cases, differences in the metabolism of NSAIDs may possibly affect renal prostaglandins, for example sulindac may have less effect because its active metabolite is highly protein bound

and does not appear in the urine in appreciable amounts,[9,26] but currently there appears to be insufficient data to distinguish between the NSAIDs. NSAIDs suppress diuretic-stimulated renin secretion and dietary salt intake may also alter the effect by varying endogenous renin activity.[32] A study in *rats* suggested that indometacin may oppose the effects of the thiazides by reducing chloride delivery to the site of thiazide action in the distal tubule.[33]

Importance and management

Overall, the evidence suggests that some patients taking thiazide diuretics can have a rise in blood pressure, and sometimes associated weight gain,[32] when given NSAIDs, but this may not always be clinically relevant. Furthermore the concurrent use of NSAIDs and diuretics may increase the risks of acute renal failure. Some consider that the use of NSAIDs should be kept to a minimum in patients taking antihypertensives.[34] The effects may be greater in the elderly and in those with blood pressures that are relatively high, as well as in those with salt imbalance such as in cardiac failure or liver disease.[31,34] However, others consider that the clinical importance of an interaction between NSAIDs and antihypertensives is less than has previously been suggested.[35] While their findings do not rule out a 2/1 mmHg increase in blood pressure with NSAIDs in treated hypertensives, they suggest that if patients in primary care have inadequate control of blood pressure, other reasons may be more likely than any effect of concurrent NSAIDs.[35] There is insufficient data at present to clearly differentiate between NSAIDs, although there is some evidence that the effects of indometacin are greatest and sulindac least. Further study is needed.

The thiazide-related diuretic metolazone may be used in conjunction with a loop diuretic in patients with congestive heart failure. In this context it is worth noting that the European Society of Cardiology (ESC) Task Force and the joint American College of Cardiology/American Heart Association both recommend avoiding NSAID use, if possible, in patients with congestive heart failure.[36,37]

For the effects of NSAIDs on other antihypertensive drug classes see 'ACE inhibitors', (p.32), 'beta blockers', (p.997), 'calcium-channel blockers', (p.1027) and 'loop diuretics', (p.1125).

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37. Swedberg K, Cleland J, Dargie H, Drexler H, Follath F, Komajda M, Tavazzi L, Smiseth OA, Gavazzi A, Haverich A, Hoes A, Jaarsma T, Korewicki J, Lévy S, Linde C, Lopez-Sendon J-L, Nieminen MS, Piérard L, Remme WJ; The Task Force for the diagnosis and treatment of CHF of the European Society of Cardiology. Guidelines for the diagnosis and treatment of chronic heart failure (update 2005). *Eur Heart J* (2005) 26, 1115–40. Available at: http://eurheartj.oxfordjournals.org/cgi/content/full/26/11/1115 (accessed 05/02/10).

Thiazide diuretics; Chlorothiazide + Fluoxetine

Fluoxetine 30 mg daily for 8 days did not affect the pharmacokinetics of a single dose of chlorothiazide 500 mg.[1] No dose adjustments would seem necessary on concurrent use.

1. Lemberger L, Bergstrom RF, Wolen RL, Farid NA, Enas GG, Aronoff GR. Fluoxetine: clinical pharmacology and physiologic disposition. *J Clin Psychiatry* (1985) 46, 14–19.

Thiazide diuretics; Hydrochlorothiazide + Phenytoin

A study in 7 healthy subjects found that pretreatment with phenytoin 100 mg three times daily for 6 days did not influence the pharmacokinetics of a single 75-mg oral dose of hydrochlorothiazide.[1]

1. Keller E, Sulzer U, Brennes M, Schollmeyer P, Hoppe-Seyler G. Disposition of hydrochlorothiazide (Hct) during phenytoin (Ph) treatment. *Klin Wochenschr* (1981) 59, 1223–4.

Thiazide diuretics; Hydrochlorothiazide + Propantheline

Propantheline can slightly increase the absorption of hydrochlorothiazide.

Clinical evidence, mechanism, importance and management

In 6 healthy fasting subjects the absorption of hydrochlorothiazide 75 mg was delayed and increased (AUC increased by 23% and urinary recovery increased by 36%) by propantheline 60 mg. It was suggested that this occurs because propantheline causes a slower delivery of the hydrochlorothiazide to its areas of absorption.[1] This small increase is unlikely to be clinically important.

1. Beermann B, Groschinsky-Grind M. Enhancement of the gastrointestinal absorption of hydrochlorothiazide by propantheline. *Eur J Clin Pharmacol* (1978) 13, 385–7.

27

Gastrointestinal drugs

The various gastrointestinal drug groups covered in this section are listed in 'Table 27.1', (below). Many of the interactions of these drugs occur by causing alterations in the absorption of other drugs. The section 'Drug absorption interactions', (p.3), discusses how these interactions occur and contains more detailed information on some of the mechanisms of interaction covered in this section.

Interactions of H_2-receptor antagonists

Cimetidine is a non-specific inhibitor of the cytochrome P450 isoenzyme-mediated hepatic metabolism of many drugs, and can therefore increase their plasma levels and/or bioavailability. These interactions are most likely to be clinically significant for drugs with a narrow therapeutic index. Famotidine, nizatidine and ranitidine do not inhibit cytochrome P450 to a clinically relevant extent and are therefore less likely than cimetidine to be involved in interactions that occur by this mechanism. However, it should be noted that the absorption of some drugs may be affected by the changes in gastric pH, which can be produced by any of the H_2-receptor antagonists. Furthermore, drug interactions may also occur because there is competition for renal tubular secretion: cimetidine, famotidine and ranitidine have all been implicated in this type of interaction.

This section is concerned with interactions that result in a change to the effect of the H_2-receptor antagonist. Interactions where H_2-receptor antagonists are affecting another drug are discussed in the section relevant to that drug.

Interactions of proton pump inhibitors

The cytochrome P450 isoenzyme CYP2C19 is the main route of metabolism of esomeprazole, lansoprazole, omeprazole, pantoprazole, and to a lesser extent rabeprazole. This isoenzyme is subject to genetic polymorphism,[1] (see 'Genetic factors in drug metabolism', (p.4), for a further explanation of polymorphism). The poor metaboliser phenotype for CYP2C19 is found in approximately 1 to 6% of Caucasians, 1 to 7.5% of Blacks and 12 to 23% of Oriental and Indian Asians.[2]

Most patients are extensive CYP2C19 metabolisers, and their major route for the metabolism of these proton pump inhibitors will be through this isoenzyme. As a consequence,[2] the levels of proton pump inhibitors in these patients are likely to be affected by drugs that inhibit or induce CYP2C19, such as 'fluvoxamine', (p.1161). Patients of the extensive metaboliser phenotype have also been shown in some studies to have a poorer clinical outcome, when compared with poor metabolisers e.g. in the eradication of *H. pylori,* as they tend to have lower therapeutic levels of proton pump inhibitors.[2-4]

Poor metabolisers, who lack CYP2C19 metabolising capacity, use alternative pathways to metabolise proton pump inhibitors, and this is mainly CYP3A4. Because poor metabolisers are more dependent on CYP3A4 for metabolism of the proton pump inhibitors the levels of proton pump inhibitors may be more significantly raised in these patients, when compared with extensive metabolisers, when they are given CYP3A4 inhibitors, such as 'clarithromycin' , (p.1160), or 'ketoconazole', (p.246).

Omeprazole and esomeprazole are also inhibitors of CYP2C19, and therefore they may increase the levels of drugs that are metabolised by this isoenzyme, such as diazepam.[1,2] Other CYP2C19 substrates are listed in 'Table 1.3', (p.6).

In vitro study suggests that some proton pump inhibitors, including omeprazole, lansoprazole and pantoprazole may possibly be P-glycoprotein substrates and inhibitors and this may be a factor in some of their interactions.[5] An example of this is the increase in lansoprazole levels caused by the P-glycoprotein inhibitor 'clarithromycin', (p.1160).

1. Robinson M, Horn J. Clinical pharmacology of proton pump inhibitors. What the practising physician needs to know. *Drugs* (2003) 63, 2739–54.
2. Desta Z, Zhao X, Shin JG, Flockhart DA. Clinical significance of the cytochrome P450 2C19 genetic polymorphism. *Clin Pharmacokinet* (2002) 41, 913–58.
3. Furuta T, Shirai N, Sugimoto M, Nakamura A, Hishida A, Ishizaki T. Influence of CYP2C19 pharmacogenetic polymorphism on proton pump inhibitor-based therapies. *Drug Metab Pharmacokinet* (2005) 20, 153–67.
4. Klotz U. Pharmacokinetic considerations in the eradication of *Helicobacter pylori. Clin Pharmacokinet* (2000) 38, 243–70.
5. Pauli-Magnus C, Rekersbrink S, Klotz U, Fromm MF. Interaction of omeprazole, lansoprazole and pantoprazole with P-glycoprotein. *Naunyn Schmiedebergs Arch Pharmacol* (2001) 364, 551–7.

Table 27.1 Gastrointestinal drugs

Group	*Drugs*
5-Aminosalicylates	Balsalazide, Mesalazine, Olsalazine, Sulfasalazine
Antidiarrhoeals	Loperamide
Antimuscarinics	Pirenzepine
Bismuth compounds	Bismuth salicylate, Bismuth subcitrate potassium, Bismuth subnitrate, Tripotassium dicitratobismuthate
H_2-receptor antagonists	Cimetidine, Famotidine, Nizatidine, Ranitidine, Roxatidine
Mucosal protectants	Carbenoxolone, Liquorice, Sucralfate
Prokinetic drugs	Cisapride, Mosapride
Proton pump inhibitors	Esomeprazole, Lansoprazole, Omeprazole, Pantoprazole, Rabeprazole

Alosetron + SSRIs

Fluvoxamine markedly increases alosetron levels. Alosetron had no clinically significant effect on fluoxetine pharmacokinetics in healthy subjects.

Clinical evidence, mechanism, importance and management

Note that isolated possible cases of serotonin syndrome have been reported when with other 5-HT_3-receptor antagonists were given with SSRIs, see 'SSRIs + 5-HT_3-receptor antagonists', p.1485.

(a) Fluoxetine

An open study in 12 healthy subjects found that alosetron 1 mg twice daily for 15 days had no clinically significant effect on the pharmacokinetics of a single 20-mg dose of fluoxetine. There was a median 3-hour delay in the time to reach peak levels of both *S*- and *R*-fluoxetine, but this was thought unlikely to be clinically relevant for a drug that requires several weeks to achieve its full therapeutic effect.[1]

(b) Fluvoxamine

The manufacturer of alosetron notes that fluvoxamine (50 mg increased to 200 mg daily for 16 days) increased the AUC of alosetron about sixfold and prolonged its half-life about threefold when a single 1-mg dose of alosetron was given on day 16. This was attributed to the potent inhibitory effect of fluvoxamine on the cytochrome P450 isoenzyme CYP1A2, by which alosetron is metabolised. These marked increases are likely to be clinically important, and the manufacturer contraindicates concurrent use of alosetron with fluvoxamine.[2]

1. D'Souza DL, Dimmitt DC, Robbins DK, Nezamis J, Simms L, Koch KM. Effect of alosetron on the pharmacokinetics of fluoxetine. *J Clin Pharmacol* (2001) 41, 455–8.
2. Lotronex (Alosetron hydrochloride). Prometheus Labs, Inc. US Prescribing information, April 2008.

Aluminium hydroxide + Ascorbic acid (Vitamin C) or Citrates

Patients with renal failure given aluminium compounds and oral citrates can develop a potentially fatal encephalopathy due to a very marked rise in blood-aluminium levels. A similar increase in aluminium levels may also occur in patients with normal renal function. There is also some evidence that aluminium compounds and ascorbic acid (vitamin C) may interact similarly.

Clinical evidence

(a) Ascorbic acid

A study in 13 healthy subjects given aluminium hydroxide 900 mg three times daily found that ascorbic acid (vitamin C) 2 g daily increased the urinary excretion of aluminium threefold.[1] Ascorbic acid significantly increases the concentration of aluminium in the liver, brain, and bones of *rats* given aluminium hydroxide.[2]

(b) Citrates

Cases of an interaction between aluminium hydroxide and oral citrates have been reported, some of which resulted in fatalities. Four patients with advanced chronic renal impairment taking aluminium hydroxide and citrate (**Shohl's**) solution died due to hyperaluminaemia.[3] When these cases were compared with another 34 renal patients, it was found that they had taken more aluminium hydroxide, more citrate, and were older. In the group as a whole, increased serum aluminium levels were correlated with increased citrate intake.[4] In a study, five healthy subjects were given aluminium hydroxide with or without citrate solution: aluminium levels were 11 micrograms/L at baseline, rising to 44 micrograms/L when aluminium hydroxide was given, and rising to 98 micrograms/L when citrate was added. Aluminium clearance also dramatically increased in the presence of citrate.[4] Another report describes this interaction in 2 patients with renal impairment, and in a possible further 6 patients, all of whom died.[5] In a further single-dose study in 6 patients with end-stage renal disease, sodium citrate with citric acid 30 mL markedly increased the AUC of aluminium (from a 30-mL dose of aluminium hydroxide gel) by 4.6-fold.[6] A number of other studies in healthy subjects have confirmed that citrate markedly increases aluminium absorption, see *Mechanism*, below.

A haemodialysis patient given **effervescent co-codamol** had a tenfold increase in serum aluminium levels. This was attributed to sodium citrate in the formulation which is used to produce the effervescence.[7]

Mechanism

Studies in healthy subjects clearly demonstrate that citrate markedly increases the absorption of aluminium from the gut.[4,8,9] The absorption is increased threefold if taken with **lemon juice**,[10] eight to tenfold if taken with **orange juice**,[11,12] and five to 50-fold if taken with citrate,[4,8,9,11] but the reason is not understood. It could be that a highly soluble aluminium citrate complex is formed.[5,8]

Importance and management

The interaction between aluminium and citrates in patients with renal impairment is established and clinically important as it is potentially fatal. Concurrent use should be strictly avoided. Remember too that some effervescent and dispersible tablets (including many proprietary non-prescription analgesics, indigestion and hangover remedies such as *Alka-Seltzer*) contain citric acid or citrates,[7,13] and they may also occur in soft drinks.[13] Haemodialysis patients should be strongly warned about these.

The interaction between aluminium and ascorbic acid is not yet well established, but the information available so far suggests that this combination should also be avoided by patients with renal impairment. It is not clear whether orange juice is also unsafe but the available evidence suggests that concurrent administration is probably best avoided.

The importance of the interaction between aluminium and citrates in subjects with normal renal function is by no means clear, because it is still not known whether increased aluminium absorption results in aluminium accumulation over the long-term in those with normal renal function.[12] Some authors have recommended that food or drinks containing citric acid (citrus fruits and fruit juices) should not be taken at the same time as aluminium-containing medicines, but that their ingestion should be separated by 2 to 3 hours.[12] However, one study in healthy subjects reported significantly raised aluminium levels when a citric acid solution and an aluminium hydroxide antacid were taken 2 hours apart.[14] Further study is needed in subjects with normal renal function to establish the clinical significance of a possible interaction.

It is worth noting that formulations of a wide range of drugs (including many non-prescription preparations) contain citrates as the effervescing or dispersing agent.

1. Domingo JL, Gomez M, Llobet JM, Richart C. Effect of ascorbic acid on gastrointestinal aluminium absorption. *Lancet* (1991) 338, 1467.
2. Domingo JL, Gomez M, Llobet JM, Corbella J. Influence of some dietary constituents on aluminum absorption and retention in rats. *Kidney Int* (1991) 39, 598–601.
3. Bakir AA, Hryhorczuk DO, Berman E, Dunea G. Acute fatal hyperaluminemic encephalopathy in undialyzed and recently dialyzed uremic patients. *Trans Am Soc Artif Intern Organs* (1986) 32, 171–6.
4. Bakir AA, Hryhorczuk DO, Ahmed S, Hessl SM, Levy PS, Spengler R, Dunea G. Hyperaluminemia in renal failure: the influence of age and citrate intake. *Clin Nephrol* (1989) 31, 40–4.
5. Kirschbaum HB, Schoolwerth AC. Acute aluminum toxicity associated with oral citrate and aluminum-containing antacids. *Am J Med Sci* (1989) 297, 9–11.
6. Rudy D, Sica DA, Comstock T, Davis J, Savory J, Schoolwerth AC. Aluminum-citrate interaction in end-stage renal disease. *Int J Artif Organs* (1991) 14, 625–9.
7. Main J, Ward MK. Potentiation of aluminium absorption by effervescent analgesic tablets in a haemodialysis patient. *BMJ* (1992) 304, 1686.
8. Coburn JW, Mischel MG, Goodman WG, Salusky IB. Calcium citrate markedly enhances aluminum absorption from aluminium hydroxide. *Am J Kidney Dis* (1991) 17, 708–11.
9. Walker JA, Sherman RA, Cody RP. The effect of oral bases on enteral aluminum absorption. *Arch Intern Med* (1990) 150, 2037–9.
10. Slanina P, Frech W, Ekström L-G, Lööf L, Slorach S, Cedergren A. Dietary citric acid enhances absorption of aluminum in antacids. *Clin Chem* (1986) 32, 539–41.
11. Weberg R, Berstad A. Gastrointestinal absorption of aluminium from single doses of aluminium containing antacids in man. *Eur J Clin Invest* (1986) 16, 428–32.
12. Fairweather-Tait S, Hickson K, McGaw B, Reid M. Orange juice enhances aluminium absorption from antacid preparation. *Eur J Clin Nutr* (1994) 48, 71–3.
13. Dorhout Mees EJ, Basçi A. Citric acid in calcium effervescent tablets may favour aluminium intoxication. *Nephron* (1991) 59, 322.
14. Mauro LS, Kuhl DA, Kirchhoff JR, Mauro VF, Hamilton RW. Impact of oral bases on aluminium absorption. *Am J Ther* (2001) 8, 21–5.

Antacids + Milk

Hypercalcaemia, alkalosis and renal impairment (milk-alkali syndrome) can develop in patients taking antacids with calcium-containing substances, including dairy products.

Clinical evidence

A man presented with nausea, vomiting, constipation, polyuria and polydipsia, which was diagnosed as milk-alkali syndrome, due to daily treatment with 6 tablets of *Caved-S* and 3.5 pints of milk, for dyspepsia related to a peptic ulcer.[1] This dose of *Caved-S* meant he was taking 600 mg of **aluminium hydroxide**, 1.2 g of **magnesium carbonate**, 600 mg of **sodium bicarbonate** and 2.28 g of **deglycyrrhizinised liquorice** daily.[1] Another case report describes a 42-year-old man who presented with confusion, agitation, involuntary movements of his limbs, severe dehydration, and metabolic and respiratory alkalosis. He had taken large amounts of a **calcium**/**magnesium carbonate**-containing antacid preparation (*Rennies)* and had also consumed at least 3 litres of diary products each day for upper abdominal complaints. Milk-alkali syndrome was diagnosed and he was successfully treated with isotonic saline and potassium.[2] A pregnant woman developed vomiting, drowsiness, abdominal pain and acute pancreatitis after excessive antacid use. She had been taking up to 10 tablets of *Rennies* antacid (**calcium**/**magnesium carbonate**), containing about 3 g of elemental calcium with up to 3 glasses of milk each day.[3]

In a study in 125 patients with non end-stage renal disease, milk-alkali syndrome was found to be the cause of hypercalcaemia in 11 (8.8%) of the patients: 9 had severe hypercalcaemia (serum calcium greater than 3.5 mmol/L).[4] Two cases have also been reported in patients taking standard doses of **calcium carbonate** who also had other risk factors for developing severe hypercalcaemia and milk-alkali syndrome (such as concurrent medications, acute renal impairment, volume depletion).[5] Several other cases have been reported in recent years involving excessive use of non-prescription **calcium carbonate**,[6-8] one of which was in a pregnant woman.[7]

Mechanism

High intake and absorption of calcium can suppress the parathyroid hormone, which leads to bicarbonate retention by the kidneys, leading to metabolic and respiratory alkalosis. The alkalosis also causes reduced excretion of calcium by the kidneys. Hypermagnesaemia may also have a part to play.

Importance and management

The milk-alkali syndrome was a common adverse effect of antacid use when it was the primary treatment of peptic ulcer disease, but it has become very uncommon with the advent of H_2-receptor antagonists and proton pump inhibitors. However, the above cases illustrate that while taking antacids, even well within the recommended dosage range, as in the first case, it is still possible to develop a serious and potentially life-threatening reaction if the intake of calcium is high. This should be borne in mind in patients who take medications containing calcium, such as antacids or supplements for the prophylaxis of osteoporosis, and also consume large quantities of dairy products in their diet. Note that many calcium-containing antacids are freely available without prescription. Chronic milk-alkali syndrome can lead to the formation of calcification and kidney damage, which may be irreversible. The quantity of calcium ingested does not appear to be directly correlated to either the development or severity of milk-alkali syndrome, which has been reported with an intake of between 4 g to 60 g of calcium carbonate.[3] However, a safe maximum calcium intake of 1.2 to 1.5 g of elemental calcium (3 to 3.75 g of calcium carbonate) has been suggested.[3]

1. Gibbs CJ, Lee HA. Milk-alkali syndrome due to Caved-S. *J R Soc Med* (1992) 85, 498–9.
2. Verburg FA, van Zanten RAA, Brouwer RML, Woittiez AJJ, Veneman TF. Een man met een ernstig klassiek melk-alkalisyndroom en een maagcarcinoom. *Ned Tijdschr Geneeskd* (2006) 150, 1624–7.
3. Gordon MV, Hamblin PS, McMahon LP. Life-threatening milk-alkali syndrome resulting from antacid ingestion during pregnancy. *Med J Aust* (2005) 182, 350–351
4. Picolos MK, Lavis VR, Orlander PR. Milk–alkali syndrome is a major cause of hypercalcaemia among non-end-stage renal disease (non-ESRD) inpatients. *Clin Endocrinol (Oxf)* (2005) 63, 566–76.
5. Picolos MK, Orlander PR. Calcium carbonate toxicity: the updated milk-alkali syndrome; report of 3 cases and review of the literature. *Endocr Pract* (2005) 11, 272–280.
6. McGuinness B, Logan JI. Milk alkali syndrome. *Ulster Med J* (2002) 71, 132–5.
7. Ennen CS, Magann EF. Milk-alkali syndrome presenting as acute renal insufficiency during pregnancy. *Obstet Gynecol* (2006) 108, 785–6.
8. George S, Clark JDA. Milk alkali syndrome – an unusual syndrome causing an unusual complication. *Postgrad Med J* (2000) 76, 422–4.

Aprepitant + CYP2C9 substrates

Aprepitant is an inducer of the cytochrome P450 isoenzyme CYP2C9, and slightly reduces the plasma levels of substrates of this isoenzyme such as 'warfarin', (p.432), and 'tolbutamide' (p.588). The manufacturers therefore recommend caution when aprepitant is given with other drugs that are known to be metabolised by CYP2C9, because of the possibility that their plasma levels may be reduced.[1,2] They specifically mention phenytoin. However, phenytoin is also an inducer of CYP3A4 and the manufacturers predict that it will decrease the levels of aprepitant, and might reduce its efficacy, see 'Aprepitant + CYP3A4 inducers', below.[1,2] Consequently, the UK manufacturer advises avoiding the concurrent use of phenytoin.[1] Other CYP2C9 substrates are listed in 'Table 1.3', (p.6).

1. Emend (Aprepitant). Merck Sharp & Dohme Ltd. UK Summary of product characteristics, July 2009.
2. Emend (Aprepitant). Merck & Co., Inc. US Prescribing information, July 2009.

Aprepitant + CYP3A4 inducers

Rifampicin markedly reduced the AUC of aprepitant, and reduced efficacy would be expected. The concurrent use of aprepitant and other potent inducers of CYP3A4 should be avoided.

Clinical evidence, mechanism, importance and management

The manufacturers note that when a single 375-mg dose of aprepitant was given on day 9 of a 14-day regimen of **rifampicin** 600 mg daily, the AUC of aprepitant was decreased by about 91%, and the half-life decreased by about 68%.[1,2]

Rifampicin is an inducer of the cytochrome P450 isoenzyme CYP3A4, by which aprepitant is metabolised. Concurrent use therefore decreases aprepitant levels

Although not assessed, this marked reduction in aprepitant levels could result in reduced efficacy. In the UK, the manufacturer recommends that concurrent use of aprepitant and potent inducers of CYP3A4, such as **rifampicin**, be avoided.[1] They also name **phenytoin** (see also 'Aprepitant + CYP2C9 substrates', above), **carbamazepine**, and **phenobarbital**, and also recommend that concurrent use of **St John's wort** is avoided.[1] **Primidone** is metabolised to phenobarbital and is therefore likely to interact similarly. Other inducers of CYP3A4 are listed in 'Table 1.4', (p.6).

1. Emend (Aprepitant). Merck Sharp & Dohme Ltd. UK Summary of product characteristics, July 2009.
2. Emend (Aprepitant). Merck & Co., Inc. US Prescribing information, July 2009.

Aprepitant + CYP3A4 inhibitors

Ketoconazole markedly increases aprepitant levels. Other potent inhibitors of CYP3A4 are predicted to interact similarly.

Clinical evidence, mechanism, importance and management

The manufacturers note that when a single 125-mg dose of aprepitant was given on day 5 of a 10-day course of **ketoconazole** 400 mg daily, the AUC of aprepitant was increased by about fivefold, and the half-life by about threefold.[1,2]

Ketoconazole is an inhibitor of the cytochrome P450 isoenzyme CYP3A4, by which aprepitant is metabolised. Concurrent use therefore raises aprepitant levels.

Although the effect of these increases has not been assessed, such marked increases in levels could increase adverse effects. The manufacturers recommend caution when aprepitant is given with **ketoconazole** and other drugs that are potent inhibitors of CYP3A4. They specifically name **protease inhibitors** (the US manufacturer names **nelfinavir** and **ritonavir**), **clarithromycin**, **itraconazole**, **nefazodone**,[1,2] **troleandomycin**,[2] **telithromycin**, **posaconazole**, and **voriconazole.**[1].

For the effect of **diltiazem** (a moderate CYP3A4 inhibitor), see 'Calci-

um-channel blockers + Aprepitant', p.1026. Other inhibitors of CYP3A4 are listed in 'Table 1.4', (p.6).

1. Emend (Aprepitant). Merck Sharp & Dohme Ltd. UK Summary of product characteristics, July 2009.
2. Emend (Aprepitant). Merck & Co., Inc. US Prescribing information, July 2009.

Aprepitant + CYP3A4 substrates

Aprepitant can increase the levels of CYP3A4 substrates in the short-term, then reduce them within 2 weeks. Concurrent use of aprepitant with pimozide, terfenadine, astemizole or cisapride is contraindicated.

Clinical evidence, mechanism, importance and management

In the first few days of use, aprepitant 125 mg on day 1 followed by 80 mg daily for 4 days markedly increased levels of midazolam, a probe drug substrate for the cytochrome P450 isoenzyme CYP3A4. Then, within 2 weeks, a reduction in levels was seen, see 'Benzodiazepines + Aprepitant', p.840. This effect was not seen with a dose regimen of 40 mg on day 1 followed by 25 mg daily for 4 days. Aprepitant is therefore both a dose-dependent inhibitor and an inducer of CYP3A4.

Because of this, aprepitant is expected to increase drug levels of other CYP3A4 substrates by up to about threefold, and the manufacturer recommends caution.[1,2] They specifically recommend caution with **ergot derivatives**.[1] Moreover, the manufacturers specifically contraindicate the concurrent use of aprepitant with **pimozide**, **terfenadine**, **astemizole** or **cisapride**, because of the risk of life-threatening torsade de pointes arrhythmias with increased levels.

For a list of CYP3A4 substrates, see 'Table 1.4', (p.6). Within 2 weeks of aprepitant therapy, a reduced level of CYP3A4 substrates might occur, and caution is also advised during this time.

For recommendations regarding antineoplastics that are CYP3A4 substrates, see 'Antineoplastics + Aprepitant', p.701.

1. Emend (Aprepitant). Merck Sharp & Dohme Ltd. UK Summary of product characteristics, July 2009.
2. Emend (Aprepitant). Merck & Co., Inc. US Prescribing information, July 2009.

Bismuth compounds + Food

Food may reduce the absorption of bismuth.

Clinical evidence, mechanism, importance and management

In a study in healthy subjects given **tripotassium dicitratobismuthate** (containing approximately 216 mg bismuth) 2 hours before a standard breakfast, peak plasma levels of bismuth were found to be on average 64 micrograms/L around 30 minutes later; one subject had bismuth level of 232 micrograms/L and ten others had a level greater than 50 micrograms/L. However, when the same bismuth compound was taken immediately after a standard breakfast, the bismuth levels were found to be lower (an average of 10.9 micrograms/mL, one subject levels were 120 micrograms/mL). In contrast, basic **bismuth carbonate** (equivalent to 160 mg bismuth) produced very low systemic levels of bismuth (no patient had a level greater than 2.7 micrograms/L) and food did not significantly affect its absorption.[1] The manufacturers recommend that **tripotassium dicitratobismuthate** (*De-Noltab*, containing 120 mg of bismuth per tablet, usual dose of up to 4 tablets daily) should be taken half an hour before each of the three main meals of the day and 2 hours after the last meal of the day or taken twice daily, half an hour before both breakfast and the evening meal.[2]

The manufacturers of *Pylorid* (**ranitidine bismuth citrate**) noted that food causes a decrease in bismuth absorption which is not of clinical relevance, but because of limited data that suggest increased ulcer healing when *Pylorid* is given with food, they noted that it should preferably be taken with food.[3]

Food reduced the bioavailability of a single tablet containing a combination of **bismuth subcitrate potassium**, metronidazole and tetracycline in one study. However, the efficacy of this combined preparation for eradication of *Helicobacter pylori* does not seem to be affected (eradication rates reported at nearly 90%) and the authors suggest that this prolonged local exposure in the stomach may be beneficial.[4] Again the manufacturers note that reduced absorption is not considered clinically significant and they recommend that *Pylera* (**bismuth subcitrate potassium**) should be given after meals and at bedtime.[5]

1. Madaus S, Schulte-Frohlinde E, Scherer C, Kämmereit A, Schusdziarra V, Classen M. Comparison of plasma bismuth levels after oral dosing with basic bismuth carbonate or tripotassium dictrato bismuthate. *Aliment Pharmacol Ther* (1992) 6, 241–9.
2. De-Noltab (Tripotassium dictratobismuthate). Astellas Pharma Ltd. UK Summary of product characteristics, July 2007.
3. Pylorid Tablets (Ranitidine bismuth citrate). GlaxoSmithKline UK. UK Summary of product characteristics, December 2005.
4. Spénard J, Aumais C, Massicotte J, Brunet J-S, Tremblay C, Grace M, Lefebvre M. Effects of food and formulation on the relative bioavailability of bismuth biskalcitrate, metronidazole, and tetracycline given for *Helicobacter pylori* eradication. *Br J Clin Pharmacol* (2005) 60, 374–7.
5. Pylera (Bismuth subcitrate potassium, metronidazole, and tetracycline hydrochloride). Axcan Pharma Inc. US Prescribing information, February 2007.

Bismuth compounds + H_2-receptor antagonists

Ranitidine possibly causes an increase in the absorption of bismuth from tripotassium dicitratobismuthate, but not bismuth salicylate or bismuth subnitrate. Any increase is considered unlikely to be clinically relevant with recommended short courses for *H. pylori* eradication. Other H_2-receptor antagonists would be expected to interact similarly.

Clinical evidence, mechanism, importance and management

In 12 healthy subjects the AUC of a single 240-mg dose of **tripotassium dicitratobismuthate** (TDB, *De Noltabs*), was increased fourfold by two 300-mg doses of ranitidine (taken the night before and 2 hours before the bismuth compound). The maximum serum levels were approximately doubled. The same regimen of ranitidine had no significant effect on the absorption of bismuth from **bismuth salicylate** (*Pepto-Bismol*) or **bismuth subnitrate** (*Roter* tablets).[1]

The authors suggest that the reduction in gastric acidity maintains TDB in its colloidal form, which is more likely to be absorbed, and that this may result in increased bismuth toxicity.[1] Other H_2-receptor antagonists, and other drugs that reduce gastric acidity would be expected to interact similarly (see also 'Bismuth compounds + Proton pump inhibitors', below).

However, the manufacturers of TDB say that the toxic range of bismuth is arbitrary and a small increase in absorption is not clinically relevant, except perhaps in patients with renal failure, in whom this bismuth compound should be avoided in any case.[2] Note that a complex of ranitidine with bismuth and citrate (**ranitidine bismuth citrate**) is available in many countries and is a recommended constituent in one of the triple therapy regimens for *H. pylori* eradication. As with all bismuth compounds, it is recommended that this is used only for limited periods: a maximum of 16 weeks (two 8-week courses or four 4-week courses) in a 12-month period.[3]

1. Nwokolo CU, Prewett EJ, Sawyerr AM, Hudson M, Pounder RE. The effect of histamine H_2-receptor blockade on bismuth absorption from three ulcer-healing compounds. *Gastroenterology* (1991) 101, 889–94.
2. Yamanouchi Pharma Ltd. Personal communication, November 1994.
3. Pylorid Tablets (Ranitidine bismuth citrate). GlaxoSmithKline UK. UK Summary of product characteristics, December 2005.

Bismuth compounds + Proton pump inhibitors

Omeprazole markedly increases the absorption and bioavailability of bismuth. Other proton pump inhibitors are expected to interact similarly. However, this is probably unlikely to be clinically relevant.

Clinical evidence

In a randomised study, 34 healthy subjects were given a triple therapy capsule *Helizide* (containing **bismuth subcitrate potassium** 140 mg, metronidazole 125 mg, and tetracycline 125 mg) at a dose of three capsules four times daily, with or without omeprazole 20 mg twice daily for 6 days. Omeprazole increased the maximum plasma levels and AUC of bismuth by about threefold. However, the maximum plasma level achieved was 25.5 micrograms/L, which was still well below 50 micrograms/L, a level reported to be highly unlikely to cause toxicity.[1] The authors also state that in clinical studies in which *Helizide* was given with omeprazole for

10 days to several hundred patients,[2] no patient showed signs of encephalopathy, a notable toxic adverse effect of bismuth.[1]

In an earlier single-dose study in 6 healthy subjects, a single 240-mg dose of **tripotassium dicitratobismuthate** was taken 1 hour after the last dose of a 1-week course of omeprazole 40 mg daily. Omeprazole increased the AUC of bismuth fourfold, and increased the maximum plasma levels from 36.7 to 86.7 micrograms/L, which the authors pointed out approaches the considered 'toxic range' for bismuth (100 micrograms/L and above).[3]

Mechanism

The solubility and absorption of some bismuth compounds are known to be increased by decreased acidity of the stomach.[1] See also 'Bismuth compounds + H_2-receptor antagonists', p.1145).

Importance and management

The authors of the single-dose study recommended that the dosage of tripotassium dicitratobismuthate should be halved when given with omeprazole because of the possibility of systemic bismuth toxicity.[3] However, an increased risk of toxicity has not been seen in subsequent studies using bismuth subcitrate potassium for up to 10 days.[1,2] The manufacturers of tripotassium dicitratobismuthate say that the toxic range of bismuth is arbitrary and the small increase in absorption is not clinically relevant, except perhaps in patients with renal failure, in whom this bismuth compound should be avoided in any case.[4] No clinically significant effect would be expected if combined treatment is limited to the recommended 2-week regimen for resistant *Helicobacter pylori* infection. As this interaction is due to changes in gastric pH other proton pump inhibitors would be expected to interact similarly.

1. Spénard J, Aumais C, Massicotte J, Tremblay C, Lefebvre M. Influence of omeprazole on bioavailability of bismuth following administration of a triple capsule of bismuth biskalcitrate, metronidazole, and tetracycline. *J Clin Pharmacol* (2004) 44, 640–5.
2. O'Morain C, Borody T, Farley A, De Boer WA, Dallaire C, Schuman R, Piotrowski J, Fallone CA, Tytgat G, Mégraud F, Spénard J. Efficacy and safety of single-triple capsules of bismuth biskalcitrate, metronidazole and tetracycline, given with omeprazole, for the eradication of Helicobacter pylori: an international multicentre study. *Aliment Pharmacol Ther* (2003) 17, 415–20.
3. Treiber G, Walker S, Klotz U. Omeprazole-induced increase in the absorption of bismuth from tripotassium dicitrato bismuthate. *Clin Pharmacol Ther* (1994) 55, 486–91.
4. Yamanouchi Pharma Ltd. Personal communication, November 1994.

Carbenoxolone + Antacids

There is some evidence that antacids may possibly reduce the bioavailability of carbenoxolone liquid.

Clinical evidence, mechanism, importance and management

The bioavailability of carbenoxolone in a liquid formulation was found to be approximately half that of carbenoxolone in granular and capsule formulations when each preparation was given with an **aluminium/magnesium hydroxide** antacid.[1] The extent to which antacids might reduce the ulcer-healing effects of carbenoxolone liquid seems not to have been assessed, but consider the possibility of a reduction in its efficacy if an antacid is also given.

1. Crema F, Parini J, Visconti M, Perucca E. Effetto degli antiacidi sulla biodisponibilità del carbenoxolone. *Farmaco (Prat)* (1987) 42, 357–64.

Carbenoxolone + Antihypertensives

Carbenoxolone causes fluid retention and raises blood pressure in some patients. This may be expected to oppose the effects of antihypertensive drugs. The potassium-depleting effects of carbenoxolone and diuretics such as the thiazides or loop diuretics can be additive. Both spironolactone and amiloride can oppose the ulcer-healing effects of carbenoxolone.

Clinical evidence, mechanism, importance and management

(a) Antihypertensives, general

Carbenoxolone can raise blood pressure. Five out of 10 patients taking carbenoxolone 300 mg daily, and 2 out of 10 patients taking carbenoxolone 150 mg daily, had a rise in their diastolic blood pressure of 20 mmHg or more.[1] Other reports[2-8] confirm that fluid retention and hypertension occur in those taking carbenoxolone, with the reported incidence of hypertension varying from as low as 4%[8] to as high as 50%,[7] and fluid retention occurring in 0%[2] to 46% of patients.[7] The reason for the blood pressure rise is that carbenoxolone has mineralocorticoid-like activity and therefore causes sodium and water retention. There appear to be few direct reports of adverse interactions between antihypertensives and carbenoxolone. Patients taking carbenoxolone should have regular checks on their weight and blood pressure, and carbenoxolone should be used with caution, if at all, in those with cardiac disease such as hypertension or congestive heart failure (see also, Diuretics, below).

(b) Diuretics

Spironolactone[3] (an aldosterone antagonist) and **amiloride**[9] are best avoided with carbenoxolone because they oppose its ulcer-healing effects, but there is a case report of the successful use of **spironolactone** in a patient with carbenoxolone-associated hypertension and hypokalaemia.[10] **Thiazide diuretics** have been used to control the oedema and hypertension caused by carbenoxolone. However, if these or other potassium-depleting diuretics (see 'Table 26.1', (p.1121)) are used it should be remembered that the potassium-losing effects of the carbenoxolone and the diuretic may be additive, and therefore a potassium supplement may be needed to prevent hypokalaemia. For example, rhabdomyolysis and acute tubular necrosis associated with severe hypokalaemia occurred in a patient given carbenoxolone and **chlortalidone**, without a potassium supplement.[11] Laryngospasm and stridor have been reported in a patient secondary to hypokalaemia and alkalosis caused by long-term use of **furosemide** and a carbenoxolone-containing antacid (*Pyrogastrone*).[12] Possible alternatives to carbenoxolone are the H_2-receptor antagonists, or the proton pump inhibitors, which do not appear to interact with antihypertensives.

1. Turpie AGG, Thomson TJ. Carbenoxolone sodium in the treatment of gastric ulcer with special reference to side-effects. *Gut* (1965) 6, 591.
2. Bank S, Marks IN. Maintenance carbenoxolone sodium in the prevention of gastric ulcer recurrence. In: Baron A, Sullivan S, eds. Carbenoxolone Sodium: London: Butterworths; 1970. p. 103–16.
3. Doll R, Langman MJS, Shawdon HH. Treatment of gastric ulcer with carbenoxolone: antagonistic effect of spironolactone. *Gut* (1968) 9, 42–5.
4. Montgomery RD, Cookson JB. Comparative trial of carbenoxolone and a deglycyrrhizinated liquorice preparation (Caved-S). *Clin Trials J* (1972) 9, 33–5.
5. Langman MJS, Knapp DR, Wakley EJ. Treatment of chronic gastric ulcer with carbenoxolone and gefarnate: a comparative trial. *BMJ* (1973) 3, 84–6.
6. Horwich L, Galloway R. Treatment of gastric ulceration with carbenoxolone sodium: clinical and radiological evaluation. *BMJ* (1965) 2, 1274–7.
7. Fraser PM, Doll R, Langman MJS, Misiewicz JJ, Shawdon HH. Clinical trial of a new carbenoxolone analogue (BX-24), zinc sulphate, and vitamin A in the treatment of gastric ulcer. *Gut* (1972) 13, 459–63.
8. Montgomery RD. Side effects of carbenoxolone sodium: a study of ambulant therapy of gastric ulcer. *Gut* (1967) 8, 148–50.
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11. Descamps C, Vandenbroucke JM, van Ypersele de Strihou C. Rhabdomyolysis and acute tubular necrosis associated with carbenoxolone and diuretic treatment. *BMJ* (1977) 1, 272.
12. Sarkar SK. Stridor due to drug-induced hypokalaemic alkalosis. *J Laryngol Otol* (1987) 101, 197–8.

Carbenoxolone + Phenytoin

A single 100-mg dose of phenytoin had no significant effect on the half-life of a single 100-mg dose of carbenoxolone in 4 healthy subjects.[1] This limited evidence would seem to suggest that there is no reason for avoiding the concurrent use of these two drugs.

1. Thornton PC, Papouchado M, Reed PI. Carbenoxolone interactions in man - preliminary report. *Scand J Gastroenterol* (1980) 15 (Suppl 65), 35–9.

Carbenoxolone + Sulfonylureas

Chlorpropamide appears to reduce the serum levels of carbenoxolone. Tolbutamide does not appear to have any significant effect on the pharmacokinetics of carbenoxolone.

Clinical evidence, mechanism, importance and management

A single 500-mg dose of **tolbutamide** had no significant effect on the half-life of a single 100-mg dose of carbenoxolone in 4 healthy subjects, whereas a single 250-mg dose of **chlorpropamide** delayed the absorption

of carbenoxolone and reduced its plasma levels in 6 patients taking carbenoxolone 100 mg three times daily.[1] The clinical importance of this latter interaction is uncertain.

1. Thornton PC, Papouchado M, Reed PI. Carbenoxolone interactions in man - preliminary report. *Scand J Gastroenterol* (1980) 15 (Suppl 65), 35–9.

Cisapride + Miscellaneous

In many countries cisapride has been withdrawn from the market, or is only available for restricted use because of its potential to cause torsade de pointes arrhythmias, especially when cisapride serum levels are elevated.[1] This can lead to cardiac arrest and sudden death. The interactions of cisapride and their importance and management are summarised in 'Table 27.2', (p.1148).

1. Ahmad SR, Wolfe SM. Cisapride and torsades de pointes. *Lancet* (1995) 345, 508.

Enteral feeds + Aluminium compounds and/or Sucralfate

Aluminium-containing antacids and sucralfate can interact with high-protein liquid enteral feeds to produce an obstructive plug.

Clinical evidence

(a) Aluminium-containing antacids

Three patients, who were being fed with a liquid high-protein nutrient (*Fresubin liquid*) through an enteral tube, developed an obstructing protein-aluminium-complex oesophageal plug when intermittently given an aluminium/magnesium hydroxide antacid (*Alucol-Gel*).[1] Another report also describes blockage of a nasogastric tube in a patient given aluminium hydroxide (*Aludrox*) and *Nutrison*.[2]

(b) Sucralfate alone or with aluminium-containing antacids

A number of reports describe the development of hard putty-like or creamy precipitations and encrustations that have blocked the oesophagus or stomach of patients given sucralfate with enteral feeds (*Ensure Plus*,[3] *Fresubin plus F*,[4] *Glucerna*,[5] *Jevity*,[5] or *Osmolite*[6]). Another patient developed this precipitate when given *Isocal* and sucralfate with aluminium/magnesium hydroxide.[7] Similarly, a patient receiving *Pulmocare* nasogastric feed, sucralfate and aluminium hydroxide gel also developed an oesophageal bezoar, which was analysed and found to contain components of both the drugs and the enteral feed.[8]

Data from the French Pharmacovigilance system database found 16 adults and 5 newborn babies who developed bezoars while taking sucralfate; nasogastric feeding was identified as a risk factor.[9]

Mechanism

It seems that a bezoar (a relatively insoluble complex) forms between the protein in the enteral feeds, and the aluminium from the antacids or sucralfate (sucralfate is about 18% aluminium). It thickens when the pH falls.[3]

Importance and management

An established and clinically important interaction that can result in the blockage of enteral or nasogastric tubes. The authors of one report say that high molecular protein solutions should not be mixed with antacids or followed by antacids, and if an antacid is needed, it should be given some time after the nutrients and the tube should be vigorously flushed beforehand.[1] The authors of another report say that they feed for 18 hours daily and then give the sucralfate overnight without problems.[2] The manufacturers recommend separating the administration of sucralfate suspension and enteral feeds given by nasogastric tube by one hour.[10]

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2. Tomlin ME, Dixon S. Aluminium and nasogastric feeds. *Pharm J* (1996) 256, 40.
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4. Vohra SB, Strang TI. Sucralfate therapy - a caution. *Br J Intensive Care* (1994) 4, 114.
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7. Algozzine GJ, Hill G, Scoggins WG, Marr MA. Sucralfate bezoar. *N Engl J Med* (1983) 309, 1387.
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9. Guy C, Ollagnier M. Sucralfate et bézoard: bilan de l'enquête officielle de pharmacovigilance et revue de la littérature. *Therapie* (1999) 54, 55–8.
10. Antepsin Suspension (Sucralfate). Chugai Pharma UK Ltd. UK Summary of product characteristics, November 2007.

H_2-receptor antagonists + Antacids

The absorption of cimetidine, famotidine, nizatidine, and ranitidine may possibly be reduced to some extent by antacids, but it seems doubtful if this significantly reduces their effects. Roxatidine absorption appears not to be affected by antacids. Cimetidine appears not to interfere with the effectiveness of *Gaviscon* (sodium alginate compound).

Clinical evidence

(a) Cimetidine

When 12 healthy subjects were given oral cimetidine 300 mg four times daily for 5 doses, with and without 30 mL of *Mylanta II* (**aluminium/magnesium hydroxide** mixture), the absorption of cimetidine was unaffected.[1] No interaction was found with cimetidine in single-dose studies using **aluminium phosphate**[2,3] or **aluminium/magnesium hydroxide**[4,5] antacids.

In contrast, a number of other single-dose studies indicated that antacids reduce the absorption of cimetidine. The AUCs of 200- to 800-mg doses of cimetidine were reduced by an average of 19 to 34% by 10 to 45 mL doses of a variety of **aluminium/magnesium**-containing antacids.[6-10] When the antacids were given 1 to 3 hours after cimetidine 'marginal' or insignificant reductions occurred in the AUCs.[7,11,12]

Gaviscon (**sodium alginate/antacid**) is an anti-reflux preparation that needs a small amount of gastric acid to be present in order for the alginic acid 'raft' to form. A study in 12 healthy subjects designed to find out if an H_2-receptor antagonist would alter the effectiveness of *Liquid Gaviscon* found that cimetidine 400 mg four times daily for 7 days caused some slight changes in gastric emptying, but the distribution of the *Gaviscon* in the fundus of the stomach was not altered.[13]

The pharmacokinetics of a 200-mg dose of cimetidine were not significantly changed by [**simeticone**] 2.25 g in 11 healthy subjects.[14]

(b) Famotidine

Mylanta II (**aluminium/magnesium hydroxide** mixture) 30 mL reduced the AUC and peak plasma levels of famotidine by about one-third when both drugs were taken simultaneously, but no significant interaction occurred when the antacid was taken 2 hours after famotidine.[15] Another study found that the maximum plasma levels of famotidine were reduced by about 25% by *Mylanta II* in 17 healthy subjects.[16] *Mylanta Double Strength* (**aluminium/magnesium hydroxide** with **simeticone**) was found to reduce the absorption of famotidine by 19%, a difference that was considered unimportant.[10] Two chewable tablets of *Mylanta II* were found to have no effect on the pharmacokinetics or pharmacodynamics of famotidine 10 or 20 mg in 18 healthy subjects.[17]

(c) Nizatidine

Mylanta Double Strength (**aluminium/magnesium hydroxide** with **simeticone**) reduced the absorption of nizatidine by 12%, which was considered clinically insignificant.[10] In a study in 11 healthy subjects a single 30-mL dose of *Gelusil* (**aluminium/magnesium hydroxide** with **simeticone**) reduced the mean AUC and maximum serum levels of nizatidine (given simultaneously) by 13% and 17%, respectively.[18] Another study found that the pharmacokinetics of nizatidine were not affected by an **aluminium/magnesium hydroxide** antacid (*Maalox)* although an increase in the time to peak effect of nizatidine was seen.[19]

(d) Ranitidine

In 6 healthy subjects, *Mylanta II* (**aluminium/magnesium hydroxide** mixture) 30 mL reduced the peak plasma levels and AUC of a single 150-mg dose of ranitidine by about one-third.[20] *Mylanta Double Strength* (**aluminium/magnesium hydroxide** with **simeticone**) reduced the absorption of ranitidine by 26%, which was not thought to be clinically significant.[10] Another study found that **aluminium/magnesium**-containing antacids reduced the

Table 27.2 Summary of the interactions of cisapride

Interacting drugs	*Reported effects*	*Action*	*Refs*
Alcohol	Cisapride increases gastric emptying and can modestly increase serum alcohol levels. A modest 22% increase in the AUC of cisapride seen in one study.	Unlikely to be significant, however the sedative effects might be accelerated. Unknown significance; monitor patient for sedation.	1-5
Antacids Aluminium [hydr]oxide and magnesium hydroxide	No effect on cisapride absorption seen.	None.	6
Antiepileptics e.g. Phenytoin	Increase in gastrointestinal motility caused by cisapride may affect the rate and/or extent of absorption, which may be important for some drugs with a narrow therapeutic index, such as some antiepileptics. However, no available case reports to suggest this is a problem, and one case reporting no interaction.	Uncertain. Monitor antiepileptic drug levels as usual practice. Advise the patient to report any increase in adverse effects.	1, 7
Antimuscarinics e.g. Disopyramide	Cisapride increases gastric emptying but antimuscarinics slow gastric emptying. **Disopyramide** absorption and serum levels were increased by cisapride in one study.	The clinical outcome is uncertain but caution is warranted if increased levels of the other drug likely to be significant e.g. **Disopyramide** is contraindicated as it can prolong the QT interval.	8
Butyrophenones e.g. Bromperidol, Haloperidol	Increased psychotic symptoms and bromperidol levels occurred in one case report. No significant pharmacokinetic interaction between cisapride and either bromperidol or haloperidol in a study in schizophrenic patients, but possible worsening of psychotic symptoms seen when cisapride was given with haloperidol.	Significance uncertain, but probably small.	9, 10
Ciclosporin	An increase in AUC and serum levels of ciclosporin has been reported.	Monitor ciclosporin levels more frequently.	11
CYP3A4 inhibitors: **Macrolides** e.g. Clarithromycin, Erythromycin **Azole antifungals** e.g. Ketoconazole **Protease inhibitors** **Nefazodone** **Diltiazem** **Cimetidine** **See also Table 1.4, p.6**	Increased levels of cisapride result in an increase in the risk of QT prolongation and life-threatening ventricular arrhythmias e.g. *torsade de pointes*.	Avoid.	1, 12-22
Diazepam	Accelerated absorption of diazepam reported. Transient increase in sedation possible.	Monitor the patient and advise that sedation may occur more quickly.	1, 23
Digoxin	Small reduction in the AUC and serum levels of digoxin seen in one study.	Unlikely to be clinically significant.	24
Diltiazem	A case of syncope and prolonged QT interval reported – see also CYP3A4 inhibitors above.	See CYP3A4 inhibitors above.	25
Drugs that prolong the QT interval	Increased risk of QT prolongation and life-threatening ventricular arrythmias.	Avoid. Should not be used with other drugs that prolong the QT interval.	1, 16
Esomeprazole	An increase in AUC and elimination half-life of cisapride reported, but no increase in serum levels. No QT-prolonging effects seen.	Unlikely to be clinically significant.	1, 26
Fluoxetine	No effect on the QT interval seen.	None.	27
Grapefruit juice	Significant increases in cisapride levels seen but high inter-subject variability occurred. No QT interval changes were seen.	May be of more significance in patients taking higher doses of cisapride or also taking other interacting drugs. Avoid concurrent use if possible.	28-30
H_2-receptor antagonists e.g. Cimetidine, ranitidine	Increase in cisapride levels and reduction in cimetidine and ranitidine bioavailability seen.	Unlikely to be clinically significant. For cimetidine, see also CYP3A4 inhibitors, above.	1, 31-35
Morphine	An increase in peak morphine serum levels was seen but with no increase in the adverse effects of morphine.	Uncertain but be aware in case of increased morphine adverse effects.	36
Nifedipine	An increase in nifedipine levels with increased nifedipine effects seen, probably due to increased absorption.	Monitor patient and adjust the nifedipine dose accordingly.	37
Pantoprazole	Small reduction in cisapride levels and no QT interval effects seen.	None.	38

Continued

Table 27.2 Summary of the interactions of cisapride (continued)

Interacting drugs	*Reported effects*	*Action*	*Refs*
Paracetamol	No significant effect on the pharmacokinetics of paracetamol was found in one study but another small study found that the metabolism of paracetamol was reduced.	Unlikely to be clinically significant.	39, 40
Propranolol	No change in levels or effect of propranolol.	None.	41
Red wine	Minor changes in cisapride levels seen in one single-dose study.	Significance is unclear.	30
Simvastatin	Slightly increased cisapride levels and reduced simvastatin levels.	Unlikely to be generally significant although it may be prudent to check that simvastatin remains effective.	42
Warfarin and related anticoagulants	**Warfarin**: A small but insignificant increase in INR was seen in healthy subjects, but one case report describes a large rise in INR. **Acenocoumarol**: Increased anticoagulant effect reported, which resolved when cisapride stopped. **Phenoprocoumon**: No significant change in anticoagulant effects.	It seems prudent to monitor patients taking anticoagulants who are given cisapride until their INR is stable.	1, 43-46

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Continued

Table 27.2 Summary of the interactions of cisapride (continued)

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absorption of ranitidine by up to almost 60%.[9] Yet another study showed that **aluminium phosphate** reduced the bioavailability of ranitidine by 30%.[21] In contrast, one study found no significant changes in the pharmacokinetics of ranitidine given with an **aluminium/magnesium hydroxide** antacid (*Maalox*).[19]

(e) Roxatidine

In a crossover study, 24 healthy subjects were given roxatidine 150 mg with 10 mL of *Maalox* (**aluminium/magnesium hydroxide**) four times daily. The pharmacokinetics of roxatidine were unchanged, apart from a clinically insignificant increase in its half-life.[22]

Mechanism

Not fully understood. Changes in gastric pH caused by the antacid, and retarded gastric motility have been suggested as potential mechanisms. An *in vitro* study showed no absorption interaction occurred between cimetidine and antacids.[5]

Importance and management

A modest reduction in the bioavailability of cimetidine, famotidine, nizatidine and ranitidine can occur with some antacids although this appears to be more likely when larger doses of antacids are used. None of these interactions are well established and evidence that the effects of the H_2-receptor antagonists are reduced seems to be lacking. If the antacids are given 1 to 2 hours before or after the H_2-receptor antagonist (if fasting), or 1 hour after (if the H_2-receptor antagonist is taken with food), no reduction in absorption should occur.[7,15,16,23]

Given the evidence available it seems unlikely that a clinically significant interaction will occur between any H_2-receptor antagonist and standard doses of an antacid.

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H_2-receptor antagonists + Metoclopramide

Metoclopramide reduces the bioavailability of cimetidine. Ranitidine may increase the bioavailability and half-life of metoclopramide.

Clinical evidence

(a) Cimetidine

In a study in healthy subjects, a 14-mg dose of a liquid formulation of metoclopramide (given a two 7-mg doses, 10 minutes before and 30 minutes after cimetidine) reduced the bioavailability of **cimetidine** by 22%, although this result did not reach statistical significance.[1] In another study in healthy subjects, the AUC of a single 200-mg dose of **cimetidine** was reduced by about 30% by a single 20-mg dose of metoclopramide.[2] Another study found that **cimetidine** bioavailability was not significantly affected when it was given 2 hours before metoclopramide.[3]

(b) Ranitidine

In a single-dose study in healthy subjects given ranitidine 300 mg and metoclopramide 10 mg, the time to maximum serum levels of ranitidine was reduced from 2.3 to 1.4 hours by metoclopramide. The AUC and maximum serum level of ranitidine were not significantly decreased.[4] In a study in healthy subjects, ranitidine 150 mg twice daily for 5 days increased the AUC of a single 20-mg dose of metoclopramide by about 13% and increased its half-life from 5.6 to 6.7 hours.[5]

Mechanism, importance and management

Reduced gastrointestinal transit time produced by metoclopramide may have led to the reduction in cimetidine bioavailability.[2] Similarly, the shortened time to maximum ranitidine levels may be due to accelerated gastric emptying.[4] However, the clinical effects of these results do not ap-

pear to be significant, particularly as there appears to be a lack of reports of H_2-receptor antagonist treatment failure when metoclopramide has also been taken.

The increase in the bioavailability of metoclopramide seen in the study with ranitidine is unlikely to be significant.

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H_2-receptor antagonists + Probenecid

Probenecid markedly decreases the renal clearance of famotidine and modestly reduces the renal clearance of cimetidine. However, these effects are not expected to result in adverse clinical effects.

Clinical evidence, mechanism, importance and management

In a randomised, crossover study, 6 healthy subjects were given probenecid 500 mg every 6 hours for 13 doses, with a single 300-mg intravenous dose of **cimetidine** 3 hours after the last probenecid dose. Probenecid reduced the renal clearance of **cimetidine** by 22%, without affecting its overall clearance.[1] Probenecid 1.5 g increased the AUC of a single 20-mg dose of **famotidine** in 8 healthy subjects by 81%, and reduced the renal tubular clearance by 89%.[2] It has been suggested that probenecid inhibits the renal secretion of **cimetidine** and famotidine, thereby reducing their renal clearance. This is consistent with the way that probenecid affects some other drugs. The effects of **famotidine** would be expected to be increased, but dose-related toxicity arising from this interaction seems unlikely. The effects of **cimetidine** are unlikely to be significantly altered. There would therefore seem to be no reason for avoiding concurrent use. Other H_2-receptor antagonists are also renally excreted and therefore they may behave similarly.

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2. Inotsume N, Nishimura M, Nakano M, Fujiyama S, Sato T. The inhibitory effect of probenecid on renal excretion of famotidine in young, healthy volunteers. *J Clin Pharmacol* (1990) 30, 50–56.

H_2-receptor antagonists + Rifampicin (Rifampin)

No clinically significant interaction appears to occur between rifampicin and cimetidine or ranitidine.

Clinical evidence, mechanism, importance and management

(a) Cimetidine

In a study, 12 patients given daily doses of rifampicin 8 mg/kg, isoniazid 8 mg/kg and ethambutol 25 mg/kg for at least 14 days, and 13 untreated control subjects were given a single 300-mg dose of intravenous cimetidine. In the patients receiving antimycobacterials, the non-renal clearance of cimetidine was increased by 52% but the total clearance and volume of distribution were unchanged. This reduction in renal clearance may have been associated with age-related impairment of renal function (although the study did exclude patients with a glomerular filtration rate of less than 60 mL/minute), but it was suggested that the increased non-renal clearance may have been due to enzyme induction of cimetidine metabolism.[1] As total clearance was unchanged this interaction seems unlikely to be clinically significant.

(b) Ranitidine

In a controlled study, 112 patients with pulmonary tuberculosis were treated in 2 groups, one with a daily regimen of rifampicin 10 mg/kg, isoniazid 300 mg and ethambutol 20 mg/kg and ranitidine 150 mg twice daily, and the other with the same antimycobacterials but without ranitidine. The pharmacokinetics of rifampicin (as measured by the total and unchanged urinary excretion) were not affected by ranitidine. No changes occurred in the incidence of adverse hepatic reactions, while gastrointestinal reactions were reduced.[2] There would seem to be no reason for avoiding the use of ranitidine, or any other H_2-receptor antagonists, in patients taking rifampicin.

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2. Purohit SD, Johri SC, Gupta PR, Mehta YR, Bhatnagar M. Ranitidine-rifampicin interaction. *J Assoc Physicians India* (1992) 40, 308–10.

H_2-receptor antagonists + Sucralfate

Most *in vitro* and human studies have found that sucralfate does not affect the absorption of either cimetidine,[1-3] ranitidine,[4] or roxatidine,[5] but two studies found 22 to 29% reductions in ranitidine bioavailability due to the concurrent use of sucralfate,[6,7] which would not be expected to be clinically significant. There is no clear reason for avoiding concurrent use.

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2. D'Angio R, Mayersohn M, Conrad KA, Bliss M. Cimetidine absorption in humans during sucralfate coadministration. *Br J Clin Pharmacol* (1986) 21, 515–20.
3. Beck CL, Dietz AJ, Carlson JD, Letendre PW. Evaluation of potential cimetidine sucralfate interaction. *Clin Pharmacol Ther* (1987) 41, 168.
4. Mullersman G, Gotz VP, Russell WL, Derendorf H. Lack of clinically significant in vitro and in vivo interactions between ranitidine and sucralfate. *J Pharm Sci* (1986) 75, 995–8.
5. Seibert-Grafe M, Pidgen A. Lack of effect of multiple dose sucralfate on the pharmacokinetics of roxatidine acetate. *Eur J Clin Pharmacol* (1991) 40, 637–8.
6. Maconochie JG, Thomas M, Michael MF, Jenner WR, Tanner RJN. Ranitidine sucralfate interaction study. *Clin Pharmacol Ther* (1987) 41, 205.
7. Kimura K, Sakai H, Yoshida Y, Kasano T, Hirose M. Effects of concomitant drugs on the blood concentration of a histamine H_2 antagonist (the 2nd report) - concomitant or time lag administration of ranitidine and sucralfate. *Nippon Shokakibyo Gakkai Zasshi* (1986) 83, 603–7.

H_2-receptor antagonists + Tobacco or Nicotine

Smoking may reduce the plasma levels of cimetidine and ranitidine, but does not appear to alter the effects of famotidine. Cimetidine, and to a lesser extent ranitidine, reduce the clearance of nicotine in non-smokers, but there is some evidence to suggest that cimetidine has no effect on nicotine clearance in smokers.

Clinical evidence

(a) Nicotine

Cimetidine 600 mg twice daily for one day, given before nicotine (1 microgram/kg per minute given intravenously for 30 minutes), reduced the nicotine clearance in 6 healthy non-smokers by 27 to 30%. **Ranitidine** 300 mg twice daily, taken for one day, reduced the clearance of nicotine by about 7 to 10%.[1] See also tobacco, below.

(b) Tobacco

In one study, tobacco smokers were given single oral doses of either **ranitidine** 150 mg or **cimetidine** 200 mg on two separate days. On one of the days they were allowed to smoke as normal and on the other they were not allowed to smoke. Peak levels for both drugs occurred sooner and were higher on the smoking day than on the non-smoking day. However, the plasma levels of the H_2-receptor antagonists, after peak levels were achieved, were lower. No effect was seen when intravenous **cimetidine** or **ranitidine** were given.[2]

A study in heavy smokers (more than 20 cigarettes per day for at least 1 year) given cimetidine 400 mg three times daily for 2 weeks found no reduction in the clearance of **nicotine** or in the number of cigarettes smoked, when compared with placebo.[3]

There was no difference in the pharmacokinetics and gastric acid-lowering effect of **famotidine** between 12 healthy smokers and 8 non-smokers.[4]

Mechanism, importance and management

The authors of one of the above studies[3] noted that tobacco smoking induces nicotine metabolism. This may at least partially explain the lack of effect of cimetidine on nicotine clearance seen in their previous study in non-smokers.[1] On balance cimetidine and other H_2-receptor antagonists probably have little effect on nicotine replacement therapy or tobacco smoking.

The healing of duodenal ulcers in patients taking H_2-receptor antagonists

such as cimetidine,[5,6] famotidine,[7] **nizatidine**[8] and ranitidine[6,7] is slower, and ulcer recurrence is more common, in smokers than in non-smokers. It is quite possible that this is due to smoking being a risk factor for the occurrence of duodenal ulcers[5,7-9] rather than a significant interaction between smoking and H_2-receptor antagonists.

1. Bendayan R, Sullivan JT, Shaw C, Frecker RC, Sellers EM. Effect of cimetidine and ranitidine on the hepatic and renal elimination of nicotine in humans. *Eur J Clin Pharmacol* (1990) 38, 165–9.
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5. Hetzel DJ, Korman MG, Hansky J, Shearman DJ, Eaves ER, Schmidt GT, Hecker R, Fitch RJ. The influence of smoking on the healing of duodenal ulcer treated with oxmetidine or cimetidine. *Aust N Z J Med* (1983) 13, 587–90.
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8. Battaglia G. Risk factors of relapse in gastric ulcer: a one-year, double-blind comparative study of nizatidine versus placebo. *Ital J Gastroenterol* (1994) 26 (1 Suppl 1), 19–22.
9. Boyd EJS, Wilson JA, Wormsley KG. Smoking impairs therapeutic gastric inhibition. *Lancet* (1983) i, 95–7.

H_2-receptor antagonists; Cimetidine + Phenobarbital

Phenobarbital modestly reduces the AUC of cimetidine, although this is probably not clinically relevant.

Clinical evidence, mechanism, importance and management

In 8 healthy subjects, phenobarbital 100 mg daily for 3 weeks reduced the AUC of a single 400-mg oral dose of cimetidine by 15%, and the time during which the plasma concentrations of the cimetidine exceeded 0.5 micrograms/mL (regarded as therapeutically desirable) was reduced by 11%.[1]

Phenobarbital apparently stimulates the enzymes in the gut wall so that the metabolism of the cimetidine is increased. Thus the amount of cimetidine absorbed and released into the circulation is reduced.

Direct information is very limited, but the effect of phenobarbital on cimetidine levels is small and unlikely to be clinically important. No special precautions seem to be necessary.

1. Somogyi A, Thielscher S, Gugler R. Influence of phenobarbital treatment on cimetidine kinetics. *Eur J Clin Pharmacol* (1981) 19, 343–7.

H_2-receptor antagonists; Cimetidine + Propantheline

Propantheline reduces the bioavailability of cimetidine.

Clinical evidence, mechanism, importance and management

In a single-dose study in healthy subjects, propantheline 30 mg reduced the AUC and peak plasma levels of cimetidine 200 mg by about 22% and 33%, respectively. It was suggested that the reduced bioavailability of cimetidine possibly due to delayed gastric emptying, decreased gastrointestinal motility, and reduced mixing of intestinal contents caused by the propantheline.[1] The clinical significance of this single dose study is unclear. However, there do not appear to be any clinical reports of treatment failure when both drugs have been used concurrently.

1. Kanto J, Allonen H, Jalonen H, Mäntylä R. The effect of metoclopramide and propantheline on the gastrointestinal absorption of cimetidine. *Br J Clin Pharmacol* (1981) 11, 629–31.

$5\text{-}HT_3$-receptor antagonists + Aprepitant

Aprepitant appears to have no clinically relevant effect on the pharmacokinetics of dolasetron, granisetron, ondansetron or palonosetron.

Clinical evidence and mechanism

(a) Dolasetron

In a study in 12 healthy subjects, aprepitant 125 mg on day one, then 80 mg on days 2 and 3 had no effect on the pharmacokinetics of a single 100-mg oral dose of dolasetron given on day one, regardless of CYP2D6 metaboliser type.[1]

(b) Granisetron

In a study in healthy subjects, aprepitant 125 mg on day one, then 80 mg on days 2 and 3 had no effect on the pharmacokinetics of oral granisetron 2 mg given on day one.[2]

(c) Ondansetron

In a study in healthy subjects, aprepitant 375 mg on day one, then 250 mg on days 2 to 5 caused a minor 15% increase in the AUC of intravenous ondansetron 32 mg given on day one.[2]

(d) Palonosetron

Aprepitant 125 mg on day one, then 80 mg on days 2 and 3 had no effect on the pharmacokinetics of a single 250-microgram intravenous dose of palonosetron given to healthy subjects on day one.[3]

Importance and management

No important pharmacokinetic interaction appears to occur between the $5\text{-}HT_3$-receptor antagonists and aprepitant. Therefore, no dosage adjustment is required when aprepitant is given with dolasetron, granisetron, ondansetron, or palonosetron.

1. Li SX, Pequignot E, Panebianco D, Lupinacci P, Majumdar A, Rosen L, Ahmed T, Royalty JE, Rushmore TH, Murphy MG, Petty KJ. Lack of effect of aprepitant on hydrodolasetron pharmacokinetics in CYP2D6 extensive and poor metabolizers. *J Clin Pharmacol* (2006) 46, 792–801.
2. Blum RA, Majumdar A, McCrea J, Busillo J, Orlowski LH, Panebianco D, Hesney M, Petty KJ, Goldberg MR, Murphy MG, Gottesdiener KM, Hustad CM, Lates C, Kraft WK, Van Buren S, Waldman SA, Greenberg HE. Effects of aprepitant on the pharmacokinetics of ondansetron and granisetron in healthy subjects. *Clin Ther* (2003) 25, 1407–19.
3. Shah AK, Hunt TL, Gallagher SC, Cullen MT. Pharmacokinetics of palonosetron in combination with aprepitant in healthy volunteers. *Curr Med Res Opin* (2005) 21, 595–601.

$5\text{-}HT_3$-receptor antagonists + Cimetidine

Cimetidine has no clinically significant effect on the pharmacokinetics of dolasetron or granisetron.

Clinical evidence, mechanism, importance and management

(a) Dolasetron

A study in 18 healthy subjects given dolasetron 200 mg daily found that cimetidine 300 mg four times daily for 7 days increased the AUC and maximum plasma level of the active metabolite of dolasetron, hydrodolasetron, by 24% and 15%, respectively, probably due to the inhibitory effect of cimetidine on the cytochrome P450-mediated metabolism of dolasetron. As 400-mg oral doses of dolasetron have been shown to be well tolerated (the usual oral dose is up to 200 mg) these changes were not considered to be clinically significant.[1] Therefore no dolasetron dosage adjustments appear to be necessary if cimetidine and dolasetron are used concurrently.

(b) Granisetron

In a study[2] in 12 healthy subjects, pretreatment with cimetidine 200 mg four times daily for 8 days had no effect on the pharmacokinetics of a single 40-microgram/kg intravenous dose of granisetron given on day 8. Therefore, no granisetron dose adjustments are likely to be necessary if cimetidine is given.

1. Dimmitt DC, Cramer MB, Keung A, Arumugham T, Weir SJ. Pharmacokinetics of dolasetron with coadministration of cimetidine or rifampin in healthy subjects. *Cancer Chemother Pharmacol* (1999) 43, 126–32.
2. Youlten L. The effect of repeat dosing with cimetidine on the pharmacokinetics of intravenous granisetron in healthy volunteers. *J Pharm Pharmacol* (2004) 56, 169–75.

$5\text{-}HT_3$-receptor antagonists + Drugs that prolong the QT interval

The $5\text{-}HT_3$-receptor antagonists dolasetron, granisetron, ondansetron, tropisetron have been reported to cause minor

increases in the QTc interval. Palonosetron has no clinically significant effect on the QT interval.

Clinical evidence, mechanism, importance and management

The 5-HT_3-receptor antagonists are now known to cause small increases (generally not exceeding 15 milliseconds) in the QTc interval.[1] It has been concluded that this class effect is too small to be of clinical relevance,[1,2] and that there is insufficient evidence to differentiate the 5-HT_3-receptor antagonists by this effect.[3] In a more recent well-controlled study in 221 healthy subjects, intravenous **palonosetron** 250 micrograms, 750 micrograms and 2.25 mg had no significant effect on the QT interval, when compared with that of moxifloxacin as a positive control.[4] Nevertheless, the manufacturers issue differing guidance about concurrent use with other QT prolonging drugs as follows:

- **Dolasetron**: the UK manufacturer contraindicates[5] the concurrent use of dolasetron and **class I** or **class III antiarrhythmics**, and recommends caution with other drugs that prolong ECG intervals in patients at risk. The US manufacturer advises caution with all drugs that may prolong the QT interval. They include **diuretics**, with the potential for causing electrolyte abnormalities.[6]
- **Granisetron**: neither the UK nor the US manufacturers mention QT prolongation.[7,8]
- **Ondansetron**: the UK manufacturer recommends caution in patients treated with **antiarrhythmics** or **beta blockers**,[9] whereas the US manufacturer does not issue any cautions regarding QT-prolongation.[10]
- **Palonosetron**: the UK manufacturer recommends caution with other drugs that increase the QT interval.[11] The US manufacturer previously advised caution with drugs that prolong the QT interval, specifically mentioning **antiarrhythmics** and **diuretics** with the potential for causing electrolyte abnormalities.[12] However, on the basis of the new data mentioned above, this warning has now been deleted.[4]
- **Tropisetron**: the UK manufacturer recommends care when it is used with other drugs that are likely to prolong the QT interval, and specifically mentions **antiarrhythmics** and **beta blockers**.[13]

For further information about drug interactions involving the QT interval see 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290.

1. Navari RM, Koeller JM. Electrocardiographic and cardiovascular effects of the 5-hydroxytryptamine$_3$ receptor antagonists. *Ann Pharmacother* (2003) 37,1276–86.
2. Kovac AL. Benefits and risks of newer treatments for chemotherapy-induced and postoperative nausea and vomiting. *Drug Safety* (2003) 26, 227–59.
3. Navari RM, Koeller JM. Comment: electrocardiographic and cardiovascular effects of the 5-hydroxytryptamine-3 receptor antagonists. Authors' reply. *Ann Pharmacother* (2003) 37, 1918–19.
4. Aloxi (Palonosetron hydrochloride). MGI Pharma Inc. US Prescribing information, February 2008.
5. Anzemet (Dolasetron mesilate). Amdipharm. UK Summary of product characteristics, May 2006.
6. Anzemet Tablets (Dolasetron mesylate). Sanofi-Aventis US LLC. US Prescribing information, August 2008.
7. Kytril Tablets (Granisetron hydrochloride). Roche Products Ltd. UK Summary of product characteristics, July 2007.
8. Kytril (Granisetron hydrochloride). Roche Laboratories Inc. US Prescribing information, November 2005.
9. Zofran Tablets (Ondansetron). GlaxoSmithKline UK. UK summary of product characteristics, October 2006.
10. Zofran Tablets (Ondansetron hydrochloride). GlaxoSmithKline. US Prescribing information, February 2006.
11. Aloxi (Palonosetron hydrochloride). Cambridge Laboratories. UK Summary of product characteristics, March 2005.
12. Aloxi (Palonosetron hydrochloride). MGI Pharma Inc. US Prescribing information, January 2006.
13. Navoban (Tropisetron hydrochloride). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, August 2006.

5-HT_3-receptor antagonists + Enzyme inducers

Rifampicin (rifampin) causes a minor reduction in dolasetron levels and a modest reduction in ondansetron levels, and may affect granisetron and tropisetron similarly, but does not appear to alter palonosetron levels. Phenobarbital causes a minor reduction in the levels of granisetron.

Clinical evidence, mechanism, importance and management

(a) Dolasetron

In a study in 17 healthy subjects given dolasetron 200 mg daily, **rifampicin** (**rifampin**) 600 mg daily for 7 days decreased the AUC and maximum plasma level of the active metabolite of dolasetron, hydrodolasetron, by 28% and 17%, respectively, probably due to induction of hydrodolasetron metabolism by **rifampicin**.[1] These changes were not considered to be clinically significant and therefore no dosage adjustments appear necessary if **rifampicin** and dolasetron are used concurrently.

(b) Granisetron

The US manufacturer notes that, in a pharmacokinetic study, **phenobarbital** increased the clearance of granisetron by 25%. They say that the relevance of this change is unknown,[2] but such a modest change is unlikely to be clinically important.

(c) Ondansetron

In a study in 10 healthy subjects, pretreatment with **rifampicin** 600 mg once daily for 5 days markedly decreased the AUC of a single 8-mg dose of oral ondansetron by 65% and intravenous ondansetron by 48%. This is most likely due to the induction of CYP3A4-mediated metabolism of ondansetron by **rifampicin**. The authors concluded that ondansetron may not be as effective if given to patients taking **rifampicin**.[3] Nevertheless, the US manufacturer says that, although the potent CYP3A4 inducers **phenytoin**, **carbamazepine**, and **rifampicin** increased ondansetron clearance, on the basis of available data, no ondansetron dose adjustment is recommended for patients taking these drugs.[4]

(d) Palonosetron

The UK manufacturer notes that, in a population pharmacokinetic analysis, **dexamethasone** and **rifampicin** had no effect on palonosetron clearance.[5] Therefore, no palonosetron dose adjustment is likely to be necessary when given with these drugs.

(e) Tropisetron

The manufacturer states that drugs known to induce hepatic enzymes might lower tropisetron plasma concentrations. However, they say that such changes are unlikely to be of practical importance with the recommended dosage regimen.[6]

1. Dimmitt DC, Cramer MB, Keung A, Arumugham T, Weir SJ. Pharmacokinetics of dolasetron with coadministration of cimetidine or rifampin in healthy subjects. *Cancer Chemother Pharmacol* (1999) 43, 126–32.
2. Kytril (Granisetron hydrochloride). Roche Laboratories Inc. US Prescribing information. November 2005.
3. Villikka K, Kivistö KT, Neuvonen PJ. The effect of rifampin on the pharmacokinetics of oral and intravenous ondansetron. *Clin Pharmacol Ther* (1999) 65, 377–81.
4. Zofran Tablets (Ondansetron hydrochloride). GlaxoSmithKline. US Prescribing information, February 2006.
5. Aloxi (Palonosetron hydrochloride). Cambridge Laboratories. UK Summary of product characteristics, March 2005.
6. Navoban (Tropisetron hydrochloride). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, August 2006.

5-HT_3-receptor antagonists + Food or Antacids

Food does not affect the absorption of dolasetron. Food slightly increases the bioavailability of ondansetron, but an antacid was found to have no effect.

Clinical evidence, mechanism, importance and management

(a) Dolasetron

In a single-dose study, 23 healthy subjects were given 200 mg of dolasetron orally either alone, or following a **high-fat breakfast** (containing fat 55 g, protein 33 g and carbohydrate 58 g). Although there was a slight delay in absorption, dosing with a meal and dosing without a meal were considered to be bioequivalent. Therefore, dolasetron may be given without regard to meals.[1]

(b) Ondansetron

When 12 healthy subjects were given an 8 mg ondansetron tablet 5 minutes after a **meal**, its bioavailability was only slightly increased (AUC raised by 17%). The concurrent use of an **aluminium**/**magnesium hydroxide** antacid (*Maalox*) had no effect on the bioavailability of ondansetron.[2] Therefore, no precautions appear to be needed when ondansetron is given with an antacid, and it may be taken without regard to meals.

1. Lippert C, Keung A, Arumugham T, Eller M, Hahne W, Weir S. The effect of food on the bioavailability of dolasetron mesylate tablets. *Biopharm Drug Dispos* (1998) 19, 17–19.
2. Bozigian HP, Pritchard JF, Gooding AE, Pakes GE. Ondansetron absorption in adults: effect of dosage form, food, and antacids. *J Pharm Sci* (1994) 83, 1011–13.

5-HT$_3$-receptor antagonists; Dolasetron + Miscellaneous

Atenolol modestly reduced the clearance of the active metabolite of dolasetron, but verapamil had no effect. One patient taking verapamil and given dolasetron experienced heart block.

Clinical evidence, mechanism, importance and management

(a) Atenolol

The US manufacturer[1] notes that atenolol reduced the clearance of the active metabolite of dolasetron, hydrodolasetron, by 27%. This change is not likely to be clinically significant.

(b) Verapamil

The US manufacturer notes that, in one case, a 61-year-old woman taking verapamil developed complete heart block following the use of dolasetron,[1] although this was not proven to be as a result of an interaction. In other patients taking verapamil, the clearance of hydrodolasetron (the active metabolite of dolasetron) was unchanged.[1]

1. Anzemet Tablets (Dolasetron mesylate). Sanofi-Aventis US LCC. US Prescribing information, August 2008.

5-HT$_3$-receptor antagonists; Palonosetron + Metoclopramide

Metoclopramide 10 mg four times daily did not alter the pharmacokinetics of a single 750-microgram intravenous dose of palonosetron in healthy subjects.[1] Therefore, no dosage adjustment appears to be necessary with concurrent use of metoclopramide and palonosetron.

1. Aloxi (Palonosetron hydrochloride). MGI Pharma Inc. US Prescribing information, February 2008.

Domperidone + CYP3A4 inhibitors

Ketoconazole and erythromycin, both inhibitors of CYP3A4, increase the plasma levels of domperidone about threefold. Additive QT prolongation may also occur on the concurrent use of domperidone and ketoconazole or erythromycin.

Clinical evidence

(a) Erythromycin

In a study, healthy subjects were given domperidone 10 mg four times daily and erythromycin 500 mg three times daily, alone and in combination. The maximum plasma level and AUC of domperidone were increased about threefold by erythromycin. In this study, domperidone and erythromycin alone were found to increase the QTc interval by 2.5 milliseconds and 4.9 milliseconds, respectively, whereas the mean increase in the QTc interval on concurrent use was 9.9 milliseconds, which was greater than the additive effect of each drug alone.[1]

(b) Ketoconazole

In a study, healthy subjects took domperidone 10 mg four times daily and ketoconazole 200 mg twice daily, alone and in combination. The maximum plasma level and AUC of domperidone were increased about threefold by ketoconazole. In this study, domperidone and ketoconazole alone were found to increase the QTc interval by 1.6 milliseconds and 3.8 milliseconds, respectively, whereas the mean increase in the QTc interval on concurrent use was 9.8 milliseconds, which was greater than the additive effect of each drug alone.[1]

Mechanism

Domperidone is metabolised by the cytochrome P450 isoenzyme CYP3A4, which is inhibited by drugs such as erythromycin and ketoconazole. Concurrent use therefore increases domperidone levels, which increases its modest effects on the QT interval. Giving erythromycin or ketoconazole with.domperidone therefore has more than additive effects on the QT interval.

Importance and management

Evidence for an interaction between domperidone and erythromycin or ketoconazole is limited. The manufacturer advises that the concurrent use of domperidone with other drugs that are potent inhibitors of CYP3A4 and that also prolong the QT interval should be avoided. They specifically name erythromycin,[1,2] ketoconazole[1,2] and **ritonavir**.[2] This seems to be a very cautious approach, but may be prudent because alternatives to these combinations would usually be available. The increase in the QT interval due to increased exposure to domperidone caused by CYP3A4 inhibition alone would probably not be clinically relevant, but when added to the increase seen with erythromycin or ketoconazole alone (which at less than 5 milliseconds would not normally be considered to be clinically important, see 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290), the increase is possibly of some concern.

1. Motilium Tablets (Domperidone maleate). McNeil Ltd. UK Summary of product characteristics, December 2009.
2. Domperidone (Domperidone maleate). Wockhardt UK Ltd. UK Summary of product characteristics, January 2008.

Loperamide + Colestyramine

An isolated report, supported by an *in vitro* study, indicates that the effects of loperamide can be reduced by colestyramine.

Clinical evidence, mechanism, importance and management

A man who had undergone extensive surgery to the gut, with the creation of an ileostomy, needed treatment for excessive fluid loss. His fluid loss was observed to be 'substantially less' when he took loperamide 2 mg every 6 hours alone, than when he took loperamide in combination with colestyramine 2 g every 4 hours.[1] The probable reason for this effect is that the colestyramine binds to loperamide in the gut, thereby reducing its activity. An *in vitro* study using 50 mL of simulated gastric fluid found that 64% of a 5.5-mg dose of loperamide was bound by 4 g of colestyramine.[1] Direct information is limited to this report, but what occurred is consistent with the way colestyramine interacts with other drugs. It has been suggested that administration of the two drugs should be separated as far as possible to prevent mixing in the gut, or that the loperamide dosage should be increased.[1] It is generally recommended that other drugs should be given 1 hour before or 4 to 6 hours after colestyramine.

1. Ti TY, Giles HG, Sellers EM. Probable interaction of loperamide and cholestyramine. *Can Med Assoc J* (1978) 119, 607–8.

Loperamide + Co-trimoxazole

Co-trimoxazole increases plasma levels of loperamide but this is not expected to be clinically significant.

Clinical evidence, mechanism, importance and management

Co-trimoxazole 960 mg twice daily was given to healthy subjects for 24 hours before and then 48 hours after they took a single 4-mg dose of loperamide (12 subjects) or loperamide oxide (a prodrug of loperamide, 10 subjects). Co-trimoxazole increased the loperamide AUC by 89% and doubled its maximum plasma levels. The loperamide oxide AUC was raised by 54% and its maximum plasma levels were raised by 41%. It is thought that co-trimoxazole inhibits the metabolism of loperamide, possibly by reducing its first pass metabolism.[1] However, despite these rises, because loperamide has a very wide margin of safety, it is thought unlikely that any dosage changes are needed.

1. Kamali F, Huang ML. Increased systemic availability of loperamide after oral administration of loperamide and loperamide oxide with cotrimoxazole. *Br J Clin Pharmacol* (1996) 41, 125–8.

Loperamide + Gemfibrozil and/or Itraconazole

Gemfibrozil and itraconazole alone or in combination significantly increase the bioavailability of loperamide.

Clinical evidence

In a placebo-controlled, crossover study, 12 healthy subjects were given a single 4-mg dose of loperamide on day 4 of taking either itraconazole 200 mg then 100 mg twice daily, gemfibrozil 600 mg twice daily, or both drugs together, each for 5 days. Itraconazole alone increased the AUC and peak levels of loperamide by 3.8-fold and 2.9-fold, respectively, and increased its half-life from 11.9 to 18.7 hours. Gemfibrozil alone increased the AUC and peak levels of loperamide by 2.2-fold and 1.6-fold, respectively, and increased its half-life from 11.9 to 16.7 hours. Itraconazole plus gemfibrozil synergistically increased the AUC and peak levels of loperamide by 12.6-fold and 4.2-fold, respectively, and increased its half-life from 11.9 to 36.9 hours.

Despite the large increases in loperamide bioavailability produced by gemfibrozil and/or itraconazole, no changes in drowsiness or psychomotor test results for loperamide were reported during concurrent treatment.

Mechanism

Loperamide is thought to be metabolised by both the cytochrome P450 isoenzymes CYP3A4 and CYP2C8, and is also a substrate for P-glycoprotein. Therefore the large increases in loperamide levels are thought to be due to CYP2C8 inhibition by gemfibrozil and CYP3A4 inhibition by itraconazole.[1] Loperamide is thought to lack CNS effects because it is a substrate for P-glycoprotein, which transports drugs out of the cells at the blood-brain barrier, thereby restricting CNS penetration.

Importance and management

The concurrent use of loperamide with gemfibrozil and/or itraconazole does not appear to produce clinically significant adverse effects, and therefore no special precautions would appear to be necessary. Consider also 'Loperamide + Protease inhibitors', p.1155.

1. Niemi M, Tornio A, Pasanen MK, Fredrikson H, Neuvonen PJ, Backman JT. Itraconazole, gemfibrozil and their combination markedly raise the plasma concentrations of loperamide. *Eur J Clin Pharmacol* (2006) 62, 463–72.

Loperamide + Protease inhibitors

Loperamide reduces the bioavailability of saquinavir by about 50%. Ritonavir increases the plasma level of loperamide without increasing its CNS adverse effects, and saquinavir similarly increases the bioavailability of loperamide. Tipranavir alone, and in combination with ritonavir, reduces the bioavailability and plasma levels of loperamide and its metabolites.

Clinical evidence

(a) Ritonavir

In a double-blind study, 12 healthy subjects were given a single 600-mg dose of ritonavir with either loperamide 16 mg or placebo. The loperamide AUC and maximum plasma level were increased threefold and 17%, respectively, by ritonavir, but no additional CNS adverse effects were seen.[1] For the effects of ritonavir given as a pharmacokinetic booster, see *Tipranavir*, below.

(b) Saquinavir

In a double-blind, placebo-controlled study, 12 healthy subjects were given single doses of either saquinavir 600 mg, loperamide 16 mg, or both drugs together. Loperamide reduced the AUC of saquinavir by about 54%. The maximum plasma level of saquinavir was also reduced by loperamide although this was not statistically significant. Saquinavir increased the AUC of loperamide by 40% and also produced a non-significant increase in the maximum level of loperamide.[2]

(c) Tipranavir

A study in 20 healthy subjects looked at the pharmacokinetics and pharmacodynamics of a single 16-mg dose of loperamide taken with either tipranavir 750 mg twice daily, ritonavir 200 mg twice daily or both drugs together. (Note that this dose of tipranavir is higher than the usual ritonavir-boosted dose of 500 mg twice daily.) Tipranavir alone *reduced* the maximum level and AUC of loperamide by 58% and 63%, respectively, whereas ritonavir *increased* these parameters by 83% and 121%, respectively. The combination of tipranavir and ritonavir, as is usual clinical practice, resulted in a net reduction in the maximum level and AUC of loperamide by 61% and 51%, respectively, similar to the effect seen with tipranavir alone. The maximum level and AUC of the metabolites of loperamide were also reduced. There were no clinically significant loperamide adverse effects on respiration or pupil contractility with either ritonavir or tipranavir alone, or in combination.[3]

Mechanism

Loperamide is primarily metabolised by the cytochrome P450 isoenzyme CYP3A4, and is thought to lack CNS effects because it is a substrate for P-glycoprotein, which transports drugs out of the cells at the blood-brain barrier, thereby restricting CNS penetration.[3] The increase in loperamide levels with ritonavir alone is thought to be due to ritonavir inhibiting its metabolism by CYP3A4. The lack of an increase in loperamide CNS effects suggests that ritonavir alone does not inhibit P-glycoprotein.[1,3]

Saquinavir probably inhibits the CYP3A4-mediated metabolism of loperamide. Loperamide reduces gastrointestinal motility and therefore may affect the absorption of some drugs. It is thought that this therapeutic action may have reduced the absorption of saquinavir leading to the reduction in its bioavailability.[2]

The reduction in loperamide levels with tipranavir alone or tipranavir with ritonavir is thought to be due to induction of gastrointestinal P-glycoprotein by tipranavir, resulting in a decrease in the systemic bioavailability of loperamide.[3] However, another study suggested that the increase in loperamide levels seen with concurrent saquinavir may be due to inhibition of CYP3A4.[2]

Importance and management

The reduced levels of saquinavir seen in the single-dose study suggest that loperamide may reduce the antiviral efficacy of saquinavir. Although the evidence is limited to this study and only a single, low-dose of unboosted saquinavir was given, it may be prudent to monitor patients taking loperamide with saquinavir to ensure that the antiviral efficacy of saquinavir is maintained. Whether loperamide would cause as large a reduction in saquinavir levels with higher doses of ritonavir-boosted saquinavir (as is usual practice) is unclear. Further study is needed. Pharmacokinetic information about other protease inhibitors appears to be lacking. However, one efficacy study reported that the viral load and CD4 count were maintained in patients treated with loperamide for **nelfinavir**-induced diarrhoea.[4]

Despite the increases in loperamide plasma levels seen in both studies with ritonavir alone, a lack of central opioid effects with loperamide (such as pupillary constriction, respiratory depression and also analgesic effects) was demonstrated. This suggests that loperamide is potentially a safe antidiarrhoeal to give with ritonavir during episodes of protease inhibitor-induced diarrhoea.[1] The increases in loperamide bioavailability seen with the single-dose saquinavir study above are also not thought to be clinically significant, although the dose of saquinavir used in this study were much smaller than that commonly used in HIV treatment regimens.[2] It would appear from the results of these studies that use of ritonavir-boosted saquinavir (as is common) with loperamide is also unlikely to lead to a clinically relevant increase in loperamide adverse effects.

The clinical relevance of the decrease in loperamide bioavailability with tipranavir alone or tipranavir with ritonavir is unknown.

1. Tayrouz Y, Ganssmann B, Ding R, Klingmann A, Aderjan R, Burhenne J, Haefeli WE, Mikus G. Ritonavir increases loperamide plasma concentrations without evidence for P-glycoprotein involvement. *Clin Pharmacol Ther* (2001) 70, 405–14.

2. Mikus G, Schmidt L, Burhenne J, Ding R, Riedel K-D, Tayrouz Y, Weiss J, Haefeli WE. Reduction of saquinavir exposure by coadministration of loperamide; a two-way pharmacokinetic interaction. *Clin Pharmacokinet* (2004) 43, 1015–24.

3. Mukwaya G, MacGregor T, Hoelscher D, Heming T, Legg D, Kavanaugh K, Johnson P, Sabo JP, McCallister S. Interaction of ritonavir-boosted tipranavir with loperamide does not result in loperamide-associated neurologic side effects in healthy volunteers. *Antimicrob Agents Chemother* (2005) 49, 4903–10.

4. Rachlis A, Gill J, Baril J-G, LeBlanc RP, Trottier B, MacLeod J, Walmsley S, Van der Vliet W, Belsky G, Burgoyne R. Effectiveness of step-wise intervention plan for managing nelfinavir-associated diarrhea: a pilot study. *HIV Clin Trials* (2005) 6, 203–12.

Loperamide + Quinidine

Quinidine increases penetration of loperamide into the brain resulting in respiratory depression.

Clinical evidence

In a study in 8 healthy subjects, a single 600-mg dose of quinidine increased the AUC of loperamide and its metabolite by 148% and 94%, respectively. Loperamide alone did not produce respiratory depression, but when given with quinidine, respiratory depression occurred, as measured by the ventilatory response of the subjects to increasing carbon dioxide concentrations.[1]

Mechanism, importance and management

Loperamide is mainly metabolised by the cytochrome P450 isoenzyme CYP3A4, and is thought to lack CNS effects because it is a substrate for P-glycoprotein, which transports drugs out of the cells at the blood-brain barrier, thereby restricting CNS penetration. The central opioid adverse effects of loperamide that occurred in the study appear to be due to central P-glycoprotein inhibition by quinidine, resulting in increased loperamide penetration into the brain, and respiratory depression.[1]

Although information is limited, it would seem prudent to be alert for the CNS adverse effects of loperamide if quinidine is given. If adverse effects are troublesome consider reducing the dose of loperamide.

1. Sadeque AJM, Wandel C, He H, Shah S, Wood AJJ. Increased drug delivery to the brain by P-glycoprotein inhibition. *Clin Pharmacol Ther* (2000) 68, 231–7.

Mesalazine (Mesalamine) + Laxatives

On theoretical grounds, formulations designed to release mesalazine in response to the higher pH in the colon should not be given with lactulose, lactitol or other preparations that lower the colonic pH. However, studies suggest that both ispaghula and lactulose do not affect the bioavailability of mesalazine.

Clinical evidence and mechanism

Asacol is a preparation of mesalazine coated with an acrylic based resin (*Eudragit S*) that disintegrates above pH 7 and thereby releases the mesalazine into the terminal ileum and colon.[1] The pH in the colon can be lowered by lactulose and lactitol, which are metabolised by gut bacteria to a number of acids (e.g. acetic, butyric, propionic, and lactic acid).[2] In healthy subjects, lactulose 30 to 80 g daily has been found to cause slight falls in colonic pH;[2,3] from about 6 to 5 in the right colon and from 7 to 6.7 in the left colon. Lactitol 40 to 180 g daily can cause similar falls in pH.[2] Ispaghula can also lower colonic pH (from 6.5 to 5.8 in the right colon, and from 7.3 to 6.6 in the left colon).[4] However, a study in patients given mesalazine found that despite this colonic acidification by ispaghula husk (*Fybogel*), the release of mesalazine appeared not to be affected, as 24-hour faecal and urinary excretion of mesalazine metabolites were unchanged.[5] Similarly, another study in 14 healthy subjects given delayed-release mesalazine (*Asacol*) 400 mg three times daily found that lactulose (15 mL increased to 30 mL twice daily) did not affect urinary or faecal excretion of mesalazine and its metabolites.[6]

Importance and management

Although on theoretical grounds ispaghula husk and lactulose might be expected to reduce the effects of mesalazine, from the above studies no interaction of clinical importance seems to occur, and there have been no reports as yet that a clinically important interaction occurs with either ispaghula husk, lactulose or lactitol. However, the UK manufacturers of *Asacol* recommend avoiding concurrent use of preparations that can lower the pH of the gut as they may reduce the efficacy of mesalazine.[1] Also note that this interaction is not mentioned by the US manufacturers of *Asacol*.[7] Furthermore, *Salofalk* is another preparation of mesalazine with a pH-dependent enteric coating.[8] This preparation disintegrates above pH 6, but no warning regarding drugs that affect the pH in the lower part of the gut is given.

1. Asacol Tablets (Mesalazine). Procter & Gamble Pharmaceuticals UK Ltd. UK Summary of product characteristics, April 2003.
2. Patil DH, Westaby D, Mahida YR, Palmer KR, Rees R, Clark ML, Dawson AM, Silk DBA. Comparative modes of action of lactitol and lactulose in the treatment of hepatic encephalopathy. *Gut* (1987) 28, 255–9.
3. Bown RL, Gibson JA, Sladen GE, Hicks B, Dawson AM. Effects of lactulose and other laxatives on ileal and colonic pH as measured by a radiotelemetry device. *Gut* (1974) 15, 999–1004.
4. Evans DF, Crompton J, Pye G, Hardcastle JD. The role of dietary fibre on acidification of the colon in man. *Gastroenterology* (1988) 94, A118.
5. Riley SA, Tavares IA, Bishai PM, Bennett A, Mani V. Mesalazine release from coated tablets: effect of dietary fibre. *Br J Clin Pharmacol* (1991) 32, 248–50.
6. Hussain FN, Ajjan RA, Moustafa M, Weir NW, Riley SA. Mesalazine release from a pH dependent formulation: effects of omeprazole and lactulose co-administration. *Br J Clin Pharmacol* (1998) 46, 173–5.
7. Asacol (Mesalamine). Procter & Gamble Pharmaceuticals. US Prescribing information, October 2007.
8. Salofalk Tablets (Mesalazine). Dr Falk Pharma UK. UK Summary of product characteristics, July 2007.

Mesalazine (Mesalamine) + Proton pump inhibitors

Omeprazole does not affect the release of mesalazine from a delayed-release preparation (*Asacol*).

Clinical evidence, mechanism, importance and management

Asacol is a preparation of mesalazine coated with an acrylic based resin (*Eudragit S*) that disintegrates above pH 7 and thereby releases the mesalazine into the terminal ileum and colon. The release is rapid at pH values of 7 and above, but it can also occur between pH 6 and 7. Since the proton pump inhibitors can raise the pH in the stomach to 6 and above, the potential exists for the premature release of mesalazine from *Asacol*. However, a study in 6 healthy subjects given *Asacol* 400 mg three times daily for 3 weeks found that when they were also given **omeprazole** 20 mg daily during the second week, and **omeprazole** 40 mg daily during the third week, the steady-state pharmacokinetics of the mesalazine remained unchanged.[1] Had mesalazine been released earlier, the absorption characteristics would have changed. There would therefore appear to be no reason for avoiding the concurrent use of *Asacol* and **omeprazole** in doses of up to 40 mg daily. On the basis of this study, it seems likely that other proton pump inhibitors will behave similarly at equivalent doses.

1. Hussain FN, Ajjan RA, Moustafa M, Weir NW, Riley SA. Mesalazine release from a pH dependent formulation: effects of omeprazole and lactulose co-administration. *Br J Clin Pharmacol* (1998) 46, 173–5.

Methylnaltrexone + Miscellaneous

Cimetidine does not have a clinically relevant effect on the pharmacokinetics of methylnaltrexone. Methylnaltrexone does not alter the pharmacokinetics of dextromethorphan.

Clinical evidence, mechanism, importance and management

(a) Cimetidine

The manufacturer notes that, in a study in 18 healthy subjects, multiple 400-mg doses of cimetidine did not cause any clinically relevant changes in the pharmacokinetics of a single dose of methylnaltrexone. There was a 42% reduction in the renal clearance of methylnaltrexone, and a small 11% reduction in its total clearance, with no clinically relevant change in either the AUC or maximum plasma levels of methylnaltrexone.[1] The reduction in methylnaltrexone renal clearance is thought to be due to inhibition of organic cation transporters by cimetidine.[1] No dose adjustment of methylnaltrexone would be expected to be needed if cimetidine is also given.

(b) Dextromethorphan

The manufacturer briefly reports that, in a study in healthy male subjects, the metabolism of dextromethorphan was unaffected by a subcutaneous 300-microgram/kg dose of methylnaltrexone bromide.[1,2] This study was conducted because, *in vitro* methylnaltrexone was a weak inhibitor of the cytochrome P450 isoenzyme CYP2D6. Dextromethorphan is a substrate of CYP2D6, and the study suggests that methylnaltrexone causes no clinically relevant inhibition of this isoenzyme. Methylnaltrexone would not be expected to alter the pharmacokinetics of other CYP2D6 substrates.

1. Relistor (Methylnaltrexone bromide). Wyeth Pharmaceuticals. UK Summary of product characteristics, July 2009.
2. Relistor (Methylnaltrexone bromide). Wyeth Pharmaceuticals Inc. US Prescribing information, June 2009.

Metoclopramide + Prochlorperazine

A single case report describes tongue swelling and respiratory obstruction in a patient given prochlorperazine and then metoclopramide.

Clinical evidence, mechanism, importance and management

A 19-year-old woman experienced progressive swelling of the tongue, partial upper-airways obstruction and a sensation of choking over a period of 12 hours after she was given intramuscular doses of metoclopramide to a total of 30 mg. She had received a 12.5-mg intramuscular dose of prochlorperazine for nausea 24 hours earlier. On examination her tongue was strikingly blue, but within 15 minutes of receiving benzatropine 2 mg it returned to its normal size and colour. The respiratory distress also disappeared.[1] The authors of the report suggested that the dystonic adverse effects of both drugs were additive, leading to the effects seen.[1] However, it should be noted that oedema of the tongue has also been described with metoclopramide alone.[2] Young patients, especially women, are particularly susceptible to the adverse effects of metoclopramide, and this patient received the standard total daily dose over just 12 hours, so an interaction is by no means established.

1. Alroe C, Bowen P. Metoclopramide and prochlorperazine: ''the blue-tongue sign''. *Med J Aust* (1989) 150, 724–5.
2. Robinson OPW. Metoclopramide—side effects and safety. *Postgrad Med J* (1973) 49 (Suppl July), 77–80.

Mosapride + Erythromycin

Erythromycin increases the plasma levels and prolongs the half-life of mosapride, but adverse cardiac effects appear to be unlikely.

Clinical evidence, mechanism, importance and management

In a study, 10 healthy subjects were given mosapride 5 mg three times daily for 14 days, with erythromycin stearate 300 mg four times daily on the last 7 days. Erythromycin increased the peak plasma levels of mosapride by 1.6-fold and increased its half-life from 1.6 to 2.4 hours. It was suggested that these pharmacokinetic changes occurred because erythromycin inhibited the metabolism of mosapride by the cytochrome P450 isoenzyme CYP3A4. This is similar to the effects seen with concurrent use of erythromycin and 'cisapride', (p.1147). However, unlike cisapride, the increases in mosapride levels seen in this study did not produce adverse changes in the ECG, including the QT interval.[1] It may be prudent to monitor concurrent use for an increase in mosapride adverse effects, and adjust the dose accordingly.

1. Katoh T, Saitoh H, Ohno N, Tateno M, Nakamura T, Dendo I, Kobayashi S, Nagasawa K. Drug interaction between mosapride and erythromycin without electrocardiographic changes. *Jpn Heart J* (2003) 44, 225–34.

Pirenzepine + Antacids

***Mylanta* reduces the bioavailability of pirenzepine by about 30%. Another antacid, *Trigastril*, modestly *increases* the bioavailability of pirenzepine, but these changes are probably of little clinical importance.**

Clinical evidence, mechanism, importance and management

In a study in 20 healthy subjects, the AUC of a single 50-mg dose of pirenzepine was reduced by about 30% by 30 mL of *Mylanta* (**aluminium/magnesium hydroxide** and **simeticone**). The antacid reduced the peak plasma levels of pirenzepine by about 45%.[1] Another study in 10 healthy subjects found that the AUC of a single 50-mg dose of pirenzepine was *increased* by almost 25% by 10 mL of an antacid (*Trigastril,* **aluminium/magnesium hydroxide**, **calcium carbonate**).[2] In practical terms these modest changes in bioavailability are probably too small to matter.

1. Matzek KM, MacGregor TR, Keirns JJ, Vinocur M. Effect of food and antacids on the oral absorption of pirenzepine in man. *Int J Pharmaceutics* (1986) 28, 151–5.
2. Vergin H, Herrlinger C, Gugler R. Effect of an aluminium-hydroxide containing antacid on the oral bioavailability of pirenzepine. *Arzneimittelforschung* (1989) 39, 520–3.

Pirenzepine + Cimetidine

The pharmacokinetics of pirenzepine and cimetidine are not affected when both drugs are given together, but pirenzepine increases the cimetidine-induced reduction in gastric acid secretion, which is an apparently advantageous interaction.[1]

1. Jamali F, Mahachai V, Reilly PA, Thomson ABR. Lack of pharmacokinetic interaction between cimetidine and pirenzepine. *Clin Pharmacol Ther* (1985) 38, 325–30.

Pirenzepine + Food

Food reduces the bioavailability of pirenzepine by about 30%, but this is probably of little clinical importance.

Clinical evidence, mechanism, importance and management

The AUC of a single 50-mg dose of pirenzepine was reduced by about 30% in 20 healthy subjects when pirenzepine was taken half-an-hour before food, or with food. Peak plasma levels were reduced by about 30% and 45%, respectively. The time to achieve peak levels was also reduced.[1] In practical terms this modest change in bioavailability is probably too small to matter. The authors of this report suggest taking pirenzepine with food because compliance is better if associated with a convenient daily ritual.[1]

1. Matzek KM, MacGregor TR, Keirns JJ, Vinocur M. Effect of food and antacids on the oral absorption of pirenzepine in man. *Int J Pharmaceutics* (1986) 28, 151–5.

Proton pump inhibitors + Antacids

***Maalox* does not appear to alter the pharmacokinetics of omeprazole, pantoprazole or rabeprazole. Antacids may cause a slight reduction in the bioavailability of lansoprazole but this is probably not clinically relevant. There is no interaction between sodium alginate and omeprazole.**

Clinical evidence, mechanism, importance and management

(a) Lansoprazole

In a study in 12 healthy subjects a single 30-mL dose of *Maalox* (**aluminium/magnesium hydroxide**) slightly reduced the AUC of a 30-mg dose of lansoprazole by 13% (not statistically significant), and reduced the maximum plasma level by 27%. However, no changes were seen when the lansoprazole was given 1 hour after the antacid.[1] Note that in this study, the bioavailability of lansoprazole was highly variable between subjects (the AUC varied by a factor of 6). In another study, **magaldrate** had no effect on the AUC of lansoprazole, but slightly reduced its maximum level by 28%; however, this change was not considered clinically relevant.[2] Nevertheless, the manufacturer recommends that antacids should not be taken within one hour of lansoprazole,[3] but on the basis of the evidence given above, this seems to be an overcautious recommendation.

(b) Omeprazole

Two single-dose studies have shown that *Maalox* suspension (**aluminium/magnesium hydroxide**) did not affect the absorption or disposition of omeprazole from an enteric-coated formulation.[4,5] Similar findings were reported for *Maalox* suspension in another single-dose study, although in contrast, this study found that *Maalox granules* reduced the AUC of omeprazole enteric-coated tablets by 74%% and significantly reduced its plasma levels.[6]

A randomised, crossover study in healthy subjects given omeprazole capsules 20 mg daily for 3 days, with two *Gaviscon* tablets (aluminium hydroxide, **magnesium trisilicate** and **sodium alginate**) on day 3, found that omeprazole did not significantly affect the alginate raft formation or the length of time the raft stayed in the stomach.[7] In another study in healthy subjects, concurrent use of *Gaviscon Advance* (**sodium alginate**) 10 mL four times daily and omeprazole (*Losec MUPS)* 20 mg daily for 3 days did not affect the pharmacokinetics of omeprazole, although it was noted that *Gaviscon Advance*, unlike *Gaviscon,* does not contain any ant-

acid.[8] No special precautions appear to be necessary if omeprazole is given with these antacids.

(c) Pantoprazole

Pantoprazole 40 mg daily was given to 24 healthy subjects with and without 10 mL of *Maalox* (**aluminium/magnesium hydroxide**). The AUC, maximum serum levels, and the half-life of pantoprazole were unchanged by the antacid.[9] No special precautions would seem to be necessary if pantoprazole is given with **aluminium/magnesium hydroxide**-containing antacids.

(d) Rabeprazole

In a single-dose study, 12 healthy subjects were, on separate occasions, given 20 mg of rabeprazole with, without, and 1-hour after a dose of an **aluminium/magnesium hydroxide** antacid (*Maalox*).[10] The antacid had no effect on the pharmacokinetics of rabeprazole, so no special precautions would seem necessary on concurrent use.

1. Delhotal-Landes B, Cournot A, Vermerie N, Dellatolas F, Benoit M, Flouvat B. The effect of food and antacids on lansoprazole absorption and disposition. *Eur J Drug Metab Pharmacokinet* (1991), Spec No 3, 315–20.
2. Gerloff J, Barth H, Mignot A, Fuchs W, Heintze K. Does the proton pump inhibitor lansoprazole interact with antacids? *Naunyn Schmiedebergs Arch Pharmacol* (1993) 347, R31.
3. Zoton FasTab (Lansoprazole). Wyeth Pharmaceuticals. UK Summary of product characteristics, August 2007.
4. Tuynman HARE, Festern HPM, Röhss K, Meuwissen SGM. Lack of effect of antacids on plasma concentrations of omeprazole given as enteric-coated granules. *Br J Clin Pharmacol* (1987) 24, 833–5.
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7. Dettmar PW, Little SL, Baxter T. The effect of omeprazole pre-treatment on rafts formed by reflux suppressant tablets containing alginate. *J Int Med Res* (2005) 33, 301–8.
8. Dettmar PW, Hampson FC, Jain A, Choubey S, Little SL, Baxter T. Administration of an alginate based gastric reflux suppressant on the bioavailability of omeprazole. *Indian J Med Res* (2006) 123, 517–24.
9. Hartmann M, Bliesath H, Huber R, Koch H, Steinijans VW, Wurst W. Lack of influence of antacids on the pharmacokinetics of the new gastric H^+/K^+-ATPase inhibitor pantoprazole. *Gastroenterology* (1994) 106 (Suppl), A91.
10. Yasuda S, Higashi S, Murakami M, Tomono Y, Kawaguchi M. Antacids have no influence on the pharmacokinetics of rabeprazole, a new proton pump inhibitor, in healthy volunteers. *Int J Clin Pharmacol Ther* (1999) 37, 249–53.

Proton pump inhibitors + Calcium-channel blockers

The clearance of both nifedipine and omeprazole is modestly reduced by their concurrent use, but these changes seem unlikely to be of clinical importance. Pantoprazole does not affect the pharmacokinetics of nifedipine. Verapamil does not appear to affect the pharmacokinetics of rabeprazole to a clinically relevant extent.

Clinical evidence, mechanism, importance and management

(a) Omeprazole

In a study in 10 healthy subjects, omeprazole 20 mg daily for 7 days reduced the clearance of **nifedipine** by 21%. In the same subjects, the clearance of a 40-mg intravenous dose of omeprazole was reduced by 14% by **nifedipine** 10 mg three times daily for 5 days.[1] In a related study, the same group of workers found that omeprazole 20 mg daily for 8 days increased the AUC of a single 10-mg dose of **nifedipine** by 26%, but blood pressure and heart rate were unchanged.[2] None of these changes are large and they seem not to be of clinical importance.

(b) Pantoprazole

In a randomised, crossover study, 24 healthy subjects were given pantoprazole 40 mg daily for 10 days, with sustained-release **nifedipine** 20 mg twice daily from day 6 to 10. The pharmacokinetics of the **nifedipine** were unchanged by the pantoprazole.[3] No special precautions would seem to be necessary if pantoprazole and **nifedipine** are given concurrently.

(c) Rabeprazole

A study in 19 healthy subjects found that **verapamil** 120 mg twice daily for 6 days did not significantly affect the pharmacokinetics of a single 20-mg dose of rabeprazole, although the levels of the inactive thioether metabolite were increased approximately twofold.

The main metabolic pathway of rabeprazole is non-enzymatic reduction to a thioether metabolite, with the cytochrome P450 isoenzymes CYP3A4 and CYP2C19 involved only to a minor extent. The results of this study indicate that verapamil does not appear to affect the minor metabolism of rabeprazole by CYP3A4, although it may affect the metabolic disposal of the inactive metabolite rabeprazole thioether.[4] In this study, subjects lacking or deficient in CYP2C19 had higher levels of rabeprazole than subjects with normal levels of CYP2C19, but this had no effect on the interaction with verapamil.

No special precautions seem likely to be necessary if rabeprazole is given with verapamil.

1. Danhof M, Soons PA, van den Berg G, Van Brummelen P, Jansen JBMJ. Interactions between nifedipine and omeprazole. *Eur J Clin Pharmacol* (1989) 36 (Suppl), A258.
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4. Shimizu M, Uno T, Yasui-Furukori N, Sugawara K, Tateishi T. Effects of clarithromycin and verapamil on rabeprazole pharmacokinetics between CYP2C19 genotypes. *Eur J Clin Pharmacol* (2006) 62, 597–603.

Proton pump inhibitors + Food

Food modestly reduces the bioavailability of lansoprazole and esomeprazole, but not omeprazole, pantoprazole, or rabeprazole. Foods such as apple sauce, apple or orange juice, and yoghurt do not seem to significantly affect the bioavailability of the contents of esomeprazole, lansoprazole or omeprazole capsules.

Clinical evidence, mechanism, importance and management

(a) Esomeprazole

In a crossover study in fasting healthy subjects, the bioavailability of the contents of an esomeprazole capsule mixed with one tablespoonful of **apple sauce** were similar to those of an intact esomeprazole capsule taken with water. **Apple sauce** was chosen because it is acidic and would therefore be unlikely to affect the enteric coat of the esomeprazole granules from the capsule.[1] An *in vitro* study found that esomeprazole enteric-coated granules from an opened capsule were stable when mixed with 100 mL tap water, **yoghurt**, **orange juice** or **apple juice**.[2] The authors suggest that it is likely that esomeprazole could be mixed with these **juices** or other **soft acidic foods** in patients who cannot swallow a capsule.[1,2] Nevertheless, for patients unable to swallow, the UK manufacturers recommend only dispersing esomeprazole *tablets* in **non-carbonated water** to avoid dissolving the enteric coating. They also note that food delays and decreases the absorption of esomeprazole *tablets*, but that this has little effect on gastric acidity.[3] The US manufacturers say that because the AUC of esomeprazole can be reduced by 43 to 53% by food, esomeprazole *capsules* and *oral suspension* should be taken at least one hour before meals.[4]

(b) Lansoprazole

A study found that food (a **standard meal**) reduced lansoprazole bioavailability by 27%.[5] Another study found a 50% reduction in lansoprazole bioavailability with food (a **standard breakfast**).[6] The authors of both these studies therefore recommended that lansoprazole should not be given with food.[5,6] The maximum plasma levels and AUC of lansoprazole are reduced by 50 to 70% when it is given 30 minutes after food. No significant effect was found when lansoprazole was given before meals.[7] The manufacturers recommend that, to achieve optimal efficacy, lansoprazole should be given in the morning at least 30 minutes before food.[7,8] However, in crossover studies in fasting healthy subjects, the bioavailability of enteric-coated granules (removed from a capsule of lansoprazole 30 mg) mixed with either **orange juice**, **tomato juice**, or with one tablespoonful of **strained pear**, **yoghurt**, **cottage cheese**, or ***Ensure* pudding** was comparable to that of an intact capsule given with water.[9,10] These studies suggest that for patients who are unable to swallow or who have difficulty swallowing, mixing the capsule contents with these specific juices or soft foods is acceptable. The US manufacturers also say that the intact contents of the *delayed-release capsules* may be mixed in with a small volume (60 mL) of **apple sauce**, ***Ensure* pudding**, **cottage cheese**, or **yoghurt**. However, the *soluble tablets* may only be dispersed in **water**, and, if given via a nasogastric tube, the tube should be flushed with water before and after administration. The *suspension* may only be mixed with **water** and must not be given through a nasogastric tube.[7]

(c) Omeprazole

In a study in healthy subjects, giving omeprazole with **breakfast** delayed its absorption, but did not affect the total amount absorbed.[11] Similarly, in another study in healthy subjects, a **standardised breakfast** did not affect the bioavailability or maximum plasma level of omeprazole (given as enteric-coated tablets), when compared with the fasting state, or when taken immediately before a meal, although the time to reach the maximum plasma level was increased.[12] Omeprazole may therefore be taken without regard to the timing of meals. For patients unable to swallow, the manufacturers recommend mixing the intact contents of the opened capsule with **non-carbonated water**, **apple**, **orange** or **pineapple juice**, **yoghurt**[13] or **apple sauce**.[13,14]

(d) Pantoprazole

The manufacturers state that food has no effect on the bioavailability of pantoprazole.[15,16] The US manufacturer recommends that the tablet is swallowed whole with water, with or without food.[15] The UK manufacturer advises taking pantoprazole before a meal, although because food has no effect on the bioavailability of pantoprazole, this is not essential.[16] The oral suspension should be taken 30 minutes before food and should only be mixed with **apple juice** or **apple sauce**.[15]

(e) Rabeprazole

A study in healthy subjects found that, although a **standard breakfast** delayed the absorption of rabeprazole, its AUC and maximum plasma level were not significantly affected.[17] The US manufacturers also report that a **high-fat meal** may delay the absorption of rabeprazole without altering its AUC and maximum serum levels.[18] Therefore the manufacturers say that rabeprazole may be taken with or without food.[18,19] The UK manufacturers note that, although food has no effect on the activity of rabeprazole, for once daily regimens they recommend taking it in the morning, before breakfast, to aid compliance.[19]

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2. Johnson DA, Roach AC, Carlsson AS, Karlsson AAS, Behr DE. Stability of esomeprazole capsule contents after in vitro suspension in common soft foods and beverages. *Pharmacotherapy* (2003) 23, 731–4.
3. Nexium Tablets (Esomeprazole magnesium trihydrate). AstraZeneca UK Ltd. UK Summary of product characteristics, September 2009.
4. Nexium (Esomeprazole magnesium). AstraZeneca. US Prescribing information, June 2009.
5. Delhotal-Landes B, Cournot A, Vermerie N, Dellatolas F, Benoit M, Flouvat B. The effect of food and antacids on lansoprazole absorption and disposition. *Eur J Drug Metab Pharmacokinet* (1991), Spec No 3, 315–20.
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7. Prevacid (Lansoprazole). Takeda Pharmaceuticals America, Inc. US Prescribing information, July 2009.
8. Zoton FasTab (Lansoprazole). Wyeth Pharmaceuticals. UK Summary of product characteristics, August 2007.
9. Chun AHC, Erdman K, Chiu YL, Pilmer BL, Achari R, Cavanaugh JH. Bioavailability of lansoprazole granules administered in juice or soft food compared to the intact capsule formulation. *Clin Ther* (2002) 24, 1322–31.
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11. Rohss K, Andren K, Heggelund A, Lagerstrom P-O, Lundborg P. Bioavailability of omeprazole given in conjunction with food. III World Conf Clin Pharmacol Ther, Stockholm July-Aug 1986. *Acta Pharmacol Toxicol (Copenh)* (1986) 85 (Suppl 5), Abstract 207.
12. Thomson ABR, Sinclair P, Matisko A, Rosen E, Andersson T, Olofsson B. Influence of food on the bioavailability of an enteric-coated tablet formulation of omeprazole under repeated dose conditions. *Can J Gastroenterol* (1997) 11, 663–7.
13. Losec Capsules (Omeprazole). AstraZeneca UK Ltd. UK Summary of product characteristics, February 2008.
14. Prilosec (Omeprazole delayed-release). AstraZeneca. US Prescribing information, April 2007.
15. Protonix (Pantoprazole sodium). Wyeth Pharmaceuticals Inc. US Prescribing information, December 2009.
16. Protium Tablets (Pantoprazole sodium sesquihydrate). Nycomed UK Ltd. UK Summary of product characteristics, January 2008.
17. Yasuda S, Ohnishi A, Ogawa T, Tomono Y, Hasegawa J, Nakai H, Shimamura Y, Morishita N. Pharmacokinetic properties of E3810, a new proton pump inhibitor, in healthy male volunteers. *Int J Clin Pharmacol Ther* (1994) 32, 466–73).
18. AcipHex (Rabeprazole sodium). Eisai Inc. US Prescribing information, January 2009.
19. Pariet (Rabeprazole sodium). Eisai Ltd. UK Summary of product characteristics, May 2009.

Proton pump inhibitors + Ginkgo (*Ginkgo biloba*)

Ginkgo induces the metabolism of omeprazole, and this might result in reduced efficacy. Other proton pump inhibitors are likely to be similarly affected.

Clinical evidence and mechanism

In one study, 18 healthy Chinese subjects were given a single 40-mg dose of omeprazole before and after a 12-day course of a standardised extract of ginkgo 140 mg twice daily. The subjects were divided into three groups: homozygous extensive CYP2C19 metabolisers (6 subjects), heterozygous extensive CYP2C19 metabolisers (5) and poor CYP2C19 metabolisers (7). The AUC of omeprazole was modestly decreased by 42%, 27% and 40%, respectively, and the plasma levels of the inactive metabolite, hydroxyomeprazole, were increased by 38%, 100%, and 232% in the three groups, respectively. Renal clearance of hydroxyomeprazole was also reduced by ginkgo. It was concluded that ginkgo increases the metabolism (hydroxylation) of omeprazole by inducing the cytochrome P450 isoenzyme CYP2C19.[1]

Importance and management

This appears to be the only study examining the effects of ginkgo on proton pump inhibitors. However, the reduction seen in the AUC of omeprazole (about 40%) suggest that there is a possibility that omeprazole will be less effective in patients taking ginkgo. As all proton pump inhibitors are metabolised by CYP2C19 to varying extents, it is likely that the effects of ginkgo seen in these studies will be similar with other proton pump inhibitors, although note that rabeprazole is much less dependent on this route of metabolism than other proton pump inhibitors.

There is insufficient evidence to generally recommend that ginkgo should be avoided in patients taking proton pump inhibitors. However, the potential reduction in the efficacy of the proton pump inhibitor should be borne in mind, particular where the consequences may be serious, such as in patients with healing ulcers.

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Proton pump inhibitors + Grapefruit juice

Grapefruit juice has little effect on the AUC of lansoprazole or omeprazole, but modestly reduces the formation of their sulfone metabolites, which is unlikely to be clinically relevant.

Clinical evidence

(a) Lansoprazole

In a randomised, crossover study 21 healthy subjects were given a single 60-mg dose of lansoprazole with either 200 mL of water or freshly-squeezed grapefruit juice. The AUC of lansoprazole was slightly increased by 18%, and the formation of the sulfone metabolite was reduced by the grapefruit juice. Metabolism to the hydroxyl metabolite was not significantly affected.[1]

(b) Omeprazole

In a single-dose study in 12 healthy subjects, grapefruit juice 300 mL had no significant effect on the AUC or half-life of omeprazole 20 mg: the results were similar in both CYP2C19 metaboliser phenotypes, as indicated by plasma levels of hydroxyomeprazole. However, there was a 20% reduction in AUC of omeprazole sulfone.[2]

Mechanism

From the studies above[1,2] it appears that grapefruit juice may have a minor inhibitory effect on the intestinal metabolism of omeprazole and lansoprazole by the cytochrome P450 isoenzyme CYP3A4 (which results in the sulfone metabolites). Grapefruit juice does not affect the metabolism (hydroxylation) of the proton pump inhibitors by CYP2C19.

Importance and management

The small changes in lansoprazole and omeprazole pharmacokinetics are not clinically relevant, so it appears that they may be taken with grapefruit juice. See also ‘Proton pump inhibitors + Food’, p.1158, for the finding

that other fruit juices had no effect on esomeprazole, lansoprazole or omeprazole bioavailability.

1. Uno T, Yasui-Furukori N, Takahata T, Sugawara K, Tateishi T. Lack of significant effect of grapefruit juice on the pharmacokinetics of lansoprazole and its metabolites in subjects with different CYP2C19 genotypes. *J Clin Pharmacol* (2005) 45, 690–4.
2. Tassaneeyakul W, Tassaneeyakul W, Vannaprasaht S, Yamazoe Y. Formation of omeprazole sulphone but not 5-hydroxyomeprazole is inhibited by grapefruit juice. *Br J Clin Pharmacol* (2000) 49, 139–44.

Proton pump inhibitors + Iron compounds

Omeprazole may impair the absorption of oral iron preparations and vegetable sources of iron.

Clinical evidence, mechanism, importance and management

Two cases of iron deficiency in patients also taking long-term **omeprazole** have been reported. In both cases the authors report that other causes of the anaemia, such as occult gastrointestinal bleeding, were ruled out by clinical and laboratory tests. The patients were taken off **omeprazole** for 2 months and continued to take the same dose of **ferrous sulfate**, with a noted improvement in both the haemoglobin and mean corpuscular volume (MCV). It was considered that hypochlorhydria induced by **omeprazole** may have impaired the absorption of oral iron preparations.[1] In another study in 7 patients with hereditary haemochromatosis, the use of either **omeprazole** 20 mg or **lansoprazole** 30 mg daily for 7 days suppressed the absorption of non-haem iron (iron of vegetable source) from a test meal.[2] The significance of this to routine clinical practice is unclear as many other factors and disease states can affect oral iron absorption. However bear these reports in mind should a patient taking a proton pump inhibitor fail to respond to oral iron therapy. Further study is needed.

1. Sharma VR, Brannon MA, Carloss EA. Effect of omeprazole on oral iron replacement in patients with iron deficiency anemia. *South Med J* (2004) 97, 887–9.
2. Hutchinson C, Geissler CA, Powell JJ, Bomford A. Proton pump inhibitors suppress absorption of dietary non-haem iron in hereditary haemochromatosis. *Gut* (2007) 56, 1291–5.

Proton pump inhibitors + Macrolides

Clarithromycin approximately doubles the serum levels of esomeprazole, lansoprazole and omeprazole, but has no significant effect on pantoprazole or rabeprazole. Lansoprazole and omeprazole may cause small rise in the serum levels of clarithromycin or its metabolite.
Limited evidence indicates that erythromycin raises serum omeprazole levels, without significantly altering its effects. Lansoprazole and omeprazole do not appear to affect the pharmacokinetics of roxithromycin.

Clinical evidence

(a) Clarithromycin

See also 'Proton pump inhibitors + Penicillins', p.1161, which describes case reports of glossitis, stomatitis and a black tongue when lansoprazole was given with antibacterial regimens including clarithromycin.

1. Esomeprazole. In a study in 18 healthy subjects the AUC, maximum serum levels and half-life of esomeprazole 40 mg once daily were increased by 70%, 18% and 35%, respectively, when clarithromycin 500 mg twice daily and amoxicillin 1 g twice daily for 7 days were also taken. When the study was repeated in 19 healthy subjects with esomeprazole 20 mg, the AUC, maximum serum levels and half-life of esomeprazole were increased by 127%, 39% and 50%, respectively. All subjects were of the CYP2C19 extensive metaboliser phenotype. Similar increases in esomeprazole levels (e.g. AUC doubled) were seen in a further 6 subjects who were of the CYP2C19 poor metaboliser phenotype. In these studies, esomeprazole did not alter clarithromycin levels.[1]

2. Lansoprazole. The AUC of a single 60-mg dose of lansoprazole was raised 1.55-fold to 1.8-fold by clarithromycin 500 mg twice daily for 6 days in both extensive and poor metabolisers of CYP2C19.[2] In another study in healthy subjects, the AUC of lansoprazole 30 mg twice daily was increased by just 25% by clarithromycin 500 mg twice daily and amoxicillin 1 g twice daily for 4 days. The AUC of the hydroxyl metabolite of clarithromycin was also increased by about 25%.[3] Another study in healthy subjects found that clarithromycin 200 mg or 400 mg twice daily for 7 days increased the maximum plasma levels of lansoprazole by around 80% and 145%, respectively.[4]

3. Omeprazole. When 11 healthy subjects taking omeprazole 40 mg daily were also given clarithromycin 500 mg every 8 hours for 5 days, the maximum plasma levels of omeprazole rose by 30% and its $AUC_{0\text{-}24}$ rose by 89%, but the effect of omeprazole on gastric pH was unchanged. The clarithromycin maximum plasma level rose by 11% and the $AUC_{0\text{-}8}$ was increased by 15%.[5] In a similar study, approximately twofold increases in the AUC of omeprazole were reported.[6] In another study in 8 subjects (all extensive metabolisers of CYP2C19), clarithromycin 500 mg twice daily for 7 days caused a similar twofold increase in the AUC of omeprazole 20 mg twice daily but did not affect the AUC of **pantoprazole** 40 mg twice daily. The levels of clarithromycin were not affected by either proton pump inhibitor.[7]

4. Rabeprazole. A study in 19 healthy subjects (14 extensive metabolisers; 5 poor metabolisers), found that, irrespective of CYP2C19 phenotype, clarithromycin 400 mg twice daily for 6 days did not significantly affect the pharmacokinetics of a single 20-mg dose of rabeprazole, although levels of the inactive thioether were increased.[8]

(b) Erythromycin

A study was undertaken in a patient to confirm the *in vitro* findings that erythromycin inhibits the metabolism of **omeprazole**. After taking 500 mg of erythromycin base and **omeprazole** 20 mg daily for 8 weeks, it was found that the AUC of **omeprazole** was increased by almost fourfold, and the metabolite of **omeprazole** was undetectable. These raised **omeprazole** levels might have been expected to increase its effectiveness, but in this patient the time during which gastric pH was less than 4 *decreased* by 22%.[9]

(c) Roxithromycin

A study of roxithromycin 300 mg twice daily, given with **omeprazole** 20 mg twice daily or with **lansoprazole** 30 mg twice daily for 6 days, found that neither proton pump inhibitor significantly affected the pharmacokinetics of roxithromycin.[10]

Mechanism

Clarithromycin appears to inhibit the metabolism of esomeprazole,[1] lansoprazole[2,4] and omeprazole[5,6] by the cytochrome P450 isoenzyme CYP3A4, one of the enzymes involved in their metabolism. Pantoprazole is metabolised by CYP2C19 only and was therefore not affected by the inhibition of CYP3A4. The main metabolic pathway of rabeprazole is non-enzymatic reduction to a thioether metabolite, with CYP3A4 and CYP2C19 involved only to a minor extent, so that rabeprazole is less affected than other proton pump inhibitors by CYP2C19 polymorphism.[8,11] See 'Gastrointestinal drugs', (p.1142), for an overview of the metabolism of proton pump inhibitors and the role of CYP2C19 polymorphism. Erythromycin interacts similarly, whereas roxithromycin has only weak effects on CYP3A4. A study also reports that increased levels of lansoprazole in the presence of clarithromycin may, in part, be due to inhibition of P-glycoprotein.[2]

Importance and management

The pharmacokinetic interactions between clarithromycin and omeprazole, esomeprazole and lansoprazole are established. However, none of the changes reported represents an adverse interaction, but they may help to explain why concurrent use is valuable in the eradication of *Helicobacter pylori*. Erythromycin is likely to interact similarly, whereas roxithromycin does not. No clinically significant interaction appears to occur between rabeprazole or pantoprazole and clarithromycin.

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Proton pump inhibitors + Penicillins

Esomeprazole, lansoprazole and omeprazole do not alter the pharmacokinetics of amoxicillin, and omeprazole does not alter bacampicillin bioavailability. Isolated reports describe glossitis, stomatitis and/or black tongue in a small number of patients given lansoprazole and antibacterials, which included amoxicillin, clarithromycin and metronidazole.

Clinical evidence and mechanism

(a) Pharmacokinetic interactions

A study in 12 healthy subjects found no significant changes in the pharmacokinetics of **amoxicillin** 1 g twice daily when it was given with **lansoprazole** 30 mg twice daily and clarithromycin 500 mg twice daily for 4 days.[1] Other randomised, crossover studies in a total of 36 healthy subjects also found no changes in the bioavailability or half-life of **amoxicillin** 1 g twice daily when it was given with clarithromycin 500 mg twice daily and **esomeprazole**, either 20 mg twice daily or 40 mg once daily for 7 days.[2]

In other studies **omeprazole** caused a few small changes in the pharmacokinetics of **bacampicillin** and **amoxicillin**, but their bioavailabilities were not reduced,[3-5] and the use of **amoxicillin** with **omeprazole** had a synergistic effect on *Helicobacter pylori* eradication.[4] Similarly, in another study, **omeprazole** 40 mg twice daily for 5 days did not affect the pharmacokinetics of **amoxicillin** 750 mg twice daily for 5 days, although the mean serum level of **omeprazole** was 12% lower and intragastric pH was slightly lower with the combination, than with **omeprazole** alone. This was felt to be partly due to suppression of *H. pylori*.[6] In a placebo-controlled study in 12 patients with non-ulcer dyspepsia, serum levels of a single dose of **amoxicillin** were not affected by pre-treatment with **omeprazole** for one week. Gastric mucosa levels of **amoxicillin** were similarly unaffected by **omeprazole**.[7]

(b) Stomatitis and similar adverse effects

Six cases of glossitis, stomatitis and/or black tongue were reported to the Sicilian Regional Pharmacovigilance Centre in patients taking **lansoprazole**, when combined with antibacterials used to treat *H. pylori* infections. All 6 patients had been given daily doses of **lansoprazole** 60 mg with clarithromycin 1 g and either metronidazole 1 g (3 patients) or **amoxicillin** 2 g (3 patients) for one week, after which the antibacterials were stopped. The **lansoprazole** was continued at 30 mg daily for periods of up to 3 weeks. The glossitis (1 patient), black tongue (3 patients) and stomatitis (2 patients) developed between days 2 and 19 of the courses of treatment.[8] In one small randomised study, nine cases of glossitis occurred when **lansoprazole** was given with **amoxicillin** but none occurred with **lansoprazole** alone.[9]

Importance and management

The incidence of glossitis, stomatitis and black tongue reported with lansoprazole and antibacterials appears to be rare. No new cases appear to have been published since these reports, even though these drug combinations are commonly used for the eradication of *H. pylori*. Just why these drugs cause these adverse effects, and whether they are due to just one drug or to an interaction is not understood. Note that the CSM in the UK have received reports of stomatitis, glossitis and a black, hairy tongue or discoloration with each of the reported drugs individually, but these are rare effects.[10]

The pharmacokinetics of amoxicillin do not appear to be affected by the concurrent use of esomeprazole, lansoprazole and omeprazole, and omeprazole was not affected by amoxicillin.

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2. Hassan-Alin M, Andersson T, Niazi M, Liljeblad M, Persson BA, Röhss K. Studies on drug interactions between esomeprazole, amoxicillin and clarithromycin in healthy subjects. *Int J Clin Pharmacol Ther* (2006) 44, 119–27.
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Proton pump inhibitors + SSRIs

Fluvoxamine markedly inhibits the metabolism of the proton pump inhibitors lansoprazole, omeprazole and rabeprazole in those of the CYP2C19 extensive metaboliser phenotype, producing levels comparable to those in poor metabolisers. Theoretically other proton pump inhibitors may be similarly affected. Omeprazole may increase escitalopram levels; esomeprazole and citalopram may also interact in this way.

Clinical evidence

(a) Escitalopram

In a study in healthy subjects,[1] **omeprazole** 30 mg daily for 6 days caused a 50% increase in the serum levels of a single 20-mg dose of escitalopram given on day 5.

(b) Fluvoxamine

Several studies in healthy subjects have investigated the effects of fluvoxamine (a CYP2C19 inhibitor) on the metabolism of proton pump inhibitors. In these studies, fluvoxamine 25 mg twice daily for 6 days had significant effects on the pharmacokinetics of three different proton pump inhibitors in patients who were of the extensive CYP2C19 metaboliser phenotype (the most common phenotype) as follows:

- **Lansoprazole**: Fluvoxamine increased the AUC and elimination half-life of a single 40-mg dose of lansoprazole by 3.8-fold and 3-fold, respectively.[2]
- **Omeprazole**: Fluvoxamine increased the AUC, half-life and maximum plasma concentration of a single 40-mg dose of omeprazole by 6-fold, 2.6-fold and 3.7-fold, respectively.[3]
- **Rabeprazole**: Fluvoxamine increased the AUC, elimination half-life and maximum plasma concentration of a single 20-mg dose of rabeprazole by 2.8-fold, 2.4-fold and 2-fold, respectively.[4]

These pharmacokinetic changes essentially had the effect of turning the extensive metabolisers into poor metabolisers.[2-4] In contrast, in patients who were of the CYP2C19 poor metabolisers phenotype, fluvoxamine did not have any significant effect on the pharmacokinetics of either of these three proton pump inhibitors.[2-4]

In an earlier study 12 healthy subjects (7 extensive metabolisers and 5 poor metabolisers of CYP2C19) were given fluvoxamine 10 to 50 mg daily for 7 days, with a single 20-mg dose of **omeprazole** on day 7. The AUC of **omeprazole** was increased by nearly threefold by fluvoxamine 10 to 20 mg and by over fourfold by fluvoxamine 25 to 50 mg (all subjects combined).[5]

Mechanism

All proton pump inhibitors are primarily metabolised by the cytochrome P450 isoenzyme CYP2C19, which is subject to genetic polymorphism,

see 'Gastrointestinal drugs', (p.1142). As fluvoxamine inhibits CYP2C19, it can increase the levels of proton pump inhibitors in patients who are extensive CYP2C19 metabolisers, but does not significantly affect the metabolism of proton pump inhibitors in patients who are poor metabolisers. Omeprazole and esomeprazole are also inhibitors of CYP2C19, and therefore may raise the levels of the SSRIs citalopram and escitalopram, which are metabolised by this route.

Importance and management

The interaction of **fluvoxamine** with proton pump inhibitors appears to be established. However, the increased levels of these proton pump inhibitors seen in extensive metabolisers taking fluvoxamine are similar to those seen in poor metabolisers not taking fluvoxamine, and are unlikely to lead to an increase in adverse effects because of the wide therapeutic margin of proton pump inhibitors.

Some studies have shown that CYP2C19 genotype is a factor in the success of proton pump inhibitor-based eradication regimens, as poor metabolisers of CYP2C19 appear to have higher *H. pylori* eradication rates with these regimens than extensive metabolisers.[6,7] Therefore, treatment of *H. pylori* is likely to be more successful in patients who are extensive metabolisers and are also taking an inhibitor of CYP2C19 such as fluvoxamine (see 'Table 1.3', (p.6), for further examples of CYP2C19 inhibitors). However, the addition of fluvoxamine to improve proton pump inhibitor-based eradication regimens is not clinically appropriate because of the risk of fluvoxamine adverse effects.

Omeprazole causes only a moderate increase in **escitalopram** levels; however, the manufacturer[8] suggests that caution is warranted and a dose adjustment of the escitalopram may be needed. The manufacturer of **esomeprazole**[9] predicts that it may raise the levels of citalopram (and therefore probably escitalopram).

1. Malling D, Poulsen MN, Søgaard B. The effect of cimetidine or omeprazole on the pharmacokinetics of escitalopram in healthy subjects. *Br J Clin Pharmacol* (2005) 60, 287–90.
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8. Cipralex (Escitalopram oxalate). Lundbeck Ltd. UK Summary of product characteristics, October 2008.
9. Nexium Tablets (Esomeprazole magnesium trihydrate). AstraZeneca UK Ltd. UK Summary of product characteristics, September 2009.

Proton pump inhibitors + St John's wort (*Hypericum perforatum*)

St John's wort induces the metabolism of omeprazole, and this might result in reduced efficacy. Other proton pump inhibitors are likely to be similarly affected.

Clinical evidence and mechanism

In a crossover study, 12 healthy subjects (6 of the extensive CYP2C19 metaboliser phenotype and 6 of the poor CYP2C19 metaboliser phenotype) were given St John's wort 300 mg three times daily or placebo for 14 days, followed by a single 20-mg dose of omeprazole on day 15. St John's wort modestly decreased the AUC of omeprazole in all subjects (by 49% in extensive metabolisers and 41% in poor metabolisers), and also increased the plasma levels of hydroxyomeprazole by 35% in those who were extensive metabolisers. It also markedly increased the levels of the inactive CYP3A4 sulfone metabolite of omeprazole in both extensive and poor metabolisers (by 148% and 132%, respectively). It was concluded that St John's wort increases the metabolism of omeprazole by inducing both CYP2C19 and CYP3A4.[1]

Importance and management

This appears to be the only study examining the effects of St John's wort on proton pump inhibitors. However, the reduction seen in the AUC of omeprazole (about 40%) suggest that there is a possibility that omeprazole will be less effective in patients taking St John's wort. As all proton pump inhibitors are metabolised by CYP2C19 to varying extents, it is likely that the effects of St John's wort seen in these studies will be similar with other proton pump inhibitors, although note that rabeprazole is much less dependent on this route of metabolism than other proton pump inhibitors.

There is insufficient evidence to suggest that St John's wort should be avoided in patients taking proton pump inhibitors. However, the potential reduction in the efficacy of the proton pump inhibitor should be borne in mind, particular where the consequences may be serious, such as in patients with healing ulcers.

1. Wang LS, Zhou G, Zhu B, Wu J, Wang JG, Abd El-Aty AM, Li T, Liu J, Yang TL, Wang D, Zhong XY, Zhou HH. St John's wort induces both cytochrome P450 3A4–catalyzed sulfoxidation and 2C19–dependent hydroxylation of omeprazole. *Clin Pharmacol Ther* (2004) 75, 191–7.

Proton pump inhibitors + Ticlopidine

Ticlopidine markedly decreases the clearance and increases the bioavailability of omeprazole in some patients.

Clinical evidence

In a study, 6 healthy subjects (all CYP2C19 extensive metabolisers, that is, those with normal levels of this isoenzyme) were given ticlopidine 100 mg three times daily with a single 40-mg dose of **omeprazole** on day 7. Ticlopidine increased the $AUC_{0\text{-}8}$ of **omeprazole** by about 76%, and reduced its clearance in 5 out of the 6 subjects.[1] In another study, 18 healthy subjects (6 of whom were CYP2C19 poor metabolisers, that is, those lacking or deficient in this isoenzyme) were given ticlopidine 200 mg daily with **omeprazole** 20 mg taken on day 8. Ticlopidine markedly increased the AUC of **omeprazole** in the 12 subjects that were CYP2C19 extensive metabolisers by about five- to sixfold, but did not alter **omeprazole** levels in the poor metaboliser group. The AUC of omeprazole in the extensive metabolisers given ticlopidine was similar to that in poor metabolisers (with or without ticlopidine). No adverse effects due to either **omeprazole** or ticlopidine were reported.[2]

Mechanism

Omeprazole is principally metabolised by the cytochrome P450 isoenzyme CYP2C19 to 5-hydroxyomeprazole, and ticlopidine is an inhibitor of this isoenzyme. People of CYP2C19 poor metaboliser phenotype have higher levels of omeprazole than extensive metabolisers, and ticlopidine effectively changes extensive metabolisers to poor metabolisers. Other proton pump inhibitors that are metabolised by CYP2C19, see 'Gastrointestinal drugs', (p.1142), would be expected to be similarly affected.

Importance and management

An interaction between omeprazole and ticlopidine is established; however, the increase in omeprazole levels reported with ticlopidine is unlikely to be of general relevance as omeprazole has a wide safety margin. No additional precautions, or an omeprazole dose reduction, appear to be necessary.

1. Tateishi T, Kumai T, Watanabe M, Nakura H, Tanaka M, Kobayashi S. Ticlopidine decreases the *in vivo* activity of CYP2C19 as measured by omeprazole metabolism. *Br J Clin Pharmacol* (1999) 47, 454–7.
2. Leiri I, Kimura M, Irie S, Urae A, Otsubo K, Ishizaki T. Interaction magnitude, pharmacokinetics and pharmacodynamics of ticlopidine in relation to CYP2C19 genotypic status. *Pharmacogenet Genomics* (2005) 15, 851–9.

Proton pump inhibitors; Omeprazole + Artemisinin

Artemisinin modestly increases the metabolism of omeprazole, but the clinical significance of this is unclear.

Clinical evidence, mechanism, importance and management

A study in 9 healthy subjects found that artemisinin 250 mg twice daily for 7 days reduced the AUC of a single 20-mg dose of omeprazole by 35%. The pharmacokinetics of the omeprazole metabolites were unchanged, but the ratio of hydroxyomeprazole to omeprazole increased 2.2-fold in those of an extensive CYP2C19 metabolisers phenotype (see 'metabolism of proton pump inhibitors', (p.1142)). This suggests that artemisinin affects the pharmacokinetics of omeprazole by inducing its metabolism by the cytochrome P450 isoenzyme CYP2C19, although other isoenzymes may also be involved. A single 250-mg dose of artemisinin had no effect on the pharmacokinetics of omeprazole, which supports the proposed mechanism of enzyme induction.[1] A subsequent study in 8 healthy subjects who were of the extensive CYP2C19 metaboliser phenotype similarly found that artemisinin 500 mg daily for 7 days decreased the AUC of both the *S*- and *R*-enantiomers of a single 20-mg dose of omeprazole to the same extent, and increased the oral clearance of both enantiomers by about threefold.[2] The clinical significance of this interaction is unclear.

1. Svensson USH, Ashton M, Hai TN, Bertilsson L, Huong DX, Huong NV, Niêu NT, Sy ND, Lykkesfeldt J, Công LD. Artemisinin induces omeprazole metabolism in human beings. *Clin Pharmacol Ther* (1998) 64, 160–67.
2. Mihara K, Svensson USH, Tybring G, Hai TN, Bertilsson L, Ashton M. Stereospecific analysis of omeprazole supports artemisinin as a potent inducer of CYP2C19. *Fundam Clin Pharmacol* (1999) 13, 671–5.

Proton pump inhibitors; Omeprazole + Disulfiram

An isolated case describes a catatonic reaction in a patient given omeprazole and disulfiram.

Clinical evidence, mechanism, importance and management

A patient who had been taking omeprazole 40 mg daily for 7 months was also given disulfiram 500 mg daily. Six days later he gradually developed confusion, which progressed to a catatonic state, with muscle rigidity and trismus (spasm of the muscles used to chew food), after 15 days. Both drugs were withdrawn and he gradually recovered. Some months later while taking disulfiram 250 mg daily, he again developed confusion, disorientation and nightmares within 72 hours of starting to take omeprazole 40 mg each morning. Again he recovered when both drugs were stopped.[1] The reason for this reaction is not understood, but the authors of the report suggest that omeprazole may have allowed the accumulation of one of the metabolites of disulfiram, carbon disulfide, which could have been responsible for the toxic effects.[1]

This is the first and only report of a possible interaction between omeprazole and disulfiram. Other patients given both drugs are said not to have shown adverse effects.[2] The general importance of this adverse interaction is therefore uncertain, but it seems likely to be small.

1. Hajela R, Cunningham G M, Kapur B M, Peachey J E, Devenyi P. Catatonic reaction to omeprazole and disulfiram in a patient with alcohol dependence. *Can Med Assoc J* (1990) 143, 1207–8.
2. Astra Pharmaceuticals Ltd. Personal communication, May 1991.

Proton pump inhibitors; Omeprazole + Metronidazole

Omeprazole has no clinically significant effect on the pharmacokinetics of oral or intravenous metronidazole.

Clinical evidence, mechanism, importance and management

In 14 healthy subjects the plasma pharmacokinetics of a single oral dose of metronidazole were unaffected by 5 days pre-treatment with **omeprazole** 20 mg twice daily.[1] Similar results were found in another study with oral and intravenous metronidazole, but when the gastric juice was further studied it was found that the transfer of metronidazole into the gastric juice following an intravenous dose dropped from 15.5 to 2.6% in the presence of **omeprazole**.[2] The significance of these findings is unclear, but the clinical relevance seems small.

See also 'Proton pump inhibitors + Penicillins', p.1161, for case reports of glossitis, stomatitis and a black tongue with lansoprazole and antibacterial regimens including metronidazole.

1. David FL, Da Silva CMF, Mendes FD, Ferraz JGP, Muscara MN, Moreno H, De Nucci G, Pedrazzoli J. Acid suppression by omeprazole does not affect orally administered metronidazole bioavailability and metabolism in healthy male volunteers. *Aliment Pharmacol Ther* (1998) 12, 349–54.
2. Jessa MJ, Goddard AF, Barrett DA, Shaw PN, Spiller RC. The effect of omeprazole on the pharmacokinetics of metronidazole and hydroxymetronidazole in human plasma. saliva and gastric juice. *Br J Clin Pharmacol* (1997) 44, 245–53.

Proton pump inhibitors; Omeprazole + Mosapride

In a study, 9 healthy subjects were given a single 20-mg dose of omeprazole alone or 1 hour before a single 5-mg dose of mosapride. The peak levels and AUC of omeprazole were increased by 45% and 65%, respectively, when given with mosapride.[1] The clinical significance of this interaction is unclear, but as omeprazole is a generally safe and well tolerated drug, no particular adverse effects would be expected.

1. Takeuchi Y, Watanabe H, Imawari M. Mosapride citrate, a serotonin HT4 selective agonist, benifitially [sic] affects pharmacokinetics of proton pump inhibitor. *Gastroenterology* (2005) 128, (Suppl 2) A-531.

Proton pump inhibitors; Omeprazole + Ranitidine

In a study in 14 healthy subjects, omeprazole 40 mg (as two 20-mg capsules containing gastro-resistant pellets) were given either alone or after ranitidine 150 mg twice daily for 5 days. The AUC and peak plasma levels of omeprazole were increased by 20% and 10%, respectively, after pre-treatment with ranitidine.[1] These changes are small and therefore unlikely to be clinically relevant.

1. Leucuta A, Vlase L, Farcau D, Nanulescu M. A pharmacokinetic interaction study between omeprazole and the H_2-receptor antagonist ranitidine. *Drug Metabol Drug Interact* (2004) 20, 273–81.

Proton pump inhibitors; Omeprazole + Tegaserod

Omeprazole may delay gastric emptying; this may be prevented by tegaserod.

Clinical evidence, mechanism, importance and management

In a study in 39 healthy male subjects, gastric emptying was assessed before and after treatment with omeprazole 20 mg twice daily, given with either tegaserod 6 mg three times daily or placebo for 14 days. Omeprazole alone significantly increased the half-life for gastric emptying and gastric retention time at 60 and 120 minutes after a test meal. Tegaserod largely prevented the development of delayed gastric emptying with omeprazole.[1] No significant adverse effects were reported in this study,[1] and it would appear that concurrent use of omeprazole with tegaserod may be beneficial.

1. Tougas G, Earnest DL, Chen Y, Vanderkoy C, Rojavin M. Omeprazole delays gastric emptying in healthy volunteers: an effect prevented by tegaserod. *Aliment Pharmacol Ther* (2005) 22, 59–65.

Sulfasalazine + Antibacterials

Ampicillin moderately reduces, and rifampicin (with ethambutol) markedly reduces, the colonic release of 5-aminosalicylic acid (the active drug) from sulfasalazine. Metronidazole appears not to interact adversely with sulfasalazine.

Clinical evidence

(a) Ampicillin

In a study in 5 healthy subjects the conversion and release of the active metabolite of sulfasalazine, 5-aminosalicylic acid, was reduced by one-third when a single 2-g dose of sulfasalazine was given after a 5-day course of ampicillin 250 mg four times daily.[1]

(b) Metronidazole

A study in 10 patients (7 with Crohn's disease and 5 with ulcerative colitis) taking long-term sulfasalazine 2 to 4 g daily found that no statistically significant changes in serum sulfapyridine levels occurred while they were also taking metronidazole 400 mg twice daily for 8 to 14 days.[2] A study in 6 patients also found that sulfasalazine 1 g twice daily had no significant effect on the pharmacokinetics of metronidazole 250 mg twice daily, when both drugs were given concurrently for 6 days.[3]

(c) Rifampicin (Rifampin)

A crossover study in 11 patients with Crohn's disease receiving long-term treatment with sulfasalazine found that rifampicin 10 mg/kg daily and ethambutol 15 mg/kg daily reduced the plasma levels of both 5-aminosalicylic acid and sulfapyridine by about 60%.[4] A similar study in patients taking sulfasalazine 1.5 g to 4 g daily found that the plasma sulfapyridine levels were reduced by 57% when patients were taking rifampicin 10 mg/kg and ethambutol 15 mg/kg daily, when compared with placebo. They also noted an increase in the erythrocyte sedimentation rate (ESR) during antibacterial treatment.[5]

Mechanism

The azo link of sulfasalazine is split by anaerobic bacteria in the colon to release sulfapyridine and 5-aminosalicylic acid, the latter being the active metabolite that acts locally in the treatment of inflammatory bowel disease. Antibacterials that decimate the gut flora can apparently reduce this conversion and this is reflected in lower plasma levels.[4,5]

Importance and management

Information is limited, but the interactions between sulfasalazine and ampicillin or rifampicin (with ethambutol) appear to be established. The extent to which these antibacterials actually reduce the effectiveness of sulfasalazine in the treatment of Crohn's disease or ulcerative colitis seems not to have been assessed, but the studies do not suggest that the outcome is worse in patients given antibacterials while taking sulfasalazine. Metronidazole does not appear to interact. Information about other antibacterials appears to be lacking, but **neomycin**, which also affects the activity of the gut microflora, has been seen to interact similarly in *animal* studies.[6]

1. Houston JB, Day J, Walker J. Azo reduction of sulphasalazine in healthy volunteers. *Br J Clin Pharmacol* (1982) 14, 395–8.
2. Shaffer JL, Kershaw A, Houston JB. Disposition of metronidazole and its effects on sulphasalazine metabolism in patients with inflammatory bowel disease. *Br J Clin Pharmacol* (1986) 21, 431–5.
3. Eradiri O, Jamali F, Thomson ABR. Interaction of metronidazole with phenobarbital, cimetidine, prednisone, and sulfasalazine in Crohn's disease. *Biopharm Drug Dispos* (1988) 9, 219–277.
4. Shaffer JL, Houston JB. The effect of rifampicin on sulphapyridine plasma concentrations following sulphasalazine administration. *Br J Clin Pharmacol* (1985) 19, 526–8.
5. Shaffer JL, Hughes S, Linaker BD, Baker RD, Turnberg LA. Controlled trial of rifampicin and ethambutol in Crohn's disease. *Gut* (1984) 25, 203–5.
6. Peppercorn MA, Goldman P. The role of intestinal bacteria in the metabolism of salicylazosulfapyridine. *J Pharmacol Exp Ther* (1972) 181, 555–62.

Sulfasalazine + Cimetidine

Cimetidine does not interact with sulfasalazine.

Clinical evidence, mechanism, importance and management

In a study, 5 patients with rheumatoid arthritis were given sulfasalazine alone, and another 9 patients were given cimetidine 400 mg three times daily for 18 weeks as well as their usual sulfasalazine. On comparing the two groups, it was found that cimetidine did not affect the plasma or urinary levels of sulfasalazine and there were no changes in blood cell counts or haemoglobin levels. It was therefore concluded that no clinically important interaction occurs between these two drugs.[1]

1. Pirmohamed M, Coleman MD, Galvani D, Bucknall RC, Breckenridge AM, Park BK. Lack of interaction between sulphasalazine and cimetidine in patients with rheumatoid arthritis. *Br J Rheumatol* (1993) 32, 222–6.

Sulfasalazine + Colestyramine

***Animal* studies show that colestyramine can bind with sulfasalazine in the gut, thereby reducing its activity, but it is not known if this also occurs in clinical use.**

Clinical evidence, mechanism, importance and management

A study in *rats* found that colestyramine binds with sulfasalazine so that the azo-bond is protected against attack by the bacteria within the gut. As a result the active 5-aminosalicylic acid is not released and the faecal excretion of intact sulfasalazine increases 30-fold.[1] It seems possible that this interaction could also occur in humans, but confirmation of this is lacking. Separating the drug dosages to prevent their admixture in the gut has proved effective with other drugs that bind with colestyramine. Standard advice is to avoid other drugs for one hour before, and 4 to 6 hours after taking colestyramine.

1. Pieniaszek HJ, Bates TR. Cholestyramine-induced inhibition of salicylazosulfapyridine (sulfasalazine) metabolism by rat intestinal microflora. *J Pharmacol Exp Ther* (1976) 198, 240–5.

Sulfasalazine + Iron compounds

Sulfasalazine and iron appear to bind together in the gut, but whether this reduces the therapeutic response to either drug is uncertain.

Clinical evidence, mechanism, importance and management

Ferrous sulfate 400 mg (containing iron 80 mg) reduced the peak serum levels of a single 50-mg/kg dose of sulfasalazine by 40% in 5 healthy subjects. The reasons for this interaction are not known, but it seems likely that sulfasalazine chelates with the iron in the gut and thereby interferes with its absorption.[1] The extent to which this suggested chelation affects the ability of the intestinal bacteria to split sulfasalazine and release its locally active metabolite, 5-aminosalicylic acid, seems not to have been studied. Therefore the effect of this interaction on the clinical response to sulfasalazine is unclear.

1. Das KM, Eastwood MA. Effect of iron and calcium on salicylazosulphapyridine metabolism. *Scott Med J* (1973) 18, 45–50.

Sulfasalazine + Zileuton

No pharmacokinetic interaction appears to occur between sulfasalazine and zileuton.

Clinical evidence, mechanism, importance and management

In a randomised, double-blind study, 14 healthy subjects were given sulfasalazine 1 g every 12 hours for 8 days, with zileuton 800 mg or a placebo every 12 hours on days 3 to 8. It was found that the pharmacokinetics of the sulfasalazine and its metabolites (sulfapyridine and *N*-acetylsulfapyridine) were not significantly changed. The study did not directly look at the pharmacokinetics of the zileuton but, when compared with a previous study, its pharmacokinetics appeared unchanged.[1] There would seem to be no reason for special precautions if both drugs are used.

1. Awni WM, Braeckman RA, Locke CS, Dubé LM, Granneman GR. The influence of multiple oral doses of zileuton on the steady-state pharmacokinetics of sulfasalazine and its metabolites, sulfapyridine and N-acetylsulfapyridine. *Clin Pharmacokinet* (1995) 29 (Suppl 2), 98–104.

28

Hormonal contraceptives and Sex hormones

The hormonal contraceptives are of two main types: the **combined hormonal contraceptives** containing both an oestrogen and a progestogen available as tablets, a patch or vaginal ring; and the **progestogen-only contraceptives**, which are available as tablets (sometimes called 'mini' pills), parenteral preparations (implants, depot injections) and intrauterine devices.

The oestrogen most commonly used in combined hormonal contraceptives is ethinylestradiol, in a usual daily dose of 20 micrograms (low-dose) or 30 or 35 micrograms (standard dose), although higher doses of ethinylestradiol may be used with liver enzyme-inducing drugs such as rifampicin (rifampin). Mestranol (a pro-drug of ethinylestradiol) is used only rarely (daily dose 50 micrograms, equivalent to about 35 micrograms of ethinylestradiol). A combined hormonal contraceptive containing the natural oestrogen, estradiol valerate, is also available, in doses of 1 to 3 mg daily.

The progestogens used in both oral combined and progestogen-only contraceptives are commonly those derived from 19-nortestosterone and can be subdivided into first generation (e.g. etynodiol diacetate, lynestrenol, norethisterone), second generation (levonorgestrel, norgestrel) and third generation (e.g. desogestrel, drospirenone, gestodene, norgestimate). Note that drospirenone is an analogue of spironolactone and also has antiandrogenic and antimineralocorticoid effects. A patch containing ethinylestradiol and norelgestromin (the active metabolite of norgestimate) and a vaginal ring containing ethinylestradiol and etonogestrel (the active metabolite of desogestrel) are also available. The progestogens used in parenteral progestogen-only contraceptives are either 19-nortestosterone derivatives (e.g. etonogestrel, norethisterone) or derived from progesterone (e.g. medroxyprogesterone acetate). Those in intrauterine devices are 19-nortestosterone derivatives (e.g. levonorgestrel).

Combined hormonal contraceptives are most usually taken cyclically for 21 days, followed by a period of 7 days during which withdrawal bleeding occurs. Some of them include 7 inert tablets to be taken at this time so that the daily routine of taking a tablet is not broken. The daily doses of both the oestrogen and progestogen can be the same (monophasic preparations), or the dose of the progestogen can vary (biphasic or triphasic). Sometimes the dose of oestrogen is also varied (sequential). The combined hormonal contraceptive patch is applied weekly for 3 weeks followed by a patch-free week. The vaginal ring is inserted for 3 weeks, followed by a one-week break before inserting a new ring. The oestrogenic and progestogenic components of these contraceptives act together to consistently suppress ovulation.

The oral progestogen-only contraceptives are taken continuously; the implants, injections or intra-uterine devices slowly release the progestogen over an extended period of time. They vary in their ability to inhibit ovulation, and not all reliably inhibit ovulation in all cycles; they probably act mainly by increasing the viscosity of the cervical mucus so that the movement of the sperm is retarded. They may also cause changes in the endometrium, which inhibit successful implantation.

Interactions

(a) Combined hormonal contraceptives

1. Altered metabolism. Almost all of the information on interactions of the hormonal contraceptives involve the oral combined hormonal contraceptives. Most of the clinically important interactions with these contraceptives involve increased metabolism. The major route for hepatic metabolism of ethinylestradiol is hydroxylation (about 30% of a dose) principally by the cytochrome P450 isoenzyme CYP3A4 and also by CYP2C9. Progestogens are also substrates for CYP3A4. Ethinylestradiol and its metabolites also undergo conjugation by sulfation and glucuronidation (via UGT1A1). Thus, enzyme inducers can increase the clearance of the contraceptive steroids and possibly increase breakthrough bleeding and decrease contraceptive efficacy (see 'Combined hormonal contraceptives + Barbiturates or Phenytoin', p.1177). The drugs that have been shown to induce the metabolism of hormonal contraceptives are listed in 'Table 28.1', (below). Intuitively, low-dose combined hormonal contraceptives might be expected to be more susceptible to drug interactions than standard-dose or high-dose preparations, but evidence to support this is scant. Conversely, inhibitors of CYP3A4 (such as some 'azoles', (p.1176)) or inhibitors of conjugation enzymes (such as some 'coxibs', (p.1181)) reduce the clearance of contraceptive steroids, and, although there is no good evidence for this, may increase the incidence of adverse effects such as nausea, breast tenderness, headaches, and potentially more serious complications such as thromboembolic events.

Table 28.1 Enzyme-inducing drugs shown to increase the metabolism of hormonal contraceptives and/or reduce their effects on the suppression of ovulation

Group	*Drugs*
Antibacterials	Rifabutin, Rifampicin (Rifampin)
Antiepileptics	Barbiturates (e.g. phenobarbital, primidone), Carbamazepine, Oxcarbazepine, Phenytoin, Rufinamide, Topiramate
Antiretrovirals	Nelfinavir, Nevirapine, Ritonavir, Ritonavir-boosted protease inhibitors
Other drugs	Aprepitant, Bosentan, Modafinil, St John's wort (*Hypericum perforatum*)

2. Enterohepatic recirculation. Some of the conjugated metabolites of ethinylestradiol undergo enterohepatic recirculation, and certain antibacterials are postulated to reduce this by inhibiting gut flora, thereby possibly decreasing contraceptive efficacy, although this is unproven (see 'Combined hormonal contraceptives + Antibacterials; Penicillins', p.1170).

3. Interaction studies. In drug interaction studies, in addition to assessing the effect on the pharmacokinetics of the contraceptive steroids, ovulation parameters are also often assessed to confirm the absence of ovulation. When evaluating drug interactions with combined hormonal contraceptives, it is important to bear in mind that they are most usually given cyclically, and that levels of the contraceptive steroids increase to steady state between about day 10 and 21 and decrease to zero in the seven-day drug free interval. In reducing contraceptive steroid levels, enzyme-inducing drugs may therefore increase the length of the pill-free interval, as well as reducing the levels at steady state. If an interacting drug is to be used continuously, such as rifampicin (rifampin) for tuberculosis, it needs to be taken with the contraceptive for at least one full cycle to assess the full effect of the drug on ovulation.

4. Other drugs affected. Increasing information is accumulating to show that hormonal contraceptives can cause clinically relevant pharmacokinetic interactions with other drugs. Ethinylestradiol appears to be a minor to modest inhibitor of the cytochrome P450 isoenzyme CYP1A2 (see 'tizanidine', (p.1572)) and an inducer of glucuronidation (see 'lamotrigine', (p.1183)), and might also have some inhibitory effect on CYP2C19

(see 'proton pump inhibitors', (p.1200)). Because of the cyclical administration of combined hormonal contraceptives, these interactions with other drugs will be cyclical (greatest at steady state, and least on the last day of the pill free interval), as has been demonstrated with 'lamotrigine', (p.1183), and this complicates their management.

(b) Progestogen-only contraceptives

There is very little direct information about interactions with the progestogen-only contraceptives (oral, parenteral, and intrauterine). It is unwise to uncritically assume that interactions known to occur with the combined hormonal contraceptives also occur with these contraceptives. However, it seems probable that an increased risk of failure with the oral and parenteral progestogen-only contraceptives is likely with drugs that cause enzyme induction (listed in 'Table 28.1', (p.1165)), which results in an increased clearance of the progestogen, with an accompanying loss of efficacy. The progestogen-releasing intrauterine system is thought to have a primarily local effect, and may not be affected by enzyme-inducers (see 'Progestogen-only contraceptives + Enzyme inducers', p.1206). However, much more study is needed to clarify the situation.

(c) Emergency hormonal contraceptives

It is not known whether interacting drugs are likely to affect the emergency hormonal contraceptives, although it is common practice that women taking enzyme-inducing drugs (see 'Table 28.1', (p.1165)) are given an increased dose to accommodate the increased rate of metabolism by the liver (see 'Emergency hormonal contraceptives + Enzyme inducers', p.1198).

The efficacy of progestogen-only emergency hormonal contraceptives is not affected by antibacterials that do not induce liver enzymes (see 'Emergency hormonal contraceptives + Antibacterials', p.1198).

(d) Hormone replacement therapy (HRT)

The preparations used for HRT contain oestrogens, either alone or combined with progestogens. They differ from the hormonal contraceptives as the most commonly used oestrogens in HRT are natural oestrogens such as estradiol and conjugated oestrogens, and their doses are generally lower than equivalent doses of ethinylestradiol used in combined hormonal contraceptives. There are only a few reports of interactions with HRT preparations, but generally they are expected to behave very much like the combined oral contraceptives.

(e) Other preparations

Cyproterone acetate combined with ethinylestradiol (co-cyprindiol) is intended for use in women with androgen-dependent skin conditions, but it also acts as an oral contraceptive and is therefore predicted to interact like conventional oestrogen-containing oral contraceptives (see 'Co-cyprindiol (Cyproterone with Ethinylestradiol) + Miscellaneous', p.1167).

1. Shader RI, Oesterheld JR. Contraceptive effectiveness: cytochromes and induction. *J Clin Psychopharmacol* (2000) 20, 119–121.
2. Shader RI, Greenblatt DJ. More on oral contraceptives, drug interactions, herbal medicines, and hormone replacement therapy. *J Clin Psychopharmacol* (2000) 20, 397–8.
3. Elliman A. Interactions with hormonal contraception. *Br J Fam Plann* (2000) 26, 109–11.
4. Zhang H, Cui D, Wang B, Han Y-H, Balimane P, Yang Z, Sinz M, Rodrigues AD. Pharmacokinetic drug interactions involving 17α-ethinylestradiol: a new look at an old drug. *Clin Pharmacokinet* (2007) 46, 133–57.

Co-cyprindiol (Cyproterone with Ethinylestradiol) + Miscellaneous

Co-cyprindiol is expected to interact with enzyme inducers in a similar manner to the oral combined hormonal contraceptives, and therefore the risk of contraceptive failure is increased. Like oral combined hormonal contraceptives, there may be rare cases of contraceptive failure with many of the antibacterials. There is some evidence that co-cyprindiol also interacts with minocycline to increase facial pigmentation.

Clinical evidence, mechanism, importance and management

Co-cyprindiol is a mixture of the anti-androgenic progestogen, cyproterone acetate 2 mg, with ethinylestradiol 35 micrograms. It is used for the treatment of acne and moderately severe hirsutism in women who may also wish to use it as an oral hormonal contraceptive.

(a) Antibacterials

Because of the possibility that the use of non-liver enzyme inducing antibacterials that reduce gut bacteria may rarely reduce the contraceptive efficacy of oral combined hormonal contraceptives such as co-cyprindiol, some authorities advise additional precautions (see the UK Faculty of Family Planning and Reproductive Health Care (FFPRHC) guidance under 'Combined hormonal contraceptives + Antibacterials; Penicillins', p.1170). Usually these precautions (additional barrier methods) are considered unnecessary after 3 weeks of concurrent use. However, the manufacturer of co-cyprindiol says that when **tetracyclines** are being taken it is advisable to use additional non-hormonal methods of contraception (except the rhythm or temperature methods) as an extremely high degree of contraceptive protection must be provided with co-cyprindiol due to the theoretical risk of cyproterone causing feminisation of a male foetus. However, they also note that oral **tetracyclines** have not actually been shown to reduce the contraceptive efficacy of co-cyprindiol. In addition co-cyprindiol may also possibly interact with **minocycline** to accentuate facial pigmentation (see 'Tetracyclines; Minocycline + Ethinylestradiol', p.393).

(b) Enzyme-inducing drugs

The contraceptive efficacy of co-cyprindiol is expected to be reduced by the same enzyme inducers (see 'Table 28.1', (p.1165)) that interact with conventional oral combined hormonal contraceptives.[1] The precautions described in this section for these contraceptives with the various drugs listed in 'Table 28.1', (p.1165), should therefore be followed, see 'Combined hormonal contraceptives + Barbiturates or Phenytoin', p.1177. Note that the efficacy of co-cyprindiol in the treatment of acne and hirsutism might also be expected to be reduced by these drugs.

(c) Other combined hormonal contraceptives

The manufacturer states that oral combined hormonal contraceptives (and presumably the combined hormonal contraceptive patch or vaginal ring) must not be taken with co-cyprindiol.[1] To do this would be analogous to doubling the ethinylestradiol dose with consequent increased risk of adverse effects. In addition, some of the progestogens in combined hormonal contraceptives have weak androgenic effects, which could oppose the benefits of cyproterone.

1. Dianette (Cyproterone with ethinylestradiol). Bayer plc. UK Summary of product characteristics, May 2008.

Combined hormonal contraceptives + Alosetron

Alosetron did not alter the pharmacokinetics or the suppression of ovulation in women given an oral combined hormonal contraceptive.

Clinical evidence, mechanism, importance and management

In a crossover study in 18 healthy women taking an oral combined hormonal contraceptive (**ethinylestradiol** 20 micrograms with **levonorgestrel** 100 micrograms), alosetron 1 mg twice daily (given alone for 7 days beginning on day 22 of one cycle and with the contraceptive from day one until day 21 of the next cycle) had no effect on the AUC of **ethinylestradiol** or **levonorgestrel**. In addition, there was no change in progesterone, FSH and LH levels, and no evidence of ovulation based on follicle size.[1] This study suggests that alosetron is unlikely to alter the efficacy of oral combined hormonal contraceptives.

1. Koch K, Campanella C, Baidoo CA, Manzo JA, Ameen VZ, Kersey KEE. Pharmacodynamics and pharmacokinetics of oral contraceptives co-administered with alosetron (Lotronex). *Dig Dis Sci* (2004) 49, 1244–9.

Combined hormonal contraceptives + Antacids

Despite *in vitro* evidence that some antacids might reduce the availability of norethisterone acetate, evidence from healthy women indicates that no pharmacokinetic interaction occurs between antacids and oral combined hormonal contraceptives containing norethisterone or levonorgestrel.

Clinical evidence, mechanism, importance and management

An *in vitro* study found that a 1% suspension of **magnesium trisilicate** in water adsorbed about 80% of **mestranol** and 50% of **norethisterone**, but minimal amounts of **ethinylestradiol**.[1,2] Similarly, another *in vitro* study reported reduced dissolution of **norethisterone acetate** from combined hormonal contraceptive tablets in the presence of **magnesium trisilicate**, **kaolin mixture**, and **aluminium hydroxide**.[3]

In contrast, a single-dose study in 12 healthy women given an oral combined hormonal contraceptive (**ethinylestradiol** 30 micrograms and either **norethisterone acetate** 1 mg or **levonorgestrel** 150 micrograms) with **magnesium trisilicate** 500 mg and **aluminium hydroxide** 250 mg, found that the AUC and peak levels of all three steroids were unchanged.[4] This is in line with common experience. There do not appear to be any reports of contraceptive failure with antacids and **norethisterone acetate** or **mestranol**-containing oral combined hormonal contraceptives. No special precautions seem to be necessary.

1. Khalil SAH, Iwuagwu M. The in vitro uptake of some oral contraceptive steroids by magnesium trisilicate. *J Pharm Pharmacol* (1976) 28 (Suppl), 47P.
2. Khalil SAH, Iwuagwu M. *In vitro* uptake of oral contraceptive steroids by magnesium trisilicate. *J Pharm Sci* (1978) 67, 287–9.
3. Fadel H, Abd Elbary A, Nour El-Din E, Kassem AA. Availability of norethisterone acetate from combined oral contraceptive tablets. *Pharmazie* (1979) 34, 49–50.
4. Joshi JV, Sankolli GM, Shah RS, Joshi UM. Antacid does not reduce the bioavailability of oral contraceptive steroids in women. *Int J Clin Pharmacol Ther Toxicol* (1986) 24, 192–5.

Combined hormonal contraceptives + Anthelmintics

The use of praziquantel or metrifonate does not appear to alter the pharmacokinetics of oral combined hormonal contraceptives.

Clinical evidence, mechanism, importance and management

A study in 25 women with early active schistosomiasis (*S. haematobium* or *S. mansoni*) without signs of liver disease and 6 healthy women found that neither the disease itself nor the concurrent use of antischistosomal drugs (a single 40-mg/kg dose of **praziquantel**, or **metrifonate** in three doses of 10 mg/kg at fortnightly intervals) had any effect on the plasma levels of steroids from an oral combined hormonal contraceptive (**ethinylestradiol** 50 micrograms with **levonorgestrel** 500 micrograms).[1] Moreover, in other studies there was no evidence that women with early active schistosomiasis without signs of liver disease[2] or with liver fibrosis with normal liver function[3] were at any greater risk of hepatic impairment while taking oral combined hormonal contraceptives. No special precautions would therefore appear necessary in women with schistosomiasis taking oral hormonal contraceptives and **praziquantel** or **metrifonate**. Note that oral hormonal contraceptives are usually considered contraindicated in schistosomiasis with liver involvement when there is cirrhosis, especially if this is severe (decompensated).

1. El-Raghy I, Back DJ, Osman F, Orme ML'E, Fathalla M. Contraceptive steroid concentrations in women with early active schistosomiasis: lack of effect of antischistosomal drugs. *Contraception* (1986) 33, 373–7.
2. Shaaban MM, Hammad WA, Fathalla MF, Ghaneimah SA, El-Sharkawy MM, Salim TH, Liao WC, Smith SC. Effects of oral contraception on liver function tests and serum proteins in women with active schistosomiasis. *Contraception* (1982) 26, 75–82.
3. Tagy AHEI, Saker ME, Moussa AA, Kolgah A. The effect of low-dose combined oral contraceptive pills versus injectable contraceptive (Depot Provera) on liver function tests of women with compensated bilharzial liver fibrosis. *Contraception* (2001) 64, 173–6.

Combined hormonal contraceptives + Antibacterials; Cephalosporins

A few anecdotal cases of oral combined hormonal contraceptive failure have been reported with cefalexin, cefalexin with clindamycin, and unspecified cephalosporins. The interaction (if such it is) appears to be very rare indeed.

Clinical evidence

Two pregnancies were attributed to the use of cephalosporins (unspecified) and an oral hormonal contraceptive (unspecified) in the adverse reactions register of the CSM in the UK for the years 1968 to 1984 (61 cases were attributed to other antibacterials).[1] One case of contraceptive failure has been attributed to **cefalexin**,[2] and one to **cefalexin** used with clindamycin.[3] One case of contraceptive failure (resulting in an ectopic pregnancy) has been attributed to the use of **cefalexin** 3 g daily for 2 weeks with an oral combined hormonal contraceptive (**ethinylestradiol** 30 micrograms with **levonorgestrel** 150 micrograms).[4]

In a case-control study, 356 women who had received oral hormonal contraceptives and antibacterials (said to be cephalosporins, penicillins, tetracyclines) were identified over a 5-year period in three dermatological practices. The contraceptive failure rate in these women (1.6% per year; 2 pregnancies occurred in women taking a cephalosporin and 3 in women taking minocycline) was indistinguishable from the failure rate seen in control patients taking oral hormonal contraceptives and no antibacterials (1% per year). All these five cases occurred after taking the antibacterial for at least 3 months.[5]

Mechanism

Suppression of intestinal bacteria, which results in reduced enterohepatic recirculation of ethinylestradiol and a fall in serum levels, is the suggested explanation for any interaction (see 'Combined hormonal contraceptives + Antibacterials; Penicillins', p.1170).

Importance and management

The reports that are summarised here are all that have been identified in the literature on the interaction between the combined hormonal contraceptives and cephalosporins. These interactions are not adequately established and the whole issue remains very controversial. Bearing in mind the extremely wide use of both groups of drugs, any increased incidence of contraceptive failure above that normally seen is clearly very low indeed. On the other hand, the personal and ethical consequences of an unwanted pregnancy can be very serious. Because of the possibility of an interaction, and for simplicity and on pragmatic grounds, the UK Faculty of Family Planning and Reproductive Health Care (FFPRHC) Clinical Effectiveness Unit recommends that patients taking any antibacterial (that does not induce liver enzymes) should use a second form of non-hormonal contraception, such as condoms, while taking a short course of less than 3 weeks of the antibacterial, and also for 7 days after it has been stopped,[6] which would apply to cephalosporins. They apply this advice to both the oral and patch form of the combined hormonal contraceptive,[6] and, therefore it should also be applied to the vaginal ring. In contrast, the WHO does not recommend any additional precautions while taking antibacterials (excluding rifampicin (rifampin)) with combined hormonal contraceptives given orally, as the patch, or as the vaginal ring.[7] For further comment and advice see also 'Combined hormonal contraceptives + Antibacterials; Penicillins', p.1170.

1. Back DJ, Grimmer SFM, Orme ML'E, Proudlove C, Mann RD, Breckenridge AM. Evaluation of Committee on Safety of Medicines yellow card reports on oral contraceptive-drug interactions with anticonvulsants and antibiotics. *Br J Clin Pharmacol* (1988) 25, 527–32.
2. DeSano EA, Hurley SC. Possible interactions of antihistamines and antibiotics with oral contraceptive effectiveness. *Fertil Steril* (1982) 37, 853–4.
3. Back DJ, Breckenridge AM, Crawford FE, MacIver M, Orme L'E, Rowe PH. Interindividual variation and drug interactions with hormonal steroids. *Drugs* (1981) 21, 46–61.
4. Friedman M, Divon M, Peretz BA. Cephalexin and Microgynon-30 do not go well together. *J Obstet Gynaecol* (1982) 2, 195–6.
5. Helms SE, Bredle DL, Zajic J, Jarjoura D, Brodell RT, Krishnarao I. Oral contraceptive failure rates and oral antibiotics. *J Am Acad Dermatol* (1997) 36, 705–10.
6. Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit. FFPRHC Guidance: Drug interactions with hormonal contraception. April 2005. Available at: http://www.ffprhc.org.uk/admin/uploads/DrugInteractionsFinal.pdf (accessed 01/02/10).
7. Reproductive Health and Research, World Health Organization. Medical eligibility criteria for contraceptive use. 3rd ed. Geneva, WHO; 2004. Available at: http://whqlibdoc.who.int/publications/2004/9241562668.pdf (accessed 01/02/10).

Combined hormonal contraceptives + Antibacterials; Macrolides

Controlled studies have not shown the macrolides clarithromycin, dirithromycin, roxithromycin and telithromycin to have any effect on contraceptive steroid levels and/or suppression of ovulation in women given combined hormonal contraceptives. In one controlled study, erythromycin modestly *increased* contraceptive steroid levels (estradiol and dienogest), but isolated anecdotal cases of failure of oral hormonal contraceptives have previously been reported with erythromycin. An isolated case of contraceptive failure has also been reported with spiramycin.

Clinical evidence

(a) Clarithromycin

Ten women taking an oral combined hormonal contraceptive (**ethinylestradiol** with **levonorgestrel** or **desogestrel**) showed a very slight but not statistically significant rise in serum **ethinylestradiol** levels while taking clarithromycin 250 mg twice daily for 7 days. No changes in **levonorgestrel** levels occurred, but levels of the active metabolite of **desogestrel** were increased. Ovulation did not occur (progesterone levels remained suppressed, and FSH and LH levels were reduced). These hormonal changes suggest that clarithromycin may even *increase* the efficacy of oral combined hormonal contraceptives.[1]

(b) Dirithromycin

Fifteen women taking an oral triphasic combined hormonal contraceptive (**ethinylestradiol** with **norethisterone**) were given dirithromycin 500 mg daily for 14 days starting on day 21 of the cycle. A small but statistically significant decrease of 7.6% occurred in the mean **ethinylestradiol** AUC, but no woman ovulated (as assessed by ultrasound and ovarian hormone levels).[2]

(c) Erythromycin

Isolated cases of contraceptive failure have been attributed to erythromycin, and two pregnancies were attributed to the use of erythromycin and an oral hormonal contraceptive (unspecified) in the adverse reactions register of the CSM in the UK for the years 1968 to 1984 (61 cases were attributed to other antibacterials).[3] Another survey of oral hormonal contraceptive failure identified one failure due to erythromycin (48 of 209 pill failures were attributed to antibacterials),[4] and break-through bleeding due to erythromycin has also been described in 2 cases.[5] Conversely, in two studies of contraceptive failures in dermatology patients, no pregnancies were identified in a total of 74 women taking erythromycin and an oral hormonal contraceptive.[6,7]

In one controlled study in postmenopausal women given an oral combined hormonal contraceptive (**estradiol** 2 mg with **dienogest** 3 mg) for 14 days, erythromycin 500 mg three times daily for 7 days increased the steady-state AUC of **estradiol** by 33% and that of **dienogest** by 63%.[8,9]

(d) Roxithromycin

While taking roxithromycin 150 mg twice daily, the anti-ovulatory effects of an oral triphasic combined hormonal contraceptive (**ethinylestradiol** with **levonorgestrel**) remained unchanged during one cycle in 21 healthy women. Efficacy was measured by monitoring ovulation, which was assessed by ultrasound and progesterone levels.[10]

(e) Spiramycin

One case of contraceptive failure has been attributed to the concurrent use of spiramycin.[11]

(f) Telithromycin

In 38 healthy women taking an oral triphasic combined hormonal contraceptive, telithromycin 800 mg daily for 10 days had no effect on the pharmacokinetics of **ethinylestradiol**, but increased the plasma levels of **levonorgestrel**. None of the women ovulated, as assessed by progesterone levels.[12]

Mechanism

The macrolides such as erythromycin might possibly be expected to suppress the bacteria responsible for the enterohepatic recycling of ethinylestradiol, but good evidence that this is clinically important is scant

(see 'Combined hormonal contraceptives + Antibacterials; Penicillins', p.1170). Erythromycin, and to a varying extent the other macrolides discussed here, also inhibit the cytochrome P450 isoenzyme CYP3A4, which is responsible for the metabolism of the contraceptive steroids. Therefore they might be expected to increase rather than reduce contraceptive efficacy. This might be expected to offset any possible reduced enterohepatic recycling.

Importance and management

Information about erythromycin is very limited, but the fact that there are only isolated reports of pregnancies with this drug, coupled with its known enzyme-inhibiting properties (demonstrated with estradiol and dienogest), suggest that it is unlikely to cause contraceptive failure. Information on the other macrolides seems to be limited to the studies cited, on the basis of which no interaction appears to be likely with clarithromycin, roxithromycin or telithromycin. Dirithromycin also appears unlikely to cause oral hormonal contraceptive failure. No cases of contraceptive failure with these macrolides appear to have been reported. If one accepts the theory that there is an as yet unidentifiable tiny group of women for whom enterohepatic recirculation of ethinylestradiol is important, then additional contraceptive precautions should be taken. However, if one tends to the theory that the anecdotal cases of contraceptive failure with non-enzyme inducing antibacterials are indistinguishable from the normal accepted failure rate, no special precautions are necessary.

In 1999, the UK Family Planning Association considered that it was almost certain that erythromycin did not interact with oral combined hormonal contraceptives.[13] However, for simplicity and on pragmatic grounds, in 2005, the UK Faculty of Family Planning and Reproductive Health Care (FFPRHC) Clinical Effectiveness Unit advised that additional contraceptives, such as condoms, should be used for short courses of all non-enzyme inducing antibacterials, see 'Combined hormonal contraceptives + Antibacterials; Penicillins', p.1170, for more detailed information. They applied this to both the oral and the patch form of the combined hormonal contraceptive,[14] and, therefore it should also be applied to the vaginal ring. In contrast, the WHO does not recommend any additional precautions while taking any antibacterials (excluding rifampicin (rifampin)) with combined hormonal contraceptives given orally, as the patch, or as the vaginal ring,[15] which seems a more logical approach for the macrolides given the data available.

For a discussion of the adverse hepatic interaction between oral hormonal contraceptives and the macrolide troleandomycin, see 'Combined hormonal contraceptives or HRT + Antibacterials; Troleandomycin', p.1174.

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Combined hormonal contraceptives + Antibacterials; Metronidazole

Isolated cases of oral combined hormonal contraceptive failure have been reported with metronidazole. The interaction (if such it is) appears to be very rare indeed. In a controlled study, metronidazole did not affect contraceptive steroid levels.

Clinical evidence, mechanism, importance and management

In 10 women taking an oral combined hormonal contraceptive, metronidazole 400 mg three times daily for 6 to 8 days had no effect on the AUC of **ethinylestradiol** and **norethisterone**. However, 2 of the 10 women had a rise in plasma progesterone levels suggesting that ovulation may have occurred. One of a further 15 women taking metronidazole and an oral combined hormonal contraceptive also appeared to ovulate. Of the 3 women who ovulated one also ovulated during a cycle while not taking metronidazole.[1] Another similar study in 10 women found that none ovulated while taking metronidazole and an oral combined hormonal contraceptive (**ethinylestradiol** with **norethisterone**).[2]

Only 3 reports of pregnancies were identified in women who took metronidazole and an oral hormonal contraceptive (unspecified) in the adverse reactions register of the CSM in the UK for the years 1968 to 1984.[3] A survey of oral hormonal contraceptive failure identified one failure due to metronidazole (48 of a total of 209 cases were attributed to antibacterials),[4] and a follow-up study identified one further case.[5] Another survey[6] found one contraceptive failure in a woman taking metronidazole, and she was also taking **doxycycline** (see 'Combined hormonal contraceptives + Antibacterials; Tetracyclines', p.1173). It is possible that these cases represent chance associations.

The interaction between metronidazole and oral combined hormonal contraceptives is not established, and the whole issue of any interaction with non-enzyme inducing antibacterials remains controversial. Bearing in mind the extremely wide use of both metronidazole and oral combined hormonal contraceptives, any increased incidence of contraceptive failure above that seen in general usage is clearly very low indeed. Nevertheless, for simplicity and on pragmatic grounds the UK Faculty of Family Planning and Reproductive Health Care (FFPRHC) Clinical Effectiveness Unit has recommended that an additional form of contraception, such as condoms, should be used for short courses of all non-enzyme inducing antibacterials,[7] which would include metronidazole. They apply this to both the oral and the patch form of the combined contraceptive and, therefore it should also be applied to the vaginal ring. In contrast, the WHO does not recommend any additional precautions while taking antibacterials (excluding rifampicin (rifampin)) with combined hormonal contraceptives given orally, as the patch, or as the vaginal ring.[8] For further comment and advice see also 'Combined hormonal contraceptives + Antibacterials; Penicillins', p.1170.

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Combined hormonal contraceptives + Antibacterials; Miscellaneous

One or two cases of contraceptive failure have been reported in patients given oral combined hormonal contraceptives and chloramphenicol, clindamycin (used with cefalexin), dapsone, fusidic acid, isoniazid, nifurtoinol and nitrofurantoin. These isolated cases are anecdotal and unconfirmed, and the interaction (if

such it is) appears to be very rare indeed. The combination of aminosalicylic acid, isoniazid and streptomycin does not appear to affect contraceptive activity.

Clinical evidence, mechanism, importance and management

One woman taking an oral combined hormonal contraceptive was briefly reported to have developed breakthrough bleeding and to have become pregnant while taking **chloramphenicol**.[1,2] One or two cases of contraceptive failure have been briefly attributed to **clindamycin** (used with cefalexin),[3] **dapsone**,[3] **fusidic acid**,[4] **isoniazid**,[3,5] **nifurtoinol**[6] and **nitrofurantoin**.[3,6] Breakthrough bleeding, due to **clindamycin** in one case and **chloramphenicol** in another case, have also been reported.[7] Conversely, no evidence of ovulation or of changes in plasma **ethinylestradiol** and **norethisterone** levels were seen in a study of 8 women taking an oral combined hormonal contraceptive with **aminosalicylic acid**, **isoniazid** and **streptomycin**.[8]

The interactions between the oral hormonal contraceptives and antibacterials summarised here are all that have been identified in the literature involving the drugs cited. These interactions are not established, and given the few anecdotal cases with each drug, could just be coincidental. With **isoniazid** in particular, there is evidence that the drug does not cause contraceptive failure when used in combination with other antimycobacterials (without rifampicin). On the other hand, the personal and ethical consequences of an unwanted pregnancy can be very serious. For simplicity and on pragmatic grounds, the UK Faculty of Family Planning and Reproductive Health Care (FFPRHC) Clinical Effectiveness Unit recommends that women taking combined hormonal contraceptives should routinely use an additional form of contraception, such as condoms, while taking a short course of any antibacterial that does not induce liver enzymes, and for 7 days after the antibacterial has been stopped.[9] For further details of this advice see 'Combined hormonal contraceptives + Antibacterials; Penicillins', below. They applied this advice to both the oral and patch form of the combined hormonal contraceptives,[9] and, therefore it should also be applied to the vaginal ring. In contrast, the WHO does not recommend any additional precautions while taking any antibiotics (excluding rifampicin (rifampin)) with combined hormonal contraceptives, given orally, as the patch, or as the vaginal ring.[10]

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Combined hormonal contraceptives + Antibacterials; Penicillins

The failure of oral combined hormonal contraceptives has been attributed to ampicillin, amoxicillin, flucloxacillin, oxacillin, phenoxymethylpenicillin, pivampicillin and talampicillin. However, the interaction (if such it is), appears to be very rare. Controlled studies have not shown any effect of ampicillin or amoxicillin on contraceptive steroid levels and the suppression of ovulation in women given these contraceptives.

Clinical evidence

(a) Oral hormonal contraceptives

1. Case reports. A case report describes 3 women taking an oral hormonal contraceptive who became pregnant when given **ampicillin**.[1] One woman had two unwanted pregnancies while taking an oral combined hormonal contraceptive (**ethinylestradiol** with **norethisterone**). On both occasions conception occurred when she was taking **ampicillin** for tonsillitis.[2] Another woman taking **ethinylestradiol** with **norethisterone** for 5 years with no history of breakthrough bleeding, lost a quantity of blood similar to a normal period loss within a day of starting to take **ampicillin** (exact dose unknown). There was no evidence of diarrhoea or vomiting in either case.[2] Two other case reports attributed contraceptive failure to **oxacillin**,[3] and to an intramuscular injection of **benethamine penicillin**, **procaine penicillin** and **benzylpenicillin**.[4]

The use of a penicillin (unspecified) was implicated in 32 pregnancies in women taking an oral hormonal contraceptive (unspecified) in the adverse reactions register of the CSM in the UK for the years 1968 to 1984 (a further 31 cases were attributed to other antibacterials).[5] In an earlier review, the penicillins in 15 cases of contraceptive failure were named as **ampicillin** (alone or with fusidic acid, tetracycline or **flucloxacillin**), **amoxicillin**, **talampicillin**, **phenoxymethylpenicillin** (one also with oxytetracycline) and 'penicillin'.[6] A survey of contraceptive failure described failures due to **amoxicillin** (16 cases), **flucloxacillin**, **phenoxymethylpenicillin**, **pivampicillin** (5 cases) and **amoxicillin** with **phenoxymethylpenicillin** (1 case),[7] and a follow-up survey identified 9 further cases involving **amoxicillin** and one with 'penicillin'.[8] Another similar survey described a total of 17 cases with **amoxicillin** and 5 cases with 'penicillin',[9] and a follow-up survey identified 8 further cases with **amoxicillin** and one case with 'penicillin'.[10]

2. Controlled studies. Three controlled studies have provided evidence that **ampicillin** does not alter the plasma levels of contraceptive steroids or reduce their anti-ovulatory effects.[11-13] In the first study, **ampicillin** 250 mg four times daily for 16 days was given to women taking **ethinylestradiol** with **etynodiol**. No women ovulated, as assessed by FSH, LH and progesterone levels. Two women had breakthrough bleeding while receiving **ampicillin**, and one had spotting while receiving placebo.[11] In another study in 7 patients and 6 healthy women, **ampicillin** 500 mg three times daily for 8 days had no significant effect on the plasma levels of **ethinylestradiol** or **levonorgestrel**. However, one woman had a large fall in **ethinylestradiol** levels. Despite this, none of the women ovulated, as assessed by progesterone levels.[12] The third study in 6 women found that **ampicillin** 1 g twice daily had no effect on the plasma levels of **ethinylestradiol** and **norethisterone**, and ovulation did not occur.[13]

(b) Vaginal ring

In a crossover study in 16 healthy women using the *NuvaRing* vaginal contraceptive ring, a 10-day course of **amoxicillin** 875 mg twice daily started on day one of a cycle did not alter the pharmacokinetics of **etonogestrel** or **ethinylestradiol**.[14]

Mechanism

Not understood. The oestrogen component of the contraceptive undergoes enterohepatic recirculation (i.e. it is repeatedly secreted in the bile as sulfate and glucuronide conjugates, which are hydrolysed by the gut bacteria before reabsorption). One idea is that if these bacteria are suppressed by the use of an antibacterial, the steroid conjugates are not hydrolysed and are therefore only poorly reabsorbed, resulting in lower than normal concentrations of circulating oestrogen in some women. This may result in inadequate suppression of ovulation.[6] However, although the penicillins reduce *urinary* oestriol secretion in pregnant women,[15-19] no marked changes in *serum* ethinylestradiol levels have been found in controlled studies in women taking an oral hormonal contraceptive with ampicillin or many other antibacterials (see 'tetracyclines', (p.1173), 'macrolides', (p.1168), 'quinolones', (p.1171)). It may be that the enterohepatic recirculation of ethinylestradiol is not clinically important: note that women with an ileostomy have normal serum contraceptive steroid levels.[20] Alternatively, it may be that the proportion of women for whom enterohepatic recirculation is important is extremely small.[20] Note that the progestogens do not take part in enterohepatic recirculation in their active forms, so the progestogenic component of the contraceptive would remain effective.

Importance and management

The interaction between combined hormonal contraceptives and penicillins is inadequately established and controversial. Almost all of the evidence is anecdotal with no controls. The total number of failures is extremely small when viewed against the number of women worldwide using combined hormonal contraceptives, so most women are apparently not at risk. If one tends to the theory that the anecdotal cases of contraceptive failure with broad-spectrum antibacterials are indistinguishable from the normal accepted failure rate, no special precautions are necessary. On the other hand, the personal and ethical consequences of an unwanted pregnancy can be very serious. If one accepts the theory that there is an as yet unidentifiable tiny group of women for whom enterohepatic recirculation of ethinylestradiol is important, then additional contraceptive precautions should be taken.

For simplicity, and on pragmatic grounds, the UK Faculty of Family Planning and Reproductive Health Care (FFPRHC) Clinical Effectiveness Unit recommends that women taking combined hormonal contraceptives should routinely use a second form of contraception, such as condoms, while taking a short course of less than 3 weeks of any antibacterial (non-enzyme inducing),[21] and for 7 days after the antibacterial has been stopped,[21] and this would include the penicillins. In addition, the FFPRHC recommends that if fewer than 7 active pills are left in the pack after the antibacterial has been stopped, the new packet should be started without a pill-free break, omitting any of the inactive tablets. For women using the combined contraceptive patch, if the 7 days after the antibacterial has been stopped runs into the usual 7 day patch-free period, a new patch should be applied when it is due to be changed and the patch-free week delayed by 7 days.[21] For women using the vaginal ring, if antibacterial (except amoxicillin, see *Amoxicillin and the need for additional precautions*, below) use runs beyond the 3 weeks of a ring-cycle, the next ring should be inserted immediately, without having the usual ring-free interval.[22] The FFPRHC also says that after 3 weeks of antibacterial treatment the gut flora becomes resistant to the antibacterial. Therefore women taking a long-term antibacterial that does not induce liver enzymes (for example, for acne), no longer need additional contraceptive protection after the initial 3 weeks of concurrent use. However, if the antibacterial is changed or another antibacterial is started, additional contraceptive cover is required. Women who have already been taking long-term antibacterials that do not induce liver enzymes, who start a combined hormonal contraceptive, do not require additional contraception, unless the antibacterial is changed.[21]

However, others have contended that these sorts of instructions may confuse patients, and complicate pill taking, and could have the opposite effect of increasing the failure rate of hormonal contraceptives.[23] Note that the WHO does not recommend any additional precautions while taking any antibacterials (excluding rifampicin (rifampin)) with combined hormonal contraceptives given orally, as the patch, or as the vaginal ring.[24]

Amoxicillin and the need for additional precautions. The UK manufacturer of the combined hormonal vaginal ring excludes amoxicillin from the advice applied to other antibacterials on the basis of the one study showing an absence of a pharmacokinetic interaction.[22] On the basis of a similar pharmacokinetic study, the FFPRHC have exempted tetracycline from the need for additional precautions with the combined hormonal contraceptive patch (see 'Combined hormonal contraceptives + Antibacterials; Tetracyclines', p.1173). If this type of study is sufficient evidence to exclude the need for additional precautions, then no additional precautions are probably required with ampicillin and oral combined hormonal contraceptives and many other antibacterials for which there are similar or better controlled studies.

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Combined hormonal contraceptives + Antibacterials; Quinolones

In controlled studies, ciprofloxacin, moxifloxacin and ofloxacin did not alter the pharmacokinetics of the contraceptive steroids or the suppression of ovulation in women taking oral combined hormonal contraceptives. No cases of contraceptive failure appear to have been reported with the quinolones. The plasma levels of moxifloxacin may be slightly reduced by oral combined hormonal contraceptives.

Clinical evidence

(a) Ciprofloxacin

No ovulation (as assessed by LH, FSH and estradiol levels) occurred in 10 healthy women taking an oral combined hormonal contraceptive (**ethinylestradiol** with **desogestrel**, **gestodene** or **levonorgestrel**) with ciprofloxacin 500 mg twice daily for 7 days (started on the first day of contraceptive intake). No breakthrough bleeding occurred.[1] Another study in 24 healthy women taking an oral combined hormonal contraceptive (**ethinylestradiol** with **desogestrel**) found that ciprofloxacin 500 mg twice daily for 10 days had no effect on the pharmacokinetics of **ethinylestradiol**. In addition, no subject ovulated, as assessed by progesterone and estradiol levels. However, 2 of the subjects were potentially ovulatory while taking a placebo instead of ciprofloxacin, as detected by an ultrasound of ovarian activity. A further 4 subjects taking ciprofloxacin and 2 taking placebo had lesser indications of ovarian activity.[2]

(b) Moxifloxacin

A placebo-controlled, crossover study in 29 young healthy women taking an oral combined hormonal contraceptive (**ethinylestradiol** with **levonorgestrel**) found that moxifloxacin 400 mg daily on cycle days 1 to 7 had no clinically relevant effect on the pharmacokinetics of either contraceptive steroid. The hormonal parameters measured (estradiol, progesterone, LH, FSH) were also unchanged by the presence of the quinolone, indicating that ovulation continued to be suppressed.[3] In another non-randomised study looking at the effects of oral combined hormonal contraceptives (unspecified) on the pharmacokinetics of a single 400-mg dose of moxifloxacin, the total oral clearance of moxifloxacin was 20% greater and its AUC and maximum plasma concentrations were 15% lower in 15 women taking oral combined hormonal contraceptives, when compared with 15 women using non-hormonal methods of contraception.[4]

(c) Ofloxacin

Ofloxacin had no effect on the suppression of ovulation in 19 women taking an oral combined hormonal contraceptive (**ethinylestradiol** with **levonorgestrel**). In this placebo-controlled, crossover study, two courses of ofloxacin 200 mg twice daily for 7 days were given on days one to 7 of two consecutive contraceptive cycles. Ovulation was assessed by ultra-

sound of the ovaries, and by measuring FSH, estradiol and progesterone levels. Four of the women had signs of ovarian activity in both the placebo and ofloxacin cycles.[5]

Mechanism

The fluoroquinolones are likely to reduce gut bacteria, and so might be expected to interrupt the enterohepatic recirculation of ethinylestradiol,[1,6] but the evidence that this is clinically important is scant (for a more detailed discussion of this mechanism see 'Combined hormonal contraceptives + Antibacterials; Penicillins', p.1170). It was suggested that ethinylestradiol might slightly decrease levels of some quinolones by inducing conjugation.[4]

Importance and management

The pharmacokinetic and pharmacodynamic data indicate a likely absence of interactions between oral combined hormonal contraceptives and these quinolones. In addition, reports of cases of contraceptive failure with these or any other quinolone antibacterial seem to be lacking. No special extra contraceptive precautions would therefore seem to be necessary during concurrent use. However, if one accepts the theory that there is an as yet unidentifiable tiny group of women for whom enterohepatic recirculation of ethinylestradiol is important, then it could be argued that insufficient patients were assessed in the above studies to include anyone from this group, and that the general precautions should be applied. However, if one tends to the theory that the anecdotal cases of contraceptive failure with antibacterials that reduce gut bacteria are indistinguishable from the normal accepted contraceptive failure rate, no special precautions are necessary with these quinolones, or indeed, any other antibacterials that do not induce liver enzymes.

However, for simplicity, and on pragmatic grounds, the UK Faculty of Family Planning and Reproductive Health Care (FFPRHC) Clinical Effectiveness Unit has recommended that additional contraceptives, such as condoms, should be used for short courses of any antibacterial, which would include the quinolones, see 'Combined hormonal contraceptives + Antibacterials; Penicillins', p.1170, for more detailed information. This applies to both the oral and the patch form of the combined hormonal contraceptive,[7] and therefore it should also be applied to the vaginal ring. Nevertheless, because the FFPRHC has excluded the need for additional precautions with tetracycline and the patch on the basis of one short pharmacokinetic study (see 'Combined hormonal contraceptives + Antibacterials; Tetracyclines', p.1173), then most of the quinolones here should be similarly exempted from the need for additional precautions with oral combined hormonal contraceptives. Note that the WHO does not recommend any additional precautions while taking any antibacterials (excluding rifampicin (rifampin)) with combined hormonal contraceptives given orally, as the patch, or as the vaginal ring.[8]

The slight reduction in moxifloxacin with oral combined hormonal contraceptives is unlikely to be clinically relevant, although the authors considered that it might be if a pathogen has only borderline sensitivity to the antibacterial.[4] However, note that changes of the magnitude seen in this study are not generally considered to be clinically relevant.

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Combined hormonal contraceptives + Antibacterials; Sulfonamides and/or Trimethoprim

Co-trimoxazole (sulfamethoxazole with trimethoprim) *increases* ethinylestradiol levels and the suppression of ovulation in women taking oral combined hormonal contraceptives. However, there are about 15 anecdotal cases on record of contraceptive failure attributed to co-trimoxazole. There are also isolated cases of contraceptive failure attributed to various sulfonamides and trimethoprim.

Clinical evidence

(a) Co-trimoxazole (Trimethoprim with Sulfamethoxazole)

In a study in 9 women taking an oral triphasic combined hormonal contraceptive (**ethinylestradiol** with **levonorgestrel**) the use of co-trimoxazole 960 mg twice daily for 7 days starting on day 10 of the cycle increased **ethinylestradiol** plasma levels by 30 to 50%. **Levonorgestrel** plasma levels remained unaltered. No subjects ovulated, as assessed by progesterone and FSH levels: FSH levels actually decreased, indicating increased suppression of ovulation.[1]

In contrast, 5 cases of oral hormonal contraceptive failure attributed to the use of co-trimoxazole were identified in the adverse reactions register of the CSM in the UK for the years 1968 to 1984 (58 cases were attributed to other antibacterials).[2,3] Contraceptive failure has been reported in another 10 patients taking co-trimoxazole,[4-8] and 3 further cases of contraceptive failure are attributed to the use of co-trimoxazole or trimethoprim.[9]

(b) Sulfonamides

One woman taking an oral combined hormonal contraceptive is briefly reported to have developed breakthrough bleeding and to have become pregnant while taking **sulfamethoxypyridazine**.[10,11] One case of a pregnancy, in a woman who had taken a sulfonamide (unspecified) and an oral hormonal contraceptive (unspecified), was identified in the adverse reactions register of the CSM in the UK for the years 1968 to 1984 (a total of 62 cases were attributed to other antibacterials).[3] Three further cases of contraceptive failure have been attributed to the use of **sulfafurazole** (**sulfisoxazole**) and a sulfonamide (unspecified).[12]

(c) Trimethoprim

Two pregnancies were attributed to the use of trimethoprim with an oral hormonal contraceptive (unspecified) in the adverse reactions register of the CSM in the UK for the years 1968 to 1984 (a total of 61 cases were attributed to other antibacterials).[3] Another survey of oral hormonal contraceptive failure identified one pregnancy due to trimethoprim (23 of a total of 137 cases were attributed to antibacterials),[6] while an earlier survey attributed 3 cases of contraceptive failure to either **co-trimoxazole** or trimethoprim.[9] One case with trimethoprim alone, and one with trimethoprim and nitrofurantoin, are briefly mentioned in another report.[7]

Mechanism

Antibacterials that decimate gut bacteria might be expected to interrupt the enterohepatic recirculation of ethinylestradiol leading to contraceptive failure, but the evidence that this is clinically important is scant (see also 'Combined hormonal contraceptives + Antibacterials; Penicillins', p.1170). A possible explanation for the rise in ethinylestradiol levels is that co-trimoxazole inhibits the liver enzymes concerned with the metabolism of this oestrogen. Therefore, as demonstrated, co-trimoxazole might be expected to increase rather than reduce the suppression of ovulation. This would be expected to offset any possible reduced enterohepatic recycling.

Importance and management

Not established. The pharmacokinetic and pharmacodynamic evidence indicates that co-trimoxazole is not likely to reduce the effectiveness of oral combined hormonal contraceptives. Although there are a number of reports of contraceptive failure attributed to co-trimoxazole, these are anecdotal and unconfirmed, whereas the controlled studies suggest *increased* contraceptive efficacy. It is probable that the cases are coincidental, and fit

within the normal failure rate of oral combined hormonal contraceptives. In 1999, the UK Family Planning Association considered that it was almost certain that co-trimoxazole and sulfonamides did not interact with oral combined hormonal contraceptives.[13] However, for simplicity and on pragmatic grounds, in 2005, the UK Faculty of Family Planning and Reproductive Health Care (FFPRHC) Clinical Effectiveness Unit advised that additional contraceptives, such as condoms, should be used for short courses of any antibacterials (non-enzyme inducing),[14] which would include co-trimoxazole, sulfonamides and trimethoprim. They applied this advice to both the oral and the patch form of the combined hormonal contraceptive, and, therefore it should also be applied to the vaginal ring. In contrast, the WHO does not recommend any additional precautions while taking any antibacterials (excluding rifampicin) with combined hormonal contraceptives given orally, as the patch, or as the vaginal ring.[15] For further comment and advice see also 'Combined hormonal contraceptives + Antibacterials; Penicillins', p.1170.

Aside from contraceptive failure the other aspect of using co-trimoxazole is the potential for increased ethinylestradiol levels. The main concern is whether this would increase the risk of adverse effects of the oestrogen, but there are no data on the clinical significance of these modest (30 to 50%) increases on various adverse effects. It could be argued that a 40% increase would turn a standard-strength contraceptive (35 micrograms) into a high-dose contraceptive (50 micrograms). Further study is needed on this issue.

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Combined hormonal contraceptives + Antibacterials; Tetracyclines

Case reports describe contraceptive failure, which was attributed to doxycycline, lymecycline, minocycline, oxytetracycline and tetracycline; some of these cases where the antibacterial was taken long-term, but the interaction (if such it is) appears to be rare. Controlled studies have not shown any effect of tetracycline or doxycycline on contraceptive steroid levels from combined hormonal contraceptives given orally, as the patch, or as the vaginal ring.

Clinical evidence

(a) Oral hormonal contraceptives

1. Case reports of pregnancy. A woman taking an oral combined hormonal contraceptive (**ethinylestradiol** with **levonorgestrel**) became pregnant, the evidence indicating that she had conceived during or in the week after taking **tetracycline** 500 mg every 6 hours for 3 days and then 250 mg every 6 hours for 2 days. There was no evidence of either nausea or vomiting, which might have been an alternative explanation for the contraceptive failure.[1] A case of breakthrough bleeding attributed to **tetracycline** was also mentioned in this report.[1] Two other case reports describe pregnancies in women taking an oral combined hormonal contraceptive and long-term **tetracycline** 500 mg daily[2] or long-term **minocycline** 100 mg daily.[3] The latter report also briefly mentions 2 cases of contraceptive failure with **doxycycline**.[3]

Twelve reports of pregnancies were attributed to the use of tetracyclines (unspecified) and an oral hormonal contraceptive (unspecified) in the adverse reactions register of the CSM in the UK for the years 1968 to 1984 (51 cases were attributed to other antibacterials).[4] In an earlier report, the tetracyclines in 6 cases were named as **tetracycline** and **oxytetracycline**.[5] A survey of oral hormonal contraceptive failure identified 7 failures due to **doxycycline**, **lymecycline** or **minocycline** (37 of a total of 163 cases were attributed to antibacterials),[6] and a follow-up survey identified 3 further cases involving short courses of **tetracycline**.[7] Similar surveys identified 5 contraceptive failures with **tetracycline**,[8-10] and 2 failures with **doxycycline**.[9] Breakthrough bleeding was attributed to **doxycycline** or **oxytetracycline** in 3 other cases.[11]

2. Case-control and cohort studies. In a dermatological practice, of 124 women taking an oral hormonal contraceptive and antibacterials (mostly tetracyclines or erythromycin), 2 became pregnant, with a calculated failure rate of 1.2%. One patient was taking long-term **minocycline** and **ethinylestradiol** with **norethisterone**, and one had taken a 5-day course of **oxytetracycline** while taking **ethinylestradiol** with **levonorgestrel**. This failure rate was reported to be sixfold higher than a normal failure rate of 0.2%.[12] However, a rate of 0.2% represents perfect rather than typical use of oral combined hormonal contraceptives. In a similar analysis,[13] one of 34 women became pregnant after taking long-term **tetracycline** and **ethinylestradiol** with **norethisterone**. This failure rate of 1.4% was not considered to be significantly different from a normal failure rate of 0.27%. In a larger, better-designed, case-control study, 356 women were identified who had received oral hormonal contraceptives and antibacterials (cephalosporins, penicillins, tetracyclines) over a 5-year period in three dermatological practices. The failure rate in these women (1.6% per year, 3 pregnancies occurred in women taking long-term **minocycline** and 2 taking a cephalosporin) was indistinguishable from the failure rate seen in control patients taking oral hormonal contraceptives and no antibacterials (1% per year).[14]

3. Controlled studies. Two controlled studies have shown that tetracyclines do not affect the pharmacokinetics of contraceptive steroids.[15,16] In the first, in 7 healthy women taking an oral combined hormonal contraceptive, **tetracycline** 500 mg every 6 hours for 10 days had no effect on the AUC of **ethinylestradiol** and **norethisterone** (measured on days one, 5 and 10).[15] Similarly, in 23 healthy women taking an oral combined hormonal contraceptive, **doxycycline** 100 mg twice daily for 7 days had no effect on the serum levels of **ethinylestradiol** and **norethisterone** (measured on days 5 to 7). In addition, ovulation did not occur, as assessed by progesterone levels, but 2 women did experience breakthrough bleeding.[16]

The pharmacokinetics of **tetracycline** (AUC_{0-4} and peak level) were not significantly different between 7 healthy women taking an oral combined hormonal contraceptive (**ethinylestradiol** with **norethisterone**) and 4 healthy women not taking any medication.[15]

(b) Patch

In a controlled study in 24 women, there was no pharmacokinetic interaction between a combined hormonal contraceptive patch (**ethinylestradiol** with **norelgestromin**) and **tetracycline**. The patch was used for one week alone, and then, one month later, for one week with **tetracycline** 500 mg four times daily started 3 days before the patch was applied.[17]

(c) Vaginal ring

In a crossover study involving 16 healthy women using the *NuvaRing* vaginal contraceptive ring, a 10-day course of **doxycycline** 200 mg on day one then 100 mg daily started on day one of a cycle did not alter the pharmacokinetics of **etonogestrel** or **ethinylestradiol**.[18]

Mechanism

Not understood. If an interaction occurs, suppression of intestinal bacteria resulting in a fall in enterohepatic recirculation of ethinylestradiol is the usual suggested explanation, but there is no evidence that this is clinically important. For a full discussion of this mechanism, see 'Combined hormonal contraceptives + Antibacterials; Penicillins', p.1170.

Importance and management

The interactions between the oral combined hormonal contraceptives and tetracyclines summarised here are all that have been identified in the literature. Much of the evidence is anecdotal with insufficient controls (if any). These interactions are not adequately established and the whole issue remains controversial. Bearing in mind the extremely wide use of both drugs, any increase in the incidence of contraceptive failure above the accepted failure rate is clearly very low indeed. On the other hand, the personal and ethical consequences of an unwanted pregnancy can be very serious. For simplicity, and on pragmatic grounds, the UK Faculty of Family Planning and Reproductive Health Care (FFPRHC) Clinical Effectiveness Unit recommends that an additional form of contraception, such as condoms, should be used while taking a short course of any antibacterial that does not induce liver enzymes, and for 7 days after the antibacterial has been stopped,[19] and this would include tetracyclines. See 'Combined hormonal contraceptives + Antibacterials; Penicillins', p.1170, for more detailed information. However, for the combined hormonal contraceptive patch, the FFPRHC specifically exclude tetracycline from the requirement for additional contraceptive protection[19] on the basis of the one short pharmacokinetic study available. Similarly, the UK manufacturer's information for the vaginal ring excludes doxycycline from the requirement for additional protection.[20] If this type of study is sufficient evidence to exclude the need for additional precautions, then no additional precautions are required with doxycycline and oral combined hormonal contraceptives containing ethinylestradiol with norethisterone on the basis of the controlled study cited. Moreover, the absence of a pharmacokinetic interaction with one tetracycline can be extrapolated to others; therefore, it would be reasonable to conclude that no additional contraceptive precautions are likely to be needed with doxycycline and the patch, and for tetracycline with the ring, etc. Note that the WHO does not recommend any additional precautions while taking any antibacterials (excluding rifampicin (rifampin)) with combined hormonal contraceptives given orally, as the patch, or as the vaginal ring.[21]

In the case of long-term use of tetracyclines for acne, at least 7 cases of contraceptive failure have been reported. Nevertheless, in statistical terms the only well-designed case-controlled study in dermatological practice indicated that the incidence of contraceptive failure due to this interaction could not be distinguished from the general and recognised failure rate of oral combined hormonal contraceptives.[14] The FFPRHC also says that after 3 weeks of antibacterial treatment the gut flora becomes resistant to the antibacterial. Therefore women taking an antibacterial long-term no longer need additional contraceptive protection after the initial 3 weeks of concurrent use, unless the antibacterial is changed.[19]

For reports of facial pigmentation due to minocycline and ethinylestradiol, see 'Tetracyclines; Minocycline + Ethinylestradiol', p.393.

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Combined hormonal contraceptives or HRT + Antibacterials; Troleandomycin

Severe pruritus and jaundice have been seen in women taking oral hormonal contraceptives shortly after starting treatment with troleandomycin. One case has also been reported with oestrogens for HRT.

Clinical evidence

A report describes 10 cases of cholestatic jaundice and pruritus in women taking oral hormonal contraceptives and troleandomycin. All had been using the contraceptive for 7 to 48 months and were given the antibacterial in daily doses of 1 to 3 g. The pruritus was intense, and started within 2 to 24 days of the first dose of troleandomycin, and preceded the jaundice. In 8 of the patients the pruritus and jaundice persisted for over a month.[1] A later report and letter by the same authors describes a total of 24 cases of this reaction.[2,3]

There are numerous other reports of this adverse reaction in a total of over 40 other women.[4-12] The adverse reactions (fatigue, anorexia, severe itching, jaundice) can begin very rapidly, sometimes even within 2 days of starting the troleandomycin, and may last up to 14 weeks or more.[3,4,12]

One report also describes a similar reaction in a 48-year-old woman taking **oestrogens** for HRT.[4]

Mechanism

Uncertain. Hepatotoxicity has been associated with the use of both types of drug, but it is not common. The reaction suggests that their damaging effects on the liver may be additive or synergistic.[10,11] Troleandomycin may cause an increase in the levels of contraceptive steroids, as it is a liver enzyme inhibitor.[12,13]

Importance and management

A well established, well documented and clinically important interaction. The incidence is unknown. Concurrent use should be avoided. Other macrolides may be suitable alternatives, but see 'Combined hormonal contraceptives + Antibacterials; Macrolides', p.1168.

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Combined hormonal contraceptives + Antihistamines

The pharmacokinetics of single doses of doxylamine and diphenhydramine do not appear to be altered by oral combined hormonal contraceptives.

Clinical evidence, mechanism, importance and management

The pharmacokinetics of a single 25-mg dose of **doxylamine** in 13 women and the pharmacokinetics of a single 50-mg dose of **diphenhydramine** in 10 women were not significantly altered by the use of low-dose oral combined hormonal contraceptives.[1] Cases of oral contraceptive failure have been attributed to the use of **doxylamine**, **chlorphenamine**, and an unnamed antihistamine,[2] but these antihistamines were all used in conjunction with penicillins, which are a possible cause of contraceptive failure (see 'Combined hormonal contraceptives + Antibacterials; Penicillins', p.1170). The effect of the antihistamines on the pharmacokinetics and pharmacodynamics of contraceptive steroids appear not to have been studied. No particular precautions would seem necessary during concurrent use.

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Combined hormonal contraceptives + Antimalarials

No clinically significant interaction appears to occur between oral combined hormonal contraceptives and chloroquine, primaquine or quinine, or between oral hormonal contraceptives and mefloquine. There is some evidence to suggest that an oral combined hormonal contraceptive modestly reduced the conversion of proguanil to its active metabolite, cycloguanil, but this may not be clinically important.

Clinical evidence and mechanism

(a) Chloroquine

A pharmacokinetic study in 12 healthy women taking an oral combined hormonal contraceptive (**ethinylestradiol** 30 micrograms with **norethisterone** 1 mg) found that the prophylactic use of chloroquine phosphate 500 mg once a week for 4 weeks caused a small 15% increase in the AUC of **ethinylestradiol**, and no change in the levels of **norethisterone**. Chloroquine use did not alter the inhibition of ovulation caused by the contraceptive, as assessed by mid-luteal progesterone levels and the lack of breakthrough spotting and bleeding. In a further group of 7 women, the same oral combined hormonal contraceptive did not alter the pharmacokinetics of a single 500-mg dose of chloroquine phosphate.[1] Another study in 6 healthy women given a single dose of an oral combined hormonal contraceptive (**ethinylestradiol** 30 micrograms with **levonorgestrel** 150 micrograms) confirmed that a single 300-mg dose of chloroquine had no significant effect on the pharmacokinetics of either the oestrogen or the progestogen.[2] Furthermore studies in *rhesus monkeys* infected with malaria, suggest that the curative efficacy of chloroquine is not altered by the use of oral combined hormonal contraceptives (**ethinylestradiol** with **norethisterone** or **norgestrel**).[3]

(b) Mefloquine

A study in 12 Thai women with falciparum malaria, 6 of whom were taking unnamed oral hormonal contraceptives, found that their response to mefloquine (parasite and fever clearance) was not affected by oral hormonal contraceptives. Similarly, the pharmacokinetics of mefloquine were not affected by oral hormonal contraceptives in patients with malaria.[4]

(c) Primaquine

A study in 6 healthy women given a single dose of an oral combined hormonal contraceptive (**ethinylestradiol** 30 micrograms with **levonorgestrel** 150 micrograms) confirmed that a single 45-mg dose of primaquine had no significant effect on the pharmacokinetics of either the oestrogen or the progestogen.[2]

(d) Proguanil

In women who were CYP2C19 extensive metabolisers (that is, those with normal levels of this isoenzyme), the use of an oral combined hormonal contraceptive (**ethinylestradiol** with **levonorgestrel**) reduced the levels of cycloguanil (the active metabolite of proguanil) by 34% after 3 weeks, when compared with the cycloguanil levels before starting the contraceptive.[5] It was suggested that the oestrogen might have inhibited the metabolism of proguanil by the cytochrome P450 isoenzyme CYP2C19. However, inhibition of CYP2C19 makes extensive metabolisers into poor metabolisers (that is, those lacking or deficient in this isoenzyme), and there is some evidence that CYP2C19 poor metaboliser status does not reduce the efficacy of proguanil for prophylaxis[6] or treatment[7] of malaria (see also 'Proguanil + Fluvoxamine', p.267).

(e) Quinine

A controlled study in Thai women found that the pharmacokinetics of a single 600-mg dose of quinine sulfate in 7 women taking oral hormonal contraceptives were not significantly different from those in 7 other women not taking contraceptives. The contraceptives being used were oral combined hormonal contraceptives in 6 women (**ethinylestradiol** with **levonorgestrel** or **norgestrel**) and a progestogen-only oral contraceptive in one (**norethisterone**).[8] There seem to be no reports that quinine affects the reliability of the oral contraceptives.

Importance and management

No clinically significant interaction appears to occur between the oral combined hormonal contraceptives and chloroquine, primaquine or quinine, or between oral hormonal contraceptives and mefloquine. There would seem to be no reason for avoiding concurrent use.

The production of the active metabolite of proguanil appears to be modestly decreased by oral combined hormonal contraceptives, and the authors of the study recommended that the dose of proguanil should be increased by 50% in women taking these contraceptives.[5] However, there is evidence that this pharmacokinetic interaction may not be clinically relevant, see also 'Proguanil + Fluvoxamine', p.267.

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Combined hormonal contraceptives + Aprepitant

Aprepitant reduced the levels of ethinylestradiol given as an oral combined hormonal contraceptive. Fosaprepitant, a prodrug of aprepitant, is expected to interact similarly.

Clinical evidence

The manufacturers[1,2] note that aprepitant 100 mg daily for 14 days given with an oral combined hormonal contraceptive (**ethinylestradiol** 35 micrograms with **norethisterone** 1 mg) decreased the AUC of **ethinylestradiol** and **norethisterone** by 43% and 8%, respectively. Reduced contraceptive steroid levels were reported in another study using a recommended antiemetic regimen including aprepitant (125 mg on the first day, then 80 mg daily for 2 days with dexamethasone 12 mg on the first day, then 8 mg daily for 3 days and ondansetron 32 mg on the first day), which was started on day 8 of a 21-day cycle of an oral combined hormonal contraceptive (**ethinylestradiol** with **norethisterone**).[1,2] Within 2 days of

starting the antiemetics (day 10) the **ethinylestradiol** AUC was reduced by 19% and the **norethisterone** level was unchanged.[2] However, the trough level of **ethinylestradiol** was reduced by as much as 64% and that of **norethisterone** by 60% during days 9 to 21.[1,2]

In yet another study, a single 40-mg dose of aprepitant was given on day 8 of a 21-day cycle of an oral combined hormonal contraceptive (**ethinylestradiol** with **norgestimate**). The AUC of **ethinylestradiol** decreased by 4% and 29% on day 8 and day 12, respectively, while the AUC of norelgestromin (the metabolite of **norgestimate**) increased by 18% on day 8 and decreased by 10% on day 12.[2]

Mechanism

During the first few days of use, aprepitant is an inhibitor of the cytochrome P450 isoenzyme CYP3A4 and therefore it would be expected to *increase* the levels of the contraceptive steroids. However, aprepitant then becomes an inducer of CYP3A4 (which usually becomes apparent after the end of a standard 3-day course), reaching a maximal inductive effect within 3 to 5 days of stopping aprepitant, and hence reduces the levels of the contraceptive steroids. This effect lasts only a few days and then reduces to become clinically insignificant within 2 weeks of stopping aprepitant.[1]

Importance and management

Although the effects of these reduced contraceptive steroids levels on ovulation were not assessed, it is likely that they could result in reduced efficacy. The manufacturer therefore recommends that alternative or additional contraceptive methods should be used during, and for 2 months (UK advice)[1] or one month (US advice)[2] after, aprepitant use. The same advice is given for **fosaprepitant**, which is a prodrug of aprepitant, for intravenous use.[3,4] This seems a sensible precaution.

1. Emend (Aprepitant). Merck Sharp & Dohme Ltd. UK Summary of product characteristics, July 2009.
2. Emend capsules (Aprepitant). Merck & Co., Inc. US prescribing information, July 2009.
3. IVEMEND (Fosaprepitant dimeglumine). Merck Sharp & Dohme Ltd. UK Summary of product characteristics, August 2009.
4. Emend for injection (Fosaprepitant dimeglumine). Merck & Co., Inc. US prescribing information, August 2009.

Combined hormonal contraceptives + Ascorbic acid (Vitamin C)

Ascorbic acid does not appear to cause a clinically important alteration in the levels of ethinylestradiol or levonorgestrel, but there are a few unconfirmed anecdotal reports of contraceptive failure associated with ascorbic acid.

Clinical evidence

One study in 5 women taking oral combined hormonal contraceptives found that ascorbic acid 1 g raised serum **ethinylestradiol** levels by 16% at 6 hours post-dose and by 48% at 24 hours post-dose.[1] However, a later well-controlled study found that ascorbic acid 1 g daily caused no significant changes in **ethinylestradiol** serum levels in 37 women taking an oral combined hormonal contraceptive (**ethinylestradiol** 30 micrograms with **levonorgestrel** 150 micrograms).[2] A similar study by the same workers found that ascorbic acid 1 g did not affect the pharmacokinetics of **levonorgestrel**.[3]

A single case report describes a woman taking an oral combined hormonal contraceptive (**ethinylestradiol** with **levonorgestrel**) who experienced heavy breakthrough bleeding in three cycles within 2 to 3 days of stopping ascorbic acid 1 g daily. This did not occur in three other cycles when no ascorbic acid was taken. It was suggested that this was due to a fall in **ethinylestradiol** levels when the vitamin C was stopped, which could increase the risk of contraceptive failure.[4] One report attributed contraceptive failure in one case to ascorbic acid and multivitamins.[5] Another two studies of pregnancies in oral hormonal contraceptive users found that vitamin C had been taken in 44 of 209 cases[6] and 15 of 137 cases,[7] although other drugs and/or factors may possibly have been involved in some of these cases.

Mechanism

Both ascorbic acid and ethinylestradiol undergo sulfate conjugation. It was suggested that large doses of ascorbic acid might compete for the metabolism of ethinylestradiol, and therefore increase its levels.[1] This would be expected to increase the efficacy of the hormonal contraceptive. However, some have suggested that enhanced levels could be followed by rebound ovulation,[4] but there is no evidence to support this.

Importance and management

Documentation about an interaction between ascorbic acid and contraceptives is limited. From the point of view of reliability, there seems to be little reason for avoiding the use of hormonal contraceptives and ascorbic acid. No special precautions are required.

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Combined hormonal contraceptives + Azoles

There are isolated reports of breakthrough bleeding and failure of oral combined hormonal contraceptives with fluconazole (including single 150 mg doses), itraconazole and ketoconazole. Conversely, fluconazole, itraconazole and voriconazole have been shown to modestly *increase* the serum levels of the contraceptive steroids. Similarly, ketoconazole markedly increased the levels of estradiol and dienogest. Be aware of the possibility of an increase in adverse effects. Intravaginal miconazole slightly increases the serum levels of ethinylestradiol and etonogestrel during the use of an intravaginal contraceptive ring. Oral combined hormonal contraceptives modestly increase voriconazole levels.

Clinical evidence

(a) Fluconazole

Up to 1990 the UK manufacturer of fluconazole had received 11 reports of menstrual disorders possibly associated with single-dose fluconazole 150 mg. Eight of these were in women taking an oral hormonal contraceptive who developed breakthrough bleeding (5 cases), no withdrawal bleeding (one case), and unintended pregnancies (2 cases).[1] Three other cases of unintended pregnancy have been very briefly mentioned elsewhere.[2]

However, one study found that a single 150-mg dose of fluconazole *increased* the AUC of **ethinylestradiol** by 29% in women taking an oral combined hormonal contraceptive (**ethinylestradiol** with **norethisterone** or **levonorgestrel**).[3] Similarly, fluconazole 300 mg once weekly for 4 weeks caused a 24% increase in the AUC of **ethinylestradiol** and a 13% increase in the AUC of **norethisterone**.[4] Moreover, the manufacturer has data on file showing that multiple doses of fluconazole 200 mg daily raised the levels of **ethinylestradiol** by 40% and of **levonorgestrel** by 24%,[5] whereas a lower dose of fluconazole (a single 50-mg dose or 50 mg of fluconazole daily for 10 days) had no significant effect on the pharmacokinetics of **ethinylestradiol** and **norgestrel**.[6] One other study in 10 women taking oral combined hormonal contraceptives found no changes in progesterone levels (suggesting no ovulation occurred) and no menstrual disorders while they were taking fluconazole 50 mg daily.[7] Furthermore, during clinical studies in which single 150-mg doses of fluconazole were used by over 700 women taking oral hormonal contraceptives, no clinical evidence of an interaction was seen.[8]

(b) Itraconazole

A 25-year-old woman who had been taking an oral combined hormonal contraceptive (**ethinylestradiol** 30 micrograms with **levonorgestrel** 150 micrograms) for a year, without problems, became pregnant when she was given itraconazole 200 mg daily for 3 months for a fungal infection.

The patient was said to be compliant, had suffered no gastrointestinal upset, and was not taking any other drugs that might have accounted for the failure of the pill.[2]

The Netherlands Pharmacovigilance Foundation (LAREB) have 9 cases of menstrual changes on their records in women taking an oral hormonal contraceptive during or after taking itraconazole 100 to 400 mg daily for one to 4 weeks. Seven women reported delayed withdrawal bleeding (2 to 5 days). In 2 of them the menstrual flow was decreased and one transiently had a positive pregnancy test after having previously experienced an intermenstrual blood loss. The remaining two reports were of amenorrhoea during one cycle, and breakthrough bleeding. The women were taking **ethinylestradiol** with either **desogestrel** or **levonorgestrel**.[9] A later extension of this report from LAREB, covering the period 1991 to 1997, describes 12 women taking contraceptives containing **ethinylestradiol** with **desogestrel**, whose withdrawal bleeding was either delayed or did not occur at all while taking itraconazole. Three other women taking **ethinylestradiol** with **levonorgestrel** had breakthrough bleeding, and yet another taking **ethinylestradiol** with **cyproterone** became pregnant while taking itraconazole.[10]

However, the manufacturer has data on file of a study showing that itraconazole 200 mg daily for 15 days had no effect on the pharmacokinetics of **ethinylestradiol**, and *increased* the bioavailability of **norethisterone** by about 40%. In this study, a single dose of **ethinylestradiol** with **norethisterone** was given before the first dose and with the last dose of itraconazole.[11]

(c) Ketoconazole

An early report described 7 out of 147 women taking oral combined hormonal contraceptives (**ethinylestradiol** with **norgestrel**) who experienced breakthrough bleeding or spotting within 2 to 5 days of starting a 5-day course of ketoconazole 400 mg daily. No pregnancies occurred.[12] One unintended pregnancy attributed to contraceptive failure due to ketoconazole has been very briefly mentioned elsewhere.[2]

In one controlled study in postmenopausal women given an oral combined hormonal contraceptive (**estradiol** 2 mg with **dienogest** 3 mg) for 14 days, ketoconazole 400 mg daily for 7 days increased the steady-state AUC of **estradiol** by 65% and that of **dienogest** by 186%.[13,14]

(d) Miconazole

A study found that both single and multiple-dose intravaginal regimens of miconazole pessaries or cream slightly increased the AUC of **ethinylestradiol** and **etonogestrel** during the use of an intravaginal ring (*NuvaRing*). The AUC over days 8 to 21 was increased by 16% for **ethinylestradiol** and 17% for **etonogestrel** with a single vaginal dose of miconazole 1.2 g given on day 8.[15]

(e) Voriconazole

The steady-state AUC of **ethinylestradiol** and **norethisterone** (given as an oral combined hormonal contraceptive) were increased by 61% and 53%, respectively, by the concurrent use of voriconazole for 4 days (400 mg twice daily on day one, then 200 mg twice daily). Moreover, the maximum levels and AUC of voriconazole were increased by 14% and 46%, respectively, by these contraceptive steroids, when compared with voriconazole given alone.[16]

Mechanism

The azole antifungals are, to varying degrees, inhibitors of the cytochrome P450 isoenzyme CYP3A4. They would therefore be expected to increase the levels of the contraceptive steroids to varying extents, as has been shown for fluconazole, itraconazole, ketoconazole, intravaginal miconazole and voriconazole. Therefore the azoles would *not* be expected to increase the incidence of breakthrough bleeding or contraceptive failure when used with combined hormonal contraceptives. It should be noted that the manufacturers list menstrual irregularities as adverse effects of itraconazole, ketoconazole and **posaconazole** irrespective of the use of hormonal contraceptives,[17-19] and menstrual disorders have also been reported with fluconazole alone.[1] The increase in voriconazole levels was expected to be due to inhibition of CYP2C19 by ethinylestradiol.[19]

Importance and management

The picture presented by these reports is somewhat confusing and contradictory. The anecdotal reports of contraceptive failure and the cases of breakthrough bleeding would suggest that these antifungals can, rarely, make oral hormonal contraception less reliable in some individuals. However, the problem with this interpretation is that the pharmacokinetic data suggest that, if anything, an *enhanced* effect of the oral combined hormonal contraceptives is likely. Note that, of all the drugs proven to decrease the efficacy of oral combined hormonal contraceptives, all have also been shown to decrease the steroid levels. Menstrual disorders have occurred with the azole antifungals alone, and may not be indicative of reduced contraceptive efficacy. As there are so few reports of pregnancy, it could just be that they fall within the accepted failure rate of oral combined hormonal contraceptives, and it was just coincidental they occurred when the antifungal was being taken. Note that the manufacturers do not advise any special precautions when taking hormonal contraceptives and these azole antifungals.[5,17,20] However, some authors have considered that the data warrant consideration being given to the use of additional contraceptive measures.[10] The theoretical teratogenic risk[5,17-20] from these azole antifungals may have a bearing on this, and the UK manufacturers of a number of the azoles recommend using effective contraception during azole treatment because of this.[5,17,19,20]

The main concern regarding the increased levels of ethinylestradiol or progestogens is whether this would increase the risk of adverse effects of these contraceptive steroids. There are no data on the effect of these modest 24 to 61% increases in steroid levels on adverse effects. It could be argued that a 40% increase for ethinylestradiol would turn a standard-strength contraceptive (35 micrograms) into a high-dose contraceptive (50 micrograms), and, indeed, in one study, the AUC of ethinylestradiol 35 micrograms with voriconazole was comparable to that seen in earlier studies with a 50 microgram dose of ethinylestradiol.[16] Further study is needed. There is also the potential for increased voriconazole adverse effects.

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18. Nizoral Tablets (Ketoconazole). Janssen-Cilag Ltd. UK Summary of product characteristics, October 2008.
19. Noxafil (Posaconazole). Schering-Plough Ltd. UK Summary of product characteristics, November 2009.
20. VFEND (Voriconazole). Pfizer Ltd. UK Summary of product characteristics, September 2009.

Combined hormonal contraceptives + Barbiturates or Phenytoin

Combined hormonal contraceptives are less reliable during the use of phenytoin, and barbiturates such as phenobarbital and primidone. Intermenstrual breakthrough bleeding and spotting can take place, and unintended pregnancies have occurred. Controlled studies have found that phenytoin and phenobarbital can reduce contraceptive steroid levels.

Clinical evidence

A woman with epilepsy taking phenytoin 200 mg and sultiame 50 mg daily (with ferrous gluconate and folic acid) became pregnant despite the regular use of an oral combined hormonal contraceptive (**ethinylestradiol** 50 micrograms with **norethisterone** 3 mg).[1] Since this first report in 1972, at least 33 pregnancies have been reported in the literature in women taking a range of oral hormonal contraceptives (mostly combined) and a barbiturate (such as **phenobarbital** or **primidone**) and/or phenytoin (see 'Table 28.2', (below)). Note that most of these cases were with an oral combined hormonal contraceptive containing at least 50 micrograms of **ethinylestradiol**. In addition, between the years 1968 to 1984, a further 39 pregnancies were reported to the CSM in the UK in women using an oral combined hormonal contraceptive while taking phenytoin (20 users) and/or **phenobarbital** (25 users) and/or **primidone** (7 users) with or without other antiepileptics.[2] In this report, over half the cases of contraceptive failure with antiepileptics related to high-dose oral combined hormonal contraceptives (50 micrograms of oestrogen).[2]

In one study, breakthrough bleeding (which was regarded as loss of reliability of the contraceptive) occurred in 30 of 51 women taking an oral combined hormonal contraceptive (**ethinylestradiol** with **norethisterone** or **mestranol** with **chlormadinone**) given **phenobarbital**.[3] In another study, 7 out of 11 patients taking **phenobarbital** and one of 2 patients taking phenytoin had breakthrough bleeding.[4] The incidence of breakthrough bleeding was 90% with preparations containing **ethinylestradiol** 30 micrograms and 29% with preparations containing **ethinylestradiol** 75 micrograms. Similarly, with preparations containing **ethinylestradiol** 50 micrograms, decreasing the dose of **norgestrel** from 500 to

Table 28.2 Case reports of pregnancies in women taking combined oral contraceptives with barbiturates and/or phenytoin

Antiepileptic	*Oestrogen*	*Progestogen*	*Number of cases*	*Refs*
Phenytoin + Sultiame	Ethinylestradiol 50 micrograms	Norethisterone 3 mg	1	1
Phenytoin + Primidone, Phenobarbital or Methylphenobarbital	Not stated	Not stated	7	2, 3
Primidone	Ethinylestradiol 50 or 100 micrograms	Norgestrel 500 micrograms or Megestrol 1 mg	2	4, 5
Phenytoin + Primidone or Phenobarbital	Ethinylestradiol 50 micrograms	Norgestrel 250 or 500 micrograms or Norethisterone 1 mg	3	4, 5
Phenytoin + Primidone or Phenobarbital + Other	Ethinylestradiol 50 micrograms	Norgestrel 500 micrograms	2	4, 5
Phenytoin + Carbamazepine	Ethinylestradiol 50 micrograms	Norgestrel 250 micrograms	1	4, 5
Primidone or Phenobarbital	Ethinylestradiol	Norgestrel	3	6
Phenobarbital or Butobarbital	Ethinylestradiol or Mestranol	Norethisterone	3	7
Phenytoin	Ethinylestradiol 100 micrograms	Dimethisterone 25 mg	1	8
Phenobarbital or Methylphenobarbital	Ethinylestradiol 50 micrograms or Mestranol 80 micrograms	Etynodiol 1 mg or Chlormadinone 2 mg	2	8
Phenytoin + Phenobarbital	Mestranol 100 micrograms	Noretynodrel 2.5 mg	1	8
Phenobarbital	Ethinylestradiol 50 micrograms	Desogestrel 75 mg	1	9
Phenytoin + Phenobarbital	Ethinylestradiol	Levonorgestrel	1	10
Phenytoin then Carbamazepine	Ethinylestradiol	Lynestrol	1	10
Phenytoin and/or phenobarbital or primidone (with or without other antiepileptics)	Ethinylestradiol 30 or 50 micrograms or Mestranol 50 micrograms	Megestrol, Norethisterone, Etynodiol, Norgestrel or Levonorgestrel	39	11
Phenytoin	Ethinylestradiol 50 micrograms	Not stated	1	12
Phenytoin	Ethinylestradiol less than 50 micrograms	Not stated	2	13
Phenobarbital	Ethinylestradiol 35 micrograms ('back up' contraception also used)	Norgestimate 180 to 250 micrograms	1*	14

*This same woman previously became pregnant while using the levonorgestrel implant, see progestogen-only contraceptives

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125 micrograms increased breakthrough bleeding from 50% to 62%.[4]

A pharmacokinetic study in 6 women taking an oral combined hormonal contraceptive found that the AUCs of **ethinylestradiol** 50 micrograms and **levonorgestrel** 250 micrograms were lowered by 49% and 42%, respectively, by phenytoin 200 to 300 mg daily for 8 to 12 weeks.[5] In another study, **phenobarbital** 30 mg twice daily did not significantly alter the plasma levels of contraceptive steroids in 4 women taking oral combined hormonal contraceptives (**ethinylestradiol** with **norethisterone** or **norgestrel**), but 2 of the women did have 54% and 60% reductions, respectively, in their **ethinylestradiol** levels. These 2 women had breakthrough bleeding, but the suppression of ovulation was maintained.[6]

Mechanism

The likeliest explanation for the unreliability and failure of oral hormonal contraceptives is that phenytoin and the barbiturates (known potent liver enzyme inducers) increase the metabolism and clearance of the contraceptive steroids from the body, thereby reducing their effects, and in some instances, allowing ovulation to occur.

Importance and management

The interactions between the oral combined hormonal contraceptives and phenobarbital and phenytoin are clinically important and fairly well documented. Primidone is metabolised to phenobarbital and appears to interact similarly. The risk of breakthrough bleeding and spotting is high (bleeding disturbances are usually regarded as an indication of reduced efficacy if cycles were previously regular[7]). However, the actual incidence of contraceptive failure when oral combined hormonal contraceptives are given with these drugs is unknown. It appears that the incidence of unintended pregnancies is quite small: in one series, a failure rate of 3.1 per 100 woman years was calculated, compared with an expected 0.7 per 100 woman years.[8] Note that this failure rate is still less than that seen with barrier methods such as condoms.

Reliable contraception in most patients is said to be achievable with ethinylestradiol 80 to 100 micrograms daily.[4,9,10] If these larger doses are required for good cycle control, there should be no increase in adverse effects because the enzyme-inducing effects of the antiepileptics reduce the blood levels of the steroids. However, note that many of the cases of unintended pregnancies cited were with products containing 50 micrograms of ethinylestradiol or more, and one review of contraceptive interactions suggested that women taking low-dose oestrogen-containing contraceptives may not be at a greater risk of an interaction.[11]

Nevertheless, as the personal and ethical consequences of an unplanned pregnancy can be very serious, it is important to take the necessary practical steps to reduce this increased risk. Moreover, pregnancy in women with epilepsy should ideally be planned so that therapy can be reviewed to minimise the risks of foetal malformation.[9] In this regard, it is of concern that some surveys have shown a lack of knowledge of these interactions and their management among prescribers,[12] and the frequent use of enzyme-inducing antiepileptics with hormonal contraceptives containing less than 50 micrograms of ethinylestradiol.[13]

The UK Faculty of Family Planning and Reproductive Health Care (FFPRHC) Clinical Effectiveness Unit have issued guidance on the use of drugs that induce liver enzymes with hormonal contraceptives, including phenytoin, phenobarbital and primidone. They recommend that:[14]

- **Copper** or **levonorgestrel-releasing intrauterine devices** (IUD) and **depot progestogen-only injections** (see 'Progestogen-only contraceptives + Enzyme inducers', p.1206), are the preferred alternative contraceptive methods, particularly for women taking the enzyme inducer in the long-term, as these are unaffected by liver-enzyme inducers.
- For the **combined hormonal contraceptives** given as a **patch**, using more than one patch is not recommended. Additional, non-hormonal methods of contraception, such as condoms, should be used by patients using the combined hormonal contraceptive patch, both when taking the liver-enzyme inducers and for at least 4 weeks after stopping the drug. If liver-enzyme inducers are to be used long-term, then alternatives to the patch should be considered.

Similar advice applies to the **vaginal ring** preparation.[15]

- Women who wish to use an oral **combined hormonal contraceptive** should take an ethinylestradiol dose of at least 50 micrograms daily (either by using two tablets of a 30-microgram preparation or one tablet of a 20-microgram preparation with one tablet of a 30-microgram preparation). The dose may be increased further above 50 micrograms if breakthrough bleeding occurs. Additional non-hormonal methods of contraception, such as condoms, should also be used by patients using oral combined hormonal contraceptives, both when taking the liver-enzyme inducers and for at least 4 weeks after stopping the drug. This advice certainly applies when taking a short-course of an enzyme-inducing drug. However, some consider that with the long-term use of enzyme-inducing antiepileptics, when oral combined hormonal contraceptives are the chosen method of contraception, additional contraceptive precautions are required only until a regular regimen has been established.[16] Alternatively, the use of a non-interacting antiepileptic drug could be considered, particularly in patients taking combined hormonal contraceptives long-term. Note that 'ethosuximide', (p.1182), 'gabapentin', (p.1183), 'levetiracetam', (p.1185), 'sodium valproate', (p.1195), 'tiagabine', (p.1193), and 'vigabatrin', (p.1196) do not appear to interact with the hormonal contraceptives.

Pill-free intervals. There are no studies to show whether omitting or reducing the pill-free interval reduces the risk of ovulation with liver enzyme inducers, so the UK Faculty of Family Planning and Reproductive Health Care (FFPRHC) Clinical Effectiveness Unit make no recommendation for this. However, enzyme-inducing drugs are likely to increase the length of the pill-free interval (see 'Interaction studies', (p.1165)), and this might contribute to their effects in reducing contraceptive efficacy. Some therefore recommend that with the enzyme-inducing antiepileptics, in addition to increasing the ethinylestradiol dose, the usual 7-day pill-free interval should be avoided, and that the pill should be taken in a tricycling regimen (i.e. a monophasic preparation continuously for 3 or 4 packets, then a short pill-free interval of 4 days).[16] Others contend that it is actually the progestogen dose that is more important in inhibiting ovulation in combined hormonal contraceptives, and that continuous use (without any pill-free interval) of a combined hormonal contraceptive containing a high dose of progestogen should be used in a woman taking an enzyme-inducing antiepileptic. However, they say that additional protection may still be worthwhile as contraceptive efficacy cannot be guaranteed.[17]

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11. Szoka PR, Edgren RA. Drug interactions with oral contraceptives: compilation and analysis of an adverse experience report database. *Fertil Steril* (1988) 49 (Suppl), S31–S38.
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Combined hormonal contraceptives + Bile-acid binding resins

Colesevelam given at the same time as an oral combined hormonal contraceptive, modestly reduces the absorption of ethinylestradiol, but has less effect when given 4 hours after the contraceptive. Colestipol and colestyramine might be expected to interact similarly.

Clinical evidence

(a) Colesevelam

The manufacturers state that, in studies in healthy subjects, colesevelam 3.75 g, taken at the same time as an oral combined hormonal contraceptive, reduced the AUC of **ethinylestradiol** 35 micrograms by 24% but had no effect on the AUC of **norethisterone** 1 mg. Giving the contraceptive 4 hours before the colesevelam reduced this effect on ethinylestradiol (AUC reduced by 12% with a 4-hour separation).[1,2]

(b) Colestyramine

A brief review of the drug interactions of contraceptives reported that the half-life of **ethinylestradiol** was reduced from 8.2 hours to 4.8 hours in a healthy subject taking 4 g of colestyramine three times daily (duration of treatment not stated).[3]

Mechanism

Colestyramine, colestipol, and colesevelam are bile-acid binding resins, intended to bind to bile acids within the gut, but they can also bind with some drugs thereby reducing the amount available for absorption. As ethinylestradiol undergoes enterohepatic circulation (i.e. after absorption it is excreted in the bile and reabsorbed), it has been suggested that its reabsorption may be reduced by these bile-acid binding resins.[3] However, separation of administration would not normally be expected to minimise the effect on enterohepatic recirculation, and, in any case, the importance of enterohepatic recirculation of ethinylestradiol to its efficacy is not established.

Importance and management

The reduction in exposure to ethinylestradiol is small when taken at the same time as colesevelam. However, on the basis of these results, the manufacturers of colesevelam recommend taking oral hormonal contraceptives at least 4 hours before colesevelam.[1,2] This might be a prudent precaution.

There appears to be no specific data relating to colestipol and only the report in one subject for colestyramine. However, as both of these drugs are known to affect the absorption of many drugs, it may be prudent to apply the standard recommendation of taking other drugs at least one hour before or 4 hours after colestipol, and one hour before or 4 to 6 hours after colestyramine, to minimise the risk of an interaction.

1. Welchol (Colesevelam hydrochloride). Daiichi Sankyo, Inc. US Prescribing information, October 2009.
2. Cholestagel (Colesevelam hydrochloride). Genzyme Therapeutics. UK Summary of product characteristics, March 2009.
3. Bolt HM. Interactions between clinically used drugs and oral contraceptives. *Environ Health Perspect* (1994) 102 (Suppl 9), 35–8.

Combined hormonal contraceptives + Candesartan

Candesartan cilexetil 8 mg daily had no effect on the pharmacokinetics of ethinylestradiol and levonorgestrel given as an oral combined hormonal contraceptive, and no ovulation occurred during concurrent use.[1] No special precautions would therefore appear to be needed if both drugs are given. Consider also 'Drospirenone-containing contraceptives or HRT + Potassium-sparing drugs', p.1197, for a possible interaction between angiotensin II receptor antagonists and drospirenone, and 'Antihypertensives + Hormonal contraceptives or HRT', p.1050.

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Combined hormonal contraceptives + Carbamazepine or Oxcarbazepine

Combined hormonal contraceptives are less reliable during treatment with carbamazepine and oxcarbazepine. Breakthrough bleeding and spotting can take place, and unintended pregnancies have occurred with carbamazepine. Controlled studies have shown that carbamazepine and oxcarbazepine can reduce contraceptive steroid levels.

Clinical evidence

(a) Carbamazepine

A pharmacokinetic study compared the effects of topiramate or carbamazepine on an oral combined hormonal contraceptive containing **ethinylestradiol** 35 micrograms with norethisterone 1 mg. In the 10 patients who received carbamazepine (600 mg daily from day one to day 21 of a cycle), the AUC of **norethisterone** and **ethinylestradiol** were reduced by 58% and 42%, respectively, on day 20 of the cycle.[1] In another earlier study, carbamazepine 300 to 600 mg daily reduced the AUC of **ethinylestradiol** by 42% and **levonorgestrel** by 40% in 4 women given a single dose of an oral combined hormonal contraceptive (**ethinylestradiol** 50 micrograms with **levonorgestrel** 250 micrograms) before and after 8 to 12 weeks of carbamazepine use.[2]

In an early study, 6 of 12 women taking an oral combined hormonal contraceptive (**ethinylestradiol** with **norethisterone**) developed spotting or breakthrough bleeding while taking carbamazepine (this is regarded as a possible loss of reliability of the contraceptive).[3] A similar study reported breakthrough bleeding in 4 of 6 patients taking carbamazepine and an oral combined hormonal contraceptive,[4] and the same author later briefly reported 37 out of 59 patients had breakthrough bleeding while taking this combination.[5]

One woman taking a low-dose oral combined hormonal contraceptive (not specified) conceived 6 weeks after starting carbamazepine, initially 200 mg daily then 600 mg daily.[6] In another case, the failure of an oral combined hormonal contraceptive containing **ethinylestradiol** 30 micrograms was attributed to carbamazepine.[7] Six pregnancies were identified in women who took carbamazepine and an oral hormonal contraceptive (unspecified) in the adverse reactions register of the CSM in the UK for the years 1968 to 1984. However, it is unclear how many of these 6 women were taking carbamazepine alone, as the authors note that some women were taking multiple antiepileptics.[8] Two further pregnancies have been reported in women taking oral combined hormonal contraceptives and antiepileptics including carbamazepine and phenytoin,[9] and one in a woman who was switched from phenytoin to carbamazepine.[10]

(b) Oxcarbazepine

Preliminary observations revealed that 4 of 6 women receiving oxcarbazepine had breakthrough bleeding when they were given an oral combined hormonal contraceptive containing **ethinylestradiol** 30 micrograms. This resolved in two women when they took double the dose of **ethinylestradiol**.[5] In a pharmacokinetic study in 10 healthy women taking an oral triphasic combined hormonal contraceptive, oxcarbazepine 300 mg three times daily for 4 weeks reduced the AUCs of **ethinylestradiol** and **levonorgestrel** by 47% and 36%, respectively. Three women had menstrual bleeding disturbances.[11] Similar results were reported in a later study with oxcarbazepine 1.2 g daily and an oral combined hormonal contraceptive (**ethinylestradiol** 50 micrograms with **levonorgestrel** 250 micrograms).[12] No cases of unintended pregnancy appear to have been published.

Mechanism

The most likely explanation for these interactions is that both carbamazepine and oxcarbazepine reduce the levels of the contraceptive steroids, presumably by inducing their metabolism. This may result in loss of contraceptive efficacy.

Importance and management

The reduction in contraceptive steroid levels caused by carbamazepine and oxcarbazepine is well established. However, the actual incidence of contraceptive failure when oral hormonal contraceptives are given with these drugs is unknown. Given the few published reports, it appears that unintended pregnancies with carbamazepine are rare, and still less frequent than that seen with barrier methods such as condoms. There appear to be no published reports of pregnancies in patients taking an oral hormonal contraceptive and oxcarbazepine. Nevertheless, given the personal and ethical consequences of an unwanted pregnancy, any reduction in contraceptive efficacy is of concern. The UK Faculty of Family Planning and Reproductive Health Care (FFPRHC) Clinical Effectiveness Unit has issued guidelines on the management of women taking liver enzyme induc-

ers such as carbamazepine or oxcarbazepine with hormonal contraceptives. These are discussed in further detail under 'Combined hormonal contraceptives + Barbiturates or Phenytoin', p.1177.

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2. Crawford P, Chadwick DJ, Martin C, Tjia J, Back DJ, Orme M. The interaction of phenytoin and carbamazepine with combined oral contraceptive steroids. *Br J Clin Pharmacol* (1990) 30, 892–6.
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Combined hormonal contraceptives + Coxibs

High-dose etoricoxib raises ethinylestradiol levels by 50 to 60%, and it may be appropriate to select a low-dose combined oral contraceptive if etoricoxib is required. Rofecoxib increases contraceptive steroid levels to a small extent. Celecoxib appears to have no effect on oral combined hormonal contraceptive levels. One case of pulmonary embolism has been reported in a patient taking valdecoxib with an oral combined hormonal contraceptive.

Clinical evidence

(a) Celecoxib

Celecoxib had no clinically significant effects on the pharmacokinetics of an oral combined hormonal contraceptive containing **ethinylestradiol** 35 micrograms with **norethisterone** 1 mg.[1]

(b) Etoricoxib

In a placebo-controlled, crossover study in women taking an oral triphasic hormonal contraceptive (**ethinylestradiol** 35 micrograms with **norethisterone** 0.5 to 1 mg) for 21 days, the addition of etoricoxib 120 mg daily taken at the same time or 12 hours after the contraceptive increased the $AUC_{0\text{-}24}$ of **ethinylestradiol** by 50% and 60%, respectively.[2] The **norethisterone** AUC showed minimal changes (9% and 22% increase). In a further study, a lower dose of etoricoxib 60 mg daily taken with the same contraceptive increased the **ethinylestradiol** AUC by 37% with a non-significant 11% increase in **norethisterone** level.[2]

(c) Rofecoxib

In a placebo-controlled, crossover study in 18 healthy women taking an oral combined hormonal contraceptive (**ethinylestradiol** 35 micrograms with **norethisterone** 1 mg), rofecoxib 175 mg daily for 2 weeks raised the AUCs of **ethinylestradiol** and **norethisterone** by 13% and 18%, respectively. No abnormal menstrual bleeding was reported.[3]

(d) Valdecoxib

A single case of left iliac vein thrombosis and bilateral multiple pulmonary emboli has been reported in a 25-year-old woman taking an oral combined hormonal contraceptive (**ethinylestradiol** with **norgestimate**) which developed within a month of starting valdecoxib 20 mg twice daily. The patient had been taking the same contraceptive (containing ethinylestradiol doses of 35 micrograms and then 25 micrograms) for 3 years before taking valdecoxib with no adverse effects. No risk factors were identified apart from prolonged stasis (a 6-hour car journey) and the hormonal contraceptive use.[4]

Mechanism

It is thought that etoricoxib increases ethinylestradiol levels because it inhibits sulfotransferase activity thereby inhibiting ethinylestradiol metabolism. Rofecoxib possibly interacts similarly, although to a lesser extent, and celecoxib appears not to interact. Coxibs as a class and some non-selective NSAIDs appear to be associated with a small increased risk of rare thrombotic events (especially myocardial infarction and stroke). Combined hormonal contraceptives are also associated with a small increased risk of rare thrombotic events. It is possible that these effects could be additive or synergistic.

Importance and management

The increase in ethinylestradiol levels with etoricoxib 120 mg daily would be expected to be similar to switching from a standard-dose contraceptive (ethinylestradiol 30 micrograms) to a high-dose preparation (50 micrograms), and could therefore have clinical consequences. The manufacturer suggests that this increase in ethinylestradiol levels should be considered when choosing the contraceptive because of the possible increased risk of adverse events such as veno-thrombotic events.[5] It may therefore be appropriate to use a contraceptive with a lower dose of ethinylestradiol if etoricoxib is required regularly, particularly at higher doses, and especially as coxibs themselves are associated with an increased risk of thrombotic events.

The small changes in ethinylestradiol levels seen with rofecoxib (now withdrawn), although statistically significant, are modest, and unlikely to be clinically important.

The general relevance of the one case of pulmonary embolism with valdecoxib (now withdrawn) and an oral combined hormonal contraceptive is unclear. However, it cannot be excluded that combined use of these two products contributed to this rare adverse effect. Note that risk factors for venous thromboembolism and cardiovascular disease are taken into account when prescribing a combined hormonal contraceptive alone, or a coxib alone, and therefore it may be prudent to re-evaluate these risks when a coxib is required in a woman using a combined hormonal contraceptive, and vice versa.

1. Celebrex (Celecoxib). Pharmacia Ltd. UK Summary of product characteristics, June 2009.
2. Schwartz J, Hunt T, Smith WB, Wong P, Larson P, Crumley T, Mehta A, Gottesdiener K, Agrawal N. The effect of etoricoxib on the pharmacokinetics of oral contraceptives in healthy participants. J Clin Pharmacol (2009) 49, 807–15.
3. Schwartz JI, Wong PH, Porras AG, Ebel DL, Hunt TR, Gertz BJ. Effect of rofecoxib on the pharmacokinetics of chronically administered oral contraceptives in healthy female volunteers. *J Clin Pharmacol* (2002) 42, 215–21.
4. Westgate EJ, Fitzgerald GA. Pulmonary embolism in a woman taking oral contraceptives and valdecoxib. *PLoS Med* (2005) 2, e197.
5. Arcoxia (Etoricoxib). Merck Sharp & Dohme Ltd. UK Summary of product characteristics, September 2009.

Combined hormonal contraceptives + Endothelin receptor antagonists

Bosentan modestly reduces the levels of ethinylestradiol and norethisterone given as an oral combined hormonal contraceptive, and is likely to reduce contraceptive efficacy. In contrast, sitaxentan increases contraceptive steroid levels, and might possibly increase adverse effects. Ambrisentan had minimal effects on the pharmacokinetics of contraceptive steroids.

Clinical evidence

(a) Ambrisentan

Ambrisentan 10 mg daily for 12 days slightly decreased the AUC of **ethinylestradiol** by 4% and slightly increased that of **norethisterone** by 14% when a single dose of an oral combined hormonal contraceptive was given to healthy women.[1,2]

(b) Bosentan

In a randomised, crossover study in 19 healthy women, a single dose of an oral combined hormonal contraceptive (**ethinylestradiol** 35 micrograms with **norethisterone** 1 mg) was given alone and on the last day of bosentan 125 mg twice daily for one week. Bosentan reduced the mean AUC of norethisterone by 14% (maximum reduction 56%) and the mean AUC of

ethinylestradiol by 31% (maximum reduction 66%). Note that there was marked inter-individual variability. The maximum concentration and half-life of both contraceptive steroids were not affected.[3]

(c) Sitaxentan

Sitaxentan increased the AUC of norethisterone by 47% and that of ethinylestradiol by 59% when healthy women were given an oral combined hormonal contraceptive containing **ethinylestradiol** 35 micrograms with **norethisterone** 1 mg. The efficacy of the contraceptive, as measured by FSH, LH, and progesterone levels, was unaffected.[4]

Mechanism

The contraceptive steroids are partially metabolised by the cytochrome P450 isoenzyme CYP3A4, and it was thought that the changes in their pharmacokinetics may have been caused by induction of CYP3A4 by bosentan. However other mechanisms could not be excluded.[3] How sitaxentan increases contraceptive steroid levels is unclear, but it has some CYP2C9 and CYP3A4/5 inhibitory activity.[4]

Importance and management

The endothelin antagonists (ambrisentan, bosentan and sitaxentan) are contraindicated in pregnancy because of their potential teratogenic effects, and for this reason, effective contraception during use is considered especially important. The clinical relevance of the reduction in contraceptive steroid levels seen with **bosentan** is not certain. Nevertheless, a 31% reduction in ethinylestradiol exposure is equivalent to changing a 30 microgram preparation to a 20 microgram preparation, and greater reductions were seen in some patients. Contraceptive failure might therefore be expected in some patients. The UK manufacturer recommends that additional or alternative methods to hormonal contraceptives (any form) are used.[5] Similarly, the US manufacturer also recommends that hormonal contraceptives (oral, injectable, implants, transdermal) should not be used as the sole form of contraception (with the exception of the levonorgestrel intrauterine system, which may be used alone).[6] Given the reduction in contraceptive steroid levels, this seems a sensible precaution.

In contrast, **sitaxentan** increases contraceptive steroid levels. The 59% increase in ethinylestradiol levels is equivalent to changing a 30 microgram preparation to a 50 microgram preparation. This might have the potential to increase adverse effects. The manufacturer specifically notes that the increase in exposure to oestrogen may increase the risk of venous thromboembolism, and in women who smoke, they recommend that prophylaxis of venous thromboembolism with vitamin K antagonists should be considered as is traditionally used in pulmonary arterial hypertension.[4] It would seem prudent to consider low-dose contraceptives and be cautious about contraceptive adverse effects.

Ambrisentan had no clinically relevant effect on the pharmacokinetics of oral combined hormonal contraceptives, and no additional precautions would seem to be necessary on concurrent use. However, as with other teratogenic drugs, the US manufacturer's advice is to use two methods of reliable contraception,[2] whereas the UK manufacturer gives no specific advice except to say that reliable contraception should be used.[1]

1. Volibris (Ambrisentan). GlaxoSmithKline UK. UK Summary of product characteristics, August 2009.
2. Letairis (Ambrisentan). Gilead Sciences, Inc. US Prescribing information, August 2009.
3. Van Giersbergen PLM, Halabi A, Dingemanse J. Pharmacokinetic interaction between bosentan and the oral contraceptives norethisterone and ethinyl estradiol. *Int J Clin Pharmacol Ther* (2006) 44, 113–18.
4. Thelin (Sitaxentan sodium). Encysive (UK) Ltd. UK Summary of product characteristics, April 2009.
5. Tracleer (Bosentan monohydrate). Actelion Pharmaceuticals UK Ltd. UK Summary of product characteristics, July 2009.
6. Tracleer (Bosentan). Actelion Pharmaceuticals US, Inc. US Prescribing information, August 2009.

Combined hormonal contraceptives + Ethosuximide

Ethosuximide probably does not alter the efficacy of oral combined hormonal contraceptives.

Clinical evidence, mechanism, importance and management

Four pregnancies were identified in women who took ethosuximide and an oral contraceptive (unspecified) in the adverse reactions register of the CSM in the UK for the years 1968 to 1984. However, the authors note that ethosuximide was the sole antiepileptic prescribed in only one of the cases reported.[1] As ethosuximide is not an inducer of hepatic enzymes, it is likely that this one case is a chance association. Another case describes pregnancy in a woman who had been taking ethosuximide, phenytoin, and phenobarbital, with an oral combined hormonal contraceptive for 6 years.[2] If indeed this case does represent an interaction, the known enzyme-inducers phenytoin and phenobarbital are more likely to be implicated than ethosuximide (see 'Combined hormonal contraceptives + Barbiturates or Phenytoin', p.1177). There do not appear to have been any pharmacokinetic or pharmacodynamic studies of the use of ethosuximide with oral contraceptives and no further case reports have been published. The UK Faculty of Family Planning and Reproductive Health Care (FFPRHC) Clinical Effectiveness Unit guidelines on the management of hormonal contraceptives and drug interactions list ethosuximide as an antiepileptic that does not induce liver enzymes.[3] No special contraceptive precautions appear to be necessary on concurrent use.

1. Back DJ, Grimmer FM, Orme ML'E, Proudlove C, Mann RD, Breckenridge AM. Evaluation of Committee on Safety of Medicines yellow card reports on oral contraceptive-drug interactions with anticonvulsants and antibiotics. *Br J Clin Pharmacol* (1988) 25, 527–32.
2. Janz D, Schmidt D. Anti-epileptic drugs and failure of oral contraceptives. *Lancet* (1974) i, 1113.
3. Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit. FFPRHC Guidance: Drug interactions with hormonal contraception. April 2005. Available at: http://www.ffprhc.org.uk/admin/uploads/DrugInteractionsFinal.pdf (accessed 01/02/10).

Combined hormonal contraceptives + Ezetimibe

Ezetimibe did not alter the pharmacokinetics of an oral contraceptive containing ethinylestradiol and norgestrel.

Clinical evidence, mechanism, importance and management

In a randomised, crossover study, 18 healthy women who had been taking an oral triphasic hormonal contraceptive (containing **ethinylestradiol** with **norgestrel**) were also given ezetimibe 10 mg daily or placebo on days 8 to 14 of two consecutive contraceptive cycles. Ezetimibe did not significantly affect the pharmacokinetics of **ethinylestradiol** or **norgestrel**.[1] Therefore, no additional precautions seem necessary if ezetimibe is given to women taking contraceptives containing these hormones.

1. Keung ACF, Kosoglou T, Statkevich P, Anderson L, Boutros T, Cutler DL, Batra V, Sellers EM. Ezetimibe does not affect the pharmacokinetics of oral contraceptives. *Clin Pharmacol Ther* (2001) 69, P55.

Combined hormonal contraceptives + Felbamate

In one study, felbamate increased the clearance of gestodene from an oral combined hormonal contraceptive without altering ovulation suppression.

Clinical evidence, mechanism, importance and management

In a randomised, placebo-controlled study 23 healthy women were given an oral combined hormonal contraceptive (**ethinylestradiol** 30 micrograms with **gestodene** 75 micrograms) for 3 months or more. During months one and 2 they were also given either felbamate in a dose of up to 2.4 g daily, or a placebo, from day 15 of month one to day 14 of month 2. None of the women showed any evidence of ovulation during the entire 3 months, although one had intermenstrual spotting. However, felbamate reduced the **gestodene** AUC by 42% and the **ethinylestradiol** AUC by 13%.[1] The reasons for this effect are not understood. What this change means in terms of the reliability of the hormonal contraceptive is not known, but some reduction in its efficacy might be expected. More study is needed to assess the clinical relevance and to see whether other progestogens are similarly affected.

1. Saano V, Glue P, Banfield CR, Reidenberg P, Colucci RD, Meehan JW, Haring P, Radwanski E, Nomeir A, Lin C-C, Jensen PK, Affrime MB. Effects of felbamate on the pharmacokinetics of a low-dose combination oral contraceptive. *Clin Pharmacol Ther* (1995) 58, 523–31.

Combined hormonal contraceptives + Gabapentin

In a controlled study, gabapentin did not alter the levels of ethinylestradiol or norethisterone in women taking an oral combined hormonal contraceptive.

Clinical evidence, mechanism, importance and management

In 13 healthy women taking an oral combined hormonal contraceptive (**ethinylestradiol** 50 micrograms with **norethisterone** 2.5 mg) gabapentin 400 mg every 8 hours for 7 days had no effect on the AUC of **ethinylestradiol** or **norethisterone**. Ovulation suppression was not assessed.[1] On this basis, the UK Faculty of Family Planning and Reproductive Health Care (FFPRHC) Clinical Effectiveness Unit guidelines on the management of hormonal contraceptives and drug interactions lists gabapentin as an antiepileptic that does not induce liver enzymes.[2] No special contraceptive precautions appear to be required during concurrent use.

1. Eldon MA, Underwood BA, Randinitis EJ, Sedman AJ. Gabapentin does not interact with a contraceptive regimen of norethindrone acetate and ethinyl estradiol. *Neurology* (1998) 50, 1146–8.
2. Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit. FFPRHC Guidance: Drug interactions with hormonal contraception. April 2005. Available at: http://www.ffprhc.org.uk/admin/uploads/DrugInteractionsFinal.pdf (accessed 01/02/10).

Combined hormonal contraceptives + Grapefruit juice

Grapefruit juice modestly increases the levels of ethinylestradiol after a single dose. A case report describes a deep vein thrombosis in a woman taking an oral combined hormonal contraceptive, for which grapefruit consumption was suggested as a contributing factor.

Clinical evidence

In 13 healthy young women given a single 50-microgram dose of ethinylestradiol, grapefruit juice increased the mean maximum plasma level and $AUC_{0\text{-}8}$ of **ethinylestradiol** by 37% and 30%, respectively, when compared with a control drink (herb tea). The mean 28% rise in the $AUC_{0\text{-}12}$ was not significant, but there was wide intersubject variation. The subjects drank grapefruit juice 100 mL or herb tea 30 minutes before the **ethinylestradiol**, a further 100 mL with the **ethinylestradiol**, and then 200 mL every 3 hours for 12 hours after taking the **ethinylestradiol**.[1] The herbal tea used was not specified.

A 42-year-old woman who had been taking an oral combined hormonal contraceptive (**ethinylestradiol** with **drospirenone**) for a year and levothyroxine for 4 years developed a deep vein thrombosis in her left leg, consistent with May-Turner syndrome. Three days earlier she had begun an aggressive weight-loss diet including 225 g of grapefruit every morning. Her only other risk factors were a 1.5-hour car journey and factor V Leiden mutation (detected on a subsequent screen). She was only slightly overweight and did not smoke.[2]

Mechanism

It is thought that the increase in ethinylestradiol bioavailability probably occurs because grapefruit juice inhibits the cytochrome P450 isoenzyme CYP3A4, mainly in the intestine, which metabolises ethinylestradiol.[1]

Deep vein thrombosis is a rare adverse effect of combined hormonal contraceptives, the risk of which appears to be higher with higher doses, and with some progestogens and in those with factor V Leiden (a type of thrombophilia). It was suggested that grapefruit may have increased ethinylestradiol levels in this patient, which enhanced hypercoagulability. This, coupled with the stasis of blood flow as a result of compression of the stenosed iliac vein, thought to be caused by hip flexion during the car journey, resulted in an acute thrombosis.[2]

Importance and management

The study suggests that drinking a litre of grapefruit juice over 12 hours might modestly increase ethinylestradiol levels, but the clinical relevance of this is uncertain. Moreover, whether the findings can be directly extrapolated to daily consumption of one glass of grapefruit juice at a similar time to the combined hormonal contraceptive is also uncertain. Further study is needed. The authors suggest that diet may be a factor in the known inter-individual variability of contraceptive steroid levels.[1] It is possible that whole grapefruit consumption may have been a contributing factor in the case of venous thrombosis, but also possible that it was just coincidental as this patient did have several other risk factors. The general relevance of this one case is therefore uncertain.

1. Weber A, Jäger R, Börner A, Klinger G, Vollanth R, Matthey K, Balogh A. Can grapefruit juice influence ethinylestradiol bioavailability? *Contraception* (1996) 53, 41–7.
2. Grande LA, Mendez RD, Krug RT, Verschuyl E-J. Attention—grapefruit! Lancet (2009) 373, 1222.

Combined hormonal contraceptives + Imatinib

A woman taking an oral combined hormonal contraceptive developed gallstones after starting imatinib.

Clinical evidence, mechanism, importance and management

A 31-year-old woman taking a low-dose oral combined hormonal contraceptive developed nausea and abdominal pain after taking imatinib 400 mg daily for 4 months. Ultrasound showed multiple gallstones and increased gallbladder wall thickness. The contraceptive was stopped, and the imatinib temporarily stopped, and the gallstones remained stable in size on periodic monitoring.[1]

Imatinib is an inhibitor of the cytochrome P450 isoenzyme CYP3A4, by which oestrogens are partially metabolised. The authors suggested that an increase in oestrogen levels could possibly lead to increased cholesterol excretion, reduced bile salt excretion and gallstone development. However, this needs confirmation. The clinical relevance of this single case report is unclear.

1. Breccia M, D'Andrea M, Alimena G. Can nifedipine and estrogen interaction with imatinib be responsible for gallbladder stone development? *Eur J Haematol* (2005) 75, 89–90.

Combined hormonal contraceptives + Lacosamide

Lacosamide did not alter the pharmacokinetics of ethinylestradiol and levonorgestrel given as an oral combined hormonal contraceptive. Suppression of ovulation was also unaffected.

Clinical evidence, mechanism, importance and management

In a study in healthy women, the pharmacokinetics of an oral combined hormonal contraceptive (**ethinylestradiol** 30 micrograms with **levonorgestrel** 150 micrograms) were not affected by lacosamide 400 mg daily (except for a minor 20% increase in the **ethinylestradiol** maximum level), and the suppression of ovulation was not altered (there were no changes in progesterone levels).[1,2] These findings indicate that no special or additional precautions are needed if oral contraceptives and lacosamide are used concurrently.

1. Vimpat (Lacosamide). UCB, Inc. US Prescribing information, January 2009.
2. Vimpat (Lacosamide). UCB Pharma Ltd. UK Summary of product characteristics, July 2009.

Combined hormonal contraceptives + Lamotrigine

In one study, lamotrigine for two weeks did not alter the plasma levels of ethinylestradiol and levonorgestrel or the suppression of ovulation in women taking an oral combined hormonal contraceptive. However, another study of six weeks use found a slight reduction in levonorgestrel levels, and some loss in suppression of FSH and LH, but no evidence of ovulation.
Combined hormonal contraceptives reduce the levels of lamotrigine, which can lead to a decrease in seizure control.

Clinical evidence

(a) Contraceptive efficacy

The preliminary results of a study suggested that lamotrigine 150 mg daily for 10 to 14 days had no significant effect on the mean plasma levels of **ethinylestradiol** and **levonorgestrel** in women taking an oral combined hormonal contraceptive (**ethinylestradiol** 30 micrograms with **levonorgestrel** 150 micrograms). No ovulation occurred (assessed by progesterone levels) and no changes in menstrual pattern were observed. Furthermore, lamotrigine did not induce hepatic enzymes (assessed by 6-β-hydroxycortisol excretion).[1] Nevertheless, another study by the manufacturer in 16 healthy women taking an oral combined hormonal contraceptive (**ethinylestradiol** 30 micrograms with **levonorgestrel** 150 micrograms) and given lamotrigine for 6 weeks (titrated to 300 mg daily) found a slight reduction in the AUC and the maximum serum levels of **levonorgestrel** of 19% and 12%, respectively, compared with hormone levels before starting lamotrigine, although this was not statistically significant. The AUC and maximum levels of **ethinylestradiol** were not affected. There was a 4.7-fold increase in FSH and 3.4-fold increase in LH; however, there was no increase in the levels of progesterone, indicating that ovulation did not occur. Intermenstrual bleeding was reported in 32% of subjects when they were taking lamotrigine, and no bleeding was reported when they were not taking lamotrigine.[2]

(b) Lamotrigine efficacy

In 2001, a case series described 6 women with epilepsy in whom lamotrigine plasma levels were decreased by 41 to 64% by an oral combined hormonal contraceptive (**ethinylestradiol** with **desogestrel** or **norethisterone**). Five had increased seizure frequency or recurrence of seizures after starting an oral hormonal contraceptive, and one had lamotrigine adverse effects on stopping the contraceptive.[3] In a subsequent study comparing lamotrigine levels in 22 women taking combined hormonal contraceptives with those in 30 women not taking contraceptives, lamotrigine levels were 54% lower in the women taking contraceptives.[4] Three further similar studies have confirmed this finding of lower levels of lamotrigine in users of oral combined hormonal contraceptives compared with non-users.[5-7] Moreover, other studies in women with epilepsy have found that lamotrigine plasma concentrations varied with combined hormonal contraceptive monthly cycles.[8,9] In one, the median lamotrigine plasma concentration was 15% higher during the hormonal contraceptive washout week than during the phase of hormonal contraceptive intake, although there was a wide interpatient variability.[8] In another, reductions in lamotrigine levels were seen within one to 3 days of starting the combined hormonal contraceptive (oral or vaginal ring), were maximal at 21 days, and increased to within 80 to 100% of baseline levels in the contraceptive-free week.[9]

In a controlled study in 16 healthy women, the maximum serum concentration and AUC of lamotrigine were decreased by about 39% and 52%, respectively while they were taking an oral combined hormonal contraceptive (**ethinylestradiol** 30 micrograms with **levonorgestrel** 150 micrograms) when compared with a 3-week period when they received lamotrigine 300 mg daily alone.[2] Similarly, in a crossover study in 7 women with epilepsy, taking lamotrigine and **ethinylestradiol** 35 micrograms with **norgestimate** 250 micrograms or placebo, lamotrigine plasma levels were 84% higher during the placebo phase, when compared with the oral hormonal contraceptive phase. Three patients experienced seizures while taking the contraceptive; two were given an increased dose of lamotrigine, and one was given clobazam.[10]

In a study in women taking lamotrigine with sodium valproate, lamotrigine dose concentration ratios did not differ between women also taking oral combined hormonal contraceptives (7) and those not taking these (15).[11]

Mechanism

The reason for the slight reduction in levonorgestrel levels with lamotrigine is unknown, and this on its own is unlikely to be clinically important. Nevertheless, the increase in FSH and LH levels and increase in intermenstrual bleeding suggest some reduction in the suppression of ovulation. Ethinylestradiol increases the glucuronidation of lamotrigine, thereby increasing its clearance. This effect is cyclical when combined hormonal contraceptives are taken cyclically (usual practice). It is suggested that, when lamotrigine glucuronidation is strongly inhibited by valproate (see 'Lamotrigine + Valproate', p.620), ethinylestradiol does not appear to have any effect.

Importance and management

The above studies show that there is some concern regarding the efficacy of oral combined hormonal contraceptives while taking lamotrigine, and, in addition, there is good evidence that combined hormonal contraceptives reduce lamotrigine levels and efficacy, in an apparent cyclical manner. Based on the small reduction in levonorgestrel levels, and the rises in FSH and LH, the manufacturer of lamotrigine suggests that the possibility of decreased contraceptive efficacy cannot be ruled out,[12,13] and the UK manufacturer actually advises that the use of non-hormonal contraceptives is preferable.[12] If a hormonal contraceptive is used as the only form of contraception, they advise that women should be alert for signs of breakthrough bleeding, which may be a sign of reduced contraceptive efficacy.[12,13] In 2005, the UK Faculty of Family Planning and Reproductive Health Care (FFPRHC) Clinical Effectiveness Unit issued guidance on the use of lamotrigine in patients taking hormonal contraceptives in response to the UK manufacturer's guidance. They concluded that there is no good evidence that non-hormonal methods of contraception are preferable in patients taking lamotrigine.[14] If an oral combined hormonal contraceptive is used with lamotrigine, the WHO recommend one with at least 30 micrograms of ethinylestradiol.[15]

When combined hormonal contraceptives are started in women already taking lamotrigine (as monotherapy or with other drugs that are *not* strong inducers or inhibitors of lamotrigine glucuronidation), the maintenance dose of lamotrigine may need to be increased by as much as twofold (according to clinical response). If this group of patients stop taking a combined hormonal contraceptive, the lamotrigine dose should be reviewed (and may need to be decreased by as much as 50%) to reduce the risk of adverse effects such as dizziness, ataxia, and diplopia occurring.[12,14] Note that apart from interindividual variations, lamotrigine plasma concentrations vary with the hormonal contraceptive monthly cycle, and this may complicate management (possible adverse effects such as during the hormone-free interval, or possible break-through seizures during the hormone-taking phase). It has been suggested that this cyclical nature of the interaction could be overcome by using a combined hormonal contraceptive continuously without a hormone-free interval.[16]

The situation is probably somewhat different in women already taking lamotrigine with a drug that strongly alters lamotrigine metabolism. In this case, the modest effect of ethinylestradiol is unlikely to be apparent. Therefore, in those already taking lamotrigine with strong inducers of lamotrigine glucuronidation, such as phenytoin and carbamazepine, changes in the dose of lamotrigine are unlikely to be necessary when starting combined hormonal contraceptives. The same appears to be true in those already taking lamotrigine with valproate, which is a strong inhibitor of lamotrigine glucuronidation.

Consider also 'Progestogen-only contraceptives + Lamotrigine', p.1208.

1. Holdich T, Whiteman P, Orme M, Back D, Ward S. Effect of lamotrigine on the pharmacology of the combined oral contraceptive pill. *Epilepsia* (1991) 32 (Suppl 1), 96.
2. Sidhu J, Job S, Singh S, Philipson R. The pharmacokinetic and pharmacodynamic consequences of the co-administration of lamotrigine and a combined oral contraceptive in healthy female subjects. *Br J Clin Pharmacol* (2006) 61, 191–9.
3. Sabers A, Buchholt JM, Uldall P, Hansen EL. Lamotrigine plasma levels reduced by oral contraceptives. *Epilepsy Res* (2001) 47, 151–4.
4. Sabers A, Öhman I, Christensen J, Tomson T. Oral contraceptives reduce lamotrigine plasma levels. *Neurology* (2003) 61, 570–1.
5. Reimers A, Helde G, Brodtkorb E. Ethinyl estradiol, not progestogens, reduces lamotrigine serum concentrations. *Epilepsia* (2005) 46, 1414–17.
6. Öhman I, Luef G, Tomson T. Effects of pregnancy and contraception on lamotrigine disposition: new insights through analysis of lamotrigine metabolites. Seizure (2008) 17, 199–202.
7. Herzog AG, Blum AS, Farina EL, Maestri XE, Newman J, Garcia E, Krishnamurthy KB, Hoch DB, Replansky S, Fowler KM, Smithson SD, Dworetzky BA, Bromfield EB. Valproate and lamotrigine level variation with menstrual cycle phase and oral contraceptive use. Neurology (2009) 72, 911–14.
8. Contin M, Albani F. Ambrosetto G, Avoni P, Bisulli F, Riva R, Tinuper P, Baruzzi A. Variation in lamotrigine plasma concentrations with hormonal contraceptive monthly cycles in patients with epilepsy. *Epilepsia* (2006) 47, 1573–5.
9. Stodieck SRG, Schwenkhagen AM. Lamotrigine plasma levels and combined monophasic oral contraceptives or a contraceptive vaginal ring. A prospective evaluation in 30 women. *Epilepsia* (2004) 45 (Suppl. 7), 187.
10. Christensen J, Petrenaite V, Atterman J, Sidenius P, Öhman I, Tomson T, Sabers A. Oral contraceptives induce lamotrigine metabolism: evidence from a double-blind, placebo-controlled trial. *Epilepsia* (2007) 48, 484–9.
11. Tomson T, Luef G, Sabers A, Pittschieler S, Öhman I. Valproate effects on kinetics of lamotrigine in pregnancy and treatment with oral contraceptives. *Neurology* (2006) 67, 1297–9.
12. Lamictal (Lamotrigine). GlaxoSmithKline UK. UK Summary of product characteristics, October 2009.
13. Lamictal (Lamotrigine). GlaxoSmithKline. US Prescribing information, September 2009.
14. Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit. Faculty statement from the CEU on changes to prescribing information for lamotrigine. August 2005. Available at: http://www.ffprhc.org.uk/admin/uploads/831_lamotrigine.pdf (accessed 01/02/10).
15. Reproductive Health and Research, World Health Organization. Medical eligibility criteria for contraceptive use. 2008 update. Geneva, WHO; 2008. Available at: http://whqlibdoc.who.int/hq/2008/WHO_RHR_08.19_eng.pdf (accessed 01/02/10)
16. Schwenkhagen AM, Stodieck SRG. Which contraception for women with epilepsy? Seizure (2008) 17, 145–50.

Combined hormonal contraceptives + Leflunomide

Leflunomide did not alter the contraceptive activity of an oral combined hormonal contraceptive in one study.

Clinical evidence, mechanism, importance and management

In a study in 32 healthy women taking a oral triphasic hormonal contraceptive (**ethinylestradiol** with **levonorgestrel**) leflunomide 100 mg daily for 3 days, then 20 mg daily for 17 days, did not reduce contraceptive activity (as assessed by progesterone levels). In addition, the pharmacokinetics of the active metabolite of leflunomide (A771726) were as expected, suggesting that the contraceptive steroid had no effect on this metabolite.[1,2] No interaction would therefore be expected.

Note that leflunomide is potentially teratogenic and therefore reliable contraception is required in women of child-bearing age both during and for about 2 years after the use of leflunomide.

1. Arava (Leflunomide). Sanofi-Aventis. UK Summary of product characteristics, September 2009.
2. Sanofi-Aventis. Personal communication. September 2009.

Combined hormonal contraceptives + Leukotriene antagonists

Montelukast and zafirlukast do not alter the pharmacokinetics of contraceptive steroids, and contraceptive activity was not altered by zafirlukast.

Clinical evidence, mechanism, importance and management

(a) Montelukast

The manufacturers of montelukast say that it does not affect the pharmacokinetics of an oral hormonal contraceptive (**ethinylestradiol** 35 micrograms with **norethisterone** 1 mg).[1,2] No special precautions are therefore needed if both drugs are given together.

(b) Zafirlukast

A single-blind, parallel-group study in 39 healthy women taking unnamed oral hormonal contraceptives found that zafirlukast 40 mg twice daily had no effect on the serum levels of **ethinylestradiol** nor on its contraceptive activity.[3] This study suggests that no special precautions are needed if both drugs are given together.

1. Singulair (Montelukast sodium). Merck Sharp & Dohme Ltd. UK Summary of product characteristics, August 2009.
2. Singulair (Montelukast sodium). Merck & Co., Inc. US Prescribing information, August 2009.
3. Accolate (Zafirlukast). AstraZeneca Pharmaceuticals LP. US Prescribing information, August 2009.

Combined hormonal contraceptives + Levetiracetam

Levetiracetam did not alter the plasma levels of ethinylestradiol and levonorgestrel given as an oral combined hormonal contraceptive. Suppression of ovulation was also unaffected.

Clinical evidence, mechanism, importance and management

The pharmacokinetics of an oral combined hormonal contraceptive (**ethinylestradiol** with **levonorgestrel**) were not affected by levetiracetam 500 mg twice daily, nor was the suppression of ovulation altered (there were no changes in LH or progesterone levels). The pharmacokinetics of levetiracetam also remained unaffected.[1] Similarly, in placebo-controlled study in 18 healthy women taking an oral combined hormonal contraceptive (**ethinylestradiol** 30 micrograms with **levonorgestrel** 150 micrograms) with levetiracetam 500 mg twice daily, levetiracetam did not affect the steady-state pharmacokinetics of either steroid, or alter the effect on the suppression of ovulation, as measured by progesterone and LH levels.[2] These findings indicate that no special or additional precautions are needed if these hormonal contraceptives and levetiracetam are used concurrently. Note that the UK Faculty of Family Planning and Reproductive Health Care (FFPRHC) Clinical Effectiveness Unit guidelines on the management of drug interactions with hormonal contraceptives lists levetiracetam as an antiepileptic that does not induce liver enzymes.[3]

1. Giuliano RA, Hiersemenzel R, Baltes E, Johnscher G, Janik F, Weber W. Influence of a new antiepileptic drug (Levetiracetam, ucb L059) on the pharmacokinetics and pharmacodynamics of oral contraceptives. *Epilepsia* (1996) 37, 90.
2. Ragueneau-Majlessi I, Levy RH, Janik F. Levetiracetam does not alter the pharmacokinetics of an oral contraceptive in healthy women. *Epilepsia* (2002) 43, 697–702.
3. Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit. FFPRHC Guidance: Drug interactions with hormonal contraception. April 2005. Available at: http://www.ffprhc.org.uk/admin/uploads/DrugInteractionsFinal.pdf (accessed 01/02/10).

Combined hormonal contraceptives + Maraviroc

Maraviroc did not alter the pharmacokinetics of an oral combined hormonal contraceptive.

Clinical evidence, mechanism, importance and management

In a study in healthy women, maraviroc 100 mg twice daily for 10 days had no effect on the AUC of the contraceptive steroids given as an oral combined hormonal contraceptive (**ethinylestradiol** 30 micrograms with **levonorgestrel** 150 micrograms) daily on days 2 to 8, when compared with a placebo.[1]

This study suggests that maraviroc is unlikely to alter the efficacy of oral combined hormonal contraceptives by a pharmacokinetic mechanism.

1. Abel S, Russell D, Whitlock LA, Ridgway CE, Muirhead GJ. Effect of maraviroc on the pharmacokinetics of midazolam, lamivudine/zidovudine, and ethinyloestradiol/levonorgestrel in healthy volunteers. Br J Clin Pharmacol (2008) 65 (Suppl 1), 19–26.

Combined hormonal contraceptives + Moclobemide

Moclobemide did not alter the effect of an oral combined hormonal contraceptive on the suppression of ovulation.

Clinical evidence, mechanism, importance and management

A study in 7 women taking oral combined hormonal contraceptives found no evidence of any significant alterations in estradiol, progesterone, FSH, or LH levels when they took moclobemide 200 mg three times daily for one cycle. This suggests that ovulation did not occur. No serious adverse reactions occurred. It was considered that the efficacy of the hormonal contraceptive is likely to be maintained during concurrent use.[1]

1. Amrein R, Güntert TW, Dingemanse J, Lorscheid T, Stabl M, Schmid-Burgk W. Interactions of moclobemide with concomitantly administered medication: evidence from pharmacological and clinical studies. *Psychopharmacology (Berl)* (1992) 106, S24–S31.

Combined hormonal contraceptives + Modafinil

Modafinil slightly reduces the levels of ethinylestradiol given as part of an oral combined hormonal contraceptive.

Clinical evidence

In 16 healthy women taking an oral combined hormonal contraceptive (**ethinylestradiol** with **norgestimate**), modafinil 200 mg daily for 7 days followed by 400 mg daily for 21 days decreased the AUC and the maximum plasma levels of **ethinylestradiol** by 18% and 11%, respectively. Increases in plasma FSH and LH were not significant.[1]

Mechanism

Modafinil is an inducer of the cytochrome P450 isoenzyme CYP3A4, which is partially responsible for the metabolism of ethinylestradiol.

Importance and management

The small changes seen in ethinylestradiol levels in the presence of modafinil are lower than those seen with other enzyme inducers known to reduce the reliability of combined hormonal contraceptives (e.g. see

'Combined hormonal contraceptives + Barbiturates or Phenytoin', p.1177). However, it cannot be ruled out that they would be sufficient to cause the failure of combined hormonal contraceptives in very rare cases. As with rufinamide (see 'Combined hormonal contraceptives + Rufinamide', p.1190), it would seem reasonable to avoid the use of contraceptives with a low 20-micrograms dose of ethinylestradiol. However, the UK manufacturer actually recommends that additional or alternative methods of contraception to hormonal contraceptives should be used during and for 2 months after stopping modafinil.[2] The US manufacturer gives similar guidance, but advises that additional or alternative contraceptive methods need only be continued for one month after stopping modafinil.[3] Note that they apply this advice to other forms of hormonal contraception including implants and patches.[3] The UK Faculty of Family Planning and Reproductive Health Care (FFPRHC) Clinical Effectiveness Unit has issued guidance on the use of liver enzyme inducers with hormonal contraceptives, see 'Combined hormonal contraceptives + Barbiturates or Phenytoin', p.1177, for further information.

1. Robertson P, Hellriegel ET, Arora S, Nelson M. Effect of modafinil on the pharmacokinetics of ethinyl estradiol and triazolam in healthy volunteers. *Clin Pharmacol Ther* (2002) 71, 46–56.
2. Provigil (Modafinil). Cephalon (UK) Ltd. UK Summary of product characteristics, November 2009.
3. Provigil (Modafinil). Cephalon, Inc. US Prescribing information, March 2008.

Combined hormonal contraceptives + Mycophenolate

Mycophenolate mofetil does not alter the pharmacokinetics of contraceptive steroids, or the suppression of ovulation, in women given oral combined hormonal contraceptives.

Clinical evidence

The manufacturer says that no pharmacokinetic interaction was seen in a single-dose study in 15 healthy women taking mycophenolate mofetil and *Orthonovum* (**ethinylestradiol** 35 micrograms with **norethisterone** 1 mg).[1]

A study of mycophenolate mofetil 1 g twice daily, given with an oral combined hormonal contraceptive (containing **ethinylestradiol** 20 to 40 micrograms and either **levonorgestrel** 50 to 150 micrograms, **desogestrel** 150 micrograms or **gestodene** 50 to 100 micrograms) over 3 consecutive menstrual cycles in 18 women not previously taking immunosuppressants, found no clinically relevant influence of mycophenolate on the suppression of ovulation by the contraceptives.[2,3] The AUC of **ethinylestradiol** and **desogestrel** were not changed, but the mean **levonorgestrel** AUC was decreased by about 15%. Note that large interpatient variability was seen in AUCs, especially for **ethinylestradiol**.[3]

Mechanism

None.

Importance and management

Mycophenolate mofetil is unlikely to reduce the contraceptive efficacy of oral combined hormonal contraceptives. The small 15% decrease in levonorgestrel levels seen is unlikely to be clinically relevant.

Note that, because mycophenolate is associated with an increased risk of pregnancy loss and of congenital malformations, the manufacturers state that effective contraception must be used before mycophenolate mofetil, during, and for 6 weeks after it has been stopped.[2,3] In this regard, the US manufacturer specifically advises that oral hormonal contraceptives should be used with caution, and additional birth control methods used.[3] Similar advice is given for mycophenolate sodium.[4,5]

1. Syntex. Data on file. A single-dose pharmacokinetic drug interaction study of oral mycophenolate mofetil and an oral contraceptive in normal subjects. (Study No. MYCS2308) 1994.
2. CellCept Tablets (Mycophenolate mofetil). Roche Products Ltd. UK Summary of product characteristics, October 2009.
3. CellCept (Mycophenolate mofetil). Roche Laboratories Inc. US Prescribing information, October 2009.
4. Myfortic (Mycophenolate sodium). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, October 2008.
5. Myfortic (Mycophenolate sodium). Novartis. US Prescribing information, October 2009.

Combined hormonal contraceptives + Nefazodone

A woman experienced increased oral combined hormonal contraceptive adverse effects while taking nefazodone.

Clinical evidence, mechanism, importance and management

Within a week of starting to take nefazodone 50 mg twice daily, a woman taking a low-dose oral combined hormonal contraceptive (**ethinylestradiol** 20 micrograms with **desogestrel** 150 micrograms) reported breast tenderness, bloating, weight gain, and increased premenstrual irritability. She had previously experienced identical symptoms while taking an oral combined hormonal contraceptive with a higher dose of oestrogen. Nefazodone was discontinued after 6 weeks, and within 24 hours the adverse effects resolved.[1] Nefazodone is a known inhibitor of the cytochrome P450 isoenzyme CYP3A4, by which **ethinylestradiol** is metabolised, and might therefore be expected to increase **ethinylestradiol** levels. However, the general importance of this isolated case is unknown. Note that nefazodone has generally been withdrawn due to adverse hepatic effects.

1. Adson DE, Kotlyar M. A probable interaction between a very low-dose oral contraceptive and the antidepressant nefazodone: a case report. *J Clin Psychopharmacol* (2001) 21, 618–19.

Combined hormonal contraceptives + NNRTIs

Nevirapine modestly reduced ethinylestradiol and norethisterone levels from an oral combined hormonal contraceptive. Efavirenz had no effect on ethinylestradiol levels and markedly decreased those of active norgestimate metabolites from an oral combined hormonal contraceptive, while ethinylestradiol had no effect on efavirenz levels. Potential contraceptive failures have been reported in two women taking efavirenz, but a low incidence of contraceptive failure was noted in one study. Etravirine slightly increased ethinylestradiol levels and did not change norethisterone levels or the suppression of ovulation in women taking an oral combined hormonal contraceptive. Delavirdine is predicted to increase ethinylestradiol levels.
Note that whatever other methods of contraception are being used, barrier methods are also advisable to reduce the risk of HIV transmission.

Clinical evidence

(a) Efavirenz

Efavirenz 400 mg daily for 10 days modestly *increased* the AUC of a single dose of **ethinylestradiol** by 37% while the maximum plasma levels remained unchanged. **Ethinylestradiol** had no effect on the AUC or maximum plasma levels of efavirenz.[1] However, in a later multiple dose study in 21 women taking an oral combined hormonal contraceptive (**ethinylestradiol** with **norgestimate**),[2,3] efavirenz 600 mg daily for 14 days had no effect on the AUC of **ethinylestradiol** and markedly *decreased* the AUC of **norelgestromin** (the principal active metabolite of norgestimate) by 64% and that of **levonorgestrel** (a secondary active metabolite) by 83%.

A retrospective review identified 22 women who were prescribed an oral hormonal contraceptive and also received an NNRTI. Two of the 16 women taking efavirenz experienced contraceptive failure. However, medication adherence could not be confirmed.[4]

As part of a 6-month clinical study in West Africa, 548 women received efavirenz with two NRTIs for HIV infection. The percentage of women using contraceptives was 58%, 70%, 77%, 79%, 80% and 80% at each month of the study (about two-thirds were using an **intramuscular progestogen** and one-third an oral **combined hormonal contraceptive**). There were just 7 pregnancies in the study, giving an overall incidence of 2.6/100 person-years.[5] The paper did not mention which, if any, contraceptives these 7 women were using at the time of conception. However, even if all these 7 pregnancies constituted failure of an oral combined hormonal contraceptive, this is still only 7 pregnancies in about 140 women over 6 months. Nevertheless, the authors note that it is possible that these women had low fertility related to their disease, and that fertility might increase over time with effective treatment.[5]

(b) Etravirine

In a study in 16 women taking an oral combined hormonal contraceptive (**ethinylestradiol** 35 micrograms **norethisterone** 1 mg), etravirine 200 mg twice daily from day one to 15 of a cycle increased the AUC of **ethinylestradiol** by 22% and did not change the AUC of **norethisterone**, when compared with a cycle without etravirine. In addition, the suppression of ovulation, as measured by FSH, LH and progesterone levels, was not altered.[6]

(c) Nevirapine

A study in 10 HIV-positive women found that nevirapine 200 mg daily for 2 weeks then twice daily for a further 2 weeks decreased the median AUC and elimination half-life of **ethinylestradiol** by 29% and 31%, respectively, and decreased the median AUC of **norethisterone** by 19%. The women received two single doses of an oral combined hormonal contraceptive (**ethinylestradiol** 35 micrograms with **norethisterone** 1 mg); 2 days before the nevirapine and on the last day of the nevirapine. Nevirapine was added to established antiretroviral therapy (commonly three drugs including nelfinavir or indinavir), which had been unchanged for at least 4 weeks.[7] A retrospective study identified 22 women who were prescribed oral hormonal contraceptives and also received an NNRTI. None of the 6 women taking nevirapine experienced contraceptive failure. However, medication adherence could not be confirmed.[4]

Mechanism

Both efavirenz and nevirapine are established inducers of the cytochrome P450 isoenzyme CYP3A4, by which ethinylestradiol is partially metabolised, and etravirine has also shown CYP3A4 inducing effects. As such they might be expected to modestly decrease contraceptive steroid levels, as has been shown for nevirapine.[7] For efavirenz, the finding of increased ethinylestradiol levels after a single ethinylestradiol dose and no change after multiple dose, is unexpected, but the marked decrease in norgestimate metabolites fits with the enzyme-inducing properties. For etravirine, the finding of a modest increase in ethinylestradiol levels with no change in norethisterone levels is also unexpected, and the mechanism is uncertain.

Importance and management

Although data are limited, the pharmacokinetic interaction with **nevirapine** is as would be predicted. Although it is not known whether these modest reductions in contraceptive levels would reduce the anti-ovulatory efficacy of the oral combined hormonal contraceptive, it would be prudent to assume they could. The manufacturers recommend that oral combined hormonal contraceptives and other hormonal methods of birth control should not be used as the sole method of contraception in women taking nevirapine. They suggest that a barrier method (e.g. condoms) should also be used, and note that this is also advisable to reduce the risk of HIV transmission.[8,9]

The original finding that **efavirenz** increased ethinylestradiol levels (after a single dose) suggested that efavirenz might not adversely alter the efficacy of oral combined hormonal contraceptives. Nevertheless, in a later study in women using these contraceptives, although efavirenz had no effect on ethinylestradiol levels, it did markedly decrease levels of the active metabolites of norgestimate, which suggests that a reduction in the activity of the contraceptive is possible. For a case of failure of the etonogestrel implant, which was attributed to efavirenz, see 'Progestogen-only contraceptives + Enzyme inducers', p.1206. The manufacturer notes that a reliable method of barrier contraception must be used in addition to other methods of contraception such as hormonal contraceptives.[3,10]

Similar advice is given by the Faculty of Family Planning and Reproductive Health Care (FFPRHC) Clinical Effectiveness Unit in the UK, who classify both efavirenz and nevirapine as drugs that can induce liver enzymes and may reduce the levels of ethinylestradiol and progestogens. They therefore recommend that their guidance on hormonal contraceptives and liver enzyme inducers is followed,[11] see 'Combined hormonal contraceptives + Barbiturates or Phenytoin', p.1177 for further detail.

For **etravirine**, based on available data, no reduction in contraceptive efficacy would be expected when using an oral combined hormonal contraceptive containing ethinylestradiol and norethisterone. The slight increase in ethinylestradiol levels (22%) is probably not clinically relevant.

The manufacturer of **delavirdine** notes that it may increase the levels of ethinylestradiol, but further study is needed to confirm and quantify this.[12] Until more is known, some caution is be prudent.

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3. Sustiva Film-coated Tablets (Efavirenz). Bristol-Myers Squibb Pharmaceuticals Ltd. UK Summary of product characteristics, July 2009.
4. Clark RA, Theall K. Population-based study evaluating association between selected antiretroviral therapies and potential oral contraceptive failure. *J Acquir Immune Defic Syndr* (2004) 37, 1219–20.
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7. Mildvan D, Yarrish R, Marshak A, Hutman HW, McDonough M, Lamson M, Robinson P. Pharmacokinetic interaction between nevirapine and ethinyl estradiol/norethindrone when administered concurrently to HIV-infected women. *J Acquir Immune Defic Syndr* (2002) 29, 471–7.
8. Viramune (Nevirapine anhydrate). Boehringer Ingelheim Ltd. UK Summary of product characteristics, May 2009.
9. Viramune (Nevirapine). Boehringer Ingelheim Pharmaceuticals, Inc. US Prescribing information, November 2008.
10. Sustiva (Efavirenz). Bristol-Myers Squibb Company. US Prescribing information, September 2009.
11. Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit. FFPRHC Guidance: Drug interactions with hormonal contraception. April 2005. Available at: http://www.ffprhc.org.uk/admin/uploads/DrugInteractionsFinal.pdf (accessed 01/02/10).
12. Rescriptor (Delavirdine mesylate). Pfizer Inc. US Prescribing information, May 2008.

Combined hormonal contraceptives + Pregabalin

Pregabalin did not affect the pharmacokinetics of the contraceptive steroids or alter the suppression of ovulation in women given ethinylestradiol and norethisterone as an oral combined hormonal contraceptive. In addition, the pharmacokinetics of pregabalin did not appear to be affected by this contraceptive.

Clinical evidence, mechanism, importance and management

In 16 healthy women, pregabalin 200 mg every 8 hours for 21 days had no effect on the steady-state pharmacokinetics of **ethinylestradiol** or **norethisterone** given as an oral combined hormonal contraceptive. In addition, the ovulation suppressant effect of the contraceptive was not reduced, as measured by progesterone levels. The pharmacokinetics of pregabalin did not appear to be affected by the contraceptive.[1] No special precautions therefore appear to be required during concurrent use.

1. Bockbrader HN, Posvar EL, Hunt T, Randinitis EJ. Pharmacokinetics of pregabalin and a concomitantly administered oral contraceptive show no-drug drug interaction. *Epilepsia* (2004) 45 (Suppl 3), 153.

Combined hormonal contraceptives + Protease inhibitors

Ritonavir and nelfinavir, given alone, markedly *reduce* the levels of ethinylestradiol. Ritonavir-boosted protease inhibitors modestly (atazanavir) to markedly (darunavir, fosamprenavir, lopinavir and tipranavir) *reduce* ethinylestradiol levels and this might result in reduced contraceptive efficacy. Conversely, indinavir alone slightly, and atazanavir or amprenavir alone modestly to markedly *increases* the levels of ethinylestradiol and norethisterone.

An oral combined hormonal contraceptive did not affect the levels of amprenavir (derived from fosamprenavir) or saquinavir, and other limited evidence suggests that hormonal contraceptives do not alter antiretroviral activity of HAART (mostly protease-inhibitor based) regimens.

Note that whatever other methods of contraception are being used, barrier methods are also advisable to reduce the risk of HIV transmission.

Clinical evidence

(a) Amprenavir

The UK manufacturer briefly noted that amprenavir *increased* the minimum plasma concentrations of **ethinylestradiol** and **norethisterone**, given as an oral combined hormonal contraceptive, by 32% and 45%, respectively. Conversely, the amprenavir minimum concentration and AUC were *decreased* by 20% and 22%, respectively.[1]

(b) Atazanavir

In a study in 22 healthy women given an oral combined hormonal contraceptive (**ethinylestradiol** with **norethisterone**), atazanavir 400 mg daily for the first 2 weeks of a cycle *increased* the levels of **ethinylestradiol** by 48% and *increased* the AUC of **norethisterone** about twofold (110%).[2] Note that, atazanavir with ritonavir decreased ethinylestradiol levels, see under *Ritonavir-boosted protease inhibitors*, below.

(c) Indinavir

Indinavir 800 mg three times daily given with an oral combined hormonal contraceptive (**ethinylestradiol** 35 micrograms with **norethisterone** 1 mg) for 8 days caused a modest 22% and 26% increase in the AUCs of ethinylestradiol and norethisterone, respectively.[3,4] In a retrospective study there were no reports of contraceptive failure in 9 patients taking indinavir (overall there were 8 contraceptive failures out of 33 women taking protease inhibitors). However, medication adherence could not be confirmed.[5]

(d) Nelfinavir

The manufacturer briefly notes that in women taking an oral combined hormonal contraceptive (**ethinylestradiol** 35 micrograms with **norethisterone** 400 micrograms) for 15 days, nelfinavir 750 mg three times daily for one week *decreased* the AUCs of **ethinylestradiol** and **norethisterone** by 47% and 18%, respectively.[6,7] In a retrospective study, 7 of 21 women taking nelfinavir experienced contraceptive failure, which was the highest rate of failure of the protease inhibitors being taken (overall there were 8 contraceptive failures out of 33 women taking protease inhibitors). However, medication adherence could not be confirmed.[5]

(e) Ritonavir

In a study in 23 healthy women ritonavir 500 mg every 12 hours for 16 days *decreased* the AUC of **ethinylestradiol** by 41% and decreased its elimination half-life from 17 hours to 13 hours. The women received a single dose of an oral combined hormonal contraceptive (**ethinylestradiol** 50 micrograms with **ethynodiol** 1 mg), 14 days before the ritonavir and on day 15 of ritonavir.[8] In a retrospective study there were no reports of contraceptive failure in 6 women taking ritonavir (overall there were 8 contraceptive failures out of 33 women taking protease inhibitors). However, medication adherence could not be confirmed.[5]

(f) Ritonavir-boosted protease inhibitors

1. Atazanavir. The manufacturer notes that when ritonavir-boosted atazanavir 100/300 mg once daily was given with an oral combined hormonal contraceptive (**ethinylestradiol** with **norgestimate**), there was a 19% decrease in the AUC of ethinylestradiol and an 85% increase in the AUC of the active metabolite of norgestimate.[9] This is in contrast to the increase seen after unboosted atazanavir, see *Atazanavir*, above

2. Darunavir. In a study in healthy women taking an oral combined hormonal contraceptive (**ethinylestradiol** with **norethisterone**), ritonavir-boosted darunavir 100/600 mg twice daily for the first 2 weeks of a cycle *decreased* the concentration of **ethinylestradiol** by 44% and *decreased* the AUC of **norethisterone** by 14%.[10]

3. Fosamprenavir. When ritonavir-boosted fosamprenavir 100/700 mg twice daily was given with an oral combined hormonal contraceptive containing **ethinylestradiol** 35 micrograms with **norethisterone** 500 micrograms daily the AUC of ethinylestradiol was *decreased* by 37% and the AUC of norethisterone *decreased* by 34%. The pharmacokinetics of amprenavir (derived from fosamprenavir) were not significantly affected; however, the AUC and maximum level of **ritonavir** were 45% and 63% higher, respectively, compared with historical data in female subjects taking fosamprenavir and ritonavir alone.[11] In this study, clinically significant increases in liver transaminases occurred in some healthy subjects.[11]

4. Lopinavir. A study in 12 healthy subjects found that ritonavir-boosted lopinavir 100/400 mg twice daily for 14 days *decreased* the AUC of **ethinylestradiol** and **norethisterone** (given as an oral combined hormonal contraceptive for 21 days) by 42% and 17%, respectively.[12]

5. Tipranavir. Ritonavir-boosted tipranavir 100/500 mg twice daily or 200/750 mg twice daily for 10 days *decreased* the AUC and maximum level of **ethinylestradiol** by about 50%, but did not significantly alter the pharmacokinetics of **norethisterone** given as a single dose of an oral combined hormonal contraceptive.[13,14] In this study, 33% of women developed a rash, which is a higher incidence than is usually seen with ritonavir-boosted tipranavir.[13]

(g) Saquinavir

A study in 8 healthy women found that the pharmacokinetics of a single 600-mg dose of saquinavir were not affected by an oral combined hormonal contraceptive containing **ethinylestradiol** 30 micrograms with **gestodene** 75 micrograms taken for 21 days.[15] In a retrospective study there was one report of contraceptive failure out of 5 women taking saquinavir (overall there were 8 contraceptive failures out of 33 women taking protease inhibitors). However, medication adherence could not be confirmed.[5]

Mechanism

Ritonavir more commonly *inhibits* the cytochrome P450 isoenzyme CYP3A4 and the results for ritonavir are the opposite of those originally predicted based on *in vitro* data showing *inhibition* of ethinylestradiol metabolism (by cytochrome P450 subfamily CYP3A-mediated 2-hydroxylation).[16] However, ethinylestradiol is also substantially metabolised by conjugation, and the clinical findings suggest that ritonavir induces glucuronosyltransferase (UGT) activity, thereby reducing ethinylestradiol levels.[8] Nelfinavir probably interacts similarly. The effect of ritonavir appears so strong that it is apparent with all ritonavir-boosted protease inhibitors studied (atazanavir, darunavir, fosamprenavir, lopinavir and tipranavir). Atazanavir alone may increase ethinylestradiol levels by inhibition of UGT.[17] Indinavir also slightly increases contraceptive steroid levels.

Importance and management

The pharmacokinetic interaction between the ethinylestradiol component of combined hormonal contraceptives and nelfinavir or ritonavir and all ritonavir-boosted protease inhibitors (atazanavir, darunavir, fosamprenavir, lopinavir and tipranavir) appears to be established and is likely to be clinically important. Similar *decreases* in the plasma levels of ethinylestradiol caused by other drugs have resulted in reduced efficacy and reliability of oral combined hormonal contraceptives, and one retrospective report suggests that this has occurred with nelfinavir.[5] If ritonavir (including all ritonavir-boosted protease inhibitors) or nelfinavir are being used would seem prudent to follow similar guidance to that used for other enzyme-inducing drugs, see 'Combined hormonal contraceptives + Barbiturates or Phenytoin', p.1177. Note that guidance from the WHO states that when an oral combined hormonal contraceptive is chosen, a preparation containing a minimum of 30 micrograms of ethinylestradiol should be used.[18] Also, whatever other methods of contraception are being used, barrier methods are always advisable to reduce the risk of HIV transmission, and the WHO notes that this will also compensate for any reduction in the effectiveness of the contraceptive.[18] With atazanavir and amprenavir, in the instances these are used *without ritonavir*, the marked increase in norethisterone and ethinylestradiol levels suggest some caution is appropriate. The US manufacturer of atazanavir recommends that an oral combined hormonal contraceptive with no more than 30 micrograms of ethinylestradiol be used,[9] whereas the UK manufacturer of atazanavir recommends avoiding oral hormonal contraceptives.[17] Note that the increases in contraceptive steroid levels with indinavir alone are unlikely to be clinically relevant.

The manufacturers of tipranavir specifically note that women using oestrogens with tipranavir may also have an increased risk of non-serious rash.[13,14]

Amprenavir levels are decreased by combined hormonal contraceptives, but the effects are modest. There is some evidence to suggest that hormonal contraceptives (including oral combined hormonal contraceptives) do not alter the antiretroviral efficacy of HAART (mostly protease-inhibitor based),[19] but evidence is preliminary and more study is needed.

1. Agenerase (Amprenavir). GlaxoSmithKline UK. UK Summary of product characteristics, February 2007.
2. Tackett D, Child M, Agarwala S, Geiger M, Geraldes M, Laura B, O'Mara E. Atazanavir: A summary of two pharmacokinetic drug interaction studies in healthy subjects. 10th Conference on Retroviruses and Opportunistic Infections, Boston, MA, 2003, abstract 543.
3. Crixivan (Indinavir sulphate). Merck Sharp & Dohme Ltd. UK Summary of product characteristics, October 2008.

4. Crixivan (Indinavir sulfate). Merck & Co., Inc. US Prescribing information, October 2009.
5. Clark RA, Theall K. Population-based study evaluating association between selected antiretroviral therapies and potential oral contraceptive failure. *J Acquir Immune Defic Syndr* (2004) 37, 1219–20.
6. Viracept (Nelfinavir mesilate). Roche Products Ltd. UK Summary of product characteristics, July 2008.
7. Viracept (Nelfinavir mesylate). Agouron Pharmaceuticals, Inc. US Prescribing information, September 2008.
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9. Reyataz (Atazanavir sulfate). Bristol-Myers Squibb. US Prescribing information, November 2009.
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11. Telzir (Fosamprenavir calcium). ViiV Healthcare UK Ltd. UK Summary of product characteristics, May 2009.
12. Bertz R, Hsu A, Lam W, Williams L, Renz C, Karol M, Dutta S, Carr R, Zhang Y, Wang Q, Schweitzer S, Foit C, Andre A, Bernstein B, Granneman GR, Sun E. Pharmacokinetic interaction between lopinavir/ritonavir (ABT-378r) and other non-HIV drugs (P291). *AIDS* (2000) 14 (Suppl 4), S100.
13. Aptivus Soft Capsules (Tipranavir). Boehringer Ingelheim Ltd. UK Summary of product characteristics, June 2009.
14. Aptivus (Tipranavir). Boehringer Ingelheim Pharmaceuticals, Inc. US Prescribing information, June 2009.
15. Fröhlich M, Burhenne J, Martin-Facklam M, Weiss J, von Wolff M, Strowitzki T, Walter-Sack I, Haefeli WE. Oral contraception does not alter single dose saquinavir pharmacokinetics in women. *Br J Clin Pharmacol* (2004) 57, 244–52.
16. Kumar GN, Rodrigues AD, Buko AM, Denissen JF. Cytochrome P450-mediated metabolism of the HIV-1 protease inhibitor ritonavir (ABT-538) in human liver microsomes. *J Pharmacol Exp Ther* (1996) 277, 423–31.
17. Reyataz (Atazanavir sulfate). Bristol-Myers Squibb Pharmaceuticals Ltd. UK Summary of product characteristics, July 2009.
18. World Health Organization. Medical eligibility criteria for contraceptive use. 2008 update. Available at: http://whqlibdoc.who.int/hq/2008/WHO_RHR_08.19_eng.pdf (accessed 01/02/10).
19. Chu JH, Gange SJ, Anastos K, Minkoff H, Cejtin H, Bacon M, Levine A, Greenblatt RM. Hormonal contraceptive use and the effectiveness of highly active antiretroviral therapy. *Am J Epidemiol* (2005) 161, 881–90.

Combined hormonal contraceptives + Remacemide

Remacemide appears not to interact with oral combined hormonal contraceptives.

Clinical evidence, mechanism, importance and management

The preliminary results of a study suggested that remacemide 200 mg twice daily for 14 days had no effect on the pharmacokinetics of **ethinylestradiol**, **desogestrel**, or **levonorgestrel**, when compared with placebo, in women taking an oral combined hormonal contraceptive (**ethinylestradiol** 30 micrograms with **levonorgestrel** 150 micrograms or **desogestrel** 150 micrograms). Inhibition of ovulation was maintained (assessed by measurement of progesterone, FSH, and LH levels).[1] It appears that no special contraceptive precautions are needed during concurrent use.

1. Blakey GE, Lockton JA, Corfield J, Oliver SD, Back D. Absence of interaction of remacemide with oral contraceptives. *Epilepsia* (1999) 40 (Suppl 2), 95.

Combined hormonal contraceptives + Retigabine

Retigabine did not alter the plasma levels of ethinylestradiol or norgestrel given as an oral combined hormonal contraceptive.

Clinical evidence, mechanism, importance and management

The preliminary results of a study suggested that retigabine 150 mg three times daily from day 10 to 13 of a cycle had no effect on the pharmacokinetics of **ethinylestradiol** or **norgestrel** in women taking an oral combined hormonal contraceptive (**ethinylestradiol** 30 micrograms with **norgestrel** 300 micrograms).[1] This suggests that no special contraceptive precautions are needed during concurrent use.

1. Paul J, Ferron GM, Richards L, Getsy J, Troy SM. Retigabine does not alter the pharmacokinetics of a low-dose oral contraceptive in women. *Neurology* (2001) 56 (Suppl 3), A335–A336.

Combined hormonal contraceptives + Rifamycins

Combined hormonal contraceptives are less reliable during treatment with rifampicin (rifampin). Breakthrough bleeding and spotting commonly occur, and pregnancy may not be prevented. Rifabutin also reduces the reliability of combined hormonal contraceptives, although it interacts to a lesser extent. Oral rifaximin appears not to alter the pharmacokinetics of contraceptive steroids.

Clinical evidence

(a) Rifabutin

In two studies, rifabutin 300 mg daily for just 10 or 14 days reduced the plasma levels of **ethinylestradiol** and **norethisterone** in women taking an oral combined hormonal contraceptive, but to about half the extent of rifampicin (rifampin). The AUC for **ethinylestradiol** decreased by about 35% in both studies, and the AUC of **norethisterone** decreased by 17%. In one study, spotting occurred in 21.7% of women when they took rifabutin (compared with 3.7% in the control cycle and 36% with rifampicin).[1] Ovulation did not occur with rifabutin or rifampicin in either study,[1,2] although in one study an increase in FSH and LH occurred with rifabutin, which was less than that seen with rifampicin.[1] It is probable that use of rifabutin long term would have a greater effect on ovulation parameters, as contraceptive steroid levels would be reduced for the whole cycle.

(b) Rifampicin (Rifampin)

1. Estradiol-containing contraceptives. In one controlled study in 16 postmenopausal women given an oral combined hormonal contraceptive (**estradiol** valerate 2 mg with **dienogest** 3 mg) for 17 days, rifampicin 600 mg daily for 5 days from day 12 to 16 decreased the steady-state AUC of **estradiol** by 44% and that of **dienogest** by 83%.[3,4]

2. Ethinylestradiol-containing contraceptives. A report in 1971 noted a marked increase in the frequency of intermenstrual breakthrough bleeding (regarded as loss of reliability of the contraceptive) in women taking an oral combined hormonal contraceptive and rifampicin.[5] In a later report by the same researchers, 62 out of 88 women taking an oral combined hormonal contraceptive had menstrual cycle disorders of various kinds (spotting, bleeding, failure to menstruate) while taking a rifampicin-based regimen for tuberculosis, compared with only one of 26 given a streptomycin-based regimen. In addition, 5 pregnancies occurred in women taking the rifampicin-based regimen.[6,7] Other case reports have confirmed this interaction, and there have been a total of at least 11 other pregnancies reported.[8-15] Oral combined hormonal contraceptives commonly mentioned in these reports include **ethinylestradiol** with **norgestrel** or **norethisterone**.[9,11-15]

There are four pharmacodynamic studies of the effects of rifampicin on oral combined hormonal contraceptives that assessed measures of ovulation (FSH, LH, progesterone),[1,2,16,17] three of which also assessed the contraceptive steroid pharmacokinetics.[1,2,17] One of these found that 11 out of 21 women taking an oral triphasic hormonal contraceptive (**ethinylestradiol** 30 to 40 micrograms with **levonorgestrel** 50 to 125 micrograms) ovulated (assessed by increased progesterone levels of above 10 nanomol/L and presence of a follicle) while taking rifampicin 300 mg daily for 21 days, and 8 had intermenstrual bleeding.[16] Similarly, in another study, 2 out of 7 women taking an oral combined hormonal contraceptive (**ethinylestradiol** 30 micrograms with **norethisterone** 1 mg) ovulated one month after starting rifampicin 8 to 10 mg/kg as part of an antimycobacterial regimen (started on day 23 of a cycle and ovulation assessed on day 19 to 23 of the next cycle). In addition, rifampicin reduced the AUC of **norethisterone** by 30% and that of **ethinylestradiol** by 12% (which was not statistically significant), although there was wide variation.[17] Conversely, two other well-controlled studies did not detect ovulation in 34 women taking an oral combined hormonal contraceptive (**ethinylestradiol** 35 micrograms with **norethisterone** 1 mg) and rifampicin 300 or 600 mg daily,[1,2] although in these studies, the rifampicin was given for just 10 or 14 days from day 1 or day 7 of the cycle. Nevertheless, both studies reported some increase in LH and FSH levels with rifampicin, and an increased incidence of spotting was noted in one of these studies (36% versus 3.7% in the control cycle).[1] Furthermore, both of these studies found that rifampicin 300 mg daily for 10 days or 600 mg daily for 14 days reduced the AUCs of **ethinylestradiol** and **norethister-**

one by about 63% and 55%, respectively. These pharmacokinetic results confirm the findings of earlier studies using single doses of contraceptive steroids.[18,19]

Rifampicin plasma levels[20] and efficacy[5] are reported to be unchanged by oral combined hormonal contraceptives.

(c) Rifaximin

In a crossover study in 26 healthy women, rifaximin 200 mg every 8 hours for 3 days had no effect on the pharmacokinetics of **ethinylestradiol**, **norgestrel** or **deacetylnorgestimate** after administration of a single dose of two tablets of an oral combined hormonal contraceptive (**ethinylestradiol** 35 micrograms with **norgestimate** 250 micrograms).[21]

Mechanism

Rifampicin (rifampin) is a potent non-specific enzyme inducer, which has been shown to increase the hydroxylation of ethinylestradiol fourfold in an *in vitro* study,[22,23] and twofold in an *in vivo* study.[24] Another study found that the metabolism of ethinylestradiol derived from mestranol was similarly affected.[25] As a result, the reduced steroid levels may be insufficient to prevent the re-establishment of a normal menstrual cycle with ovulation, which would explain the breakthrough bleeding and pregnancies that have occurred. Rifabutin similarly acts as an enzyme inducer, but it is less potent than rifampicin (about half as potent in reducing contraceptive steroid levels).[2] Rifaximin is also an inducer of cytochrome P450 isoenzymes, but its oral absorption is negligible (0.4%) and it therefore appears to have no effect on the metabolism of the contraceptive steroids.

Importance and management

The interaction between the oral combined hormonal contraceptives and **rifampicin** is well documented, well established and clinically important. Menstrual cycle disturbances of 36 to 70%,[1,5,6] and an ovulation rate of 29 to 52% when used for 21 days or more[16,17] show very clearly that women receiving oral combined hormonal contraceptives should use an alternative or additional form of contraception while taking rifampicin, and for 4 to 8 weeks after its withdrawal.[26,27] This would equally well able to other forms of combined hormonal contraceptives.

Direct information about the interaction between oral combined hormonal contraceptives and **rifabutin** seems to be limited to the pharmacodynamic studies cited, but it is supported by the well-recognised enzyme-inducing properties of rifabutin. It would clearly be prudent for women receiving rifabutin to take the same precautions as with rifampicin, although the risks are probably somewhat lower because rifabutin is a less potent enzyme inducer.

Oral **rifaximin** appears not to alter the pharmacokinetics of contraceptive steroids and would therefore not be expected to alter contraceptive efficacy.

See also 'Progestogen-only contraceptives + Enzyme inducers', p.1206.

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Combined hormonal contraceptives + Rotigotine

The manufacturer notes that the pharmacodynamics and pharmacokinetics of oral contraceptives containing ethinylestradiol 30 micrograms and levonorgestrel 150 micrograms were unaltered by the use of rotigotine 3 mg/24 hours.[1]

1. Neupro (Rotigotine). UCB Pharma Ltd. UK Summary of product characteristics, August 2009.

Combined hormonal contraceptives + Rufinamide

Rufinamide caused a modest decrease in the plasma levels of ethinylestradiol and norethisterone given as an oral combined hormonal contraceptive.

Clinical evidence, mechanism, importance and management

The preliminary results of a study in 18 healthy women taking an oral combined hormonal contraceptive suggest that rufinamide 800 mg twice daily for 14 days from day 22 of cycle one to day 7 of cycle two decreased the AUC of **ethinylestradiol** 35 micrograms by 22% and of **norethisterone** 1 mg by 14% measured on day 7 of cycle two. Inhibition of ovulation was not assessed.[1]

Rufinamide is a weak inducer of the cytochrome P450 isoenzyme CYP3A4,[2] by which the contraceptive steroids are metabolised.

These small reductions in plasma levels of the contraceptive hormones are similar to those seen with high-dose topiramate (see 'Combined hormonal contraceptives + Topiramate', p.1193) and less than those seen with carbamazepine (see 'Combined hormonal contraceptives + Carbamazepine or Oxcarbazepine', p.1180), and their clinical relevance is unknown. However, given these findings, low-dose contraceptives (**ethinylestradiol** 20 micrograms) should probably be considered unsuitable for use with rufinamide. Note that the UK manufacturer advises that the prescriber should use clinical judgement when assessing whether oral hormonal contraceptives, or the doses of the contraceptive steroid components, are adequate based on the individual patients clinical situation,[2] whereas the US manufacturer recommends that additional non-hormonal methods of contraception are used.[3] Further study is needed.

1. Svendsen KD, Choi L, Chen B-L, Karolchyk MA. Single-center, open-label, multiple-dose pharmacokinetic trial investigating the effect of rufinamide administration on Ortho-Novum 1/35 in healthy women. *Epilepsia* (1998) 39 (Suppl 6), 59.
2. Inovelon (Rufinamide). Eisai Ltd. UK Summary of product characteristics, October 2009.
3. Banzel (Rufinamide). Eisai Inc. US Prescribing information, November 2008.

Combined hormonal contraceptives + Sirolimus

Sirolimus did not alter the pharmacokinetics of a single dose of an oral combined hormonal contraceptive.

Clinical evidence, mechanism, importance and management

A single-dose study found that the pharmacokinetics of an oral combined hormonal contraceptive (**ethinylestradiol** 30 micrograms with **norgestrel** 300 micrograms) were unaffected by sirolimus,[1,2] and sirolimus whole blood exposure was unaffected by the contraceptive.[2] This suggests that the efficacy of the contraceptive is unlikely to be changed by sirolimus. Nevertheless, the UK manufacturer cautiously points out that the effects of long-term sirolimus on oral contraception are unknown.[1] Effective contraception is advised during the use of sirolimus, and for 12 weeks after sirolimus is stopped, because its effects on the foetus are uncertain.

1. Rapamune (Sirolimus). Wyeth Pharmaceuticals. UK Summary of product characteristics, April 2009.
2. Zimmerman JJ. Exposure-response relationships and drug interactions of sirolimus. *AAPS J* (2004) 6, e28.

Combined hormonal contraceptives + Spermicides

Nonoxinol-9 had no effect on the absorption of contraceptive steroids from the combined hormonal contraceptive vaginal ring.

Clinical evidence, mechanism, importance and management

In a placebo-controlled study in healthy women using the combined hormonal contraceptive vaginal ring (**ethinylestradiol** with **etonogestrel**), a single dose of a vaginal gel spermicide (4% **nonoxinol-9**) given on day 8 of a cycle had no effect on the AUC of **ethinylestradiol** or **etonogestrel** measured over three time periods (day 8 to 9, day 8 to 10 and day 8 to 21).[1]

This study suggests that **nonoxinol-9** is unlikely to alter the efficacy of the combined hormonal contraceptive ring.

1. Haring T, Mulders TMT. The combined contraceptive ring NuvaRing® and spermicide comedication. *Contraception* (2003) 67, 271–2.

Combined hormonal contraceptives + St John's wort (*Hypericum perforatum*)

St John's wort may slightly reduce the levels of desogestrel, ethinylestradiol, and norethisterone from oral combined hormonal contraceptives, although there is some evidence that an extract with low hyperforin may not interact. Both breakthrough bleeding and, more rarely, contraceptive failure have been reported in women also taking St John's wort.

Clinical evidence

(a) Controlled studies

1. Hypericin 0.3%. A study in 17 healthy women taking **ethinylestradiol** 20 micrograms with **desogestrel** 150 micrograms daily found that St John's wort (300 mg two or three times daily) did not affect the AUC or maximum levels of **ethinylestradiol**. However, the AUC and maximum levels of the active metabolite of **desogestrel** were significantly decreased, by about 40% and 20%, respectively. There was no evidence that ovulation occurred. However, the frequency of breakthrough bleeding increased significantly from 35% to around 80%.The St John's wort preparation (*Jarsin*) in this study contained a methanolic extract (LI160).[1]
Similarly, another study in 12 healthy women taking **ethinylestradiol** 35 micrograms with **norethisterone** 1 mg found that St John's wort 300 mg three times daily for 8 weeks caused some changes to the pharmacokinetics of the contraceptive steroids, but the only statistically significant changes were a 15% increase in the oral clearance of **norethisterone** and a 48% reduction in the half-life of **ethinylestradiol**. Nevertheless, no ovulation occurred, as indicated by unaffected serum levels of LH, FSH and progesterone. However there was an increase in breakthrough bleeding (7 subjects reported breakthrough bleeding while taking St John's wort compared with 2 in the control phase). A sample of the St John's wort capsules in this study (Rexall-Sundown Pharmaceuticals) were analysed and found to contain 0.37% hypericin and 3% hyperforin.[2] Furthermore, a crossover study in 16 subjects also found small reductions in the levels of low-dose **ethinylestradiol** 20 micrograms with **norethisterone** 1 mg (median reductions in AUC of 16% and 13%, respectively) while they were taking St John's wort 300 mg three times daily. Furthermore, they found increased progesterone levels of more than 3 nanograms/mL (an indication that ovulation occurred) in 3 patients while taking St John's wort compared with one subject while taking placebo. The incidence of breakthrough bleeding was also increased (56% versus 31%). This study also used an alcoholic St John's Wort extract standardised to 0.3% hypericin, which contained 3.7% hyperforin.[3] In a secondary analysis of this study, the anti-androgenic effects of **ethinylestradiol** with **norethisterone**, utilised in the treatment of hirsutism and acne, were not significantly affected by St John's wort.[4]

2. Hypericin 0.2% with low hyperforin. In a study, 16 healthy women who took **ethinylestradiol** 20 micrograms with **desogestrel** 150 micrograms daily on days one to 21 of a 28 day cycle were given an extract of St John's wort with a low hyperforin content of less than 0.2%, (Ze117, standardised to 0.2% hypericin), 250 mg twice daily on days 7 to 21. In contrast to the studies above, the AUCs of **ethinylestradiol** and the active metabolite of **desogestrel** were not significantly altered by St John's wort. None of the women experienced any breakthrough bleeding or spotting, and measurements of plasma hormone levels indicated that the contraceptive efficacy was unchanged.[5] However, this study would have been more conclusive if the extract had been given for a whole cycle and the pharmacokinetics of the steroids had been compared on the same day of each cycle.

(b) Contraceptive failure and breakthrough bleeding

Controlled studies have found that the frequency of breakthrough bleeding in women taking combined hormonal contraceptives increased significantly when St John's wort was taken, see under *Hypericin 0.3%*, above.

The Adverse Drug Reactions Database of the Swedish Medical Products Agency has on record 2 cases of pregnancy due to the failure of an oral combined hormonal contraceptive, which was attributed to the use of products containing St John's wort (*Esbericum* and *Kira*). One woman was taking **ethinylestradiol** and **norethisterone** and the other was taking **ethinylestradiol** and **levonorgestrel**.[6] This follows an earlier report from the Swedish Medical Products Agency of 8 cases of breakthrough bleeding in women aged 23 to 31 years taking long-term oral hormonal contraceptives and St John's wort. Breakthrough bleeding occurred within about a week of starting St John's wort in 5 of the cases, and was known to have resolved in 3 cases when the St John's wort was stopped.[7]

The CSM in the UK has on record a further 7 cases of pregnancy in women taking St John's wort and oral hormonal contraceptives in the 2-year period from February 2000 to February 2002.[8] Six of these women were taking oral combined hormonal contraceptives (**ethinylestradiol** with **desogestrel**, **levonorgestrel**, **norethisterone** or **norgestimate**), generally for at least 7 months before starting St John's wort. Preparations were standard dose in 5 cases (**ethinylestradiol** 30 or 35 micrograms) and low dose (20 micrograms) in one case. The unplanned pregnancies occurred after they had been taking the St John's wort for on average about 4 months (one to 9 months).[9] Another earlier brief report describes 3 women taking an oral combined hormonal contraceptive (**ethinylestradiol** 30 micrograms with **desogestrel** 150 micrograms) who developed breakthrough bleeding one week (2 cases) and 3 months (one case) after starting to take St John's wort.[10] A single case of pregnancy has also been reported in a patient taking St John's wort and **ethinylestradiol** with **dienogest**.[11] The German Federal Institute for Drugs and Medical Devices has received a total of 8 case reports of contraceptive failure in women also taking St John's wort.[12]

Mechanism

St John's wort can modestly induce the metabolism of the contraceptive steroids by the cytochrome P450 isoenzyme [CYP3A4], thereby reducing their serum levels and their effects.[7,10,13] This can lead to breakthrough bleeding and, in some cases, contraceptive failure. This is consistent with the way St John's wort appears to lower the serum levels of some other drugs. Note that St John's wort is a herbal preparation, and the specific constituents responsible for enzyme induction are currently unknown, although there is some evidence that hyperforin may be responsible. Also, the levels of individual constituents can vary between different preparations of the herb.

Importance and management

The interaction between hormonal contraceptives and St John's wort is established, although the effect on contraceptive steroid levels appears to be slight, and therefore probably not relevant in many women. Its incidence is not known but the evidence so far suggests that breakthrough bleeding may be a problem (and may be a sign of reduced efficacy), although pregnancy resulting from this interaction appears to be uncommon. However, as it is not known which patients are particularly likely to be at risk, women taking oral hormonal contraceptives should either avoid St John's wort (the recommendation of the CSM/MCA and the FFPRHC in the UK[13,14]) or follow the advice given for other enzyme-inducing drugs, see 'Combined hormonal contraceptives + Barbiturates or Phenytoin', p.1177, for details of this guidance. Given that there are many established antidepressants that do not interact with contraceptives, this would seem prudent advice. Note that the combined hormonal contraceptive patch and vaginal ring may also be affected.

Although the considerable worldwide popularity of St John's wort is fairly recent, its use has been widespread in Germany and has been used for very many years in both Germany and Austria. Nevertheless, there seems to be no published evidence that oral hormonal contraceptive failure in those countries is more frequent than anywhere else. This would seem to confirm that contraceptive failure leading to pregnancy occurring as a result of this interaction is very uncommon, although it is always possible that it has failed to be identified as a possible cause. Further study is needed to confirm whether St John's wort extracts with a low hyperforin content (0.2% as opposed to about 3%) do not interact with contraceptives, as these may be an alternative.

1. Pfrunder A, Schiesser M, Gerber S, Haschke M, Bitzer J, Drewe J. Interaction of St John's wort with low-dose oral contraceptive therapy: a randomized controlled trial. *Br J Clin Pharmacol* (2003) 56, 683–90.
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4. Fogle RH, Murphy PA, Westhoff CL, Stanczyk FZ. Does St. John's Wort interfere with the antiandrogenic effect of oral contraceptive pills? *Contraception* (2006) 74, 245–8.
5. Will-Shahab L, Bauer S, Kunter U, Roots I, Brattström A. St John's wort extract (Ze 117) does not alter the pharmacokinetics of a low-dose oral contraceptive. Eur J Clin Pharmacol (2009) 65, 287–94. Erratum: *ibid.* 541.
6. Swedish Medical Products Agency. St John's wort may influence other medication. Data on file, 2002.
7. Yue Q-Y, Bergquist C, Gerdén B. Safety of St John's wort (Hypericum perforatum). *Lancet* (2000) 355, 576–7.
8. Committee on Safety of Medicines. Personal communication, February 15th, 2002.
9. Henderson L, Yue QY, Bergquist C, Gerden B, Arlett P. St John's wort Hypericum perforatum): drug interactions and clinical outcomes. *Br J Clin Pharmacol* (2002) 54, 349–56.
10. Bon S, Hartmann K, Kuhn M. Johanniskraut: Ein Enzyminduktor? *Schweiz Apothekerzeitung* (1999) 16, 535–6.
11. Schwarz UI, Büschel B, Kirch W. Unwanted pregnancy on self-medication with St John's wort despite hormonal contraception. *Br J Clin Pharmacol* (2003) 55, 112–13.
12. Bundesinstitut für Arzneimittel und Medizinprodukte. Personal communication, March 2007.
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14. Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit. FFPRHC Guidance: Drug interactions with hormonal contraception. April 2005. Available at: http://www.ffprhc.org.uk/admin/uploads/DrugInteractionsFinal.pdf (accessed 01/02/10).

Combined hormonal contraceptives + Statins

Atorvastatin and rosuvastatin may modestly increase the plasma levels of oral combined hormonal contraceptives. Rosuvastatin pharmacokinetics and lipid-lowering effects were unaffected by an oral contraceptive containing ethinylestradiol and norgestimate. The pharmacokinetics of a single dose of pravastatin were also unaffected by oral combined hormonal contraceptives. Lovastatin and simvastatin prevented some of the adverse effects of oral combined hormonal contraceptives on lipids.

Clinical evidence

(a) Atorvastatin

A study in 12 healthy women taking an oral combined hormonal contraceptive (**ethinylestradiol** 35 micrograms with **norethisterone** 1 mg) found that atorvastatin 40 mg daily increased the AUC of **ethinylestradiol** and **norethisterone** by about 19% and 28%, respectively.[1]

(b) Lovastatin

Sixty women were randomised to receive an oral triphasic combined hormonal contraceptive (**ethinylestradiol** 30 to 40 micrograms with **levonorgestrel** 50 to 125 micrograms) alone or with lovastatin 20 mg daily for 3 months. Serum triglycerides increased in those receiving the contraceptive alone (from 90 to 157 mg/dL), but showed little change in those also receiving the lovastatin (105 to 113 mg/dL). LDL-cholesterol did not change in those given the contraceptive alone, but decreased (effect not statistically significant) in those also receiving lovastatin.[2]

(c) Pravastatin

The pharmacokinetics of a single 20-mg dose of pravastatin were found to be unaffected in 15 young women taking oral combined hormonal contraceptives (**ethinylestradiol** with **norethisterone**, **norgestrel** or **levonorgestrel**), when compared with similar women not taking contraceptives. No adverse effects attributable to concurrent use were seen.[3]

(d) Rosuvastatin

In a non-randomised study in 18 healthy women taking an oral triphasic combined hormonal contraceptive (**ethinylestradiol** 35 micrograms with **norgestimate** 180 to 250 micrograms), the addition of rosuvastatin 40 mg daily increased the AUC of **ethinylestradiol** by 26% and increased that of norgestrel, an active metabolite of norgestimate, by 34%. The contraceptive activity was unchanged as measured by FSH, LH and progesterone levels.[4] The pharmacokinetics and lipid-lowering effects of rosuvastatin were also unaffected.[4]

(e) Simvastatin

In a crossover study, 48 women with polycystic ovary syndrome received an oral combined hormonal contraceptive (**ethinylestradiol** 20 micrograms with **desogestrel** 150 micrograms) alone for 12 weeks and with simvastatin 20 mg daily for 12 weeks. Simvastatin prevented the contraceptive-induced 20% increase in triglycerides, and decreased LDL-cholesterol (the contraceptive alone increased this).[5] The effects of simvastatin alone were not assessed in this study, so it is not possible to say whether the contraceptive attenuated any of the benefits of simvastatin.

Mechanism

It is not known why atorvastatin and rosuvastatin increase levels of the contraceptive steroids.

Oral combined hormonal contraceptives are known to be associated with some adverse effects on plasma lipids, which can depend on the progestogen used. Oral contraceptives containing an androgenic progestogen probably have the greatest effects whereas non-androgenic (third generation) progestogen (e.g. desogestrel, gestodene, norgestimate) have less detrimental effects on lipids. Statins appear to attenuate some of the adverse effects of contraceptives on plasma lipids.

Importance and management

The increases in ethinylestradiol and progestogens seen with atorvastatin and rosuvastatin are only moderate and unlikely to be clinically important, but the manufacturers say that they should be considered when selecting an appropriate oral hormonal contraceptive dose for women given these statins.[6-8] If adverse effects such as nausea and breast tenderness are troublesome, it may be appropriate to select a contraceptive with a lower dose.

Note that statins are potentially teratogenic and therefore reliable contraception is required if they are used in women of child-bearing age. However, bear in mind also that the indications for statins may be a contraindication to the use of combined hormonal contraceptives, if other risk factors for arterial disease are present. This is because these contraceptives can have adverse effects on serum lipids. Statins may attenuate some of these effects.

1. Yang B-B, Siedlik PH, Smithers JA, Sedman AJ, Stern RH. Atorvastatin pharmacokinetic interactions with other CYP3A4 substrates: erythromycin and ethinyl estradiol. *Pharm Res* (1996) 13 (9 Suppl), S-437.
2. Colakoglu M, Kodama H, Tanaka T. The effect of combined medication of triphasic oral contraceptive with an anti-lipid agent, lovastatin, on plasma lipid levels. *Jpn J Fertil Steril* (1996) 41, 317–20.
3. Pan HY, Waclawski AP, Funke PT, Whigan D. Pharmacokinetics of pravastatin in elderly versus young men and women. *Ann Pharmacother* (1993) 27, 1029–33.
4. Simonson SG, Martin PD, Warwick MJ, Mitchell PD, Schneck DW. The effect of rosuvastatin on oestrogen & progestin pharmacokinetics in healthy women taking an oral contraceptive. *Br J Clin Pharmacol* (2004) 57, 279–86.
5. Banaszewska B, Pawelczyk L, Spaczynski RZ, Dziura J, Duleba AJ. Effects of simvastatin and oral contraceptive agent on polycystic ovary syndrome: prospective, randomized, crossover trial. *J Clin Endocrinol Metab* (2007) 92, 456–61.
6. Lipitor (Atorvastatin calcium trihydrate). Pfizer Ltd. UK Summary of product characteristics, December 2009.

7. Lipitor (Atorvastatin calcium). Pfizer Inc. US Prescribing information, June 2009.
8. Crestor (Rosuvastatin calcium). AstraZeneca UK Ltd. UK Summary of product characteristics, April 2009.

Combined hormonal contraceptives + Sucrose polyesters

Sucrose polyester did not alter the pharmacokinetics of the contraceptive steroids or affect the suppression of ovulation in women given oral combined hormonal contraceptives.

Clinical evidence, mechanism, importance and management

When 28 healthy women took 18 g of sucrose polyester (*Olestra*) daily for 28 days, the pharmacokinetics of the components of an oral combined hormonal contraceptive (**ethinylestradiol** 30 micrograms with **norgestrel** 300 micrograms) were unchanged. Serum progesterone levels also remained unaltered, suggesting no ovulation occurred.[1] This agrees with the findings of earlier single-dose studies, which found that sucrose polyester had no effect on the bioavailability of single doses of **ethinylestradiol** or **norethisterone**.[2] No special contraceptive precautions appear to be necessary in the presence of sucrose polyesters.

1. Miller KW, Williams DS, Carter SB, Jones MB, Mishell DR. The effect of olestra on systemic levels of oral contraceptives. *Clin Pharmacol Ther* (1990) 48, 34–40.
2. Roberts RJ, Leff RD. Influence of absorbable and nonabsorbable lipids and lipidlike substances on drug availability. *Clin Pharmacol Ther* (1989) 45, 299–304.

Combined hormonal contraceptives + Tacrolimus

Theoretically, tacrolimus may *increase* the plasma levels of hormonal contraceptives. Combined hormonal contraceptives may increase tacrolimus levels.

Clinical evidence, mechanism, importance and management

The UK manufacturer of tacrolimus says that during clinical use **ethinylestradiol** has been shown to increase tacrolimus levels to a minor extent, and that, *in vitro,* **gestodene** and **norethisterone** are potential inhibitors of tacrolimus metabolism.[1] The mechanism for this is unclear as these contraceptive steroids do not inhibit the cytochrome P450 isoenzyme CYP3A4, by which tacrolimus is principally metabolised.

In addition, tacrolimus is known to be a weak inhibitor of CYP3A4, by which contraceptive steroids are partially metabolised. Therefore, tacrolimus may reduce the clearance of hormonal contraceptives, leading to increased hormone exposure.[1] However, the extent of this interaction does not appear to have been studied, and its clinical relevance is therefore uncertain (it would be expected to be small). Nevertheless, the UK manufacturers suggest that care should be taken when deciding upon contraceptive measures.[1]

1. Prograf (Tacrolimus monohydrate). Astellas Pharma Ltd. UK Summary of product characteristics, May 2009.

Combined hormonal contraceptives + Tegaserod

Tegaserod did not alter the pharmacokinetics of the contraceptive steroids or the suppression of ovulation in women given an oral combined hormonal contraceptive.

Clinical evidence, mechanism, importance and management

In a placebo-controlled study in healthy women taking a triphasic oral combined hormonal contraceptive (**ethinylestradiol** with **levonorgestrel**), tegaserod 6 mg twice daily for a complete cycle had no effect on the AUC of **ethinylestradiol** and caused a minor 8% decrease in the AUC of **levonorgestrel**, which would not be expected to be clinically relevant. In addition, no ovulation occurred as assessed by progesterone levels.[1,2]

This study suggests that tegaserod is unlikely to alter the efficacy of combined hormonal contraceptives.

1. Zhou H, Walter YH, Hubert M, Ma P, Osborne S, Appel-Dingemanse A, McLeod JF. Tegaserod (HTF 919) does not decrease the effectiveness of an oral contraceptive when coadministered to healthy female subjects. *Gastroenterology* (2000) 118, A1207.
2. Appel-Dingemanse S. Clinical pharmacokinetics of tegaserod, a serotonin 5-HT_4 receptor partial agonist with promotile activity. *Clin Pharmacokinet* (2002) 41, 1021–42.

Combined hormonal contraceptives + Terbinafine

Terbinafine appears unlikely to interact with oral combined hormonal contraceptives.

Clinical evidence, mechanism, importance and management

An *in vitro* study in human liver microsomes found that terbinafine did not inhibit the hydroxylation of **ethinylestradiol**,[1] indicating that, in clinical use, it is unlikely to alter the pharmacokinetics of ethinylestradiol by this mechanism.

The UK manufacturer of terbinafine notes that some cases of menstrual disturbances (breakthrough bleeding and irregular cycle) have been reported in patients taking both oral contraceptives and terbinafine.[2] Nevertheless, in a post-marketing survey that included 314 patients taking both oral contraceptives and terbinafine, the rate of menstrual disorders (4.5%) was within the rate reported in the literature for patients taking oral contraceptives alone.[3] It seems unlikely that terbinafine will alter the efficacy of oral hormonal contraceptives.

1. Back DJ, Stevenson P, Tjia JF. Comparative effects of two antimycotic agents, ketoconazole and terbinafine, on the metabolism of tolbutamide, ethinyloestradiol, cyclosporin and ethoxycoumarin by human liver microsomes *in vitro*. *Br J Clin Pharmacol* (1989) 28, 166–70.
2. Lamisil Tablets (Terbinafine hydrochloride). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, September 2008.
3. O'Sullivan DP, Needham CA, Bangs A, Atkin K, Kendall FD. Postmarketing surveillance of oral terbinafine in the UK: report of a large cohort study. *Br J Clin Pharmacol* (1996) 42, 559–65.

Combined hormonal contraceptives + Tiagabine

Tiagabine did not alter the suppression of ovulation or plasma contraceptive steroid levels in women given oral combined hormonal contraceptives.

Clinical evidence, mechanism, importance and management

A study in 10 healthy women found that tiagabine 2 mg four times daily, from day 24 of one cycle to day 7 of the next cycle, had no effect on the mean plasma levels of any of the steroids in two oral combined hormonal contraceptives (**ethinylestradiol** 30 micrograms with **levonorgestrel** 150 micrograms or **desogestrel** 150 micrograms). There was no evidence that the suppression of ovulation was altered in any way (no significant changes in the plasma concentrations of progesterone, FSH, or LH were seen between the first and second cycles, and progesterone levels remained in the non-ovulatory range). Tiagabine did not induce hepatic enzymes, as assessed by 6β-hydroxycortisol excretion. Two women did develop breakthrough bleeding, but given the above findings, this was not thought to represent reduced efficacy of the contraceptive.[1] There would appear to be no reason for any special contraceptive precautions during the concurrent use of tiagabine.

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Combined hormonal contraceptives + Topiramate

Ethinylestradiol levels may be modestly reduced by high-dose topiramate, increasing the risk of breakthrough bleeding in women taking oral combined hormonal contraceptives.

Clinical evidence

In a study, 11 women with epilepsy taking sodium valproate and an oral combined hormonal contraceptive (**ethinylestradiol** 35 micrograms with **norethisterone** 1 mg) were also given three escalating doses of topiramate 200 mg, 400 mg and 800 mg daily (as two divided doses) for 28-day periods. The mean AUC of the **ethinylestradiol** fell by 18%, 21%, and 30%, with the three doses respectively. No significant changes were found in the **norethisterone** AUC. No ovulation occurred, as assessed by progestogen levels, but one patient had breakthrough bleeding.[1] A follow-up study evaluated the effect of lower doses of topiramate on the pharmacokinetics of the same oral combined hormonal contraceptive. Subjects were randomised to take daily doses of topiramate of 50 mg (11 subjects), 100 mg (10 subjects) or 200 mg (2 groups of 12 subjects). This study found minor changes in the pharmacokinetics of both **ethinylestradiol** and **norethisterone**; these changes were not statistically significant, and further reduced when the data from 2 subjects were excluded due to compliance issues (maximum decrease of 12% in the **ethinylestradiol** AUC). The authors noted that the difference between this study and the first study[1] was due to the difference in the doses of topiramate used, as topiramate is a weak liver enzyme-inducer, and this effect is dose-related.[2]

Mechanism

Not understood. It is suggested that high-dose topiramate weakly induces drug-metabolising enzymes, which increases the metabolism of the ethinylestradiol.[1,2]

Importance and management

The interaction between topiramate and the oral combined hormonal contraceptives is established. The small changes in the pharmacokinetics of the oral combined hormonal contraceptive seen here with usual therapeutic doses of topiramate (50 to 400 mg daily) are lower than those seen with other enzyme-inducing antiepileptics such as carbamazepine and phenytoin (see 'Combined hormonal contraceptives + Carbamazepine or Oxcarbazepine', p.1180, and 'Combined hormonal contraceptives + Barbiturates or Phenytoin', p.1177). However, it is possible that they would be sufficient to cause the failure of oral combined hormonal contraceptives in rare cases, particularly at high therapeutic doses of topiramate. The authors of the first study considered that an oral combined hormonal contraceptive containing at least 35 micrograms of ethinylestradiol would be suitable for women taking topiramate,[1] which seems reasonable. Nevertheless, as there is a risk of failure of contraception with the concurrent use of topiramate, and possibly more importantly, because topiramate is teratogenic, the UK manufacturer of topiramate advises the use of a non-hormonal contraceptive or a high-dose oral combined hormonal contraceptive (at least 50 micrograms of oestrogen), and also that patients should be told to report any changes in their bleeding patterns.[3] However, while recognising the possibility of decreased contraceptive efficacy, the US manufacturer gives no advice about ethinylestradiol dose.[4] The UK Faculty of Family Planning and Reproductive Health Care (FFPRHC) Clinical Effectiveness Unit has issued guidance on the use of liver enzyme inducers, including topiramate, with hormonal contraceptives, see 'Combined hormonal contraceptives + Barbiturates or Phenytoin', p.1177, for details of this guidance.

1. Rosenfeld WE, Doose DR, Walker SA, Nayak RK. Effect of topiramate on the pharmacokinetics of an oral contraceptive containing norethindrone and ethinyl estradiol in patients with epilepsy. *Epilepsia* (1997) 38, 317–23.
2. Doose DR, Wang S-S, Padmanabhan M, Schwabe S, Jacobs D, Bialer M. Effect of topiramate or carbamazepine on the pharmacokinetics of an oral contraceptive containing norethindrone and ethinyl estradiol in healthy obese and nonobese female subjects. *Epilepsia* (2003) 44, 540–9.
3. Topamax (Topiramate). Janssen-Cilag Ltd. UK Summary of product characteristics, December 2008.
4. Topamax (Topiramate). Ortho-McNeil Neurologics. US Prescribing information, May 2009.

Combined hormonal contraceptives + Triptans

Oral combined hormonal contraceptives appear to modestly raise the levels of frovatriptan, naratriptan and zolmitriptan, and slightly increase those of sumatriptan. Almotriptan, rizatriptan and sumatriptan appear not to alter the levels of contraceptive steroids. Note that use of combined hormonal contraceptives in migraine (the indication for triptans) appears to increase the risk of stroke.

Clinical evidence

(a) Almotriptan

In a well-controlled study in 21 women, a single 12.5-mg dose of almotriptan given between days 8 and 12 of a cycle had no clinically significant effect on the pharmacokinetics of an oral combined hormonal contraceptive (**ethinylestradiol** 30 micrograms with **desogestrel** 150 micrograms) taken for two cycles.[1]

(b) Frovatriptan

In a retrospective analysis of pharmacokinetic data from phase I studies, the mean maximum concentration and AUC of frovatriptan were 25% and 30% higher, respectively, in women taking oral hormonal contraceptives than in women not taking these contraceptives.[2]

(c) Naratriptan

The manufacturer notes that the clearance of naratriptan was reduced by 32% by oral hormonal contraceptives leading to a slightly higher level of naratriptan.[3] A case of ischaemic colitis has been reported in a 42-year-old woman who had been taking an oral combined hormonal contraceptive (**ethinylestradiol** 30 micrograms with **drospirenone** 3 mg) for 3 years, naratriptan 2.5 mg as needed for 18 months (maximum dose of one tablet in a day and 9 tablets in a month), and topiramate 25 mg twice daily for 4 months.[4]

(d) Rizatriptan

In a placebo-controlled study in 20 healthy young women taking an oral combined hormonal contraceptive (**ethinylestradiol** 35 micrograms with **norethisterone** 1 mg), the concurrent use of rizatriptan (6 days of 10 mg daily followed by 2 days of 10 mg every 4 hours to a total of 3 doses daily) did not affect the pharmacokinetics of either contraceptive steroid. Blood pressure, heart rate and temperature were unaffected and adverse effects were similar to those seen with placebo.[5]

(e) Sumatriptan

A study was designed to investigate the effects of an oral combined hormonal contraceptive (**ethinylestradiol** 35 micrograms with **norethisterone** 1 mg) on the pharmacokinetics of sumatriptan in 26 women who had been taking this contraceptive for at least 3 months. A single 50-mg oral dose of sumatriptan was given once after 21 days of active treatment with the contraceptive, and again after 7 days of placebo (day 28). A 16% higher AUC and a 17% higher maximum concentration of sumatriptan was noted on day 21, compared with day 29. There was an 18% reduction in the maximum concentration of **norethisterone** when it was given with sumatriptan, but no change in its AUC. Similarly, there was no change in the AUC or maximum concentration of **ethinylestradiol** when it was given with sumatriptan.[6]

In a large prospective study of subcutaneous sumatriptan, there was no difference in the incidence of cardiovascular adverse events between 1 188 patients taking oral hormonal contraceptives (types not stated) and 11 151 patients who were not taking contraceptives. Two cardiovascular adverse events occurred within 24 hours of sumatriptan use in women also using oral hormonal contraceptives. One 44-year-old women experienced angina, and the other had palpitations.[7]

(f) Zolmitriptan

The US manufacturer states that, in a retrospective analysis of pharmacokinetic data from several studies, the mean maximum concentration and AUC of zolmitriptan were 30% and 50% higher, respectively, in women taking oral hormonal contraceptives than in women not taking these contraceptives.[8] The effects of zolmitriptan on oral hormonal contraceptive steroids have not been studied.[8]

Mechanism

Uncertain, but ethinylestradiol is known to be a modest inhibitor of the cytochrome P450 isoenzyme CYP1A2, by which a number of these triptans (particularly frovatriptan and zolmitriptan) are at least partially metabolised.

Importance and management

Although data are limited, the minor to modest possible increases in frovatriptan, naratriptan, sumatriptan and zolmitriptan exposure described are not likely to produce clinically relevant adverse effects. Almotriptan, rizatriptan and sumatriptan do not appear to have any clinically important effect on levels of contraceptive steroids. The significance of the single case

report of ischaemic colitis associated with the concurrent use of naratriptan and an oral combined hormonal contraceptive is unclear. Note that ischaemic colitis has, rarely, been reported with naratriptan alone.[9] The manufacturers have found no cases of ischaemic colitis in approximately 450 women taking oral hormonal contraceptives and naratriptan, for prophylaxis for 5 to 6 days.[9]

More importantly, women who suffer from migraine and take an oral combined hormonal contraceptive are at a 6- to 14-fold increased risk of a stroke compared with those not using oral combined hormonal contraceptives who do not suffer from migraine. In addition, in women who suffer from migraine, the use of oral combined hormonal contraceptives was associated with a two- to fourfold increased risk of stroke, compared with non-users of these contraceptives.[10] Migraine with aura (which indicates ischaemia) is generally thought to be a greater risk for stroke. As a result, in the UK, the Faculty of Family Planning and Reproductive Health Care (FFPRHC) guidance states that women of all ages who currently have migraines *with* aura should not use a combined hormonal contraceptive. Women over the age of 35 years who have migraine attacks *without* aura and those of any age with a past history of migraine *with* aura should also not use combined hormonal contraceptives.[11] Women taking any hormonal contraceptive who develop migraine with aura as a new symptom should have their contraceptive choices reviewed. The FFPRHC guidance gives advice on alternative choices of contraceptive method for women with migraine or a history of migraine.[11]

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2. Buchan P. Effects of alcohol, smoking and oral contraceptives on the pharmacokinetics of frovatriptan. *Eur J Neurol* (2000) 7 (Suppl 3), 86–7.
3. Amerge (Naratriptan hydrochloride). GlaxoSmithKline. US Prescribing information, October 2007.
4. Charles JA, Pullicino PM, Stoopack PM, Shroff Y. Ischemic colitis associated with naratriptan and oral contraceptive use. *Headache* (2005) 45, 386–9.
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8. Zomig (Zolmitriptan). AstraZeneca Pharmaceuticals LP. US Prescribing information, October 2008.
9. Malone TD, Kori SH. Ischemic colitis associated with naratriptan and oral contraceptive use: A response. *Headache* (2005) 45, 1419–20.
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11. Faculty of Family Planning and Reproductive Health Care (FFPRHC) & Royal College of Obstetricians & Gynaecologists. UK Medical eligibility criteria for contraceptive use (UKMEC 2005/2006), July 2006. Available at: http://www.ffprhc.org.uk/ (accessed 05/02/10).

Combined hormonal contraceptives + Urinary antimuscarinics

Fesoterodine, solifenacin and tolterodine do not alter the pharmacokinetics of the contraceptive steroids, or their effects on the suppression of ovulation in women taking oral combined hormonal contraceptives. Darifenacin does not affect the pharmacokinetics of oral combined hormonal contraceptives. Hormonal contraceptives do not appear to alter the pharmacokinetics of oxybutynin.

Clinical evidence

(a) Darifenacin

The manufacturers note that, in a study in 22 healthy women, steady-state darifenacin 10 mg three times daily had no effect on the pharmacokinetics of an oral combined hormonal contraceptive (**ethinylestradiol** with **levonorgestrel**).[1,2]

(b) Fesoterodine

In a randomised, crossover study in 26 healthy women, fesoterodine 8 mg daily for 14 days, beginning on day one of a cycle, had no significant effect on the pharmacokinetics of an oral combined hormonal contraceptive (**ethinylestradiol** 30 micrograms with **levonorgestrel** 150 micrograms). Fesoterodine did not alter suppression of ovulation assessed by progesterone, LH or FSH levels.[3]

(c) Oxybutynin

The pharmacokinetics of a single 10-mg dose of oxybutynin as a controlled release tablet did not differ between women taking contraceptive steroids, women not taking contraceptive steroids, and men.[4]

(d) Solifenacin

In a randomised, crossover study in healthy women, solifenacin 10 mg daily for 10 days, beginning on day 12 of a cycle, had no significant effect on the pharmacokinetics of an oral combined hormonal contraceptive (**ethinylestradiol** 30 micrograms with **levonorgestrel** 150 micrograms). Solifenacin did not alter suppression of LH or FSH.[5]

(e) Tolterodine

A randomised, crossover study in 24 women found that tolterodine 2 mg twice daily on days one to 14 of two 28-day contraceptive cycles had no effect on the pharmacokinetics of the steroids in an oral combined hormonal contraceptive (**ethinylestradiol** 30 micrograms with **levonorgestrel** 150 micrograms). The pharmacokinetics of the tolterodine were also not significantly altered, and the serum levels of estradiol and progesterone indicated that suppression of ovulation continued during both periods of treatment.[6]

Mechanism

None known.

Importance and management

The evidence from these controlled studies suggest that the urinary antimuscarinics tested (darifenacin, fesoterodine, solifenacin and tolterodine) are unlikely to alter the efficacy of oral combined hormonal contraceptives. No special precautions would therefore seem to be needed if these drugs are used concurrently.

1. Enablex (Darifenacin hydrobromide). Novartis. US Prescribing information, June 2008.
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3. Malhotra B, Sachse R, Wood N. Evaluation of drug-drug interactions with fesoterodine. Eur J Clin Pharmacol (2009) 65, 551–60.
4. Lukkari E, Hakonen T, Neuvonen PJ. The pharmacokinetics of oxybutynin is unaffected by gender and contraceptive steroids. *Eur J Clin Pharmacol* (1998) 53, 351–4.
5. Taekema-Roelvink MEJ, Swart PJ, Kuipers ME, Krauwinkel WJJ, Visser N, Smulders RA. Pharmacokinetic interaction of solifenacin with an oral contraceptive containing ethinyl estradiol and levonorgestrel in healthy women: a double-blind, placebo-controlled study. *Clin Ther* (2005) 27, 1403–10.
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Combined hormonal contraceptives + Ursodeoxycholic acid (Ursodiol)

Ursodeoxycholic acid did not alter levels of ethinylestradiol from an oral combined hormonal contraceptive.

Clinical evidence, mechanism, importance and management

In a placebo-controlled study in 8 healthy women taking an oral combined hormonal contraceptive (**ethinylestradiol** with **gestodene**), ursodeoxycholic acid 8 to 10 mg/kg daily for 21 days had no effect on the AUC of **ethinylestradiol**.[1]

This study suggests that ursodeoxycholic acid is unlikely to alter the efficacy of oral combined hormonal contraceptives.

1. Baisini O, Benini F, Petraglia F, Kuhnz W, Scalia S, Marschall H-U, Brunetti G, Tauschel H-D, Lanzini A. Ursodeoxycholic acid does not affect ethinylestradiol bioavailability in women taking oral contraceptives. *Eur J Clin Pharmacol* (2004) 60, 481–7.

Combined hormonal contraceptives + Valproate

Sodium valproate does not appear to alter the efficacy of oral combined hormonal contraceptives. In one single-dose study, sodium valproate did not alter the AUC of ethinylestradiol or levonorgestrel. Ethinylestradiol may modestly reduce valproate

levels, an effect which is cyclical. There is one published case where this resulted in an increase in seizure frequency.

Clinical evidence

(a) Contraceptive efficacy

In a series of 32 patients taking an oral hormonal contraceptive, none of 7 taking sodium valproate 600 mg to 1.8 g daily had breakthrough bleeding, whereas about two-thirds of those taking carbamazepine or phenobarbital had breakthrough bleeding (a sign of possible reduced contraceptive efficacy). Most of the 7 patients taking valproate were taking oral combined hormonal contraceptives containing 50 micrograms of **ethinylestradiol**; one was taking less than 50 micrograms, and one was using an oral **progestogen-only contraceptive**. One of the 7 patients had previously experienced breakthrough bleeding while taking phenobarbital, but this stopped when it was replaced with sodium valproate. Two further patients did not have breakthrough bleeding while taking sodium valproate and benzodiazepines, but breakthrough bleeding started when phenytoin was also given.[1]

In a pharmacokinetic study, sodium valproate 200 mg twice daily had no effect on the AUC of a single dose of an oral combined hormonal contraceptive (**ethinylestradiol** 50 micrograms with **levonorgestrel** 250 micrograms) given to women with epilepsy 8 to 16 weeks after they started sodium valproate. However, a 50% *increase* in the peak plasma levels of **ethinylestradiol** was noted.[2]

Conversely, one pregnancy was identified in a woman who took sodium valproate and an oral hormonal contraceptive (unspecified) in the adverse reactions register of the CSM in the UK for the years 1968 to 1984. However, the authors consider this one case to be a chance association.[3]

(b) Valproate efficacy

In 9 women with epilepsy taking valproic acid 500 mg to 1.5 g daily, the serum levels of total and unbound valproic acid were 21% and 41% lower, respectively, during combined hormonal contraceptive intake compared with the pill-free period. These women were taking oral contraceptives containing **ethinylestradiol** and either **gestodene** (5 women) or **drospirenone** (2 women), or the transdermal patch containing **ethinylestradiol** and **norelgestromin** (2 women). The pill-free interval was 7 days in seven women and 4 days in two women.[4] In another study in 12 women taking valproate monotherapy, a very similar median 23.4% lower serum valproate level was seen during the third week of an oral combined hormonal contraceptive cycle when compared with the fourth pill-free week. These women were taking **ethinylestradiol** with either **norethisterone**, **levonorgestrel** or **norgestimate**.[5]

In one case report, lower valproate levels and more frequent seizures occurred in a woman taking an oral combined hormonal contraceptive (**ethinylestradiol** 35 micrograms with **ethynodiol** 1 mg) during the active pill phase, when compared with the inactive 7-day period. Specifically, over a 5-month period, she had 12 seizures during 105 days of active pill use and none during the 35 days of inactive pill use, and total and unbound valproate levels were 36% and 46% lower, respectively, during active pill use.[6] No further cases appear to have been published.

Mechanism

Valproate is metabolised by glucuronide conjugation, and therefore its levels may be reduced due to induction of glucuronosyltransferases by ethinylestradiol. Valproate is an inhibitor of glucuronidation, and might therefore be expected to increase ethinylestradiol levels, but only an increase in maximum levels and not the AUC was seen in the one single-dose study available.

Importance and management

Although specific data are limited, it appears that valproate is unlikely to reduce the efficacy of combined hormonal contraceptives. No special contraceptive precautions are required during concurrent use. Note that the UK Faculty of Family Planning and Reproductive Health Care (FFPRHC) Clinical Effectiveness Unit guidelines on the management of hormonal contraceptives and drug interactions lists valproate as an example of an antiepileptic that does not induce liver enzymes and causes no reduction in ethinylestradiol or progestogens.[7] The general relevance of the modest cyclical reduction in valproate levels during active pill taking, and the case report of an increase in seizure frequency is unclear, and further study is needed. However, bear the possibility of this interaction in mind.

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5. Herzog AG, Blum AS, Farina EL, Maestri XE, Newman J, Garcia E, Krishnamurthy KB, Hoch DB, Replansky S, Fowler KM, Smithson SD, Dworetzky BA, Bromfield EB. Valproate and lamotrigine level variation with menstrual cycle phase and oral contraceptive use. Neurology (2009) 72, 911–14.
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Combined hormonal contraceptives + Vigabatrin

Vigabatrin appears not to alter the pharmacokinetics of ethinylestradiol or levonorgestrel given as an oral combined hormonal contraceptive.

Clinical evidence, mechanism, importance and management

Vigabatrin 3 g daily had no statistically significant effect on the pharmacokinetics of **ethinylestradiol** and **levonorgestrel** in 13 healthy women given a single dose of an oral combined hormonal contraceptive (**ethinylestradiol** 30 micrograms with **levonorgestrel** 150 micrograms); although 2 of the women had a 39% and a 50% fall in the AUC of **ethinylestradiol**. Vigabatrin did not induce hepatic enzymes as assessed by antipyrine clearance and 6β-hydroxycortisol excretion.[1]

This study would seem to confirm the lack of reports of an interaction between hormonal contraceptives and vigabatrin, but the authors of the report introduce a small note of caution because it is not clear whether the reduced **ethinylestradiol** AUCs seen in two of the women resulted from an interaction or were simply normal individual variations.[1] Note that the UK Faculty of Family Planning and Reproductive Health Care (FFPRHC) Clinical Effectiveness Unit guidelines on the management of hormonal contraceptives and drug interactions list vigabatrin as an example of an antiepileptic that does not induce liver enzymes.[2] No special precautions are recommended.

1. Bartoli A, Gatti G, Cipolla G, Barzaghi N, Veliz G, Fattore C, Mumford J, Perucca E. A double-blind, placebo-controlled study on the effect of vigabatrin on in vivo parameters of hepatic microsomal enzyme induction and on the kinetics of steroid oral contraceptives in healthy female volunteers. *Epilepsia* (1997) 38, 702–7.
2. Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit. FFPRHC Guidance: Drug interactions with hormonal contraception. April 2005. Available at: http://www.ffprhc.org.uk/admin/uploads/DrugInteractionsFinal.pdf (accessed 01/02/10).

Combined hormonal contraceptives + Ziprasidone

Ziprasidone did not alter the levels of ethinylestradiol and levonorgestrel from an oral combined hormonal contraceptive.

Clinical evidence, mechanism, importance and management

In a placebo-controlled, crossover study, 18 healthy women taking an oral contraceptive (**ethinylestradiol** 30 micrograms with **levonorgestrel** 150 micrograms) for at least 3 cycles were also given ziprasidone 20 mg twice daily for 8 days, from day 8 to 15 of a cycle. The only change in the pharmacokinetics of the two steroids was an increase of about 30-minutes in the time to maximum plasma concentration of the **levonorgestrel**, but this is not clinically relevant. On the basis of this pharmacokinetic study,

ziprasidone appears unlikely to affect the efficacy of oral combined hormonal contraceptives.[1]

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Combined hormonal contraceptives + Zonisamide

Zonisamide did not affect the levels of ethinylestradiol or norethisterone in women taking an oral combined hormonal contraceptive, and the suppression of ovulation was not altered.

Clinical evidence, mechanism, importance and management

Zonisamide 100 mg daily titrated to 200 to 400 mg daily taken from day 15 of cycle two to day 13 of cycle three had no effect on the pharmacokinetics of **ethinylestradiol** or **norethisterone** in healthy women taking an oral combined hormonal contraceptive (**ethinylestradiol** 35 micrograms with **norethisterone** 1 mg). There was no change in FSH and LH levels, and the levels of progesterone indicated the absence of ovulation.[1] This suggests that no special contraceptive precautions are needed during concurrent use.

1. Griffith SG, Dai Y. Effect of zonisamide on the pharmacokinetics and pharmacodynamics of a combination ethinyl estradiol-norethindrone oral contraceptive in healthy women. *Clin Ther* (2004) 26, 2056–65.

Drospirenone-containing contraceptives or HRT + Potassium-sparing drugs

Drospirenone, given as the progestogen component of oral combined hormonal contraceptives or HRT, has the potential to cause hyperkalaemia and may have additive effects with other potassium-sparing drugs.

Clinical evidence

(a) Drospirenone in combined hormonal contraceptives

In a small study in 27 women with acne, there was no significant increase in serum potassium level 4 to 6 weeks after starting **ethinylestradiol** 30 micrograms with drospirenone 3 mg and **spironolactone** 100 mg daily. Although this study was non-comparative, it does provide some useful evidence about concurrent use.[1]

In a matched cohort study, there was no difference in the rate of diagnosed hyperkalaemia between 22 429 women who started contraception with **ethinylestradiol** with drospirenone and 44 858 women who started other oral hormonal contraceptives (one versus 4) over an average follow-up of 7.6 months. In addition, there was no difference in the rate of clinical outcomes that could be related to hyperkalaemia.[2]

(b) Drospirenone in HRT

In a controlled study in 24 postmenopausal women taking **enalapril** 10 mg twice daily there was no change in serum potassium levels after taking **estradiol** 1 mg with drospirenone 3 mg daily for 14 days, when compared with placebo. In addition, no subject developed hyperkalaemia (defined as serum potassium greater than 5.5 mmol/L).[3] Similarly, in a larger study in postmenopausal women taking an **ACE inhibitor** or an **angiotensin II receptor antagonist**, there was no significant difference in incidence of hyperkalaemia (potassium level 5.5 mmol/L or more) between those receiving **estradiol** 1 mg with drospirenone 3 mg daily for 28 days and placebo (7.3% versus 2.6%). This study included women with diabetes, women without diabetes, and women without diabetes who were also given a 5-day course of **ibuprofen** 400 mg three times daily.[4] Nevertheless, the UK manufacturer notes that the concurrent use of all these three types of medications together (drospirenone in HRT with an **NSAID** and an **ACE inhibitor** or **angiotensin II receptor antagonist**) may cause a small increase in serum potassium, which is more pronounced in diabetic women.[5]

In yet another study in 33 healthy postmenopausal women, there was no difference in potassium levels between the concurrent use of **estradiol** 1 mg with drospirenone 3 mg daily for 17 days and **indometacin** 50 mg three times daily for the last 5 days, and **indometacin** alone. In addition there was no difference in the incidence of hyperkalaemia (5 women versus 3 women). However, in 14 women, at least one potassium level above 4.4 mmol/L was seen both during combined treatment and with indometacin alone). Of the other women, 12 had raised potassium levels only during the combined treatment, whereas only one woman had a raised potassium levels during the use of indometacin alone,[6] which seems to suggest some additive effect.

The US manufacturer also notes a study of the effect of drospirenone 3 mg daily on serum potassium levels in women with normal renal function (11 women) and mild renal impairment (10 women) or moderate renal impairment (7 women). During the study, 7 patients continued to use **potassium-sparing drugs** (not specified). Drospirenone had no significant effect on potassium levels and no hyperkalaemia occurred. However, in 5 of the 7 patients also taking **potassium-sparing drugs**, there was a rise in potassium level of up to 0.33 mmol/L).[7]

Mechanism

Drospirenone, an analogue of spironolactone, has weak antimineralocorticoid and potassium-sparing effects, and therefore may increase the risk of hyperkalaemia if it is given with other drugs that can increase potassium levels. Drospirenone 3 mg is said to have activity similar to that of spironolactone 25 mg.[8]

Importance and management

The risk of hyperkalaemia developing in women taking the drospirenone-containing oral combined hormonal contraceptive or HRT with other drugs that can increase serum potassium appears to be low, especially if renal function is normal. However, in the UK, severe renal impairment is a contraindication to use. If the woman has mild or moderate renal impairment, it is recommended that serum potassium is measured during the first cycle/month of treatment with contraceptives or HRT containing drospirenone, especially if they are also taking any other drugs that increase serum potassium.[5,9] In the US, renal impairment [any degree] is a contraindication to the use of drospirenone preparations.[7,8]

In the US, it is recommended that consideration be given to monitoring serum potassium during the first cycle in women [with normal renal function] who regularly take any drugs that increase serum potassium (ACE inhibitors, **aldosterone antagonists**, angiotensin II receptor antagonists, **heparin**, NSAIDs, **potassium-sparing diuretics** and **potassium supplements** are named.[7,8] The same advice used to be given in the UK for all women given the drospirenone-containing oral combined hormonal contraceptive. However, for women without renal impairment, current UK advice is to monitor potassium during the first treatment cycle if they are also taking another aldosterone antagonist (e.g. spironolactone and eplerenone) or a potassium-sparing diuretic, and there is no requirement for monitoring with ACE inhibitors or NSAIDs.[9] Note that in one survey of 58 US physicians, only 40% of 466 women starting ethinylestradiol with drospirenone and taking concurrent potassium-sparing drugs had a potassium test. Physicians who did not do the test were more likely to disagree with the need for it in patients taking ACE inhibitors, angiotensin II receptor antagonists, heparin and NSAIDs.[10]

Nevertheless, for the drospirenone-containing HRT preparation, the UK manufacturer notes that the concurrent use of more than one drug that can raise potassium levels (an NSAID with an ACE inhibitor or angiotensin II receptor antagonist) may cause a small increase in serum potassium levels, which is more pronounced in diabetic women.[5]

For mention of the risks of hypertension with combined hormonal contraceptives, and the fact that drospirenone HRT appears to slightly decrease blood pressure, see ‘Antihypertensives + Hormonal contraceptives or HRT’, p.1050.

1. Krunic A, Ciurea A, Scheman A. Efficacy and tolerance of acne treatment using both spironolactone and a combined contraceptive containing drospirenone. J Am Acad Dermatol (2008) 58, 60–2.
2. Loughlin J, Seeger JD, Eng PM, Foegh M, Clifford CR, Cutone J, Walker AM. Risk of hyperkalemia in women taking ethinylestradiol/drospirenone and other oral contraceptives. Contraception (2008) 78, 377–83.
3. Karara AH, Zhang P, Blode H, Schuermann R, Preston R. Effect of drospirenone/estradiol combination product on the serum potassium of mildly hypertensive postmenopausal women maintained on enalapril maleate [Abstract 45]. *J Clin Pharmacol* (2001) 41, 1024.
4. Preston RA, White WB, Pitt B, Bakris G, Norris PM, Hanes V. Effects of drospirenone/17-beta estradiol on blood pressure and potassium balance in hypertensive postmenopausal women. *Am J Hypertens* (2005) 18, 797–804.
5. Angeliq (Drospirenone/Estradiol). Bayer plc. UK Summary of product characteristics, May 2008.
6. Schütt B, Kunz M, Blode H. Coadministration of estradiol/drospirenone and indomethacin does not cause hyperkalemia in healthy postmenopausal women: a randomized open-label crossover study. *J Clin Pharmacol* (2007) 47, 774–81.

7. Angeliq (Drospirenone/Estradiol). Bayer HealthCare Pharmaceuticals, Inc. US Prescribing information, March 2008.
8. Yasmin (Drospirenone/Ethinylestradiol). Bayer HealthCare Pharmaceuticals, Inc. US Prescribing information, April 2007.
9. Yasmin (Drospirenone/Ethinylestradiol). Bayer plc. UK Summary of product characteristics, June 2008.
10. Mona Eng P, Seeger JD, Loughlin J, Oh K, Walker AM. Serum potassium monitoring for users of ethinyl estradiol/drospirenone taking medications predisposing to hyperkalemia: physician compliance and survey of knowledge and attitudes. *Contraception* (2007) 75, 101–7.

Emergency hormonal contraceptives + Antibacterials

There is a theoretical possibility that the emergency contraceptive efficacy of norgestrel with ethinylestradiol could be affected by antibacterials such as the penicillins and tetracyclines. The efficacy of levonorgestrel given for emergency contraception is not likely to be affected by these antibacterials.

Clinical evidence, mechanism, importance and management

(a) Combined oestrogen and progestogen

The manufacturer has stated that the efficacy of **norgestrel** with **ethinylestradiol** (*Schering PC4*) may be reduced by **ampicillin** and other antibacterials.[1] This is presumably an extrapolation from the rare cases of combined hormonal contraceptive failure seen with various other antibacterials that do not induce liver enzymes, which, it has been suggested, could be due to reduced enterohepatic recycling of **ethinylestradiol** (see 'Combined hormonal contraceptives + Antibacterials; Penicillins', p.1170). However, it has been suggested that it is likely that sufficient hormone is absorbed initially for the emergency contraceptive to be effective[2] (it is taken as 2 doses within 12 hours of each other).

Note that **rifampicin** (**rifampin**) and **rifabutin** are likely to reduce the efficacy of *Schering PC4*, as they induce the metabolism of oestrogens and progestogens, see 'Emergency hormonal contraceptives + Enzyme inducers', below.

Note that the use of an oestrogen with a progestogen as an emergency contraceptive has been superseded by a progestogen-only preparation (see below), as the latter is associated with a higher efficacy and less oestrogen-related adverse effects.

(b) Progestogen only

Levonorgestrel is metabolised to inactive substances before it is conjugated,[3] and does not undergo enterohepatic recycling of the active moiety.[4] Therefore, there is no reason to expect that its efficacy as an emergency contraceptive would be affected by antibacterials that alter gut flora and do not induce liver enzymes.[4] No special precautions are necessary with these antibacterials. However, **rifampicin** (**rifampin**) and **rifabutin** are likely to reduce the efficacy of levonorgestrel given as an emergency contraceptive, as they induce the metabolism of progestogens, see 'Emergency hormonal contraceptives + Enzyme inducers', below.

1. Schering PC4 (Norgestrel/ethinylestradiol). Schering Health Care Ltd. UK Summary of product characteristics, July 1995.
2. Elliman A. Interactions with hormonal contraception. *Br J Fam Plann* (2000) 26, 109–11.
3. Levonelle One Step (Levonorgestrel). Bayer plc. UK Summary of product characteristics, November 2007.
4. Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit. FFPRHC Guidance: Drug interactions with hormonal contraception. April 2005. Available at: http://www.ffprhc.org.uk/admin/uploads/DrugInteractionsFinal.pdf (accessed 01/02/10)

Emergency hormonal contraceptives + Enzyme inducers

Two cases of pregnancy despite the use of emergency hormonal contraception were attributed to the use of St John's wort. The efficacy of both the progestogen-only and combined emergency hormonal contraceptive is likely to be reduced by enzyme inducers that have been shown to affect oral combined hormonal contraceptives, such as rifampicin (rifampin), the enzyme-inducing antiepileptics and some antiretrovirals.

Clinical evidence, mechanism, importance and management

Between 2000 and 2002 the CSM in the UK had received reports of 2 women taking **St John's wort** who became pregnant despite taking emergency hormonal contraception.[1] One of them had also been taking an oral combined hormonal contraceptive and took *Levonelle-2* (**levonorgestrel**).[1,2]

Various enzyme inducers have specifically been shown to decrease the levels of contraceptive steroids and/or reduce their effects on the suppression of ovulation when used as components of oral combined hormonal contraceptives (see 'Table 28.1', (p.1165)). This would also be expected when **ethinylestradiol** with **norgestrel**, or **levonorgestrel** alone, are used as postcoital emergency hormonal contraceptives. It would be easy to specifically evaluate the pharmacokinetic changes that occur with single doses of emergency hormonal contraceptive products when given with enzyme-inducing drugs, although no such studies appear to have been published. However, it is difficult to envisage a practical study design that would show to what extent this reduced metabolism results in reduced efficacy of emergency contraception.

In the UK in 2005, the Faculty of Family Planning and Reproductive Health Care (FFPRHC) Clinical Effectiveness Unit noted that there appeared to be no good evidence on how to manage this interaction, but they recommended increasing the contraceptive dose by approximately 50% (**levonorgestrel** 2.25 mg).[3] The BNF in the UK recommends doubling the dose (giving a single 3-mg dose of levonorgestrel).[4] A **copper IUD** may also be used as an effective alternative.[3] In some countries it is possible to buy emergency hormonal contraception without a prescription; however, in the UK it has been advised that patients taking enzyme inducers should not be supplied the emergency hormonal contraceptive but should be referred to a doctor or family planning service.[3,5] Given the potential consequences of an unwanted pregnancy, these seem sensible precautions.

1. Committee on Safety of Medicines. Personal communication, February 15th, 2002.
2. Henderson L, Yue QY, Bergquist C, Gerden B, Arlett P. St John's wort *Hypericum perforatum*): drug interactions and clinical outcomes. *Br J Clin Pharmacol* (2002) 54, 349–56.
3. Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit. FFPRHC Guidance: Drug interactions with hormonal contraception. April 2005. Available at: http://www.ffprhc.org.uk/admin/uploads/DrugInteractionsFinal.pdf (accessed 01/02/10).
4. British National Formulary. 58th ed. London: BMJ Publishing Group Ltd and RPS Publishing; 2009. p. 454.
5. Royal Pharmaceutical Society of Great Britain. Practice guidance on the supply of emergency hormonal contraception as a pharmacy medicine. September 2004. Available at: http://www.rpsgb.org/pdfs/ehcguid.pdf (accessed 01/02/10).

Emergency hormonal contraceptives; Ulipristal + Miscellaneous

The efficacy of ulipristal emergency contraception is expected to be reduced by enzyme-inducing drugs. The absorption of ulipristal may be reduced in women taking antacids, proton pump inhibitors or H_2-receptor antagonists. Ulipristal has the potential to reduce the efficacy of hormonal contraceptives, and after ulipristal emergency contraception, a non-hormonal contraceptive should be used until the next menstrual period.

Clinical evidence, mechanism, importance and management

(a) Contraceptive steroids

The manufacturer notes that ulipristal acetate binds to the progesterone receptor with high affinity, and therefore could theoretically interfere with the action of progestogen-containing products. They say that it might reduce the efficacy of **combined hormonal contraceptives** and **progestogen-only contraception**. Therefore, after using ulipristal emergency contraception, it is recommended that a reliable barrier method of contraception should be used until the next menstrual period starts.[1] In addition, the manufacturer specifically states that the concurrent use of ulipristal acetate and emergency hormonal contraception containing **levonorgestrel** is not recommended.[1]

(b) CYP3A4 inducers

The manufacturer states that ulipristal is metabolised by the cytochrome P450 isoenzyme CYP3A4 *in vitro*. No specific drug interaction studies have been performed *in vivo*; however, it is predicted that CYP3A4 inducers (the manufacturer names **rifampicin** (**rifampin**), **phenytoin**, **phenobarbital**, **carbamazepine**, **ritonavir**, and **St John's wort**) may reduce plasma concentrations of ulipristal acetate, which may result in decreased efficacy.[1] For a list of enzyme inducers that have affected combined hormonal contraceptives, see 'Table 28.1', (p.1165). However, note that not all of these drugs interact by inducing CYP3A4 (e.g. **ritonavir** probably interacts by inducing glucuronidation). Because ulipristal is a synthetic

steroid derivative, it is possible that it will undergo similar interactions.

The manufacturer advises that ulipristal should not be used for emergency contraception in women taking CYP3A4 inducers. They say that, because enzyme induction wears off slowly, effects on the plasma concentrations of ulipristal acetate may occur even if a woman has stopped taking an enzyme inducer within the last 2 to 3 weeks.[1] Until more is known, this advice is prudent.

(c) CYP3A4 inhibitors

Potent CYP3A4 inhibitors (the manufacturer names **ketoconazole**, **itraconazole**, **telithromycin**, **clarithromycin**, and **nefazodone**) are predicted to increase exposure to ulipristal acetate. The manufacturer notes that the clinical relevance of this is unknown.[1]

(d) Drugs that increase gastric pH

The manufacturer notes that drugs that increase gastric pH such as **proton pump inhibitors**, **antacids** and **H_2-receptor antagonists** may reduce the plasma concentrations of ulipristal acetate and may result in decreased efficacy. Because of this, they say that concurrent use is not recommended.[1]

1. EllaOne (Ulipristal acetate). HRA Pharma UK Ltd. UK Summary of product characteristics, May 2009.

Gestrinone + Enzyme inducers

The manufacturer says that rifampicin (rifampin) and antiepileptics may reduce the effects of gestrinone.

Clinical evidence, mechanism, importance and management

The manufacturer suggests that **rifampicin** (**rifampin**) and **antiepileptics** (not named, but by implication those that are enzyme inducers, see 'Table 28.1', (p.1165)) may accelerate the metabolism of gestrinone.[1] Be aware that gestrinone may not be as effective if any of these drugs are given concurrently.

1. Dimetriose (Gestrinone). Sanofi-Aventis. UK Summary of product characteristics, February 2008.

Hormonal contraceptives + Danazol or Gestrinone

There is a theoretical risk that the effects of danazol or gestrinone and hormonal contraceptives might be altered or reduced by concurrent use.

Clinical evidence, mechanism, importance and management

(a) Danazol

Danazol inhibits ovulation, but it is not considered reliable enough to be used as a hormonal contraceptive.[1-3] Danazol should not be used during pregnancy, because it can cause virilisation of a female foetus. The manufacturer advises the use of reliable non-hormonal contraceptive methods while taking danazol,[4] and by inference the avoidance of hormonal contraceptives. They state that there is a theoretical risk that danazol and exogenously administered oestrogens and/or progestogens, including oral hormonal contraceptives, might possibly compete for the same oestrogen, progestogen, and androgen receptors, thereby altering the effects of both drugs.[3] This would also apply to other hormonal contraceptives such as progestogen implants and injections. However, as yet there appears to be no direct evidence that any interaction actually occurs.

(b) Gestrinone

Although gestrinone, at the dose used for endometriosis, can inhibit ovulation, it is not sufficiently reliable to be used as a contraceptive. The manufacturer strongly emphasises the importance of using a barrier method of contraception while taking gestrinone because they say that not only are the effects of gestrinone possibly modified by oral hormonal contraceptives, but its use in pregnancy is totally contraindicated (high doses have been shown to be embryotoxic in some *animal* species).[5]

1. Greenblatt RB, Oettinger M, Borenstein R, Bohler CS-S. Influence of danazol (100 mg) on conception and contraception. *J Reprod Med* (1974) 13, 201–3.
2. Colle ML, Greenblatt RB. Contraceptive properties of danazol. *J Reprod Med* (1976) 17, 98–102.
3. Sterling-Winthrop, Personal communication 1990.
4. Danol (Danazol). Sanofi-Aventis. UK Summary of product characteristics, July 2007.
5. Dimetriose (Gestrinone). Sanofi-Aventis. UK Summary of product characteristics, February 2008.

Hormonal contraceptives + Griseofulvin

The effects of the oral hormonal contraceptives may possibly be disturbed (either intermenstrual bleeding or amenorrhoea) if griseofulvin is taken concurrently. A few isolated reports describe women taking oral hormonal contraceptives who became pregnant while taking griseofulvin.

Clinical evidence

In 1984, regulatory authorities in the UK and the Netherlands noted that they had received a total of 22 reports of possible interactions between oral hormonal contraceptives and griseofulvin. These included 15 reports of transient intermenstrual bleeding and 5 of amenorrhoea, occurring during the first or second cycle, after griseofulvin 500 mg to 1 g daily was started. Four of these patients were rechallenged with griseofulvin (2 with intermenstrual bleeding and 2 with amenorrhoea) and all developed their original reactions. The other two women were reported to have become pregnant while taking griseofulvin and a sulfonamide ('co-trimoxazole', (p.1172) in one instance and an unknown sulfonamide in the other).[1] One other case of contraceptive failure has been reported from an analysis of the database of the CSM in the UK from 1968 to 1984,[2] but note this case may be included in the two already reported.[1] One other case report describes a woman taking an oral triphasic combined hormonal contraceptive who became pregnant about 2 months after she started to take griseofulvin 330 mg twice daily,[3] and another report describes a woman taking an oral hormonal contraceptive who became pregnant 6 weeks after starting to take griseofulvin 500 mg daily for 3 months and a 7-day course of erythromycin.[4] Note that erythromycin has also been reported to interact, see 'Combined hormonal contraceptives + Antibacterials; Macrolides', p.1168. Irregular menses and reduced menstrual flow have been described in another woman taking an oral combined hormonal contraceptive (**ethinylestradiol** 35 micrograms with **norethisterone** 500 micrograms to 1 mg) with griseofulvin 250 to 500 mg daily. When the contraceptive was substituted with another with more oestrogen (**ethinylestradiol** 50 micrograms with **norgestrel** 500 micrograms), the menstrual cycle became normal again.[5]

Mechanism

Not understood. Early evidence led to the suggestion that griseofulvin may possibly induce the activity of the liver enzymes concerned with the metabolism of the contraceptive steroids, thereby reducing their effects.[1] For this reason, griseofulvin has often been classified as an enzyme inducer. However, there is no *in vitro* or clinical evidence to support this. The apparent lack of interactions of griseofulvin with many other drugs that are substrates of liver enzymes suggests that griseofulvin is not a clinically important enzyme inducer, although this can only be confirmed by a controlled clinical study.

Importance and management

Information about an interaction between griseofulvin and oral hormonal contraceptives is very limited, but there is some evidence to suggest that menstrual disturbances may occur. The risk of contraceptive failure is uncertain but probably very small. However, it is important to ensure adequate contraception during and for one month after taking griseofulvin because it can induce aneuploidy (abnormal segregation of chromosomes during cell division), which carries the potential risk of teratogenicity.[6] Therefore, for maximal contraceptive protection, additional contraceptive measures (such as a barrier method) should be used routinely with oral combined hormonal or progestogen-only contraceptives while taking griseofulvin and for one month afterwards. Note that some UK authorities[7] also recommend additional contraceptive precautions on the basis of griseofulvin being an enzyme inducer, but see *Mechanism*, above.

It has been suggested that **progestogen-only oral contraceptives** are not the contraceptive of choice in those taking griseofulvin, not because of reduced efficacy, but because of increased menstrual irregularities.[8]

1. van Dijke CPH, Weber JCP. Interaction between oral contraceptives and griseofulvin. *BMJ* (1984) 288, 1125–6.

2. Back DJ, Grimmer SFM, Orme ML'E, Proudlove C, Mann RD, Breckenridge AM. Evaluation of Committee on Safety of Medicines yellow card reports on oral contraceptive-drug interactions with anticonvulsants and antibiotics. *Br J Clin Pharmacol* (1988) 25, 527–32.
3. Côté J. Interaction of griseofulvin and oral contraceptives. *J Am Acad Dermatol* (1990) 22, 124–5.
4. Bollen M. Use of antibiotics when taking the oral contraceptive pill. *Aust Fam Physician* (1995) 24, 928–9.
5. McDaniel PA, Caldroney RD. Oral contraceptives and griseofulvin interaction. *Drug Intell Clin Pharm* (1986) 20, 384.
6. Committee on Safety of Medicines/Medicines Control Agency. Griseofulvin (Fulcin, Grisovin): contraceptive precautions. *Current Problems* (1996) 22, 8.
7. Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit. FFPRHC Guidance: Drug interactions with hormonal contraception. April 2005. Available at: http://www.ffprhc.org.uk/admin/uploads/DrugInteractionsFinal.pdf (accessed 01/02/10).
8. McCann MF, Potter LS. Progestin-only contraception: a comprehensive review. *Contraception* (1994) 50 (Suppl 1), S1–S198.

Hormonal contraceptives + NRTIs

There do not appear to have been any reports of hormonal contraceptive failure or a reduction in the efficacy of NRTIs during concurrent use. Tenofovir does not appear to affect the pharmacokinetics of ethinylestradiol or norgestimate. Hormonal contraception (oral combined hormonal contraceptives or medroxyprogesterone acetate) did not alter the pharmacokinetics of zidovudine.
Note that whatever other methods of contraception are being used, barrier methods are also advisable to reduce the risk of HIV transmission.

Clinical evidence and mechanism

(a) Tenofovir

In a study in 20 women taking an oral combined hormonal contraceptive containing **ethinylestradiol** and **norgestimate**, tenofovir 300 mg daily for 7 days had no effect on the pharmacokinetics of **ethinylestradiol** or **norgestimate**. The pharmacokinetics of tenofovir were also not affected when compared with historical data.[1]

(b) Zidovudine

In a study in 14 women, there was no difference in the AUCs of either plasma zidovudine or intracellular zidovudine phosphorylates when zidovudine 200 mg three times daily for 7 days was given before or after starting hormonal contraception. One dose of the zidovudine was given intravenously. There was a modest 40% increase in the AUC ratio of glucuronidated zidovudine to zidovudine after intravenous administration only; however, this was not statistically significant. Six women were given an oral combined hormonal contraceptive (**ethinylestradiol** 35 micrograms **norethisterone** 1 mg) and 8 women were given depot **medroxyprogesterone acetate**. There were no differences in any of the pharmacokinetic parameters between the two types of contraceptive, although note that the study was insufficiently powered to reliably assess this.[2] It had been expected that contraception would increase the zidovudine AUC because an *in vitro* study found that **ethinylestradiol** inhibited the glucuronidation of zidovudine by 50% or more.[3] Although the clinical study only included a small number of women taking the oral combined hormonal contraceptive, it does discount a marked effect of this on zidovudine levels. Note also that other drugs that had a similar effect *in vitro* did not alter zidovudine pharmacokinetics in subsequent clinical studies, see 'NRTIs; Zidovudine + Drugs that inhibit glucuronidation', p.960.

Importance and management

Tenofovir does not appear to alter the pharmacokinetics of oral combined contraceptives, and would not therefore be expected to alter their efficacy by this mechanism. Oral combined hormonal contraceptives and medroxyprogesterone acetate do not appear to alter zidovudine levels. There appears to be no published evidence at present of any clinically relevant interactions between the other NRTIs (**abacavir**, **didanosine**, **emtricitabine**, **lamivudine**, **stavudine** and **zalcitabine**) and hormonal contraceptives, and note that no pharmacokinetic interaction would be expected. A study[4] found no evidence to suggest that hormonal contraceptives (mostly oral combined hormonal contraceptives or depot medroxyprogesterone acetate) affect the efficacy of HAART. The specific HAART drugs were not named; however, most patients were noted to be on a regimen containing an NRTI and a protease inhibitor, but no NNRTI.

Note that whatever other methods of contraception are being used, barrier methods are also advisable to reduce the risk of HIV transmission.

1. Kearney BP, Isaacson E, Sayre J, Cheng AK. Tenofovir DF and oral contraceptives: Lack of a pharmacokinetic drug interaction. *Intersci Conf Antimicrob Agents Chemother* (2003) 43, 37.
2. Aweeka FT, Rosenkranz SL, Segal Y, Coombs RW, Bardeguez A, Thevanayagam L, Lizak P, Aberg J, Watts DH; NIAID AIDS Clinical Trials Group. The impact of sex and contraceptive therapy on the plasma and intracellular pharmacokinetics of zidovudine. *AIDS* (2006) 20, 1833–41.
3. Sim SM, Back DJ, Breckenridge AM. The effect of various drugs on the glucuronidation of zidovudine (azidothymidine, AZT) by human liver microsomes. *Br J Clin Pharmacol* (1991) 32, 17–21.
4. Chu JH, Gange SJ, Anastos K, Minkoff H, Cejtin H, Bacon M, Levine A, Greenblatt RM. Hormonal contraceptive use and the effectiveness of highly active antiretroviral therapy. *Am J Epidemiol* (2005) 161, 881–90.

Hormonal contraceptives + Orlistat

Studies suggest that orlistat does not alter the suppression of ovulation in women taking oral combined hormonal contraceptives. However, isolated pregnancies have occurred with oral contraceptives in women also taking orlistat, and the UK manufacturer says that severe orlistat-induced diarrhoea might be a risk for this.

Clinical evidence

Two groups of 10 healthy women taking an oral combined hormonal contraceptive were given **orlistat** 120 mg three times daily or a placebo on days one to 23 of two menstrual cycles.[1] Orlistat had no effect on ovulation (measured by LH and progesterone levels). The contraceptives used all subjects contained **ethinylestradiol**, but the progestogens differed: 10 contained **desogestrel**, 4 **levonorgestrel**, 3 **gestodene**, 2 **cyproterone acetate** and one **lynestrenol**. However, there is a brief published case of a woman who had been taking an oral low dose combined hormonal contraceptive (**ethinylestradiol** 20 micrograms with **desogestrel** 150 micrograms) for 2 years who was found to be pregnant within 9 weeks of starting to take orlistat 120 mg three times daily.[2]

Mechanism

The UK manufacturers state that orlistat may indirectly reduce the bioavailability of oral hormonal contraceptives (as it can cause severe diarrhoea), and that this may lead to unexpected pregnancies in individual cases.[3] The one published case does not mention to what extent the woman had orlistat-induced diarrhoea.

Importance and management

It seems feasible that if orlistat causes significant diarrhoea this could increase the risk of contraceptive failure with oral hormonal contraceptives, whether combined or progestogen-only. Therefore, the UK manufacturer recommends using an additional contraceptive in case patients develop severe diarrhoea.[3] Note that the contraceptive effect of the combined hormonal contraceptive given as a patch is said not to be affected by diarrhoea.

1. Hartmann D, Güzelhan C, Zuiderwijk PBM, Odink J. Lack of interaction between orlistat and oral contraceptives. *Eur J Clin Pharmacol* (1996) 50, 421–4.
2. Peleg R. Caution when using oral contraceptive pills with orlistat. *Isr Med Assoc J* (2000) 2, 712.
3. Xenical (Orlistat). Roche Products Ltd. UK Summary of product characteristics, March 2009.

Hormonal contraceptives + Proton pump inhibitors

Lansoprazole and pantoprazole did not appear to alter the effect of oral combined hormonal contraceptives on the suppression of ovulation. Oral combined hormonal contraceptives modestly inhibit the metabolism of omeprazole, but the levonorgestrel progestogen-only pill appears to have no effect.

Clinical evidence

(a) Lansoprazole

In a placebo-controlled, crossover study, 24 healthy women were given an oral combined hormonal contraceptive (**ethinylestradiol** 30 micrograms with **levonorgestrel** 150 micrograms) for two monthly cycles, with and

without lansoprazole 60 mg daily. The levels of the oral hormonal contraceptive steroids were not significantly altered by lansoprazole, nor were endogenous progesterone levels raised, suggesting that ovulation did not occur.[1] The manufacturer has information about three other unpublished studies in a total of 59 women, which have also found no evidence to suggest that lansoprazole interacts with oral hormonal contraceptives in any way which would affect their reliability.[2]

(b) Omeprazole

A study in 10 healthy women given an oral combined hormonal contraceptive (**ethinylestradiol** 40 micrograms with **levonorgestrel** 75 micrograms) for 10 days found that the contraceptive increased the AUC of a single 40-mg dose of omeprazole (*Losec MUPS*) by 38%. This increase was not seen when the subjects were given **levonorgestrel** 60 micrograms daily alone for 10 days, taken as two tablets of a progestogen-only oral contraceptive.[3] Similarly, in a pharmacokinetic probe study in 10 women, an oral combined hormonal contraceptive (**ethinylestradiol** 35 microrams with **norgestimate** 180 to 250 micrograms) caused about a 50% increase in the ratio of omeprazole to its metabolite 5-hydroxyomeprazole, which indicates an inhibition of omeprazole metabolism.[4] This confirms earlier similar findings of a higher omeprazole to hydroxyomeprazole ratio in women taking oral hormonal contraceptives compared with non-users of these contraceptives.[5]

(c) Pantoprazole

A study over four menstrual cycles was completed by 64 women. The women were confirmed to be ovulating before taking a low-dose oral triphasic hormonal contraceptive (**ethinylestradiol** with **levonorgestrel**), and not ovulating during contraceptive use. They continued not ovulating when pantoprazole 40 mg daily was given, so it was concluded that pantoprazole does not affect the efficacy of oral hormonal contraception.[6]

Mechanism

Ethinylestradiol appears to be a minor to modest inhibitor of the cytochrome P450 isoenzyme CYP2C19, by which omeprazole is principally metabolised.[4,5] As this is also the main route of metabolism of most of the other proton pump inhibitors (see 'Gastrointestinal drugs', (p.1142)), they may be similarly affected. Levonorgestrel does not have this effect.

Importance and management

The proton pump inhibitors tested (lansoprazole, pantoprazole) do not appear to alter the suppression of ovulation in women taking oral combined hormonal contraceptives and would therefore not be expected to alter their reliability. There is nothing to suggest that omeprazole will be any different.

Oral combined hormonal contraceptives cause a modest increase in omeprazole levels (and may similarly affect some other proton pump inhibitors), but this is unlikely to be clinically relevant. The progestogen-only oral contraceptive containing levonorgestrel does not have this effect.

1. Fuchs W, Sennewald R, Klotz U. Lansoprazole does not affect the bioavailability of oral contraceptives. *Br J Clin Pharmacol* (1994) 38, 376–80.
2. Wyeth, Personal communication, February 1998.
3. Palovaara S, Tybring G, Laine K. The effect of ethinyloestradiol and levonorgestrel on the CYP2C19-mediated metabolism of omeprazole in healthy female subjects. *Br J Clin Pharmacol* (2003) 56, 232–7.
4. Shelepova T, Nafziger AN, Victory J, Kashuba ADM, Rowland E, Zhang Y, Sellers E, Kearns G, Leeder JS, Gaedigk A, Bertino JS. Effect of a triphasic oral contraceptive on drug-metabolizing enzyme activity as measured by the validated Cooperstown 5+1 cocktail. *J Clin Pharmacol* (2005) 45, 1413–21.
5. Laine K, Tybring G, Bertilsson L. No sex-related differences but significant inhibition by oral contraceptives of CYP2C19 activity as measured by the probe drugs mephenytoin and omeprazole in healthy Swedish white subjects. *Clin Pharmacol Ther* (2000) 68, 151–9.
6. Middle MV, Müller FO, Schall R, Hundt HKL, Mogilnicka EM, Beneke PC. Effect of pantoprazole on ovulation suppression by a low-dose hormonal contraceptive. *Clin Drug Invest* (1995) 9, 54–6.

Hormonal contraceptives + Retinoids

There seems to be no evidence that the reliability of the oral combined hormonal contraceptives is affected by acitretin, etretinate or isotretinoin. It is unclear whether the effects of the progestogen-only oral contraceptives are altered by acitretin, but, in any case, progestogen-only oral contraceptives are not generally considered reliable enough for use with these teratogenic drugs. The adverse effects of isotretinoin on lipids may be additive with those of oral contraceptives.

Clinical evidence

(a) Combined hormonal contraceptives

1. Acitretin. Eight women taking an oral combined hormonal contraceptive (**ethinylestradiol** with **levonorgestrel**) were given acitretin 25 to 40 mg daily for at least two cycles. The suppression of ovulation in response to the contraceptive was not affected by acitretin, as assessed by plasma progesterone levels.[1]

2. Etretinate. In a study in 12 women taking an oral combined hormonal contraceptive (**ethinylestradiol** with **levonorgestrel**, **norethisterone**, **norgestrel**, or **cyproterone**) the use of **etretinate** 0.7 to 1 mg/kg did not affect the suppression of ovulation in response to the contraceptive.[2]

3. Isotretinoin. A pharmacokinetic study in 9 women taking an oral combined hormonal contraceptive found that the plasma levels of **ethinylestradiol** and **levonorgestrel** were not significantly changed in the first and third cycle after starting isotretinoin 500 micrograms/kg when compared with before starting the retinoid. Suppression of ovulation was maintained.[3] In another study in 26 women taking an oral triphasic combined hormonal contraceptive (**ethinylestradiol** 35 micrograms with **norethisterone** 500 micrograms to 1 mg), the pharmacokinetics of the contraceptive steroids were almost identical when isotretinoin 1 mg/kg daily was also given. The only changes were a 9% decrease in the ethinylestradiol AUC on day 6 (but not day 20), and an 11% decrease in the maximum level of norethisterone on day 20. FSH showed a significant 44% decline (day 20) after starting isotretinoin, suggesting a greater suppression of ovulation, but there was no significant changes in LH or progesterone. However large inter-patient variability in the results was noted and 2 patients had increases in progesterone levels, possibly indicating that ovulation had occurred, one of these in the phase before isotretinoin treatment (noted to be non-compliant), and one during isotretinoin.[4]

The US manufacturer notes that pregnancies have occurred in women taking isotretinoin while using combined hormonal contraceptives, given orally, as the patch, or as the vaginal ring, and that these reports are more frequent in women using only one form of contraception.[5]

The adverse effects of isotretinoin and combined hormonal contraceptives on plasma lipids may be additive. A case-control study found that women who had hypertriglyceridaemia and/or hypercholesterolaemia while taking isotretinoin were 2 to 12 times as likely to be also taking an oral hormonal contraceptive.[6]

(b) Progestogen-only contraceptives

One woman taking an oral progestogen-only contraceptive (**levonorgestrel** 30 micrograms) had a significant increase in her progesterone levels after 3 cycles while taking **acitretin** 400 micrograms/kg daily. Plasma progesterone levels rose from 2.15 nanograms/mL before taking the **acitretin** to 3.87 to 13.46 nanograms/mL with **acitretin**. This rise in progesterone levels was taken as evidence that ovulation had occurred.[1]

The US manufacturer notes that pregnancies have occurred in women taking **isotretinoin** while using contraceptive implants or injections.[5]

Mechanism, importance and management

The available data suggest that these retinoids do not usually alter the efficacy of oral combined hormonal contraceptives. The case with acitretin suggests that it might reduce the efficacy of progestogen-only oral contraceptives. However, note that progestogen-only oral contraceptives do not reliably suppress ovulation in all cycles, and that this is not considered their primary mechanism of action (see 'Hormonal contraceptives and sex hormones', (p.1165)). The single report cannot therefore be taken as proof that acitretin reduces the efficacy of progestogen-only contraceptives.

Also note that because the retinoids are established human teratogens, it is very important that women taking them do not become pregnant. For this reason, progestogen-only oral contraceptives are generally not considered suitable for use with retinoids.[7] Unless contraindicated, oral combined hormonal contraceptives were considered the method of choice.[7-9] The oral combined hormonal contraceptive should be started one month before the retinoids and continued for one month after stopping isotretinoin,[8,9] and for 2 years after stopping etretinate or acitretin.[7] In the US, it is standard practice to mandate that a second form of contraception, such as a barrier method, should also be used.[5] This is also preferred by the UK manufacturer of isotretinoin.[10] This is because, even though hormonal methods of contraception are highly effective, they do, on rare occasions, fail.[8] The very small reduction in ethinylestradiol levels seen in one study with isotretinoin is unlikely to be clinically relevant. However, because of this small reduction and the wide variability in hormonal levels, the

authors state that their results reinforce the advice of using two forms of contraception,[4] one of which should usually be a barrier method, such as condoms.[5] Note that an oral contraceptive containing a non-androgenic (third generation) progestogen (e.g. desogestrel, gestodene, norgestimate) is preferred, as these have less detrimental effects on lipids,[7] and some favour the use of the anti-androgen cyproterone.[9]

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5. Accutane (Isotretinoin). Roche Laboratories Inc. US Prescribing information, November 2008.
6. Chen Y, Xue S, Dai W, LaBraico J. Evaluation of serum triglyceride and cholesterol levels from isotretinoin therapy with concomitant oral contraceptives. *Pharmacoepidemiol Drug Safety* (1995) 4, 91–6.
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Hormonal contraceptives + Thalidomide

The pharmacokinetics of ethinylestradiol and norethisterone are not affected by thalidomide. The concurrent use of combined hormonal contraceptives and thalidomide is associated with a theoretical increased risk of thromboembolic events in some patients.

Clinical evidence, mechanism, importance and management

In studies in 10 women who had undergone surgical sterilisation and 10 postmenopausal women, the pharmacokinetics of single doses of **ethinylestradiol** 70 micrograms with **norethisterone** 2 mg were not affected by pretreatment with thalidomide 200 mg daily for 3 weeks.[1,2]

These studies indicate that thalidomide is unlikely to have a pharmacokinetic interaction with hormonal contraceptives.

Note that thalidomide is a powerful teratogen, and therefore it is essential that women of child-bearing age use reliable contraception while taking this drug. The UK manufacturer advises one reliable method,[3] whereas the US manufacturer mandates two reliable forms of contraception.[4] Moreover, the UK manufacturer considers that the increased risk of thromboembolic events in patients receiving thalidomide for multiple myeloma might be further increased by the use of **combined hormonal contraceptives**, so they do not recommend these contraceptives. They state that, if a hormonal contraceptive is used, progestogen-only contraceptives should be used, and they specifically recommend implants, depot injections, the levonorgestrel intrauterine system or an oral progestogen that inhibits ovulation (oral desogestrel).[3] However, the US manufacturer makes no mention of the theoretical increased risk of thrombosis specifically with combined hormonal contraceptives, and does not exclude their use (in conjunction with another form of contraception).[4] It must also be borne in mind that the reliability of hormonal contraceptives may be compromised by the concurrent use of drugs other than thalidomide.

1. Trapnell CB, Donahue SR, Collins JM, Flockhart DA, Thacker D, Abernethy DR. Thalidomide does not alter the pharmacokinetics of ethinyl estradiol and norethindrone. *Clin Pharmacol Ther* (1998) 64, 597–602.
2. Scheffler MR, Colburn W, Kook KA, Thomas SD. Thalidomide does not alter estrogen-progesterone hormone single dose pharmacokinetics. *Clin Pharmacol Ther* (1999) 65, 483–90.
3. Thalidomide Celgene (Thalidomide). Celgene Ltd. UK Summary of product characteristics, August 2009.
4. Thalomid (Thalidomide). Celgene Corporation. US Prescribing information, February 2007.

Hormonal contraceptives + Tobacco or Nicotine

There is some evidence that smoking tobacco increases the risk of breakthrough bleeding with oral combined hormonal contraceptives, although smoking appears not to alter contraceptive steroid levels. The risk of cardiovascular disease in women taking combined hormonal contraceptives is greatly increased if they smoke, particularly in the older age group. Progestogen-only contraceptives are an alternative. Combined hormonal contraceptives may modestly increase nicotine metabolism.

Clinical evidence

(a) Cardiovascular effects

Early after the introduction of oral combined hormonal contraceptives it was realised that they increase the risk of cardiovascular effects such as thromboembolism, myocardial infarction, and stroke, and that the risks were markedly increased in women who also smoked.[1-5] For example, one of these studies found a relative risk of non-fatal myocardial infarction in women taking an oral hormonal contraceptive of 4.5 in non-smokers and 39 in heavy smokers.[4] Another study found a relative risk of subarachnoid haemorrhage in women taking oral hormonal contraceptives of 6.5 for non-smokers and 22 for smokers.[5] Heavy smokers (who smoke more than 15 cigarettes daily) have a threefold increased risk of myocardial infarction and a twofold increase in the risk of stroke compared with non-smokers, and these risks are further increased by the use of oral combined hormonal contraceptives.[6] A study involving 17 032 women aged 25 to 39 years at entry, who had used oral hormonal contraceptives (mainly containing 50 micrograms of oestrogen), a diaphragm, or an intrauterine device, found that the risk of death from ischaemic heart disease was slightly, but not statistically significantly, raised in all oral hormonal contraceptive users. However, smoking had a substantial effect on mortality from ischaemic heart disease; in heavy smokers (more that 15 cigarettes daily) the mortality rate ratios for oral hormonal contraceptive use for 48 months or less, for 49 to 96 months, and for 97 months or more compared with non-use were 2.4, 4.8, and 2.8, respectively.[7]

(b) Contraceptive efficacy

An analysis of data from three large clinical studies in a total of 2956 women found that smoking was associated with an increased incidence of spotting and bleeding in users of oral combined hormonal contraceptives. The relative risk was 1.3 during the first cycle of use and increased to 1.9 by the sixth cycle.[8] Similarly, in a study of women who became pregnant while taking oral hormonal contraceptives, smokers were more likely to have menstrual disturbances, and smokers taking an oral combined hormonal contraceptive had a 20% greater pill failure rate than expected,.[9] This association was not noted for **progestogen-only oral contraceptive** failure.[9] Conversely, in a large cohort study in the UK, the failure rate of oral hormonal contraceptives was not increased in smokers.[10] In one study in 311 women taking oral hormonal contraceptives, plasma levels of **ethinylestradiol** and **norgestrel** were similar in smokers and non-smokers,[11] and another study found only a small increase in **ethinylestradiol** clearance in smokers.[12]

(c) Nicotine metabolism

In a non-randomised comparison, the metabolism of nicotine after a single intravenous infusion was modestly faster in 53 women using oral hormonal contraceptives than in 153 women not using these contraceptives. This was demonstrated by a 28% faster clearance, and a 19% shorter half-life, of nicotine. In the 50 women using oral combined hormonal contraceptives, nicotine clearance was 30% faster, whereas in the just 3 women who were taking a **progestogen-only contraceptive**, nicotine clearance appeared to be 12% slower. Nevertheless, there was no difference in mean daily cigarette consumption between women using oral hormonal contraceptives and those not.[13] Another study presented similar findings that nicotine metabolism was faster in girls using hormonal contraception than those not using these contraceptives.[14]

Mechanism

The cardiovascular effects reported do not appear to be attributable to any effect of smoking on the metabolism of contraceptives steroids (see below). Rather, the adverse effects of oral combined hormonal contraceptives on cardiovascular risk factors, such as plasma lipids and coagulation parameters, appear to be additive or synergistic with those of smoking.

Smoking does not appear to alter the levels of contraceptive steroids to a clinically relevant extent. Nicotine is metabolised by cytochrome P450 isoenzyme CYP2A6 to cotinine. The limited available evidence suggests

that this may be modestly induced by oral combined hormonal contraceptives.

Importance and management

The cardiovascular interaction between smoking and **combined hormonal contraceptives** is well established. In the UK, the Faculty of Family Planning and Reproductive Health Care (FFPRHC) Clinical Effectiveness Unit and Royal College of Obstetricians and Gynaecologists guidelines on criteria for the use of contraceptives recommend that the combined hormonal contraceptive should not be used in women aged over 35 years who are current smokers or who stopped smoking less than one year ago as the risks, particularly of cardiovascular disease, outweigh the benefits.[6,15] Women over the age of 35 years with no additional risk factors (such as diabetes, hypertension etc.) and who stopped smoking more than one year ago may consider using a combined hormonal contraceptive. This is because the risk of cardiovascular disease reduces by as much as 50% one year after stopping smoking, although it may not become comparable to that of a non-smoker for up to 4 to 10 years.[6,15] Women aged under 35 years who smoke and have no other associated risk factors may use a combined hormonal contraceptive, but should be informed about the increased risk of cardiovascular disease. Any woman with multiple risk factors for cardiovascular disease (older age, smoking, diabetes, hypertension, obesity, family history of arterial disease, migraine) should not take the combined hormonal contraceptive.[15,16] The BNF in the UK recommends that women who smoke 40 or more cigarettes a day should not receive oral combined hormonal contraceptives.[16] In women who smoke, for whom an oral combined hormonal contraceptive is not contraindicated, ones with the lowest doses of ethinylestradiol may be safer.[17] In the UK, **progestogen-only oral contraceptives** are considered suitable for women who are heavy smokers,[15] although it should be remembered that they have a higher failure rate than the oral combined hormonal contraceptives.

Smoking may increase the incidence of breakthrough bleeding. This may decrease the acceptability of the oral hormonal contraceptive, and lead to the use of less effective contraceptive methods.[8] However, it also raises the question of whether smoking increases the failure rate of oral hormonal contraceptives. The only evidence that this may occur is anecdotal. Further study is needed.

Oral combined hormonal contraceptives might modestly increase nicotine metabolism, but the relevance of this to **nicotine replacement therapy**, if any, remains to be determined.

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5. Petitti DB, Wingerd J. Use of oral contraceptives, cigarette smoking, and risk of subarachnoid haemorrhage. *Lancet* (1978) ii, 234–6.
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9. Sparrow MJ. Pregnancies in reliable pill takers. *N Z Med J* (1989) 102, 575–7.
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11. Crawford FE, Back DJ, Orme ML'E, Breckenridge AM. Oral contraceptive steroid plasma concentrations in smokers and non-smokers. *BMJ* (1981) 282, 1829–30.
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14. Berlin I, Gasior MJ, Moolchan ET. Sex-based and hormonal contraception effects on the metabolism of nicotine among adolescent tobacco-dependent smokers. *Nicotin Tob Res* (2007) 9, 493–8.
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HRT + Ascorbic acid (Vitamin C)

There is some evidence that ascorbic acid may modestly increase estradiol levels in women receiving HRT.

Clinical evidence

In 25 postmenopausal women receiving *transdermal* **estradiol** HRT, ascorbic acid 500 mg twice daily for one month caused a non-significant 21% increase in plasma **estradiol** levels. However, in the 9 women with initially low **estradiol** levels, ascorbic acid doubled the levels, and this was statistically significant.[1]

Mechanism

Ascorbic acid may reverse the oxidation of the oestrogens.[1]

Importance and management

Evidence for an interaction between ascorbic acid and HRT appears to be limited to this one study. The authors say that their findings do not support the general use of ascorbic acid as an adjuvant to HRT, but that further study is needed. No special precautions are required.

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HRT + Azoles

Ketoconazole modestly increased the levels of estrone, a metabolite of estradiol.

Clinical evidence, mechanism, importance and management

A study in 6 postmenopausal women given a single 2-mg dose of **estradiol** found that **ketoconazole** 100 mg twice daily for 4 days increased the AUC and maximum plasma levels of **estrone** (a metabolite of estradiol) by 16% and 30%, respectively.[1] These small increases are unlikely to be clinically relevant.[1]

1. Annas A, Carlström K, Alván G, AL-Shurbaji A. The effect of ketoconazole and diltiazem on oestrogen metabolism in postmenopausal women after single dose oestradiol treatment. *Br J Clin Pharmacol* (2003) 56, 334–6.

HRT + Enzyme inducers

Enzyme inducers that increase the metabolism of contraceptive steroids might also be expected to reduce the efficacy of HRT. An isolated case describes reduced efficacy of oral conjugated oestrogens in a patient taking phenytoin.

Clinical evidence, mechanism, importance and management

A report describes a 28-year-old woman taking oral **conjugated oestrogens** (*Premarin*) 1.25 mg daily after hysterectomy and ovariectomy, who had a dramatic increase in the incidence of hot flushes when she began to take **phenytoin** 300 mg daily. Her estrone and estradiol levels were found to be very low, and they subsequently increased four- to sixfold after the **phenytoin** was stopped, at which point the incidence of hot flushes decreased.[1] This seems to be the only report of this interaction, and there do not appear to be any pharmacokinetic drug interaction studies of HRT preparations with enzyme inducing drugs. Nevertheless, **rifampicin** (**rifampin**) caused a 44% reduction in the AUC of **estradiol** used as the oestrogen component of an oral combined hormonal contraceptive, which is similar to its interaction with ethinylestradiol, see 'Combined hormonal contraceptives + Rifamycins', p.1189. Therefore, it is not unreasonable to assume that other enzyme inducers that increase the metabolism of contraceptive steroids (see 'Table 28.1', (p.1165)) would also increase the metabolism of oestrogens used for HRT. These drugs may therefore reduce the efficacy of HRT preparations. This would be most likely to be noticed where HRT is prescribed for menopausal vasomotor symptoms, but might

be difficult to detect where the indication is osteoporosis. The interaction is not relevant to HRT applied locally for menopausal vaginitis. Further study is needed to confirm the importance of this possible interaction.

1. Notelovitz M, Tjapkes J, Ware M. Interaction between estrogen and Dilantin in a menopausal woman. *N Engl J Med* (1981) 304, 788–9.

HRT + Grapefruit juice

Grapefruit juice caused a minor increase in estrogen levels after a single oral dose of estradiol. One epidemiological study found that the consumption of whole grapefruit caused a minor increased risk for breast cancer, and that this was additive with the effect of HRT, whereas another similar study did not confirm this.

Clinical evidence

In a study in 8 women given a single 2-mg dose of **estradiol**, simultaneous administration of 200 mL of **grapefruit juice** produced a small 16% increase in the AUC of estrone, a metabolite of **estradiol**, and a 40% increase (not statistically significant) in the AUC of **estradiol**.[1]

In a large cohort study, eating more than a quarter of a **whole grapefruit** per day increased the relative risk of breast cancer in current users of HRT by about one-third (relative risk 2.55 versus 2.01 in users of oestrogen and progestogen, and 2.12 versus 1.56 in users of oestrogen alone). A similar increased risk of breast cancer with grapefruit was seen in women not using HRT (1.44 versus 1). This study was unable to assess the effect of **grapefruit juice**, because the original dietary questionnaire had combined this with orange juice.[2] In contrast, a later very similar study did not find an association between eating the same amount of whole grapefruit daily and breast cancer, including in women taking HRT.[3]

Mechanism

It appears that grapefruit juice has some minor inhibitory effect on the metabolism of estradiol (see also 'Combined hormonal contraceptives + Grapefruit juice', p.1183). Increasing oestrogen levels may increase the risk of adverse effects, including estrogen-associated breast cancer.

Importance and management

The small pharmacokinetic study provides some reassurance that grapefruit juice has only a minor effect on oestrogen levels after estradiol administration. However, a larger study is needed to provide a more conclusive picture. One epidemiological study found that the risk of breast cancer with daily consumption of whole grapefruit caused a minor increased risk of breast cancer that was additive with the effect of menopausal HRT. However, the effect was very much smaller than the increased risk with HRT alone. Moreover, another study did not find an association between grapefruit and breast cancer risk. Interpretation of these studies is complicated by the fact they did not control for grapefruit juice consumption.

1. Schubert W, Cullberg G, Edgar B, Hedner T. Inhibition of 17β-estradiol metabolism by grapefruit juice in ovariectomized women. *Maturitas* (1994) 20, 155–63.
2. Monroe KR, Murphy SP, Kolonel LN, Pike MC. Prospective study of grapefruit intake and risk of breast cancer in postmenopausal women: the Multiethnic Cohort Study. *Br J Cancer* (2007) 97, 440–5.
3. Spencer EA, Key TJ, Appleby PN, van Gils CH, Olsen A, Tjønneland A, Clavel-Chapelon F, Boutron-Ruault M-C, Touillaud M, Sánchez M-J, Bingham S, Khaw KT, Slimani N, Kaaks R, Riboli E. Prospective study of the association between grapefruit intake and risk of breast cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC). Cancer Causes Control (2009) 20, 803–9.

HRT + NSAIDs

Etoricoxib appears to raise the levels of conjugated oestrogens from HRT. The findings of one observational study raise the possibility that the risk of myocardial infarction might be higher with the concurrent use of NSAIDs and HRT.

Clinical evidence

High-dose etoricoxib 120 mg daily for 28 days taken with HRT containing 0.625 mg of conjugated oestrogens (*Premarin)* increased the AUC of unconjugated estrone, equilin and 17-β estradiol by 41%, 76%, and 22%, respectively.[1]

In a large population-based epidemiological study, the odds ratio of a myocardial infarction was increased in women taking HRT with an NSAID (1.7), was lower in women taking HRT without an NSAID (0.64) and unchanged in women taking an NSAID with no HRT (1.02), relative to women not taking HRT or an NSAID. In this study, the three most widely used NSAIDs, **diclofenac**, **ibuprofen**, and **naproxen**, accounted for 75% of NSAID use.[2]

Mechanism

Etoricoxib inhibits the conjugation of oestrogens by sulfation (see also 'Combined hormonal contraceptives + Coxibs', p.1181. It was suggested that NSAIDs might inhibit the postulated beneficial atheroprotective effects of estrogens.[2] However, it is also possible that the rare adverse cardiovascular effects of HRT and NSAIDs could be additive or synergistic.

Importance and management

The levels of these oestrogens with high-dose etoricoxib are less than half those seen with twice the dose of conjugated oestrogens (1.25 mg) taken alone.[1] The effects of usual recommended lower doses of etoricoxib have not been studied. The manufacturers say that these increases should be taken into account when selecting HRT in patients taking etoricoxib, because of the possible increased risk of HRT adverse effects.[1]

The findings of the epidemiological study suggest that the concurrent use of HRT and NSAIDs might have adverse cardiovascular effects. The authors suggested that this showed that NSAIDs possibly inhibit the beneficial effects of HRT,[2] but subsequent randomised studies have not shown HRT to have beneficial cardiovascular effects, and may possibly even cause an increase in cardiovascular events in the first year of use. An alternative hypothesis is that the rare adverse cardiovascular effects of HRT could be additive or synergistic with the small increased risk of rare thrombotic events (especially myocardial infarction and stroke) seen with coxibs and some NSAIDs. Further study is needed.

1. Arcoxia (Etoricoxib). Merck Sharp & Dohme Ltd. UK Summary of product characteristics, September 2009.
2. García Rodríguez LA, Egan K, FitzGerald GA. Traditional nonsteroidal anti-inflammatory drugs and postmenopausal hormone therapy: a drug-drug interaction? *PLoS Med* (2007) 4, e157.

HRT + Senna

Senna does not appear to affect the pharmacokinetics of estradiol.

Clinical evidence

In a clinical study in 19 women, the maximum daily tolerated dose of senna tablets (*Senokot*) was taken for 10 to 12 days with a single 1.5-mg dose of **estradiol glucuronide** given 4 days before the end of the assessment period. Senna had no significant effect on the median AUC of estradiol or estrone.[1]

Mechanism

It was thought that reducing intestinal transit time with senna might lead to reduced blood levels of estradiol.

Importance and management

This limited evidence suggests that there is unlikely to be a clinically relevant pharmacokinetic interaction between anthraquinone-containing laxatives and estradiol.

1. Lewis SJ, Oakey RE, Heaton KW. Intestinal absorption of oestrogen: the effect of altering transit-time. *Eur J Gastroenterol Hepatol* (1998) 10, 33–9.9512951

HRT + Triptans

The manufacturer briefly notes that HRT did not appear to affect the pharmacokinetics of naratriptan.[1]

1. Amerge (Naratriptan hydrochloride). GlaxoSmithKline. US Prescribing information, October 2007.

IUDs; Copper + Anti-inflammatory drugs

There are a few early reports suggesting that the very occasional contraceptive failure of a copper IUD may have been due to an interaction with a corticosteroid, aspirin or NSAID.

Clinical evidence, mechanism, importance and management

The cases of 4 women who, despite being fitted with copper IUDs, each had two successive pregnancies have been reported. Two were taking **corticosteroids** regularly and the other two often took **aspirin** for migraine.[1,2] Unwanted pregnancies have also been reported in 3 women with copper IUDs who were taking **corticosteroids**,[3-5] and in 2 women taking NSAIDs (**indomethacin** and **naproxen**).[5] A later case-control study found that **aspirin** and NSAIDs were used more frequently in 717 women who became pregnant while using IUDs than in 717 non-pregnant IUD users (the majority of IUDs were copper). The difference was significant only for **aspirin** (102 IUD failures, 59 control failures). It is possible that this finding could have resulted from bias in recall or reporting.[2] The suggested mechanism for any interaction was that part of the efficacy of copper IUDs may be based on local inflammatory effects, and that anti-inflammatory drugs might reduce this.

The evidence for this possible interaction is very slim and inconclusive, and there appear to be no further reports of any problems. Modern copper-containing IUDs are one of the most effective methods of contraception. Also, intermittent use of anti-inflammatory drugs such as NSAIDs is widespread. A recent Cochrane Database Systematic Review of studies on the use of NSAIDs to reduce pain and/or bleeding with IUDs recommends the use of NSAIDs as first-line drugs to reduce these adverse effects.[6] One manufacturer of copper IUDs states that the evidence does not justify general precautions.[7] No special precautions therefore appear to be necessary.

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2. Papiernik R, Rozenbaum H, Amblard P, Dephot N, de Mouzon J. Intra-uterine device failure: relation with drug use. *Eur J Obstet Gynecol Reprod Biol* (1989) 32, 205–12.
3. Inkeles DM, Hansen RI. Unexpected pregnancy in a woman using an intrauterine device and receiving steroid therapy. *Ann Ophthalmol* (1982) 14, 975.
4. Zerner J, Miller AB, Festino MJ. Failure of an intrauterine device concurrent with administration of corticosteroids. *Fertil Steril* (1976) 27, 1467–8.
5. Thomas P-R, Stérilet et anti-inflammatoires: à propos de quatre observations. *Concours Med* (1977) 45, 7095–6.
6. Grimes DA, Hubacher D, Lopez LM, Schulz KF. Non-steroidal anti-inflammatory drugs for heavy bleeding or pain associated with intrauterine-device use. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 04/01/07).
7. NOVA T 380 (copper containing intrauterine contraceptive device). Schering Health Care Limited. Technical data sheet, May 2003.

Medroxyprogesterone or Megestrol + Aminoglutethimide

Aminoglutethimide markedly reduces the plasma levels of medroxyprogesterone and megestrol given orally. Intravenous medroxyprogesterone acetate appears not to be affected.

Clinical evidence

(a) Medroxyprogesterone acetate

In 6 postmenopausal women with breast cancer aminoglutethimide 250 mg two to four times daily approximately halved the plasma levels of medroxyprogesterone acetate 500 mg three times daily.[1] Another study in 6 postmenopausal women found that aminoglutethimide 250 mg four times daily reduced medroxyprogesterone levels by 63% after oral, but not intravenous, use.[2] In another study in 6 women with advanced breast cancer, it was found that as the dose of aminoglutethimide was gradually reduced from 250 mg twice daily and finally withdrawn, the plasma levels of medroxyprogesterone steadily climbed to three times their initial level, although the dose remained constant at a total of 800 mg daily.[3]

(b) Megestrol

Aminoglutethimide 250 mg four times daily reduced the serum levels of megestrol 160 mg daily by 78% in 6 postmenopausal women.[2]

Mechanism

The most likely reason for this interaction is that aminoglutethimide acts as an enzyme inducer, increasing the metabolism of the progestogens, thereby decreasing their levels. When the aminoglutethimide is withdrawn, the enzyme induction ceases, and the progestogen level rises.

Importance and management

Both interactions appear to be established and are possibly clinically important. A 50% reduction in the plasma levels of medroxyprogesterone and megestrol should be expected during concurrent use, and this may reduce the adrenal suppressive effect.[1] The authors of one report[3] say that to achieve adequate plasma medroxyprogesterone acetate levels in breast cancer (above 100 nanograms/mL) a daily dose of 800 mg of *Provera* is probably necessary in the presence of aminoglutethimide 125 or 250 mg twice daily. This is double the usual recommended dose for this condition.

Note that intravenous medroxyprogesterone does not appear to be affected. It is therefore uncertain whether depot medroxyprogesterone acetate will be affected, although the manufacturer includes the possibility of the interaction in their product information.[4,5] However, if the mechanism for the aminoglutethimide interaction is correct (enzyme induction), this suggests that depot medroxyprogesterone would be unlikely to be affected, as it is said not to interact with enzyme inducers, see 'Progestogen-only contraceptives + Enzyme inducers', p.1206.

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Progestogen-only contraceptives + Antibacterials

The reliability of progestogen-only methods of hormonal contraception are probably not affected by antibacterials that do not induce liver enzymes, such as the penicillins and tetracyclines.

Clinical evidence

Four of the 63 contraceptive failures attributed to antibacterials in the records of the CSM in the UK for 1968 to 1984 occurred with a progestogen-only contraceptive (unspecified).[1] In another study, 2 of 37 cases of contraceptive failure attributed to antibacterials occurred with a progestogen-only contraceptive (unspecified).[2]

Note that, pharmacokinetic data show that the progestogen component (**levonorgestrel**, **norethisterone**) of oral *combined* hormonal contraceptives is not affected by **ampicillin**,[3,4] **clarithromycin**,[5] **doxycycline**,[6] **metronidazole**,[4] **moxifloxacin**,[7] or **tetracycline**;[8] whereas **desogestrel** exposure was slightly increased by **clarithromycin**,[5] and **levonorgestrel** exposure was slightly increased by **telithromycin**.[9] The progestogen component of the vaginal ring (**etonogestrel**) was not affected by **ampicillin** or **doxycycline**.[10]

Mechanism

The mechanism behind the rare cases of failure of oral *combined* hormonal contraceptives seen with various non-enzyme-inducing antibacterials is postulated to be reduced enterohepatic recycling of ethinylestradiol (see 'Combined hormonal contraceptives + Antibacterials; Penicillins', p.1170). As progestogens are largely metabolised to inactive substances before they are conjugated, they do not undergo enterohepatic recycling of the active substance. Progestogens are partially metabolised by the cytochrome P450 isoenzyme CYP3A4, so antibacterials that inhibit this isoenzyme, such as some of the macrolides, may actually increase progestogen exposure.

Importance and management

There is no reason to expect that the contraceptive efficacy of the various progestogen-only contraceptive methods (tablets, implants, injections, IUDs) would be affected by antibacterials that alter gut flora and do not induce liver enzymes.

It is generally accepted that no interaction occurs,[11] and it is likely that the few cases seen with progestogen-only contraceptives are chance associations.[1] In the UK, the Faculty of Family Planning and Reproductive Health Care (FFPRHC) Clinical Effectiveness Unit does not recommend any additional contraceptive precautions when antibacterials that do not induce liver enzymes are taken with any method of progestogen-only hormonal contraception, including the emergency contraceptive pill.[12] However, note that rifampicin (rifampin) and rifabutin are likely to reduce the efficacy of some forms of progestogen-only contraceptives, as they induce the metabolism of progestogens, see 'Progestogen-only contraceptives + Enzyme inducers', p.1206.

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Progestogen-only contraceptives + Azoles

In one study itraconazole markedly increased the levels of the active metabolite of desogestrel, whereas fluconazole had no effect.

Clinical evidence

In a crossover study in 11 healthy women, **itraconazole** 200 mg daily for 4 days increased the AUC of 3-keto-desogestrel (etonogestrel) by about 72% after a single 150-microgram oral dose of **desogestrel** was given one hour after the last itraconazole dose. There was no change in 3-keto-desogestrel maximum level or elimination half-life. Conversely, **fluconazole** 200 mg daily for 4 days had no effect.[1]

Note that, pharmacokinetic data show that the AUC of **norethisterone** (given as the progestogen component of an oral *combined* hormonal contraceptive) is increased by **voriconazole** (53%)[2] and **itraconazole** (40%),[3] but only minimally by **fluconazole** (13%).[4] Similarly, **levonorgestrel** was only modestly affected by **fluconazole** (24%)[5] and **etonogestrel** was only modestly affected by **miconazole** (17%).[6]

Mechanism

Itraconazole is principally an inhibitor of the cytochrome P450 isoenzyme CYP3A4, whereas fluconazole is principally an inhibitor of CYP2C9. The data here suggest that the active metabolite of desogestrel, 3-keto-desogestrel (etonogestrel) is mainly metabolised by CYP3A4.

Importance and management

Although based on a single-dose study, the available information suggests that fluconazole is unlikely to alter the efficacy of the desogestrel progestogen-only contraceptive by a pharmacokinetic mechanism. However, the marked increase in levels of the active metabolite of desogestrel with itraconazole suggests that itraconazole (and other potent CYP3A4 inhibitors) might increase the incidence of adverse effects of desogestrel. Further study is needed.

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Progestogen-only contraceptives + Enzyme inducers

The contraceptive efficacy of oral progestogen-only contraceptives, levonorgestrel implants, and etonorgestrel implants is probably reduced by enzyme inducers, and there are a number of reports of pregnancies in women given these contraceptives with an enzyme-inducing antiepileptic, St John's wort, rifampicin (rifampin) or efavirenz. Conversely, the efficacy of medroxyprogesterone depot injection may not be affected by enzyme inducers, and no pharmacokinetic interaction has been seen with this contraceptive and efavirenz, nevirapine and nelfinavir. Similarly, the contraceptive reliability of the norethisterone depot injection and the levonorgestrel-releasing intrauterine system is not thought to be affected by enzyme inducers.

Clinical evidence, mechanism, importance and management

(a) Implants

In a study, a **levonorgestrel** implant (*Norplant*) was inserted in 8 women taking enzyme-inducing antiepileptics (**phenytoin** and/or **carbamazepine**) and 10 women taking no other drugs. At 3, 6 and 9 months after insertion, plasma **levonorgestrel** levels were 38% lower in the 6 women taking **phenytoin** alone or in combination with **carbamazepine** or valproate than in the women not taking these enzyme inducers. Low **levonorgestrel** levels were also seen in the two women taking **carbamazepine** alone. Two of the women became pregnant (one taking **phenytoin** 25 mg daily, occurring about 11 months after insertion of the implant, and one taking **phenytoin** 400 mg daily with **carbamazepine** 400 mg daily, occurring 20 months after insertion of the implant).[1]

In three other cases women using **levonorgestrel** implants with enzyme-inducing antiepileptics became pregnant.[2-4] In one, a woman taking **phenytoin** 300 mg daily became pregnant 9 months after the insertion of the implant. **Levonorgestrel** levels increased by 50% after discontinuation of the **phenytoin**, and progesterone levels fell, suggesting greater suppression of ovulation.[2] Similarly, one woman taking **phenobarbital** 210 mg daily became pregnant about 17 months after the insertion of the **levonorgestrel** implant (this woman subsequently also became pregnant while using an oral combined hormonal contraceptive containing 35 micrograms of ethinylestradiol and a back up method).[3] Another report[4] briefly mentions that one woman taking enzyme-inducing antiepileptics became pregnant while using a **levonorgestrel** implant, and mentions that the manufacturer had 30 other similar cases on file as of 1995.

There are 4 published case reports of pregnancy in women using the **etonogestrel** implant (*Implanon*) with enzyme-inducing drugs. Once case occurred in a patient taking **carbamazepine** 600 mg daily, 1 month after insertion of the implant.[5] A pregnancy (ectopic) that occurred in a woman who had received the implant was considered to be due to the use of **rifampicin** (**rifampin**).[6] Another pregnancy occurred in a woman who had been fitted with this implant for approximately 2 years, about 6 months after starting **rifampicin** 300 mg twice daily for hidradenitis suppurativa.[7] There is also a case of contraceptive failure (ectopic pregnancy) in a woman taking **efavirenz**, lamivudine and zidovudine, 2.5 years after insertion of the **etonorgestrel** implant.[8]

In addition, an Australian post-marketing report for the 3 years from May 2001 describes 8 other cases of contraceptive failure with the **etonorgestrel** implant in patients who were taking enzyme-inducing antiepileptics (7 of the 8 were taking **carbamazepine**).[9] An updated report in 2007 gives 32 pregnancies in users of the **etonorgestrel** implant possi-

bly related to other medicines (26 with **carbamazepine**, 4 with **phenytoin**, one with **methylphenobarbital** and one with **rifampicin**.[10]

The data here show that contraceptive failure can occur with the progestogen implants (both **levonorgestrel** and **etonorgestrel**) if potent enzyme inducers are also taken. Limited evidence from the one study with the **levonorgestrel** implant suggests that the incidence might be high (2 out of 8 women). In the UK, the Faculty of Family Planning and Reproductive Health Care (FFPRHC) Clinical Effectiveness Unit recommends that the progestogen-only implant may be continued with short courses of enzyme inducers, but only if additional contraceptive methods such as condoms are used during and for at least 4 weeks after the drug is stopped. They recommend that alternatives to the progestogen-only implant should be considered with the long-term use of liver enzyme inducers.[11] A list of enzyme inducers can be found in 'Table 28.1', (p.1165)).

(b) Injectable preparations

1. Medroxyprogesterone acetate depot. In a study in women taking NRTIs with **efavirenz** (17), **nevirapine** (16), or **nelfinavir** (21), there was no significant change in the pharmacokinetics of depot medroxyprogesterone acetate 150 mg, when compared with 16 women not taking any antiretrovirals or taking just NRTIs. Suppression of ovulation was maintained. Furthermore, viral load and CD4 counts were not altered.[12,13] In another similar study, there was no difference in pharmacokinetics of depot medroxyprogesterone acetate between 15 women taking **efavirenz** plus two NRTIs (lamivudine and zidovudine) compared with 15 women not taking any antiretrovirals. No ovulation occurred in the women taking the antiretrovirals.[14] For mention of another study that found a low incidence of pregnancy in women taking an **efavirenz**-based regimen and using an intramuscular progestogen or an oral combined hormonal contraceptive, see 'Combined hormonal contraceptives + NNRTIs', p.1186.

The UK manufacturer states that the clearance of medroxyprogesterone acetate is approximately equal to hepatic blood flow, and as such, would not be expected to be affected by drugs that alter hepatic enzyme activity.[15] Whatever the explanation, the limited data with the antiretrovirals above seems to support a lack of an interaction. Therefore, the UK manufacturer says that no dose adjustment is needed,[15] and this is also the advice given by the FFPRHC,[11] although some have recommended giving the injection more frequently.[16]

2. Norethisterone depot. There are data showing that **rifamycins** and **carbamazepine** can reduce the plasma levels of norethisterone when it is used as a component of an oral combined hormonal contraceptive (see 'Combined hormonal contraceptives + Rifamycins', p.1189, and 'Combined hormonal contraceptives + Carbamazepine or Oxcarbazepine', p.1180). The UK manufacturer of *Noristerat* notes that enzyme inducers may theoretically reduce the efficacy of the norethisterone enantate injection.[17] Nevertheless, the dose of norethisterone provided by the depot injection is very much higher than that provided by oral combined hormonal contraceptives, and it is therefore possible that it remains effective even in women taking enzyme-inducing drugs.[18]

It has been recommended by some that the interval between injections be shortened in women taking enzyme-inducing drugs. However, in the UK, the guidance from the FFPRHC Clinical Effectiveness Unit is to continue with the normal injection schedule for norethisterone.[11]

(c) Oral progestogen-only contraceptives

In a review of pregnancies reported to the CSM in the UK between the years 1968 to 1984 in women taking antiepileptics and oral hormonal contraceptives, 3 cases were identified in women taking progestogen-only pills (progestogen not stated). The antiepileptics used in these specific cases were not stated, but most of the women were taking enzyme-inducing antiepileptics such as **phenytoin**, **phenobarbital**, **primidone** and **carbamazepine** (alone or as combinations).[19] In 2002, the UK regulatory authority had one case on record of an unplanned pregnancy that occurred 4 months after starting **St John's wort** in a woman who had been taking **norethisterone** for 2 years.[20]

There do not appear to have been any clinical pharmacokinetic studies of enzyme inducers with any of the oral progestogen-only contraceptives (**desogestrel**, **levonorgestrel**, **norethisterone**). Nevertheless, various enzyme inducers have specifically been shown to decrease the levels of these progestogens when used as components of oral combined hormonal contraceptives (see 'Table 28.1', (p.1165)). Therefore, it can be assumed that there is also a risk of contraceptive failure with oral progestogen-only contraceptives.[21] This is of particular concern as oral progestogen-only contraceptives are not as effective as oral combined hormonal contraceptives, especially the **levonorgestrel** and **norethisterone** preparations, which are given in very low doses that do not consistently inhibit ovulation. Some have suggested at least doubling the dose of the oral progestogen-only contraceptive.[22] However, others consider that this is not an option as it tends to increase the rate of irregular bleeding (a common adverse effect of these contraceptives). They consider that oral progestogen-only contraceptives are not suitable for use in women taking enzyme-inducing antiepileptics,[18,21] and this is the view taken in the UK by the FFPRHC.[11]

(d) Progestogen-releasing intrauterine system (IUS)

Some enzyme inducers increase the metabolism and reduce the efficacy of the oral combined hormonal contraceptives (see 'Table 28.1', (p.1165), for a list). The manufacturer has not studied the influence of these drugs on the pharmacokinetics of the **levonorgestrel**-releasing IUS (*Mirena*).[23] The systemic absorption of **levonorgestrel** from the IUS leads to lower blood levels than are seen with standard oral progestogen-only contraceptives, and many women using a **levonorgestrel** IUS continue to ovulate. Thus, the contraceptive effects of the **levonorgestrel** IUS are thought to be mainly local,[23] and it might therefore not be as susceptible to enzyme-inducing drugs.[18] Nevertheless, the manufacturer has said that they cannot be sure that the foreign body effect (i.e. the effect whereby the presence of the IUS prevents implantation) and/or locally acting hormone will provide reliable contraception when systemic hormone levels and suppression of ovaries are reduced by drug interactions.[24] However, this appears to be overly cautious. In a pilot study in 47 women (most with epilepsy) using a **levonorgestrel** IUS with at least one enzyme-inducing drug there was only one apparent contraceptive failure for 1075 months of use for contraception. This occurred 2 years after insertion of the IUS in a 42-year-old woman taking **primidone** 500 mg daily and **phenytoin** 300 mg daily. In this study, enzyme-inducing drugs being taken were **carbamazepine**, **efavirenz**, **nevirapine**, **phenytoin**, **phenobarbital**, **primidone**, **rifabutin**, **ritonavir** and **topiramate**.[25]

In the UK, the FFPRHC Clinical Effectiveness Unit considers that the **levonorgestrel**-releasing IUS is unlikely to be affected by enzyme inducers and recommends that no additional contraceptive protection is required.[11] It is therefore a suitable contraceptive for women taking these drugs.[18]

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Progestogen-only contraceptives + Lamotrigine

Preliminary evidence suggests that desogestrel might increase lamotrigine levels and adverse effects. However, there was no difference in lamotrigine levels between non-users of hormonal contraceptives and users of the levonorgestrel IUD, or a variety of other progestogen-only contraceptives in two other studies.

Clinical evidence

In a preliminary report[1] of one study in 10 women stable taking lamotrigine, an oral progestogen-only contraceptive, **desogestrel** 75 micrograms daily for 12 weeks, caused a 20 to 100% increase in lamotrigine levels in 7 out of the 10 women. The increase in maximum levels was said to be greater than the increase in trough levels, and some women (number not stated) had dose-dependent increases in lamotrigine adverse effects about 30 minutes to 3 hours after their lamotrigine dose. The increase in lamotrigine dose occurred about 2 weeks after starting the desogestrel, and increased up to weeks 8 to 12.

In another study which compared lamotrigine levels in 16 women taking progestogen-only contraceptives with those in 18 women not using hormonal contraceptives, the lamotrigine serum-concentration to dose ratio did not differ between the two groups. The progestogen-only contraceptives used included oral **desogestrel** (3 women), oral **norethisterone** (one woman), **etonogestrel** implant (7 women), **levonorgestrel** implant (one woman), depot **medroxyprogesterone acetate** (one woman) or the **levonorgestrel** IUD (3 women). There were no obvious differences between these contraceptives, although the number of women in each group is too limited to be certain.[2] In another similar study, there was no difference in the lamotrigine serum-concentration to dose ratio between 12 women with a **levonorgestrel** IUD and 20 women not using hormonal contraception.[3]

Mechanism

Unknown. In contrast to the finding here for continuous desogestrel alone, a combined hormonal contraceptive containing ethinylestradiol and desogestrel caused a reduction in lamotrigine levels, see ‘Combined hormonal contraceptives + Lamotrigine’, p.1183.

Importance and management

There are very limited data on the effect of using progestogen-only contraceptives with lamotrigine. Available data suggest that the levonorgestrel IUD has no effect on lamotrigine levels, but that desogestrel might increase them in some women. This is in contrast to the effects of combined hormonal contraceptives, which are known to decrease lamotrigine levels, as a result of the ethinylestradiol component (see ‘Combined hormonal contraceptives + Lamotrigine’, p.1183). Until more is known, it may be prudent to increase monitoring of lamotrigine levels and efficacy when desogestrel is started or stopped.

There are no data on whether the efficacy of progestogen-only contraceptives is altered by lamotrigine. In one study with a combined oral contraceptive there was a slight reduction in levonorgestrel levels combined with an increase in FSH and LH levels and an increase in intermenstrual bleeding, which suggests some reduction in suppression of the hypothalamic-pituitary-ovarian axis. However, the clinical relevance of this is uncertain. If one assumes that some reduction in the efficacy of hormonal contraceptives is likely, then the advice given for other enzyme-inducing drugs should be followed. Namely, the efficacy of high-dose injectable progestogens (medroxyprogesterone acetate and norethisterone) and the levonorgestrel IUD is unlikely to be affected, whereas the efficacy of oral pills and the implants may be. See ‘Progestogen-only contraceptives + Enzyme inducers’, p.1206, for a further discussion.

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Immunosuppressants

The immunosuppressants dealt with in this section are principally used for diseases considered to have an auto-immune component or in organ and tissue transplantation. They include the corticosteroids, calcineurin inhibitors (ciclosporin and tacrolimus), monoclonal antibodies (e.g. basiliximab), cytokine modulators (e.g. etanercept and infliximab) and various others, as classified in 'Table 29.1', (below). When any of these drugs acts as the interacting agent the relevant monograph is categorised in the section dealing with the drug whose effects are changed. The cytotoxic drugs that are also used for immunosuppression (e.g. azathioprine, cyclophosphamide and methotrexate) are found in the section on antineoplastic drugs.

Immunosuppressant interactions

A. Pharmacological interactions

The most important pharmacological interactions of these drugs relate to their immunosuppressant effects. These will be additive with other immunosuppressants and, for example, increases the risk of infection. The risk of this sort of interaction obviously depends on the potency of the immunosuppressant and the duration of use. The additive risk can be such that certain combinations should be avoided, e.g. anakinra with TNF antagonists such as 'etanercept', (p.1273). Similarly, the use of live vaccines is not usually recommended in patients receiving immunosuppressants, see 'Immunosuppressants + Vaccines', p.1276.

B. Pharmacokinetic interactions

Many of the potent immunosuppressants discussed in this section have their doses titrated carefully to a given pharmacological effect or therapeutic level. For this reason, the use of drugs that cause a modest pharmacokinetic interaction may have clinically relevant consequences.

(a) Calcineurin inhibitors

1. Ciclosporin. Ciclosporin undergoes extensive metabolism, principally by the hepatic cytochrome P450 isoenzyme CYP3A4. The primary route of its excretion is biliary. Hence, drugs may alter ciclosporin levels by inhibiting or inducing its metabolism or altering its biliary secretion. An important dose-related adverse effect of ciclosporin is nephrotoxicity (raised serum creatinine and urea levels). In the transplant setting, the ciclosporin dose adjustments are usually based on the monitoring of its levels and serum creatinine. In general, trough levels (pre-dose levels, C_0) are measured in whole blood. More recently, there has been interest in the use of monitoring ciclosporin levels 2 hours post dose (C_2 levels). With the lower doses of ciclosporin used in various autoimmune disorders, the dose is usually titrated to efficacy, and ciclosporin levels are not necessarily routinely monitored.
Ciclosporin is itself an inhibitor of P-glycoprotein and also a modest inhibitor of CYP3A4. It may therefore have pharmacokinetic interactions with other drugs (covered in other sections). More recently, it has been found that ciclosporin may also interacts with some drugs via inhibition of drug transporter proteins.

2. Tacrolimus. Tacrolimus is a substrate of the cytochrome P450 isoenzyme CYP3A4 and P-glycoprotein, principally in the intestine. This is demonstrated by the fact that inhibitors or inducers of this isoenzymes and drug transporter increase or decrease the oral bioavailability of tacrolimus to a greater extent than they alter its clearance. In general, interactions of tacrolimus are similar to those of ciclosporin. Tacrolimus doses are adjusted on the basis of therapeutic drug monitoring. Tacrolimus is itself a modest inhibitor of CYP3A4.

(b) Corticosteroids

Some corticosteroids such as methylprednisolone are substrates for the cytochrome P450 isoenzyme CYP3A4 and therefore may interact with CYP3A4 inhibitors or inducers e.g. 'azoles', (p.1257), 'macrolides', (p.1264), or 'rifampicin (rifampin)', (p.1270). Inhaled corticosteroids e.g. fluticasone may, in certain circumstances, also interact, see 'Corticosteroids + Protease inhibitors', p.1268.

(c) Monoclonal antibodies

Monoclonal antibodies generally have few reported interactions, partly because studies can be difficult to design due to long elimination half-lives, and also because metabolising enzymes are generally not involved in monoclonal antibody elimination.

(d) Mycophenolate

Mycophenolate is rapidly hydrolysed to the active mycophenolic acid, which is subsequently metabolised by glucuronidation by glucuronyl-

Table 29.1 Immunosuppressant drugs†

Group	*Drugs*
Corticosteroids	
Glucocorticoids	Beclometasone, Budesonide, Ciclesonide, Deflazacort, Dexamethasone, Fluticasone, Hydrocortisone, Methylprednisolone, Prednisolone, Prednisone, Triamcinolone
Mineralocorticoids	Aldosterone, Fludrocortisone, Liquorice
Monoclonal antibodies	
Tumour necrosis factor (TNF) antagonists	Adalimumab, Certolizumab pegol, Golimumab, Infliximab
Miscellaneous	Abatacept, Anakinra, Basiliximab, Daclizumab, Muromonab-CD3, Natalizumab, Rituximab, Tocilizumab
Other immunosuppressants	
Calcineurin inhibitors	Ciclosporin (Cyclosporine), Tacrolimus
Tumour necrosis factor (TNF) antagonists	Etanercept
Miscellaneous	Everolimus, Leflunomide (DMARD), Mycophenolate, Sirolimus

†For other immunosuppressants that may also be used as cytotoxics, such as azathioprine, cyclophosphamide, methotrexate and mercaptopurine, see under Antineoplastics.

transferases (UGT enzymes). Drugs that induce or inhibit glucuronidation may interact with mycophenolate. The glucuronide metabolite undergoes enterohepatic recycling being cleaved by gut bacteria to mycophenolic acid, which is then reabsorbed leading to a second peak in plasma levels. Drugs that interfere with this process, such as bile acid sequestrants and some antibacterials, may reduce this enterohepatic recycling. Mycophenolate is not metabolised by the cytochrome P450 isoenzyme system, so is not subject to interactions via this system. Note that blood levels of mycophenolic acid are not routinely monitored.

(e) Sirolimus and related drugs

Sirolimus (previously known as rapamycin) is a substrate of CYP3A4 and P-glycoprotein, principally in the intestine. It is therefore subject to drug interactions similar to those of tacrolimus. Its doses are adjusted on the basis of therapeutic drug monitoring. **Everolimus** is an analogue of sirolimus that was developed to improve the oral bioavailability of sirolimus. **Temsirolimus** is an ester prodrug of sirolimus. They therefore interact similarly to sirolimus.

Abatacept + Miscellaneous

An increased risk of serious infection is reported if abatacept is given with tumour necrosis factor antagonists. Abatacept does not appear to affect the clearance of methotrexate, NSAIDs or corticosteroids. Live vaccines should not been given to patients taking abatacept.

Clinical evidence, mechanism, importance and management

(a) Anakinra

The US manufacturer recommends that anakinra is not given with abatacept because of insufficient information regarding the safety and efficacy of using these two drugs together.[1]

(b) Tumour necrosis factor antagonists

In clinical studies it was noted that tumour necrosis factor antagonists did not alter the clearance of abatacept.[1,2] However, patients who received treatment with abatacept and unnamed tumour necrosis factor antagonists [e.g. infliximab, adalimumab] experienced a higher incidence of infections and serious infections, 63% and 4.4%, respectively, when compared with treatment with tumour necrosis factor antagonists alone, 43% and 0.8%, respectively.[1] The manufacturers say that concurrent use is not recommended.[1,2]

(c) Vaccines

As no data are available on the use of live vaccines in patients receiving abatacept, the manufacturers recommend that live vaccines should not be given concurrently or within 3 months of discontinuation of abatacept. The response to some vaccines may be reduced.[1,2]

(d) Other drugs

The manufacturers note that population pharmacokinetic data suggests that the clearance of abatacept is not affected by **corticosteroids**, **methotrexate**, or **NSAIDs**.[1,2] There were no safety issues noted when abatacept was given with **sulfasalazine**, **hydroxychloroquine** or **leflunomide**.[2]

1. Orencia (Abatacept). Bristol-Myers Squibb. US Prescribing information, April 2008.
2. Orencia (Abatacept). Bristol-Myers Squibb Pharmaceuticals Ltd. UK Summary of product characteristics, May 2009.

Anakinra + Miscellaneous

Live vaccines should not be given with anakinra. No interaction has been reported between anakinra and corticosteroids, NSAIDs or other antirheumatics. The use of anakinra with infliximab increases the risk of severe infection.

Clinical evidence, mechanism, importance and management

(a) Methotrexate

The manufacturers note that, in studies in *rats* concurrent use of methotrexate with anakinra did not affect the clearance of either drug or result in an increase in their adverse effects.[1,2] The clinical safety and efficacy of the combined use of anakinra and methotrexate has been proven in clinical studies,[2] and concurrent use is licensed.[1,2]

(b) Vaccines

The manufacturer states that live vaccines should not be given to patients receiving anakinra as the clinical safety of concurrent use has not been established. Patients may be at risk of developing generalised infections. The manufacturers also note that vaccination may be less effective in patients receiving anakinra.[1,2]

(c) Other drugs

The manufacturers state that no interaction has been reported between anakinra and **corticosteroids**, **NSAIDs** or other disease-modifying anti-rheumatic drugs (DMARDs).[2] **Infliximab** inhibits the activity of tumour necrosis factor (TNFα). In clinical studies the use of anakinra with another TNFα inhibitor, etanercept, has been associated with an increased risk of serious infection and neutropenia and no additional benefit, when compared to the use of these drugs alone.[3,4] As a result of this the manufacturers of **infliximab** note that similar toxicity may occur if anakinra is given with **infliximab** and therefore advise against concurrent use.[3,4]

1. Kineret (Anakinra). Amgen. US Prescribing information.
2. Kineret (Anakinra). Biovitrum AB. Summary of product characteristics, March 2007.
3. Remicade (Infliximab). Schering-Plough Ltd. UK Summary of product characteristics, March 2009.
4. Remicade (Infliximab). Centocor, Inc. US Prescribing information, April 2009.

Ciclosporin + ACE inhibitors or Angiotensin II receptor antagonists

Acute renal failure developed in four kidney transplant patients taking ciclosporin when they were given enalapril. Oliguria was seen in another patient taking ciclosporin with captopril. Other studies have found no significant changes in renal function with candesartan and losartan or with enalapril. Hyperkalaemia may develop in patients taking ACE inhibitors or angiotensin II receptor antagonists with ciclosporin.

Clinical evidence

(a) ACE Inhibitors

Two kidney transplant patients taking ciclosporin developed acute renal failure 10 to 42 days after starting to take **enalapril** 5 to 10 mg twice daily. Recovery was complete when the **enalapril** was stopped in one of the patients, and when both **enalapril** and ciclosporin were stopped in the other. The latter patient had no problems when ciclosporin was restarted. In both cases renal function had recovered after 10 to 30 days. Neither had any previous evidence of renal artery stenosis or chronic rejection, which are conditions known to predispose to renal failure during the use of an ACE inhibitor. Two other patients appeared to tolerate concurrent use well.[1] Two further kidney transplant patients developed acute renal failure when given **enalapril**. Neither had renal arterial stenosis or acute rejection.[2] The manufacturer briefly mentions that transient oliguria was seen in a kidney transplant patient given ciclosporin and **captopril**.[3]

A study in 13 kidney transplant patients taking ciclosporin found that concurrent treatment with **enalapril** 5 or 10 mg daily for 3 weeks caused a larger increase in potassium levels (mean increase of 0.5 mmol/L) than in those patients given **losartan** 50 mg daily (mean increase of 0.2 mmol/L). Potassium levels were not increased above 5.5 mmol/L in any of the patients studied. Uric acid levels were also increased by **enalapril** but decreased by **losartan**, although this was not statistically significant. No changes in ciclosporin trough levels were seen during the study and the serum creatinine levels remained stable.[4] Another study in kidney transplant patients taking ciclosporin with either **enalapril** (33 patients) or **enalapril** plus amlodipine (32 patients) found that the potassium and serum creatinine levels did not increase in the group given **enalapril** and amlodipine whereas they increased by 0.2 mmol/L and 9 micromol/L, respectively, in the group given **enalapril** alone. Ciclosporin levels remained stable in all patients.[5]

(b) Angiotensin II receptor antagonists

A study in kidney transplant patients taking ciclosporin with **losartan** found that the serum creatinine level was only slightly and non-significantly increased in 5 patients. Losartan was stopped in 3 patients because of a rise in creatinine levels. Transient hyperkalaemia (potassium above 5.5 mmol/L) developed in 4 patients but the potassium had fallen to below 5.5 mmol/L by week 12 in all patients. Ciclosporin levels remained stable during the study and no significant dose changes were made, although one patient was withdrawn from the study due to ciclosporin toxicity which the authors state was not related to the use of losartan.[6] Another study in 14 kidney transplant patients taking ciclosporin with **losartan** 50 to 100 mg daily for 8 weeks found serum creatinine, potassium and ciclosporin levels were unaffected.[7] Another study in 41 kidney transplant patients with proteinuria taking ciclosporin found that the addition of **candesartan** 4 to 12 mg daily had no significant effects on the creatinine clearance or ciclosporin levels.[8]

Mechanism

Not understood. One suggestion is that ciclosporin reduces renal blood flow and reduces perfusion through the glomerulus, which is worsened when angiotensin II is inhibited by the ACE inhibitor.[1] One study suggest-

ed that the larger increase in potassium levels may be related to changes in aldosterone levels seen with enalapril.[4]

Importance and management

There have been few specific case reports of renal failure and hyperkalaemia with ciclosporin and ACE inhibitors or angiotensin II receptor antagonists. Data from the few examples of efficacy studies cited above, suggest that the incidence of renal failure and hyperkalaemia is low, nevertheless care and good monitoring are needed if ACE inhibitors or angiotensin II receptor antagonists and ciclosporin are used concurrently. Also note that the manufacturers of ciclosporin warn about the possible increased risk of hyperkalaemia when ciclosporin is used with ACE inhibitors or angiotensin II receptor antagonists.[9,10] Monitor potassium levels more closely in the initial weeks of concurrent use, bearing in mind that an increase in potassium levels may be due to worsening renal function as well as these drugs.

1. Murray BM, Venuto RC, Kohli R, Cunningham EE. Enalapril-associated renal failure in renal transplants: possible role of cyclosporine. *Am J Kidney Dis* (1990) 16, 66–9.
2. Garcia TM, da Costa JA, Costa RS, Ferraz AS. Acute tubular necrosis in kidney transplant patients treated with enalapril. *Ren Fail* (1994) 16, 419–23.
3. Cockburn I. Cyclosporine A: a clinical evaluation of drug interactions. *Transplant Proc* (1986) 18 (Suppl 5), 50–5.
4. Schmidt A, Gruber U, Böhmig G, Köller E, Mayer G. The effect of ACE inhibitor and angiotensin II receptor antagonist therapy on serum uric acid levels and potassium homeostasis in hypertensive renal transplant recipients treated with CsA. *Nephrol Dial Transplant* (2001) 16, 1034–7.
5. Halimi JM, Giraudeau B, Buchler M, Al-Najjar A, Etienne I, Laouad I, Bruyere F, Lebranchu Y. Enalapril/amlodipine combination in cyclosporine-treated renal transplant recipients: a prospective randomized trial. *Clin Transplant* (2007) 21, 277–84.
6. del Castillo D, Campistol JM, Guirado L, Capdevilla L, Martínez JG, Pereira P, Bravo J, Pérez R. Efficacy and safety of losartan in the treatment of hypertension in renal transplant patients. *Kidney Int* (1998) 54, (Suppl 68) S135–S139.
7. Tylicki L, Biedunkiewicz B, Chamienia A, Wojnarowski K, Zdrojewski Z, Rutkowski B. Randomized placebo-controlled study on the effects of losartan and carvedilol on albuminuria in renal transplant recipients. *Transplantation* (2006) 81, 52–6.
8. Omoto K, Tanabe K, Tokumoto T, Shimmura H, Ishida H, Toma H. Use of candesartan cilexetil decreases proteinuria in renal transplant patients with chronic allograft dysfunction. *Transplantation* (2003) 76, 1170–4.
9. Neoral (Ciclosporin). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, May 2009.
10. Neoral (Ciclosporin). Novartis Pharmaceuticals Corporation. US Prescribing information, October 2009.

Ciclosporin + Acetazolamide

There is some limited evidence to suggest that oral acetazolamide can cause a marked and rapid rise in ciclosporin levels, possibly accompanied by renal toxicity.

Clinical evidence, mechanism, importance and management

A study in 3 men found that 72 hours after they started taking acetazolamide (dose not stated) their trough serum ciclosporin levels rose by more than sixfold, from a range of 54 to 270 nanograms/mL up to a range of 517 to 1827 nanograms/mL.[1] Another man with a heart transplant had a fivefold increase in his serum ciclosporin levels, marked renal impairment, and neurotoxicity when he was given oral acetazolamide for raised intra-ocular pressure secondary to panuveitis.[2] The increase in ciclosporin serum levels has also been seen in *animal* studies.[3]

Information seems to be limited to these reports but it seems that the concurrent use of ciclosporin and acetazolamide should be closely monitored, being alert of the need to reduce the ciclosporin dose. The interaction can apparently develop very rapidly.

1. Tabbara KF, Al-Faisal Z, Al-Rashed W. Interaction between acetazolamide and cyclosporine. *Arch Ophthalmol* (1998) 116, 832–3.
2. Keogh A, Esmore D, Spratt P, Savdie E, McClusky P, Chang V. Acetazolamide and cyclosporine. *Transplantation* (1988) 46, 478–9.
3. El-Sayed YM, Tabbara KF, Gouda MW. Effect of acetazolamide on the pharmacokinetics of cyclosporin in rabbits. *Int J Pharmaceutics* (1995) 121, 181–6.

Ciclosporin + Aciclovir and related drugs

Aciclovir does not normally seem to affect ciclosporin levels or worsen renal function on concurrent use, but cases of nephrotoxicity and increased ciclosporin levels have been reported. Valaciclovir, a prodrug of aciclovir, is expected to interact similarly. Limited evidence suggests ganciclovir does not affect ciclosporin levels or worsen renal function on concurrent use. However, four patients given ciclosporin and ganciclovir developed an acute but reversible eye movement disorder.

Clinical evidence

(a) Aciclovir

A retrospective study in kidney transplant patients taking ciclosporin (serum levels in the range 100 to 250 nanograms/mL) found that in 12 patients, oral aciclovir 800 mg four times daily for 3 months had no significant effect on their ciclosporin serum levels or on nephrotoxicity when compared with 9 control subjects.[1] No significant changes in renal function were seen in 11 patients taking ciclosporin when they were given intravenous aciclovir 750 to 1500 mg/m^2 daily for at least 7 days to treat herpes infections.[2] No significant changes in serum creatinine or ciclosporin levels were seen during the 14 days following kidney transplant in 17 patients given aciclovir 800 mg daily.[3] Fifty-three kidney transplant patients were given ciclosporin and aciclovir 800 mg to 3.2 g daily for 12 weeks. The aciclovir was withdrawn from 2 patients because of unexplained and temporary increases in serum creatinine levels. The serum ciclosporin levels were not reported.[4] Five patients (2 adults and 3 children) taking ciclosporin, prednisone and azathioprine were given aciclovir 200 mg five times daily for 6 days for herpes zoster or chicken pox. Ciclosporin serum levels remained unchanged and renal function improved.[5]

In contrast to the cases cited above, 3 of 7 bone marrow transplant patients given ciclosporin and intravenous aciclovir 500 mg/m^2 every 8 or 12 hours (depending on renal function) developed nephrotoxicity, which was fatal in one case. Histological evidence suggested ciclosporin nephrotoxicity.[6] The manufacturer briefly notes that an increase in serum creatinine was seen in patients taking ciclosporin in one report, and increased aciclovir levels accompanied by reversible acute tubular necrosis in another.[7] Yet another report describes a threefold increase in ciclosporin serum levels, which occurred when a child with a heart transplant was given intravenous aciclovir.[8]

(b) Ganciclovir

In a retrospective analysis, 7 patients taking ciclosporin with ganciclovir 3 mg/kg every 12 hours for 5 to 7 days during antirejection therapy with antithymocyte globulin or muromonab-CD3 had no significant change in their ciclosporin levels (increase of 7.8%) and the ciclosporin dose was not altered. In these patients, serum creatinine levels remained stable.[9]

Another retrospective study identified 582 allogeneic bone marrow transplant patients taking ciclosporin and about 45% of whom were given ganciclovir at some time during the first 3 months after the transplant. Four patients (0.7%) developed an acute eye movement disorder (unilateral or bilateral sixth nerve palsies) within 4 to 34 days of starting ganciclovir. Three of the four patients also had bilateral ptosis, which resolved 24 to 48 hours after withdrawal of both drugs from 3 patients and after the withdrawal of just ciclosporin from the other patient. Objective eye movement abnormality with diplopia recurred in one patient when both drugs were restarted, but not when ciclosporin alone was given.[10]

Mechanism

The renal toxicity of aciclovir and related drugs may occasionally be additive or synergistic with that of ciclosporin. The reason for the eye movement disorders with ganciclovir is not known but the authors of the report suggest an interaction as eye movement disorders are not known to occur with either drug alone.[10]

Importance and management

The evidence available indicates that ciclosporin levels and renal function are usually unaltered by the concurrent use of aciclovir, but the handful of cases where problems have arisen clearly indicate that renal function should be well monitored. One group of workers suggest that aciclovir, in doses of 250 mg/m^2 by slow infusion, does not adversely affect renal function in well-hydrated patients taking ciclosporin if their ciclosporin levels are carefully monitored.[2] Similar precautions should be used with **valaciclovir**, a prodrug of aciclovir. Note that the manufacturers recommend that renal function is closely monitored if high doses of valaciclovir (more than 4 g daily),[11] or aciclovir infusion[12] are given with drugs that affect renal function, such as ciclosporin.

Limited evidence suggests that ganciclovir does not alter ciclosporin levels or renal function, but, like aciclovir, ganciclovir can cause increases in

serum creatinine and accumulates in renal impairment, so some caution is warranted on concurrent use. The same advice would appear to apply to **valganciclovir**, the prodrug of ganciclovir.

The report of eye movement disorders with ganciclovir cited here seems to be the only report of this interaction; therefore its general relevance is uncertain.

1. Dugandzic RM, Sketris IS, Belitsky P, Schlech WF, Givner ML. Effect of coadministration of acyclovir and cyclosporine on kidney function and cyclosporine concentrations in renal transplant patients. *DICP Ann Pharmacother* (1991) 25, 316–7.
2. Johnson PC, Kumor K, Welsh MS, Woo J, Kahan BD. Effects of coadministration of cyclosporine and acyclovir on renal function of renal allograft recipients. *Transplantation* (1987) 44, 329–31.
3. Stoffel M, Squifflet JP, Pirson Y, Lamy M, Alexandre GPJ. Effectiveness of oral acyclovir prophylaxis in renal transplant recipients. *Transplant Proc* (1987) 19, 2190–3.
4. Balfour HH, Chace BA, Stapleton JT, Simmons RL, Fryd DS. A randomized, placebo-controlled trial of oral acyclovir for the prevention of cytomegalovirus disease in recipients of renal allografts. *N Engl J Med* (1989) 320, 1381–7.
5. Hayes K, Shakuntala V, Pingle A, Dhawan IK, Masri MA. Safe use of acyclovir (Zovirax) in renal transplant patients on cyclosporine A therapy: case reports. *Transplant Proc* (1992) 24, 1926.
6. Shepp DH, Dandliker PS, Meyers JD. Treatment of varicella-zoster virus infection in severely immunocompromised patients: a randomized comparison of acyclovir and vidarabine. *N Engl J Med* (1986) 314, 208–12.
7. Cockburn I. Cyclosporine A: a clinical evaluation of drug interactions. *Transplant Proc* (1986) 18 (Suppl 5), 50–5.
8. Boardman M, Yodur Purdy C. Cyclosporine and aciclovir; report of a drug interaction. Am Soc Hosp Pharmacists Midyear Clinical Meeting, Dallas, Texas. December 1988, Abstract SP-16.
9. Cantarovich M, Latter D. Effect of prophylactic ganciclovir on renal function and cyclosporine levels after heart transplantation. *Transplant Proc* (1994) 26, 2747–8.
10. Openshaw H, Slatkin NE, Smith E. Eye movement disorders in bone marrow transplant patients on cyclosporin and ganciclovir. *Bone Marrow Transplant* (1997) 19, 503–5.
11. Valtrex (Valaciclovir). GlaxoSmithKline UK. UK Summary of product characteristics, August 2008.
12. Aciclovir sterile concentrate. Hospira UK Ltd. UK Summary of product characteristics, February 2008.

Ciclosporin + Alcohol

An isolated report describes a marked increase in serum ciclosporin levels in a patient after an episode of binge drinking, but a subsequent study found that moderate, single doses of alcohol in other patients had no such effect. A large amount of red wine, taken concurrently with ciclosporin in the fasted state, decreased ciclosporin bioavailability.

Clinical evidence

The serum ciclosporin levels of a kidney transplant patient doubled, from 101 nanograms/mL to 205 nanograms/mL, and remained high for about 4 days after he went on a 2-day alcohol binge. However, a subsequent study in 8 other patients with kidney transplants found no changes in serum ciclosporin or creatinine levels when they took their regular dose of ciclosporin followed by 50 mL of 100% alcohol in orange juice consumed over a one-hour period (about equivalent to 4 oz of whisky).[1]

A crossover study in 12 fasted, healthy subjects given a single 8 mg/kg dose of ciclosporin (*Sandimmun*) with water or 350 mL (12 oz) of Californian red wine found that red wine caused a 50% increase in the oral clearance of ciclosporin. The ciclosporin AUC was reduced by 30% and the maximum blood levels were reduced by 38% (from 1258 to 779 micrograms/L), but there was no change in elimination half-life. There was a high degree of variability, with increases in oral clearance ranging from 1.5 to 129%, with Caucasians experiencing a greater degree of change than Asians. In this study, half of the wine was consumed 15 minutes before the ciclosporin, and the other half was consumed at the same time as taking ciclosporin and in the 15 minutes afterwards. In their discussion the authors briefly note that, in a separate study of theirs, white wine did not have an effect on ciclosporin clearance.[2]

Mechanism

The mechanism by which red wine decreases ciclosporin absorption is not known. White wine[2] and pure alcohol[1] do not appear to affect ciclosporin pharmacokinetics, so the interaction is not believed to be an effect of alcohol itself. Antioxidants in red wine such as resveratrol may inactivate the cytochrome P450 isoenzyme CYP3A4, but this would be expected to increase ciclosporin levels. The solubility of ciclosporin is decreased in red wine, and it is possible that substances in red wine bind ciclosporin in the gastrointestinal tract and reduce its bioavailability.[2] Another study by the same authors suggested that ciclosporin absorption is possibly impaired by P-glycoprotein induction by red wine.[3]

A study in *animals* found that pretreatment with oral ciclosporin had no effect on the pharmacokinetics of alcohol or acetaldehyde. This suggests that any difference in the alcohol consumption of patients taking ciclosporin is unlikely to have a pharmacokinetic basis.[4]

Importance and management

The authors of the first study[1] say that they currently advise their kidney transplant patients to avoid heavy drinking, but that an occasional drink probably does not affect ciclosporin levels. The second study[2] suggests that it may be wise to avoid red wine close to a ciclosporin dose. However, it cannot be assumed that this interaction would occur with an occasional single glass of red wine taken with a meal and separate from ciclosporin dosing, and the mechanism of reduced absorption suggests this would be unlikely. Note that patients may be advised to avoid alcohol if they are taking ciclosporin after transplantation.

1. Paul MD, Parfrey PS, Smart M, Gault H. The effect of ethanol on serum cyclosporine A levels in renal transplant patients. *Am J Kidney Dis* (1987) 10, 133–5.
2. Tsunoda SM, Harris RZ, Christians U, Velez RL, Freeman RB, Benet LZ, Warshaw A. Red wine decreases cyclosporine bioavailability. *Clin Pharmacol Ther* (2001) 70, 462–7.
3. Tsunoda SM, Christians U, Velez RL, Benet LZ, Harris RZ. Red wine (RW) effects on cyclosporine (CyA) metabolites. *Clin Pharmacol Ther* (2000) 67, 150.
4. Giles HG, Orrego H, Sandrin S, Saldivia V. The influence of cyclosporine on abstinence from alcohol in transplant patients. *Transplantation* (1990) 49, 1201–2.

Ciclosporin + Alfalfa (*Medicago sativa*) and Black cohosh (*Cimicifuga racemosa*)

An isolated report describes acute rejection and vasculitis with black cohosh and/or alfalfa in a renal transplant patient taking ciclosporin.

Clinical evidence

A stable kidney transplant patient taking azathioprine 50 mg daily and ciclosporin 75 mg twice daily began to take alfalfa and black cohosh supplements (specific products not stated) on medical advice for severe menopausal symptoms. Her serum creatinine rose from between about 97 to 124 micromol/L up to 168 micromol/L after 4 weeks and, to 256 micromol/L after 6 weeks with no associated change in her ciclosporin levels. Biopsy revealed severe acute rejection with vasculitis and she was treated with corticosteroids and anti-T lymphocyte immunoglobulin with partial improvement in renal function.[1]

Mechanism

Alfalfa has been reported to cause worsening of lupus and immunostimulation and it was suggested that immunostimulation may have contributed to the acute rejection in this patient.[1]

Importance and management

The evidence for an interaction between alfalfa and/or black cohosh and immunosuppressants is limited, with the mechanism suggesting that alfalfa is the more likely culprit, although an effect of black cohosh cannot be ruled out. As the effects were so severe in this case it would seem prudent to avoid the use of alfalfa supplements in patients receiving immunosuppressants for serious indications, such as organ or tissue transplantation. Similarly, it would seem prudent to avoid the use of alfalfa in those taking immunosuppressants for indications such as eczema, psoriasis or rheumatoid arthritis; however, if these patients particularly wish to take alfalfa a short-term trial of concurrent use is likely to be less hazardous, but patients should be counselled about the possible risks (i.e. loss of disease control).

1. Light TD, Light JA. Acute renal transplant rejection possibly related to herbal medications. *Am J Transplant* (2003) 3, 1608–9.

Ciclosporin + Allopurinol

Isolated cases of markedly raised ciclosporin levels have been reported in patients given standard doses of allopurinol for the treatment of gout. However, in two clinical studies, a trend towards lower ciclosporin levels with low-dose allopurinol has been seen.

Clinical evidence, mechanism, importance and management

The ciclosporin levels of a kidney transplant patient rose by about threefold, accompanied by an increase in serum creatinine from 124 micromol/L to 194 micromol/L, after allopurinol 100 mg daily was taken for 12 days for the treatment of gout.[1] Another previously stable kidney transplant patient had a two- to threefold rise in her ciclosporin level when allopurinol 200 mg daily was given for gout. Her serum creatinine remained unchanged throughout.[2] The general importance of these two reports of increased ciclosporin levels is unknown, although increases in ciclosporin levels are associated with increased risk of nephrotoxicity.

Two clinical studies in kidney transplant patients taking ciclosporin, azathioprine and prednisolone, with low-dose allopurinol 25 mg daily or on alternate days to improve the efficacy of azathioprine, found a reduction in ciclosporin levels (32% in one group), as well as a beneficial reduction in the acute rejection rate.[3] Note that azathioprine levels can be raised significantly by allopurinol usually requiring a dose reduction, see 'Thiopurines + Allopurinol', p.773. The case reports above and the clinical studies are probably insufficient to recommend increased monitoring of ciclosporin levels in all patients given allopurinol, but bear them in mind in the event of an unexpected response to treatment.

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Ciclosporin + Amiodarone

Increased ciclosporin serum levels have been reported in patients starting amiodarone, and nephrotoxicity has occurred as a result of increased levels. Conversely, one report describes slightly lower ciclosporin levels and increased amiodarone levels and another case describes pulmonary toxicity in patients stopping amiodarone and starting ciclosporin.

Clinical evidence

Eight patients with heart transplants and 3 patients with heart-lung transplants taking ciclosporin were also given amiodarone (dose not stated) for atrial flutter or fibrillation. Their serum ciclosporin levels rose by 9% despite a 13 to 14% reduction in the ciclosporin dose, serum creatinine levels rose by 38% (from 157 to 216 micromol/L), and blood urea nitrogen rose by 30%.[1] In another report, one patient is said to have had a 50% decrease in the clearance of ciclosporin when given amiodarone (1 g, then 600 mg daily for 5 days, then 400 mg daily).[2] Eight other patients with heart or heart-lung transplants were effectively treated with amiodarone (dose not stated) for atrial flutter and/or atrial fibrillation, but they had a 31% rise in their serum ciclosporin levels, from 248 nanograms/mL to 325 nanograms/mL despite a 44% reduction in the ciclosporin dose (from 6.2 to 3.5 mg/kg daily). Serum creatinine levels increased by 39%.[3] The serum ciclosporin levels of a kidney transplant patient doubled when amiodarone 600 mg twice daily was given.[4]

In contrast, in 5 heart transplant patients in whom amiodarone was discontinued and ciclosporin subsequently initiated, the metabolism of ciclosporin appeared to be increased for 4 to 5 weeks compared with patients who had not received amiodarone (total plasma metabolites 1437 nanograms/mL and 720 nanograms/mL, respectively). The mean maintenance ciclosporin level was only slightly reduced, in those who had received amiodarone compared with those who had not been given amiodarone (225 nanograms/mL and 240 nanograms/mL, respectively).[5] In this study, 2 patients had amiodarone levels monitored, and it was found that the plasma levels of amiodarone and its main metabolite, desethylamiodarone were increased over 4 to 5 weeks. During this period increased adverse effects, including pulmonary toxicity in one patient, were seen.[5]

Mechanism

Uncertain. It has been suggested that increased ciclosporin levels are a result of a reduction in the metabolism of ciclosporin by amiodarone.[2] Conversely, in the one report suggesting decreased ciclosporin levels and increased amiodarone levels, it was suggested that blocking of P-glycoprotein in the intestinal mucosa and liver by both amiodarone and ciclosporin may result in decreased excretion and increased toxicity of amiodarone as well as accumulation of ciclosporin metabolites.[5]

Importance and management

The increase in ciclosporin levels on starting amiodarone would appear to be an established and clinically important interaction. Concurrent use need not be avoided but close monitoring is needed and ciclosporin dose reductions may also be required to minimise the potential nephrotoxicity. Remember to re-adjust the ciclosporin dose if the amiodarone is stopped, bearing in mind that it may take weeks before amiodarone is totally cleared from the body.

The general significance of the increase in amiodarone levels, apparent decrease in ciclosporin levels and the occurrence of pulmonary toxicity in patients who had stopped amiodarone and started ciclosporin is unclear.

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Ciclosporin + Amphotericin B

There is some good evidence to suggest that the risk of nephrotoxicity is increased if ciclosporin and amphotericin B are used concurrently. However, other limited evidence suggests that the concurrent use of a liposomal form of amphotericin B (*AmBisome*) with ciclosporin does not increase nephrotoxicity or hepatotoxicity. Ciclosporin blood levels may be increased or decreased by amphotericin B.

Clinical evidence

(a) Ciclosporin levels

A retrospective analysis in allogeneic bone marrow transplant patients found that those patients taking high-dose prednisone with a continuous infusion of ciclosporin and prophylactic amphotericin B 5 to 10 mg daily had 13 to 23% lower plasma levels of ciclosporin in the first 4 weeks post-transplant when compared with those given the same GVHD (graft-versus-host-disease) prophylactic regimen who did not receive amphotericin B. No obvious dose reductions or changes in renal function were noted in these patients. It was also noted in this study that patients with ciclosporin plasma levels of 500 nanograms/mL had a 2.2-fold increased risk of developing GVHD when compared with patients with levels of 1000 nanograms/mL.[1] Similarly, a 23-year-old man had a reduction in his blood level of ciclosporin from about 100 nanograms/mL to 50 nanograms/mL within 10 days of starting intravenous amphotericin B.[2]

In contrast, a study in 187 transplant patients given an average dose of ciclosporin 10 mg/kg daily found that ciclosporin blood levels increased significantly from 275 nanograms/mL to 328 nanograms/mL during the use of liposomal amphotericin B (*AmBisome)* and decreased to 242 nanograms/mL one week after amphotericin B was stopped.[3] A retrospective study in 22 patients who had undergone allogeneic stem cell transplants found a non-significant increase in mean ciclosporin blood levels (from 259 nanograms/mL to 296 nanograms/mL) when given amphotericin B (0.6 to 2 mg/kg daily for 3 to 112 days). However, a lower maximum mean ciclosporin blood level of 775 nanograms/mL was seen in those patients who received amphotericin B compared with 1240 nanograms/mL in 62 patients receiving ciclosporin without amphotericin B, although again the difference was not significant.[4]

(b) Toxic effects

1. Nephrotoxicity. The concurrent use of ciclosporin and amphotericin B increased the incidence of nephrotoxicity in 47 patients with bone marrow transplants. Out of 10 patients who had received both drugs, 5 doubled and 3 tripled their serum creatinine levels within 5 days. In contrast, only 8 out of 21 (38%) taking ciclosporin alone and 3 out of 16 (19%) taking meth-

otrexate and amphotericin B doubled their serum creatinine within 14 to 30 days and 5 days, respectively.[5] Similarly, in a retrospective study, 14 potential drug-drug interactions were identified in patients given both ciclosporin and amphotericin B, and of these, 7 resulted in a clinically significant interaction (raised creatinine in all cases, with one patient developing nephrotoxicity).[6]

Two studies of the risk factors associated with amphotericin B identified the concurrent use of ciclosporin as posing a particularly significant risk for the development of the moderate to severe nephrotoxicity seen in 8 to 12% of patients given amphotericin B.[7,8] Two other studies in bone marrow transplant patients taking ciclosporin found that amphotericin B contributed significantly to nephrotoxicity and renal failure.[9,10] Renal impairment can apparently develop even after amphotericin B has been withdrawn.[9] Marked nephrotoxicity is described in one patient in another report.[11] A retrospective study of patients taking ciclosporin also found an increase in creatinine levels during the concurrent use of a continuous infusion of amphotericin B (*Fungizone*) in 22 patients (compared with 62 patients taking ciclosporin alone); however, severe reductions in renal function (creatinine clearance less than 30 mL/minute) were not found.[4] A study including 8 severely ill infants undergoing bone marrow transplantation for severe immunodeficiency, found no evidence of significant nephrotoxicity or hepatotoxicity when liposomal amphotericin B (*AmBisome*) was given with ciclosporin. The average course of treatment lasted for 29 days.[12]

2. Neurotoxicity. An isolated case report described severe tremors, later becoming myoclonic, attributed to the concurrent use of liposomal amphotericin B (*AmBisome*) and ciclosporin. Serum ciclosporin levels were unaltered and creatinine levels only rose slightly.[13] This alleged neurotoxicity was challenged in a letter citing 187 transplant patients who had received ciclosporin and *AmBisome*, none of whom developed neurotoxicity attributable to an interaction.[14]

3. Other adverse effects. In a retrospective analysis in bone marrow transplant patients, renal tubular acidosis and hypomagnesaemia were noted to be the most common adverse effects of the concurrent use of low-dose amphotericin B 5 to 10 mg daily with ciclosporin.[1]

Mechanism

Amphotericin B and ciclosporin are both nephrotoxic, and their adverse effects on the kidneys might be additive. The mechanism of the effects of amphotericin B on ciclosporin blood levels is not understood, especially as contrasting effects have been noted. However, in one *animal* study, amphotericin B decreased ciclosporin bioavailability by inducing the cytochrome P450 subfamily CYP3A and P-glycoprotein.[2]

Importance and management

The increased nephrotoxicity associated with ciclosporin and amphotericin B appears to be established and clinically important. The authors of one report[5] suggest that, in patients needing amphotericin B, renal toxicity may be decreased without losing the immunosuppressant effect of ciclosporin by withholding ciclosporin until the serum level is less than about 150 nanograms/mL.

The reports supporting a lack of significant nephrotoxicity all used liposomal amphotericin B, a formulation that is recommended when amphotericin toxicity (particularly nephrotoxicity) is considered to be a significant risk. This would seem to suggest that in patients taking ciclosporin, the less nephrotoxic forms of amphotericin B are advisable. Renal function should be closely monitored during concurrent use.

The changes in ciclosporin blood levels reported with amphotericin B are inconsistent. However, these studies should be borne in mind when using both drugs, and ciclosporin levels as well as renal function and electrolytes should be closely monitored.

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8. Harbarth S, Pestotnik SL, Lloyd JF, Burke JP, Samore MH. The epidemiology of nephrotoxicity associated with conventional amphotericin B therapy. *Am J Med* (2001) 111, 528–34.
9. Tutschka PJ, Beschorner WE, Hess AD, Santos GW. Cyclosporin-A to prevent graft-versus-host-disease: a pilot study in 22 patients receiving allogeneic marrow transplants. *Blood* (1983) 61, 318–25.
10. Miller KB, Schenkein DP, Comenzo R, Erban JK, Fogaren T, Hirsch CA, Berkman E, Rabson A. Adjusted-dose continuous-infusion cyclosporin A to prevent graft-versus-host disease following allogeneic bone marrow transplantation. *Ann Hematol* (1994) 68, 15–20.
11. Conti DJ, Tolkoff-Rubin NE, Baker GP, Doran M, Cosimi AB, Delmonico F, Auchincloss H, Russell PS, Rubin RH. Successful treatment of invasive fungal infection with fluconazole in organ transplant recipients. *Transplantation* (1989) 48, 692–5.
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Ciclosporin + Anabolic steroids or Androgens

The ciclosporin levels of two patients were raised when they were also given methyltestosterone. Hepatotoxicity has been seen in three patients given ciclosporin and norethandrolone.

Clinical evidence

(a) Methyltestosterone

A man with a kidney transplant who had been stable taking ciclosporin, prednisolone and azathioprine for 23 months was given methyltestosterone 5 mg three times daily for impotence. After 4 weeks he developed anorexia and pruritus. He was found to have a raised bilirubin level and his ciclosporin level had risen from 70 nanograms/mL to 252 nanograms/mL, with an accompanying decrease in his renal function. The methyltestosterone was withdrawn and he was later restabilised.[1] Another case describes abnormally high ciclosporin levels (in excess of 2000 nanograms/mL) when a patient taking methyltestosterone was given ciclosporin 15 mg/kg daily.[2]

(b) Norethandrolone

Three out of four patients with bone marrow aplasia taking ciclosporin and prednisone developed liver toxicity. The adverse effects developed in 2 of them when norethandrolone was added. No toxicity occurred when they were given either of the drugs alone.[3] A 14-year-old girl developed jaundice associated with toxic hepatitis during the post-transplant period, which was attributed to the concurrent use of ciclosporin and norethandrolone.[4]

Mechanism

Uncertain. In the first case, the increase in ciclosporin levels was attributed to cholestatic jaundice brought on by the methyltestosterone.[1] Both norethandrolone and ciclosporin are known to be hepatotoxic, so additive hepatotoxicity may occur.

Importance and management

Information is limited. However, it would seem prudent to avoid the use of androgens or anabolic steroids in patients taking ciclosporin wherever possible. If no alternative is available, it may be prudent to increase the frequency of liver function monitoring.

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Ciclosporin + Antibacterials; Aminoglycosides

Studies indicate that nephrotoxicity may be increased by the concurrent use of ciclosporin and gentamicin. This has also been seen with tobramycin. Cases of renal impairment have been reported when ciclosporin was given with amikacin and gentamicin.

Clinical evidence

A comparative study in patients given **gentamicin** 30 mg with lincomycin just before kidney transplantation found that the concurrent use of ciclosporin increased the incidence of nephrotoxicity from 5% to 67%.[1] When **gentamicin** and lincomycin were replaced with ampicillin, ceftazidime and lincomycin the incidence of nephrotoxicity was 10%.[1] Another study describes increased nephrotoxicity associated with the concurrent use of ciclosporin and **tobramycin** in bone marrow transplant recipients.[2,3]

One case report describes reversible acute worsening of renal function in a kidney transplant patient receiving ciclosporin with **gentamicin**,[4] and another case report describes impaired renal function in a heart transplant patient taking ciclosporin and given **amikacin**.[5]

A retrospective analysis of the medical records of bone marrow transplant patients suggested that aminoglycosides can be safely given with a continuous infusion of ciclosporin without excessive nephrotoxicity, if the patient is carefully monitored.[6]

Mechanism

Uncertain. As both ciclosporin and the aminoglycosides can individually be nephrotoxic, it seems that their toxicities can be additive.

Importance and management

Established and clinically important interactions. In general the concurrent use of two drugs with nephrotoxic potential should be avoided; however the concurrent use of ciclosporin and aminoglycosides is clinically valuable. Renal function should be monitored with either drug alone, but if concurrent use is undertaken then it would seem prudent to increase the frequency of this monitoring.

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2. Hows JM, Chipping PM, Fairhead S, Smith J, Baughan A, Gordon-Smith EC. Nephrotoxicity in bone marrow transplant recipients treated with cyclosporin A. *Br J Haematol* (1983) 54, 69–78.
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Ciclosporin + Antibacterials; Aztreonam

Aztreonam does not appear to alter ciclosporin levels.

Clinical evidence, mechanism, importance and management

A study in 20 kidney transplant patients taking ciclosporin found that when aztreonam (dose not stated) was added for the treatment of various infections the ciclosporin serum levels were not significantly changed. The ciclosporin blood levels before, during, and after aztreonam treatment were 517 nanograms/mL, 534 nanograms/mL, and 592 nanograms/mL, respectively.[1] On the basis of this study it appears that no ciclosporin dose adjustment is needed on the concurrent use of aztreonam.

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Ciclosporin + Antibacterials; Cephalosporins

Isolated case reports suggest that ceftazidime, ceftriaxone, and latamoxef may increase ciclosporin levels, whereas one report suggests ceftazidime, ceftriaxone, and cefuroxime do not, although ceftazidime caused deterioration in some measures of renal function.

Clinical evidence, mechanism, importance and management

Two kidney transplant patients had two- to fourfold rises in ciclosporin blood levels within 2 to 3 days of starting **ceftriaxone** 1 g twice daily. Levels fell when the antibacterial was stopped. The reason for this effect is uncertain but it was suggested that **ceftriaxone** possibly inhibits the metabolism of ciclosporin by the liver.[1] However, a report of 51 kidney transplant patients stated that **ceftriaxone** and **cefuroxime** had no effect on ciclosporin blood levels and also that they were not nephrotoxic. This report also stated that **ceftazidime** did not affect serum ciclosporin levels, but it increased blood urea nitrogen and creatinine levels, indicating that it was nephrotoxic.[2] A report briefly mentions that **ceftazidime** and **latamoxef** have also been implicated in an increase in ciclosporin plasma levels.[3] However, the manufacturers of **ceftazidime** state that there is no evidence to suggest that **ceftazidime** itself is nephrotoxic when used in the recommended doses, although dose adjustment is required in renal impairment.[4] A study in 28 bone marrow transplant patients taking ciclosporin found no evidence that **ceftazidime** 2 g three times daily worsened renal function.[5]

Information about these cephalosporins is very limited indeed. The general relevance of these reports is uncertain, but bear them in mind in the event of unexpected response to treatment.

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Ciclosporin + Antibacterials; Chloramphenicol

A marked rise in ciclosporin levels has been reported in patients who have also been given intravenous or oral chloramphenicol.

Clinical evidence

A retrospective study identified 3 transplant patients taking ciclosporin who had received a total of 6 courses of intravenous chloramphenicol, each lasting for at least 12 days. By day 4 of concurrent use ciclosporin blood levels had increased on average by about 40%. Ciclosporin doses tended to be slightly reduced over the course of treatment, and by day 10, ciclosporin levels were about 31% below baseline.[1]

A woman with a heart-lung transplant and with a trough ciclosporin level of 84 nanograms/mL started to take oral chloramphenicol (dose not stated) to treat an infection with *Xanthomonas maltophilia*. On the next day the ciclosporin levels had risen to 240 micrograms/L. The chloramphenicol was continued but the ciclosporin dose was reduced from 300 to 225 mg daily. By day 8 the ciclosporin levels were back within the therapeutic range.[2]

Two kidney transplant patients had marked increases in ciclosporin blood levels (almost doubled in one case) when they were given chloramphenicol for urinary tract infections.[3]

There is another report of this interaction, but the case is greatly complicated by the presence of ciprofloxacin, vancomycin, ceftazidime, and a recent course of rifampicin (rifampin) taken by the patient.[4]

Mechanism

Uncertain. The authors suggest that chloramphenicol might reduce the metabolism of ciclosporin by the liver.[4]

Importance and management

Information seems to be limited to these reports, so although the interaction appears to be established, its incidence is obviously uncertain. It would be prudent to monitor ciclosporin levels if systemic chloramphenicol is added, being alert for the need to reduce the ciclosporin dose. The

retrospective study highlights the need to monitor levels closely throughout the whole chloramphenicol course.[1] It seems doubtful that there would be enough chloramphenicol absorbed from eye drops to interact with ciclosporin, but this needs confirmation.

1. Mathis AS, Shah N, Knipp GT, Friedman GS. Interaction of chloramphenicol and the calcineurin inhibitors in renal transplant recipients. *Transpl Infect Dis* (2002) 4, 169–74.
2. Steinfort CL, McConachy KA. Cyclosporin-chloramphenicol drug interaction in a heart-lung transplant recipient. *Med J Aust* (1994) 161, 455.
3. Zawadzki J, Prokurat S, Smirska E, Jelonek A. Interaction between cyclosporine A and chloramphenicol after kidney transplantation. *Pediatr Nephrol* (1991) 5, C49.
4. Bui LL, Huang DD. Possible interaction between cyclosporine and chloramphenicol. *Ann Pharmacother* (1999) 33, 252–3.

Ciclosporin + Antibacterials; Clindamycin

Two patients had a marked reduction in their serum ciclosporin levels when they took clindamycin.

Clinical evidence, mechanism, importance and management

A lung transplant patient receiving ciclosporin in a dose to maintain levels of 100 to 150 nanograms/mL required ciclosporin dose increases to achieve this level when clindamycin 600 mg three times daily was given. Initially the levels were almost halved by the addition of clindamycin. Ciclosporin was reduced to the original dose when the clindamycin was stopped.[1] In a second lung transplant patient, the use of clindamycin 600 mg three times daily necessitated ciclosporin dose increases from 325 mg daily to 1.1 g daily over 4 weeks to maintain serum levels of about 200 nanograms/mL.

The reasons for the interaction are not understood, but the authors suggest close monitoring of ciclosporin levels to prevent under-dosing if clindamycin is given;[1] however, this seems exceptionally cautious as these two cases appear to be all that have been reported.

1. Thurnheer R, Laube I, Speich R. Possible interaction between clindamycin and cyclosporin. *BMJ* (1999) 319, 163.

Ciclosporin + Antibacterials; Imipenem with Cilastatin

Several transplant patients with impaired renal function have experienced adverse CNS effects (including convulsions and tremors) while taking imipenem with cilastatin and ciclosporin. Imipenem with cilastatin appears to decrease the nephrotoxicity of ciclosporin, but its effect on ciclosporin levels is uncertain.

Clinical evidence

(a) Ciclosporin levels

In one heart transplant patient, the dose of ciclosporin required to maintain a therapeutic level needed to be reduced from 240 mg to 180 mg daily when imipenem with cilastatin was given for mediastinitis.[1] Another patient had a rise in ciclosporin blood levels from about 400 nanograms/mL to 1000 nanograms/mL in the 4 days after receiving two doses of imipenem with cilastatin. This patient also developed CNS toxicity, see *CNS effects and seizures*, below.[2]

Conversely, in a randomised controlled study of the use of imipenem with cilastatin to reduce ciclosporin nephrotoxicity, there was no difference in the ciclosporin levels or dose between the 10 patients who received imipenem with cilastatin and the 10 patients who received placebo.[3] Similar findings were reported in another study.[4]

However, in a retrospective analysis, mean ciclosporin levels were *lower* in 64 patients given imipenem with cilastatin (208 nanograms/mL) than in the 40 patients who were not given imipenem with cilastatin (265 nanograms/mL). No difference in the incidence of graft versus host disease was found between the two groups.[5]

(b) CNS effects and seizures

A kidney transplant patient taking ciclosporin developed a urinary-tract infection for which she was given imipenem with cilastatin 500 mg intravenously every 12 hours (dose adjusted for renal function). About 20 minutes after the second dose she became confused, disorientated, agitated, and developed motor aphasia and intense tremor. This was interpreted as being a combination of the adverse CNS effects of both drugs. The imipenem and cilastatin was not given again, and the effects subsided over the next few days.[2] This patient also developed raised ciclosporin levels, see *Ciclosporin levels*, above.[2]

Similarly, 4 transplant patients who were taking ciclosporin developed seizures when they were given imipenem with cilastatin 1 g daily, and a fifth patient developed myoclonia. These patients all had chronic renal impairment.[6] Moreover, in one randomised study of the use of imipenem with cilastatin to reduce ciclosporin nephrotoxicity, 2 patients were withdrawn from the study because of seizures.[3]

In contrast, in an analysis of the incidence of seizure in patients who had been given ciclosporin and imipenem with cilastatin or either drug alone, there was no difference between the groups. Three of 77 patients (3.8%) given ciclosporin alone and 2 of 45 patients (4.4%) who were given ciclosporin and imipenem with cilastatin had seizures, whereas none of the 44 patients who received imipenem with cilastatin alone had seizures.[7]

(c) Reduction in nephrotoxicity

Various randomised prospective studies and retrospective studies have been published suggesting that serum creatinine levels are lower and the risk of acute renal failure is reduced in patients given ciclosporin and imipenem with cilastatin. In a meta-analysis of the data, the odds ratio for developing acute renal failure was 0.24 with the combination compared with ciclosporin alone.[8]

Mechanism

Focal tremors, myoclonus and convulsions are known adverse effects of imipenem with cilastatin and are most likely to occur in patients with renal impairment. Ciclosporin can also cause tremor, and rarely, convulsions, hence the effects of both drugs might be additive.

Cilastatin might possibly reduce the nephrotoxicity of ciclosporin because of its effect as an inhibitor of dehydropeptidase I, an enzyme found in the brush border of the renal tubules. Alternatively, it has been suggested it might reduce nephrotoxicity by reducing the levels of ciclosporin by altering ciclosporin metabolism,[9,10] but evidence for reduced ciclosporin levels is not conclusive.

Importance and management

An interaction between imipenem with cilastatin and ciclosporin leading to an increase in CNS adverse effects is not established. What occurred may simply represent the increased risk of seizures when imipenem with cilastatin is used in patients with renal impairment. The manufacturers of imipenem with cilastatin recommend that patients who develop focal tremors, myoclonus and convulsions while receiving the antibacterial should be started on an antiepileptic drug. If symptoms persist the dose should be reduced, or the drug withdrawn.[11,12]

The effect of imipenem with cilastatin on ciclosporin levels is uncertain, but bear these reports in mind if unexpected effects are seen with concurrent use.

Note that the risk of nephrotoxicity is possibly reduced in patients taking ciclosporin given cilastatin, although the use of imipenem with cilastatin for this purpose is investigational.

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Ciclosporin + Antibacterials; Macrolides

Ciclosporin levels can be markedly raised by clarithromycin, erythromycin, josamycin, pristinamycin, and possibly midecamycin. Rokitamycin, telithromycin and troleandomycin are predicted to interact similarly. Roxithromycin appears to interact minimally, while no interaction is normally seen with azithromycin, dirithromycin or spiramycin, although there are two isolated reports of an interaction with azithromycin.

Clinical evidence

(a) Azithromycin

In a study in 8 healthy subjects were given ciclosporin 3.75 to 7.5 mg/kg alone and then after taking azithromycin 500 mg initially then 250 mg daily for 4 days. Azithromycin did not alter ciclosporin levels.[1] Similarly, in another controlled study in 8 patients with kidney transplants stabilised on ciclosporin, there was no clinically relevant change in ciclosporin levels after azithromycin 500 mg daily for 3 days (7% increase in AUC).[2] A number of other studies have also found no evidence of a clinically significant interaction between ciclosporin and azithromycin used for respiratory tract infections (dose not stated)[3] or for ciclosporin-induced gingival overgrowth (500 mg daily for 3 days).[4,5] However, there are two isolated reports describing a marked increase in ciclosporin levels in 2 patients, which were attributed to the use of azithromycin (500 mg on day one, then 250 mg daily for 4 days;[6] and 500 mg daily for 9 days[7]).

(b) Clarithromycin

In a study in 8 healthy subjects, ciclosporin 3.75 to 7.5 mg/kg was given alone and after clarithromycin 250 mg every 12 hours for 7 days. The maximum ciclosporin levels were raised by 50% by clarithromycin. In another study, a mean 30% reduction in the dose of ciclosporin was needed in 6 transplant patients also given clarithromycin.[8] Clarithromycin 500 mg twice daily as part of a *Helicobacter pylori* eradication regimen caused a two- to threefold increase in ciclosporin levels in 27 kidney transplant patients.[9,10] The ciclosporin levels in 4 renal transplant patients with stable renal function increased by about 72% when clarithromycin 250 mg twice daily for 6 days was added to treat gingival hyperplasia. Ciclosporin levels returned to baseline levels within 7 days of stopping clarithromycin. Only two patients required a ciclosporin dose reduction.[11]

Numerous case reports also describe this interaction: the AUC or levels of ciclosporin have been increased two- to threefold,[12-15] with changes being seen within 3 to 6 days of clarithromycin 250 or 500 mg twice daily being started.[12,15] Another patient had a seven- to twelvefold rise in serum ciclosporin levels and acute renal failure within 3 weeks of starting to take clarithromycin 1 g daily.[16] Another case report in a heart transplant patient taking ciclosporin found that the addition of rifampicin to clarithromycin negated the increase in ciclosporin levels seen with clarithromycin alone, and the ciclosporin dose requirement with both clarithromycin and rifampicin was similar to that before clarithromycin or rifampicin were started.[17]

(c) Dirithromycin

In a study in 8 healthy subjects, dirithromycin 500 mg daily for 14 days did not significantly affect the pharmacokinetics of a single 15-mg/kg oral dose of ciclosporin.[18]

(d) Erythromycin

A study in 9 transplant patients taking ciclosporin found that erythromycin increased the mean trough serum levels of 3 kidney transplant patients sevenfold (from 147 to 1125 nanograms/mL), and of 6 heart transplant patients four- to fivefold (from 185 to 815 nanograms/mL). Acute nephrotoxicity occurred in all 9 patients, and 7 had mild to severe hepatotoxicity caused by the increased ciclosporin levels.[19]

Markedly raised ciclosporin blood levels and/or toxicity have been described in a number of other studies and case reports with erythromycin given orally or intravenously to about 50 other patients.[20-35] The interaction has also been demonstrated in controlled studies in healthy subjects.[1,36] Oral erythromycin may possibly have a greater effect than intravenous erythromycin.[31,37]

Erythromycin-related ototoxicity, possibly associated with the use of ciclosporin, has been reported in liver transplant patients.[38]

(e) Josamycin

A man with a renal transplant who was taking azathioprine, prednisone and ciclosporin 330 mg daily had a marked rise in his plasma ciclosporin levels from about 90 nanograms/mL to 600 nanograms/mL when he took josamycin 2 g daily for 5 days. He responded in the same way when later rechallenged with josamycin. Another patient also reacted in the same way.[39] Two- to fourfold rises in ciclosporin levels have been seen in 9 other patients given josamycin 2 to 3 g (50 mg/kg) daily.[40-42] Another patient had a 40% rise in ciclosporin levels when given josamycin 500 mg twice daily.[43]

(f) Midecamycin

The steady-state ciclosporin blood levels of 10 kidney transplant patients were roughly doubled when they took midecamycin 800 mg twice daily.[44] A 43-year-old kidney transplant patient taking ciclosporin, azathioprine and prednisone, began further treatment on day 27 after the transplant with midecamycin diacetate 600 mg twice daily and co-trimoxazole three times daily for pneumonia. By day 33 the concentration/dose ratio of ciclosporin had doubled, and ciclosporin levels had reached 700 nanograms/mL, accompanied by a rise in serum creatinine levels. When the midecamycin was replaced by cefuroxime, the concentrations of both ciclosporin and creatinine fell to their former levels within 3 days.[45] Ciclosporin levels in another kidney transplant patient taking ciclosporin 120 mg twice daily increased from 95 nanograms/mL to 380 nanograms/mL 3 days after starting midecamycin 800 mg twice daily.[46] Blood levels of ciclosporin in a kidney transplant patient also increased from 97 nanograms/mL to 203 nanograms/mL 4 days after starting midecamycin diacetate 600 mg twice daily.[47]

(g) Pristinamycin

A kidney transplant patient had a tenfold increase in plasma ciclosporin levels from 30 nanograms/mL to 290 nanograms/mL after taking pristinamycin 2 g daily for 8 days. Blood creatinine levels rose from 75 micromol/L to 120 micromol/L. Another patient given pristinamycin 1.25 g had a rise in ciclosporin levels from 78 nanograms/mL to 855 nanograms/mL after 6 days. Ciclosporin and creatinine levels fell to normal levels within 2 days of stopping both drugs.[48]

In a study in 10 patients, pristinamycin 50 mg/kg daily raised the ciclosporin blood levels by 65% (from 560 to 925 nanograms/mL). Ciclosporin levels fell when the pristinamycin was stopped.[49] Within 5 days of starting to take pristinamycin 4 g daily the ciclosporin levels of another patient more than doubled. His serum creatinine levels also rose. Both fell back to baseline levels within 3 days of stopping the antibacterial.[50]

(h) Roxithromycin

Eight patients with heart transplants taking ciclosporin 8 mg/kg daily, prednisolone and azathioprine for at least one month, were given roxithromycin 150 mg twice daily for 11 days. A 38% rise in plasma ciclosporin levels occurred at the time the roxithromycin was given, and a 60% rise occurred 4 hours later. Ciclosporin levels fell again when roxithromycin was stopped. A small (10%) increase in serum creatinine levels occurred, but there was no evidence of a deterioration in renal function.[51] One study in kidney transplant patients taking ciclosporin found that the half-life of roxithromycin was doubled, from 17 to 34.4 hours.[52]

(i) Spiramycin

The ciclosporin plasma levels of 6 heart transplant patients taking corticosteroids, azathioprine and ciclosporin remained unchanged when they were given spiramycin 3 million units twice daily for 10 days.[53] Similarly, no interaction was found between ciclosporin and spiramycin in other studies in patients with renal transplants.[54-57]

Mechanism

In vitro studies with human liver microsomes have found that clarithromycin, erythromycin, josamycin, rokitamycin, roxithromycin and troleandomycin (but not spiramycin) inhibit ciclosporin metabolism, which is catalysed by the cytochrome P450 subfamily CYP3A.[16,58] This would be expected to result in raised ciclosporin levels. Telithromycin is also an inhibitor of CYP3A4 and may increase ciclosporin levels.[59,60] Erythromycin[31,35] and clarithromycin[14] also possibly increase the absorption of ciclosporin from the gut by inhibiting the cytochrome P450 isoen-

zyme CYP3A4 in the gut wall or increasing uptake by inhibiting P-glycoprotein.

Azithromycin is believed to be metabolised by routes independent of the cytochrome P450 enzyme system. Intravenous azithromycin was thought to have increased ciclosporin levels through P-glycoprotein inhibition and/or competition for biliary excretion in one case report.[7]

Importance and management

The interaction between ciclosporin and **erythromycin** or **clarithromycin** is well documented, well established and potentially serious. If concurrent use is thought appropriate, monitor the ciclosporin blood levels closely and reduce the dose as required; a reduction of about 35% may be needed.[33] The dose should be increased again when the macrolide is stopped. The effect of intravenous erythromycin is less than oral erythromycin so if the route of administration is changed, be alert for the need to change the ciclosporin dose.[31,37]

Information about the interactions with **josamycin**, **midecamycin**, and **pristinamycin** is much more limited, but as they appear to behave like erythromycin, the same precautions should be taken. There seems to be no direct clinical information about **telithromycin**, **troleandomycin** and **rokitamycin** but they would also be expected to interact like erythromycin. Note that troleandomycin is usually a more potent inhibitor of CYP3A4 than erythromycin, so it may be expected to have a larger effect on ciclosporin levels.

Dirithromycin and **spiramycin** do not appear to interact with ciclosporin, and **roxithromycin** appears only to interact very minimally. Also bear in mind that roxithromycin serum levels may be increased.

Most evidence indicates that azithromycin does not affect ciclosporin levels, although some authors[7] recommend increased monitoring because of the isolated reports of increased ciclosporin levels. Bear the case reports in mind should an unexplained increase in ciclosporin levels occur on concurrent use.

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Ciclosporin + Antibacterials; Metronidazole

Three reports describe an increase in ciclosporin levels in patients given metronidazole.

Clinical evidence, mechanism, importance and management

The ciclosporin blood levels of a kidney transplant patient rose from 850 nanograms/mL to 1930 nanograms/mL when metronidazole 2.25 g daily and cimetidine 800 mg daily were started. The ciclosporin levels then fell to about 1500 nanograms/mL when the metronidazole dose was

halved and cimetidine was stopped. Because the levels of ciclosporin were still so high, the dose of ciclosporin was reduced from 7.1 to 5.7 mg/kg daily, which resulted in a further decrease in the ciclosporin level to about 1200 to 1380 nanograms/mL. When metronidazole was stopped, the ciclosporin levels fell to a range of 501 to 885 nanograms/mL.[1]

Another kidney transplant patient developed a raised serum creatinine (increased from 223 micromol/L to 304 micromol/L) with virtually doubled ciclosporin blood levels when metronidazole 1.5 g daily was given.[2]

Ciclosporin levels in yet another kidney transplant patient doubled (from 134 to 264 micrograms/L) accompanied by a modest elevation in serum creatinine when metronidazole 400 mg three times daily was also given. The levels fell again when metronidazole was stopped.[3]

These three cases appear to be the only reports of an interaction, one of which is confused by the presence of cimetidine (see also 'Ciclosporin + H_2-receptor antagonists', p.1241). There is insufficient evidence to advocate monitoring every patient given the combination, but it would be prudent to at least bear this interaction in mind if using metronidazole in patients taking ciclosporin.

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Ciclosporin + Antibacterials; Penicillins

Ampicillin does not interact adversely with ciclosporin. Limited evidence suggests that intravenous flucloxacillin might decrease ciclosporin levels. Increased nephrotoxicity has been seen in lung transplant patients given prophylactic nafcillin, whereas an isolated report describes a fall in ciclosporin levels in a patient treated with nafcillin. A case of raised ciclosporin levels in a patient taking ticarcillin has been described.

Clinical evidence

(a) Ampicillin

Seventy-one kidney transplant patients taking ciclosporin had no changes in serum urea, creatinine or ciclosporin levels when ampicillin was given.[1]

(b) Flucloxacillin

In a retrospective study in 7 kidney transplant recipients, it was noted that the use of intravenous flucloxacillin for septicaemia reduced ciclosporin trough levels by 55%. The ciclosporin dose needed to be increased 2.2-fold, but despite this, biopsy-proven rejection occurred in 3 patients within 10 days of starting flucloxacillin. Ciclosporin trough levels returned to normal within about 2 days of stopping the flucloxacillin.[2]

(c) Nafcillin

A retrospective study of 19 lung transplant patients taking ciclosporin found that those given nafcillin for one week as prophylaxis against staphylococci had a greater degree of renal impairment than those not taking nafcillin. Serum creatinine levels rose steadily over 6 days until the nafcillin was stopped, whereas patients not taking nafcillin had no changes in creatinine levels. Three of the nafcillin group temporarily needed haemodialysis. Ciclosporin doses in the nafcillin group were higher but the blood levels in both groups were not significantly different. The incidence of viral infections was also greater in the nafcillin group.[3]

A kidney transplant patient taking ciclosporin and prednisone experienced a marked fall in her serum ciclosporin levels on two occasions when given nafcillin 2 g every 6 hours. Trough blood levels fell from 229 nanograms/mL to 119 nanograms/mL after 3 days, and then to 68 nanograms/mL after 7 days of nafcillin and rose when the nafcillin was stopped. On the second occasion ciclosporin levels fell from 272 nanograms/mL to 42 nanograms/mL after 9 days of treatment with nafcillin.[4]

(d) Ticarcillin

A patient had a rise in his plasma ciclosporin levels from 90 nanograms/mL to 230 nanograms/mL within 5 days, and from 120 nanograms/mL to 300 nanograms/mL within 10 days, of starting ticarcillin 10 g daily.[5]

Mechanism

The authors of the study using nafcillin[3] suggest that it may have interfered with the ciclosporin assay, resulting in an underestimate of the actual levels, so that the nephrotoxicity was simply due to higher ciclosporin levels.[3] The fall in ciclosporin levels in the individual patient taking nafcillin[4] is not understood, nor is the rise in levels seen in the patient taking ticarcillin.[5] *In vitro* evidence[6] suggests that flucloxacillin at high concentrations might act as an inducer of the cytochrome P450 isoenzyme CYP3A4 and P-glycoprotein, both of which are involved in the metabolism of ciclosporin. However, in clinical use, there is little evidence to suggest that flucloxacillin interacts in this way.

Importance and management

Information seems to be limited to the studies and cases cited. No special precautions would seem necessary with ampicillin, but an alternative to nafcillin would seem prudent. The general importance of the interaction with flucloxacillin is uncertain given that flucloxacillin is not generally considered to affect the metabolism of other drugs. However, in light of these findings, it might be prudent to bear the possibility of an interaction in mind if high-dose intravenous flucloxacillin is required. Further study is required to establish an interaction. The isolated report with ticarcillin is of unknown general significance.

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Ciclosporin + Antibacterials; Quinolones

Ciclosporin levels are normally unchanged by the use of ciprofloxacin, but increased levels and nephrotoxicity may occur in a small number of patients. There is also some evidence that the immunosuppressant effects of ciclosporin are reduced by ciprofloxacin. One study, and two case reports describe rises in ciclosporin levels in patients given norfloxacin, but another study found no change. Similar results have been found with levofloxacin. No significant pharmacokinetic interaction appears to occur between ciclosporin and enoxacin, ofloxacin, pefloxacin and trovafloxacin.

Clinical evidence

(a) Ciprofloxacin

A single-dose study in 10 healthy subjects found that after taking ciprofloxacin 500 mg twice daily for 7 days the pharmacokinetics of oral ciclosporin 5 mg/kg were unchanged.[1] Five other studies confirm the lack of a pharmacokinetic interaction in:

- kidney transplant patients taking ciprofloxacin 750 mg twice daily for 13 days;[2]
- kidney transplant patients taking ciprofloxacin 500 mg twice daily for 7 days;[3]
- bone marrow transplant patients given ciprofloxacin 500 mg twice daily for 4 days;[4]
- heart transplant patients given ciprofloxacin 250 to 500 mg for 7 to 140 days;[5]
- heart transplant patients given ciprofloxacin 800 mg to 1.5 g daily.[6]

There were no changes in serum ciclosporin levels or evidence of nephrotoxicity.

In contrast, a handful of cases of nephrotoxicity have been reported, with three cases of increased ciclosporin levels.[7,8] A heart transplant patient developed acute renal failure within 4 days of being given ciprofloxacin 750 mg every 8 hours.[9] Another patient who had undergone a kidney transplant developed reversible nephrotoxicity.[10] Decreased renal function in a heart-lung transplant patient has been described in another report.[7] This patient and another also had increased ciclosporin blood levels

when given ciprofloxacin 500 mg three times daily.[7] Acute interstitial nephritis in a heart transplant patient has also been reported.[11-13] A patient taking ciclosporin for red cell aplasia had an increase in ciclosporin levels from 120 nanograms/mL to 297 nanograms/mL, requiring a dose reduction from 250 mg to 200 mg daily, when intravenous ciprofloxacin 200 mg two or three times daily [exact dose unclear] was started. A ciclosporin dose increase back to 250 mg daily was required when the ciprofloxacin course was finished.[8]

A case-control study in 42 kidney transplant patients suggested that the proportion of cases experiencing at least one episode of biopsy-proved rejection within one to 3 months of receiving a transplant were significantly greater in those who had taken ciprofloxacin (45%) than in those who had not (19%). There was also a marked increase in the incidence of rejection associated with ciprofloxacin use (29%) compared with the controls (2%).[14]

(b) Enoxacin

Enoxacin 400 mg twice daily for 5 days had little effect on either blood or plasma levels of single doses of ciclosporin in 10 healthy subjects.[15]

(c) Levofloxacin

In a study in 12 healthy subjects, levofloxacin 500 mg twice daily for 6 days had no effect on the pharmacokinetics of ciclosporin when a single dose of the oral solution (*Sandimmune*) was given on day 5.[16] A case report in a patient taking oral ciclosporin 250 mg daily (as the emulsion formulation) found no change in ciclosporin levels when he was given intravenous levofloxacin 500 mg daily for 9 days.[8]

In contrast, in a study in 5 kidney transplant patients taking ciclosporin (microemulsion formulation), the AUC was increased by 26% and the trough level by 36% when levofloxacin 500 mg twice daily for 6 days was taken for a urinary-tract infection. The authors concluded that this interaction may be clinically significant, and warned about extrapolating the results from single-dose studies in healthy subjects (as above) to patients with transplants.[17]

(d) Norfloxacin

In a retrospective analysis, 6 kidney transplant patients given norfloxacin 400 mg twice daily for 3 to 23 days for urinary tract infections,[18] and 4 heart transplant patients given norfloxacin 400 mg for 7 to 140 days had no changes in their serum ciclosporin levels.[5] However, two reports describe rises, one marked, in serum ciclosporin levels in a heart transplant patient and a kidney transplant patient given norfloxacin.[19] Similarly, a retrospective study of paediatric kidney transplant patients, found that the ciclosporin dose at discharge was lower in 5 children who were also taking norfloxacin 5 to 10 mg/kg daily compared with a control group of 6 children not taking norfloxacin (4.5 mg/kg versus 7.4 mg/kg daily).[20]

(e) Ofloxacin

Thirty-nine patients with kidney transplants taking ciclosporin and prednisolone had no evidence of nephrotoxicity nor of any other interaction when they were given ofloxacin 100 to 400 mg daily for periods of 3 to 500 days.[21]

(f) Pefloxacin

A study in kidney transplant patients taking corticosteroids, azathioprine and ciclosporin found that the pharmacokinetics of the ciclosporin were not significantly changed by pefloxacin 400 mg twice daily for 4 days.[22]

(g) Trovafloxacin

A placebo-controlled crossover study in 7 stable kidney transplant patients taking ciclosporin (*Sandimmune*) found that the pharmacokinetics of ciclosporin were not significantly altered by trovafloxacin 200 mg daily for 7 days.[23]

Mechanism

Uncertain. On the basis of *in vitro* analysis, it was suggested that norfloxacin inhibits the cytochrome P450 isoenzyme CYP3A4, which would result in a reduction in ciclosporin metabolism.[20] However, there is no direct evidence from a controlled study that norfloxacin raises ciclosporin levels, and norfloxacin is not known as a clinically important inhibitor of CYP3A4, so further study is needed.

The interaction between ciclosporin and ciprofloxacin resulting in increased rejection episodes, may possibly be due to some antagonism by ciprofloxacin of the ciclosporin-dependent inhibition of interleukin-2, which thereby opposes its immunosuppressant action.[14]

Importance and management

Information seems to be limited to these reports. Evidence for an interaction between ciclosporin and levofloxacin or norfloxacin is limited and a significant pharmacokinetic interaction seems generally unlikely. However, as some changes in ciclosporin levels have been reported, it would be prudent to bear the possibility of an interaction in mind should any unexplained change in ciclosporin levels occur in patients taking either of these quinolones. No pharmacokinetic interaction usually occurs between ciclosporin and ciprofloxacin but very occasionally and unpredictably an increase in serum ciclosporin levels and/or nephrotoxicity occurs. There is also some evidence that the immunosuppressant effects of ciclosporin may be reduced.[14] Bear these interactions in mind if both drugs are given.

There seem to be no reports of problems with the concurrent use of ciclosporin and enoxacin, ofloxacin, pefloxacin or trovafloxacin.

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Ciclosporin + Antibacterials; Quinupristin/Dalfopristin

Quinupristin/dalfopristin increased the AUC and maximum levels of single-dose ciclosporin in healthy subjects. In an isolated case report, quinupristin/dalfopristin increased ciclosporin levels by about threefold. There is limited evidence suggesting that ciclosporin might increase the risk of myalgia and/or arthralgia occurring with quinupristin/dalfopristin.

Clinical evidence

(a) Ciclosporin levels

In a study in 24 subjects given a single 300-mg dose of ciclosporin, taken 1.5 hours before the fourth of 9 infusions of quinupristin/dalfopristin (7.5 mg/kg given at intervals of 8 hours), the AUC and maximum blood levels of ciclosporin were increased by 63% and 30%, respectively, and ciclosporin clearance was decreased by 34%.[1]

A kidney transplant patient taking ciclosporin with trough blood levels of between 80 and 105 nanograms/mL developed a vancomycin-resistant enterococcal infection. After a series of antibacterials had failed to clear the infection she was given intravenous quinupristin/dalfopristin 300 mg every 8 hours. After 3 days of treatment her ciclosporin trough level rose to almost 300 nanograms/mL. A ciclosporin dose reduction from 75 to 50 mg twice daily returned her levels to baseline. However, 2 days after the antibacterials were discontinued she was found to have a trough ciclosporin level of only 34 nanograms/mL. She was subsequently restabilised on her original dose of ciclosporin.[2]

(b) Myalgias or arthralgias

In a case-control study[3] of 50 patients receiving quinupristin/dalfopristin 7.5 mg/kg every 8 hours, 10 of the 25 patients who experienced arthralgia or myalgia were also taking ciclosporin, and the risk of these adverse effects with concurrent use was associated with an odds ratio of 3.8.

Mechanism

Quinupristin/dalfopristin inhibits the cytochrome P450 isoenzyme CYP3A4, by which ciclosporin is metabolised.[4] Myalgias and/or arthralgias are common in patients receiving quinupristin/dalfopristin and their aetiology is uncertain.[4]

Importance and management

The available evidence suggests that quinupristin/dalfopristin is likely to increase ciclosporin levels. The manufacturers advise that ciclosporin levels are closely monitored during concurrent use,[4,5] which would seem prudent. Ciclosporin dose reductions may be necessary. Bear in mind the possibility that ciclosporin use might increase the risk of myalgias and/or arthralgias with quinupristin/dalfopristin. The manufacturer notes that improvement has been noted in some patients with this adverse effect when the quinupristin/dalfopristin dose frequency has been extended.[4]

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Ciclosporin + Antibacterials; Sulfonamides and/or Trimethoprim

In isolated cases, sulfadiazine given orally or sulfadimidine given intravenously with trimethoprim have caused a reduction in ciclosporin levels. Sulfametoxydiazine possibly caused a minor reduction in ciclosporin levels in one case. Co-trimoxazole increases serum creatinine levels in kidney transplant patients taking ciclosporin. Isolated reports have shown a similar effect with trimethoprim.

Clinical evidence

(a) Co-trimoxazole

A large-scale study in 132 kidney transplant patients taking ciclosporin encompassing 33 876 patient days found that the concurrent use of co-trimoxazole was effective and well tolerated. Ciclosporin pharmacokinetics remained unchanged. A 15% rise in serum creatinine levels occurred, which reversed when the co-trimoxazole was stopped. This rise was not interpreted as a sign of nephrotoxicity but appeared to be due to inhibition of the tubular excretion of creatinine by the co-trimoxazole.[1]

Other reports describe a few patients given ciclosporin with co-trimoxazole who developed rises in creatinine levels (interpreted as evidence of nephrotoxicity),[2-5] interstitial nephritis,[6] granulocytopenia and thrombocytopenia.[7,8]

(b) Sulfadiazine or Sulfametoxydiazine

Three heart transplant patients treated for toxoplasmosis had a reduction in their ciclosporin levels when they were given sulfadiazine 4 or 6 g daily. Their dose to ciclosporin level ratios rose by 58%, 82%, and 29%. Two had previously been given sulfametoxydiazine and this had caused a minor reduction in ciclosporin levels in one of them.[9]

(c) Sulfadimidine with Trimethoprim

A heart transplant patient taking ciclosporin and prednisolone developed undetectable serum ciclosporin levels 7 days after starting intravenous sulfadimidine 2 g four times daily and **trimethoprim** 300 to 500 mg twice daily. Doubling the ciclosporin dose had little effect and evidence of transplant rejection was seen. Within 10 days of starting to take the antibacterials orally instead of intravenously the serum ciclosporin levels returned to roughly their former levels and the rejection problems disappeared.[10]

Another report by some of the same authors describes a similar marked fall in serum ciclosporin levels in 5 heart transplant patients (one of them the same as the report already cited[10]) when given sulfadimidine and **trimethoprim** intravenously.[11]

(d) Trimethoprim

In 4 kidney transplant patients taking ciclosporin, serum creatinine concentrations rose during the use of trimethoprim. Renal function deteriorated within 2 or 3 days of starting trimethoprim and returned to normal within a week of stopping this antibacterial.[12]

Mechanism

Uncertain. Co-trimoxazole and trimethoprim can raise serum creatinine levels, possibly due to inhibition of creatinine secretion by the kidney tubules.[13] The reduction in serum ciclosporin levels apparently caused by the sulfonamides is not understood.

Importance and management

The documentation is only moderate, and these interactions are not firmly established. Be aware that intravenous sulfadimidine with trimethoprim may cause a marked reduction in serum ciclosporin levels with accompanying inadequate immunosuppression. Sulfadiazine may also reduce ciclosporin levels. The evidence suggests that oral sulfadimidine with trimethoprim, sulfametoxydiazine, and co-trimoxazole do not interact adversely and are normally safe and effective, although toxicity can apparently occur in a small number of patients. Until more information is available it would be prudent to monitor ciclosporin levels if any sulphonamide is added to established treatment with ciclosporin. The manufacturers recommend close monitoring of renal function when ciclosporin is used with co-trimoxazole[14,15] or trimethoprim[14] and this would seem a prudent precaution.

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14. Neoral (Ciclosporin). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, May 2009.
15. Neoral (Ciclosporin). Novartis Pharmaceuticals Corporation. US Prescribing information, October 2009.

Ciclosporin + Antibacterials; Vancomycin

Vancomycin may increase the risk of nephrotoxicity when it is given with ciclosporin.

Clinical evidence, mechanism, importance and management

In a subgroup analysis of bone marrow transplant patients who were taking ciclosporin, there was a 42% decrease in creatinine clearance in those receiving intravenous vancomycin 15 mg/kg every 12 hours compared with a 15% decrease in those receiving teicoplanin. All patients also received tobramycin and piperacillin.[1]

Both vancomycin and ciclosporin can individually be nephrotoxic, and this study provides some evidence that their toxicities can be additive. Bear in mind the possibility of increased nephrotoxicity if vancomycin is required in a patient taking ciclosporin.

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Ciclosporin + Antidiabetics

Some preliminary evidence suggests that glibenclamide (glyburide) can moderately increase ciclosporin levels. Glipizide approximately doubled ciclosporin levels in 2 patients, but one study found no interaction. A single-dose study found ciclosporin significantly increased repaglinide bioavailability, but not all studies have found this effect. Pioglitazone is not expected to alter ciclosporin levels.

Clinical evidence, mechanism, importance and management

Note that one of the rare adverse effects of ciclosporin is hyperglycaemia, and therefore, even in the absence of a pharmacokinetic interaction, ciclosporin might interfere with diabetic control. However, the effect is rare, and does not justify an increase in monitoring all patients. Studies investigating the effects of specific antidiabetics on ciclosporin are discussed below.

(a) Pioglitazone

In vitro and human studies have shown that pioglitazone does not affect cytochrome P450 isoenzymes, including CYP3A4. Therefore no interaction would be expected with ciclosporin, which is mainly metabolised by CYP3A4.[1]

(b) Repaglinide

A placebo-controlled study in 12 healthy subjects given ciclosporin 100 mg twice daily for two doses, with a single 250-microgram dose of repaglinide on day 2, found that ciclosporin significantly increased the maximum plasma level and AUC of repaglinide by 175% and 244%, respectively. It was suggested that ciclosporin inhibited the metabolism of repaglinide by the cytochrome P450 isoenzyme CYP3A4 as well as affecting the hepatic uptake of repaglinide by organic anion transporters.[2,3]

In a study in kidney transplant patients stabilised on immunosuppressants, 7 patients taking ciclosporin had no significant changes in ciclosporin blood levels and no dose changes were required on starting repaglinide 1 to 3 mg daily (mostly as monotherapy, but in a few cases given with either metformin or rosiglitazone).[4] Six of the 7 patients had a successful outcome. This success rate was higher than that seen with tacrolimus (8 of 14), and others have suggested that this might have been due to the pharmacokinetic interaction, which results in increased repaglinide levels.[3] However, commenting further, the authors noted that they were unable to demonstrate a consistent, increased blood glucose-lowering effect with the concurrent use of repaglinide and ciclosporin when compared with tacrolimus and repaglinide, and that there was no obvious difference in the median repaglinide dose.[5] It is therefore difficult to draw any significant conclusions from this study.

The large increases in repaglinide levels seen in the single-dose study in healthy subjects might well be clinically relevant in some patients. Because of this, the possibility of an increased blood-glucose-lowering effect should be borne in mind if ciclosporin is added to the established use of repaglinide. Patients should be advised to report any adverse effects, particularly an increase in the number of hypoglycaemic events.

In the clinical study where repaglinide was given to patients stabilised on ciclosporin, ciclosporin levels were unaffected. However, note that, in this study repaglinide was started at a low dose and titrated upwards as necessary.[5] It may therefore be prudent to introduce repaglinide in this way.

Note that the UK manufacturer of repaglinide suggests avoiding its use with ciclosporin, and recommends close monitoring if concurrent use is necessary.[6]

(c) Sulfonylureas

A review of 6 post-transplant patients with diabetes,taking ciclosporin found that their steady-state plasma ciclosporin levels rose by 57% when they were given **glibenclamide** (**glyburide**). Hepatic and renal function were unchanged. The reason for this reaction is not known, but it was suggested that **glibenclamide** possibly inhibits the cytochrome P450 isoenzyme CYP3A4, the major isoenzyme involved in the metabolism of ciclosporin, resulting in a reduction in its clearance.[7] However, glibenclamide is not known to be a CYP3A4 inhibitor.

Ciclosporin blood levels in 2 patients were more than doubled, and they needed reductions of 20 to 30% in their ciclosporin dose when they were also given **glipizide** 10 mg daily.[8] In contrast, a study in 11 post-transplant patients with diabetes found no significant alterations in ciclosporin pharmacokinetics when **glipizide** was given.[9]

These interactions are unconfirmed and of uncertain clinical significance. There is insufficient evidence to recommend increased monitoring, but be aware of the potential for an interaction in the case of an unexpected response to treatment. Information about other sulfonylureas appears not to be available.

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Ciclosporin + Antiepileptics

Ciclosporin levels are markedly reduced by carbamazepine, phenobarbital, and phenytoin. The dose of ciclosporin may need to be increased two- to fourfold to maintain adequate immunosuppression. Oxcarbazepine caused a small decrease in ciclosporin levels in one case. Valproate appears not to affect ciclosporin levels but two case reports suggest that it may damage renal grafts and cause hepatotoxicity in patients taking ciclosporin.

Clinical evidence

(a) Carbamazepine

The ciclosporin serum levels of a kidney transplant patient fell from 346 nanograms/mL to 64 nanograms/mL within 3 days of starting to take carbamazepine 200 mg three times daily. A week later serum levels had fallen to 37 nanograms/mL. They rose again when the carbamazepine was stopped but fell once more when it was restarted and the ciclosporin dose was increased to keep the levels within the therapeutic range.[1]

The mean average steady-state blood levels of ciclosporin (adjusted for dose) in a group of 3 children with kidney transplants taking carbamazepine were 50% lower than in 3 other matched patients not taking carbamazepine.[2] This interaction has also been described in four other individual patients.[3-5] One needed her ciclosporin dose to be doubled in order to maintain adequate blood levels while taking carbamazepine 800 mg daily.[3] When the carbamazepine was replaced by sodium valproate in 3 patients, the ciclosporin doses could be reduced to their previous level.[3,4]

(b) Oxcarbazepine

A kidney transplant patient taking ciclosporin 270 mg daily and valproate, gabapentin, prednisone, doxepin, allopurinol, levothyroxine and pravastatin was also given oxcarbazepine. Fourteen days later, with the dose of oxcarbazepine at 750 mg daily, the ciclosporin trough level fell below 100 nanograms/mL and after a further 2 days was 87 nanograms/mL. The ciclosporin dose was increased to 290 mg daily and the oxcarbazepine dose reduced to 600 mg daily. Ciclosporin levels then remained stable above 100 nanograms/mL and seizure frequency was reduced by 95%.[6]

(c) Phenobarbital

A 4-year-old child with a bone marrow transplant who was receiving phenobarbital 50 mg twice daily had serum ciclosporin levels of less than 60 nanograms/mL even after raising the ciclosporin dose to 18 mg/kg daily. When the phenobarbital dose was reduced to 25% of the original dose the trough serum ciclosporin levels rose to 205 nanograms/mL.[7] Another report describes a patient whose ciclosporin levels increased from 512 nanograms/mL to 810 nanograms/mL after phenytoin and phenobarbital were replaced by sodium valproate.[8]

A threefold increase in ciclosporin clearance was seen in a child with a kidney transplant while taking phenobarbital.[9] Reductions in ciclosporin levels due to phenobarbital have been described in other patients.[10-13]

(d) Phenytoin

The observation that patients taking ciclosporin needed marked dose increases while taking phenytoin[14] prompted a further controlled study in 6 healthy subjects.[15] Phenytoin 300 or 400 mg daily reduced the maximum ciclosporin blood levels and AUC by 37% (from 1325 to 831 micrograms/L) and 47%, respectively.[15]

Other reports describe patients who needed two- to fourfold increases in their ciclosporin doses when they were given phenytoin,[16-19] and one patient who had variable ciclosporin levels and a rejection episode in the first 10 days after a kidney transplant while taking phenytoin.[20]

Another report describes an increase in ciclosporin levels from 512 nanograms/mL to 810 nanograms/mL after phenytoin and phenobarbital were replaced by sodium valproate.[8]

A report of severe gingival overgrowth in a kidney transplant patient was attributed to the additive adverse effects of ciclosporin and phenytoin. Ciclosporin was replaced by tacrolimus, which may have fewer oral adverse effects, and almost complete reversal of gingival overgrowth was achieved within 6 months.[21]

(e) Sodium valproate

In four cases an interacting antiepileptic was successfully replaced by sodium valproate,[3,4,8] see *Carbamazepine*, *Phenobarbital* and *Phenytoin*, above. However, sodium valproate may not always be without problems because interstitial nephritis was suspected in one patient with a renal graft taking ciclosporin and valproate,[10] and fatal valproate-induced hepatotoxicity occurred in another patient taking ciclosporin.[22]

Mechanism

It is thought that phenytoin,[14,15] carbamazepine[1,2] and phenobarbital[7,11] increase the metabolism of ciclosporin by cytochrome P450 in the liver (most probably the isoenzyme CYP3A4) thereby decreasing its serum levels. Oxcarbazepine produced only a small reduction in ciclosporin levels in one case, and the effect is probably due to more modest induction of the cytochrome P450 subfamily CYP3A.[6] Phenytoin also possibly reduces the absorption of ciclosporin.[23]

Importance and management

None of these interactions is extensively documented, but all appear to be established and of clinical importance. Serum ciclosporin levels should be well monitored if carbamazepine, phenobarbital or phenytoin are added and the ciclosporin dose increased appropriately. **Primidone** is metabolised to phenobarbital, and **fosphenytoin** is a prodrug of phenytoin and would therefore also be expected to reduce ciclosporin levels. Information about oxcarbazepine is very limited but small reductions in its dose, together with an increase in ciclosporin dose, may be adequate to control any interaction; however, more study is required.[6] The effects of the interaction may persist for a week or more after the anticonvulsant is withdrawn. Sodium valproate seems not to alter ciclosporin levels, but the case reports of nephritis and hepatotoxicity suggest some caution is warranted.

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Ciclosporin + Antimycobacterials

Ciclosporin levels are markedly reduced by rifampicin and transplant rejection can rapidly develop. One case report suggests that rifabutin interacts, although to a lesser extent. Topical rifamycin has been reported to reduce ciclosporin levels in one patient. Ethambutol and isoniazid do not generally appear to interact with ciclosporin although case reports have described alterations in ciclosporin levels.

Clinical evidence

(a) Rifabutin

The clearance of ciclosporin in a patient with a kidney transplant doubled when isoniazid, ethambutol, pyridoxine and rifampicin 600 mg daily were given. When these drugs were replaced by rifabutin 150 mg and clofazimine 100 mg daily, the ciclosporin clearance fell to about its former levels, but after about 3 weeks the clearance was about 20% greater than before the antimycobacterial drugs were given.[1]

(b) Rifampicin (Rifampin)

A study in 39 kidney transplant patients taking ciclosporin at a mean dose of 158 mg daily found that the ciclosporin dose needed to be increased by between 150 to 525 mg daily (an average dose of 469 mg daily) when rifampicin 450 to 600 mg daily was taken as part of a regimen for tubercu-

losis. An increased incidence of acute rejection occurred during treatment with ciclosporin and rifampicin and 16 patients had kidney graft failure and needed to go back on haemodialysis because of this interaction.[2]

A heart transplant patient taking ciclosporin started taking rifampicin 600 mg daily with amphotericin B for the treatment of an *Aspergillus fumigatus* infection. Within 11 days her serum ciclosporin levels had fallen from 473 nanograms/mL to less than 31 nanograms/mL and severe acute graft rejection occurred. The dose of ciclosporin was increased stepwise and the levels climbed to a plateau before suddenly falling again. The dose had to be increased to more than 30 mg/kg daily to achieve serum levels in the range 100 to 300 nanograms/mL.[3]

A considerable number of other reports about individual patients, both adult and paediatric, confirm that a very marked fall in serum ciclosporin levels occurs, often to undetectable levels, accompanied by transplantation rejection in many instances, if rifampicin is given either intravenously or orally without raising the ciclosporin dose.[1,4-28] Ciclosporin levels become toxic within 2 weeks of stopping rifampicin unless the previously adjusted ciclosporin dose is reduced.[4,6]

Three patients needed increases in the dose of ciclosporin when given rifampicin, despite the additional use of erythromycin, which normally reduces ciclosporin requirements.[19,29,30] Another patient whose ciclosporin levels had been raised by clarithromycin had a fall in their levels when rifampicin was added.[31] For further information on the effects of the macrolides on ciclosporin levels, see 'Ciclosporin + Antibacterials; Macrolides', p.1218.

(c) Rifamycin sodium

Rifamycin sodium used to irrigate a wound has been reported to reduce the serum levels of ciclosporin in a kidney transplant patient.[32]

(d) Other antituberculars

Isoniazid[12,22,23,33] and **ethambutol**[22,23] do not normally interact with ciclosporin. However, there is one case report describing a patient who had a gradual rise in serum ciclosporin levels when isoniazid and ethambutol were stopped,[14] and another which attributed a marked rise in ciclosporin levels to the use of isoniazid.[34] Successful treatment of tuberculosis in heart and kidney transplant patients has also been reported using **isoniazid**, **ethambutol**, '**pyrazinamide**', (p.1250), and **streptomycin**.[35]

Mechanism

Rifampicin (rifampin) induces the cytochrome P450 isoenzyme CYP3A4, by which ciclosporin is metabolised resulting in a marked increase in ciclosporin clearance. In addition, rifampicin decreases ciclosporin absorption by inducing its metabolism by the gut wall,[36] thus producing a significant fall in ciclosporin levels. The drug transporter protein P-glycoprotein may also be involved in this interaction. Rifabutin has some enzyme-inducing effects but the extent is quite small compared with rifampicin, and the onset may be delayed.[37]

Importance and management

The interaction between ciclosporin and rifampicin (rifampin) is very well documented, well established and clinically important, and transplant rejection may occur unless the ciclosporin dose is markedly increased. In one study 27% of patients taking rifampicin lost grafts due to rejection, and this was directly attributed to the interaction.[22] The interaction develops within a few days (within a single day in one case[20]). If the concurrent use of rifampicin is essential, monitor the effects closely and increase the ciclosporin dose appropriately: three- to fivefold dose increases (sometimes increasing the dose frequency from two to three times daily) have proved to be effective, with daily monitoring. Remember also to reduce the ciclosporin dose when rifampicin is stopped to reduce the risk of ciclosporin toxicity.

The authors of one large study concluded that it is better to avoid rifampicin in patients taking ciclosporin and to use other antimycobacterials instead.[22] They found that the use of three antitubercular drugs (not including rifampicin) for at least 9 months reduced mortality. Other reports similarly found that regimens without rifampicin were suitable for the treatment of tuberculosis in transplant patients.[23,35] Another suggested alternative is to replace the ciclosporin with a different non-interacting immunosuppressant, such as azathioprine and low-dose prednisolone, if rifampicin is needed.[13]

Other rifamycins may also be an option; limited evidence from one case suggests that rifabutin interacts minimally. However, the manufacturer[38] and the CSM in the UK[39] caution about the possibility of an interaction, and close monitoring of ciclosporin levels would still be advisable.

Topical rifamycin interacted like rifampicin in one patient when it was applied to a wound.[32]

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Ciclosporin + Azoles

The evidence suggests that all the azole antifungals can raise ciclosporin levels to a greater or lesser degree. Ketoconazole may cause five- to tenfold rises, while itraconazole, fluconazole and voriconazole may cause two- to threefold rises. A case report suggests that intravenous miconazole interacts similarly and, in theory, miconazole oral gel may also interact. Posaconazole may also modestly raise ciclosporin levels. Rhabdomyolysis has been reported with the combination of ciclosporin and itraconazole, but four of these cases were complicated by the presence of statins.

Clinical evidence

(a) Fluconazole

Oral fluconazole 200 mg daily for 14 days roughly doubled the ciclosporin trough blood levels of 8 kidney transplant patients stabilised on oral ciclosporin, from 27 to 58 nanograms/mL. The AUC increased by 80% but serum creatinine levels were unchanged.[1,2]

Other reports describe two- to threefold rises in ciclosporin blood levels in kidney transplant patients within 6 to 11 days of starting treatment with fluconazole 100 to 300 mg daily.[3-9] One patient developed nephrotoxicity, which resolved when the doses of both drugs were reduced.[10]

In contrast, some patients have had little or no changes in serum ciclosporin or creatinine levels when fluconazole was given.[7,8,11-15] It has been suggested that the interaction is dose-dependent.[8] In addition, the route of administration might influence the interaction. For example, there was only a 20% increase in ciclosporin levels when intravenous ciclosporin was given with high-dose intravenous fluconazole, which was not considered clinically relevant.[16] In a retrospective study in patients receiving intravenous ciclosporin, the ciclosporin blood level rose slightly (from 362 nanograms/mL to 394 nanograms/mL)when intravenous fluconazole was switched to oral fluconazole.[17] One study found a lack of interaction in females and African-American patients, suggesting that gender and ethnicity may also be factors.[18]

(b) Itraconazole

In 4 heart-lung, 2 heart and one lung transplant patient an average 56% reduction (range 33 to 84%) in the ciclosporin doses were needed when itraconazole (dose not stated) was given. Serum creatinine levels rose temporarily until the ciclosporin dose had been readjusted.[19] Two- to threefold rises in ciclosporin levels were seen in another 2 patients given itraconazole 200 mg daily,[20,21] and in one case the raised levels persisted for more than 4 weeks after the itraconazole was stopped.[21] Intravenous itraconazole 200 mg twice daily for 2 days then 200 mg daily caused a mean 80% increase in the levels of ciclosporin in 8 patients receiving intravenous ciclosporin.[22]

Other case reports and studies suggest that dose reductions of about 50 to 80% (where stated) were needed when patients taking ciclosporin were given itraconazole.[23-27] Enhanced itraconazole absorption in the presence of a carbonated drink that increased stomach acidity was found to allow decreases in the ciclosporin dose and increases in its dose interval.[28]

These reports contrast with another describing 14 bone marrow transplant patients taking ciclosporin. Those given itraconazole 100 mg twice daily had no significant changes in ciclosporin or creatinine serum levels.[29] Another patient required only a 10% reduction in ciclosporin dose when given itraconazole 400 mg daily for 40 days.[7]

Rhabdomyolysis has been reported in 3 lung transplant patients[23,30] and 2 heart transplant patients[31,32] when itraconazole was given with ciclosporin. However, in three of these cases the concurrent use of simvastatin and in one case concurrent simvastatin and gemfibrozil would also have been factors,[23,30-32] as both ciclosporin and itraconazole can increase simvastatin levels (see 'Statins + Ciclosporin', p.1326, and also 'Statins + Azoles', p.1321).

In a pharmacokinetic study in patients undergoing stem cell transplantation, the AUC of itraconazole after a single 200-mg intravenous dose did not differ before and after patients were stabilised on ciclosporin. However, the median AUC of the main active itraconazole metabolite, hydroxyitraconazole, was increased by 49%. This is probably not clinically relevant, but may have a bearing in situations when itraconazole levels are monitored.[33]

(c) Ketoconazole

Ketoconazole 200 mg daily caused a marked and rapid rise in the ciclosporin blood levels of 36 renal transplant patients. On the basis of experience with previous patients, the ciclosporin dose was reduced by 70% when ketoconazole was started, and after a year the dose reduction was 85% (from 420 mg to 66 mg daily). Minimal nephrotoxicity was seen.[34-36] A study in children with nephrotic syndrome found the addition of ketoconazole allowed a ciclosporin dose reduction of about 37%. They also found that those given ketoconazole (153 patients) had a lower frequency of renal impairment, were more likely to be able to stop taking steroids and had a better chance of staying in remission than those not given ketoconazole (54 patients).[37] Another similar study by this same research group found comparable results.[38]

Other reports[7,39-52] describe essentially similar rises in ciclosporin levels during the use of ketoconazole. The effects of ketoconazole on ciclosporin were found to be slightly increased (from 80 to 85% or from 77 to 84%) when diltiazem was also given.[26,53]

In a retrospective study an increased incidence of severe liver toxicity was seen in patients also taking ketoconazole when the method of monitoring ciclosporin levels was switched from trough levels (C_0) to taking levels 2 hours post dose (C_2). Liver toxicity developed in 26% of patients monitored solely using C_2 levels compared with no patients monitored using C_0 and C_2 levels.[54] For mention of a report of seizures occurring when ketoconazole was added to ciclosporin and high-dose methylprednisolone, see 'Ciclosporin + Corticosteroids', p.1235.

Topical ketoconazole 2% cream did not alter the response to oral ciclosporin 1 mg/kg daily in the treatment of contact allergic dermatitis.[55]

(d) Miconazole

A single case report describes a rise of about 65% in ciclosporin serum levels within 3 days of intravenous miconazole 1 g every 8 hours being started. Ciclosporin levels rose again during subsequent treatment with miconazole.[56]

(e) Posaconazole

Posaconazole 200 mg daily for 10 days was given to 4 heart transplant patients receiving stable doses of ciclosporin. Three of the 4 required modest dose reductions of between 14 and 29% to maintain ciclosporin levels.[57] In another report, increased ciclosporin levels occurred in just one of 12 transplant patients given posaconazole 800 mg daily. In this patient, the ciclosporin dose was decreased by 45% on starting posaconazole, and the ciclosporin level was normal 17 days later (193 nanograms/mL) at discharge. However, 7 days later the patient had altered mental status and very high ciclosporin levels. She had thrombotic thrombocytopenic purpura and pancytopenia and eventually died. The authors said it is not clear if this case represents a patient medication error, or an interaction.[58] The UK manufacturer also reports cases of ciclosporin toxicity that resulted in significant adverse effects, including nephrotoxicity and one fatal case of leukoencephalopathy, which occurred in posaconazole efficacy studies.[59]

(f) Voriconazole

In a placebo-controlled, crossover study, 14 kidney transplant patients receiving stable doses of ciclosporin were given voriconazole 200 mg every 12 hours for 15 doses. Of the 14 patients, 7 discontinued treatment during the voriconazole phase due to adverse effects, 4 due to raised ciclosporin levels (mean 2.48-fold), one due to raised liver function, one due to asthenia, dyspnoea and oedema, and one due to an underlying condition unrelated to the voriconazole. In the remaining 7 patients voriconazole increased the AUC of ciclosporin by 70%.[60] Ciclosporin levels were significantly *reduced* in a bone marrow transplant patient, from a range of 150 to 184 nanograms/mL to 56 to 111 nanograms/mL, when prophylactic voriconazole was *stopped* due to abnormal liver function tests. The levels returned to range when the voriconazole was restarted.[61]

Mechanism

The azole antifungals inhibit the cytochrome P450 isoenzyme CYP3A4, by which ciclosporin is metabolised, and as a result ciclosporin blood levels rise. The azoles vary in the potency of their effects on CYP3A4, see 'Azoles', (p.233). One review lists them in relative order of their effects on ciclosporin metabolism (most potent first): ketoconazole, followed by

itraconazole and voriconazole (roughly equipotent), and then fluconazole.[62] Further study into the relative potency of posaconazole is required.[62]

Fluconazole and ketoconazole also appear to inhibit the metabolism of ciclosporin by the gut wall.[16,50]

Importance and management

All the available azole antifungals can raise ciclosporin levels to varying degrees. The interaction between ciclosporin and **ketoconazole** is very well established and clinically important. Ciclosporin blood levels rise rapidly and sharply, but they can be controlled by reducing the ciclosporin dose by about 70 to 80%[7,24,34,41,51] thereby preventing kidney damage. A ciclosporin dose reduction of 68 to 89% was required over a 13-month period in one study, with no adverse changes in immunosuppressive activity, resulting in a total cost saving of about 65%, partially offset because of the need for more frequent patient follow-up and the cost of the ketoconazole.[34,35] Other studies have also suggested that this interaction can be exploited to make cost savings.[51,63,64] Reviews of the pros and cons of concurrent use have been published.[36,65] Ketoconazole may possibly have a kidney protective effect.[34,35] A study in kidney transplant patients suggested that variability in absorption and in the response to metabolic inhibition by ketoconazole made the ciclosporin blood level response difficult to predict and monitor.[66] There are also other confounding factors. For example, a patient who was given ketoconazole to increase ciclosporin levels was subsequently given famotidine. The famotidine raised gastric pH, which resulted in a reduction in the ketoconazole absorption, and the ciclosporin levels consequently fell.[67] Bear in mind the possibility that, in patients taking ketoconazole. monitoring the use of ciclosporin with ciclosporin levels taken 2 hours post-dose may not be the best method.[54,68]

Information about the use of ciclosporin with **fluconazole** or **itraconazole** is less extensive, but concurrent use should be closely monitored, being alert for the need to reduce the ciclosporin dose, in some cases by up to 50% or more, although some patients may demonstrate no significant changes at all. There is also some evidence that in the case of fluconazole, the interaction may possibly depend on its dose,[8] gender and ethnicity,[18] and the route of ciclosporin[16] or fluconazole[17] administration. Ciclosporin may increase the levels of the hydroxy metabolite of itraconazole, but the relevance of this is uncertain.

The interaction between *intravenous* **miconazole** and ciclosporin may be potentially serious and of clinical importance. There is no evidence of an interaction with other forms of miconazole. However, a large proportion of miconazole *oral* gel (both prescription and non-prescription doses) may be swallowed and therefore adequate systemic absorption may occur for interactions with other medications. The manufacturers of miconazole oral gel recommend close monitoring and possible dose reduction of ciclosporin if given concurrently.[69] An interaction with *intravaginal* miconazole would not normally be expected because its systemic absorption is usually very low (less than 2%) in healthy women of child-bearing age.[70] Similarly, an interaction with topical miconazole creams would also not be expected.

The manufacturers of **voriconazole** suggest that the dose of ciclosporin should be halved when initiating voriconazole, and that ciclosporin levels should be carefully monitored during voriconazole treatment. It is important that the ciclosporin dose is increased again as necessary if voriconazole is withdrawn.[71,72]

The manufacturers of **posaconazole** recommend that the dose of ciclosporin should be reduced by about 25% when posaconazole is started, with careful monitoring of ciclosporin levels and further dose adjustment as needed, including when posaconazole is stopped.[59,73] However, the authors of one review state that pre-emptive ciclosporin dose reductions when starting azoles are not standard practice among transplant clinicians, because of the concern of an increased risk of rejection[62] (due to subtherapeutic ciclosporin levels). Whatever is done, close monitoring is necessary. In addition, note that the UK manufacturer of posaconazole predicts that its levels will increased by ciclosporin as a result of P-glycoprotein inhibition.[59]

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Ciclosporin + Basiliximab

Ciclosporin levels and adverse effects may be altered by basiliximab.

Clinical evidence, mechanism, importance and management

A study in 39 paediatric kidney transplant patients taking ciclosporin found that, in 24 patients who were also given basiliximab 10 or 20 mg on days 0 and 4 after transplantation, lower doses of ciclosporin resulted in significantly higher ciclosporin trough levels and some evidence of early ciclosporin toxicity within the first 10 days. At days 28 to 50, ciclosporin levels declined and 20% higher doses were required to maintain adequate trough levels in the basiliximab group.[1] Another study, in 54 paediatric liver transplant patients, found that the addition of basiliximab to ciclosporin and corticosteroids did not significantly alter the overall ciclosporin dose requirements. However, 9 patients given basiliximab experienced acute rejection at 21 to 28 days after transplantation, and this was associated with low ciclosporin trough levels, requiring an increased ciclosporin dose in 6 of the 9 patients.[2] It was suggested that the effect on ciclosporin was due to an interleukin-2 receptor mediated alteration of the cytochrome P450 enzyme system.[1] This was considered to only play a minor role in the liver transplant patients because of significantly lower target trough levels in these patients.[2] However, a further study found no increase in rejection rates between days 28 to 50 in kidney transplant patients given basiliximab and ciclosporin.[3]

The authors of the first study[1] recommend that the initial dose of ciclosporin should be limited to 400 mg/m^2 in children receiving kidney transplants who are also given basiliximab. Dose reductions were not considered necessary by other authors, but close monitoring was recommended.[2,3]

A retrospective analysis of kidney transplant patients compared the rates of acute rejection within 6 months in patients given ciclosporin, mycophenolate mofetil and prednisone, with or without basiliximab. Overall the rates of acute rejection were 11% and 23% in the basiliximab and no-basiliximab groups, respectively. In 74 patients not given basiliximab, low therapeutic ciclosporin exposure on day 3 was associated with increased acute rejection within the first 6 months post-transplantation (45% with ciclosporin AUC less than 4400 nanogram.h/mL compared with 15% with a ciclosporin AUC of greater than 4400 nanogram.h/mL). In 93 patients given basiliximab, rates of acute rejection were similar (about 10%) in patients with low or therapeutic ciclosporin exposure at day 3. It was suggested that achieving early ciclosporin therapeutic targets may not be required if basiliximab is also used.[4]

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Ciclosporin + Benzbromarone

Benzbromarone does not appear to interact with ciclosporin.

Clinical evidence, mechanism, importance and management

Twenty-five kidney transplant patients taking ciclosporin were given benzbromarone 100 mg daily to treat hyperuricaemia. The plasma uric acid levels decreased from 579 micromol/L to 313 micromol/L and the 24-hour urinary uric acid secretion rose from 2082 micromol to 3233 micromol after 4 weeks of treatment. The plasma uric acid levels normalised in 21 of the patients who had creatinine clearances of over 25 mL/minute. No significant adverse effects developed and the ciclosporin serum levels remained unchanged. The authors of the report emphasise the advantages of benzbromarone over allopurinol because of its efficacy, lack of significant adverse effects and because, unlike allopurinol, it does not interact with azathioprine, which often accompanies ciclosporin treatment.[1]

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Ciclosporin + Berberine

Berberine appears to increase the bioavailability and trough blood levels of ciclosporin.

Clinical evidence, mechanism, importance and management

A study in 6 kidney transplant patients looked at the effects of berberine on the pharmacokinetics of ciclosporin. The patients were taking ciclosporin 3 mg/kg twice daily for an average of 12 days before berberine 200 mg three times daily for 12 days was added. The AUC and trough blood levels of ciclosporin were increased by 35% and 88%, respectively. The peak ciclosporin level was decreased but this was not statistically significant.[1] A clinical study by the same authors in 52 kidney transplant patients stable taking ciclosporin and given berberine 200 mg three times daily for 3 months found that the ciclosporin trough levels were increased by about 24% when the berberine-treated group was compared with 52 similar patients taking ciclosporin without berberine. The ciclosporin levels in 8 patients fell after berberine was stopped. Creatinine clearance was not significantly altered, and no serious adverse effects were reported.[1]

A single-dose study in healthy subjects found conflicting results. Six subjects given a single 6-mg/kg dose of ciclosporin daily found that berberine 300 mg twice daily, taken for 10 days before the dose of ciclosporin, had no significant effects on the pharmacokinetics of ciclosporin. However, a separate study in another 6 subjects given a single 3-mg/kg dose of ciclosporin found that a single 300-mg dose of berberine increased the AUC of ciclosporin by 19%. No adverse events were reported in this study.[2]

Mechanism

The mechanism for the increase in ciclosporin levels seen in the clinical studies is unclear, although it has been suggested that it may be due to inhibition of CYP3A by berberine.

Animal studies[3,4] suggest that ciclosporin may also affect the handling of berberine possibly by inhibiting P-glycoprotein, therefore affecting its intestinal absorption and its distribution into the bile and liver.

Importance and management

Although the increase in ciclosporin levels is not sufficiently severe to suggest that the concurrent use of berberine should be avoided, it may make ciclosporin levels less stable. If concurrent use is undertaken, ciclosporin levels should be well monitored, and the dose of ciclosporin adjusted accordingly.

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3. Tsai P-L, Tsai T-H. Hepatobiliary excretion of berberine. *Drug Metab Dispos* (2004) 32, 405–12.
4. Pan G-Y, Wang G-J, Liu X-D, Fawcett JP, Xie Y-Y. The involvement of P-glycoprotein in berberine absorption. *Pharmacol Toxicol* (2002) 91, 193–7.

Ciclosporin + Beta blockers

Carvedilol may modestly increase ciclosporin levels in some patients. In general, atenolol and metoprolol do not appear to interact with ciclosporin.

Clinical evidence

A study in 21 kidney transplant patients found that when **atenolol** was gradually replaced by **carvedilol** in a stepwise manner, starting with **carvedilol** 6.25 mg daily, gradually increasing to 50 mg daily, the ciclosporin dose had to be gradually reduced. At 90 days the ciclosporin dose had been reduced by 20% (from 3.7 to 3 mg/kg daily) to maintain levels within the therapeutic range but considerable inter-individual variations were seen.[1] A retrospective study in 12 heart transplant patients found that **carvedilol** increased the ciclosporin level in 10 patients from a mean of 257 nanograms/mL to 380 nanograms/mL. This required a mean dose reduction of 31 mg daily (10%). In the same study, 20 patients taking **metoprolol** were also assessed. Twelve patients had a decrease and 8 patients an increase in their ciclosporin levels, although the overall mean change was only 1 nanogram/mL. However, in one case, metoprolol appears to have increased the ciclosporin levels from about 300 nanograms/mL to 900 nanograms/mL, but insufficient detail is given to be able to assess this finding. None of these changes with **metoprolol** required any significant ciclosporin dose alterations (mean dose alteration 0.03%).[2] A study in 30 kidney transplant patients found no change in the ciclosporin levels of those taking **atenolol** 25 to 100 mg daily.[3]

Mechanism

Carvedilol appears to increase ciclosporin levels by inhibiting P-glycoprotein.[4]

Importance and management

The modest interaction of carvedilol with ciclosporin would appear to be established. The manufacturers of carvedilol recommend close monitoring of ciclosporin levels with appropriate dose adjustment when carvedilol is added,[5,6] which seems prudent. In general it appears that no ciclosporin dose adjustment would be expected to be needed in patients taking metoprolol. Atenolol does not appear to interact with ciclosporin.

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5. Eucardic (Carvedilol). Roche Products Ltd. UK Summary of product characteristics, July 2007.
6. Coreg (Carvedilol). GlaxoSmithKline. US Prescribing information, June 2009.

Ciclosporin + Bifendate

Two case reports suggest that bifendate can cause a gradual fall in the serum levels of ciclosporin, and a modest reduction in ciclosporin levels was seen in one study in healthy subjects.

Clinical evidence

Two kidney transplant patients were successfully treated with ciclosporin and prednisolone for 30 months and 36 months. When they were given bifendate 75 mg daily for the treatment of chronic hepatitis, both of them had a gradual fall in their trough serum ciclosporin levels. The ciclosporin levels of the first patient fell from 97.7 nanograms/mL to 78 nanograms/mL at 4 weeks, and fell further, to 49 nanograms/mL, at 6 weeks. The other patient had a fall from 127.5 nanograms/mL to 70.5 nanograms/mL at 8 weeks and to 45 nanograms/mL at 16 weeks. The ciclosporin doses remained unchanged throughout, and despite the low serum levels that occurred, no graft rejection was seen. When the bifendate was stopped, ciclosporin levels gradually climbed again, at about the same rate as their decline, to about their former levels.[1] In a subsequent placebo-controlled study in 18 healthy subjects, bifendate 15 mg three times daily for 14 days decreased the AUC of ciclosporin by 10 to 38% after a single oral dose of ciclosporin, and increased the oral clearance by 10 to 32%.[2]

Mechanism

The reasons for this interaction are not understood. It is possible that bifendate is acting as an inducer of the cytochrome P450 isoenzyme CYP3A4,[2] which is the major isoenzyme involved in ciclosporin metabolism.

Importance and management

The available information suggests that a modest interaction might occur between bifendate and ciclosporin, therefore it would be prudent to monitor the outcome, being alert for the need to increase the ciclosporin dose if bifendate is used. Bifendate is derived from *Schisandra* therefore, until more is known, it might be wise to extend this caution to all herbal preparations containing *Schisandra*. However, in contrast to the above data, an extract from *Schisandra sphenanthera* increased the levels of tacrolimus, which is also a substrate of CYP3A4, see 'Tacrolimus + Schisandra', p.1308.

1. Kim YS, Kim DH, Kim DO, Lee BK, Kim KW, Park JN, Lee JC, Choi YS, Rim H. The effect of diphenyl-dimethyl-dicarboxylate on cyclosporine-A blood level in kidney transplants with chronic hepatitis. *Korean J Intern Med* (1997) 12, 67–9.
2. Zeng Y, He YJ, He FY, Fan L, Zhou HH. Effect of bifendate on the pharmacokinetics of cyclosporine in relation to the CYP3A4*18B genotype in healthy subjects. Acta Pharmacol Sin (2009) 30, 478–84.

Ciclosporin + Bile acids or Ursodeoxycholic acid (Ursodiol)

Ursodeoxycholic acid unpredictably increases the absorption and raises the levels of ciclosporin in some but not all patients. Bile acids (cholic and dehydrocholic acids) appear not to interact with ciclosporin.

Clinical evidence

(a) Bile acids

In a study, 11 healthy subjects were given a single oral dose of ciclosporin on three occasions: while fasting, with breakfast, and with breakfast plus bile acid tablets (**cholic acid** 400 mg, **dehydrocholic acid** 100 mg): the mean ciclosporin AUCs were 7283 nanograms/mL, 7453 nanograms/mL and 9078 nanograms/mL, respectively, indicating that the bile acids increased the absorption of ciclosporin by 22%.[1] However, a related study in 19 transplant patients found that their 12-hour trough ciclosporin serum levels were unchanged by the concurrent use of this dose of bile acids over an 8-day period.[1]

(b) Ursodeoxycholic acid (Ursodiol)

When a heart transplant patient who had previously had his entire ileum removed and about one metre of the residual jejunum anastomosed to the transverse colon started taking ursodeoxycholic acid 1 to 2 g daily, it was possible to reduce his ciclosporin dose from 1.6 to 1.2 g daily. However, when the ursodeoxycholic acid was stopped, his ciclosporin serum levels became subtherapeutic and severe acute rejection developed. The ciclosporin levels rose when ursodeoxycholic acid was restarted, and the ciclosporin AUC was increased by more than threefold.[2] Similarly, the trough serum ciclosporin levels of a patient with chronic active hepatitis C increased from 150 nanograms/mL to 500 nanograms/mL when he was given ursodeoxycholic acid, and it was necessary to halve his daily ciclosporin dose to keep the ciclosporin levels at 150 nanograms/mL.[3]

In contrast, various other studies[4-6] and one case report[7] have shown little or no effect of ursodeoxycholic acid on ciclosporin levels. In one of these in liver transplant patients, there was no difference in ciclosporin (*Sandimmun*) dose requirements between 17 patients given ursodeoxycholic acid 15 mg/kg daily for 3 months and 16 patients given placebo.[6] Similarly, in 7 liver transplant patients there were no statistically significant changes in mean ciclosporin levels when a single 600-mg dose of ursodeoxycholic acid was given at the same time as the ciclosporin (*Sandimmun*).[4] Yet another study in 12 liver transplant patients, 6 of whom were cholestatic, found that ciclosporin (*Sandimmun*) was absorbed more rapidly after a single dose of ursodeoxycholic acid in 8 patients, but, although 7 patients had some rise in their AUC, the mean 24-hour AUC was not significantly changed. There was no consistent improvement in ciclosporin pharmacokinetics in the cholestatic patients.[5]

Furthermore, variable effects were seen in another study using the microemulsion formulation of ciclosporin (*Neoral*) in liver transplant recipients. Ursodeoxycholic acid appeared to *reduce* the absorption rate and bioavailability of ciclosporin in 9 patients without cholestasis, but increased the absorption rate and bioavailability in 3 cholestatic patients.[8]

Mechanism

When an interaction occurs it is thought to do so because the ursodeoxycholic acid improves micellation of the oil-containing oral ciclosporin formulation so that its absorption is increased.[2]

Importance and management

Information is limited but bile acids do not appear to interact with ciclosporin. However, the effects of the interaction with ursodeoxycholic acid appears to be variable and unpredictable. It would therefore be prudent to monitor the effects of adding or stopping ursodeoxycholic acid in any patient taking ciclosporin, being alert for the need to adjust the ciclosporin dose.

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Ciclosporin + Bupropion

An isolated case describes a large decrease in ciclosporin levels when a 10-year-old boy was given bupropion.

Clinical evidence, mechanism, importance and management

A 10-year-old boy, who had received a heart transplant 6 years previously, started taking bupropion 75 mg twice daily in addition to his usual transplant medication, which included ciclosporin. After taking bupropion for 22 days, his ciclosporin level was found to be only 39 nanograms/mL. The last level taken before bupropion treatment had been 197 nanograms/mL. Despite an increase in his ciclosporin dose from 420 to 500 mg daily, the ciclosporin levels fell further, to 27 nanograms/mL. The ciclosporin dose was then increased to 550 mg daily and bupropion was stopped.[1]

The reason for this probable interaction is unclear, although an interaction via the cytochrome P450 isoenzyme CYP3A4 is a possibility. This appears to be the only reported case of an interaction between ciclosporin and bupropion, and its general importance is unknown.

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Ciclosporin + Calcium-channel blockers

Diltiazem, nicardipine and verapamil markedly raise ciclosporin levels, but also appear to possess kidney protective effects. Nifedipine normally appears not to interact, but rises and falls in ciclosporin levels have been seen in a few patients. Amlodipine has modestly increased ciclosporin levels in some studies, but not in others, and it may also have kidney protective properties. A single case describes elevated ciclosporin levels caused by nisoldipine. Felodipine, isradipine, lacidipine and nitrendipine normally appear not to raise ciclosporin levels. Ciclosporin has been seen to markedly increase lercanidipine levels, and modestly increase felodipine levels. The concurrent use of calcium-channel blockers and ciclosporin increases the risk of gingival overgrowth.

Clinical evidence

(a) Ciclosporin levels and nephrotoxicity

1. Amlodipine. Ten hypertensive patients with kidney transplants taking ciclosporin (3 of them also taking azathioprine) were given amlodipine 5 to 10 mg daily for 4 weeks. The hypertension was well controlled, the drugs were well tolerated, and the pharmacokinetics of ciclosporin were unaltered by amlodipine.[1] However, another study in 11 hypertensive kidney transplant patients found that amlodipine, given for 7 weeks, increased the ciclosporin levels by an average of 40%, without affecting creatinine levels.[2] A review identified two other studies that have found increases in ciclosporin levels of 23% and 43% with amlodipine, whereas four studies have found no change.[3] Amlodipine is reported to reduce ciclosporin-associated nephrotoxicity in a study in patients with psoriasis,[4] and in a review of kidney transplant recipients.[3]

2. Diltiazem. A pharmacokinetic study in 9 patients taking ciclosporin found that the addition of diltiazem 180 mg daily increased the trough blood level, maximum blood level and half-life of ciclosporin by 112%, 37%, and 43%, respectively.[5] Sixty-five kidney transplant patients taking ciclosporin and diltiazem were found to need less ciclosporin when compared with 63 control patients not given diltiazem (7.3 mg/kg daily compared with 9 mg/kg daily). There were considerable individual differences in dose requirements.[6] Other studies clearly confirm that diltiazem can raise ciclosporin blood levels.[7-32] In some cases the ciclosporin blood levels were not only controlled by reducing the ciclosporin dose by 30 to 60%, but it appeared that diltiazem had a kidney protective role (reduced nephrotoxicity, fewer rejection episodes and haemodialysis sessions).[11,22,33-37] Another study found that a reduction in ciclosporin dose of about 21% was required for both men and women during the long-term use of diltiazem 90 mg twice daily, despite reports of higher activity of the cytochrome P450 isoenzyme CYP3A4 in women than in men.[38]

3. Felodipine. Thirteen kidney transplant patients had no significant changes in their serum ciclosporin levels when they took felodipine 2.5 to 10 mg daily; serum creatinine levels were also unchanged. Mean blood pressures fell from 161/100 mmHg to 152/90 mmHg.[39] Another study found no significant changes in ciclosporin levels in patients also given felodipine.[40] A single 10-mg dose of felodipine was found to have beneficial effects on blood pressure, renal haemodynamics, and renal tubular sodium and water handling in kidney transplant patients taking ciclosporin. The effects of long-term use were not studied.[41] A single-dose study in 12 healthy subjects found that the maximum serum levels of ciclosporin 5 mg/kg were slightly raised by 16% by felodipine 10 mg, while the AUC and maximum plasma level of felodipine were raised by 58% and 151%, respectively, but blood pressures were unchanged.[42] The same group of researchers also briefly described acute and short-term studies in groups of kidney transplant patients and dermatological patients, which found that felodipine 5 to 10 mg reduced blood pressure and opposed ciclosporin nephrotoxicity.[43] A study in heart transplant patients taking ciclosporin found that felodipine attenuated the hypertrophic effects of ciclosporin on transplanted hearts.[44]

4. Isradipine. Twelve kidney transplant patients had no changes in their ciclosporin levels over 4 weeks while taking up to 2.5 mg of isradipine twice daily.[45] Similar findings are noted in another study.[40] Three other studies in 31 kidney transplant patients confirmed that ciclosporin blood levels are unchanged by isradipine and blood pressures are reduced.[46-48]

5. Lacidipine. Ten kidney transplant patients taking ciclosporin, prednisone and azathioprine started taking lacidipine 4 mg daily. A very small increase in the trough blood levels (6%) and AUC (14%) of the ciclosporin occurred. The blood pressures fell from 142/93 mmHg to 125/79 mmHg, and the 14-hour urinary output rose from 1401 mL to 2050 mL.[49]

6. Lercanidipine. The manufacturer notes that, in healthy subjects given lercanidipine and ciclosporin simultaneously, the plasma levels of lercanidipine were raised threefold by ciclosporin, and the ciclosporin AUC was raised by 21% by lercanidipine. When the ciclosporin was given 3 hours after the lercanidipine, the levels of lercanidipine did not change, and the AUC of ciclosporin increased by 27%.[50]

7. Nicardipine. In a study in 9 patients, nicardipine 20 mg three times daily increased the ciclosporin blood levels by 110% (from 226 to 430 nanograms/mL, range 24 to 341%). Their serum creatinine concentrations rose from 136 micromol/L to 147 micromol/L.[51] Other studies have found increases in serum ciclosporin levels, in some cases as much as two- to threefold, when nicardipine was given.[52-58]

8. Nifedipine. Five of 9 patients who had an increase in ciclosporin levels with nicardipine (see *Nicardipine*, above) had no interaction when they were given nifedipine.[51] No changes in ciclosporin levels were seen in other studies,[36,59-63] but raised[17,20] and reduced levels[64] have been reported in others. Two studies found that nifedipine appeared to protect patients against ciclosporin-induced nephrotoxicity.[65,66] However, there is some evidence that the adverse effects of nifedipine such as flushing and rash may be increased.[67] For a discussion of gingival overgrowth, see under *Gingival overgrowth*, below.

9. Nisoldipine. A 46-year-old man taking azathioprine, prednisolone and ciclosporin after a kidney transplant 18 months previously was given nisoldipine 5 mg twice daily. During the following month his ciclosporin levels rose from a range of 100 to 150 micrograms/L up to 200 micrograms/L and an increase in serum creatinine levels occurred. His ciclosporin dose was gradually reduced from 325 to 250 mg daily, and his ciclosporin and creatinine levels returned to the acceptable range.[68]

10. Nitrendipine. Nitrendipine 20 mg daily for 3 weeks had no significant effect on the ciclosporin blood levels in 16 kidney transplant patients.[69]

11. Verapamil. Twenty-two kidney transplant patients given ciclosporin and verapamil had ciclosporin blood levels that were 50 to 70% higher than in 18 other patients not given verapamil, despite similar ciclosporin doses in both groups. Serum creatinine levels were lower in those taking verapamil. Moreover, only 3 of the 22 patients had rejection episodes within 4 weeks compared with 10 out of 18 patients not given verapamil.[70] Other studies have found that verapamil 120 to 320 mg daily can increase, double or even triple ciclosporin blood levels in individual patients with kidney or heart transplants.[24,40,62,64,71-75]

(b) Gingival overgrowth

Both ciclosporin and calcium-channel blockers are well-known to be associated with gingival overgrowth in transplant recipients, and there is evidence that concurrent use exacerbates this effect. In a randomised, controlled study, **nifedipine** increased the frequency and severity of gingival overgrowth seen with ciclosporin. After 3 months of treatment, 0 of 15 patients taking ciclosporin (17 mg/kg daily gradually reduced to 7 mg/kg daily) had moderate to severe overgrowth (grade 3 or 4) compared with 9 of 17 patients receiving the same ciclosporin regimen with **nifedipine**.[76] Many other cohort studies (two are cited as examples[77,78]) but by no means all (one is cited as an example[79]) have reported similar findings for **nifedipine**.

There are fewer data on other individual calcium-channel blockers. In one cohort study in patients taking ciclosporin, there was a higher incidence of gingival overgrowth in those receiving **amlodipine** than in those receiving **nifedipine** (72% versus 53%).[80] Conversely, in another cohort study, the incidence of gingival overgrowth was higher with **nifedipine** (86%) than **amlodipine** (47%) or **verapamil** (35%).[81] In one study of **verapamil**, patients taking the combination had a slightly higher incidence and severity of gingival overgrowth than ciclosporin alone, but this was not statistically significant.[82] In another study, **diltiazem** did not increase gingival overgrowth, but neither did **nifedipine**.[79]

Various other cohort studies have found that calcium-channel blockers as a class (individual drugs not specified) are associated with an increased risk of gingival overgrowth when used with ciclosporin. One is cited as an example.[83]

Mechanism

The increased ciclosporin levels are largely due to inhibition of ciclosporin metabolism by the cytochrome P450 isoenzyme CYP3A4 in the liver. Diltiazem and verapamil are moderate CYP3A4 inhibitors, however other calcium-channel blockers do not generally cause significant inhibition of CYP3A4, see 'Calcium-channel blockers', (p.1025). Diltiazem also appears to reduce ischaemia-induced renal tubular necrosis.[84] Other calcium-channel blockers also seem to have a kidney-protective effect. The raised felodipine and lercanidipine levels are possibly due to competitive inhibition by ciclosporin of intestinal and liver metabolism (by CYP3A4), or inhibition of P-glycoprotein. Whether ciclosporin affects other calcium-channel blockers similarly does not appear to have been studied.

Both ciclosporin and calcium-channel blockers can cause gingival overgrowth, and this effect is probably additive.

Importance and management

The **pharmacokinetic interactions** of ciclosporin with diltiazem, nicardipine and verapamil are established and relatively well documented. Concurrent use need not be avoided, but ciclosporin levels should be well monitored and dose reductions made as necessary. Even though ciclosporin blood levels are increased, these calcium-channel blockers appear to have a kidney protective effect. One study[85] noted that, although calcium-channel blockers increase ciclosporin blood levels, this is of no harm to the patient, as no changes in renal function were observed. With diltiazem and verapamil the ciclosporin dose can apparently be reduced by about 25 to 50% and possibly more with nicardipine. One case suggests that this is also true with nisoldipine. Several studies suggest that substantial cost savings can be made by giving either diltiazem[13,86,87] or verapamil[24] with ciclosporin. Take care not to substitute one diltiazem product for another after the patient has been stabilised because there is evidence that their bioequivalence differences may alter the extent of the interaction.[27,88] The situation with nifedipine is not totally clear (no effect or decreases or increases), but it appears to have a kidney protective effect[63] as does felodipine. The situation with amlodipine is also uncertain, but isradipine, lacidipine and nitrendipine appear to be non-interacting alternatives. Many of the calcium-channel blockers have a kidney protective effect. The increase in lercanidipine levels is such that the manufacturer says that lercanidipine and ciclosporin should not be given together,[50] and the manufacturer of ciclosporin recommends caution.[89] Ciclosporin modestly increases felodipine levels, which would not be clinically relevant, and its effect on the levels of other calcium-channel blockers does not appear to have been studied.

The increased risk of **gingival overgrowth** when calcium-channel blockers are used with ciclosporin also appears to be established, with most data relating to nifedipine. Note that the UK manufacturer of ciclosporin specifically recommends avoiding nifedipine in patients who develop gingival overgrowth whilst taking ciclosporin.[89] It might be prudent to apply this to all calcium-channel blockers, when possible. Note that tacrolimus has been suggested as an alternative to ciclosporin,

although it is not entirely free from gingival adverse effects. The ACE inhibitors may be suitable alternatives to the calcium-channel blockers, but they are not entirely free of problems when used with ciclosporin (see 'Ciclosporin + ACE inhibitors or Angiotensin II receptor antagonists', p.1211). Note that a useful paper about minimising the risk of gingival overgrowth and its management has been published.[90]

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Ciclosporin + Chlorambucil

An isolated report describes a reduction in ciclosporin levels in a patient given chlorambucil.

Clinical evidence, mechanism, importance and management

A woman with B-chronic lymphocytic leukaemia and autoimmune haemolytic anaemia controlled with ciclosporin started taking chlorambucil 5 mg daily because of disease progression. When she reached a total cumulative dose of chlorambucil of 200 mg she suddenly relapsed, and her serum ciclosporin levels were found to have dropped to 60 nanograms/mL from a range of 200 to 400 nanograms/mL. The ciclosporin levels remained low despite a doubling of the ciclosporin dose and withdrawal of the chlorambucil. Only after one month did the anaemia respond and the ciclosporin levels rise again.[1] This appears to be an isolated report so the general significance of this interaction is unclear.

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Ciclosporin + Chloroquine or Hydroxychloroquine

Three transplant patients had rapid rises in ciclosporin levels, with evidence of nephrotoxicity in two of them, when they were given chloroquine. Neither chloroquine nor hydroxychloroquine altered the incidence of raised creatinine levels seen with low-dose ciclosporin in rheumatoid arthritis.

Clinical evidence

(a) Chloroquine

A kidney transplant patient taking ciclosporin, azathioprine and prednisolone had a threefold rise in ciclosporin blood levels, from 148 nanograms/mL to 420 nanograms/mL, accompanied by a rise in serum creatinine levels within 48 hours of starting chloroquine 900 mg daily for suspected malarial fever. On days 2 and 3 the chloroquine dose was reduced to 300 mg daily. The ciclosporin and creatinine returned to their former levels 7 days after the chloroquine was stopped.[1]

When another kidney transplant patient taking ciclosporin, azathioprine and prednisolone was given chloroquine 100 mg daily for 6 days, his ciclosporin serum levels rose from 105 nanograms/mL to 470 nanograms/mL and his serum creatinine levels rose from 200 micromol/L to 234 micromol/L, accompanied by a rise in blood pressure from 130/80 mmHg to 160/100 mmHg. These changes reversed when the chloroquine was stopped, and occurred again when chloroquine was restarted.[2] The ciclosporin serum levels of another patient were doubled by chloroquine 100 mg daily.[3]

A randomised, controlled study in 88 patients with recent onset rheumatoid arthritis found that the addition of ciclosporin (1.25 or 2.5 mg/kg daily) to chloroquine 100 mg daily was moderately effective, but changes in serum creatinine levels occurred. In the presence of chloroquine, the creatinine was not significantly altered by placebo or ciclosporin 1.25 mg/kg, but was raised by 10 micromol/L by ciclosporin 2.5 mg/kg, indicating that some renal effects can occur.[4] However, as there was no group given ciclosporin alone, it is not possible to say if the renal effects were due to an interaction with chloroquine, or just due to ciclosporin alone. The results of a further study suggest that they were probably due to ciclosporin alone: there was no difference in the incidence of increased creatinine levels between rheumatoid arthritis patients taking ciclosporin 2.5 mg/kg daily alone or the same dose of ciclosporin with chloroquine 150 mg daily. Note that in this study, there was no advantage to using the combination.[5]

(b) Hydroxychloroquine

In a randomised study in rheumatoid arthritis patients receiving ciclosporin 3 mg/kg daily alone or the same dose of ciclosporin with hydroxychloroquine 400 mg daily, there was no difference in incidence of renal impairment or in temporary or permanent reductions in ciclosporin dose between the groups. Note that in this study, there was no advantage to using the combination.[6]

Mechanism

The reason for the increased ciclosporin levels in these few cases is not understood.

Importance and management

Information is limited, but it would be prudent to monitor for increases in serum ciclosporin levels when chloroquine is given to patients receiving high ciclosporin doses. In the setting of the use of low-dose ciclosporin in rheumatoid arthritis, neither chloroquine nor hydroxychloroquine appear to contribute to the known adverse effects of ciclosporin on creatinine and renal function.

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Ciclosporin + Cinacalcet

Cinacalcet does not appear to affect ciclosporin trough levels. In some studies it has caused a slight decrease in renal function in patients taking ciclosporin.

Clinical evidence

In a pharmacokinetic study in 8 kidney transplant patients taking ciclosporin, cinacalcet 30 mg daily for 6 days had no effect on the pharmacokinetics of ciclosporin, but there was a minor 9% increase in the AM19 metabolite of ciclosporin. The increase in this metabolite correlated with a small decrease in renal function (from 78 to 72 mL/minute).[1]

In clinical use, no changes in ciclosporin trough levels have been seen. For example, in one 3-month study in 13 transplant patients, there was no change in ciclosporin trough levels after one, 2 and 3 months use of cinacalcet 30 mg daily.[2] In two other reports, no change in ciclosporin dose was needed in patients when they were given cinacalcet, initially 30 mg daily then titrated to effect, for 6 months.[3,4] One of these studies did find a decrease in glomerular filtration rate and a modest increase in serum creatinine levels (from 140 micromol/L to 153 micromol/L at 2 months and 148 micromol/L at 3 months).[2] Another found that serum creatinine and creatinine clearance were stable during 6 months use of cinacalcet.[3]

Mechanism

The slight impairment in renal function in patients taking ciclosporin might be due to cinacalcet increasing levels of the ciclosporin AM19 metabolite, but the mechanism for this is unclear.

Importance and management

Cinacalcet does not appear to alter ciclosporin levels, and so no ciclosporin dose adjustment is likely to be necessary with concurrent use. Further study is needed to establish any possible impairment of renal function when cinacalcet is used with ciclosporin and to assess its clinical relevance. Until more is known, bear the possibility of adverse renal effects in mind.

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Ciclosporin + Clodronate

Clodronate does not appear to alter ciclosporin blood levels.

Clinical evidence, mechanism, importance and management

Ten heart transplant patients taking ciclosporin, azathioprine and diltiazem were also given clodronate 800 mg daily for one week. No statistically significant differences were seen in their ciclosporin blood levels or AUCs. Three of them were also taking simvastatin, two were taking ranitidine and one was taking propafenone, furosemide and cyclophosphamide. There would seem to be no reason for avoiding concurrent use, but the authors of the report suggest that longer-term use of clodronate should be well monitored.[1] There seems to be no information about other bisphosphonates.

1. Baraldo M, Furlanut M, Puricelli C. No effect of clodronate on cyclosporin A blood levels in heart transplant patients simultaneously treated with diltiazem and azathioprine. *Ther Drug Monit* (1994) 16, 435.

Ciclosporin + Clonidine

A child taking ciclosporin had a marked rise in his ciclosporin blood levels when clonidine was also given.

Clinical evidence, mechanism, importance and management

A 3-year-old kidney transplant patient taking ciclosporin, azathioprine and prednisone was given a combination of propranolol, hydralazine, furosemide and nifedipine postoperatively in an attempt to control his blood pressure. Minoxidil was added, but was considered unacceptable because of adverse cosmetic effects. When it was replaced with clonidine, the ciclosporin levels increased about threefold to 927 nanograms/mL, despite a ciclosporin dose reduction. Ciclosporin levels returned to the patient's normal range of 150 to 300 nanograms/mL when the clonidine was withdrawn, and blood pressure was controlled by the addition of an ACE inhibitor. It was suggested that clonidine inhibited the metabolism of ciclosporin by cytochrome P450.[1]

As this appears to be the only report of an interaction, there is insufficient evidence to recommend routinely increasing the monitoring of ciclosporin levels in every patient taking these drugs. However, the possibility of an interaction should still be considered if both drugs are given.

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Ciclosporin + Coenzyme Q_{10} (Ubidecarenone)

Coenzyme Q_{10} did not alter ciclosporin levels in a clinical study.

Clinical evidence, mechanism, importance and management

In a study in 11 renal transplant patients, coenzyme Q_{10} 30 mg three times daily for 4 weeks did not alter the serum levels of creatinine or ciclosporin (137 to 155 nanograms/mL). This suggests no ciclosporin dose adjustment is likely to be needed on the concurrent use of coenzyme Q_{10}.[1]

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Ciclosporin + Colchicine

A number of cases of serious muscle disorders (myopathy, rhabdomyolysis), a few with multiple organ failure, have been seen when colchicine and ciclosporin were given concurrently. Ciclosporin toxicity has also been seen rarely.

Clinical evidence

A patient taking ciclosporin, azathioprine, prednisone and colchicine 1.2 mg daily immediately after a renal transplant developed colchicine neuromyopathy (possibly rhabdomyolysis), ciclosporin nephrotoxicity and liver function abnormalities within 31 days.[1] Many other reports have described myopathy (muscle weakness, myalgia) or rhabdomyolysis in patients who took ciclosporin and colchicine,[2-13] some with multiple organ failure.[13] These have occurred after just 3 days of colchicine administration[6] or after many months of combined use.[9,12] At the time of the development of toxicity, ciclosporin levels were normal in many cases,[4,6,10,13] but raised in some.[9] Raised creatine kinase levels have been a feature of many cases, but not all.[12] The incidence of myopathy may be high. For example, in one retrospective study, 5 of 10 renal transplant patients who had received colchicine with ciclosporin experienced muscular symptoms after a mean of 12 months of colchicine therapy. This improved after colchicine withdrawal.[8] In another study in four renal transplant patients with familial Mediterranean fever taking colchicine, an attempt to replace azathioprine with ciclosporin failed after 3 weeks because of pronounced adverse effects even before achieving therapeutic levels of ciclosporin. These included elevations in serum creatinine, liver enzymes and bilirubin, and one patient was hospitalised for general muscle weakness and severe myalgia.[4]

Another kidney transplant patient had a transient rise (lasting 2 to 3 days) in serum creatinine and ciclosporin blood levels, from 100 to 200 nanograms/mL up to 1519 nanograms/mL one day after receiving a total of 4 mg of colchicine.[14]

Mechanism

Myotoxiciy is a known adverse effect of colchicine alone, which is more common in renal impairment because this reduces its excretion. Myopathy has also occurred with ciclosporin alone.[2,15] The myotoxic effects of both ciclosporin and colchicine might be additive or synergistic.[16] In addition, patients taking ciclosporin who develop ciclosporin-impaired renal function are likely to accumulate colchicine and be at greater risk of colchicine toxicity.[16] Moreover, ciclosporin might directly increase colchicine levels, because it inhibits P-glycoprotein and might thereby impair colchicine excretion.[10]

Importance and management

The overall picture presented by these reports is not totally clear. However, it appears that the risk of colchicine-induced muscle toxicity is increased in patients taking ciclosporin. If concurrent use is thought to be appropriate, it should be very carefully monitored because the outcome can be serious. Patients should be reminded to report any unexplained muscle pain, tenderness or weakness or dark urine.

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Ciclosporin + Colestyramine

Colestyramine does not appear to alter ciclosporin levels.

Clinical evidence, mechanism, importance and management

Five transplant patients taking ciclosporin and colestyramine had their colestyramine suspended for one week. It was then restarted for one week, and given simultaneously with ciclosporin on the day of testing. There was no difference in the peak and trough levels of ciclosporin and a non-significant average increase (6%) in the AUC of ciclosporin, but one patient had a 55% increase and another a 23% decrease in the AUC of ciclosporin.[1] In another pharmacokinetic study in 6 kidney transplant patients, colestyramine 4 g daily caused no significant change in the ciclosporin AUC, peak and trough levels.[2] Ciclosporin was given at 8 am and 8 pm, with colestyramine taken at noon. Similarly, in a 12 month efficacy study, 18 heart transplant patients taking ciclosporin were randomised to receive colestyramine 4 g twice daily taken one to 2 hours after ciclosporin. Colestyramine had no effect on ciclosporin levels.[3]

In general, it appears that colestyramine has little effect on ciclosporin absorption. However, the occasional patient may be affected, and therefore, because of the clinical consequences of the loss of ciclosporin efficacy, it would seem prudent to separate the administration of colestyramine and ciclosporin. It is usually advised that colestyramine is given one hour before or 4 to 6 hours after other drugs.

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Ciclosporin + Corticosteroids

Some evidence suggests that ciclosporin levels are raised or unchanged by high-dose methylprednisolone or reduced by prednisone. Ciclosporin can reduce the clearance of corticosteroids. Convulsions have been described during the concurrent use of ciclosporin and high-dose methylprednisolone, and the incidence of diabetes mellitus may also be increased. One case of osteonecrosis has been reported with high-dose topical betamethasone and ciclosporin.

Clinical evidence

(a) Betamethasone

A patient with psoriasis taking ciclosporin and applying an average of betamethasone 30 mg daily (as 15 g to 150 g of topical betamethasone 0.05% cream or ointment) developed avascular osteonecrosis of the femoral heads of both hip joints.[1]

(b) Methylprednisolone

A study found that the pharmacokinetics of methylprednisolone in patients taking ciclosporin and azathioprine varied widely between individual kidney transplant patients, but the mean values were similar to those found in normal subjects.[2] Another later study by the same research group confirmed that ciclosporin did not appear to affect methylprednisolone pharmacokinetics.[3]

The plasma ciclosporin levels of 22 out of 33 patients were reported to be more than doubled by intravenous methylprednisolone used for acute graft rejection, and the ciclosporin dose needed to be reduced in 6 patients.[4,5] Others have similarly observed that high doses of methylprednisolone increased or more than doubled ciclosporin levels.[6-8] However, a study found that trough ciclosporin levels were unchanged when an intravenous dose of ciclosporin was given with high-dose intravenous methylprednisolone, although the clearance of ciclosporin was slightly increased (by 20%) in 8 out of 9 patients.[9] In another analysis of the use of methylprednisolone in 17 rejection episodes in 13 patients, there was no change in ciclosporin levels before during and after methylprednisolone in most cases. Rises in ciclosporin levels occurred only in 3 rejection episodes in 3 patients, and these were not attributed to an interaction.[10]

A report describes 4 young patients (aged 10, 12, 13 and 18 years) who had undergone bone marrow transplants for severe aplastic anaemia and who developed convulsions when given high-dose methylprednisolone (5 to 20 mg/kg daily) and ciclosporin.[11] Convulsions also occurred in a 25-year-old woman given ciclosporin with high-dose methylprednisolone.[12] In another report, seizures occurred in 3 patients taking ciclosporin and high-dose methylprednisolone only after ketoconazole was added to permit a reduction in ciclosporin dose.[13]

A study of 314 kidney transplant patients during the period 1979 to 1987 found that the incidence of diabetes mellitus in those given ciclosporin and methylprednisolone was twice that of other patients given azathioprine and methylprednisolone. The diabetes developed within less than 2 months.[14]

(c) Prednisolone or Prednisone

A pharmacokinetic study in 40 patients found that the clearance of prednisolone was about 30% lower in those taking ciclosporin when compared with those taking azathioprine.[15] Another study in patients with kidney transplants by the same group of researchers reported a 25% lower clearance of prednisolone in the presence of ciclosporin.[16]

Other studies confirm that the clearance of prednisolone is about one-third lower in patients also taking ciclosporin and that it is lower at 3 to 6 months than at 2 to 4 weeks.[4,17] As a result, some patients develop signs of steroid toxicity (cushingoid symptoms and impaired glucose metabolism).[4] In contrast, these studies have all been questioned by the authors of another study, who found that the metabolism of prednisolone after an oral and intravenous dose did not differ between patients taking ciclosporin and those taking azathioprine.[18] Similarly, another study found no change in the pharmacokinetics of intravenous prednisolone before and after starting ciclosporin.[19]

A comparative study over a year, in two groups of kidney transplant patients taking ciclosporin and azathioprine, one group with and the other without prednisone, found that those taking prednisone had lower trough ciclosporin levels (about 10 to 20%) despite using the same or higher doses of ciclosporin.[20]

There is other evidence that low-dose prednisolone does not increase the immunosuppression of ciclosporin, but it can reduce ciclosporin nephrotoxicity.[21]

Mechanism

Uncertain. Some evidence suggests that ciclosporin reduces the metabolism of the corticosteroids by the liver thereby raising their levels,[4] but not all studies have found an interaction. *In vitro*, methylprednisolone inhibited the metabolism of ciclosporin.[22] There is some evidence that prednisolone-induced changes in lipoproteins may correlate with the changes in ciclosporin levels.[23] Corticosteroids are known to cause osteonecrosis and ciclosporin may depress bone resorption as well as bone remodelling.[1]

Importance and management

None of these adverse interactions is well established. Concurrent use is common and advantageous but be alert for any evidence of increased ciclosporin and corticosteroid effects.

It is not clear whether high-dose corticosteroids cause a rise in

ciclosporin levels or not. If they do, the authors of one report point out that this interaction could possibly lead to a misinterpretation of clinical data as a rise in serum creatinine levels in patients with kidney transplants is assumed to be due to rejection, unless proven otherwise. If a corticosteroid is then given, this could lead to increased ciclosporin levels, which might lead to the rejection episode being re-interpreted as ciclosporin nephrotoxicity.[5] It has been suggested that ciclosporin levels measured by [the non-specific] RIA (radioimmunoassay) method should be interpreted with caution in patients taking high-dose corticosteroids as the levels of ciclosporin metabolites, which can interfere with the test, may be altered.[9] However, a study using both [the non-specific] RIA method and HPLC did not find a difference in the interaction between the two methods.[10]

The contribution of ciclosporin and high-dose *topical* corticosteroid to the development of osteonecrosis in the isolated case report is not known.

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Ciclosporin + Coumarins

A case report describes reduced ciclosporin levels and reduced warfarin efficacy in patients given both drugs concurrently. A further report describes a rise in serum ciclosporin levels when an unnamed anticoagulant was given. Other reports describe increased or decreased acenocoumarol effects and decreased ciclosporin levels in two patients given both drugs.

Clinical evidence

(a) Acenocoumarol

The anticoagulant dose of a patient taking acenocoumarol needed to be *reduced* by about half to maintain a therapeutic INR when he was given ciclosporin after a kidney transplant. The required dose of ciclosporin slightly decreased.[1] A patient taking acenocoumarol 32 mg per week was given ciclosporin for nephrotic syndrome. After 10 days his acenocoumarol dose needed to be *increased* to maintain a therapeutic INR, and the ciclosporin level was considered too low so the dose was increased from 100 to 150 mg daily. However, a further 10 days later (after the increase in the acenocoumarol dose) the ciclosporin level was even lower. Eventually the patient achieved therapeutic levels in the presence of acenocoumarol with a ciclosporin dose of 200 mg daily.[2]

(b) Warfarin

A man with erythrocyte aplasia effectively treated with ciclosporin for 18 months, relapsed within a week of starting warfarin. His ciclosporin levels had fallen from a range of 300 to 350 nanograms/mL down to 170 nanograms/mL. He responded well when the ciclosporin dose was increased from 3 to 7 mg/kg daily, but his prothrombin activity rose from 17% to 64% and he needed an increase in the warfarin dose to achieve satisfactory anticoagulation.[3] The patient was also taking phenobarbital. A woman with angioimmunoblastic T-cell lymphoma receiving chemotherapy developed a deep vein thrombosis and was therefore given heparin and later warfarin. When ciclosporin 300 mg daily was added, her INR decreased by about 40% and she needed a progressive warfarin dose increase from 18.75 to 27.5 mg per week.[4] Another report briefly states that the serum ciclosporin levels rose in a patient given a warfarin derivative.[5]

Mechanism

Unknown. Ciclosporin is an inhibitor of the cytochrome P450 isoenzyme CYP3A4 and of P-glycoprotein, but this isoenzyme and drug transporter have only a very minor role in coumarin metabolism. Warfarin is not known to affect the pharmacokinetics of other drugs.

Importance and management

Information about the interactions of the coumarins and ciclosporin seems to be limited to these few reports. They simply serve to emphasise the need to monitor concurrent use because the outcome is clearly uncertain.

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Ciclosporin + Cyclophosphamide

Cyclophosphamide was found to reduce ciclosporin levels in a retrospective study.

Clinical evidence, mechanism, importance and management

A retrospective study in stem cell transplant patients found that the ciclosporin levels in 47 patients whose pre-transplant conditioning regimens contained cyclophosphamide were lower (149.7 nanograms/mL) than those in 56 patients whose regimens did not contain cyclophosphamide (217.3 nanograms/mL). However, there was no difference in the incidence of acute graft versus host disease of grade 2 or higher.[1] The reason for this possible interaction is not understood, and its clinical relevance is uncertain. Further study is needed.

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Ciclosporin + Danazol

Marked increases in ciclosporin levels have been reported in patients taking danazol.

Clinical evidence

A 15-year-old girl, one-year post kidney transplant, taking ciclosporin and prednisone, had a marked rise in serum ciclosporin levels over about

2 weeks (from a range of 250 to 325 micromol/L up to 680 to 860 micromol/L) when she was given danazol 200 mg twice daily, even though the ciclosporin dose was reduced from 350 to 250 mg daily.[1]

Similar rises in ciclosporin levels were seen in another patient, from about 400 to 600 nanograms/mL on one occasion, and from 150 to about 450 nanograms/mL on another occasion, over about a 6-week period when danazol 400 mg daily and later 600 mg daily was given.[2] A 12-year-old boy needed a reduction in his ciclosporin dose from 10 to 2 mg/kg daily when danazol 400 mg twice daily was added.[3] A marked rise in ciclosporin blood levels has been described in 2 other patients when given danazol 200 mg three or four times daily.[4,5]

A pharmacokinetic study in one kidney transplant patient found that danazol 200 mg three times daily given with ciclosporin 120 mg twice daily, reduced the ciclosporin clearance by 50%, prolonged its half-life by 66%, and raised its AUC by 65% when compared with a 20% higher ciclosporin dose of 150 mg twice daily.[6]

A patient with aplastic anaemia taking ciclosporin was given danazol 200 mg daily for pancytopenia and endometriosis. Within 4 days the patient had epigastric pain, and elevated serum ciclosporin and creatinine levels. Danazol was stopped and the ciclosporin dose was halved. Two weeks later abrupt severe hepatic injury occurred and the patient died of liver failure, although this was thought to be due to danazol toxicity rather than the interaction.[7]

Mechanism

Uncertain. It has been suggested that danazol raises ciclosporin levels by inhibiting its metabolism, possibly by inhibiting the cytochrome P450 isoenzyme CYP3A4.[3] However, further study is needed to confirm this suggestion.

Importance and management

Although the information seems to be limited to these few reports the interaction is established. The ciclosporin levels of any patient who is given danazol should be carefully monitored, and dose adjustments made as necessary.

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Ciclosporin + Disopyramide

An isolated report describes the development of nephrotoxicity, which was attributed to an interaction between ciclosporin and disopyramide.

Clinical evidence, mechanism, importance and management

Ten months after receiving a kidney transplant, a 40-year-old woman taking ciclosporin and methylprednisolone developed premature ventricular beats and was given oxprenolol. After 2 months she had shown no improvement so she started taking disopyramide 100 mg three times daily. Over the next week her serum creatinine rose from 88 micromol/L to 159 micromol/L, at which point the disopyramide was stopped, and her renal function returned to normal over the next week. As she had previously been stable taking ciclosporin, and, as nephrotoxicity had not been reported with disopyramide, an interaction was suspected.[1]

This interaction is unconfirmed and of uncertain clinical significance. There is insufficient evidence to recommend increased monitoring, but be aware of the potential for an interaction in the case of an unexpected response to treatment.

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Ciclosporin + Diuretics

Isolated cases of nephrotoxicity have been described when patients taking ciclosporin were given either amiloride with hydrochlorothiazide, metolazone, or mannitol. Furosemide can possibly protect the kidneys against ciclosporin damage. The concurrent use of ciclosporin with thiazides, but not loop diuretics, may increase magnesium levels. The concurrent use of ciclosporin with potassium-sparing diuretics may cause hyperkalaemia. Eplerenone does not appear to affect the pharmacokinetics of ciclosporin and may reduce ciclosporin nephrotoxicity.

Clinical evidence, mechanism, importance and management

(a) Nephrotoxicity

A 39-year-old man taking ciclosporin, whose second kidney transplant functioned subnormally, and who required treatment for hypertension with atenolol and minoxidil, developed ankle oedema, which was resistant to **furosemide**, despite doses of up to 750 mg daily. When **metolazone** 2.5 mg daily was added for 2 weeks his serum creatinine levels more than doubled (from 193 to 449 micromol/L). When **metolazone** was stopped the creatinine levels fell again. Ciclosporin serum levels were unchanged and neither graft rejection nor hypovolaemia occurred.[1]

The kidney transplant of another patient taking ciclosporin almost ceased to function when **mannitol** was given, and a biopsy indicated severe ciclosporin nephrotoxicity. Transplant function recovered when the **mannitol** was stopped.[2]

A woman taking ciclosporin had a rise in serum creatinine levels from 121 micromol/L to 171 micromol/L three weeks after she started to take *Moduretic* (**amiloride** with [**hydro**]**chlorothiazide**). Trough serum ciclosporin levels were unchanged.[3]

One clinical study suggested that furosemide may have a protective effect against ciclosporin-induced nephrotoxicity.[4]

(b) Magnesium wasting

Although ciclosporin and **loop diuretics** are both known to cause magnesium wasting, a review of magnesium serum levels, magnesium replacement doses and diuretic use in 50 heart transplant recipients indicated that magnesium requirements were not altered by the use of ciclosporin with **loop diuretics**. However, the use of **thiazides** with ciclosporin resulted in *increases* in serum magnesium and decreases in magnesium replacement.[5] Electrolytes, including magnesium, should be monitored as a matter of routine in patients taking ciclosporin with loop or thiazide diuretics.

(c) Hyperkalaemia

No clinically significant pharmacokinetic interaction was noted when **eplerenone** was given with ciclosporin.[6] It has been suggested that aldosterone receptor blockade with **eplerenone** might reduce ciclosporin nephrotoxicity by reducing aldosterone-mediated renal vasoconstriction.[7]

Note that ciclosporin alone can cause hyperkalaemia, especially if renal function is impaired, and the risk might be additive with potassium-sparing drugs. Because of this, the US manufacturers suggest that ciclosporin should not be used with **potassium-sparing diuretics**,[8] whereas the UK manufacturers suggest that caution is required on concurrent use, with close control of potassium levels.[9] Very careful monitoring would appear prudent if concurrent use is considered essential.

1. Christensen P, Leski M. Nephrotoxic drug interaction between metolazone and cyclosporin. *BMJ* (1987) 294, 578.
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8. Neoral (Ciclosporin). Novartis Pharmaceuticals Corporation. US Prescribing information, October 2009.
9. Neoral (Ciclosporin). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, May 2009.

Ciclosporin + Endothelin receptor antagonists

Bosentan decreases ciclosporin levels. Ciclosporin markedly increases sitaxentan and bosentan levels. Ambrisentan may be similarly affected.

Clinical evidence

(a) Bosentan

In a study designed to assess the effects of bosentan on ciclosporin renal toxicity, 7 healthy subjects were given bosentan 500 mg and ciclosporin 300 mg, both twice daily, for 7 days. Bosentan did maintain renal plasma flow, which is markedly decreased by ciclosporin. However, bosentan was calculated to have reduced the AUC of ciclosporin by about 50%. In addition, bosentan had no effect on the ciclosporin-induced rise in blood pressure, and headache, nausea, and vomiting were a problem with the combination. Moreover, the steady-state AUC of bosentan was raised 70%, when compared with the AUC of a single dose of bosentan.[1]

It should be noted that bosentan induces its own metabolism, and after 7 days, plasma levels are about 50 to 65% of those seen after a single dose.[2] Therefore, the effect of ciclosporin on the bosentan AUC may be twice those described in this study (i.e. up to a fourfold increase in the AUC of bosentan). The manufacturers of bosentan say that when bosentan is given with ciclosporin its plasma levels were markedly raised (30-fold after a single dose and three- to fourfold at steady state).[2,3]

(b) Sitaxentan

Sitaxentan does not alter ciclosporin levels. However, ciclosporin increases sitaxentan trough levels sixfold.[4]

Mechanism

Uncertain. Bosentan probably reduces ciclosporin levels because it is an inducer of the cytochrome P450 isoenzyme CYP3A4, by which ciclosporin is metabolised. Ciclosporin modestly inhibits CYP3A4, by which bosentan is partly metabolised, but the rise in bosentan levels seen suggests another mechanism is involved. *In vitro* study shows that ciclosporin inhibits the hepatic uptake of bosentan by the organic anion transporting polypeptides (OATPs), and this might explain the interaction.[5] This mechanism has also been suggested for the interaction with sitaxentan.[4] The UK manufacturer lists ciclosporin as an example of a drug, like bosentan, that inhibits the bile salt export pump, and is therefore expected to increase the risk of liver toxicity when used with bosentan.[2]

Importance and management

Although the data are limited, a pharmacokinetic interaction would appear to be established, resulting in reduced ciclosporin levels, and markedly increased bosentan levels. Because of this, the manufacturers of bosentan contraindicate the combination.[2,3] In addition, the UK manufacturer also states that the concurrent use of ciclosporin may increase the risk of liver toxicity.[2] Other endothelin receptor antagonists are less well studied, but the concurrent use of sitaxentan and ciclosporin is similarly contraindicated.[4] There appears to be even less information about **ambrisentan**, but the manufacturers note that it is a substrate of a number of drug transporters. Therefore they advise caution in patients also taking drugs that affect transporter proteins, such as ciclosporin, which is known to inhibit P-glycoprotein.[6,7]

The concurrent use of **tacrolimus** or **sirolimus** with bosentan has not been studied. Based on the information available for ciclosporin, the UK manufacturer of bosentan advises against concurrent use, but if this is required, close monitoring of bosentan adverse effects and immunosuppressant levels is recommended.[2] The US manufacturer of bosentan recommends caution with tacrolimus.[3]

1. Binet I, Wallnöfer A, Weber C, Jones R, Thiel G. Renal hemodynamics and pharmacokinetics of bosentan with and without cyclosporine A. *Kidney Int* (2000) 57, 224–31.
2. Tracleer (Bosentan monohydrate). Actelion Pharmaceuticals UK Ltd. UK Summary of product characteristics, July 2009.
3. Tracleer (Bosentan). Actelion Pharmaceuticals US, Inc. US Prescribing information, August 2009.
4. Thelin (Sitaxentan sodium). Encysive (UK) Ltd. UK Summary of product characteristics, April 2009.
5. Treiber A, Schneiter R, Häusler S, Stieger B. Bosentan is a substrate of human OATP1B1 and OATP1B3: inhibition of hepatic uptake as the common mechanism of its interactions with cyclosporin A, rifampicin, and sildenafil. *Drug Metab Dispos* (2007) 35, 1400–7.
6. Letairis (Ambrisentan). Gilead Sciences, Inc. US Prescribing information, August 2009.
7. Volibris (Ambrisentan). GlaxoSmithKline UK. UK Summary of product characteristics, August 2009.

Ciclosporin + Epoetins

It has been suggested that epoetin alfa might alter ciclosporin levels.

Clinical evidence, mechanism, importance and management

Some UK manufactures of epoetin alfa say that, since ciclosporin is bound by red blood cells there is potential for a drug interaction. They recommend that, if epoetin alfa is given, ciclosporin levels should be monitored and the ciclosporin dose adjusted as the haematocrit rises.[1,2]

This is a theoretical interaction, and there does not appear to be any published data to suggest a significant interaction occurs in practice, and the manufacturers of other epoetins make no mention of such an interaction. Furthermore, it seems likely that any rise in the haematocrit will be sufficiently slow that any interaction would be picked up by routine ciclosporin monitoring.

1. Eprex (Epoetin alfa). Janssen-Cilag Ltd. UK Summary of product characteristics, April 2009.
2. Binocrit (Epoetin alfa). Sandoz Ltd. UK Summary of product characteristics, November 2008.

Ciclosporin + Fibrates

The use of bezafibrate with ciclosporin has resulted in significantly increased serum creatinine levels. Reductions, no change, or increased ciclosporin levels have also been seen. The use of fenofibrate has also been associated with reduced renal function and possibly reduced ciclosporin levels. Three studies found no pharmacokinetic interaction between ciclosporin and gemfibrozil while a fourth found gemfibrozil caused a significant reduction in ciclosporin levels and an increase in serum creatinine in some patients.

Clinical evidence

(a) Bezafibrate

A kidney transplant patient had a rise in his previously stable ciclosporin blood levels from a range of 150 to 200 nanograms/mL to about 340 nanograms/mL over a 6-week period after bezafibrate 200 mg twice daily was given. The rise was accompanied by increases in blood urea nitrogen and creatinine levels. Renal biopsy found evidence of possible ciclosporin toxicity, and rejection. The patient recovered when the bezafibrate was stopped.[1]

Two other transplant patients (one kidney and the other heart) had a reversible deterioration in renal function when they were given bezafibrate. This was severe in one, and it occurred on two occasions in the other patient. Neither had any changes in ciclosporin blood levels.[2,3] Two other similar cases have been reported, one of whom was subsequently given gemfibrozil without problems.[4]

Another study over 3 months in 40 heart transplant patients taking ciclosporin found that bezafibrate was associated with a rise in serum creatinine levels, although none of the patients had to be withdrawn from the study. The ciclosporin level tended to be lower (198 nanograms/mL at baseline, compared with 144 nanograms/mL after 3 months).[5]

(b) Fenofibrate

In a study in 10 heart transplant patients, fenofibrate 200 mg daily for 2 weeks effectively reduced the blood cholesterol levels from 7.7 mmol/L to 6.5 mmol/L without significantly altering ciclosporin blood levels over a 2-week period. The only possible adverse effect was an increase in creatinine levels from 145 mmol/L to 157 mmol/L, suggesting some possible nephrotoxicity. No other clinically adverse effects were seen. However, the authors of this study suggested that longer follow-up studies were needed to confirm the safety of using these drugs together.[6] They followed this up with a one-year study[7] in 43 heart transplant patients, only 14 of whom completed the study (67% withdrew for various reasons). Fourteen patients had a rise in blood creatinine levels and a decrease in renal func-

tion, which improved when the fenofibrate was stopped. There was also some evidence of a reduction in ciclosporin levels in 5 patients, who developed rejection, and 14 patients, who had to stop fenofibrate because ciclosporin levels could not be maintained without adversely affecting renal function.

(c) Gemfibrozil

Forty kidney transplant patients taking ciclosporin had a reduction in their hypertriglyceridaemia when gemfibrozil 900 mg daily for 6 months or 600 mg twice daily for 4 months was added, and their ciclosporin blood levels and serum creatinine levels remained unaltered.[8] Two other studies similarly found that gemfibrozil did not affect ciclosporin blood levels.[9,10]

However, in contrast to these findings, another study in 7 kidney transplant patients with hyperlipidaemia found that gemfibrozil 450 mg once or twice daily was associated with a decline in trough ciclosporin levels. Levels declined from 93 nanograms/mL to 76 nanograms/mL after 6 weeks of concurrent use, and after dose increases in 3 patients, the level at 3 months was 88 nanograms/mL. In 8 similar patients not given gemfibrozil, and with the same ciclosporin dose throughout, trough levels changed from 99 nanograms/mL to 98 nanograms/mL at 6 weeks and to 123 nanograms/mL at 3 months. In 2 patients there was a significant increase in serum creatinine, and biopsy revealed chronic rejection in one and ciclosporin toxicity in the other. The study was stopped at 6 months because a drug interaction was suspected.[11]

Mechanism

The mechanism of the interaction between ciclosporin and the fibrates is not known, but changes in distribution of lipoproteins during treatment with fibrates may cause changes in the free fraction of ciclosporin. Ciclosporin absorption may also be reduced.

Importance and management

Neither the incidence nor the reasons for these reactions are known, but because the outcome is uncertain and potentially serious, keep a close check on the effects of adding a fibrate, particularly bezafibrate or fenofibrate, to ciclosporin in any patient. The UK manufacturer of ciclosporin suggests close monitoring of renal function during concurrent use, and withdrawal of the fibrate should significant impairment occur.[12]

1. Hirai M, Tatuso E, Sakurai M, Ichikawa M, Matsuya F, Saito Y. Elevated blood concentrations of cyclosporine and kidney failure after bezafibrate in renal graft recipient. *Ann Pharmacother* (1996) 30, 883–4.
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10. Pflugfelder PW, Huff M, Oskalns R, Rudas L, Kostuk WJ. Cholesterol-lowering therapy after heart transplantation: a 12-month randomized trial. *J Heart Lung Transplant* (1995) 14, 613–22.
11. Fehrman-Ekholm I, Jogestrand T, Angelin B. Decreased cyclosporine levels during gemfibrozil treatment of hyperlipidemia after kidney transplantation. *Nephron* (1996) 72, 483.
12. Neoral (Ciclosporin). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, May 2009.

Ciclosporin + Food

Food can slightly decrease the bioavailability of ciclosporin from the *Neoral* formulation and slightly increase the bioavailability of ciclosporin from the *Cicloral* formulation. Lipid admixtures for parenteral nutrition appear not to affect intravenous ciclosporin pharmacokinetics.

Clinical evidence

(a) Oral ciclosporin

1. Food or Milk. In early studies with oral ciclosporin,[1] presumably the *Sandimmun* formulation, food and milk increased its bioavailability. For example, patients taking ciclosporin with milk had a 39% higher AUC after food and 23% higher AUC when fasting, compared with other patients taking ciclosporin with orange juice (which is known not to interact, see 'Ciclosporin + Grapefruit and other fruit juices', p.1240). Food more than doubled the AUC of ciclosporin (bioavailability increased from about 21% to 53%) and almost tripled its maximum serum levels, from 783 nanograms/mL to 2062 nanograms/mL.[2] Similarly, when 18 patients with kidney transplants were given ciclosporin mixed with 240 mL of chocolate milk and taken with a standard hospital breakfast, their peak ciclosporin levels rose by 31% (from 1120 to 1465 nanograms/mL), trough blood levels rose by 17% (from 228 to 267 nanograms/mL), and the AUC rose by 45%. Very considerable individual variations occurred.[3]

The *Neoral* formulation was developed to increase ciclosporin bioavailability and reduce variability in absorption,[4] and has now replaced the oral *Sandimmun* formulation. The *Neoral* formulation is less affected by food.[4] With the *Neoral* formulation, the manufacturer notes that food slightly decreases the ciclosporin AUC and maximum level. Giving a dose of ciclosporin within 30 minutes after eating a high-fat meal (669 kcal, 45 grams fat) decreased the ciclosporin AUC by 13% and maximum level by 33%. The effects of a low fat meal (667 kcal, 15 grams fat) were similar.[5]

In a study using the *Cicloral* formulation, the ciclosporin AUC was increased by 21% and the maximum level by 32% when the capsules were taken immediately after a fat-rich breakfast when compared with the fasting state in healthy subjects.[6]

2. Soft drinks. A lung transplant patient taking ciclosporin had large variations in his ciclosporin levels, which ranged between 319 and 761 nanograms/mL, on discharge from hospital, which were unexplained by changes in his current medication or ciclosporin dose changes. It was found that on the days when the ciclosporin levels were increased, the patient had drunk a citrus soft drink (*Sun Drop*) at breakfast. These fluctuations resolved when he stopped drinking the soft drink.[7] However, a subsequent pharmacokinetic study in 12 healthy subjects found that neither *Sun Drop* nor another citrus soft drink, *Fresca*, had any significant effects on the pharmacokinetics of a single 2.5-mg/kg dose of ciclosporin. Both *Sun Drop* and *Fresca* were tested, and found to contain bergamottin 0.078 and 6.5 mg/L, respectively (note that grapefruit contains about 5.6 mg/L). The authors note that factors such as genetic and disease-related variability in ciclosporin metabolism as well as changes in the bergamottin content between batches of the drinks may account for the contrasting results.[8] For more discussion about the effects of grapefruit and other fruit juices see also 'Ciclosporin + Grapefruit and other fruit juices', p.1240.

(b) Intravenous ciclosporin

A study in 10 patients undergoing bone-marrow transplantation and given isocaloric and isonitrogenous parenteral nutrition with or without lipids found that ciclosporin pharmacokinetics after intravenous administration were not affected by lipid-enriched admixtures.[9]

Mechanism

The *Neoral* formulation of ciclosporin contains ethanol as a volatile cosolvent, and undergoes a microemulsification process with fluid in the gastrointestinal tract; therefore, its absorption is less affected by food than the old oral *Sandimmun* formulation.[4] The authors of the report of an interaction with a citrus soda drink confirmed with the manufacturers that it contained furanocoumarins such as bergamottin which are thought to inhibit CYP3A4,[7,8] the major isoenzyme involved in the metabolism of ciclosporin. Compare also 'Ciclosporin + Grapefruit and other fruit juices', p.1240.

Importance and management

Food has a minor effect on the extent of absorption of ciclosporin from the *Neoral* formulation. Nevertheless, in the US the manufacturer recommends that it should be taken on a consistent schedule in relation to time

of day and meals.[5] However, in the UK the manufacturer makes no reference to timing in relation to meals.[4] Similarly, the effect of absorption of ciclosporin from the *Cicloral* formulation is minimal, but the authors of the study suggest that it should be taken on a consistent schedule in relation to time of day and meals.[6]

Lipid admixtures in parenteral nutrition do not appear to affect ciclosporin pharmacokinetics and it is speculated that they may protect against ciclosporin-induced nephrotoxicity. Close supervision and monitoring is required. There is insufficient evidence to allow extrapolation of the results to bone-marrow transplant recipients with risk factors such as dyslipidaemia, liver, or renal impairment.[9]

The isolated report[7] of an interaction between a citrus soft drink (containing furanocoumarins) and ciclosporin was not confirmed by a subsequent single-dose pharmacokinetic study in healthy subjects[8] and therefore its significance is unclear. The case does highlight the influence diet can have on ciclosporin and it should be borne in mind should any unexpected changes in ciclosporin levels occur.

1. Keogh A, Day R, Critchley L, Duggin G, Baron D. The effect of food and cholestyramine on the absorption of cyclosporine in cardiac transplant recipients. *Transplant Proc* (1988) 20, 27–30.
2. Gupta SK, Benet LZ. Food increases the bioavailability of cyclosporin in healthy volunteers. *Clin Pharmacol Ther* (1989) 45,148.
3. Ptachcinski RJ, Venkataramanan R, Rosenthal JT, Burckart GJ, Taylor RJ, Hakala TR. The effect of food on cyclosporine absorption. *Transplantation* (1985) 40, 174–6.
4. Neoral (Ciclosporin). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, May 2009.
5. Neoral (Ciclosporin). Novartis Pharmaceuticals Corporation. US Prescribing information, October 2009.
6. Kees F, Mair G, Dittmar M, Bucher M. Cicloral versus Neoral: a bioequivalence study in healthy volunteers on the influence of a fat-rich meal on the bioavailability of Cicloral. *Transplant Proc* (2004) 36, 3234–8.
7. Johnston PE, Milstone A. Probable interaction of bergamottin and cyclosporine in a lung transplant recipient. *Transplantation* (2005) 79, 746.
8. Schwarz UI, Johnston PE, Bailey DG, Kim RB, Mayo G, Milstone A. Impact of citrus soft drinks relative to grapefruit juice on ciclosporin disposition. *Br J Clin Pharmacol* (2006) 62, 485–91.
9. Santos P, Lourenço R, Camilo ME, Oliveira AG, Figueira I, Pereira ME, Ferreira B, Carmo JA, Lacerda JMF. Parenteral nutrition and cyclosporine: do lipids make a difference? A prospective randomized crossover trial. *Clin Nutr* (2001) 20, 31–6.

Ciclosporin + Foscarnet

Acute but reversible renal failure occurred in two transplant patients when foscarnet was given with ciclosporin.

Clinical evidence

A man with a kidney transplant taking corticosteroids and ciclosporin developed a cytomegalovirus infection that was treated with foscarnet 85 mg/kg daily. Despite efforts to minimise the nephrotoxic effects of foscarnet (hydration with 2.5 litres of isotonic saline daily and nifedipine 80 mg the day before and during treatment) the patient developed non-oliguric worsening of his renal function after 8 days. Nine days after stopping foscarnet, the former renal function was restored.[1]

A liver transplant patient taking steroids, azathioprine and ciclosporin was given foscarnet 180 mg/kg daily for a hepatitis B infection. Acute renal failure occurred 5 days after the foscarnet was started, and renal function was restored 10 days after the foscarnet was stopped. The ciclosporin blood levels were therapeutic and not significantly altered at any time in either patient.[1]

Mechanism

Not understood. It seems that the nephrotoxic effects of ciclosporin and foscarnet may be additive.

Importance and management

Direct information appears to be limited to this report, but it is consistent with the known potential toxicity of both drugs. Acute renal failure can clearly occur despite the preventative measures taken. The authors of this report[1] say that monitoring of renal function is mandatory when both drugs are given.

1. Morales JM, Muñoz MA, Fernández Zataraín G, Garcia Cantón C, García Rubiales MA, Andrés A, Aguado JM, Pinto IG. Reversible acute renal failure caused by the combined use of foscarnet and cyclosporin in organ transplanted patients. *Nephrol Dial Transplant* (1995) 10, 882–3.

Ciclosporin + *Geum chiloense*

A single case report describes a marked and rapid increase in the ciclosporin levels of a man after he drank an infusion of *Geum chiloense.*

Clinical evidence, mechanism, importance and management

A 54-year-old kidney transplant patient taking ciclosporin, prednisone, azathioprine, diltiazem and nifedipine had a sudden and very marked rise in his ciclosporin levels from his usual range of 60 to 90 [nanograms/mL] up to a range of 469 to 600 [nanograms/mL]. He had been taking ciclosporin 2 to 3 mg/kg daily for 15 months since the transplant. His serum creatinine levels were found to be 115 micromol/L. It eventually turned out that about 2 weeks earlier he had started to drink an infusion of *Geum chiloense* (or *Geum quellyon*), a herbal remedy claimed to increase virility and to treat prostatism. When the herbal remedy was stopped, his serum ciclosporin levels rapidly returned to their normal values. The reasons for this apparent interaction are not known.[1]

This appears to be the only case on record but it serves, along with reports about other herbs, to emphasise that herbal remedies may not be safe just because they are 'natural'. In this instance the herbal remedy markedly increased the potential nephrotoxicity of the ciclosporin. Patients should be warned.

1. Duclos J, Goecke H. "Hierba del clavo" *(Geum chiloense)* interfiere niveles de ciclosporin: potencial riesgo para trasplantados. *Rev Med Chil* (2001) 129, 789–90.

Ciclosporin + Grapefruit and other fruit juices

Grapefruit juice, and possibly pomelo juice, but not cranberry or orange juices, can increase the bioavailability of oral ciclosporin.

Clinical evidence

(a) Cranberry juice

In a single-dose study in healthy subjects, cranberry juice 240 mL did not have any significant effects on ciclosporin pharmacokinetics when given at the same time as ciclosporin (*Neoral*).[1]

(b) Grapefruit juice

Many single and multiple-dose pharmacokinetic studies in healthy subjects,[2-5] transplant recipients,[6-11] and other patients with autoimmune diseases[12,13] have shown that if oral ciclosporin is taken at the same time as 150 to 250 mL (5 to 8 ozs) of grapefruit juice, the trough and peak blood levels and the bioavailability of ciclosporin may be significantly increased. The increases reported vary considerably: increases in trough blood levels range from about 15 to 85%,[6,8-11,13] increases in peak blood levels range from 4 to 43%,[2-4,7-11,13] and increases in AUCs range from about 15 to 59%.[2-4,7-11,13,14] In one other study where grapefruit juice was given every 3 hours for 30 hours, with a dose of ciclosporin given at 7.5 hours separated by 1.5 hours from the grapefruit juice, the maximum levels of ciclosporin increased by 22% and the AUC by just 7% (not statistically significant).[15] Where stated, these studies were with the original *Sandimmun* formulation of ciclosporin.

A few studies have looked at the effect of grapefruit juice on the microemulsion formulation of ciclosporin (*Neoral*) in healthy subjects[14,16] or transplant patients.[17,18] In these studies, when grapefruit juice was taken at the same time as ciclosporin, the AUC was increased by 25 to 47% and the maximum levels were largely unchanged (2 to 10% increase). In one study using an intravenous control, grapefruit juice increased the bioavailability of ciclosporin from 38% to 55%.[14] A further study found a greater effect in African-American subjects: the peak levels and AUC were increased by 39% and 60%, respectively, compared with smaller increases of 8% and 44% in Caucasian subjects.[16]

In a study comparing two oral liquid formulations in 6 paediatric kidney transplant patients, giving ciclosporin oral solution (*Sandimmun*) simultaneously with grapefruit juice produced a significant increase (109%) in the 12-hour trough level although the AUC was not significantly changed. When ciclosporin was given as the microemulsion (*Neoral*), grapefruit juice did not significantly affect the pharmacokinetics of ciclosporin.[19]

Grapefruit juice has no effect on ciclosporin levels when the ciclosporin is given *intravenously*.[3]

(c) Orange juices

In single-dose studies in healthy subjects, ciclosporin levels were unaffected by simultaneous administration of orange juice,[2,5,20] tangerine juice,[20] or Seville (bitter) orange juice.[4]

(d) Pomelo juice

In a single-dose study in 12 healthy subjects, pomelo juice 240 mL slightly increased the AUC and maximum level of ciclosporin by about 19% and 12%, respectively, when given at the same time as the ciclosporin (*Neoral*).[1]

Mechanism

It is suggested that grapefruit juice inhibits the activity of the cytochrome P450 isoenzyme CYP3A4, predominantly in the gut wall. Ciclosporin is primarily metabolised by CYP3A4 and so its bioavailability rises; however, because grapefruit juice has minor effects on hepatic CYP3A4 this effect is not seen with intravenous use. A number of active constituents of grapefruit juice have been suggested, but it is probably the furanocoumarins (which include bergamottin and 6',7'-dihydroxybergamottin) that are responsible for this interaction because a furanocoumarin-free grapefruit juice did not interact.[5] Another *in vitro* study suggested that 6',7'-dihydroxybergamottin is not responsible.[4] More study is needed. Pomelo is related to grapefruit and therefore potentially interacts by the same mechanism.

Importance and management

The interaction between grapefruit juice and ciclosporin is established and clinically important, and results in increases in the bioavailability of oral ciclosporin. Patients taking ciclosporin should be warned about drinking grapefruit juice because increased ciclosporin levels are associated with increased nephrotoxicity. In general, grapefruit juice should be avoided. It has been suggested that separation of administration could minimise this interaction. However, apart from one study,[15] all the data relate to drinking grapefruit juice around the same time as taking the ciclosporin dose. The study that separated administration (by 1.5 hours) still found a minor interaction. However, in this study a large quantity of grapefruit juice was consumed over 30 hours, and the study did not test simultaneous administration for comparison. It is therefore unclear if separation of administration would reduce or negate the effect of grapefruit juice on ciclosporin.

It has been suggested[2] that the interaction between grapefruit juice and ciclosporin could be exploited to save money. One group of authors has suggested that grapefruit juice is roughly as effective as diltiazem in raising ciclosporin blood levels, and has the advantage of being inexpensive, nutritious and lacking the systemic effects of diltiazem and ketoconazole which have been used in this way. However, it has also been pointed out that it may be risky to try to exploit this interaction because the increases appear to be so variable and difficult, if not impossible, to control. This is because batches of grapefruit juice vary so much, and also considerable patient variation occurs with this interaction.[21-23] Grapefruit juice has been used to improve ciclosporin efficacy in two patients with psoriasis[24] and four patients with autoimmune haematological disorders.[4]

The US manufacturer suggests that patients taking ciclosporin should avoid **whole grapefruit**, as well as the juice.[25]

The significance of the single report of the small increases in ciclosporin bioavailability and blood levels seen with pomelo juice in healthy subjects is unclear.[1] However, a similar interaction has been seen in a kidney transplant patient taking tacrolimus, see 'Tacrolimus + Grapefruit and other fruit juices', p.1301. There is insufficient evidence to recommend avoiding pomelo juice or pomelo fruit when taking ciclosporin but bear this potential interaction in mind. More study is needed.

Both cranberry juice and orange juices do not appear to interact with ciclosporin.

1. Grenier J, Fradette C, Morelli G, Merritt GJ, Vranderick M, Ducharme MP. Pomelo juice, but not cranberry juice, affects the pharmacokinetics of cyclosporine in humans. *Clin Pharmacol Ther* (2006) 79, 255–62.
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Ciclosporin + Griseofulvin

An isolated report describes decreased ciclosporin levels in a patient given griseofulvin, whereas another report found no interaction.

Clinical evidence, mechanism, importance and management

A 57-year-old-man, who had been stable for almost one year taking ciclosporin, azathioprine and prednisolone following a kidney transplant, was given griseofulvin 500 mg daily for onychomycosis. Two weeks later his trough ciclosporin levels had dropped from 90 nanograms/mL to 50 nanograms/mL and remained low, despite an increase in his ciclosporin dose from 2.8 to 4.8 mg/kg. When the griseofulvin was later stopped, his ciclosporin levels rose to over 200 nanograms/mL and his dose of ciclosporin was readjusted.[1] In contrast, the authors of another report noted that there was no appreciable interaction when griseofulvin 1 g daily for 8 weeks was used to treat tinea capitis in a kidney transplant patient taking ciclosporin, and graft function remained stable.[2]

The first case appears to be the only report of an interaction with griseofulvin, and its general significance is unclear.

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Ciclosporin + H_2-receptor antagonists

Reports are inconsistent. Cimetidine has been reported to increase ciclosporin levels in some studies, whereas others found no interaction. Ranitidine, and probably famotidine, do not appear to affect ciclosporin levels. Both cimetidine and ranitidine

have been reported to cause an increase in serum creatinine levels, in some but not all studies. Isolated cases of thrombocytopenia and hepatotoxicity have been reported with ranitidine and ciclosporin.

Clinical evidence

(a) Cimetidine

A study in 5 liver transplant patients taking ciclosporin found that cimetidine 800 mg given every 12 hours for 3 doses raised peak ciclosporin levels, but no changes in trough levels were seen after 4 hours. Similarly, no change in trough ciclosporin levels was seen in 2 patients who received cimetidine 400 mg four times daily for 4 weeks, and the conclusion was reached that it was safe to use cimetidine over at least a 4-week period.[1] However, a retrospective study reported that heart transplant patients taking cimetidine had a lower dose/level quotient leading to higher ciclosporin blood levels for the same dose.[2] Similarly, a study in 6 healthy subjects found a 30% rise in the AUC of ciclosporin 300 mg given after a 3-day course of cimetidine 400 mg daily.[3] Raised ciclosporin blood levels have also been seen in a patient given cimetidine and metronidazole[4] (see 'Ciclosporin + Antibacterials; Metronidazole', p.1219).

Cimetidine or **ranitidine** increased the mean serum creatinine levels in 7 kidney transplant patients taking ciclosporin by 41% (from 202 to 285 micromol/L). All of the patients had a rise, whereas only 2 out of 5 other patients with heart transplants had a rise in their serum creatinine levels when given either cimetidine or **ranitidine**, nevertheless the mean rise was 37% (from 152 to 209 micromol/L). Ciclosporin levels were not altered.[5] Another study in 7 kidney transplant patients given cimetidine 400 mg daily for 7 days reported a transient minor increase in creatinine serum levels at days 2 and 5, which was not statistically significant. Again ciclosporin levels were not altered.[6] Similarly, in two studies in healthy subjects, cimetidine did not alter ciclosporin blood levels.[7,8]

(b) Famotidine

Several studies have reported that famotidine does not affect ciclosporin blood levels.[9-11] No significant changes in the pharmacokinetics of ciclosporin was seen in a single-dose study in 8 healthy subjects[8] and no changes in serum creatinine or BUN levels were seen in 7 kidney transplant patients.[11] However, a study of heart transplant patients given famotidine found slightly higher ciclosporin blood levels for a given ciclosporin dose.[2]

(c) Ranitidine

One report (see *Cimetidine* above), where the effects of cimetidine and ranitidine were examined together, suggests that ranitidine raises creatinine levels in patients taking ciclosporin, without affecting ciclosporin levels.[5] Similarly, several other reports suggest that ranitidine does not alter ciclosporin blood levels.[6,12-15] Two also note that ranitidine does not alter creatinine levels[6,13] or inulin clearance.[13]

A report describes thrombocytopenia in a man taking ciclosporin after a kidney transplant who was given ranitidine.[16] Another patient experienced hepatotoxicity while taking ciclosporin with ranitidine.[17]

Mechanism

t has been suggested that any rise in serum creatinine levels could simply be because these H_2-receptor antagonists compete with creatinine for secretion by the kidney tubules, and therefore rises are not an indicator of nephrotoxicity[18,19]

Importance and management

Information about the possible interaction of ciclosporin and cimetidine are inconsistent, but there appear to be very few reports of confirmed toxicity. Most of the evidence suggests that famotidine does not affect ciclosporin levels, and ranitidine does not appear to affect ciclosporin levels. The reported increases in serum creatinine levels seen with the H_2-receptor antagonists may not be a reflection of increased nephrotoxicity (see *Mechanism*). Thus there is little to suggest that concurrent use should be avoided, but good initial monitoring is possibly advisable with cimetidine.

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Ciclosporin + Hormonal contraceptives and Progestogens

Isolated reports describe hepatotoxicity and raised ciclosporin levels in two patients taking ciclosporin when given oral combined hormonal contraceptives. A couple of reports also describe some increase in ciclosporin levels with norethisterone.

Clinical evidence

(a) Contraceptives

A woman with uveitis taking ciclosporin 5 mg/kg daily had an increase in her trough plasma ciclosporin levels (roughly doubled) on two occasions within 8 to 10 days of starting an oral contraceptive (**ethinylestradiol** 30 micrograms with **levonorgestrel** 150 micrograms). She also experienced nausea, vomiting and hepatic pain, and had evidence of severe hepatotoxicity (very marked increases in AST and ALT, and rises in serum bilirubin and alkaline phosphatase).The woman had previously taken this oral contraceptive for 5 years without problems.[1]

Another report describes hepatotoxicity in a patient taking ciclosporin 2 weeks after she started an oral contraceptive (**ethinylestradiol** 30 micrograms with **desogestrel** 150 micrograms). The contraceptive was stopped, and liver enzyme levels promptly started to fall, but ciclosporin levels continued to rise, and peaked about 10 days later, at a level about threefold higher than they had been.[2]

(b) Norethisterone

A 15-year-old girl taking ciclosporin who had a marked increase in serum ciclosporin levels when she was given danazol (see 'Ciclosporin + Danazol', p.1236), continued to have elevated levels, but not as high, when the danazol was replaced by norethisterone 5 mg three times daily. The levels returned to her previous normal range when the norethisterone was stopped.[3] Two women had a mild rise in ciclosporin levels with no changes in creatinine levels when they were given norethisterone 10 mg daily for 10 days.[4] No changes in ciclosporin levels were seen in another patient who was intermittently given norethisterone.[5]

Mechanism

Uncertain. It seems possible that some of these compounds inhibit the metabolism of ciclosporin by the liver, thereby leading to an increase in its serum levels. The mechanism of the hepatotoxicity is not understood, but in some cases it seems that it occurs simply as a rare adverse effect of the sex hormone.

Importance and management

This interaction between ciclosporin and oral combined hormonal contraceptives or norethisterone is unconfirmed and of uncertain clinical significance. There is insufficient evidence to recommend increased monitoring but be aware of the potential for an interaction in the case of an unexpected response to treatment.

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Ciclosporin + Lamivudine

Lamivudine did not alter ciclosporin levels in kidney transplant patients.

Clinical evidence, mechanism, importance and management

In a study, the ciclosporin levels of 4 kidney transplant patients taking were unchanged when lamivudine 100 to 150 mg daily was added to treat chronic hepatitis B. Normal graft function was maintained.[1] Another study in 15 kidney transplant patients also found that lamivudine 50 to 100 mg daily for 4 to 29 months did not affect ciclosporin levels and no acute rejection was seen.[2] Therefore, no ciclosporin dose adjustment seems to be necessary on the concurrent use of lamivudine.

1. Jung YO, Lee YS, Yang WS, Han DJ, Park JS, Park S-K. Treatment of chronic hepatitis B with lamivudine in renal transplant recipients. *Transplantation* (1998) 66, 733–7.
2. Mouquet C, Bernard B, Poynard T, Thibault V, Opolon P, Coriat P, Bitker MO. Chronic hepatitis B treatment with lamivudine in kidney transplant patients. *Transplant Proc* (2000) 32, 2762.

Ciclosporin + Melphalan

Melphalan may increase the nephrotoxic effects of ciclosporin.

Clinical evidence, mechanism, importance and management

A comparative study found that 13 out of 17 patients receiving bone marrow transplants and given ciclosporin 12.5 mg/kg daily with high-dose melphalan (single injection of 140 to 250 mg/m^2) developed renal failure, compared with no cases of renal failure in 7 other patients given melphalan but no ciclosporin.[1] In another study, one out of 4 patients given both drugs developed nephrotoxicity.[2] Renal function should be monitored closely on concurrent use. Note that melphalan is an established part of conditioning regimens given before bone marrow transplantation, for which ciclosporin is used to prevent graft-versus-host disease.

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2. Dale BM, Sage RE, Norman JE, Barber S, Kotasek D. Bone marrow transplantation following treatment with high-dose melphalan. *Transplant Proc* (1985) 17, 1711–13.

Ciclosporin + Methotrexate

Previous or concurrent treatment with methotrexate may possibly increase the risk of liver and other toxicity in those given ciclosporin. Ciclosporin might cause a moderate rise in serum methotrexate levels, but methotrexate does not appear to affect the pharmacokinetics of ciclosporin.

Clinical evidence

(a) Bone marrow transplant

In a pilot study of the use of reduced-dose ciclosporin and methotrexate for the control of acute graft-versus-host disease in bone marrow transplant patients, a 50% lower ciclosporin dose (1.5 mg/kg/day) appeared to be as effective and appeared to be associated with reduced hepatotoxicity. The methotrexate doses were 10 to 15 mg/m^2 on days 1, 3, 6, and 11 after grafting.[1] Another study in three bone marrow transplant patients found that low-dose methotrexate (15 mg/m^2 on day 1, and 10 mg/m^2 on days 3, 6 and 11) given with ciclosporin did not significantly affect clinical care and no interaction of clinical significance was seen.[2] Nevertheless, in a large retrospective study of kidney function impairment post-haematopoietic stem cell transplantation, the main cause of acute renal failure was found to be ciclosporin use. The concurrent use of methotrexate in patients taking ciclosporin was also found to be associated with an increased risk of acute renal failure in the first 100 days (hazard ratio 1.9).[3]

(b) Psoriasis

A limited comparative study in patients with chronic plaque psoriasis suggested that the previous use of methotrexate, which can cause liver damage, possibly increases the risk of ciclosporin toxicity (higher ciclosporin blood levels and serum creatinine levels, hypertension).[4] This was confirmed by another study in 4 patients with resistant psoriasis taking ciclosporin 2.5 to 5 mg/kg daily in whom the addition of methotrexate 2.5 mg every 12 hours for three doses at weekly intervals increased creatinine levels and liver enzymes (AST, ALT), which resulted in the study being stopped.[5] Nevertheless, successful concurrent use has been described. In one such study in patients with poorly controlled disease on maximum tolerated doses of ciclosporin or methotrexate alone, concurrent use allowed the reduction in dose of the established drug with better control of psoriasis. However, in 6 of 12 patients receiving both drugs for longer than a year, renal impairment developed, which responded to a reduction in the ciclosporin dose in 3 patients, remained stable in 2 patients, and necessitated the withdrawal of ciclosporin in one patient. There was no evidence of impaired liver function.[6]

(c) Rheumatoid arthritis

An open-label pharmacokinetic study in 26 patients with rheumatoid arthritis taking methotrexate 7.5 to 22.5 mg weekly with ciclosporin 1.5 mg/kg every 12 hours for 14 days, found that the AUC of the weekly dose of methotrexate increased by 26%, whereas the plasma levels of its major metabolite (7-hydroxymethotrexate), which is much less active and may be associated with toxicity, were reduced by 80%.[7] Another study in patients with rheumatoid arthritis found that the pharmacokinetics of ciclosporin after the first dose did not differ between those who had been receiving intramuscular methotrexate 10 mg each week for 6 months and those not receiving methotrexate.[8]

A number of efficacy studies have evaluated the concurrent use of methotrexate and ciclosporin in rheumatoid arthritis. In one, there was no difference in the incidence of renal impairment, or patient withdrawals between patients taking ciclosporin 3 mg/kg daily alone or the same dose of ciclosporin with methotrexate 7.5 to 10 mg weekly. However, there was a tendency for more patients to require dose modification when they were given both drugs (56% versus 28%).[9] In another study, there was no difference in ciclosporin dose between 60 patients receiving ciclosporin alone and 60 patients receiving ciclosporin with methotrexate. However, hypertension or an increase in serum creatinine, or both, were more often a reason for discontinuation in the group given both drugs (9 patients versus 2 patients).[10]

Mechanism

Not understood.

Importance and management

The reports cited here give an inconsistent picture. Patients receiving ciclosporin should routinely be monitored for renal adverse effects, and those receiving methotrexate routinely monitored for hepatotoxicity. If both drugs are used concurrently it may be worth increasing the frequency of this monitoring to aid rapid detection of any adverse effects.

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Ciclosporin + Methoxsalen

In a single-dose study, oral methoxsalen slightly increased the bioavailability of ciclosporin.

Clinical evidence, mechanism, importance and management

In a single-dose study in 12 healthy subjects, oral methoxsalen 40 mg increased the AUC and peak plasma level of ciclosporin 200 mg by about 14% and 8%, respectively, when given at the same time. In two subjects the ciclosporin AUCs increased by 80% and 2.7-fold, respectively. The half-life and time to peak levels were not affected. As methoxsalen absorption is subject to high interindividual variation, this particular study was unable to detect a significant difference in methoxsalen pharmacokinetics, although ciclosporin tended to reduce the AUC and peak levels of methoxsalen by 25% and 35%, respectively.[1]

Methoxsalen may interact by reducing the absorption of ciclosporin. Further study is required to see if this interaction is clinically significant. Until more is known, bear this interaction in mind in patients taking ciclosporin if its levels are increased.

1. Rheeders M, Bouwer M, Goosen TC. Drug-drug interaction after single oral doses of the furanocoumarin methoxsalen and cyclosporine. *J Clin Pharmacol* (2006) 46, 768–75.

Ciclosporin + Methylphenidate

In an isolated case, the ciclosporin levels of a 10-year-old-boy were raised by 50% after he started to take methylphenidate.

Clinical evidence, mechanism, importance and management

A 10-year-old boy who had received a heart transplant 6 years previously, started taking methylphenidate 5 mg twice daily in addition to his transplant medication, which included ciclosporin. After 4 days his ciclosporin level was found to have risen, from 195 nanograms/mL to 302 nanograms/mL. His ciclosporin dose was therefore reduced from 550 to 500 mg daily, and at the same time the methylphenidate was increased to 7.5 mg twice daily. As the next ciclosporin level was still elevated at 251 nanograms/mL, the ciclosporin dose was further reduced to 450 mg daily. The boy then remained on this dose of ciclosporin with acceptable levels, despite further dose increases in the methylphenidate to an eventual dose of 20 mg daily.[1]

The reason for this probable interaction is unclear. This appears to be the only reported case of an interaction between ciclosporin and methylphenidate, and its general importance is unknown.

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Ciclosporin + Metoclopramide

Metoclopramide moderately increases the absorption of ciclosporin and raises its blood levels.

Clinical evidence, mechanism, importance and management

When 14 kidney transplant patients were given metoclopramide their peak ciclosporin blood levels were increased by 46% (from 388 to 567 nanograms/mL) and the ciclosporin AUC was increased by 22%. The dose of metoclopramide was 10 mg by mouth 30 minutes before, 5 mg with, and 5 mg 30 minutes after the morning dose of ciclosporin, which was given after breakfast.[1] Ciclosporin is largely absorbed by the small intestine so the likely mechanism for this interaction is increased absorption of ciclosporin because metoclopramide hastens gastric emptying.

The clinical importance of this interaction is uncertain. Concurrent use should be well monitored to ensure that any increase in ciclosporin peak levels does not increase adverse effects. Note that the increase in the AUC of ciclosporin is only modest.

1. Wadhwa NK, Schroeder TJ, O'Flaherty E, Pesce AJ, Myre SA, First MR. The effect of oral metoclopramide on the absorption of cyclosporine. *Transplant Proc* (1987) 19, 1730–3.

Ciclosporin + Minoxidil

The concurrent use of ciclosporin and minoxidil can cause excessive hairiness (hypertrichosis).

Clinical evidence, mechanism, importance and management

Six male kidney transplant patients taking ciclosporin (blood levels of 100 to 200 nanograms/mL) were given methyldopa, a diuretic and minoxidil 15 to 40 mg daily for intractable hypertension. After 4 weeks of treatment all of them complained of severe and unpleasant hypertrichosis (excessive hairiness). Two months after stopping minoxidil the hypertrichosis had significantly improved.[1] Both ciclosporin and minoxidil cause hypertrichosis and it would seem that their effects may be additive. The authors of the report point out that this is not a life-threatening problem, but it limits the concurrent use of these drugs in both men and women.[1]

1. Sever MS, Sonmez YE, Kocak N. Limited use of minoxidil in renal transplant recipients because of the additive side-effects of cyclosporine on hypertrichosis. *Transplantation* (1990) 50, 536.

Ciclosporin + Modafinil

Ciclosporin levels were reported to be reduced by modafinil in one patient.

Clinical evidence, mechanism, importance and management

A kidney transplant patient, stable for 9 years taking ciclosporin 200 mg daily, developed Gélineau's syndrome (narcoleptic syndrome) and was given modafinil 200 mg daily. Within a few weeks her ciclosporin blood levels were noted to have fallen, and it was necessary to raise her ciclosporin dose stepwise to 300 mg daily before her blood levels were back to their former values.[1]

Modafinil is a known modest inducer of the cytochrome P450 isoenzyme CYP3A4, the major enzyme involved in the metabolism of ciclosporin. Concurrent use therefore increases ciclosporin metabolism and decreases its levels.

Evidence is limited to this single case report, but, on the basis of the proposed mechanism, a modest interaction would be expected. It would seem prudent to anticipate a reduction in ciclosporin levels if modafinil is used and adjust the ciclosporin dose as necessary. **Armodafinil**, the *R*-isomer of modafinil, would be expected to interact similarly.

1. Le Cacheux Ph, Charasse C, Mourtada R, Muh Ph, Boulahrouz R, Simon P. Syndrome de Gélineau chez une transplantée rénale. Mise en évidence d'une interaction cyclosporine-modafinil. *Presse Med* (1997) 26, 466.

Ciclosporin + Muromonab-CD3

Muromonab-CD3 appears to increase ciclosporin blood levels, and there is an increased risk of reactivation of viral infections with combined use.

Clinical evidence, mechanism, importance and management

In the preliminary report of a retrospective review, when 5 mg of muromonab-CD3 was given daily for 10 days to 10 kidney transplant patients to treat acute rejection, their mean trough ciclosporin levels on day 8 were higher than before the muromonab-CD3 was started, despite a 50% reduction in the ciclosporin dose. When the muromonab-CD3 was withdrawn,

the ciclosporin dose needed to be increased again.[1] The manufacturer notes that there is an increased risk of reactivation of cytomegalovirus when an immunosuppressive regimen including ciclosporin is used after an anti-lymphocyte antibody such as muromonab-CD3.[2]

The reasons for the rise in ciclosporin levels are not understood. Muromonab-CD3 augments the immunosuppressant effects of ciclosporin and consequently increases the risk of infection and reactivation of viral infections. Note that the authors of the first study say that ciclosporin doses are routinely reduced before use of muromonab-CD3 to avoid over-immunosuppression, and therefore the relevance of their retrospective findings on ciclosporin levels is uncertain.

1. Vrahnos D, Sanchez J, Vasquez EM, Pollak R, Maddux MS. Cyclosporine levels during OKT3 treatment of acute renal allograft rejection. *Pharmacotherapy* (1991) 11, 278.
2. Orthoclone OKT3 (Muromonab-CD3). Ortho Biotech. US Prescribing information, November 2004.

Ciclosporin + Nefazodone

Four cases of raised ciclosporin levels have been seen in patients taking nefazodone and ciclosporin, one with raised creatinine levels and tremor, and one with raised liver enzymes.

Clinical evidence

A kidney transplant patient had a 70% rise in trough serum ciclosporin levels within 3 days of starting to take nefazodone 25 mg twice daily.[1] Another kidney transplant patient had a two- to threefold rise in ciclosporin levels associated with raised creatinine levels and marked generalised tremors after starting nefazodone 100 mg twice daily. The patient was eventually stabilised on a 50% lower dose of ciclosporin.[2] Similarly, a heart transplant patient taking ciclosporin had a tenfold increase in ciclosporin levels shortly after the addition of nefazodone 150 mg twice daily. Levels returned to baseline over 6 days after nefazodone was stopped.[3] A patient taking nefazodone developed significantly raised liver enzymes (AST and ALT) one month after kidney transplantation. His ciclosporin level was high, at 614 nanograms/mL, and both ciclosporin and nefazodone were stopped. He had previously taken nefazodone uneventfully, and subsequently took ciclosporin uneventfully, so the raised liver enzymes were attributed to a pharmacokinetic interaction between the two drugs.[4]

Mechanism

Nefazodone is an inhibitor of the cytochrome P450 isoenzyme CYP3A4, the main isoenzyme by which ciclosporin is metabolised. Concurrent use can therefore lead to increased ciclosporin levels.

Importance and management

Although the evidence is limited, it appears that nefazodone can cause a marked rise in ciclosporin levels, with an increase in adverse effects. Alternative antidepressants should probably be given, or concurrent use very well monitored. Note that nefazodone has generally been withdrawn due to its adverse effects on the liver.

1. Helms-Smith KM, Curtis SL, Hatton RC. Apparent interaction between nefazodone and cyclosporine. *Ann Intern Med* (1996) 125, 424.
2. Vella JP, Sayegh MH. Interactions between cyclosporine and newer antidepressant medications. *Am J Kidney Dis* (1998) 31, 320–3.
3. Wright DH, Lake KD, Bruhn PS, Emery RW. Nefazodone and cyclosporine drug-drug interaction. *J Heart Lung Transplant* (1999) 18, 913–15.
4. Garton T, Nefazodone and CYP450 3A4 interactions with cyclosporine and tacrolimus. *Transplantation* (2002) 74, 745.

Ciclosporin + NNRTIs

Efavirenz, and to a lesser extent nevirapine, appear to decrease the levels of ciclosporin. The ciclosporin levels of one patient dramatically decreased following the addition of efavirenz. Etravirine is also predicted to interact in this way. In contrast, delavirdine is predicted to inhibit the metabolism of ciclosporin and increase its levels.

Clinical evidence

A patient was diagnosed as HIV-positive 3 years after a kidney transplant, for which he was taking ciclosporin. He was started on **efavirenz** 600 mg daily, lamivudine and zidovudine, and 7 days later, after an initial rise, his ciclosporin level dropped from about 203 nanograms/mL to 80 nanograms/mL. A nadir of 50 nanograms/mL was reached one month later.[1] In a study in 35 HIV-infected patients, ciclosporin was added to established antiretroviral therapy after liver or kidney transplantation. Patients taking **efavirenz** required much higher ciclosporin doses than those taking **nevirapine** (275 mg twice daily compared to 189 mg twice daily at week 2 and 279 mg twice daily compared to 147 mg twice daily at week 12). Patients taking **nevirapine** had similar ciclosporin levels and dose requirements to patients not infected with HIV taking ciclosporin. Dose requirements in the **efavirenz** patients were also much higher than those in patients taking any other antiretroviral. Ciclosporin levels were about 30% lower with **efavirenz** than with **nevirapine** (91 nanograms/mL compared with 130 nanograms/mL at week 2, and 84 nanograms/mL compared with 116 nanograms/mL at week 12).[2] The same authors reported the results of the first 18 patients recruited into this study in an earlier paper, and showed that at 2 years the required ciclosporin dose was slightly lower in patients taking these NNRTIs (1.7 mg/kg compared with 2.6 mg/kg).[3] There were minimal changes in the pharmacokinetics of the NNRTIs during the study.

Mechanism

Efavirenz, etravirine and nevirapine induce the cytochrome P450 isoenzyme CYP3A4 (although etravirine is only a weak inducer[4]). Ciclosporin is extensively metabolised by CYP3A4, so concurrent use would be expected to decrease ciclosporin levels. Note that delavirdine inhibits CYP3A4 and is predicted to increase ciclosporin levels.[5]

Importance and management

The available evidence suggests that **efavirenz** decreases ciclosporin levels and increases the ciclosporin dose requirements. **Nevirapine** may also affect ciclosporin levels but it appears that its effects on ciclosporin levels are much less than those of efavirenz. The manufacturer[4] of **etravirine** predicts that it will also affect ciclosporin levels. Note that as etravirine is only a weak inducer of CYP3A4, any reduction in ciclosporin levels would be expected to be much less than that seen with efavirenz. As subtherapeutic levels of ciclosporin may have significant consequences, including transplant rejection, it would be prudent to monitor ciclosporin levels closely in patients given efavirenz, etravirine or nevirapine.

In contrast, **delavirdine** is predicted to increase ciclosporin levels and so a dose reduction of ciclosporin may be needed. As increased levels may lead to toxicity, it would be prudent to monitor ciclosporin levels and renal function closely in patients also given delavirdine.

1. Tseng A, Nguyen ME, Cardella C, Humar A, Conly J. Probable interaction between efavirenz and cyclosporine. *AIDS* (2002) 16, 505–6.
2. Frassetto LA, Browne M, Cheng A, Wolfe AR, Roland ME, Stock PG, Carlson L, Benet LZ. Immunosuppressant pharmacokinetics and dosing modifications in HIV-1 infected liver and kidney transplant recipients. *Am J Transplant* (2007) 7, 2816–20.
3. Frassetto L, Baluom M, Jacobsen W, Christians U, Roland ME, Stock PG, Carlson L, Benet LZ. Cyclosporine pharmacokinetics and dosing modifications in human immunodeficiency virus-infected liver and kidney transplant recipients. *Transplantation* (2005) 80, 13–17.
4. Intelence (Etravirine). Janssen-Cilag Ltd. UK Summary of product characteristics, November 2009.
5. Rescriptor (Delavirdine mesylate). Pfizer Inc. US Prescribing information, May 2008.

Ciclosporin + NSAIDs, Aspirin or Paracetamol (Acetaminophen)

NSAIDs sometimes reduce renal function in individual patients, which is reflected in serum creatinine level rises and possibly in changes in ciclosporin levels, but concurrent use can also be uneventful. Diclofenac levels can be doubled by ciclosporin. There is an isolated report of colitis in a child treated with ciclosporin and diclofenac or indometacin.

Clinical evidence

(a) Aspirin

In a study in healthy subjects, no pharmacokinetic interaction was found when ciclosporin was given with aspirin 960 mg three times daily.[1]

(b) Diclofenac

A study in 20 patients with rheumatoid arthritis given ciclosporin and diclofenac found that 7 of them had a high probability of an interaction (rises in serum creatinine levels and blood pressures), and 9 possibly had an interaction.[2] A kidney transplant patient taking ciclosporin, digoxin, furosemide, prednisolone, and spironolactone had a marked rise in serum creatinine levels immediately after starting to take diclofenac 25 mg three times daily. A fall in serum ciclosporin levels from 409 nanograms/mL to 285 nanograms/mL also occurred.[3] Increased nephrotoxicity was seen in another patient taking ciclosporin for idiopathic uveitis when diclofenac 150 mg daily was given.[4]

A 6-month study in 20 patients with severe rheumatoid arthritis given diclofenac 100 to 200 mg with ciclosporin 3 mg/kg daily found that the AUC of diclofenac was doubled and serum creatinine levels increased from 71 micromol/L to 88.4 micromol/L. The overall pattern of adverse events and laboratory abnormalities were similar to those in patients with rheumatoid arthritis treated with ciclosporin and other NSAIDs. It was suggested that it would be prudent to start with low doses of diclofenac and to monitor well.[5] A study in 24 healthy subjects found that diclofenac 50 mg every 8 hours for 8 days caused no changes in the pharmacokinetics of ciclosporin, but there was some inconclusive evidence that diclofenac serum levels were increased.[6]

A child with rheumatoid arthritis taking ciclosporin 10 mg/kg daily developed colitis when diclofenac was given. The NSAID was stopped and her symptoms resolved while the ciclosporin was continued.[7]

(c) Dipyrone (Metamizole sodium)

A placebo-controlled, crossover study in 6 kidney and 2 heart transplant patients taking ciclosporin, found that while they were taking dipyrone 500 mg three times daily for 4 days the pharmacokinetics of ciclosporin (AUC, trough and peak blood levels, elimination half-life) were unchanged, but the time to reach maximum blood levels was slightly prolonged, from 2.1 hours to 3.8 hours. It is not known what the effects of more prolonged use might be.[8]

(d) Indometacin

A study in 16 healthy subjects found that indometacin 100 mg twice daily for 9 days reduced the maximum blood levels of a single 300-mg dose of ciclosporin by 18% and slowed its absorption (time to maximum concentration increased by 30 minutes) but the extent of absorption was not changed, indicating the absence of a clinically relevant pharmacokinetic interaction. Further, the pharmacokinetics of indometacin were not affected by ciclosporin.[9] A study in rheumatoid arthritis patients taking ciclosporin 2.5 mg/kg daily, found that creatinine clearances were reduced by 6% in those taking indometacin 50 mg four times daily, but this was not considered to be clinically important.[10] An experimental study in healthy subjects found that ciclosporin 10 mg/kg twice daily for 4 days had no effect on effective renal plasma flow or the glomerular filtration rate, but when indometacin 50 mg twice daily was added the effective renal plasma flow fell by 32% and the glomerular filtration rate fell by 37%.[11]

A child with rheumatoid arthritis taking ciclosporin 10 mg/kg daily developed colitis when indometacin was given. The NSAID was stopped and her symptoms resolved while the ciclosporin was continued.[7]

(e) Ketoprofen

A study in rheumatoid arthritis patients taking ciclosporin 2.5 mg/kg daily, found that creatinine clearances were reduced by 2.3% in those taking ketoprofen 50 mg four times daily, but this was not considered to be clinically important.[10] Another report describes increased serum creatinine levels in a patient with rheumatoid arthritis who took ciclosporin and ketoprofen.[12]

(f) Mefenamic acid

The ciclosporin blood levels in a renal transplant patient doubled, accompanied by a rise in creatinine levels from 113 micromol/L to 168 micromol/L, within a day of starting to take mefenamic acid. Levels fell to normal within a week of stopping the mefenamic acid.[13]

(g) Naproxen

When 11 patients with rheumatoid arthritis taking ciclosporin were given naproxen and sulindac, their serum creatinine levels increased by 24% and renal function was reduced (glomerular filtration rate reduced from 98 mL/minute at baseline to 67 mL/minute).[14]

(h) Paracetamol (Acetaminophen)

A study in rheumatoid arthritis patients taking ciclosporin 2.5 mg/kg daily, found that creatinine clearances were reduced by 3.5% in those taking paracetamol 650 mg four times daily, but this was not considered to be clinically important.[10]

(i) Piroxicam

Piroxicam is reported to have increased the serum creatinine levels of a patient with rheumatoid arthritis by an unknown amount (but classed as a significant adverse event). This resolved when the piroxicam was withdrawn.[12] A study in healthy subjects given piroxicam 20 mg daily for 11 days and a single 300-mg dose of ciclosporin on day 10 found no clinically relevant pharmacokinetic interaction.[9]

(j) Sulindac

A study in rheumatoid arthritis patients taking ciclosporin 2.5 mg/kg daily, found that the creatinine clearance was reduced by 2.6% in those taking sulindac 100 mg four times daily, but this was not considered to be clinically important.[10]

A kidney transplant patient had a rise in serum creatinine levels when sulindac was used. Ciclosporin blood levels fell and rose again when the sulindac was stopped.[3] Another report states that the ciclosporin levels of a woman with a kidney transplant were more than doubled within 3 days of her starting to take sulindac 150 mg twice daily.[15] When 11 patients with rheumatoid arthritis taking ciclosporin were given sulindac and naproxen their serum creatinine levels increased by 24% and renal function was reduced (glomerular filtration rate reduced from 98 mL/minute at baseline to 67 mL/minute).[14]

Another report describes a patient with rheumatoid arthritis taking ciclosporin who developed increased serum creatinine levels when given ketoprofen, but not when given sulindac.[12]

Mechanism

Uncertain. One idea is that intact kidney prostacyclin synthesis is needed to maintain the glomerular filtration rate and renal blood flow in patients given ciclosporin, which may possibly protect the kidney from the development of ciclosporin-induced nephrotoxicity. If NSAIDs that inhibit prostaglandin production in the kidney are given, the nephrotoxic effects of the ciclosporin manifest themselves, possibly independently of changes in serum ciclosporin levels.[3] A study in *rats* found that indometacin and ciclosporin together can cause rises in serum creatinine levels that are much greater than with either drug alone.[16]

Ciclosporin may decrease the first-pass metabolism of NSAIDs that are metabolised in this way, such as diclofenac.[17]

The occurrence of colitis in a child receiving ciclosporin and either diclofenac or indometacin appeared to be independent of changes in ciclosporin levels and may be a result of additive effects of both drugs.[7]

Importance and management

Information about the individual NSAIDs listed here is sparse, but when viewed as a group, the overall picture appears to be that concurrent use in rheumatoid arthritis need not be avoided but renal function should be very well monitored. The UK manufacturer of ciclosporin also specifically recommends that patients with rheumatoid arthritis taking ciclosporin and an NSAID should have their liver function measured as well as renal function, because hepatotoxicity is a potential adverse effect of both drugs.[17] It has been suggested that gastrointestinal symptoms should also be carefully evaluated.[7] It is clearly difficult to generalise about what will or will not happen if any particular NSAID is given, but in the case of diclofenac, as its serum levels can be doubled by ciclosporin, it has been recommended that doses at the lower end of the range should be used initially.[5] The UK manufacturer recommends halving the diclofenac dose, and using lower than usual doses of other NSAIDs in patients also taking ciclosporin.[17]

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3. Harris KP, Jenkins D, Walls J. Nonsteroidal antiinflammatory drugs and cyclosporine. A potentially serious adverse interaction. *Transplantation* (1988) 46, 598–9.
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11. Sturrock NDC, Lang CC, Struthers AD. Indomethacin and cyclosporin together produce marked renal vasoconstriction in humans. *J Hypertens* (1994) 12, 919–24.
12. Ludwin D, Bennett KJ, Grace EM, Buchanan WA, Bensen W, Bombardier C, Tugwell PX. Nephrotoxicity in patients with rheumatoid arthritis treated with cyclosporine. *Transplant Proc* (1988) 20 (Suppl 4), 367–70.
13. Agar JWMacD. Cyclosporin A and mefenamic acid in a renal transplant patient. *Aust N Z J Med* (1991) 21, 784–5.
14. Altman RD, Perez GO, Sfakianakis GN. Interaction of cyclosporine A and nonsteroidal anti-inflammatory drugs on renal function in patients with rheumatoid arthritis. *Am J Med* (1992) 93, 396–402.
15. Sesin GP, O'Keefe E, Roberto P. Sulindac-induced elevation of serum cyclosporine concentration. *Clin Pharm* (1989) 8, 445–6.
16. Whiting PH, Burke MD, Thomson AW. Drug interactions with cyclosporine. Implications from animal studies. *Transplant Proc* (1986) 18 (Suppl 5), 56–70.
17. Neoral (Ciclosporin). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, May 2009.

Ciclosporin + Opioids

An isolated report describes neuropsychosis in a patient who was given intravenous ciclosporin and morphine. A single case report describes a patient taking ciclosporin who developed opioid withdrawal on stopping low-dose, transdermal fentanyl.

Clinical evidence, mechanism, importance and management

A patient who underwent kidney transplantation was given ciclosporin 6 mg/kg daily by intravenous infusion over 2 hours and intravenous methylprednisolone postoperatively. He also received patient-controlled analgesia (PCA) as bolus doses of **morphine** 0.5 mg to a total dose of 13 mg on the first day and 11 mg on the second day. On the third day he developed insomnia, anxiety, amnesia, aphasia and severe confusion. The morphine was discontinued and the symptoms subsided after treatment with propofol, diazepam and haloperidol. It was suggested that ciclosporin may have decreased the excitation threshold of neuronal cells, which potentiated the dysphoric effects of **morphine**.[1]

A patient taking ciclosporin following a stem cell transplant developed opioid withdrawal symptoms when transdermal **fentanyl** 25 micrograms/hour was discontinued. The authors suggested that, as withdrawal symptoms are not usual at this dose of fentanyl, ciclosporin may have raised **fentanyl** levels by inhibiting the cytochrome P450 isoenzyme CYP3A4 by ciclosporin. However, they also note that other factors may have played a role, such as the physical and mental status of the patient after the stem cell transplant.[2]

These appear to be isolated cases and almost certainly not of general importance.

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2. Tsutsumi Y, Kanamori H, Tanaka J, Asaka M, Imamura M, Masauzi N. Withdrawal symptoms from transdermal fentanyl (TDF) after an allogeneic blood stem cell transplant. *Pain Med* (2006) 7, 164–5.

Ciclosporin + Orlistat

The absorption of ciclosporin is markedly reduced by orlistat, and cases of low levels have been reported with both the microemulsion formulation (*Neoral*) and the oil formulation (*Sandimmun*), including an episode of acute graft rejection.

Clinical evidence

In the first year after orlistat approval in the US, the FDA in the US noted that they had received six reports of transplant recipients who developed subtherapeutic ciclosporin trough levels (formulation not mentioned) soon after starting to take orlistat.[1] A number of reports have also been published, both with the *Sandimmun* and *Neoral* formulations, as outlined below.

1. Neoral formulation. In a pharmacokinetic study in healthy subjects given low-dose ciclosporin 50 mg twice daily, orlistat 120 mg three times daily with meals reduced the trough level and AUC of ciclosporin by 27% and 34%, respectively, when ciclosporin was also taken with meals. When ciclosporin was taken 3 hours after meals, the reduction in ciclosporin trough levels was similar.[2]

A heart transplant patient taking ciclosporin had an unexpected non-significant acute rejection episode noted on routine endocardial biopsy, with very low trough ciclosporin levels of 38 nanograms/mL, 24 days after starting to take orlistat. Ciclosporin trough levels returned to previous levels of between 90 to 110 nanograms/mL when the orlistat was stopped, suggesting that orlistat had caused about a 60% drop in ciclosporin levels.[3]

Another similar report describes one patient who was found to have about a 50% reduction in ciclosporin levels 44 days after starting orlistat 120 mg twice daily (lunch and dinner), and another who had a 45% reduction in ciclosporin levels, noted 6 days after starting orlistat 120 mg three times daily.[4] One patient who was unable to achieve therapeutic ciclosporin levels after starting orlistat 360 mg daily while taking the *Sandimmun* formulation (see below) was subsequently stabilised on the *Neoral* formulation at a 50% higher dose than his original *Sandimmun* dose.[5]

2. Sandimmun formulation. In a heart transplant patient taking ciclosporin, orlistat 120 mg three times daily for 2 weeks was found to have reduced the trough blood levels of ciclosporin by 50%, to 50 nanograms/mL. A subsequent pharmacokinetic study in this patient confirmed that orlistat reduced the trough and peak levels and the AUC of ciclosporin by 47%, 86% and 75%, respectively.[6] In a further patient taking ciclosporin 250 mg daily, orlistat 360 mg daily reduced the ciclosporin levels by 67% (from 150 to 50 nanograms/mL). Increasing the dose of ciclosporin did not result in an increased level, so the patient was given *Neoral* instead (see above).[5] Another heart transplant patient had a progressive reduction in her ciclosporin level when she started to take orlistat 120 mg three times daily (28% reduction at 5 days and 46% at 10 days), despite taking the orlistat 2 hours before the ciclosporin. Stopping the breakfast dose of orlistat did not result in increased ciclosporin levels, but levels did return to normal when orlistat was stopped. Note that this patient was also reported to have severe diarrhoea secondary to poor adherence to a low-fat diet when taking orlistat, which may have contributed to the low ciclosporin levels seen.[7]

Mechanism

Orlistat inhibits pancreatic lipase and prevents the absorption of dietary fat and lipophilic molecules such as ciclosporin. Absorption of ciclosporin from the oil suspension formulation (*Sandimmun*) is more dependent on the lipid absorption stage and thus may be more affected by orlistat than the microemulsion form (*Neoral*).[5]

Importance and management

An established interaction, that has the potential to be clinically important. It has been suggested that the effects of the interaction may be reduced by using the microemulsion formulation of ciclosporin (*Neoral*),[5] which has generally replaced the corn oil suspension (*Sandimmun*). However, close monitoring is required if the two drugs are used together, either in the standard or microemulsion form, because there is still a risk of subtherapeutic levels. Some authors recommend avoidance of the combination.[4,6] The UK manufacturer of orlistat does not recommend concurrent use, but notes that if it is unavoidable more frequent ciclosporin monitoring is recommended.[8] The US manufacturer also advises against concurrent use. They recommend taking ciclosporin at least 2 hours before or 2 hours after orlistat to reduce the chance of an interaction, and that ciclosporin levels should be monitored more frequently in patients whose levels are being monitored.[9] However, there is evidence that separation of doses does not avoid the interaction.[2,7]

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8. Xenical (Orlistat). Roche Products Ltd. UK Summary of product characteristics, March 2009.
9. Xenical (Orlistat). Roche Pharmaceuticals. US Prescribing information, July 2008.

Ciclosporin + Oxybutynin

Oxybutynin did not appear to affect ciclosporin levels in two children.

Clinical evidence, mechanism, importance and management

In a retrospective analysis, one child with a kidney transplant taking ciclosporin had no change in his ciclosporin level and dose over the 2 months before and the 2 months after he started taking oxybutynin 2 mg twice daily. Another patient had no change in ciclosporin levels and dose over the 3 months before and 3 months after stopping oxybutynin 5 mg twice daily.[1]

Although the evidence is limited, it suggests that oxybutynin is unlikely to have an important effect on ciclosporin levels.

1. Springate JE. Oxybutynin does not affect cyclosporin blood levels. *Ther Drug Monit* (2001) 23, 155–6.

Ciclosporin + Pancreatic enzymes

Pancreatic enzyme extracts do not increase the bioavailability of ciclosporin in cystic fibrosis patients.

Clinical evidence, mechanism, importance and management

A study in heart-lung transplant patients with cystic fibrosis found that they needed almost five times the oral dose of ciclosporin than other patients, confirming other studies in these patients that had found a very much reduced bioavailability of oral ciclosporin. This is probably a reflection of the generally poor digestion and absorption in cystic fibrosis patients. The addition of pancreatic enzymes (*Creon*) was not found to improve this poor ciclosporin bioavailability. No adverse effects were reported.[1]

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Ciclosporin + Phosphodiesterase type-5 inhibitors

Sildenafil and vardenafil do not alter ciclosporin levels.

Clinical evidence

(a) Sildenafil

In a clinical study in 5 kidney transplant recipients, sildenafil 25 to 100 mg in repeated doses had no effect on the AUC, trough or maximum levels of ciclosporin over 8 weeks.[1] Similarly, in other clinical studies, sildenafil 50 or 100 mg in repeated doses for 72 hours to 4 weeks had no effect on ciclosporin trough levels.[2-4] No significant changes in blood pressure were reported in one of these studies.[3]

(b) Vardenafil

In a study in 14 renal transplant patients, vardenafil 10 or 20 mg (maximum frequency of once in 24 hours) in repeated doses during a 4-week period had no effect on levels or required dose of ciclosporin and no change in renal function was reported.[5]

Mechanism

None.

Importance and management

No significant pharmacokinetic interaction appears to occur between ciclosporin and sildenafil or vardenafil. Therefore, no ciclosporin dose adjustment would be expected to be necessary in patients taking these drugs. In two studies with 'tacrolimus', (p.1305), there was a decrease in blood pressure with sildenafil; but this was not seen n the one study that assessed this effect. Nevertheless, it has been suggested that sildenafil be started at a low dose in all kidney transplant patients, with the dose increased according to efficacy and tolerability.[6]

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5. Demir E, Balal M, Paydas S, Sertdemir Y, Erken U. Efficacy and safety of vardenafil in renal transplant recipients with erectile dysfunction. *Transplant Proc* (2006) 38, 1379–81.
6. Barry JM. Treating erectile dysfunction in renal transplant recipients. *Drugs* (2007) 67, 975–83.

Ciclosporin or Tacrolimus + Potassium compounds

Ciclosporin and tacrolimus alone can cause or worsen pre-existing hyperkalaemia, and the concurrent use of potassium compounds may exacerbate this.

Clinical evidence, mechanism, importance and management

Both ciclosporin and tacrolimus can cause hyperkalaemia.[1,2] Hyperkalaemia can in itself be a sign of worsening renal function but may be exacerbated by ciclosporin or tacrolimus. This can be worsened further by the use of potassium supplements.

Note that potassium levels are usually routinely monitored during the use of ciclosporin and tacrolimus, and this monitoring should probably be increased if other drugs that affect potassium levels, such as potassium supplements, are also given. The UK manufacturer of tacrolimus recommends that patients should avoid a high potassium intake, such as in supplements.[1]

1. Prograf (Tacrolimus monohydrate). Astellas Pharma Ltd. UK Summary of product characteristics, May 2009.
2. Neoral (Ciclosporin). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, May 2009.

Ciclosporin + Prazosin

Preliminary studies found that prazosin caused a small reduction in the glomerular filtration rate in kidney transplant patients taking ciclosporin.

Clinical evidence, mechanism, importance and management

A study in 8 kidney transplant patients found that prazosin 1 mg twice daily for one week did not alter their ciclosporin blood levels, and arterial blood pressures and renal vascular resistance were reduced. However, the glomerular filtration rate (GFR) was reduced by about 10% (from 47 to 42 mL/minute).[1] Previous studies in kidney transplant patients taking azathioprine, prednisone and prazosin found no reduction in GFR.[2] There would seem to be no strong reason for totally avoiding prazosin in patients taking ciclosporin, but the authors of the report point out that the fall in GFR makes prazosin a less attractive antihypertensive than a calcium-channel blocker.

1. Kiberd BA. Effects of prazosin therapy in renal allograft recipients receiving cyclosporine. *Transplantation* (1990) 49, 1200–1.
2. Curtis JR, Bateman FJA. Use of prazosin in management of hypertension in patients with chronic renal failure and in renal transplant recipients. *BMJ* (1975) 4, 432.

Ciclosporin + Probucol

Probucol modestly to markedly reduces blood ciclosporin levels.

Clinical evidence

A study in 6 heart transplant patients taking ciclosporin found that the concurrent use of probucol 500 mg every 12 hours decreased trough whole blood ciclosporin levels by 42% from 139 nanograms/mL to 81 nanograms/mL, and reduced the AUC_{0-9} by 28%. The clearance was increased by 60% and volume of distribution also increased.[1] Another study similarly found that 9 out 10 kidney transplant patients had a reduction in their trough blood ciclosporin levels while taking probucol.[2]

In 5 patients with nephrotic syndrome, probucol 250 to 500 mg daily decreased trough ciclosporin levels by 36 to 56%.[3] Although not specified, it is assumed that these studies used the original *Sandimmun* formulation. The same group of workers found that in 4 patients with nephrotic syndrome taking ciclosporin (*Neoral*), probucol 500 mg daily decreased the trough ciclosporin levels by 17 to 30%.[4]

Mechanism

Not understood. Probucol appears to reduce the absorption of ciclosporin. Evidence from *in vitro* and *animal* studies found that probucol does not affect ciclosporin absorption via P-glycoprotein-mediated transport.[5]

Importance and management

Information appears to be limited to these studies, but the interaction appears to be established. The ciclosporin dose may need to be increased if probucol is added. Monitor the effects and adjust the dose appropriately. Note that one group of researchers consider that *Neoral* is less affected than *Sandimmun*.[4]

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3. Wakasugi H, Yoshimoto M, Aoki M, Osawa R, Futami T, Ono T, Muso E, Inui K. Effect of probucol on the concentration of cyclosporin A in patients with nephrotic syndrome. *Nippon Jinzo Gakkai Shi* (2001) 43, 595–9.
4. Wakasugi H, Yoshimoto M, Ono T, Muso E, Inui K. Effect of probucol on the blood concentration of cyclosporin A in patients with nephrotic syndrome: a case study with a microemulsion formulation (Neoral). *Nippon Jinzo Gakkai Shi* (2002) 44, 792–7.
5. Sugimoto K-I, Sudoh T, Tsuruoka S, Yamamoto Y, Maezono S, Watanabe Y, Fujimura A. Effect of probucol on oral bioavailability of cyclosporine A. *Eur J Pharm Sci* (2004) 22, 71–7.

Ciclosporin + Propafenone

In an isolated report, propafenone caused a 60% increase in the ciclosporin levels of a patient.

Clinical evidence, mechanism, importance and management

A heart transplant patient taking ciclosporin, azathioprine and prednisolone developed ventricular tachycardia 9 months after transplantation, for which he was given propafenone 600 or 750 mg daily. After the first day, his ciclosporin level had risen from about 160 nanograms/mL to 190 nanograms/mL, and after 5 days the levels had reached around 260 nanograms/mL. Over the same time period his serum creatinine rose from 168 micromol/L to 212 micromol/L. His ciclosporin dose was reduced from 240 mg daily to a final dose of 200 mg daily after which his renal function and ciclosporin levels were re-established at about the level before propafenone was started.[1] The authors suggest that propafenone interferes with the metabolism of ciclosporin by affecting hepatic cytochrome P450, or that propafenone may enhance the absorption of ciclosporin. Information appears to be limited to this one report, the general importance of which is unknown.

1. Spes CH, Angermann CE, Horn K, Strasser T, Mudra H, Landgraf R, Theisen K. Ciclosporin-propafenone interaction. *Klin Wochenschr* (1990) 68, 872.

Ciclosporin + Protease inhibitors

Protease inhibitors can markedly increase the levels of ciclosporin. This has been demonstrated for fosamprenavir, indinavir, nelfinavir, saquinavir, and ritonavir-boosted amprenavir, indinavir and lopinavir. Some evidence suggests that ciclosporin may increase indinavir, nelfinavir and saquinavir levels, but in one study, this effect was not sustained.

Clinical evidence

(a) Fosamprenavir

An HIV-positive patient taking ciclosporin 250 to 350 mg twice daily (to maintain a therapeutic ciclosporin trough level of 300 to 400 nanograms/mL) was restarted on his usual HAART regimen of tenofovir, lamivudine and fosamprenavir 1.4 g twice daily on day 12 post-liver transplantation. Within 2 days, the ciclosporin level had increased to 600 nanograms/mL, requiring a ciclosporin dose reduction to 100 mg twice daily; a reduction of about 70%.[1]

(b) Nelfinavir

A pilot study in 7 HIV-positive subjects taking nelfinavir 1.25 g twice daily found that a single 4-mg/kg oral dose of ciclosporin slightly increased the time to maximum serum level for nelfinavir from 2.6 to 3.2 hours. The AUC of nelfinavir was also increased by 55%, but this was not statistically significant. In the same study, a single 2-mg/kg intravenous dose of ciclosporin given over 2.5 hours had little effect on the pharmacokinetics of oral nelfinavir. The pharmacokinetics of oral ciclosporin in this study did not appear to differ from that seen in healthy subjects in other studies, but there was high inter-individual variability.[2] However, in another study by this research group, when ciclosporin was added to established antiretroviral therapy after liver or kidney transplantation in 35 HIV-positive patients, those taking protease inhibitor-based regimens (not specified) required a marked reduction in ciclosporin dose and about a 50% increase in dosing interval at week 2 when compared with those taking an NNRTI-based regimen.[3] Furthermore, the same authors reported the results of the first 18 patients recruited into this study in an earlier paper, and showed that in 5 patients taking nelfinavir or **indinavir**-based antiretroviral regimens, the required ciclosporin dose decreased by 85% from 1.3 mg/kg to just 0.2 mg/kg in the 2 years after transplantation. The AUC of the protease inhibitor generally increased in the first few weeks after starting ciclosporin, but gradually returned to baseline by week 28.[4]

(c) Ritonavir-boosted regimens

Three HIV-positive patients who had undergone liver transplantation required reductions in their ciclosporin doses when they started taking ritonavir-boosted **lopinavir** based HAART. One patient taking ciclosporin 150 mg twice daily had an increase in his ciclosporin levels to 900 nanograms/mL when HAART was started, and needed a dose reduction of 95% to maintain a usual ciclosporin trough level of 75 to 150 nanograms/mL. A second patient also required a similar reduction. The third patient needed a dose reduction of 80% when taking ritonavir-boosted **lopinavir**, but no further ciclosporin dose alteration was needed when his treatment was changed to ritonavir-boosted **indinavir**.[5] In a similar case, a reduction in ciclosporin dose from 200 to 350 mg twice daily to just 25 mg twice daily was required on restarting a ritonavir-boosted **amprenavir** containing regimen (about a 90% reduction).[1] Likewise, a study in 35 HIV-positive patients given ciclosporin post-transplant, found a greater reduction in ciclosporin dose requirements when ritonavir was given with protease inhibitors (not specified) than when the protease inhibitors were given alone (25 mg twice daily compared with 57 to 75 mg twice daily).[3]

(d) Saquinavir

An HIV-positive patient taking lamivudine and zidovudine, and ciclosporin for a kidney transplant, started taking saquinavir 1.2 g three times daily. Within 2 days he started to complain of fatigue, headache and gastrointestinal discomfort. On investigation his ciclosporin level was found to have risen from a range of 150 to 200 nanograms/mL up to 580 nanograms/mL, and his saquinavir AUC was increased 4.3-fold (by comparison with subjects not taking ciclosporin). His ciclosporin dose was reduced by 50% from 150 mg twice daily to 75 mg twice daily, and his saquinavir dose was reduced to 600 mg three times daily, which resulted in ciclosporin levels similar to those achieved previously.[6]

Mechanism

All protease inhibitors can inhibit the cytochrome P450 isoenzyme CYP3A4 to varying degrees, see 'Antivirals', (p.913). Ciclosporin is extensively metabolised by CYP3A4, so any inhibition of this isoenzyme is likely to increase ciclosporin levels. Ciclosporin is also a modest inhibitor of CYP3A4 and P-glycoprotein, which may explain the raised nelfinavir and saquinavir levels.

Importance and management

An established interaction. The inhibition of ciclosporin metabolism by protease inhibitors may lead to marked increases in ciclosporin levels. Therefore ciclosporin levels should be carefully monitored and the dose adjusted accordingly during concurrent use, bearing in mind that large dose reductions may be required in some patients. The dose reductions needed in the various case reports have been 80 to 95% for ritonavir-boosted regimens, 85% for nelfinavir or indinavir, 67% for fosamprenavir and 50% for saquinavir. The clinical significance of the effects of ciclosporin on saquinavir or nelfinavir pharmacokinetics is unclear, but in one study the effect was not sustained.

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Ciclosporin + Proton pump inhibitors

Omeprazole does not normally appear to affect ciclosporin levels, but there is an isolated report of doubled ciclosporin levels in one patient, and, conversely, more than halved ciclosporin levels in another. Pantoprazole does not appear to affect ciclosporin levels.

Clinical evidence

(a) Omeprazole

In a placebo-controlled study, ten kidney transplant patients had no clinically or statistically significant changes in trough ciclosporin levels when given omeprazole 20 mg daily for 2 weeks.[1] Eight kidney transplant patients given omeprazole 20 mg daily for 6 days similarly had no significant changes in ciclosporin levels when compared with control patients not taking omeprazole.[2] No significant changes in ciclosporin levels were seen in another kidney transplant patient when omeprazole 20 mg daily was given for 8 weeks.[3]

However, in one retrospective analysis, the dose of ciclosporin required to give a specific level was 28% lower in 21 patients taking omeprazole (dose not stated), when compared with 139 patients not taking omeprazole.[4] There is also a case in which the ciclosporin blood levels of a liver transplant patient roughly doubled (from a range of 187 to 261 nanograms/mL up to 510 nanograms/mL) about 2 weeks after omeprazole 40 mg daily was started. His ciclosporin levels were readjusted by reducing the dose from 130 to 80 mg twice daily. The levels then remained steady at about 171 nanograms/mL for the following 4 months.[5] In contrast, the serum ciclosporin levels of a bone marrow transplant patient fell from 254 nanograms/mL to about 100 nanograms/mL over 14 days in the presence of omeprazole 40 mg daily. The ciclosporin levels increased rapidly when omeprazole was stopped.[6]

(b) Pantoprazole

Two studies in kidney transplant patients found that pantoprazole 40 mg daily did not affect ciclosporin blood levels when given in the evening,[7] or when both drugs were given together in the morning.[8]

Mechanism

Not understood.

Importance and management

There is good evidence that omeprazole 20 mg daily does not alter the pharmacokinetics of ciclosporin, and also evidence that pantoprazole 40 mg daily does not interact. There is no explanation for the opposite findings (an increase or decrease in ciclosporin levels) from the two isolated case reports in patients given omeprazole 40 mg daily. The concurrent use of ciclosporin and these proton pump inhibitors need not be avoided, but it may be prudent to consider the possibility of an interaction if patients taking higher doses of omeprazole have otherwise unexplained changes in ciclosporin levels..

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Ciclosporin + Pyrazinamide

Pyrazinamide does not normally appear to interact with ciclosporin, but one isolated report suggests that it may possibly have contributed to the effects of rifampicin in one patient, which resulted in lowered ciclosporin levels. Another patient developed toxic myopathy, which was attributed to the use of pyrazinamide with ciclosporin.

Clinical evidence, mechanism, importance and management

A number of reports mention that anti-tuberculosis regimens containing pyrazinamide and without rifampicin, do not appear to alter ciclosporin levels in kidney transplant patients, and some are cited as examples.[1-3] These regimens frequently consisted of combinations of pyrazinamide, ethambutol, isoniazid and streptomycin. In one early report, a 12-year-old girl with a kidney transplant taking ciclosporin and prednisolone had a rejection episode while taking rifampicin and isoniazid, apparently due to the fall in serum ciclosporin levels caused by the rifampicin. The rejection settled when the rifampicin was replaced by pyrazinamide.[1] However, an anecdotal report suggested that when pyrazinamide was given with rifampicin and isoniazid it appeared to add to the effects of the rifampicin causing an additional reduction in ciclosporin blood levels.[4] Another report attributed the development of toxic myopathy in a kidney transplant patient to the concurrent use of pyrazinamide and ciclosporin.[5]

There would seem to be no reason for avoiding pyrazinamide in patients taking ciclosporin, but be aware of these rare complications.

1. Coward RA, Raftery AT, Brown CB. Cyclosporin and antituberculous therapy. *Lancet* (1985) i, 1342–3.
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3. Vachharajani TJ, Oza UG, Phadke AG, Kirpalani AL. Tuberculosis in renal transplant recipients: rifampicin sparing treatment protocol. *Int Urol Nephrol* (2002) 34, 551–3.
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Ciclosporin + Quinine

An isolated case suggests that quinine reduces ciclosporin levels.

Clinical evidence, mechanism, importance and management

A man with a kidney transplant and mild cerebral falciparum malaria had a gradual decrease in his ciclosporin blood levels, from 328 nanograms/mL to 107 nanograms/mL over 7 days, when he was given quinine 600 mg every 8 hours. A gradual rise in the ciclosporin levels occurred when the quinine was stopped.[1]

The reason for this apparently isolated report is unclear and its general importance is unknown. There is insufficient evidence to recommend

increased monitoring, but be aware of the potential for an interaction in the case of an unexpected response to treatment. The effects of lower quinine doses used for cramps are unclear.

1. Tan HW, Ch'ng SL. Drug interaction between cyclosporine A and quinine in a renal transplant patient with malaria. *Singapore Med J* (1991) 32, 189–90.

Ciclosporin + Red yeast rice (*Monascus purpureus*)

Red yeast rice has been reported to cause rhabdomyolysis in a kidney transplant patient taking ciclosporin.

Clinical evidence, mechanism, importance and management

A kidney transplant patient taking ciclosporin 300 mg daily developed asymptomatic rhabdomyolysis when she started to take a herbal preparation of red yeast rice containing rice fermented with red yeast, beta-sitosterol, danshen root (*Salvia mitorriza*) and garlic bulb (*Allium sativum*). Two months later, her creatine phosphokinase rose to 1050 units/L but reduced to 600 units/L 2 weeks after stopping the herbal preparation. It is thought that a component of the red yeast rice called monacolin K (identical to lovastatin) probably caused the muscle toxicity.[1] Although this appears to be an isolated case it would be expected to be generally significant as ciclosporin is well known to interact with the statins, and this interaction appeared to be mediated by a statin-like component. Concurrent use need not be avoided, but it would seem prudent to discuss the potential effects with patients and describe the symptoms of myopathy. Patients should report any unexplained muscle pain, tenderness or weakness.

1. Prasad GVR, Wong T, Meliton G, Bhaloo S. Rhabdomyolysis due to red yeast rice (*Monascus purpureus*) in a renal transplant recipient. *Transplantation* (2002) 74, 1200–1.

Ciclosporin + Retinoids

An increase in ciclosporin blood levels in one patient was attributed in part to starting etretinate. Two patients had an increase in their ciclosporin levels while taking isotretinoin, although in neither case was this attributed to an interaction. Another patient taking both drugs had no alteration in ciclosporin levels.

Clinical evidence

(a) Etretinate

In one case, a woman with generalised pustular psoriasis taking ciclosporin 200 mg daily had a considerable rise in her ciclosporin blood levels from 176 micrograms/L to 540 micrograms/L 7 days after the ciclosporin dose was increased to 300 mg daily and 3 days after etretinate 50 mg daily was added. An interaction was suspected as contributing to this effect because it was found possible to reduce the ciclosporin dose gradually to 150 mg daily (accompanied by a fall in the trough ciclosporin blood levels to 168 micrograms/L), without any loss in the control of the disease.[1] In small studies or case reports, etretinate has been considered to have a ciclosporin-sparing effect,[2-4] or to have modest or no additional benefit.[5,6].

(b) Isotretinoin

A 27-year old man with a heart transplant taking ciclosporin was given isotretinoin 40 mg daily for 2 months, then 80 mg daily up to 20 weeks. His ciclosporin trough levels remained within the recommended range, and there was no evidence of graft rejection.[7] Another man with a heart transplant taking ciclosporin received isotretinoin 1 mg/kg daily for 4 months. His daily ciclosporin dose was reduced from 7 mg/kg to 6 mg/kg one month after starting isotretinoin because of a rise in ciclosporin level to 587 nanograms/mL. However, it was noted that this may have had nothing to do with the isotretinoin, because the patient required alterations in ciclosporin dose in 3 instances before isotretinoin was started. No laboratory abnormalities or ciclosporin toxicity were seen, and the heart transplant function remained satisfactory.[8] A 13-year-old girl with aplastic anaemia, who was taking ciclosporin, was given isotretinoin 40 mg daily for 20 weeks. She had a threefold increase in her trough ciclosporin level at week 17, which was considered probably unrelated to isotretinoin, and was managed by reducing her ciclosporin dose. Serum lipids did not change during concurrent use.[9]

Mechanism

Uncertain. An *in vitro* study using human liver microsomes found that concentrations of 100 micromol of acitretin, etretinate and isotretinoin inhibited the total ciclosporin metabolism and total primary ciclosporin metabolite production to the same extent (32 to 45%).[1] These figures suggest that the retinoids may inhibit ciclosporin metabolism. However, another *in vitro* study using human liver microsomes did not find that etretinate inhibits the metabolism of ciclosporin.[10]

Importance and management

From the one published case, it is unclear if etretinate has any effect on ciclosporin levels. Similarly, from the cases presented, it is also unclear if isotretinoin alters ciclosporin levels. However, the potential for an interaction cannot entirely be dismissed. Note, that it has been suggested that serum lipids should be monitored if isotretinoin is given with ciclosporin because both drugs can cause an increase in lipids.[7]

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2. Korstanje MJ, Bessems PJMJ, van de Staak WJBM. Combination therapy cyclosporin-etretinate effective in erythrodermic psoriasis. *Dermatologica* (1989) 179, 94.
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10. Webber IR, Back DJ. Effect of etretinate on cyclosporin metabolism *in vitro*. *Br J Dermatol* (1993) 128, 42–4.

Ciclosporin + Sevelamer

Sevelamer did not appear to alter ciclosporin levels in one study; however, a case report describes markedly reduced ciclosporin levels within 6 days of starting sevelamer.

Clinical evidence

In a study in 18 kidney transplant patients taking ciclosporin (with 9 patients also taking mycophenolate), the pharmacokinetics of ciclosporin were unchanged after they took sevelamer as a single 1.6- or 1.2-g dose and when this dose of sevelamer was given three times daily for 4 days.[1] Eight of the patients were children (average age 12 years). The largest change was a 9% decrease in the ciclosporin AUC after 4 days of sevelamer use, but this was not statistically significant. The AUC of one metabolite of ciclosporin, AM1, was reduced by about 30%. In this study, ciclosporin was taken at the same time as sevelamer.[1] In contrast, a transplant patient taking ciclosporin 60 mg daily needed a dose increase to 85 mg daily to maintain ciclosporin levels within about 6 days of starting sevelamer 806 mg three times daily. Her trough ciclosporin level fell from about 79 nanograms/mL, to 62 nanograms/mL on day one, to 42 nanograms/mL on day 3, and then to 35 nanograms/mL on day 6 (figures taken from a graph). When the sevelamer was stopped after 50 days because of gastrointestinal intolerance, ciclosporin levels rose, but then fell again on restarting sevelamer.[2]

Mechanism

Sevelamer may bind with ciclosporin in the gut preventing ciclosporin absorption.[2,3] It may also bind with the ciclosporin metabolite AM1 secreted in the bile, so preventing its reabsorption.[1]

Importance and management

The first study did not find a clinically relevant interaction with 4 days of sevelamer use, but the case report appears to contradict this finding. The reasons for this are unclear. The manufacturers of sevelamer recommend that drugs for which a reduction in bioavailability could be clinically important should be taken at least one hour before or 3 hours after sevelamer, or consideration should be given to monitoring blood levels of these drugs.[4,5] The UK manufacturer specifically names ciclosporin and recommends that close monitoring should be considered both on concurrent use and when sevelamer is stopped.[4] Until more is known, this would appear to be prudent. Further study is required with longer-term administration and to evaluate whether separating doses minimises the extent of the interaction.

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2. Guillen-Ananya M-A, Jadoul M. Drug interaction between sevelamer and cyclosporin. *Nephrol Dial Transplant* (2004) 19, 515.
3. Wauters J-P, Uelinger D, Marti H-P. Drug interaction between sevelamer and cyclosporin. *Nephrol Dial Transplant* (2005) 20, 660–1.
4. Renagel (Sevelamer). Genzyme Therapeutics. UK Summary of product characteristics, July 2009.
5. Renagel (Sevelamer hydrochloride). Genzyme. US Prescribing information, November 2007.

Ciclosporin + Sibutramine

One case report describes an increase in ciclosporin levels when orlistat was stopped and sibutramine started. Ciclosporin is predicted to raise sibutramine levels.

Clinical evidence

A kidney transplant patient taking ciclosporin 100 mg twice daily was changed from orlistat to sibutramine 10 mg daily, as orlistat for 27 months had been unsuccessful. One week later her trough ciclosporin level had increased from 79 nanograms/mL to 152 nanograms/mL and her ciclosporin daily dose was reduced by 25 mg. Her ciclosporin level was still raised one week later (at 162 nanograms/mL) and her ciclosporin daily dose was again reduced by 25 mg. No increase in blood pressure or serum creatinine occurred, and the ciclosporin trough levels remained stable over the following 10 months.[1]

Mechanism

Unknown. The authors propose a mechanism via inhibition of the cytochrome P450 isoenzyme CYP3A4;[1] however, sibutramine is not an inhibitor of this isoenzyme.[2] Note that the UK manufacturer of sibutramine predicts that ciclosporin may lead to an increase in levels of the active metabolites of sibutramine, by inhibiting CYP3A4,[2] although note that ciclosporin is only a modest inhibitor of this isoenzyme.

Importance and management

This appears to be the only case report of an increase in ciclosporin levels with sibutramine, and therefore its general relevance is uncertain. The fact that the patient had previously been taking orlistat, which can markedly reduce ciclosporin levels, raises the possibility that the increase in ciclosporin levels in this case was due to stopping orlistat rather than starting sibutramine, but insufficient information was presented to evaluate this possibility. For further information on the interaction of orlistat with ciclosporin, see 'Ciclosporin + Orlistat', p.1247.

The UK manufacturer of sibutramine recommends caution on the concurrent use of ciclosporin because of the possibility of increased sibutramine levels and adverse effects.[2] Further study is needed.

1. Clerbaux G, Goffin E, Pirson Y. Interaction between sibutramine and cyclosporine. *Am J Transplant* (2003) 3, 906.
2. Reductil (Sibutramine hydrochloride monohydrate). Abbott Laboratories Ltd. UK Summary of product characteristics, October 2007.

Ciclosporin + Somatostatin analogues

Octreotide causes a marked reduction in ciclosporin levels and inadequate immunosuppression may result. Lanreotide is predicted to interact similarly.

Clinical evidence

A diabetic man with kidney and pancreatic segment transplants was successfully immunosuppressed with azathioprine, methylprednisolone and ciclosporin. When he was also given subcutaneous **octreotide** 100 micrograms twice daily to reduce fluid collection around the pancreatic graft, his trough ciclosporin blood levels fell below the assay detection limit of 50 nanograms/mL. Serum creatinine increased dramatically, which was interpreted as a selective rejection episode of the kidney transplant. Nine other patients with diabetes similarly treated with **octreotide** for peripancreatic fluid collection and fistulas after pancreatic transplantation also had significant falls in their ciclosporin blood levels within 24 to 48 hours, in 3 of them to undetectable levels.[1] A similar interaction was seen in another patient.[2]

Mechanism

Uncertain. A suggestion is that the octreotide reduces the intestinal absorption of ciclosporin.[1,2]

Importance and management

The interaction between octreotide and ciclosporin is established and clinically important, although the documentation is limited. The authors of one report recommend that before giving octreotide the oral dose of ciclosporin should be increased on average by 50% and the serum levels monitored daily.[1] The manufacturer of **lanreotide** says that, as with other somatostatin analogues, it may reduce the absorption of ciclosporin from the gut.[3] As yet there appear to be no reports of this interaction in practice; however, it would be prudent to monitor the outcome of the use of lanreotide with ciclosporin.

1. Landgraf R, Landgraf-Leurs MMC, Nusser J, Hillebrand G, Illner W-D, Abendroth D, Land W. Effect of somatostatin analogue (SMS 201–995) on cyclosporine levels. *Transplantation* (1987) 44, 724–5.
2. Rosenberg L, Dafoe DC, Schwartz R, Campbell DA, Turcotte JG, Tsai S-T, Vinik A. Administration of somatostatin analog (SMS 201–995) in the treatment of a fistula occurring after pancreas transplantation. Interference with cyclosporine suppression. *Transplantation* (1987) 43, 764–6.
3. Somatuline LA (Lanreotide acetate). Ipsen Ltd. UK Summary of product characteristics, August 2003.

Ciclosporin + SSRIs

A small study found no evidence of an interaction between fluoxetine and ciclosporin although one case of doubled ciclosporin levels has been seen. One case of increased ciclosporin levels with an increase in serum creatinine has been reported with fluvoxamine. Limited evidence suggests that citalopram, paroxetine and sertraline do not interact. Serotonin syndrome has been seen in one patient taking ciclosporin and sertraline and another taking ciclosporin and escitalopram.

Clinical evidence

(a) Citalopram

In 5 transplant patients the pharmacokinetics of ciclosporin were not significantly affected by citalopram 10 to 20 mg daily.[1]

(b) Escitalopram

An 84-year-old woman with a kidney transplant taking ciclosporin developed delirium associated with hyperthermia 6 months after starting escitalopram, titrated to 15 mg daily, which was attributed to serotonin syndrome. Her condition improved rapidly on stopping escitalopram.[2]

(c) Fluoxetine

A small, retrospective study in 9 liver transplant and 4 heart transplant patients found no evidence that fluoxetine 5 to 20 mg daily increased ciclosporin blood levels.[3] Another patient had just a minimal 7% increase in ciclosporin levels after starting fluoxetine 20 mg daily.[4] However, the ciclosporin blood levels of a heart transplant patient were doubled by fluoxetine 20 mg daily for 10 days. They fell when the ciclosporin dose was reduced and needed to be increased again when fluoxetine was stopped.[5]

(d) Fluvoxamine

A kidney transplant patient had an approximate 60% increase in ciclosporin blood levels, an increase in serum creatinine levels and fine

tremor 2 weeks after starting fluvoxamine 100 mg daily. The ciclosporin dose was subsequently reduced by 33%.[6]

(e) Paroxetine

Two patients had minimal changes in ciclosporin levels (7.5% decrease and a 23% increase) after starting paroxetine 20 mg daily.[4]

(f) Sertraline

A 53-year-old man taking ciclosporin following a kidney transplant developed serotonin syndrome 5 days after starting to take sertraline 50 mg daily. This resolved on stopping the sertraline.[7]

Three patients had just minimal changes in ciclosporin levels (11.5% increase, 10 to 12% decrease, 9 to 17% decrease) after starting sertraline (25 mg daily, 50 to 100 mg daily, 50 mg daily, respectively).[4] One report briefly mentions that a patient taking ciclosporin had her antidepressant medication switched from nefazodone to sertraline, because sertraline did not affect ciclosporin levels.[8]

Mechanism

Fluvoxamine is a minor inhibitor of the cytochrome P450 isoenzyme CYP3A4, the main isoenzyme by which ciclosporin is metabolised. Concurrent use may therefore lead to increased ciclosporin levels. Fluoxetine is considered a weak inhibitor of CYP3A4 and may interact possibly raise ciclosporin levels by this mechanism. Citalopram, paroxetine and sertraline do not usually inhibit CYP3A4, and would therefore not be expected to interact.

Serotonin syndrome is a rare adverse effect, usually, but not always, associated with the use of more than one serotonergic drug (see 'serotonin syndrome', (p.9)). On the basis that ciclosporin has been reported to increase serotonin turnover within the brain in *mice*, the reaction was attributed to an interaction between the SSRIs and ciclosporin in one of the cases described.[7] However, serotonin syndrome has occurred with SSRIs alone, so ciclosporin may not have played any role in these cases.

Importance and management

Evidence is limited. From the one case with fluvoxamine, it appears that this SSRI can cause a clinically significant increase in ciclosporin levels, resulting in an increase in adverse effects. Concurrent use should be closely monitored, or a non-interacting antidepressant used. Fluoxetine has been used without interaction, but in one case, ciclosporin levels were doubled, so some caution would seem prudent. Citalopram, paroxetine and sertraline do not appear to affect ciclosporin levels to a clinically relevant extent, and may therefore be suitable alternatives. Escitalopram, the *S*-isomer of citalopram, would also not be expected to interact.

The relevance of ciclosporin to the occurrence of serotonin syndrome with escitalopram and sertraline in the two cases cited is uncertain.

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2. Lang PO, Hasso Y, Hilleret H, Vogt-Ferrier N. Serotonin syndrome as a result of escitalopram and cyclosporin combination in an 84-year-old woman. Rev Med Interne (2008) 29, 583–6.
3. Strouse TB, Fairbanks LA, Skotzko CE, Fawzy FI. Fluoxetine and cyclosporine in organ transplantation: failure to detect significant drug interactions or adverse clinical events in depressed organ recipients. *Psychosomatics* (1996) 37, 23–30.
4. Markowitz JS, Gill HS, Hunt NM, Monroe RR Jr, DeVane CL. Lack of antidepressant-cyclosporine pharmacokinetic interactions. *J Clin Psychopharmacol* (1998) 18, 91–3.
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Ciclosporin + St John's wort (*Hypericum perforatum*)

Marked reductions in ciclosporin blood levels and transplant rejection can occur within a few weeks of starting St John's wort.

Clinical evidence

A marked fall in ciclosporin blood levels in one kidney transplant patient was identified as being due to the addition of St John's wort extract 300 mg three times daily. When the St John's wort was stopped the ciclosporin levels rose. The authors of this report identified another 35 kidney and 10 liver transplant patients whose ciclosporin levels had fallen by an average of 49% (range 30 to 64%) after starting St John's wort. Two of them had rejection episodes.[1,2] In addition, subtherapeutic ciclosporin levels in 7 kidney transplant patients,[3-7] one liver transplant patient,[8] and 6 heart transplant patients[9-11] have been attributed to self-medication with St John's wort. Acute graft rejection episodes occurred in 7 cases,[3,5,7-9,11] and one patient subsequently developed chronic rejection, requiring a return to dialysis.[5] Another case of subtherapeutic ciclosporin levels occurred in a kidney transplant patient during the concurrent use of a herbal tea containing St John's wort. The patient's ciclosporin levels remained subtherapeutic despite a ciclosporin dose increase from 150 to 250 mg daily. The levels recovered within 5 days of stopping the herbal tea and the ciclosporin dose was reduced to 175 mg daily.[12]

These case reports are supported by a small study in which 11 kidney transplant patients, with stable dose requirements for ciclosporin, were given St John's wort extract (*Jarsin 300*) 600 mg daily for 14 days. Pharmacokinetic changes were noted 3 days after the St John's wort was added. By day 10 the ciclosporin dose had to be increased from an average of 2.7 to 4.2 mg/kg daily in an attempt to keep ciclosporin levels within the therapeutic range. Two weeks after the St John's wort was stopped, only 3 patients had been successfully re-stabilised on their baseline ciclosporin dose. Additionally, the pharmacokinetics of various ciclosporin metabolites were substantially altered.[13]

Another study in 10 kidney transplant patients stable taking ciclosporin found that the content of hyperforin in the St John's wort affected the extent of the interaction with ciclosporin. In patients taking St John's wort with a high hyperforin content (hyperforin 7 mg; hypericin 0.45 mg) the reduction in the $AUC_{0\text{-}12}$ of ciclosporin was 45% greater than that in patients taking St John's wort with a low hyperforin content (hyperforin 0.1 mg; hypericin 0.45 mg). The maximum blood ciclosporin level and the trough ciclosporin level were also reduced by 36% and 45%, respectively, in the patients taking the higher hyperforin-containing St John's wort preparation, when compared with the patients taking the preparation with a lower hyperforin content. The patients taking the high-hyperforin preparation required a mean ciclosporin dose increase of 65% whereas the patients taking the low-hyperforin preparation did not require any ciclosporin dose alterations.[14]

Mechanism

St John's wort is a known inducer of the cytochrome P450 isoenzyme CYP3A4 by which ciclosporin is metabolised. Concurrent use therefore reduces ciclosporin levels. It has also been suggested that St John's wort affects ciclosporin reabsorption by inducing the drug transporter protein, P-glycoprotein, in the intestine.[9,13]

Importance and management

An established and clinically important interaction. The incidence is not known, but all transplant patients taking ciclosporin should avoid St John's wort because of the potential severity of this interaction. Transplant rejection can develop within 3 to 4 weeks. It is possible to accommodate this interaction by increasing the ciclosporin dose[11] (possibly about doubled) but this raises the costs of an already expensive drug. Also, the varying content of natural products would make this hard to monitor. The advice of the CSM in the UK is that patients receiving ciclosporin should avoid or stop taking St John's wort. In the latter situation, the ciclosporin blood levels should be well monitored and the dose adjusted as necessary.[15] The study described above suggests that increased monitoring will be needed for at least 2 weeks after the St John's wort is stopped.[13] There appears to be no information on the clinical relevance of this interaction in patients taking ciclosporin for reasons other than immunosuppression following transplantation. Nevertheless, because of the large reduction in ciclosporin levels seen, treatment failure seems likely, and therefore it would also seem prudent for these patient to avoid the use of St John's wort.

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2. Breidenbach T, Kliem V, Burg M, Radermacher J, Hoffmann MW, Klempnauer J. Profound drop of cyclosporin A whole blood trough levels caused by St John's wort (Hypericum perforatum). *Transplantation* (2000) 69, 2229–30.
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6. Moschella PA-C, Jaber BL. Interaction between cyclosporine and Hypericum perforatum (St John's wort) after organ transplantation. *Am J Kidney Dis* (2001) 38, 1105–7.
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Ciclosporin + Sucrose polyesters

Sucrose polyesters (e.g. *Olestra*) may modestly reduce the bioavailability and peak levels of ciclosporin.

Clinical evidence, mechanism, importance and management

In a study in 7 kidney transplant patients aged 9 to 18 years, a single 0.35-g/kg dose (maximum of 16 g) of sucrose polyesters (*Olestra*), reduced the ciclosporin AUC and peak levels by almost 19% and 27%, respectively, when taken at the same time as the usual dose of ciclosporin (*Neoral*). Ciclosporin trough levels and elimination rate were not affected by sucrose polyesters.[1] The reduced bioavailability was thought to be due to sucrose polyesters reducing the absorption of ciclosporin. Sucrose polyesters (*Olestra*) is marketed as a non-absorbable, non-calorific fat ingredient in snack foods. The authors note that it is mainly consumed by children and adolescents, with the age group of 13 to 17-year-olds being reported to eat 16.2 g of *Olestra* per snack, and therefore this interaction could be of particular significance for young transplant patients taking ciclosporin.[1] However, note that changes in the AUC of ciclosporin of this size are very modest.

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Ciclosporin + Sulfasalazine

An isolated report describes elevated ciclosporin levels in a kidney transplant patient that developed when sulfasalazine was stopped.

Clinical evidence, mechanism, importance and management

A patient with a kidney transplant was taking azathioprine, ciclosporin, prednisone and sulfasalazine 1.5 g daily. After initial adjustments the dose of ciclosporin remained at 480 mg daily for 8 months. The dose of prednisone was reduced and treatment stopped at 8 months, and azathioprine was stopped at 12 months, without any need to adjust the ciclosporin dose. However, when sulfasalazine was stopped 13.5 months after transplantation, the mean ciclosporin level increased from 205 nanograms/mL to 360 nanograms/mL within 5 days, and to 389 nanograms/mL after 10 days. The ciclosporin dose was reduced over the following 2 months from 9.6 mg/kg to 5.6 mg/kg to maintain blood levels at about 200 nanograms/mL.[1] The mechanism for this interaction is not understood, although the time course of the interaction, noted after 5 days, probably excludes decreased absorption.

Information appears to be limited to this isolated case report. There is insufficient evidence to recommend increased monitoring in all patients, but be aware of the potential for an interaction in the case of an unexpected response to treatment.

1. Du Cheyron D, Debruyne D, Lobbedez T, Richer C, Ryckelynck J-P, Hurault de Ligny B. Effect of sulfasalazine on cyclosporin blood concentration. *Eur J Clin Pharmacol* (1999) 55, 227–8.

Ciclosporin + Sulfinpyrazone

Sulfinpyrazone can reduce ciclosporin levels, and episodes of transplant rejection have occurred as a result of this interaction.

Clinical evidence

A study in 120 heart transplant patients found that sulfinpyrazone 200 mg daily was effective in the treatment of hyperuricaemia. The mean uricaemia over 4 to 8 months fell by 22% (from 0.51 to 0.4 mmol/L) but unexpectedly the mean trough ciclosporin levels fell by 39% (from 183 to 121 micrograms/L) despite a 7.7% increase in the ciclosporin daily dose. Two of the patients developed rejection: one after 4 months of taking sulphinpyrazone when the ciclosporin levels fell to 50 micrograms/L, and the other after 7 months of taking sulfinpyrazone, when the ciclosporin levels fell to 20 micrograms/L.[1]

Another report describes a patient who needed unusually high doses of ciclosporin while taking sulfinpyrazone,[2] while yet another report describes *increased* ciclosporin levels in a patient taking sulfinpyrazone. In this latter case there is the possibility that the findings may have been an artefact due to interference with the assay method.[3]

Mechanism

Not understood.

Importance and management

Information appears to be limited to these reports, but the interaction would seem to be established and clinically important. If sulfinpyrazone is added to established treatment with ciclosporin, be alert for the need to raise the ciclosporin dose. The mean fall in trough ciclosporin levels seen in the major study cited was 39%.[1] This study does comment on how quickly this interaction develops, but the two cases of transplant rejection occurred after 4 months and 7 months, which implies that it can possibly be slow. Long-term monitoring would therefore be a prudent precaution.

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Ciclosporin + Terbinafine

Terbinafine does not appear to have a clinically significant effect on ciclosporin levels in most patients.

Clinical evidence

In a study in 20 healthy subjects, terbinafine 250 mg daily for 6 to 7 days decreased the mean AUC of a single 300-mg dose of ciclosporin by 13% and decreased its maximum blood level by 14%. It was suggested that as the *Sandimmun* formulation was used in the study, inter- and intra-individual variations in ciclosporin absorption caused these differences, rather than any drug interaction.[1] This study has been briefly reported elsewhere.[2] Another study in 11 patients with kidney, heart or lung transplants found that terbinafine 250 mg daily for 12 weeks caused a small but clinically irrelevant decrease in serum ciclosporin levels.[3] Similarly, another study in 30 kidney transplant patients taking ciclosporin and given terbinafine 250 mg daily for 6 to 12 weeks found no significant interaction and none of the patients required ciclosporin dose changes.[4] However, in another report in 4 kidney transplant patients taking ciclosporin, ciclosporin levels were reduced when they were given terbinafine 250 mg daily for fungal skin and nail infections. In 3 of the patients, ciclosporin levels remained within the therapeutic range and therefore no dose adjustment was needed. In the remaining patient, an increase in the ciclosporin dose was required to maintain levels within the therapeutic range, and then a reduction in the ciclosporin dose was needed on stopping terbinafine.[5]

Mechanism

These studies broadly confirm previous *in vitro* work with human liver microsomal enzymes, which found that terbinafine either does not inhibit or causes only modest inhibition of ciclosporin metabolism.[6-8]

Importance and management

In general, the changes in the pharmacokinetics of ciclosporin seen with terbinafine are not clinically unimportant. However, it may be prudent to bear the possibility of an interaction in mind, particularly in patients whose ciclosporin levels are at the lower end of the therapeutic range.

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Ciclosporin + Ticlopidine

Three case reports describe marked falls in ciclosporin levels, and one study noted that trough ciclosporin levels were halved by ticlopidine. However, the interaction was not confirmed in a later randomised, controlled study.

Clinical evidence

The ciclosporin blood levels of a patient with nephrotic syndrome were roughly halved on two occasions when he was given ticlopidine 500 mg daily.[1] Another two patients with kidney transplants had similar falls (one patient on two occasions) when ticlopidine 250 mg or 500 mg daily was given.[2,3] In one of these cases, there was a progressive decrease in ciclosporin levels during 4 months of ticlopidine use, requiring an progressive increase in the ciclosporin dose after 2 months of concurrent use. When aspirin was substituted for ticlopidine, ciclosporin levels rose, and the ciclosporin dose was reduced.[3] Similar findings were reported in an uncontrolled study in 12 heart transplant patients taking ciclosporin, who were given ticlopidine 250 mg twice daily. After 3 months, the mean whole blood trough ciclosporin levels were noted to be halved from 136 nanograms/mL to 72 nanograms/mL, without a change in the mean ciclosporin dose. One case of acute rejection occurred, with a ciclosporin level of 74 nanograms/mL.[4] However, in a randomised, placebo-controlled study by the same group in 20 heart transplant patients, the pharmacokinetics of ciclosporin were not altered by ticlopidine at the lower dose of 250 mg daily for 14 days. The mean decrease in trough level and AUC of ciclosporin were 20% and 14%, respectively, which was not statistically significant. Nevertheless, one patient was withdrawn from the study after 3 days because of a 60% fall in ciclosporin levels.[5]

Mechanism

Not understood.

Importance and management

Information appears to be limited to the reports cited, and the reason for the marked difference between the controlled study and the other study and reports is not certain. However, the controlled study used a low dose of ticlopidine and just 2 weeks of concurrent use, whereas in the other study and reports the interaction was noted after a few months of concurrent use. For this reason, it would be prudent to closely monitor ciclosporin levels, both when ticlopidine is first added, and for the first few months of concurrent use.

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2. Verdejo A, de Cos MA, Zubimendi JA. Probable interaction between cyclosporin A and low dose ticlopidine. *BMJ* (2000) 320, 1037.
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4. de Lorgeril M, Boissonnat P, Dureau G, Guidollet J, Renaud S. Evaluation of ticlopidine, a novel inhibitor of platelet aggregation, in heart transplant recipients. *Transplantation* (1993) 55, 1195–6.
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Ciclosporin + Trimetazidine

Trimetazidine does not appear to alter the pharmacokinetics or immunosuppressive effects of ciclosporin.

Clinical evidence, mechanism, importance and management

In a study in 12 kidney transplant patients taking ciclosporin, trimetazidine 40 mg twice daily for 5 days caused no changes in the pharmacokinetics of ciclosporin, and there were no alterations in interleukin-2 concentrations or soluble interleukin-2 receptors.[1] An associated study by the same group of workers using two models (the lymphoproliferative response of normal human lymphocytes to phytohaemagglutinin and a delayed *mouse* hypersensitivity model), similarly found that trimetazidine did not interfere with the effects of ciclosporin.[2] It was concluded on the basis of these two studies that the concurrent use of ciclosporin and trimetazidine need not be avoided.

1. Simon N, Brunet P, Roumenov D, Dussol B, Barre J, Duche JC, Albengres E, D'Athis Ph, Crevat A, Berland Y, Tillement JP. The effects of trimetazidine-cyclosporin A coadministration on interleukin 2 and cyclosporin A blood levels in renal transplant patients. *Therapie* (1995) 50 (Suppl), 498.
2. Albengres E, Tillement JP, d'Athis P, Salducci D, Chauvet-Monges AM, Crevat A. Lack of pharmacodynamic interaction between trimetazidine and cyclosporin A in human lymphoproliferative and mouse delayed hypersensitivity response models. *Fundam Clin Pharmacol* (1996) 10, 264–8.

Ciclosporin + Vitamins

In two studies, ciclosporin levels were increased by vitamin E in a water-soluble formulation, while in another study vitamin E modestly decreased the ciclosporin AUC. Other studies have also found modestly reduced ciclosporin levels with vitamin E combined with vitamin C, with or without betacarotene.

Clinical evidence

(a) Vitamin E alone

Ten healthy subjects were given a single 10-mg/kg oral dose of ciclosporin (*Sandimmun* formulation) with and without a 0.1-mL/kg oral dose of vitamin E (d-alpha tocopheryl polyethylene glucose 1000 succinate; *Liqui-E*). The AUC of the ciclosporin increased by 60%.[1] In a further study in liver transplant patients, this same formulation of vitamin E (*Liqui-E*) decreased the required dose of oral ciclosporin [probably the *Sandimmun* formulation] by 28% in 19 adults and 32% in 7 children.[2]

In contrast, another study in 12 healthy subjects found that vitamin E (ACO, Sweden) 800 units daily for 6 weeks modestly reduced the AUC of a single 5-mg/kg dose of ciclosporin (*Neoral* formulation) by 21%. In this study, vitamin E did not significantly attenuate the transient reduction in renal plasma flow and glomerular filtration rate (GFR) seen with ciclosporin.[3]

(b) Vitamin E with Vitamin C

A study in 10 kidney transplant patients taking ciclosporin found that the addition of an antioxidant vitamin supplement (product not specified) for 6 months containing vitamin C 500 mg, vitamin E 400 units and **betacarotene** (vitamin A precursor) 6 mg daily reduced the ciclosporin blood level by 24%. An associated improvement in renal function, indicated by an increase in glomerular filtration rate of 17%, was also seen and may have been associated with reduced ciclosporin levels.[4] In a placebo-controlled study in 56 kidney transplant patients taking ciclosporin with vitamin C 1 g daily and vitamin E 300 mg daily, trough ciclosporin levels were

decreased in the group given vitamins, when compared with the placebo group (14 micrograms/L decrease compared with 10 micrograms/L increase, respectively, from baseline values). A reduction in serum creatinine was also seen.[5] Similarly, in a retrospective study of 22 heart transplant patients, vitamin E 400 units twice daily with vitamin C 500 mg twice daily taken at the same time as ciclosporin, decreased trough ciclosporin levels by about 28%. The reduction in levels was more marked in the 6 patients taking the *Sandimmun* preparation than in the 16 patients taking the *Neoral* preparation, but the difference was not statistically significant (42% versus 25%).[6]

Mechanism

Unknown. The formulation of the vitamin E and of the ciclosporin appears to affect the interaction, suggesting that reduction in levels occurs as a result of altered absorption.

Importance and management

The clinical significance of these studies is unclear, and there appear to be no published case reports of any adverse effects due to this interaction. However, in some patients, changes in ciclosporin levels may significantly affect immunosuppression, and dose modification may be required. If vitamin E and C are used in transplant patients taking ciclosporin, ciclosporin levels should be well monitored. In addition, it may be prudent to question patients about their intake of vitamin supplements before starting or when taking ciclosporin, particularly if a sudden or unexplained reduction in stable ciclosporin levels occurs. More study is needed, particularly with regard to the concurrent use of standard, commercially available multivitamin preparations, which generally contain much lower doses of vitamin C and E than described here.

1. Chang T, Benet LZ, Hebert MF. The effect of water-soluble vitamin E on cyclosporine pharmacokinetics in healthy volunteers. *Clin Pharmacol Ther* (1996) 59, 297–303.
2. Pan SH, Lopez RR Jr, Sher LS, Hoffman AL, Podesta LG, Makowka L, Rosenthal P. Enhanced oral cyclosporine absorption with water-soluble vitamin E early after liver transplantation. *Pharmacotherapy* (1996) 16, 59–65.
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4. Blackhall ML, Fassett RG, Sharman JE, Geraghty DP, Coombes JS. Effects of antioxidant supplementation on blood cyclosporin A and glomerular filtration rate in renal transplant recipients. *Nephrol Dial Transplant* (2005) 20, 1970–75.
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Corticosteroids + Aminoglutethimide

The effects of dexamethasone, but not hydrocortisone, can be reduced or abolished by aminoglutethimide.

Clinical evidence

(a) Dexamethasone

In a study in 6 patients, aminoglutethimide 500 to 750 mg daily reduced the half-life of dexamethasone 1 mg from 264 to 120 minutes.[1] In another 22 patients it was found that larger doses of dexamethasone (1.5 to 3 mg daily) compensated for the increased dexamethasone metabolism caused by aminoglutethimide and complete adrenal suppression was achieved over a prolonged period.[1] Another study found a fourfold increase in dexamethasone clearance in 10 patients taking aminoglutethimide 1 g daily.[2]

A patient, dependent on dexamethasone due to brain oedema caused by a tumour, deteriorated rapidly, with headache and lethargy, when aminoglutethimide was also given. The problem was solved by withdrawing the aminoglutethimide and temporarily increasing the dexamethasone dosage from 6 to 16 mg daily.[3]

(b) Hydrocortisone

One study found that aminoglutethimide did not affect the response to hydrocortisone, and that hydrocortisone 40 mg was adequate replacement therapy in patients taking aminoglutethimide 1 g daily. In this study, aminoglutethimide did not affect the half-life of ^{3}H-cortisol, which suggests that it does not affect hydrocortisone metabolism.[2] Hydrocortisone 30 mg daily is normally adequate replacement in patients taking aminoglutethimide.[4]

Mechanism

Aminoglutethimide is an enzyme inducer and it seems likely that it interacts with dexamethasone by increasing its hepatic metabolism and clearance, thereby reducing its effects.[5]

Importance and management

Information is limited but the interaction between dexamethasone and aminoglutethimide is established. The reduction in the serum corticosteroid levels can be enough to reduce or even abolish the effects of corticosteroid replacement therapy,[1] or to cause the loss of control of a disease condition.[3] This has been successfully accommodated by increasing the dosage of the dexamethasone. Hydrocortisone is routinely used with aminoglutethimide as replacement therapy, and would seem to be a suitable alternative to dexamethasone, where clinically appropriate. Other synthetic corticosteroids are predicted to interact in the same way as dexamethasone, but this needs confirmation.

1. Santen RJ, Lipton A, Kendall J. Successful medical adrenalectomy with amino-glutethimide. Role of altered drug metabolism. *JAMA* (1974) 230, 1661–5.
2. Santen RJ, Wells SA, Runić S, Gupta C, Kendall J, Rudy EB, Samojlik E. Adrenal suppression with aminoglutethimide. I. Differential effects of aminoglutethimide on glucocorticoid metabolism as a rationale for use of hydrocortisone. *J Clin Endocrinol Metab* (1977) 45, 469–79.
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4. Cytadren (Aminoglutethimide). Novartis Pharmaceuticals Corporation. US Prescribing information, March 2002.
5. Santen RJ, Brodie AMH. Suppression of oestrogen production as treatment of breast carcinoma: pharmacological and clinical studies with aromatase inhibitors. *Clin Oncol* (1982) 1, 77–130.

Corticosteroids + Antacids

The absorption of prednisone, and probably prednisolone, can be reduced by large doses of aluminium/magnesium hydroxide antacids; small doses of antacid do not appear to interact. Dexamethasone absorption is reduced by magnesium trisilicate.

Clinical evidence

(a) Dexamethasone

In 6 healthy subjects, **magnesium trisilicate** 5 g in 100 mL of water considerably reduced the bioavailability of a single 1-mg oral dose of dexamethasone. Using the urinary excretion of 11-hydroxycorticosteroids as a measure, the reduction in bioavailability was about 75%.[1]

(b) Prednisolone

A study in 8 healthy subjects given a single 20-mg dose of prednisolone found that 30 mL of **Magnesium Trisilicate Mixture BP** or *Aludrox* (**aluminium hydroxide gel**) caused small changes in peak prednisolone levels and absorption, but these did not reach statistical significance. However, one subject given **magnesium trisilicate** had considerably reduced prednisolone levels.[2] **Aluminium phosphate** has also been found not to affect prednisolone absorption.[3,4]

(c) Prednisone

In a study in 5 patients and 2 healthy subjects, *Gastrogel* (**aluminium/magnesium hydroxide** and **magnesium trisilicate**) 20 mL had no significant effect on the serum levels, half-life or AUC of prednisone 10 or 20 mg.[5] In contrast, another study in healthy subjects and patients given 60 mL of *Aldrox* or *Melox* (both containing **aluminium/magnesium hydroxide**) found that the bioavailability of prednisone 10 mg was reduced by 30% on average, and even by 40% in some individuals.[6]

Mechanism

The reduction in dexamethasone absorption is attributed to adsorption onto the surface of the magnesium trisilicate.[1,7]

Importance and management

Information seems to be limited to these studies. The indication is that large doses of some antacids can reduce the bioavailability of corticosteroids, but small doses do not, although this needs confirmation. One man-

ufacturer of dexamethasone suggests that the doses of antacid should be spaced as far as possible from the dexamethasone dose,[8] while another suggests an interval of at least 2 hours.[9] In other similar antacid interactions 2 to 3 hours is usually sufficient. The manufacturer of **deflazacort** also suggests an interval of at least 2 hours between giving deflazacort and an antacid.[10] Concurrent use should be monitored to confirm that the therapeutic response is adequate. Information about the interaction of other corticosteroids and antacids is lacking.

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8. Dexamethasone Tablets. Organon Laboratories Ltd. UK Summary of product characteristics, March 2008.
9. Dexsol Oral Solution (Dexamethasone sodium phosphate). Rosemont Pharmaceuticals Ltd. UK Summary of product characteristics, March 2008.
10. Calcort (Deflazacort). Shire Pharmaceuticals Ltd. UK Summary of product characteristics, February 2008.

Corticosteroids + Antithyroid drugs

Prednisolone clearance is increased by the use of carbimazole or thiamazole.

Clinical evidence

A comparative study was conducted in three groups of euthyroid women:

Group 1 – eight women taking **levothyroxine** with **thiamazole** 2.5 mg daily or **carbimazole** 5 mg daily for Graves' ophthalmology,

Group 2 – six women taking **levothyroxine** who had undergone subtotal thyroidectomy for Graves' disease, and

Group 3 – six healthy women.

It was found that the clearance of a 540-microgram/kg dose of intravenous **prednisolone** in those in group 1 was much greater than in groups 2 and 3 (0.37, 0.24 and 0.2 L/h.kg, respectively). After 6 hours the plasma **prednisolone** levels in group 1 were only about 10% of those in the healthy women (group 3) and were undetectable after 8 hours, whereas total and unbound **prednisolone** levels were much higher and measurable over the 10 hour study period in those women who had not taken **thiamazole** or **carbimazole**.[1] In another group of previously hyperthyroid patients, now euthyroid because of **carbimazole** treatment, the total **prednisolone** clearance was 0.4 L/hour.[1]

Mechanism

Not established. It seems possible that thiamazole and carbimazole increase the metabolism of prednisolone by the liver microsomal enzymes, thereby increasing its clearance.

Importance and management

Direct information seems to be limited to this study, although the authors point out that there is a clinical impression that higher doses of prednisolone are needed in patients with Graves' disease. Be alert for the need to use higher doses of prednisolone in patients taking either thiamazole or carbimazole. Also note that a hypothyroid state may increase corticosteroid effects, and thus corticosteroids are cautioned in hypothyroid patients.

1. Legler UF. Impairment of prednisolone disposition in patients with Graves' disease taking methimazole. *J Clin Endocrinol Metab* (1988) 66, 221–3.

Corticosteroids + Aprepitant

In the short term, aprepitant (and therefore fosaprepitant) increases the plasma levels of dexamethasone and methylprednisolone.

Clinical evidence

(a) Dexamethasone

In a crossover study in 20 healthy subjects, aprepitant 125 mg on day one and 80 mg on days 2 to 5, given with a standard dexamethasone regimen (20 mg on day one, and 8 mg on days 2 to 5) increased the dexamethasone AUC 2.2-fold. When the same dose of aprepitant was given with a reduced-dose dexamethasone regimen (12 mg on day one, and 4 mg on days 2 to 5), the AUC of dexamethasone was similar to that seen with the standard dexamethasone regimen given alone. All regimens in this study also included intravenous ondansetron 32 mg, given on day one.[1]

(b) Methylprednisolone

In a crossover study in 10 healthy subjects, aprepitant 125 mg on day one and 80 mg on days 2 and 3, given with a methylprednisolone regimen (125 mg intravenously on day one, and 40 mg orally on days 2 and 3), increased the AUC of methylprednisolone 1.3-fold on day one and 2.5-fold on day 3.[1]

Mechanism

Aprepitant is a moderate inhibitor of the cytochrome P450 isoenzyme CYP3A4, and probably raises levels of these corticosteroids in the short term, by inhibiting their metabolism via CYP3A4. However, aprepitant is also a mild inducer of CYP3A4 with a transient effect that may only become apparent after the end of treatment with aprepitant. The maximal effect is seen 3 to 5 days after stopping treatment and is clinically insignificant within 2 weeks, see 'Benzodiazepines + Aprepitant', p.840.

Importance and management

An established interaction of clinical importance. The manufacturers[2,3] recommend that the usual dose of dexamethasone should be reduced by about 50% when given with aprepitant (although note that the dose given in the manufacturer's dexamethasone/aprepitant antiemetic regimen accounts for the interaction). The manufacturers also recommend that the usual dose of intravenous methylprednisolone should be reduced by approximately 25%, and the usual oral dose by approximately 50%, when given with aprepitant. However, the manufacturer[2] also notes that during continuous treatment with methylprednisolone, corticosteroid levels may be expected to *decrease* at later time points within 2 weeks of starting aprepitant and the effect is expected to be greater if methylprednisolone is given orally rather than intravenously.

Fosaprepitant is a prodrug of aprepitant, and therefore similar precautions are appropriate in the presence of these corticosteroids.

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2. Emend (Aprepitant). Merck Sharp & Dohme Ltd. UK Summary of product characteristics, July 2009.
3. Emend (Aprepitant). Merck & Co., Inc. US Prescribing information, July 2009.

Corticosteroids + Azathioprine

In a study in 11 subjects, a single dose of azathioprine did not appear to affect the pharmacokinetics of prednisolone given as a single oral dose of prednisone.[1]

1. Frey FJ, Lozada F, Guentert T, Frey BM. A single dose of azathioprine does not affect the pharmacokinetics of prednisolone following oral prednisone. *Eur J Clin Pharmacol* (1981) 19, 209–12.

Corticosteroids + Azoles; Itraconazole

There is some evidence to suggest that itraconazole can increase the levels and/or effects of inhaled budesonide, fluticasone, the active metabolite of ciclesonide, deflazacort, dexamethasone and methylprednisolone, and, to a lesser extent, prednisolone and prednisone. A few case reports describe the development of secondary Cushing's syndrome in patients taking itraconazole with budesonide, fluticasone or deflazacort.

Clinical evidence

(a) Budesonide

A 70-year-old patient receiving long-term treatment for asthma, which included inhaled budesonide 1.2 to 1.6 mg daily, developed Cushing's syndrome after taking itraconazole 200 mg twice daily for 8 weeks for a fungal infection of the skin and subcutaneous tissues. Corticosteroid levels may already have been increased as the patient was also taking 'diltiazem', (p.1261), with the effects becoming more pronounced after starting itraconazole. Budesonide and itraconazole were discontinued but she subsequently required long-term oral hydrocortisone for secondary adrenal insufficiency.[1]

Two other reports describe the development of Cushing's syndrome in patients with cystic fibrosis given inhaled budesonide, and then itraconazole for bronchopulmonary aspergillosis.[2] One patient was also taking clarithromycin, which may have contributed to the increased budesonide effects (see 'Corticosteroids + Macrolides', p.1264). The other patient was a 4-year-old boy who developed Cushing's syndrome 2 weeks after starting to take itraconazole 200 mg daily and inhaled budesonide 400 micrograms daily.[3]

In a double-blind, randomised, crossover study, 10 healthy subjects were given 1 mg of inhaled budesonide over a period of 2 minutes after taking itraconazole 200 mg daily for 5 days. The AUC of budesonide was increased 4.2-fold by the itraconazole, and the plasma cortisol levels of the patients were suppressed, indicating an increased budesonide effect.[4] Another study compared the results of the ACTH (tetracosactide) test in 25 patients taking itraconazole 400 to 600 mg daily and high-dose inhaled budesonide 800 micrograms to 1.6 mg daily with patients receiving either drug alone. Adrenal insufficiency was detected in 44% of those taking both drugs, but in none of the patients taking itraconazole or budesonide alone.[5]

(b) Ciclesonide

The manufacturer notes that giving itraconazole with ciclesonide may increase the exposure to the active metabolite of ciclesonide (seen with ketoconazole) and that the risk of systemic adverse effects of corticosteroids may be increased.[6]

(c) Deflazacort

A patient with cystic fibrosis taking deflazacort 15 mg daily developed Cushing's syndrome within 2 months of starting to take itraconazole 200 mg twice daily. The patient recovered within 4 months of stopping the itraconazole and reducing the dose of deflazacort to 12 mg daily.[7]

(d) Dexamethasone

A study in 8 healthy subjects found that itraconazole 200 mg daily for 4 days increased the AUC, peak plasma level, and elimination half-life of a single 4.5-mg dose of dexamethasone 3.7-fold, 1.7-fold, and 2.8-fold, respectively. In another phase of the study itraconazole decreased the systemic clearance of intravenous dexamethasone 5 mg by 68% and increased the AUC and elimination half-life 3.3-fold and 3.2-fold, respectively. The adrenal-suppressant effects of dexamethasone were enhanced by itraconazole.[8]

(e) Fluticasone

A case report describes profound adrenal suppression with secondary Cushing's syndrome in a patient with cystic fibrosis given itraconazole 200 mg twice daily and low-dose inhaled fluticasone 250 micrograms daily.[9] Another report describes a patient with asthma who had been taking inhaled fluticasone 1 to 1.5 mg twice daily for 2 years who developed secondary Cushing's syndrome and adrenal suppression 6 weeks after starting to take itraconazole (initially 100 mg daily then 200 mg daily).[10]

(f) Methylprednisolone

A study in 14 healthy subjects found that itraconazole 400 mg for one day and then 200 mg daily for the next 3 days, increased the AUC of a single 48-mg dose of methylprednisolone more than 2.5-fold.[11] Other studies in healthy subjects have found that itraconazole decreases the clearance, and increases the elimination half-life and AUC of both oral and intravenous methylprednisolone. Enhanced adrenal suppression also occurred.[12,13]

A man with a lung transplant taking methylprednisolone, ciclosporin and azathioprine was given itraconazole 200 mg twice daily to treat a suspected *Aspergillus fumigatus* infection. Three weeks later signs of corticosteroid toxicity developed, namely myopathy (confirmed by electromyography) and diabetes mellitus. Ten days after stopping the itraconazole the muscle force had improved and the daily dose of insulin had decreased from 120 units to 20 units.[14]

(g) Prednisolone or Prednisone

Six patients with allergic bronchopulmonary aspergillosis (3 with underlying cystic fibrosis and 3 with severe asthma) were given itraconazole 200 mg twice daily for one to 6 months. Four of the patients, who were also taking systemic prednisone, were able to reduce the corticosteroid dosage by 44% (from 43 mg daily to 24 mg daily) without any clinical deterioration.[15] Another study in healthy subjects found no clinically significant pharmacokinetic interaction between itraconazole (400 mg on day one then 200 mg daily for 3 days) and a single 60-mg dose of prednisone.[11]

A study in 10 healthy subjects found that itraconazole 200 mg daily for 4 days increased the AUC of a single 20-mg oral dose of prednisolone by 24%, but this was considered to be of limited clinical significance.[16]

Mechanism

It seems probable that itraconazole inhibits the metabolism of these corticosteroids by the cytochrome P450 isoenzyme CYP3A4 in the liver leading to higher levels and therefore increased effects. The active metabolite of ciclesonide is also metabolised by CYP3A4.[6] Prednisolone is less likely than methylprednisolone to interact with CYP3A4 inhibitors.[16]

Importance and management

These interactions appear to be established. There is currently too little data to assess the incidence, but it would be prudent to monitor the outcome of giving itraconazole with deflazacort, dexamethasone or methylprednisolone, being alert for the need to reduce the steroid dosage. The manufacturer of ciclesonide suggests that the concurrent use of itraconazole should be avoided unless the benefits outweigh the risks.[6]

Adrenal function should also be monitored in patients receiving inhaled budesonide or fluticasone given itraconazole, as Cushing's syndrome has been reported in a few patients during concurrent use. The manufacturer of budesonide suggests avoiding the concurrent use of itraconazole, but if this is not possible, the time interval between giving the interacting drugs should be as long as possible and a reduction in the dose of budesonide should also be considered.[17] Similarly, the manufacturer of fluticasone recommends caution, and, if possible, the avoidance of long-term treatment with itraconazole.[18]

Itraconazole appears to interact with prednisone and prednisolone to a lesser extent, but the effects may still be clinically important in some patients; consider this interaction as a possible cause if corticosteroid adverse effects develop. Information about other corticosteroids is lacking but good monitoring for increased systemic effects seems advisable as most are metabolised, at least in part, by CYP3A4.

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17. Pulmicort CFC-free Inhaler (Budesonide). AstraZeneca UK Ltd. UK Summary of product characteristics, May 2009.
18. Flixotide Evohaler (Fluticasone propionate). Allen & Hanburys Ltd. UK Summary of product characteristics, February 2009.

Corticosteroids + Azoles; Ketoconazole

Ketoconazole reduces the metabolism and clearance of methylprednisolone. Ketoconazole may increase levels of the active metabolite of ciclesonide. Ketoconazole modestly increases the systemic effect of inhaled budesonide and possibly fluticasone, and markedly increases the AUC of oral budesonide. The situation with prednisone and prednisolone is uncertain: studies have shown some moderate pharmacokinetic effects, but this does not appear to alter the action of either drug.

Clinical evidence

(a) Budesonide

In a study, 16 healthy subjects were given a single 1-mg inhaled dose of budesonide after taking ketoconazole 200 mg daily for 2 days. Plasma cortisol levels and urinary cortisol excretion were used as a measure of how much budesonide was absorbed systemically. Ketoconazole was found to cause a 37% decrease in the $AUC_{0\text{-}24}$ of cortisol, which suggests an increase in systemic budesonide levels.[1]

Another study, in 8 healthy subjects, found that the AUC of a single 3-mg oral dose of budesonide was increased 6.5-fold when it was given with the last dose of ketoconazole 200 mg daily for 4 days. When budesonide was given 12 hours before the last dose of ketoconazole, the AUC was increased 3.8-fold.[2]

(b) Ciclesonide

The manufacturer notes that, in an interaction study, the use of ketoconazole with ciclesonide increased the exposure to the active metabolite of ciclesonide approximately 3.5-fold and that there is an increased risk of systemic adverse effects of corticosteroids.[3]

(c) Fluticasone

In a study, 16 healthy subjects were given a single 500-microgram inhaled dose of fluticasone after taking ketoconazole 200 mg daily for 2 days. Plasma cortisol levels and urinary cortisol excretion were used as a measure of how much fluticasone was absorbed systemically, and it was found that ketoconazole had no effect on fluticasone absorption.[1] However, the manufacturer of fluticasone cites a study in which the exposure to fluticasone was increased by 150% by ketoconazole, which resulted in reductions in plasma cortisol levels.[4]

(d) Methylprednisolone

In 6 healthy subjects ketoconazole 200 mg daily for 6 days increased the mean AUC of a single 20-mg intravenous dose of methylprednisolone by 135% and decreased its clearance by 60%. The 24-hour cortisol AUC was reduced by 44%.[5] These findings were confirmed in another study by the same group of workers.[6]

(e) Prednisolone or Prednisone

In 10 healthy subjects ketoconazole 200 mg daily for 6 to 7 days caused a 50% rise in the levels of both total and unbound prednisolone, following a dose of either oral prednisone (which is metabolised to prednisolone) or intravenous prednisolone.[7] In contrast, two other studies found that ketoconazole 200 mg daily for 6 days did not affect either the pharmacokinetics or the pharmacodynamics of prednisolone, as measured by the suppressive effects on serum cortisol, blood basophil and helper T-lymphocyte values of prednisolone.[8,9]

Mechanism

Ketoconazole inhibits the cytochrome P450 isoenzyme CYP3A4 in the intestinal wall and liver so that the metabolism of some corticosteroids is reduced and therefore their levels increase. The active metabolite of ciclesonide is also metabolised by CYP3A4,[3] and it may therefore be similarly affected.

Importance and management

The interaction between methylprednisolone and ketoconazole appears to be established and clinically important. A 50% reduction in the dose of methylprednisolone was recommended by the authors of one study.[6] It has been pointed out that increased corticosteroid serum levels have an increased immunosuppressive effect, which may be undesirable in those with a fungal infection needing treatment with ketoconazole.[7] The situation with prednisone and prednisolone is as yet uncertain,[10,11] and more study is needed.

The study using inhaled budesonide indicates that ketoconazole increases the systemic effect of inhaled budesonide. Some manufacturers[12,13] recommend that, if the combination cannot be avoided, the interval between giving the two drugs should be as great as possible; a reduction in the dose of budesonide should also be considered. In addition, a significant interaction may occur with oral budesonide; the effects of ketoconazole on budesonide appear to be reduced by about half by separating the administration of the two drugs by 12 hours.[2] One manufacturer suggests reducing the oral budesonide dose if adverse effects occur.[14]

The situation with inhaled fluticasone is less clear, with one study finding an effect and another finding no effect. The manufacturer of fluticasone suggests that caution is warranted and, where possible, long-term concurrent use should be avoided.[4] Similarly, the manufacturer of ciclesonide suggests that it should not be used with ketoconazole unless the benefits outweigh the risks.[3]

It would seem prudent to bear this possible interaction in mind if ketoconazole is added to treatment with any systemic or inhaled corticosteroid. Patients should be warned to be alert for any evidence of increased corticosteroid effects (such as moon face, weight gain, hyperglycaemia) and to seek medical advice if these occur.

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2. Seidegård J. Reduction of the inhibitory effect of ketoconazole on budesonide pharmacokinetics by separation of their time of administration. *Clin Pharmacol Ther* (2000) 68, 13–17.
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4. Flixotide Evohaler (Fluticasone propionate). Allen & Hanburys Ltd. UK Summary of product characteristics, February 2009.
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12. Pulmicort CFC-free Inhaler (Budesonide). AstraZeneca UK Ltd. UK Summary of product characteristics, May 2009.
13. Novolizer (Budesonide). Meda Pharmaceuticals. UK Summary of product characteristics, March 2008.
14. Entocort CR Capsules (Budesonide). AstraZeneca UK Ltd. UK Summary of product characteristics, July 2008.

Corticosteroids + Azoles; Voriconazole

Voriconazole increases plasma levels of prednisolone but not to a clinically significant extent. A case report notes that voriconazole appears not to interact with oral hydrocortisone.

Clinical evidence

In healthy subjects, voriconazole 200 mg twice daily for 30 days increased the maximum plasma levels and AUC of a single 60-mg dose of **prednisolone** by 11% and 34%, respectively.[1,2]

A patient who developed Cushing's syndrome and secondary adrenal insufficiency during treatment with itraconazole and inhaled budesonide was given oral **hydrocortisone** replacement. The patient was then also

given voriconazole 200 mg twice daily for 3 months without any apparent effects on the **hydrocortisone**.[3]

Mechanism

Voriconazole is an inhibitor of the cytochrome P450 isoenzyme CYP3A4, but its inhibitory effects are much less than those of itraconazole.[3] Therefore voriconazole is less likely than 'itraconazole', (p.1257), or 'ketoconazole', (p.1259) to affect the pharmacokinetics of the corticosteroids, many of which are metabolised, at least in part, by CYP3A4.

Importance and management

No dose adjustment of the corticosteroid is said to be necessary if voriconazole is given with prednisolone,[1,2] and this also appears to be the case if voriconazole is given with hydrocortisone.[3] The effects of voriconazole on other corticosteroids does not appear to have been studied.

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2. VFEND (Voriconazole). Pfizer Inc. US Prescribing information, December 2009.
3. Bolland MJ, Bagg W, Thomas MG, Lucas JA, Ticehurst R, Black PN. Cushing's syndrome due to interaction between inhaled corticosteroids and itraconazole. *Ann Pharmacother* (2004) 38, 46–9.

Corticosteroids + Barbiturates

The therapeutic effects of systemic dexamethasone, methylprednisolone, prednisone and prednisolone are decreased by phenobarbital. Other barbiturates, including primidone, and some other corticosteroids probably interact similarly.

Clinical evidence

(a) Dexamethasone

A 14-year-old girl with congenital adrenal hyperplasia taking dexamethasone rapidly became over-treated (weight gain, signs of hypercortisolism) when **primidone** 250 mg twice daily was withdrawn over a month. Satisfactory control was only achieved when the dexamethasone dosage was reduced threefold.[1] A reduction in the effects of dexamethasone has been described when another patient with congenital adrenal hyperplasia was given **primidone** for petit mal seizures.[2] A patient with pemphigus vulgaris failed to respond to large doses of corticosteroids including **prednisolone** 100 mg daily or dexamethasone 30 mg daily when he was given **phenobarbital** and phenytoin. Dramatic improvement occurred following gradual discontinuation of the antiepileptic drugs.[3]

(b) Methylprednisolone

Phenobarbital increased the clearance of intravenous methylprednisolone in asthmatic children by 209%, but had no significant effect on the bioavailability of oral methylprednisolone.[4]

(c) Prednisolone

Phenobarbital increased the clearance of intravenous prednisolone in asthmatic children by 41%, but had no significant effect on the bioavailability of oral prednisolone.[4] Another study, in renal transplant patients, found that prednisolone elimination is increased by **phenobarbital**.[5]

Nine patients with rheumatoid arthritis taking prednisolone 8 to 15 mg daily had strong evidence of clinical deterioration (worsening joint tenderness, pain, morning stiffness, fall in grip strength) when they took **phenobarbital** for 2 weeks (plasma levels 0 to 86.2 micromol/L). The prednisolone half-life fell by 25%.[6]

For mention of a patient with pemphigus vulgaris, who was unresponsive to prednisolone following antiepileptic treatment including phenobarbital, see under *Dexamethasone*, above.

(d) Prednisone

In a group of 75 children with kidney transplants taking azathioprine and prednisone, the incidence of graft failure was increased in 11 epileptic children taking **phenobarbital** 60 to 120 mg daily. Two of the 11 children were also taking phenytoin 100 mg daily.[7] Three prednisone-dependent patients with bronchial asthma taking prednisone 10 to 40 mg daily had a marked worsening of their symptoms within a few days of starting to take **phenobarbital** 120 mg daily. There was a deterioration in pulmonary function tests (FEV_1, degree of bronchospasm) and a rise in eosinophil counts, all of which improved when the **phenobarbital** was stopped. The prednisone clearance was increased by the **phenobarbital**.[8] In contrast, the prednisone requirements of asthmatic children were unaltered when they took a compound preparation containing **phenobarbital** 24 mg daily.[9]

Mechanism

Phenobarbital is a recognised potent liver enzyme inducer that increases the metabolism of corticosteroids, thereby reducing their effects. Pharmacokinetic studies have shown that phenobarbital reduces the half-lives of these corticosteroids and increases their clearances by 40 to 209%.[4,8,10] Primidone interacts in a similar way because it is metabolised in the body to phenobarbital.[1]

Importance and management

The interaction between the corticosteroids and phenobarbital is well documented, well established and clinically important. Concurrent use need not be avoided but the outcome should be monitored. Increase the corticosteroid dosage as necessary. The extent of the increase is variable, but dexamethasone,[8] **hydrocortisone**,[11] methylprednisolone,[4,10] prednisone[7,8] and prednisolone[4,6] are all known to be affected. Prednisolone is less affected than methylprednisolone and may therefore be preferred in some situations. Be alert for the same interaction with other corticosteroids and other barbiturates, which also are enzyme-inducers, although direct evidence seems to be lacking. The dexamethasone adrenal suppression test may be expected to be unreliable in those taking phenobarbital, just as it is with phenytoin, another potent enzyme-inducer. See 'Corticosteroids + Phenytoin', p.1267.

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6. Brooks PM, Buchanan WW, Grove M, Downie WW. Effects of enzyme induction on metabolism of prednisolone. Clinical and laboratory study. *Ann Rheum Dis* (1976) 35, 339–43.
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8. Brooks SM, Werk EE, Ackerman SJ, Sullivan I, Thrasher K. Adverse effects of phenobarbital on corticosteroid metabolism in patients with bronchial asthma. *N Engl J Med* (1972) 286, 1125–8.
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11. Burstein S, Klaiber EL. Phenobarbital-induced increase in 6-β-hydroxycortisol excretion: clue to its significance in human urine. *J Clin Endocrinol Metab* (1965) 25, 293–6.

Corticosteroids + Bile-acid binding resins

Colestyramine and possibly colestipol reduce the absorption of oral hydrocortisone. Some other corticosteroids may possibly be affected, although colestyramine does not appear to affect prednisolone absorption.

Clinical evidence

(a) Colestyramine

In 10 healthy subjects, colestyramine 4 g reduced the AUC of a 50-mg oral dose of **hydrocortisone** by 43%. Peak **hydrocortisone** levels were reduced and delayed (by about 50 minutes).[1] Two of the subjects were given both 4 g and 8 g of colestyramine, and their AUCs were reduced by 47% and 59% by the 4-g dose and by 97% and 86% by the 8-g dose.[1]

In contrast, an 8-g dose of colestyramine did not affect the bioavailability of **prednisolone** in 2 patients receiving long-term **prednisolone**.[2]

(b) Colestipol

A man with hypopituitarism taking **hydrocortisone** 20 mg each morning and 10 mg each evening became lethargic, ataxic, and developed headaches (all signs of **hydrocortisone** insufficiency) within 4 days of starting to take colestipol 15 g three times daily for hypercholesterolaemia. He responded rapidly when given intravenous **hydrocortisone** 100 mg, and was discharged with the colestipol replaced by a statin.[3]

Mechanism

It seems that hydrocortisone can become bound to colestyramine or colestipol in the gut, thereby reducing its absorption.[1,4]

Importance and management

Information is limited, but the interactions of colestipol and colestyramine with hydrocortisone appear to be established (they are consistent with the interactions of both of these bile-acid resins with other drugs). Separate the administration of the drugs as much as possible to minimise admixture in the gut, although the authors of one report warn that this may not necessarily avoid this interaction because their data show that the colestyramine may remain in the gut for a considerable time.[1] The usual recommendation is to give other drugs one hour before or 4 to 6 hours after taking colestyramine, and one hour before or 4 hours after taking colestipol. Monitor the effects and increase the hydrocortisone dosage, or use an alternative to colestyramine, if necessary. Some manufacturers of other corticosteroids including **budesonide** and **dexamethasone** have suggested that colestyramine may potentially reduce the absorption of the corticosteroid,[5,6] and it would therefore be prudent to separate administration. One manufacturer advises taking oral budesonide and colestyramine at least 2 hours apart.[5] Prednisolone may be a non-interacting alternative, but the evidence for this is extremely limited.

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5. Budenofalk Gastro-resistant Capsules (Budesonide). Dr. Falk Pharma UK Ltd. UK Summary of product characteristics, April 2009.
6. Dexsol Oral Solution (Dexamethasone sodium phosphate). Rosemont Pharmaceuticals Ltd. UK Summary of product characteristics, March 2008.

Corticosteroids + Carbamazepine

The clearance of dexamethasone, methylprednisolone, prednisolone, and probably some other corticosteroids, can be increased in patients taking carbamazepine. The results of the dexamethasone suppression test may be invalid in those taking carbamazepine.

Clinical evidence

(a) Dexamethasone

A study in 8 healthy subjects found that, in the presence of carbamazepine 800 mg daily, the dosage of dexamethasone needed to suppress cortisol secretion (as part of the dexamethasone adrenal suppression test) was increased two- to fourfold.[1] A further study found that it took 2 to 13 days for false-positive results to occur after carbamazepine was started, and 3 to 12 days to recover when the carbamazepine was stopped.[2] A report describes two patients suspected of having Cushing's syndrome because the overnight suppression test with dexamethasone 1 mg had not suppressed their cortisol levels. Further investigation found no clinical evidence of Cushing's syndrome and the false-positive test results were attributed to the fact that both patients were taking carbamazepine 400 mg three times daily at the time of the test. The test was repeated in one of the patients 3 weeks after carbamazepine was stopped and it indicated normal cortisol suppression.[3]

(b) Prednisolone

A study in 8 patients receiving long-term treatment with carbamazepine found that the elimination half-life of prednisolone was about 45 minutes shorter, and its clearance was 42% higher, than in 9 healthy subjects not taking carbamazepine.[4]

A study in asthmatic children found that carbamazepine increased the clearance of intravenous prednisolone by 79% and increased the clearance of intravenous **methylprednisolone** by 342%.[5] A patient taking carbamazepine and valproate required high-dose prednisolone (20 to 60 mg daily) for polymyalgia rheumatica. It was noted that when carbamazepine was discontinued her response to prednisolone improved, allowing the dose to be reduced to 20 mg then 10 mg daily.[6]

Mechanism

Carbamazepine induces liver enzymes, which results in the increased metabolism of the corticosteroids.

Importance and management

Information is limited but the interaction appears to be established. Patients taking carbamazepine are likely to need increased doses of dexamethasone, methylprednisolone or prednisolone. Prednisolone is less affected than methylprednisolone and may therefore be preferred in some situations. The same interaction seems likely with other corticosteroids but more study is needed to confirm this. Note that **hydrocortisone** and **prednisone** are affected by another potent enzyme inducer, phenobarbital (see 'Corticosteroids + Barbiturates', p.1260), and would therefore also be expected to interact with carbamazepine.

1. Köbberling J, v zur Mühlen A. The influence of diphenylhydantoin and carbamazepine on the circadian rhythm of free urinary corticoids and on the suppressibility of the basal and the 'impulsive' activity by dexamethasone. *Acta Endocrinol (Copenh)* (1973) 72, 308–18.
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Corticosteroids + Diltiazem

Diltiazem increases the AUC of intravenous and oral methylprednisolone, and the metabolism of oral prednisone is also reduced by diltiazem.

Clinical evidence

In a study, 5 healthy subjects were given diltiazem 180 mg daily for 4 days, with and without *intravenous* **methylprednisolone** 300 micrograms/kg (based on ideal body-weight) on day 5. Diltiazem increased the AUC of **methylprednisolone** by 50%, prolonged its half-life by 37% and reduced the **methylprednisolone** clearance by 33%. Although the morning cortisol concentration was only 12% of that during the placebo phase, overall the suppressive effects of **methylprednisolone** on cortisol excretion were unchanged.[1] Another similar study in which patients were given diltiazem and a single 16-mg oral dose of **methylprednisolone** found much larger effects: the AUC of **methylprednisolone** was increased 2.6-fold, and the morning cortisol excretion was only 12% of that in the absence of diltiazem,[2] suggesting an enhanced effect.

Another study in healthy subjects found that diltiazem 180 mg daily for 3 days inhibited the metabolism of a single 15-mg oral dose of **prednisone**; the AUC of **prednisolone** (the major active metabolite of prednisone) was increased by 21%.[3]

Mechanism

Diltiazem is a moderate inhibitor of the cytochrome P450 isoenzyme CYP3A4. As methylprednisolone is mainly metabolised by CYP3A4, any inhibition of its activity would be expected to raise the corticosteroid levels.[1,2] Prednisolone is less dependent on CYP3A4 for metabolism, and is therefore more modestly affected. It has been suggested that P-glycoprotein may also play a role in the interaction with methylprednisolone.[1,2] Inhibition of intestinal/hepatic CYP3A4 may increase the oral bioavailability of methylprednisolone, which could contribute to the pharmacokinetic differences seen in the interaction when methylprednisolone is given orally rather than intravenously.

Importance and management

Information about the interaction between diltiazem and methylprednisolone seems limited to these two studies, but the effect of concurrent use is clear. However, the clinical significance of the raised methylprednisolone levels has not been established. Monitoring for an increase in the

adverse effects of methylprednisolone, as suggested by one of the authors, seems a prudent measure.[1] Similarly, prednisone/prednisolone bioavailability might possibly be affected by diltiazem but the effect is modest, and possibly not clinically relevant.

1. Booker BM, Magee MH, Blum RA, Lates CD, Jusko WJ. Pharmacokinetic and pharmacodynamic interactions between diltiazem and methylprednisolone in healthy volunteers. *Clin Pharmacol Ther* (2002) 72, 370–82.
2. Varis T, Backman JT, Kivistö KT, Neuvonen PJ. Diltiazem and mibefradil increase the plasma concentrations and greatly enhance the adrenal-suppressant effect of oral methylprednisolone. *Clin Pharmacol Ther* (2000) 67, 215–21.
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Corticosteroids + Diuretics; Potassium-depleting

Both corticosteroids and the loop or thiazide diuretics can cause potassium loss, severe depletion is therefore possible if they are used together.

Clinical evidence, mechanism, importance and management

There seem to be no formal clinical studies about the extent of the additive potassium depletion that can occur when potassium-depleting diuretics and corticosteroids are given together, but an exaggeration of the potassium loss undoubtedly occurs (e.g. seen with **hydrocortisone** and **furosemide**[1]). One study looking at hypokalaemia with potassium-depleting diuretics found that corticosteroids were a significant risk factor for hypokalaemic events; 20% of patients taking a potassium-depleting diuretic developed hypokalaemia, whereas 31% of patients taking a potassium-depleting diuretic and a corticosteroid developed hypokalaemia.[2] Hypokalaemia in patients taking potassium-depleting diuretics should be corrected before a corticosteroid is started. Concurrent use should be well monitored and the potassium intake increased as appropriate to balance this loss.

The greatest potassium loss occurs with the naturally occurring corticosteroids such as **cortisone** and **hydrocortisone**. **Corticotropin** (**ACTH**), which is a pituitary hormone, and **tetracosactrin** (a synthetic polypeptide) stimulate corticosteroid secretion by the adrenal cortex and can thereby indirectly cause potassium loss. **Fludrocortisone** also causes potassium loss. The synthetic corticosteroids (glucocorticoids) have a less marked potassium-depleting effect and are therefore less likely to cause problems. These include **betamethasone**, **dexamethasone**, **prednisolone**, **prednisone** and **triamcinolone**.

The potassium-depleting diuretics (i.e. **loop diuretics** or **thiazide** and related diuretics) are listed in 'Table 26.1', (p.1121). **Acetazolamide**, a weak diuretic, has also been predicted to cause hypokalaemia in the presence of corticosteroids. However, hypokalaemia seen with **acetazolamide** is rarely clinically significant, and therefore any risk is lower.

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Corticosteroids + Ephedrine

Ephedrine increases the clearance of dexamethasone.

Clinical evidence, mechanism, importance and management

Nine asthmatic patients had a 40% increase in the clearance and a similar reduction in the half-life of **dexamethasone** when they were given ephedrine 100 mg daily for 3 weeks.[1] This would be expected to reduce the overall effects of **dexamethasone**, but this requires confirmation. Be alert for any evidence that the **dexamethasone** effects are reduced if both drugs are given; an increase in the dexamethasone dose might be necessary. It is not clear whether other corticosteroids behave similarly.

1. Brooks SM, Sholiton LJ, Werk EE, Altenau P. The effects of ephedrine and theophylline on dexamethasone metabolism in bronchial asthma. *J Clin Pharmacol* (1977) 17, 308–18.

Corticosteroids + Fluoxetine

Fluoxetine does not affect the pharmacokinetics of prednisolone or its effects on cortisol suppression.

Clinical evidence, mechanism, importance and management

In healthy subjects, fluoxetine 20 mg daily for 5 days then 60 mg daily for 9 days did not significantly affect the pharmacokinetics of a single 40-mg dose of **prednisolone succinate**, given as an intravenous bolus, or the duration of cortisol suppression in response to the **prednisolone**.[1] Although fluoxetine has some inhibitory effect on the cytochrome P450 isoenzyme CYP3A4, and thus may inhibit the metabolism of corticosteroids that are CYP3A4 substrates, its effects are weak and not usually clinically relevant. Furthermore, **prednisolone** is only partly metabolised by this route.[2] No clinically important interaction is likely if **prednisolone** and fluoxetine are given concurrently. The situation with other corticosteroids that may be more likely to interact (e.g. **methylprednisolone**, which is mainly metabolised by CYP3A4) is not known.

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Corticosteroids + Grapefruit juice

Grapefruit juice moderately increases the plasma levels of budesonide and methylprednisolone. Grapefruit juice does not affect the pharmacokinetics of prednisolone or prednisone.

Clinical evidence, mechanism, importance and management

(a) Budesonide

In a study in 8 healthy subjects giving budesonide (*Entocort EC*) capsules with concentrated grapefruit juice resulted in a twofold increase in the bioavailability of budesonide, compared with enteric-coated budesonide alone. Similar results were obtained with a plain capsule formulation, but the clearance, volume of distribution and half-life of budesonide given intravenously were not altered by grapefruit juice. These results suggest that grapefruit juice increases the systemic availability of budesonide capsules due to inhibition of intestinal CYP3A4 activity.[1] One of the manufacturers of budesonide therefore advises that regular ingestion of grapefruit or grapefruit juice should be avoided in connection with budesonide administration.[2] Another manufacturer of oral and rectal budesonide also recommends avoidance of concurrent use.[3,4]

(b) Methylprednisolone

In a crossover study, 10 healthy subjects were given either double-strength grapefruit juice 200 mL, or water, three times daily for 2 days. On day 3, grapefruit juice 200 mL or water was given with, 30 minutes and 90 minutes after a single 16-mg dose of methylprednisolone. Grapefruit juice increased the AUC and peak plasma level of methylprednisolone by 75% and 27%, respectively. The time to reach peak levels was increased from 2 to 3 hours and the elimination half-life was increased by 35%. Plasma cortisol levels after methylprednisolone was given with grapefruit juice or water were not significantly different, although grapefruit juice slightly decreased plasma cortisol levels before the morning dose of methylprednisolone. As the effects on plasma cortisol levels were slight, this interaction is unlikely to be of clinical significance in most patients, although the authors note that in some sensitive subjects large amounts of grapefruit juice might enhance the effects of oral methylprednisolone.[5]

(c) Prednisolone or Prednisone

A study in 12 kidney transplant patients taking ciclosporin and corticosteroids found that grapefruit juice, given every 3 hours for 30 hours, increased ciclosporin levels, but had no significant effect on the AUC of prednisolone or prednisone It was concluded that grapefruit juice does not affect the metabolism of prednisolone or prednisone.[6] No special precautions are therefore needed if patients drink grapefruit juice while taking these corticosteroids.

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4. Budenofalk Rectal Foam (Budesonide). Dr. Falk Pharma UK Ltd. UK Summary of product characteristics, October 2007.
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Corticosteroids + H_2-receptor antagonists

Cimetidine does not appear to interact with budesonide, dexamethasone prednisolone, or prednisone, and ranitidine does not interact with prednisone.

Clinical evidence, mechanism, importance and management

A double-blind crossover study in 9 healthy subjects found that **cimetidine** 300 mg every 6 hours or **ranitidine** 150 mg twice daily for 4 days did not significantly alter the pharmacokinetics of prednisolone after a single 40-mg oral dose of **prednisone**.[1] **Prednisone** is a pro-drug, which must be converted to prednisolone within the body to become active.

Another double-blind, crossover study found that **cimetidine** 1 g daily only caused minor changes in plasma **prednisolone** levels following a 10-mg dose of enteric-coated **prednisolone**.[2] Similarly, **cimetidine** has been reported to have a slight but clinically insignificant effect on the pharmacokinetics of oral **budesonide**.[3] Another study found that **cimetidine** 600 mg twice daily for 7 days had no effect on the pharmacokinetics of a single 8-mg intravenous dose of **dexamethasone sodium phosphate**.[4]

Dosage adjustments therefore seem unlikely to be necessary if any of these corticosteroids are given with cimetidine or other H_2-receptor antagonists.

Drugs such as cimetidine, which inhibit the cytochrome P450 isoenzyme CYP3A4, might be expected to decrease the rate of metabolism of corticosteroids, such as **methylprednisolone**, that are largely metabolised by this route. However, information appears to be lacking, and cimetidine has only weak to modest effects on this isoenzyme. Therefore no clinically significant interaction is anticipated.

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Corticosteroids + Hormonal contraceptives or Sex hormones

The serum levels of cloprednol, methylprednisolone, prednisolone, prednisone, and possibly other corticosteroids are increased by combined hormonal contraceptives. In theory, both the therapeutic and toxic effects would be expected to be increased, but in practice it is uncertain whether these changes are important. Total serum cortisol levels may also be increased by hormonal contraceptives. Fluocortolone and oral budesonide levels were not affected by oral contraceptives. Prasterone did not affect the pharmacokinetics of prednisone or the effects of its metabolite, prednisolone, on cortisol secretion. Progesterone appears not to affect the metabolism of prednisolone.

Clinical evidence

(a) Hormonal contraceptives

1. Budesonide. The plasma levels of oral budesonide 4.5 mg daily for 7 days, and cortisol suppression were no different in 20 women taking an oral contraceptive (**ethinylestradiol**/**desogestrel**) when compared with 20 women not taking an oral contraceptive.[1]

2. Cloprednol. The clearance of cloprednol 20 mg was decreased by about one-third in 7 women taking an oral contraceptive (**ethinylestradiol**/**norethisterone**), when compared with women not taking an oral contraceptive.[2]

3. Corticotropin. In a study in 11 healthy women who were not taking hormonal contraceptives, the mean basal concentration of total serum cortisol was 454 nanomol/L, but when the women took combined hormonal contraceptives orally for 3 months the cortisol level increased to 861 nanomol/L. After a low-dose (1 microgram) corticotropin (ACTH) test, using **tetracosactide** (*Synacthen*), the mean serum cortisol level at 30 minutes increased to 652 nanomol/L and 1374 nanomol/L before and after hormonal contraceptive use, respectively. The basal plasma concentration of corticotropin also increased from 17.2 to 38.2 nanograms/L after hormonal contraceptive use. However, the basal and corticotropin-stimulated salivary cortisol was not significantly different between the baseline period and the hormonal contraceptive period.[3]

4. Fluocortolone. A study in 7 women found that the pharmacokinetics of fluocortolone 20 mg were unaffected by an oral contraceptive (**ethinylestradiol**/**norethisterone**).[4]

5. Methylprednisolone. A study in two groups of 6 patients found that the clearance of methylprednisolone was decreased to about half in the group taking oral contraceptives (**ethinylestradiol/levonorgestrel**), when compared with the group not taking oral contraceptives. The oral contraceptive group were less sensitive to the suppressive effects of methylprednisolone on the secretion of cortisol, and had more suppression of basophils, but no changes in the T-helper cell response patterns.[5]

6. Prednisolone. In a placebo-controlled study, 20 healthy women took an oral contraceptive (**ethinylestradiol**/**desogestrel** 30/150 micrograms) for at least 4 months before being given prednisolone 20 mg daily for 7 days. The prednisolone AUC and steady-state levels were 2.3-fold higher, when compared with those in 20 women not taking oral contraceptives.[1] Several other studies have found similar results, with the prednisolone AUC increasing 1.6- to 6-fold,[6,7] and the clearance reducing by about 35 to 85% in the presence of oral contraceptives containing **ethinylestradiol** or **mestranol** and various progestogens such as **levonorgestrel**, **norgestrel** and **norethisterone**.[6-11] Similarly, a 2.3-fold increase in the AUC of prednisolone and a 45% decrease in its clearance was seen when **prednisone** was given to 10 women (9 taking an oral combined hormonal contraceptive and one taking ethinylestradiol).[12]

(b) Prasterone

In a study in 14 healthy women, prasterone 200 mg daily for one menstrual cycle (approximately 28 days) did not affect the pharmacokinetics of a single 20-mg dose of **prednisone** or its inhibition of cortisol secretion.[13]

(c) Progesterone

Intravenous and oral **prednisolone** were given to 6 post-menopausal women before and after they took progesterone 5 mg for 2 months. The pharmacokinetics of **prednisolone** were not significantly altered by progesterone.[14]

Mechanism

Not fully understood. The possibilities include a change in the metabolism of the corticosteroids, or in their binding to serum proteins.[12] The absence of an interaction with progesterone suggests that the oestrogenic component of the oral contraceptive is possibly responsible for any interaction.[14] Endogenous and synthetic oestrogens appear to cause an increase in the plasma concentration of cortisol binding globulin, which results in an elevation of the total cortisol level.[3]

Importance and management

It is established that the pharmacokinetics of some corticosteroids are affected by combined hormonal contraceptives, but the clinical importance of any such changes is not known. The therapeutic and adverse effects would be expected to be increased but there appear to be no clinical reports of adverse reactions arising from concurrent use. In fact the authors of one study[5] concluded that women can be dosed similarly with methylprednisolone irrespective of contraceptive use.

However, until more is known it would be prudent to bear this interaction in mind when using any corticosteroid and combined hormonal contraceptive together. Only prednisone, prednisolone, cloprednol and methylprednisolone have been reported to interact although some other corticosteroids possibly behave similarly, the exceptions apparently being fluocortolone and oral budesonide.

Total serum cortisol levels may be increased by hormonal contracep-

tives, but the unbound fraction of cortisol appears to be unaffected.[3] Progesterone appears not to interact with prednisolone.

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Corticosteroids + Liquorice

Liquorice can delay the clearance of prednisolone and hydrocortisone. Dexamethasone may attenuate the mineralocorticoid effects of glycyrrhizin. Liquorice, if given in large quantities with corticosteroids, may cause additive hypokalaemia.

Clinical evidence, mechanism, importance and management

Liquorice has a great number of active compounds of different classes that act in different ways. The most important constituent is usually considered to be glycyrrhizin (glycyrrhizic or glycyrrhizinic acid).

(a) Dexamethasone

In a parallel group study, 6 patients were given **glycyrrhizin** 225 mg daily for 7 days, and 6 patients were given the same dose of **glycyrrhizin** and dexamethasone 1.5 mg daily for 7 days. The mineralocorticoid effects of **glycyrrhizin** were significantly reduced by dexamethasone; cortisol plasma concentrations and urinary excretions were reduced by up to 70%.[1]

(b) Hydrocortisone

Glycyrrhizin slightly increased the AUC of cortisol by 14% in 4 patients with adrenocorticol insufficiency taking oral hydrocortisone 20 to 40 mg daily. Note that **glycyrrhizin** had no effect on endogenous cortisol levels in 7 control subjects without adrenal insufficiency.[2] In a study in 23 healthy subjects, topical **glycyrrhetinic acid** markedly potentiated the activity of topical hydrocortisone, as assessed by cutaneous vasoconstrictor effect.[3]

(c) Prednisolone

A study in 6 healthy subjects found that after taking four 50-mg oral doses of **glycyrrhizin** at 8-hourly intervals, followed by a bolus injection of prednisolone hemisuccinate 96 micrograms/kg, the AUC of total prednisolone was increased by 50% and the AUC of free prednisolone was increased by 55%.[4] This confirms previous findings with **glycyrrhizin** 200 mg given by intravenous infusion.[5]

Glycyrrhizin slightly increased the AUC of prednisolone by about 16 to 20% in 12 patients who had been taking oral prednisolone 10 to 30 mg daily for at least 3 months.[2]

Mechanism

Inhibition of 11 β-hydroxysteroid dehydrogenase by glycyrrhetinic acid may slightly delay the clearance of hydrocortisone and prednisolone and thereby enhance their effects. However, note that whether a mineralocorticoid or glucocorticoid is a substrate for this enzyme system depends on its chemical structure. Therefore, it cannot be assumed that liquorice will inhibit the inactivation of all corticosteroids.

Dexamethasone appears to attenuate the mineralocorticoid effects of glycyrrhizin because it suppresses endogenous cortisol secretion (causes adrenal suppression). Other corticosteroids would be expected to interact similarly if given in adrenal-suppressant doses.

Deglycyrrhizinated liquorice would not have these effects.

Importance and Management

The clinical importance of these observations is uncertain. Doses of corticosteroids sufficient to cause adrenal suppression would be expected to reduce the mineralocorticoid activity of liquorice, but mineralocorticoid activity might still occur. Glycyrrhizin (an active constituent of liquorice) and its metabolite glycyrrhetinic acid slightly increased the plasma levels of hydrocortisone and prednisolone and markedly potentiated the cutaneous effects of hydrocortisone. This suggests that liquorice will slightly potentiate the effects of these steroids. However, this might not apply to other corticosteroids (see *Mechanism*, above). Nevertheless, it might be prudent to monitor the concurrent use of liquorice and corticosteroids, especially if liquorice ingestion is prolonged or if large doses are taken, as additive effects on water and sodium retention, and potassium depletion may occur.

Note that several manufacturers of corticosteroids comment that the hypokalaemic effects of **carbenoxolone**, a synthetic derivative of glycyrrhizic acid, may be enhanced by corticosteroids.

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Corticosteroids + Macrolides

Troleandomycin and, to a lesser extent, clarithromycin and erythromycin can reduce the clearance of methylprednisolone, thereby increasing both its therapeutic and adverse effects; azithromycin does not appear to affect the pharmacokinetics of methylprednisolone. A patient receiving long-term clarithromycin developed Cushing's syndrome after using inhaled budesonide. There appears to be no pharmacokinetic interaction between erythromycin and inhaled ciclesonide or fluticasone. Similarly, prednisolone appears not to be affected by macrolides, except possibly in those patients also taking enzyme-inducers such as phenobarbital. Isolated case reports describe the development of acute mania and psychosis in two patients, apparently due to an interaction between prednisone and clarithromycin.

Clinical evidence

(a) Budesonide

A 40-year-old woman with cystic fibrosis given **clarithromycin** 500 mg twice daily for 4 years for a *Mycobacterium abscessus* infection developed Cushing's syndrome with adrenal suppression 6 weeks after starting to use inhaled budesonide 400 micrograms daily. A slow rise in morning free cortisol levels was found 4 weeks after stopping budesonide. She died 8 weeks later of severe respiratory failure.[1]

(b) Ciclesonide

In a crossover study, healthy subjects were given a single 500-mg dose of **erythromycin** and inhaled ciclesonide 640 micrograms, alone or together. Concurrent use did not alter the pharmacokinetics of either drug.[2]

(c) Fluticasone

In a multiple-dose study, giving **erythromycin** 333 mg three times daily did not affect the pharmacokinetics of inhaled fluticasone propionate 500 micrograms twice daily.[3]

(d) Methylprednisolone

1. Azithromycin. A review by the manufacturers briefly mentions that azithromycin does not alter the pharmacokinetics of methylprednisolone.[4]

2. Clarithromycin. A study in 6 asthmatic patients found that clarithromycin 500 mg twice daily for 9 days reduced the clearance of a single dose of methylprednisolone by 65% and resulted in significantly higher plasma methylprednisolone levels.[5]

3. Erythromycin. A study in 9 asthmatic patients aged 9 to 18 years found that after taking erythromycin 250 mg four times daily for a week, the clearance of methylprednisolone was decreased by 46% (range 28 to 61%) and the half-life was increased by 47%, from 2.3 to 3.5 hours.[6]

4. Troleandomycin. A pharmacokinetic study in 4 children and 6 adult corticosteroid-dependent asthmatics found that troleandomycin 14 mg/kg daily for one week increased the half-life of methylprednisolone by 88%, from 2.46 to 4.63 hours, and reduced the total body clearance by 64%. All 10 had cushingoid symptoms (cushingoid faces and weight gain), which resolved when the methylprednisolone dosage was reduced, without any loss in the control of the asthma.[7] Another study found that the dose of methylprednisolone could be reduced by 50% in the presence of troleandomycin, without loss of disease control.[8] Other studies have found similar effects.[9-14] However, a randomised, placebo-controlled, 2-year study found that although troleandomycin modestly reduced the required dose of methylprednisolone, this did not reduce corticosteroid-related adverse effects.[14] A case report describes a fatal varicella infection attributed to the potentiation of steroid effects by troleandomycin.[15]

(e) Prednisolone or Prednisone

1. Clarithromycin. A 30-year-old woman with no history of mental illness was treated for acute sinusitis with prednisone 20 mg daily for 2 days, followed by 40 mg daily for a further 2 days and clarithromycin 1 g daily. After 5 days she stopped taking both drugs (for unknown reasons), but a further 5 days later she was hospitalised with acute mania (disorganised thoughts and behaviour, pressured speech, increased energy, reduced need for sleep and labile effect). She spontaneously recovered after a further 5 days and had no evidence of psychiatric illness 4 months later.[16] A 50-year-old man with emphysema was given prednisone 20 mg daily to improve dyspnoea. After about 2 weeks he was also given clarithromycin 500 mg twice daily for purulent bronchitis. Shortly afterwards his family noticed psychiatric symptoms characterised by paranoia, delusions and what was described as dangerous behaviour. He recovered following treatment with low-dose olanzapine, a gradual reduction of the prednisone dosage and discontinuation of the clarithromycin. An interaction was suspected as the patient had previously received prednisone on a number of occasions without the development of psychosis.[17]

A study in 6 asthmatic patients found that clarithromycin 500 mg twice daily for 9 days had no significant effect on prednisone pharmacokinetics.[5]

2. Troleandomycin. A study found that prednisolone clearance was not affected by troleandomycin in 3 patients, but was reduced by about 50% by troleandomycin in one patient who was also taking **phenobarbital**, which is an enzyme inducer.[9]

Mechanism

The available evidence suggests that clarithromycin, erythromycin and troleandomycin can inhibit the metabolism of methylprednisolone. The volume of distribution is also decreased.[6,7,9,18] Clarithromycin may inhibit the metabolism of budesonide.[1]

Importance and management

Information about the clarithromycin or erythromycin interactions with methylprednisolone is much more limited than with the interaction between troleandomycin and methylprednisolone, but they all appear to be established and of clinical importance. The effect should be taken into account during concurrent use and appropriate dosage reductions made to avoid the development of corticosteroid adverse effects. The authors of one study[7] suggest that this reduction should be empirical, based primarily on clinical symptoms. Another group found that a 68% reduction in methylprednisolone dosage was possible within 2 weeks.[11] Troleandomycin appears to have a greater effect than erythromycin or clarithromycin.

Prednisolone seems not to interact with troleandomycin and may be a non-interacting alternative to methylprednisolone, except possibly in those taking enzyme-inducers (e.g. phenobarbital). Nevertheless, one manufacturer of prednisolone advises caution with the concurrent use of CYP3A4 inhibitors including troleandomycin and says that dosages of the corticosteroid may need to be decreased.[19] The available evidence suggests that potent CYP3A4 inhibitors (such as troleandomycin) present the greatest risk.

The evidence for the interaction leading to psychosis between prednisone and clarithromycin is limited and its general importance is uncertain, but prescribers should be aware of the reports of psychosis if both drugs are used together. Note that psychosis is a rare adverse effect of high-dose corticosteroids given alone.

One case report indicates that clarithromycin may enhance the effects of inhaled budesonide and although the authors suggest that prolonged use of clarithromycin and the terminal condition of the patient may have been factors, they advise close monitoring if the combination is used.[1] One manufacturer of budesonide advises that potent inhibitors of CYP3A4 (they name clarithromycin) should be avoided.[20] However, given the evidence available, this seems a very cautious approach.

Some other manufacturers of corticosteroids, including **dexamethasone** and **hydrocortisone** have also mentioned the potential for increased plasma concentrations of corticosteroids with macrolides such as erythromycin. In general the concurrent use of these corticosteroids and CYP3A4-inhibiting macrolides need not be avoided, but it would seem prudent to monitor for corticosteroid adverse effects and suspect an interaction if symptoms occur. In most cases the interaction should be manageable by reducing the dose of the corticosteroid until the macrolide is withdrawn.

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20. Budenofalk Rectal Foam (Budesonide). Dr. Falk Pharma UK Ltd. UK Summary of product characteristics, October 2007.

Corticosteroids + Mifepristone

The UK manufacturer of mifepristone says that, due to the antiglucocorticoid activity of mifepristone, the efficacy of long-term corticosteroids (including inhaled corticosteroids) may be decreased during the 3 to 4 days following intake of mifepristone.[1] Patients taking corticosteroids should be monitored during this time, and consideration given to increasing the corticosteroid dose. However, the US manufacturer contraindicates the use of

mifepristone in patients receiving long-term corticosteroid therapy.[2]

1. Mifegyne (Mifepristone). Exelgyn Laboratories. UK Summary of product characteristics, May 2008.
2. Mifeprex (Mifepristone). Danco Laboratories, LLC. US Prescribing information, July 2005.

Corticosteroids + Nefazodone

Nefazodone inhibits the metabolism of methylprednisolone and prolongs its effects on cortisol suppression.

Clinical evidence

In healthy subjects, nefazodone (initial dose of 100 mg, increased to 150 mg, then 200 mg, twice daily, for a total of 9 days) increased the AUC of a single 600-microgram/kg intravenous dose of **methylprednisolone** twofold and increased its half-life from 2.3 to 3.3 hours. **Methylprednisolone** clearance was decreased by about 50%. The duration of cortisol suppression after **methylprednisolone** alone was 23.3 hours, which increased to more than 32 hours when nefazodone was also given.[1]

Mechanism

Nefazodone probably inhibits the metabolism of methylprednisolone by the cytochrome P450 isoenzyme CYP3A4.[1]

Importance and management

At clinically relevant doses nefazodone decreases methylprednisolone clearance and significantly prolongs methylprednisolone-induced cortisol suppression. Care is recommended during concurrent use.[1] Note that many other corticosteroids are metabolised, at least in part, by the same route as methylprednisolone, and may therefore also be expected to interact to some extent, although this needs confirmation. Note that nefazodone has been generally withdrawn from the market because of adverse hepatic effects.

1. Kotlyar M, Brewer ER, Golding M, Carson SW. Nefazodone inhibits methylprednisolone disposition and enhances its adrenal-suppressant effect. *J Clin Psychopharmacol* (2003) 23, 652–6.

Corticosteroids + NNRTIs

Delavirdine may increase the levels of dexamethasone and possibly other corticosteroid, whereas the plasma levels of dexamethasone, prednisolone, and possibly other corticosteroids, may be decreased by efavirenz or nevirapine.
Dexamethasone may decrease the plasma levels of delavirdine and etravirine, and prednisone may increase the incidence and severity of rash associated with the use of nevirapine.

Clinical evidence, mechanism, importance and management

(a) Delavirdine

The manufacturer of delavirdine says that it should be used with caution with **dexamethasone** because delavirdine may be less effective due to decreased plasma concentrations.[1] This is presumably because delavirdine is primarily metabolised by the cytochrome P450 isoenzyme CYP3A4,[1] which is said to be induced by **dexamethasone**.[2] However, evidence of **dexamethasone** having clinically relevant interactions as a result of this mechanism is generally lacking. The levels of **dexamethasone** may possibly be increased by delavirdine, due to inhibition of CYP3A4.[2] There appears to be little information about other corticosteroids and delavirdine, but many corticosteroids (particularly **methylprednisolone**) are metabolised, at least in part, by CYP3A4 and therefore their levels may also be raised to some extent by delavirdine. Be alert for increased corticosteroid adverse effects.

(b) Efavirenz or Nevirapine

Systemic **dexamethasone** levels may be decreased by efavirenz or nevirapine due to induction of CYP3A4,[2] by which dexamethasone is metabolised.

A study in HIV-positive subjects given a single 20-mg dose of **prednisone**, found that efavirenz, as part of antiretroviral medication, decreased the AUC of **prednisolone** by about 20%, when compared with similar patients who were not taking antiretrovirals; however, this was not statistically significant. When the patients taking efavirenz were compared with patients receiving lopinavir boosted with ritonavir there was a 40% reduction in the AUC of **prednisolone**. This indicates that **prednisolone** concentrations may fluctuate widely when HIV-positive individuals established on efavirenz change to lopinavir/ritonavir or *vice versa*.[3]

Corticosteroids may be used to treat rash associated with efavirenz,[4] however, the manufacturers of nevirapine warn that **prednisone** 40 mg daily for the first 14 days of nevirapine use has not been shown to reduce the incidence of nevirapine-associated rash and may be associated with an increase in incidence and severity of rash during the first 6 weeks of nevirapine use.[5,6] The US manufacturer therefore states that the use of **prednisone** to prevent nevirapine-associated rash is not recommended.[6]

There appears to be little information about other corticosteroids and efavirenz of nevirapine, but many corticosteroids (particularly **methylprednisolone**) are metabolised, at least in part, by CYP3A4. Dosage increases of the corticosteroid may possibly be needed if efavirenz or nevirapine are started, stopped, or the doses changed.

(c) Etravirine

The manufacturer of etravirine says that it should be used with caution with **dexamethasone** because etravirine may be less effective due to decreased plasma concentrations. They advise that alternatives to dexamethasone should be considered if possible, particularly for long-term use.[7] This is presumably because etravirine is metabolised by the cytochrome P450 isoenzyme CYP3A4,[1] which is said to be induced by **dexamethasone**.[2] However, evidence of **dexamethasone** having clinically relevant interactions as a result of this mechanism is generally lacking.

1. Rescriptor (Delavirdine mesylate). Pfizer Inc. US Prescribing information, May 2008.
2. de Maat MMR, Ekhart GC, Huitema ADR, Koks CHW, Mulder JW, Beijnen JH. Drug interactions between antiretroviral drugs and comedicated agents. *Clin Pharmacokinet* (2003) 42, 223–82.
3. Busse KH, Formentini E, Alfaro RM, Kovacs JA, Penzak SR. Influence of antiretroviral drugs on the pharmacokinetics of prednisolone in HIV-infected individuals. J Acquir Immune Defic Syndr (2008) 48, 561–6.
4. Sustiva Film-coated Tablets (Efavirenz). Bristol-Myers Squibb Pharmaceuticals Ltd. UK Summary of product characteristics, June 2009.
5. Viramune (Nevirapine anhydrate). Boehringer Ingelheim Ltd. UK Summary of product characteristics, May 2009.
6. Viramune (Nevirapine). Boehringer Ingelheim Pharmaceuticals, Inc. US Prescribing information, November 2008.
7. Intelence (Etravirine). Janssen-Cilag Ltd. UK Summary of product characteristics, November 2009.

Corticosteroids + NSAIDs

Corticosteroids or NSAIDs alone may be risk factors for gastrointestinal bleeding and ulceration. The concurrent use of NSAIDs and corticosteroids increases the risk of gastrointestinal bleeding and probably ulceration.
Ibuprofen, indometacin and naproxen may increase the levels of free prednisolone, and the plasma levels of diclofenac are modestly increased by triamcinolone. Dexamethasone and prednisone do not appear to affect the levels of oxyphenbutazone.

Clinical evidence, mechanism, importance and management

(a) Gastrointestinal bleeding and ulceration

A retrospective study of about 20 000 patients who had taken corticosteroids found that the incidence of upper gastrointestinal bleeding resulting in hospitalisation was very low in outpatients taking corticosteroids for dermatitis and asthma. Bleeding occurred in only 45 (0.23%) of the patients. However, the risk of bleeding was increased if the patients were also taking aspirin or other NSAIDs (incidence rate of 5.1 per 10 000 person-months, compared with 2.2 per 10 000 person-months in those who did not take NSAIDs).[1] This is consistent with the results of another study in patients taking **prednisone** and **indometacin**.[2]

A case-control study reviewed 1415 patients aged 65 years or older, hospitalised between 1984 and 1986 for peptic ulcer or upper gastrointestinal haemorrhage of unknown cause, and 7063 control patients. The relative risk for the development of peptic ulcer disease was estimated to be 2 in those taking oral corticosteroids; however, for those corticosteroid users not receiving NSAIDs it was 1.1 and the estimated risk was only increased in those taking corticosteroids with NSAIDs (relative

risk 4.4). It was estimated that patients taking corticosteroids with NSAIDs have an approximately 15-fold greater risk for peptic ulcer disease than patients taking neither drug.[3]

Another study compared 1121 patients aged 60 years or over who were admitted to hospital with bleeding peptic ulcers, with 989 control patients, to investigate factors other than NSAIDs that may have contributed to the risk of bleeding.[4] The risk (calculated as odds ratio) was about threefold greater for the use of corticosteroids alone, but when corticosteroids were used with NSAIDs, the risk was ninefold greater.[4]

NSAIDs alone increase the risk of gastrointestinal adverse effects.[5-8] Most patients with NSAID-associated ulcers are elderly: this is because there is a greater prevalence of ulcer disease in the elderly, and they are more likely to be taking NSAIDs and to be sensitive to them.[7] A history of ulcer disease is a further risk factor.[7] Corticosteroids alone are reported not to be a risk factor in some studies,[1,9] while other studies found they were a risk factor for gastrointestinal adverse effects.[4,10] However, several studies have found that the risk of gastrointestinal adverse effects is increased by the combined use of corticosteroids and NSAIDs[3,4,11,12] and caution with concurrent use has been suggested.[3] It may be prudent to consider the use of gastroprotection in patients taking NSAIDs and corticosteroids, especially if they are elderly.

(b) Pharmacokinetic interactions

A patient with rheumatoid arthritis taking **prednisolone** 5 to 10 mg daily with the intermittent use of an NSAID (aspirin 700 mg to 2.8 g daily, **ibuprofen** 400 mg to 1.2 g daily, or **naproxen** 250 to 500 mg daily), developed osteonecrosis of the upper third of the femoral head, which was attributed to increased free levels of **prednisolone** due to protein-binding displacement by the NSAID.[13] A study in 11 patients with stable rheumatoid disease regularly taking a corticosteroid found that **indometacin** 75 mg or **naproxen** 250 mg twice daily for 2 weeks did not alter the total plasma levels of a single 7.5-mg dose of **prednisolone** but the amount of unbound (free) **prednisolone** increased by 30 to 60%.[14] The probable reason for this effect is that these NSAIDs displace both administered and endogenous corticosteroids from their plasma protein binding sites. In a double-blind, crossover study 12 healthy subjects were given **rofecoxib** 250 mg daily or placebo for 14 days, with a single 30-mg dose of either intravenous **prednisolone** or oral **prednisone** on days 10 and 14. **Rofecoxib** did not affect the pharmacokinetics of the corticosteroids, even at a dose 10 times greater than that used clinically.[15]

In a double-blind, crossover study in healthy subjects given a single intramuscular dose of **diclofenac** 75 mg, the use of **triamcinolone** 40 mg increased the maximum plasma levels of **diclofenac** by 24%. This was possibly due to an increased rate of absorption. Other pharmacokinetic parameters of **diclofenac** were not significantly changed.[16] In another study, neither **prednisone** 5 mg nor **dexamethasone** 1.5 mg daily were found to affect **oxyphenbutazone** levels.[17]

The majority of these pharmacokinetic interactions seem unlikely to be of clinical significance, but they may well contribute to the adverse effects of both drugs, particularly the corticosteroids. No particular action appears to be necessary to account for these pharmacokinetic effects.

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Corticosteroids + Phenytoin

The therapeutic effects of dexamethasone, fludrocortisone, methylprednisolone, prednisolone, prednisone, and probably other corticosteroids, can be markedly reduced by phenytoin. One study suggested that dexamethasone may modestly increase serum phenytoin levels, but another study and two case reports of patients with brain metastases suggest that a *decrease* can occur. The results of the dexamethasone adrenal suppression test may prove to be unreliable in those taking phenytoin.

Clinical evidence

Several studies suggest that phenytoin may affect the half-life and clearance of a number of corticosteroids. These are shown in 'Table 29.2', (below). Other information regarding specific corticosteroids is given in the sections below.

Table 29.2 A comparison of the effects of phenytoin on the pharmacokinetics of different corticosteroids (after Petereit and colleagues[1])

Corticosteroid	*Daily dosage of phenytoin (mg)*	*Half-life without phenytoin (minutes)*	*Decreased half-life with phenytoin (%)*	*Increased mean clearance rate with phenytoin (%)*	*Refs*
Dexamethasone	300	250	51	140	2
Hydrocortisone	300 to 400	60 to 90	15	25	3
Methylprednisolone	300	165	56	130	4
Prednisolone	300	190 to 240	45	77	3
Prednisone	Prednisolone is the biologically active metabolite of prednisone so that the values for prednisone and prednisolone should be similar				5

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(a) Dexamethasone

1. Dexamethasone levels/response. A comparative pharmacokinetic study in 6 neurological or neurosurgical patients taking oral dexamethasone and phenytoin found that the average amount of dexamethasone that reached the general circulation was a quarter of that observed in 9 other patients taking dexamethasone alone (mean oral bioavailability fractions of 0.21 and 0.84, respectively).[1] Another report describes patients who needed increased doses of dexamethasone while taking phenytoin,[2] and a patient with pemphigus vulgaris failed to respond to large doses of corticosteroids including **prednisolone** 100 mg daily or dexamethasone 30 mg daily when he took phenytoin and phenobarbital. Dramatic improvement occurred following gradual discontinuation of the antiepileptic drugs.[3]

A study in 7 patients found that phenytoin 300 to 400 mg daily reduced the plasma cortisol levels in response to dexamethasone from 220 to 190 microgram/L, compared with a mean reduction from 180 to 40 microgram/L in the absence of phenytoin.[4] Other studies confirmed that, in patients taking long-term phenytoin, plasma cortisol and urinary 17-hydroxycorticosteroid levels were suppressed far less than might be expected with small doses of dexamethasone (500 micrograms every 6 hours for 8 doses), but with larger doses (2 mg every 6 hours for 8 doses) suppression was normal.[5] However, one case describes a patient in whom even 16 mg of dexamethasone failed to cause cortisol depression while she was taking phenytoin, but when she was re-tested in the absence of phenytoin only 1 mg of dexamethasone was needed to elicit a response.[6]

Phenytoin levels. A study into epilepsy prophylaxis post-trauma found that the serum phenytoin levels in those taking dexamethasone 16 to 150 mg (mean 63.6 mg) were 40% higher than in those taking phenytoin alone (17.3 micrograms/mL compared with 12.5 micrograms/mL). The phenytoin was given as a loading dose of 11 mg/kg intravenously and then 13 mg/kg intramuscularly.[7] Conversely, a retrospective study of 40 patient records (diagnosis unspecified) indicated that dexamethasone reduced serum phenytoin levels: the serum phenytoin levels of 6 patients receiving fixed doses of phenytoin were halved by dexamethasone.[8] Another report describes a patient with brain metastases who required over 8 mg/kg of phenytoin (600 mg) to achieve therapeutic phenytoin levels in the presence of dexamethasone 16 mg. When the dexamethasone was increased to 28 mg daily he experienced seizures, and an increase in his phenytoin dose from 600 mg to 1 g only resulted in an increase in his levels from 13.9 to 16.4 micrograms/mL.[9] Another patient, also with a brain metastasis, needed a large dose of phenytoin (greater than 10 mg/kg) while taking dexamethasone. He had an almost fourfold rise in serum phenytoin levels when dexamethasone was stopped.[10]

(b) Other corticosteroids

The **fludrocortisone** dosages of two patients required 4-fold and 10- to 20-fold increases, respectively, in the presence of phenytoin.[11]

Renal allograft survival is decreased in patients taking **prednisone** and phenytoin, due (it is believed) to a reduction in the immunosuppressant effects of the corticosteroid.[12] For mention of a patient with pemphigus vulgaris who did not respond to corticosteroids including **prednisolone** when he was also treated with drugs including phenytoin, see under *Dexamethasone*, above.

Mechanism

Phenytoin is a potent liver enzyme inducer that increases the metabolism of the corticosteroids so that they are cleared from the body more quickly, reducing both their therapeutic and adrenal suppressant effects.

Importance and management

The fall in serum corticosteroid levels is established and of clinical importance in systemic treatment, but it seems unlikely to affect the response to steroids given topically or by inhalation, intra-articular injection or enema.[13] The interaction can be accommodated in several ways:

- Increase the corticosteroid dosage proportionately to the increase in clearance (see 'Table 29.2', (p.1267)). With prednisolone an average increase of 100% (range 58 to 260% in 5 subjects) proved effective.[13] A fourfold increase may be necessary with dexamethasone,[1] and much greater increases have been required with fludrocortisone.[11]
- Exchange the corticosteroid for another that is less affected (see 'Table 29.2', (p.1267)). A comparative study in children found that **methylprednisolone** was more affected than prednisolone.[14] In another case the exchange of dexamethasone 16 mg daily for prednisone 100 mg daily was successful.[15]
- Exchange the phenytoin for another antiepileptic: barbiturates (including primidone[16]) and carbamazepine, are also enzyme-inducers, but valproate is a possible non-interacting alternative,[2] where clinically appropriate. However, remember that corticosteroids should only be given to epileptics with care and good monitoring because of the risk that they will exacerbate the disease condition.

The effects of phenytoin on the dexamethasone adrenal suppression test can apparently be accommodated by using larger than usual doses of dexamethasone (2 mg every 6 hours for 8 doses)[5] or by an overnight test using 50 mg of hydrocortisone.[17]

The reports on the changes in serum phenytoin levels are inconsistent (both increases and decreases have been seen). The effects of concurrent use should be closely monitored.

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Corticosteroids + Protease inhibitors

Several cases of Cushing's syndrome have been seen in patients using inhaled or intranasal fluticasone when ritonavir was also given. In healthy subjects given fluticasone propionate intranasally, ritonavir increased fluticasone propionate plasma concentrations several hundred fold, resulting in markedly reduced serum cortisol concentrations. Ritonavir may reduce the clearance of prednisone, prednisolone and some other corticosteroids. Ritonavir and nelfinavir may increase levels of the active metabolite of ciclesonide. Dexamethasone may reduce the levels of indinavir, saquinavir and possibly darunavir.

Clinical evidence

(a) Fluticasone

Case reports of adverse effect. An HIV-positive 32-year-old man who had been using intranasal fluticasone 200 micrograms twice daily for 3 years for allergic rhinitis, developed a cushingoid face and gained 6.5 kg in weight within 5 months of starting to take **ritonavir**, zidovudine and lamivudine.[1] Another HIV-positive man receiving inhaled beclometasone 400 to 800 micrograms daily for asthma and intranasal fluticasone 800 micrograms daily for allergic rhinitis was also given **ritonavir**, **saquinavir**, stavudine and nevirapine, after which he developed mild cushingoid facial changes. Both patients had high plasma levels of fluticasone. The problems resolved when the fluticasone was withdrawn. A third HIV-positive patient receiving inhaled beclometasone and intranasal fluticasone as well as **ritonavir**, zidovudine and lamivudine, had increased fluticasone levels but no signs of Cushing's syndrome.[1]

A further 6 HIV-positive patients taking protease inhibitors, including low

doses of **ritonavir**, and with HIV-lipodystrophy developed symptomatic Cushing's syndrome when given inhaled fluticasone. All had adrenal suppression, and after withdrawal of fluticasone, 3 patients required oral corticosteroids for several months. Exacerbation of pre-existing diabetes mellitus occurred in one patient and 4 patients had osteoporosis (1 with fractures). Diagnosis was made more difficult by the lipodystrophy masking the Cushingoid features.[2] Another report describes exacerbation of AIDS-associated Kaposi sarcoma together with iatrogenic Cushing syndrome in a patient receiving **ritonavir**-boosted **atazanavir** and fluticasone. Discontinuation of the fluticasone resulted in resolution of the cutaneous Kaposi sarcoma.[3]

There are reports of at least 12 other patients, including 4 children or adolescents,[4-6] who have developed Cushing's syndrome within 2 to 5 months of using regimens of inhaled[4-12] or intranasal[13] fluticasone, with **ritonavir**,[6,13] and the following ritonavir-boosted protease inhibitors: **amprenavir**,[7,11] **atazanavir**,[12] **indinavir**,[11] **lopinavir**,[4,5,9] **saquinavir**,[8] or **lopinavir** with **saquinavir**.[10] The interaction was confirmed in one patient by replacing the **ritonavir** with nevirapine for 3 weeks and then restarting the **ritonavir**.[13]

2. Pharmacokinetic studies. In a crossover study in 18 healthy subjects, fluticasone propionate nasal spray 200 micrograms was given daily for 7 days. Plasma fluticasone propionate levels were undetectable in most subjects, and when they were detectable, maximum levels averaged 11.9 picograms/mL. After the addition of **ritonavir** 100 mg twice daily for 7 days, the maximum plasma levels of fluticasone propionate increased to 318 picograms/mL and the AUC increased approximately 370-fold. The serum cortisol AUC decreased by 86%.[14]

(b) Prednisolone or Prednisone

A study in healthy subjects found that the AUC of a single 20-mg dose of prednisone, given before and on days 4 and 14 of a 14.5 day course of **ritonavir** 200 mg twice daily, was increased by about 30% by the **ritonavir**. The apparent oral clearance of prednisolone was reduced from 8.84 L/hour to 6.45 L/hour and 6.88 L/hour on days 4 and 14, respectively.[15] A further study in HIV-positive subjects found that **lopinavir**/**ritonavir** increased the AUC of a single 20-mg dose of prednisolone compared with the AUC in subjects not receiving antiretroviral medications, although this was not statistically significant.[16]

Mechanism

Ritonavir, and all protease inhibitors, inhibit the cytochrome P450 isoenzyme CYP3A4 to varying degrees. Fluticasone is metabolised by this isoenzyme and therefore the protease inhibitors cause its plasma levels to rise. The active metabolite of ciclesonide is also metabolised by CYP3A4,[17] and is therefore similarly affected. Prednisolone is less dependent on CYP3A4 for metabolism, and is therefore only modestly affected.

Importance and management

The interaction between ritonavir and **fluticasone** appears to be established and clinically important. The incidence is not known, but any patient using these two drugs should be very well monitored for any signs of corticosteroid overdose. The problem may take months to manifest itself. It has been suggested that if an inhaled corticosteroid is required by a patient taking ritonavir, a corticosteroid that is not a substrate for CYP3A4 (e.g. beclometasone)[18] or one with less systemic availability should be given at the lowest effective dose.[19] The manufacturers of fluticasone inhaler[14,20] and nasal spray[21,22] advise against their concurrent use with ritonavir unless the potential benefit is considered to outweigh the risk of systemic corticosteroid adverse effects; similar advice has been given by the manufacturers of protease inhibitors boosted with ritonavir.

Ritonavir may increase the levels of **prednisone** and **prednisolone** and some manufacturers of **betamethasone**,[23] **budesonide**,[24] **ciclesonide**,[17] or **dexamethasone**[25,26] predict a similar interaction. As a result, concurrent use is not generally recommended due to the increased risk of systemic adverse effects of corticosteroids, but if the combination is essential careful monitoring would be prudent. The need for dosage reduction of the corticosteroid should be borne in mind. Note that, of the protease inhibitors, **nelfinavir**, like ritonavir, is a highly potent inhibitor of CYP3A4, and therefore similar precautions to those advised with ritonavir would seem prudent if nelfinavir is given with one of these corticosteroids. Other protease inhibitors have less effect on CYP3A4, but some monitoring would still seem appropriate, particularly as low-dose ritonavir is often used with these protease inhibitors as a pharmacological booster.

The manufacturers of **dexamethasone** note that it is a modest inducer of CYP3A4 and state that it may reduce the plasma levels of indinavir or saquinavir.[26] Similar warnings are given by the manufacturer of **darunavir**.[18] The clinical outcome of this predicted effect is unknown, but until more is known, it would seem prudent to monitor antiviral efficacy if these combinations are used.

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18. Prezista (Darunavir ethanolate). Janssen-Cilag Ltd. UK Summary of product characteristics, October 2009.
19. Li AM. Ritonavir and fluticasone: beware of this potentially fatal combination. *J Pediatr* (2006) 148, 294–5.
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26. Dexamethasone Tablets. Organon Laboratories Ltd. UK Summary of product characteristics, March 2008.

Corticosteroids + Proton pump inhibitors

Lansoprazole appears to have no effect on the pharmacokinetics of prednisolone following a single dose of prednisone. Omeprazole has no effect on oral budesonide or prednisone pharmacokinetics in healthy subjects, but an isolated and unexplained report describes a reduction in the effects of prednisone in a patient taking omeprazole.

Clinical evidence, mechanism, importance and management

(a) Lansoprazole

A placebo-controlled, randomised study in 18 healthy subjects found that lansoprazole 30 mg daily had no effect on the absorption of a single 40-mg oral dose of **prednisone**. Furthermore, the biotransformation of prednisone to **prednisolone**, and the pharmacokinetics of prednisolone were not affected.[1]

(b) Omeprazole

A placebo-controlled, randomised study in 18 healthy subjects found that omeprazole 40 mg daily had no effect on the pharmacokinetics of **prednisolone** after a single 40-mg dose of **prednisone**.[1] This contrasts with an isolated and unexplained report of a patient suffering from pemphigus who was given **prednisone** 1 mg/kg daily with, a week later, ranitidine 200 mg daily for a gastric ulcer. Four weeks later, when the skin lesions were well controlled, it was decided to replace the ranitidine with omeprazole 40 mg daily. Within 4 days the skin lesions began to worsen progressively, although the **prednisone** dosage remained unchanged. After 3 weeks it was decided to stop the omeprazole and restart the ranitidine because an adverse interaction between the **prednisone** and the omeprazole was suspected. Within about a week, the skin condition had begun to improve.[2] The suggested explanation for the interaction is that the omeprazole inhibited the liver enzyme (11β-hydroxylase) that normally converts **prednisone** into its active form (prednisolone) resulting in inadequate treatment of the pemphigus.[2]

A placebo-controlled, randomised study in 11 healthy subjects found that omeprazole 20 mg daily for 5 days had no effect on the pharmacokinetics of a single 9-mg dose of **budesonide** (*Entocort CR* capsules).[3]

It would seem that adverse interactions between oral **budesonide** or **prednisone** and omeprazole are unlikely, but the isolated case should be borne in mind in the event of an unexpected response to treatment.

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Corticosteroids + Rifampicin (Rifampin)

The effects of systemic cortisone, dexamethasone, fludrocortisone, hydrocortisone, methylprednisolone, prednisone and prednisolone can be markedly reduced by rifampicin, but aldosterone appears not to be affected. Rifabutin and rifapentine are predicted to interact similarly, all be it to a lesser extent.

Clinical evidence

(a) Aldosterone

In 7 patients with Addison's disease due to tuberculosis, there were no changes in the pharmacokinetics of intravenous aldosterone after they were also given rifampicin 600 mg daily for 6 days.[1]

(b) Cortisone and Fludrocortisone

A patient with Addison's disease taking cortisone and fludrocortisone had typical signs of corticosteroid overdosage when the rifampicin he was taking was replaced by ethambutol,[2] suggesting that the rifampicin had reduced the levels of these corticosteroids. Another Addisonian patient needed an increase in her dosage of cortisone from 37.5 mg daily to 50 mg daily, and fludrocortisone 100 micrograms daily, when rifampicin 450 mg daily was started.[3] A patient had an Addisonian crisis when rifampicin was added to treatment with **dexamethasone** and fludrocortisone.[4]

(c) Dexamethasone

Rifampicin markedly increases the clearance of dexamethasone.[5,6] A patient had an Addisonian crisis when rifampicin was added to treatment with dexamethasone and **fludrocortisone**.[4]

(d) Hydrocortisone

A metabolic study in an Addisonian patient taking hydrocortisone found that rifampicin shortened its half-life and reduced its AUC.[7]

(e) Other corticosteroids

A child with nephrotic syndrome taking **prednisolone**, and accidentally given a BCG vaccine, was given rifampicin and isoniazid to prevent possible dissemination of the vaccine. When the nephrotic condition did not respond, the prednisolone dosage was raised from 2 to 3 mg/kg daily without any evidence of corticosteroid overdosage. Later when the rifampicin and isoniazid were withdrawn, remission of the nephrotic condition was achieved with the original dosage of prednisolone.[8] A number of other reports describe a reduction in the response to **prednisone**, **prednisolone** or **methylprednisolone** in patients given rifampicin.[4,9-17] Pharmacokinetic studies in patients have shown that the AUC of **prednisolone** is reduced by about 60% by rifampicin, and its half-life is decreased by 40% to 60%.[11,15,18]

Mechanism

Rifampicin is a potent liver enzyme inducer, which increases the metabolism of the corticosteroids by the liver,[10] thereby decreasing their levels and reducing their effects.

Importance and management

The interactions between the corticosteroids and rifampicin are established, well documented and clinically important. The need to increase the dosages of cortisone, dexamethasone, fludrocortisone, hydrocortisone, methylprednisolone, prednisolone and prednisone should be expected if rifampicin is given. It has been suggested that as an initial adjustment the dosage of prednisolone should be increased two- to threefold, and reduced proportionately if the rifampicin is withdrawn.[10,11,18,19] In the case of prednisolone the interaction develops maximally by 14 days and disappears about 14 days after withdrawal of the rifampicin.[20]

There seems to be no direct information about corticosteroids other than those mentioned here, but be alert for them to be similarly affected. Systemic corticosteroids are usually considered as contraindicated, or only to be used with great care, in patients with active or quiescent tuberculosis.

It is not clear whether any of the topically applied corticosteroids will interact with rifampicin, but any clinically significant interaction would be expected to be very rare.

There does not seem to be any information regarding the other rifamycins, **rifabutin** (a weak enzyme inducer) and **rifapentine** (a moderate enzyme inducer). However, the UK manufacturers and the CSM in the UK warn that rifabutin may possibly reduce the effects of a number of drugs,[21,22] including corticosteroids,[21] and therefore some caution is probably prudent.

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Corticosteroids + Somatropin

Corticosteroid doses may possibly require increasing if somatropin is also given. Corticosteroid replacement therapy may attenuate the growth promoting effects of somatropin.

Clinical evidence, mechanism, importance and management

One manufacturer of somatropin says that it inhibits 11β-hydroxysteroid dehydrogenase type 1 (11βHSD-1) in adipose and hepatic tissue and may affect the metabolism of cortisol and cortisone.[1] Limited *in vitro*[2] and *in vivo*[3] data also indicate that somatropin may be an inducer of cytochrome P450 isoenzymes and that it may increase the clearance of drugs that are metabolised by CYP3A4 enzymes, including a number of corticosteroids.[1-4] The clinical significance of this is unknown, but careful monitoring is advisable. Somatropin has been reported to induce a modest reduction of serum cortisol levels in growth hormone deficient patients receiving adrenal substitution treatment.[2] Therefore, patients receiving corticosteroid replacement therapy may require an increase in their maintenance or stress doses of corticosteroid if they are given somatropin;[1,2] this may be especially true for patients taking **cortisone acetate** and **prednisone** since conversion of these drugs to their biologically active metabolites is dependent on the activity of the 11βHSD-1 enzyme.[1]

In addition, glucocorticoid therapy may attenuate the growth promoting effects of somatropin.[1,2,4] Therefore, glucocorticoid replacement therapy should be carefully adjusted in patients with growth hormone and glucocorticoid deficiency to avoid both hypoadrenalism and an inhibitory effect on growth.[1]

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Corticosteroids + St John's wort (*Hypericum perforatum*)

St John's wort does not appear to affect the pharmacokinetics of prednisone or its metabolite, prednisolone.

Clinical evidence

In a pharmacokinetic study, 8 healthy subjects were given a single 20-mg oral dose of **prednisone** before, and at the end, of a 28-day course of St John's wort 300 mg three times daily. The pharmacokinetics of **prednisone**, and its metabolite **prednisolone**, were not significantly affected by St John's wort. The St John's wort extract was standardised to contain hypericin 0.3% and a minimum of 4% hyperforin.[1]

Mechanism

It was thought that St John's wort, a known inducer of the cytochrome P450 isoenzyme CYP3A4, would increase the metabolism of prednisone and prednisolone and reduce their levels. While prednisone and prednisolone are substrates of CYP3A4, it is not a major metabolic pathway as they have been shown to be only modestly affected by potent CYP3A4 inhibitors in healthy subjects.

Importance and management

St John's wort does not appear to induce the metabolism of a single dose of prednisone, or its metabolite prednisolone, in healthy subjects; however, further study is needed to clarify significance of this in patients receiving long-term prednisone.

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Corticosteroids + Sucralfate

Sucralfate does not appear to affect the pharmacokinetics of prednisone to a clinically relevant extent.

Clinical evidence, mechanism, importance and management

In 12 healthy subjects, sucralfate 1 g every 6 hours had no significant effect on the pharmacokinetics of a single 20-mg dose of **prednisone**; however, the peak plasma levels were delayed by about 45 minutes when the drugs were given at the same time, but not when the sucralfate was given 2 hours after the **prednisone**.[1] No particular precautions are likely to be needed in patients given both drugs. Information about other corticosteroids is lacking.

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Corticosteroids + Tobacco

The pharmacokinetics of dexamethasone, prednisone and prednisolone do not appear to be affected by smoking. Cigarette smoking in asthma is associated with a reduced sensitivity to corticosteroids.

Clinical evidence, mechanism, importance and management

Studies have shown that cigarette smoking impairs the efficacy of inhaled corticosteroids,[1-4] including **beclometasone,**[1,2] **budesonide**[3] and **fluticasone**.[4] One study showed that smokers with mild persistent asthma were insensitive to the therapeutic effect of low-doses of inhaled corticosteroids, although some benefit was observed with high-doses of inhaled corticosteroids.[2] However, another study found that neither lung function nor eosinophil markers changed in smokers, even when high doses of inhaled corticosteroids were given.[3]

Active smoking also impairs the therapeutic response to short-term oral corticosteroids in chronic asthma. In a study in asthmatic patients, **prednisolone** 40 mg daily for 14 days significantly improved FEV_1 in patients who had never smoked, but had no effect on smokers, when compared with placebo.[5] Ex-smokers who had stopped smoking for more than one year showed a trend towards improvement in asthma control after **prednisolone** treatment.[5] However, in another study there was no change in airway corticosteroid responses in patients who had only stopped smoking for 6 weeks, although baseline lung function had improved.[6]

In addition, the insensitivity to corticosteroids in smokers with asthma appears to affect tissue sites other than the airways; the cutaneous vasoconstrictor response to topical **beclometasone** is reduced in smokers with asthma, when compared with patients with asthma who have never smoked.[7] In a study in asthmatic patients who smoked, the vasoconstrictor response to topical **beclometasone** improved in those who had stopped smoking for 6 weeks, compared with those who continued to smoke.[6]

A study involving 18 healthy subjects, half of whom were smokers, found that smoking had no overall effect on the pharmacokinetics of oral or intravenous **dexamethasone**, oral **prednisone**, or intravenous **prednisolone**.[8]

Cigarette smoking is an important factor associated with corticosteroid resistance in asthmatics. The mechanism behind the reduced sensitivity to corticosteroids in smokers is not fully understood, but may possibly be due to increased oxidative stress resulting in reduced histone deacetylase activity, airway inflammation, and/or impaired glucocorticoid receptor function. There is some evidence that smoking cessation may at least partially restore corticosteroid responsiveness.[9-11] These findings reinforce the need for those with airways disease, including asthma, to give up smoking tobacco.

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Corticosteroids + Vaccines

Patients who are immunised with live vaccines while receiving immunosuppressive doses of corticosteroids may develop generalised, possibly life-threatening, infections. Corticosteroids may attenuate the response to vaccination.

Clinical evidence, mechanism, importance and management

The use of corticosteroids can reduce the number of circulating lymphocytes and suppress the normal immune response, so that concurrent immunisation with live vaccines can lead to generalised infection. It has been suggested that **prednisone** in doses of greater than 10 to 15 mg daily will suppress the immune response, whereas doses of up to 40 to 60 mg on alternate days probably will not,[1] although this is debated.

A patient with lymphosarcoma and hypogammaglobulinaemia, taking **prednisone** 15 mg daily, developed a generalised vaccinial infection when she was given **smallpox vaccine**.[2] A fatal vaccinial infection developed following **smallpox vaccination** in another patient taking **cortisone**.[3] This type of problem can be controlled with immunoglobulin to give cover against a general infection while immunity develops, and this has been successfully used in steroid-dependent patients needing **smallpox vaccination**.[4]

The principles applied to **smallpox** may be generally applicable to other live attenuated vaccines (e.g. **measles**, **mumps**, **rubella**, **poliomyelitis**, **BCG**), but no studies seem to have been done to establish what is safe.[1]

It is generally accepted that patients taking immunosuppressants should not be given live vaccines. Problems with topical or inhaled steroids in normal dosages seem unlikely because the amounts absorbed are relatively small.[1] However, this needs confirmation. The UK Department of Health contraindicates the use of live vaccines in all patients receiving systemic high-dose steroids, until at least 3 months after treatment has been stopped.[5] This includes children who receive **prednisolone**, orally or rectally, at a daily dose (or its equivalent) of 2 mg/kg per day for at least one week, or 1 mg/kg per day for one month. For adults, immunosuppression should be considered in those who receive at least 40 mg of **prednisolone** per day for more than one week.

Note that immunosuppression caused by corticosteroids may also attenuate the response to other vaccines. In one study patients given a higher dose of **prednisolone** per kg had a reduced antibody response to **influenza vaccine**, and those given a daily dose had a reduced response, when compared with those given an alternate day schedule.[6] Consider also 'Immunosuppressants + Vaccines', p.1276.

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Corticosteroids + Zileuton

No clinically relevant pharmacokinetic interaction occurs between prednisone and zileuton.

Clinical evidence, mechanism, importance and management

In a randomised, crossover study, 16 healthy subjects were given zileuton 600 mg every 6 hours for a week, with either a 40-mg dose of **prednisone** or placebo on day 6. The pharmacokinetics of both drugs were slightly altered but this was not considered to be clinically relevant. The half-life of **prednisolone** (derived from **prednisone**) increased from 2.8 to 2.9 hours, while the zileuton AUC and the time to achieve maximum serum levels were decreased by 13% and 26%, respectively. It was concluded that concurrent use carries a minimal risk of a clinically important pharmacokinetic interaction.[1] No special precautions would appear to be needed if both drugs are given.

1. Awni WM, Cavanaugh JH, Tzeng T-B, Witt G, Granneman GR, Dubé LM. Pharmacokinetic interactions between zileuton and prednisone. *Clin Pharmacokinet* (1995) 29 (Suppl 2), 105–111.

Corticosteroids; Dexamethasone + Asparaginase

Recent treatment with asparaginase may reduce dexamethasone clearance.

Clinical evidence, mechanism, importance and management

A study in 214 children with acute lymphoblastic leukaemia found that there was considerable inter- and intrapatient variability in the pharmacokinetics of dexamethasone 8 mg/m^2 daily on days 1 and 8 of an 8-day re-induction course of dexamethasone: more than a tenfold variability in systemic exposure to the drug was found. Much of the variability in dexamethasone clearance was accounted for by variability in serum albumin concentrations, which in turn were affected by the intensity of previous asparaginase treatment. Hypoalbuminaemia, a biomarker of asparaginase activity, was associated with a low dexamethasone apparent clearance, whilst higher apparent clearance of dexamethasone was associated with a greater serum albumin concentration and also with younger children (who tended to be treated in the low-risk group).[1] The authors of the report suggest that this interaction may be, at least in part, responsible for the variability in response to dexamethasone in this patient group. More study is needed.

1. Yang L, Panetta JC, Cai X, Yang W, Pei D, Cheng C, Kornegay N, Pui C-H, Relling MV. Asparaginase may influence dexamethasone pharmacokinetics in acute lymphoblastic leukemia. J Clin Oncol (2008) 26, 1932–9.

Corticosteroids; Dexamethasone + Caffeine

The results of the dexamethasone suppression test can be falsified by the acute ingestion of caffeine but long-term caffeine use does not appear to have an effect.

Clinical evidence, mechanism, importance and management

In a placebo-controlled study, 22 healthy subjects and 6 depressed patients were given a single 480-mg dose of caffeine at 2 pm, following a single 1-mg dose of dexamethasone given at 11 pm the previous evening. Caffeine significantly increased the cortisol levels following the dexamethasone dose: cortisol levels taken at 4 pm were about 146 nanomol/L with caffeine, compared with about 64 nanomol/L with placebo.[1] Thus the equivalent of about 4 to 5 cups of coffee may effectively falsify the results of the dexamethasone suppression test. However, in a study in 121 patients with depression, there was no correlation between long-term low to high intake of caffeine (6 mg to 2.3 g daily) and cortisol levels at 8 am, 4 pm or 11 pm on the day after a 1-mg dose of dexamethasone was given (at 11 pm the previous evening). It was suggested that long-term caffeine intake produces tolerance to the effects of acute caffeine on the hypothalamic-pituitary adrenal (HPA) axis.[2]

1. Uhde TW, Bierer LM, Post RM. Caffeine-induced escape from dexamethasone suppression. *Arch Gen Psychiatry* (1985) 42, 737–8.
2. Lee MA, Flegel P, Cameron OG, Greden JF. Chronic caffeine consumption and the dexamethasone suppression test in depression. *Psychiatry Res* (1988) 24, 61–5.

Corticosteroids; Dexamethasone + Valspodar

Dexamethasone does not affect the pharmacokinetics of valspodar. Valspodar modestly increases the AUC of dexamethasone.

Clinical evidence, mechanism, importance and management

In a crossover study, healthy fasting subjects were given single doses of dexamethasone 8 mg and valspodar 400 mg either alone or together. Dexamethasone had no effect on the pharmacokinetics of valspodar. The AUC of dexamethasone was increased by 24% by valspodar. This change is modest and therefore dosage alterations are probably not required if concurrent use is of a short duration.[1]

1. Kovarik JM, Purba HS, Pongowski M, Gerbeau C, Humbert H, Mueller EA. Pharmacokinetics of dexamethasone and valspodar, a P-glycoprotein (*mdr1*) modulator: implications for coadministration. *Pharmacotherapy* (1998) 18, 1230–6.

Etanercept + Methotrexate

Methotrexate does not appear to alter the pharmacokinetics of etanercept.

Clinical evidence, mechanism, importance and management

A double-blind study in 98 patients with rheumatoid arthritis receiving subcutaneous etanercept 25 mg twice weekly, or etanercept with oral methotrexate (median weekly dose of 20 mg) found that the pharmacokinetics of etanercept were not altered by methotrexate.[1] No particular precautions or dosage adjustments appear to be necessary on concurrent use.

1. Zhou H, Mayer PR, Wajdula J, Fatenejad S. Unaltered etanercept pharmacokinetics with concurrent methotrexate in patients with rheumatoid arthritis. *J Clin Pharmacol* (2004) 44, 1235–43.

Etanercept + Miscellaneous

A higher incidence of malignancies has been reported in patients with Wegener's granulomatosis when given both cyclophosphamide and etanercept. A reduced neutrophil count may occur in patients taking etanercept with sulfasalazine. No interactions have been found when etanercept was given with salicylates other than sulfasalazine, corticosteroids, or NSAIDs.

Clinical evidence, mechanism, importance and management

(a) Cyclophosphamide

The US manufacturer says that etanercept is not recommended in patients receiving cyclophosphamide. They state that in a study in patients with Wegener's granulomatosis, the addition of etanercept to standard treatment, including cyclophosphamide, was associated with a higher incidence of non-cutaneous solid malignancies.[1]

(b) Sulfasalazine

A study in patients taking sulfasalazine found that when etanercept was also given, patients had a decrease in neutrophil counts, when compared to other groups of patients receiving either drug alone. The clinical significance of this finding is not known.[1,2]

(c) Other drugs

The UK manufacturer notes that no interactions have been found when etanercept was given with **corticosteroids**, **salicylates** (except *sulfasalazine*, see above), **NSAIDs** or other analgesics.[2]

1. Enbrel (Etanercept). Amgen Inc. & Wyeth Pharmaceuticals. US Prescribing information, April 2009.
2. Enbrel (Etanercept). Wyeth Pharmaceuticals. UK Summary of product characteristics, May 2009.

Everolimus + Calcium-channel blockers

Increased levels of both everolimus and verapamil can occur on concurrent use. Diltiazem might be expected to increase everolimus levels, although there was no clear evidence of an interaction in a population model. In this model, there was also no evidence of an interaction with amlodipine, isradipine or nifedipine.

Clinical evidence

A study in 16 healthy subjects given a single 2-mg dose of everolimus before and on day 2 of a 6-day course of **verapamil** 80 mg three times daily found that verapamil increased the AUC and peak blood level of everolimus 3.5-fold and 2.3-fold, respectively. Everolimus also increased the plasma levels of verapamil 2.3-fold.[1]

In a pharmacokinetic modelling study, the difference in everolimus clearance in 5 patients taking **verapamil** was not statistically significant. In addition, there was no clear evidence of an effect on everolimus clearance for **diltiazem** in 22 patients or the dihydropyridines, **amlodipine**, **isradipine**, or **nifedipine** in 267 patients.[2] These suggested findings require confirmation.

Mechanism

Verapamil is an inhibitor of the cytochrome P450 isoenzyme CYP3A4, the isoenzyme primarily involved in the metabolism of everolimus, and also inhibits P-glycoprotein, a transporter for which everolimus is a substrate. Therefore concurrent use raises everolimus levels. It is not known exactly why verapamil levels are raised. Diltiazem is also an inhibitor of the cytochrome P450 isoenzyme CYP3A4 and so might be expected to interact similarly, although the modelling study cited did not find any effect. Further study is needed.

Importance and management

If verapamil is given with everolimus, it would seem prudent to monitor everolimus blood levels as well as monitor for adverse effects due to verapamil, such as hypotension, flushing and oedema, and adjust the dose of both drugs as needed. The UK manufacturer recommends that, in patients given everolimus for renal cell carcinoma and also taking verapamil or diltiazem, an everolimus dose reduction from 10 mg daily to 5 mg daily or 5 mg on alternate days should be considered. However, they state that this dose decrease is a prediction and therefore good monitoring is still required.[3] Note that the US manufacturer advises avoiding the concurrent use of both of these calcium-channel blockers.[4]

One manufacturer[5] also lists **nicardipine**, but note that the degree of inhibition of CYP3A4 is less than that of diltiazem and verapamil.

Amlodipine, isradipine, and nifedipine do not appear to interact with everolimus, although this ideally needs confirmation in formal pharmacokinetic studies.

1. Kovarik JM, Beyer D, Bizot MN, Jiang Q, Allison MJ, Schmouder RL. Pharmacokinetic interaction between verapamil and everolimus. *Br J Clin Pharmacol* (2005) 60, 434–7.
2. Kovarik JM, Hsu C-H, McMahon L, Berthier S, Rordorf C. Population pharmacokinetics of everolimus in de novo renal transplant patients: impact of ethnicity and comedications. *Clin Pharmacol Ther* (2001) 70, 247–54.
3. Afinitor (Everolimus). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, October 2009.
4. Afinitor (Everolimus). Novartis. US Prescribing information, March 2009.
5. Certican (Everolimus). Novartis Pharmaceuticals Australia Pty Ltd. Australian product information, March 2008.

Everolimus + Ciclosporin

Ciclosporin increases the AUC of everolimus. Although everolimus appears to have no relevant effects on ciclosporin levels, concurrent use might potentiate ciclosporin-induced renal toxicity.

Clinical evidence

(a) Effects on ciclosporin

In a phase I pharmacokinetic study in 7 patients stable taking ciclosporin, there was no change in ciclosporin pharmacokinetics when they were given a single-dose of everolimus ranging from 0.25 to 15 mg.[1] Similarly, in a placebo-controlled study in 54 kidney transplant patients taking ciclosporin (93% also taking prednisone), everolimus 0.75 to 10 mg daily in single or divided doses had no consistent, clinically relevant effect on ciclosporin levels in 44 patients when compared with the 10 patients given placebo. However, because of wide interpatient variability, there is a possibility that an interaction could occur in some patients.[2] Another study in 101 kidney transplant patients taking ciclosporin and prednisone with everolimus 0.5 to 2 mg twice daily for one year also found no evidence that everolimus affected ciclosporin pharmacokinetics.[3]

(b) Effects on everolimus

The possibility of a drug interaction was assessed in a crossover study in 24 healthy subjects who were given a single 2-mg dose of everolimus, alone and with single doses of ciclosporin, either *Neoral* (microemulsion) 175 mg or *Sandimmun* (corn oil suspension) 300 mg. *Neoral* increased the peak levels and AUC of everolimus by 82% and 168%, respectively. *Sandimmun* did not affect the peak levels of everolimus but increased its AUC by 74%.[4]

In a pharmacokinetic study in 6 heart transplant recipients taking everolimus, trough concentrations of everolimus were almost halved from 4.2 micrograms/L to 2.3 micrograms/L when ciclosporin was stopped and tacrolimus was started. The AUC of everolimus was similarly decreased by about 50% and its maximum level was decreased by 35%.[5]

Mechanism

Not fully understood. Ciclosporin is a modest inhibitor of the cytochrome P450 isoenzyme CYP3A4 and of P-glycoprotein, of which everolimus is a substrate. Why the *Neoral* formulation had a greater effect than the *Sandimmun* formulation is unclear.

Importance and management

Information on the effects of ciclosporin on the pharmacokinetics of everolimus appear to be limited; however, the studies suggest that ciclosporin may increase everolimus levels to a clinically relevant extent. Therefore, it would be prudent to monitor everolimus levels with concurrent use of these drugs, and adjust the everolimus dose as necessary. The UK manufacturer recommends that, in patients given everolimus for renal cell carcinoma and also taking ciclosporin, an everolimus dose reduction from 10 mg daily, to 5 mg daily or 5 mg on alternate days, should be considered. However, they state that this dose decrease is a prediction and therefore good monitoring is still required.[6] Bear in mind that one study found that the *Neoral* formulation may have a greater effect than the *Sandimmun* formulation.

It would appear that, in general, everolimus has no clinically significant effects on the pharmacokinetics of ciclosporin. However, one manufacturer cautions that everolimus may potentiate the renal toxicity of ciclosporin. They recommend that renal function should be monitored, and that reduction of the ciclosporin dose should be considered in patients with raised serum creatinine. They say that, in renal transplantation, everolimus should not be used long term with full doses of ciclosporin.[7]

1. Kirchner GI, Winkler M, Mueller L, Vidal C, Jacobsen W, Franzke A, Wagner S, Blick S, Manns MP, Sewing K-F. Pharmacokinetics of SDZ RAD and cyclosporin including their metabolites in seven kidney graft patients after the first dose of SDZ RAD. *Br J Clin Pharmacol* (2000) 50, 449–54.
2. Budde K, Lehne G, Winkler M, Renders L, Lison A, Fritsche L, Soulillou J-P, Fauchald P, Neumayer H-H, Dantal J and RADW 102 Renal Transplant Study Group. Influence of everolimus on steady-state pharmacokinetics of cyclosporine in maintenance renal transplant patients. *J Clin Pharmacol* (2005) 45, 781–91.
3. Kovarik JM, Kahan BD, Kaplan B, Lorber M, Winkler M, Rouilly M, Gerbeau C, Cambon N, Boger R, Rordorf C on behalf of the Everolimus Phase II Study Group. Longitudinal assessment of everolimus in de novo renal transplant recipients over the first post-transplant year: pharmacokinetics, exposure-response relationships, and influence of cyclosporine. *Clin Pharmacol Ther* (2001). 69, 48–56.
4. Kovarik JM, Kalbag J, Figueiredo J, Rouilly M, O'Bannon LF, Rordorf C. Differential influence of two cyclosporine formulations on everolimus pharmacokinetics: a clinically relevant pharmacokinetic interaction. *J Clin Pharmacol* (2002) 42, 95–9.
5. Brandhorst G, Tenderich G, Zittermann A, Oezpeker C, Koerfer R, Oellerich M, Armstrong VW. Everolimus exposure in cardiac transplant recipients is influenced by concomitant calcineurin inhibitor. Ther Drug Monit (2008) 30, 113–16.
6. Afinitor (Everolimus). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, October 2009.
7. Certican (Everolimus). Novartis Pharmaceuticals Australia Pty Ltd. Australian product information, March 2008.

Everolimus + Food

A high-fat meal slightly reduces the exposure to everolimus.

Clinical evidence

In a single-dose study in 24 healthy subjects, giving everolimus 2 mg tablets with a high-fat breakfast reduced the maximum everolimus level by 60% and delayed the time to maximum level by about 1.25 hours when compared with the fasting state.[1] However, the everolimus AUC was reduced by just 16%. Similarly, in a study in 6 transplant patients taking ciclosporin and everolimus 2.5 mg daily, giving everolimus with a high-fat meal reduced the maximum level and AUC of everolimus by 53% and 21%, respectively, without altering the trough level.[1]

Mechanism

Unknown.

Importance and management

The available evidence suggests that food has little effect on the exposure to everolimus. Nevertheless, the UK manufacturer recommends that everolimus is taken consistently either with or without food, to minimise variability.[2]

1. Kovarik JM, Hartmann S, Figueiredo J, Rordorf C, Golor G, Lison A, Budde K, Neumayer HH. Effect of food on everolimus absorption: quantification in healthy subjects and a confirmatory screening in patients with renal transplants. *Pharmacotherapy* (2002) 22, 154–9.
2. Afinitor (Everolimus). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, October 2009.

Everolimus + Ketoconazole and other CYP3A4 inhibitors

Ketoconazole, a potent inhibitor of CYP3A4, very markedly increases everolimus levels. A report describes reduced everolimus clearance in a patient also given itraconazole, and another patient was treated with a markedly reduced everolimus dose while receiving voriconazole. Other inhibitors of CYP3A4 and/or P-glycoprotein are predicted to increase everolimus levels.

Clinical evidence

In a study, 12 healthy subjects were given a single 1-mg dose of everolimus on day 4 of an 8-day course of **ketoconazole** 200 mg twice daily. Ketoconazole increased the AUC, peak blood level and half-life of everolimus by 15-fold, 3.9-fold, and 1.9 fold, respectively.[1]

Similarly, in a pharmacokinetic modelling study, a patient taking **itraconazole** with everolimus, ciclosporin and prednisone had a 74% lower everolimus clearance. However, everolimus clearance was reduced by a non-significant 7% in 16 patients who were also taking **fluconazole**.[2] In one severely-ill patient receiving intravenous **fluconazole**, the authors stated that everolimus was started at about a 50 to 75% lower dose than usual (0.75 mg twice daily), and this maintained everolimus levels within the desired range.[3] However, note that the starting dose of 0.75 mg twice daily used in this study is the recommended initial dose in kidney and heart transplant patients.[4] When fluconazole was switched to **voriconazole**, the everolimus dose was reduced to just 0.25 mg daily, with everolimus levels remaining within the therapeutic range, although the concentration-dose ratio suggested that 0.25 mg twice daily might have been more appropriate.[3]

Mechanism

Everolimus, a derivative of sirolimus, is a substrate for the cytochrome P450 isoenzyme CYP3A4 and P-glycoprotein. The azole antifungals inhibit CYP3A4, to varying degrees (consider 'azole antifungals', (p.233)), and therefore inhibit everolimus metabolism.

Importance and management

The pharmacokinetic interaction with ketoconazole was very marked, and likely to be clinically important. One group recommends that, given the magnitude of the interaction, ketoconazole should be avoided if possible in patients taking everolimus.[5] The manufacturers also advise avoiding the concurrent use of ketoconazole; and also itraconazole, **posaconazole** and voriconazole.[6,7] If these azoles must be given with everolimus, patients should have their everolimus levels monitored closely and the dose reduced as necessary.

On the basis of the interaction with the azoles and its likely mechanism, the manufacturers predict that other moderate or potent CYP3A4 and/or P-glycoprotein inhibitors will interact similarly. They name **aprepitant**, **delavirdine**, **fluconazole**, **grapefruit juice**, **nefazodone**, the protease inhibitors **amprenavir**, **atazanavir**, **darunavir**, **fosamprenavir**, **indinavir**, **nelfinavir**, **ritonavir** and **saquinavir**.[6,7] The US manufacturers suggest that the concurrent use of everolimus and moderate or potent CYP3A4 inhibitors should be avoided. The UK manufacturers similarly

advise that potent CYP3A4 inhibitors should be avoided, but suggest that some moderate inhibitors (they name **amprenavir**, **fosamprenavir**, and **fluconazole**) can be used with monitoring and an appropriate dose reduction. They recommend an everolimus dose reduction from 10 mg daily to 5 mg daily or 5 mg on alternate days should be considered in patients with renal cell carcinoma; but note that this dose decrease is a prediction.[7] Remember to readjust the everolimus dose if needed when these drugs are stopped.

For further information about the CYP3A4 inhibitors clarithromycin, erythromycin, and telithromycin, see also 'Everolimus + Macrolides', below, and for diltiazem and verapamil, see 'Everolimus + Calcium-channel blockers', p.1273.

1. Kovarik JM, Beyer D, Bizot MN, Jiang Q, Shenouda M, Schmouder RL. Blood concentrations of everolimus are markedly increased by ketoconazole. *J Clin Pharmacol* (2005) 45, 514–8.
2. Kovarik JM, Hsu C-H, McMahon L, Berthier S, Rordorf C. Population pharmacokinetics of everolimus in de novo renal transplant patients: impact of ethnicity and comedications. *Clin Pharmacol Ther* (2001) 70, 247–54.
3. Pea F, Baccarani U, Tavio M, Cojutti P, Adani GL, Londero A, Baraldo M, Franceschi L, Furlanut M, Viale P. Pharmacokinetic interaction between everolimus and antifungal triazoles in a liver transplant patient. Ann Pharmacother (2008) 42, 1711–16.
4. Certican (Everolimus). Novartis Pharmaceuticals Australia Pty Ltd. Australian product information, March 2008.
5. Rothenburger M, Zuckermann A, Bara C, Hummel M, Strüber M, Hirt S, Lehmkuhl H; Certican Consensus Study Group. Recommendations for the use of everolimus (Certican) in heart transplantation: results from the second German-Austrian Certican Consensus Conference. *J Heart Lung Transplant* (2007) 26, 305–11.
6. Afinitor (Everolimus). Novartis. US Prescribing information, March 2009.
7. Afinitor (Everolimus). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, October 2009.

Everolimus + Macrolides

Erythromycin increased everolimus levels in one study. Other macrolides probably interact similarly.

Clinical evidence

In a study, 16 healthy subjects were given a single 4-mg dose of everolimus before and on day 5 of a 9-day course of **erythromycin** 500 mg three times daily. The peak blood levels and AUC of everolimus were increased twofold and 4.4-fold, respectively, and its half-life was prolonged by 39%.[1] In a pharmacokinetic modelling study, 9 patients were identified who had received a macrolide antibacterial. Those patients receiving **erythromycin** had a 22% lower clearance of everolimus, and those receiving **azithromycin** had an 18% lower clearance.[2]

Mechanism

Erythromycin probably inhibits the metabolism of everolimus by the cytochrome P450 isoenzyme CYP3A4, of which it is a moderate inhibitor. Everolimus is also a substrate for P-glycoprotein, and various macrolides (such as erythromycin, clarithromycin and possibly azithromycin) are inhibitors of this drug transporter.

Importance and management

The interaction of everolimus with erythromycin is likely to be clinically relevant. The authors recommend that appropriate everolimus dose reductions based on frequently monitored blood levels should be made when patients are given erythromycin.[1] The UK manufacturer recommends that, in patients taking everolimus for renal cell carcinoma and also given erythromycin, an everolimus dose reduction from 10 mg daily, to 5 mg daily or 5 mg on alternate days, should be considered. However, they state that this dose decrease is a prediction and therefore good monitoring is still required.[3] Note that the US manufacturer advises avoiding the concurrent use of erythromycin.[4]

Other macrolides that inhibit CYP3A4 and/or P-glycoprotein would be expected to interact similarly, although the extent of any effect may vary. Therefore if concurrent use with everolimus is considered necessary, everolimus levels should also be closely monitored and the dose adjusted as required. Note that the manufacturers advise avoiding the concurrent use of **clarithromycin** and **telithromycin**.[3,4]

1. Kovarik JM, Beyer D, Bizot MN, Jiang Q, Shenouda M, Schmouder R. Effect of multiple-dose erythromycin on everolimus pharmacokinetics. *Eur J Clin Pharmacol* (2005) 61, 35–8.
2. Kovarik JM, Hsu C-H, McMahon L, Berthier S, Rordorf C. Population pharmacokinetics of everolimus in de novo renal transplant patients: impact of ethnicity and comedications. *Clin Pharmacol Ther* (2001) 70, 247–54.
3. Afinitor (Everolimus). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, October 2009.
4. Afinitor (Everolimus). Novartis. US Prescribing information, March 2009.

Everolimus + Rifampicin (Rifampin) and other CYP3A4 inducers

Rifampicin (a CYP3A4 and P-glycoprotein inducer) markedly reduces the bioavailability and increases the clearance of everolimus. Other inducers of CYP3A4 and P-glycoprotein are predicted to interact similarly.

Clinical evidence

In a study, 12 healthy subjects were given a single 4-mg dose of everolimus before and after taking rifampicin 600 mg daily for 7 days. Rifampicin increased the clearance of everolimus by 172%, and decreased its AUC and peak blood levels by 63% and 58%, respectively, although there was a large inter-individual variation in the AUC.[1]

Mechanism

Everolimus is metabolised by the cytochrome P450 isoenzyme CYP3A4 and is a substrate for P-glycoprotein, therefore induction of both CYP3A4 and P-glycoprotein by rifampicin may increase the metabolism and reduced the bioavailability of everolimus.

Importance and management

The interaction between everolimus and rifampicin is likely to be clinically important, and may lead to treatment failure. If concurrent use is necessary, it would be prudent to increase the dose of everolimus and monitor levels very closely. One group has suggested a two- to threefold increase in everolimus dose when used with rifampicin.[2] The US manufacturer predicts that **rifabutin** will interact similarly.[3] However, note that rifabutin is a less potent enzyme inducer than rifampicin, so would not be expected to reduce everolimus bioavailability to the same extent.

On the basis of the interaction with rifampicin the manufacturers advise avoiding concurrent use with potent CYP3A4 inducers: they name **carbamazepine**, **phenytoin** (and therefore probably **fosphenytoin**), **phenobarbital** (and therefore probably **primidone**),[3,4] **efavirenz**, **nevirapine**, and **St John's wort**.[4] However, if concurrent use is necessary, everolimus levels should be closely monitored and adjusted as necessary. The manufacturers recommend that, in patients given everolimus for renal cell carcinoma, an everolimus dose increase from 10 mg daily to 20 mg daily, in steps of 5 mg (starting on day 4 of concurrent use), should be considered. However, they state that this dose increase is a prediction and therefore good monitoring is still required.[3,4] Remember to adjust the everolimus dose when rifampicin, rifabutin or other CYP3A4 inducers are stopped.

The US manufacturer[3] also lists **dexamethasone** as a potent CYP3A4 inducer; however, note that clinically significant interactions with dexamethasone as a result of this mechanism appear to be rare.

For a list of CYP3A4 inducers, see 'Table 1.4', (p.6). What should be remembered is that the extent of the inducing effects of these drugs is not identical, so that very marked effects like those observed with rifampicin may not occur; nevertheless the interaction may still be clinically important.

1. Kovarik JM, Hartmann S, Figueiredo J, Rouilly M, Port A, Rordorf C. Effect of rifampicin on apparent clearance of everolimus. *Ann Pharmacother* (2002) 36, 981–5.
2. Rothenburger M, Zuckermann A, Bara C, Hummel M, Strüber M, Hirt S, Lehmkuhl H; Certican Consensus Study Group. Recommendations for the use of everolimus (Certican) in heart transplantation: results from the second German-Austrian Certican Consensus Conference. *J Heart Lung Transplant* (2007) 26, 305–11.
3. Afinitor (Everolimus). Novartis. US Prescribing information, March 2009.
4. Afinitor (Everolimus). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, October 2009.

Everolimus + Tacrolimus

No significant pharmacokinetic interaction appears to occur between everolimus and tacrolimus.

Clinical evidence

(a) Effect on everolimus

In one study, 8 transplant patients taking tacrolimus were changed from mycophenolate to everolimus 1.5 mg twice daily. After everolimus had been taken for 10 days the tacrolimus dose was halved. There was no difference in the pharmacokinetics of everolimus between the full-dose tacrolimus and half-dose tacrolimus periods (trough level 3.3 nanograms/mL compared with 3 nanograms/mL). In addition, the everolimus trough level and AUC were about 2.5-fold lower than in a previous study of patients taking the same dose of everolimus with ciclosporin, which is known to increase everolimus levels.[1] In another study, trough concentrations of everolimus were almost halved (from 4.2 to 2.3 nanograms/mL) when ciclosporin was stopped and tacrolimus was started in 6 heart transplant recipients taking everolimus. The AUC of everolimus was similarly decreased by about 50% and its maximum level was decreased by 35%.[2]

(b) Effect on tacrolimus

In a study in 8 transplant patients taking tacrolimus, there was no statistically significant change in the tacrolimus trough level (7.9 nanograms/mL compared with 8.4 nanograms/mL) and its AUC when mycophenolate was replaced with everolimus 1.5 mg twice a day.[1] Similarly, there was no change in tacrolimus pharmacokinetics in 6 transplant patients taking tacrolimus when azathioprine was replaced with everolimus 1.5 mg twice daily.[2]

Mechanism

None.

Importance and management

The limited available data suggest that there is no clinically significant pharmacokinetic interaction between tacrolimus and everolimus. The consequence of this is that higher everolimus doses are likely to be required in patients taking tacrolimus than in those patients taking ciclosporin. For further discussion on the effect of ciclosporin on everolimus levels, see 'Everolimus + Ciclosporin', p.1273.

1. Kovarik JM, Curtis JJ, Hricik DE, Prescovitz MD, Scantlebury V, Vasquez A. Differential pharmacokinetic interaction of tacrolimus and cyclosporine on everolimus. *Transplant Proc* (2006) 38, 3456–8.
2. Brandhorst G, Tenderich G, Zittermann A, Oezpeker C, Koerfer R, Oellerich M, Armstrong VW. Everolimus exposure in cardiac transplant recipients is influenced by concomitant calcineurin inhibitor. Ther Drug Monit (2008) 30, 113–16.

Immunosuppressants + Vaccines

The body's immune response is suppressed by immunosuppressants such as ciclosporin, mycophenolate, sirolimus, and tacrolimus. The antibody response to vaccines may be reduced, although even partial protection may be of benefit. In general, the use of live attenuated vaccines is considered contraindicated because of the possible risk of generalised infection. Inactivated vaccines may be used.

Clinical evidence

(a) Diphtheria, tetanus, and inactivated polio vaccines

In a case-control review, organ transplant recipients taking immunosuppressants, tetanus vaccines[1,2] and inactivated polio vaccines[1] produced protective antibody titres. The response to diphtheria vaccine was lower than in healthy controls[1] and the antibody titre had fallen below the protective level by 12 months in 38% of patients in one study,[1] and 24% in another.[2] Note that live polio vaccines are not recommended in immunosuppressed patients (see *Live vaccines*, below).

(b) Hepatitis vaccines

The antibody response to **hepatitis B vaccine** is generally poor in patients taking immunosuppressants after organ transplantation,[3,4] although one research group reported a sustained antibody response in half of their patients,[5] and an overall 85% seroconversion rate was seen in one study in children (aged between 4 and 16 years).[6] In this latter study,[6] children receiving **ciclosporin** monotherapy had a higher seroconversion rate (100%) than those receiving **ciclosporin** and **corticosteroids** (84%) and those receiving **ciclosporin**, **azathioprine**, and **corticosteroids** (66%). The antibody response to **hepatitis A vaccine** in patients taking immunosuppressants after organ transplantation is variable,[7-9] and declines quicker than in healthy controls.[9] In kidney transplant recipients, there is some evidence that the response is inversely related to the number of immunosuppressant drugs.[8]

(c) Influenza vaccine

A number of studies have been published on the efficacy of influenza vaccination in organ transplant recipients taking immunosuppressants. Many have found a reduction in the proportion of patients developing a protective antibody titre compared with healthy control subjects,[10,11] whereas some have found no reduction.[12] A few studies have looked at the effects of individual drugs in the immunosuppressive regimen. In one comparative study in 59 kidney transplant patients, 21 patients taking **ciclosporin** and **prednisone** had a significantly lower immune response to influenza vaccine (inactivated trivalent) than 38 patients taking **azathioprine** and **prednisone** or 29 healthy subjects taking no drugs. All of the immune response measurements were reduced by 20 to 30% in those taking **ciclosporin**.[13] In another study, 13 patients taking **mycophenolate**, **ciclosporin**, and **prednisolone** had a marked reduction in antibody response to influenza vaccine, when compared with 25 patients taking **ciclosporin**, **azathioprine** and **prednisolone**.[14] In yet another study, patients taking **ciclosporin** had lower antibody responses when compared with patients taking **tacrolimus**.[15] Confirmation of the practical importance of the reduced antibody titre in some patients is described in a case report of a heart transplant patient taking **ciclosporin** who did not respond to influenza vaccination while taking **ciclosporin** and **prednisone**. He had two episodes of influenza, one serologically confirmed, and it was later shown that vaccination had not resulted in seroconversion.[16] Similarly, a patient taking **tacrolimus** after a liver transplant developed influenza A myocarditis despite prophylactic vaccination.[17]

(d) Live vaccines

The use of live vaccines in patients receiving corticosteroids has caused generalised infection, see 'Corticosteroids + Vaccines', p.1272. Similarly, the use of live vaccines in patients taking other immunosuppressants is not recommended: probably as a consequence of this there are few published reports about the use of live vaccines with immunosuppressants. One study found that **measles vaccine** was effective in 7 of 18 children under 3 years old after liver transplantation, and that there were no complications directly attributable to the vaccine.[18]

(e) Measles, mumps and rubella vaccines

A small study in 10 children with juvenile idiopathic arthritis found that low-dose methotrexate or methotrexate with **etanercept** 400 micrograms/kg twice weekly for at least 6 months before measles, mumps and rubella (MMR) revaccination did not interfere significantly with the immune response to revaccination, when compared with healthy children. Neither vaccine failure nor occurrence of overt measles, mumps and rubella or secondary severe infections was observed within 6 months of MMR revaccination. However, further studies are needed to provide a safety basis for the use of MMR vaccine in juvenile idiopathic arthritis.[19]

(f) Pneumococcal vaccines

Good responses to pneumococcal vaccines have been seen in patients taking immunosuppressant drugs after organ transplantation,[10,20] but protective antibody titres may not persist as long as in healthy subjects.[21]

Mechanism

Immunosuppression by these drugs diminishes the ability of the body to respond immunologically both to transplants and to vaccination.

Importance and management

These are established and clinically important interactions. The UK Department of Health[22] recommends that live vaccines should not be used in the following individuals:

- Patients who have received a solid organ transplant and are currently on immunosuppressive treatment.
- Patients who have received a bone marrow transplant, until at least 12 months after finishing all immunosuppressive treatment. Patients may lose their antibodies against most diseases and should be considered for re-immunisation under specialist supervision.

- Patients taking other immunosuppressive drugs such as ciclosporin, methotrexate, cyclophosphamide, leflunomide, and cytokine inhibitors [presumably including etanercept] should not be given live vaccines during or for up to 6 months after treatment has stopped.

They recommend that immunosuppressed patients be given inactivated vaccines in accordance with national recommendations, bearing in mind that they may not achieve as good an antibody response.
They say that, in individuals about to start immunosuppressive treatments, inactivated vaccines should ideally be given at least 2 weeks before immunosuppressive therapy is started, and in the case of live vaccines, a longer period before immunosuppression commences may be desirable.
The proportion of patients developing protective antibody titres to vaccines is often reduced in patients taking immunosuppressants. Nevertheless, for many vaccines, the reduced response seen is still considered clinically useful, and, for example, in the case of kidney transplant patients,[22] and in patients who are immunosuppressed (either by drugs or disease), influenza vaccination is actively recommended.[22] Pneumococcal vaccine should also be given to these patients. If a vaccine is given, it may be prudent to monitor the response, so that alternative prophylactic measures can be considered where it is considered inadequate. For influenza vaccine, one suggestion is that if patients remain unprotected after a single vaccination and a booster dose, amantadine 200 mg daily should be given during an influenza epidemic. It will protect against influenza A but not B infection.[16] Note that, even where effective antibody titres are produced, these may not persist as long as in healthy subjects, and more frequent booster doses may be required.

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Leflunomide + Infliximab

An isolated report describes a delayed hypersensitivity reaction in a boy receiving leflunomide and infliximab. However, one study suggests that concurrent use does not increase the rate of adverse effects.

Clinical evidence, mechanism, importance and management

In a 30-week study, 72 patients with active rheumatoid arthritis who had received oral leflunomide for at least 16 weeks were given infliximab 3 mg/kg intravenously at weeks 0, 2, 6, 14, and 22. Serious adverse events occurred in 16 patients (22%), but the combination did not appear to increase the rate of toxicities or result in unexpected adverse events.[1] However, a 17-year-old boy with refractory psoriatic arthritis developed a unique cutaneous hypersensitivity reaction, manifesting as a vasculitic-like skin rash, after he had been receiving infliximab and leflunomide for 9 months. The rash cleared within 2 months of discontinuing treatment.[2] The general relevance of this isolated case is unclear.

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Leflunomide + Itraconazole

A case of fatal fulminant hepatic failure has been reported in a patient taking leflunomide and itraconazole.

Clinical evidence, mechanism, importance and management

A 68-year-old woman who had been taking leflunomide 10 mg daily for about 4 months started taking itraconazole 300 mg daily for a fungal infection. About one month later her leflunomide dose was increased to 20 mg daily, and liver function tests were normal. The following month, she developed abdominal pain, vomiting, and weakness. Despite symptomatic treatment and washout with colestyramine, fatal fulminant hepatic failure occurred. The authors of the report attribute the reaction to additive hepatotoxicity between the leflunomide and itraconazole.[1] This interaction serves to highlight the cautions about the use of leflunomide with other hepatotoxic drugs, see *Alcohol* under 'Leflunomide + Miscellaneous', p.1278, and 'Leflunomide + Methotrexate', below.

1. Legras A, Bergemer-Fouquet A-M, Jonville-Bera A-P. Fatal hepatitis with leflunomide and itraconazole. *Am J Med* (2002) 113, 352–3.

Leflunomide + Methotrexate

Methotrexate may increase leflunomide hepatotoxicity and haematotoxicity.

Clinical evidence, mechanism, importance and management

No pharmacokinetic interaction was seen in patients taking methotrexate (mean dose 17.2 mg per week) with leflunomide (100 mg daily for 2 days as a loading dose followed by 10 to 20 mg daily).[1] However, elevated liver enzyme levels have been seen following concurrent use.[2,3] By March 2001, the EMEA was aware of 129 cases of serious hepatic reactions in patients taking leflunomide, and 78% of these were in patients also taking other hepatotoxic medications. In patients with elevated liver function tests, 58% were also taking methotrexate and/or NSAIDs.[4]

Pancytopenia has also been associated with the use of leflunomide with methotrexate.[5,6] The Australian Adverse Drug Reactions Advisory Committee (ADRAC) received 11 reports of pancytopenia associated with the use of leflunomide during its first 31 months of marketing and in 9 of these cases, the patients were also taking methotrexate. In 2 cases, methotrexate was added to leflunomide and in the other 7 cases methotrexate use preceded leflunomide use. In 5 of these cases methotrexate had been taken in weekly doses for a mean of 336 weeks (range 103 to 650 weeks) without the development of pancytopenia; however, when leflunomide was added the blood dyscrasia developed within 6 to 78 weeks. Of the total 394 re-

ports describing any type of adverse reaction associated with leflunomide over the 31-month study period, 128 reports (32.5%) also recorded methotrexate being taken concurrently.[6] Another report describes 5 cases of severe pancytopenia occurring within 23 days to 4 years of starting leflunomide and methotrexate.[7]

Due to the possible risks of additive or synergistic liver toxicity or haematotoxicity, particularly when used long-term, the UK manufacturer says that the concurrent use of methotrexate is not advisable.[2] The US manufacturer says that if concurrent use is undertaken, long-term monitoring should be increased to monthly intervals.[3] Close liver enzyme and haematological monitoring is also recommended if switching between these drugs, and colestyramine or activated charcoal washout is recommended as it may decrease the risk of toxicity when switching from leflunomide to methotrexate.[2,3]

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Leflunomide + Miscellaneous

The serum levels of the active metabolite of leflunomide are reduced by activated charcoal and colestyramine. The concurrent use of alcohol may increase the risk of hepatotoxicity, although limited alcohol consumption appears to have little effect on liver enzyme values in patients taking leflunomide. The manufacturers predict interactions between leflunomide and phenytoin or tolbutamide, and advise caution with rifampicin (rifampin) as it may increase leflunomide metabolite levels. Concurrent use with other DMARDs (other than methotrexate) has not been studied, but is not recommended by the manufacturer. No clinically relevant interaction occurs with cimetidine, corticosteroids or NSAIDs.

Clinical evidence, mechanism, importance and management

(a) Alcohol

The UK manufacturer says that because of the potential for additive hepatotoxic effects, it is recommended that alcohol should be avoided by patients taking leflunomide.[1] However, one study suggested that self-reported alcohol consumption had no significant influence on ALT levels in rheumatoid arthritis patients taking leflunomide[2] and the British Society for Rheumatology guidelines recommend that patients taking leflunomide should be asked to limit alcohol intake to 4 to 8 units a week.[3]

(b) Charcoal or Colestyramine

Studies in healthy subjects found that colestyramine 8 g three times daily for 24 hours reduced the plasma levels of the active metabolite of leflunomide (A771726) by 40% after 24 hours and by 49 to 65% after 48 hours.[1,4]

Treatment with activated charcoal 50 g every 6 hours for 24 hours, either orally or by nasogastric tube, reduced A771726 levels by 37% after 24 hours and by 48% after 48 hours.[1,4]

These drugs are thought to bind with A771726 in the gut, reducing plasma levels by a gastrointestinal dialysis mechanism and/or by interrupting the enterohepatic cycle.[1] Patients should therefore not be given either colestyramine or activated charcoal with leflunomide, unless the intention is to remove the leflunomide,[1] for example following overdosage or when switching from leflunomide to another DMARD (see *DMARDs*, below), or where there is any other good reason to clear leflunomide from the body more quickly.[1,4]

(c) Cimetidine

The manufacturers say that no clinically significant interaction occurs between leflunomide and cimetidine.[1,4]

(d) Corticosteroids

The manufacturers say that corticosteroids may continue to be used if leflunomide is given.[1,4]

(e) CYP2C9 substrates

The manufacturers advise caution if leflunomide is given with **phenytoin** or **tolbutamide**.[1] The reason is that the active metabolite of leflunomide (A771726) has been shown by *in vitro* studies to be an inhibitor of the cytochrome P450 isoenzyme CYP2C9, which is concerned with the metabolism of these two drugs. If this inhibition were to occur *in vivo* it could possibly lead to a decrease in their metabolism and an increase in their toxicity. Although so far there appear to be no clinical reports of an interaction, the manufacturers made a similar prediction with warfarin, another CYP2C9 substrate, which has, in isolated cases, been borne out in practice, see 'Coumarins + Leflunomide', p.475.

(f) DMARDs

The manufacturers say that the concurrent use of leflunomide and other DMARDs (they list **azathioprine**, **chloroquine**, **hydroxychloroquine**, intramuscular or oral **gold** and **penicillamine**) has not yet been studied,[1,4] but the UK manufacturer says that combined use is not advisable because of the increased risk of serious adverse reactions (haemo- or hepatotoxicity).[1] As the active metabolite of leflunomide has a long half-life of 1 to 4 weeks, a washout with colestyramine or activated charcoal is recommended and the manufacturers say that this may decrease the risk of toxicity if patients are to be given other DMARDs.[1,4]

See also 'Leflunomide + Methotrexate', p.1277.

(g) NSAIDs

Leflunomide inhibits the activity of the cytochrome P450 isoenzyme CYP2C9 *in vitro* and might therefore be expected to increase the serum levels of NSAIDs that are metabolised by this isoenzyme. In addition, the metabolite of leflunomide (A771726) is extensively bound to protein and may displace other highly protein-bound drugs. Leflunomide displaced **diclofenac** and **ibuprofen** *in vitro*, but the effect was not considered to be clinically relevant.[1] The manufacturers say that no safety problems were seen in clinical studies with leflunomide and NSAIDs. No special precautions would seem to be needed if any of these or any other NSAID drugs are given concurrently with leflunomide.[1]

(h) Rifampicin (Rifampin)

When a single dose of leflunomide was given to subjects after taking multiple-dose rifampicin, the peak levels of the active metabolite of leflunomide (A771726) were increased by 40% but the AUC was unchanged.[1,4] There would seem to be no reason for avoiding concurrent use, but the US manufacturer advises caution as metabolite levels may build up over time.[4] It may be prudent to increase the frequency of leflunomide monitoring if these two drugs are used together.

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Leflunomide + Tegafur with Uracil

A case of peripheral neuropathy has been reported in a patient taking leflunomide and tegafur with uracil.

Clinical evidence, mechanism, importance and management

A 75-year-old man with rectal cancer was given a 28-day course of tegafur 200 mg three times daily (with uracil) and calcium folinate 30 mg daily. Treatment was withheld because of an episode of minor duodenal bleeding and 3 months later he was given leflunomide 100 mg daily for 3 days followed by 20 mg daily to treat rheumatoid arthritis. A further two courses of tegafur and uracil (separated by 7 days) were given because of tumour progression, after which the patient had increasing numbness of the lower extremities, diagnosed as polyneuropathy. He also had severe diar-

rhoea and hand-foot syndrome. These symptoms had not occurred when tegafur and uracil had been given without leflunomide, and hence an interaction was suspected.

Tegafur is a prodrug of fluorouracil, which is given with uracil to prevent fluorouracil degradation (by inhibiting dihydropyrimidine dehydrogenase). Both tegafur with uracil and leflunomide may cause neurotoxicity and therefore the effects seen may have occurred as a result of simple additive toxicity. The authors suggested that leflunomide may increase fluorouracil toxicity by increasing its conversion to fluorouracil monophosphate, or by enhancing the effect of uracil by additional inhibition of dihydropyrimidine dehydrogenase.[1] This is an isolated case and its general importance is unclear.

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Monoclonal antibodies + Azathioprine or Mercaptopurine

Infliximab may increase serum levels of azathioprine metabolites, and giving azathioprine and mercaptopurine with infliximab may be associated with higher trough levels of infliximab. Adalimumab clearance is not affected by azathioprine or mercaptopurine and basiliximab clearance is only modestly affected by azathioprine.
A rare T-cell lymphoma has been reported in adolescents and young adults given infliximab and azathioprine or mercaptopurine and serious infection may be associated with the use of natalizumab and azathioprine or mercaptopurine.

Clinical evidence, mechanism, importance and management

(a) Adalimumab

In a study of the pharmacokinetics of adalimumab, the concurrent use of either azathioprine (36 patients) or mercaptopurine (23 patients) slightly lowered or had no impact on adalimumab clearance.[1]

(b) Basiliximab

Azathioprine, added to regimens including basiliximab, ciclosporin microemulsion and corticosteroids reduced the clearance of basiliximab by 22%.[2-4] However, the use of basiliximab in triple regimens with azathioprine did not increase adverse effects or infections.[2,3] No dose adjustment is considered necessary if basiliximab is added to triple-immunosuppression regimens including ciclosporin, corticosteroids and azathioprine.[3,4]

(c) Infliximab

In 32 patients with Crohn's disease taking azathioprine (mean dose 2.81 mg/kg) and with stable levels of 6-tioguanine nucleotides (the active metabolites of azathioprine), an infusion of infliximab 5 mg/kg over 2 hours resulted in a significant increase in 6-tioguanine nucleotide levels in 21 patients after 1 to 3 weeks, when compared with pre-infusion levels. The leucocyte count was significantly decreased and mean corpuscular volume increased. Significant increases in 6-tioguanine nucleotides were associated with good tolerance and a favourable response to infliximab. These changes were transient even in patients who received two additional infusions of infliximab over the following 6 weeks: levels returned to normal 3 months after the first infusion.[5]

The manufacturers state that rare post-marketing cases of an aggressive and usually fatal hepatosplenic T-cell lymphoma have been reported in adolescent and young adult patients with Crohn's disease who were given infliximab. All cases occurred in patients also receiving azathioprine or mercaptopurine, either with or immediately before the use of infliximab. A causal relationship is unclear.[6,7] Up until October 2006, the Adverse Event Reporting System (AERS) database of the FDA in the US had received 8 case reports of hepatosplenic T-cell lymphoma associated with infliximab use in young patients being treated for Crohn's disease or ulcerative colitis; all had received concurrent azathioprine and/or mercaptopurine.[8] Further study has suggested that, in patients with Crohn's disease, continuing azathioprine or mercaptopurine with infliximab beyond 6 months offers no clear benefit over infliximab monotherapy, but is associated with a higher median infliximab trough level and decreased C-reactive protein level.[9]

No dosage adjustments appear to be necessary with the concurrent use of azathioprine or mercaptopurine, but the long-term benefits of treatment need further study.

(d) Natalizumab

In clinical studies in patients with Crohn's disease, the concurrent use of natalizumab with long-term mercaptopurine and azathioprine did not result in an increase in overall infections, when compared with natalizumab alone.[10] Nevertheless, in patients with Crohn's disease the manufacturer states that natalizumab should not be used in combination with azathioprine or mercaptopurine, because of the potential for increased risk of progressive multifocal leukoencephalopathy and other infections.[10]

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6. Remicade (Infliximab). Schering-Plough Ltd. UK Summary of product characteristics, March 2009.
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10. Tysabri (Natalizumab). Biogen Idec Inc. US Prescribing information, October 2008.

Monoclonal antibodies + Cytochrome P450 substrates

Although the manufacturers of golimumab and tocilizumab predict that they may interact with substrates of the cytochrome P450 isoenzyme system there appears to be no clinical data to confirm this.

Clinical evidence, mechanism, importance and management

(a) Golimumab

The manufacturer notes that golimumab, a tumour necrosis factor antibody, is expected to reverse the suppression of cytochrome P450 isoenzymes caused by tumour necrosis factor-alpha. They therefore advise that patients taking drugs metabolised cytochrome P450 that have a narrow therapeutic window (they name **ciclosporin**, **theophylline** and **warfarin**) should be monitored when golimumab is started or stopped, as they may require a dosage increase to ensure efficacy.[1] At present there appears to be no *in vitro* or clinical data to confirm these predicted interactions. Furthermore, other tumour necrosis factor antibodies, such as infliximab, do not appear to have these effects in practice.

(b) Tocilizumab

Tocilizumab, an interleukin-6 inhibitor, can reverse the suppression of cytochrome P450 isoenzymes caused by interleukin. *In vitro* studies have shown that tocilizumab can reverse this effect on the cytochrome P450 isoenzymes CYP1A2, CYP2C9, CYP2C19, and CYP3A4, and that levels of these isoenzymes may return to normal values and their metabolic capacity may increase. The manufacturer therefore advises that patients taking drugs metabolised by these isoenzymes (they name **theophylline** (CYP1A2), **warfarin** (CYP2C9), **phenytoin** (CYP2C19), **atorvastatin**, **benzodiazepines** [e.g. midazolam], **calcium-channel blockers**, and **ciclosporin** (CYP3A4)) should be monitored as they may require a dosage increase to ensure efficacy. At present there appears to be no clinical data to confirm these predictions; however, until more is known, it would be

prudent to consider the possibility of an interaction if clinical symptoms suggest that the levels of these drugs have been reduced. Note that as tocilizumab has a long half-life, any clinically relevant effect on cytochrome P450 isoenzymes will persist for up to several weeks after it has been stopped.[2]

1. Simponi (Golimumab). Centocor Ortho Biotech Inc. US Prescribing information, April 2009.
2. RoActemra (Tocilizumab). Roche Registration Ltd. Summary of product characteristics, January 2009.

Monoclonal antibodies + Methotrexate

The clearance of adalimumab may be decreased by methotrexate. Concurrent use may decrease antibody formation and result in elevations in liver enzymes. The concurrent use of methotrexate with natalizumab is predicted to increase the risk of developing infections, some of which may be severe. Several other monoclonal antibodies do not appear to interact with methotrexate, and some are specifically licensed for concurrent use.

Clinical evidence, mechanism, importance and management

(a) Adalimumab

In 45 patients with rheumatoid arthritis taking stable doses of methotrexate for at least 3 months, the mean clearance of a single intravenous dose of adalimumab was decreased by approximately 22%, when compared with 89 similar patients who did not receive methotrexate.[1] Another study found that giving adalimumab to patients taking methotrexate had no statistically significant effect on the pharmacokinetics of methotrexate.[2] No dose adjustment of either adalimumab or methotrexate is considered necessary when they are given concurrently.[3]

The manufacturers say that giving adalimumab in the absence of methotrexate resulted in increased formation of antibodies, increased clearance and reduced efficacy of adalimumab.[3,4] Elevations in liver enzymes have been observed with adalimumab alone, but appear to be more frequent in patients who have received both adalimumab and methotrexate.[3,4] It may therefore be prudent to increase the frequency of liver enzyme monitoring if both drugs are given.

(b) Rituximab

A study in 38 patients with highly active rheumatoid arthritis found that the pharmacokinetics of rituximab were not altered by the concurrent use of methotrexate.[5]

(c) Tocilizumab

The manufacturer reports that a single 10 mg/kg dose of tocilizumab had no clinically relevant effect on the overall exposure to methotrexate (given weekly at a dose of 10 to 25 mg weekly). They also state that, in population pharmacokinetic analyses, methotrexate had no significant effect on the clearance of tocilizumab. Therefore, no dose adjustments appear to be necessary should tocilizumab be given with weekly methotrexate. Note that it is licensed for concurrent use with methotrexate.[6]

(d) Other monoclonal antibodies

Although specific interaction studies appear to be lacking certolizumab pegol[7] and golimumab[8] have been safely given with methotrexate in clinical studies. Note that certolizumab pegol and golimumab are specifically licensed for use with methotrexate.

In clinical studies, the concurrent use of natalizumab with methotrexate did not increase the risk of infection when compared with natalizumab alone. However, the US manufacturer specifically advises against the concurrent use of natalizumab with methotrexate due to the risk of progressive multifocal leukoencephalopathy (a viral infection that can lead to severe disability and death) and other infections, which have been associated with the use of natalizumab in immunosuppressed patients.[9]

1. Velagapudi RB, Noertersheuser PA, Awni WM, Fischkoff SA, Kupper H, Granneman RG, van de Putte LBA, Keystone EC. Effect of methotrexate coadministration on the pharmacokinetics of adalimumab (Humira, Abbott) following a single intravenous injection. *Arthritis Rheum* (2003) 48 (Suppl), S141.
2. Weisman MH, Moreland LW, Furst DE, Weinblatt ME, Keystone EC, Paulus HE, Teoh LS, Velagapudi RB, Noertersheuser PA, Granneman GR, Fischkoff SA, Chartash EK. Efficacy, pharmacokinetic, and safety assessment of adalimumab, a fully human anti-tumor necrosis factor-alpha monoclonal antibody, in adults with rheumatoid arthritis receiving concomitant methotrexate: a pilot study. *Clin Ther* (2003) 25, 1700–21.
3. Humira (Adalimumab). Abbott Laboratories. US Prescribing information, March 2009.
4. Humira (Adalimumab). Abbott Laboratories Ltd. UK Summary of product characteristics, December 2009.
5. Davies B, Shaw T. Rituximab pharmacokinetic characteristics are not influenced by combination with methotrexate or cyclophosphamide. *Ann Rheum Dis* (2004) 63, FRI0128.
6. RoActemra (Tocilizumab). Roche Registration Ltd. Summary of product characteristics, January 2009.
7. Cimzia (Certolizumab pegol). UCB Inc. US Prescribing information, December 2008.
8. Simponi (Golimumab). Centocor Ortho Biotech Inc. US Prescribing information, April 2009.
9. Tysabri (Natalizumab). Biogen Idec Inc. US Prescribing information, October 2008.

Monoclonal antibodies + Miscellaneous

Monoclonal antibodies appear to increase the risk of infection in patients receiving drugs that are known to alter immune function (e.g. antineoplastics, immunosuppressants). They may also increase the risk of malignancy in predisposed individuals (e.g. tobacco smokers).

Clinical evidence, mechanism, importance and management

For a list of drugs that are not expected to interact with monoclonal antibodies, see 'Table 29.3', (p.1281).

(a) Antineoplastics

A study in 37 patients with highly active rheumatoid arthritis found that the pharmacokinetics of **rituximab** were not altered by the concurrent use of **cyclophosphamide**.[1]

The UK manufacturer of **natalizumab** contraindicates the concurrent use of immunosuppressant drugs, or other drugs that modulate the immune response, due to the increased risk of opportunistic infections, particularly progressive multifocal leukoencephalopathy (PML). They specifically name **cyclophosphamide** and **mitoxantrone**.[2] However, PML has developed in 2 patients taking **natalizumab** as monotherapy[3] and the US manufacturer says that the number of cases is too low to suggest that concurrent use of immunosuppressant drugs increases the risk of PML. Nevertheless, they suggest that concurrent use should be avoided wherever possible.[4] See also 'Monoclonal antibodies + Methotrexate', above, and 'Monoclonal antibodies + Azathioprine or Mercaptopurine', p.1279.

(b) Corticosteroids

In clinical studies in patients with multiple sclerosis, short courses of corticosteroids were not associated with an increased rate of infection and therefore can be used in combination with **natalizumab**.[2,4] Furthermore, in clinical studies in patients with Crohn's disease, the concurrent use of natalizumab with long-term corticosteroids did not result in an increase in overall infections, when compared with **natalizumab** alone.[4] Nevertheless, it has been advised that care should be taken with patients who have previously received immunosuppressants, to allow sufficient time for immune function recovery to occur.[2,5]

(c) Glatiramer acetate

The UK manufacturer of **natalizumab** contraindicates its concurrent use with the immunomodulator glatiramer acetate,[2] because of the potential for an increase in the risk of infections.

(d) Muromonab-CD3

The manufacturers of **basiliximab** say that patients in phase 3 studies received **basiliximab** with muromonab-CD3 for episodes of rejection, with no increase in adverse events or infections. Human antimurine antibody responses were reported in 2 of 138 patients receiving basiliximab and 4 of 34 patients receiving both **basiliximab** and muromonab-CD3. Therefore, the manufacturers say that if **basiliximab** has been given, muromonab-CD3 or other murine antilymphocytic antibody preparations can still subsequently be given.[6,7]

In a clinical study in heart transplant patients taking ciclosporin, mycophenolate mofetil, and corticosteroids, the use of **daclizumab** was associated with an increase in infection-related deaths. Furthermore, concurrent use of another antilymphocyte (such as muromonab-CD3 or antithymocyte immunoglobulin) appeared to be associated with a higher incidence of fatal infection: 8 of 40 patients died, compared with 2 of 37 who received an antilymphocyte and placebo. The manufacturer suggested that the concurrent use of **daclizumab** with another antilymphocyte antibody in patients receiving intensive immunosuppression may be a factor leading to fatal infection.[8] Caution may be warranted.

Table 29.3 Drugs that are not expected to interact with monoclonal antibodies as listed by the manufacturers

	Adalimumab[1]	*Basiliximab*[2,3]	*Infliximab*[4,5]	*Tocilizumab*[6]
Aminosalicylates	May be continued during treatment with adalimumab.		Infliximab levels unaffected by baseline aminosalicylate use.	
Analgesics		No increase in adverse effects with unspecified analgesics.	Infliximab clearance not affected by NSAIDs (population pharmacokinetic data).	Tocilizumab clearance not affected by NSAIDs (population pharmacokinetic data).
Antibacterials		No increase in adverse effects with unspecified antibacterials.	Infliximab levels unaffected by baseline ciprofloxacin or metronidazole use.	
Antifungals		No increase in adverse effects with unspecified antifungals.		
Antivirals		No increase in adverse effects with unspecified antivirals.		
Beta blockers		No increase in adverse effects with unspecified beta blockers.		
Calcium-channel blockers		No increase in adverse effects with unspecified calcium-channel blockers.		
Corticosteroids	May be continued during treatment with adalimumab.		Infliximab levels unaffected by baseline prednisolone use.	Tocilizumab clearance not affected (population pharmacokinetic data).
Diuretics		No increase in adverse effects with unspecified diuretics.		
Proton pump inhibitors			Infliximab clearance not affected by omeprazole (population pharmacokinetic data).	

1. Humira (Adalimumab). Abbott Laboratories. US Prescribing information, November 2009.
2. Simulect (Basiliximab). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, October 2008.
3. Simulect (Basiliximab). Novartis Pharmaceuticals Corporation. US Prescribing information, September 2005.
4. Remicade (Infliximab). Centocor Ortho Biotech, Inc. US Prescribing information, November 2009.
5. Xu Z, Seitz K, Fasanmade A, Ford J, Williamson P, Xu W, Davis HM, Zhou H. Population pharmacokinetics of infliximab in patients with ankylosing spondylitis. *J Clin Pharmacol* (2008) 48, 681–95.
6. RoActemra (Tocilizumab). Roche Products Ltd. UK Summary of product characteristics, November 2009.

(e) Mycophenolate

Mycophenolate mofetil, added to regimens including **basiliximab**, ciclosporin microemulsion and corticosteroids, reduced the clearance of **basiliximab** by 51%.[6,7,9] However, the use of basiliximab in triple regimens with mycophenolate did not increase adverse effects or infections.[6,7] No dose adjustment is considered necessary if **basiliximab** is added to triple-immunosuppression regimens including ciclosporin, corticosteroids and mycophenolate mofetil.[7,9]

A study in 75 renal transplant recipients given immunosuppressants, including mycophenolate mofetil, found that **daclizumab** had no effect on the pharmacokinetics of its active metabolite, mycophenolic acid. The pharmacokinetics of **daclizumab** were comparable with historical data, suggesting that mycophenolate mofetil did not affect the clearance of **daclizumab**. The addition of **daclizumab** to immunosuppressant treatment including mycophenolate mofetil did not appear to result in any increase in adverse events.[10] However, in one clinical study in heart transplant patients taking ciclosporin, mycophenolate mofetil, and corticosteroids, the use of **daclizumab** was associated with an increase in infection-related deaths.[8]

(f) Tobacco

In a study in patients with moderate to severe chronic obstructive pulmonary disease (COPD), more malignancies were reported in patients given **infliximab** than in control patients: all patients had a history of heavy smoking. The manufacturer suggests caution when considering the use of **infliximab** in patients with an increased risk for malignancy due to heavy smoking.[11] Furthermore, because of these findings, the manufacturer of **adalimumab** suggests caution in patients with COPD, as well as in patients with increased risk for malignancy due to heavy smoking.[12] Note that both **infliximab** and **adalimumab** are both tumour necrosis factor antibodies.

1. Davies B, Shaw T. Rituximab pharmacokinetic characteristics are not influenced by combination with methotrexate or cyclophosphamide. *Ann Rheum Dis* (2004) 63, FRI0128.
2. Tysabri (Natalizumab). Biogen Idec Ltd. UK Summary of product characteristics, January 2009.
3. Food and Drug Administration. Natalizumab (marketed as Tysabri) information. FDA Alert, August 2008. Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm126592.htm (accessed 05/02/10).
4. Tysabri (Natalizumab). Biogen Idec Inc. US Prescribing information, October 2008.
5. Ilanjian H, Shane R. Washout period for immune-modifying drugs before natalizumab therapy. Am J Health-Syst Pharm (2008) 65, 18–19.
6. Simulect (Basiliximab). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, October 2008.
7. Simulect (Basiliximab). Novartis Pharmaceuticals Corporation. US Prescribing information, September 2005.
8. Zenapax (Daclizumab). Roche Pharmaceuticals. US Prescribing information, September 2005.
9. Kovarik JM, Pescovitz MD, Sollinger HW, Kaplan B, Legendre C, Salmela K, Book BK, Gerbeau C, Girault D, Somberg K; on behalf of the Simulect Phase IV Study Group. Differential influence of azathioprine and mycophenolate mofetil on the disposition of basiliximab in renal transplant patients. *Clin Transplant* (2001) 15, 123–30.
10. Pescovitz MD, Bumgardner G, Gaston RS, Kirkman RL, Light S, Patel IH, Nieforth K, Vincenti F. Pharmacokinetics of daclizumab and mycophenolate mofetil with cyclosporine and steroids in renal transplantation. *Clin Transplant* (2003) 17, 511–17.
11. Remicade (Infliximab). Schering-Plough Ltd. UK Summary of product characteristics, March 2009.
12. Humira (Adalimumab). Abbott Laboratories Ltd. UK Summary of product characteristics, December 2009.

Monoclonal antibodies + Tumour necrosis factor antagonists

The use of tumour necrosis factor antagonists with monoclonal antibodies can increase the incidence of neutropenia and severe infections.

Clinical evidence, mechanism, importance and management

A short-term study in patients with active Crohn's disease receiving **infliximab**, found that addition of **natalizumab** did not result in any significant safety concerns and the proportion of patients who experienced adverse effects associated with infection was comparable with patients who received infliximab alone.[1]

Despite one study suggesting safe effective use, it is generally recommended that the concurrent use of tumour necrosis factor antagonists should be avoided with monoclonal antibodies, because of the increased risk of neutropenia and severe infections.

1. Sands BE, Kozarek R, Spainhour J, Barish CF, Becker S, Goldberg L, Katz S, Goldblum R, Harrigan R, Hilton D, Hanauer SB. Safety and tolerability of concurrent natalizumab treatment for patients with Crohn's disease not in remission while receiving infliximab. *Inflamm Bowel Dis* (2007) 13, 2–11.

Monoclonal antibodies + Vaccines

Live vaccines should not be given to patients receiving monoclonal antibodies.

Clinical evidence, mechanism, importance and management

In general, there is little experience of the concurrent use of live vaccines with monoclonal antibodies. Therefore, many manufacturers of monoclonal antibodies (such as **adalimumab**, **certolizumab**, **golimumab**, **infliximab**, **tocilizumab**) recommend that live vaccines are not given to patients receiving a monoclonal antibody, because of the risk of generalised infection. Information about the use of other vaccines with monoclonal antibodies is similarly sparse. The manufacturer of **adalimumab** reports that, in a study in 226 patients with rheumatoid arthritis, the antibody response to **pneumococcal vaccine** and **influenza trivalent vaccine** did not differ between patients given adalimumab and patients given placebo.[1] Similarly, in a study in patients, **golimumab** had no significant effect on the response to **pneumococcal vaccine**. The fact that patients who also received methotrexate had a lower response to vaccination acted as a positive control.[2] The manufacturers advise that vaccines, other than live vaccines, may be given to patients receiving **adalimumab**[1] or **golimumab**.[2] However, it is also recommended that, if possible, patients with juvenile idiopathic arthritis are brought up-to-date with all standard scheduled immunisations before starting **adalimumab**.[1]

1. Humira (Adalimumab). Abbott Laboratories Ltd. UK Summary of product characteristics, December 2009.
2. Simponi (Golimumab). Centocor Ortho Biotech Inc. US Prescribing information, April 2009.

Monoclonal antibodies; Muromonab-CD3 + Indometacin

One report suggested that indometacin may possibly increase the incidence of encephalopathy and psychosis in patients given muromonab-CD3.

Clinical evidence, mechanism, importance and management

A study of patient records found that 4 out of a total of 55 kidney transplant patients (7.3%) given muromonab-CD3 and indometacin 50 mg orally or rectally every 6 to 8 hours for 48 to 72 hours developed serious encephalopathy and psychosis, compared with only 2 out of 173 patients (1.2%) who had received muromonab-CD3 without indometacin.[1]

This appears to be an isolated report, and its general significance is unknown. Indometacin has been used to reduce the adverse effects of muromonab-CD3, and in one analysis, concurrent use was associated with reduced fever, headache, and gastrointestinal disturbances.[2] Muromonab-CD3 alone is associated with encephalopathy and other CNS adverse effects, and the manufacturer warns that patients should be closely monitored for these effects.[3]

1. Chan GL, Weinstein SS, Wright CE, Bowers VD, Alveranga DY, Shires DL, Ackermann JR, LeFor WW, Kahana L. Encephalopathy associated with OKT3 administration. Possible interaction with indomethacin. *Transplantation* (1991) 52, 148–50.
2. Gaughan WJ, Francos BB, Dunn SR, Francos GC, Burke JF. A retrospective analysis of indomethacin on adverse reactions to orthoclone OKT3 in the therapy of acute renal allograft rejection. *Am J Kidney Dis* (1994) 24, 486–90.
3. Orthoclone OKT3 (Muromonab-CD3). Ortho Biotech. US Prescribing information, November 2004.

Monoclonal antibodies; Natalizumab + Interferon beta

Two cases of progressive multifocal leukoencephalopathy occurred in patients receiving natalizumab with interferon beta. Concurrent use does not cause a clinically relevant change in the pharmacokinetics of either drug.

Clinical evidence, mechanism, importance and management

In a study in 38 patients with multiple sclerosis who were receiving interferon beta-1a 30 micrograms weekly, 15 patients were given a single 3-mg/kg dose of natalizumab and 21 patients were given a single 6-mg/kg dose of natalizumab. There was no significant change in the pharmacokinetics of interferon beta, although there were large variations in interferon beta levels between patients. Using historical control data interferon beta did not cause a clinically significant increase in the exposure to natalizumab 6 mg, when compared with natalizumab alone.[1]

Two cases of progressive multifocal leukoencephalopathy (PML) occurred in patients with relapsing multiple sclerosis who were receiving natalizumab with interferon beta-1a.[2] The use of natalizumab has been associated with an increased risk of PML[3,4] but no causal link has been confirmed with the concurrent use interferon beta; however, the UK manufacturer contraindicates the use of natalizumab with beta interferons.[3]

1. Vollmer TL, Phillips JT, Goodman AD, Agius MA, Libonati MA, Giacchino JL, Grundy JS. An open-label safety and drug interaction study of natalizumab (Antegren™) in combination with interferon-beta (Avonex®) in patients with multiple sclerosis. *Multiple Sclerosis* (2004) 10, 511–20.
2. Rudick RA, Stuart WH, Calabresi PA, Confavreux C, Galetta SL, Radue E-W, Lublin FD, Weinstock-Guttman B, Wynn DR, Lynn F, Panzara MA, Sandrock AW, for the SENTINEL Investigators. Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. *N Engl J Med* (2006) 354, 911–23.
3. Tysabri (Natalizumab). Biogen Idec Ltd. UK Summary of product characteristics, January 2009.
4. Tysabri (Natalizumab). Biogen Idec Inc. US Prescribing information, October 2008.

Mycophenolate + Aciclovir and related drugs

The concurrent use of aciclovir or ganciclovir and mycophenolate mofetil does not appear to significantly affect the pharmacokinetics of either drug. There are reports of neutropenia in patients taking mycophenolate with valaciclovir, ganciclovir or valganciclovir.

Clinical evidence, mechanism, importance and management

(a) Aciclovir or Valaciclovir

In a crossover study, healthy subjects were given a single-dose of oral aciclovir 800 mg and mycophenolate mofetil 1 g, both together and alone. The renal clearances of both drugs were not significantly altered by concurrent use. The AUC of aciclovir was increased by about 17% (not statistically significant), that of mycophenolic acid was increased by about 9% (not significant), and that of the glucuronide metabolite of mycophenolate was increased by about 9%. It was concluded that none of these changes was likely to be clinically significant.[1,2] In another single-dose study in healthy subjects, a 31% increase in the AUC of aciclovir was seen when it was given with mycophenolate mofetil: there were no changes to mycophenolic acid pharmacokinetics. The concurrent use of valaciclovir 2 g with mycophenolate mofetil 1 g did not alter aciclovir pharmacokinetics, and the only change in mycophenolate pharmacokinetics was a 12% decrease in AUC of its glucuronide metabolite.[3] None of these changes are likely to be clinically important in patients with normal renal function. The manufacturers of mycophenolate state that, in renal impairment there may be competition for tubular secretion, and that further increases in the concentrations of both aciclovir and mycophenolate may occur.[4,5]

A case report describes a kidney transplant patient taking, amongst other drugs, mycophenolate mofetil 1 g twice daily, who developed neutropenia after starting valaciclovir 6 g daily for prophylactic treatment of a cytomegalovirus infection after successful treatment with ganciclovir. The neutropenia resolved on stopping the valaciclovir. The authors suggested that mycophenolate may increase the haematotoxic effect of valaciclovir especially at high doses.[6] Neutropenia is a rare adverse effect of valaciclovir alone. Bear the possibility of an interaction in mind should neutropenia occur with the combination.

(b) Ganciclovir or Valganciclovir

A crossover study in 12 transplant patients found no pharmacokinetic interaction between a single 1.5-g oral dose of mycophenolate mofetil and intravenous ganciclovir 5 mg/kg, but the renal clearance of ganciclovir was slightly reduced, by 12%.[7] However, the manufacturers predict that, due to competition for renal tubular secretion, the concurrent use of these two drugs may result in increases in ganciclovir levels and in the levels of the inactive metabolite of mycophenolate. They suggest careful monitoring in patients with renal impairment given both drugs.[4,5] These cautions are also applied to the ganciclovir prodrug, valganciclovir.[4,5]

Five cases of neutrophil dysplasia in transplant patients appeared to be related to the concurrent use of ganciclovir and mycophenolate, rather than to the use of mycophenolate alone.[8] In three retrospective analyses, the use of valganciclovir with mycophenolate appeared to be associated with an increased risk of myelotoxicity.[9-11] In one study, there was some evidence that this more frequent with higher dose valganciclovir (900 mg versus 450 mg daily).[11] This emphasises the need for caution with concurrent use. The UK manufacturer of valganciclovir says that as both mycophenolate mofetil and ganciclovir have the potential to cause neutropenia and leucopenia, patients should be monitored for additive toxicity.[12]

1. Shah J, Juan D, Bullingham R, Wong B, Wong R, Fu C. A single dose drug interaction study of mycophenolate mofetil and acyclovir in normal subjects. *J Clin Pharmacol* (1994) 34, 1029.
2. Syntex. A single-dose, pharmacokinetic drug interaction study of oral mycophenolate mofetil and oral acyclovir in normal subjects. Data on file, 1994.
3. Gimenez F, Foeillet E, Bourdon O, Weller S, Garret C, Bidault R, Singlas E. Evaluation of pharmacokinetic interactions after oral administration of mycophenolate mofetil and valaciclovir or aciclovir to healthy subjects. *Clin Pharmacokinet* (2004) 43, 685–92.
4. CellCept Tablets (Mycophenolate mofetil). Roche Products Ltd. UK Summary of product characteristics, October 2009.
5. CellCept (Mycophenolate mofetil). Roche Laboratories Inc. US Prescribing information, October 2009.
6. Royer B, Zanetta G, Bérard M, Davani S, Tanter Y, Rifle G, Kantelip J-P. A neutropenia suggesting an interaction between valacyclovir and mycophenolate mofetil. *Clin Transplant* (2003) 17, 158–61.
7. Wolfe EJ, Mathur V, Tomlanovich S, Jung D, Wong R, Griffy K, Aweeka FT. Pharmacokinetics of mycophenolate mofetil and intravenous ganciclovir alone and in combination in renal transplant recipients. *Pharmacotherapy* (1997) 17, 591–8.
8. Kennedy GA, Kay TD, Johnson DW, Hawley CM, Campbell SB, Isbel NM, Marlton P, Cobcroft R, Gill D, Cull G. Neutrophil dysplasia characterised by a pseudo-Pelger–Huet anomaly occurring with the use of mycophenolate mofetil and ganciclovir following renal transplantation: a report of five cases. *Pathology* (2002) 34, 263–6.
9. Rerolle JP, Szelag JC, Le Meur Y. Unexpected rate of severe leucopenia with the association of mycophenolate mofetil and valganciclovir in kidney transplant recipients. *Nephrol Dial Transplant* (2007) 22, 671–2.
10. Manuel O, Venetz JP, Fellay J, Wasserfallen JB, Sturzenegger N, Fontana M, Matter M, Meylan PR, Pascual M. Efficacy and safety of universal valganciclovir prophylaxis combined with a tacrolimus/mycophenolate-based regimen in kidney transplantation. *Swiss Med Wkly* (2007) 137, 669–76.
11. Brum S, Nolasco F, Sousa J, Ferreira A, Possante M, Pinto JR, Barroso E, Santos JR. Leukopenia in kidney transplant patients with the association of valganciclovir and mycophenolate mofetil. Transplant Proc (2008) 40, 752–4.
12. Valcyte (Valganciclovir hydrochloride). Roche Products Ltd. UK Summary of product characteristics, September 2007.

Mycophenolate + Allopurinol

No clinically relevant interactions have been seen between mycophenolate mofetil and allopurinol.

Clinical evidence, mechanism, importance and management

A study in 5 kidney transplant patients with gouty arthritis, who were switched from azathioprine to mycophenolate mofetil 2 g daily (to avoid the risk of an interaction between azathioprine and allopurinol), found that no adverse effects occurred when they were given allopurinol 100 or 200 mg daily. On average, 10 weeks after the switch had taken place, uricaemia had fallen by 21%, mean serum creatinine levels were only slightly raised (by 12%,) and white cell counts were unchanged.[1] Another study in 19 kidney transplant patients taking mycophenolate 2 g daily, ciclosporin and prednisolone also found a significant reduction in uricaemia without any adverse effects on white cell count, after allopurinol 100 mg daily was also taken for 60 days.[2]

No special precautions would therefore seem necessary if allopurinol is used with mycophenolate, although the authors of both studies suggest that long-term randomised studies are needed to confirm safety.

1. Jacobs F, Mamzer-Bruneel MF, Skhiri H, Thervet E, Legendre Ch, Kreis H. Safety of the mycophenolate mofetil-allopurinol combination in kidney transplant recipients with gout. *Transplantation* (1997) 64, 1087–8.
2. Navascués RA, Gómez E, Rodriguez M, Laures AS, Baltar J, Grande JA. Safety of the allopurinol-mycophenolate mofetil combination in the treatment of hyperuricemia of kidney transplant patients. *Nephron* (2002) 91, 173–4.

Mycophenolate + Antacids

An aluminium/magnesium hydroxide antacid modestly reduced the absorption of mycophenolate in two studies.

Clinical evidence, mechanism, importance and management

In a study in 10 patients, 10 mL of an **aluminium/magnesium hydroxide** antacid (*Maalox TC*) taken four times daily with a single 2-g dose of mycophenolate mofetil (*Cellcept*), reduced the AUC of mycophenolic acid (the active form of the drug) by 17% and its maximum plasma concentration by 38%.[1] Similarly, the manufacturer of mycophenolate sodium (*Myfortic*) noted that a single 30-mL dose of an **aluminium/magnesium hydroxide** antacid reduced the AUC and maximum level of mycophenolic acid by about 37% and 25%, respectively.[2,3]

The clinical significance of this reduction has not been assessed, but the reductions seen in the *Myfortic* study in particular could well be clinically important. The US manufacturer of *Cellcept* says that **aluminium/magnesium** antacids can be used in patients taking mycophenolate, but that they should not be given simultaneously.[4] With many other (but not all) antacid interactions, a 2-hour separation is usually sufficient to avoid an interaction. Similarly, the US manufacturer of *Myfortic* also advises against simultaneous administration.[3] The UK manufacturer of *Myfortic* says that aluminium-magnesium containing antacids may be used intermittently for the treatment of occasional dyspepsia. However their long-term daily use with *Myfortic* is not recommended due to the potential for decreased mycophenolic acid exposure and reduced efficacy.[2] It would seem prudent to check that the immunosuppressant effects of mycophenolate remain adequate in the presence of this or any other antacid.

1. Bullingham R, Shah J, Goldblum R, Schiff M. Effects of food and antacid on the pharmacokinetics of single doses of mycophenolate mofetil in rheumatoid arthritis patients. *Br J Clin Pharmacol* (1996) 41, 513–16.
2. Myfortic (Mycophenolate sodium). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, October 2008.
3. Myfortic (Mycophenolate sodium). Novartis. US Prescribing information, October 2009.
4. CellCept (Mycophenolate mofetil). Roche Laboratories Inc. US Prescribing information, October 2009.

Mycophenolate + Antibacterials

Amoxicillin with clavulanic acid, ciprofloxacin, the combination of norfloxacin with metronidazole, and a selective bowel decontamination regimen of nystatin, tobramycin and cefuroxime have all modestly reduced mycophenolate bioavailability. No interaction appears to occur between mycophenolate and co-trimoxazole.

Clinical evidence

(a) Co-trimoxazole (Sulfamethoxazole with Trimethoprim)

In a study in healthy subjects,[1] co-trimoxazole 960 mg twice daily for 10 days had no effect on the AUC or maximum level of mycophenolic acid, when a single-dose of mycophenolate mofetil 1.5 g was given on day 8.

(a) Metronidazole

A study in 9 healthy subjects found that metronidazole 500 mg three times daily for 5 days reduced the AUC of a single 1-g oral dose of mycophenolate mofetil, given 2 hours after metronidazole on day 4, by 19%. The AUC of the glucuronide metabolite was also reduced, by 27%. When norfloxacin 400 mg twice daily was also given, the AUC of mycophenolate and its glucuronide metabolite were reduced by 33% and 41%, respectively.[2]

(b) Penicillins

In a study in kidney transplant patients taking mycophenolate, mycophenolic acid trough levels were monitored in patients receiving **amoxicillin** with **clavulanic acid** 375 mg three times daily for 7 days (20 patients) or for 14 days or more (17 patients). In both groups the trough mycophenolic acid levels were about 50% lower 3 days after starting the antibacterial, and they were still at this level on day 7. Three days after stopping the antibacterial in the 7-day group, the trough levels had returned to baseline. On day 14 in the longer-term group, the trough levels had *risen*, and were just 19% lower than baseline.[3]

(c) Quinolones

A study in 11 healthy subjects found that **norfloxacin** 400 mg twice daily reduced the AUC of a single 1-g oral dose of mycophenolate mofetil, given 2 hours after the antibacterial on day 4, by 10%. The AUC of the glucuronide metabolite was also reduced by 10%. When metronidazole 400 mg twice daily was also given, the AUC of mycophenolate and its glucuronide metabolite were reduced by 33% and 41%, respectively.[2]

In a study in kidney transplant patients taking mycophenolate, mycophenolic acid trough levels were monitored in patients receiving **ciprofloxacin** 500 mg twice daily for 7 days (24 patients) or for 14 days or more (21 patients). In both groups the trough levels were about 35 to 40% lower 3 days after starting **ciprofloxacin**, and they were still at this level on day 7. Three days after stopping **ciprofloxacin** in the 7-day group, the trough levels had returned to baseline. On day 14 in the longer-term group, the trough levels had *risen*, and were just 17% lower than baseline.[3]

(d) Rifampicin (Rifampin)

For the effect of rifampicin on the pharmacokinetics of mycophenolate, see 'Mycophenolate + Rifampicin (Rifampin)', p.1287.

(e) Selective bowel decontamination

Six liver transplant patients were given a regimen for selective bowel decontamination for 21 days after the transplant, which consisted of **nystatin**, **tobramycin** and **cefuroxime** and also received mycophenolate mofetil 1 g twice daily. The AUC of mycophenolic acid was measured when the patients were taking the antibacterials (one measurement between day 17 and 20, at which time mycophenolate had been given for at least 10 days) and then again after stopping the antibacterials (one measurement between day 23 and 29). The AUC was 31% lower while taking the antibacterials, although this did not reach statistical significance. However, the reduction in $AUC_{6\text{-}12}$ of 57% was statistically significant.[4]

Mechanism

Mycophenolic acid is metabolised to the glucuronide conjugate, which is excreted in bile and urine. Gut bacteria that express the beta-glucuronidase enzyme (mostly Gram-negative anaerobes) cleave the glucuronide conjugate allowing free mycophenolic acid to be reabsorbed (enterohepatic recirculation). Antibacterials that decimate gut bacteria can reduce this enterohepatic recirculation leading to lower levels of mycophenolic acid.[2,3] However, the effect may lessen over time as the bowel flora recover even with continued use of the antibacterial.[3]

Importance and management

The available evidence suggests that antibacterials that can decimate gut bacteria might reduce levels of mycophenolic acid by up to one-third or one-half. In the study assessing the time course of this effect during an antibacterial course, the effect was rapid, occurring within 3 days of starting the antibacterial and recovering within 3 days of stopping it. Also, interestingly, the effect lessened with continued use of the antibacterial beyond 7 days.

The clinical relevance of these reductions has not been assessed. One manufacturer considers that a change in the dose of mycophenolate should not normally be necessary, in the absence of clinical evidence of graft dysfunction, if amoxicillin with clavulanic acid or ciprofloxacin are also given. However, close clinical monitoring is advisable during the concurrent use of the antibacterial, and shortly after it is stopped.[5] The available evidence suggests that this advice should be applied to any antibacterial that affects gut flora. Note that the US manufacturer considers that the combination of metronidazole and norfloxacin should not be used with mycophenolate mofetil.[1]

1. CellCept (Mycophenolate mofetil). Roche Laboratories Inc. US Prescribing information, October 2009.
2. Naderer OJ, Dupuis RE, Heinzen EL, Wiwattanawongsa MS, Johnson MW, Smith PC. The influence of norfloxacin and metronidazole on the disposition of mycophenolate mofetil. *J Clin Pharmacol* (2005) 45, 219–26.
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4. Schmidt LE, Rasmussen A, Nørrelykke MR, Poulsen HE, Hansen BA. The effect of selective bowel decontamination on the pharmacokinetics of mycophenolate mofetil in liver transplant recipients. *Liver Transpl* (2001) 7, 739–42.
5. CellCept Tablets (Mycophenolate mofetil). Roche Products Ltd. UK Summary of product characteristics, October 2009.

Mycophenolate + Azathioprine

The manufacturers of mycophenolate have recommended that it should not be given with azathioprine because they say that concurrent use has not been studied,[1-4] and as both drugs inhibit purine metabolism,[4] they have the potential to cause bone marrow suppression.[1]

1. CellCept (Mycophenolate mofetil). Roche Laboratories Inc. US Prescribing information, October 2009.
2. CellCept Tablets (Mycophenolate mofetil). Roche Products Ltd. UK Summary of product characteristics, October 2009.
3. Myfortic (Mycophenolate sodium). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, October 2008.
4. Myfortic (Mycophenolate sodium). Novartis. US Prescribing information, October 2009.

Mycophenolate + Ciclosporin or Tacrolimus

Ciclosporin reduces the levels of mycophenolic acid. Tacrolimus may increase mycophenolic acid levels in some patient groups.

Clinical evidence

(a) Mycophenolate with Ciclosporin or Tacrolimus

A study in 78 kidney transplant patients taking corticosteroids with mycophenolate 1 g two or three times daily, and also taking either ciclosporin (68 patients) or tacrolimus (10 patients), found lower trough levels of the active metabolite, mycophenolic acid, and higher levels of the glucuronide metabolite in patients taking ciclosporin during the first 3 months post-transplant, when compared with those taking tacrolimus. Of interest, of the 11 patients that changed from ciclosporin to tacrolimus during the study, 5 patients subsequently required mycophenolate dose reductions because of adverse effects.[1] Another study found that despite a higher dose of mycophenolate, patients also taking ciclosporin had a 50% lower trough mycophenolic acid level when compared with those taking mycophenolate with tacrolimus.[2] Other studies have found similar results.[3-5] In another study, 12 stable kidney transplant patients taking ciclosporin (*Neoral*) were given enteric-coated mycophenolate sodium (*Mycofortic*) 720 mg twice daily for 14 days. After pharmacokinetic assessment, they were then changed over to tacrolimus with the same dose and formulation of mycophenolate sodium. This study found that when tacrolimus was given the mycophenolic acid AUC was 20% greater than when ciclosporin was taken, but maximum concentration of mycophenolic acid was 24% greater with ciclosporin than with tacrolimus.[6] However, a study in 22 kidney transplant patients taking mycophenolate found that neither ciclosporin (13 patients) nor tacrolimus (9 patients) affected the plasma levels of mycophenolic acid. Levels of the glucuronide metabolite were increased by ciclosporin but not tacrolimus.[7] The manufacturers report that in one study in kidney transplant patients receiving ciclosporin and mycophenolate mofetil, the AUC of mycophenolic acid was increased by about 30% when ciclosporin was replaced by tacrolimus.[8]

(b) Mycophenolate with Ciclosporin

There are reports that the trough levels of the active metabolite of mycophenolate, mycophenolic acid, may be reduced in the presence of ciclosporin.[9] In a study, 52 kidney transplant patients were given mycophenolate mofetil 1 g twice daily with ciclosporin and prednisone. Six months after transplantation 19 patients continued triple therapy, 19 discontinued ciclosporin and 14 discontinued prednisone. Three months later, patients in whom ciclosporin had been discontinued had higher trough mycophenolic acid levels compared with the other groups of patients. Discontinuing ciclosporin resulted in almost a doubling of mycophenolic acid trough levels.[10] Other studies note similar effects on mycophenolic acid levels in adult[11] and paediatric patients.[12]

A study in 33 children taking ciclosporin with prednisolone and 15 children additionally taking mycophenolate mofetil found that the ciclosporin levels 2 hours after the ciclosporin dose, was significantly reduced in those patients taking mycophenolate.[13] Another study in children found similar results.[14]

(c) Mycophenolate with Tacrolimus

A study in stable kidney transplant patients taking tacrolimus long-term found that the addition of mycophenolate mofetil resulted in a increase in the tacrolimus AUC, but this was not considered significant.[15] Another

study in kidney transplant patients found no change in tacrolimus levels when mycophenolate was given.[8] However, a 20% increase in tacrolimus levels has been reported in a study in liver transplant patients given mycophenolate 1.5 g twice daily.[8]

Mechanism

Mycophenolate is hydrolysed to its active drug, mycophenolic acid. This then undergoes glucuronidation by glucuronosyltransferases (UGT) to form an inactive glucuronide metabolite. This metabolite is then either excreted in urine or undergoes enterohepatic recirculation, where it is converted back into the active form, mycophenolic acid. Ciclosporin is thought to inhibit the enterohepatic conversion of the glucuronide metabolite back to the active metabolite, mycophenolic acid, leading to lower levels of mycophenolic acid.[8]

Tacrolimus may inhibit UGT which metabolises mycophenolic acid to the glucuronide metabolite,[1,7] and may also interfere with the enterohepatic recycling of the glucuronide metabolite.[8]

Importance and management

The addition of mycophenolate to ciclosporin has been found to reduce the incidence of rejection episodes in kidney transplant patients[16] and it is licensed for concurrent use.[8] From the studies above, ciclosporin appears to reduce the levels of the active metabolite, mycophenolic acid, and increase the levels of the glucuronide metabolite (which is associated with mycophenolate adverse effects). The UK manufacturers point out that as efficacy studies were conducted in patients taking ciclosporin, mycophenolate and corticosteroids, the finding that ciclosporin reduces the mycophenolic acid AUC by 19 to 38% does not affect the recommended dose requirements.[8] They also state that ciclosporin pharmacokinetics are not affected by mycophenolate.[8,17] However, this is in contrast to the studies in children reported above.[13,14] It has also been observed that the use of triple therapy with corticosteroids, ciclosporin and mycophenolate mofetil rather than with azathioprine makes it possible to use a lower dose of ciclosporin.[18] However, other studies have noted that adjusting ciclosporin doses affects mycophenolic acid levels, and therefore the overall effect on immunosuppression needs careful monitoring.[12]

The significance of the reported increases in mycophenolic acid levels with concurrent tacrolimus is not clear, and the manufacturers note that the benefit of concurrent use with tacrolimus has not been established.[8,17] There are also inherent problems in interpretation of the results of studies comparing ciclosporin or tacrolimus with mycophenolate.[2,4,19,20] It has been suggested that the changes in mycophenolic acid trough levels are because tacrolimus increases mycophenolic acid levels;[4] however, another interpretation may be that the differences in mycophenolic acid trough levels and AUCs seen are because ciclosporin decreases mycophenolic acid exposure.[19]

Patients taking either ciclosporin or tacrolimus with mycophenolate should have their immunosuppressive response closely monitored, particularly if changing from ciclosporin to tacrolimus or *vice versa*, and dose adjustment of mycophenolate should be considered if patients develop mycophenolate-related adverse effects (such as diarrhoea, vomiting and leucopenia) on switching from ciclosporin to tacrolimus.

1. Mandla R, Midtvedt K, Line P-D, Hartmann A, Bergan S. Mycophenolic acid clinical pharmacokinetics influenced by a cyclosporine C2 based immunosuppressive regimen in renal allograft recipients. *Transpl Int* (2006) 19, 44–53.
2. Gerbase MW, Fathi M, Spiliopoulos A, Rochat T, Nicod LP. Pharmacokinetics of mycophenolic acid associated with calcineurin inhibitors: long-term monitoring in stable lung recipients with and without cystic fibrosis. *J Heart Lung Transplant* (2003) 22, 587–90.
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8. CellCept Tablets (Mycophenolate mofetil). Roche Products Ltd. UK Summary of product characteristics, October 2009.
9. Weber SW, Keller F. Low mycophenolate predose levels with cyclosporine co-medication. *Kidney Blood Press Res* (1999) 22, 390.
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17. Myfortic (Mycophenolate sodium). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, October 2008.
18. Sanz Moreno C, Gomez Sanchez M, Fdez Fdez J, Botella J. Cyclosporine A (CsA) needs are reduced with substitution of azathioprine (Aza) by mycophenolate mofetil (MMF). *Nephrol Dial Transplant* (1998) 13, A260.
19. van Gelder T, Smak Gregoor PJH, Weimar W. Letter to the editor. *Ther Drug Monit* (2000) 22, 639.
20. Hübner GI, Sziegoleit W. Response to letter from van Gelder. *Ther Drug Monit* (2000) 22, 498–9.

Mycophenolate + Colestyramine

Colestyramine modestly reduces the AUC of mycophenolic acid after administration of mycophenolate.

Clinical evidence

In a study in healthy subjects, colestyramine 4 g three times daily for 4 days reduced the AUC of mycophenolic acid by 37% (range 10 to 61%) after they took a single 1.5-g oral dose of mycophenolate mofetil one hour after the first colestyramine dose on day 2.[1-3] There was no difference in the maximum level, and the main difference was a reduction in mycophenolic acid levels from 6 hours onwards.[3]

Mechanism

Mycophenolic acid is metabolised to the glucuronide conjugate, which is excreted in bile and urine. Gut bacteria cleave the glucuronide conjugate allowing free mycophenolic acid to be reabsorbed (enterohepatic recirculation). Colestyramine appears to reduce the enterohepatic recirculation of mycophenolate.[3]

Importance and management

The clinical importance of the reduction in mycophenolic acid levels has not been assessed; however, enterohepatic recirculation of mycophenolic acid varies widely between individuals,[3] and therefore this interaction may well be significant in some patients. If colestyramine is considered essential, it would seem prudent to confirm that the immunosuppressant effects of mycophenolate remain adequate. Separating the administration of colestyramine and mycophenolate is not likely to eliminate this interaction. Note that the US manufacturers of mycophenolate advise avoiding the concurrent use of colestyramine[2,4] and other drugs that bind to bile acids, such as **bile-acid binding resins** or oral **activated charcoal**.[4]

1. CellCept Tablets (Mycophenolate mofetil). Roche Products Ltd. UK Summary of product characteristics, October 2009.
2. CellCept (Mycophenolate mofetil). Roche Laboratories Inc. US Prescribing information, October 2009.
3. Bullingham RE, Nicholls AJ, Kamm BR. Clinical pharmacokinetics of mycophenolate mofetil. *Clin Pharmacokinet* (1998) 34, 429–55.
4. Myfortic (Mycophenolate sodium). Novartis. US Prescribing information, October 2009.

Mycophenolate + Corticosteroids

One study suggests that methylprednisolone might modestly decrease mycophenolate levels, but a similar study suggests that

it does not. In another study, prednisone did not alter mycophenolate levels.

Clinical evidence, mechanism, importance and management

(a) Methylprednisolone

In a study in kidney transplant patients taking mycophenolate, ciclosporin and methylprednisolone, the dose-normalised mycophenolic acid AUC was 35% lower in the first month when patients were receiving higher doses of methylprednisolone (about 16 mg daily) than at 6 months when lower maintenance doses of methylprednisolone (8 mg daily) were being used. In addition, plasma levels of the glucuronide metabolite were 2.7-fold higher in the first month than at 6 months. Moreover, in those patients in whom methylprednisolone was tapered and discontinued, there was a 56% and 31% increase in trough levels and AUC of mycophenolic acid, respectively. This difference was apparent even when controlling for 'ciclosporin', (p.1284), exposure.[1]

In contrast, in another very similar study, the authors reported that methylprednisolone dose or withdrawal had no effect on mycophenolic acid trough concentrations or AUC.[2]

(b) Prednisone

In a study in patients taking triple therapy (mycophenolate, ciclosporin and prednisone), trough mycophenolate acid levels did not differ between 19 patients who continued this therapy and 14 patients who discontinued prednisone.[3]

Mechanism

Corticosteroids might induce the glucuronidation of mycophenolic acid, thereby decreasing its levels.[1]

Importance and management

It is unclear from these studies whether corticosteroids can alter mycophenolate levels, but the extent was modest in the one study that did find a decrease, and probably of limited clinical relevance. The combination is in general clinical use.

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3. Smak Gregoor PJH, de Sévaux RGL, Hené RJ, Hesse CJ, Hilbrands LB, Vos P, van Gelder T, Hoitsma AJ, Weimar W. Effect of cyclosporine on mycophenolic acid trough levels in kidney transplant recipients. *Transplantation* (1999) 68, 1603–6.

Mycophenolate + Food

Food had no effect on the extent of absorption of mycophenolate mofetil or mycophenolate sodium, but markedly delayed absorption with mycophenolate sodium.

Clinical evidence, mechanism, importance and management

(a) Mycophenolate mofetil

In a study in 10 rheumatoid arthritis patients, there was no difference in the AUC of mycophenolic acid when a single 2-g dose of mycophenolate mofetil (*Cellcept*) was given in the fasting state or immediately after a high-fat breakfast. The time to maximum level was delayed from one to two hours and there was a slight 24% reduction in the maximum level, suggesting some delay in absorption. There was also a slight 14% increase in the AUC of the glucuronide metabolite.[1] Similarly, the manufacturers report that, in a further study in kidney transplant patients, there was no change in extent of absorption (AUC), but there was a more marked 40% reduction in maximum levels.[2,3] It is doubtful if this is clinically relevant, but note that the US manufacturer recommends that mycophenolate mofetil is taken on an empty stomach. They say that, in stable kidney transplant patients, mycophenolate mofetil can be taken with food if necessary.[2]

(b) Mycophenolate sodium

The manufacturer reports that no difference was seen in the AUC of mycophenolic acid when a single dose of mycophenolate sodium (*Myfortic*) was given in the fasting state or immediately after a high-fat meal. However, there was a 33% decrease in the maximum concentration and a 5-hour delay in the time to maximum level suggesting significant delay in absorption.[4,5] Some patients had a time to maximum level of greater than 15 hours, which can lead to an absorption overlap from one dose interval to the next.[4] Because of this, the UK manufacturer recommends that patients take mycophenolate sodium consistently, either with or without food.[4] However, the US manufacturer advises that, to avoid the variability in absorption between doses, mycophenolate sodium (*Myfortic*) should be taken on an empty stomach, one hour before or 2 hours after food intake.[5]

1. Bullingham R, Shah J, Goldblum R, Schiff M. Effects of food and antacid on the pharmacokinetics of single doses of mycophenolate mofetil in rheumatoid arthritis patients. *Br J Clin Pharmacol* (1996) 41, 513–6.
2. CellCept (Mycophenolate mofetil). Roche Laboratories Inc. US Prescribing information, October 2009.
3. CellCept Tablets (Mycophenolate mofetil). Roche Products Ltd. UK Summary of product characteristics, October 2009.
4. Myfortic (Mycophenolate sodium). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, October 2008.
5. Myfortic (Mycophenolate sodium). Novartis. US Prescribing information, October 2009.

Mycophenolate + Iron compounds

Most studies have found that oral iron has no significant effect on the absorption of mycophenolate mofetil.

Clinical evidence, mechanism, importance and management

In the first study of the effect of iron on mycophenolate levels, a single 1050-mg dose of sustained-release **ferrous sulfate** (210 mg of elemental iron; *Fero-Gradumet*) reduced the AUC and maximum levels of mycophenolic acid by more than 90% when given at the same time as a single 1-g dose of mycophenolate mofetil in 7 healthy fasting subjects.[1] However, this finding was not replicated in an identical study in which 16 healthy fasting subjects were given a single 1-g dose of mycophenolate mofetil with sustained-release **ferrous sulfate** (210 mg elemental iron; *Ferro-Gradumet*). There was no change in the AUC of mycophenolic acid.[2]

Moreover, three studies in kidney transplant patients taking mycophenolate have also not identified an interaction.[3-5] In one study in 10 kidney transplant patients taking mycophenolate mofetil 1 g daily, a single 105-mg dose of elemental iron (as **ferrous sulfate** in *Ferro-Gradumet*) had no effect on the absorption of mycophenolate in the fasted state, either when given at the same time, or 4 hours apart.[3] Similarly, another study in 40 kidney transplant patients found that two sustained-release tablets of **ferrous sulfate** (*Ferrogradumet*) daily, given either at the same time or 4 hours after the morning dose of mycophenolate (for 5 days after kidney transplantation), had no significant effect on the absorption of mycophenolate 1 g twice daily, when compared with patients not given an iron supplement. In addition, the groups appeared comparable in terms of incidence of rejection and adverse effects, although the study was not big enough to properly assess this.[4] A further study in 5 transplant patients, found no change in the mycophenolic acid AUC when slow-release **ferrous sulfate** was given daily for 7 days, either at the same time as the morning dose of mycophenolate mofetil or 2 hours afterwards. With a **polysaccharide iron complex**, the mean mycophenolic acid AUC was modestly increased by 22% when it was given 2 hours after mycophenolate mofetil, with no change when given at the same time.[5]

The reason why the first study had such a different finding to all the others is unknown, but it has been suggested that there may have been a problem with the assay.[2]

On balance, it would appear that oral iron compounds do not alter the pharmacokinetics of mycophenolate, and that no special precautions are required if an iron supplement is needed in a patient taking mycophenolate.

1. Morii M, Ueno K, Ogawa A, Kato R, Yoshimura H, Wada K, Hashimoto H, Takeda M, Tanaka K, Nakatani T, Shibakawa M. Impairment of mycophenolate mofetil absorption by iron ion. *Clin Pharmacol Ther* (2000) 68, 613–16.
2. Ducray PS, Banken L, Gerber M, Boutouyrie B, Zandt H. Absence of an interaction between iron and mycophenolate mofetil absorption. *Br J Clin Pharmacol* (2006) 62, 492–5.
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Mycophenolate + Methotrexate

A study in patients with rheumatoid arthritis found that the concurrent use of methotrexate and mycophenolate mofetil was well tolerated and there were no pharmacokinetic interactions.[1] There would appear to be no need for dose adjustments if both drugs are given for rheumatoid arthritis.

1. Yocum D, Kremer J, Blackburn W, Caldwell J, Furst D, Nunez M, Zuzga J, Zeig S, Gutierrez M, Merrill J, Dumont E, B Leishman. Cellcept® (mycophenolate mofetil - MMF) and methotrexate (MTX) safety and pharmacokinetic (PK) interaction study in rheumatoid arthritis patients. *Arthritis Rheum* (1999) 42 (9 Suppl), S83.

Mycophenolate + Polycarbophil calcium

Polycarbophil calcium reduced the bioavailability of mycophenolate in one study in healthy subjects.

Clinical evidence, mechanism, importance and management

A study in 5 healthy subjects given a single 1-g dose of mycophenolate alone or with polycarbophil calcium 2.4 g found that the AUC and peak serum levels of mycophenolic acid were reduced by about 51% and 69%, respectively. The authors suggest that this interaction was probably the result of reduced absorption due to chelate-complex formation between mycophenolate and the calcium ions, which they also demonstrated in an *in vitro* study. It was concluded that mycophenolate and polycarbophil calcium should not be taken at the same time.[1] A suitable interval was not specified, but a separation of 2 hours has been suggested with antacids, which may interact by a similar mechanism (see 'Mycophenolate + Antacids', p.1283). Further study is needed, especially as this study used the same assay method as that in a study with iron, the validity of which has been questioned.

1. Kato R, Ooi K, Ikura-Morii M, Tsuchishita Y, Hashimoto H, Yoshimura H, Uenishi K, Kawai M, Tanaka K, Ueno K. Impairment of mycophenolate mofetil absorption by calcium polycarbophil. *J Clin Pharmacol* (2002) 42, 1275–80.

Mycophenolate + Probenecid

Probenecid might increase mycophenolic acid levels.

Clinical evidence, mechanism, importance and management

In *animals*, probenecid increased the AUC of mycophenolic acid twofold and the AUC of its glucuronide metabolite threefold.[1] This was thought to be because probenecid competitively inhibits the renal excretion of the glucuronide metabolite of mycophenolate.[1] However, as there appear to be no clinical reports of an interaction, the clinical significance of this is unclear. Further study is needed.

1. CellCept (Mycophenolate mofetil). Roche Laboratories Inc. US Prescribing information, October 2009.

Mycophenolate + Proton pump inhibitors

Lansoprazole, but not rabeprazole, might modestly reduce mycophenolic acid levels.

Clinical evidence, mechanism, importance and management

In a retrospective study in 22 kidney transplant patients taking mycophenolate mofetil and tacrolimus, **lansoprazole** 30 mg daily reduced the dose-adjusted maximum level and trough level of mycophenolic acid by 32% and 45%, respectively, when compared with a control group of 22 patients not taking a proton pump inhibitor. The dose-adjusted AUC was 25% lower, but this was not statistically significant. The interaction tended to be greater in intermediate CYP2C19 metabolisers than in extensive metabolisers (i.e. the interaction was greater in those with lower levels of this isoenzyme).[1] In the same study, there was no difference in mycophenolic acid pharmacokinetics between 17 patients taking **rabeprazole** 10 mg daily and the control group.[1]

The exact mechanism for this interaction and the differences seen is uncertain it may be related to gastric pH and therefore the differing acid-suppressant effects of the doses studied. It is unclear if the modest differences in mycophenolic acid levels reported with **lansoprazole** are of clinical relevance and a controlled study is needed to confirm these results. Until more is known, it would seem prudent to bear the possibility of an interaction in mind in patients taking **lansoprazole**.

1. Miura M, Satoh S, Inoue K, Kagaya H, Saito M, Suzuki T, Habuchi T. Influence of lansoprazole and rabeprazole on mycophenolic acid pharmacokinetics one year after renal transplantation. Ther Drug Monit (2008) 30, 46–51.

Mycophenolate + Rifampicin (Rifampin)

In a controlled study, rifampicin slightly reduced the levels of mycophenolic acid (the active metabolite of mycophenolate) and markedly increased the levels of the acyl-glucuronide metabolite, which may be associated with mycophenolate adverse effects. One case report describes markedly increased mycophenolate dose requirements in a patient taking rifampicin.

Clinical evidence

A heart-lung transplant patient taking tacrolimus 7 mg twice daily and mycophenolate mofetil 1 g twice daily was given rifampicin 600 mg daily, pyrazinamide 1 g daily, isoniazid 300 mg daily and pyridoxine 250 mg weekly for a suspected mycobacterial infection. As expected, the tacrolimus dose needed to be substantially increased when rifampicin was started, and the rifampicin dose was reduced to 450 mg daily to try to minimise the interaction. However, the mycophenolate mofetil dose also needed to be increased threefold to 6 g daily without achieving an adequate level (target trough plasma level of 2.5 micrograms/mL). Rifampicin was then stopped and the patient continued taking isoniazid and pyrazinamide. Pharmacokinetic analysis of mycophenolate before and 13 days after rifampicin was stopped, found that the dose-corrected trough level of mycophenolic acid increased 18-fold and the $AUC_{0\text{-}12}$ increased threefold after stopping rifampicin.[1]

However, a subsequent study by the same authors in 8 kidney transplant patients taking mycophenolate 750 mg to 1 g twice daily found that rifampicin 600 mg daily for 8 days decreased the $AUC_{0\text{-}12}$ and peak levels of mycophenolic acid by just 18% and 19%, respectively. The $AUC_{0\text{-}12}$ of the inactive 7-*O*-glucuronide metabolite was increased by 34%, and the $AUC_{0\text{-}12}$ and peak levels of the acyl-glucuronide metabolite were significantly increased by 193% and 121%, respectively. The acyl-glucuronide metabolite has been associated with an increase in mycophenolate adverse effects, but this was not seen in this study.[2]

Mechanism

The exact mechanism of this interaction is unknown. Mycophenolate is a prodrug and is metabolised to its active form, mycophenolic acid, which undergoes glucuronidation by glucuronosyltransferases (UGTs) in the liver, kidney and intestine to its inactive 7-*O*-glucuronide metabolite. The authors of these reports suggest that rifampicin induces intestinal, kidney and liver glucuronidation of mycophenolic acid by UGT and reduces its enterohepatic recirculation and absorption.[1,2]

Importance and management

These appear to be the only reports of an interaction between rifampicin and mycophenolate. However, the effects of reduced mycophenolic acid levels could be significant in terms of acute graft rejection. Also the increases in the levels of the acyl-glucuronide metabolite could put the patient at greater risk of adverse effects, although as mentioned, this was not seen in these studies. Mycophenolate should be monitored closely during the concurrent use of rifampicin and the dose adjusted as required, both on starting or stopping rifampicin. For a discussion of the effects of antibacterials on mycophenolate via an effect on gut bacteria, see 'Mycophenolate + Antibacterials', p.1283.

1. Kuypers DRJ, Verleden G, Naesens M, Vanrenterghem Y. Drug interaction between mycophenolate mofetil and rifampin: possible induction of uridine diphosphate-glucuronosyltransferase. *Clin Pharmacol Ther* (2005) 78, 81–8.
2. Naesens M, Kuypers DRJ, Streit F, Armstrong VW, Oellerich M, Verbeke K, Vanrenterghem Y. Rifampin induces alterations in mycophenolic acid glucuronidation and elimination: implications for drug exposure in renal allograft recipients. *Clin Pharmacol Ther* (2006) 80, 509–21.

Mycophenolate + Sevelamer

The short-term use of sevelamer moderately reduces mycophenolic acid levels.

Clinical evidence, mechanism, importance and management

In a pharmacokinetic study, 3 adult and 6 paediatric kidney transplant patients taking mycophenolate and ciclosporin were given sevelamer (at the same time), either as a single 1.6-g dose in the adults, or a single 1.2-g dose in the children, or for 4 days (same dose given three times daily). The average age of the children was 12 years. The single dose of sevelamer reduced the AUC of mycophenolic acid by 25%, and multiple-dosing of sevelamer reduced its AUC by 30%. The interaction was thought to be due to sevelamer reducing the absorption of mycophenolate.[1] The UK manufacturer notes that no graft rejection occurred in this study.[2]

The clinical significance of this modest interaction is unclear. However, until more is known, it would seem prudent to monitor mycophenolic acid levels in any patient given sevelamer. The UK manufacturer[2] of mycophenolate mofetil recommends that drugs for which a reduction in bioavailability could be clinically important, should be taken at least one hour before or three hours after taking sevelamer. One US manufacturer advises taking mycophenolate 2 hours before sevelamer.[3]

Further study is required with longer-term administration and to evaluate if separation of doses is an effective way of reducing the interaction.

1. Pieper A-K, Buhle F, Bauer S, Mai I, Budde K, Haffner D, Neumayer H-H, Querfeld U. The effect of sevelamer on pharmacokinetics of cyclosporin A and mycophenolate-mofetil after renal transplantation. *Nephrol Dial Transplant* (2004) 19, 2630–3.
2. CellCept Tablets (Mycophenolate mofetil). Roche Products Ltd. UK Summary of product characteristics, October 2009.
3. CellCept (Mycophenolate mofetil). Roche Laboratories Inc. US Prescribing information, October 2009.

Mycophenolate + Sirolimus

Higher levels of mycophenolic acid have been seen in kidney transplant patients taking mycophenolate with sirolimus when compared with similar patients taking mycophenolate with ciclosporin.

Clinical evidence

A study in 12 kidney transplant patients taking mycophenolate 1 g twice daily at the same time as sirolimus (dose adjusted to attain therapeutic trough blood levels of 10 to 15 nanograms/mL) for 30 days found that the $AUC_{0\text{-}9}$ of the active metabolite of mycophenolate, mycophenolic acid, was 50% higher in the sirolimus-treated group when compared with a similar group of 19 patients taking ciclosporin instead of sirolimus.[1] Similarly, in a study in 13 kidney transplant patients taking mycophenolate 1 g twice daily with sirolimus (trough blood levels of 10 to 20 nanograms/mL), the mycophenolic acid trough levels and AUC were significantly higher in patients taking sirolimus, compared with a similar group of 17 patients given ciclosporin, although peak mycophenolic acid levels were similar. Mycophenolate dose reductions were required in 2 patients in the first month, another 3 patients in the second month and 6 patients in the third month (total of 11 patients), compared with the ciclosporin group where only 5 patients needed mycophenolate dose reductions. A higher incidence of leucopenia at months one and 2 after transplantation was reported in patients taking sirolimus, rather than ciclosporin, with mycophenolate.[2]

Another study in 11 kidney transplant patients taking low-dose mycophenolate 500 mg twice daily with low-dose sirolimus (mean dose of between 3.6 to 4.3 mg daily adjusted to achieve a trough blood level of 5 to 10 nanograms/mL) found that the sirolimus-based regimen had a 4.4-fold higher dose-adjusted mycophenolic acid trough level than those found in another similar group of 10 patients taking a ciclosporin-based regimen.[3]

Yet another study in 15 kidney transplant patients taking mycophenolate with sirolimus looked at the effects of sirolimus on mycophenolate dose regimens of 500 mg, 750 mg, and 1 g twice daily and compared them with the effects of ciclosporin on mycophenolate 1 g twice daily in 12 similar patients. They found that mycophenolate 750 mg twice daily with sirolimus produced a comparable $AUC_{0\text{-}12}$ and trough mycophenolic acid levels to mycophenolate 1 g twice daily with ciclosporin.[4] Another study also found that exposure to mycophenolic acid was about 70 to 100% higher in 30 patients given sirolimus than in 15 given ciclosporin, and exposure to the glucuronide metabolite was lower. Moreover, biopsy proven rejection was higher in the sirolimus group (40% versus 13.3%).[5]

Mechanism, importance and management

Ciclosporin is known to inhibit the metabolism of mycophenolate, producing lower levels of mycophenolic acid, see 'Mycophenolate + Ciclosporin or Tacrolimus', p.1284. Whether sirolimus specifically raises mycophenolic acid levels compared with mycophenolate taken on its own is unclear; however, raised mycophenolic acid levels have been associated with an increased risk of adverse effects.[1-3] The authors of one of the studies suggest that the mycophenolate dose should be reduced from 1 g to 750 mg twice daily in patients taking sirolimus, as this produced comparable mycophenolic acid levels to the recommended dose of mycophenolate 1 g twice daily with ciclosporin.[4]

However, until further information is available, patients taking mycophenolate and changed from ciclosporin to sirolimus should be closely monitored for mycophenolate adverse effects (such as diarrhoea, vomiting and leucopenia), and the dose of mycophenolate reduced accordingly.

1. Picard, N, Prémaud, Rousseau A, Le Meur Y, Marquet P. A comparison of the effect of ciclosporin and sirolimus on the pharmacokinetics of mycophenolate in renal transplant patients. *Br J Clin Pharmacol* (2006) 62, 477–84.
2. Büchler M, Lebranchu Y, Bénéton M, Le Meur Y, Heng AE, Westeel PF, le Guellec C, Libert F, Hary L, Marquet P, Paintaud G. Higher exposure to mycophenolic acid with sirolimus than with cyclosporine cotreatment. *Clin Pharmacol Ther* (2005) 78, 34–42.
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5. Pescovitz MD, Vincenti F, Hart M, Melton L, Whelchel J, Mulgaonkar S, McKay D, Leung M, Calleja E, Bouw MR. Pharmacokinetics, safety, and efficacy of mycophenolate mofetil in combination with sirolimus or ciclosporin in renal transplant patients. *Br J Clin Pharmacol* (2007) 64, 758–71.

Mycophenolate + St John's wort (*Hypericum perforatum*)

St John's wort does not appear to alter the pharmacokinetics of mycophenolate.

Clinical evidence

In a pharmacokinetic study, 8 stable kidney transplant patients taking mycophenolate 1 to 2 g daily and tacrolimus were given 600 mg of St John's wort extract (*Jarsin 300*) daily for 14 days. The levels of mycophenolic acid, the main metabolite of mycophenolate, were measured before St John's wort was started, on day 14, and two weeks after St John's wort was stopped. The pharmacokinetics of mycophenolic acid were unchanged throughout the study, and no dosage adjustments were needed in any of the 8 patients.[1]

Mechanism

No mechanism. St John's wort is an inducer of the cytochrome P450 isoenzyme CYP3A4, and P-glycoprotein. As mycophenolate is not significantly metabolised or transported by these routes, an interaction would not be expected.

Importance and management

St John's wort does not appear to affect the pharmacokinetics of mycophenolate and therefore no additional precautions seem necessary on concurrent use.

1. Mai I, Störmer E, Bauer S, Krüger H, Budde K, Roots I. Impact of St John's wort treatment on the pharmacokinetics of tacrolimus and mycophenolic acid in renal transplant patients. *Nephrol Dial Transplant* (2003) 18, 819–22.

Mycophenolate + Voriconazole

Voriconazole does not alter the pharmacokinetics of mycophenolate.

Clinical evidence, mechanism, importance and management

In a study, voriconazole had no effect on the pharmacokinetics of a single 1-g dose of mycophenolate.[1] Similarly, the AUC, trough levels and maximum levels of mycophenolic acid did not change in a kidney transplant patient 7 days after stopping a 3-month course of voriconazole.[2] Mycophenolate is not metabolised by the cytochrome P450 system and is not a substrate for P-glycoprotein, so would not be expected to be affected by drugs that affect this isoenzyme and drug transporter, such as voriconazole.

No pharmacokinetic interaction occurs, so no dose adjustment of mycophenolate should be necessary on concurrent use.

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2. Kuypers DR, Claes K, Evenepoel P, Vanrenterghem Y. Clinically relevant drug interaction between voriconazole and tacrolimus in a primary renal allograft recipient. *Transplantation* (2006) 81, 1750–2.

Sirolimus and related drugs + ACE inhibitors or Angiotensin II receptor antagonists

Angioedema has been reported in patients taking everolimus, sirolimus or temsirolimus with ACE inhibitors.

Clinical evidence

(a) Everolimus

One report described 6 cases of tongue angioedema in 114 patients given everolimus, all of whom were taking an ACE inhibitor (**enalapril**, **ramipril**) or angiotensin II receptor antagonists (**losartan**). All 6 required hospitalisation. In 5 patients, concurrent use was continued and there had been no recurrences (15 to 126 days follow-up). One patient had two recurrences (day 42 and 67) and everolimus was discontinued.[1] Two other similar cases were briefly mentioned in a consensus conference report.[2] The manufacturer of everolimus lists angioneurotic oedema as a common adverse reaction, which predominantly occurs in patients also receiving an ACE inhibitor.[3]

(b) Sirolimus

A study in 52 kidney transplant patients taking sirolimus 2 to 5 mg daily with **ramipril** 2.5 to 5 mg daily found that 5 of these patients developed non-life threatening tongue oedema within one month of starting **ramipril**. All of these patients had taken **ramipril** before their transplant without any adverse effects or signs of angioedema. The tongue oedema resolved within 2 weeks of stopping ramipril. The authors noted that at that time all 5 patients were taking sirolimus 5 mg daily and ramipril 5 mg daily, with their sirolimus levels in the higher end of the range between 16 and 20 nanograms/mL. Three months after their transplant, when sirolimus had been stabilised at a lower dose of 2 to 4 mg daily, resulting in blood levels of 8 to 12 nanograms/mL, ramipril was restarted at 2.5 mg daily with no adverse effects.[4]

A kidney transplant patient taking sirolimus 9 mg daily developed non-pitting oedema of the eyelid, cheek and lips when he started to take **ramipril** (dose not specified).[5] Another kidney transplant patient who had taken **enalapril** 2.5 mg daily for 2 months developed erythematous skin lesions with non-pitting oedema of the neck, face and chest 9 days after she was switched from tacrolimus to sirolimus 2 mg daily. Symptoms resolved in both patients when the ACE inhibitor was stopped and corticosteroid therapy was increased.[5]

(c) Temsirolimus

The manufacturers of temsirolimus note that angioneurotic oedema-type reactions (including delayed reactions occurring 2 months following initiation of therapy[6]) have been observed in some patients who were given temsirolimus with ACE inhibitors.[6,7]

Mechanism

ACE inhibitors alone can cause angioedema, and this has also been reported for sirolimus (rarely[8]) and everolimus (common with ACE inhibitors[3]). It is therefore possible that the risk of angioedema might be increased by the concurrent use of ACE inhibitors. Although angioedema is not specifically listed as an adverse effect of temsirolimus, facial oedema is common, and as temsirolimus is a pro-drug of sirolimus, the risk of angioedema cannot be ruled out.[6,7]

Importance and management

These reports suggest that it would be prudent to be more alert to the possibility of angioedema when either starting an ACE inhibitor in a patient already taking everolimus, sirolimus or temsirolimus or when starting these immunosuppressants in a patient taking an ACE inhibitor. The effect may be dose-related, with higher doses of both drugs potentially posing a greater risk.

1. Fuchs U, Zittermann A, Berthold HK, Tenderich G, Deyerling KW, Minami K, Koerfer R. Immunosuppressive therapy with everolimus can be associated with potentially life-threatening lingual angioedema. *Transplantation* (2005) 79, 981–3.
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3. Certican (Everolimus). Novartis Pharmaceuticals Australia Pty Ltd. Australian product information, March 2008.
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5. Burdese M, Rossetti M, Guarena C, Consiglio V, Mezza E, Soragna G, Gai M, Segoloni GP, Piccoli GB. Sirolimus and ACE-inhibitors: a note of caution. *Transplantation* (2005) 79, 251–2.
6. Torisel (Temsirolimus). Wyeth Pharmaceuticals. UK Summary of product characteristics, August 2009.
7. Torisel (Temsirolimus). Wyeth Pharmaceuticals Inc. US Prescribing information, September 2008.
8. Rapamune (Sirolimus). Wyeth Pharmaceuticals. UK Summary of product characteristics, April 2009.

Sirolimus or Tacrolimus + Amiodarone

A case report describes increased sirolimus and tacrolimus levels in a paediatric patient and another case report describes markedly elevated tacrolimus levels in an adult, both associated with the concurrent use of amiodarone.

Clinical evidence

A 2-year-old heart transplant patient taking tacrolimus 20 micrograms/kg daily was given amiodarone to control ventricular arrhythmias. Her tacrolimus trough levels were reported as within the target range of 8 to 10 micrograms/L on both day one and day 3 after starting amiodarone. She was then switched from tacrolimus to sirolimus 60 micrograms/kg daily, increased to 120 micrograms/kg after 2 days, with tacrolimus continued until therapeutic sirolimus levels were achieved. The sirolimus levels and tacrolimus levels 9 days after starting amiodarone were found to be 53 micrograms/L and 13 micrograms/L, respectively. Subsequent sirolimus doses were put on hold and tacrolimus was stopped. The sirolimus levels were raised for a further 14 days. Sirolimus was restarted at a lower dose (30 micrograms/kg daily) but the levels remained above 10 micrograms/L and the sirolimus dose was reduced further to 20 micrograms/kg daily.[1]

A 73-year-old kidney transplant patient, who had been taking ciclosporin and amiodarone long-term, had the ciclosporin switched to tacrolimus 7 mg daily. About 3 months later he was found to have a markedly raised tacrolimus level of 63 nanograms/mL. The tacrolimus dose was reduced to 2 mg daily, with a resulting level of 12.9 nanograms/mL.[2]

Mechanism

The elevated levels of tacrolimus and sirolimus were attributed to an interaction with amiodarone, which can inhibit the cytochrome P450 isoenzyme CYP3A4, and affect P-glycoprotein, which have effects on the metabolism and clearance of sirolimus and tacrolimus.[1]

Importance and management

The authors of the first report advise that, because of the long half-life of sirolimus, and the difficulty in reducing elevated levels quickly, prescribers should consider reducing sirolimus and tacrolimus doses before starting amiodarone[1] rather than waiting for the interaction to occur. They also advise more frequent monitoring of sirolimus and tacrolimus levels if amiodarone is also given. Although there are limited data, given that a similar interaction has been reported with ciclosporin (see 'Ciclosporin + Amio-

darone', p.1214), which is metabolised in a similar way to sirolimus and tacrolimus, this would seem prudent.

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Sirolimus + Azoles

Sirolimus levels are very markedly raised by ketoconazole, posaconazole and voriconazole. Itraconazole appears to interact similarly. Two case reports suggest that fluconazole can markedly raise sirolimus levels. Clotrimazole and miconazole oral gel are predicted to interact similarly.

Clinical evidence

(a) Fluconazole

A kidney transplant patient taking sirolimus was given fluconazole 200 mg daily for oesophageal candidiasis. As an interaction was anticipated, the sirolimus dose was reduced from 4 to 3 mg daily. After 4 days the sirolimus level had risen from about 10 micrograms/L to 22.8 micrograms/L. The dose of sirolimus was then reduced to 2 mg daily, but by the seventh day of fluconazole use the sirolimus level had reached 35 micrograms/L, after which they began to fall. The patient then had a hyperkalaemic arrest and died.[1] The sirolimus levels of another kidney transplant patient were raised almost fivefold about 3 weeks after she started to take fluconazole.[2]

(b) Itraconazole

A heart transplant patient needed only half of his normal sirolimus dose to maintain about the same trough levels when he took itraconazole 400 mg daily for a year.[2] A kidney transplant patient taking sirolimus 5 mg daily was given an initial dose of itraconazole 600 mg daily on post-transplant day 10 followed by 400 mg daily. The sirolimus trough level was subtherapeutic at 6.8 nanograms/mL one day after starting itraconazole so the sirolimus dose was increased to 10 mg daily. However, the sirolimus level then increased rapidly and reached a level of 82.5 nanograms/mL 6 days later.[3] A haematopoietic stem cell transplant patient taking itraconazole 200 mg twice daily was changed from tacrolimus to sirolimus 7 mg daily. The sirolimus dose was reduced to 5 mg daily 6 days later because the sirolimus level was 17.5 nanograms/mL (therapeutic range 5 to 15 nanograms/mL). As the sirolimus level was found to be 35.6 nanograms/mL two days later sirolimus was stopped until the level had fallen back to the therapeutic range. Sirolimus was subsequently restarted, with the dose adjusted to between 0.5 mg and 2 mg daily according to levels.[4]

(c) Ketoconazole

A pharmacokinetic study in 23 healthy subjects found that while taking ketoconazole 200 mg daily for 10 days, the maximum serum levels and AUC of a single 5-mg dose of sirolimus were increased 4.3-fold and 10.9-fold, respectively.[5] In a study in 6 kidney transplant patients, ciclosporin was stopped because of toxicity or rejection episodes, and sirolimus was started. The subjects were given about a 75 to 87% lower than recommended dose of sirolimus (250 to 500 micrograms daily) along with ketoconazole 100 to 200 mg daily, adjusted to maintain sirolimus levels within the therapeutic range. The serum creatinine levels of the patients improved and reduced from 230 micromol/L to 194 micromol/L.[6]

(d) Posaconazole

In a study in healthy subjects, posaconazole 400 mg given orally twice daily for 16 days increased the maximum serum levels and AUC of a single 2-mg dose of sirolimus about 6.7-fold and 8.9-fold, respectively.[7]

(e) Voriconazole

The manufacturers report that voriconazole 400 mg twice daily for one day, then 200 mg twice daily for 8 days, markedly raised the maximum serum levels and AUC of a single 2-mg dose of sirolimus about 7-fold and 11-fold, respectively.[8,9] In a retrospective study of allogeneic haematopoietic stem cell transplant patients, 11 patients were found to have received both sirolimus and voriconazole for a median of 33 days (range, 3 to 100 days). Three patients had increased trough sirolimus levels of between 10 and 19 nanograms/mL and serious toxicity occurred in 2 of them. The other 8 patients had their sirolimus dose reduced by 90% when voriconazole was started, in anticipation of the interaction, and in these patients, trough sirolimus levels were similar to those before voriconazole was started: no significant toxicity from either drug occurred.[10] A patient taking sirolimus, who had markedly raised sirolimus levels with itraconazole, was given voriconazole, and the sirolimus dose was decreased from 1.5 mg daily to 0.5 mg daily in anticipation of a similar interaction. The sirolimus trough level was 6.4 nanograms/mL (about the patients' usual range) two days after starting voriconazole.[4]

A case report describes a heart transplant patient who was given two doses of voriconazole 400 mg then 200 mg twice daily for 16 days. When sirolimus was started a dose of 1 mg gave a sirolimus trough level of 12.8 nanograms/mL, but after the voriconazole was stopped a dose of 3 mg only gave trough sirolimus levels of 7.4 nanograms/mL.[2] Voriconazole has been reported to markedly raise sirolimus levels in a number of other patients.[2,11]

Mechanism

Ketoconazole, itraconazole, posaconazole and voriconazole are potent inhibitors of the cytochrome P450 isoenzyme CYP3A4, the isoenzyme that is at least partly responsible for the metabolism of sirolimus.[9] Therefore these azoles probably cause raised sirolimus levels by inhibiting its metabolism. Fluconazole and miconazole also inhibit CYP3A4, but are less potent than ketoconazole. Hence sirolimus levels rise when fluconazole is given, but the rise is not as great as that seen with ketoconazole. Sirolimus is also a substrate for P-glycoprotein and, as azole antifungals may inhibit intestinal P-glycoprotein, this may also contribute to the interaction by increasing the oral bioavailability of sirolimus.[3]

Importance and management

The interactions between the azole antifungals and sirolimus are established and of clinical importance. The rises in sirolimus levels caused by **voriconazole** might be too large to be easily accommodated by reducing the dose of the sirolimus, although one study found that an initial empiric reduction in sirolimus dose by 90% at the start of treatment with voriconazole was adequate. However, more study is required to confirm the safety of such regimens.[10] Note that the concurrent use of sirolimus is contraindicated by the manufacturers of **voriconazole**,[8,12] and not recommended by the manufacturers of sirolimus.[9,13]

The rises in sirolimus levels with **ketoconazole** and **posaconazole** are of a similar magnitude to those seen with voriconazole, and, although data are more limited, **itraconazole** also appears to interact to the same extent. If these azoles are required in a patient taking sirolimus, a pre-emptive sirolimus dose reduction would appear to be prudent, and trough sirolimus levels should be very closely monitored both during use and after they are stopped. About an 80% reduction in sirolimus dose was used in one study with ketoconazole.[6] However, note that the manufacturers of sirolimus say that concurrent use of sirolimus with ketoconazole, and itraconazole is not recommended.[9,13] Similar advice is also given by the manufacturers of **posaconazole**.[7,14] If the combination is unavoidable, the UK manufacturers advise aiming for trough sirolimus levels in the upper part of the therapeutic range. This is because there is a change in the disposition of sirolimus which means that lower levels, even within the therapeutic range, may be subtherapeutic.[7]

Fluconazole, although a weaker inhibitor of CYP3A4 than ketoconazole, voriconazole or itraconazole, has been reported to interact in two cases. **Clotrimazole**[9,13] (presumably systemic clotrimazole) may also interact similarly. Sirolimus plasma levels should be closely monitored during treatment with and following the withdrawal of both of these antifungals.

There appear to be no reports of an interaction between **miconazole** and sirolimus. However, a large proportion of miconazole oral gel (both prescription and non-prescription doses) may be swallowed and therefore adequate systemic absorption may occur to produce an interaction. The manufacturers of miconazole oral gel recommend close monitoring and possible dose reduction of sirolimus if both drugs are given.[15] An interaction with intravaginal miconazole would not normally be expected because its systemic absorption is usually very low (less than 2%).[16]

1. Cervelli MJ. Fluconazole-sirolimus drug interaction. *Transplantation* (2002) 74, 1477–8.
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8. VFEND (Voriconazole). Pfizer Inc. US Prescribing information, December 2009.
9. Rapamune (Sirolimus). Wyeth Pharmaceuticals. UK Summary of product characteristics, April 2009.
10. Marty FM, Lowry CM, Cutler CS, Campbell BJ, Fiumara K, Baden LR, Antin JH. Voriconazole and sirolimus coadministration after allogeneic hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant* (2006) 12, 552–9.
11. Mathis AS, Shah NK, Friedman GS. Combined use of sirolimus and voriconazole in renal transplantation: a report of two cases. *Transplant Proc* (2004) 36, 2708–9.
12. VFEND (Voriconazole). Pfizer Ltd. UK Summary of product characteristics, September 2009.
13. Rapamune (Sirolimus). Wyeth Pharmaceuticals Inc. US Prescribing information, November 2009.
14. Noxafil (Posaconazole). Schering-Plough. US Prescribing information, February 2009.
15. Daktarin Oral Gel (Miconazole). Janssen-Cilag Ltd. UK Summary of product characteristics, September 2008.
16. Daneshmend TK. Systemic absorption of miconazole from the vagina. *J Antimicrob Chemother* (1986) 18, 507–11.

Sirolimus + Calcium-channel blockers

Sirolimus modestly raised verapamil levels, but did not appear to affect diltiazem levels. Diltiazem and verapamil raise sirolimus levels. Nicardipine is predicted to interact similarly. Nifedipine appears not to interact with sirolimus.

Clinical evidence

(a) Diltiazem

A randomised, crossover study in 18 healthy subjects found that a single 120-mg oral dose of diltiazem increased the AUC and the maximum serum levels of a single 10-mg oral dose of sirolimus by 60% and 43%, respectively. The pharmacokinetics of diltiazem and its metabolites were unchanged.[1] Similarly, in a study in 76 patients given sirolimus 2 mg daily alone for 28 days then with diltiazem 180 mg daily after coronary stenting, blood levels of sirolimus were increased by 50%, from 6.2 nanograms/mL to 9.3 nanograms/mL.[2]

(b) Nifedipine

In a study comparing 16 patients taking nifedipine and sirolimus with 10 patients taking sirolimus alone, there were no significant differences in sirolimus pharmacokinetics between the two groups.[3] Similarly, in a study in healthy subjects, there was no pharmacokinetic interaction between nifedipine and sirolimus.[4]

(c) Verapamil

In 26 healthy subjects, the concurrent use of sirolimus oral solution 2 g daily and verapamil 180 mg every 12 hours to steady-state resulted in an increase in the sirolimus maximum levels and AUC of 2.3-fold and 2.2-fold, respectively. In addition, there was a 50% increase in the maximum levels and AUC of the active *S*-verapamil isomer.[5,6]

Mechanism

Diltiazem and verapamil inhibit the cytochrome P450 isoenzyme CYP3A4 in the intestinal wall and liver, which is the primary route of sirolimus metabolism. Verapamil may also inhibit P-glycoprotein activity, which leads to increased sirolimus absorption. It is not known why verapamil levels were raised. Nifedipine is not an inhibitor of CYP3A4 or P-glycoprotein.

Importance and management

The pharmacokinetic interactions between sirolimus and diltiazem or verapamil would appear to be established. The manufacturers recommend whole blood monitoring and a possible sirolimus dose reduction (based on sirolimus levels) if diltiazem or verapamil are used concurrently.[5,6] The clinical relevance of the modest increase in verapamil levels is uncertain, but bear it in mind in the event of an increase in adverse effects due to verapamil, such as hypotension, flushing and oedema. The manufacturers note that other calcium-channel blockers that inhibit CYP3A4 might interact similarly, and they specifically name **nicardipine**,[5,6] although note that other calcium-channel blockers do not usually act as CYP3A4 inhibitors.

1. Böttinger Y, Säwe J, Brattström C, Tollemar J, Burke JT, Häss G, Zimmerman JJ. Pharmacokinetic interaction between single oral doses of diltiazem and sirolimus in healthy volunteers. *Clin Pharmacol Ther* (2001) 69, 32–40.
2. Rodríguez AE, Rodríguez Alemparte M, Vigo CF, Fernández Pereira C, Llauradó C, Vetcher D, Pocovi A, Ambrose J. Role of oral rapamycin to prevent restenosis in patients with de novo lesions undergoing coronary stenting: results of the Argentina single centre study (ORAR trial). *Heart* (2005) 91, 1433–7.
3. Zimmerman JJ, Kahan BD. Pharmacokinetics of sirolimus in stable renal transplant patients after multiple oral dose administration. *J Clin Pharmacol* (1997) 37, 405–15.
4. Zimmerman JJ. Exposure-response relationships and drug interactions of sirolimus. *AAPS J* (2004) 6, 1–12.
5. Rapamune (Sirolimus). Wyeth Pharmaceuticals Inc. US Prescribing information, November 2009.
6. Rapamune (Sirolimus). Wyeth Pharmaceuticals. UK Summary of product characteristics, April 2009.

Sirolimus + Ciclosporin

Ciclosporin markedly raises sirolimus levels, and this effect is approximately halved if sirolimus is given at least 4 hours after ciclosporin. Concurrent use for longer than 3 to 4 months possibly increases renal toxicity, and should be used with caution only when the benefits outweigh the risks. Sirolimus does not appear to alter blood ciclosporin levels in the short-term.

Clinical evidence

(a) Effects on ciclosporin

In a placebo-controlled study in kidney transplant patients, when sirolimus was added to a regimen including ciclosporin and a corticosteroid for 2 weeks, the steady-state ciclosporin levels remained unchanged. Blood pressure, glomerular filtration rate, creatinine levels, triglyceride levels and liver enzymes (ALT, AST) were unchanged.[1] Similarly, in a 2-week pharmacokinetic study in 40 kidney transplant patients, sirolimus 0.5 to 6.5 mg/m^2 given twice daily did not affect the pharmacokinetics of ciclosporin 75 to 400 mg twice daily. The patients were also taking prednisone.[2] In a related study in kidney transplant patients, a single dose of sirolimus had no effect on ciclosporin pharmacokinetics.[3] Similarly, in another study in healthy subjects, single doses of sirolimus did not affect the pharmacokinetics of a single dose of ciclosporin (*Neoral*) when given either at the same time or 4 hours apart.[4]

Nevertheless, the US manufacturer notes that in kidney transplant patients taking ciclosporin (*Neoral*) and sirolimus (taken 4 hours after ciclosporin) over a 6-month period, the oral clearance of ciclosporin was decreased, and lower doses of ciclosporin were needed to maintain therapeutic levels.[5]

In contrast, there is an isolated report of a kidney transplant patient who had a marked rise in ciclosporin levels shortly after starting sirolimus 2 mg daily. Within 2 weeks of starting the sirolimus, she was readmitted to hospital with signs of ciclosporin toxicity, including raised creatinine and urea, high blood pressure, and increased ciclosporin level (536 nanograms/mL). The ciclosporin dose was reduced from 400 to 300 mg daily, sirolimus was continued, and her ciclosporin level fell to 276 nanograms/mL. The sirolimus levels remained at 5.2 to 10.6 nanograms/mL, within the therapeutic range.[6]

(b) Effects on sirolimus

In a single-dose study in healthy subjects, ciclosporin (*Neoral*) given 4 hours before sirolimus increased the maximum serum levels of sirolimus by 40% and increased its AUC by 80%. When the drugs were given at the same time, the effect was even greater, with a 2.2-fold increase in maximum sirolimus level and 3.3-fold increase in the AUC.[4] This study confirmed the findings of a previous multiple-dose study in kidney transplant recipients,[7] and similar results have been seen in another study (40% increase when sirolimus was given 6 hours after ciclosporin).[8] When sirolimus was taken at the same time or 2 hours after ciclosporin, the AUC of sirolimus was increased by 183% and 141%, respectively, but when sirolimus was given 2 hours before the ciclosporin there was no effect on its AUC or peak plasma levels.[9] The US manufacturer of sirolimus also presents data showing that ciclosporin oral solution (*Sandimmune*) given at the same time as sirolimus, increased sirolimus trough levels by 67 to 86% in 150 patients with psoriasis.[5]

(c) Renal toxicity

The manufacturers note that, in clinical studies in patients with kidney transplants, the concurrent use of ciclosporin and sirolimus for more than 6 months and up to 36 months was associated with an increase in serum creatinine and a decrease in glomerular filtration rate when compared with patients treated with ciclosporin and placebo.[5,9] The difference in glomerular filtration rate was about 5.5 mL/minute (10%) at 12 and 36 months.[5] In patients in whom ciclosporin was successfully withdrawn, glomerular filtration rates were higher than in those maintained on ciclosporin.[5,9]

Mechanism

It appears that ciclosporin inhibits the metabolism of sirolimus by the cytochrome P450 isoenzyme CYP3A4 in the gut and liver leading to increased sirolimus levels[4,5,9] and inhibits P-glycoprotein leading to increased sirolimus absorption. There is some experimental evidence to suggest that sirolimus may increase ciclosporin renal toxicity by increasing intracellular ciclosporin levels in the renal epithelial cells by inhibiting P-glycoprotein.[10]

Importance and management

The effect of ciclosporin on sirolimus levels is an established interaction. The manufacturers recommend that, to minimise the interaction, sirolimus should be given 4 hours after microemulsion ciclosporin, and consistently, either with or without food.[5,9] Despite this, it may still be necessary to reduce the sirolimus dose,[4] and blood levels of sirolimus should be monitored and the dose adjusted to maintain levels of 4 to 12 nanograms/mL.[9] Renal function should be closely monitored, and if serum creatinine levels increase, discontinuation of sirolimus or ciclosporin should be considered.[5] Moreover, the manufacturers do not recommend continued use of the combination long-term,because higher serum creatinine levels and lower glomerular filtration rates have been seen.[5,9] Ciclosporin should be gradually discontinued over 4 to 8 weeks increasing the sirolimus dose to obtain higher trough sirolimus levels of 12 to 20 nanograms/mL.[9] In general, the sirolimus dose will need to be raised fourfold to take into account the absence of the interaction (twofold increase) and the need for increased immunosuppression (twofold increase).[9]

The UK manufacturer does not recommend the use of sirolimus in high-risk patients (e.g. those with renal impairment, markers of rejection of multi-organ transplants) as insufficient numbers of this type of patient were studied.[9] However, the US manufacturer states that it may be used in combination with ciclosporin in high-risk patients for up to one year.

The concurrent use of both drugs increases the risk of developing calcineurin inhibitor-induced haemolytic uraemic syndrome, thrombotic thrombocytopenic purpura, and thrombotic microangiopathy.[5,9] An increased risk of hepatic artery thrombosis, leading to graft loss and/or death in most cases, has also been seen in clinical studies in *de novo* liver transplant patients taking sirolimus with ciclosporin, and the manufacturers do not recommend using sirolimus in liver or lung transplant patients as safety and effectiveness have not been proven.[5,9]

1. Murgia MG, Jordan S, Kahan BD. The side effect profile of sirolimus: a phase I study in quiescent cyclosporine-prednisone-treated renal transplant patients. *Kidney Int* (1996) 49, 209–16.
2. Zimmerman JJ, Kahan BD. Pharmacokinetics of sirolimus in stable renal transplant patients after multiple oral dose administration. *J Clin Pharmacol* (1997) 37, 405–15.
3. Ferron GM, Mishina EV, Zimmerman JJ, Jusko WJ. Population pharmacokinetics of sirolimus in kidney transplant patients. *Clin Pharmacol Ther* (1997) 61, 416–28.
4. Zimmerman JJ, Harper D, Getsy J, Jusko WJ. Pharmacokinetic interactions between sirolimus and microemulsion cyclosporine when orally administered jointly and 4 hours apart in healthy volunteers. *J Clin Pharmacol* (2003) 42, 1168–76.
5. Rapamune (Sirolimus). Wyeth Pharmaceuticals Inc. US Prescribing information, November 2009.
6. Dąbrowska-Zamojcin E, Pawlik A, Domański L, Różański J, Droździk M. Cyclosporine and sirolimus interaction in a kidney transplant patient. *Transplant Proc* (2005) 37, 2317–19.
7. Kaplan B, Meier-Kriesche H-U, Napoli KL, Kahan BD. The effects of relative timing of sirolimus and cyclosporine microemulsion formulation coadministration on the pharmacokinetics of each agent. *Clin Pharmacol Ther* (1998) 63, 48–53.
8. Wu FLL, Tsai M-K, Chen RR-L, Sun S-W, Huang J-D, Hu R-H, Chen K-H, Lee P-H. Effects of calcineurin inhibitors on sirolimus pharmacokinetics during staggered administration in renal transplant recipients. *Pharmacotherapy* (2005) 25, 646–53.
9. Rapamune (Sirolimus). Wyeth Pharmaceuticals. UK Summary of product characteristics, April 2009.
10. Anglicheau D, Pallet N, Rabant M, Marquet P, Cassinat B, Méria P, Beaune P, Legendre C, Thervet E. Role of P-glycoprotein in cyclosporine cytotoxicity in the cyclosporine-sirolimus interaction. *Kidney Int* (2006) 70, 1019–25.

Sirolimus + Corticosteroids

Intravenous methylprednisolone appears to have no effect on trough sirolimus levels. Sirolimus slightly increased prednisolone levels (derived from prednisone).

Clinical evidence, mechanism, importance and management

(a) Methylprednisolone

When 14 patients taking sirolimus (and also taking either azathioprine or mycophenolate) were given methylprednisolone as a daily intravenous bolus for one to 5 days (total dose of between 500 mg and 3 g) the sirolimus trough concentrations were not significantly altered.[1] No sirolimus dose adjustment appears to be necessary on concurrent use.[1]

(b) Prednisolone or Prednisone

In a study in kidney transplant patients taking ciclosporin and prednisone 5 to 20 mg daily, only minor to moderate changes occurred in the pharmacokinetics of the metabolite, prednisolone, when sirolimus 6 to 13 mg/m^2 daily was given for 2 weeks.[2] The maximum plasma prednisolone levels were raised by 14%, and the AUC was raised by 18%. The clinical relevance of these findings is uncertain, but they are likely to be minor.

1. Bäckman L, Kreis H, Morales JM, Wilczek H, Taylor R, Burke JT. Sirolimus steady-state trough concentrations are not affected by bolus methylprednisolone therapy in renal allograft recipients. *Br J Clin Pharmacol* (2002) 54, 65–8.
2. Jusko WJ, Ferron GM, SM Mis, Kahan BD, Zimmerman JJ. Pharmacokinetics of prednisolone during administration of sirolimus in patients with renal transplants. *J Clin Pharmacol* (1996) 36, 1100–6.

Sirolimus + Co-trimoxazole

A single dose of co-trimoxazole did not alter sirolimus levels in one study.

Clinical evidence, mechanism, importance and management

In a study in 15 kidney transplant patients who had started sirolimus one week previously, there was no change in the AUC and maximum level of sirolimus after the first daily dose of oral co-trimoxazole (sulfamethoxazole with trimethoprim) 480 mg when compared with the day before.[1] There was also no change in serum creatinine levels between these two days, although a slight mean 4.3% increase was seen in 9 of the 15 patients on the following day.

The evidence suggests that co-trimoxazole does not have a marked effect on the pharmacokinetics of sirolimus and that no sirolimus dose adjustment is likely to be needed with concurrent use. However, the authors note that it does not rule out the possibility that longer-term concurrent use might lead to increases in sirolimus levels, particularly if renal function is impaired leading to co-trimoxazole accumulation.[1]

1. Böttiger Y, Brattström C, Bäckman L, Claesson K, Burke JT. Trimethoprim-sulphamethoxazole does not affect the pharmacokinetics of sirolimus in renal transplant recipients. *Br J Clin Pharmacol* (2005) 60, 566–9.

Sirolimus + Food

A high-fat meal modestly increased the exposure to sirolimus in one study.

Clinical evidence

In a single-dose study in healthy subjects, giving a non-aqueous solution of sirolimus with a high-fat breakfast reduced the maximum sirolimus level by 34%, delayed the time to maximum level by about 2 hours, and increased the AUC by 34%, when compared with the fasting state. There was no change in the elimination half-life of sirolimus.[1] In a similar study using sirolimus tablets, the maximum level and AUC of sirolimus were increased by 65% and 23%, respectively, by a high-fat meal.[2] The extent of this interaction was considered minor when compared with the large variability in sirolimus levels between subjects.[1] Nevertheless, the manu-

facturer recommends that sirolimus solution or tablets should be taken consistently either with or without food, to minimise variability.[2,3]

1. Zimmerman JJ, Ferron GM, Lim HK, Parker V. The effect of a high-fat meal on the oral bioavailability of the immunosuppressant sirolimus (rapamycin). *J Clin Pharmacol* (1999) 39, 1155–61.
2. Rapamune (Sirolimus). Wyeth Pharmaceuticals. UK Summary of product characteristics, April 2009.
3. Rapamune (Sirolimus). Wyeth Pharmaceuticals Inc. US Prescribing information, November 2009.

Sirolimus + Macrolides

Erythromycin markedly increased sirolimus levels in healthy subjects, and there is a report of two patients who had large elevations in their sirolimus levels when they were given erythromycin. Similarly, there is a case report of clarithromycin causing a marked increase in sirolimus levels and renal impairment. Many other macrolides are expected to interact similarly.

Clinical evidence

(a) Clarithromycin

A kidney transplant patient taking sirolimus 2 mg daily and with stable but poor renal function (creatinine clearance 14 mL/minute) was given clarithromycin 250 mg twice daily for a week. At the end of the week, her trough sirolimus level was found to have risen markedly by 8.4-fold (from 6.2 to 52.2 nanograms/mL) and there was a sharp fall in her creatinine clearance to 6.8 mL/minute. Sirolimus was temporarily stopped until trough levels fell to low normal (8 days), and the creatinine clearance gradually improved.[1]

(b) Erythromycin

The manufacturers report that, in 24 healthy subjects, the concurrent use of erythromycin 800 mg three times daily with sirolimus oral solution 2 mg daily resulted in a significant increase in the peak blood levels and AUC of sirolimus, of 4.2- and 4.4-fold, respectively. The peak plasma levels and AUC of erythromycin were also increased, by 60% and 70%, respectively.[2,3]

A case report describes 2 patients taking sirolimus who were also given erythromycin 1 g three times daily for suspected Legionella pneumonia. Despite marked reductions in the sirolimus dose (actual reductions not stated), the sirolimus levels of both patients rose fivefold.[4]

Mechanism

Erythromycin and clarithromycin are inhibitors of the cytochrome P450 isoenzyme CYP3A4, which is the main enzyme responsible for the metabolism of sirolimus, and are also said to be inhibitors of P-glycoprotein, which is involved in the transport of sirolimus. Therefore they probably inhibited the metabolism of sirolimus and increased its bioavailability, causing the levels to rise. The mechanism behind sirolimus increasing erythromycin levels is uncertain.

Importance and management

The pharmacokinetic interaction leading to an increase in sirolimus levels would appear to be established and of clinical importance. Single-dose sirolimus also raised **erythromycin** levels, and although the increase seen is probably of little clinical relevance, further study is needed to see if a greater effect occurs on repeated use. The manufacturers of sirolimus differ in their recommendations for erythromycin use: in the US it is advised that erythromycin is avoided,[3] whereas in the UK the advice is to monitor sirolimus levels and decrease the dose of both drugs as appropriate.[2] In both countries, the advice is to avoid the use of **clarithromycin** and also **telithromycin** in patients taking sirolimus.[2,3] The manufacturers of sirolimus also name **troleandomycin** as a moderate inhibitor of CYP3A4, which may possibly interact.[2,3] However, note that troleandomycin tends to be a more potent inhibitor of CYP3A4 than clarithromycin. On the basis of the available data, if any macrolide is considered essential in a patient taking sirolimus, it would be prudent to decrease the sirolimus dose and closely monitor levels.

1. Capone D, Palmiero G, Gentile A, Basile V, Federico S, Sabbatini M, Potenza M, Perfetti A, Pieri M, Tarantino G. A pharmacokinetic interaction between clarithromycin and sirolimus in kidney transplant recipient. *Curr Drug Metab* (2007) 8, 379–81.
2. Rapamune (Sirolimus). Wyeth Pharmaceuticals. UK Summary of product characteristics, April 2009.
3. Rapamune (Sirolimus). Wyeth Pharmaceuticals Inc. US Prescribing information, November 2009.
4. Claesson K, Brattström C, Burke JT. Sirolimus and erythromycin interaction: two cases. *Transplant Proc* (2001) 33, 2136.

Sirolimus and related drugs + Miscellaneous

Cimetidine is predicted to increase levels of everolimus, sirolimus and temsirolimus, and grapefruit juice might also interact. No pharmacokinetic interaction appears to occur between sirolimus and aciclovir, digoxin or glibenclamide (glyburide). It has been suggested that cisapride, danazol, etravirine, metoclopramide and bromocriptine might interact with everolimus and sirolimus. Temsirolimus is a prodrug of sirolimus, and may therefore be expected to share some of its interactions.

Clinical evidence, mechanism, importance and management

(a) Aciclovir

In a study in healthy subjects, there was no pharmacokinetic interaction between aciclovir and sirolimus.[1]

(b) Digoxin

In a study in healthy subjects, there was no pharmacokinetic interaction between digoxin and sirolimus.[1]

(d) Glibenclamide (Glyburide)

In a study in healthy subjects, there was no pharmacokinetic interaction between glibenclamide and sirolimus.[1]

(e) Grapefruit juice

Grapefruit juice inhibits CYP3A4 (potentially raising sirolimus levels), and so the manufacturers recommend that concurrent use should be avoided.[2,3]

(f) NNRTIs

The manufacturer of **etravirine** predicts that it will induce the metabolism of sirolimus by the cytochrome P450 isoenzyme CYP3A4 and thus reduce sirolimus levels. However, note that etravirine is only a weak inducer of this isoenzyme.[4] The manufacturer advises caution on concurrent use and, until more is known, close monitoring of sirolimus levels would seem prudent. Until the extent of any interaction is established, similar caution may be appropriate if etravirine is given with **everolimus** and **temsirolimus**.

(g) Prokinetic drugs

The manufacturers of sirolimus note that **cisapride** and **metoclopramide** may increase sirolimus levels, although there do not appear to be any published reports of this interaction.[2,3] The manufacturer of **everolimus** also lists **cisapride** and **metoclopramide** as potentially interacting.[5]

(h) Other drugs

The manufacturers of **everolimus** and sirolimus list **bromocriptine**, **cimetidine**, and **danazol** as drugs that might increase sirolimus levels,[2,3,5] on the basis of these drugs being moderate or weak inhibitors of the cytochrome P450 isoenzyme CYP3A4.[2,5] However a significant interaction with **bromocriptine** would not generally be expected as it is not usually considered to be a clinically relevant CYP3A4 inhibitor. The UK manufacturer of **temsirolimus** contraindicates **cimetidine** on the basis that it is a potent inhibitor of CYP3A4.[6] However, **cimetidine** is a moderate non-specific inhibitor of cytochrome P450, and would be expected to cause only a minor interaction via this mechanism. Some caution might therefore be appropriate with cimetidine if it is given with sirolimus, **everolimus** or **temsirolimus**.

1. Zimmerman JJ. Exposure-response relationships and drug interactions of sirolimus. *AAPS J* (2004) 6, 1–12.
2. Rapamune (Sirolimus). Wyeth Pharmaceuticals. UK Summary of product characteristics, April 2009.
3. Rapamune (Sirolimus). Wyeth Pharmaceuticals Inc. US Prescribing information, November 2009.
4. Intelence (Etravirine). Janssen-Cilag Ltd. UK Summary of product characteristics, November 2009.
5. Certican (Everolimus). Novartis Pharmaceuticals Australia Pty Ltd. Australian product information, March 2008.
6. Torisel (Temsirolimus). Wyeth Pharmaceuticals. UK Summary of product characteristics, August 2009.

Sirolimus + Phenytoin

Two case reports describe increased sirolimus dose requirements in the presence of phenytoin.

Clinical evidence

An 11-year-old girl with a kidney transplant taking phenytoin started taking sirolimus 30 micrograms/kg twice daily following an episode of acute rejection. The dose of sirolimus was increased tenfold over the next few weeks in an attempt to achieve the target trough level of 10 to 20 nanograms/mL, and two further episodes of acute rejection occurred. About one month after the sirolimus had been started, tacrolimus was added, and her phenytoin was stopped. Over the next few weeks her sirolimus level rose to about 40 nanograms/mL. The patient subsequently recovered.[1]

A 62-year-old woman started taking phenytoin 100 mg twice daily because she developed a seizure disorder following a liver transplant. At this time she was taking ciclosporin, but it was decided to start sirolimus because of neurological complications. The initial sirolimus dose of 5 mg daily produced subtherapeutic sirolimus levels. She was subsequently stabilised taking sirolimus 15 mg daily, with trough levels of less than 5 nanograms/mL. Phenytoin was stopped, and about 5 days later her trough sirolimus level was found to be around 15 to 20 nanograms/mL. After a further 5 days, the sirolimus dose was reduced to 10 mg daily.[2]

Mechanism

Sirolimus is extensively metabolised by the cytochrome P450 isoenzyme CYP3A4 in the intestinal wall and is a substrate for P-glycoprotein. Phenytoin and other antiepileptics that induce the activity of this isoenzyme and transporter protein would be expected to lower sirolimus levels.

Importance and management

These appear to be the only reports of an interaction between sirolimus and phenytoin, but they are consistent with the way both drugs are known to interact. It would therefore seem prudent to closely monitor sirolimus levels in any patient in whom phenytoin is started or withdrawn, and to adjust the sirolimus dose as necessary.

1. Hodges CB, Maxwell H, Beattie TJ, Murphy AV, Jindal RM. Use of rapamycin in a transplant patient who developed ciclosporin neurotoxicity. *Pediatr Nephrol* (2001) 16, 777–8.
2. Fridell JA, Jain AKB, Patel K, Virji M, Rao KN, Fung JJ, Venkataramanan R. Phenytoin decreases the blood concentrations of sirolimus in a liver transplant recipient: a case report. *Ther Drug Monit* (2003) 25, 117–19.

Sirolimus + Protease inhibitors

Nelfinavir markedly increased the levels of sirolimus in one patient. Other protease inhibitors are predicted interact similarly.

Clinical evidence, mechanism, importance and management

An HIV-positive, liver transplant patient taking sirolimus 5 mg daily was given **nelfinavir** 250 mg twice daily (one-fifth of the normal dose), lamivudine and zidovudine. Three weeks later, because of a reduced full blood count, her sirolimus blood levels were checked, and found to be 24.7 nanograms/mL. Her sirolimus dose was reduced to 3 mg daily and then 2 mg daily and her levels rechecked 5 days later. The trough sirolimus level was found to be 4.6 nanograms/mL, which was almost fivefold higher than the trough levels of 3 control patients taking sirolimus 5 to 7 mg daily but not taking nelfinavir. The peak level and AUC of sirolimus were also much higher in the patient taking nelfinavir.[1]

The manufacturers point out that sirolimus is extensively metabolised by the cytochrome P450 isoenzyme CYP3A4 and cleared by P-glycoprotein, so drugs such as the protease inhibitors, which inhibit the activity of this isoenzyme and drug transporter may raise sirolimus levels.[2,3] On the basis of the interaction with ketoconazole (see 'Sirolimus + Azoles', p.1290), they advise against the concurrent use of potent inhibitors of CYP3A4.[2,3] This would generally be expected to include the protease inhibitors (ritonavir is the most potent CYP3A4 inhibitor known). However, the UK manufacturer of sirolimus[3] lists the protease inhibitors as moderate or weak inhibitors of CYP3A4. The US manufacturer[2] suggests that the protease inhibitors (they specifically name **indinavir** and **ritonavir**) may significantly increase in sirolimus levels, and suggest that if both drugs are given it would be prudent to very closely monitor sirolimus levels and adjust the dose of sirolimus as necessary.

1. Jain AKB, Venkataramanan R, Fridell JA, Gadomski M, Shaw LM, Ragni M, Korecka M, Fung J. Nelfinavir, a protease inhibitor, increases sirolimus levels in a liver transplantation patient: a case report. *Liver Transpl* (2002) 8, 838–40.
2. Rapamune (Sirolimus). Wyeth Pharmaceuticals Inc. US Prescribing information, November 2009.
3. Rapamune (Sirolimus). Wyeth Pharmaceuticals. UK Summary of product characteristics, April 2009.

Sirolimus + Repaglinide

Repaglinide does not appear to alter sirolimus levels.

Clinical evidence, mechanism, importance and management

In a study in kidney transplant patients stabilised on immunosuppressants, the concurrent use of repaglinide in the 5 patients taking sirolimus did not appear to cause any significant changes in sirolimus blood levels and no sirolimus dose changes were required on starting repaglinide 1 to 3 mg daily (mostly as monotherapy but a few patients were also given either metformin or rosiglitazone).[1] It would appear from the limited data from this observational study, that a significant pharmacokinetic interaction between sirolimus and repaglinide does not occur, however this ideally needs confirmation in a pharmacokinetic study.

1. Türk T, Peitruck F, Dolff S, Kribben A, Janssen OE, Mann K, Philipp T, Heemann U, Witzke O. Repaglinide in the management of new-onset diabetes mellitus after renal transplantation. *Am J Transplant* (2006) 6, 842–6.

Sirolimus + Rifampicin (Rifampin) and other CYP3A4 inducers

Rifampicin (a potent CYP3A4 inducer) markedly decreases sirolimus levels. Rifabutin and rifapentine are predicted to interact similarly, although to a lesser extent. Other CYP3A4 inducers are also predicted to interact similarly.

Clinical evidence

A clinical study in 14 healthy subjects found that **rifampicin** 600 mg daily for 6 days increased the clearance of a single 10-mg oral dose of sirolimus 5.5-fold, and reduced the AUC and maximum serum levels of sirolimus by 82% and 71%, respectively.[1,2]

Mechanism

Sirolimus is extensively metabolised by the cytochrome P450 isoenzyme CYP3A4 in the intestinal wall and liver, and is also a substrate for the drug transporter protein P-glycoprotein: drugs such as rifampicin that induce the activity of this isoenzyme and drug transporter would be expected to lower sirolimus levels.[1,2]

Importance and management

This interaction is likely to result in markedly reduced sirolimus trough levels and efficacy. The manufacturers say that concurrent use is not recommended, and that alternatives to rifampicin should be used.[1,2] **Rifabutin**[1,2] and **rifapentine**[2] are predicted to also lower sirolimus levels, but this will probably be to a lesser extent than with rifampicin. Nevertheless, the concurrent use of **rifabutin** is also not recommended.[1,2]

On the basis of the interaction with rifampicin, the manufacturers state that the concurrent use of potent CYP3A4 inducers should be avoided, and cautions the use of other CYP3A4 inducers.[1,2] They specifically mention **St John's wort**, **carbamazepine**, phenytoin and **phenobarbital** (see 'Sirolimus + Phenytoin', above, for case reports of this interaction). It would certainly be prudent to monitor sirolimus levels closely if any of these drugs are used concurrently. What should be remembered is that the extent of the inducing effects of these drugs is not identical, so that very marked effects like those observed with rifampicin may not occur; never-

theless the interaction may still be clinically important. For a list of CYP3A4 inducers, see 'Table 1.4', (p.6).

1. Rapamune (Sirolimus). Wyeth Pharmaceuticals. UK Summary of product characteristics, April 2009.
2. Rapamune (Sirolimus). Wyeth Pharmaceuticals Inc. US Prescribing information, November 2009.

Tacrolimus + ACE inhibitors or Angiotensin II receptor antagonists

Candesartan and losartan do not appear to affect the pharmacokinetics of tacrolimus, although concurrent use may increase the risk of hyperkalaemia.

Clinical evidence

A study in 12 kidney transplant patients taking tacrolimus twice daily for 12 days with **candesartan** (2 mg daily for 3 days, then 4 mg daily for 3 days, and then 16 mg daily for 3 days) found that the pharmacokinetics of tacrolimus were unchanged. Renal function remained stable and unchanged, and no adverse effects were reported.[1] Another study in a group of 21 kidney transplant patients taking tacrolimus found no significant change in serum creatinine or the levels of tacrolimus when they also took **candesartan** 4 to 12 mg daily for one year. Serum potassium levels were reported to have increased by an average of 0.34 mmol/L, although it is unclear from the study if this was specifically in the tacrolimus group or also included another group taking candesartan and ciclosporin.[2]

A study in kidney transplant patients taking tacrolimus and given **losartan** 50 mg daily for 12 weeks (some receiving 100 mg daily from week 8) for hypertension found no significant changes in the tacrolimus levels. Transient hyperkalaemia occurred in 4 of the 67 patients.[3]

Mechanism

Both ACE inhibitors and angiotensin II receptor antagonists can raise potassium levels, and this effect might be additive with that of tacrolimus.

Importance and management

No pharmacokinetic interaction is anticipated. However, as tacrolimus may cause nephrotoxicity and hyperkalaemia, bear in mind the possibility of additive effects if ACE inhibitors or angiotensin II receptor antagonists are also given.

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Tacrolimus + Antacids

Aluminium/magnesium hydroxide caused a minor increase in tacrolimus levels in one study. There is some evidence to suggest that sodium bicarbonate may possibly reduce the tacrolimus levels.

Clinical evidence

(a) Aluminium/magnesium antacids

In an early *in vitro* study, **aluminium hydroxide** gel and **magnesium oxide** caused a significant reduction in tacrolimus concentrations due to pH-mediated degradation, leading to the suggestion that the administration of antacids and tacrolimus should be separated until data from clinical studies became available.[1] However, in a crossover study in healthy subjects, a single dose of **aluminium/magnesium hydroxide** slightly *increased* the mean AUC of tacrolimus by 21% and decreased the mean peak level of tacrolimus by 10%.[2] Moreover, a retrospective study in 18 kidney transplant patients found that the concurrent use of antacid medications (H_2-receptor antagonists, **magnesium oxide**, sodium bicarbonate or proton pump inhibitors) did not reduce tacrolimus blood levels and no patients required a tacrolimus dose increase,[3] although interpretation of this study is limited by the broad range of drugs considered together.

(b) Sodium bicarbonate

A review very briefly states that widely variable trough plasma tacrolimus levels have been seen in patients taking sodium bicarbonate close to the time when the tacrolimus was given, and that the use of sodium bicarbonate results in lower blood levels of tacrolimus. No details were given.[4] It was suggested that their administration should be separated by at least 2 hours[4] However, a retrospective study in 18 renal transplant patients found that the concurrent use of antacid medications (H_2-receptor antagonists, magnesium oxide, sodium bicarbonate or proton pump inhibitors) did not reduce tacrolimus blood levels and no patient required a tacrolimus dose increase,[3] although interpretation of this study is limited by the broad range of drugs considered together.

Mechanism

Unknown.

Importance and management

More study is needed to confirm and assess the extent and clinical importance of these interactions, but the best available evidence suggests that aluminium/magnesium hydroxide might cause a minor increase in tacrolimus levels, which is probably unlikely to be clinically relevant. Nevertheless, it would seem prudent to bear this in mind if tacrolimus is given with any antacids, and be alert for the need to separate the doses by at least 2 hours.

1. Steeves M, Abdallah HY, Venkataramanan R, Burckart GT, Ptachcinski RJ, Abu-Elmagd K, Jain AK, Fung F, Todo S, Starzl TE. In-vitro interaction of a novel immunosuppressant, FK506, and antacids. *J Pharm Pharmacol* (1991) 43, 574–7.
2. Prograf (Tacrolimus). Astellas Pharma US Inc. US Prescribing information, August 2009.
3. Chisholm MA, Mulloy LL, Jagadeesan M, DiPiro JT. Coadministration of tacrolimus with anti-acid drugs. *Transplantation* (2003) 76, 665–6.
4. Venkataramanan R, Swaminathan A, Prasad T, Jain A, Zuckerman S, Warty V, McMichael J, Lever J, Burckart G, Starzl T. Clinical pharmacokinetics of tacrolimus. *Clin Pharmacokinet* (1995) 29, 404–30.

Tacrolimus + Antiepileptics; Enzyme-inducing

An isolated report describes an increase in phenytoin levels attributed to the use of tacrolimus. Phenytoin decreased tacrolimus levels in three cases, and has been used to reduce tacrolimus levels after an overdose. Phenobarbital has also been used for this purpose. Carbamazepine is predicted to interact similarly.

Clinical evidence

(a) Phenobarbital

In a 4-month-old liver transplant recipient with tacrolimus toxicity, intravenous phenobarbital 5 mg/kg was used to try to increase the tacrolimus clearance. The half-life of tacrolimus was calculated as 70 to 235 hours before phenobarbital administration, and 13 to 30 hours during phenobarbital administration.[1] Two other infants were similarly treated, resulting in about three to fivefold decreases in the tacrolimus half-life.[2]

(b) Phenytoin

1. Phenytoin levels. A kidney transplant patient taking phenytoin 500 and 600 mg on alternate days (and also taking azathioprine, bumetanide, digoxin, diltiazem, heparin, insulin and prednisone) had his immunosuppressant changed from ciclosporin, to tacrolimus 14 to 16 mg daily. About 7 weeks later he presented to hospital because of a fainting episode and his phenytoin levels were found to have risen from 18.4 micrograms/mL to 36.2 micrograms/mL. The phenytoin was temporarily stopped until his serum levels had fallen, and he was then discharged on a reduced phenytoin dose of 400 and 500 mg on alternate days with no further problems.[3] The presumption is that the fainting episode was due to the raised serum phenytoin levels.

2. Tacrolimus levels. In one kidney transplant patient taking phenytoin, tacrolimus 250 micrograms/kg daily was needed to give a blood level of 9 nanograms/mL. Three months later phenytoin was gradually stopped, with gradual tapering of the tacrolimus dose. The patient was eventually stabilised with a tacrolimus dose of 160 micrograms/kg daily giving a blood level of 11 nanograms/mL.[4] Similarly, two other cases of about two- to threefold increases in tacrolimus requirements while taking pheny-

toin 200 mg daily and decreased requirements on stopping have been reported.[5] In another patient, variable tacrolimus doses and levels were seen in the post-transplant period while taking phenytoin, and phenytoin was eventually tapered and replaced with oxcarbazepine.[6]
Another report describes the use of an intravenous phenytoin infusion to treat acute tacrolimus overdoses in 2 patients, with the aim of enhancing tacrolimus metabolism.[7]

Mechanism

Tacrolimus is extensively metabolised by the cytochrome P450 isoenzyme CYP3A4, and phenytoin and phenobarbital are known inducers of this system, and are therefore predicted to decrease tacrolimus levels. In the case of raised phenytoin levels, it was suggested that tacrolimus might have inhibited the metabolism of phenytoin, although other factors may have had some part to play.[3]

Importance and management

Information is limited, but based on the known metabolism of these drugs it would be prudent to monitor tacrolimus levels in all patients given phenytoin or phenobarbital. The manufacturers suggest that **carbamazepine** will interact similarly.[8,9] It would certainly be prudent to monitor tacrolimus levels closely if any of the enzyme-inducing antiepileptics (including the prodrug of phenytoin, **fosphenytoin**; and **primidone**, which is metabolised to phenobarbital) are used concurrently.

Similarly, until more is known, based on the single case of phenytoin toxicity, it may also be advisable to monitor phenytoin levels in patients taking tacrolimus.

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Tacrolimus + Azoles

The azole antifungals increase tacrolimus levels, to varying degrees, and tacrolimus dose reductions may be needed. There is some evidence (using fluconazole and ketoconazole) that the levels of tacrolimus after intravenous administration are less affected by the azoles. In theory it is possible that miconazole oral gel may also interact with tacrolimus.

Clinical evidence

(a) Clotrimazole

In a study in 35 kidney transplant patients taking tacrolimus 150 micrograms/kg twice daily, patients were randomised to receive either clotrimazole lozenges 10 mg three times daily (17 patients) or nystatin oral suspension (control group, 18 patients). Clotrimazole markedly increased tacrolimus trough blood levels from a mean of about 15 nanograms/mL up to 53 nanograms/mL at day 5, whereas tacrolimus levels were not affected by nystatin. By day 7, patients in the clotrimazole group were found to require significantly lower tacrolimus doses than those in the nystatin group.[1] In a further pharmacokinetic study by this research group, in 6 patients, a 5-day course of clotrimazole lozenges markedly increased the AUC and trough levels of tacrolimus about 2.5-fold.[2]

Similarly, in a liver transplant patient the trough plasma levels of tacrolimus 6 mg daily rose from 3.5 nanograms/mL to 5.6 nanograms/mL within a day of clotrimazole 10 mg four times daily being started, and reached more than 9 nanograms/mL within 8 days. Later studies and rechallenge confirmed that clotrimazole was responsible for the rise in tacrolimus levels. The tacrolimus AUC was nearly doubled.[3]

(b) Fluconazole

1. Oral tacrolimus. Twenty organ transplant patients (11 liver, 6 kidney, 2 heart and one bone marrow) taking tacrolimus were also given fluconazole 100 or 200 mg daily for various fungal infections. On day one the median plasma trough levels of those given fluconazole 100 mg rose by 40%, and in those taking 200 mg it rose 3.1-fold. The dose of tacrolimus was reduced to accommodate this rise: the median dose reduction was 56% (range 0 to 88%). The highest tacrolimus level was seen within 3 days. A pharmacokinetic study in one patient found that when fluconazole 100 mg daily was stopped, the tacrolimus AUC fell by about 60%.[4] In two other studies, patients given fluconazole required a reduction of 40% or 47% (increased to 65% at 3 months) in tacrolimus dose to achieve similar trough levels.[5,6]
Other studies in adult[7] and paediatric patients[8] and individual case reports[9,10] have confirmed that tacrolimus levels are increased by oral fluconazole, increasing the risk of nephrotoxicity.[8-10] A bone-marrow transplant patient taking tacrolimus and given fluconazole for oral candidiasis experienced headache and was found to have glycosuria, increased serum creatinine and Pelger-Huet anomaly of granulocytes, which disappeared after tacrolimus was discontinued. The effects were thought to be due to tacrolimus toxicity due to an interaction with fluconazole.[11] In yet another study in patients receiving oral tacrolimus, both oral and intravenous fluconazole appeared to increase tacrolimus trough levels to a similar extent,[12] but other studies suggest that an interaction with intravenous tacrolimus may be smaller than with oral tacrolimus, see *Intravenous tacrolimus*, below.

2. Intravenous tacrolimus. When intravenous tacrolimus was given with intravenous fluconazole 400 mg, the steady-state levels of tacrolimus were only slightly increased (by about 16%), which was considered to be clinically unimportant.[13] In a retrospective study in patients receiving intravenous tacrolimus, the tacrolimus blood level rose slightly (from 17.4 nanograms/mL to 18.8 nanograms/mL) when they were switched from intravenous to oral fluconazole.[14]

(c) Itraconazole

A study in 40 lung transplant patients taking tacrolimus with prophylactic itraconazole 200 mg twice daily for 6 months found that when itraconazole was stopped the mean tacrolimus dose needed to maintain therapeutic levels increased by 76% (to 5.74 mg daily). The adverse effects and rejection rate were not affected by itraconazole.[15] Similar findings were reported in two other studies in heart and lung transplant patients, who required about one-third of the tacrolimus dose while taking itraconazole.[16,17]

Various cases of this interaction have also been reported. The trough blood levels of tacrolimus in a heart-lung transplant patient increased threefold (from 16 to 57 nanograms/mL) and serum creatinine levels also rose after she was given itraconazole 200 mg daily.[18] A kidney transplant patient taking tacrolimus 6 mg daily was given itraconazole 100 mg twice daily for a urinary candida infection. Within a day, the tacrolimus trough levels increased from 12.6 nanograms/mL to 21 nanograms/mL and the tacrolimus dose needed to be progressively reduced to 3 mg daily. Four days after the itraconazole was discontinued tacrolimus had to be progressively increased back to its initial dose.[19] The interaction has been reported in three other transplant recipients.[17,20-22] Similarly, in a study in 9 patients, intravenous itraconazole 200 mg twice daily for 2 days then 200 mg daily caused a mean 83% increase in the levels of *intravenous* tacrolimus.[23]

(d) Ketoconazole

In a kidney transplant patient taking tacrolimus and prednisone, the addition of ketoconazole 200 mg daily resulted in an increase in tacrolimus blood levels from 11.1 nanograms/mL to 27.9 nanograms/mL, despite a 45% decrease in the dose of tacrolimus. Eventually the dose of tacrolimus had to be reduced by 80% to keep the levels within the therapeutic range. Tacrolimus levels decreased to 5.8 nanograms/mL within a week of discontinuing ketoconazole and so the dose was raised.[24] Similarly, in a study in 11 kidney transplant patients taking tacrolimus, the concurrent use of ketoconazole 87 mg daily allowed a reduction in the tacrolimus dose of about 75 to 80%.[25] In another similar study, a reduction in the tacrolimus dose of about 50% was needed with ketoconazole 100 mg daily.[26] A pharmacokinetic study in 6 healthy subjects found that ketoconazole 200 mg orally at bedtime for 12 days increased the bioavailability of a single 100-microgram/kg dose of oral tacrolimus from 14% to 30%.[27] The man-

ufacturer notes that the clearance of *intravenous* tacrolimus was not significantly changed by ketoconazole, although it was highly variable between patients.[28]

(e) Posaconazole

In a study in healthy subjects, the peak blood level and AUC of a single 50 microgram/kg dose of tacrolimus were increased by 2.2-fold and 4.6-fold, respectively, when posaconazole 400 mg twice daily was given for 7 days.[29]

In another report, increased tacrolimus levels occurred in just 2 of 10 transplant patients given posaconazole 800 mg daily, occurring after 17 days and 39 days of concurrent use. One of these patients had acute renal impairment.[30] The manufacturer notes that, in clinical efficacy studies, clinically important interactions with tacrolimus, resulting in hospitalisation and/or posaconazole discontinuation, were reported.[31]

(f) Voriconazole

A small study comparing the tacrolimus levels of two patients, one taking voriconazole 200 mg twice daily and the other taking placebo, found that the tacrolimus levels were nearly tenfold higher in the patient taking voriconazole. This was originally designed as a larger study, but the study was stopped after the finding in these initial two subjects.[32] Another study in 14 healthy subjects found that voriconazole 400 mg twice daily on day one, then 200 mg twice daily for 6 days increased the AUC and maximum plasma levels of a single 100 microgram/kg dose of tacrolimus 3.2-fold and 2.3-fold, respectively.[33]

A liver transplant patient taking tacrolimus was hospitalised with multiple complaints, and was found to have a high tacrolimus level. Tacrolimus was withheld and later restarted at 3 mg daily and then gradually reduced to 1.5 mg daily. When voriconazole 400 mg twice daily was started, the tacrolimus dose was reduced by one-third to 0.5 mg daily, but eventually needed to be reduced to 0.15 mg daily (a 90% reduction in the overall dose) as a result of rising tacrolimus levels.[34] A kidney transplant patient taking tacrolimus 2 mg daily had an increase in tacrolimus levels from less than 12 nanograms/mL to 25 nanograms/mL when voriconazole 4 mg/kg twice daily was added. His renal function also worsened. The tacrolimus dose was eventually reduced to 0.5 mg on alternate days, with an improvement in his renal function.[35] Another similar case has been reported.[36] A case of thrombotic microangiopathy and severe leukoencephalopathy was attributed to tacrolimus toxicity in a patient who had no tacrolimus dose reduction when given voriconazole.[37]

Painful neuromuscular disorders occurred in 9 of 27 patients taking tacrolimus who were also treated with voriconazole. Tacrolimus levels were maintained within the therapeutic range. At the time of onset of the symptoms, trough voriconazole levels were higher than in the patients without symptoms. Patients completely recovered when voriconazole was stopped. It was suggested that tacrolimus triggered voriconazole neurotoxicity, and that this does not appear to occur if voriconazole doses are adjusted to maintain voriconazole trough levels below 1.5 mg/mL.[38]

Mechanism

Fluconazole, itraconazole, ketoconazole, posaconazole and voriconazole inhibit the metabolism of tacrolimus by the gut wall and/or liver by the cytochrome P450 isoenzyme CYP3A4, and/or inhibit the activity of P-glycoprotein so that more tacrolimus is absorbed.[13,19,27,32] Intravenous tacrolimus is less affected as it does not undergo first-pass metabolism in the gut,[13]

Importance and management

The evidence suggests that all azoles can markedly raise tacrolimus levels. The interaction between tacrolimus and **fluconazole** is established, clinically important and can develop rapidly (within 3 days). Fluconazole generally only inhibits CYP3A4 at high doses (greater than 200 mg daily), and the authors of one of the reports say that up to 200 mg of oral fluconazole daily can be used safely and effectively provided that the tacrolimus dose is reduced by half;[4] however, note that clinically relevant, although less dramatic rises, do occur with lower fluconazole doses. Concurrent use should be closely monitored and the tacrolimus dose adjusted as required. One study specifically examining dose adjustments suggested that fluconazole can be safely used if 60% of the original tacrolimus dose is given.[5] If tacrolimus is given intravenously, no clinically important interaction appears to occur.[13]

The interactions of tacrolimus with **itraconazole** and **ketoconazole** also appear to be established, and the UK manufacturer of tacrolimus states that nearly all patients will require tacrolimus dose reductions when given these drugs.[39]

The manufacturers of **posaconazole** recommend that the tacrolimus dose is initially reduced (they suggest by about two-thirds) in patients given posaconazole, with further dose adjustments made as required on the basis of close monitoring of tacrolimus levels both during concurrent use and after the antifungal is stopped.[40] Similarly, the manufacturers of **voriconazole** advise reducing the tacrolimus dose by two-thirds when starting voriconazole, closely monitoring tacrolimus levels throughout, and increasing the tacrolimus dose in response to levels obtained when voriconazole is stopped.[41,42] Note that, greater reductions in the dose of tacrolimus may be needed in some patients.[32,34] However, the authors of one review state that pre-emptive tacrolimus dose reductions when starting azoles are not standard practice among transplant clinicians, because of the concern of an increased risk of rejection[43] (due to subtherapeutic tacrolimus levels). Whatever is done, close monitoring is necessary.

Information about oral **clotrimazole** is more limited, but on the basis of the case report and studies cited it would be prudent to monitor tacrolimus levels, and adjust the dose as necessary. No interaction would generally be expected with clotrimazole used topically (e.g. pessaries or cream), as the systemic absorption is usually low.

In vitro studies with human liver microsomes have shown that **miconazole**[44] also inhibits liver and small intestine microsomes that metabolise tacrolimus and it seems possible that it may interact like fluconazole but this needs confirmation. There appear to be no clinical reports of an interaction between miconazole and tacrolimus. However, a large proportion of miconazole oral gel (both prescription and non-prescription doses) may be swallowed and therefore adequate systemic absorption may occur to produce an interaction. The manufacturer of miconazole oral gel recommends close monitoring and a possible dose reduction of tacrolimus if both drugs are given concurrently.[45] An interaction with intravaginal miconazole would not normally be expected because its systemic absorption is usually very low (less than 2%) in healthy women of child-bearing age.[46] No interaction would be expected if miconazole is applied to the skin.

Remember to readjust the dose of tacrolimus when the azole antifungal is stopped.

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Tacrolimus + Basiliximab

Basiliximab increases tacrolimus levels and adverse effects.

Clinical evidence, mechanism, importance and management

A study in 12 adult kidney transplant patients found that trough tacrolimus levels on day 3 were increased by 63% in patients also given basiliximab, and in 50% of these patients this was associated with the development of acute tubular necrosis. By day 30, tacrolimus trough levels showed a downward trend in the group receiving basiliximab, despite similar dose requirements to those on day 10. Tacrolimus dose requirements were lower in the group receiving basiliximab throughout the 60-day study period, when compared with the control group.[1] Dose reductions were not considered necessary by the authors, but close monitoring was recommended.[1]

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Tacrolimus + Calcium-channel blockers

Nifedipine may cause a moderate rise in tacrolimus levels and also appears to be kidney protective. Marked rises in tacrolimus levels have been reported in a few cases with diltiazem, although one study found no interaction. There is an isolated case of increased levels with felodipine. Nicardipine, verapamil, and possibly nilvadipine, are predicted to interact similarly.

Clinical evidence

(a) Diltiazem

A liver transplant patient taking tacrolimus 8 mg twice daily had an increase in his tacrolimus trough blood levels from 12.9 nanograms/mL to 55 nanograms/mL within 3 days of starting diltiazem (initially 5 to 10 mg/hour intravenously for one day, then 30 mg orally every 8 hours). The patient became delirious, confused and agitated. Both drugs were stopped, and over the next 3 days his mental state improved and his tacrolimus levels fell to 6.7 nanograms/mL. Tacrolimus was then restarted, gradually increasing to a dose of 5 mg twice daily, which produced levels of 9 to 10 nanograms/mL.[1] Another report briefly mentions that one kidney transplant patient with acute tacrolimus nephrotoxicity required a 66% tacrolimus dose reduction after starting diltiazem.[2] Diltiazem was thought to have contributed to a case of very high tacrolimus levels in a patient also taking 'protease inhibitors', (p.1305), but ritonavir alone could equally well have been responsible.

Similarly, a study in 2 liver and 2 kidney transplant patients found that diltiazem increased the AUC of tacrolimus. In the kidney transplant patients the increase appeared to be dose-related; a 20 mg dose of diltiazem caused a 26% and 67% rise, while a 180 mg dose caused a 48% and 177%, rise in each patient, respectively. The liver transplant patients did not have any alteration in the AUC of tacrolimus until they were given higher doses of diltiazem; one patient had an 18% rise following a 120 mg dose, the other a 22% rise following a 180 mg dose.[3]

However, in a study in liver transplant patients given tacrolimus, there was no difference in the required tacrolimus dose at day 3, day 7, month one and month 3 between 7 patients also given modified-release diltiazem 90 mg daily when compared with 7 patients not given diltiazem.[4] The authors of the other study[3] suggested that this lack of effect may have been because only 90 mg of diltiazem was used.

(b) Felodipine

A 13-year-old boy taking tacrolimus 4 mg twice daily was given felodipine 2.5 mg daily 15 days after receiving a kidney transplant. Two weeks later his tacrolimus level was reported as greater than 30 nanograms/mL (previous levels ranged from 10.6 to 20 nanograms/mL), and despite a reduction in the dose of tacrolimus to 3 mg twice daily, a subsequent tacrolimus level was 53.9 nanograms/mL. He was eventually stabilised at the original tacrolimus levels with tacrolimus 500 micrograms twice daily. When felodipine was stopped several months later, his tacrolimus dose needed to be raised to maintain therapeutic levels.[5]

(c) Nifedipine

A one-year retrospective study of two groups of liver transplant patients found that in the 22 patients taking nifedipine 30 or 60 mg daily there was a 55% increase in the tacrolimus blood levels after one month. By 6 months the tacrolimus dose had been reduced by a total of 25.5% in the nifedipine group and by 12 months by 31.4% when compared with the group not taking nifedipine. The nifedipine group also had improved renal function (lowered serum creatinine).[6]

Mechanism

Diltiazem and verapamil are established moderate inhibitors of the cytochrome P450 isoenzyme CYP3A4, and verapamil is known to also inhibit P-glycoprotein. Tacrolimus is a substrate for this isoenzyme and transporter protein, and diltiazem and verapamil would therefore be expected to reduce the metabolism and clearance of tacrolimus leading to increased blood levels. Nifedipine and felodipine are not known to act as inhibitors of drug metabolism, and the reasons for the potential interactions described are unclear. However, an early *in vitro* study using human liver microsomes did find inhibition of tacrolimus metab-

olism by nifedipine and nilvadipine,[7] although there is some doubt about the clinical relevance of these findings.

Importance and management

Information about an interaction between tacrolimus and **diltiazem** is limited. However, given that diltiazem is known to affect one of the main routes of tacrolimus metabolism and that marked rises in tacrolimus levels have been seen in some patients, it would seem wise to closely monitor tacrolimus levels when this drug is started or stopped. **Verapamil** would also be expected to interact with tacrolimus (see *Mechanism*) and the manufacturers of tacrolimus state that interactions have been reported.[8,9] Similar precautions to those advised for diltiazem would be prudent with concurrent use.

Limited evidence from one retrospective study suggests that **nifedipine** might interact with tacrolimus. However, the increase seems slow, and it seems likely that any decrease in the dose requirements of tacrolimus will be detected by routine monitoring.

There is only one isolated case report with **felodipine**, and no interaction is established; however, some manufacturers of felodipine advise monitoring tacrolimus levels if felodipine is given and a dose adjustment as required.[10,11] Published information about other calcium-channel blockers appears to be lacking, but the manufacturers of tacrolimus[8,9] say that interactions have occurred with **nicardipine**, and the UK manufacturer additionally suggests that **nilvadipine** may interact similarly, based on *in vitro* data.[9]

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Tacrolimus + Chloramphenicol

A marked rise in tacrolimus trough levels has been reported in several patients who were given systemic chloramphenicol.

Clinical evidence

A retrospective study identified 3 patients taking tacrolimus who had received a total of 5 courses of intravenous chloramphenicol, each lasting for at least 12 days. Tacrolimus trough blood levels were doubled by day 2, and had risen by 207% at their peak, on day 6. The tacrolimus dose had been decreased by about one-third by day 12, and the tacrolimus levels returned to around the baseline value.[1]

An adolescent patient with a kidney transplant developed toxic tacrolimus levels on the second day of starting chloramphenicol for a vancomycin-resistant enterococcal infection. The tacrolimus dose had to be reduced by 83% to achieve safe serum levels, and it was found that the dose-adjusted tacrolimus AUC was 7.5-fold greater in the presence of chloramphenicol.[2] Another report describes a similar interaction in a liver transplant patient taking tacrolimus 4 mg twice daily. The patient was given intravenous chloramphenicol, but at the unintentionally high dose of 1850 mg every 6 hours. After about 3 days the patient complained of lethargy, fatigue, headaches and tremors, so both drugs were stopped. His tacrolimus trough level had increased from a range of 9 to 11 nanograms/mL to more than 60 nanograms/mL. Seven days after chloramphenicol had been stopped his tacrolimus level was 8.2 nanograms/mL and his symptoms had resolved.[3] Another case report in a kidney-pancreas transplant patient taking tacrolimus 4 mg twice daily found that the addition of oral chloramphenicol 750 mg four times daily increased the tacrolimus trough blood level to more than 30 micrograms/L within 3 days. After 10 days, the dose of tacrolimus was reduced to 1.5 mg twice daily and the tacrolimus level fell to between 18 and 25 micrograms/L. Chloramphenicol was stopped 5 days later and the tacrolimus dose was increased to 3 mg twice daily. However, the tacrolimus level fell to below 5 micrograms/L for several days leading to an episode of acute organ rejection. The tacrolimus level then returned to within the therapeutic range and the patient stabilised.[4]

Mechanism

The authors suggest that chloramphenicol increased tacrolimus levels by rapidly inhibiting its metabolism.[2]

Importance and management

These appear to be the only reports of this interaction, but it is expected to be an interaction of general importance. It would be prudent to monitor the outcome closely if systemic chloramphenicol is given to any patient taking tacrolimus, being alert for the need to reduce the tacrolimus dose. It seems doubtful if a clinically relevant interaction will occur with topical chloramphenicol because the dose and systemic absorption are small, but this needs confirmation.

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Tacrolimus + Ciclosporin

The manufacturers say that tacrolimus and ciclosporin should not be used concurrently because of the increased risk of nephrotoxicity.

Clinical evidence, mechanism, importance and management

One study found that, in patients with normal bilirubin levels, the half-life of ciclosporin was prolonged from a range of 6 to 15 hours up to 26 to 74 hours, and the ciclosporin serum levels, measured by a fluorescent polarisation immunoassay, were raised by tacrolimus.[1] On the other hand another study found no changes in the pharmacokinetics of ciclosporin, as measured by HPLC, in patients given tacrolimus, but creatinine levels were almost doubled (suggesting kidney damage),[2] which confirmed a previous report suggesting that severe renal impairment may develop when both drugs are given.[3] Tacrolimus levels may also be raised by ciclosporin.[4]

The manufacturers of tacrolimus say that it should not be given with ciclosporin because of the risk of additive/synergistic nephrotoxicity, and, if ciclosporin is being replaced by tacrolimus, 12 to 24 hours should elapse between stopping one drug and starting the other. If ciclosporin levels are raised, the introduction of tacrolimus should be further delayed.[4,5]

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5. Prograf (Tacrolimus monohydrate). Astellas Pharma Ltd. UK Summary of product characteristics, May 2009.

Tacrolimus + Cinacalcet

In a controlled study, cinacalcet had little effect on the pharmacokinetics of tacrolimus. However, a case report describes a marked fall in tacrolimus levels in a patient who started to take cinacalcet.

Clinical evidence

In a pharmacokinetic study in 6 kidney transplant patients taking tacrolimus, cinacalcet 30 mg daily for 7 days had minimal effects on the pharmacokinetics of tacrolimus. There was an average 14% reduction in the AUC of tacrolimus, with no change in the trough level and no change in the renal function.[1]

In clinical studies, no change in tacrolimus dose was needed in 5 patients when they were given cinacalcet, 30 mg daily then titrated to effect, for 6 months.[2,3]

However, there is one case report of a woman taking tacrolimus 4 mg twice daily who had a marked fall in tacrolimus levels (from 6.3 to 2.6 micrograms/L) one week after starting to take cinacalcet 30 mg daily. Increasing the dose of tacrolimus to 6 mg twice daily led to levels within the therapeutic range. Because of a rise in serum creatinine, cinacalcet was withdrawn and her tacrolimus levels rose from 6.6 micrograms/L to 8 micrograms/L. No further tacrolimus dose adjustment was required.[4]

Mechanism

The reason for the slight reduction in tacrolimus exposure in the pharmacokinetic study is unknown. Whether the marked reduction in the case report was actually due to cinacalcet, and the mechanism for this effect, is unknown. Cinacalcet is not an inhibitor of the cytochrome P450 isoenzyme CYP3A4, by which tacrolimus is principally metabolised and therefore this mechanism is not involved.

Importance and management

The minor reduction in tacrolimus levels in the pharmacokinetic study are unlikely to be clinically relevant, and this seems to be borne out in the few patients in clinical studies taking tacrolimus who were given cinacalcet for 6 months. However, the case report of a marked reduction in levels introduces a note of caution. Until further clinical experience is gained, it would be prudent to monitor tacrolimus levels more closely with concurrent use.

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4. Maass E, Mueller GA, Heller T, Koziolek MJ. Decrease in serum tacrolimus level and rise in serum creatinine under late addition of cinacalcet in a renal transplant recipient with hyperparathyroidism: a case report. *Transplant Proc* (2007) 39, 3468–70.

Tacrolimus + Corticosteroids

The concurrent use of tacrolimus and corticosteroids is very common but some evidence suggests that methylprednisolone may alter tacrolimus pharmacokinetics. Prednisone appears to reduce the levels of tacrolimus.

Clinical evidence, mechanism, importance and management

A review of early studies of tacrolimus stated that serum levels were said to have been increased on 10 occasions, decreased on 5 occasions, and unaltered on 2 occasions by **methylprednisolone**.[1]

In a randomised study conducted over 3 months, 31 patients receiving tacrolimus, mycophenolate and daclizumab were compared with 34 patients receiving tacrolimus, mycophenolate and **prednisone**. Higher tacrolimus doses were required to maintain therapeutic tacrolimus levels in the **prednisone** group. This reached a maximum after one month, when a 30% larger tacrolimus dose was necessary.[2] A further study found that patients taking higher doses of **prednisone** (more than 0.25 mg/kg daily) also needed larger doses of tacrolimus to maintain therapeutic trough blood levels. The authors considered that this was possibly due to induction of the cytochrome P450 isoenzyme CYP3A4 by **prednisone** and recommended that tacrolimus levels be closely monitored and adjusted according to any changes in corticosteroid dose.[3]

The concurrent use of tacrolimus and corticosteroids common and advantageous but be alert for any evidence of altered tacrolimus effects.

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Tacrolimus + Danazol

An isolated report describes an increase in tacrolimus levels in a patient given danazol.

Clinical evidence, mechanism, importance and management

In a kidney transplant patient, the trough serum levels of tacrolimus 10 mg daily rose from 0.7 nanograms/mL to 2.7 nanograms/mL within 4 days of danazol 400 mg to 1.2 g daily being started. Despite a reduction in the danazol dose to 600 mg and then 400 mg daily, her tacrolimus levels and serum creatinine remained high for one month until the danazol was withdrawn.[1]

The reason for this effect is not known, but the authors suggest that danazol possibly inhibits the metabolism (demethylation and hydroxylation) of tacrolimus by the liver so that it is cleared from the body more slowly.[1]

Although this is an isolated case, it seems possible that it will be of general significance (compare 'Ciclosporin + Danazol', p.1236). Monitor the effects of concurrent use in any patient, reducing the tacrolimus dose as necessary.

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Tacrolimus + Echinocandins

Caspofungin slightly decreases tacrolimus levels. Anidulafungin and micafungin do not appear to affect tacrolimus pharmacokinetics, and tacrolimus does not affect the pharmacokinetics of anidulafungin, caspofungin, or micafungin.

Clinical evidence, mechanism, importance and management

(a) Anidulafungin

Thirty-five healthy subjects were given a single 5-mg oral dose of tacrolimus 3 days before and on day 10 of a course of intravenous anidulafungin (200 mg loading dose and then 100 mg daily). Anidulafungin did not have any significant effects on the pharmacokinetics of tacrolimus and no serious adverse effects were reported. The pharmacokinetics of anidulafungin were not affected by tacrolimus.[1] No additional monitoring would seem to be required with this combination; however, bear in mind that the study above was a single-dose study in healthy subjects. Ideally, more study is required in patients taking long-term tacrolimus.

(b) Caspofungin

The preliminary results of one study in healthy subjects suggest that caspofungin reduces the AUC of tacrolimus by a modest 20%,[2] and reduces the trough tacrolimus levels by 26%.[3] Tacrolimus did not alter the pharmacokinetics of caspofungin.[2] However, in another study in 17 transplant patients taking tacrolimus, just 3 required a tacrolimus dose adjustment (no details given) when also given caspofungin.[4] In a small retrospective study of liver transplant patients, the concurrent use of tacrolimus and caspofungin did not appear to be associated with elevations of liver enzymes.[5]

The manufacturers of caspofungin advise that standard monitoring of tacrolimus levels should be undertaken if caspofungin is given, and the tacrolimus dose should be adjusted as appropriate.[3,6]

(c) Micafungin

Twenty-six healthy subjects were given single 5-mg doses of tacrolimus alone, after intravenous micafungin 100 mg, and one day after intravenous micafungin 100 mg daily for 5 days. The pharmacokinetics of tacrolimus were not affected by micafungin, and single-dose tacrolimus had no effects on the pharmacokinetics of micafungin.[7] Similarly, in a clinical study of patients given micafungin, there was no difference in micafungin blood levels, bilirubin or creatinine clearance between 7 patients taking tac-

rolimus (14 samples) and 22 patients not taking tacrolimus (26 samples).[8] No additional monitoring would seem to be required with this combination.

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3. Cancidas (Caspofungin acetate). Merck Sharp & Dohme Ltd. UK Summary of product characteristics, July 2009.
4. Veroux M, Macarone M, Fiamingo P, Cappello D, Gagliano M, Di Mare M, Vizcarra D, Spataro M, Giuffrida G, Sorbello M, Severino V, Veroux P. Caspofungin in the treatment of azole-refractory esophageal candidiasis in kidney transplant recipients. *Transplant Proc* (2006) 38, 1037–9.
5. Saner F, Gensicke J, Rath P, Fruhauf N, Gu Y, Paul A, Radtke A, Malagó M, Broelsch C. Safety profile of concomitant use of caspofungin and cyclosporine or tacrolimus in liver transplant patients. *Infection* (2006) 34, 328–32.
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Tacrolimus + Food

Food decreases the rate and extent of tacrolimus absorption.

Clinical evidence

In a single-dose study in healthy subjects, giving tacrolimus capsules with a high-fat breakfast reduced the maximum tacrolimus level by 77%, delayed the time to maximum level by about 5 hours, and decreased the AUC by 33%, when compared with the fasting state. There was no change in the elimination half-life.[1] Slightly less marked findings were noted with a low-fat, high carbohydrate breakfast (65% and 26% reductions in maximum level and AUC, respectively, and about a 2 hour delay in time to maximum level.[1]

In another study in healthy subjects, taking tacrolimus 1.5 hours after a meal resulted in the same reduction in the AUC as when it was given immediately after a meal (39%), but the decrease in maximum level was slightly less (63% versus 71%).[2]

The manufacturers report that, in a study in 11 liver transplant patients, taking tacrolimus 15 minutes after a high-fat breakfast resulted in a 27% decrease in the AUC and 50% decrease in maximum levels when compared with the fasted state.[2,3] However, the effect was less pronounced in a study in kidney transplant patients given tacrolimus immediately after a continental breakfast, the AUC of tacrolimus was reduced by 2 to 12% and its maximum level was reduced by 15 to 38%.[3]

Mechanism

Unknown.

Importance and management

The extent of this interaction is likely to be clinically relevant.[1] The UK manufacturer advises that tacrolimus is taken on an empty stomach at least one hour before or 2 to 3 hours after a meal to optimise absorption.[3]

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2. Prograf (Tacrolimus). Astellas Pharma US Inc. US Prescribing information, August 2009.
3. Prograf (Tacrolimus monohydrate). Astellas Pharma Ltd. UK Summary of product characteristics, May 2009.

Tacrolimus + Grapefruit and other fruit juices

Grapefruit juice can markedly increase the levels of tacrolimus. Pomelo may interact similarly. An isolated case describes an increase in tacrolimus levels in a patient eating grapefruit marmalade.

Clinical evidence

(a) Grapefruit juice

Eight liver transplant patients were given 12 oz (about 360 mL) of grapefruit juice twice daily, which they drank within 45 minutes of taking their dose of tacrolimus. After one week it was found that their 12-hour trough, and one-hour and 4-hours post-dose tacrolimus levels were raised by 300%, 195%, and 400%, respectively. Two patients had headaches, one had diarrhoea and one had an increased creatinine level that reversed, but none developed irreversible toxicity. Two of the patients continued to drink the grapefruit juice and it was possible to halve their tacrolimus dose.[1] Similarly, 6 kidney transplant patients had their dose of tacrolimus reduced by an average of 40% after drinking 100 mL of grapefruit juice daily for 5 days.[2]

A hospitalised liver transplant patient was advised to drink grapefruit juice in an effort to increase her tacrolimus trough blood levels, which were subtherapeutic (below 5 nanograms/mL) despite a dose of tacrolimus 10 mg daily. She drank 250 mL of grapefruit juice four times over 3 days during which time the tacrolimus level did not increase. However, one week after she stopped the grapefruit juice the tacrolimus level was found to have increased to 37 nanograms/mL.[3]

(b) Other grapefruit products

A 52-year-old man with a liver transplant, stabilised on tacrolimus 3 mg twice daily, began to feel anxious and febrile with continued trembling and blurred vision. Within 5 days he deteriorated and developed severe left chest pain. His tacrolimus whole blood level was found to be markedly raised to 55.4 micrograms/L from a previous therapeutic level (between 8 and 13 micrograms/L), and he had renal impairment (serum creatinine of 174 micromols/L). It transpired that during the week preceding the onset of symptoms he had eaten more than 1.5 kg of a home-made marmalade, which was made with more than 50% grapefruit.

(c) Pomelo

A case report describes a kidney transplant patient taking tacrolimus whose tacrolimus level rose from a range of 8 to 10 nanograms/mL up to 25.2 nanograms/mL after he ate about 100 g of pomelo (*Citrus grandis*, a fruit related to grapefruit).[4]

Mechanism

Grapefruit juice inhibits the activity of the cytochrome P450 isoenzyme CYP3A4, mainly in the gut wall. Tacrolimus is primarily metabolised by CYP3A4 and so its bioavailability rises. Pomelo is related to grapefruit and therefore potentially interacts by the same mechanism. *In vitro*, pomelo juice and grapefruit juice extracts inhibited the cytochrome P450 isoenzyme CYP3A4, and had a lesser effect on P-glycoprotein (pomelo weaker than grapefruit).[5] However, the reason for the delayed rise in tacrolimus levels in the liver transplant patient is unclear.[3]

Importance and management

In practical terms the authors of the first report suggest that this interaction means that the dose of tacrolimus can possibly be reduced (to save money) although there is a clear need to monitor the effects closely not only because of the inter-individual factors affecting tacrolimus dosing but also because of the difficulties of standardising grapefruit juice.[1] However, the manufacturers of tacrolimus suggest that the combination should be avoided.[6,7] This would appear prudent. Patients should be informed of the potential risk of this interaction.

The case report with grapefruit marmalade appears to be isolated. As such, it requires confirmation by further study. Note that in this case, the patient consumed an unusually large amount of marmalade (estimated 14 dessert spoonfuls (15 g) daily). More modest consumption (a spoonful of about 15 g daily) would appear unlikely to interact.

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2. Michelangelo V, Piero D, Elisa C, Enrico S, Mauro B, Pietro B. Grapefruit juice and kinetics of tacrolimus. *J Am Soc Nephrol* (2001) 12, 862A.
3. Fukatsu S, Fukudo M, Masuda S, Yano I, Katsura T, Ogura Y, Oike F, Takada Y, Inui K-I. Delayed effect of grapefruit juice on pharmacokinetics and pharmacodynamics of tacrolimus in a living-donor liver transplant recipient. *Drug Metab Pharmacokinet* (2006) 21, 122–5.
4. Egashira K, Fukuda E, Onga T, Yogi Y, Matsuya F, Koyabu N, Ohtani H, Sawada Y. Pomelo-induced increase in the blood level of tacrolimus in a renal transplant patient. *Transplantation* (2003) 75, 1057.
5. Egashira K, Ohtani H, Itoh S, Koyabu N, Tsujimoto M, Murakami H, Sawada Y. Inhibitory effects of pomelo on the metabolism of tacrolimus and the activities of CYP3A4 and P-glycoprotein. *Drug Metab Dispos* (2004) 32, 828–33.

6. Prograf (Tacrolimus). Astellas Pharma US Inc. US Prescribing information, August 2009.
7. Prograf (Tacrolimus monohydrate). Astellas Pharma Ltd. UK Summary of product characteristics, May 2009.

Tacrolimus + H_2-receptor antagonists

Cimetidine might slightly increase tacrolimus levels, but famotidine and ranitidine do not appear to interact.

Clinical evidence

(a) Cimetidine

In a retrospective study in 48 kidney transplant patients, patients switched from cimetidine 400 mg daily to omeprazole 20 mg daily had a 15% decrease in their dose to weight-normalised tacrolimus trough levels.[1]

(b) Famotidine

In a transplant patient taking tacrolimus 8 mg daily with lansoprazole, tacrolimus levels of 12 to 15.4 nanograms/mL were achieved. However, when lansoprazole was replaced by famotidine, the tacrolimus levels were reduced to 8 nanograms/mL.[2,3] Another similar case has been reported.[4] In another patient, a slight decrease in tacrolimus levels (from a range of 8.3 to 8.5 nanograms/mL down to a range of 6.2 to 8.4 nanograms/mL) was seen when rabeprazole was switched to famotidine.[3]

(c) Ranitidine

In one case report, a marked increase in tacrolimus levels occurred when ranitidine was switched to omeprazole.[5]

Mechanism

Cimetidine is a known minor inhibitor of various cytochrome P450 isoenzymes, and so might be expected to slightly increase tacrolimus levels. The *decreased* tacrolimus levels in one study when stopping cimetidine and starting omeprazole would seem to support this suggestion (although the authors concluded that omeprazole may have induced tacrolimus metabolism, but this would be unexpected for omeprazole, see 'Tacrolimus + Proton pump inhibitors', p.1306). Other H_2-receptor antagonists do not inhibit any cytochrome P450 isoenzymes.

Importance and management

There is very little information available regarding an interaction between tacrolimus and the H_2-receptor antagonists. Cimetidine might slightly increase tacrolimus levels, although this may be of little general relevance. Other H_2-receptor antagonists are not expected to interact to a clinically relevant extent. The studies above found that when a proton pump inhibitor was substituted with ranitidine or famotidine, the increased tacrolimus levels caused by the proton pump inhibitor were not sustained by the H_2-receptor antagonist, supporting this predicted lack of an interaction. For more information on the modest interaction of the proton pump inhibitors with tacrolimus, see 'Tacrolimus + Proton pump inhibitors', p.1306.

1. Lemahieu WPD, Maes BD, Verbeke K, Vanrenterghem Y. Impact of gastric acid suppressants on cytochrome P450 3A4 and P-glycoprotein: consequences for FK506 assimilation. *Kidney Int* (2005) 67, 1152–60.
2. Homma M, Itagaki F, Yuzawa K, Fukao K, Kohda Y. Effects of lansoprazole and rabeprazole on tacrolimus blood concentration: case of a renal transplant recipient with CYP2C19 gene mutation. *Transplantation* (2002) 73, 303–4.
3. Itagaki F, Homma M, Yuzawa K, Fukao K, Kohda Y. Drug interaction of tacrolimus and proton pump inhibitors in renal transplant recipients with CYP2C19 gene mutation. *Transplant Proc* (2002) 34, 2777–8.
4. Takahashi K, Motohashi H, Yonezawa A, Okuda M, Ito N, Yamamoto S, Ogawa O, Inui K. Lansoprazole-tacrolimus interaction in Japanese transplant recipient with CYP2C19 polymorphism. *Ann Pharmacother* (2004) 38, 791–4.
5. Takahashi K, Yano I, Fukuhara Y, Katsura T, Takahashi T, Ito N, Yamamoto S, Ogawa O, Inui K. Distinct effects of omeprazole and rabeprazole on the tacrolimus blood concentration in a kidney transplant recipient. *Drug Metab Pharmacokinet* (2007) 22, 441–4.

Sirolimus or Tacrolimus + Imatinib

Imatinib modestly increases tacrolimus levels and is predicted to increase sirolimus levels.

Clinical evidence, mechanism, importance and management

One study, in patients with leukaemia who had undergone stem cell transplantation, found that the levels of tacrolimus were increased by 25 to 33% within 72 hours of starting imatinib. An empiric tacrolimus dose reduction of 25% at the start of imatinib treatment was found to prevent further serum level fluctuations.[1]

Imatinib is an inhibitor of the cytochrome P450 isoenzyme CYP3A4, and it would therefore be expected to increase the levels of immunosuppressants metabolised in this way (such as ciclosporin, tacrolimus and sirolimus.[2] P-glycoprotein might also be involved.

Although data is limited, based on the likely mechanism and increase in levels reported when imatinib was taken with other CYP3A4 substrates (such as simvastatin, see 'Statins + Imatinib', p.1337), it would be prudent to monitor tacrolimus, **ciclosporin** and sirolimus levels on starting or stopping imatinib.

1. Sheth SR, Hicks K, Ippoliti C, Giralt , Champlin RE, Anderlini P. Safety, tolerability, and drug interactions of adjuvant imatinib mesylate (Gleevec) within the first 100 days following stem cell transplantation (SCT) in patients with Ph+ CML and PH+ ALL at high risk for recurrence. *Blood* (2002) 100, Abstract 2500.
2. Gleevec (Imatinib mesylate). Novartis Pharmaceuticals Corporation. US Prescribing information, May 2009.

Tacrolimus + Macrolides

Patients have had marked increases in tacrolimus levels accompanied by evidence of renal toxicity when they were also given erythromycin. The same interaction has been seen in patients given clarithromycin, and is predicted with josamycin and troleandomycin. One case report describes an increase in tacrolimus levels when azithromycin was given.

Clinical evidence

(a) Azithromycin

One report briefly describes a patient taking tacrolimus following a bone marrow transplant who took a 10-day course of azithromycin (dose not stated) without any significant alteration in his serum creatinine or trough tacrolimus levels.[1] However, in another case report, a patient who had been given intravenous tacrolimus 20 micrograms/kg had an increase in tacrolimus levels from a range of 15.8 to 17.5 nanograms/mL to greater than 30 nanograms/mL 3 days after azithromycin 500 mg daily was started.[2]

(b) Clarithromycin

A woman with a kidney transplant taking tacrolimus, prednisone and azathioprine was given clarithromycin 500 mg twice daily for 4 days, then 250 mg daily to treat a severe *Mycoplasma pneumoniae* infection. Despite a 64% reduction in the dose of the tacrolimus, the trough tacrolimus concentrations rose sharply, from 2.8 nanograms/mL to 36.1 nanograms/mL by day 6 and creatinine levels increased from 309 micromol/L to 442 micromol/L. The tacrolimus dose was further reduced and then stopped, and not restarted until clarithromycin treatment was completed.[3] In another 2 kidney transplant patients, tacrolimus levels increased by 146% and 131%, following 9 doses of clarithromycin 250 mg. Creatinine levels increased by 91% and 30%, respectively.[4] Similarly, the tacrolimus levels of a bone marrow transplant patient rose from below 1.1 nanograms/mL to 10.1 nanograms/mL after he took clarithromycin 500 mg twice daily for about 4 days.[1] A similar increase in tacrolimus levels has been reported in a heart transplant patient, despite an initial 33% reduction in the tacrolimus dose in anticipation of the interaction,[5] and in another kidney transplant patient.[6]

(c) Erythromycin

A liver transplant patient taking tacrolimus 6 mg twice daily for one year had a marked rise in serum tacrolimus levels from about 1.4 nanomol/L to 6.5 nanomol/L when intravenous ampicillin with sulbactam 3 g every 6 hours and oral erythromycin 250 mg every 6 hours were given for 4 days to treat pneumonia. Renal toxicity, demonstrated by increased blood urea and creatinine levels also occurred. Erythromycin was stopped, and the next day tacrolimus was also stopped. Over the next week the tacrolimus plasma levels, creatinine levels, and blood urea nitrogen fell.[7] A kidney transplant patient had an increase in his plasma tacrolimus levels from 1.3 nanograms/mL to 8.5 nanograms/mL 4 days after starting erythromycin 400 mg four times daily. His serum creatinine levels almost doubled.[8] A man with a kidney transplant had a sixfold rise in tacrolimus blood levels when he took erythromycin.[9] Another similar case has been described.[10] Two children aged 3 and 7 years also had rises in tacrolimus

blood levels, which were accompanied by renal toxicity when erythromycin was added.[11]

Mechanism

The macrolides inhibit tacrolimus metabolism by the cytochrome P450 subfamily CYP3A and inhibit its transport by P-glycoprotein. Azithromycin is less likely to interact with tacrolimus because it does not inhibit this subfamily,[12] although, as it might inhibit P-glycoprotein, an interaction cannot be entirely ruled out.

Importance and management

Direct information about an interaction between tacrolimus and the macrolides seems to be limited to these case reports. However, what is known is in line with the way both tacrolimus and these macrolides are known to interact with other drugs. It would therefore be prudent to closely monitor the effects of adding clarithromycin or erythromycin in any patient, being alert for the need to reduce the tacrolimus dose to avoid nephrotoxicity. Remember to reduce the tacrolimus dose when the macrolide is stopped. Most other macrolides would also be expected to interact, although they do not all behave identically. The manufacturers of tacrolimus name **josamycin**[13] and **troleandomycin**.[13,14] Note that troleandomycin is considered to be a more potent inhibitor of CYP3A4 than erythromycin, and may produce a greater increase in tacrolimus levels. Similar precautions would also be prudent with **telithromycin**.[15]

Azithromycin would appear less likely to interact, but the case report of increased tacrolimus levels should be borne in mind.

1. Ibrahim RB, Abella EM, Chandrasekar PH. Tacrolimus-clarithromycin interaction in a patient receiving bone marrow transplantation. *Ann Pharmacother* (2002) 36, 1971–2.
2. Mori T, Aisa Y, Nakazato T, Yamazaki R, Ikeda Y, Okamoto S. Tacrolimus-azithromycin interaction in a recipient of allogeneic bone marrow transplantation. *Transpl Int* (2005) 18, 757–8.
3. Wolter K, Wagner K, Philipp T, Fritschka E. Interaction between FK 506 and clarithromycin in a renal transplant patient. *Eur J Clin Pharmacol* (1994) 47, 207–8.
4. Gómez G, Álvarez ML, Errasti P, Lavilla FJ, García N, Ballester B, García I, Purroy A. Acute tacrolimus nephrotoxicity in renal transplant patients treated with clarithromycin. *Transplant Proc* (1999) 31, 2250–1.
5. Kunicki PW, Sobieszczańska-Malek M. Pharmacokinetic interaction between tacrolimus and clarithromycin in a heart transplant patient. *Ther Drug Monit* (2005) 27, 107–8.
6. Katari SR, Magnone M, Shapiro R, Jordan M, Scantlebury V, Vivas C, Gritsch A, McCauley J, Starzl T, Demetris J, Randhawa PS. Clinical features of acute reversible tacrolimus (FK 506) nephrotoxicity in kidney transplant recipients. *Clin Transplant* (1997) 11, 237–42.
7. Shaeffer MS, Collier D, Sorrell MF. Interaction between FK506 and erythromycin. *Ann Pharmacother* (1994) 28, 280–1.
8. Jensen C, Jordan M, Shapiro R, Scantelbury V, Hakala T, Fung J, Stasrzl T, Venkataramanan R. Interaction between tacrolimus and erythromycin. *Lancet* (1994) 344, 825.
9. Padhi ID, Long P, Basha M, Anandan JV. Interaction between tacrolimus and erythromycin. *Ther Drug Monit* (1997) 19, 120–2.
10. Moreno M, Latorre C, Manzanares C, Morales E, Herrero JC, Dominguez-Gil B, Carreño A, Cubas A, Delgado M, Andres A, Morales JM. Clinical management of tacrolimus drug interactions in renal transplant patients. *Transplant Proc* (1999) 31, 2252–3.
11. Furlan V, Perello L, Jacquemin E, Debray D, Taburet A-M. Interactions between FK506 and rifampicin or erythromycin in pediatric liver recipients. *Transplantation* (1995) 59, 1217–18.
12. Paterson DL, Singh N. Interactions between tacrolimus and antimicrobial agents. *Clin Infect Dis* (1997) 25, 1430–40.
13. Prograf (Tacrolimus monohydrate). Astellas Pharma Ltd. UK Summary of product characteristics, May 2009.
14. Prograf (Tacrolimus). Astellas Pharma US Inc. US Prescribing information, August 2009.
15. Ketek (Telithromycin). Sanofi-Aventis. UK Summary of product characteristics, June 2009.

Tacrolimus + Metoclopramide

In an isolated case, metoclopramide may have increased tacrolimus levels, resulting in tacrolimus toxicity and acute renal failure.

Clinical evidence, mechanism, importance and management

A case report describes a liver transplant patient taking tacrolimus up to 28 mg twice daily (and several other drugs), whose subtherapeutic tacrolimus levels were increased when she took metoclopramide for gastric dysmotility (initially 10 mg four times daily, then 20 mg four times daily). Her tacrolimus trough levels increased from less than 2 nanograms/mL to greater than 30 nanograms/mL within 5 to 6 days, and she developed tremor, weakness, nausea, vomiting, diarrhoea and acute renal failure. The authors considered that the increase in tacrolimus levels was due to metoclopramide, possibly due to its effects in increasing gut motility and hence, tacrolimus absorption. However, several other factors may have contributed, such as diarrhoea and the use of cimetidine and ketoconazole, both of which can inhibit the metabolism of tacrolimus and increase its levels.[1]

This appears to be the only reported case of tacrolimus toxicity with metoclopramide, and because of the number of complicating factors, it is by no means established. Its general significance is unclear.

1. Prescott WA, Callahan BL, Park JM. Tacrolimus toxicity associated with concomitant metoclopramide therapy. *Pharmacotherapy* (2004) 24, 532–7.

Tacrolimus + Metronidazole

Two case reports describe increases in tacrolimus levels in patients also given metronidazole.

Clinical evidence

A kidney transplant patient taking tacrolimus 3 mg twice daily had a three-fold increase in his tacrolimus levels when he was given metronidazole 500 mg four times daily for 14 days. His trough level increased from 9.2 nanograms/mL to 26.3 nanograms/mL within 4 days of starting the metronidazole, requiring a tacrolimus dose reduction to 1 mg twice daily. Five days after stopping the metronidazole his trough level had returned to 9.2 nanograms/mL and his dose was increased back up to 2 mg twice daily.[1] A similar increase in tacrolimus trough levels was seen in a kidney transplant patient taking tacrolimus 3 mg in the morning and 2 mg at night. His tacrolimus level rose from 9 nanograms/mL to nearly 18 nanograms/mL when he started taking metronidazole 400 mg three times daily for a *C. difficile* infection. The tacrolimus dose was reduced to 1 mg twice daily and the tacrolimus level fell to 8.1 nanograms/mL. When the metronidazole was stopped, his tacrolimus level decreased further, to 5.2 nanograms/mL, and his tacrolimus dose needed to be increased to 2 mg twice daily.[2]

Mechanism

Unknown. It was suggested that metronidazole might be a weak inhibitor of the cytochrome P450 isoenzyme CYP3A4 or an inhibitor of P-glycoprotein.[1] As tacrolimus is metabolised by CYP3A4 and is also a substrate for P-glycoprotein, one or both of these mechanisms may be involved in this interaction.

Importance and management

These two cases appear to be the only reports of a possible interaction between tacrolimus and metronidazole. There is insufficient evidence to advocate monitoring in every patient given the combination, but it would be prudent to at least bear this interaction in mind if using metronidazole in patients taking tacrolimus.

1. Page RL, Klem PM, Rogers C. Potential elevation of tacrolimus trough concentrations with concomitant metronidazole therapy. *Ann Pharmacother* (2005) 39, 1109–13.
2. Herzig K, Johnson DW. Marked elevation of blood cyclosporin and tacrolimus levels due to concurrent metronidazole therapy. *Nephrol Dial Transplant* (1999) 14, 521–3.

Tacrolimus + Miscellaneous

The manufacturers advise caution on the concurrent use of tacrolimus with anticoagulants, antidiabetics, nephrotoxic and neurotoxic drugs, and also with various drugs that might alter tacrolimus metabolism.

Clinical evidence, mechanism, importance and management

(a) Isoniazid

The UK manufacturer of tacrolimus states that isoniazid has the potential to decrease tacrolimus levels.[1] However, note that there is little to suggest that isoniazid has any enzyme-inducing effects.

(b) Neurotoxicity or nephrotoxicity

The manufacturers of tacrolimus predict that there may be additive neuro- or nephrotoxicity on the concurrent use of **aciclovir**,[1] **aminoglycosides**,[1,2] **co-trimoxazole**,[1] **ganciclovir**,[1] **gyrase inhibitors**,[1] **NSAIDs**[1] (see 'Tacrolimus + NSAIDs', p.1304) or vancomycin.[1] They also note that nephrotoxicity has been seen when **amphotericin B** was given with tacrolimus.[1]

(c) Protein-binding interactions

Because tacrolimus is extensively bound to plasma proteins, the UK manufacturer mentions the possibility of protein-binding interactions with oral

anticoagulants or **antidiabetics**,[1] but this has largely been discredited as a mechanism, see 'Protein-binding interactions', (p.3).

(d) Other drugs

On the basis of *in vitro* studies, the UK manufacturer of tacrolimus suggests that **bromocriptine**, **dapsone**, **ergotamine**, **lidocaine**, **midazolam**, **quinidine** and **tamoxifen** might inhibit tacrolimus metabolism.[1] The US manufacturer mentions **bromocriptine** may increase tacrolimus levels.[2] These predictions are as yet unconfirmed, and note that these drugs are not generally considered to be associated with clinically significant interactions by inhibition of the cytochrome P450 isoenzyme CYP3A4, which is the main isoenzyme involved in tacrolimus metabolism.

1. Prograf (Tacrolimus monohydrate). Astellas Pharma Ltd. UK Summary of product characteristics, May 2009.
2. Prograf (Tacrolimus). Astellas Pharma US Inc. US Prescribing information, August 2009.

Tacrolimus + NNRTIs

Limited evidence from case reports suggests that efavirenz increases tacrolimus clearance. Nevirapine possibly has less effect. Etravirine is predicted to interact similarly, whereas delavirdine is predicted to decrease tacrolimus clearance.

Clinical evidence

(a) Efavirenz

A kidney transplant patient taking efavirenz 600 mg daily and two nucleoside analogues needed a much larger than expected tacrolimus dose of 24 mg daily to maintain a tacrolimus level of 12.5 nanograms/mL.[1,2] In another study in 4 transplant patients taking stable doses of tacrolimus and various other drugs including fluconazole, the addition of efavirenz and two nucleoside analogues had little effect on the required dose of tacrolimus, but the calculated oral clearance of tacrolimus was almost doubled. In two of these patients for whom a detailed pharmacokinetic analysis was available, one had a 51% decrease in tacrolimus trough level (from 16.1 to 7.9 nanograms/mL) and the other just a 12% decrease in the tacrolimus trough level.[3]

(b) Nevirapine

One case report mentions that a liver transplant patient taking nevirapine and dual nucleoside analogues was maintained on tacrolimus 1 mg daily.[4] In another report, two kidney transplant patients taking nevirapine and dual nucleoside analogues were maintained on tacrolimus 4 mg daily.[1,2]

(c) NNRTIs with protease inhibitors

Adding an NNRTI (efavirenz or nevirapine) to a protease inhibitor required a modest 40% increase in the tacrolimus dose to 1 mg, and a big decrease in the dosing interval (every 12 hours instead of once every 80 hours).[5]

Mechanism

Efavirenz, etravirine and nevirapine generally act as inducers of the cytochrome P450 isoenzyme CYP3A4 by which tacrolimus is metabolised (although note that etravirine is only a weak inducer[6]). As such, they would be expected to decrease tacrolimus levels. The effect of efavirenz in one study may have been attenuated by fluconazole (which may inhibit CYP3A4). NNRTIs slightly attenuated the effect of protease inhibitors on tacrolimus metabolism.

Note that delavirdine *inhibits* CYP3A4 and is predicted to *increase* tacrolimus levels.[7]

Importance and management

There is some evidence that efavirenz increases the clearance of tacrolimus and increases the required dose, whereas there is limited evidence that nevirapine has little effect on the required dose. However, until further data becomes available, it would seem prudent to closely monitor tacrolimus levels in any patient given efavirenz or nevirapine, because of the possibility they may decrease tacrolimus levels. The effect of etravirine on tacrolimus metabolism has not been studied. The manufacturer[6] predicts that it will decrease tacrolimus levels; however, this is likely to be to a lesser degree than efavirenz or nevirapine.

In contrast, delavirdine is predicted to increase tacrolimus levels and so may require tacrolimus dose reductions. Until further information is available, it would be prudent to monitor tacrolimus levels closely in patients also given delavirdine.

1. Jain AK, Venkataramanan R, Shapiro R, Scantlebury VP, Potdar S, Bonham CA, Pokharna R, Rohal S, Ragni M, Fung JJ. Interaction between tacrolimus and antiretroviral agents in human immunodeficiency virus-positive liver and kidney transplantation patients. *Transplant Proc* (2002) 34, 1540–1.
2. Jain AK, Venkataramanan R, Shapiro R, Scantlebury VP, Potdar S, Bonham CA, Ragni M, Fung JJ. The interaction between antiretroviral agents and tacrolimus in liver and kidney transplant patients. *Liver Transpl* (2002) 8, 841–5.
3. Teicher E, Vincent I, Bonhomme-Faivre L, Abbara C, Barrail A, Boissonnas A, Duclos-Vallée JC, Taburet AM, Samuel D, Vittecoq D. Effect of highly active antiretroviral therapy on tacrolimus pharmacokinetics in hepatitis C virus and HIV co-infected liver transplant recipients in the ANRS HC-08 study. *Clin Pharmacokinet* (2007) 46, 941–52.
4. Gow PJ, Mutimer D. Liver transplantation for an HIV-positive patient in the era of highly active antiretroviral therapy. *AIDS* (2001) 15, 291–2.
5. Frassetto LA, Browne M, Cheng A, Wolfe AR, Roland ME, Stock PG, Carlson L, Benet LZ. Immunosuppressant pharmacokinetics and dosing modifications in HIV-1 infected liver and kidney transplant recipients. *Am J Transplant* (2007) 7, 2816–20.
6. Intelence (Etravirine). Janssen-Cilag Ltd. UK Summary of product characteristics, November 2009.
7. Rescriptor (Delavirdine mesylate). Pfizer Inc. US Prescribing information, May 2008.

Tacrolimus + NSAIDs

Two liver transplant patients taking tacrolimus developed acute renal failure after also taking ibuprofen. However, the concurrent use of an NSAID use did not appear to be a contributor to tacrolimus renal toxicity in a study in rheumatoid arthritis patients.

Clinical evidence

Two patients with liver transplants taking tacrolimus developed acute but reversible renal failure, one after taking four **ibuprofen** tablets (strength not stated) and the other after taking three 400-mg tablets of **ibuprofen** taken over 24 hours. Both had stable renal function before taking **ibuprofen**.[1]

However, in another study of the use of tacrolimus in patients with rheumatoid arthritis, the concurrent use of an NSAID use did not appear to influence the renal toxicity of tacrolimus. In this study, increases in creatinine levels of 40% or more above baseline occurred in 9% of patients receiving tacrolimus 1 mg daily, 19% of patients receiving 3 mg daily, and 28% of patients receiving 5 mg daily, and required tacrolimus discontinuation in 2 patients taking 3 mg daily and 7 patients taking 5 mg daily. Stable NSAID therapy (specific drugs not stated) was used in 68 to 81% of patients. The frequency of NSAID use was not higher in patients who developed creatinine elevations, nor was it higher in those who discontinued tacrolimus because of creatinine elevations (about half of the patients who discontinued tacrolimus were taking NSAIDs).[2]

Mechanism

NSAIDs are known to inhibit prostaglandin synthesis and as a result may decrease renal blood flow, which in certain circumstances can lead to renal failure. Renal impairment is more likely to occur in the presence of renal vasoconstrictors. Tacrolimus is known to cause renal vasoconstriction and thus the combined effects of ibuprofen and tacrolimus may have led to acute renal failure. Both patients also had a degree of liver impairment, which the authors suggest may have potentiated the toxicity of tacrolimus with ibuprofen.[1]

Importance and management

Renal impairment with tacrolimus is well known and renal function should be routinely monitored. Whether NSAIDs can contribute to this is uncertain. However, the risk of renal impairment may be increased by other nephrotoxic drugs, and the UK manufacturer lists NSAIDs in this category.[3] Some caution would seem appropriate with concurrent use, taking into account the usual precautions for both NSAIDs and tacrolimus in renal impairment.

1. Sheiner PA, Mor E, Chodoff L, Glabman S, Emre S, Schwartz ME, Miller CM. Acute renal failure associated with the use of ibuprofen in two liver transplant recipients on FK506. *Transplantation* (1994) 57, 1132–3.
2. Furst DE, Saag K, Fleischmann MR, Sherrer Y, Block JA, Schnitzer T, Rutstein J, Baldassare A, Kaine J, Calabrese L, Dietz F, Sack M, Senter RG, Wiesenhutter C, Schiff M, Stein CM, Satoi Y, Matsumoto A, Caldwell J, Harris RE, Moreland LW, Hurd E, Yocum D, Stamler DA. Efficacy of tacrolimus in rheumatoid arthritis patients who have been treated unsuccessfully with methotrexate: a six-month, double-blind, randomized, dose-ranging study. *Arthritis Rheum* (2002) 46, 2020–8.
3. Prograf (Tacrolimus monohydrate). Astellas Pharma Ltd. UK Summary of product characteristics, May 2009.

Tacrolimus + Nystatin

Nystatin oral suspension did not alter tacrolimus levels in one study.

Clinical evidence, mechanism, importance and management

In a study, 18 kidney transplant patients taking tacrolimus 150 micrograms/kg twice daily were given nystatin oral suspension 5 mL four times daily for the prophylaxis of oral thrush immediately following transplantation. Tacrolimus levels measured on days 1, 3, 5 and 7 were not affected by the use of nystatin.[1] It would appear that nystatin has no significant affect on the absorption of tacrolimus, and therefore no tacrolimus dose adjustment would appear to be necessary on concurrent use.

1. Vasquez EM, Pollak R, Benedetti E. Clotrimazole increases tacrolimus blood levels: a drug interaction in kidney transplant patients. *Clin Transplant* (2001) 15, 95–9.

Tacrolimus + Orlistat

In patients adhering to recommended dietary fat intake, orlistat does not appear to significantly affect the pharmacokinetics of tacrolimus, although small dose adjustments may be needed in some patients.

Clinical evidence, mechanism, importance and management

In a study in 12 liver transplant patients taking tacrolimus with orlistat 120 mg three times daily for 6 months, there was no statistically significant difference in the tacrolimus dose or trough-level to daily-dose ratio at any time point. However, 4 patients required a reduction and 2 required an increase in their tacrolimus dose, although these adjustments were only minor dose changes. No elevations in liver enzymes were seen and no episodes of rejection occurred. No diarrhoea was reported by the patients in this study, which suggests that the patients adhered well to the dietary advice regarding fat intake. In this study, patients took their morning tacrolimus dose 30 minutes before orlistat, and then ate breakfast after a further 30 minutes. In the evening the patients took orlistat 30 minutes before dinner, and took their evening dose of tacrolimus 2 hours later.[1] The authors concluded that orlistat could be safely used in patients taking tacrolimus provided that tacrolimus levels are carefully monitored. They do however caution that there is a possibility that transplant patients who do not follow dietary fat advice and develop diarrhoea or steatorrhoea when taking orlistat may need a more marked adjustment of their tacrolimus dose.[1]

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Tacrolimus + Phosphodiesterase type-5 inhibitors

Sildenafil does not affect the pharmacokinetics of tacrolimus. The levels of sildenafil were reported to be higher in patients taking tacrolimus than in healthy subjects. A marked blood pressure drop occurred when both drugs were given in one study, and two patients required modification of their antihypertensives in another. Vardenafil does not appear to affect tacrolimus levels.

Clinical evidence

(a) Sildenafil

In 10 men with erectile dysfunction taking tacrolimus after a kidney transplant, a single 50-mg dose of sildenafil did not affect the pharmacokinetics of tacrolimus. When the pharmacokinetics of sildenafil were compared with those quoted by the manufacturer for healthy subjects, it was found that the maximum plasma concentration and AUC of sildenafil were increased by 44% and 90%, respectively, in patients taking tacrolimus. The AUC of the sildenafil metabolite was also raised. Apart from the pharmacokinetic effects, it was noted that the mean blood pressure dropped by 27/20 mmHg after sildenafil was given.[1] A subsequent study by the same authors in 9 men with erectile dysfunction taking tacrolimus after a kidney transplant, found that sildenafil 25 mg daily for 9 days had no significant effects on the trough levels or half-life of tacrolimus. Mean arterial blood pressure was reduced (by 1 to 7 mmHg, but this was not statistically significant), and 2 patients required a reduction in dose of their antihypertensives.[2]

Another study in 4 patients taking tacrolimus found that sildenafil 50 or 100 mg did not affect tacrolimus trough levels.[3]

(b) Vardenafil

In a study in kidney transplant patients, vardenafil 10 or 20 mg (maximum frequency of once in 24 hours) in repeated doses during a 4-week period had no effect on the levels or required dose of tacrolimus, and no change in renal function was reported.[4]

Mechanism

There are several possible reasons for the apparent increase in sildenafil levels in transplant patients other than a direct effect of tacrolimus. The pharmacokinetic data quoted by the manufacturer are from healthy subjects, not patients, and the patients in the study were taking a multitude of other drugs, some of which could have affected sildenafil.

Importance and management

It would appear that sildenafil does not affect tacrolimus levels; however, given the reduction in blood pressure seen in two studies,[1,2] it may be prudent to start patients on a 25-mg dose of sildenafil, as the authors of this study advise, and increase the dose according to efficacy and tolerability. Vardenafil also does not appear to affect tacrolimus levels, but the effects on blood pressure do not appear to have been studied.

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4. Demir E, Balal M, Paydas S, Sertdemir Y, Erken U. Efficacy and safety of vardenafil in renal transplant recipients with erectile dysfunction. *Transplant Proc* (2006) 38, 1379–81.

Tacrolimus + Potassium-sparing diuretics

The concurrent use of tacrolimus and potassium-sparing diuretics may cause hyperkalaemia.

Clinical evidence, mechanism, importance and management

Tacrolimus alone can cause hyperkalaemia, especially if renal function is impaired, and the risk might be additive with potassium-sparing drugs. Because of this, the manufacturers suggest that tacrolimus should not be used with potassium-sparing diuretics,[1,2] such as **amiloride**, **triamterene**, and **spironolactone**.[2] **Eplerenone** may also cause hyperkalaemia, and similar precaution would seem appropriate. It would be prudent to closely monitor potassium levels and renal function if the concurrent use of any of these diuretics is considered essential.

1. Prograf (Tacrolimus). Astellas Pharma US Inc. US Prescribing information, August 2009.
2. Prograf (Tacrolimus monohydrate). Astellas Pharma Ltd. UK Summary of product characteristics, May 2009.

Tacrolimus + Protease inhibitors

Protease inhibitors markedly inhibit the metabolism of tacrolimus and increase its levels. The available evidence suggests the effect is most apparent with ritonavir-boosted regimens.

Clinical evidence

In transplant patients taking tacrolimus and started on a protease inhibitor-based regimen, the tacrolimus dose was reduced by 80% (to 700 micrograms) and the dosing interval markedly increased to just once every 80 hours. This effect was attenuated somewhat when 'NNRTIs', (p.1304), were additionally given.[1] In another case series, the average

tacrolimus dose was 1 to 3 mg *weekly* in patients taking a protease inhibitor (mostly nelfinavir).[2] Another report briefly mentions that 4 HIV-positive kidney transplant patients taking a protease inhibitor (not specified) required a dramatic tacrolimus dose reduction, and 3 of them needed a change from a protease inhibitor to an NNRTI.[3]

(a) Fosamprenavir

Four transplant patients needed an average threefold increase in the dose of tacrolimus (from about 290 to 880 micrograms daily) when their protease inhibitor was changed from **nelfinavir** to fosamprenavir.[4]

(b) Nelfinavir

An HIV-positive patient, with hepatitis C following a liver transplant, was given stavudine, lamivudine, and nelfinavir 500 mg three times daily. Tacrolimus 6 mg daily was started postoperatively, but high blood levels were observed and the dose was reduced over the next 3 months to a maintenance dose of 500 micrograms *weekly*, which achieved levels of 7 to 25.9 nanograms/mL.[5] In one case series, the required dose of tacrolimus varied between 500 micrograms once every 5 days and 1 mg every other day in 4 patients taking nelfinavir-based antiretroviral regimens.[6,7] Similar decreased tacrolimus dose requirements have been noted in other patients given nelfinavir (500 micrograms every 3 days[8] or weekly[9] or a 75 to 93% reduction in daily dose[10]).

A brief report describes petit mal seizures brought on by high tacrolimus levels, which were thought to be due to an interaction with nelfinavir.[11] One report mentions a patient who developed acute cellular rejection progressing to chronic rejection due to low tacrolimus levels when nelfinavir was stopped without an increase in the tacrolimus dose.[2]

(c) Ritonavir-boosted protease inhibitors

1. Lopinavir. A liver transplant patient taking tacrolimus 5 mg twice daily (to give a tacrolimus trough blood level of 10.6 nanograms/mL) had a large increase in tacrolimus levels to 78.5 nanograms/mL when ritonavir-boosted lopinavir was started, despite a tacrolimus dose reduction to 6 mg daily. Tacrolimus neurotoxicity developed, but no nephrotoxicity was seen. The patient was eventually stabilised taking tacrolimus 500 micrograms *weekly* while taking ritonavir-boosted lopinavir.[9] Two other patients taking ritonavir-boosted lopinavir developed raised tacrolimus levels and were eventually stabilised on tacrolimus doses of 500 micrograms to 1 mg weekly.[9,12] A further patient was unable to tolerate tacrolimus with ritonavir-boosted lopinavir and was switched to nelfinavir.[9] In seven liver transplant patients taking tacrolimus, the tacrolimus dose needed to be reduced by 99% (to about 20 to 250 micrograms daily) when ritonavir-boosted lopinavir was started. Maintenance doses of tacrolimus in these patients varied from 500 micrograms to 1.5 mg, given between once weekly and just once every 25 days.[10]

2. Saquinavir. A case report describes an HIV-positive patient taking ritonavir-boosted saquinavir 100/800 mg twice daily who developed a very high tacrolimus level (200 micrograms/L) 5 days after starting tacrolimus 5 mg twice daily after a kidney transplant. The tacrolimus dose was reduced tenfold to 500 micrograms twice daily, and by 15 months post-transplant he was stabilised on just 500 micrograms *weekly*.[13] In another case, a patient had a tacrolimus level of 10.9 nanograms/mL while taking tacrolimus 4 mg twice daily without antiretrovirals. When he was given ritonavir-boosted saquinavir, a reduced dose of tacrolimus 1 mg twice daily resulted in tacrolimus levels in excess of 120 nanograms/mL, with severe and prolonged toxicity.[8]

Mechanism

All protease inhibitors are, to varying degrees, potent inhibitors of the cytochrome P450 isoenzyme CYP3A4, by which tacrolimus is metabolised. It therefore seems likely that the protease inhibitors reduced tacrolimus metabolism resulting in the extremely high levels seen. The protease inhibitors also inhibit P-glycoprotein, of which tacrolimus is a substrate. It has been suggested that this could lead to increased levels of unmetabolised tacrolimus in the bile which may be reabsorbed through the enterohepatic circulation system, thus further increasing tacrolimus levels.[9]

Importance and management

An established and clinically important interaction. When protease inhibitors, particularly ritonavir, are given to patients taking tacrolimus, a marked reduction in the dose of tacrolimus is required, with close and frequent monitoring of tacrolimus levels. One centre found that the average tacrolimus dose needed was just 1 mg to 3 mg *weekly* in patients taking a protease inhibitor-based HAART regimen (mostly nelfinavir).[2] In another centre, the average tacrolimus dose required was 700 micrograms every 80 hours (3.3 days).[1] In yet another centre, in patients specifically taking ritonavir-boosted lopinavir, the required tacrolimus dose was just 0.5 to 1.5 mg given between once *weekly* and just once every 25 days.[10] The effect of fosamprenavir appears to be less than that of nelfinavir.[4]

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Tacrolimus + Proton pump inhibitors

Lansoprazole may increase tacrolimus levels, and the extent of the interaction might depend on the metaboliser status of the patient. Pantoprazole and omeprazole are predicted to interact similarly, although there is some evidence of a lack of interaction for both these drugs. Rabeprazole does not appear to have a clinically significant effect on tacrolimus levels.

Clinical evidence

(a) Lansoprazole

A 57-year-old woman taking tacrolimus following a kidney transplant started taking lansoprazole 30 mg daily 19 days after her transplant because of a peptic ulcer. After 3 days her tacrolimus trough level rose from a range of 16.3 to 17.6 nanograms/mL up to 26.7 nanograms/mL. The tacrolimus dose was reduced, and levels of 12 to 15.4 nanograms/mL were achieved. When lansoprazole was replaced by famotidine, the tacrolimus levels reduced to 8 nanograms/mL[1,2] Two other very similar cases have been reported in Japanese transplant patients,[3,4] and in all these cases the patients were CYP2C19 poor metabolisers (those lacking or deficient in this isoenzyme).

In a pharmacokinetic study in 19 healthy Japanese subjects, lansoprazole 30 mg daily for 4 days increased the $AUC_{0\text{-}8}$ of tacrolimus by 48% and decreased its clearance by 31% when a single 2-mg dose of tacrolimus was given with the lansoprazole on day 4. When divided by CYP2C19 metaboliser status, the increase in AUC was 52% greater in the 11 intermediate or poor metabolisers, than in the 8 extensive metabolisers (that is, those with normal levels of this isoenzyme), although there was wide variability between subjects.[5] However, in another study in 40 transplant patients taking tacrolimus and lansoprazole 30 mg daily, the degree of the interaction appeared to be influenced more by CYP3A5 genetic polymorphisms than CYP2C19 genetic polymorphisms.[6]

(b) Omeprazole

In a study in 51 kidney transplant patients taking tacrolimus and omeprazole 20 mg daily for 6 months after transplantation, there was no differ-

ence in the tacrolimus level to dose ratio in the 3 months before stopping omeprazole and the 3 months after stopping omeprazole.[7] However, a retrospective study in 48 kidney transplant patients found that when patients switched from cimetidine 400 mg daily to omeprazole 20 mg daily there was a 15% decrease in the dose to weight-normalised tacrolimus trough levels.[8]

In contrast, a case report of a 13-year-old transplant patient, describes a marked increase in tacrolimus trough levels (from around 10 nanograms/mL up to 28 nanograms/mL) and an increase in serum creatinine when omeprazole 20 mg daily was started, both of which resolved on stopping the omeprazole. This patient was not a CYP2C19 poor metaboliser.[9] Another similar case is reported (genetic status unknown).[10]

(c) Pantoprazole

A study in 6 transplant patients taking tacrolimus found that pantoprazole 40 mg daily for 5 days did not significantly affect the trough levels of tacrolimus.[11]

(d) Rabeprazole

One patient who had a rise in tacrolimus levels while taking lansoprazole was later given rabeprazole 10 mg daily without any alteration in tacrolimus levels.[1,2] Two other reports also describe a lack of interaction between rabeprazole and tacrolimus.[4,10] Another report describes a patient who had no significant alteration in tacrolimus levels when rabeprazole 10 mg daily was started and stopped.[2]

In a pharmacokinetic study in 15 healthy Japanese subjects, rabeprazole 10 mg daily for 4 days slightly increased the AUC_{0-8} of tacrolimus by 18% when a single-dose of tacrolimus 2 mg was given with the rabeprazole on day 4, but this change was not statistically significant.[5]

Mechanism

Uncertain. In some of the cases and one study, the interaction with lansoprazole was greatest in patients with decreased activity of the cytochrome P450 isoenzyme CYP2C19, by which lansoprazole (and also esomeprazole, omeprazole and pantoprazole) is mainly metabolised. When levels of this isoenzyme are low, lansoprazole levels are much higher, and it has been suggested that this might be sufficient to inhibit tacrolimus metabolism by CYP3A4 and/or affect transport by P-glycoprotein (which is inhibited to some extent by all the proton pump inhibitors).[5] If this is the mechanism, then **esomeprazole**, omeprazole and **pantoprazole** would be expected to interact similarly. Nevertheless, one study suggested that CYP3A5 metaboliser status was more important than CYP2C19 metaboliser status or P-glycoprotein.[6] Rabeprazole is principally metabolised non-enzymatically and seems less likely to interact,[1,2,5] although one study found no difference between rabeprazole and lansoprazole.[6]

The *decreased* tacrolimus levels in one study with omeprazole was thought to be due to induction of CYP3A4 by omeprazole,[8] but may have been more to do with stopping the cimetidine (a known enzyme inhibitor) than an effect of omeprazole. Further study is required.

Importance and management

The incidence of the interaction between tacrolimus and lansoprazole is unknown. There is some evidence that it is most likely in those with decreased CYP2C19 activity,[5] although not all evidence supports this.[6,9] As metaboliser status is rarely known, it is not possible to predict which patients would be affected. No interaction was seen in the one study with pantoprazole or one study with omeprazole, although there are a couple of case reports with omeprazole. Some evidence suggests that rabeprazole is less likely to interact and may be a suitable alternative, but not all evidence supports this. Further detailed pharmacokinetic study is required for all proton pump inhibitors. Until more is known, bear the possibility of an interaction in mind and give consideration to increasing the monitoring of tacrolimus levels when any of these drugs are started or stopped, taking into account the significance of a potential increase in levels to the individual patient.

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Tacrolimus + Quinolones

Levofloxacin modestly increased the bioavailability of tacrolimus in one study.

Clinical evidence, mechanism, importance and management

A study in 5 kidney transplant patients found that **levofloxacin** 500 mg twice daily for 5 days increased the AUC_{0-12} of tacrolimus by about 27%.[1] The authors concluded that levofloxacin inhibits the metabolism of tacrolimus, but levofloxacin is not a known inhibitor of the principal mechanisms of tacrolimus elimination (the cytochrome P450 isoenzyme CYP3A4 and P-glycoprotein).

The one available study suggests that a modest increase in tacrolimus levels might occur in patients given levofloxacin, but this is probably not likely to be clinically relevant for a short course of the antibacterial. Nevertheless, the authors of this study suggest that close monitoring would be appropriate if tacrolimus is given with levofloxacin.[1] Further study is needed.

1. Federico S, Carrano R, Capone D, Gentile A, Palmiero G, Basile V. Pharmacokinetic interaction between levofloxacin and ciclosporin or tacrolimus in kidney transplant recipients: ciclosporin, tacrolimus and levofloxacin in renal transplantation. *Clin Pharmacokinet* (2006) 45, 169–75.

Tacrolimus + Quinupristin/Dalfopristin

Quinupristin/dalfopristin may modestly increase tacrolimus levels. There is limited evidence suggesting that tacrolimus might increase the risk of myalgia and/or arthralgia occurring with quinupristin/dalfopristin.

Clinical evidence

The manufacturer states that the concurrent use of quinupristin/dalfopristin has been reported to increase the trough levels of tacrolimus by 15%.[1]

In an analysis of myalgia and/or arthralgia occurring with quinupristin/dalfopristin in cancer patients, the use of tacrolimus within the month preceding treatment was associated with a higher risk. Seven (35%) of the patients experiencing myalgia and/or arthralgia had received tacrolimus compared with 4 (11%) of those not experiencing myalgia and/or arthralgia.[2]

Mechanism

Quinupristin/dalfopristin is an inhibitor of the cytochrome P450 isoenzyme CYP3A4, the main isoenzyme involved in the metabolism of tacrolimus.[1,3] Concurrent use therefore leads to decreased tacrolimus metabolism and increased levels. Myalgia and/or arthralgia are common in patients receiving quinupristin/dalfopristin and their aetiology is uncertain. It was suggested that tacrolimus-induced impairment in biliary function/cholestasis might predispose patients to develop myalgia and/or arthralgia with quinupristin/dalfopristin.[2]

Importance and management

Although the increase in trough tacrolimus levels with quinupristin/dalfopristin is modest, it might be prudent to monitor tacrolimus levels more closely during concurrent use.[1,3] Bear in mind the possibility that tacrolimus use might increase the risk of myalgia and/or arthralgia with quinupristin/dalfopristin. The US manufacturer of quinupristin/dalfopristin notes that improvement has been noted in some patients with this adverse effect when the dose frequency has been extended.[3]

1. Synercid (Quinupristin/Dalfopristin). Monarch Pharmaceuticals Ireland Ltd. UK Summary of product characteristics, March 2005.
2. Raad I, Hachem R, Hanna H. Relationship between myalgias/arthralgias occurring in patients receiving quinupristin/dalfopristin and biliary dysfunction. *J Antimicrob Chemother* (2004) 53, 1105–8.
3. Synercid (Quinupristin/Dalfopristin). DSM Pharmaceuticals, Inc. US Prescribing information, November 2007.

Tacrolimus + Repaglinide

Repaglinide does not appear to alter tacrolimus levels.

Clinical evidence, mechanism, importance and management

In a study in kidney transplant patients stabilised on immunosuppressants, the concurrent use of repaglinide in the 14 patients taking tacrolimus did not appear to cause any significant changes in tacrolimus blood levels and no tacrolimus dose changes were required on starting repaglinide 1 to 3 mg daily (mostly as monotherapy but a few patients were also given either metformin or rosiglitazone).[1] It would appear from the limited data from this observational study, that a significant pharmacokinetic interaction between tacrolimus and repaglinide does not occur; however, this ideally needs confirmation in a pharmacokinetic study.

1. Türk T, Peitruck F, Dolff S, Kribben A, Janssen OE, Mann K, Philipp T, Heemann U, Witzke O. Repaglinide in the management of new-onset diabetes mellitus after renal transplantation. *Am J Transplant* (2006) 6, 842–6.

Tacrolimus + Rifamycins

A number of liver transplant patients have needed markedly increased tacrolimus doses when rifampicin (rifampin) was added. A pharmacokinetic study found that rifampicin increases the clearance and decreases the bioavailability of intravenous and oral tacrolimus. One case report demonstrates that rifabutin does not interact to the same extent as rifampicin (rifampin).

Clinical evidence

(a) Rifabutin

A renal transplant patient developed low tacrolimus levels (3.7 to 5.5 nanograms/mL) despite an increase in dose from 16 to 60 mg daily while taking rifampicin 600 mg daily. When the rifabutin was substituted for rifampicin, the tacrolimus doses were gradually reduced to 20 mg daily with serum levels between 10 and 15 nanograms/mL.[1]

(b) Rifampicin (Rifampin)

The trough tacrolimus blood levels of a 10-year-old boy with a liver transplant fell from 10 nanograms/mL to unmeasurable levels within 2 days of rifampicin 150 mg twice daily being started. His tacrolimus dose was therefore doubled from 4 to 8 mg twice daily. When rifampicin was later stopped, the tacrolimus dose had to be reduced to 3 mg twice daily to keep the blood levels in the region of 10 nanograms/mL.[2]

Various other similar cases have been reported.[1,3-7] In one of these, a tenfold increase in the tacrolimus dose was needed to keep trough blood levels within the target range when rifampicin was started. However, despite levels within the acceptable range, a biopsy showed suspected tacrolimus nephrotoxicity, which was considered to be possibly due to the cumulative tacrolimus dose, or to high levels of tacrolimus metabolites (which were not measured).[5] In another case, a decrease in tacrolimus levels from 9.2 nanograms/mL to 1.4 nanograms/mL occurred just 2 days after starting rifampicin. Rifampicin was stopped and replaced by pyrazinamide, with a gradual return to the baseline tacrolimus level.[6] In yet another case, the effect of rifampicin was so potent that the use of either 'fluconazole', (p.1296), or 'clarithromycin', (p.1302), both known inhibitors of tacrolimus metabolism, did not increase tacrolimus levels.[7]

A study in 6 healthy subjects supports the findings of these case reports. In the study, rifampicin 600 mg daily for 18 days markedly decreased the AUC of tacrolimus after both oral and intravenous administration (by 68% and 35%, respectively). The oral bioavailability of tacrolimus was halved.[8]

Mechanism

This interaction is thought to occur because rifampicin (rifampin), a known enzyme inducer, increases the metabolism of tacrolimus by the cytochrome P450 isoenzyme CYP3A4 in the liver and small bowel, and induces P-glycoprotein, so that tacrolimus is cleared more rapidly. Rifabutin is a less potent enzyme inducer than rifampicin, and therefore has less effect on tacrolimus metabolism.

Importance and management

An established and clinically important interaction. Anticipate the need to increase the dose of tacrolimus, sometimes markedly, if rifampicin (rifampin) is also given. Note that if the interaction is not managed well in patients given tacrolimus post-transplant, there is a risk of transplant rejection.

The one case report with rifabutin suggests that any interaction with tacrolimus is much less marked than with rifampicin. Nevertheless, until the situation is clearer, it would be prudent to closely monitor concurrent use with other rifamycins (for example, **rifapentine** is a moderate CYP3A4 inducer), being alert for the need to increase the tacrolimus dose.

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Tacrolimus + Schisandra

Schisandra greatly increases tacrolimus levels and its adverse effects.

Clinical evidence

In a pharmacokinetic study, 12 healthy subjects were given an extract of *Schisandra sphenanthera* (containing 33.75 mg schizandrin) twice daily for 14 days, with a single 2-mg oral dose of tacrolimus on day 14. The extract of *Schisandra sphenanthera* increased the AUC and maximum plasma concentrations of tacrolimus by 164% and 227%, respectively, but did not alter its half-life. Six of the 12 subjects experienced indigestion, and burning hands and feet, one hour after both medicines were given. These symptoms resolved over 10 hours.[1]

Mechanism

Not established. P-glycoprotein is involved in the intestinal absorption of tacrolimus. It is therefore possible that the inhibition of P-glycoprotein by schizandrin, and possibly other related compounds, may have resulted in increased absorption of tacrolimus. The authors also suggest that the metabolism of tacrolimus, which is a substrate of the cytochrome P450 isoenzyme CYP3A4, may have been inhibited by schisandra. However, one *animal* study suggests that this effect on CYP3A4 may not be clinically relevant.[2]

Importance and management

An interaction between schisandra and tacrolimus seems fairly well established, although the mechanism is not fully established. Concurrent use

appears to result in a large rise in tacrolimus levels, accompanied by an increase in tacrolimus adverse effects. If the use of both medicines is considered desirable it would seem prudent to monitor the outcome of concurrent use closely, adjusting the tacrolimus dose as necessary. It is important to note that, although the schisandra product used in the study was standardised for schizandrin content, this constituent has not been established as the cause of the interaction. Therefore the extent of the interaction may vary between different schisandra products, and different batches of the same schisandra product. This may make this interaction difficult to standardise for, and therefore it may be prudent to avoid concurrent use where tacrolimus blood levels are critical, such as in organ transplantation.

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Tacrolimus + Sevelamer

Sevelamer may reduce the absorption of tacrolimus.

Clinical evidence, mechanism, importance and management

A kidney transplant patient had a progressive reduction in his tacrolimus levels requiring an increase in his tacrolimus dose after he started to take sevelamer 800 mg three times daily. A pharmacokinetic study in the same patient found that the peak tacrolimus level was increased from 9.9 nanograms/mL to 13.1 nanograms/mL, and the AUC_{0-7} was increased 2.4-fold, three days after sevelamer was stopped.[1] Sevelamer can bind with drugs in the gut and prevent their absorption, and this may have lead to the reduction in tacrolimus levels seen.

This appears to be the only case report of an interaction between these two drugs, but sevelamer has been seen to have similar effects on the absorption of a number of other drugs. It is recommended that any drug for which a reduction in the bioavailability may be clinically significant (the UK manufacturer specifically names tacrolimus[2]) should be taken at least one hour before or 3 hours after sevelamer, or their concentrations should be monitored.[2,3] Tacrolimus levels should be closely monitored and the dose adjusted as needed if concurrent use is required or if sevelamer is stopped.

1. Merkle M, Wornle M, Rupprecht HD. The effect of sevelamer on tacrolimus target levels. *Transplantation* (2005) 80, 707.
2. Renagel (Sevelamer). Genzyme Therapeutics. UK Summary of product characteristics, July 2009.
3. Renagel (Sevelamer hydrochloride). Genzyme. US Prescribing information, November 2007.

Tacrolimus + Sirolimus

No pharmacokinetic interaction occurred between tacrolimus and sirolimus in healthy subjects, but there is clinical evidence that sirolimus may modestly reduce tacrolimus blood levels. Tacrolimus does not appear to alter sirolimus levels.

Clinical evidence and mechanism

A single-dose study in 28 healthy subjects found that, compared with either drug alone, there was no pharmacokinetic interaction between sirolimus and tacrolimus when they were given either at the same time or 4 hours apart.[1] A study in 18 liver transplant and 7 kidney-pancreas transplant patients taking tacrolimus and sirolimus found no difference in the pharmacokinetics of either drug when the drugs were taken either simultaneously or 4 hours apart. No nephrotoxicity was seen.[2]

However, subsequent studies have found decreases in tacrolimus levels due to the concurrent use of sirolimus. A study in 7 children with kidney transplants taking tacrolimus and prednisone found that the addition of sirolimus to treat chronic allograft nephropathy resulted in a decrease in dose-normalised tacrolimus trough blood levels from 0.14 kg/L, to 0.1 kg/L on day 3 and to 0.08 kg/L on day 28. All patients required a tacrolimus dose increase, with a mean increase of about 70% (range 22 to 245%) in order to keep the tacrolimus blood levels above 3 nanograms/mL. This was thought to be due to a reduction in the bioavailability of tacrolimus rather than increased excretion.[3] Another study in 28 kidney transplant patients taking tacrolimus and given sirolimus 500 micrograms, 1 mg, or 2 mg daily also found an initial reduction in the tacrolimus level with the first dose. The tacrolimus levels recovered, but a trend towards reduced tacrolimus levels was seen with continued dosing. Tacrolimus did not appear to alter sirolimus levels, when compared with previous data in studies with sirolimus alone.[4] The US manufacturer of tacrolimus includes a study in which use of tacrolimus and sirolimus (2 or 5 mg daily) in stable kidney transplant patients decreased the AUC and trough level of tacrolimus by about 30% relative to tacrolimus alone. With a lower dose of 1 mg of sirolimus daily, the tacrolimus AUC and trough level decreased by about 3% and 11%, respectively.[5]

A study in 16 adult kidney transplant patients taking tacrolimus and fixed-dose sirolimus 500 micrograms or 2 mg daily found a significant, dose-dependent increase in the AUC of tacrolimus of 16% and 31%, respectively, and an increase in the peak levels of tacrolimus of 19% and 33%, respectively, when sirolimus was stopped.[6]

A retrospective study in adult kidney transplant patients taking tacrolimus and sirolimus found that concurrent use may be associated with extensive tubular cell injury and a unique form of cast nephropathy.[7]

The manufacturers of sirolimus note that clinical studies in *de novo* liver transplant patients have found an increased risk of hepatic artery thrombosis when tacrolimus is also given,[8,9] and in the US concurrent use is not recommended in this patient group.[9] The US manufacturer of sirolimus also notes that a study in *de novo* liver transplant patients found an increased risk of graft loss and mortality in patients also taking tacrolimus.[9]

Moreover, the US manufacturer of tacrolimus notes that the use of full-dose tacrolimus with sirolimus 2 mg daily in heart transplant recipients was associated with increased risk of wound healing complications, impaired renal function, and post-transplant insulin-dependent diabetes mellitus, and is not recommended.[5]

Importance and management

The controlled pharmacokinetic study shows that no interaction appears to occur; however, there is clinical evidence of increased tacrolimus dose requirements on starting sirolimus. As both tacrolimus and sirolimus are given as individualised doses based on target blood levels, any change in required dose on concurrent use should be identified with routine monitoring.

Note that, the US manufacturer of tacrolimus actually recommends avoiding use with sirolimus on the basis of questions regarding safety and efficacy of the combination.[5]

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3. Filler G, Womiloju T, Feber J, Lepage N, Christians U. Adding sirolimus to tacrolimus-based immunosuppression in pediatric renal transplant recipients reduces tacrolimus exposure. *Am J Transplant* (2005) 5, 2005–10.
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5. Prograf (Tacrolimus). Astellas Pharma US Inc. US Prescribing information, August 2009.
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8. Rapamune (Sirolimus). Wyeth Pharmaceuticals. UK Summary of product characteristics, April 2009.
9. Rapamune (Sirolimus). Wyeth Pharmaceuticals Inc. US Prescribing information, November 2009.

Tacrolimus + SSRIs and related antidepressants

Marked increases in tacrolimus levels and toxicity were observed when three patients were also given nefazodone. Fluvoxamine is predicted to increase tacrolimus levels. Paroxetine and sertraline may not interact with tacrolimus, but the situation is not clear.

Clinical evidence

A kidney transplant patient taking tacrolimus 5 mg daily developed delirium and renal failure 4 weeks after starting to take **nefazodone** 150 mg daily. The tacrolimus levels had been 9.4 nanograms/mL some 3 months earlier when he was taking tacrolimus 6 mg daily, but in the presence of **nefazodone** the tacrolimus level increased to 46.4 nanograms/mL with a tacrolimus dose of 5 mg daily and his serum creatinine had doubled. Within 2 days of the tacrolimus dose being reduced to 3 mg daily, the tacrolimus level had fallen to 29.6 nanograms/mL. **Nefazodone** was then

replaced by **paroxetine** 20 mg daily. After 3 days the tacrolimus dose was increased to 5 mg daily and satisfactory levels of 12.4 nanograms/mL were achieved.[1]

A kidney transplant patient taking prednisone, azathioprine and tacrolimus 5 mg daily for 2 years experienced headache, confusion and 'grey areas' in her vision within one week of starting **nefazodone** 50 mg twice daily in place of **sertraline**. Her serum creatinine had risen from 132 micromol/L to 195 micromol/L and her trough tacrolimus level was greater than 30 nanograms/mL. **Nefazodone** was replaced by **sertraline**, and tacrolimus was withheld for 4 days. Signs of tacrolimus-induced neurotoxicity disappeared within 36 hours, and the serum creatinine and tacrolimus levels returned to the levels seen before **nefazodone** was started within 2 weeks.[2]

Another patient developed raised liver enzymes and raised tacrolimus levels after taking **nefazodone** and tacrolimus for 2 weeks. When the **nefazodone** was stopped his liver enzymes normalised over the next 5 days, and his tacrolimus levels fell from 23 nanograms/mL to 9.5 nanograms/mL over 10 days.[3]

Mechanism

Tacrolimus is metabolised by the cytochrome P450 isoenzyme CYP3A4, which is inhibited by nefazodone. Concurrent use therefore results in increased levels of tacrolimus. Paroxetine and sertraline do not have significant effects on CYP3A4 and are therefore not expected to interact with tacrolimus.

Importance and management

Information appears to be limited but what is known indicates that tacrolimus levels or at least signs of tacrolimus toxicity should be well monitored if nefazodone is also given. In view of the narrow therapeutic index of tacrolimus, it may be advisable to avoid nefazodone. Note that nefazodone has generally been withdrawn due to adverse hepatic effects.

Fluvoxamine is a minor to moderate inhibitor of CYP3A4[4] and so theoretically could affect the metabolism of tacrolimus. Close monitoring of tacrolimus levels would therefore be prudent. Paroxetine and sertraline and possibly other SSRIs may be suitable alternative antidepressants, but the evidence is sparse, so additional monitoring may still be warranted.[1] Further study on the use of antidepressants with tacrolimus is needed.

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2. Olyaei AJ, deMattos AM, Norman DJ, Bennett WM. Interaction between tacrolimus and nefazodone in a stable renal transplant recipient. *Pharmacotherapy* (1998) 18, 1356–9.
3. Garton T, Nefazodone and CYP450 3A4 interactions with cyclosporine and tacrolimus. *Transplantation* (2002) 74, 745.
4. Faverin (Fluvoxamine maleate). Solvay Healthcare Ltd. UK Summary of product characteristics, June 2009.

Tacrolimus + St John's wort (*Hypericum perforatum*)

St John's wort decreases tacrolimus levels.

Clinical evidence

In a clinical study, 10 healthy subjects were given a single 100-microgram/kg dose of tacrolimus alone, or after they took St John's wort 300 mg three times daily for 14 days. On average St John's wort decreased the maximum blood level of tacrolimus by 65% and decreased its AUC by 32%. However, the decrease in AUC ranged from 15 to 64%, with one patient having a 31% *increase* in AUC.[1] Similar results have been found in a study in 10 kidney transplant patients given St John's wort (*Jarsin300*) 600 mg daily for 2 weeks. In order to achieve target levels, the tacrolimus dose was increased in all patients, from a median of 4.5 mg daily to 8 mg daily. Two weeks after stopping St John's wort, tacrolimus doses were reduced to a median of 6.5 mg daily, and then to the original dose of 4.5 mg daily after about 4 weeks.[2]

A case report describes a 65-year-old patient taking tacrolimus following a kidney transplant. The patient started to take St John's wort (*Neuroplant*) 600 mg daily, and after one month the tacrolimus trough blood levels had dropped from a range of 6 to 10 nanograms/mL down to 1.6 nanograms/mL, with an unexpected improvement in creatinine levels. When the St John's wort was stopped, tacrolimus levels and creatinine returned to the previous range. Subsequently a lower target range of tacrolimus was set.[3]

Mechanism

St John's wort induces the cytochrome P450 isoenzyme CYP3A4 and affects the transporter protein P-glycoprotein. CYP3A4 and P-glycoprotein are involved in the metabolism and clearance of tacrolimus, so an increase in their effects would be expected to result in a decrease in tacrolimus levels.[1,3]

Importance and management

Although the evidence currently seems limited to these reports the interaction between tacrolimus and St John's wort has been predicted from the pharmacokinetics of these two drugs. Given the unpredictability of the interaction (and the variability in content of St John's wort products) it would seem prudent to avoid St John's wort in transplant patients, and possibly other types of patient taking tacrolimus. If St John's wort is started or stopped, monitor tacrolimus levels and adjust the dose accordingly.

1. Hebert MF, Park JM, Chen Y-L, Akhtar S, Larson AM. Effects of St John's wort (Hypericum perforatum) on tacrolimus pharmacokinetics in healthy volunteers. *J Clin Pharmacol* (2004) 44, 89–94.
2. Mai I, Störmer E, Bauer S, Krüger H, Budde K, Roots I. Impact of St John's wort treatment on the pharmacokinetics of tacrolimus and mycophenolic acid in renal transplant patients. *Nephrol Dial Transplant* (2003) 18, 819–22.
3. Bolley R, Zülke C, Kammerl M, Fischereder M, Krämer BK. Tacrolimus-induced nephrotoxicity unmasked by induction of the CYP3A4 system with St John's wort. *Transplantation* (2002) 73, 1009.

Tacrolimus + Theophylline

An isolated report suggests that theophylline may increase tacrolimus levels.

Clinical evidence

A kidney transplant patient taking tacrolimus 7 mg daily was given theophylline 600 mg daily to treat post-transplant erythrocytosis. After one month serum creatinine levels increased from 110 micromol/L to 145 micromol/L and the tacrolimus trough blood level increased to 16 nanograms/mL, from a range of 5 to 15 nanograms/mL. The theophylline dose was reduced to 300 mg daily on 4 days of each week and one month later the serum creatinine was 175 micromol/L and the trough tacrolimus level was 48.5 nanograms/mL. Theophylline was discontinued and the renal function and trough tacrolimus levels rapidly returned to normal. The pharmacokinetics of tacrolimus were later assessed in the same patient. Theophylline 125 mg daily for 4 days was associated with an almost fivefold increase in the AUC of tacrolimus and an increase in the peak tacrolimus blood levels from 19.3 nanograms/mL to 37.4 nanograms/mL, without significant alterations in renal function on this occasion.[1]

Mechanism

Unclear. An *in vitro* study found that tacrolimus and theophylline each exhibited a negligible effect on the metabolism of the other drug.[2] However, the authors of the case report suggest that theophylline levels in their patient could have been sufficient to inhibit the cytochrome P450 isoenzyme-mediated metabolism of tacrolimus,[1] but note that there is no direct evidence to suggest that theophylline acts this way.

Importance and management

Direct information regarding an increase in tacrolimus levels caused by an interaction with theophylline seems to be limited to this single case report. The authors concluded that low-dose theophylline may be given to transplant patients with erythrocytosis provided that tacrolimus levels are closely monitored.[1] However, this interaction is unconfirmed and of uncertain clinical significance. There is insufficient evidence to recommend increased monitoring in every patient, but be aware of the potential for an interaction in the case of an unexpected response to treatment.

1. Boubenider S, Vincent I, Lambotte O, Roy S, Hiesse C, Taburet A-M, Charpentier B. Interaction between theophylline and tacrolimus in a renal transplant patient. *Nephrol Dial Transplant* (2000) 15, 1066–8.
2. Matsuda H, Iwasaki K, Shiraga T, Tozuka Z, Hata T, Guengerich FP. Interactions of FK506 (tacrolimus) with clinically important drugs. *Res Commun Mol Pathol Pharmacol* (1996) 91, 57–64.

Temsirolimus + Ketoconazole and other CYP3A4 inhibitors

Ketoconazole (a potent CYP3A4 inhibitor) markedly increases the levels of temsirolimus and its active metabolite, sirolimus. Other potent CYP3A4 inhibitors are expected to interact similarly.

Clinical evidence

To determine the effect of ketoconazole on the pharmacokinetics of temsirolimus, 14 healthy subjects were given a single 5-mg intravenous dose of temsirolimus alone, or 2 hours after the first dose of ketoconazole 400 mg daily for 7 days. There was no significant change in the pharmacokinetics of temsirolimus, but the maximum plasma level and AUC of the active metabolite, sirolimus, were increased 2.2-fold and 3.2-fold, respectively.[1] In a study of *oral* temsirolimus (not the clinically used route of administration), ketoconazole 200 mg daily for 10 days increased the AUC of temsirolimus 2 mg given on day 5 sevenfold and increased that of the sirolimus metabolite ninefold.[2]

Mechanism

Ketoconazole is a potent inhibitor of the cytochrome P450 isoenzyme CYP3A4 and P-glycoprotein. Temsirolimus is metabolised by CYP3A4 to sirolimus, which is the major metabolite after intravenous administration, and is equipotent to temsirolimus.[3] Sirolimus is itself also metabolised by CYP3A4, and appears to be more sensitive to CYP3A4 inhibition than temsirolimus. Both sirolimus and temsirolimus are also substrates of P-glycoprotein. Ketoconazole had a much greater effect on oral temsirolimus than intravenous temsirolimus suggesting that intravenous administration bypasses significant gastrointestinal metabolism.

Importance and management

Although the evidence is limited, based on the likely mechanisms and large increases seen in the studies above, an interaction between ketoconazole and temsirolimus would appear to be established. As all of the azoles inhibit CYP3A4 to various degrees, see 'azole antifungals', (p.233), they would be expected to interact similarly. Note that the intravenous study used a very low dose of temsirolimus, and it is possible that increased exposure to sirolimus with the clinically recommended doses of intravenous temsirolimus would give rise to greater increases in toxicity. The authors suggest reducing the temsirolimus dose by half if they are also given potent inhibitors of CYP3A4. They also advise, that if the CYP3A4 inhibitor is stopped, a one week washout period should be allowed before increasing temsirolimus back up to the original dose.[1] The manufacturers of temsirolimus predict that other potent inhibitors of CYP3A4 (they name ketoconazole, **itraconazole**, **voriconazole**, **atazanavir**, **indinavir**, **nelfinavir**, **ritonavir**, **saquinavir**, **telithromycin**, and **nefazodone**) will interact similarly.[3,4] However, the UK manufacturer advises avoiding concurrent use, whereas the US manufacturer suggests considering halving the temsirolimus dose.[4]

The UK manufacturer[3] also suggests that the concurrent use of temsirolimus and moderate inhibitors of CYP3A4 (they name **aprepitant** [and therefore probably **fosaprepitant** should be considered], **fluconazole**, **amiodarone**, **erythromycin**, **diltiazem**, **verapamil**, **fluvoxamine**, and **grapefruit juice**) should be used with caution in patients taking temsirolimus 25 mg [weekly], and should be avoided in patients taking doses of greater than 25 mg weekly. Note that grapefruit juice may have little effect, as the main interactions of grapefruit juice are with orally administered drugs, and temsirolimus bypasses gastrointestinal metabolism because it is used intravenously. Also note that aprepitant has a mild *inducing* effect on CYP3A4, which usually occurs 3 to 5 days after it has been stopped, and fluvoxamine is generally considered to have weak effects on CYP3A4. Both manufacturers also mention **clarithromycin** as a potentially interacting drug, but in the US it is considered to be a potent CYP3A4 inhibitor, whereas in the UK it is considered to be a moderate CYP3A4 inhibitor.

1. Boni JP, Leister C, Burns , Hug B. Differential effects of ketoconazole on exposure to temsirolimus following intravenous infusion of temsirolimus. Br J Cancer (2008) 98, 1797–1802.
2. Shu C, Afsharvand M, Raible D, Zhou J. Effect of ketoconazole on the temsirolimus pharmacokinetic profile in healthy subjects. *Clin Pharmacol Ther* (2005) P34.
3. Torisel (Temsirolimus). Wyeth Pharmaceuticals. UK Summary of product characteristics, August 2009.
4. Torisel (Temsirolimus). Wyeth Pharmaceuticals Inc. US Prescribing information, September 2008.

Temsirolimus + Rifampicin (Rifampin) and other CYP3A4 inducers

Rifampicin, phenytoin and carbamazepine (all potent CYP3A4 inducers) markedly reduce levels of the active metabolite of temsirolimus, sirolimus, after administration of intravenous temsirolimus. Other potent CYP3A4 inducers are expected to interact similarly.

Clinical evidence

(a) Antiepileptics

In a study in patients with malignant gliomas, the maximum tolerated dose of intravenous temsirolimus was 250 mg in patients taking enzyme-inducing antiepileptics compared with 170 mg in patients taking non-enzyme-inducing antiepileptics. The sum of the AUC of temsirolimus and sirolimus was 50% lower in the patients taking enzyme-inducing antiepileptics, despite taking a higher temsirolimus dose. At comparable doses, the AUC for temsirolimus did not differ between the groups, but that for sirolimus was 53% lower in the enzyme-inducing antiepileptic group. The majority of the patients in the enzyme-inducing antiepileptics group were taking **phenytoin** (47%): other drugs used being **carbamazepine**, **oxcarbazepine**, **fosphenytoin**, **phenobarbital** and **primidone**.[1]

In another similar study, the AUC of sirolimus was 43% lower in 11 patients receiving **carbamazepine** or **phenytoin** than in 14 patients not receiving enzyme inducers. The AUC of temsirolimus was 15% lower (not statistically significant).[2]

(b) Rifampicin

In a study in healthy subjects, a single dose of oral or intravenous temsirolimus was given on the sixth day of rifampicin 600 mg daily for 14 days. With *intravenous* temsirolimus, rifampicin reduced the maximum plasma level and AUC of sirolimus by 65% and 56%, respectively, but had no effect on the pharmacokinetics of temsirolimus. With *oral* temsirolimus, rifampicin had a similar effect on sirolimus pharmacokinetics (63% and 60% reduction in maximum level and AUC, respectively) and also reduced the temsirolimus maximum level and AUC, by 41% and 30%, respectively.[2]

Mechanism

Rifampicin and some antiepileptics (carbamazepine, phenytoin, phenobarbital, primidone) are potent inducers of the cytochrome P450 isoenzyme CYP3A4 and P-glycoprotein. Temsirolimus is metabolised by CYP3A4 to sirolimus, which is the major metabolite after intravenous administration, and is equipotent to temsirolimus.[3] Sirolimus is itself metabolised by CYP3A4, and appears to be more sensitive to CYP3A4 induction than temsirolimus. Both sirolimus and temsirolimus are also substrates of P-glycoprotein. Rifampicin had a much greater effect on oral temsirolimus than intravenous, suggesting that intravenous administration bypasses significant gastrointestinal metabolism.

Importance and management

The reductions seen in the levels of the active metabolite of temsirolimus after intravenous administration (the usual clinical route) with the enzyme-inducing antiepileptics or rifampicin are less than after oral temsirolimus, but could well be clinically important. The manufacturers advise avoiding other drugs that are potent inducers of CYP3A4 and they name **carbamazepine**, **phenobarbital**, **phenytoin** and **rifampicin**.[3,4] It would seem prudent to also apply this to **primidone**, which is metabolised to phenobarbital, and **fosphenytoin**, which is a prodrug of phenytoin. In the UK, in patients given temsirolimus for renal cell cancer, they recommend avoidance only if the CYP3A4 inducer is continued beyond an initial 5 to 7 days. However, for patients given temsirolimus for mantle cell lymphoma, concurrent use is not recommended because of the higher dose of temsirolimus used for this condition.[3] The US manufacturer additionally lists **rifabutin** and **dexamethasone**. However, note that clinically significant interactions with dexamethasone as a result of this mechanism

appear to be rare. If treatment with a CYP3A4 inducer is essential, the US manufacturer recommends that the dose of temsirolimus in patients with renal cell cancer should be doubled while the CYP3A4 inducer is being taken and readjusted when the inducer is stopped.[4]

It is also recommended that **St John's wort** is avoided by patients taking temsirolimus.[3,4] For a list of CYP3A4 inducers, see 'Table 1.4', (p.6). What should be remembered is that the extent of the inducing effects of these drugs is not identical, so that marked effects like those observed with rifampicin may not occur; nevertheless the interaction may still be clinically important.

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3. Torisel (Temsirolimus). Wyeth Pharmaceuticals. UK Summary of product characteristics, August 2009.
4. Torisel (Temsirolimus). Wyeth Pharmaceuticals Inc. US Prescribing information, September 2008.

Temsirolimus + Sunitinib

Unexpected dose-limiting toxicity was seen in a phase I study in which temsirolimus was given with sunitinib.

Clinical evidence, mechanism, importance and management

In a phase I study, two of the first 3 patients who received treatment with intravenous temsirolimus 15 mg weekly and oral sunitinib 25 mg daily for 19 to 21 days of a 4 week course, experienced dose-limiting toxicities (including erythematous rash, thrombocytopenia, gout and cellulitis requiring hospitalisation).[1] The study was terminated early because of the toxicity seen at these low starting doses of both drugs. This specific regimen should not be used.

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Lipid regulating drugs

This section is concerned with the drugs that are used for dyslipidaemias (i.e. disturbed levels of lipids in the blood). In the very broadest of terms (and ideally) they lower the blood levels of cholesterol and low-density lipoprotein (LDL), and raise those of high-density lipoprotein (HDL). Such drugs include the statins (more properly known as HMG-CoA (hydroxymethylglutaryl-coenzyme A) reductase inhibitors), fibrates, ezetimibe, bile-acid binding resins (e.g. colestipol, colestyramine) and nicotinic acid (niacin) and related drugs. These are listed in 'Table 30.1', (below). Bile acids (e.g. ursodeoxycholic acid), which affect cholesterol levels in the bile are also included in this chapter. Where lipid regulating drugs or bile acids affect other drugs, the interactions are covered elsewhere.

Table 30.1 Lipid-regulating drugs

Group	*Drugs*
Bile-acid binding resins	Colesevelam, Colestilan, Colestipol, Colestyramine
Fibrates	Bezafibrate, Ciprofibrate, Clofibrate, Fenofibrate, Gemfibrozil
Statins	Atorvastatin, Fluvastatin, Lovastatin, Pitavastatin, Pravastatin, Rosuvastatin, Simvastatin
Miscellaneous	Acipimox, Ezetimibe, Nicotinic acid, Omega-3 marine triglycerides

(a) Statins

1. Muscle and liver toxicity. Statins are generally well tolerated, but have two major but relatively uncommon adverse effects. They raise liver enzymes, and can cause skeletal muscle disorders (e.g. myalgia, myopathy and rhabdomyolysis). Rhabdomyolysis is a syndrome resulting from skeletal muscle injury, which results in the release of the enzyme creatine kinase (among other things) into the circulation. Creatine kinase (CK) is also known as creatine phosphokinase (CPK). Both terms are used throughout the text, the choice being dependent on the term used in the source quoted. Reports of muscle disorders associated with statins have not always been consistent in their definitions, although the generally accepted definition of myopathy is myalgia (muscle pain or soreness), weakness, and/or cramps plus a CK level greater than 10 times the upper limit of normal; rhabdomyolysis has been defined as a CK level of greater than 10,000 units/L or a CK level greater than 10 times the upper level or normal with worsening renal function and/or a requirement for medical intervention with intravenous hydration.[1] As well as elevated creatine kinase levels, signs and symptoms of rhabdomyolysis include muscle pain and weakness and reddish-brown urine (myoglobinuria).[2]

Just how statins cause muscle disorders is as yet unclear, although it is thought to be connected to elevated statin levels[3] and may vary with individual statins, due to lipophilicity and pharmacokinetic differences. Similarly, elevated hepatic transaminases are dose dependent, although progression to liver failure is exceedingly rare.[4] Any pharmacokinetic interaction that results in a marked rise in statin levels is therefore to be regarded seriously.

One of the ways blood statin levels can become elevated is if the interacting drug inhibits the metabolism of the statin, with the result that it is cleared from the body more slowly and it begins to accumulate (see pharmacokinetics below). The overall risk of myopathy with the statins at standard therapeutic doses is quite low and commonly quoted as 0.01 to 0.1%, although in clinical studies involving patients taking statins muscle symptoms have been reported to occur in 1.5 to 3% of patients.[1] A further report[5] puts the incidence of mild myopathies with a statin alone as up to 7%, whilst another observational study found mild to moderate muscular symptoms occurred in 10.5% of patients given a high dose of a statin.[6] However, it has been estimated that for every 15 million prescriptions there is only one occurrence of severe muscle damage.[7] The incidence seems to rise markedly if other interacting drugs are being taken concurrently. Thus a literature review of published reports for the period 1985 to 2000 found 15 cases of rhabdomyolysis with statins alone, but 54 cases when then statin was given with other drugs.[3] Other patient-related risk factors for myopathy include:[4]

- advanced age (especially greater than 70 to 80 years),
- frailty,
- multisystem disease (e.g. chronic renal impairment, especially due to diabetes),
- perioperative periods,
- hypothyroidism,
- alcohol abuse,
- female sex.

In order to reduce the risk of myopathy the CSM in the UK have advised that statins should be used with care in patients who are at increased risk of this adverse effect. Among other risk factors, they mention the concurrent use of fibrates (such as 'gemfibrozil', (p.1332)), 'ciclosporin', (p.1326), 'macrolides', (p.1337), 'azoles', (p.1321), and 'protease inhibitors', (p.1341). They also recommend that patients should be made aware of the risks of myopathy and rhabdomyolysis, and asked to promptly report muscle pain, tenderness, or weakness, especially if this is accompanied by malaise, fever, or dark urine.[8] The American College of Cardiology/American Heart Association/National Heart, Lung and Blood Institute (ACC/AHA/NHLBI) Clinical Advisory on Statins[4] and the National Lipid Association Safety Assessment Task Force[1] give some important safety recommendations, which are useful in the context of interactions:

- Routine monitoring of creatine kinase is of little value in the absence of clinical symptoms.
- If a patient has intolerable muscle symptoms or a creatine kinase value 10 times the upper limit of normal, and is symptomatic, statin treatment should be immediately discontinued.
- If a patient has symptoms of muscle pain with a creatine kinase of up to 10 times the upper limit of normal they should be monitored closely. Statin therapy may be continued at the same or reduced doses and symptoms and creatine kinase levels may be used as the clinical guide to stop or continue treatment.
- If progressive creatine kinase elevations occur consider a dose reduction or temporary discontinuation of the statin.
- Liver transaminase levels should be obtained during routine general evaluation of patients being considered for statin therapy.
- Liver enzyme values of up to 3 times the upper limit of normal do not represent a contraindication to treatment but patients should be carefully monitored.

2. Pharmacokinetics. Lovastatin and simvastatin are extensively metabolised by the cytochrome P450 isoenzyme CYP3A4 so that drugs that can inhibit this enzyme can cause marked rises in blood statin levels. Atorvas-

tatin is also metabolised by CYP3A4, but to a lesser extent than lovastatin or simvastatin. Some of the statins are not metabolised by this isoenzyme so they interact differently. Fluvastatin is metabolised primarily by CYP2C9 (with a minor contribution from other isoenzymes, including CYP3A4), only 10% of rosuvastatin is metabolised, and the isoenzymes involved appear to be CYP2C9 and CYP2C19, while the cytochrome P450 system does not appear to be significantly involved in the metabolism of pravastatin or pitavastatin.[9,10]

Hepatic uptake and biliary excretion are also important in statin elimination, and multiple uptake transporters including the organic anion transporting polypeptide (OATP) 1B1 (also known as OATP-C, OATP2, and LST-1) play an important role in the clearance of statins; atorvastatin, pitavastatin, pravastatin and rosuvastatin have all been reported to be OATP1B1 substrates.[10] The statins are also P-glycoprotein substrates, and may therefore interact due to competition for this carrier, generally resulting in altered oral bioavailability.[9] However, *in vitro* study has suggested that, due to the low affinity of atorvastatin and simvastatin for P-glycoprotein this is unlikely to be a clinically significant cause of statin drug interactions.[11] Some metabolites of atorvastatin, lovastatin and simvastatin have been shown to inhibit P-glycoprotein, while fluvastatin and pravastatin seem to have little effect.[12] There appears to be no data on the effect of rosuvastatin on P-glycoprotein.[13]

(b) Bile-acid binding resins

Bile-acid binding resins lower cholesterol by binding with bile acids in the gastrointestinal tract to form an insoluble complex that is excreted in the faeces. This predisposes them to interactions by binding with other drugs in the same way as they do with bile acids, which prevents absorption or local action of the affected drug. A new bile-acid binding resin, colesevelam, is supposed to be devoid of clinically significant drug-binding interactions.[14]

(c) Ezetimibe

Ezetimibe is a cholesterol absorption inhibitor, and, as this term suggests, it (and the major metabolite), ezetimibe glucuronide, impair the intestinal absorption of cholesterol, both from the diet and biliary cholesterol.[15] The absorption of other fats is not affected. Ezetimibe has not been found to have significant effects on cytochrome P450, suggesting it is unlikely to interact by this mechanism.

(d) Fibrates

Fibrates are protein-bound drugs that are metabolised by the cytochrome P450 isoenzyme CYP3A4. They are not generally recognised as inhibitors of this enzyme. Although protein binding contributes to their interactions, this mechanism alone does not usually lead to serious interactions. This leaves their mechanism of interaction largely unexplained, although it has been suggested that they may act as inhibitors of glucuronidation.[16] Fibrates do not all share the same pharmacokinetic interactions, for example gemfibrozil inhibits CYP2C8 as well as OATP1B1, and seems to increase the plasma levels of most statins, whereas bezafibrate and fenofibrate have less effect on statin bioavailability.[17] As with the statins (see above), fibrates are also recognised as causing myopathies, and the risk of this appears to be greatly increased when they are given with statins, see 'Statins + Fibrates', p.1332.

(e) Nicotinic acid (Niacin)

Nicotinic acid has little effect on the cytochrome P450 isoenzyme system and is therefore unlikely to result in significant pharmacokinetic interactions. It may possibly increase the risk of myopathies when given with statins, see 'Statins + Nicotinic acid (Niacin)', p.1339. Also note that although no interaction has been shown with **acipimox**, the manufacturer recommends caution with drugs that interact with nicotinic acid.[18] This is because nicotinic acid is an analogue of **acipimox**, and so may share its interactions.

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3. Omar MA, Wilson JP, Cox TS. Rhabdomyolysis and HMG-CoA reductase inhibitors. *Ann Pharmacother* (2001) 35, 1096–1107.
4. Pasternak RC, Smith SC, Bairey-Merz CN, Grundy SM, Cleeman JI, Lenfant C. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *J Am Coll Cardiol* (2002) 40, 567–72.
5. Ucar M, Mjörndal T, Dahlqvist R, HMG-CoA reductase inhibitors and myotoxicity. *Drug Safety* (2000) 22, 441–57.
6. Bruckert E, Hayem G, Dejager S, Yau C, Bégaud B. Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients—the PRIMO study. *Cardiovasc Drugs Ther* (2005) 19, 403–14.
7. Thompson, PD, Clarkson PM, Rosenson RS; the National Lipid Association's Muscle Safety Expert Panel. An Assessment of statin safety by muscle experts. *Am J Cardiol* (2006) 97 (Suppl), 69C–76C.
8. Committee on Safety of Medicines/Medicines Control Agency. HMG CoA reductase inhibitors (statins) and myopathy. *Current Problems* (2002) 28, 8–9.
9. Williams D, Feely J. Pharmacokinetic-pharmacodynamic drug interactions with HMG-CoA reductase inhibitors. *Clin Pharmacokinet* (2002) 41, 343–70.
10. Shitara Y, Sugiyama Y. Pharmacokinetic and pharmacodynamic alterations of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors: drug-drug interactions and interindividual differences in transporter and metabolic enzyme functions. *Pharmacol Ther* (2006) 112, 71–105.
11. Hochman JH, Pudvah N, Qiu J, Yamazaki M, Tang C, Lin JH, Prueksaritanont T. Interactions of human P-glycoprotein with simvastatin, simvastatin acid, and atorvastatin. *Pharm Res* (2004) 21, 1686–91.
12. Bogman K, Peyer AK, Török M, Küsters E, Drewe J. HMG-CoA reductase inhibitors and P-glycoprotein modulation. *Br J Pharmacol* (2001) 132, 1183–92.
13. Roach AE, Tsikouris JP, Haase KK. Rosuvastatin. A new HMG-CoA reductase inhibitor for hypercholesterolemia. *Formulary* (2002) 37, 179–85.
14. Donovan JM, Stypinski D, Stiles MR, Olson TA, Burke SK. Drug interactions with colesevelam hydrochloride, a novel, potent lipid-lowering agent. *Cardiovasc Drugs Ther* (2000) 14, 681–90.
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17. Neuvonen PJ, Niemi M, Backman JT. Drug interactions with lipid-lowering drugs: mechanisms and clinical relevance. *Clin Pharmacol Ther* (2006) 80, 565–81.
18. Olbetam (Acipimox). Pharmacia Ltd. UK Summary of product characteristics, May 2007.

Acipimox + Colestyramine

Colestyramine does not appear to significantly affect the pharmacokinetics of acipimox.

Clinical evidence, mechanism, importance and management

A randomised, crossover study, in 7 healthy subjects given acipimox 150 mg with three 4-g doses of colestyramine (taken concurrently, and then 8 and 16 hours later), found that the pharmacokinetics of acipimox were slightly but not significantly altered by colestyramine.[1] There would seem to be no good reason for avoiding concurrent use.

1. de Paolis C, Farina R, Pianezzola E, Valzelli G, Celotti F, Pontiroli AE. Lack of pharmacokinetic interaction between cholestyramine and acipimox, a new lipid lowering agent. *Br J Clin Pharmacol* (1986) 22, 496–7.

Colestyramine + Food

A study in 10 patients with type IIA hyperlipoproteinaemia found that the efficacy of colestyramine in controlling total cholesterol and low density lipoprotein levels was unaltered whether the colestyramine was taken with or before meals.[1]

1. Sirtori M, Pazzucconi F, Gianfranceschi G, Sirtori CR. Efficacy of cholestyramine does not vary when taken before or during meals. *Atherosclerosis* (1991) 88, 249–52.

Ezetimibe + Antacids

The bioavailability of ezetimibe does not appear to be affected to a clinically significant extent by aluminium/magnesium hydroxide-containing antacids.

Clinical evidence, mechanism, importance and management

A study in 12 healthy subjects found that giving ezetimibe 10 mg with 20 mL of an **aluminium**/**magnesium** [hydroxide]-containing antacid (*Supralox*) did not affect the AUC of ezetimibe or conjugated ezetimibe metabolites, although the mean maximum plasma concentration of total ezetimibe (ezetimibe plus conjugated ezetimibe) decreased by about 30% and the time to maximum plasma concentration of ezetimibe increased from 1.5 to 3 hours.[1] However, these changes would not be expected to be clinically relevant and therefore ezetimibe may be given without regard to the timing of aluminium/magnesium hydroxide-containing antacids.

1. Courtney RD, Kosoglou T, Statkevich P, Boutros T, Maxwell SE, Pember L, Batra VK. Effect of antacid on the pharmacokinetics of ezetimibe. *Clin Pharmacol Ther* (2002) 71, P80.

Ezetimibe + Antiretrovirals

In one study ezetimibe did not appear to interact with HAART including lopinavir and nevirapine.

Clinical evidence, mechanism, importance and management

In a study, 19 HIV-positive patients (18 on stable HAART) who had poorly controlled antiretroviral-associated dyslipidaemia despite the use of pravastatin 20 mg daily, were also given ezetimibe 10 mg daily. After 6, 12, or 24 weeks of concurrent use, there were significant declines in LDL-cholesterol levels, compared to baseline values, irrespective of antiretroviral type (protease inhibitor or NNRTI). No differences were observed in **lopinavir** or **nevirapine** minimum plasma levels measured just before and 12 weeks after ezetimibe introduction. The addition of ezetimibe appeared to be well tolerated.[1] This study suggests that these antiretrovirals do not alter the efficacy of ezetimibe: concurrent use appears to be beneficial.

1. Negredo E, Moltó J, Puig J, Cinquegrana D, Bonjoch A, Pérez-Álvarez N, López-Blázquez R, Blanco A, Clotet B, Rey-Joly C. Ezetimibe, a promising lipid-lowering agent for the treatment of dyslipidaemia in HIV-infected patients with poor response to statins. *AIDS* (2006) 20, 2159–64.

Ezetimibe + Bile-acid binding resins

Colestyramine reduces ezetimibe exposure.

Clinical evidence, mechanism, importance and management

In a study, 8 otherwise healthy hypercholesterolaemic subjects were given colestyramine 4 g twice daily with ezetimibe 10 mg daily for 14 days. Concurrent use decreased the AUC of total ezetimibe (ezetimibe plus glucuronide metabolite) by 56%.[1] The manufacturers suggest that this interaction may reduce the expected additive effects of ezetimibe and colestyramine on LDL-cholesterol reduction, and recommend that ezetimibe should be taken at least 2 hours before or 4 hours after bile-acid binding resins.[2,3] Note that ezetimibe undergoes enterohepatic recirculation, so separating administration may not fully resolve this interaction.

1. Kosoglou T, Statkevich P, Reyderman L, Pember LJC, Maxwell SE, Courtney R, Krishna G, Cutler DL. Effects of selected drugs on exposure to ezetimibe. *Eur Heart J* (2003) 24 (Suppl), 462.
2. Zetia (Ezetimibe). Merck/Schering-Plough Pharmaceuticals. US Prescribing information, July 2009.
3. Ezetrol (Ezetimibe). MSD-SP Ltd. UK Summary of product characteristics, July 2009.

Ezetimibe + Ciclosporin

The levels of ezetimibe may be greatly increased by ciclosporin. Ezetimibe may have a small effect on ciclosporin levels.

Clinical evidence, mechanism, importance and management

(a) Effect on ciclosporin

A randomised, crossover study in 12 healthy subjects found that ezetimibe 20 mg daily for 8 days increased the AUC of a single 100-mg dose of ciclosporin by 15%. The authors noted that it would be difficult to determine the outcome of long-term concurrent use, but the modest effect seen suggested that caution was necessary if the combination was given.[1] However, a 15% increase in the AUC of a narrow therapeutic index drug like ciclosporin is not usually considered to be clinically significant. Furthermore, an efficacy study noted that in 16 renal transplant patients the addition of ezetimibe 10 mg daily had no effect on ciclosporin levels.[2] Nevertheless, the manufacturers of ezetimibe recommend monitoring ciclosporin levels in patients given ezetimibe.[3,4]

(b) Effect on ezetimibe

In one study, 8 stable renal transplant patients taking ciclosporin were given a single 10-mg dose of ezetimibe. When compared with other data from healthy control subjects, the AUC of ezetimibe was found to be 3.4-fold higher in the patients taking ciclosporin.[5]

A case report describes a heart transplant patient taking ciclosporin 100 mg twice daily with atorvastatin 40 mg daily. As his LDL-cholesterol was inadequately lowered by the atorvastatin, and greater doses had not been tolerated due to elevated creatine kinase levels, ezetimibe 10 mg daily was added. His LDL-cholesterol then decreased from 126 mg/dL to 51 mg/dL (target less than 100 mg/dL), and so his dose of ezetimibe was decreased to 5 mg daily.[6] The authors of this case report note that only about 50% of heart transplant patients are able to achieve LDL-cholesterol of less than 100 mg/dL and attribute the effects seen in their patient to an interaction. However, the validity of any interaction has been debated,[7,8] and an efficacy study in which renal transplant patients taking ciclosporin and a statin were given ezetimibe 10 mg daily noted an enhanced but not excessive effect on lipids.[2]

A further patient, with severe renal impairment taking multiple drugs including ciclosporin, had a 12-fold increase in the AUC of ezetimibe.[5]

Therefore, it seems that ciclosporin can greatly raise ezetimibe levels, possibly resulting in an increased effect on lipid reduction. If concurrent use is necessary, until the effects of concurrent treatment are better established, it would seem prudent to monitor the effects on lipid levels, anticipating the need to reduce the dosage of ezetimibe. The authors of the case report cited suggest that, in patients taking ciclosporin, ezetimibe should be started at a dose of 5 mg daily or less, with careful monitoring if the dose is increased.[8]

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2. Kohnle M, Pietruck F, Kribben A, Philipp T, Heemann U, Witzke O. Ezetimibe for the treatment of uncontrolled hypercholesterolemia in patients with high-dose statin therapy after renal transplantation. *Am J Transplant* (2006) 205–8.
3. Ezetrol (Ezetimibe). MSD-SP Ltd. UK Summary of product characteristics, July 2009.
4. Zetia (Ezetimibe). Merck/Schering-Plough Pharmaceuticals. US Prescribing information, July 2009.
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Ezetimibe + Cimetidine

In a study in 12 healthy subjects, cimetidine 400 mg twice daily for 7 days caused a small increase in the peak plasma level and AUC of ezetimibe 10 mg daily, but the overall bioavailability was not affected to a clinically significant extent. The combination was well tolerated.[1] No dosage adjustments therefore seem necessary on concurrent use.

1. Krishna G, Kosoglou T, Ezzet F, Pember L, Statkevich P, Boutros T, Maxwell SE, Basso L, Batra VK. Effect of cimetidine on the pharmacokinetics of ezetimibe. *AAPS PharmSci* (2001) 3; 3.

Ezetimibe + Food

The bioavailability of ezetimibe does not appear to be affected to a clinically significant extent by food.

Clinical evidence, mechanism, importance and management

A study in 18 healthy subjects found that the AUC of a single 10-mg dose of ezetimibe was not significantly affected by a high-fat or non-fat meal, when compared with the fasting state. The maximum plasma concentration of ezetimibe was increased by about 40% by the high-fat meal and slightly reduced by the non-fat meal, but these changes were not considered to be clinically significant due to the considerable overlap in the data. Ezetimibe can therefore be given without regard to meals.[1]

1. Courtney RD, Kosoglou T, Statkevich P, Boutros T, Maxwell SE, Batra VK. Effect of food on the oral bioavailability of ezetimibe. *Clin Pharmacol Ther* (2002) 71, P80.

Ezetimibe + Rifampicin (Rifampin)

Single-doses of rifampicin increase ezetimibe levels without altering its effects on sterols, whereas multiple doses of rifampicin decrease ezetimibe levels and almost totally abolish its effects.

Clinical evidence

In a single-dose study investigating the disposition of ezetimibe, 8 healthy subjects were given ezetimibe 20 mg with rifampicin 600 mg. Rifampicin increased the ezetimibe maximum serum levels about 2.5-fold, without affecting the AUC. The maximum serum levels of ezetimibe glucuronide (the major active metabolite of ezetimibe) were similarly increased, and its AUC was also increased, about twofold. The sterol-lowering effects of ezetimibe were also more rapid in the presence of rifampicin, but the overall effect was unchanged, possibly because ezetimibe and its glucuronide were excreted more rapidly.[1] In another study by the same researchers, subjects were given rifampicin 600 mg daily for 8 days, with a single 20-mg dose of ezetimibe given 12 hours after the last dose of rifampicin. Both the AUC and maximum serum levels of ezetimibe and its glucuronide were *decreased* (AUC decreased by more than 50%) and the effect of ezetimibe on sterols was almost completely abolished.[2]

Mechanism

The raised ezetimibe levels seen in the single-dose study are thought to occur because rifampicin enhances the absorption of ezetimibe, probably by inhibiting intestinal P-glycoprotein, and another transporter protein, MRP2. However, inhibition of MRP2 appears to reduce enterohepatic circulation, which is needed for the long duration of ezetimibe effects, and therefore shortens the sterol-lowering effects of ezetimibe.[1] It seems likely that the balance of these factors is altered when rifampicin is given in multiple doses, which leads to a reduction in the effects of ezetimibe. Other factors are possibly also involved.[2]

Importance and management

Information about the interaction between ezetimibe and rifampicin appears to be limited to these studies, which were primarily designed to investigate ezetimibe disposition. However, it seems likely that the effects of ezetimibe will be reduced in patients who are also given multiple doses of rifampicin. If both drugs are given it would be prudent to closely monitor the effects on lipid levels.

1. Oswald S, Giessmann T, Luetjohann D, Wegner D, Rosskopf D, Weitschies W, Siegmund W. Disposition and sterol-lowering effect of ezetimibe are influenced by single-dose coadministration of rifampin, an inhibitor of multidrug transport proteins. *Clin Pharmacol Ther* (2006) 80, 477–85.
2. Oswald S, Haenisch S, Fricke C, Sudhop T, Remmler C, Giessmann T, Jedlitschky G, Adam U, Dazert E, Warzok R, Wacke W, Cascorbi I, Kroemer HK, Weitschies W, von Bergmann K, Siegmund W. Intestinal expression of P-glycoprotein (*ABCB1*), multidrug resistance associated protein 2 (*ABCC2*), and uridine diphosphate–glucuronosyltransferase 1A1 predicts the disposition and modulates the effects of the cholesterol absorption inhibitor ezetimibe in humans. *Clin Pharmacol Ther* (2006) 79, 206–17.

Fibrates + Bile-acid binding resins

Colestyramine does not alter the pharmacokinetics of clofibrate when both drugs are given at the same time. Similarly colestipol does not alter the pharmacokinetics of clofibrate or fenofibrate, and colesevelam does not alter the pharmacokinetics of fenofibrate. Colestipol can reduce the absorption of gemfibrozil if both drugs are given at the same time, but not if they are given 2 hours apart. A similar interaction may occur between bezafibrate and colestyramine.

Clinical evidence, mechanism, importance and management

(a) Bezafibrate

The manufacturer of bezafibrate recommends that there should be a 2-hour interval between giving an ion-exchange resin [such as **colestyramine**] and bezafibrate, as the absorption of bezafibrate may otherwise be impaired.[1]

(b) Clofibrate

In a study in 24 healthy subjects **colestipol** 10 g daily did not alter the pharmacokinetics of clofibrate 500 mg daily, when both drugs were given at the same time, for 6 days.[2] In a study in 6 patients **colestyramine** 4 g four times daily had no effect on the fasting plasma levels, urinary and faecal excretion, or the half-life of clofibrate 1 g twice daily. In this study, the morning and evening doses of **colestyramine** were taken at the same time as the clofibrate.[3]

(c) Fenofibrate

In a 6-day study in 6 healthy subjects the pharmacokinetics of fenofibrate were not altered to a clinically relevant extent, when **colestipol** 10 g daily was given at the same time as fenofibrate 200 mg in the morning, and **colestipol** 5 g daily was given at the same time as fenofibrate 100 mg in the evening.[4] In a randomised, crossover study 27 healthy subjects took fenofibrate 160 mg with **colesevelam** 3.75 g, four hours before **colesevelam**, or alone. **Colesevelam** caused some slight changes in the pharmacokinetics of fenofibrate when both drugs were given at the same time but this was not considered to be clinically significant.[5]

(d) Gemfibrozil

A study in 10 patients with raised serum cholesterol and triglyceride levels found that if gemfibrozil 600 mg was given alone, 2 hours before or 2 hours after **colestipol** 5 g, the AUCs of gemfibrozil were similar. However, when both drugs were given at the same time, the AUC of gemfibrozil was reduced by about one-third.[6] Another study found that giving gemfibrozil at the same time as **colestipol** enhanced the LDL-lowering effects of both drugs, but tended to mitigate the HDL-raising effects of the gemfibrozil.[7] Combined use is effective, but information is very limited about the clinical importance of the reduction in gemfibrozil bioavailabil-

ity. However, the interaction can be avoided by separating the administration of the two drugs by at least 2 hours.

1. Bezalip Tablets (Bezafibrate). Actavis UK Ltd. UK Summary of product characteristics, October 2009.
2. DeSante KA, DiSanto AR, Albert KS, Weber DJ, Welch RD, Vecchio TJ. The effect of colestipol hydrochloride on the bioavailability and pharmacokinetics of clofibrate. *J Clin Pharmacol* (1979) 19, 721–25.
3. Sedaghat A, Ahrens EH. Lack of effect of cholestyramine on the pharmacokinetics of clofibrate in man. *Eur J Clin Invest* (1975) 5, 177–85.
4. Harvengt C, Desager JP. Lack of pharmacokinetic interaction of colestipol and fenofibrate in volunteers. *Eur J Clin Pharmacol* (1980) 17, 459–63.
5. Jones MR, Baker BA, Mathew P. Effect of colesevelam HCl on single-dose fenofibrate pharmacokinetics. *Clin Pharmacokinet* (2004) 43, 943–50.
6. Forland SC, Feng Y, Cutler RE. Apparent reduced absorption of gemfibrozil when given with colestipol. *J Clin Pharmacol* (1990) 30, 29–32.
7. East C, Bilheimer DW, Grundy SM. Combination drug therapy for familial combined hyperlipidemia. *Ann Intern Med* (1988) 109, 25–32.

Fibrates + Colchicine

Case reports suggest that the concurrent use of fibrates and colchicine can result in rhabdomyolysis or neuromyopathy.

Clinical evidence

A 40-year-old man with chronic hepatitis and nephrotic syndrome, who had been taking colchicine 500 micrograms three times daily uneventfully for 2 to 3 years, started taking **gemfibrozil** 600 mg twice daily. About one month later he presented with muscle pain and dark brown urine, and had an elevated serum creatine kinase level of 3 559 units/L, and he was diagnosed as having rhabdomyolysis. Both drugs were stopped, and he recovered over the following 9 days.[1] Another case report describes neuromyopathy (creatine kinase level 15 084 units/L), in a patient who had been taking **bezafibrate** 400 mg daily with colchicine 3 mg daily for 14 days.[2] This patient was known to have renal impairment.

Mechanism

Colchicine alone can, rarely, cause myopathy. However, it is more common in those given colchicine long term (as in the case with gemfibrozil), in high dose, or in the presence or renal impairment (as in the case with bezafibrate).[2] As the fibrates can also, rarely, cause myopathy, an additive or synergistic effect seems possible.

Importance and management

Although information seems limited to these two cases, the effects seen are known to be associated with both colchicine and the fibrates, so an interaction, all be it rare, seems to be established. It would be prudent to suspect this interaction in any patient presenting with muscle pain or a raised creatine kinase level. The section on 'muscle toxicity', (p.1313), discusses risk factors for myopathy and it would seem prudent to be aware of these when prescribing the combination, as both patients in the cases above had other risk factors for rhabdomyolysis.

1. Atmaca H, Sayarlioğlu H, Külah E, Demircan N, Akpolat T. Rhabdomyolysis associated with gemfibrozil-colchicine therapy. *Ann Pharmacother* (2002) 36, 1719–21.
2. Sugie M, Kuriki A, Arai D, Ichikawa H, Kawamura M. A case report of acute neuromyopathy induced by concomitant use of colchicine and bezafibrate. *No To Shinkei* (2005) 57, 785–90.

Fibrates + Diuretics

Treatment with clofibrate in patients with nephrotic syndrome receiving furosemide has sometimes led to marked diuresis with severe and disabling adverse muscular effects. An isolated report describes rhabdomyolysis in a patient taking bezafibrate and furosemide.

Clinical evidence

(a) Bezafibrate

An isolated report attributed a case of acute renal failure and rhabdomyolysis to treatment with bezafibrate 400 mg daily and **furosemide** 25 mg on alternate days.[1]

(b) Clofibrate

Three patients with hyperlipoproteinaemia secondary to nephrotic syndrome, taking **furosemide** 80 to 500 mg daily, developed severe muscle pain, low lumbar backache, stiffness, and general malaise with pronounced diuresis within 3 days of starting to take clofibrate 1 to 2 g daily. Similarly, a patient taking **bendroflumethiazide** 10 mg daily developed adverse muscle effects within 3 days of starting to take clofibrate 2 g daily. Of these 4 patients, 3 had documented raised serum transaminases or creatine phosphokinase, and 3 were also taking **spironolactone** 75 or 100 mg daily.

Two other patients had raised levels of serum transaminases or creatine phosphokinase while taking clofibrate with **furosemide**.

Further study in 4 of the 6 patients discussed above and 4 healthy controls, found that free serum clofibrate was markedly higher in the patients, and this correlated with low serum albumin. Urinary clofibrate excretion was markedly delayed.[2]

Mechanism

Not understood. The marked diuresis may have been due to competition and displacement of the furosemide by the clofibrate from its plasma protein binding sites. Clofibrate occasionally causes muscle toxicity, which could have been exacerbated by the urinary loss of sodium and potassium and the increase in the half-life of clofibrate. The reason for the rhabdomyolysis attributed to bezafibrate and furosemide is unknown.

Importance and management

The clinical documentation for an interaction between diuretics and fibrates seems to be limited to these reports. In the case of clofibrate and furosemide it appears to be a combination of a drug-drug interaction, with or without a drug-disease interaction (clofibrate with nephrotic syndrome). The authors of one report[2] suggest that serum proteins and renal function should be checked before giving clofibrate to any patient. If serum albumin is low, the total daily dosage of clofibrate should not exceed 500 mg for each 1 g per 100 mL of the albumin concentration. However, note that this guidance is old. The general importance of the isolated case of rhabdomyolysis with bezafibrate and furosemide is expected to be small.

1. Venzano C, Cordì GC, Corsi L, Dapelo M, De Micheli A, Grimaldi GP. Un caso di rabdomiolisi acuta con insufficienza renale acuta da assunzione contemporanea di furosemide e bezafibrato. *Minerva Med* (1990) 81, 909–11.
2. Bridgman JF, Rosen SM, Thorp JM. Complications during clofibrate treatment of nephrotic-syndrome hyperlipoproteinaemia. *Lancet* (1972) ii, 506–9.

Fibrates + Ezetimibe

Fenofibrate and gemfibrozil may increase ezetimibe levels, but ezetimibe does not alter fenofibrate or gemfibrozil pharmacokinetics. The concurrent use of ezetimibe and a fibrate may increase cholesterol excretion into the bile, which increases the risk of gallstone formation.

Clinical evidence

(a) Fenofibrate

In a randomised, crossover study, 18 healthy subjects were given ezetimibe 10 mg daily with fenofibrate 145 mg daily for 10 days, or either drug alone. Ezetimibe did not affect the AUC of fenofibrate, but fenofibrate increased the total AUC of ezetimibe and ezetimibe-glucuronide by 50%.[1] In a randomised, placebo-controlled study, 32 otherwise healthy patients with hypercholesterolaemia were given fenofibrate 200 mg daily, ezetimibe 10 mg daily, both drugs in combination, or placebo daily; each for 14 days. The combination was well tolerated, and resulted in an increased reduction in LDL-cholesterol than that achieved by either ezetimibe or fenofibrate alone. Concurrent use had no effect on the pharmacokinetics of fenofibrate, whereas the AUCs of ezetimibe and its glucuronide metabolite were increased by about 50%.[2] A further efficacy and safety study, in 172 patients with mixed hyperlipidaemia taking ezetimibe 10 mg daily with fenofibrate 160 mg daily for 12 weeks, found that the concurrent use of fenofibrate with ezetimibe did not seem to influence the adverse effects beyond those noted with fenofibrate alone and no cases of rhabdomyolysis or myopathy were recorded. However, both drugs were discontinued in one patient because of cholelithiasis, which was managed with a cholecystectomy.[3] In a 48-week extension phase of this study, the combination of fenofibrate and ezetimibe was well tolerated and more efficacious than fenofibrate alone.[4]

(b) Gemfibrozil

In a randomised, crossover study, 12 healthy subjects were given ezetimibe 10 mg daily with gemfibrozil 600 mg twice daily for 7 days, or either drug alone. Ezetimibe did not affect the AUC of gemfibrozil, but gemfibrozil increased the total AUC of ezetimibe and ezetimibe glucuronide by about 70%.[5]

Mechanism, importance and management

Despite these seemingly favourable results, the manufacturers of ezetimibe state that the safety of combined use with fibrates is not yet established[6,7] and the US manufacturer further says that the concurrent use of ezetimibe and fibrates (other than fenofibrate) is not recommended.[7] This is because both fibrates and ezetimibe may increase cholesterol excretion into the bile, which could promote the production of gallstones.[6,7] The manufacturers recommend that if gallstones or gall bladder disease is suspected in a patient receiving ezetimibe and fenofibrate then the combination should be discontinued.[6,7]

1. Gustavson LE, Schweitzer SM, Burt DA, Achari R, Rieser MJ, Edeki T, Chira T, Yannicelli HD, Kelly MT. Evaluation of the potential for pharmacokinetic interaction between fenofibrate and ezetimibe: a phase I, open-label, multiple-dose, three-period crossover study in healthy subjects. *Clin Ther* (2006) 28, 373–87.
2. Kosoglou T, Statkevich P, Fruchart J-C, Pember LJC, Reyderman L, Cutler DL, Guillaume M, Maxwell SE, Veltri EP. Pharmacodynamic and pharmacokinetic interaction between fenofibrate and ezetimibe. *Curr Med Res Opin* (2004) 20, 1197–1207.
3. Farnier M, Freeman MW, Macdonell G, Perevozskaya I, Davies MJ, Mitchel YB, Gumbiner B, for the Ezetimibe Study Group. Efficacy and safety of the coadministration of ezetimibe with fenofibrate in patients with mixed hyperlipidaemia. *Eur Heart J* (2005) 26, 897–905.
4. McKenney JM, Farnier M, Lo K-W, Bays HE, Perevozkaya I, Carlson G, Davies MJ, Mitchel YB, Gumbiner B. Safety and efficacy of long-term co-administration of fenofibrate and ezetimibe in patients with mixed hyperlipidemia. *J Am Coll Cardiol* (2006) 47, 1584–7.
5. Reyderman L, Kosoglou T, Statkevich P, Pember L, Boutros T, Maxwell SE, Affrime M, Batra V. Assessment of a multiple-dose drug interaction between ezetimibe, a novel selective cholesterol absorption inhibitor and gemfibrozil. *Int J Clin Pharmacol Ther* (2004) 42, 512–18.
6. Ezetrol (Ezetimibe). MSD-SP Ltd. UK Summary of product characteristics, July 2009.
7. Zetia (Ezetimibe). Merck/Schering-Plough Pharmaceuticals. US Prescribing information, July 2009.

Fibrates + Nifedipine

It has been suggested that three cases of rhabdomyolysis occurred because of an interaction between bezafibrate and nifedipine, but it seems more likely that the dose of bezafibrate was too high.

Clinical evidence, mechanism, importance and management

Rhabdomyolysis developed in 4 of 5 patients undergoing CAPD, who were given **bezafibrate** 200 to 400 mg daily for raised cholesterol and triglyceride levels. Of these, 2 patients were also taking nifedipine, and one patient was also taking nifedipine and lovastatin. Raised creatine kinase levels developed within 8 to 16 days of concurrent use, and resolved within 48 hours of stopping the **bezafibrate**. The authors suggest that nifedipine may have competed with **bezafibrate** for metabolism by the cytochrome P450 isoenzyme CYP3A4. They therefore say that patients with renal failure needing a fibrate should avoid taking CYP3A4 substrates.[1] However, note that there appear to be no interactions reported for bezafibrate as a result of CYP3A4 inhibition. Furthermore, the recommended dose for **bezafibrate** in dialysis patients is 200 mg every 72 hours.[2] It therefore appears likely that the high dose, and not an interaction, was responsible for the rhabdomyolysis.

1. Weissgarten J, Zaidenstein R, Fishman S, Dishi V, Michovitz-Koren M, Averbukh Z, Golik A. *Perit Dial Int* (1999) 19, 180–2.
2. Bezalip Tablets (Bezafibrate). Actavis UK Ltd. UK Summary of product characteristics, October 2009.

Fibrates + Probenecid

Plasma clofibrate levels can be approximately doubled by probenecid.

Clinical evidence, mechanism, importance and management

A pharmacokinetic study in 4 healthy subjects taking clofibrate 500 mg every 12 hours found that probenecid 500 mg every 6 hours for 7 days almost doubled the steady-state clofibric acid levels, from 72 mg/L to 129 mg/L, and raised the free clofibric acid levels from 2.5 mg/L to 9.1 mg/L. The suggested reason is that probenecid reduces the renal and metabolic clearance of clofibrate by inhibiting its conjugation with glucuronic acid.[1] The clinical importance of this interaction is uncertain, but it may be prudent to be alert for increased clofibrate adverse effects (e.g. gastrointestinal disturbances, headache, fatigue) and review treatment if these become a problem. There appears to be no information about other fibrates and probenecid.

1. Veenendaal JR, Brooks PM, Meffin PJ. Probenecid-clofibrate interaction. *Clin Pharmacol Ther* (1981) 29, 351–8.

Fibrates + Rifampicin (Rifampin)

Limited evidence suggests that rifampicin can reduce the plasma levels of the active metabolite of clofibrate. In contrast, rifampicin does not appear to affect gemfibrozil pharmacokinetics.

Clinical evidence, mechanism, importance and management

(a) Clofibrate

In a study in 5 healthy subjects, the steady-state plasma levels of the active metabolite of clofibrate, chlorophenoxyisobutyric acid (CIPB), was reduced by 35% after they took rifampicin 600 mg daily for 7 days.[1] This reduction in CIPB levels appears to occur because its metabolism by the liver and/or the kidneys is increased.[1] On the basis of this study it would seem prudent to monitor serum lipid levels of patients taking clofibrate if rifampicin is added, and to increase the clofibrate dosage if necessary. More study is needed to establish this interaction.

(b) Gemfibrozil

In a study in 10 healthy subjects, rifampicin 600 mg daily for 6 days did not significantly affect the pharmacokinetics of gemfibrozil 600 mg.[2] No dosage adjustment therefore seems necessary if both drugs are given.

1. Houin G, Tillement J-P. Clofibrate and enzymatic induction in man. *Int J Clin Pharmacol Ther Toxicol* (1978) 16, 150–4.
2. Forland SC, Feng Y, Cutler RE. The effect of rifampin on the pharmacokinetics of gemfibrozil. *J Clin Pharmacol* (1988) 28, 930.

Fibrates; Ciprofibrate + Ibuprofen

An isolated report describes a patient taking ciprofibrate who developed acute renal failure and rhabdomyolysis, which was, in part, attributed to the use of ibuprofen.

Clinical evidence, mechanism, importance and management

A 29-year-old man with type M hyperlipidaemia[1] who had been taking ciprofibrate for 6 months (current dose 200 mg daily) began to take ibuprofen 200 mg and then 400 mg daily for a painful heel. The pain became general, his urine turned 'muddy', he complained of having a 'stiff body'. After a dose of a contrast medium he developed acute renal failure. His serum creatinine concentration was found to be 647 micromol/L and his creatine kinase was 13 740 units/L. He subsequently made a full recovery (treatment not stated).

The reasons for this reaction are not known, but the authors of the report postulate that the ibuprofen displaced the ciprofibrate from its binding sites, thereby turning a safe dose into a toxic one.[1] However, it should be said that this mechanism of interaction is rarely important on its own, so it seems likely that some other factors may have contributed to what happened. The authors also note that, during the time this patient was treated, the recommended dose of ciprofibrate was reduced from 200 mg daily to 100 mg daily, due to a high incidence of rhabdomyolysis.

This is an isolated case, and an interaction is by no means established. It therefore seems unlikely to be of general relevance.

1. Ramachandran S, Giles PD, Hartland A. Acute renal failure due to rhabdomyolysis in presence of concurrent ciprofibrate and ibuprofen treatment. *BMJ* (1997) 314, 1593.

Fibrates; Clofibrate + Hormonal contraceptives

Combined hormonal contraceptives increase the clearance of clofibrate but the significance of this is unclear.

Clinical evidence, mechanism, importance and management

A comparative study in men, women, and women taking oral combined hormonal contraceptives found that the clearance of clofibrate was increased by 48% in those taking combined oral contraceptives, apparently due to an increase in clofibrate glucuronidation.[1] Another study found that oral combined hormonal contraceptives increased the excretion of clofibric acid glucuronide (the pharmacologically active form of clofibrate) by 25%.[2] None of these studies addressed the question of whether concurrent use significantly reduces clofibrate efficacy, but it would seem prudent to be aware that increases in blood lipid levels could be possible.

1. Miners JO, Robson RA, Birkett DJ. Gender and oral contraceptive steroids as determinants of drug glucuronidation: effects on clofibric acid elimination. *Br J Clin Pharmacol* (1984) 18, 240–43.
2. Liu H-F, Magdalou J, Nicolas A, Lafaurie C, Siest G. Oral contraceptives stimulate the excretion of clofibric acid glucuronide in women and female rats. *Gen Pharmacol* (1991) 22, 393–7.

Fibrates; Fenofibrate + Donepezil

Dropped head syndrome occurred in a patient given donepezil and fenofibrate.

Clinical evidence, mechanism, importance and management

A 77-year-old patient who had been taking fenofibrate for 10 years presented with a dropped head 6 months after starting to also take donepezil. Clinical examination showed muscle weakness and pain with swallowing difficulties, and serum muscle enzymes were increased. Donepezil and fenofibrate were discontinued and the symptoms disappeared with slow normalisation of creatine kinase. It was suggested that this effect occurred because both drugs have a potential action on muscle fibres through different mechanisms.[1]

This appears to be an isolated case report and its general relevance is unknown.

1. Polivka M, Ducros A, Perchaud V, Guittard M, Amarenco P, Mikol J. Drop head syndrome during a combined treatment by donepezil and fenofibrate. *Brain Pathol* (2000) 10, 545.

Fibrates; Gemfibrozil + Antacids

Aluminium-containing antacids can reduce the absorption of gemfibrozil.

Clinical evidence, mechanism, importance and management

A study in patients with kidney and liver disease found that the concurrent use of antacids (**aluminium hydroxide**, **aluminium magnesium silica hydrate**) reduced the maximum plasma levels of gemfibrozil by about 50 to 70%, and reduced its AUC by about 30 to 60%. The precise values are not given in the text. The reasons for these reductions are not known, but it was suggested that the gemfibrozil is adsorbed onto the antacids in the gut. The authors recommend that gemfibrozil is given 1 to 2 hours before antacids.[1] More study is needed to confirm these findings.

1. Knauf H, Kölle EU, Mutschler E. Gemfibrozil absorption and elimination in kidney and liver disease. *Klin Wochenschr* (1990) 68, 692–8.

Fibrates; Gemfibrozil + Interferon alfa

An isolated report describes severe gastrointestinal symptoms and raised liver enzymes potentially due to an interaction between interferon alfa and gemfibrozil.

Clinical evidence

A 43-year-old man receiving interferon alfa-2b and a melanoma vaccine (melanoma theraccine) for malignant melanoma was given gemfibrozil 600 mg twice daily for interferon-induced hypertriglyceridaemia. About one month later, he developed severe gastrointestinal symptoms, consisting of nausea and decreased appetite, and raised liver enzymes. The dose of gemfibrozil was reduced to 300 mg daily and, 3 weeks later, his symptoms and liver enzyme levels had significantly improved. The patient had been receiving the same dose of interferon alfa for 6 months without any adverse effects.

Mechanism

Unknown. The adverse effects seen are known to occur with both gemfibrozil and interferon alfa alone, so it was suggested that what occurred was due to the additive effects of both drugs. However, an effect of gemfibrozil alone, and an interaction involving the melanoma vaccine was not ruled out. Furthermore, the potential for a pharmacokinetic interaction was not examined.[1]

Importance and management

Evidence for an interaction between interferon alfa and gemfibrozil appears to be limited to this case report, and is not established. Nevertheless, as gastrointestinal adverse effects and raised liver enzymes are known adverse effects of both drugs it would be prudent to use some caution if both drugs are given. It seems likely that any interaction would be detected by routine monitoring associated with the use of interferon alfa, but consider increasing the frequency of monitoring in stabilised patients if gemfibrozil is started.

1. Wong S-F, Jakowatz JG, Taheri R. Potential drug-drug interaction between interferon alfa-2b and gemfibrozil in a patient with malignant melanoma. *Clin Ther* (2005) 27, 1942–8.

Fibrates; Gemfibrozil + Psyllium

When 10 healthy subjects took gemfibrozil 600 mg with, or 2 hours after, psyllium 3 g in 240 mL of water, the AUC of gemfibrozil was reduced by about 10%.[1] This reduction is almost certainly too small to be clinically significant. Note that the name psyllium may cover several *Plantago* species including *Plantago ovata*, also known as ispaghula.

1. Forland SC, Cutler RE. The effect of psyllium on the pharmacokinetics of gemfibrozil. *Clin Res* (1990) 38, 94A.

Nicotinic acid (Niacin) + Aspirin

Aspirin reduces the flushing reaction that often occurs with nicotinic acid, but there is some evidence that it can also increase nicotinic acid plasma levels.

Clinical evidence, mechanism, importance and management

Nicotinic acid (a 70 to 100 micrograms/kg per minute infusion over 6 hours) was given to 6 healthy subjects. Two hours after the infusion was started, oral aspirin 1 g was also given. The plasma nicotinic acid levels rose markedly, and its clearance was reduced by 30 to 54%.[1] It was thought that the salicylate competes with nicotinic acid for metabolism by glycine conjugation in the liver so that the clearance of nicotinic acid is reduced, resulting in a rise in its levels. The clinical importance of this effect when aspirin is given to reduce the annoying nicotinic acid flushing reaction[2] is not known. However, as nicotinic acid is titrated upwards, according to efficacy and tolerability, any increase in its levels caused by aspirin is probably naturally accounted for.

1. Ding RW, Kolbe K, Merz B, de Vries J, Weber E, Benet LZ. Pharmacokinetics of nicotinic acid-salicylic acid interaction. *Clin Pharmacol Ther* (1989) 46, 642–7.
2. Jungnickel PW, Maloley PA, Vander Tuin EL, Peddicord TE, Campbell JR. Effect of two aspirin pretreatment regimens on niacin-induced cutaneous reactions. *J Gen Intern Med* (1997) 12, 591–6.

Nicotinic acid (Niacin) + Nicotine

An isolated report describes an unpleasant flushing reaction that developed when a woman taking nicotinic acid started to use nicotine transdermal patches.

Clinical evidence, mechanism, importance and management

A case report describes a woman who had taken nicotinic acid 250 mg twice daily for 3 years without problems, as well as nifedipine, ranitidine, colestyramine and ferrous sulfate. Following laryngectomy for cancer of the larynx, she restarted all of the drugs except the colestyramine and began to use nicotine transdermal patches 21 mg daily to try to give up

smoking. On several occasions, shortly after taking the nicotinic acid, she developed unpleasant flushing episodes lasting about 30 minutes. No further episodes developed when the nicotinic acid was stopped.[1] The reasons are not understood, but flushing is a very common adverse effect of nicotinic acid, and it would seem that in this case the nicotine patch may have been responsible for its emergence. A comment on this report suggests that this reaction may possibly have an immunological basis.[2] Either way, this reaction is more unpleasant than serious.

1. Rockwell KA. Potential interaction between niacin and transdermal nicotine. *Ann Pharmacother* (1993) 27, 1283–4.
2. Sudan BJL. Comment: niacin, nicotine, and flushing. *Ann Pharmacother* (1994) 28, 1113.

Statins + ACE inhibitors

In general the statins do not appear to interact adversely with the ACE inhibitors. An isolated report describes severe hyperkalaemia in a diabetic given lisinopril with lovastatin, and acute pancreatitis has been attributed to the use of lisinopril with atorvastatin.

Clinical evidence, mechanism, importance and management

Retrospective analysis of clinical study data found no evidence that the safety or efficacy of **fluvastatin** was altered by the use of unspecified ACE inhibitors.[1] Another retrospective analysis of clinical study data found no evidence that the safety of **lovastatin** was altered by the use of unspecified ACE inhibitors in 142 patients.[2] Likewise, another study found that the addition of **lovastatin** 20 mg daily to **lisinopril** therapy, for 6 weeks, was well tolerated and there was a substantial reduction in serum cholesterol levels without any clinically relevant effect on the antihypertensive efficacy of lisinopril.[3] However, one study in 70 patients taking **enalapril** or **lisinopril** found that the addition of **lovastatin** or **pravastatin** caused a greater reduction in blood pressure compared with ACE inhibitor alone.[4] A study in healthy subjects found that **simvastatin** had no effect on the pharmacokinetics or ACE-inhibitory effects of **ramipril** or its metabolites.[5] Similarly, no evidence of clinically important adverse interactions was found when **moexipril** was used with **cholesterol-lowering drugs** [not specifically named].[6] An isolated report describes a type I diabetic (receiving insulin) with hypertension and hyperlipidaemia who developed myositis and severe hyperkalaemia (serum potassium 8.4 mmol/L) when given **lovastatin** 20 to 40 mg daily with **lisinopril** 50 mg daily. His serum potassium returned to about 5.5 mmol/L after the **lovastatin** was stopped and the dosage of **lisinopril** lowered (to 20 mg daily). About 3 months later, the patient resumed taking the **lovastatin**, but after only 2 doses he again had severe myositis and hyperkalaemia, which resolved after the **lovastatin** was discontinued. The reason seemed to be a combination of the potassium-sparing effects of the **lisinopril**, the release of intracellular potassium into the blood stream associated with the myositis caused by the **lovastatin**, and a predisposition to hyperkalaemia due to the diabetes and mild renal impairment.[7] Another case report describes the development of acute pancreatitis in a patient who had been taking **lisinopril** 10 mg daily with **atorvastatin** 20 mg daily for 9 months. No other cause for the pancreatitis was identified, and both drugs alone have, rarely, been associated with the development of pancreatitis.[8] These are unusual cases and, given the widespread concurrent use of drugs from these classes they seem unlikely to be of general importance. No special precautions would seem to be necessary if ACE inhibitors are given with statins.

1. Peters TK, Jewitt-Harris J, Mehra M, Muratti EN. Safety and tolerability of fluvastatin with concomitant use of antihypertensive agents. An analysis of a clinical trial database. *Am J Hypertens* (1993) 6, 346S–352S.
2. Pool JL, Shear CL, Downton M, Schnaper H, Stinnett S, Dujovne C, Bradford RH, Chremos AN. Lovastatin and coadministered antihypertensive/cardiovascular agents. *Hypertension* (1992) 19, 242–8.
3. Os I, Bratland B, Dahlöf B, Gisholt K, Syvertsen J-O, Tretli S. Effect and tolerability of combining lovastatin with nifedipine or lisinopril. *Am J Hypertens* (1993) 6, 688–92.
4. Spósito AC, Mansur AP, Coelho OR, Nicolau JC, Ramires JAF. Additional reduction in blood pressure after cholesterol-lowering treatment by statins (lovastatin or pravastatin) in hypercholesterolemic patients using angiotensin-converting enzyme inhibitors (enalapril or lisinopril). *Am J Cardiol* (1999) 83, 1497–9.
5. Meyer BH, Scholtz HE, Müller FO, Luus HG, de la Rey N, Seibert-Grafe M, Eckert HG, Metzger H. Lack of interaction between ramipril and simvastatin. *Eur J Clin Pharmacol* (1994) 47, 373–5.
6. Univasc (Moexipril hydrochloride). Schwarz Pharma. US Prescribing information, June 2008.
7. Edelman S, Witztum JL. Hyperkalemia during treatment with HMG-CoA reductase inhibitor. *N Engl J Med* (1989) 320, 1219–20.
8. Kanbay M, Sekuk H, Yilmaz U, Gur G, Boyacioglu S. Acute pancreatitis associated with combined lisinopril and atorvastatin therapy. *Dig Dis* (2005) 23, 92–4.

Statins + Amiodarone

There is some evidence of a high incidence of myopathy when amiodarone is given with high doses of simvastatin or possibly atorvastatin. Cases of myopathy and rhabdomyolysis have been reported in patients taking amiodarone and a statin.

Clinical evidence

The manufacturers of **simvastatin** note that in an ongoing unpublished clinical study, myopathy (clinically significant muscle pain with a creatine kinase concentration at least 10 times the upper limit of normal[1]) has been reported in 6% of patients receiving simvastatin 80 mg daily with amiodarone.[2,3] There is some evidence from reports to the FDA in the US that the concurrent use of **simvastatin** (or **atorvastatin**) with amiodarone is associated with a higher incidence of muscle toxicity than **pravastatin** with amiodarone. The percentage of reports of muscle, liver, pancreas, and bone marrow toxicity associated with the concurrent use of statins and amiodarone was 1% for **simvastatin**, 0.7% for **atorvastatin**, and 0.4% for **pravastatin**.[4]

A study in 12 healthy subjects found that amiodarone 400 mg daily for 3 days significantly increased the bioavailability of a single 40-mg dose of **simvastatin**; the mean AUC of simvastatin and simvastatin acid were increased by 73% and 78%, respectively. However, amiodarone had no clinically relevant effect on the pharmacokinetics of a single 40-mg dose of **pravastatin**.[5]

A 63-year-old man with diabetes developed diffuse muscle pain with generalised muscular weakness 4 weeks after starting to take **simvastatin** 40 mg daily, and about 2 weeks after starting to take amiodarone (1 g daily for 10 days, then 200 mg daily thereafter). There was a marked increase in creatine kinase, which normalised after stopping both drugs.[6] A 77-year-old man taking multiple medications including amiodarone 100 mg daily and **simvastatin** 20 mg daily, developed increasing lower-extremity pain and darkening of his urine 3 weeks after his simvastatin dose was increased to 40 mg daily. He was diagnosed with rhabdomyolysis secondary to **simvastatin** use,[7] although a later comment suggested that amiodarone could have contributed.[8] Two other cases of rhabdomyolysis in patients taking amiodarone with **simvastatin**[9,10] (one involving clarithromycin)[10] have also been reported. One of these patients had pneumonia,[10] and the other diabetes,[9] both of which have been suggested as risk factors for rhabdomyolysis. Another case report describes rhabdomyolysis in a 72-year-old HIV-positive man taking amiodarone who began taking **simvastatin** 80 mg daily about 3 weeks before his symptoms started. He was also taking atazanavir and delavirdine, so it is difficult to directly attribute this reaction to an interaction with amiodarone.[11]

Asymptomatic elevated serum transaminase levels, which were attributed to an interaction between **rosuvastatin** and amiodarone, have also been reported in a 73-year-old woman with diabetes and hypothyroidism who had recently undergone surgery.[12] However, diabetes, hypothyroidism and the peri-operative period are all associated with an increased risk of myopathy, so this case may not have occurred as a result of an interaction.

Mechanism

Amiodarone is an inhibitor of various cytochrome P450 isoenzymes. Whether it inhibits the metabolism of simvastatin and other extensively-metabolised statins, and thereby increases the risk of muscle toxicity, is not known. Amiodarone alone may sometimes cause myopathy.

Importance and management

An interaction between simvastatin and amiodarone appears to be established. Some manufacturers recommend that the dose of simvastatin should not exceed 20 mg daily in patients also taking amiodarone, unless the clinical benefit is likely to outweigh the increased risk of myopathy and rhabdomyolysis.[2,3] **Lovastatin** is metabolised in the same way as simvastatin, and shares many of its interactions: the manufacturer of lovastatin suggests a maximum dose of 40 mg daily in the presence of amiodarone.[13] Atorvastatin is also metabolised (at least in part) by CYP3A4 inhibitors and the UK manufacturer of atorvastatin suggests that, although interaction studies have not been conducted, amiodarone may possibly result in increased exposure to atorvastatin; lipid levels should be monitored to ensure that the lowest dose necessary of atorvastatin is used.[14]

As a general rule, any patient given simvastatin, lovastatin or atorvastatin should be told to report any signs of myopathy and possible rhabdomyolysis (i.e. otherwise unexplained muscle pain, tenderness or weakness or dark coloured urine). If myopathy does occur, the statin should be stopped immediately. See also 'muscle toxicity', (p.1313), for further guidance on monitoring and risk factors for muscle toxicity.

Rosuvastatin and pravastatin undergo limited metabolism by the cytochrome P450 isoenzyme system and are therefore considered less likely to interact.

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14. Lipitor (Atorvastatin calcium trihydrate). Pfizer Ltd. UK Summary of product characteristics, December 2009.

Statins + Angiotensin II receptor antagonists

Irbesartan, telmisartan and valsartan appear not to alter the pharmacokinetics of simvastatin, simvastatin does not significantly affect the pharmacokinetics of valsartan, fluvastatin does not alter the pharmacokinetics of losartan or its active metabolite, and olmesartan appears not to interact with pravastatin.

Clinical evidence, mechanism, importance and management

(a) Fluvastatin

In a crossover study, 12 healthy subjects were given **losartan** 50 mg in the morning for 7 days, followed by fluvastatin 40 mg at bedtime for 7 days, and then both drugs together for another 7 days. It was found that the steady-state pharmacokinetics of **losartan** and its active metabolite, E-3174, were not significantly altered by fluvastatin.[1] The findings of this study indicate that a clinically relevant pharmacokinetic interaction is unlikely, and no **losartan** dose adjustment is required on combined use.

(b) Pravastatin

The manufacturer of **olmesartan** states that it has no clinically relevant interaction with pravastatin in healthy subjects.[2]

(c) Simvastatin

A study in 12 healthy subjects found that **irbesartan** 300 mg had no significant effect on the pharmacokinetics of a single 50-mg dose of simvastatin, or its metabolite simvastatin acid, and the combination was well tolerated.[3] No clinically relevant interaction was noted when **telmisartan** was given with simvastatin.[4] In a randomised study, 18 healthy subjects were given **valsartan** 160 mg daily with simvastatin 40 mg daily for 7 days. Although some changes occurred in the pharmacokinetics of both drugs these were small and not considered to be clinically relevant.[5]

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Statins + Antacids

Aluminium/magnesium hydroxide antacids cause a moderate reduction in the bioavailability of atorvastatin, pravastatin, and rosuvastatin, but the lipid-lowering efficacy of atorvastatin and pravastatin is not affected.

Clinical evidence, mechanism, importance and management

In a multiple-dose study, 18 patients were given **atorvastatin** 10 mg daily for 15 days with 30 mL of an **aluminium/magnesium hydroxide** antacid *(Maalox TC)* four times daily for a further 17 days. The maximum serum levels and AUC of **atorvastatin** were reduced by 34%, and the absorption rate was also reduced by the antacid. However, the LDL-cholesterol reduction remained the same.[1] In another study, giving an **aluminium/magnesium hydroxide** antacid *(Maalox TC)* 15 mL four times daily, one hour before a single 20-mg dose of **pravastatin**, reduced the bioavailability of **pravastatin** by 28%. This change was less than that seen with food, which did not alter **pravastatin** efficacy.[2] There is therefore no need to avoid the concurrent use of **aluminium/magnesium hydroxide** antacids, nor does the dosage of **atorvastatin** or **pravastatin** need to be raised.

In a randomised study, 14 healthy subjects were given a single 20-mL dose of an **aluminium/magnesium hydroxide** antacid (*Maalox*); either with, or 2 hours after, a single 40-mg dose of **rosuvastatin**. The antacid reduced the AUC of **rosuvastatin** by 54% when given simultaneously, and by 22% when given 2 hours after the **rosuvastatin**.[3] On this basis, the authors concluded that antacids should be given at least 2 hours after **rosuvastatin**, which seems prudent advice.

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3. Martin PD, Schneck DW, Dane AL, Warwick MJ. The effect of a combination antacid preparation containing aluminium hydroxide and magnesium hydroxide on rosuvastatin pharmacokinetics. Curr Med Res Opin (2008) 24, 1231–5.

Statins + Aspirin

Aspirin 324 mg did not significantly affect the pharmacokinetics of a single 20-mg dose of pravastatin.[1] In a study in 73 patients, the addition of atorvastatin or pravastatin did not interfere with the anti-aggregatory effect of aspirin (with clopidogrel).[2] An isolated report describes acute pancreatitis possibly associated with the long-term use of aspirin 100 mg daily and atorvastatin 40 mg daily.[3] This is not expected to be of general relevance.

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Statins + Azoles

Fluconazole modestly increases the levels of fluvastatin, slightly increases the levels of rosuvastatin, but does not affect pravastatin levels. Miconazole would be expected to interact similarly.
Itraconazole causes a marked rise in the serum levels of atorvastatin, lovastatin and simvastatin, a minimal to modest rise in pravastatin levels, but no change in fluvastatin or rosuvastatin

levels. Ketoconazole, posaconazole and voriconazole would be expected to interact similarly.
Case reports describe rhabdomyolysis associated with the use of statins and azoles.

Clinical evidence

(a) Atorvastatin

A case report describes a 76-year-old man taking multiple medications, including long-term **fluconazole** 150 mg daily had his treatment with pravastatin 80 mg daily changed to atorvastatin 40 mg daily due to a lack of response. Within one week he began to feel tired, and 3 weeks later he was admitted to hospital with dyspnoea, myopathy, rhabdomyolysis and renal failure. Although both drugs were stopped he later died of multi-organ failure. The authors considered an interaction between atorvastatin and **fluconazole** as the most likely explanation for the rhabdomyolysis.[1]

Ten healthy subjects were given **itraconazole** 200 mg daily for 5 days with a single 40-mg dose of atorvastatin on day 4. The **itraconazole** increased the AUC of atorvastatin acid and atorvastatin lactone fourfold and threefold, respectively, and increased their half-lives threefold and twofold, respectively. The AUC values of active and total HMG-CoA reductase inhibitors were increased by 60% and 70%, respectively.[2] Raised atorvastatin levels have been seen in other studies with itraconazole.[3,4]

In a review of the FDA spontaneous reports of statin-associated rhabdomyolysis covering the period November 1997 to March 2000, an azole antifungal was potentially implicated in 2 cases of rhabdomyolysis involving atorvastatin.[5]

(b) Fluvastatin

A randomised study in 12 healthy subjects found that **fluconazole** (400 mg on day 1 followed by 200 mg daily for 3 days) increased the AUC of a single 40-mg dose of fluvastatin by 84% and increased its maximum plasma level by 44%. The pharmacokinetics of the **fluconazole** were unaffected.[6] In a similar study, **itraconazole** 100 mg daily for 4 days did not significantly affect the pharmacokinetics of fluvastatin, apart from a small increase in its half-life.[7]

(c) Lovastatin

In a placebo-controlled, crossover study, 12 healthy subjects were given **itraconazole** 200 mg daily for 4 days with a single 40-mg oral dose of lovastatin on day 4. On average the peak plasma concentration and the 24-hour AUC of the lovastatin were increased more than 20-fold. The peak plasma concentration of the active metabolite of lovastatin, lovastatin acid, was increased 13-fold (range 10 to 23-fold) and its AUC was increased 20-fold. The creatine kinase activity of one subject increased 10-fold, but in the other 11 subjects it remained unchanged.[8] Another study also found similar pharmacokinetic changes.[7] Two reports describe rhabdomyolysis in patients taking lovastatin and **itraconazole**,[8,9] which, in one case, developed after 2 weeks of concurrent use.[9]

Another patient who had received lovastatin for several years was diagnosed with hepatitis and rhabdomyolysis about 4 weeks after **ketoconazole** 400 mg three times daily was started.[10]

In a review of the FDA spontaneous reports of statin-associated rhabdomyolysis covering the period November 1997 to March 2000, an azole antifungal was potentially implicated in 6 cases of rhabdomyolysis involving lovastatin.[5]

(d) Pravastatin

A randomised, double-blind study in 12 healthy subjects found that **fluconazole** (400 mg on day 1 followed by 200 mg daily for 3 days) had no significant effect on the pharmacokinetics of a single 40-mg dose of pravastatin.[6]

In a study in 10 healthy subjects, the AUC of a single 40-mg dose of pravastatin was increased by 71% by **itraconazole** 200 mg daily for 4 days, although this did not reach statistical significance.[11] In a similar study, the same dosage of **itraconazole** caused a modest 51% increase in the AUC of pravastatin.[3] In contrast, one study in 104 subjects found that **itraconazole** had no effect on pravastatin pharmacokinetics.[4]

(e) Rosuvastatin

In a study in 14 healthy subjects, **fluconazole** 200 mg daily for 11 days increased the AUC and maximum plasma concentration of a single 80-mg dose of rosuvastatin (given on day 8) by 14% and 9%, respectively. The proportion of circulating active HMG-CoA reductase inhibitors was not affected by **fluconazole**.[12] In similar studies by the same workers, **itraconazole**[13] and **ketoconazole**[14] also had no clinically significant effect on the levels of rosuvastatin.

(f) Simvastatin

An 83-year-old man who had been taking multiple medications including simvastatin 40 mg daily for 2 years was given **fluconazole** 400 mg daily as part of a prophylactic regimen against chemotherapy-induced neutropenic sepsis. After one week he developed generalised muscle weakness and was found to have brown urine and an elevated serum creatine kinase. His medication was stopped, and he was treated with hydration and diuretics, after which his symptoms resolved.[15] A similar case of rhabdomyolysis has been reported in another taking patient simvastatin and **fluconazole**.[16]

In a two-phase crossover study, 10 healthy subjects were given **itraconazole** 200 mg daily or a placebo for 4 days, with a single 40-mg dose of simvastatin on day 4. The peak serum levels of total simvastatin acid (simvastatin acid plus simvastatin lactone) were increased 17-fold and the AUC was increased 19-fold. The maximum serum levels and the AUC of total HMG-CoA reductase inhibitors increased about 3-fold and 5-fold, respectively.[11] Five case reports describe rhabdomyolysis in patients taking simvastatin and **itraconazole**.[17-21] Symptoms started within 2 to 3 weeks of concurrent use.[17,18] Four of these cases were complicated by the presence of ciclosporin, which may also cause rhabdomyolysis with simvastatin (see 'Statins + Ciclosporin', p.1326). Gemfibrozil was also taken in one of these cases.[21] An otherwise healthy subject with hypercholesterolaemia also had an increase in simvastatin serum levels, from 0.5 to 6.5 nanogram/mL within a day of starting **itraconazole** 200 mg daily.[18]

Five cases of rhabdomyolysis have been reported in patients taking simvastatin, which developed between 7 days and 4 weeks after starting **ketoconazole**.[22-25]

In a review of the FDA spontaneous reports of statin-associated rhabdomyolysis covering the period November 1997 to March 2000, an azole antifungal was potentially implicated in 4 cases of rhabdomyolysis involving simvastatin.[5]

Mechanism

Fluconazole (and **miconazole**) inhibits the cytochrome P450 isoenzymes CYP2C9 and has moderate inhibitory effects on CYP3A4, whereas itraconazole and ketoconazole are potent inhibitors of CYP3A4. Consequently they interact differently with the various statins depending on which isoenzymes are involved in the metabolism of the statins in question: this has been shown in several studies.[3,6,7] The more dependent the statin is on metabolism by an isoenzyme, the greater its interaction in the presence of an inhibitor of this isoenzyme. Thus, itraconazole has a greater effect on simvastatin than atorvastatin, and has less effect on fluvastatin than fluconazole. See 'Lipid regulating drugs', (p.1313), for further discussion on the metabolism of the statins, and 'azole antifungals', (p.233), for the enzyme-inhibitory effects of the azoles. Raised statin levels are known to be associated with the development of myopathy and rhabdomyolysis.

Importance and management

An established interaction of clinical importance, which differs depending on the drug pair used. The differing risks and management of the various drug pairs are discussed below. See also 'muscle toxicity', (p.1313), for further guidance on monitoring, and risk factors for muscle toxicity.

1. Lovastatin or Simvastatin. The very marked increases in levels of lovastatin and simvastatin that can occur considerably increase the risk of severe muscle damage and therefore the use of these statins with **itraconazole** or **ketoconazole** should be avoided. If a short course of an azole antifungal is considered essential, the manufacturers suggest temporary withdrawal of the statin.[26-28] The manufacturers of **voriconazole** predict that it will interact similarly, but they suggest that a dose adjustment [reduction] of the statin should be considered during concurrent use.[29,30] Similarly the US manufacturer of **posaconazole** suggests a dose reduction of lovastatin and simvastatin,[31] whereas the UK manufacturer contraindicates concurrent use.[32] **Fluconazole**, particularly in high dose (greater than 200 mg daily), and **miconazole** (including the oral gel, which can be absorbed sufficiently to have enzyme-inhibitory effects), have the potential to interact similarly, but probably to a lesser extent. Nevertheless, cases of rhabdomyolysis have been reported with fluconazole and therefore it would be prudent to monitor for muscle toxicity. Note that the UK manufacturers of miconazole oral gel contraindicate concurrent use.[33]

2. Atorvastatin. Although the increase in the levels of atorvastatin are not as great as those with lovastatin or simvastatin, they are still marked, and concurrent use of an azole antifungal with atorvastatin should only be undertaken if the benefits outweigh the risks.[34] Lower doses of atorvastatin,[34,35] or alternatively (for short courses of **itraconazole** or **ketoconazole**) a temporary suspension of treatment with atorvastatin may be considered.[35] The UK manufacturer of atorvastatin says that in the case of itraconazole (and therefore probably ketoconazole), the maintenance dose of atorvastatin should not exceed 40 mg daily.[35] As a general rule, any patient given atorvastatin with an azole should be told to report any signs of myopathy and possible rhabdomyolysis (i.e. otherwise unexplained muscle pain, tenderness or weakness or dark coloured urine). If myopathy does occur, the statin should be stopped immediately. Note that the US manufacturer of **posaconazole**[31] and the manufacturers of **voriconazole**[29,30] suggest considering a dosage reduction of statins metabolised via CYP3A4, such as atorvastatin, although the UK manufacturer of posaconazole[32] contraindicates concurrent use.

Fluconazole, particularly in high dose (greater than 200 mg daily), and **miconazole** (including the oral gel, which can be absorbed sufficiently to have enzyme-inhibitory effects), have the potential to interact similarly, but probably to a lesser extent. Nevertheless, a case of rhabdomyolysis has been reported with fluconazole and therefore it would be prudent to monitor for muscle toxicity.

3. Fluvastatin. The clinical relevance of the modest changes in fluvastatin levels with **fluconazole** is unclear. Note that in a review of the FDA spontaneous reports of statin-associated rhabdomyolysis for the period November 1997 to March 2000, azole antifungals were not identified as a potentially interacting drug in any of the reports for fluvastatin.[5] However, fluconazole, **miconazole** (and to some extent **voriconazole**) are inhibitors of CYP2C9 by which fluvastatin is metabolised and so a degree of caution seems warranted. Therefore, any patient given fluvastatin and one of these azoles (including miconazole in preparations such as the oral gel, which is can be absorbed in sufficient quantities to have enzyme-inhibitory effects) should be told to report any signs of myopathy and possible rhabdomyolysis (i.e. otherwise unexplained muscle pain, tenderness or weakness or dark coloured urine). If myopathy does occur, the statin should be stopped immediately. Other azoles would not be expected to interact.

4. Pravastatin. The clinical relevance of the modest changes in pravastatin levels with different azole antifungals seems likely to be small, and a clinically significant interaction would not be expected. Note that in a review of the FDA spontaneous reports of statin-associated rhabdomyolysis for the period November 1997 to March 2000, azole antifungals were not identified as a potentially interacting drug in any of the reports for pravastatin.[5]

5. Rosuvastatin. The small increase in rosuvastatin levels with fluconazole is not considered to be clinically relevant. Other azoles would not be expected to interact.

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34. Lipitor (Atorvastatin calcium). Pfizer Inc. US Prescribing information, June 2009.
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Statins + Beta blockers

Propranolol does not cause any clinically relevant changes to the pharmacokinetics of fluvastatin, lovastatin or pravastatin. The concurrent use of simvastatin and talinolol does not affect the pharmacokinetics of either drug. In clinical studies, the safety and efficacy of statins were not altered by the concurrent use of beta blockers as a class.

Clinical evidence, mechanism, importance and management

In a study in 24 healthy subjects, the pharmacokinetics of a single 40-mg dose of **fluvastatin** was not affected by the concurrent use of **propranolol** 40 mg every 12 hours for 3 days.[1] Similarly, the same dose of **propranolol** caused less than an 18% reduction in the AUC of **lovastatin** 20 mg and its metabolites, and modestly reduced the AUC of **pravastatin** 20 mg and its metabolites by 16 to 23%.[2] These changes are small and unlikely to be clinically relevant. In another study in healthy subjects the pharmacokinetics of **simvastatin** and **talinolol** were not affected during the concurrent use of these drugs.[3]

Retrospective analysis of clinical study data found no evidence that the safety or efficacy of **fluvastatin** was altered by the use of beta blockers (unspecified).[4] Similarly, in another analysis, there was no evidence that the safety or efficacy of **lovastatin** was altered by cardioselective beta blockers (primarily **atenolol**, **metoprolol** and **labetalol**) or non-selective beta blockers (primarily **propranolol**, **nadolol** and **timolol**).[5]

No special precautions would seem to be necessary if beta blockers are given concurrently with statins.

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Statins + Bile-acid binding resins

Although colestyramine and colestipol reduce plasma fluvastatin and pravastatin levels, the overall total lipid-lowering effect is increased by concurrent use. Colestipol appears to interact with atorvastatin similarly. Colesevelam appears not to interact with atorvastatin, lovastatin or simvastatin.

Clinical evidence

(a) Atorvastatin

A study in which atorvastatin 40 mg daily and **colestipol** 10 mg twice daily were given concurrently found that although the serum levels of atorvastatin were reduced by about 25%, the total reduction in the LDL-cholesterol levels was greater than when each drug was given alone.[1,2]

(b) Fluvastatin

In a study in 19 healthy subjects, **colestyramine** 8 g given at the same time as fluvastatin 20 mg decreased the AUC and the maximum plasma levels of fluvastatin by 89% and 96%, respectively. When the fluvastatin was given 2 hours after the **colestyramine**, the AUC and the maximum plasma levels of fluvastatin were reduced by just over 50%.[3] In another study in 20 healthy subjects, the AUC and maximum plasma levels of fluvastatin were reduced by 51% and 82%, respectively, when fluvastatin was taken 4 hours after **colestyramine** 8 g and a meal.[3]

Despite these marked reductions in fluvastatin bioavailability, other studies in large numbers of hypercholesterolaemic patients have found that the concurrent use of **colestyramine** and fluvastatin actually has additive lipid-lowering effects.[3,4] In the first of these studies, fluvastatin was given 4 hours after **colestyramine**,[3] but the other study did not indicate whether or not doses were separated.[4]

(c) Lovastatin

A crossover study in 22 healthy subjects found that the pharmacokinetics of lovastatin 20 mg given with a meal were not significantly affected when **colesevelam** 2.25 g was given at the same time.[5]

(d) Pravastatin

In a randomised study, 33 patients with primary hypercholesterolaemia were given pravastatin 5, 10, or 20 mg twice daily before their morning and evening meals for 4 weeks, and then for a further 4 weeks they also took **colestyramine** 24 g daily. The **colestyramine** was taken at least an hour after the pravastatin. Despite the fact that **colestyramine** reduced the bioavailability of pravastatin by 18 to 49%, the reduction in blood lipid levels was enhanced by concurrent use.[6] A related study in 18 subjects found that **colestyramine** reduced the bioavailability of pravastatin by about 40% when given at the same time, but only small and clinically insignificant pharmacokinetic changes occurred when the pravastatin was given one hour before, or 4 hours after the **colestyramine**.[7] Similarly, a multicentre study in 311 patients found that the combined use of pravastatin 40 mg daily and **colestyramine** 12 g daily was highly effective in the treatment of hypercholesterolaemia. The **colestyramine** was taken at least one hour after the pravastatin.[8]

In a study in 18 subjects, **colestipol** reduced the bioavailability of pravastatin by about 50%, but no reduction in bioavailability was seen when pravastatin was given 1 hour before **colestipol** and a meal.[7]

Mechanism

It seems probable that these bile-acid binding resins bind with statins in the gut and thereby reduce the amount of statin available for absorption.

Importance and management

The interactions of colestipol and colestyramine with the statins are established but of only relatively minor importance. Although colestipol modestly decreased atorvastatin bioavailability it appears that atorvastatin may be used with bile acid-binding resins for additive effect. Similarly, despite the reduction in the bioavailability of pravastatin caused by colestyramine or colestipol, the overall lipid-lowering effect is increased by concurrent use.[6,8] The effects of the interaction can be minimised by separating their administration as described above. This can be achieved by taking the colestyramine or colestipol with meals, and the pravastatin at bedtime. Likewise, any interaction between fluvastatin and colestyramine can be minimised by taking fluvastatin at least one hour before or 4 hours after colestyramine.

There would appear to be no reason for avoiding concurrent use of lovastatin and colesevelam. The manufacturer of colesevelam says that its concurrent use with atorvastatin, lovastatin or simvastatin in clinical studies shows that colesevelam can be dosed at the same time as the statin.[9]

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Statins + Bosentan

Bosentan modestly reduces the AUC of simvastatin and its active metabolite, which could lead to a reduction in simvastatin efficacy. Other statins metabolised by the same route as simvastatin may be similarly affected.

Clinical evidence

In a three-way, crossover study, 9 healthy subjects were given either bosentan 125 mg twice daily for 5.5 days, simvastatin 40 mg daily for 6 days, or both treatments together. Simvastatin had no effect on the pharmacokinetics of bosentan, but bosentan reduced the AUC of simvastatin and its β-hydroxyacid metabolite by 34% and 46%, respectively.[1]

Mechanism

Bosentan is known to be a mild inducer of the cytochrome P450 isoenzyme CYP3A4, which is involved in the metabolism of simvastatin. Induction of simvastatin metabolism may have led to the reduced levels seen.

Importance and management

Evidence is limited to this study, but the interaction found is in line with the way both drugs are known to interact. A 40% reduction in the AUC of simvastatin is potentially clinically significant. If bosentan and simvastatin are used concurrently it would seem prudent to monitor the outcome to ensure that simvastatin is effective. Other statins metabolised by the same route as simvastatin (that is, predominantly by CYP3A4) are likely to interact similarly, and the same precautions described for simvastatin would seem appropriate. See 'Lipid regulating drugs', (p.1313), for more information on the metabolism of the statins. **Atorvastatin** seems unlikely to be affected to the same extent, but bear this interaction in mind if lipid-lowering targets are not met.

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Statins + Calcium-channel blockers

Marked rises in statin plasma levels have been seen when lovastatin or simvastatin were given with diltiazem, and when simvastatin was given with verapamil. Isolated cases of rhabdomyolysis have occurred as a result of these interactions. However, overall, it seems that problems with combinations of statins and calcium-channel blockers (particularly the dihydropyridine-type) are rare, especially if the lowest possible dose of statin is used.

Clinical evidence

(a) Atorvastatin

1. Amlodipine. One manufacturer reports that amlodipine 10 mg increased the AUC of an 80-mg dose of atorvastatin by 18%,[1] which would not be expected to be clinically relevant. A randomised study involving 1660 patients with hypertension and dyslipidaemia, found that various combinations of amlodipine 5 or 10 mg, atorvastatin 10, 20, 40, or 80 mg or placebo, for 8 weeks, were well tolerated and without adverse pharmacodynamic interaction. Atorvastatin did not modify the effect of amlodipine on systolic blood pressure, and amlodipine did not adversely affect the overall lipid-lowering capacity of atorvastatin. In addition, all treatments were well tolerated and the occurrence of adverse effects or laboratory abnormalities was similar in patients given both drugs and patients receiving either amlodipine or atorvastatin alone.[2]

2. Diltiazem. One manufacturer reports that diltiazem 240 mg increased the AUC of a 40-mg dose of atorvastatin by 51%.[1] A 60-year-old man taking atorvastatin 20 mg daily developed rhabdomyolysis 3 weeks after diltiazem was started.[3] Another similar case has also been reported.[4]

3. Verapamil. A study in 12 healthy subjects found that atorvastatin increased the AUC of verapamil by 43%.[5]

(b) Fluvastatin

A retrospective study of the effects of antihypertensives on the efficacy of fluvastatin found that the concurrent use of unspecified calcium-channel blockers did not significantly affect the safety or lipid-lowering effects of fluvastatin, although there was a trend towards enhanced lowering of triglycerides.[6]

(c) Lovastatin

A retrospective study of the effects of lovastatin and antihypertensive medication found that when calcium-channel blockers (**diltiazem**, **nifedipine** or **verapamil**) were used in combination with lovastatin there was an additional 3 to 5% lowering in the LDL-cholesterol, which was of marginal significance.[7] Another study found that the use of lovastatin 20 mg daily with **nifedipine** for 6 weeks was well tolerated and there was a substantial reduction in serum cholesterol levels without any impact on the antihypertensive efficacy of nifedipine.[8]

Pharmacokinetic studies have shown that oral **diltiazem** increases the AUC and maximum serum levels of lovastatin about fourfold.[9,10] In another study, in 12 healthy subjects, lovastatin 20 mg and **isradipine** 5 mg were given alone or together for 5 days. **Isradipine** reduced the AUC of lovastatin by 40%, in males but not females.[11]

(d) Pravastatin

A study in 10 healthy subjects found that sustained-release **diltiazem** 120 mg twice daily had no effect on the pharmacokinetics of a single 20-mg dose of pravastatin.[9] Similarly, a study in 15 healthy subjects found that extended-release **verapamil** 480 mg daily for 3 days did not affect the pharmacokinetics of pravastatin 40 mg daily.[12]

(e) Simvastatin

1. Amlodipine. In a study in 8 patients taking simvastatin 5 mg daily, the addition of amlodipine 5 mg daily for 4 weeks increased the maximum levels and AUC of simvastatin by a modest 40% and 30%, respectively, without affecting the lipid profiles of the patients.[13]

2. Diltiazem. In a study, 10 healthy subjects were given sustained-release diltiazem 120 mg twice daily for 2 weeks followed by a single 20-mg dose of simvastatin. Diltiazem caused about a fivefold increase in the simvastatin AUC, a fourfold increase in its maximum serum levels, and a 2.5-fold increase in its half-life.[14] A further study in 11 subjects found that the concurrent use of simvastatin 5 mg daily and diltiazem 30 mg three times daily resulted in a twofold increase in the AUC and maximum plasma level of simvastatin acid (the active metabolite of simvastatin), and a 20% decrease in the AUC and maximum plasma level of diltiazem.[15]

The clinical relevance of the diltiazem interaction has been demonstrated in a 53-year-old man, who developed rhabdomyolysis 3 months after diltiazem 30 mg four times daily was added to established treatment with simvastatin 40 mg daily. Both drugs were discontinued and he recovered over the following 10 days.[16] Other similar cases have also been reported.[4,17,18]

3. Lacidipine. In a randomised, crossover study, simvastatin 40 mg daily was given for 8 days, with or without lacidipine 4 mg daily. Lacidipine raised the AUC of simvastatin by 35%.[19]

4. Verapamil. A study in which 12 subjects were given verapamil 80 mg three times daily, found a 4.6-fold increase in the AUC of simvastatin and a 2.8-fold increase in the AUC of simvastatin acid (the active metabolite of simvastatin). In addition, there was a 2.6-fold increase in the maximum serum levels of simvastatin, and about a twofold increase in its half-life.[20] Similarly, a study in 12 healthy subjects found that extended-release verapamil 480 mg daily for 3 days caused a fivefold increase in the maximum serum levels of simvastatin 40 mg, and about a fourfold increase in its AUC.[12]

The clinical relevance of the verapamil interaction has been demonstrated in a 63-year-old man, who developed rhabdomyolysis about 1 month after extended-release verapamil 240 mg daily was added to established treatment with simvastatin 40 mg daily and ciclosporin. Verapamil and simvastatin were discontinued and he recovered over the following 14 days.[21]

Mechanism

Diltiazem and verapamil inhibit the cytochrome P450 isoenzyme CYP3A4, which is responsible for the metabolism of lovastatin, simvastatin and to an extent, atorvastatin. Therefore concurrent use of these drugs results in an increase in the levels of the statin. One study found that oral, but not intravenous diltiazem interacts, suggesting that it is CYP3A4 in the gut wall that is the site of the interaction.[22] Isradipine and lovastatin are both metabolised by CYP3A4, and therefore the modest interaction may have occurred as a result of competition for metabolism. A similar mechanism probably accounts for the modest interaction between simvastatin and lacidipine or amlodipine. Note that fluvastatin, pravastatin and **rosuvastatin** are not significantly metabolised by CYP3A4 and so are less likely to interact with diltiazem or verapamil. See 'Lipid regulating drugs', (p.1313), and 'Calcium-channel blockers', (p.1025), for more information about the way these groups of drugs are metabolised.

Importance and management

Interactions between the statins and calcium-channel blockers are established, but the effects are not usually clinically relevant. Even with those pairs of drugs where the increases in plasma levels are quite large (such as when simvastatin is given with diltiazem or verapamil) problems seem to be very rare. Indeed an analysis of the 4S study and the Heart Protection Study (which used maximum simvastatin doses of 40 mg) found no evidence that the concurrent use of a calcium-channel blocker increases the risk of myopathy.[23] However, with higher doses of simvastatin, the risk of myopathy is increased with concurrent verapamil and possibly diltiazem: the incidence of myopathy with an 80-mg dose of simvastatin appears to be doubled by verapamil and diltiazem, but is still low, at 1%.[24] Therefore, although concurrent use need not be avoided, it has been suggested that treatment with a statin metabolised by CYP3A4 (see 'statins', (p.1313)) in a patient taking diltiazem or verapamil should be at the lowest possible dose; in patients already taking statins, the dose of the statin may need to be considerably reduced.[20]

The manufacturers of simvastatin and lovastatin recommend the following dose restrictions:

- maximum dose of 40 mg of simvastatin in the presence of diltiazem,[24]
- maximum dose of 20 mg of simvastatin in the presence of verapamil,[24,25]
- maximum dose of 40 mg of lovastatin in the presence of verapamil.[26]

Fluvastatin, pravastatin and rosuvastatin appear less likely to interact with diltiazem or verapamil. See also 'muscle toxicity', (p.1313), for further guidance on monitoring and risk factors for muscle toxicity.

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Statins + Carbamazepine

Carbamazepine dramatically reduces simvastatin levels. Other statins metabolised in the same way as simvastatin may be similarly affected.

Clinical evidence

In a randomised, crossover study, 12 healthy subjects were given carbamazepine 200 mg daily for 2 days, then 300 mg twice daily for 12 days, with a single 80-mg dose of **simvastatin** 12 hours after the last dose of carbamazepine. The AUC and maximum serum levels of **simvastatin** were reduced by 75% and 68%, respectively, and the AUC and maximum serum levels of simvastatin acid (the active metabolite of **simvastatin**) were reduced by 82% and 69%, respectively.[1]

Mechanism

Carbamazepine is a known potent inducer of the cytochrome P450 isoenzyme CYP3A4 by which simvastatin is metabolised. Carbamazepine therefore increases simvastatin metabolism, leading to reduced levels.

Importance and management

Although this appears to be the only study, the effects of concurrent use are consistent with both the way carbamazepine interacts with many other CYP3A4 substrates and the way simvastatin interacts with other CYP3A4 inducers. The effects of simvastatin are likely to be greatly reduced with concurrent use and a dose increase seems likely to be necessary. Monitor concurrent use to check simvastatin is effective. Statins metabolised by the same route as simvastatin may also have their levels reduced, at least modestly. In contrast, it seems unlikely that other statins that are not metabolised by CYP3A4, will interact, and they may therefore be preferable. However, this needs confirmation. See 'statins', (p.1313), for more information on the metabolism of the various statins.

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Statins + Ciclosporin

Ciclosporin can cause marked rises in the plasma levels of atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin, and for some of the statins this has led to the development of serious myopathy (rhabdomyolysis) and renal failure. The plasma levels of ciclosporin appear not to be affected by fluvastatin, lovastatin, pravastatin, or rosuvastatin, but some moderate changes in ciclosporin levels have been seen when atorvastatin or simvastatin were given.

Clinical evidence

(a) Atorvastatin

1. Effect on ciclosporin. In a study of 10 patients taking ciclosporin following a kidney transplant, 4 had increases in their trough ciclosporin levels of between 26 and 54% when atorvastatin 10 mg was added, necessitating a dosage reduction of ciclosporin. No changes were seen in 6 other patients, and the incidence of adverse effects was no greater than in a control transplant group not given atorvastatin.[1] When atorvastatin 10 mg daily was given to 21 renal transplant patients taking ciclosporin, the maximum serum levels of ciclosporin generally decreased (by a mean of 13.5%). However, 4 patients needed a *decrease* in their ciclosporin dose and one patient needed an increase.[2] A follow-up study suggested that atorvastatin does not, on average, affect ciclosporin pharmacokinetics in renal transplant patients, although the influence of atorvastatin on the ratio between ciclosporin and a major metabolite (AM9) showed large interindividual variability.[3] Another study suggested that atorvastatin causes a negligible increase in ciclosporin levels in liver transplant patients.[4]

2. Effect on atorvastatin. In an open study the concurrent use of atorvastatin 10 mg daily with ciclosporin resulted in a more than sevenfold increase in atorvastatin levels (data calculated from figures), when compared with historical controls not taking ciclosporin.[2] A further analysis of this study has been reported elsewhere,[5] suggesting that ciclosporin may cause an 8.7-fold increase in the AUC of atorvastatin acid. A pharmacokinetic study in 13 healthy subjects found that the short-term use of ciclosporin (2 doses 12 hours apart) increased the AUC of atorvastatin acid 15-fold.[6]
A case of rhabdomyolysis has been described in a woman who took atorvastatin 10 mg daily and ciclosporin for 2 months. She had also been taking modified-release diltiazem 240 mg daily.[7] In a review of the FDA spontaneous reports of statin-associated rhabdomyolysis covering the period November 1997 to March 2000, ciclosporin was potentially implicated in 5 cases of rhabdomyolysis involving atorvastatin.[8]

(b) Fluvastatin

1. Effect on ciclosporin. When fluvastatin 20 mg daily was given to 16 patients taking ciclosporin 21 to 103 months after renal transplantation, no significant changes were seen in their ciclosporin levels.[9,10] Similar results were seen in other studies, one using fluvastatin 20 mg twice daily,[11] and one in 17 renal transplant recipients taking extended-release fluvastatin 80 mg daily.[12]

2. Effect on fluvastatin. In a double-blind study, 52 heart transplant patients taking ciclosporin were randomised to receive fluvastatin 40 mg daily for 1 year, or placebo. Fluvastatin had a positive effect on lipid profiles, and, although creatine phosphokinase levels rose, the maximum reached was 4.5 times normal, which did not require cessation of the fluvastatin and normalised without intervention. There was no increase in the reported rate of myalgia, and no patients developed rhabdomyolysis.[13]
In 20 renal transplant patients taking ciclosporin, the AUC and maximum serum concentration of fluvastatin 20 mg daily were found to be about 94% and 30% higher, respectively, than in historical control patients not taking ciclosporin.[14] Results from another study in renal transplant patients taking ciclosporin and fluvastatin 80 mg found a twofold increase in fluvastatin exposure, when compared with historical data.[12] Similarly, the AUC and maximum serum concentration of fluvastatin 40 mg daily for 4 weeks were threefold and sixfold greater in heart transplant patients taking ciclosporin than in healthy subjects not given ciclosporin.[15] One study reported 2 patients with mild myalgia without creatine phosphokinase rises, and a patient with elevated creatine phosphokinase without myalgia, when fluvastatin 20 mg daily was given with ciclosporin.[14] Further studies suggest that concurrent use does not affect creatine phosphokinase or result in additional adverse effects.[9-11]

(c) Lovastatin

1. Effect on ciclosporin. Ciclosporin and creatine phosphokinase levels were not significantly changed in 6 renal transplant patients taking ciclosporin and lovastatin (10 mg for 8 weeks, then 20 mg for 12 weeks).[16] Similar results were found in another study.[17]

2. Effect on lovastatin. In 6 patients taking ciclosporin the plasma levels of lovastatin 10 to 20 mg daily were about the same as those seen in healthy subjects taking lovastatin 40 mg alone (i.e. the levels were increased up to fourfold by ciclosporin).[16] In another study in 21 renal transplant patients taking ciclosporin, the maximum serum levels and AUC of lovastatin 20 mg daily were 40 and 47% higher, respectively, after 28 days of concurrent use than on day 1 (suggesting accumulation) and were estimated to be 20-fold higher than values reported in healthy subjects not taking ciclosporin.[18] A further study found that the AUC of lovastatin was five times greater in patients taking ciclosporin than in patients not taking ciclosporin, irrespective of whether the patients had received a transplant or were receiving other immunosuppressants.[19]

There are at least 9 documented cases of rhabdomyolysis, often resulting in acute renal failure, in patients taking ciclosporin and lovastatin.[20-24] In each of these cases the patient was taking lovastatin 40 to 80 mg daily. Several other studies suggest that this interaction may be dose-related. In one study, 15 patients taking ciclosporin were given lovastatin 20 mg daily without problem, but 4 of 5 other patients, who were given lovastatin 40 to 80 mg, daily developed rhabdomyolysis, which was associated with renal failure in two of them.[25] In a further study 24 patients were given lovastatin 10 or 20 mg daily in addition to ciclosporin. Of the 12 receiving the 20-mg dose, 7 developed either myalgia and muscle weakness or raised creatine phosphokinase levels, but only one patient from the 10-mg group did.[26] The incidence of myopathies with lovastatin is about 0.1 to 0.2%,[18] but in the presence of ciclosporin the incidence is said to be as high as 30%.[27]

(d) Pravastatin

1. Effect on ciclosporin. Several studies have shown no significant change in ciclosporin levels in patients also taking pravastatin.[18,28,29]

2. Effect on pravastatin. A study in 19 paediatric and adolescent cardiac transplant patients (mean age 12.1 years) found that triple immunosuppressant therapy (17 patients taking ciclosporin) raised the maximum levels and AUC of pravastatin 10 mg daily for 8 weeks by about eightfold and tenfold, respectively, when compared with control subjects not receiving immunosuppressants. There was extremely large intersubject variation in the pravastatin AUC and maximum levels.[30] Similar results have been found in other studies in adults.[31,32] Although a study in patients taking ciclosporin found that the AUC of pravastatin 20 mg daily did not differ between day 1 and day 28 of therapy (suggesting no accumulation), the AUC values were estimated to be five to sevenfold higher than in patients not taking ciclosporin.[18]

A report describes asymptomatic rhabdomyolysis in a heart transplant patient taking ciclosporin, who had taken pravastatin 40 mg daily for more than 3 years.[33] In a review of the FDA spontaneous reports of statin-associated rhabdomyolysis covering the period November 1997 to March 2000, ciclosporin was potentially implicated in 2 cases of rhabdomyolysis involving pravastatin.[8]

Several studies have shown no rises in creatine phosphokinase levels,[28,34,35] and no increase in adverse effects[18,34,36] when pravastatin in doses of 10 to 40 mg daily was given with ciclosporin.

(e) Rosuvastatin

In an open-label study 10 stable heart transplant patients taking ciclosporin were given rosuvastatin 10 mg daily for 10 days. When compared to healthy historical controls, the rosuvastatin maximum levels and $AUC_{0\text{-}24}$ were found to have been increased by 10.6-fold and 7.1-fold, respectively. Rosuvastatin had little effect on ciclosporin levels.[37]

(f) Simvastatin

1. Effect on ciclosporin. A study found that the ciclosporin levels of 12 renal transplant patients fell from 334 to 235 micrograms/L after simvastatin 5 to 15 mg daily was added.[38] A retrospective study by the same authors confirmed these results in 12 patients.[38] In contrast, a single-dose pharmacokinetic study suggested that simvastatin increases the maximum levels and AUC of ciclosporin by a modest 8% and 13%, respectively.[39] Another study reported no significant change in ciclosporin levels over a period of 9 months in patients also taking simvastatin 10 mg daily, and no clinical signs of myopathy were observed.[29]

2. Effect on simvastatin. A group of 20 heart transplant patients were given simvastatin 10 mg daily and ciclosporin over a period of 4 months. The plasma levels of simvastatin acid were at least 6 times higher in 7 patients taking ciclosporin than in 7 control patients not taking ciclosporin. Significant changes in ALT levels and creatine kinase were seen, but the combination was well tolerated.[40] Another study, comparing 5 renal transplant patients taking ciclosporin and simvastatin 20 mg daily with 5 renal transplant patients not given ciclosporin, found that the AUC and maximum serum levels of simvastatin were 2.5-fold and 2-fold greater, respectively, in the patients taking ciclosporin.[41] In a third study, low-dose simvastatin 10 mg daily was well tolerated over 8 months in heart transplant patients receiving ciclosporin.[42]

There are at least 6 documented cases of rhabdomyolysis,[43-47] one of which was fatal,[44] in patients given ciclosporin and simvastatin. A further case of rhabdomyolysis occurred in a patient taking ciclosporin and amlodipine about 2 months after his statin was changed from atorvastatin 20 mg daily to simvastatin 40 mg daily.[48] Yet another case has been reported in a patient who had received ciclosporin and a statin (fluvastatin then pravastatin) for several years. Onset of muscle pain occurred about 2 months after simvastatin was substituted for pravastatin and 2 weeks after verapamil was added to his treatment : the effect was attributed to multiple drug interactions[49] (see also 'Statins + Calcium-channel blockers', p.1324). In a review of the FDA spontaneous reports of statin-associated rhabdomyolysis covering the period November 1997 to March 2000, ciclosporin was potentially implicated in 31 cases of rhabdomyolysis involving simvastatin.[8]

Mechanism

Complex and not fully understood. Ciclosporin appears to cause an increased systemic exposure to statins regardless of their main route of metabolism. However, the more marked rises in statin levels and/or toxicity (rhabdomyolysis) may occur because ciclosporin and some statins (e.g. lovastatin and simvastatin) compete for the same metabolising enzyme, the cytochrome P450 isoenzyme CYP3A4. The extent of the interaction seems to depend on the relative affinities of the different statins for this isoenzyme, and also on whether they can be metabolised by alternative pathways. P-glycoprotein and other transporter proteins such as the organic anion transporting polypeptide (OATP) 1B1 also have a part to play, especially in the raised statin levels seen with atorvastatin, and rosuvastatin. See 'Lipid regulating drugs', (p.1313), for more information about the metabolism of the statins.

Importance and management

The interacting effect of ciclosporin on the statins is well documented, well established and clinically important. Concurrent use need not be avoided but it should be very well monitored, a precautionary recommendation being to start (or reduce) the statin to the lowest daily dose appropriate to the patient's condition.[50,51]

For patients taking ciclosporin, the manufacturers of **atorvastatin**[52,53] and **simvastatin**[54,55] suggest that the statin dose should not exceed 10 mg daily, and the manufacturer of **lovastatin**[50] suggests its dose should not exceed 20 mg daily. The UK manufacturer of **pravastatin** suggests a starting dose of 20 mg.[51] The US manufacturer of **rosuvastatin** states that the dose of rosuvastatin should be limited to 5 mg daily,[56] whereas the UK manufacturer contraindicates concurrent use.[57]

Any patient given ciclosporin with a statin should be told to report any signs of myopathy and possible rhabdomyolysis (i.e. otherwise unexplained muscle pain, tenderness or weakness or dark coloured urine). If myopathy does occur, withdrawing the statin has been shown to resolve the symptoms. See also 'muscle toxicity', (p.1313), for further guidance on monitoring and risk factors for muscle toxicity.

Alterations in ciclosporin levels with the statins are generally small and seem likely to be identified by routine ciclosporin monitoring. However, note that, of the statins, simvastatin, and possibly atorvastatin have somewhat larger effects, and an increase in the frequency of ciclosporin monitoring may be desirable if these statins are used.

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Statins + Cilostazol

Cilostazol may increase the plasma levels of lovastatin (and therefore probably simvastatin).

Clinical evidence

In a study in 13 healthy subjects, a single 80-mg oral dose of **lovastatin** was given before, and then on the final day of a 7-day treatment period with cilostazol 100 mg twice daily. The AUCs of **lovastatin** and its beta-hydroxy acid metabolite were increased by about 60% and 70%, respectively, by cilostazol, but the maximum plasma levels were unaffected.[1] At the end of this study (day 9), 12 subjects were given **lovastatin** 80 mg with a larger 150-mg dose of cilostazol. It was found that the maximum level and the AUC of the **lovastatin** metabolite were increased about twofold, suggesting that larger cilostazol doses may have a greater effect.[1] Lovastatin decreased the absorption of cilostazol by about 15%, but this was not considered to be clinically relevant.[1]

Mechanism

Lovastatin is metabolised by the cytochrome P450 isoenzyme CYP3A4 and it would appear that cilostazol can modestly inhibit this enzyme. **Simvastatin** is metabolised by the same route as lovastatin, and may therefore be expected to interact similarly.

Importance and management

Evidence for an interaction between cilostazol and lovastatin appears to be limited to this one study. The increases in lovastatin levels described here are much lower than those seen with moderate CYP3A4 inhibitors (e.g. see 'Statins + Calcium-channel blockers', p.1324) but the authors of the study still suggest that the dose of lovastatin may need to be reduced if cilostazol is also taken. This appears over-cautious. However, it may be prudent to remind patients to report any signs of myopathy and possible rhabdomyolysis (i.e. otherwise unexplained muscle pain, tenderness or weakness or dark coloured urine), especially if other risk factors are present. Similar advice should probably be given with concurrent use of cilostazol and simvastatin. If myopathy does occur, the statin should be

stopped immediately. See also 'muscle toxicity', (p.1313), for further guidance on monitoring, and risk factors for muscle toxicity.

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Statins + Colchicine

Several case reports describe myopathy or rhabdomyolysis in patients given colchicine with atorvastatin, fluvastatin, pravastatin or simvastatin. It seems possible that this interaction could occur with colchicine and any statin.

Clinical evidence

(a) Atorvastatin

A 45-year-old man with nephrotic syndrome who had been taking colchicine 1.5 mg daily for 3 years without adverse effects, began to experience lower extremity weakness, muscle pain and gait instability about 2 weeks after he started taking atorvastatin 10 mg daily. Two weeks later rhabdomyolysis was diagnosed, with acute renal failure and an elevated creatine kinase level of more than fifty times the reference values. After withdrawal of colchicine and atorvastatin, his creatine kinase levels and muscle strength improved, but he then developed septic shock as a result of hospital-acquired pneumonia and died.[1]

(b) Fluvastatin

A 70-year-old man who had been taking fluvastatin 80 mg daily for 2 years started taking colchicine 1.5 mg daily for an attack of gouty arthritis. Within 3 days he felt nauseous and began to develop muscle pains and weakness. On admission to hospital he was found to have acute renal failure and a raised creatine kinase, and was diagnosed with rhabdomyolysis. Both drugs were stopped and he recovered over 19 days. He was eventually restabilised on fluvastatin without incident.[2]

(c) Pravastatin

A 65-year-old woman who had been taking pravastatin 20 mg daily for 6 years was given colchicine 1.5 mg daily for an episode of gout. Within 20 days she had developed muscle weakness in the legs and had a slightly raised creatine kinase. A diagnosis of myopathy was made and so both the colchicine and pravastatin were stopped. The weakness resolved over the following week. The colchicine was subsequently given alone, and myopathy did not occur.[3]

(d) Simvastatin

A 70-year-old man with chronic renal failure who had been taking simvastatin (dose not stated) for 2 years was given colchicine 500 micrograms twice daily for gout. Within 2 weeks he developed muscle weakness, which was diagnosed as myopathy. Both drugs were stopped and the symptoms resolved.[4] Another report describes rhabdomyolysis in a 61-year-old woman with mild renal impairment taking simvastatin 40 mg daily, who was also taking colchicine 600 micrograms twice daily. Two weeks later, the simvastatin dose was doubled to 80 mg daily. About one week after this, the patient began to experience increasing muscle weakness in her lower extremities, progressing to an inability to stand up or walk; on admission to hospital her creatine kinase levels were substantially increased. Both drugs were discontinued and within 2 weeks the muscle weakness had resolved and the creatine kinase levels had returned to the expected range. Simvastatin was restarted at 80 mg daily and allopurinol initiated; 6 months later, she was asymptomatic with normal creatine kinase levels.[5] A further report describes a similar case of rhabdomyolysis in a 79-year-old man with mild, chronic renal impairment after he had taken simvastatin 40 mg daily and colchicine (initially 600 micrograms daily, increased to twice daily after 4 days).[6]

Mechanism

It has been suggested that the interaction between colchicine and simvastatin or atorvastatin could occur due to competition for metabolism by the cytochrome P450 isoenzyme CYP3A4.[1,4,5] However, as the interaction has also been seen with fluvastatin and pravastatin, which are not metabolised in this way, this seems unlikely to be the full explanation. P-glycoprotein has also been implicated.[1,3] Colchicine alone can, rarely, cause myopathy. However, it is more common in those given colchicine long term, in high dose, or in the presence of renal impairment.[3] As the statins can also cause myopathy, an additive or synergistic effect seems possible.[2]

Importance and management

Although this interaction is rare, it is serious. Given the evidence available it seems likely to occur with all statins, although this has not been clearly demonstrated. All patients taking statins should be warned about the symptoms of myopathy and told to report muscle pain or weakness. It would be prudent to reinforce this advice if they are given colchicine. See also 'muscle toxicity', (p.1313), for further guidance on monitoring and risk factors for muscle toxicity.

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Statins + Danazol

Severe rhabdomyolysis and myoglobinuria developed in a man taking lovastatin about two months after danazol was added. Other reports describe similar interactions with danazol in another patient taking lovastatin and a man taking simvastatin.

Clinical evidence

(a) Lovastatin

A 72-year-old man taking atenolol, aspirin, dipyridamole and lovastatin 20 mg twice daily was admitted to hospital after complaining of myalgia over the last 12 days, and brown urine over the last 5 days. He was diagnosed with severe rhabdomyolysis and myoglobinuria. About 2 months previously he had started taking danazol 200 mg three times daily and prednisone, and one month previously he had received a 10-day course of doxycycline 100 mg twice daily. The aspirin and lovastatin were stopped (danazol was stopped 4 days before admission and the doxycycline was stopped 5 days before the onset of symptoms), and all the symptoms resolved. Laboratory tests were normal within 2 weeks.[1] A similar case has been reported in a woman with end-stage renal disease, who was given danazol 600 mg daily, with the addition of lovastatin 40 mg daily, 5 weeks before admission. The authors note that both drugs had been previously tolerated when given alone, but it should be noted that the lovastatin had been given in a lower dose of 20 mg daily.[2]

(b) Simvastatin

A 68-year-old man who had been taking simvastatin 40 mg daily long-term without problem developed rhabdomyolysis (progressive muscle pain and weakness, tea-coloured urine, renal impairment, and a raised creatine phosphokinase) within 3 weeks of starting to take danazol 200 mg three times daily. He was given haemodialysis and subsequently recovered.

Mechanism

It has been suggested that danazol was hepatotoxic, which led to decreased lovastatin metabolism, or that the danazol had a direct toxic effect on the muscles.[1] However, it has also been suggested that danazol is an inhibitor of the cytochrome P450 isoenzyme CYP3A4 by which simvastatin and lovastatin are metabolised. This could result in raised statin levels, and therefore myopathy and rhabdomyolysis.[1,3] This seems a more likely explanation for the effects seen, but this suggestion needs confirmation.

Importance and management

These appear to be the only reports of this apparent interaction, but the pharmacokinetic basis of the interaction seems to be established. The benefits of combining lovastatin or simvastatin with danazol should be weighed against the potential risks and low doses should be used. The US manufacturer of lovastatin[4] suggests that the dose should be started at

10 mg daily, and should not exceed 20 mg daily in the presence of danazol. Similarly, the US manufacturer[5] of simvastatin suggests that the dose should be started at 5 mg daily, and both manufacturers state that the simvastatin dose should not exceed 10 mg daily in the presence of danazol.[5,6] It would seem prudent to monitor for symptoms of myopathy and tell patients to report any unexplained muscle pain, tenderness or weakness. The authors of the lovastatin report[1] point out that, as in this case, severe lovastatin muscle toxicity may be very slow to develop. See also 'muscle toxicity', (p.1313), for further guidance on monitoring, and risk factors for muscle toxicity.

The statins that are not significantly metabolised by CYP3A4 (**fluvastatin**, **pravastatin**, **rosuvastatin**) are not expected to interact.

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Statins + Dipeptidylpeptidase-4 inhibitors

Saxagliptin, sitagliptin and vildagliptin do not alter the pharmacokinetics of simvastatin. Sitagliptin use was considered a possible contributing factor to two cases of statin-induced rhabdomyolysis (one with lovastatin and one with simvastatin). Simvastatin does not alter the pharmacokinetics of saxagliptin or vildagliptin.

Clinical evidence

(a) Saxagliptin

In a study in 23 healthy subjects, when saxagliptin 10 mg daily and **simvastatin** 40 mg daily were given together for 4 days there was no change in the pharmacokinetics of **simvastatin**, when compared with **simvastatin** alone. In addition, there was no change in the AUC of saxagliptin, and just a minor 21% increase in the saxagliptin maximum level, when compared with saxagliptin alone.[1]

(b) Sitagliptin

In a study in 12 healthy subjects, sitagliptin 200 mg daily for 5 days did not alter the pharmacokinetics of simvastatin acid or simvastatin lactone when a single 20-mg dose of **simvastatin** was given on day 5. In addition, there was no alteration in plasma inhibition of HMG-CoA reductase.[2]

Two cases of possible interactions have been reported.[3,4] In one, a 76-year-old man with chronic renal impairment and numerous other medical conditions was admitted with rhabdomyolysis and acute renal failure. His medications included antihypertensives, amiodarone, **simvastatin**, ezetimibe and sitagliptin. Four months previously, his simvastatin dose had been increased from 40 to 80 mg daily and ezetimibe 10 mg daily added. Six weeks previously, he had started sitagliptin 50 mg daily, increased to 100 mg daily 3 weeks later. Various medications were stopped including sitagliptin, simvastatin and ezetimibe, and he made a full recovery. He was later given **lovastatin** 10 mg daily.[3] In another case, a 75-year-old woman with normal renal function who had been taking **lovastatin** 40 mg daily for 12 years and diltiazem 240 mg daily (last dose adjustment 10 months previously) presented with weakness and was diagnosed with rhabdomyolysis secondary to statin use. Nineteen days earlier she had started sitagliptin 100 mg daily and after 14 days this was replaced with glimepiride 1 mg daily. A statin was not restarted.[4]

(c) Vildagliptin

In a study in 24 healthy subjects, there was no change in the pharmacokinetics of vildagliptin, **simvastatin** or its active metabolite, compared with either drug given alone, when vildagliptin 100 mg daily and **simvastatin** 80 mg daily were given together for 7 days.[5]

Mechanism

Saxagliptin, sitagliptin and vildagliptin do not affect the cytochrome P450 isoenzyme CYP3A4, by which simvastatin is principally metabolised, therefore no pharmacokinetic interaction was anticipated, and the controlled studies available confirm this. In the case of rhabdomyolysis with simvastatin, it was suggested that too high a dose of sitagliptin for the degree of renal impairment possibly contributed to renal impairment, which reduced simvastatin clearance.[3] However, it is also possible that the effect was due to using too high a dose of simvastatin with amiodarone.[6] In the second case with lovastatin, diltiazem could have caused this interaction, but the authors discounted this on the basis of the time frame since the diltiazem dose increase.[4] For more information on the interactions of amiodarone and diltiazem with the statins, see 'Statins + Amiodarone', p.1320, and 'Statins + Calcium-channel blockers', p.1324.

Importance and management

It appears that saxagliptin, sitagliptin and vildagliptin have no effect on the pharmacokinetics of simvastatin, and no interaction as a result of altered levels would therefore be expected. However, two possible cases of rhabdomyolysis with sitagliptin and a statin have been reported. One case could equally well have been caused by other factors, but another explanation for the other case is less clear. These cases are insufficient evidence to issue a general caution, but bear them in mind in the event of an unexpected response to treatment.

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Statins + Distigmine

A case report describes rhabdomyolysis associated with the use of pravastatin and distigmine.

Clinical evidence, mechanism, importance and management

An isolated report describes a 70-year-old woman taking **pravastatin**, colestyramine and distigmine 10 mg daily who was admitted to hospital with symptoms including reduced urine output and muscle weakness. She was found to have a creatine kinase level of 4,069 units/L (reference range 45 to 163 units/L) and was diagnosed with rhabdomyolysis, which was thought to have been due to the pravastatin and colestyramine. These drugs were discontinued immediately, but 2 days later the patient's creatine kinase level remained elevated, and so the distigmine was also discontinued. After 3 days the creatine kinase levels had fallen, and had returned to the expected range after a further 8 days.[1] The authors of the report attributed the rhabdomyolysis to distigmine, with a possible contribution from pravastatin, based on the fall in the CK levels after its discontinuation, and recommend caution if distigmine is given with any statin. However, the patient had seemingly taken both drugs uneventfully for more than 18 months, distigmine is not normally associated with myopathy, it is unknown whether the creatine kinase levels would have dropped without the withdrawal of the distigmine, and the dose of pravastatin was not stated. Therefore an interaction is far from established. The current evidence is too slim to warrant any action if both drugs are taken.

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Statins + Diuretics

In clinical studies, the safety and efficacy of statins were not altered by the concurrent use of diuretics. Reversible diabetes mellitus developed in a woman taking cyclothiazide with triamterene when she was also given pravastatin. No clinically relevant pharmacokinetic interaction occurs between simvastatin and eplerenone.

Clinical evidence, mechanism, importance and management

(a) Lovastatin

Retrospective analysis of clinical study data[1] found no evidence that the safety or efficacy of lovastatin was altered by the use of **potassium-sparing diuretics** (hydrochlorothiazide with **triamterene** or **amiloride**), or **thiazide diuretics** (mostly **hydrochlorothiazide**). Another retrospective study of 19 patients found that the addition of lovastatin to diuretic treatment caused an initial 30% fall in total serum cholesterol levels for one month, followed by a rise of about 20%. In a further 13 patients, the addition of diuretic treatment to lovastatin caused a 20% fall in total serum cholesterol for one month followed by a 20% rise back to baseline values. The diuretics used were **furosemide** (16 patients), **triamterene** with **hydrochlorothiazide** (7), **hydrochlorothiazide** (8), **indapamide** (1). The fall and subsequent rise in serum cholesterol levels occurred in all of the patients except just the one taking **indapamide**.[2] The reason for this initial fall in cholesterol, particularly when the diuretic was added to the statin, is unknown, and the findings of this study are difficult to interpret.

(b) Pravastatin

A 63-year-old woman who had been taking **cyclothiazide** with **triamterene**, and acebutolol, for 4 years, developed polyuria and polydipsia, which gradually worsened, within 3 weeks of starting to take pravastatin 20 mg daily. After another 4 months she was hospitalised with hyperglycaemia, which was treated with insulin and later glibenclamide (glyburide). The **cyclothiazide** with **triamterene** and pravastatin were stopped and gradually the diabetic symptoms began to abate. Five weeks after admission she was discharged without the need for any antidiabetic treatment with the diabetes fully resolved.[3] The detailed reasons for this reaction are not understood, but it would seem that the pravastatin increased the potential of the thiazide diuretic to raise blood glucose levels to the point where frank diabetes developed. This is an isolated case and its general importance is likely to be small. Indeed, a study involving dyslipidaemic, hypertensive patients found that captopril, **hydrochlorothiazide** and pravastatin were effective and well tolerated by the 128 patients taking this combination, and there was no significant change in glucose levels.[4]

(c) Simvastatin

In 18 healthy subjects simvastatin 40 mg daily had no effect on the pharmacokinetics of **eplerenone** 100 mg daily. The maximum level and AUC of simvastatin were decreased by 32% and 14%, respectively, but this was not considered to be clinically relevant.[2]

(d) Other statins

Retrospective analysis of clinical study data found no evidence that the safety or efficacy of **fluvastatin** was altered by the use of unspecified **diuretics**.[5]

The bulk of the evidence suggests no special precautions are necessary if diuretics are given concurrently with statins.

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Statins + Everolimus

In a single-dose study in healthy subjects, everolimus did not cause a clinically relevant alteration in the pharmacokinetics or HMG-CoA reductase activity of atorvastatin or pravastatin. Everolimus pharmacokinetics were unaltered by the statins.[1] Dosage adjustments therefore seem unlikely to be necessary on concurrent use.

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Statins + Ezetimibe

Ezetimibe does not appear to have adverse pharmacokinetic interactions with atorvastatin, fluvastatin, lovastatin, pitavastatin, rosuvastatin or simvastatin. However, some evidence suggests that concurrent use may increase the risk of myopathy.

Clinical evidence

(a) Atorvastatin

In a three-arm study, patients were given atorvastatin 80 mg daily, atorvastatin 80 mg daily with ezetimibe 10 mg daily, or atorvastatin 40 mg daily with ezetimibe 10 mg daily. No difference in adverse events was noted between each of the three groups and there were no significant elevations in creatine kinase. No cases of myopathy or rhabdomyolysis occurred, and the combination was well tolerated.[1] Similarly, an efficacy study found that ezetimibe did not worsen statin intolerance or toxicity in 628 patients with hypercholesterolaemia who were taking atorvastatin.[2] However, a case report describes a 43-year-old man taking atorvastatin 80 mg daily who developed severe muscle pain with elevated creatine kinase levels 3 weeks after he started taking ezetimibe 10 mg daily. Symptoms resolved when both drugs were withdrawn and he later restarted the atorvastatin without problems.[3] Other similar cases have also been reported, in patients taking ezetimibe 10 mg daily and atorvastatin 40 mg or 80 mg daily.[4,5]

(b) Fluvastatin

In a randomised study 32 otherwise healthy subjects with hypercholesterolaemia were given either ezetimibe 10 mg daily, fluvastatin 20 mg daily or both drugs in combination for 14 days. The pharmacokinetics of ezetimibe were not significantly affected by fluvastatin, but ezetimibe appeared to modestly decrease fluvastatin bioavailability: this was not considered to be clinically significant. The combination was well tolerated, with no evidence of increased incidence of adverse effects, and an enhanced lowering of LDL-cholesterol was noted, which was considered to be clinically favourable.[6] Similarly, another study in 199 patients with a history of muscle-related adverse effects with other statins, found that fluvastatin alone or in combination with ezetimibe were well tolerated for 12 weeks: the incidence of muscle-related adverse effects were 24%, 17%, and 14% in patients who received ezetimibe 10 mg daily, prolonged-release fluvastatin 80 mg daily, or both drugs, respectively.[7] However, a case report describes a 52-year-old man taking fluvastatin 80 mg daily who developed elevated creatine kinase levels 8 weeks after ezetimibe 10 mg daily was added. His creatine kinase levels returned to normal 4 weeks after the ezetimibe was withdrawn.[3]

(c) Lovastatin

In a randomised, crossover study, 18 healthy subjects were given either ezetimibe 10 mg daily, lovastatin 20 mg daily or both drugs in combination for 7 days. The combination was well tolerated, and no significant pharmacokinetic interaction was noted.[8]

(d) Pitavastatin

A review of ezetimibe[9] cites an unpublished study in which 18 healthy subjects were given ezetimibe 10 mg and pitavastatin 2 mg, alone and together. Concurrent use did not affect the pharmacokinetics of either drug.

(e) Rosuvastatin

In a placebo-controlled study 12 otherwise healthy subjects with hypercholesterolaemia were given ezetimibe 10 mg daily with rosuvastatin 10 mg daily for 14 days. The combination was well tolerated (no significant changes in liver enzymes or creatine phosphokinase noted), the pharmacokinetics of both drugs were not significantly changed, and an enhanced lowering of LDL-cholesterol was noted, which was considered to be clinically favourable.[10]

(f) Simvastatin

In a three-arm study, patients were given simvastatin 80 mg daily, simvastatin 80 mg daily with ezetimibe 10 mg daily, or simvastatin 40 mg daily with ezetimibe 10 mg daily. No difference in adverse events was noted between each of the 3 groups and there were no significant elevations in creatine kinase. No cases of myopathy or rhabdomyolysis occurred, and the combination was well tolerated.[1] Another study in patients with primary hypercholesterolaemia found a similar safety profile between simvastatin 10, 20, 40 or 80 mg daily taken as monotherapy (560 subjects) or in combination with ezetimibe 10 mg daily (544 subjects) for up to

6 months.[11] A further observational study in 25 heart transplant recipients (all of whom were receiving ciclosporin) found that ezetimibe 10 mg daily combined with simvastatin 10 or 20 mg daily was well tolerated.[12] A retrospective analysis of 17 studies found that overall, muscle related adverse effects, including myopathy, were no more common in patients taking ezetimibe with simvastatin than in those taking simvastatin alone. The incidence of myopathy was 0.08% (2 of 2563) in those taking simvastatin alone and 0.04% (2 of 4558) in those taking ezetimibe with simvastatin. However, these findings should be interpreted with caution as the studies were not specifically designed to detect muscle toxicity. In addition, many patients were excluded if they had other medical conditions, such as renal impairment, or if they were taking other potentially interacting medication.[13] In another study, ezetimibe 0.25 mg, 1 mg or 10 mg daily had no effect on the pharmacokinetics of simvastatin 10 mg daily, when both drugs were given for 14 days. In addition, 10 and 20-mg doses of simvastatin were well tolerated in combination with ezetimibe.[14]

(g) Unnamed statins

The manufacturers of ezetimibe note that, in controlled clinical studies, the incidence of consecutive elevations (3 or more times the upper limit of normal) in hepatic transaminase levels was 1.3% for patients taking a statin with ezetimibe and 0.4% for patients taking statins alone. These elevations in transaminases were generally asymptomatic, and resolved spontaneously, either with continued treatment or after the drugs were stopped.[15,16] Creatine phosphokinase levels greater than 10 times the upper limit of normal were reported in 1 of 917 (0.1%) patients given ezetimibe and a statin, 4 of 1674 (0.2%) patients given ezetimibe alone, and 4 of 929 (0.4%) patients given a statin alone.[15,16]

Mechanism, importance and management

The available evidence suggests that on the whole the concurrent use of a statin with ezetimibe does not result in a change in the pharmacokinetics of either drug. However, there is some evidence to suggest that, rarely, concurrent use may increase the risk of myopathy. Therefore any patient taking a statin who is also given ezetimibe should be told to report any signs of myopathy and possible rhabdomyolysis (i.e. otherwise unexplained muscle pain, tenderness or weakness or dark coloured urine). See also 'muscle toxicity', (p.1313), for further guidance on monitoring, and risk factors for muscle toxicity. Note that a combination preparation containing simvastatin and ezetimibe is widely available.

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Statins + Fibrates

The plasma levels of lovastatin, simvastatin, atorvastatin, pitavastatin and pravastatin are increased by gemfibrozil, the levels of fluvastatin are increased by bezafibrate, and the levels of pravastatin are increased by fenofibrate. Both statins and fibrates are known to cause rhabdomyolysis, and their concurrent use increases the risk of this reaction, especially if plasma levels of the statin are also raised.

Clinical evidence

A. Bezafibrate

(a) Fluvastatin

In one study bezafibrate 200 mg three times daily increased the AUC and maximum levels of fluvastatin 20 mg daily by about 50 to 60%. Bezafibrate pharmacokinetics were not affected.[1]

(b) Lovastatin

In a study in 11 healthy subjects the pharmacokinetics of a single 40-mg dose of lovastatin were not altered by bezafibrate 400 mg daily for 3 days.[2]

B. Ciprofibrate

The manufacturer of fluvastatin reports that the concurrent use of ciprofibrate has no effect on the bioavailability of fluvastatin.[1]

C. Fenofibrate

(a) Atorvastatin

A 58-year-old man who had been taking atorvastatin 10 mg daily for 4 months developed rhabdomyolysis-induced acute renal failure one month after starting to take fenofibrate 200 mg daily. He recovered within a month, after treatment with diuretics and haemodialysis.[3]

(b) Fluvastatin

A single-dose study in 24 healthy subjects found that there was no significant pharmacokinetic interaction between fenofibrate 160 mg and fluvastatin 40 mg. Fenofibrate increased the AUC of fluvastatin by about 15%, but fluvastatin had little effect on fenofibric acid exposure.[4]

(c) Pitavastatin

In a crossover study in 24 healthy subjects, fenofibrate 160 mg daily increased the AUC of pitavastatin 4 mg by 18%, without affecting its maximum levels.[5]

(d) Pravastatin

A single-dose study in 23 healthy subjects found that the concurrent use of pravastatin 40 mg and fenofibrate 201 mg had no effect on the pharmacokinetics of either drug, but a moderate increase in the formation of a non-toxic pravastatin metabolite was seen. This was not thought to be clinically important.[6] In a multiple-dose study, pravastatin 40 mg daily was given to 23 healthy subjects with fenofibrate 160 mg daily. Fenofibrate increased the maximum levels and AUC of pravastatin by about 40% and 30%, respectively. Similar increases were seen for the main pravastatin metabolite. The combination was well tolerated, and the increases were considered to be modest.[7] However, a case report describes a patient taking fenofibrate 300 mg daily, who developed rhabdomyolysis after starting to take pravastatin 10 mg daily.[8] In another report, a 56-year-old woman who had taken pravastatin 20 mg daily for 12 years, developed severe rhabdomyolysis-induced acute renal failure about 2 months after starting to take fenofibrate 200 mg daily. She recovered in about 2 weeks after treatment with diuretics and haemodialysis.[3]

(e) Rosuvastatin

In a study in 14 healthy subjects, fenofibrate 67 mg three times daily and rosuvastatin 10 mg daily for 7 days resulted in only minor changes in fenofibric acid and rosuvastatin exposure, when compared with either drug given alone.[9] However, a 68-year-old man taking rosuvastatin 10 mg daily developed myopathy about 3 weeks after fenofibrate 160 mg was added. Rhabdomyolysis was diagnosed and both drugs were stopped, resulting in marked clinical improvement within 24 hours.[10]

(f) Simvastatin

In a randomised, crossover study 25 healthy subjects were given simvastatin 80 mg daily with fenofibrate 160 mg daily for 7 days. The phar-

macokinetics of both drugs and their main metabolites (as assessed in 12 subjects) were unchanged by concurrent use. All 25 subjects were assessed for safety, and the combination was found to be well tolerated.[11] Similarly, an 18-week, multicentre study (the SAFARI trial) investigated the efficacy and tolerability of simvastatin 20 mg and fenofibrate 160 mg daily. In the 411 patients who received both drugs concurrently, no drug-related serious adverse events were observed and there were no instances of clinical myopathy or severe abnormalities in liver function.[12] One manufacturer of simvastatin says that when simvastatin and fenofibrate are given concurrently, there is no evidence that the risk of myopathy exceeds the sum of the individual risks of each drug.[13] However, one 70-year-old man with diabetes and hypothyroidism, who was taking medication including simvastatin 40 mg, developed bilateral leg myalgia 2 weeks after fenofibrate 160 mg was started. Two weeks later he was found to have raised creatinine and creatine phosphokinase (CPK) levels and rhabdomyolysis was diagnosed. The fenofibrate and simvastatin were discontinued and, with hydration, the myalgia resolved; his creatinine levels returned to baseline over the next week and serum CPK returned to baseline within 4 weeks.[14]

D. Gemfibrozil

(a) Atorvastatin

A pharmacokinetic study in 10 healthy subjects found that gemfibrozil 600 mg twice daily increased the AUC of atorvastatin and its metabolites by 24% and 30 to 80%, respectively, which was considered a moderate increase.[15] A 43-year-old woman with multiple medical problems was taking gemfibrozil 600 mg twice daily. After a recurrent attack of pancreatitis, atorvastatin 10 mg and glibenclamide (glyburide) 2.5 mg, both twice daily, were added. About 3 weeks later she developed brown and turbid urine (suggesting urinary myoglobin), creatine kinase levels of 4633 units/L and had myalgia: she was diagnosed as having rhabdomyolysis. Her serum creatine kinase levels rapidly fell when the atorvastatin and gemfibrozil were withdrawn.[16]

In a case series of 10 patients taking a statin who experienced myopathy and presented for muscle biopsy, one patient taking gemfibrozil developed gradual onset of weakness over a 3-month period after his dose of atorvastatin was increased from 10 mg to 20 mg.[17]

(b) Fluvastatin

In a randomised, crossover study, 15 patients were given fluvastatin 20 mg and gemfibrozil 600 mg twice daily. The pharmacokinetics of both gemfibrozil and fluvastatin were unchanged by concurrent use and no significant adverse effects were noted.[18] However, a case report describes serious hepatocellular injury, and rhabdomyolysis causing acute renal failure, in a patient one month after she started to take fluvastatin 80 mg daily and gemfibrozil 1.2 g daily; she was not using any other medications.[19]

(c) Lovastatin

In a pharmacokinetic study, 11 healthy subjects were given gemfibrozil 1.2 g daily for 3 days, with a single 40-mg dose of lovastatin on day 3. The AUC and maximum plasma level of lovastatin acid (a metabolite) were nearly threefold greater in the presence of gemfibrozil.[2]

By 1990 the FDA had documented 12 case reports of severe myopathy or rhabdomyolysis associated with the concurrent use of lovastatin and gemfibrozil. The mean serum creatine kinase levels of the patients reached 15 250 units/L. Four of those tested had myoglobinuria and five had acute renal failure.[20] Other cases of rhabdomyolysis associated with the concurrent use of these drugs have been reported,[21-26] five involving renal failure.[21-23,25] A review of the concurrent use of a statin and a fibrate identified additional cases of rhabdomyolysis involving gemfibrozil and lovastatin, mainly with lovastatin doses of 40 mg daily and above.[27] Further cases of rhabdomyolysis have been seen in patients taking lovastatin and gemfibrozil, with ciclosporin,[28] or niacin.[29]

Many reports suggest there is insufficient benefit to warrant combining lovastatin and gemfibrozil,[20,30] although in contrast, some describe apparently safe and effective concurrent use under very well controlled conditions,[31-33] although muscle symptoms and/or elevated creatine phosphokinase levels, without rhabdomyolysis, were seen in up to 9% of cases.

(d) Pitavastatin

In a crossover study in 24 healthy subjects, the concurrent use of pitavastatin 4 mg daily and gemfibrozil 600 mg twice daily increased the AUC and maximum level of pitavastatin by 45% and 31%, respectively.[5]

(e) Pravastatin

In a study in 18 healthy subjects gemfibrozil 600 mg caused no clinically significant changes in the bioavailability of a single 20-mg dose of pravastatin.[34] However, another study using pravastatin 40 mg found that the AUC and maximum levels of pravastatin were increased roughly twofold by gemfibrozil.[35] A 12-week study with pravastatin 40 mg daily and gemfibrozil 600 mg twice daily found that marked abnormalities in creatine kinase concentrations (four times the pretreatment values) occurred in 1 of 71 patients taking pravastatin alone, 1 of 73 patients taking placebo, 2 of 72 patients taking gemfibrozil alone, and 4 of 75 patients taking gemfibrozil with pravastatin. The differences between treatments were not statistically significant. Two patients taking gemfibrozil with pravastatin had these drugs withdrawn because of asymptomatic creatine kinase elevations. Severe myopathy or rhabdomyolysis was not seen in any patient, although 14 patients had musculoskeletal pain, but in most cases this was not considered to be related to treatment.[36]

(f) Rosuvastatin

In a randomised, crossover study, 20 healthy subjects were given gemfibrozil 600 mg twice daily for 7 days, with a single 80-mg dose of rosuvastatin on day 4. The AUC of rosuvastatin was increased by 88% (11 subjects assessed) and the maximum level of rosuvastatin was increased 2.21-fold. Three subjects had asymptomatic increases in ALT levels (less than 2.5 times upper limit of normal).[37]

(g) Simvastatin

A 62-year-old man with diabetes taking simvastatin 20 mg daily and gemfibrozil 600 mg daily (as well as acenocoumarol, glibenclamide (glyburide) and diclofenac) was hospitalised because of melaena, generalised myalgia, malaise and brown urine. Laboratory tests confirmed the diagnosis of rhabdomyolysis. He recovered when the simvastatin and gemfibrozil were stopped.[38] Another diabetic patient had been taking simvastatin and gemfibrozil 600 mg daily for two and a half years (as well as felodipine, indapamide, calcium carbonate, bumetanide, psyllium, acenocoumarol and insulin). She complained of tiredness, generalised myalgia and anuria 3 months after her dosage of simvastatin had been increased to 80 mg daily. Rhabdomyolysis with renal impairment were diagnosed and confirmed. She recovered when the simvastatin and gemfibrozil were stopped.[38] Four further cases of rhabdomyolysis have been reported in patients taking simvastatin, 3 weeks to 3 months after starting gemfibrozil.[39-42] One of these cases was fatal.[39]

A pharmacokinetic study found that when gemfibrozil was given with simvastatin the AUC of simvastatin acid (an active metabolite of simvastatin) was increased nearly threefold and the peak concentration was approximately doubled.[43]

In a case series of 10 patients taking a statin who experienced myopathy and presented for muscle biopsy, two patients taking gemfibrozil gradually developed myopathy while also taking simvastatin 80 mg daily.[17]

E. Unspecified Fibrates or Statins

In a review[44] of the FDA spontaneous reports of statin-associated rhabdomyolysis covering the period November 1997 to March 2000, fibrates (unspecified) were potentially implicated in 10 of 73 cases of rhabdomyolysis seen with **atorvastatin**, 4 of 10 with **fluvastatin**, 5 of 40 with **lovastatin**, 6 of 71 with **pravastatin**, and 33 of 215 with **simvastatin**. Another review using data from the adverse event reporting system of the FDA concluded that the concurrent use of **fenofibrate** with a statin results in fewer reports of rhabdomyolysis than the concurrent use of **gemfibrozil** and a statin (0.58 cases per million prescriptions and 8.6 cases per million prescriptions, respectively).[45]

Mechanism

Complex and not fully understood. Myopathy can occur with statins and fibrates alone and their effects may therefore be additive or synergistic. There is also evidence that some fibrates may inhibit the metabolism of the statins, but *not* by inhibiting the cytochrome P450 isoenzyme CYP3A4.[2,43] More recent study has shown that gemfibrozil may inhibit the glucuronidation of some of the statin metabolites, and that gemfibrozil and gemfibrozil glucuronide are inhibitors of some of the CYP2C isoenzymes e.g. CYP2C8.[46,47] Other evidence suggests that drug transporter proteins, such as the organic anion transporting polypeptide OATP1B1 (also known as OATP2 and OATP-C), may also be involved.[35,37,48,49] However, a pharmacokinetic interaction with statins does not appear to be a group effect of the fibrates, for example, bezafibrate does not affect the bioavailability of lovastatin.

Importance and management

There are many studies showing efficacious use of many pairs of statins and fibrates, and the overall incidence of myopathy with a statin and a fibrate has been put at 0.12%, although this may be an underestimate as many of the studies excluded patients with renal or liver impairment and thyroid dysfunction.[27] In addition, evaluation of the data is difficult as there has been no standard definition of myopathy. Another retrospective review of patients with myopathy suggested an incidence of 0.12% with statins alone and 0.22% with statins combined with an interacting drug, including fibrates.[50] A further study estimated that, compared with statin monotherapy, the concurrent use of a statin and a fibrate was associated with a 5.5-fold increase in the risk of rhabdomyolysis. In addition, the use of a statin with a fibrate increased the risk twofold when compared with a fibrate alone.[51] Therefore, the risks of these combinations are evident, at least for individual patients.

The pharmacokinetic interaction varies between the different statins and fibrates with gemfibrozil affecting the bioavailability of most statins (except fluvastatin), and other fibrates such as fenofibrate less likely to cause a pharmacokinetic interaction. In addition, individual fibrates have different safety profiles: for example, a review of adverse events submitted to the FDA over a 5-year period suggested that fenofibrate had a higher rate of liver-related adverse effects than gemfibrozil and gemfibrozil had a higher rate of muscle-related adverse effects than fenofibrate.[52] Therefore, individual combinations of statins and fibrates are associated with different levels of risk.

General recommendations. In general, concurrent use of a stain and a fibrate should only be undertaken if the benefits of treatment outweigh the risks. Monitoring of creatine kinase has been suggested in patients taking a statin with a fibrate, but this will not necessarily identify all cases of developing rhabdomyolysis. As a general rule, any patient given a statin and a fibrate should be told to report any signs of myopathy and possible rhabdomyolysis (i.e. otherwise unexplained muscle pain, tenderness or weakness or dark coloured urine). If myopathy does occur, the statin should be stopped immediately. See also 'muscle toxicity', (p.1313), for further guidance on monitoring and risk factors for muscle toxicity.

Simvastatin and Lovastatin. The interactions of lovastatin and simvastatin with fibrates, particularly **gemfibrozil**, are established and clinically important. The FDA discourage the concurrent use of lovastatin with gemfibrozil in any patient, but suggest that it should be completely avoided in patients with compromised liver or renal function.[20] The manufacturers of lovastatin and simvastatin recommend that combined use with gemfibrozil should generally be avoided, but if the benefits are considered to outweigh the risks, a low dose of the statin should be used. In the presence of gemfibrozil, the maximum generally recommended dose for lovastatin is 20 mg and for simvastatin is 10 mg.[13,53,54] For **other fibrates**, the manufacturers recommend caution, and similarly suggest that if the benefits are considered to outweigh the risks, a low dose of the statin should be used: the same maximum statin doses are generally recommended,[13,53] although **fenofibrate** has been excluded from this recommendation for simvastatin.[13] Note that the manufacturer of **bezafibrate** contraindicates the use of a statin if a number of conditions considered to be risk factors for myopathy (such as renal impairment and hypothyroidism) are present.[55]

Atorvastatin. If the concurrent use of atorvastatin and a fibrate is unavoidable, the manufacturers suggest that lower doses of atorvastatin should be considered; in the UK a starting dose of 10 mg is specifically mentioned.[56,57] Note that the manufacturer of **bezafibrate** contraindicates the use of a statin if a number of conditions considered to be risk factors for myopathy (such as renal impairment and hypothyroidism) are present.[55]

Rosuvastatin. The manufacturers of rosuvastatin also suggest that combination with **gemfibrozil** should be avoided, but if the benefits outweigh the risks, the US manufacturer recommends a maximum dose of 10 mg of rosuvastatin.[58] Further, the UK manufacturer recommends starting with a 5-mg dose of rosuvastatin, and contraindicates the 40-mg dose, in any patient taking a fibrate.[59] Note that the manufacturer of **bezafibrate** contraindicates the use of a statin if a number of conditions considered to be risk factors for myopathy (such as renal impairment and hypothyroidism) are present.[55]

Other statins. The manufacturer of **bezafibrate** contraindicates the use of a statin if a number of conditions considered to be risk factors for myopathy (such as renal impairment and hypothyroidism) are present.[55]

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Statins + Fibre or Pectin

Pectin and oat bran can reduce the cholesterol-lowering effects of lovastatin.

Clinical evidence, mechanism, importance and management

The serum LDL-cholesterol levels of 3 patients taking lovastatin 80 mg daily showed a marked 42% rise from 4.48 mmol/L to 6.36 mmol/L when they were also given pectin 15 g daily. One patient had a 59% rise in LDL-cholesterol.[1] Two other patients taking lovastatin had a rise in LDL-cholesterol from 5.03 mmol/L to 6.54 mmol/L when they were also given **oat bran** 50 to 100 g daily. One patient had a 41% rise in LDL-cholesterol.[1] When the pectin and **oat bran** were stopped, the serum levels of the LDL-cholesterol fell.

It is presumed that both pectin and **oat bran** reduced the absorption of lovastatin from the gut.[1] Evidence is still very limited but if patients are adding these fibres to their diets it would seem prudent to separate the ingestion of lovastatin by as much as possible. The effect of these fibres on other statins does not appear to have been studied.

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Statins + Fusidic acid

Rhabdomyolysis has been described in patients given atorvastatin or simvastatin with fusidic acid.

Clinical evidence, mechanism, importance and management

A 66-year-old man with a renal transplant and diabetes, taking various drugs, was given **atorvastatin** 10 mg daily for hyperlipidaemia. Six weeks later, because of a resistant infection, clindamycin and ciprofloxacin were discontinued and fusidic acid 1.5 g daily was started. At this time serum creatine kinase was 54 units/L. Two weeks later the patient was admitted with progressive muscle weakness and pain in both legs. His serum creatine kinase was 3550 units/L, and he also had raised myoglobin levels. Both continued to rise for 5 days after the **atorvastatin** and fusidic acid were stopped, and then gradually returned to normal over one week. Serum levels of both fusidic acid and **atorvastatin** were higher than expected, and it was considered that an interaction was likely.[1]

A 78-year-old woman who had been taking **simvastatin** 10 mg daily for 10 months, developed rhabdomyolysis 15 days after starting to take fusidic acid. She recovered after stopping both drugs.[2] Another case of rhabdomyolysis and acute renal failure occurred postoperatively in a 71-year-old man taking multiple drugs including fusidic acid and **simvastatin** 40 mg daily. He recovered after withdrawal of the simvastatin.[3] Other cases of rhabdomyolysis, following the use of fusidic acid with **atorvastatin** or **simvastatin** have also been reported.[4,5] This includes a case where simvastatin was originally considered to be interacting with tacrolimus rather than fusidic acid, see 'Statins + Tacrolimus', p.1344.

The clinical significance of this possible interaction is unclear. It would seem wise to remind patients taking either **atorvastatin** or **simvastatin** with fusidic acid to be on the look out for the symptoms of myopathy and rhabdomyolysis (i.e. otherwise unexplained muscle pain, tenderness or weakness or dark coloured urine). If myopathy does occur, the statin should be stopped immediately. See also 'muscle toxicity', (p.1313), for further guidance on monitoring, and risk factors for muscle toxicity.

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Statins + Grapefruit and other fruit juices

Large amounts of grapefruit juice markedly increase the plasma levels of lovastatin and simvastatin, and also increase the plasma levels of atorvastatin. Pitavastatin and pravastatin seem not to interact. The clinical significance of the possible effects of pomegranate juice on rosuvastatin, and orange juice on pravastatin are unclear.

Clinical evidence

(a) Atorvastatin

Twelve healthy subjects were given 200 mL of double-strength grapefruit juice three times daily for 5 days. On day 3 they were given a single 40-mg dose of atorvastatin with the grapefruit juice then two more 200-mL doses of grapefruit juice, one after 30 minutes and the other after 90 minutes. The $AUC_{0\text{-}72}$ of atorvastatin acid and total HMG-CoA reductase inhibitors were increased 2.5-fold and by 50%, respectively.[1] Other studies, using 250 mL of single-strength grapefruit three times a day, have found broadly similar increases in atorvastatin levels.[2,3] In contrast, the manufacturers report that one 240-mL glass of grapefruit juice has a more modest effect, causing an increase of only 37% in the AUC of atorvastatin.[4]

(b) Lovastatin

Ten healthy subjects were given 200 mL of double-strength grapefruit juice three times daily for 3 days. On day 3 they took lovastatin 80 mg with 200 mL of grapefruit juice, then two more 200-mL doses of grapefruit juice, one after 30 minutes and the other after 90 minutes. The mean peak serum levels of the lovastatin and its active metabolite, lovastatin acid, were increased 12-fold and fourfold, respectively, and the mean AUCs were increased 15-fold and fivefold, respectively.[5] However, another study in which lovastatin 40 mg was given the evening after single-strength grapefruit juice was taken with breakfast found that the AUC and maximum serum level of lovastatin were approximately doubled, and the AUC and maximum serum level of lovastatin acid were only increased by 60%.[6] It has been suggested that if the grapefruit juice had been given at the same time as the lovastatin in the latter study[6] then much greater increases in the AUC and maximum serum levels would have been found.[7]

(c) Pitavastatin

A study in 8 healthy Japanese men found that 250 mL of single-strength grapefruit juice three times daily for 4 days had a minimal effect on the pharmacokinetics of a single dose of pitavastatin 4 mg given on day 4. The AUC of pitavastatin acid was increased by 13% and the change in the maximum plasma concentration was negligible.[2]

(d) Pravastatin

Grapefruit juice did not significantly affect the pharmacokinetics of a single 40-mg dose of pravastatin. In this study, 200 mL of double-strength grapefruit juice was given three times daily for 2 days, and then on the third day 200 mL was given with the pravastatin and again after 30 and

90 minutes.[1] A further study using 10 mg of pravastatin similarly found that grapefruit juice did not significantly affect pravastatin pharmacokinetics.[3]

In a study in 14 healthy subjects a total of 800 mL of **orange juice**, was given over about 3 hours, starting 15 minutes before a 10-mg dose of pravastatin. **Orange juice** increased the $AUC_{0\text{-}4}$ of pravastatin by a modest 50%, without affecting the maximum pravastatin levels.[8]

(e) Rosuvastatin

A case report describes a 48-year-old man taking ezetimibe 10 mg daily, and rosuvastatin 5 mg on alternate days, who developed rhabdomyolysis within 3 weeks of starting to drink 200 mL of **pomegranate juice** twice weekly. Although the patient had been stable taking ezetimibe with rosuvastatin for 15 months he had a history of myopathy with statins and had an elevated creatine kinase before statin treatment was started.[9]

(f) Simvastatin

Ten healthy subjects were given 200 mL of double-strength grapefruit juice three times daily for 2 days. On day 3 they took 60 mg of simvastatin with 200 mL of grapefruit juice, then two more 200-mL doses of grapefruit juice, one after 30 minutes and the other after 90 minutes. The mean peak serum levels of the simvastatin and simvastatin acid were increased ninefold and sevenfold, respectively, and the mean AUCs were increased 16-fold and sevenfold, respectively.[10] In a further study by the same research group, when simvastatin was given 24 hours after the last dose of grapefruit juice (same dosage regimen as the previous study) the effect was only 10% of that observed during concurrent use, and had disappeared within 3 to 7 days.[11] However, the manufacturers of simvastatin note that drinking 240 mL of standard grapefruit juice in the morning and taking simvastatin in the evening increased the exposure to simvastatin by 90%.[12] Another study found as little as 200 mL of grapefruit juice daily for 3 days could increase the maximum levels of a single 40-mg dose of simvastatin taken on day 3, and its metabolite, simvastatin acid, up to about fourfold.[13]

A case report describes rhabdomyolysis in a patient taking simvastatin 80 mg daily (dose increased 6 months before presentation), which occurred 4 days after she started to eat one fresh grapefruit a day.[14]

Mechanism

It seems that some components of the grapefruit juice (including furanocoumarin derivatives and flavonoids such as naringenin), inhibit the activity of the cytochrome P450 isoenzyme CYP3A4 in the gut wall, thereby reducing the metabolism of the affected statins as they are absorbed, and allowing more to pass into the body. See 'Lipid regulating drugs', (p.1313), for more information about the metabolism of the statins.

Importance and management

Information about the interaction of statins and grapefruit juice seems to be mainly limited to pharmacokinetic reports (i.e. few adverse case reports) but they are consistent with the way other CYP3A4 inhibitors interact with the statins. Large increases in the serum levels of **lovastatin** and **simvastatin** are potentially hazardous because elevated statin levels carry the risk of toxicity (muscle damage and the possible development of rhabdomyolysis). As even small quantities of grapefruit juice taken in the morning can significantly affect simvastatin levels the UK manufacturer says that concurrent use should generally be avoided.[15] In the US the manufacturers suggest that intake of grapefruit juice should be restricted to less than one quart [roughly 1 litre] daily.[12,16] See also 'muscle toxicity', (p.1313), for further guidance on monitoring and risk factors for muscle toxicity.

The modest increase in **atorvastatin** levels when taken with usual doses of grapefruit juice seems less likely to be clinically relevant, but the UK manufacturer suggests that large quantities (not defined) are not recommended.[4] In general, the occasional glass of grapefruit juice would not appear to be a problem. **Pitavastatin** and **pravastatin** seem not to interact. Information about other statins appears to be lacking, but no interaction would be expected with **fluvastatin** or **rosuvastatin**, as these statins are not significantly metabolised by CYP3A4.

The interaction of **pomegranate juice** with rosuvastatin and ezetimibe seems to be limited to one case report, which is clouded by other possible contributory factors. Furthermore, although pomegranate juice has been shown to inhibit CYP3A4,[9] rosuvastatin is not metabolised by this route. Although it is possible that other mechanisms may be responsible, no firm conclusions can be drawn from this case.

The interaction of pravastatin with **orange juice** would be expected to be of little clinical significance in most patients, but this needs confirmation.

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15. Simvador (Simvastatin). Discovery Pharmaceuticals Ltd. UK Summary of product characteristics, March 2009.
16. Mevacor (Lovastatin). Merck & Co., Inc. US Prescribing information, September 2008.

Statins + H_2-receptor antagonists or Proton pump inhibitors

No clinically significant interaction usually appears to occur between cimetidine and atorvastatin, fluvastatin, or pravastatin; between ranitidine and fluvastatin; or between omeprazole and fluvastatin.

Clinical evidence, mechanism, importance and management

(a) Atorvastatin

In a crossover study, 12 healthy subjects were given atorvastatin for 15 days with and without **cimetidine** 300 mg four times daily. **Cimetidine** had no effect on the maximum serum levels or AUC of atorvastatin. **Cimetidine** had little effect on the lipid-lowering ability of atorvastatin, except that the reduction in triglycerides was slightly less, but this difference was considered to be of little clinical significance.[1] There would appear to be no reason for avoiding concurrent use.

Esomeprazole has been implicated in a case of rhabdomyolysis involving atorvastatin and clarithromycin. See 'Statins + Macrolides', p.1337.

(b) Fluvastatin

The manufacturers of fluvastatin say that its bioavailability is increased by **cimetidine**, **omeprazole**, and **ranitidine** (AUC increased by 24 to 33%[2]), but they say that this is of no clinical relevance.[3] No dose adjustments would seem to be necessary on concurrent use.

(c) Pravastatin

Cimetidine 300 mg four times daily for 3 days increased the bioavailability of a single 20-mg dose of pravastatin by 58%. The dose of pravastatin was given on day 3, one hour after the first dose of **cimetidine**.[4] However, the manufacturers say that it is unlikely that the changes caused by **cimetidine** will affect the clinical efficacy of pravastatin.[4]

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3. Lescol (Fluvastatin sodium). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, March 2009.
4. ER Squibb. A report on the comparative pharmacokinetics of pravastatin in the presence and absence of cimetidine or antacids in healthy male subjects. Data on file (Protocol No 27, 201-43), 1988.

Statins + Imatinib

Imatinib raises simvastatin serum levels, increasing the risk of toxicity. It seems likely that statins metabolised in the same way as simvastatin may also be similarly affected.

Clinical evidence, mechanism, importance and management

In a single-dose study, 20 patients with chronic myeloid leukaemia were given **simvastatin** 40 mg before and on the last day of a 7-day course of imatinib 400 mg daily. Imatinib increased the maximum serum levels of **simvastatin** twofold and the AUC threefold. The authors conclude that caution is warranted if **simvastatin** and imatinib are taken concurrently.[1]

Imatinib inhibits the cytochrome P450 isoenzyme CYP3A4,[1] by which **simvastatin** is metabolised. It therefore seems likely that **lovastatin** will be similarly affected, and **atorvastatin** may be affected to some extent. These rises increase the risk of statin toxicity (myopathy and rhabdomyolysis).

As a general rule, any patient given imatinib with **simvastatin** (or **lovastatin**, and probably **atorvastatin**) should be told to report any signs of myopathy and possible rhabdomyolysis (i.e. otherwise unexplained muscle pain, tenderness or weakness or dark coloured urine). If myopathy does occur, the statin should be stopped immediately. See also 'muscle toxicity', (p.1313), for further guidance on monitoring, and risk factors for muscle toxicity.

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Statins + Macrolides

Cases of acute rhabdomyolysis have been reported between lovastatin and azithromycin, clarithromycin, or erythromycin and between simvastatin and clarithromycin or roxithromycin. Macrolide antibacterials have also been potentially implicated in cases of rhabdomyolysis with atorvastatin and pravastatin. Pharmacokinetic studies suggest that many macrolides increase the levels of atorvastatin, lovastatin and simvastatin.

Clinical evidence

(a) Azithromycin

1. Atorvastatin. In a randomised study, two groups of 12 healthy subjects were given atorvastatin 10 mg daily for 8 days with azithromycin 500 mg daily or placebo for the final 3 days. When the azithromycin group were compared with the placebo group no change in atorvastatin pharmacokinetics were noted.[1]

2. Lovastatin. A 51-year-old man who had been taking lovastatin 40 mg daily for 5 years developed muscle aches and fever one day after finishing a 5-day course of azithromycin 250 mg daily. His creatine phosphokinase levels were elevated and he was diagnosed as having rhabdomyolysis. This patient was also taking colestyramine, diltiazem, doxazosin, glibenclamide (glyburide), 'thyroid', allopurinol, naproxen, prednisone, loratadine and inhaled beclometasone.[2]

(b) Clarithromycin

1. Atorvastatin. In a randomised study, two groups of 12 healthy subjects were given atorvastatin 10 mg daily for 8 days with clarithromycin 500 mg twice daily or placebo for the final 3 days. When the clarithromycin group were compared with the placebo group the atorvastatin AUC was 82% higher and the maximum serum levels 50% higher.[1] In another randomised study, 15 healthy subjects were given atorvastatin 80 mg daily with clarithromycin 500 mg twice daily for 8 days. Clarithromycin increased the AUC of atorvastatin fourfold.[3]

Two case reports describe rhabdomyolysis in patients taking atorvastatin with clarithromycin,[4,5] although both of these cases were complicated by the presence of other drugs (efavirenz/lopinavir/ritonavir,[5] **esomeprazole**[4]) which may also have contributed to the interaction.

2. Lovastatin. A 76-year-old woman who had been taking lovastatin 40 mg daily for 5 years developed muscle pain and weakness 2 days after completing a 10-day course of clarithromycin 500 mg twice daily. Later, when hospitalised, she was found to have elevated creatine phosphokinase levels and was diagnosed as having acute rhabdomyolysis.[2] Another case report describes rhabdomyolysis in a patient taking lovastatin and clarithromycin. This patient was also taking gemfibrozil, which may have played a part in the interaction.[6]

3. Pravastatin. In a randomised study, 15 healthy subjects were given pravastatin 40 mg daily with clarithromycin 500 mg twice daily for 8 days. Clarithromycin increased the AUC of pravastatin twofold.[3]

4. Simvastatin. A preliminary report of a pharmacokinetic study suggests that clarithromycin 500 mg twice daily for 7 days can cause an eightfold increase in the AUC and maximum levels of a single 40-mg dose of simvastatin.[7] In a randomised study, 15 healthy subjects were given simvastatin 40 mg daily with clarithromycin 500 mg twice daily for 8 days. Clarithromycin increased the AUC of simvastatin tenfold.[3]

A case report describes a 64-year-old man with multiple pathologies, including renal impairment, developed rhabdomyolysis 3 weeks after clarithromycin was added to his treatment, which included simvastatin 80 mg daily.[8] Other reports describe 5 further cases of rhabdomyolysis in patients taking simvastatin,[9-13] which in some cases occurred within days of the clarithromycin being started. In 3 of these cases the patients were also taking amiodarone,[11] or ciclosporin,[10,12] which may also have had some part to play in the reaction.

(c) Erythromycin

1. Atorvastatin. In a study, 12 healthy subjects were given a single 10-mg dose of atorvastatin on day 7 of an 11-day course of erythromycin 500 mg four times daily. The maximum serum levels of atorvastatin were raised by 38% and the AUC was raised by 33% by the erythromycin.[14]

2. Fluvastatin. The manufacturer reports a study in which the steady-state plasma levels of fluvastatin 40 mg daily were not affected by a single 500-mg dose of erythromycin.[15]

3. Lovastatin. A man taking lovastatin 20 mg three times daily, diltiazem, allopurinol and aspirin developed progressive weakness and diffuse myalgia after taking erythromycin 500 mg every 6 hours for 13 days. When admitted to hospital his creatine kinase level was high (35 200 units/L) and his urine was reddish-brown. The rhabdomyolysis was treated by stopping the lovastatin, and by giving furosemide with vigorous intravenous hydration.[16] A woman who had been taking lovastatin for 7 years developed multiple organ toxicity (rhabdomyolysis, acute renal failure, pancreatitis, livedo reticularis and raised aminotransferase levels) when erythromycin was added.[17] Four other cases of rhabdomyolysis attributed to an interaction between lovastatin and erythromycin have been reported,[17-19] although it should be noted that one of these patients[18] was also taking ciclosporin, which may have contributed to the effects seen.

In a study, 6 healthy subjects were given lovastatin 40 mg daily for 14 days, with erythromycin 500 mg three times daily for the last 7 days. The erythromycin caused the maximum serum levels and AUC of lovastatin to rise more than fivefold.[20]

4. Pravastatin. In a study, 6 healthy subjects were given pravastatin 40 mg daily for 14 days, with erythromycin 500 mg three times daily for the last 7 days. The pharmacokinetics of the pravastatin remained unchanged.[20] However, in another study, erythromycin caused a 70% increase in the AUC and a 2.2-fold increase in the maximum level of pravastatin.[21]

5. Rosuvastatin. In a study in 11 healthy subjects, erythromycin 500 mg four times daily for 7 days did not raise the levels of a single 80-mg dose of rosuvastatin. In fact, rosuvastatin levels were slightly lowered, although this was not considered to be of clinical relevance if short-term courses of erythromycin are used.[22]

6. Simvastatin. An 83-year-old man receiving multiple medication, who had been taking simvastatin 80 mg daily for at least 5 years, developed rhabdomyolysis about 2 weeks after he completed a 14-day course of erythromycin 500 mg four times daily (given intravenously for 2 days then orally for 10 days) for atypical pneumonia.[13]

A study in which 12 subjects were given erythromycin 500 mg three times daily, found a 6.2-fold increase in the AUC of a single 40-mg dose of simvastatin, and a 3.4-fold increase in its maximum serum levels. The major active metabolite, simvastatin acid, was similarly affected.[23]

(d) Roxithromycin

1. Lovastatin. In a randomised, crossover study, 12 healthy subjects were given lovastatin 80 mg either alone or following 5 days of pre-treatment with roxithromycin 300 mg four times daily. Roxithromycin increased the

maximum level and AUC of lovastatin acid by 38% and 42%, respectively, and decreased the maximum level and AUC of lovastatin lactone by a similar amount.[24]

2. Simvastatin. A 73-year-old woman, who had been stable for 6 months while taking a combination of gemfibrozil 600 mg twice daily, simvastatin 80 mg daily and diltiazem, developed muscular weakness and myalgia 7 days after starting roxithromycin. All drugs were stopped, and initially she developed myoglobinuria and had a further elevation in her creatine kinase level, but this normalised over the following 18 days. She was discharged after 6 weeks, by which time she had regained full strength.[25]

(e) Telithromycin

In a randomised, crossover study, 14 healthy subjects were given telithromycin 800 mg daily for 5 days, with a single 40-mg dose of **simvastatin** either with, or 12 hours after, the last dose of telithromycin. Although separating administration decreased the effect of telithromycin on **simvastatin** levels by over 50%, the AUC and maximum serum levels of **simvastatin** were still raised 4-fold and 3.4-fold, respectively.[26]

(f) Unspecified macrolides

In a review of the FDA spontaneous reports of statin-associated rhabdomyolysis covering the period November 1997 to March 2000, macrolide antibacterials (unspecified) were potentially implicated in 13 of 73 cases of rhabdomyolysis seen with **atorvastatin**, 11 of 40 with **lovastatin**, 6 of 71 with **pravastatin**, and 10 of 215 with **simvastatin**.[27]

Mechanism

Most macrolides inhibit the cytochrome P450 isoenzyme CYP3A4, by which lovastatin, simvastatin and, to some extent, atorvastatin are metabolised. Hence the concurrent use of a macrolide raises the levels of these statins, leading in some instances to toxicity (myopathy and rhabdomyolysis). No interaction would be expected with pravastatin because it is not metabolised by CYP3A4, (although a moderate effect has been found with clarithromycin but it is possible that another mechanism may be responsible), no interaction would be expected with rosuvastatin as it is minimally metabolised, and no interaction would be expected with azithromycin (and possibly **dirithromycin** and **spiramycin**) as these macrolides not appear to inhibit CYP3A4 to any great extent. See 'Lipid regulating drugs', (p.1313), for a more detailed discussion of statin metabolism.

Importance and management

Information about the interactions between statins and macrolide antibacterials seems to be limited to the reports cited here. In general it appears that the macrolides raise the levels of statins metabolised by CYP3A4 (i.e. atorvastatin, lovastatin and simvastatin), but not all patients are affected. One study found a large interpatient variation in results,[23] which may account for this. It should be noted that the manufacturers of **lovastatin** and **simvastatin** contraindicate the concurrent use of these drugs with clarithromycin, erythromycin or telithromycin, and that the statin must be temporarily withdrawn if these antibacterials are required.[28-30]

The risk is smaller with atorvastatin, but as the cases illustrate adverse interactions are possible. The manufacturers of **atorvastatin** therefore recommend that concurrent use with clarithromycin or erythromycin should only be undertaken if the benefits outweigh the risks and that lower doses of atorvastatin should be considered.[31,32] The manufacturers of atorvastatin also suggest that the maintenance dose of atorvastatin should not exceed 20 mg daily if clarithromycin is also given or alternatively (for short courses of antibiotic) a temporary suspension of treatment with atorvastatin may be considered.[31,32] Note that the manufacturer of telithromycin specifically contraindicates atorvastatin.[33]

Pravastatin, **rosuvastatin** and **fluvastatin** are not significantly metabolised by CYP3A4, and so would not be expected to interact with macrolides via this mechanism, but potential cases have been identified with pravastatin.

To be on the safe side, any patient taking pravastatin who is given a macrolide (except probably azithromycin, dirithromycin or spiramycin) should be warned to be alert for any signs of myopathy (i.e. otherwise unexplained muscle pain, tenderness or weakness or dark coloured urine). If myopathy does occur, the statin should be stopped immediately. See also 'muscle toxicity', (p.1313), for further guidance on monitoring, and risk factors for muscle toxicity.

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9. Kahri AJ, Valkonen MM, Vuoristo MKE, Pentikäinen PJ. Rhabdomyolysis associated with concomitant use of simvastatin and clarithromycin. *Ann Pharmacother* (2004) 38, 719.
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27. Omar MA, Wilson JP. FDA adverse event reports on statin-associated rhabdomyolysis. *Ann Pharmacother* (2002) 36, 288–95.
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29. Simvador (Simvastatin). Discovery Pharmaceuticals Ltd. UK Summary of product characteristics, March 2009.
30. Zocor (Simvastatin). Merck & Co., Inc. US Prescribing information, June 2008.
31. Lipitor (Atorvastatin calcium). Pfizer Inc. US Prescribing information, June 2009.
32. Lipitor (Atorvastatin calcium trihydrate). Pfizer Ltd. UK Summary of product characteristics, December 2009.
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Statins + Nefazodone

Nefazodone has been implicated in cases of muscle toxicity and rhabdomyolysis in patients taking simvastatin, lovastatin, and possibly pravastatin.

Clinical evidence

(a) Lovastatin

In a review of the FDA spontaneous reports of statin-associated rhabdomyolysis, covering the period November 1997 to March 2000, nefazodone was potentially implicated in 2 cases of rhabdomyolysis involving lovastatin.[1]

(b) Pravastatin

A 74-year-old man taking atenolol, aspirin and pravastatin had his treatment with citalopram replaced by nefazodone 50 mg twice daily. Because the possibility of an interaction was suspected, his plasma creatine kinase levels were monitored and were found to be 877 units/L (reference range 0 to 190 units/L) at 36 hours. Lactate dehydrogenase, aspartate aminotransferase and alanine aminotransferase were all slightly elevated and

this was interpreted as indicating muscle toxicity. The nefazodone was withdrawn and although creatine kinase levels were falling they were still above the normal range when the pravastatin was withdrawn 14 days later. Pravastatin was subsequently re-introduced, and then venlafaxine 75 mg twice daily was added without problems.[2] However, the diagnosis of muscle toxicity has been questioned, and, because pravastatin levels were not measured, the possibility of an interaction has also been questioned.[3]

(c) Simvastatin

A 44-year-old man who had uneventfully taken simvastatin 40 mg daily for 19 weeks developed 'tea-coloured' urine, initially misdiagnosed as a urinary tract infection, a month after starting to take nefazodone 100 mg twice daily. A month later he was also complaining of severe myalgias of the thighs and calves, and was found to have muscle weakness and tenderness. Laboratory tests confirmed a diagnosis of rhabdomyolysis and myositis. He was asymptomatic within 3 weeks of stopping both drugs, and remained problem-free 5 weeks after restarting simvastatin 40 mg daily.[4] A further case of rhabdomyolysis has been reported in a 72-year-old man taking simvastatin. Symptoms developed 6 weeks after nefazodone was initiated (2 weeks after a dose increment). He recovered with rehydration after the nefazodone was stopped.[5] Other similar cases have also been reported,[6,7] and a review of the FDA spontaneous reports of statin-associated rhabdomyolysis, covering the period November 1997 to March 2000, nefazodone was potentially implicated in 2 cases of rhabdomyolysis involving simvastatin.[1]

Mechanism

Uncertain. The suggestion is that nefazodone (an inhibitor of the cytochrome P450 isoenzyme CYP3A4, an enzyme involved in the metabolism of simvastatin) caused a marked increase in the serum levels of simvastatin with accompanying toxicity.[4] The same mechanism might also account for the interaction with lovastatin, but the explanation for the case with pravastatin is less clear. See, 'Lipid regulating drugs', (p.1313), for a more detailed discussion of statin metabolism.

Importance and management

Information about interactions between nefazodone and the statins seems to be limited to these reports, but they are in line with the way lovastatin, simvastatin and **atorvastatin** are known to interact with other drugs. The manufacturers of lovastatin and simvastatin either advise avoiding or contraindicate the combination.[8-10] Some caution is probably prudent with atorvastatin, as it is also metabolised by CYP3A4, and a dose reduction should be considered. Patients given atorvastatin with nefazodone should be told to report any signs of myopathy and possible rhabdomyolysis (i.e. otherwise unexplained muscle pain, tenderness or weakness or dark coloured urine). If myopathy does occur, the statin should be stopped immediately. See also 'muscle toxicity', (p.1313), for further guidance on monitoring, and risk factors for muscle toxicity.

Other statins seem unlikely to interact. Note that in 2003 nefazodone was withdrawn in many countries due to cases of liver toxicity.

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Statins + Nicotinic acid (Niacin)

The risk of muscle toxicity may possibly be increased in patients taking a statin with nicotinic acid, but there appear to be only isolated reports of rhabdomyolysis in patients given these drugs.

Clinical evidence

(a) Lovastatin

A 43-year-old man taking lovastatin 40 mg twice daily developed rhabdomyolysis, which was attributed to the addition of nicotinic acid, titrated up to 2.5 g daily.[1] A similar reaction occurred in a 54-year-old man taking lovastatin 120 mg daily and nicotinic acid 3 g daily,[2] as well as in a 53-year-old man with a heart transplant taking multiple medications including ciclosporin, nicotinic acid 1.5 g daily and lovastatin 40 mg twice daily.[3] Myositis has also been briefly reported in a patient taking lovastatin and nicotinic acid.[1]

A combined preparation of lovastatin/nicotinic acid is marketed (*Advicor*, USA), and in a 52-week study investigating efficacy and tolerability, none of the 814 patients experienced drug-induced myopathy (myalgia and elevated creatine kinase levels greater than 10 times the upper limit of normal), although 7 patients were withdrawn from the study due to elevated creatine kinase levels.[4] A similar study reported that the risk of adverse events with extended-release nicotinic acid/lovastatin did not exceed the risks associated with the individual drug components; discontinuation of treatment due to muscle ache occurred in 2 of 57 patients (4%) taking nicotinic acid 1 g/lovastatin 20 mg, in 0 of 57 patients taking nicotinic acid 2 g/lovastatin 40 mg, in 1 of 61 patients (2%) taking nicotinic acid alone, and in 4 of 61 patients (7%) taking lovastatin alone.[5] Furthermore, a review of the use of extended-release niacin with lovastatin found that myalgia, which was reported in 3% of patients, tended to be associated with higher initial doses of statins.[6] In a review of the FDA spontaneous reports of statin-associated rhabdomyolysis covering the period November 1997 to March 2000, nicotinic acid was identified as a potentially interacting drug in 1 of 40 cases for lovastatin.[7] However, a later study using the FDA adverse event reporting system (1999 to March 2005) found no evidence of a clinically significant adverse drug interaction between extended-release nicotinic acid and lovastatin, and the rate of serious adverse event reports associated with the combination was similar to that of lovastatin or extended-release nicotinic acid alone.[8]

(b) Other statins

In contrast to the use of lovastatin, there do not appear to be any published reports of myopathy occurring with nicotinic acid and any other statin. Indeed, the manufacturers of **fluvastatin**[9] and **pravastatin**[10] report clinical studies in which nicotinic acid was given with pravastatin and myopathy was not observed. Furthermore, nicotinic acid does not alter the bioavailability of **fluvastatin**[11] or **pravastatin**.[12] The HDL-atherosclerosis treatment study (HATS) found that patients taking **simvastatin** (mean dose 13 mg daily) with nicotinic acid (mean dose 2.4 g daily) for 3 years had similar adverse effects and abnormal laboratory findings, when compared with patients who received placebo: symptoms of fatigue, nausea and/or muscle aches occurred in 9% versus 5% of patients, and creatine phosphokinase levels greater than twice the upper limit of normal occurred in 3% versus 4% of patients, respectively.[13]

In a review of the FDA spontaneous reports of statin-associated rhabdomyolysis covering the period November 1997 to March 2000, nicotinic acid was identified as a potentially interacting drug in 2 of 215 cases for **simvastatin** and 1 of 71 cases for **pravastatin**. Nicotinic acid was not identified as an interacting drug in any reports for **atorvastatin** or **fluvastatin**.[7]

Mechanism

Unknown. Additive muscle toxicity has been suggested.

Importance and management

The reports describing an adverse interaction between nicotinic acid and a statin are isolated and it is by no means certain that nicotinic acid contributed to what happened. For example, in one case, ciclosporin may have been a contributory factor (consider also 'Statins + Ciclosporin', p.1326) and myopathy is known to occur with lovastatin alone,[14] with a reported incidence of 0.1%. Furthermore, in a report covering recommendations to healthcare professionals regarding the safety of nicotinic acid, it was proposed that, on the basis of almost two decades of clinical evidence, the use of nicotinic acid with a statin does not potentiate statin-related myopathic reactions. In addition, it was suggested that isolated case reports of myopathy, including rhabdomyolysis, with the concurrent use of nicotinic acid and a statin might have been related to other drug interactions or possibly hepatic toxicity from earlier forms of nicotinic acid with subsequent

decreased hepatic extraction of statins and increased peripheral blood statin levels.[15]

Nevertheless, the manufacturer of lovastatin recommends a maximum dose of 20 mg in patients taking nicotinic acid in doses of 1 g or more daily.[16] Similarly the UK manufacturer of simvastatin recommends a maximum dose of 10 mg in patients taking nicotinic acid in doses of 1 g or more daily.[17] The manufacturers of atorvastatin[18,19] and rosuvastatin[20] also suggest that the lowest statin dose should be used, or a statin dose reduction considered. Patients should be told to report otherwise unexplained muscle pain, tenderness or weakness or dark coloured urine). See also 'muscle toxicity', (p.1313), for further guidance on monitoring, and risk factors for muscle toxicity.

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4. Kashyap ML, McGovern ME, Berra K, Guyton JR, Kwiterovich PO, Harper WL, Toth PD, Favrot LK, Kerzner B, Nash SD, Bays HE, Simmons PD. Long-term safety and efficacy of a once-daily niacin/lovastatin formulation for patients with dyslipidaemia. *Am J Cardiol* (2002) 89, 672–8.
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10. Pravachol (Pravastatin sodium). Bristol-Myers Squibb Company. US Prescribing information, March 2007.
11. Smith HT, Jokubaitis LA, Troendle AJ, Hwang DS, Robinson WT. Pharmacokinetics of fluvastatin and specific drug interactions. *Am J Hypertens* (1993) 6, 375S–382S.
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14. Bilheimer DW. Long term clinical tolerance of lovastatin (mevinolin) and simvastatin (epistatin). An overview. *Drug Invest* (1990) 2 (Suppl 2), 58–67.
15. Guyton JR, Bays HE. Safety considerations with niacin therapy. *Am J Cardiol* (2007) 99 (Suppl), 22C–31C.
16. Mevacor (Lovastatin). Merck & Co., Inc. US Prescribing information, September 2008.
17. Simvador (Simvastatin). Discovery Pharmaceuticals Ltd. UK Summary of product characteristics, March 2009.
18. Lipitor (Atorvastatin calcium trihydrate). Pfizer Ltd. UK Summary of product characteristics, December 2009.
19. Lipitor (Atorvastatin calcium). Pfizer Inc. US Prescribing information, June 2009.
20. Crestor (Rosuvastatin calcium). AstraZeneca. US Prescribing information, February 2009.

Statins + NNRTIs

Delavirdine is expected to raise the levels of atorvastatin, fluvastatin, simvastatin and lovastatin. This expectation is supported by a case of rhabdomyolysis, which developed in a patient taking atorvastatin and delavirdine. Efavirenz (and possibly nevirapine) *lower* the levels of atorvastatin, simvastatin, and pravastatin. Etravirine lowers atorvastatin levels and is predicted to lower simvastatin and lovastatin levels. Etravirine is also predicted to raise fluvastatin levels.

Clinical evidence, mechanism, importance and management

(a) Delavirdine

An isolated case report describes a 63-year-old HIV-positive man, who had been taking **atorvastatin** 20 mg daily with indinavir, lamivudine and stavudine, and who was admitted to hospital 2 months after indinavir was replaced with delavirdine. He had a one-month history of malaise, muscle pain, vomiting, and dark urine. Laboratory tests confirmed a diagnosis of rhabdomyolysis, and he was found to have acute renal failure. All drugs were withheld, and he gradually recovered over the following month. It was suggested that delavirdine inhibited the metabolism of **atorvastatin**,[1] probably by the cytochrome P450 isoenzyme CYP3A4. The manufacturer of delavirdine reports that it may be expected to increase the plasma levels of **atorvastatin**. They advise caution, due to the risk of rhabdomyolysis, and suggest using the lowest possible dose of **atorvastatin** with careful monitoring.[2] See 'muscle toxicity', (p.1313), for further guidance on monitoring, and risk factors for muscle toxicity. The same advice is given for **fluvastatin**,[2] which is metabolised by the cytochrome P450 isoenzyme CYP2C9, which delavirdine is known to inhibit.

Simvastatin and **lovastatin** are metabolised in a similar way to **atorvastatin**, and would therefore be expected to interact to a similar, if not greater magnitude. Indeed, a case report describes rhabdomyolysis in a patient taking **simvastatin**, delavirdine, atazanavir and amiodarone, see 'Statins + Protease inhibitors', p.1341.

The manufacturer of delavirdine recommends that it should not be used concurrently with either **simvastatin** or **lovastatin**.[2]

(b) Efavirenz

In an open-label study, 42 healthy subjects were given efavirenz 600 mg daily for 11 days, with **atorvastatin** 10 mg daily, **simvastatin** 40 mg daily, or **pravastatin** 40 mg daily for the last 2 days. Efavirenz reduced the AUC of **simvastatin** and its active metabolites by about 45 to 55%, reduced the AUC of **atorvastatin** and its active metabolites by 35 to 45%, and reduced the AUC of **pravastatin** by about 40%. The pharmacokinetics of efavirenz were not changed. Decreases in LDL-cholesterol were attenuated when efavirenz was given with **simvastatin**.[3] The changes with **atorvastatin** and **simvastatin** were expected, as efavirenz induces the cytochrome P450 isoenzyme CYP3A4, by which **simvastatin**, and to an extent **atorvastatin** are metabolised. The authors note that similar results would be expected with **nevirapine**, which also induces CYP3A4. The reasons for the reduction in the **pravastatin** AUC are less clear, as it is not metabolised by CYP3A4.[3]

It would seem prudent to monitor the lipid-profile of patients taking efavirenz and any of these statins, although bear in mind that NNRTIs are often used with 'protease inhibitors', (p.1341), which dramatically raise the levels of some statins.

(c) Etravirine

The manufacturers report a study in which 16 healthy subjects were given **atorvastatin** 40 mg daily with etravirine. Etravirine pharmacokinetics were unaffected, but the AUC of **atorvastatin** was modestly decreased, by 37%, and the AUC of its hydroxy metabolite was modestly raised, by 27%.[4,5] These effects probably occur because etravirine induces the cytochrome P450 isoenzyme CYP3A4 by which **atorvastatin** is metabolised. The manufacturers reasonably predict that the levels of other statins metabolised by CYP3A4 (i.e. **lovastatin** and **simvastatin**) may be similarly affected.[4,5]

Etravirine is also an inhibitor of the cytochrome P450 isoenzyme CYP2C9 by which **fluvastatin** is metabolised. The manufacturers therefore predict that **fluvastatin** levels may be raised by etravirine.[4,5]

The manufacturers recommend monitoring the concurrent use of etravirine and any of these statins, and adjusting the dose according to clinical response. The US manufacturers predict that **rosuvastatin** will not interact; however the UK manufacturers suggest that an interaction is possible. This seems highly unlikely, as less than 10% of **rosuvastatin** is metabolised. No interaction is expected between etravirine and **pravastatin**. Therefore these **pravastatin** or **rosuvastatin** may prove to be suitable alternatives.

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4. Intelence (Etravirine). Tibotec, Inc. US Prescribing information, November 2009.
5. Intelence (Etravirine). Janssen-Cilag Ltd. UK Summary of product characteristics, November 2009.

Statins + Orlistat

Orlistat has no clinically relevant effect on the pharmacokinetics of atorvastatin, pravastatin or simvastatin.

Clinical evidence, mechanism, importance and management

(a) Atorvastatin

In a randomised study, 32 healthy subjects were given atorvastatin 20 mg daily for 6 days, with or without orlistat 120 mg three times daily for 6 days. Orlistat had no significant effect on the pharmacokinetics of atorvastatin.[1]

(b) Pravastatin

In a placebo-controlled, crossover study in 24 subjects with mild hypercholesterolaemia, orlistat 120 mg three times daily was reported to have no effect on the pharmacokinetics, or lipid-lowering effects, of pravastatin 40 mg daily, when both drugs were given for 6 days.[2]

A review includes brief details of a comparative study in two groups of healthy subjects given pravastatin, either with orlistat or placebo. After 10 days there was no significant difference in the pravastatin AUC between the groups, but the maximum serum concentration did show a tendency to be higher in the orlistat group.[3]

(c) Simvastatin

In a placebo-controlled, randomised study in 29 healthy subjects orlistat 120 mg three times daily had no effect on the pharmacokinetics of simvastatin 40 mg daily.[4]

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2. Oo CY, Akbari B, Lee S, Nichols G, Hellmann CP. Effect of orlistat, a novel anti-obesity agent, on the pharmacokinetics and pharmacodynamics of pravastatin in patients with mild hypercholesterolaemia. *Clin Drug Invest* (1999) 17, 217–23.
3. Guerciolini R. Mode of action of orlistat. *Int J Obes* (1997) 21 (Suppl 3), S12–S23.
4. Zhi J, Moore R, Kanitra L, Mulligan TE. Effects of orlistat, a lipase inhibitor, on the pharmacokinetics of three highly lipophilic drugs (amiodarone, fluoxetine, and simvastatin) in healthy volunteers. *J Clin Pharmacol* (2003) 43, 428–34.

Statins + Phenytoin

A number of isolated case reports describe a reduced cholesterol-lowering effect of simvastatin, fluvastatin and atorvastatin in patients taking phenytoin. The concurrent use of phenytoin and fluvastatin modestly raises the levels of both drugs.

Clinical evidence

A 50-year-old woman taking **simvastatin** 10 mg daily had her antiepileptic medication changed from sodium valproate to phenytoin 325 mg daily. Over the following 3 months her total cholesterol rose from 9.4 mmol/L to 15.99 mmol/L. The dose of **simvastatin** was gradually increased to 40 mg daily without a significant effect on her cholesterol levels. Despite further changes (to **fluvastatin** 40 mg daily, then to **atorvastatin** 80 mg daily) her cholesterol level remained above 10 mmol/L. Finally phenytoin was discontinued and her cholesterol dropped to 6.24 mmol/L with **atorvastatin** 80 mg daily.[1] Similarly, a 78-year-old woman, who had been stable on multiple drugs including **simvastatin** 40 mg and phenytoin 300 mg daily for several years, was admitted to hospital after she inadvertently omitted her diuretic and mistakenly took extra phenytoin for a week: her phenytoin levels and also her cholesterol levels were found to be raised. The phenytoin was withheld and the cholesterol levels decreased gradually along with the reduction in phenytoin levels.[2] A further case describes a 61-year-old man taking long-term phenytoin and phenobarbital who had a lack of significant improvement in lipid profiles while taking **atorvastatin** 40 mg for 8 weeks then 80 mg daily, even with the addition of ezetimibe 10 mg daily and nicotinic acid (niacin), titrated up to 2 g daily. His phenytoin was discontinued and 2 months later his LDL-cholesterol levels had decreased by about 50%.[3]

The addition of modified-release phenytoin 300 mg daily to **fluvastatin** 40 mg daily increased the maximum levels and AUC of **fluvastatin** by 27% and 40%, respectively, and increased the maximum levels and AUC of phenytoin by 5% and 20%, respectively.[4]

Mechanism

It seems possible that phenytoin induced the metabolism of simvastatin and atorvastatin by the cytochrome P450 isoenzyme CYP3A4, so that they were cleared from the body more quickly and were therefore less effective. The increase in fluvastatin levels and phenytoin levels seen in the study probably occurs because both drugs are metabolised by the cytochrome P450 isoenzyme CYP2C9.

Importance and management

Evidence of an interaction between phenytoin and atorvastatin or simvastatin currently appears to be limited to these few reports and their general significance remains unclear. However, if lipid levels remain significantly elevated in a patient taking phenytoin, it might be worth considering switching to a statin that is not significantly metabolised by the cytochrome P450 enzyme system (see 'statins', (p.1313)).

There is a small risk that the concurrent use of fluvastatin and phenytoin could result in myopathy. Patients should be told to report any signs of myopathy and possible rhabdomyolysis (i.e. otherwise unexplained muscle pain, tenderness or weakness or dark coloured urine). If myopathy does occur, the statin should be stopped immediately. See also 'muscle toxicity', (p.1313), for further guidance on monitoring, and risk factors for muscle toxicity. The alteration in phenytoin levels caused by fluvastatin seems unlikely to be clinically significant, although the manufacturer of fluvastatin cautiously recommends monitoring phenytoin when fluvastatin is started or the dose is altered.[4]

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Statins + Phosphodiesterase type-5 inhibitors

A man taking simvastatin developed symptoms of rhabdomyolysis after taking a single dose of sildenafil. The pharmacokinetics of atorvastatin and sildenafil do not appear to be altered by concurrent use, and tadalafil does not alter lovastatin pharmacokinetics.

Clinical evidence

(a) Sildenafil

A 76-year-old man who had been taking **simvastatin** 10 mg daily for 3 years, presented at a clinic with a 3-day history of severe and unexplained muscle aches, particularly in the lower part of his legs and feet. The problem had started within 10 hours of taking a single 50-mg dose of sildenafil. When examined he showed no muscle tenderness or swelling but his creatine phosphokinase level was slightly raised (406 units/L). There was also a mild elevation of blood urea nitrogen and an increase in creatinine and potassium levels. A tentative diagnosis of rhabdomyolysis was made, there being no other obvious identifiable cause for the myalgia. Both **simvastatin** and sildenafil were stopped, and he made a full recovery.[1] A study in 24 healthy subjects found that the pharmacokinetics of sildenafil (single 100-mg dose) and **atorvastatin** (10 mg daily for 7 days) were unchanged by concurrent use.[2]

(b) Tadalafil

In a study in 16 healthy subjects, tadalafil 20 mg daily for 14 days did not affect the pharmacokinetics of a 40-mg dose of **lovastatin**.[3]

Mechanism, importance and management

The reasons for this possible interaction are not known. This is as yet an isolated case, and no broad generalisations can be based on such slim evidence. Based on this evidence no further precautions currently seem necessary.

1. Gutierrez CA. Sildenafil-simvastatin interaction: possible cause of rhabdomyolysis? *Am Fam Physician* (2001) 63, 636–7.
2. Chung M, DiRico A, Calcagni A, Messig M, Scott R. Lack of a drug interaction between sildenafil and atorvastatin. *J Clin Pharmacol* (2000) 40, 1057.
3. Ring BJ, Patterson BE, Mitchell MI, Vandenbranden M, Gillespie J, Bedding AW, Jewell H, Payne CD, Forgue ST, Eckstein J, Wrighton SA, Phillips DL. Effect of tadalafil on cytochrome P450 3A4-mediated clearance: studies in vitro and in vivo. *Clin Pharmacol Ther* (2005) 77, 63–75.

Statins + Protease inhibitors

The levels of simvastatin and/or atorvastatin are markedly increased by darunavir, lopinavir, saquinavir and tipranavir (all boosted with ritonavir), or nelfinavir alone. Several cases of rhabdomyolysis have been attributed to this interaction. Lovastatin would be expected to interact similarly. Rosuvastatin appears to be moderately affected by protease inhibitors, and pravastatin is usually only modestly affected, although there can be large inter-

individual variations. There do not appear to be any reports of interactions with fluvastatin and protease inhibitors.

Clinical evidence

(a) Atazanavir

A 72-year-old HIV-positive man with coronary artery disease taking multiple medications including atazanavir 400 mg daily and delavirdine 600 mg twice daily presented with muscle pain, fatigue and dark orange urine. He had been taking atorvastatin 40 mg daily for 2 years without any adverse effects, but 27 days earlier had been switched to **simvastatin** 80 mg daily. Furthermore, amiodarone had also been started 19 days earlier. The patient was diagnosed with rhabdomyolysis and acute renal failure probably due to an interaction between simvastatin and atazanavir and/or amiodarone,[1] see also 'Statins + Amiodarone', p.1320. Note that delavirdine may also increase simvastatin plasma levels, see 'Statins + NNRTIs', p.1340.

(b) Darunavir with Ritonavir

In a study, ritonavir-boosted darunavir 100/300 mg twice daily increased the AUC and minimum levels of **atorvastatin** 10 mg daily by three- to fourfold. Ritonavir-boosted darunavir 100/600 mg twice daily increased the AUC of a single 40-mg dose of **pravastatin** fivefold in some patients, although the majority of patients experienced no increase.[2,3]

(c) Indinavir

In a non-randomised study, patients receiving HAART were given **pravastatin** or **fluvastatin**. Neither of the statins altered the pharmacokinetics of indinavir, the combination was well tolerated, and no increase in adverse events was seen.[4]

(d) Lopinavir with Ritonavir

In a study, 24 healthy subjects were given either **atorvastatin** 20 mg daily or **pravastatin** 20 mg daily for 4 days during a 14-day course of lopinavir/ritonavir 400/100 mg twice daily. The maximum serum levels and AUC of **atorvastatin** were increased 4.7- to 5.9-fold and the maximum serum levels and AUC of **pravastatin** were only increased by about 30%. **Atorvastatin** and **pravastatin** had no effect on the pharmacokinetics of lopinavir or ritonavir.[5] A study in 22 HIV-positive patients found that lopinavir/ritonavir concentrations were not affected by **rosuvastatin** 10 to 40 mg daily over a 12-week period, but rosuvastatin levels appeared to be increased by about 60%, when compared with data from healthy subjects.[6] Another study in 15 healthy subjects found that lopinavir/ritonavir 400/100 mg twice daily increased the AUC and maximum plasma concentration of **rosuvastatin** 20 mg daily twofold and fivefold, respectively.[7]

(e) Nelfinavir

In an open label study, 31 healthy subjects were given either **atorvastatin** 10 mg daily or **simvastatin** 20 mg daily for 28 days, with nelfinavir 1.25 g twice daily for the last 14 days. Nelfinavir increased the maximum serum levels and AUC of **atorvastatin** approximately twofold and the maximum serum levels and AUC of **simvastatin** approximately sixfold. No significant adverse effects, or any signs of rhabdomyolysis were noted throughout the study.[8]

One study found that nelfinavir 750 mg three times daily increased the maximum serum levels and AUC of **pravastatin** 40 mg daily by 29% and 35%, respectively, and increased the maximum serum levels and AUC of **atorvastatin** 40 mg daily by 32% and 209%, respectively.[9] A further study, in which 14 healthy subjects took nelfinavir 1.25 g twice daily for 12 days, with **pravastatin** 40 mg daily for the final 4 days, found that the AUC of **pravastatin** ranged from a decrease of 65% to an increase of 11%, and the maximum serum levels ranged from a decrease of 77% to an increase of 154%.[10]

In another study, 14 healthy subjects were given nelfinavir 1.25 g twice daily for 18 days, with **pravastatin** 40 mg daily for the last 4 days. No significant change was noted in the pharmacokinetics of nelfinavir, nor of its major metabolite.[11]

A case report describes a 70-year-old HIV-positive man taking nelfinavir who developed rhabdomyolysis and died, about 3 weeks after being given **simvastatin** 80 mg daily. He had previously tolerated both **pravastatin** 40 mg daily and **simvastatin** 10 mg daily.[12]

(f) Ritonavir

A 51-year-old woman was admitted to hospital with a 4-day history of muscular aches and weakness. Among other drugs, she had been taking zidovudine, lamivudine, indinavir, and **simvastatin** for 2 years. Ritonavir 100 mg twice daily had been added to her usual regimen 2 weeks previously. The rhabdomyolysis was therefore attributed to an interaction between ritonavir and **simvastatin**.[13] Another similar case has also been reported.[14] See also (b) and (d) above and (g) and (h) below for interactions of ritonavir combined with other protease inhibitors.

(g) Saquinavir with Ritonavir

Ritonavir 300 mg twice daily and saquinavir 400 mg twice daily were given to healthy subjects for 3 days, after which the dose was increased to ritonavir 400 mg twice daily and saquinavir 400 mg twice daily for a further 11 days. On the last 4 days **atorvastatin**, **pravastatin**, or **simvastatin** (all 40 mg daily) were also given. The mean **pravastatin** AUC was approximately halved (13 subjects), the mean **atorvastatin** AUC was increased approximately fourfold (14 subjects) and the mean **simvastatin** acid AUC was increased approximately 32-fold (14 subjects). No cases of rhabdomyolysis were noted.[11]

(h) Tipranavir with Ritonavir

Tipranavir with ritonavir has been found to increase the plasma levels of a single dose of **atorvastatin** by eight- to tenfold. The pharmacokinetics of tipranavir are not affected by **atorvastatin**.[15] The manufacturer of tipranavir says that the plasma levels of both tipranavir and **rosuvastatin** are increased when rosuvastatin and ritonavir-boosted tipranavir are given concurrently.[16]

(i) Unnamed antiretrovirals

A study found that although **rosuvastatin** 10 or 20 mg was effective in lowering lipid parameters in HIV-positive patients (84% taking protease inhibitors), the lipid changes were smaller than those found in subjects not infected with HIV.[17]

Mechanism

Many protease inhibitors, especially ritonavir, are known to be potent inhibitors of the cytochrome P450 isoenzyme CYP3A4. The levels of statins metabolised by this isoenzyme (notably simvastatin, lovastatin and to some extent atorvastatin) are therefore increased. See 'Lipid regulating drugs', (p.1313) for information on the metabolism of the individual statins. The exact mechanism of the interaction with rosuvastatin is unknown, but may be the result of transporter inhibition. Fluvastatin and pravastatin are less likely to be affected by protease inhibitors because they are not significantly metabolised by CYP3A4, or any of the other isoenzymes that ritonavir can inhibit.

Importance and management

The interactions of the protease inhibitors and simvastatin appear to be established by the pharmacokinetic studies cited here, and supported by a few case reports. It is generally recommended that **simvastatin** and **lovastatin**, which is similarly metabolised, should be avoided in patients taking protease inhibitors.

The interactions of **atorvastatin** with protease inhibitors are also established. Concurrent use should only be undertaken if the benefits outweigh the risks and atorvastatin should be used in low doses (e.g. 10 mg) with care; the US manufacturer says that in the presence of a ritonavir-boosted protease inhibitor, for doses of atorvastatin exceeding 20 mg, appropriate clinical assessment is recommended to ensure the lowest dose necessary is used.[18]

The US manufacturer of **rosuvastatin** states that the dose should be limited to 10 mg daily in patients taking lopinavir/ritonavir.[19] However, the UK manufacturer of rosuvastatin says that the concurrent use of protease inhibitors is not recommended.[20]

Pravastatin, **fluvastatin** or low-dose atorvastatin have been recommended as first-line agents in HIV-positive patients receiving protease inhibitors.[21] Pravastatin and fluvastatin can probably be used without dose adjustments with most protease inhibitors, but monitoring is needed to confirm this as one study with nelfinavir and pravastatin[10] suggested a trend towards *reduced* pravastatin efficacy, while a small number of patients had *increased* pravastatin levels when they were given darunavir. Until more is known, it would seem prudent to initiate the concurrent use of pravastatin and a protease inhibitor at the lowest dose of pravastatin.

As a general rule, any patient given a statin and a protease inhibitor should be told to report any signs of myopathy and possible rhabdomyolysis (i.e. otherwise unexplained muscle pain, tenderness or weakness or dark coloured urine). If myopathy does occur, the statin should be stopped

immediately. See also 'muscle toxicity', (p.1313), for further guidance on monitoring, and risk factors for muscle toxicity.

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Statins + Ranolazine

Ranolazine may increase the levels of simvastatin. Other statins that are similarly metabolised may also be affected.

Clinical evidence

In an open-label study, simvastatin 80 mg daily was given with ranolazine 1 g twice daily for 4 days. Simvastatin had no effect on the pharmacokinetics of ranolazine, but ranolazine increased the maximum plasma levels of simvastatin and its active metabolites by up to about twofold and increased its AUC by 40 to 60%.[1]

Mechanism

Simvastatin is a substrate of the cytochrome P450 isoenzyme CYP3A4, of which ranolazine is a moderate inhibitor. Concurrent use can therefore increase the levels of simvastatin and its active metabolite. Note that, **lovastatin** is also predominantly metabolised by CYP3A4 and **atorvastatin** is metabolised, in part, by CYP3A4.

Importance and management

Evidence for an interaction between the statins and ranolazine appears to be limited to this one study, but an interaction appears to be established. The increased simvastatin levels seen appear to be modest; however, they may be clinically significant in some patients. All patients taking statins should be warned about the symptoms of myopathy and told to report muscle pain or weakness. It would be prudent to reinforce this advice to patients given simvastatin or lovastatin, and possibly atorvastatin, if they are given ranolazine.

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Statins + Rifampicin (Rifampin)

Rifampicin lowers the serum levels of atorvastatin, fluvastatin, pravastatin, and simvastatin, and may increase or decrease the levels of rosuvastatin in some subjects.

Clinical evidence

It was briefly mentioned in a review by the manufacturer of **fluvastatin** that rifampicin reduced the AUC and the maximum serum levels of **fluvastatin** by 51% and 59%, respectively. No further study details were given.[1] In a randomised, crossover study in 10 healthy subjects, 5 days of pretreatment with rifampicin 600 mg daily reduced the AUCs of **simvastatin** and simvastatin acid by 87% and 93%, respectively.[2] A study of the same design with a 40-mg dose of **atorvastatin** found that rifampicin decreased the AUC of **atorvastatin** by 80% and decreased the AUCs of its two active metabolites by 43% and 81%, respectively. There was considerable intersubject variation in these values.[3] In a further study by the same authors, this time with **pravastatin** 40 mg, it was found that rifampicin reduced the AUC of **pravastatin** by 31%, but again there were large interindividual differences in the results, with some subjects having an *increase* in AUC.[4]

In a randomised, placebo-controlled study, 18 healthy subjects were given rifampicin 450 mg daily for 6 days, with a single 20-mg dose of **rosuvastatin** on day 7. The mean AUC of **rosuvastatin** was not altered by rifampicin; however, 3 subjects had an increase in the AUC of **rosuvastatin** of more than 50% and 3 subjects had an decrease in the AUC of **rosuvastatin** of more than 50%.[5]

Mechanism

Rifampicin is a known inducer of cytochrome P450 isoenzymes, including CYP3A4 and CYP2C9 by which a number of the statins are metabolised (see 'statins', (p.1313)). Rifampicin also has effects on drug transporter proteins (OATP, P-glycoprotein) and it seems possible that this may account for its interaction with statins that are not greatly metabolised by the cytochrome P450 enzyme system.

Importance and management

Evidence appears to be limited to the pharmacokinetic studies cited, which do not assess the clinical relevance of the pharmacokinetic interactions seen between rifampicin and a number of the statins. Nevertheless an interaction appears to be established. It might therefore be necessary to increase the dosage of atorvastatin, fluvastatin, simvastatin, and possibly pravastatin in some subjects, if rifampicin is given concurrently, but the efficacy of this approach needs confirmation.

The situation with rosuvastatin is less clear. Until more is known it would seem prudent to be alert both for the need to increase the rosuvastatin dose or an increase in rosuvastatin adverse effects if rifampicin is also given.

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4. Kyrklund C, Backman JT, Neuvonen M, Neuvonen PJ. Effect of rifampicin on pravastatin pharmacokinetics in healthy subjects. *Br J Clin Pharmacol* (2004) 57, 181–7.
5. Zhang W, Deng S, Chen X-P, Zhou G, Xie H-T, He F-Y, Cao D, Li Y-J, Zhou H-H. Pharmacokinetics of rosuvastatin when coadministered with rifampicin in healthy males: a randomized, single-blind, placebo-controlled, crossover study. Clin Ther (2008) 30, 1283–9.

Statins + Risperidone

A schizophrenic patient taking risperidone developed rhabdomyolysis when simvastatin was added.

Clinical evidence

A 22-year-old patient with schizophrenia taking risperidone 4 mg daily and clonazepam 2 mg daily for about 4 weeks started taking **simvastatin** 10 mg daily. After about 5 days later he experienced pain in his right ankle and heel, which increased in severity and spread proximally, accompanied by swelling and a rash over the affected area. In addition, his creatine phosphokinase levels were dramatically raised (12, 408 units/L). The simvastatin was discontinued and rhabdomyolysis associated with an acute compartment syndrome was diagnosed, requiring emergency surgery.

Mechanism

It was suggested that the risperidone might have reduced the metabolism of the simvastatin by the cytochrome P450 system, causing increased plasma concentration of the statin and resulting in muscle injury. However, simvastatin is metabolised by CYP3A4 and risperidone via CYP2D6, and to a lesser extent CYP3A4, and risperidone is not known to directly inhibit CYP3A4. Nevertheless, risperidone might compete with simvastatin for this isoenzyme, and this may become clinically relevant in a patient who is lacking or totally deficient in CYP2D6, when CYP3A4 would become more important in the metabolism of risperidone.[1]

Importance and management

Evidence for an interaction between simvastatin and risperidone is limited to this case report. As the patient did not receive simvastatin alone, an interaction is not established. Nevertheless, the authors advise caution regarding the selection of statins that are metabolised via CYP3A4 in patients taking risperidone, and suggest that statins that are not significantly metabolised by cytochrome P450 may be a safer alternative (see 'statins', (p.1313), for a further discussion of statin metabolism). However, it seems somewhat premature to take precautions in all patients based on this isolated case report.

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Statins + St John's wort (*Hypericum perforatum*)

St John's wort modestly decreases the plasma level of simvastatin and may reduce the lipid-lowering effects of atorvastatin. An isolated report also unexpectedly suggests that rosuvastatin may also interact. St John's wort does not appear to affect the pharmacokinetics of pravastatin.

Clinical evidence

In a placebo-controlled, crossover study, 16 healthy subjects took St John's wort 300 mg three times daily for 14 days. On day 14 **simvastatin** 10 mg was given to 8 subjects and **pravastatin** 20 mg was given to the other 8 subjects. St John's wort did not affect the plasma concentration of **pravastatin**, but it tended to reduce the **simvastatin** AUC and significantly reduced the AUC of its active metabolite, simvastatin hydroxy acid, by 62%.[1]

In a crossover study in 24 patients with hypercholesterolaemia taking long-term **simvastatin** 10 to 40 mg daily (an average dose of 20.8 mg daily), St John's wort (*Movina*) 300 mg twice daily for 4 weeks, significantly raised the levels of total cholesterol from 4.56 mmol/L (pre-treatment) to 5.08 mmol/L and LDL-cholesterol from 2.30 mmol/L to 2.72 mmol/L. The authors equate the magnitude of the increased LDL-cholesterol levels to a halving of the effects of **simvastatin**.[2]

In a similar study by the same authors, 16 patients with hypercholesterolaemia taking long-term **atorvastatin** 10 to 40 mg daily (an average dose of 14.4 mg daily), were given St John's wort (*Movina*) 300 mg twice daily for 4 weeks. St John's wort significantly raised the levels of total cholesterol from 4.76 mmol/L (pre-treatment) to 5.1 mmol/L and LDL-cholesterol from 2.39 mmol/L to 2.66 mmol/L. The levels of **atorvastatin** were not measured in this study. The authors equate the magnitude of the increased LDL-cholesterol levels to a loss of a third of the effects of **atorvastatin**. No adverse effects were reported.[3]

A case report describes a 59-year-old man who was taking **rosuvastatin** 10 mg daily with satisfactory lipid levels. Six months later, a routine blood test indicated that his total cholesterol had risen from 4.27 mmol/L to 6.1 mmol/L. On questioning he said that he had been taking a supplement containing St John's wort 600 mg daily. He stopped taking the supplement, and 4 months later his cholesterol levels had reduced to about the former level.[4]

Mechanism

The reason for this interaction is unknown. St John's wort may reduce the levels of simvastatin and its metabolite by inducing the cytochrome P450 isoenzyme CYP3A4 or by having some effect on P-glycoprotein. Rosuvastatin does not appear to be a P-glycoprotein substrate; the authors of the study suggest that CYP2C9 and CYP2C19 may have been involved, but as rosuvastatin is less than 10% metabolised this seems unlikely.

Importance and management

Although the evidence is limited, it appears that St John's wort may reduce the efficacy of atorvastatin and simvastatin, which may result in a clinically relevant increase in total cholesterol and LDL-cholesterol levels, depending on the patients baseline result and medical history. It may be prudent to consider an interaction if lipid-lowering targets are not met, and advise the patient to stop taking St John's wort or adjust the dose of statin, as needed.

No significant interaction would be expected with pravastatin as it is not primarily metabolised by CYP3A4, and this was demonstrated in the study above. Similarly, no significant interaction would be expected with rosuvastatin, but the case report adds a note of caution.

1. Sugimoto K, Ohmori M, Tsuruoka S, Nishiki K, Kawaguchi A, Harada K, Arakawa M, Sakomoto K, Masada M, Miyamori I, Fujimura A. Different effects of St John's wort on the pharmacokinetics of simvastatin and pravastatin. *Clin Pharmacol Ther* (2001) 70, 518–24.
2. Eggertsen R, Andreasson Å, Andrén L. Effects of treatment with a commercially available St John's Wort product (Movina®) on cholesterol levels in patients with hypercholesterolemia treated with simvastatin. *Scand J Prim Health Care* (2007) 25, 154–9.
3. Andrén L, Andreasson Å, Eggertsen R. Interaction between a commercially available St. John's wort product (Movina) and atorvastatin in patients with hypercholesterolemia. *Eur J Clin Pharmacol* (2007) 63, 913–16.
4. Gordon RY, Becker DJ, Rader DJ. Reduced efficacy of rosuvastatin by St John's wort. Am J Med (2009) 122, e1–e2.

Statins + Tacrolimus

An isolated case report attributes rhabdomyolysis to an interaction between tacrolimus and simvastatin. Tacrolimus does not appear to affect atorvastatin pharmacokinetics.

Clinical evidence, mechanism, importance and management

A pharmacokinetic study in 13 healthy subjects found that the short-term use of tacrolimus (2 doses 12 hours apart) did not affect the pharmacokinetics of **atorvastatin**.[1]

A 51-year-old woman, who was taking tacrolimus after a kidney transplant, started taking **simvastatin** 10 mg daily following a stroke. After 5 months, the dose was increased to 20 mg daily, and fusidic acid was started for osteomyelitis. Muscle pain developed 2 weeks later, and after a further 3 weeks she was admitted to hospital, when her creatine kinase level was found to be 24 000 units/mL (normal range 10 to 70 units/mL) and she had renal impairment. The **simvastatin** and fusidic acid were immediately stopped and the patient recovered over the following 2 weeks. She was later treated with a combination of **fluvastatin**, tacrolimus and fusidic acid without incident, leading the authors to suspect that the rhabdomyolysis was caused by an interaction between **simvastatin** and tacrolimus.[2] However, note that fusidic acid, has been implicated in a number of cases of rhabdomyolysis with statins, including simvastatin, see 'Statins + Fusidic acid', p.1335, many of which were only reported subsequent to this case. It therefore now seems more likely that the reaction seen in this case was actually an interaction between fusidic acid and simvastatin.

1. Lemahieu WPD, Hermann M, Asberg A, Verbeke K, Holdaas H, Vanrenterghem Y, Maes BD. Combined therapy with atorvastatin and calcineurin inhibitors: no interactions with tacrolimus. *Am J Transplant* (2005) 5, 2236–43.
2. Kotanko P, Kiristis W, Skrabal F. Rhabdomyolysis and acute renal graft impairment in a patient treated with simvastatin, tacrolimus, and fusidic acid. *Nephron* (2002) 90, 234–5.

Statins + Vaccines

A study suggests that influenza vaccination does not precipitate myopathy in patients taking statins, although one possible case

has been reported. Atorvastatin does not appear to affect the antibody response to hepatitis A vaccination.

Clinical evidence, mechanism, importance and management

An isolated report describes a patient who had uneventfully taken cerivastatin and bezafibrate for 2 months, who developed rhabdomyolysis after being given an **influenza vaccine**. The patient developed diffuse myalgia within 24 hours of the vaccination. Initially he attributed the myalgia to the vaccination, but he developed increasing muscular weakness, which rendered him unable to get out of bed 3 days post vaccination.[1] In contrast, in a study in 98 outpatients receiving **influenza vaccination**, there was no indication that **influenza vaccine** caused clinical or laboratory evidence of myopathy in patients taking statins. Only 2 patients experienced myopathy (one of 52 taking statins and one of 46 controls). Creatine phosphokinase levels were measured in all the patients, before and after vaccination: no significant differences were identified.[2] Considering the number of patients taking statins who also receive influenza vaccination, there seems to be little evidence to suggest there is a problem.

Statins appear to have immunomodulatory properties, but **atorvastatin** was reported to have no effect on the antibody response to **hepatitis A vaccine** in healthy young subjects.[3]

On the whole the evidence suggests that no interaction occurs with statins and influenza or hepatitis A vaccines. The case report involving cerivastatin and influenza vaccine seems unlikely to be of general significance: an interaction between cerivastatin and bezafibrate (which sometimes takes some months to develop, see 'Statins + Fibrates', p.1332) cannot be ruled out; and cerivastatin alone is known to be associated with severe myopathy, an adverse effect that led to its general withdrawal from the market.

1. Plotkin E, Bernheim J, Ben-Chetrit S, Mor A, Korzets Z. Influenza vaccine–a possible trigger of rhabdomyolysis induced acute renal failure due to the combined use of cerivastatin and bezafibrate. *Nephrol Dial Transplant* (2000) 15, 740–1.
2. Chazan B, Weiss R, Tabenkin H, Mines M, Raz R. Influenza vaccine does not produce myopathy in patients taking statins. *J Fam Pract* (2002) 51, 986–8.
3. Packard RRS, Schlegel S, Senouf D, Burger F, Sigaud P, Perneger T, Siegrist C-A, Mach F. Atorvastatin treatment and vaccination efficacy. *J Clin Pharmacol* (2007) 47, 1022–7.

Statins + Vitamin E substances

Supplementation with antioxidants including vitamin E appears to reduce the beneficial effect of statins on HDL-cholesterol. However, one study suggests that alpha-tocopherol alone may not adversely affect HDL-cholesterol.

Clinical evidence, mechanism, importance and management

In a coronary artery disease intervention study over 12 months, patients taking antioxidants (vitamin E, **vitamin C**, **betacarotene** and **selenium**) in combination with **simvastatin** and nicotinic acid (niacin) were found to have a smaller increase in HDL–cholesterol when compared with those receiving the statin and nicotinic acid alone.[1] Similarly, in a 3-year, placebo-controlled, study (The HDL-Atherosclerosis Treatment Study; HATS) involving 160 patients, the protective increase in HDL2 cholesterol found in patients taking **simvastatin** and nicotinic acid was attenuated by the concurrent use of antioxidants (**betacarotene**, **selenium**, **vitamin C** and vitamin E). Coronary artery stenosis *progressed* by 3.9% with placebo, 1.8% with antioxidants, and 0.7% with **simvastatin**, nicotinic acid and antioxidants, and *regressed* by 0.4% with simvastatin and nicotinic acid alone. Thus the benefit of regression of coronary stenosis seen with **simvastatin** and nicotinic acid was lost when antioxidants were also given.[2] A further placebo-controlled study found that vitamin E supplementation (equivalent to *d*-α-tocopherol 268 mg daily) for 8 weeks did not affect total or LDL-cholesterol levels in hypercholesterolaemic patients taking **lovastatin** or **simvastatin**. There was a small decrease in HDL-cholesterol levels during vitamin E supplementation, which was not sufficient to change the ratio of total cholesterol to HDL–cholesterol (a measure of cardiac risk) and was not sustained.[3] However, another study concluded that high-dose *d*-alpha-tocopherol for 2 years in patients with coronary artery disease taking concurrent statin therapy did not affect HDL-cholesterol.[4]

The available evidence suggests that some types of antioxidant use may decrease the response to statins, but the use of vitamin E alone may not have this effect. More study is needed to confirm to suitability of different types and doses of antioxidant supplementation.

1. Cheung MC, Zhao X-Q, Chait A, Albers JJ, Brown BG. Antioxidant supplements block the response of HDL to simvastatin-niacin therapy in patients with coronary artery disease and low HDL. *Arterioscler Thromb Vasc Biol* (2001) 21, 1320–6.
2. Brown BG, Zhao X-Q, Chait A, Fisher LD, Cheung MC, Morse JS, Dowdy AA, Marino EK, Bolson EL, Alaupovic P, Frohlich J, Serafini L, Huss-Frechette E, Wang S, DeAngelis D, Dodek A, Albers JJ. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. *N Engl J Med* (2001) 345, 1583–92.
3. Leonard SW, Joss JD, Mustacich DJ, Blatt DH, Lee YS, Traber MG. Effects of vitamin E on cholesterol levels of hypercholesterolemic patients receiving statins. *Am J Health-Syst Pharm* (2007) 64, 2257–66.
4. Singh U, Otvos J, Dasgupta A, de Lemos JA, Devaraj S, Jialal I. High-dose α-tocopherol therapy does not affect HDL subfractions in patients with coronary artery disease on statin therapy. *Clin Chem* (2007) 53, 525–8.

Statins; Atorvastatin + Sirolimus

A case report describes a patient who developed elevated sirolimus levels after atorvastatin was started.

Clinical evidence, mechanism, importance and management

A case report describes a patient who had undergone a pancreatic islet transplant and who had been stable taking sirolimus 8 to 11 mg daily for 5 months. A routine lipid evaluation at 6 months found raised cholesterol and triglyceride levels, and so atorvastatin was started. Six weeks later the trough sirolimus level was 20.5 nanograms/mL (target 7 to 10 nanograms/mL) and so the sirolimus dose was reduced. Further reductions were subsequently needed, and 3 months after the atorvastatin was started the sirolimus dose had been halved.[1] The authors suggested that the atorvastatin competed with sirolimus for metabolism by the cytochrome P40 isoenzyme CYP3A4, which resulted in reduced sirolimus metabolism and the elevated levels seen.[1] However, alone, competition for the same route of metabolism rarely seems to result in a clinically relevant elevation in the levels of either drug. This case report seems to be the only evidence of an interaction and so its general significance is unknown, it seems likely to be small.

1. Barshes NR, Goodpastor SE, Goss JA, DeBakey ME. Sirolimus-atorvastatin drug interaction in the pancreatic islet transplant recipient. *Transplantation* (2003) 76, 1649–50.

Statins; Pravastatin + Mianserin

An isolated report describes rhabdomyolysis attributed to the long-term concurrent use of pravastatin and mianserin, triggered by a cold.

Clinical evidence, mechanism, importance and management

An isolated report describes a 72-year-old woman taking pravastatin 20 mg daily and mianserin 10 mg daily for 2 years, who was hospitalised because of weakness in her legs that began 2 days previously, shortly after she developed a cold. She could stand, but was unable to walk unaided. Laboratory data revealed evidence of increased serum enzymes, all of which suggested rhabdomyolysis. Within a week of stopping the pravastatin the leg weakness had disappeared and all of the laboratory results had returned to normal. The authors of the report attributed the toxicity to the long-term use of both drugs, ageing and the development of a cold.[1] However, what part these factors and/or the presence of mianserin actually played in the development of this toxicity is not known. It seems unlikely that this case is of general significance.

1. Takei A, Chiba S. Rhabdomyolysis associated with pravastatin treatment for major depression. *Psychiatry Clin Neurosci* (1999) 53, 539.

Statins; Pravastatin + Probucol

In a study in 20 healthy subjects, probucol 500 mg did not cause any clinically significant changes in the bioavailability of a single 20-mg dose of pravastatin.[1]

1. ER Squibb. A report on the bioavailability of pravastatin in the presence and absence of gemfibrozil or probucol in healthy male subjects. Data on file (Protocol No 27, 201-18), 1988.

Statins; Simvastatin + Fish oils

In a randomised, crossover study in 23 subjects, omega-3-acid ethyl esters (*Omacor*) 4 g daily did not significantly affect the pharmacokinetics of simvastatin 80 mg daily when both drugs were given together for 14 days. The combination was also well tolerated.[1] No dosage adjustments would appear to be necessary on concurrent use.

1. McKenney JM, Swearingen D, Di Spirito M, Doyle R, Pantaleon C, Kling D, Shalwitz RA. Study of the pharmacokinetic interaction between simvastatin and prescription omega-3-acid ethyl esters. *J Clin Pharmacol* (2006) 46, 785–91.

Ursodeoxycholic acid (Ursodiol) + Bile-acid binding resins

The absorption of ursodeoxycholic acid can be more than halved by the simultaneous dosing of colestilan or colestyramine, and its efficacy might be reduced.

Clinical evidence

(a) Colestilan

Following a test meal with an overnight fast, 5 healthy subjects were given 200 mg of ursodeoxycholic acid alone or with 1.5 g of colestilan granules. It was found that the ursodeoxycholic acid serum levels at 30 minutes were reduced by more than 50% by colestilan in 4 out of the 5 subjects; the mean ursodeoxycholic acid level was decreased from 9.2 micromol/L to 3.4 micromol/L.[1]

(b) Colestyramine

In a study in 5 healthy subjects the simultaneous administration of colestyramine 4 g daily with ursodeoxycholic acid reduced the fasting serum levels of ursodeoxycholic acid by about 60%. Separating administration by 5 hours tended to diminish the reduction in ursodeoxycholic acid levels (serum levels reduced by less than 40%).[2]

Mechanism

It seems likely that the bile-acid binding resins bind with ursodeoxycholic acid (a bile acid) in the intestine and thereby reduce its absorption.

Importance and management

The interactions of colestilan and colestyramine with ursodeoxycholic acid would appear to be established, and are probably clinically important. One UK manufacturer of ursodeoxycholic acid actually advises that **colestipol** and colestyramine should be avoided, as they may limit its effectiveness.[3] Note that it is usually recommended that other drugs are given 1 hour before or 4 to 6 hours after colestyramine, and 1 hour before or 4 hours after colestipol. However, the authors of the reports recommend that, in order to reduce the effects of this interaction, administration of ursodeoxycholic acid and the bile-acid binding resin should be separated,[1,2] by at least 2 hours.[1]

1. Takikawa H, Ogasawara T, Sato A, Ohashi M, Hasegawa Y, Hojo M. Effect of colestimide on intestinal absorption of ursodeoxycholic acid in men. *Int J Clin Pharmacol Ther* (2001) 39, 558–60.
2. Rust C, Sauter GH, Oswald M, Büttner J, Kullak-Ublick GA, Paumgartner G, Beuers U. Effect of cholestyramine on bile acid pattern and synthesis during administration of ursodeoxycholic acid in man. *Eur J Clin Invest* (2000) 30, 135–9.
3. Urdox (Ursodeoxycholic acid). Wockhardt UK Ltd. UK Summary of product characteristics, March 2008.

Ursodeoxycholic acid (Ursodiol) + Miscellaneous

Antacids are expected to decrease ursodeoxycholic acid absorption. The concurrent use of fibrates is predicted to decrease the efficacy of ursodeoxycholic acid.

Clinical evidence, mechanism, importance and management

(a) Antacids

Some antacids have been shown to adsorb bile acids *in vitro* and some manufacturers of ursodeoxycholic acid[1-3] suggest that these antacids (a number of manufacturers specifically mention aluminium-based antacids) may be expected to interfere with absorption in the same manner as bile-acid binding resins (see 'Ursodeoxycholic acid (Ursodiol) + Bile-acid binding resins', p.1346). One manufacturer advises that antacids should be avoided when ursodeoxycholic acid is given, as they may reduce efficacy.[4] However, most absorption interactions with antacids can be managed by separating administration (2 to 3 hours is usually sufficient).

(b) Fibrates

The manufacturers of ursodeoxycholic acid[1-4] recommend that it should not be taken with certain blood cholesterol-lowering agents (some name clofibrate), which may counteract its effectiveness by increasing cholesterol elimination in the bile and thus encourage gallstone formation. Note that, all fibrates increase cholesterol elimination, and may therefore be expected to interact similarly.

1. Ursofalk Capsules (Ursodeoxycholic acid). Dr. Falk Pharma UK Ltd. UK Summary of product characteristics, December 2004.
2. Urso 250 (Ursodeoxycholic acid). Axcan Scandipharm Inc. US Prescribing information, March 2008.
3. Destolit (Ursodeoxycholic acid). Norgine Ltd. UK Summary of product characteristics, January 2009.
4. Urdox (Ursodeoxycholic acid). Wockhardt UK Ltd. UK Summary of product characteristics, March 2008.

Ursodeoxycholic acid (Ursodiol) + Oestrogens

Ursodeoxycholic acid does not affect the bioavailability of ethinylestradiol. However, oestrogens are predicted to decrease the effectiveness of ursodeoxycholic acid.

Clinical evidence, mechanism, importance and management

In a placebo-controlled study, 8 healthy women were given an oral hormonal contraceptive (**ethinylestradiol**/gestodene 30/75 micrograms daily) with ursodeoxycholic acid 8 to 10 mg/kg daily for 21 days. Ursodeoxycholic acid was found not to affect the bioavailability of **ethinylestradiol**. Mean serum triglyceride levels increased from 58.3 mg/dL at the start of the study, to 91.4 mg/dL and 88.6 mg/dL, during **ethinylestradiol** treatment with placebo and ursodeoxycholic acid, respectively.[1]

The study indicates that contraceptive efficacy would not be affected by ursodeoxycholic acid, although further study is required to evaluate the combination in patients with cholestatic liver disease, as there is some evidence to suggest that these patients may metabolise bile salt acids differently.[1] In addition, some manufacturers of ursodeoxycholic acid recommend that drugs such as **oestrogens**, which increase cholesterol elimination in the bile and gallstone formation, should not be taken with ursodeoxycholic acid[2,3] as they may reduce its effectiveness.[4]

1. Baisini O, Benini F, Petraglia F, Kuhnz W, Scalia S, Marschall HU, Brunetti G, Tauschel HD, Lanzini A. Ursodeoxycholic acid does not affect ethinylestradiol bioavailability in women taking oral contraceptives. *Eur J Clin Pharmacol* (2004) 60, 481–7.
2. Ursofalk Capsules (Ursodeoxycholic acid). Dr. Falk Pharma UK Ltd. UK Summary of product characteristics, December 2004.
3. Destolit (Ursodeoxycholic acid). Norgine Ltd. UK Summary of product characteristics, January 2009.
4. Urso 250 (Ursodeoxycholic acid). Axcan Scandipharm Inc. US Prescribing information, March 2008.

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Lithium

Lithium is used in the management of mania, bipolar disorder (formerly manic depression) and recurrent depressive illnesses. The dose of lithium is adjusted to give therapeutic serum concentrations of 0.4 to 1 mmol/L, although it should be noted that this is the range used in the UK, and other ranges have been quoted.

Lithium is given under close supervision with regular **monitoring** of serum concentrations because there is a narrow margin between therapeutic concentrations and those that are toxic. Initially weekly monitoring is advised, dropping to every 3 months for those on stable regimens. It is usual to take serum lithium samples about 10 to 12 hours after the last oral dose.

Adverse effects that are not usually considered serious include nausea, weakness, fine tremor, mild polydipsia and polyuria. If serum concentrations rise into the 1.5 to 2 mmol/L range, toxicity usually occurs, and may present as lethargy, drowsiness, coarse hand tremor, lack of coordination, muscular weakness, increased nausea and vomiting, or diarrhoea. Higher levels result in neurotoxicity, which manifests as ataxia, giddiness, tinnitus, confusion, dysarthria, muscle twitching, nystagmus, and even coma or seizures. Cardiovascular symptoms may also develop and include ECG changes and circulatory problems, and there may be a worsening of polyuria.[1-3] Lithium levels of over 2 mmol/L can be extremely dangerous and therefore require urgent attention. Chronic lithium toxicity has been reported to have a 9% mortality, whilst acute toxicity has a 25% mortality.[4] However, patients with chronic lithium toxicity are more likely to experience severe symptoms at lower serum lithium levels. Concurrent medications, older age and prior neurological illness may increase the susceptibility to lithium toxicity.[5]

In addition to the effects described above, lithium can induce diabetes insipidus and hypothyroidism in some patients, and is contraindicated in those with renal or cardiac insufficiency.

Just how lithium exerts its beneficial effects is not known, but it may compete with sodium ions in various parts of the body, and it alters the electrolyte composition of body fluids.

Interactions

Many of the interactions involving lithium occur because of altered serum lithium concentrations. Lithium is mainly excreted by the kidney; it undergoes glomerular filtration and then tubular reabsorption, and competes with sodium for this process. Therefore, drugs that affect renal excretion (e.g. thiazides, see 'Lithium + Diuretics; Thiazide and related', p.1357) or electrolyte balance (e.g. sodium compounds, see 'Lithium + Sodium compounds', p.1364) are likely to interact. Drug interactions may be an important cause of lithium neurotoxicity occurring when serum lithium levels are within the therapeutic range.[6] This tends to occur with centrally active drugs, including many antipsychotics (see. 'Antipsychotics + Lithium', p.834), carbamazepine (see 'Lithium + Carbamazepine', p.1354), and a number of antidepressants (see 'Lithium + SSRIs', p.1365, and 'Lithium + Tricyclic and related antidepressants', p.1367). Most of the interactions involving lithium are discussed in this section but a few are found elsewhere in this publication. Virtually all of the reports are concerned with the carbonate, but sometimes lithium is given as the acetate, aspartate, chloride, citrate, gluconate, orotate or sulfate instead. There is no reason to believe that these lithium compounds will interact any differently to lithium carbonate.

1. Finley PR, Warner MD, Peabody CA. Clinical relevance of drug interactions with lithium. *Clin Pharmacokinet* (1995) 29, 172–91.
2. Camcolit (Lithium carbonate). Norgine Ltd. UK Summary of product characteristics, January 2009.
3. Lithobid (Lithium carbonate). Noven Therapeutics. US Prescribing Information, May 2009.
4. Vipond AJ, Bakewell S, Telford R, Nicholls AJ. Lithium toxicity. *Anaesthesia* (1996) 51, 1156–8.
5. Chen K-P, Shen WW, Lu M-L. Implication of serum concentration monitoring in patients with lithium intoxication. *Psychiatry Clin Neurosci* (2004) 58, 25–9.
6. Emilien G, Maloteaux JM. Lithium neurotoxicity at low therapeutic doses. Hypotheses for causes and mechanism of action following a retrospective analysis of published case reports. *Acta Neurol Belg* (1996) 96, 281–93.

Lithium + ACE inhibitors

ACE inhibitors can raise lithium levels, and in some individuals two- to fourfold increases have been recorded. Cases of lithium toxicity have been reported in patients given captopril, enalapril or lisinopril (and possibly perindopril). One analysis found an increased relative risk for lithium toxicity requiring hospitalisation in elderly patients newly started on an ACE inhibitor.

Clinical evidence

An analysis of 10 615 elderly patients receiving lithium found that 413 (3.9%) were admitted to hospital at least once for lithium toxicity during a 10-year study period. The prescriptions for any ACE inhibitor (not specifically named) were compared between these 413 hospitalised patients and 1651 control patients. For any use of ACE inhibitor (63 cases and 110 controls) there was an increased relative risk of hospitalisation for lithium toxicity of 1.6. When patients who had started taking an ACE inhibitor within the last month were evaluated (14 cases and 5 controls), a dramatically increased risk of lithium toxicity was found (relative risk 7.6).[1]

Studies and case reports of the interaction between lithium and specific named ACE inhibitors are outlined in the subsections below.

(a) Captopril

A patient taking lithium carbonate developed a serum lithium level of 2.35 mmol/L and toxicity (tremor, dysarthria, digestive problems) within 10 days of starting to take captopril 50 mg daily. He was restabilised on half his previous dose of lithium.[2] A retrospective study also reports a case of increased lithium levels with captopril (see under *Lisinopril*, below).

(b) Enalapril

A woman taking lithium carbonate developed signs of lithium toxicity (ataxia, dysarthria, tremor, confusion) within 2 to 3 weeks of starting to take enalapril 20 mg daily. After 5 weeks her plasma lithium levels had risen from 0.88 mmol/L to 3.3 mmol/L, and moderate renal impairment was noted.[3] No toxicity occurred when the enalapril was later replaced by nifedipine.[3] Lithium toxicity following the use of enalapril, and associated in some cases with a decrease in renal function, has been seen in another 5 patients,[4-8] and a reduced lithium dose was found adequate in another patient.[9] Enalapril 5 mg daily for 9 days had no effect on the mean serum lithium levels of 9 healthy male subjects. However, one subject had a 31% increase in lithium levels.[10]

A retrospective study also reports several cases of increased lithium levels with enalapril (see under *Lisinopril*, below).

(c) Lisinopril

A retrospective study of patient records identified 20 patients who were stabilised on lithium and then started taking an ACE inhibitor (13 given lisinopril, 6 enalapril and one captopril). Their serum lithium levels rose by an average of 35% (from 0.64 to 0.86 mmol/L) and there was a 26% decrease in lithium clearance. Signs and symptoms suggestive of toxicity (increased tremor, confusion, ataxia), necessitating a dose reduction or lithium withdrawal, developed in four (20%) of these patients. In 3 patients the development of the interaction was delayed for several weeks.[11]
A woman taking lithium developed lithium toxicity and a trough serum lithium level of 3 mmol/L within 3 weeks of stopping clonidine and starting lisinopril 20 mg daily.[12] Other reports similarly describe acute lithium toxicity in 5 patients when they were given lisinopril.[8,13-16] One of them was also taking verapamil,[15] which has also been shown to interact with lithium, but not usually to raise lithium levels (see 'Lithium + Calcium-channel blockers', p.1353), and one patient experienced an increase in lithium levels on changing from fosinopril to lisinopril.[16] A case report describes toxic lithium levels of 2.04 mmol/L, without any signs of lithium toxicity in a woman taking lithium 900 mg daily with lisinopril 10 mg daily. Her lithium levels fell to 1.45 mmol/L on reducing the lithium dose to 600 mg daily, but when she took this dose without lisinopril, her lithium levels were 0.86 mmol/L.[17]

(d) Perindopril

A patient taking lithium developed toxicity 3 months after starting to take perindopril and bendroflumethiazide,[18] which may also interact, see 'Lithium + Diuretics; Thiazide and related', p.1357.

Mechanism

Not fully understood. It has been suggested that as both ACE inhibitors and lithium cause sodium to be lost in the urine, and also ACE inhibitors reduce thirst stimulation, fluid depletion can occur. The normal compensatory reaction for fluid depletion is constriction of the efferent renal arterioles to maintain the glomerular filtration rate, but this mechanism is blocked by the ACE inhibitor. In addition, lithium and sodium ions are competitively reabsorbed, mainly in the proximal tubule, and with less sodium available, more lithium is retained. Consequently the renal excretion of lithium falls and toxicity develops.

Importance and management

The interaction between lithium and the ACE inhibitors is established and of clinical importance, although it seems that the incidence of adverse effects as a result of this interaction is probably small. It has been suggested that concurrent use should be avoided, or only undertaken with caution and close monitoring. However, although lithium levels can rise, this is not always of clinical importance, but it should be noted that the risk of lithium toxicity increases when other risk factors are also present.

Risk factors for increased lithium toxicity include: advanced age,[1,11] congestive heart failure,[10,12] renal impairment[7,12] and volume depletion.[6,12] Some consider these to be contraindications to the use of lithium.[7,12] Only captopril, enalapril, lisinopril (and possibly perindopril) have been reported to interact, but it seems likely, given the proposed mechanism, that this interaction will occur with any other ACE inhibitor. Therefore if any ACE inhibitor is added to established lithium treatment, monitor well for symptoms of lithium toxicity (see 'Lithium', (p.1347)) and consider measuring lithium levels more frequently. Be alert for the need to reduce the lithium dose (possibly by between one-third to one-half).[12,14] The development of the interaction may be delayed, so monitoring lithium levels every week[12] or every two weeks[11] for several weeks has been advised.

1. Juurlink DN, Mamdani MM, Kopp A, Rochon PA, Shulman KI, Redelmeier DA. Drug-induced lithium toxicity in the elderly: a population-based study. *J Am Geriatr Soc* (2004) 52, 794–8.
2. Pulik M, Lida H. Interaction lithium-inhibiteurs de l'enzyme de conversion. *Presse Med* (1988) 17, 755.
3. Douste-Blazy P, Rostin M, Livarek B, Tordjman E, Montastruc JL, Galinier F. Angiotensin converting enzyme inhibitors and lithium treatment. *Lancet* (1986) i, 1448.
4. Mahieu M, Houvenagel E, Leduc JJ, Choteau P. Lithium-inhibiteurs de l'enzyme conversion: une association á éviter? *Presse Med* (1988) 17, 281.
5. Drouet A, Bouvet O. Lithium et inhibiteurs de l'enzyme de conversion. *Encephale* (1990) 16, 51–2.
6. Navis GJ, de Jong PE, de Zeeuw D. Volume homeostasis, angiotensin converting enzyme inhibition, and lithium therapy. *Am J Med* (1989) 86, 621.
7. Simon G. Combination angiotensin converting enzyme inhibitor/lithium therapy contraindicated in renal disease. *Am J Med* (1988) 85, 893–4.
8. Correa FJ, Eiser AR. Angiotensin-converting enzyme inhibitors and lithium toxicity. *Am J Med* (1992) 93, 108–9.
9. Ahmad S. Sudden hypothyroidism and amiodarone-lithium combination: an interaction. *Cardiovasc Drugs Ther* (1995) 9, 827–8.
10. DasGupta K, Jefferson JW, Kobak KA, Greist JH. The effect of enalapril on serum lithium levels in healthy men. *J Clin Psychiatry* (1992) 53, 398–400.
11. Finley PR, O'Brien JG, Coleman RW. Lithium and angiotensin-converting enzyme inhibitors: evaluation of a potential interaction. *J Clin Psychopharmacol* (1996) 16, 68–71.
12. Baldwin CM, Safferman AZ. A case of lisinopril-induced lithium toxicity. *DICP Ann Pharmacother* (1990) 24, 946–7.
13. Griffin JH, Hahn SM. Lisinopril-induced lithium toxicity. *DICP Ann Pharmacother* (1991) 25, 101.
14. Anon. ACE inhibitors and lithium toxicity. *Biol Ther Psychiatry* (1988) 11, 43.
15. Chandragiri SS, Pasol E, Gallagher RM. Lithium, ACE inhibitors, NSAIDs, and verapamil. A possible fatal combination. *Psychosomatics* (1998) 39, 281–2.
16. Meyer JM, Dollarhide A, Tuan I-L. Lithium toxicity after switch from fosinopril to lisinopril. *Int Clin Psychopharmacol* (2005) 20, 115–18.
17. Teitelbaum M. A significant increase in lithium levels after concomitant ACE inhibitor administration. *Psychosomatics* (1993) 34, 450–3.
18. Vipond AJ, Bakewell S, Telford R, Nicholls AJ. Lithium toxicity. *Anaesthesia* (1996) 51, 1156–8.

Lithium + Acetazolamide

There is some evidence that the excretion of lithium can be increased by the short-term use of acetazolamide. However, lithium toxicity has been seen in one patient given both drugs for a month.

Clinical evidence, mechanism, importance and management

A single-dose study in 6 subjects given lithium 600 mg ten hours before acetazolamide 500 or 750 mg found a 31% increase in the urinary excretion of lithium.[1] A case report describes a woman who was successfully treated for a lithium overdose with acetazolamide, intravenous fluids, sodium bicarbonate, potassium chloride and mannitol.[2]

Paradoxically, lithium toxicity occurred in another patient after a month of treatment with acetazolamide. Lithium levels rose from 0.8 to 5 mmol/L, although it should be noted that the later measurement was taken 8 hours post-dose.[3] See 'Lithium', (p.1347) for details of lithium monitoring.

1. Thomsen K, Schou M. Renal lithium excretion in man. *Am J Physiol* (1968) 215, 823–7.
2. Horowitz LC, Fisher GU. Acute lithium toxicity. *N Engl J Med* (1969) 281, 1369.
3. Gay C, Plas J, Granger B, Olie JP, Loo H. Intoxication au lithium. Deux interactions inédites: l'acétazolamide et l'acide niflumique. *Encephale* (1985) 11, 261–2.

Lithium + Aciclovir

An isolated case report describes lithium toxicity caused by high-dose intravenous aciclovir.

Clinical evidence, mechanism, importance and management

A 42-year-old woman taking lithium carbonate 450 mg twice daily developed signs of lithium toxicity 6 days after starting treatment with intravenous aciclovir 10 mg/kg, which was given every 8 hours for a severe herpes zoster infection following chemotherapy. Her serum lithium levels had risen over fourfold to 3.4 mmol/L. The reasons for this interaction are unknown but the authors of the report suggest that aciclovir may have inhibited the renal excretion of lithium.[1]

This appears to be the first and only report of this interaction, but it would now be prudent to monitor for symptoms of lithium toxicity (see *Interactions*, under 'Lithium', (p.1347)) and consider monitoring lithium levels if high-dose intravenous aciclovir is given to any patient. The report recommends measuring lithium levels every second or third day.[1] Oral aciclovir is predicted not to interact because of its low bioavailability, and no interaction would be expected with topical aciclovir as the plasma levels achieved by this route are minimal.

1. Sylvester RK, Leitch J, Granum C. Does acyclovir increase serum lithium levels? *Pharmacotherapy* (1996) 16, 466–8.

Lithium + Amisulpride

Amisulpride does not appear to affect the pharmacokinetics of lithium. However, lithium may increase the plasma levels of amisulpride.

Clinical evidence, mechanism, importance and management

In a placebo-controlled study in 24 healthy subjects, lithium carbonate 500 mg twice daily was given for 7 days to obtain stable lithium serum levels, and then amisulpride 100 mg twice daily was added for a further 7 days. Amisulpride appeared to have no effect on lithium pharmacokinetics.[1] In a pharmacokinetic analysis of amisulpride levels in patients with schizophrenia or schizoaffective disorder, dose-corrected amisulpride plasma levels were 80% higher in 3 patients taking lithium than in 13 patients taking amisulpride alone.[2] In a further study by the same authors, 7 patients who had been taking amisulpride 250 to 1200 mg daily for between 9 and 110 days were given lithium carbonate 450 to 1125 mg daily. Dose-corrected plasma levels of amisulpride were increased by about 8 to 56% (mean 31%) by lithium, taken for between 3 and 73 days. There was a positive correlation between the duration of lithium treatment and the increase in amisulpride levels.[3]

Evidence for an interaction between amisulpride and lithium is limited, but it appears to be established. Although the mean increase in amisulpride levels would not be expected to be clinically significant, the authors of the study suggest that increases of up to 56% could result in increased adverse effects. It would therefore seem prudent to monitor concurrent use for amisulpride adverse effects (extrapyramidal effects, insomnia, constipation) and consider reducing the amisulpride dose if these become troublesome.

1. Canal M, Legangneux E, van Lier JJ, van Vliet AA, Coulouvrat C. Lack of effect of amisulpride on the pharmacokinetics and safety of lithium. *Int J Neuropsychopharmacol* (2003) 6, 103–9.
2. Bergemann N, Kopitz J, Kress KR, Frick A. Plasma amisulpride levels in schizophrenia or schizoaffective disorder. *Eur Neuropsychopharmacol* (2004) 14, 245–50.
3. Bergemann N, Abu-Tair F, Kress KR, Parzer P, Kopitz J. Increase in plasma concentration of amisulpride after addition of concomitant lithium. *J Clin Psychopharmacol* (2007) 27, 546–9.

Lithium + Angiotensin II receptor antagonists

Case reports describe lithium toxicity in patients given candesartan, losartan, valsartan, and possibly irbesartan. Other angiotensin II receptor antagonists would be expected to interact similarly.

Clinical evidence

(a) Candesartan

A 58-year-old woman taking long-term lithium for depression (stable serum lithium levels between 0.6 and 0.7 mmol/L), and unnamed calcium-channel blockers for hypertension, was additionally given candesartan 16 mg daily. She was hospitalised 8 weeks later with a 10-day history of ataxia, increasing confusion, disorientation and agitation, and was found to have a serum lithium level of 3.25 mmol/L. She recovered completely when all the drugs were stopped. She was later restabilised on her original lithium dose with a change to urapidil for her hypertension.[1]

(b) Irbesartan

A report describes a 74-year-old woman with increased lithium levels of 2.3 mmol/L and symptoms of lithium toxicity, which were associated with the use of several drugs including irbesartan, lisinopril, escitalopram, levomepromazine, furosemide and spironolactone. It was suggested that these drugs could have delayed lithium excretion or worsened neurotoxic effects. An increase in the lisinopril dose and the addition of irbesartan several weeks before admission may have contributed to the lithium toxicity.[2]

(c) Losartan

An elderly woman taking lithium carbonate developed lithium toxicity (ataxia, dysarthria, and confusion) after starting to take losartan 50 mg daily. Her serum lithium levels rose from 0.63 mmol/L to 2 mmol/L over 5 weeks. The lithium and losartan were stopped and her symptoms had disappeared 2 days later. When lithium was restarted and the losartan was replaced by nicardipine, her lithium levels were restabilised at 0.77 mmol/L within 2 weeks.[3]

(d) Valsartan

A woman with a long history of bipolar disorder was treated with lithium carbonate (serum levels consistently at 0.9 mmol/L) and a number of other drugs (L-tryptophan, lorazepam, glibenclamide, conjugated oestrogens and ciprofloxacin). Two weeks before being hospitalised for a manic relapse she was additionally started taking valsartan 80 mg daily. While in hospital the ciprofloxacin was stopped, lorazepam was replaced by zopiclone, and quetiapine was added. On day 3 of her hospitalisation her serum lithium levels were 1.1 mmol/L and she became increasingly delirious, confused and ataxic over the next week. By day 11 her serum lithium levels had risen to 1.4 mmol/L. When an interaction was suspected, the valsartan was replaced by diltiazem. She later recovered and was stabilised on her original lithium carbonate dose with lithium levels of 0.8 mmol/L.[4] A second case describes a woman taking lithium 600 mg daily who experienced an increase in lithium serum levels to 1.72 mmol/L after she started to take valsartan 80 mg daily. She demonstrated signs of lithium toxicity including ataxia, limb rigidity and falls. Previously, her lithium levels had been stable between 0.62 and 0.87 mmol/L when she took lithium in doses of 900 mg to 1.2 g daily.[5]

Mechanism

Not fully understood. It could be that, as with the ACE inhibitors, angiotensin II receptor antagonists inhibit aldosterone secretion, resulting in increased sodium loss by the renal tubules. This causes lithium retention and thus an increase in lithium levels. However, angiotensin II receptor antagonists have less effect on aldosterone than the ACE inhibitors, making a clinically significant interaction less likely. *Animal* studies show that

ramipril,[6] but not losartan,[7] decreases the excretion of lithium by the kidney, which would support this idea.

Importance and management

Direct information about interactions between lithium and angiotensin II receptor antagonists seems to be limited to these reports, although the interaction has been predicted to occur with all drugs of this class. Such sparse evidence is not enough to recommend contraindicating the concurrent use of angiotensin II receptor antagonists with lithium, especially as an interaction is less likely than with the ACE inhibitors (see *Mechanism*, above), although some manufacturers do not recommend the combination. One report suggests weekly monitoring for the first month of concurrent use,[4] but any rise in serum lithium levels may be gradual so that toxicity might take as long as 3 to 7 weeks to develop fully. Be mindful that the lithium dose may need to be decreased.

Patients taking lithium should be aware of the symptoms of lithium toxicity and told to report them immediately should they occur. This should be reinforced when they are given angiotensin II receptor antagonists. As with ACE inhibitors (see 'Lithium + ACE inhibitors', p.1348), the risk of lithium toxicity would be expected to increase when risk factors such as advanced age, renal insufficiency, heart failure and volume depletion are also present.

1. Zwanzger P, Marcuse A, Boerner RJ, Walther A, Rupprecht R. Lithium intoxication after administration of AT_1 blockers. *J Clin Psychiatry* (2001) 62, 208–9.
2. Spinewine A, Schoevaerdts D, Mwenge GB, Swine C, Dive A. Drug-induced lithium intoxication: a case report. *J Am Geriatr Soc* (2005) 53, 360–1.
3. Blanche P, Raynaud E, Kerob D, Galezowski N. Lithium intoxication in an elderly patient after combined treatment with losartan. *Eur J Clin Pharmacol* (1997) 52, 501.
4. Leung M, Remick RA. Potential drug interaction between lithium and valsartan. *J Clin Psychopharmacol* (2000) 20, 392–3.
5. Su Y-P, Chang C-J, Hwang T-J. Lithium intoxication after valsartan treatment. *Psychiatry Clin Neurosci* (2007) 61, 204.
6. Barthelmebs M, Grima M, Imbs J-L. Ramipril-induced decrease in renal lithium excretion in the rat. *Br J Pharmacol* (1995) 116, 2161–5.
7. Barthelmebs M, Alt-Tebacher M, Madonna O, Grima M, Imbs J-L. Absence of a losartan interaction with renal lithium excretion in the rat. *Br J Pharmacol* (1995) 116, 2166–9.

Lithium + Antibacterials

A retrospective study of patients receiving long-term lithium found that concurrent medication, especially antibacterials, tended to be associated with a higher risk of elevated serum lithium levels.

Clinical evidence, mechanism, importance and management

A multicentre, retrospective study of patients receiving long-term lithium found 51 patients with elevated serum lithium levels (greater than or equal to 1.3 mmol/L) which was at least 50% greater than the previous serum level. Fifteen patients had taken potentially interacting medication and, of these, 7 patients had taken antibacterials (6 different unnamed antibacterials). It was suggested that the underlying infection, associated fever and poor fluid intake might have contributed to the elevated lithium levels in these patients rather than the use of the antibacterial *per se*.[1]

1. Wilting I, Movig KLL, Moolenaar M, Hekster YA, Brouwers JRBJ, Heerdink ER, Nolen WA, Egberts ACG. Drug-drug interactions as a determinant of elevated lithium serum levels in daily clinical practice. *Bipolar Disord* (2005) 7, 274–80.

Lithium + Antibacterials; Co-trimoxazole or Trimethoprim

Two reports describe lithium toxicity in three patients given co-trimoxazole; in two of these patients toxicity was paradoxically accompanied by a fall in lithium levels. A further report describes lithium toxicity accompanied by an increase in lithium levels in a patient given trimethoprim.

Clinical evidence, mechanism, importance and management

Two patients stabilised on lithium carbonate (serum level 0.75 mmol/L) had signs of lithium toxicity (tremor, fasciculations, muscular weakness, dysarthria, apathy) within a few days of being given co-trimoxazole (dose not stated), yet their serum lithium levels were found to have fallen to about 0.4 mmol/L. Within 48 hours of withdrawing the co-trimoxazole, the signs of toxicity had gone, and their serum lithium concentrations had returned to their former level.[1] Another report very briefly states that ataxia, tremor and diarrhoea developed in a patient taking lithium and timolol when co-trimoxazole was given.[2]

A 40-year-old woman taking lithium 1.2 g daily, experienced nausea, diarrhoea, malaise, difficulty concentrating, trembling, an uncertain gait and muscle spasms after trimethoprim 300 mg daily was started; her serum lithium levels appeared to be elevated. She made a good recovery following rehydration.[3]

The reasons for this interaction are not understood, although trimethoprim may affect the renal excretion of lithium.[3] The general importance of this interaction is uncertain. If concurrent use is undertaken it would clearly be prudent to monitor the clinical response, as it would appear that in this situation serum level monitoring might not always be a reliable guide to toxicity. Consider also 'Lithium + Antibacterials', above.

1. Desvilles M, Sevestre P. Effet paradoxal de l'association lithium et sulfaméthoxazol-triméthoprime. *Nouv Presse Med* (1982) 11, 3267–8.
2. Edwards IR. Medicines Adverse Reactions Committee: eighteenth annual report, 1983. *N Z Med J* (1984) 97, 729–32.
3. de Vries PL. Lithiumintoxicatie bij gelijktijdig gebruik van trimethoprim. *Ned Tijdschr Geneeskd* (2001) 145, 539–40.

Lithium + Antibacterials; Linezolid

Two cases describe serotonin syndrome in patients taking linezolid and lithium, although in both cases other potentially interacting drugs were also taken.

Clinical evidence, mechanism, importance and management

A retrospective review of adverse events reported to the FDA in the US, identified 29 cases of serotonin syndrome involving linezolid. One patient had received lithium; their other medication included bupropion, sertraline and trazodone.[1] A case report also describes serotonin syndrome occurring in a 36-year-old woman after linezolid was added to her drug regimen, which also included lithium, venlafaxine, and imipramine.[2]

Although the use of linezolid was implicated in both of these cases, it is unclear what part lithium had to play, although cases of serotonin syndrome have been reported when lithium is taken with other drugs affecting serotonin, see 'Lithium + SSRIs', p.1365. However, in both of the cases cited above, other drugs were also taken which are known to result in serotonin syndrome with linezolid and therefore the general significance of these cases is unclear. For more information on serotonin syndrome, see under 'Additive or synergistic interactions', (p.9).

1. Lawrence KR, Adra M, Gillman PK. Serotonin toxicity associated with the use of linezolid: a review of postmarketing data. *Clin Infect Dis* (2006) 42, 1578–83.
2. Miller DG, Lovell EO. Antibiotic-induced serotonin syndrome. J Emerg Med (2008) [EPub ahead of print].

Lithium + Antibacterials; Metronidazole

The lithium levels of three patients rose, to toxic levels in two cases, after they took metronidazole. Renal impairment was also reported in two of these patients.

Clinical evidence, mechanism, importance and management

A 40-year-old woman taking lithium carbonate 1.8 g daily, levothyroxine 150 micrograms daily and propranolol 60 mg daily developed signs of lithium toxicity (ataxia, rigidity, poor cognitive function, impaired coordination) after completing a one-week course of metronidazole 500 mg twice daily. Her serum-lithium levels had risen by 46% (from 1.3 to 1.9 mmol/L).[1] Another report describes 2 patients whose serum-lithium levels rose by about 20% and 125%, 5 to 12 days, after they finished a one-week course of metronidazole 750 mg or 1 g daily, respectively, in divided doses.[2] A degree of renal impairment occurred during concurrent use and was still present 5 to 6 months later.[2] In contrast, one other patient is said to have taken both drugs together uneventfully.[1]

There seems to be no reason for avoiding concurrent use, but the outcome should be well monitored. Some have recommended that a reduction in the lithium dose should be considered, especially in patients maintained at relatively high serum lithium levels.[1,2] Patients taking lithium should be aware of the symptoms of lithium toxicity and told to report them immediately should they occur. This should be reinforced when they are given

metronidazole. The authors of one of the reports also recommend frequent analysis of creatinine and electrolyte levels and urine osmolality in order to detect any renal problems in patients taking this combination.[2] Consider also 'Lithium + Antibacterials', p.1350.

1. Ayd FJ. Metronidazole-induced lithium intoxication. *Int Drug Ther Newslett* (1982) 17, 15–16.
2. Teicher MH, Altesman RI, Cole JO, Schatzberg AF. Possible nephrotoxic interaction of lithium and metronidazole. *JAMA* (1987) 257, 3365–6.

Lithium + Antibacterials; Quinolones

An isolated case of lithium toxicity has been reported in a patient taking lithium and levofloxacin. Another possible case has been reported with ciprofloxacin.

Clinical evidence, mechanism, importance and management

A 56-year-old man taking lithium carbonate 400 mg three times daily for a bipolar disorder was admitted to hospital with bronchitis. He was given **levofloxacin** 300 mg daily, and within 2 days was noted to have developed gait ataxia, dysarthria, coarse tremor, dizziness, vomiting, and confusion. Lithium toxicity was suspected, and because of the time course of the symptoms, an interaction with **levofloxacin** was considered responsible. Serum lithium levels were found to have risen from 0.89 mmol/L (measured 2 weeks previously) to 2.53 mmol/L, and a reduction in his renal function was noted. Both drugs were stopped and the patient recovered over the following 4 days. His lithium level was found to be 1.12 mmol/L at that time.[1]

The mechanism of this interaction between lithium and **levofloxacin** is unclear, and this appears to be the only report. However, it would seem prudent to bear this interaction in mind if a patient taking lithium is given **levofloxacin**. Patients taking lithium should be aware of the symptoms of lithium toxicity and told to report them immediately should they occur. This should be reinforced when they are given **levofloxacin**. For a report of lithium toxicity with raised lithium levels in a patient taking **ciprofloxacin** and nimesulide, which was attributed to the NSAID, see *Nimesulide*, under 'Lithium + NSAIDs', p.1360, and consider also 'Lithium + Antibacterials', p.1350.

1. Takahashi H, Higuchi H, Shimizu T. Severe lithium toxicity induced by combined levofloxacin administration. *J Clin Psychiatry* (2000) 61, 949–50.

Lithium + Antibacterials; Spectinomycin

An isolated case report describes a patient who developed lithium toxicity when given spectinomycin.

Clinical evidence, mechanism, importance and management

A woman developed lithium toxicity (tremor, nausea, vomiting, ataxia and dysarthria) when given spectinomycin injections (dose not stated) in addition to her long-term treatment with lithium.[1] Her serum-lithium levels had risen from a range of 0.8 to 1.1 mmol/L up to 3.2 mmol/L. Spectinomycin reduces urinary output, and so it was suggested that a reduced renal clearance of lithium led to these elevated levels. Information seems to be limited to this report, but it would seem prudent to bear this interaction in mind in any patient given both drugs.

Consider also 'Lithium + Antibacterials', p.1350.

1. Conroy RW. Quoted as a personal communication by Ayd FJ. Possible adverse drug-drug interaction report. *Int Drug Ther Newslett* (1978) 13, 15.

Lithium + Antibacterials; Tetracyclines

The concurrent use of lithium and the tetracyclines is normally uneventful, but two isolated reports describe increased lithium levels and lithium toxicity, one in a woman taking tetracycline, and the other in a man taking doxycycline. An isolated case of pseudotumor cerebri occurred in one patient taking lithium and minocycline.

Clinical evidence

(a) Doxycycline

A man receiving long-term treatment with lithium carbonate became confused within a day of starting to take doxycycline 100 mg twice daily. By the end of a week he had developed symptoms of lithium toxicity (ataxia, dysarthria, worsened tremor, fatigue, etc.). His serum lithium levels had risen from a range of 0.8 to 1.1 mmol/L up to 1.8 mmol/L; his renal function remained normal. He recovered when the doxycycline was withdrawn.[1]

(b) Minocycline

A case report describes pseudotumor cerebri in an obese 15-year-old girl taking lithium, 4 months after she started taking minocycline 75 mg twice daily for acne.[2]

(c) Tetracycline

An isolated report describes a woman who had been taking lithium for 3 years, with serum levels within the range of 0.5 to 0.84 mmol/L. Within 2 days of starting to take a sustained-release form of tetracycline (*Tetrabid*) her serum lithium levels had risen to 1.7 mmol/L, and 2 days later they had further risen to 2.74 mmol/L. By then she had clear symptoms of lithium toxicity (slight drowsiness, slurring of the speech, fine tremor and thirst).[3] In contrast, 13 healthy subjects taking lithium carbonate 450 mg twice daily or 900 mg daily had a small 8% reduction in serum lithium levels (from 0.51 to 0.47 mmol/L) when they were given tetracycline 500 mg twice daily for 7 days.[4] The incidence of adverse reactions remained largely unchanged, except for a slight increase in CNS and gastrointestinal adverse effects.

Mechanism

Not understood. One suggested reason for increased serum lithium levels is that tetracycline (known to have nephrotoxic potential) may have adversely affected the renal clearance of lithium.[3]

Importance and management

These adverse interaction reports describing a possible interaction between lithium and the tetracyclines are isolated and unexplained. Two reports make the point that these drugs are commonly used for acne caused by lithium,[1,5] so any common interaction resulting in raised lithium levels would be expected to have come to light by now. The case of pseudotumor cerebri also appears rare, but note that the female gender, obesity, and minocycline use alone are risk factors for its development and so greater caution may be warranted in this type of patient.[2] The authors advise frequent enquiry about headaches and visual changes.

There would seem to be no reason for avoiding the concurrent use of lithium and tetracycline, doxycycline or minocycline, but be aware of the potential for a rare interaction. One manufacturer advises increased frequency of lithium level monitoring when a tetracycline is started or stopped.[6] Consider also 'Lithium + Antibacterials', p.1350.

1. Miller SC. Doxycycline-induced lithium toxicity. *J Clin Psychopharmacol* (1997) 17, 54–5.
2. Jonnalagadda J, Saito E, Kafantaris V. Lithium, minocycline, and pseudotumor cerebri. *J Am Acad Child Adolesc Psychiatry* (2005) 44, 209.
3. McGennis AJ. Lithium carbonate and tetracycline interaction. *BMJ* (1978) 2, 1183.
4. Fankhauser MP, Lindon JL, Connolly B, Healey WJ. Evaluation of lithium–tetracycline interaction. *Clin Pharm* (1988) 7, 314–17.
5. Jefferson JW. Lithium and tetracycline. *Br J Dermatol* (1982) 107, 370.
6. Camcolit (Lithium carbonate). Norgine Ltd. UK Summary of product characteristics, January 2009.

Lithium + Aripiprazole

Lithium does not affect the pharmacokinetics of aripiprazole to a clinically significant extent. A case report describes neuroleptic malignant syndrome in a patient taking aripiprazole and lithium.

Clinical evidence, mechanism, importance and management

In a study, 7 healthy subjects were given aripiprazole 30 mg daily for 5 weeks, with lithium carbonate slow-release tablets 1.2 to 1.8 g daily (to give a plasma level of 1 to 1.4 mmol/L) during weeks 3 to 5. The AUC and maximum plasma concentrations of aripiprazole were increased by 15% and 19%, respectively.[1] Results from a routine therapeutic drug monitoring service suggest that aripiprazole levels are increased by 34% by lithium.[2]

Moderately severe neuroleptic malignant syndrome developed in a patient with bipolar disorder within 3 weeks of starting aripiprazole in a dose of 5 mg daily titrated slowly up to 15 mg twice daily and lithium which was increased to 600 mg twice daily. The patient improved over 4 days after aripiprazole was discontinued and lithium withheld and after a further 3 days lithium was restarted. The use of lithium may have increased the risk of this syndrome with aripiprazole.[3]

The concurrent use of lithium and aripiprazole modestly increases the plasma levels of both drugs, but these increases are not considered to be clinically significant. The case describing neuroleptic malignant syndrome is isolated, and as this effect can occur in response to one antipsychotic drug there would seem no need to take additional precautions if both aripiprazole and lithium are taken.

1. Citrome L, Josiassen R, Bark N, Salazar DE, Mallikaarjun S. Pharmacokinetics of aripiprazole and concomitant lithium and valproate. *J Clin Pharmacol* (2005) 45, 89–93.
2. Castberg I, Spigset O. Effects of comedication on the serum levels of aripiprazole: evidence from a routine therapeutic drug monitoring service. *Pharmacopsychiatry* (2007) 40, 107–10.
3. Ali S, Pearlman RL, Upadhyay A, Patel P. Neuroleptic malignant syndrome with aripiprazole and lithium: a case report. *J Clin Psychopharmacol* (2006) 26, 434–6.

Lithium + Aspirin or other Salicylates

No clinically significant pharmacokinetic interaction appears to occur between aspirin, lysine aspirin or sodium salicylate and lithium.

Clinical evidence, mechanism, importance and management

In a steady-state study, 10 healthy women with average plasma lithium levels of 0.63 mmol/L had a slight 6% rise in their renal excretion of lithium when they were given aspirin 1 g four times daily for 7 days. However, no statistically significant alteration in lithium levels was found.[1]

No change in serum lithium levels was seen in 7 patients taking lithium when they were given aspirin 975 mg four times daily for 6 days.[2] Another report states that aspirin 600 mg four times daily had no effect on the absorption or renal excretion of single doses of lithium carbonate given to 6 healthy subjects.[3] Further reports describe no change in serum lithium levels with **lysine aspirin**,[4] intravenous aspirin,[5] or intravenous **sodium salicylate**.[5] However, lithium clearance was slightly reduced by 22% by intravenous **sodium salicylate**,[5] and a study in one healthy subject found a 32% increase in mean serum lithium levels (from 0.41 to 0.54 mmol/L) after 5 days' use of oral aspirin (975 mg four times daily for 2 days, then 650 mg four times daily for 3 days).[6]

Note that pyrexia, for which aspirin and other related drugs may be taken, can itself alter fluid and electrolyte balance and thereby cause elevated lithium levels.

1. Reimann IW, Diener U, Frölich JC. Indomethacin but not aspirin increases plasma lithium ion levels. *Arch Gen Psychiatry* (1983) 40, 283–6.
2. Ragheb MA. Aspirin does not significantly affect patients' serum lithium levels. *J Clin Psychiatry* (1987) 48, 425.
3. Bikin D, Conrad KA, Mayersohn M. Lack of influence of caffeine and aspirin on lithium elimination. *Clin Res* (1982) 30, 249A.
4. Singer L, Imbs JL, Danion JM, Singer P, Krieger-Finance F, Schmidt M, Schwartz J. Risque d'intoxication par le lithium en cas de traitement associé par les anti-inflammatoires non stéroïdiens. *Therapie* (1981) 36, 323–6.
5. Reimann IW, Golbs E, Fischer C, Frölich JC. Influence of intravenous acetylsalicylic acid and sodium salicylate on human renal function and lithium clearance. *Eur J Clin Pharmacol* (1985) 29, 435–41.
6. Bendz H, Feinberg M. Aspirin increases serum lithium ion levels. *Arch Gen Psychiatry* (1984) 41, 310–11.

Lithium + Baclofen

The hyperkinetic symptoms of two patients with Huntington's chorea were aggravated within a few days of starting to take lithium and baclofen.

Clinical evidence, mechanism, importance and management

A patient with Huntington's chorea, taking lithium and haloperidol, was also given baclofen, and another patient taking imipramine, clopenthixol, chlorpromazine and baclofen was also given lithium. Within a few days both patients had a severe aggravation of their hyperkinetic symptoms, which disappeared within 3 days of withdrawing the baclofen.[1] Other patients with Huntington's chorea had no major changes in their mental state or movement disorders when given up to 90 mg of baclofen daily,[2,3] which suggests that an interaction with lithium may have been the cause of the hyperkinesis in these two patients. On the basis of this very limited evidence it would seem prudent to monitor the effects of concurrent use and consider stopping one of the drugs if hyperkinesis develops.

1. Andén N-E, Dalén P, Johansson B. Baclofen and lithium in Huntington's chorea. *Lancet* (1973) ii, 93.
2. Barbeau A. G.A.B.A. and Huntington's chorea. *Lancet* (1973) ii, 1499–1500.
3. Paulson GW. Lioresal in Huntington's disease. *Dis Nerv Syst* (1976) 37, 465–7.

Lithium + Benzodiazepines

Neurotoxicity and increased lithium levels were reported in several patients when clonazepam was given to patients taking lithium, and increased lithium levels have been described in one patient taking bromazepam. An isolated case of serious hypothermia has been reported during the concurrent use of lithium and diazepam. Alprazolam seems unlikely to cause a clinically important rise in lithium levels.

Clinical evidence, mechanism, importance and management

(a) Alprazolam

In 10 healthy subjects taking lithium carbonate 900 mg to 1.5 g daily, alprazolam 2 mg daily for 4 days slightly increased the steady-state AUC of lithium by about 8% and reduced its urinary recovery from 93.6% to 78.2%. It was suggested that these changes were unlikely to be clinically significant, but confirmation of this is needed.[1]

(b) Bromazepam

A case report describes a patient taking lithium carbonate 900 mg daily, whose lithium levels rose from 1.12 mmol/L to 1.4 mmol/L within 4 days of starting to take bromazepam 18 mg daily. His lithium dose was reduced to 500 mg daily, which resulted in his lithium level returning to its former value.[2]

(c) Clonazepam

A retrospective study of patient records revealed 5 patients with bipolar affective disorder, taking lithium carbonate 900 mg to 2.4 g daily, who had developed a reversible neurotoxic syndrome with ataxia, dysarthria, drowsiness and confusion when they were given clonazepam 2 to 16 mg daily. In one case the clonazepam was added to their antipsychotics (chlorpromazine, perphenazine, haloperidol) and in 4 cases the clonazepam replaced the antipsychotic treatment. In all cases the lithium levels rose, and in two of these cases they reached toxic levels. The authors of the report suggest that the neurotoxicity was caused either by the increase in lithium levels, or by synergistic toxicity; however, the use of antipsychotics may also have increased CNS sensitivity. It was recommended that lithium levels should be measured more frequently if clonazepam is added, and the effects of concurrent use well monitored.[3]

(d) Diazepam

A patient who was described as having profound mental retardation had occasional hypothermic episodes (below 35°C) while taking lithium and diazepam, but not while taking either drug alone. After taking lithium carbonate 1 g and diazepam 30 mg daily for 17 days, the patient's temperature fell from 35.4°C to 32°C over 2 hours, and she became comatose with reduced reflexes, dilated pupils, a systolic blood pressure of 40 to 60 mmHg, a pulse rate of 40 bpm and no piloerector response.[4] The reasons for this reaction are not known. This is an isolated case and therefore no general recommendations can be made. There seems to be no evidence of this adverse interaction with any of the other benzodiazepines.

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2. Raudino F. Interazione fra benzodiazepine e livelli plasmatici di sali di litio. *Clin Ter* (1981) 98, 683–5.
3. Koczerginski D, Kennedy SH, Swinson RP. Clonazepam and lithium—a toxic combination in the treatment of mania? *Int Clin Psychopharmacol* (1989) 4, 195–9.
4. Naylor GJ, McHarg A. Profound hypothermia on combined lithium carbonate and diazepam treatment. *BMJ* (1977) 3, 22.

Lithium + Caffeine

The heavy consumption of caffeine-containing drinks may cause a small to moderate reduction in serum lithium levels.

Clinical evidence

An early single-dose study found that the intake of xanthines such as caffeine caused an increase in lithium excretion.[1] In contrast, another single-dose study did not find any significant changes in the urinary clearance of lithium in 6 subjects given caffeine 200 mg four times daily compared with a caffeine-free control period.[2] However, a study in 11 psychiatric patients taking lithium 600 mg to 1.2 g daily who were also regular **coffee** drinkers (4 to 8 cups daily containing 70 to 120 mg of caffeine per cup), serum lithium levels rose by an average of 24% when the **coffee** was withdrawn, although the levels of 3 patients did not change.[3] These findings are consistent with another report of 2 patients with lithium-induced tremors that were aggravated when they stopped drinking large amounts of **coffee**. One of the patients had a 50% rise in lithium levels, and required a reduction in lithium dose from 1.5 g daily to 1.2 g daily.[4]

Mechanism

It is not clear exactly how caffeine affects the excretion of lithium by the renal tubules, but other xanthines have a similar effect (see 'Lithium + Theophylline', p.1366).

Importance and management

The weight of evidence suggests that, although there is no need for those taking lithium to avoid caffeine (from caffeine-containing herbs, coffee, tea, cola drinks etc.), they should stick to a moderate intake, and in cases where a reduction in caffeine intake is desirable, it should be withdrawn cautiously. This is particularly important in those whose serum lithium levels are already high, because of the risk of toxicity. When caffeine is withdrawn it may be necessary to reduce the dose of lithium. In addition, remember that there is a caffeine-withdrawal syndrome (headache and fatigue being the major symptoms) that might worsen some of the major psychiatric disorders (such as affective and schizophrenic disorders)[3] for which lithium is given.

1. Thomsen K, Schou M. Renal lithium excretion in man. *Am J Physiol* (1968) 215, 823–7.
2. Bikin D, Conrad KA, Mayersohn M. Lack of influence of caffeine and aspirin on lithium elimination. *Clin Res* (1982) 30, 249A.
3. Mester R, Toren P, Mizrachi I, Wolmer L, Karni N, Weizman A. Caffeine withdrawal increases lithium blood levels. *Biol Psychiatry* (1995) 37, 348–50.
4. Jefferson JW. Lithium tremor and caffeine intake: two cases of drinking less and shaking more. *J Clin Psychiatry* (1988) 49, 72–3.

Lithium + Calcitonin (Salcatonin)

A study in 4 women found that calcitonin caused a small reduction in serum lithium levels.

Clinical evidence

Prompted by the occasional observation of decreased serum lithium levels in outpatients receiving calcitonin, a study was undertaken in 4 women with bipolar depression. The patients, who had been taking lithium for 10 years, were also given salmon calcitonin 100 units subcutaneously for three consecutive days for postmenopausal osteoporosis. It was found that their serum lithium levels fell, on average, from 0.73 mmol/L to 0.59 mmol/L. The clearance of lithium in the urine was tested in 2 of the patients, and both had increases (9.8% and 16.2%).[1]

Mechanism

Not known. Increased renal excretion and possibly some reduced intestinal absorption of the lithium have been suggested by the authors of the report.[1]

Importance and management

Information seems to be limited to this study, which only lasted for 3 days. The study found only a small fall in serum lithium levels, and did not assess the effect on the control of depression. It seems unlikely that this interaction will be clinically important in most patients, but as some patients may be affected, monitor the outcome of concurrent use, and consider monitoring lithium levels if an interaction is suspected.

1. Passiu G, Bocchetta A, Martinelli V, Garau P, Del Zompo M, Mathieu A. Calcitonin decreases lithium plasma levels in man. Preliminary report. *Int J Clin Pharmacol Res* (1998) 18, 179–81.

Lithium + Calcium-channel blockers

The concurrent use of lithium and verapamil can be uneventful, but neurotoxicity (ataxia, movement disorders, tremors) with unchanged lithium levels has been reported in a few patients. Reduced and increased lithium levels have also occurred with verapamil. An acute parkinsonian syndrome and marked psychosis has been seen in at least one patient taking lithium and diltiazem. Reduced lithium clearance, and one possible case of increased lithium levels have been reported with nifedipine.

Clinical evidence

(a) Diltiazem

A woman stable on lithium for several years developed marked psychosis and parkinsonism within a week of starting to take diltiazem 30 mg three times daily.[1] An acute parkinsonism syndrome developed in a 58-year-old man taking lithium and tiotixene within 4 days of starting 30 mg of diltiazem three times daily.[2] However, this report has been questioned as the symptoms may have been attributable to an adverse effect of the tiotixene, and, even if the lithium toxicity was genuine, it is thought to have been more likely due to recent increases in the lithium dose, or the patient's diuretic therapy than diltiazem.[3]

(b) Nifedipine

In a study of patients with essential hypertension, two doses of nifedipine 20 mg did not affect single-dose lithium clearance, but nifedipine 40 to 80 mg daily for 6 and 12 weeks was found to decrease single-dose lithium clearance by 30%.[4] A man, taking lithium carbonate 1.5 g daily with a level of 0.8 mmol/L, developed ataxia and dysarthria 7 days after starting nifedipine 30 mg daily for 48 hours, then 60 mg daily. His lithium dose was reduced by 40%, but his serum lithium level first increased to 1.1 mmol/L (about 2 weeks after starting the nifedipine), before restabilising at 0.9 mmol/L.[5] In contrast, a patient taking lithium, who developed dysarthria and ataxia after verapamil was added to her treatment (see *Verapamil*, below), was subsequently well controlled while taking lithium and nifedipine 40 mg daily.[6]

(c) Verapamil

A 42-year-old woman taking lithium carbonate 900 mg daily developed toxicity (nausea, vomiting, muscular weakness, ataxia and tinnitus) within 9 days of starting to take verapamil 80 mg three times daily. Her bipolar depressive disorder improved even though her serum lithium levels remained unchanged at 1.1 mmol/L. The toxicity disappeared within 48 hours of stopping the verapamil, but her disorder worsened. The same pattern was repeated when verapamil was restarted and then withdrawn.[7] Another 3 cases of movement disorders (including ataxia, tremors and choreoathetosis) resulting from the concurrent use of lithium and verapamil have also been reported,[6,8,9] two of which had documented unchanged serum lithium levels.[6,8] In one case the patient was restabilised by halving the dose of lithium.[8]

Conversely, a patient stable taking lithium 900 mg to 1.2 g daily for over 8 years had a marked fall in his serum lithium levels from about 1.04 mmol/L to 0.5 mmol/L when he was given verapamil 80 mg four times daily. He was restabilised on approximately double the dose of lithium.[10] Another patient had an increased lithium clearance when he took verapamil for 3 days, and he had a fall in his serum lithium levels, from 0.61 mmol/L to 0.53 mmol/L.[10]

In addition to unchanged or decreased lithium levels with verapamil, one manufacturer notes that increased lithium levels have occurred.[11]

Two cases of bradycardia have been reported when verapamil was added to lithium treatment; in one case the patient's heart rate returned to normal on stopping verapamil, in the other case the patient, who was also taking propranolol, developed asymptomatic class I atrioventricular ectopy and died following a myocardial infarction.[12]

Mechanism

Not understood. However, it has been suggested that calcium-channel blockers and lithium affect neurotransmitter production[1,2,9] (several pathways have been described), which results in CNS sensitivity. This produces movement disorders, which are said to mimic lithium toxicity. In most of the cases mentioned above, symptoms of toxicity were present at therapeutic lithium levels, which would support this suggested mechanism. It

is unclear whether the cases of bradycardia are attributable to an interaction between lithium and verapamil, or the effects of verapamil alone. The contribution of propranolol in the second case may also be significant, see 'Beta blockers + Calcium-channel blockers; Verapamil', p.1003.

Importance and management

The neurotoxic adverse reactions cited above for lithium and verapamil contrast with two other case reports describing uneventful concurrent use.[13,14] Variable reports of altered serum lithium levels have also occurred. This unpredictability emphasises the need to monitor the effects closely where it is thought appropriate to give lithium and verapamil. Only a couple of isolated reports of neurotoxicity have been reported with lithium and diltiazem, and their general relevance is uncertain, but bear them in mind in the event of an unexpected response to treatment. Some limited data suggest that nifedipine may slightly reduce lithium clearance, and the clinical relevance of this is also uncertain.

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2. Valdiserri EV. A possible interaction between lithium and diltiazem: case report. *J Clin Psychiatry* (1985) 46, 540–1.
3. Flicker MR, Quigley MA, Caldwell EG. Diltiazem-lithium interaction: an opposing viewpoint. *J Clin Psychiatry* (1988) 49, 325–6.
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7. Price WA, Giannini AJ. Neurotoxicity caused by lithium-verapamil synergism. *J Clin Pharmacol* (1986) 26, 717–19.
8. Price WA, Shalley JE. Lithium-verapamil toxicity in the elderly. *J Am Geriatr Soc* (1987) 35, 177–8.
9. Helmuth D, Ljaljevic Z, Ramirez L, Meltzer HY. Choreoathetosis induced by verapamil and lithium treatment. *J Clin Psychopharmacol* (1989) 9, 454–5.
10. Weinrauch LA, Belok S, D'Elia JA. Decreased serum lithium during verapamil therapy. *Am Heart J* (1984) 108, 1378–80.
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12. Dubovsky SL, Franks RD, Allen S. Verapamil: a new antimanic drug with potential interactions with lithium. *J Clin Psychiatry* (1987) 48, 371–2.
13. Brotman AW, Farhadi AM, Gelenberg AJ. Verapamil treatment of acute mania. *J Clin Psychiatry* (1986) 47, 136–8.
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Lithium + Carbamazepine

Although the concurrent use of lithium and carbamazepine is beneficial in many patients, it may increase the risk of neurotoxicity. Sinus node dysfunction has also occurred in a few patients. An isolated report describes a patient who had a marked rise in lithium levels and lithium toxicity, which was apparently caused by carbamazepine-induced renal impairment.

Clinical evidence

(a) Neurotoxicity with normal drug levels

A patient taking lithium 1.8 g daily developed severe neurotoxicity (ataxia, truncal tremors, nystagmus, limb hyperreflexia, muscle fasciculation) within 3 days of starting to take carbamazepine 600 mg daily. Blood levels of both drugs remained within the therapeutic range. The symptoms resolved when each drug was withdrawn in turn, and recurred within 3 days of restarting concurrent treatment.[1] Five patients with rapid-cycling bipolar disorder developed similar neurotoxic symptoms (confusion, drowsiness, generalised weakness, lethargy, coarse tremor, hyperreflexia, cerebellar signs) when they were given lithium carbonate with carbamazepine (doses not stated). Plasma levels of both drugs remained within the accepted range.[2] Other reports describe adverse neurological effects during the concurrent use of lithium and carbamazepine, which were also not accompanied by significant changes in lithium levels,[3-7] although in one patient raised serum levels of both drugs were seen.[8] A systematic search through the Medline database, for reports of neurotoxic adverse effects in patients taking lithium at low therapeutic concentrations, found a total of 41 cases over approximately 30 years from 1966. Carbamazepine had been taken concurrently in 22% of these cases, in some instances with other potentially interacting drugs.[9] Another retrospective study of 46 patients with type I bipolar disorder found significant benefits of the long-term concurrent use of lithium and carbamazepine, compared with lithium (31 patients) or carbamazepine (15 patients) alone. However, rates of adverse effects increased 2.5-fold compared with monotherapy, and there were particular excesses of tremor and drowsiness.[10]

In other patients the concurrent use of lithium and carbamazepine was said to be well tolerated and beneficial,[11,12] but one report suggests that the doses may need to be carefully titrated to avoid adverse effects.[13]

(b) Sinus node dysfunction

A 9-year study in a psychiatric hospital found that, of 5 patients taking lithium who developed sinus node dysfunction, 4 were also taking carbamazepine.[14]

(c) Toxic lithium levels

An isolated case report describes carbamazepine-induced acute renal failure, which resulted in a 3.5-fold rise in lithium levels and lithium toxicity 3 weeks after carbamazepine was started.[15]

Mechanism

Not understood. A paper that plotted the serum levels of lithium and carbamazepine on a two-dimensional graph did not find any evidence of synergistic toxicity.[16] Sinus node dysfunction can be caused by either lithium or carbamazepine, but this is rare. However, the effects may possibly be additive.

Importance and management

The neurotoxic interaction between lithium and carbamazepine is established, but its incidence is not known. The incidence of severe neurotoxicity may be quite small, but increased mild adverse events such as tremor and drowsiness seem to be fairly common.[10] The authors of one paper suggest that the risk factors appear to be a history of neurotoxicity with lithium, and compromised medical or neurological function.[2] If concurrent use is undertaken, the outcome should be closely monitored. This is particularly important because neurotoxicity can develop even though the levels remain within the accepted therapeutic range. If severe neurotoxicity develops the lithium treatment should be discontinued promptly, whatever the lithium level.[9] The manufacturers of **oxcarbazepine**[17] predict that it may interact similarly, and therefore it would seem prudent to take similar precautions to those suggested for carbamazepine.

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16. McGinness J, Kishimoto A, Hollister LE. Avoiding neurotoxicity with lithium-carbamazepine combinations. *Psychopharmacol Bull* (1990) 26, 181–4.
17. Trileptal (Oxcarbazepine). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, March 2009.

Lithium + Cisplatin

Isolated case reports describe either a fall or no alteration in lithium levels in patients given cisplatin. However, note that cisplatin-induced renal impairment may cause an increase in lithium levels.

Clinical evidence, mechanism, importance and management

The serum lithium levels of a woman taking lithium carbonate 300 mg four times daily fell, over a period of 2 days, from 1 mmol/L to 0.3 mmol/L, and from 0.8 mmol/L to 0.5 mmol/L, on two occasions when given cisplatin (100 mg/m^2 intravenously over 2 hours). To prevent cisplatin-induced renal toxicity, she was also given a fluid load over a total of 24 hours, which included one litre of sodium chloride 0.9% over 4 hours, one litre of mannitol 20% over 4 hours, and one litre of dextrose 5% in sodium chloride 0.9%. Serum lithium levels returned to normal at the end of 2 days. No change in the control of the psychotic symptoms was seen.[1] A man had a transient 64% decrease in serum lithium levels, without perceptible clinical consequences, during the first of four courses of cisplatin, bleomycin, and etoposide. The effect became less pronounced during the subsequent courses.[2] It is not clear whether the fall in serum lithium levels in these cases was due to increased renal clearance caused by the cisplatin or the sodium load, dilution from the fluid load, or a combination of all three factors.

In contrast, one patient had no clinically significant changes in her serum lithium levels when given cisplatin, but 2 months later her deteriorating renal function resulted in a rise in her serum lithium levels.[3]

None of these interactions was of great clinical importance, but the authors of the first report pointed out that some regimens of cisplatin involve the use of higher doses (40 mg/m^2 daily) with a sodium chloride 0.9% fluid load over 5 days, and under these circumstances it would be prudent to monitor the serum lithium levels carefully. Concurrent use should be monitored in all patients.

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Lithium + Clozapine

A few patients given lithium carbonate and clozapine have experienced adverse reactions including myoclonus, neuroleptic malignant syndrome, seizures, delirium, and psychoses.

Clinical evidence

A review of the medical records of 44 patients taking clozapine and lithium identified 28 patients who had experienced an adverse effect, three of which were possibly associated with the drug combination. There were two reports of myoclonus and one of a grand mal seizure.[1] A retrospective study using both Medline and the spontaneous reporting system of the FDA in the US, over the period 1969 to 1994, identified 237 cases of severe neurotoxicity involving lithium, with 188 involving lithium with antipsychotics and of these, 6 involved clozapine.[2,3]

Four out of 10 patients taking lithium carbonate (mean dose of 1.4 g daily) and clozapine (mean maximum dose 900 mg daily) developed reversible neurological symptoms including involuntary jerking of the limbs and tongue, facial spasm, tremor, confusion, generalised weakness, stumbling gait, leaning and falling to the right. One of them also became delirious. Serum lithium levels remained unchanged, and the problems resolved when the lithium was stopped. Three of the four had a recurrence of the symptoms when rechallenged with the drug combination.[4]

A man with poorly controlled schizophrenia, taking clozapine 750 mg daily for 6 weeks, was given lithium, initially 900 mg and then subsequently 1.2 g daily. His serum lithium level was 0.86 mmol/L. Within one week he began to experience paroxysmal jerky movements of his upper and lower extremities lasting about 30 minutes. This myoclonus resolved when both drugs were stopped, and did not recur when clozapine was restarted alone.[5] Another patient taking lithium developed neuroleptic malignant syndrome (stiffness, rigidity, tachycardia, diaphoresis, hypertension) 3 to 4 weeks after clozapine was added. The symptoms disappeared within 2 to 3 days of stopping the clozapine.[6] An elderly man also developed neuroleptic malignant syndrome 3 days after starting to take clozapine 25 mg daily. He was also taking carbamazepine, and had stopped taking lithium 3 days earlier.[7] A number of other case reports describe adverse neurological effects in patients taking clozapine and lithium. These include neurotoxic symptoms (ataxia, coarse tremor, myoclonus, facial spasm, and increased deep tendon reflex) which developed after 3 days of concurrent use,[8] psychosis and raised lithium levels,[9] and two cases of seizures (one within 4 days of concurrent use).[10]

It has been suggested that lithium may help to protect patients from the adverse effects of clozapine, in particular agranulocytosis.[11] However, lithium is thought to have masked a clozapine-induced agranulocytosis in a 59-year-old woman who developed leucopenia and subsequently agranulocytosis after 40 days of treatment with lithium and clozapine.[12]

Mechanism

Not understood.

Importance and management

An interaction between clozapine and lithium appears to be established; however, not all patients are affected. It is not clear just why some patients develop a toxic reaction when given both drugs, and others do not, and it is also not clear which patients are at risk. One group of workers suggest that lithium levels of no more than 0.5 mmol/L may give therapeutic benefits while minimising adverse effects.[4]

The concurrent use of clozapine and lithium should therefore be well monitored for adverse effects, particularly for evidence of neuroleptic malignant syndrome, which appears to be the most common adverse effect reported. An interaction with clozapine leading to increased lithium levels is not established: there appears to be only one case report describing this effect.

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12. Valevski A, Modai I, Lahav M, Weizman A. Clozapine-lithium combined treatment and agranulocytosis. *Int Clin Psychopharmacol* (1993) 8, 63–5.

Lithium + Corticosteroids

Corticosteroids may disturb electrolyte balance, which in theory could affect serum lithium levels, but there do not appear to be any reports of significant interactions. A case report suggests that lithium caused resistance to corticosteroid treatment in a patient with Addison's disease.

Clinical evidence, mechanism, importance and management

A patient with systemic lupus erythematosus suffering from steroid-induced depression and moderate renal impairment was given lithium 600 mg daily and her depression improved. However, serum lithium levels increased from 0.4 to 0.8 mmol/L within one week and the lithium treatment caused an exacerbation of a finger tremor. The lithium was discontinued and then restarted at 400 mg daily, resulting in serum levels of 0.4 mmol/L, which improved her depression and was associated with only a fine finger tremor. Three other patients with steroid-induced depression were also successfully treated with lithium.[1] One case describes a 29-year-old patient taking several drugs including **fludrocortisone** 150 micrograms daily and **hydrocortisone** 40 mg daily for Addison's disease and also taking lithium carbonate 1.2 g daily for bipolar disorder. He was admitted to hospital with an Addisonian crisis and a plasma sodium level of 117 mmol/L, but this normalised (to 130 mmol/L) within 48 hours of stopping his medication and treatment with intravenous **hydrocortisone** and hypertonic fluids. Lithium levels remained within the therapeutic range. Hyponatraemia developed a second time when treatment was re-

instated, and again, resolved within 48 hours after stopping lithium.[2]

Two UK manufacturers warn that drugs affecting electrolyte balance, such as corticosteroids, may alter lithium excretion and should therefore be avoided,[3,4] but other manufacturers do not appear to specifically mention this potential interaction. An early study in *rats* reported increased lithium clearance with **methylprednisolone**.[5] The available evidence is insufficient to recommend routine monitoring. However, it may be prudent to consider monitoring lithium effects in patients with renal impairment, or other conditions pre-disposing to lithium toxicity, taking levels if early symptoms suggest a potential problem.

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4. Li-Liquid (Lithium citrate tetrahydrate). Rosemont Pharmaceuticals Ltd. UK Summary of product characteristics, July 2009.
5. Imbs JL, Singer L, Danion JM, Schmidt M, Zawilslak R. Effects of indomethacin and methylprednisolone on renal elimination of lithium in the rat. *Int Pharmacopsychiatry* (1980) 15, 143–9.

Lithium + Diuretics; Loop

The concurrent use of lithium carbonate and furosemide can be safe and uneventful, but serious lithium toxicity has been described. Bumetanide interacts similarly. The risk of lithium toxicity with a loop diuretic is greatly increased during the first month of concurrent use.

Clinical evidence

An analysis of 10 615 elderly patients receiving lithium found that 413 patients (3.9%) were admitted to hospital at least once for lithium toxicity during a 10-year study period. The prescriptions for any loop diuretic (not specifically named) were compared between these 413 hospitalised patients and 1 651 control patients. For any use of a loop diuretic (54 cases and 71 controls) there was an increased relative risk of hospitalisation for lithium toxicity of 1.7. When patients who were newly started on a loop diuretic were analysed (12 cases and 6 controls), a dramatically increased risk of lithium toxicity within a month of initiating treatment was found (relative risk 5.5).[1] Reports relating to specific named loop diuretics are discussed below.

(a) Bumetanide

Bumetanide has been responsible for the development of lithium toxicity in 2 patients[2,3] one of whom was following a salt-restricted diet,[3] which has also been implicated in episodes of lithium toxicity, see 'Lithium + Sodium compounds', p.1364.

(b) Furosemide

Six healthy subjects stabilised on lithium carbonate 300 mg three times daily (mean serum levels 0.43 mmol/L) were given furosemide 40 mg daily for 14 days. Five experienced some minor adverse effects, probably attributable to the furosemide, without significant changes in serum lithium levels, but one subject experienced such a marked increase in the toxic effects of lithium that she withdrew from the study after taking both drugs for only 5 days. Her serum lithium levels were found to have risen from 0.44 mmol/L to 0.71 mmol/L.[4]

There are another 4 case reports of individual patients who experienced serious lithium toxicity or other adverse reactions when given lithium and furosemide.[5-8] One of the patients was also following a salt-restricted diet,[5] which has also been implicated in episodes of lithium toxicity, see 'Lithium + Sodium compounds', p.1364. In contrast, 6 patients who had been stabilised on lithium for over 6 years had no significant changes in their serum lithium levels over a 12-week period while taking furosemide 20 to 80 mg daily.[9] Other studies in healthy subjects also found no significant changes in lithium levels when furosemide 40 or 80 mg daily was given.[10,11]

Mechanism

Not fully understood. If and when a rise in serum lithium levels occurs, it may be related to the salt depletion that can accompany the use of furosemide (for a more detailed explanation see 'Lithium + Sodium compounds', p.1364). As with the thiazides (see 'Lithium + Diuretics; Thiazide and related', p.1357), such an interaction would take a few days to develop. This may explain why one study in subjects given a single dose of lithium did not find any effect of furosemide on the urinary excretion of lithium.[12]

Importance and management

Information about an interaction between loop diuretics and lithium seems to be limited to the reports cited. The incidence of this interaction is uncertain and its development unpredictable. It would be imprudent to give furosemide or bumetanide to patients stabilised on lithium unless the effects can be well monitored, because some patients may develop serious toxicity. Patients taking lithium should be aware of the symptoms of lithium toxicity (see 'Lithium', (p.1347)) and told to report them immediately should they occur. Consider increased monitoring of lithium levels in patients newly started on this combination.

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Lithium + Diuretics; Potassium-sparing

There is evidence that the excretion of lithium can be increased by triamterene. In contrast, lithium levels may rise if spironolactone is used: eplerenone is predicted to interact similarly. Amiloride appears not to interact with lithium.

Clinical evidence and mechanism

(a) Amiloride

Amiloride has been found to have no significant effect on serum lithium levels when used in the treatment of lithium-induced polyuria.[1,2] Similarly, in a study to investigate the effect of amiloride on urine osmolality in 11 patients taking lithium, there was no change in the lithium plasma levels after they took amiloride 5 mg daily for 2 weeks, then 10 mg daily for 4 weeks.[3] One review briefly mentions a case report in which amiloride was successfully used as a replacement for bendroflumethiazide, which had caused lithium toxicity.[4] However, one manufacturer[5] suggests that, as a diuretic, amiloride reduces the renal clearance of lithium, thereby increasing the risk of lithium toxicity. There appears to be no evidence to confirm this alleged interaction.

(b) Spironolactone

One study found that spironolactone had no statistically significant effect on the excretion of lithium,[6] whereas in another report, the use of spironolactone 100 mg daily was accompanied by a rise in serum lithium levels from 0.63 mmol/L to 0.9 mmol/L. The levels continued to rise for several days after the spironolactone was stopped.[7]

(c) Triamterene

Triamterene, given to a patient taking lithium while following a salt-restricted diet, is said to have led to a strong lithium diuresis.[8] Similarly, triamterene increased lithium excretion in 8 healthy subjects.[9]

Importance and management

Amiloride, spironolactone and triamterene have been available for a very considerable time and it might have been expected that by now any serious adverse interactions with lithium would have emerged, but information is very sparse. None of the reports available gives a clear indication of the

outcome of concurrent use, but some monitoring would be a prudent precaution with any potassium-sparing diuretic. No interaction study has been undertaken with lithium and **eplerenone**.[10,11] The manufacturers suggest that lithium levels should be monitored frequently if eplerenone is also given,[10,11] although, in the UK, the manufacturer advises avoidance of the combination.[11] They state that this is because raised lithium levels have occurred with related drugs such as the ACE inhibitors and diuretics.

Patients taking lithium should be aware of the symptoms of lithium toxicity (see 'Lithium', (p.1347)) and told to report them immediately should they occur.

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4. Aronson JK, Reynolds DJM. ABC of monitoring drug therapy. Lithium. *BMJ* (1992) 305, 1273–6.
5. Amilamont (Amiloride hydrochloride). Rosemont Pharmaceuticals Ltd. UK Summary of product characteristics, August 2009.
6. Thomsen K, Schou M. Renal lithium excretion in man. *Am J Physiol* (1968) 215, 823–7.
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10. Inspra (Eplerenone). Pfizer Inc. US Prescribing information, April 2008.
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Lithium + Diuretics; Thiazide and related

Thiazide and related diuretics can cause a rapid rise in lithium levels, leading to toxicity unless the lithium dose is reduced appropriately.

Clinical evidence

A retrospective analysis of 10 615 elderly patients receiving lithium found that 413 (3.9%) were admitted to hospital at least once for lithium toxicity during a 10-year study period. The prescriptions for a thiazide-type diuretic were compared between these 413 hospitalised patients and 1 651 control patients. For any use of a thiazide diuretic (16 cases and 37 controls) there was a non-significant increased relative risk of 1.3 for hospitalisation due to lithium toxicity. When treatment for patients who were newly started on a thiazide diuretic was analysed (5 cases and 6 controls), the increased relative risk of toxicity was also non-significant (1.3). The authors considered that these findings suggest that the use of thiazide diuretics and lithium may not be as hazardous as previously thought. However, the authors also suggest that another explanation is that clinicians were aware of the potential interaction and so adjusted doses or observed patients more closely in the outpatient setting, thereby avoiding any hospitalisations for toxicity.[1]

Case reports and studies for named thiazide diuretics are outlined below.

(a) Bendroflumethiazide

A study in 22 patients, who had been taking either bendroflumethiazide 2.5 mg daily or hydroflumethiazide 25 mg daily for at least 2 months, found that these diuretics caused a 24% reduction in the urinary clearance of a single 600-mg dose of lithium carbonate.[2] There is also a case report of a roughly twofold increase in serum lithium levels,[3] and a case of lithium toxicity with a roughly threefold increase in serum lithium levels mentioned in a review article,[4] both after bendroflumethiazide was started in patients taking lithium. In a further case, lithium toxicity, with serum lithium levels of 4.28 mmol/L was detected 3 months after the addition of bendroflumethiazide.[5] However, this case was complicated by the presence of perindopril, which might also raise lithium levels, as has occurred with other ACE inhibitors, see 'Lithium + ACE inhibitors', p.1348.

In contrast to these reports, one single-dose study found that bendroflumethiazide 7.5 mg given 10 hours after lithium carbonate 600 mg had no effect on lithium clearance.[6] However, it seems unlikely that single-dose studies will detect an interaction (see *Mechanism* below).

(b) Chlorothiazide

A single 300-mg dose of lithium carbonate was given to 4 healthy subjects alone and following 7 days of treatment with chlorothiazide 500 mg daily. Lithium-plasma levels were increased and lithium clearance was decreased by about 26% following chlorothiazide treatment.[7]

Lithium toxicity developed in a patient taking lithium after she was given chlorothiazide, spironolactone and amiloride.[8] The lithium levels rose from 0.6 mmol/L to 2.2 mmol/L. A 54-year-old patient developed nephrogenic diabetes insipidus when she took lithium carbonate. The addition of chlorothiazide reduced her polyuria, but resulted in an elevation in her lithium level from 1.3 mmol/L to more than 2 mmol/L, with accompanying signs of toxicity. The patient was later successfully treated with chlorothiazide and a reduced dose of lithium.[9]

(c) Chlortalidone

A 58-year-old woman developed lithium toxicity within 10 days of starting chlortalidone (dose unknown).[10] Her lithium levels rose from 0.8 mmol/L to 3.7 mmol/L.

(d) Hydrochlorothiazide

In a placebo-controlled study, the serum lithium levels of 13 healthy subjects taking lithium 300 mg twice daily rose by 23% (from 0.3 to 0.37 mmol/L), when they were given hydrochlorothiazide 25 mg twice daily for 5 days.[11] Similar results were found in another small study.[12] In addition to these studies at least 6 cases of lithium toxicity have been seen when hydrochlorothiazide was given to patients taking lithium.[13-17] Hydrochlorothiazide was either given with amiloride,[13-15] spironolactone[16] or triamterene.[17] See also 'Lithium + Diuretics; Potassium-sparing', p.1356.

(e) Hydroflumethiazide

A study in 22 patients who had been taking either bendroflumethiazide 2.5 mg daily or hydroflumethiazide 25 mg daily for at least 2 months found that these diuretics caused a 24% reduction in the urinary clearance of a single 600-mg dose of lithium carbonate.[2]

(f) Indapamide

A 64-year-old man developed lithium toxicity one week after starting to take indapamide 5 mg daily.[18] His serum lithium level was 3.93 mmol/L.

Mechanism

Not fully understood. The interaction occurs even though the thiazides and related diuretics exert their major actions in the distal part of the kidney tubule whereas lithium is mainly reabsorbed in the proximal part. However, thiazide diuresis is accompanied by sodium loss which, within a few days, is compensated by retention of sodium, this time in the proximal part of the tubule. As both sodium and lithium ions are treated similarly, the increased reabsorption of sodium would include lithium as well, hence a significant and measurable reduction in its excretion.[5,19]

Importance and management

Established, well-documented and potentially serious interactions. The rise in serum lithium levels and the accompanying toxicity develops most commonly within about a week to 10 days,[4,7,9-11,13,17] although it has apparently been seen after 19 days[16] and even 3 months.[5] Not every patient necessarily develops a clinically important interaction, but it is not possible to predict which patients will be affected. The lack of serious cases of toxicity in the case-control study either suggests the interaction is rare, or that appropriate precautions are used when the combination is prescribed.[1]

Although only the diuretics named above have been implicated in this interaction, it seems likely that all thiazides and related diuretics will interact similarly. None of the thiazide or related diuretics should be given to patients taking lithium unless the serum lithium levels can be closely monitored and appropriate downward dose adjustments made. Patients taking lithium should be aware of the symptoms of lithium toxicity (see 'Lithium', (p.1347)) and told to report them immediately should they occur.

The concurrent use of lithium and thiazides, under controlled conditions, has been advocated for certain psychiatric conditions and for the control of lithium-induced nephrogenic diabetes insipidus. A successful case is described above.[9] It has been suggested that a 40 to 70% reduction in the lithium dose would be needed with doses of 0.5 to 1 g of chlorothiazide,[20,21] but it would seem sensible to base any dose adjustments on individual lithium levels.

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11. Crabtree BL, Mack JE, Johnson CD, Amyx BC. Comparison of the effects of hydrochlorothiazide and furosemide on lithium disposition. *Am J Psychiatry* (1991) 148, 1060–3.
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17. Mehta BR, Robinson BHB. Lithium toxicity induced by triamterene-hydrochlorothiazide. *Postgrad Med J* (1980) 56, 783–4.
18. Hanna ME, Lobao CB, Stewart JT. Severe lithium toxicity associated with indapamide therapy. *J Clin Psychopharmacol* (1990) 10, 379–80.
19. Schwarcz G. The problem of antihypertensive treatment in lithium patients. *Compr Psychiatry* (1982) 23, 50–54.
20. Himmelhoch JM, Poust RI, Mallinger AG, Hanin I, Neil JF. Adjustment of lithium dose during lithium-chlorothiazide therapy. *Clin Pharmacol Ther* (1977) 22, 225–7.
21. Himmelhoch JM, Forrest J, Neil JF, Detre TP. Thiazide-lithium synergy in refractory mood swings. *Am J Psychiatry* (1977) 134, 149–52.

Lithium + Gabapentin

Gabapentin did not alter the pharmacokinetics of single-dose lithium in patients with normal renal function.

Clinical evidence, mechanism, importance and management

In a double-blind study, 13 patients with normal renal function were given a single 600-mg dose of lithium, either with or without gabapentin at steady state. Gabapentin did not significantly alter the pharmacokinetics of the lithium, and no increase in adverse effects was noted on concurrent use. Ideally, longer-term studies are needed to confirm this lack of interaction, especially in patients with impaired renal function as both drugs are eliminated by renal excretion.[1] However, on the basis of the information from this report, no lithium dose adjustment would be expected to be necessary on concurrent use.

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Lithium + Herbal medicines

A woman developed lithium toxicity after taking a herbal diuretic remedy. A brief report describes mania in a patient taking lithium who also took St John's wort.

Clinical evidence, mechanism, importance and management

(a) Herbal diuretics

A 26-year-old woman who had been taking lithium 900 mg twice daily for 5 months, with hydroxyzine, lorazepam, propranolol, risperidone and sertraline, came to an emergency clinic complaining of nausea, diarrhoea, unsteady gait, tremor, nystagmus and drowsiness (all symptoms of lithium toxicity). Her lithium level, which had previously been stable at 1.1 mmol/L was found to be 4.5 mmol/L. For the past 2 to 3 weeks she had been taking a non-prescription **herbal diuretic** containing **corn silk**, ***Equisetum hyemale***, **juniper**, **ovate buchu**, **parsley** and **bearberry**, all of which are believed to have diuretic actions. The other ingredients were bromelain, paprika, potassium and vitamin B_6.[1]

The most likely explanation for what happened is that the **herbal diuretic** caused the lithium toxicity. It is impossible to know which herb or combination of herbs actually caused the toxicity, or how, but this case once again emphasises that herbal remedies are not risk-free just because they are natural. It also underscores the need for patients to avoid self-medication without first seeking informed advice and supervision if they are taking potentially hazardous drugs like lithium.

(b) St John's wort (Hypericum perforatum)

A search of Health Canada's database of spontaneous adverse reactions identified one case in which St John's wort was suspected of inducing mania in a patient also taking lithium.[2] The reasons for this effect are unknown, although it seems likely that the symptoms could be due to the effects of both lithium and St John's wort on serotonin. No further details were given of this case.

1. Pyevich D, Bogenschutz MP. Herbal diuretics and lithium toxicity. *Am J Psychiatry* (2001) 158, 1329.
2. Natural health products and adverse reactions. *Can Adverse React News* (2004) 14, 2–3. Available at: http://www.hc-sc.gc.ca/dhp-mps/medeff/bulletin/ (accessed 08/02/10).

Lithium + Iodides

The hypothyroid and goitrogenic effects of lithium carbonate and iodides may be additive if they are given concurrently.

Clinical evidence

A man with normal thyroid function showed evidence of hypothyroidism after 3 weeks of treatment with lithium carbonate 750 mg to 1.5 g daily. After two further weeks, during which he was also given **potassium iodide**, the hypothyroidism became even more marked, but resolved completely within 2 weeks of the withdrawal of both drugs. This patient was studied before the potential risk of hypothyroidism with iodine was well recognised.[1] Another report also describes a case of hypothyroidism associated with the use of lithium carbonate and **potassium iodide**.[2]

In a study of the possible effects of iodide intake on thyroid function in 10 patients receiving lithium, 3 to 5 weeks of **potassium iodide** caused hypothyroidism in 2 patients and hyperthyroidism in one. Little effect on thyroid function was seen in 5 control patients given **potassium iodide** without lithium.[3] A case of hypothyroidism involving lithium and a product containing **isopropamide iodide** with haloperidol (*Vesalium*) has also been reported.[4,5]

Mechanism

Lithium accumulates in the thyroid gland and blocks the release of the thyroid hormones by thyroid-stimulating hormone, and can therefore cause clinical hypothyroidism.[1,6-13] The prevalence of hypothyroidism may be higher in women, in middle age,[13] and in countries with a higher level of nutritional iodine.[14] Potassium iodide temporarily prevents the production of thyroid hormones but, as time goes on, synthesis recommences. Thus, both lithium and iodide ions can depress the production or release of the hormones and therefore have additive hypothyroid effects.

Importance and management

The pharmacological interaction of altered thyroid function with lithium and iodides would appear to be established. However, the clinical use of iodides is now very limited (mostly to the pre-operative treatment of thyrotoxicosis). It is therefore unlikely that iodides will be used in patients taking lithium. However, note that patients taking lithium are advised against the regular use of some preparations of povidone iodine, such as sprays that may be used as disinfectants for minor wounds.[15] Where countries are adopting iodization programmes to prevent iodine deficiency, there may be an increased risk of clinical hypothyroidism in patients taking lithium.[14] Lithium-induced hypothyroidism can be treated with levothyroxine replacement.

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2. Jorgensen JV, Brandrup F, Schroll M. Possible synergism between iodine and lithium carbonate. *JAMA* (1973) 223, 192–3.
3. Spaulding SW, Burrow GN, Ramey JN, Donabedian RK. Effect of increased iodide intake on thyroid function in subjects on chronic lithium therapy. *Acta Endocrinol (Copenh)* (1977) 84, 290–6.
4. Luby ED, Schwartz D, Rosenbaum H. Lithium-carbonate-induced myxedema. *JAMA* (1971) 218, 1298–9.
5. Wiener JD. Lithium carbonate-induced myxedema. *JAMA* (1972) 220, 587.
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7. Shopsin B, Blum M, Gershon S. Lithium-induced thyroid disturbance: case report and review. *Compr Psychiatry* (1969) 10, 215–23.
8. Emerson CH, Dyson WL, Utiger RD. Serum thyrotropin and thyroxine concentrations in patients receiving lithium carbonate. *J Clin Endocrinol Metab* (1973) 36, 338–46.
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10. Villeneuve A, Gautier J, Jus A, Perron D. Effect of lithium on thyroid in man. *Lancet* (1973) ii, 502.
11. Lloyd GG, Rosser RM, Crowe MJ. Effect of lithium on thyroid in man. *Lancet* (1973) ii, 619.
12. Bocchetta A, Bernardi F, Pedditzi M, Loviselli A, Velluzzi F, Martino E, Del Zompo M. Thyroid abnormalities during lithium treatment. *Acta Psychiatr Scand* (1991) 83, 193–8.
13. Johnston AM, Eagles JM. Lithium-associated clinical hypothyroidism: prevalence and risk factors. *Br J Psychiatry* (1999) 175, 336–9.
14. Leutgeb U. Ambient iodine and lithium-associated clinical hypothyroidism. *Br J Psychiatry* (2000) 176, 495–6.
15. Betadine Dry Powder Spray (Povidone iodine). Molnlycke Health Care. UK Summary of product characteristics, April 2006.

Lithium + Ispaghula (Psyllium)

In an isolated case, the withdrawal of ispaghula husk resulted in an increase in lithium levels. Psyllium slightly reduced the absorption of lithium in a study in healthy subjects.

Clinical evidence

A 47-year-old woman who had recently started taking lithium was found to have a blood lithium level of 0.4 mmol/L five days after an increment in her lithium dose and whilst also taking one teaspoonful of ispaghula husk twice daily. The ispaghula husk was stopped 3 days later and lithium levels measured 4 days later were found to be 0.76 mmol/L.[1] A study in 6 healthy subjects similarly found that the absorption of lithium (as measured by the urinary excretion) was reduced by about 14% by psyllium.[2]

Mechanism

Not understood. One idea is that the absorption of the lithium from the gut is reduced by psyllium and ispaghula.[1,2]

Importance and management

Information is very limited and the general importance of this interaction is uncertain, but it would seem prudent to bear this interaction in mind in patients taking lithium who are given ispaghula or psyllium preparations. If an interaction is suspected consider monitoring lithium levels and separating the administration of the two drugs by at least an hour, or use an alternative laxative.

1. Perlman BB. Interaction between lithium salts and ispaghula husk. *Lancet* (1990) 335, 416.
2. Toutoungi M, Schulz P, Widmer J, Tissot R. Probable interaction entre le psyllium et le lithium. *Therapie* (1990) 45, 358–60.

Lithium + Lamotrigine

Lamotrigine does not appear to cause a clinically significant alteration in lithium levels. Delirium has been reported in one patient taking both drugs.

Clinical evidence, mechanism, importance and management

In a randomised, two-period, crossover study, 20 healthy men were given 2 g of anhydrous lithium gluconate (9.8 mmol of lithium) every 12 hours for 11 doses, either with or without lamotrigine 100 mg daily. It was found that the serum lithium levels were decreased by about 8% by lamotrigine, but these small changes were not considered to be clinically relevant.[1]

A 2002 review of the few published reports on the use of lithium with lamotrigine suggested that concurrent use appears to be well tolerated.[2] However, one woman taking lithium who had been taking lamotrigine 50 mg for 4 weeks, experienced delirium when the dose of lamotrigine was increased to 150 mg daily. The symptoms disappeared when the lamotrigine dose was reduced to 100 mg daily.[3] It is not clear whether these effects were directly caused by the concurrent use of lithium and lamotrigine. However; the author of the review considered that if cognitive adverse effects occur, it might be worth considering a reduction in the dose of either or both drugs.[2]

1. Chen C, Veronese L, Yin Y. The effects of lamotrigine on the pharmacokinetics of lithium. *Br J Clin Pharmacol* (2000) 50, 193–5.
2. Pies R. Combining lithium and anticonvulsants in bipolar disorder: a review. *Ann Clin Psychiatry* (2002) 14, 223–32.
3. Sporn J, Sachs G. The anticonvulsant lamotrigine in treatment-resistant manic-depressive illness. *J Clin Psychopharmacol* (1997) 17, 185–9.

Lithium + Mazindol

An isolated report describes a case of lithium toxicity, which was attributed to the concurrent use of mazindol.

Clinical evidence, mechanism, importance and management

A bipolar depressive woman, stabilised on lithium carbonate, had signs of lithium toxicity (sluggishness, ataxia) within 3 days of starting to take mazindol 2 mg daily. After 9 days she developed twitching, limb rigidity and muscle fasciculation, and was both dehydrated and stuporose. Her serum lithium levels were found to have risen from a range of 0.4 to 1.3 mmol/L up to 3.2 mmol/L. The mazindol was stopped, and she recovered over the next 48 hours whilst being rehydrated.[1] It is not known whether this was a direct interaction between the two drugs, but the authors suggest that the anorectic effect of mazindol led to this toxicity [i.e. the reduced intake of sodium and water caused a reduction in the renal excretion of lithium]. There seem to be no other reports of interactions between lithium and other anorectic drugs confirming this possibility.

This is an isolated case and its general importance is uncertain, but bear it in mind in the case of an unexpected response to treatment. Note that stimulants such as mazindol are no longer generally recommended as appetite suppressants.[2]

1. Hendy MS, Dove AF, Arblaster PG. Mazindol-induced lithium toxicity. *BMJ* (1980) 280, 684–5.
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Lithium + Methyldopa

Symptoms of lithium toxicity, not always associated with raised lithium levels, have been described in four patients and four healthy subjects when they were also given methyldopa.

Clinical evidence

A woman with manic depression, taking lithium carbonate 900 mg daily was hospitalised for signs of manic decompensation and her lithium dose was increased to 1.8 g daily. When she was also given methyldopa 1 g daily for hypertension, she developed signs of lithium toxicity (blurred vision, hand tremors, mild diarrhoea, confusion, and slurred speech), even though her serum lithium levels were within the range of 0.5 to 0.7 mmol/L. The methyldopa was then stopped and the lithium carbonate dose reduced to 1.5 g daily. Ten days later the lithium level was 1.4 mmol/L, and the lithium dose was decreased to 900 mg daily.[1] Later the author of this report demonstrated this interaction on himself.[2] He took lithium carbonate 150 mg four times daily for a week (lithium level 0.5 mmol/L), and then added methyldopa 250 mg every 8 hours. Within 2 days, signs of lithium toxicity had clearly developed, and the following day his lithium level had increased to 0.8 mmol/L. He then stopped the methyldopa, and about 36 hours later his lithium level was 0.7 mmol/L.

There are three other cases of patients who took methyldopa with lithium, and developed symptoms of lithium toxicity. In one of these cases the patient had lithium levels within the normal therapeutic range,[3] but in the other two the lithium levels increased to 1.5 mmol/L and 1.87 mmol/L.[4,5] A small study in 3 healthy subjects also found that the concurrent use of lithium and methyldopa resulted in increased confusion, sedation and dysphoria.[6]

Mechanism

Not understood. Both a central effect and an effect on renal excretion have been proposed.[3-5]

Importance and management

Information appears to be limited to the reports cited, but the interaction would seem to be established. If both drugs are given then the effects should be closely monitored. Serum lithium measurements may be unreliable because symptoms of toxicity can occur even though the levels remain within the normally accepted therapeutic range.

1. Byrd GJ. Methyldopa and lithium carbonate: suspected interaction. *JAMA* (1975) 233, 320.
2. Byrd GJ. Lithium carbonate and methyldopa: apparent interaction in man. *Clin Toxicol* (1977) 11, 1–4.

3. Osanloo E, Deglin JH. Interaction of lithium and methyldopa. *Ann Intern Med* (1980) 92, 433–4.
4. O'Regan JB. Adverse interaction of lithium carbonate and methyldopa. *Can Med Assoc J* (1976) 115, 385–6.
5. Yassa R. Lithium-methyldopa interaction. *Can Med Assoc J* (1986) 134, 141–2.
6. Walker N, White K, Tornatore F, Boyd JL, Cohen JL. Lithium-methyldopa interactions in normal subjects. *Drug Intell Clin Pharm* (1980) 14, 638–9.

Lithium + Mirtazapine

No pharmacokinetic or pharmacodynamic interactions appeared to occur between lithium and mirtazapine in one study in healthy subjects.

Clinical evidence, mechanism, importance and management

In a randomised, double-blind, crossover study, 12 healthy subjects were given lithium carbonate 600 mg daily or placebo for 10 days, with a single 30-mg dose of mirtazapine on day 10. The pharmacokinetics of both mirtazapine and lithium were unaltered by concurrent use. In addition, no pharmacodynamic changes, as studied by psychometric testing, were identified.[1] The UK manufacturer of mirtazapine warns of the potential for serotonin syndrome in patients also taking lithium.[2] There do not appear to be any reports of this reaction with lithium and mirtazapine, but consider also 'Lithium + SSRIs', p.1365, and 'Lithium + Venlafaxine', p.1368.

1. Sitsen JMA, Voortman G, Timmer CJ. Pharmacokinetics of mirtazapine and lithium in healthy male subjects. *J Psychopharmacol* (2000) 14, 172–6.
2. Zispin (Mirtazapine). Organon Laboratories Ltd. UK Summary of product characteristics, February 2009.

Lithium + Nefazodone

No pharmacokinetic interaction appears to occur between lithium and nefazodone.

Clinical evidence, mechanism, importance and management

In a study in 12 healthy subjects, nefazodone 200 mg twice daily was given alone for 5 days. After a washout period, lithium was given for 11 days, in escalating doses from 250 mg twice daily to 500 mg twice daily. When therapeutic steady-state lithium levels were achieved nefazodone 200 mg twice daily was added for 5 days. The pharmacokinetics of both nefazodone and lithium were unaltered by concurrent use, although there were some small changes in the pharmacokinetics of the nefazodone metabolites. However, as concurrent use was well tolerated, no dose adjustments were considered necessary on concurrent use.[1]

1. Laroudie C, Salazar DE, Cosson J-P, Cheuvart B, Istin B, Girault J, Ingrand I, Decourt J-P. *Eur J Clin Pharmacol* (1999) 54, 923–8.

Lithium + NSAIDs

NSAIDs may increase lithium levels leading to toxicity, but there is great variability between different NSAIDs and also between individuals taking the same NSAID. For example, studies have found that celecoxib causes a modest 17% increase in lithium levels, yet case reports describe increases of up to 344%. Similar effects occur with other NSAIDs, and it seems likely that all NSAIDs will interact similarly. However, note that sulindac seems unique in that it is the only NSAID that has also been reported to cause a decrease in lithium levels.

Clinical evidence

A retrospective analysis of 10 615 elderly patients receiving lithium found that 413 (3.9%) were admitted to hospital at least once for lithium toxicity during a 10-year study period. The prescriptions for any NSAID were compared between these 413 hospitalised patients and 1 651 control patients. For any use of an NSAID (63 cases and 187 controls) there was no increased relative risk of hospitalisation for lithium toxicity (relative risk 1.1). Similarly, when patients who were newly started on an NSAID were analysed (4 cases and 17 controls), there was still no increased risk (relative risk 0.6). The authors considered that these findings suggest that the use of NSAIDs and lithium may not be as hazardous as previously thought, although they do suggest that another explanation could be that clinicians were aware of the potential interaction and so adjusted doses or observed patients more closely in the outpatient setting, thereby avoiding any hospitalisations for toxicity.[1]

Case reports and studies about individual, named NSAIDs are outlined in the following subsections, and 'Table 31.1', (p.1361) summarises the effects of NSAIDs on lithium concentrations.

(a) Celecoxib

A 58-year-old woman, with a stable serum lithium level of between 0.5 and 0.9 mmol/L, developed renal impairment associated with severe lithium toxicity, within 5 days of starting to take celecoxib 400 mg twice daily. Her lithium level was 4 mmol/L. Of note, and a possible contributory factor, was the presence of ibuprofen, which she had taken with her lithium for several years without incident.[2]

In addition to 3 of the cases in 'Table 31.1', (p.1361), in January 2003, a review of the Adverse Event Reporting System database of the FDA in the US found 2 cases of increased lithium levels and symptoms of lithium toxicity in patients who also took celecoxib.[3]

(b) Flurbiprofen

A woman who was taking lithium carbonate 600 mg twice daily, with serum levels of 0.5 to 0.9 mmol/L, started to take flurbiprofen 200 mg daily. Within 4 days she became sleepy, hypotensive, and experienced nausea and vomiting, and tremor. Her serum lithium level had risen to 1.3 mmol/L. Seven days after stopping all treatment her lithium level had fallen to 0.5 mmol/L.[4]

(c) Ibuprofen

Three patients stabilised on lithium, with plasma levels of 0.7 to 0.9 mmol/L, were given ibuprofen 1.2 or 2.4 g daily for 7 days. The serum lithium levels of one patient rose from 0.8 to 1 mmol/L and he experienced nausea and drowsiness. The two other patients, including the one taking the 1.2-g ibuprofen dose, did not show this interaction.[5]

Three other case reports describe patients with symptoms of lithium toxicity that occurred within one to 7 days of them starting to take ibuprofen 1.2 g daily.[6-8] In another case, episodes of unsteadiness and tremor associated with raised lithium levels were attributed to varying use of prescribed ibuprofen 400 mg three times daily.[9]

(d) Indometacin

A case report describes lithium toxicity in a man given indometacin 50 mg every 6 hours. Three days after he started the indometacin his serum creatinine was raised, and 9 days later he had symptoms of lithium toxicity and was found to have a lithium level of 3.5 mmol/L. It was suggested that the indometacin caused renal impairment, which led to lithium retention and toxicity.[10] A study in 7 healthy subjects given a 200-mmol and 40-mmol sodium diet found that indometacin 50 mg three times daily for 4 doses increased mean plasma concentrations of a single 400-mg dose of lithium carbonate by 20% and 26%, respectively. Indometacin reduced lithium clearance by 16% and 28%, and fractional renal lithium reabsorption increased from 71% to 75% and from 75% to 81% during the high- and low-sodium diets, respectively.[11]

(e) Ketorolac

An 80-year-old man taking haloperidol, procyclidine, clonazepam, aspirin, digoxin and lithium (serum lithium levels between 0.5 and 0.7 mmol/L) was additionally given indometacin 100 mg daily for arthritis, which was replaced, after 13 days, by ketorolac 30 mg daily. The next day his serum lithium level was 0.9 mmol/L and 6 days later 1.1 mmol/L. Subsequently the patient developed severe nausea and vomiting, and both drugs were stopped.[12]

(f) Mefenamic acid

Acute lithium toxicity, accompanied by a sharp deterioration in renal function, was seen in a patient taking lithium carbonate with mefenamic acid 500 mg three times daily for 2 weeks. Withdrawal of the drugs and subsequent rechallenge confirmed this interaction.[13] Another case of toxicity was seen in a patient taking lithium who was given mefenamic acid. Her renal function was impaired when the lithium was started, but it had been stable for about 6 months before the NSAID was added.[14] A brief report also mentions another case of this interaction.[15]

(g) Niflumic acid

An isolated report describes lithium toxicity in a woman who took niflumic acid (said to be three capsules daily) for 7 days with the addition of

Table 31.1 Summary of the effects of NSAIDs on lithium levels

NSAID	*Dose*	*Subjects*	*Increase in lithium levels*	*Time to symptoms or increase in levels*	*Refs*
Celecoxib	200 to 800 mg daily	4 cases	56 to 248%	10 days to 10 weeks	1, 2
	200 mg twice daily	Study in healthy subjects	17%		3, 4
Diclofenac	75 mg daily	Case	86%	25 days	5
	50 mg three times daily	Study in 5 healthy subjects	26%	7 to 10 days	6
Flurbiprofen	200 mg twice daily	Case	44 to 160%	4 days	7
	100 mg twice daily	Placebo-controlled study in 11 otherwise healthy subjects with bipolar disorder	19%	7 days	8
Ibuprofen	1.6 to 1.8 g daily in divided doses	Studies in 11 healthy subjects and 9 subjects with bipolar disorder	12 to 67%	6 to 9 days	9, 10
Indometacin	150 mg daily	Studies in 9 healthy subjects and 6 subjects with bipolar disorder	30 to 61%	6 to 10 days	11-13
Ketoprofen	400 mg daily	Case	About 90%	3 weeks	14
Ketorolac	60 mg daily	Case	50%	3 weeks	15
	40 mg daily	Study in 5 healthy subjects	29%	5 days	16
Lornoxicam	4 mg twice daily	Study in 12 healthy subjects	20% (61% in one subject)	7 days	17
Meloxicam	15 mg daily	Study in 16 healthy subjects	21%	14 days	18
Naproxen	220 or 250 mg three times daily	Study in 9 healthy subjects and 7 bipolar or schizoaffective disorder	0 to 42%	5 to 6 days	19, 20
Phenylbutazone	750 mg daily (suppositories)	Case	106%	36 hours	21
	100 mg three times daily	Study in 5 subjects with bipolar disorder	0 to 15%	6 days	22
Piroxicam	20 mg daily	2 cases	130 to 235%	1 to 2 months	23, 24
Rofecoxib	Not stated or 25 mg once or twice daily	7 cases	58 to 448%	6 days to about 3 months	2, 25
	50 mg [daily]	Study in 10 healthy subjects	Unstated rise in 9 subjects, of these 3 were withdrawn early with levels of 1.26 mmol/L or more	Up to 5 days	26

1. Gunja N, Graudins A, Dowsett R. Lithium toxicity: a potential interaction with celecoxib. *Intern Med J* (2002) 32, 494-5.
2. Phelan KM, Mosholder AD, Lu S. Lithium interaction with the cyclooxygenase 2 inhibitors rofecoxib and celecoxib and other non-steroidal anti-inflammatory drugs. *J Clin Psychiatry* (2003) 64, 1328-34.
3. Celebrex (Celecoxib). Pharmacia Ltd. UK Summary of product characteristics, June 2009.
4. Celebrex (Celecoxib). Pfizer Inc. US Prescribing Information, June 2009.
5. Monji A, Maekawa T, Miura T, Nishi D, Horikawa H, Nakagawa Y, Tashiro N. Interactions between lithium and non-steroidal antiinflammatory drugs. *Clin Neuropharmacol* (2002) 25, 241-2.
6. Reimann IW, Frölich JC. Effects of diclofenac on lithium kinetics. *Clin Pharmacol Ther* (1981) 30, 348-52.
7. Aktepe E, Özkorumak E, Kandil S. Lithium interaction with flurbiprophen: a case report. *Klinik Psikofarmakoloji Bülteni* (2007) 17, 83–6.
8. Hughes BM, Small RE, Brink D, McKenzie ND. The effect of flurbiprofen on steady-state plasma lithium levels. *Pharmacotherapy* (1997) 17, 113-20.
9. Kristoff CA, Hayes PE, Barr WH, Small RE, Townsend RJ, Ettigi PG. Effect of ibuprofen on lithium plasma and red blood cell concentrations. *Clin Pharm* (1986) 5, 51-5.
10. Ragheb M. Ibuprofen can increase serum lithium level in lithium-treated patients. *J Clin Psychiatry* (1987) 48, 161-3.
11. Ragheb M, Ban TA, Buchanan D, Frolich JC. Interaction of indomethacin and ibuprofen with lithium in manic patients under a steady-state lithium level. *J Clin Psychiatry* (1980) 41, 397-8.
12. Frölich JC, Leftwich R, Ragheb M, Oates JA, Reimann I, Buchanan D. Indomethacin increases plasma lithium. *BMJ* (1979) 1, 1115-16.
13. Reimann IW, Diener U, Frölich JC. Indomethacin but not aspirin increases plasma lithium ion levels. *Arch Gen Psychiatry* (1983) 40, 283-6.
14. Singer L, Imbs JL, Danion JM, Singer P, Krieger-Finance F, Schmidt M, Schwartz J. Risque d'intoxication par le lithium en cas de traitement associé par les anti-inflammatories non stéroïdiens. *Therapie* (1981) 36, 323-6.
15. Iyer V, Ketorolac (Toradol®) induced lithium toxicity. *Headache* (1994) 34, 442-4.
16. Cold JA, ZumBrunnen TL, Simpson MA, Augustin BG, Awad E, Jann MW. Increased lithium serum and red blood cell concentrations during ketorolac coadministration. *J Clin Psychopharmacol* (1998) 18, 33-7.
17. Ravic M, Salas-Herrera I, Johnston A, Turner P, Foley K, Rosenow D. Influence of lornoxicam a new non-steroidal anti-inflammatory drug on lithium pharmacokinetics. *Hum Psychopharmacol* (1993) 8, 289-92.
18. Türck D, Heinzel G, Luik G. Steady-state pharmacokinetics of lithium in healthy volunteers receiving concomitant meloxicam. *Br J Clin Pharmacol* (2000) 50, 197-204.
19. Ragheb M, Powell AL. Lithium interaction with sulindac and naproxen. *J Clin Psychopharmacol* (1986) 6, 150-4.
20. Levin GM, Grum C, Eisele G. Effect of over-the-counter dosages of naproxen sodium and acetaminophen on plasma lithium concentrations in normal volunteers. *J Clin Psychopharmacol* (1998) 18, 237-40.
21. Singer L, Imbs JL, Schmidt M, Mack G, Sebban M, Danion JM. Baisse de la clearance rénale du lithium sous l'effet de la phénylbutazone. *Encephale* (1978) 4, 33-40.
22. Ragheb M. The interaction of lithium with phenylbutazone in bipolar affective patients. *J Clin Psychopharmacol* (1990) 10, 149-150.

Continued

Table 31.1 Summary of the effects of NSAIDs on lithium levels (continued)

23. Kelly CB, Cooper SJ. Toxic elevation of serum lithium concentration by non-steroidal anti-inflammatory drugs. *Ulster Med J* (1991) 60, 240-2.
24. Harrison TM, Wynne Davies D, Norris CM. Lithium carbonate and piroxicam. *Br J Psychiatry* (1986) 149, 124-5.
25. Rätz Bravo AE, Egger SS, Crespo S, Probst WL, Krähenbühl S. Lithium intoxication as a result of an interaction with rofecoxib. *Ann Pharmacother* (2004) 38, 1189-93.
26. Sajbel TA, Carter GW, Wiley RB. Pharmacokinetic effects of rofecoxib therapy on lithium. *Pharmacotherapy* (2001) 21, 380.

aspirin 1.5 g daily after 5 days. Her serum lithium levels rose from 0.8 mmol/L to 1.6 mmol/L.[16]

(h) Nimesulide

A 42-year-old woman taking lithium was given nimesulide 100 mg and ciprofloxacin 250 mg, both twice daily, for flank pain and dysuria. After 72 hours, she developed symptoms of lithium toxicity and the dose of lithium was reduced. After 98 hours she had vomiting, ataxia, and oliguria, and lithium levels were found to be 3.23 mmol/L (previous level 1.08 mmol/L) and her serum creatinine was raised.[17]

(i) Oxyphenbutazone

In an apparently isolated case, a 49-year-old woman is reported to have developed nausea and vomiting associated with a rise in lithium levels following the addition of oxyphenbutazone suppositories 500 mg daily. She responded well to a reduction in the lithium dose.[18]

(j) Parecoxib

The manufacturer of parecoxib says that valdecoxib, the main active metabolite of parecoxib, has been shown to cause decreases in the clearance of lithium (serum clearance reduced by 25%, renal clearance reduced by 30%), resulting in a 34% increase in exposure.[19]

(k) Piroxicam

A 56-year-old woman, taking lithium for over 9 years, with levels usually between 0.8 and 1 mmol/L, experienced lithium toxicity (unsteadiness, trembling, confusion) and was admitted to hospital on three occasions after taking piroxicam. Her serum levels on two occasions had risen to 2.7 mmol/L and 1.6 mmol/L, although in the latter instance the lithium had been withdrawn the day before the levels were taken. In a subsequent study her serum lithium levels rose from 1 mmol/L to 1.5 mmol/L after she took piroxicam 20 mg daily.[20] Two other case reports describe lithium toxicity, which occurred 4 weeks and 4 months after piroxicam was started.[21,22]

(l) Rofecoxib

A 73-year-old man, with lithium levels of between 0.6 and 0.9 mmol/L for the past 13 years, developed symptoms of lithium toxicity (serum lithium level 1.5 mmol/L) within 9 days of starting to take rofecoxib 12.5 mg daily. An interaction was strongly suspected. However, it should be noted that the patient had required his lithium dose to be successively decreased over the 13 years to maintain his lithium levels within the desired range. Captopril 6.25 mg daily had also been started during this time,[23] although it is unclear whether it had a part to play either in the lithium dose reduction or the development of an interaction. In addition to 6 of the cases in 'Table 31.1', (p.1361), in January 2003, a review of the Adverse Event Reporting System database of the FDA in the US found 7 cases of increased serum lithium concentrations after the addition of rofecoxib.[3]

(m) Sulindac

1. Lithium levels reduced. A patient stabilised on lithium had a marked fall in serum lithium levels from 0.65 mmol/L to 0.39 mmol/L after 2 weeks of the concurrent use of sulindac 100 mg twice daily. Her serum lithium levels gradually climbed over the next 6 weeks to 0.71 mmol/L and restabilised without any change in the dose of either lithium or sulindac. She needed amitriptyline for depression while the lithium levels were low, but bouts of depression had not been uncommon, even when lithium levels were stable.[24] The serum lithium levels of another patient were approximately halved a week after his dose of sulindac was doubled to 200 mg twice daily. He continued taking both drugs, but a higher dose of lithium was needed.[24]

2. Lithium levels unaffected. Two small studies (in a total of 10 patients)[25,26] and a case report[27] found that serum lithium levels were unaffected by the use of sulindac.

3. Lithium levels increased. Two patients developed increased serum lithium levels, apparently due to the use of sulindac.[28] In one case the lithium levels rose from 1 mmol/L to 2 mmol/L after 19 days of treatment with sulindac 150 mg twice daily, and symptoms of toxicity were seen. The levels fell to 0.8 mmol/L within 5 days of stopping the sulindac. The other patient had a rise from 0.9 mmol/L to 1.7 mmol/L within a week of adding sulindac 150 mg twice daily. The sulindac was continued and the lithium dose was reduced from 1.8 g daily to 1.5 g daily. The serum lithium levels fell and were 1.2 mmol/L at 37 days and 1 mmol/L at 70 days. No symptoms of lithium toxicity occurred.[28]

(n) Tiaprofenic acid

A 79-year-old woman taking lithium (as well as fosinopril, nifedipine, oxazepam and haloperidol) had a rise in her trough serum lithium levels from 0.36 mmol/L to 0.57 mmol/L within 3 days of starting to take tiaprofenic acid 200 mg three times daily. The serum lithium levels had risen to 0.65 mmol/L by the next day and, despite halving the lithium dose, were found to be 0.69 mmol/L five days later. These rises were attributed to an interaction with the tiaprofenic acid exacerbated by the fosinopril,[29] see 'Lithium + ACE inhibitors', p.1348.

Mechanism

Not understood. It has been suggested that the interacting NSAIDs inhibit the synthesis of the renal prostaglandins (PGE_2) so that the renal blood flow is reduced, thereby reducing the renal excretion of the lithium. In addition, reduced renal PGE_2 levels may be associated with increased reabsorption of sodium and lithium. However, this fails to explain why aspirin, which blocks renal prostaglandin synthesis by 65 to 70%, does not usually affect serum lithium levels, see 'Lithium + Aspirin or other Salicylates', p.1352.

Importance and management

The interaction between NSAIDs and lithium is well established, although the incidence is unknown. The increase in serum lithium levels appears to vary between the different NSAIDs and also between individuals taking the same NSAID (see 'Table 31.1', (p.1361)). Factors such as advanced age, impaired renal function, decreased sodium intake, volume depletion, renal artery stenosis, and heart failure increase the risk.

The documentation of these interactions is variable and limited, and although only some NSAIDs have been shown to interact, it seems likely that they will all interact to a greater or lesser extent. What is known indicates that most NSAIDs should be avoided, especially if other risk factors are present, unless serum lithium levels can be very well monitored (initially every few days) and the dose reduced appropriately. The effects of sulindac appear to be unpredictable (serum levels raised, lowered or unchanged) so that good monitoring is still necessary.

Patients taking lithium should be aware of the symptoms of lithium toxicity (see 'Lithium', (p.1347)) and told to report them immediately should they occur. This should be reinforced when they are given an NSAID. The situation with regards to single doses of NSAIDs is less clear. As many cases have demonstrated a rise in lithium levels within a matter of days, those buying non-prescription NSAIDs should be advised to only intermittently self-medicate with NSAIDs (i.e. very short-term use), or preferably to use a non-interacting alternative, such as paracetamol, see 'Lithium + Paracetamol (Acetaminophen)', p.1363. The same advice regarding an awareness of lithium toxicity should be reinforced. If any of the pre-disposing conditions that increase the risk of toxicity are present it may be safer to avoid concurrent use unless monitoring can be undertaken.

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Lithium + Olanzapine

Several case reports suggest that some patients taking olanzapine and lithium may develop adverse reactions (neuroleptic malignant syndrome or serotonin syndrome, encephalopathy, priapism) without raised serum lithium levels. One study found no pharmacokinetic interaction between the drugs, but another analysis suggested that lithium may reduce olanzapine plasma levels.

Clinical evidence, mechanism, importance and management

A 16-year-old boy taking lithium 1.2 g daily, with a therapeutic serum lithium level, developed neuroleptic malignant syndrome (generalised rigidity, urinary retention, fever, tachycardia) about 2 weeks after his olanzapine dose was increased from 10 to 20 mg daily. Both drugs were stopped, and the symptoms resolved over 8 days. He had previously taken olanzapine and lithium separately without problem.[1]

A 59-year-old man who had been diagnosed with encephalopathy and confusion while taking a combination of carbamazepine, haloperidol and lithium (at a level within the therapeutic range), developed similar symptoms when he was later given lithium with olanzapine.[2] Another elderly patient who had taken lithium for 7 years, developed severe delirium and extrapyramidal symptoms after the addition of olanzapine. Serum lithium levels were found to be 3 mmol/L.[3] The serotonin syndrome developed in a woman with bipolar affective disorder taking lithium and citalopram after olanzapine was also given. She became increasingly irritable 3 months after starting the combination and one month later (4 days after increasing the dose of olanzapine from 15 to 20 mg and stopping the citalopram) she became severely agitated, confused and was sweating profusely with hyperreflexia, tremor and a low-grade fever. The symptoms resolved on cessation of her medication.[4] Citalopram may have contributed to this reaction, as the serotonin syndrome has been reported with the concurrent use of 'lithium and SSRIs', (p.1365).

A case of non-ketotic hyperosmolar syndrome has been reported in a non-diabetic patient taking olanzapine, lithium and valproic acid. Symptoms began only 5 days after the olanzapine was started.[5] Priapism, which was reversed by surgical detumescence, occurred when a 30-year-old man took olanzapine with lithium.[6]

In an open-label study, 12 healthy subjects took a single 32.4-mmol dose of lithium with olanzapine 10 mg, and after a washout period, olanzapine 10 mg daily for 8 days, with a single 32.4-mmol dose of lithium on the last day. No pharmacokinetic interactions were detected.[7] However, an analysis of olanzapine levels in schizophrenic patients found that the concurrent use of lithium was associated with lower olanzapine plasma levels.[8]

The case reports detailed above suggest that some patients taking olanzapine and lithium may develop a pharmacodynamic interaction. Concurrent use of lithium and olanzapine need not be avoided but be aware that there is some risk of developing adverse reactions to the combination. The presence of other serotonergic drugs (e.g. antidepressants such as SSRIs) or dopamine antagonists (e.g. antipsychotics such as haloperidol) is likely to increase the risk of an interaction.

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Lithium + Paracetamol (Acetaminophen)

Paracetamol appears not to alter lithium levels.

Clinical evidence, mechanism, importance and management

A study in 9 healthy subjects given lithium carbonate 300 mg every 12 hours to achieve steady state, followed by the addition of 650 mg of paracetamol every 6 hours for 5 days, found no evidence that paracetamol increased serum lithium levels. Six subjects had no change in lithium levels, one subject had a 0.1 mmol/L decrease, and two had a 0.1 mmol/L increase.[1] One patient whose serum lithium level doubled while taking rofecoxib was later given paracetamol without any problems.[2] No precautions seem necessary on concurrent use.

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Lithium + Phenytoin

Symptoms of lithium toxicity (sometimes with unchanged lithium levels) have been seen in a few patients taking lithium and phenytoin, although the interaction has not been clearly demonstrated.

Clinical evidence, mechanism, importance and management

A patient with a history of depression and convulsions was given increasing doses of lithium carbonate and phenytoin over a period of about 4 years. Although the serum levels of both drugs remained within the therapeutic range, he eventually began to develop symptoms of lithium toxicity (thirst, polyuria, polydipsia and tremor) that disappeared when the lithium was stopped. Later, when lithium was restarted, the symptoms returned, this time abating when the phenytoin was replaced by carbamazepine. The patient then claimed that he felt normal for the first time in years.[1] Another report describes symptoms of lithium toxicity in a patient with lithium levels within the therapeutic range. This patient was also taking phenytoin.[2]

In a further case[3] a man taking phenytoin became ataxic within 3 days of starting to take lithium. He had no other toxic symptoms and his serum lithium level was 2 mmol/L. However, as he only ever took lithium in the presence of phenytoin, it is not possible to say whether the effects were as a result of an interaction, or whether toxic levels would have occurred with the lithium alone. Another similar case has also been reported.[4]

Information seems to be limited to these reports and none of them presents a clear picture of the role of phenytoin in the reactions

described.[1-4] The interaction is not well established. Patients taking lithium should be aware of the symptoms of lithium toxicity and told to report them immediately should they occur. This should be reinforced when they are given phenytoin. Increased serum lithium monitoring does not appear to be of value in this situation as the interaction occurred in patients with lithium levels within the normally accepted range.

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Lithium + Propranolol

One study suggests that propranolol may decrease the clearance of lithium. An isolated report describes a patient taking lithium who developed marked bradycardia after he took propranolol 30 mg daily.

Clinical evidence, mechanism, importance and management

A study in lithium-treated patients with manic depression found that the clearance of lithium was about 20% lower in 23 patients also taking propranolol than in 292 similar patients taking lithium alone.[1] However, the clinical effects of this difference were not evaluated, so the significance of this finding is unclear. A 70-year-old man who had been stable on lithium for 16 years was started on propranolol 30 mg daily for lithium-induced tremor. Six weeks later he was hospitalised because of vomiting, dizziness, headache and a fainting episode. His pulse rate was 35 to 40 bpm and his serum lithium level was 0.3 mmol/L. When later discharged taking lithium without propranolol his pulse rate had risen to a range of 64 to 80 bpm.[2]

The authors of the case report attribute the bradycardia to an interaction with lithium, as the low dose of propranolol was considered unlikely to cause bradycardia alone. They also point out that both drugs affect the movement of calcium across cell membranes, which could account for the decreased contraction rate of the heart muscle, and thus bradycardia in this patient. They suggest careful monitoring in elderly patients with atherosclerotic cardiovascular problems.[2]

The general importance of this interaction, if it is such, is uncertain, but it seems possible with all beta blockers because they can all cause bradycardia. However, as beta blockers are used to treat lithium-induced tremor, any serious problem would be expected to have come to light by now.

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Lithium + Quetiapine

Quetiapine does not appear to affect serum lithium levels in one study, and concurrent use did not increase the incidence of extrapyramidal symptoms in another study. An isolated report describes the development of delirium in a patient given quetiapine and lithium.

Clinical evidence, mechanism, importance and management

A patient with a long history of schizoaffective disorder stopped his medication and 2 months later developed psychosis, mood instability and psychomotor agitation. He was given an initial dose of quetiapine 50 mg daily which was increased over 7 days to 700 mg daily. He became sedated but as he was still experiencing mood fluctuations he was also given lithium carbonate 900 mg daily. Two days later he became confused, disorientated with cloudy consciousness and had short-term memory disturbances, visual hallucinations and agitation. The lithium serum level was 0.6 mmol/L. Quetiapine and lithium were stopped. He was treated with diazepam and the delirium gradually resolved. It was noted that lithium may induce delirium when given in combination with other drugs and that it may occur when lithium levels are within the therapeutic range.[1]

The steady-state serum lithium levels of 10 patients with schizophrenia, schizoaffective or bipolar disorder were studied before, during, and after the concurrent use of quetiapine 250 mg three times daily. Quetiapine increased the AUC and maximum serum levels of lithium by 12% and 4.5%, respectively, but this was not statistically significant. Concurrent use was well tolerated.[2]

A randomised, placebo-controlled study found that the incidence of extrapyramidal symptoms in patients receiving quetiapine with lithium was similar to that in patients receiving placebo with lithium.[3]

Although the studies suggest no special precautions would appear to be necessary on concurrent use, the isolated case report of delirium should be borne in mind if this combination is used.

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Lithium + Risperidone

There appears to be no pharmacokinetic interaction between risperidone and lithium, although a number of case reports describe adverse effects (e.g. extrapyramidal symptoms) when both drugs are given.

Clinical evidence, mechanism, importance and management

In a study 13 patients were given lithium and a conventional antipsychotic for at least 5 days on days 1 and 2 of the study. On study day 3, the patients were given lithium and risperidone 1 mg twice daily. The risperidone dose was increased to 2 mg twice daily on day 4 and then to 3 mg twice daily on days 5 to 9. The steady-state pharmacokinetics of lithium were not affected by the switch to risperidone and the plasma levels of risperidone and 9-hydroxyrisperidone were comparable to historical levels in subjects taking risperidone alone.[1]

A case report describes a 42-year-old woman taking lithium 800 mg daily who developed extrapyramidal adverse effects of the mouth after risperidone was started. Three days after her risperidone dose had reached 5 mg daily, she experienced an abrupt onset of abnormal peri-oral movements. Her serum lithium level was 0.7 mmol/L. Symptoms resolved after intravenous promethazine was given.[2] Another case report describes a non-diabetic patient, who developed diabetic ketoacidosis 2 years after starting treatment with risperidone and lithium. During this acute illness he also experienced neuroleptic malignant syndrome and a myocardial infarction. The authors considered the combination of these two drugs was a causative factor, as the patient was able to continue taking lithium alone with no recurrence of this condition, or the need for antidiabetic medication.[3] In a further case, a man taking lithium developed somnolence, confusion, delirium, fever and a rise in creatinine phosphokinase levels when risperidone was given.[4]

The study suggests that dose adjustments are unlikely to be necessary in patients given lithium and risperidone. The case reports serve as a reminder to be alert for adverse effects if both drugs are given.

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Lithium + Sodium compounds

The ingestion of marked amounts of sodium can prevent the establishment or maintenance of adequate lithium levels. Conversely, dietary salt restriction can cause lithium levels to rise to toxic concentrations if the lithium dose is not reduced appropriately.

Clinical evidence

(a) Lithium response reduced by the ingestion of sodium

A 35-year-old man who started to take lithium carbonate 250 mg four times a day, had a serum lithium level of 0.5 mmol/L by the following

morning. When the dose frequency was progressively increased to five, and later six times daily, his serum lithium levels did not exceed 0.6 mmol/L because, unknown to his doctor, he was also taking **sodium bicarbonate**. The patient's wife said he had been taking "**Soda Bic**" for years but since he started taking lithium he had been "shovelling it in". When the **sodium bicarbonate** was stopped, relatively stable serum lithium levels of 0.8 mmol/L were achieved with the initial dose of lithium carbonate.[1]

An investigation to find out why a number of inpatients were unable either to reach or maintain adequate therapeutic serum lithium levels over a period of 2 months, revealed that a clinic nurse had been giving the patients *Efferdex*, a product containing about 50% **sodium bicarbonate**, because the patients complained of nausea. The reduction in the expected serum lithium levels was as much as 40% in some cases.[2]

Other studies confirm that the serum lithium levels can fall, and the effectiveness of treatment can lessen, if the intake of sodium is increased.[3-6]

(b) Lithium response increased by sodium restriction

The serum lithium levels of 4 patients rose more rapidly and achieved a higher peak when salt was restricted to less than 10 mmol of sodium per day compared with the situation when the patients took a **dietary salt supplement**.[7]

Mechanism

The situation is complex and not fully established, but the mechanism can be broadly described in simplistic terms. Sodium balance is controlled by the kidney; if the serum sodium is low the kidney can reabsorb more sodium to maintain the balance. The kidney excretes and reabsorbs both lithium and sodium, but it does not appear to clearly distinguish between lithium and sodium ions. Therefore, if a patient taking lithium restricts sodium intake, the kidney may reabsorb both sodium and lithium, causing a rise in serum lithium levels. A corresponding decrease in lithium levels can occur when sodium intake is supplemented.[8,9]

Importance and management

Well established and clinically important interactions. The establishment and maintenance of therapeutic serum lithium levels can be jeopardised if the intake of sodium is altered. Warn patients not to take non-prescription antacids or urinary alkalinisers without first seeking informed advice. Sodium bicarbonate comes in various guises and disguises e.g. *Alka-Seltzer* (55.8%), *Andrews Salts* (22.6%), *Eno* (46.4%), *Jaap's Health Salts* (21.3%), *Peptac* (28.8%). Substantial amounts of sodium also occur in some **urinary alkalinising agents** (e.g. *Citralka*, *Citravescent*).[10] There are many similar preparations available throughout the world. An antacid containing **aluminium**/**magnesium hydroxide** with simeticone has been found to have no effect on the bioavailability of lithium carbonate,[11] so that antacids of this type would appear to be safer alternatives.

Patients already stabilised on lithium should not begin to limit their intake of salt unless their serum lithium levels can be monitored and suitable dose adjustments made, because their lithium levels can rise quite rapidly.

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Lithium + SSRIs

The concurrent use of lithium and SSRIs can be advantageous and uneventful, but various kinds of neurotoxicities have occurred. Isolated reports describe the development of symptoms similar to those of serotonin syndrome in patients taking lithium and fluoxetine, fluvoxamine, paroxetine and possibly citalopram. In addition, increases and decreases in serum lithium levels have been seen with fluoxetine.

Clinical evidence

(a) Citalopram

In a study in 8 healthy subjects, no pharmacokinetic changes were seen when lithium 30 mmol/day (as lithium sulfate 1.98 g daily) was added to citalopram 40 mg daily.[1] Another study, in 24 patients who had previously not responded to citalopram alone, found that the concurrent use of citalopram 40 or 60 mg and lithium carbonate 800 mg daily was effective and did not increase adverse effects.[2] For a report describing serotonin syndrome in a patient with bipolar affective disorder taking lithium, citalopram and olanzapine, see 'Lithium + Olanzapine', p.1363.

(b) Fluoxetine

A woman with bipolar affective disorder, successfully maintained for 20 years on lithium carbonate 1.2 g daily, developed stiffness of her arms and legs, dizziness, unsteadiness in walking and speech difficulties within a few days of starting fluoxetine 20 mg daily. Her serum lithium levels had risen from a range of 0.75 to 1.15 mmol/L up to 1.7 mmol/L. The lithium dose was reduced to 900 mg daily and the fluoxetine withdrawn. Within 7 days, the toxic symptoms had disappeared and the lithium levels had fallen to 0.9 mmol/L.[3] Two other patients had increases in serum lithium levels of about 45% and 70% (but no lithium toxicity) about a month after starting fluoxetine 20 mg daily or 40 mg daily, respectively. The problem resolved when the lithium dose was reduced by 40% and 30%, respectively, and in the second case, the fluoxetine was withdrawn. Both patients also developed mania, either after readjustment of the lithium dose or during concurrent use.[4]

In contrast, a study in 10 healthy subjects who took a single 32.4-mmol dose of lithium acetate alone, with a single 60-mg dose of fluoxetine, or with fluoxetine 60 mg after pretreatment with fluoxetine 20 mg three times daily for 7 days, found no significant changes in the distribution or elimination of lithium. Lithium levels were lower in the first 4 hours after it was taken with the single dose of fluoxetine than when it was taken alone or at fluoxetine steady-state, but all levels remained within the therapeutic range.[5] The US manufacturer of fluoxetine[6] says that the concurrent use of these two drugs has resulted in both increased and decreased serum lithium concentrations.

Toxicity (confusion, ataxia, coarse tremor, incoordination, movement disorders, fever) was seen in a patient when lithium was added to treatment with fluoxetine, although the serum lithium levels remained within the therapeutic range.[7] A woman taking clonazepam who started taking fluoxetine 20 mg then 40 mg daily, developed tremor and ataxia 6 days after lithium carbonate 100 mg increased to 400 mg daily was added. The problems resolved when the lithium and fluoxetine were withdrawn.[8] Extrapyramidal adverse effects and ataxia were seen in one patient taking lithium and fluoxetine, and dystonia occurred in another patient who was also taking carbamazepine, captopril and trimipramine.[9] The development of serotonin syndrome is also reported to have occurred in 2 patients taking lithium and fluoxetine.[10,11] Heat stroke developed in a man taking lithium and fluoxetine, attributed to synergistic impairment of his temperature regulatory system by the two drugs.[12] Absence seizures occurred in another patient given both drugs.[13]

(c) Fluvoxamine

A woman taking fluvoxamine became somnolent within a day of starting to take lithium. The lithium level 20 hours after the last dose was 0.2 mmol/L. She recovered when both drugs were stopped and she was discharged taking lithium alone. The excessive somnolence was considered to have been possibly caused by increased serotonin levels caused by this drug combination.[14] A woman taking long-term lithium started taking fluvoxamine 50 mg daily, increased to 200 mg daily over 10 days. She gradually developed tremor, difficulties in making fine hand movements, impaired motor co-ordination and hyperreflexia. Serum lithium levels remained therapeutic throughout. The reaction was interpreted as a mild form of serotonin syndrome.[15]

By 1989, the CSM in the UK had received 19 reports of adverse reactions when fluvoxamine was given with lithium (5 reports of convulsions and one of hyperpyrexia).[16]

In contrast to these reports, a study in 6 patients found that lithium (dosed to achieve plasma levels of 0.3 to 0.65 mmol/L) and fluvoxamine 100 to 150 mg daily (for between 3 and 23 weeks) was safe and effective, and no

adverse interaction of any kind occurred.[17] Another study in 6 depressed patients found that lithium did not affect the pharmacokinetics of fluvoxamine 100 mg daily and concurrent use was more effective than fluvoxamine alone.[18] It would seem therefore that concurrent use can be valuable, but there is a clear need to monitor the outcome so that any problems can be quickly identified.

(d) Paroxetine

A study in 14 patients taking lithium found that tremor increased significantly when paroxetine 20 to 40 mg daily was added. The greatest increments occurred approximately 3 weeks after concurrent use was started, but tremor activity was still significantly greater than baseline after 6 weeks. No patient discontinued treatment because of the increase in tremor.[19]

A 59-year-old woman with a long-standing bipolar disorder who had taken paroxetine 10 mg increased to 30 mg daily for 3 weeks, developed symptoms suggestive of serotonin syndrome (shivering, tremor of her arms and legs, flushed face, agitation, and some impairment of mental focussing) after lithium 400 mg daily was added.[20] Her serum lithium and paroxetine levels were found to be 0.63 mmol/L and 690 nanograms/mL, respectively (the latter being sixfold higher than the upper levels seen in other patients). The paroxetine dose was reduced to 10 mg daily, which decreased the paroxetine serum levels to 390 nanograms/mL, whereupon she became symptom-free and her depression was relieved. It is not clear whether this reaction was due to an interaction as she never took the higher dose of paroxetine in the absence of lithium.

There is a report of seizures, unsteady gait and blurred speech in a patient with bipolar disorder and cystic fibrosis taking lithium and paroxetine; both drugs were discontinued. However, this patient was abusing oxycodone and clonazepam and was also taking a variety of anti-asthma medications (salbutamol, salmeterol, budesonide, montelukast and cromoglicate), so the exact cause of the seizures is unclear.[21]

(e) Sertraline

In a randomised, placebo-controlled study, 16 healthy subjects were given lithium 600 mg twice daily for 9 days. On day 8, half of the subjects received two 100-mg doses of sertraline 8 hours apart, while the other half received placebo. Sertraline caused reduced steady-state lithium levels by 1.4%, and increased the renal excretion of lithium, but neither of these changes was statistically significant. However, there was a high incidence of adverse effects (mainly tremor and nausea) on concurrent use: tremor occurred in 7 out of the 8 taking sertraline, whereas no adverse effects were reported in the placebo group.[22]

Severe priapism occurred in a patient taking lithium carbonate 600 mg daily within 2 weeks of having the dose of sertraline increased from 50 to 100 mg daily. It was not clear whether this was purely a reaction to the increased sertraline dose, although it was suggested that the effect may have been due to the serotonergic effects of both drugs.[23]

Mechanism

Not fully understood although it seems likely that many of the symptoms could be due to the effects of both lithium and SSRIs on serotonin.

Importance and management

The concurrent use of lithium and an SSRI can be uneventful. A review of the safety of the concurrent use of lithium and the SSRIs identified 503 subjects who had received the combination without any evidence of serious adverse events.[24] However, occasionally and unpredictably adverse reactions develop, but the precise incidence is not known. If lithium is used in conjunction with an SSRI be alert for any evidence of toxicity. The symptoms may include tremor, dysarthria, ataxia, confusion, and many other symptoms of serotonin syndrome (see also *Serotonin syndrome*, under 'Additive or synergistic interactions', (p.9)). Heat stroke has also been seen and the serum lithium levels may rise. It would clearly be prudent to monitor concurrent use carefully.

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Lithium + Theophylline

Lithium levels are moderately reduced by 20 to 30% by the concurrent use of theophylline, which may cause patients to relapse.

Clinical evidence

The serum lithium levels of 10 healthy subjects taking lithium carbonate 900 mg daily fell by 20 to 30%, and the urinary clearance increased by 30%, when they were given theophylline (*Theo-dur*). Steady-state theophylline levels of 5.4 to 12.7 micrograms/mL were achieved, and it was noted that higher theophylline levels were strongly correlated with increased lithium clearance.[1] This study has been reported in brief elsewhere.[2]

A man taking theophylline was diagnosed with a bipolar disorder and started taking lithium while in hospital for an exacerbation of COPD. When the dose of theophylline was raised, because of a worsening in his condition, his lithium dose also had to be increased to control the emergence of manic symptoms. He received a maximum theophylline dose of 1.5 g daily, during which time he needed 2.7 g of lithium daily. When the theophylline was stopped, he only needed around 1.5 g of lithium daily to control his manic symptoms.[3] Two studies support the evidence from these cases, with the finding that lithium excretion is increased by about 50% by aminophylline or theophylline.[4,5]

Mechanism

Uncertain. Theophylline has an effect on the renal clearance of lithium.

Importance and management

Information is very limited but the interaction between aminophylline or theophylline and lithium appears to be established. Depressive and manic relapses may occur if the dose of lithium is not raised appropriately when these drugs are given. Serum lithium levels should be monitored if theophylline or aminophylline is stopped, started, or if the dose is altered.

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Lithium + Topiramate

Two isolated reports describe elevated lithium levels and evidence of toxicity in patients also taking topiramate. No important pharmacokinetic interaction has been seen in healthy subjects.

Clinical evidence, mechanism, importance and management

A 42-year-old woman with type II bipolar disorder started taking lithium carbonate 1.5 g and topiramate 500 mg daily, resulting in a steady-state trough serum lithium level of 0.5 mmol/L after 10 days. She was also started taking citalopram 10 mg daily. The patient raised the topiramate dose to 800 mg daily in an attempt to lose weight, and 5 weeks later began to complain of severe anorexia, nausea, fatigue and impaired concentration. She had managed to lose 35 lb (almost 16 kg) of weight she had gained whilst taking a previous drug combination. When examined she was lethargic, with tremors, nystagmus, bradycardia and memory loss. Her trough serum lithium level had risen by 180% to 1.4 mmol/L. The symptoms disappeared over 4 days when the lithium was stopped. Two months later she was stabilised once again on lithium carbonate 1.2 g and topiramate 500 mg daily, with a steady-state serum lithium level of 0.5 mmol/L.[1]

Another report describes a case of increased lithium levels and toxicity (worsening concentration, confusion, lethargy) after topiramate was given to a patient taking lithium. The lithium was stopped and then restarted at half the original dose, which produced therapeutic lithium levels of 0.67 mmol/L. In addition, while maintaining the dose of lithium at 450 mg daily, further increases in the topiramate dose from 75 to 125 mg daily over 4 weeks resulted in parallel elevations of lithium levels (from 0.67 to 0.92 mmol/L).[2]

However, a review of the pharmacokinetic interactions of topiramate reported a study that had found that there was little pharmacokinetic interaction with lithium when topiramate (50 mg twice daily titrated to 100 mg twice daily) was given to 12 healthy subjects receiving lithium carbonate 300 mg two or three times daily [dosing frequency unclear]. The AUC of lithium was about 18% lower and the clearance 22% higher. When compared with historical data, the clearance of topiramate appeared to be lower in the presence of lithium.[3]

The reasons for these reactions are not known, but topiramate is mainly eliminated by renal excretion and high doses of topiramate may competitively interfere with lithium excretion.[1] Similarly, lithium may affect topiramate clearance.[3] Some of the toxicity could have been due to the adverse effects of either drug, with the weight loss in the first case possibly disturbing the sodium excretion, which could have affected the loss of lithium in the urine.

These cases highlight the possible risk of elevated serum lithium levels especially if high doses of topiramate are used. Patients taking lithium should be aware of the symptoms of lithium toxicity and told to report them immediately should they occur. This should be reinforced when they are given topiramate. The authors of two reports suggest that lithium levels should be monitored in patients newly started on this combination and the dose of topiramate and/or lithium carefully adjusted to minimise adverse effects.[4,5]

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Lithium + Tricyclic and related antidepressants

The concurrent use of a tricyclic antidepressant and lithium can be successful in some patients, but others may develop adverse effects, a few of them severe. Cases of neurotoxicity, serotonin syndrome, and neuroleptic malignant syndrome have been reported.

Clinical evidence

A study in 14 treatment-resistant depressed patients aged between 61 and 82 years found that 7 patients had complete improvement and 3 patients had partial improvement, 3 to 21 days after lithium was added to treatment with the tricyclic or related antidepressants. Lithium adverse effects occurred in 6 patients; 4 of whom stopped lithium as a result. One of them was successfully restarted at a lower dose. Tremor was the most frequent adverse effect, and reversible neurotoxicity with a stroke-like syndrome was the most severe. The antidepressants used were **amitriptyline**, **doxepin**, **maprotiline** and **trazodone**.[1]

A meta-analysis of 9 studies on the acute treatment of unipolar or bipolar depression indicated that the concurrent use of a mood stabiliser (lithium in 6 studies) and a tricyclic antidepressant was associated with an increased risk of switches into (hypo)mania, when compared with a mood stabiliser alone. It was suggested that monotherapy with a mood stabiliser should be tried to see if it is effective, before adding an antidepressant. Tricyclics were considered to be second-line antidepressants, with SSRIs the preferred choice.[2]

Reports relating to specific tricyclics are outlined below.

(a) Amitriptyline

A study in 17 lithium-maintained patients found that tremor increased significantly when amitriptyline 75 to 150 mg daily was added. The greatest increments occurred within approximately 3 weeks of starting concurrent use, but tremor activity was still significantly greater than baseline after 6 weeks. No patient discontinued treatment because of the increase in tremor.[3] Seizures occurred in a patient taking amitriptyline 300 mg daily, 13 days after lithium carbonate 300 mg three times daily was started. After recovery, concurrent use was resumed, but further seizures occurred 10 days later. Her lithium levels were 0.9 mmol/L three days before this second episode. She later took amitriptyline 500 mg daily without adverse effect.[4] Another patient developed neuroleptic malignant syndrome after one week of treatment with lithium carbonate 300 mg and amitriptyline 25 mg, both three times daily. The patient had also received chlorpromazine for one week, just before the concurrent use of lithium and amitriptyline was started.[5] No pharmacokinetic interaction was found in 10 therapy-resistant patients with major depression who were given amitriptyline and lithium for 4 weeks.[6]

(b) Amoxapine

An analysis of the spontaneous reporting system of the FDA in the US identified one case of neurotoxicity involving the use of amoxapine and lithium.[7]

(c) Clomipramine

A depressed man taking clomipramine 175 mg, levomepromazine 25 mg and flunitrazepam 2 mg daily, started taking lithium 600 mg daily. About one week later, after his dose of lithium was raised to 1 g daily he developed serotonin syndrome (myoclonus, shivering, tremors, incoordination). Due to this reaction, and because his serum lithium levels were 1.6 mmol/L, the lithium was stopped. Serotonin syndrome then abated. The clomipramine dose was reduced, but some mild symptoms remained until the clomipramine was stopped. He responded well to lithium 600 mg daily alone, without developing serotonin syndrome.[8]

(d) Doxepin

A 64-year-old man developed periods of confusion and disorientation within 2 weeks of starting to take lithium 300 mg twice daily with doxepin 100 mg at bedtime. He was admitted to hospital because of urinary retention, and he was also lethargic and became confused, but despite the withdrawal of both drugs he developed a condition similar to neuroleptic malignant syndrome (fever, muscle rigidity, changes in consciousness, autonomic dysfunction), which was successfully treated with dantrolene.[9]

(e) Nortriptyline

A 65-year-old woman developed tremor, memory difficulties, disorganised thinking and auditory hallucinations when given lithium carbonate 300 mg twice daily (lithium level 0.82 mmol/L) and nortriptyline 50 mg daily. However, because she only ever received lithium with nortriptyline, the possibility that this was an effect of lithium alone cannot be excluded.[10]

Mechanism

Not fully understood. Tremor is a relatively frequent adverse effect of both lithium and antidepressants with serotonergic properties. It might be expected that the concurrent use of lithium (which is itself serotonergic) with such antidepressants will enhance not only efficacy, but also increase the incidence of adverse effects.[3] For more information about serotonin syndrome, see 'Additive or synergistic interactions', (p.9).

Importance and management

The concurrent use of lithium and tricyclics can be valuable, but the reports cited here clearly show the need to monitor the outcome closely so that any problems can be dealt with quickly. The incidence of these serious reactions is not known.

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Lithium + Triptans

In two cases patients taking lithium developed symptoms suggestive of serotonin syndrome after taking sumatriptan.

Clinical evidence, mechanism, importance and management

A comprehensive literature search published in 1998 identified several cases of adverse events reported with **sumatriptan** and lithium, although in most cases other medications were also being taken. Two patients taking **sumatriptan** and lithium concurrently were identified with symptoms suggestive of serotonin syndrome, but the symptoms were mild to moderate and self-limiting. The number of patients taking lithium and **sumatriptan** was not stated, so the incidence of this effect is unknown.[1] The conclusion was reached that **sumatriptan** can be used cautiously in patients receiving lithium.[1] There seem to be no other reports of problems with lithium and triptans. However, note that, rarely, the use of lithium or triptans with other drugs has led to serotonin syndrome. For more information about serotonin syndrome, see under 'Additive or synergistic interactions', (p.9).

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Lithium + Valproate

No clinically relevant adverse interaction appears to occur between lithium carbonate and valproate.

Clinical evidence, mechanism, importance and management

In a crossover study, 16 healthy subjects were given valproate (as valproate semisodium) or a placebo twice daily for 12 days, to which lithium carbonate 300 mg three times daily was added on days 6 to 10. The valproate serum levels and AUC rose slightly, while the serum lithium levels were unaltered. Adverse events did not change significantly. It was concluded that the concurrent use of these drugs is safe.[1] A review on the efficacy of the concurrent use of lithium and an antiepileptic in bipolar disorder lists several studies in which the combination of valproate (as valproate semisodium) and lithium was used. On the whole concurrent use was considered safe and well tolerated, although a few patients discontinued treatment due to adverse effects, which included gastrointestinal symptoms and raised liver transaminases. It was, however, difficult to know if these adverse effects were due to the individual drugs or the result of an interaction. Other adverse effects that have been reported on concurrent use include tremor, cognitive impairment and alopecia.[2]

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Lithium + Venlafaxine

Symptoms similar to those of serotonin syndrome have developed in a few patients taking lithium with venlafaxine. No clinically significant pharmacokinetic interaction usually appears to occur between these two drugs.

Clinical evidence

In an open study of 13 patients with major depression who did not respond to a 4-week course of venlafaxine 300 mg daily, lithium was added and continued for 4 weeks. After 12 days of concurrent use, 2 patients experienced symptoms of hypomania, marked nausea and trembling (considered to be a moderate form of serotonin syndrome), and had to stop lithium. Their lithium plasma levels were within the therapeutic range (0.83 and 0.77 mmol/L on day 7). Lithium was well tolerated by most of the other patients, with trembling being the most frequent adverse effect (4 out of 11).[1]

A case report describes a 50-year-old woman who developed serotonin syndrome 45 days after starting to take lithium and venlafaxine (and within 10 days of the most recent dose increase of venlafaxine). Both drugs were immediately stopped and she recovered over the next 4 to 5 days. Plasma levels of venlafaxine, its metabolite *O*-desmethylvenlafaxine, and lithium had remained within the normal therapeutic ranges throughout. As she had previously experienced profound adverse effects with two different SSRIs, the authors concluded that the patient was unusually sensitive to serotonergic medication.[2] Another case report describes a 71-year-old woman who developed signs of serotonin syndrome a few days after dose increases of venlafaxine from 75 mg to 150 mg daily and lithium carbonate 400 mg to 600 mg daily. She had only been taking the combination for a few days in total when serotonin syndrome developed. Her lithium levels remained within the therapeutic range, but her venlafaxine levels were 239 micrograms/L, (reference range 10 to 200 micrograms/L). She recovered within 3 days of stopping treatment with venlafaxine and lithium. Subsequently, when taking venlafaxine alone, her levels were within the reference range.[3]

In a pharmacokinetic study, 12 healthy subjects were given a single 600-mg dose of lithium carbonate on day one and day 8, with venlafaxine 50 mg every 8 hours for 7 days from day 4. The renal clearance of venlafaxine was reduced by about 50% and that of its active metabolite, *O*-desmethylvenlafaxine, was reduced by 15%. Neither of these changes was considered to be clinically relevant, as the total clearance was not affected. The maximum serum levels of the lithium were increased by about 10%, and the time to reach this was reduced by about 30 minutes, but these changes would not be expected to be clinically relevant, and the other pharmacokinetic parameters of lithium were unchanged.[4]

Mechanism, importance and management

The general picture that emerges from these reports is that normally no clinically important pharmacokinetic interaction occurs if venlafaxine and lithium are used together, but in some rare cases, serotonin syndrome may occur. The reason for the raised venlafaxine levels seen in one of the cases is unclear.[3] There seems to be no good reason for avoiding concurrent use, but be aware that an interaction is possible and monitor the outcome carefully. For more information about serotonin syndrome, see under 'Additive or synergistic interactions', (p.9).

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2. Mekler G, Woggon B. A case of serotonin syndrome caused by venlafaxine and lithium. *Pharmacopsychiatry* (1997) 30, 272–3.
3. Adan-Manes J, Novalbos J, López-Rodríguez R, Ayuso-Mateos JL, Abad-Santos F. Lithium and venlafaxine interaction: a case of serotonin syndrome. *J Clin Pharm Ther* (2006) 31, 397–400.
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Lithium + Ziprasidone

Ziprasidone does not appear to alter the pharmacokinetics of lithium. However, a neuroleptic malignant syndrome occurred in one patient taking both drugs.

Clinical evidence, mechanism, importance and management

A randomised, placebo-controlled study in 25 healthy subjects taking lithium carbonate 450 mg twice daily for 15 days, found that ziprasidone 20 mg twice daily on days 9 to 11, followed by 40 mg twice daily on days 12 to 15, caused only a small increase in the steady-state serum-lithium levels (14% compared with 11% in the placebo group). A 5% reduction in renal clearance was seen in the ziprasidone group and a 9% reduction was seen in the placebo group. These differences were neither statistically nor clinically significant.[1]

A case report describes a patient taking lithium 450 mg twice daily, divalproex sodium, and a number of other drugs, who started to take ziprasidone 80 mg twice daily orally with intramuscular ziprasidone 20 mg as needed. He became somnolent, was unable to walk and follow commands. His respiratory rate was increased (28 breaths/minute), his blood pressure was decreased (68/40 mmHg), and his temperature was raised (39.4°C) and had a raised white cell count. He had a high urine output and an elevated lithium level of 2.07 mmol/L and so diabetes insipidus secondary to lithium was suspected. He was also diagnosed with neuroleptic malignant syndrome.[2] The authors note that both ziprasidone and lithium (particularly in toxicity) are associated with the neuroleptic malignant syndrome. Although a reaction to ziprasidone was suspected they note that in interaction with lithium cannot be excluded.[2]

This is an isolated case and an interaction is not established. As neuroleptic malignant syndrome can occur in response to one antipsychotic drug there would seem no need to take additional precautions if both ziprasidone and lithium are taken.

1. Apseloff G, Mullet D, Wilner KD, Anziano RJ, Tensfeldt TG, Pelletier SM, Gerber N. The effects of ziprasidone on steady-state lithium levels and renal clearance of lithium. *Br J Clin Pharmacol* (2000) 49 (Suppl 1), 61S–64S.
2. Borovicka MC, Bond LC, Gaughan KM. Ziprasidone- and lithium-induced neuroleptic malignant syndrome. *Ann Pharmacother* (2006) 40, 139–42.

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MAOIs

The intended target of the MAOIs (monoamine oxidase inhibitors) is monoamine oxidase within the brain, but monoamine oxidase is also found in other parts of the body. Particularly high concentrations occur in the gut and liver, where it acts as a protective detoxifying enzyme against tyramine and possibly other potentially hazardous amines, which exist in foods that have undergone bacterial degradation. There are at least two forms of monoamine oxidase: MAO-A metabolises (deaminates) noradrenaline (norepinephrine) and serotonin (5-HT), while MAO-B metabolises phenylethylamine. Substances like tyramine and dopamine are metabolised by both forms of MAO.

The older MAOIs (see 'Table 32.1', below) are non-selective or non-specific, and inhibit both isoenzymes A and B. They are irreversible and long acting, because the return of monoamine oxidase activity depends upon the regeneration of new enzymes. As a result their effects (both beneficial and adverse) can last for 2 to 3 weeks after they have been withdrawn. Tranylcypromine differs in being a more reversible inhibitor of MAO, so the onset and disappearance of its actions are quicker than the other non-selective MAOIs. However, its effects still last for a number of weeks after withdrawal (e.g. see 'MAOIs or RIMAs + Tyramine-rich foods', p.1395), so it is still effectively an irreversible inhibitor, and is usually classified as such. These non-selective MAOIs cause serious and potentially life-threatening hypertensive reactions if they are given with the sympathomimetics found in some proprietary 'cough and cold remedies', (p.1388), and with 'tyramine-rich foods', (p.1395), and 'drinks', (p.1393).

Some of the newer and more recently developed drugs with MAO inhibitory activity (see 'Table 32.1', below) interact to a lesser extent than the older MAOIs. This is because they are largely selective. One group of these selective inhibitors targets MAO-A, and are relatively rapidly reversible; inhibition of this enzyme is responsible for the antidepressant effect. These selective MAO-A inhibitors (moclobemide, toloxatone) have been given the acronym RIMAs (Reversible Inhibitors of Monoamine oxidase A). They leave MAO-B largely uninhibited so that there is still a metabolic pathway available for the breakdown of amines, such as tyramine, that can cause a rise in blood pressure. In practical terms this means that the amount of tyramine needed to cause a hypertensive crisis is about tenfold greater than with the non-selective MAOIs (see 'tyramine-rich foods', (p.1395)).

The other newer selective MAOIs that specifically inhibit MAO-B are ineffective for the treatment of depression and are mainly used for Parkinson's disease, and so are covered elsewhere, see 'Antiparkinsonian and related drugs', (p.784). In low doses they inhibit MAO-B, leaving MAO-A largely uninhibited. However, selegiline loses some of its selectivity at doses of more than 10 mg daily and will therefore be subject to the same interactions as the non-selective MAOIs. Rasagiline is another irreversible selective inhibitor of MAO-B used for Parkinson's disease.

Some other drugs covered elsewhere in this publication also have MAOI activity. Furazolidone is an antiprotozoal with MAOI activity. Linezolid is an oxazolidinone antibacterial with weak, reversible non-selective MAOI activity. Interactions typical of MAOIs might therefore occur with these drugs.

The product information issued by manufacturers frequently contains warnings about real and alleged interactions with MAOIs. Blackwell,[1] who has done much work on the interactions of the MAOIs, has rightly pointed out that the MAOIs are among the drugs that accumulate much myth and misinformation. He notes that the MAOIs have developed such a sinister reputation that manufacturers often issue a reflexive admonition to avoid the concurrent use of MAOIs with new drugs.

This means that many of the warnings about potential interactions with the MAOIs may lack a sound scientific basis. However, equally this does not mean that the proven serious life-threatening interactions that are associated with the MAOIs should be dismissed, and it should be noted that any drug with indirectly-acting sympathomimetic activity is likely to interact.

1. Blackwell B. Monoamine oxidase inhibitor interactions with other drugs. *J Clin Psychopharmacol* (1991) 11, 55–59.

Table 32.1 Monoamine oxidase inhibitors (MAOIs)†

Irreversible non-selective MAO-inhibitors (MAO-A and MAO-B)	*Reversible Inhibitors of MAO-A (RIMAs)*	*Irreversible inhibitors of MAO-B**
Iproniazid	Brofaromine	Rasagiline
Isocarboxazid	Moclobemide	Selegiline
Mebanazine	Toloxatone	
Nialamide		
Phenelzine		
Tranylcypromine		

*MAO-B inhibitors are used in Parkinson's disease, so are covered elsewhere

†Furazolidone, a non-selective MAOI used as an antiprotozoal, and linezolid, a weak, reversible non-selective MAOI, used as an antibacterial, are covered elsewhere

MAOIs + Antihistamines

The alleged interaction between the MAOIs and antihistamines appears to be based on a single *animal* study, and is probably more theoretical than real. There appear to be some exceptions, based on the additional properties of some specific antihistamines (cyproheptadine and promethazine).

Clinical evidence, mechanism, importance and management

A number of lists, charts and books about adverse interactions suggest that potentially serious interactions can occur between the MAOIs and the antihistamines. This appears to be based on a study in *rabbits* from 1972, which showed that some antihistamines (notably alkylamine antihistamines such as **chlorphenamine**, **brompheniramine**, and also **diphenhydramine**) produced a fatal hyperpyrexia, thought to be due to serotonin potentiation, when given intravenously to **phenelzine** pretreated *rabbits*.[1] This reaction was considered to be similar to that seen with 'pethidine (meperidine)', (p.1381), or the 'tricyclics', (p.1391). However, in over 20 years since the publication of this data, the manufacturers of various antihistamines did not identify any clinical reports of adverse interactions attributed to the use of any antihistamine with an MAOI.[2-6] Nevertheless, the UK manufacturers of most of the sedating antihistamines (**alimemazine**, **brompheniramine**, **chlorphenamine**, **diphenhydramine**) state that MAOIs may intensify the antimuscarinic effect of antihistamines, and many contraindicate or caution concurrent use.[7-10] No such warning is given for non-sedating antihistamines. In fact, brompheniramine and chlorphenamine have been specifically mentioned by one author as being suitable for the management of rhinitis associated with the common cold in patients taking MAOIs.[11]

There would appear to be no good reason to avoid the concurrent use of sedating or non-sedating antihistamines and MAOIs, although note that there other properties should be considered: because cyproheptadine has specific serotonin antagonist properties, and promethazine is a phenothiazine, they may interact differently, see 'MAOIs or RIMAs + Antihistamines; Cyproheptadine', below, and 'MAOIs or RIMAs + Antipsychotics', below.

1. Sinclair JG. Antihistamine-monoamine oxidase inhibitor interaction in rabbits. *J Pharm Pharmacol* (1972) 24, 955–61.
2. Intercare Products (Sandoz). Personal communication, May 1995.
3. Rhône-Poulenc Rorer, Personal communication, December 1997.
4. Glaxo Wellcome. Personal communication, December 1995.
5. Stafford Miller. Personal communication, November 1995.
6. Hoechst Roussel. Personal communication, November 1995.
7. Nytol (Diphenydramine hydrochloride). GlaxoSmithKline Consumer Healthcare. UK Summary of product characteristics, February 2002.
8. Piriton (Chlorphenamine maleate). GlaxoSmithKline Consumer Healthcare. UK Summary of product characteristics, October 2004.
9. Dimotane Plus Paediatric (Brompheniramine maleate). Wyeth Pharmaceuticals. UK Summary of product characteristics, June 2003.
10. Vallergan Tablets (Alimemazine). Sanofi-Aventis. UK Summary of product characteristics, January 2007.
11. Jenike MA. Alcohol and antihistamines not contraindicated with MAOIs? *Am J Psychiatry* (1983) 140, 1107.

MAOIs or RIMAs + Antihistamines; Cyproheptadine

Isolated reports describe delayed hallucinations in a patient taking phenelzine and cyproheptadine, and the rapid re-emergence of depression when two other patients taking brofaromine or phenelzine were given cyproheptadine.

Clinical evidence

A woman who had responded well to **brofaromine** rapidly became depressed again when she took cyproheptadine. She had to be hospitalised due to suicidal ideation, but eventually she responded to treatment and she then took **brofaromine** with cyproheptadine for 6 months.[1] A man whose depression responded well to **phenelzine** 75 mg daily was given cyproheptadine 4 mg to treat associated sexual dysfunction and anorgasmia. Within 3 days of adding the cyproheptadine his depression returned, but the anorgasmia did not improve. When the cyproheptadine was stopped his depression was relieved.[2] Hallucinations developed in a woman taking **phenelzine** 2 months after cyproheptadine was started.[3]

Mechanism

Cyproheptadine is a serotonin antagonist. The reversal of the effects of the brofaromine was therefore attributed by the authors of one report[1] to the blockage of 5-HT (serotonin) receptors by cyproheptadine (brofaromine has both MAO-A inhibitory and 5-HT uptake inhibitory properties).

Cyproheptadine also appears to block the activity of serotonin reuptake inhibitors (see 'SSRIs + Cyproheptadine', p.1482).

Importance and management

Information seems to be limited to these reports but it would be prudent to be alert for a reduction in efficacy or an adverse response if cyproheptadine is given with any MAOI or RIMA. The manufacturer of cyproheptadine actually contraindicates concurrent use with MAOIs.[4] However, there appears to be no reason why cyproheptadine cannot be used to treat the serotonin syndrome occurring in a patient taking an MAOI.

The UK manufacturer of cyproheptadine also says that MAOIs prolong and intensify the antimuscarinic effects of antihistamines,[4] but there seems to be no clinical data to support this suggestion with cyproheptadine or any other antihistamine, see 'MAOIs + Antihistamines', above.

1. Katz RJ, Rosenthal M. Adverse interaction of cyproheptadine with serotonergic antidepressants. *J Clin Psychiatry* (1994) 55, 314–15.
2. Zubieta JK, Demitrack MA. Depression after cyproheptadine: MAO treatment. *Biol Psychiatry* (1992) 31, 1177–8.
3. Kahn DA. Possible toxic interaction between cyproheptadine and phenelzine. *Am J Psychiatry* (1987) 144, 1242–3.
4. Periactin (Cyproheptadine hydrochloride). Merck Sharp & Dohme Ltd. UK Summary of product characteristics, January 2004.

MAOIs + Antimuscarinics

No adverse interactions between the MAOIs and antimuscarinics have been reported, although the possibility has been suggested.

Clinical evidence, mechanism, importance and management

A hyperthermic reaction has been reported in some *animals* given **tranylcypromine** or **nialamide** with **procyclidine** or **benzatropine**. It was considered that this might be due to an exaggerated dopamine response.[1] However, there do not appear to be any reports of such an interaction occurring clinically. Nevertheless, the manufacturer of procyclidine,[2] and some manufacturers of irreversible non-selective MAOIs (isocarboxazid and phenelzine)[3,4] advise caution because of the possibility that the concurrent use of an antimuscarinic and an MAOI may lead to increased antimuscarinic effects. This is presumably because, in theory, inhibition of drug-metabolising enzymes by MAOIs may possibly enhance the effects of antimuscarinics.

1. Pedersen V, Nielsen IM. Hyperthermia in rabbits caused by interaction between M.A.O.I.s, antiparkinson drugs, and neuroleptics. *Lancet* (1975) i, 409–10.
2. Kemadrin (Procyclidine hydrochloride). GlaxoSmithKline UK. UK Summary of product characteristics, May 2008.
3. Isocarboxazid. Cambridge Laboratories. UK Summary of product characteristics, March 2000.
4. Nardil (Phenelzine sulfate). Concord Pharmaceuticals Ltd. UK Summary of product characteristics, July 2003.

MAOIs or RIMAs + Antipsychotics

The concurrent use of MAOIs and phenothiazines is usually safe and effective. However, rarely, cases of possible neuroleptic malignant syndrome or hyperpyrexia have been reported when MAOIs were given with chlorpromazine, levomepromazine or trifluoperazine. Some of these cases were fatal. Chlorpromazine has been successfully used for treatment of serotonin syndrome occurring with MAOIs and other drugs.
Moclobemide has been given with various antipsychotics without a significant interaction, although adverse effects were increased. However, one case describes a fatal overdose which was attributed to an interaction between moclobemide and perazine.

Clinical evidence

(a) MAOIs

MAOIs and phenothiazines have been safe and effective when used together in the treatment of psychiatric conditions, particularly in the form

of a preparation containing both **tranylcypromine** and **trifluoperazine**,[1-3] which is still marketed in some countries. There is also a report of the beneficial use of **tranylcypromine** with **chlorpromazine**.[4]

However, rarely, cases suggestive of neuroleptic malignant syndrome or similar have been reported. In one case, a 70-year-old woman taking **isocarboxazid** 10 mg daily and **chlorpromazine** 25 mg three times daily, suddenly developed dyspnoea, tachycardia, pyrexia, muscular rigidity, hypotension, and became comatose. Her condition initially improved over 24 hours, but she later died from acute renal failure as a result of rhabdomyolysis. Throughout the previous 2 years of inpatient care, the patient had received neuroleptics intermittently and had developed an unexplained toxic confusional state on 6 occasions, which suggested that neuroleptic malignant syndrome had a milder chronic course in this patient before the full acute syndrome developed.[5] In another case, a woman presented with symptoms of neuroleptic malignant syndrome one week after starting **tranylcypromine**/**trifluoperazine** 10/1 mg and immediately after doubling the dose. She was intubated and treated with dantrolene and intravenous sodium bicarbonate, and made a full recovery.[6] Interpretation of her case is complicated by the fact she had been previously taking imipramine, and was switched to tranylcypromine/trifluoperazine without a break (see also 'MAOIs or RIMAs + Tricyclic and related antidepressants', p.1391). One study mentions an unexplained fatality in a woman who suddenly developed hyperthermia and coma while taking **levomepromazine** and **pargyline**.[7] Another report briefly mentions a woman who developed fatal hyperthermia while taking **levomepromazine** and **tranylcypromine**,[8] and a fatality following the use of an unnamed MAOI/phenothiazine combination.[8] Note that **chlorpromazine**[9] has 5-HT antagonist activity, and has been successfully used in the treatment of severe serotonin syndrome occurring with 'MAOIs and tricyclic antidepressants', (p.1391).

One early reviewer stated that MAOIs increase the potency of phenothiazine derivatives such that their initial dose should be reduced by three-quarters. He briefly mentions a case of a patient taking long-term **perphenazine** who developed a Parkinson-like syndrome with extrapyramidal symptoms a few hours after starting an MAOI.[10] The US manufacturer notes that, based on the increased incidence of extrapyramidal effects reported with concurrent use of some MAOIs and phenothiazines, this possibility should be considered with **promethazine**,[11] whilst the UK manufacturer contraindicates the use of **promethazine** with MAOIs and for 14 days after stopping treatment with an MAOI.[12] Also note that it has been suggested that MAOIs may intensify the antimuscarinic effects of **promethazine** (a phenothiazine antihistamine),[12] but evidence for this is largely lacking (see 'MAOIs + Antihistamines', p.1371).

A report attributes 2 cases of fatal fulminant hepatitis to an interaction between **iproniazid** and **prochlorperazine**.[13]

A single report[14] describes a woman taking an MAOI who developed a severe occipital headache after taking 30 mL of a paediatric cough linctus. Initially this interaction was attributed to **promethazine**, but it is now known that the linctus in question contained phenylpropanolamine, which is much more likely to have been the cause.[15] See 'MAOIs or RIMAs + Sympathomimetics; Indirectly-acting', p.1388 for the interaction with phenylpropanolamine.

Four days after the withdrawal of **phenelzine** and **perphenazine**, a patient was given operative premedication of **droperidol** 20 mg and hyoscine 400 micrograms, orally. About 2 hours later he was observed to be pale, sweating profusely and slightly cyanosed, with a blood pressure of 75/60 mmHg and a pulse rate of 60 bpm. He was not excitable, and no changes in respiration were seen. The blood pressure gradually rose to 115/80 mmHg over the next 45 minutes, but did not return to his normal level of 160/100 mmHg for 36 hours. The same premedication was given 11 days later without any adverse effects.[16] The response was attributed to the residual effects of **phenelzine** treatment.

(b) RIMAs

The manufacturer of **moclobemide** noted that in 1992 there were data available from 110 patients given **moclobemide** 150 to 400 mg daily with various antipsychotics, namely **acepromazine**, **aceprometazine**, **alimemazine**, **bromperidol**, **chlorpromazine**, **chlorprothixene**, **clothiapine**, **clozapine**, **cyamemazine**, **flupenthixol**, **fluphenazine**, **fluspirilene**, **haloperidol**, **levomepromazine**, **penfluridol**, **pipamperone**, **prothipendyl**, **sulpiride**, **thioridazine**, or **zuclopenthixol**. There was no evidence of any clinically relevant interactions, but there was some evidence that hypotension, tachycardia, sleepiness, tremor and constipation were more common, suggesting synergistic adverse effects.[17] A fatal case of overdose with **moclobemide** and **perazine** was attributed to synergistic effects resulting in functional cardiovascular disorder.[18]

Mechanism

Neuroleptic malignant syndrome (NMS) is a rare condition associated with a reduction in dopamine activity in the brain, which has occurred with a wide variety of dopamine antagonists including the phenothiazines. It is unclear what role, if any, is played by the MAOIs in the few possible cases cited here. Note that MAOIs can cause the similar serotonin syndrome, and it is important to differentiate between the two conditions, especially since phenothiazines would aggravate NMS, but can successfully treat the serotonin syndrome.

Importance and management

No special precautions would normally seem to be necessary during the concurrent use of MAOIs and phenothiazines. However, bear in mind that serious, sometimes fatal, cases of neuroleptic malignant syndrome or hyperpyrexia have rarely occurred when an MAOI was given with chlorpromazine, levomepromazine or trifluoperazine. The role of the MAOI in these cases is unclear. Chlorpromazine has been used successfully to treat serotonin syndrome occurring with MAOIs and other serotonergic drugs, but note that it should be avoided if neuroleptic malignant syndrome is a possible diagnosis, or if the patient is hypotensive.

1. Winkelman NW. Three evaluations of a monoamine oxidase inhibitor and phenothiazine combination (a methodological and clinical study). *Dis Nerv Syst* (1965) 26, 160–4.
2. Chesrow EJ, Kaplitz SE. Anxiety and depression in the geriatric and chronically ill patient. *Clin Med* (1965) 72, 1281–4.
3. Janecek J, Schiele BC, Bellville T, Anderson R. The effects of withdrawal of trifluoperazine on patients maintained on the combination of tranylcypromine and trifluoperazine. A double blind study. *Curr Ther Res* (1963) 5, 608–15.
4. Bucci L. The negative symptoms of schizophrenia and the monoamine oxidase inhibitors. *Psychopharmacology (Berl)* (1987) 91, 104–8.
5. Jones EM, Dawson A. Neuroleptic malignant syndrome: a case report with post-mortem brain and muscle pathology. *J Neurol Neurosurg Psychiatry* (1989) 52, 1006–9.
6. Lappa A, Podestà M, Capelli O, Castagna A, Di Placido G, Alampi D, Semeraro F. Successful treatment of a complicated case of neuroleptic malignant syndrome. *Intensive Care Med* (2002) 28, 976–7.
7. Barsa JA, Saunders JC. A comparative study of tranylcypromine and pargyline. *Psychopharmacologia* (1964) 6, 295–8.
8. McQueen EG. New Zealand Committee on Adverse Drug Reactions: fourteenth annual report 1979. *N Z Med J* (1980) 91, 226–9.
9. Graham PM. Successful treatment of the toxic serotonin syndrome with chlorpromazine. *Med J Aust* (1997) 166, 166–7.
10. Kline NS. Psychopharmaceuticals: effects and side effects. *Bull WHO* (1959) 21, 397–410.
11. Phenergan (Promethazine). Wyeth Pharmaceuticals Inc. US Prescribing information, July 2005.
12. Phenergan (Promethazine hydrochloride). Sanofi-Aventis. UK Summary of product characteristics, March 2007.
13. Capron J-P, Gineston J-L, Opolon P, Dupas J-L, Denis J, Quénum C, Lorriaux A. Hépatite fulminante mortelle due a l'association iproniazide-prochlorpérazine: deux cas. *Gastroenterol Clin Biol* (1980) 4, 123–7.
14. Mitchell L. Psychotropic drugs. *BMJ* (1968) 1, 381.
15. Griffin JP, D'Arcy PF eds. A Manual of Adverse Drug Interactions. 2nd ed Bristol: Wright; 1979. p. 174.
16. Penlington GN. Droperidol and monoamine-oxidase inhibitors. *BMJ* (1966) 1, 483–4.
17. Amrein R, Güntert TW, Dingemanse J, Lorscheid T, Stabl M, Schmid-Burgk W. Interactions of moclobemide with concomitantly administered medication: evidence from pharmacological and clinical studies. *Psychopharmacology (Berl)* (1992) 106, S24–S31.
18. Musshoff F, Varchmin-Schultheiss K, Madea B. Suicide with moclobemide and perazine. *Int J Legal Med* (1998) 111, 196–8.

MAOIs + Barbiturates

Although the MAOIs can enhance and prolong the activity of barbiturates in *animals*, only a few isolated cases of adverse responses attributed to an interaction have been described.

Clinical evidence

One reviewer[1] briefly mentions that on three or four occasions patients taking an MAOI continued, without the prescriber's knowledge, to take their usual barbiturate hypnotic and thereby '…unknowingly raised their dose of barbiturate by five to ten times, and as a consequence barely managed to stagger through the day.' No details are given, so it is not known whether the serum barbiturate levels of these patients were measured, or whether the raised levels are only a surmise.

A patient taking **tranylcypromine** 10 mg three times daily was inadvertently given intramuscular **amobarbital sodium** 250 mg for sedation. Within an hour she became ataxic, and fell to the floor, repeatedly hitting her head. After complaining of nausea and dizziness the patient became semicomatose and remained in that state for a further 36 hours. To what extent the head trauma played a part is uncertain.[2]

A man taking **amobarbital sodium** 195 mg at night suffered severe headache, and became confused after also taking **phenelzine** 15 mg three times daily for 4 weeks. On admission to hospital he was comatose, and he had a temperature of 40°C, blood pressure of 150/90 mmHg, tachycardia, stertorous respiration, fixed dilated pupils, exaggerated tendon reflexes and extensor plantar responses. His condition deteriorated and he died 2 hours after admission.[3] Pathology suggested a rise in intracranial pressure was responsible. The authors attribute this response to the drugs, but do not rule out a possible contribution of alcohol.[3]

Mechanism

Not known. *Animal* studies[2,4] show that MAOIs prolong the activity of barbiturates, and that this is possibly because they inhibit the metabolism of barbiturates by a mechanism independent of MAO inhibition. Whether this occurs in man as well is uncertain.

Importance and management

The evidence for these interactions seems to be confined to a few unconfirmed anecdotal reports. There is no well-documented evidence showing that concurrent use should be avoided, although some caution is clearly appropriate. For mention of successful anaesthesia including the use of **thiopental** in patients taking MAOIs, see 'Anaesthetics, general + MAOIs and related drugs', p.112.

1. Kline NS. Psychopharmaceuticals: effects and side effects. *Bull WHO* (1959) 21, 397–410.
2. Domino EF, Sullivan TS, Luby ED. Barbiturate intoxication in a patient treated with a MAO inhibitor. *Am J Psychiatry* (1962) 118, 941–3.
3. MacLeod I. Fatal reaction to phenelzine. *BMJ* (1965) 1, 1554.
4. Buchel L, Lévy J. Mécanisme des phénomènes de synergie du sommeil expérimental. II. Étude des associations iproniazide-hypnotiques, chez le rat et la souris. *Arch Sci Physiol (Paris)* (1965) 19, 161–79.

MAOIs or RIMAs + Benzodiazepines

Isolated cases of adverse reactions (chorea, severe headache, facial flushing, and severe oedema) attributed to interactions between phenelzine and chlordiazepoxide, clonazepam or nitrazepam, and between isocarboxazid and chlordiazepoxide have been described. Evidence from clinical studies suggests that there is no interaction between moclobemide and benzodiazepines, although one study found a slight progressive worsening in driving performance.

Clinical evidence and mechanism

(a) MAOIs

A patient who had been taking **phenelzine** 45 mg daily for 9 years developed a severe occipital headache after taking 500 micrograms of clonazepam. A similar but milder headache occurred the next night when she again took clonazepam 500 micrograms. No blood pressure measurements were taken.[1] Another report describes facial flushing in a patient taking clonazepam, which occurred after **phenelzine** was started, and which responded to a reduction in the clonazepam dose.[2]

A patient with depression responded well when given **phenelzine** 15 mg and chlordiazepoxide 10 mg three times a day, but 4 to 5 months later developed choreiform movements of moderate severity, and slight dysarthria. These symptoms subsided when both drugs were withdrawn.[3]

Two patients taking chlordiazepoxide and either **phenelzine** or **isocarboxazid** developed severe oedema, which was attributed to the use of the combination.[4,5]

A patient became unconscious and hyperreflexic, with a low blood pressure (100/60 mmHg), increased heart rate (100 bpm), and increased temperature (38.4°C) about 29 hours after taking an overdose of **phenelzine** and chlordiazepoxide.[6] Another report briefly mentions a case of prolonged coma lasting 3 days in a patient who overdosed with **phenelzine** and chlordiazepoxide.[7]

A patient taking **phenelzine** 30 mg twice daily started to take nitrazepam 5 mg at night and the dose was gradually increased to 15 mg at night over 2 months. He developed MAOI toxicity (excessive sweating, postural hypotension) within 10 days of increasing his dose of nitrazepam to 15 mg daily. Both drugs were stopped and he recovered after 3 days. The **phenelzine** was restarted 2 weeks later without problems. It was suggested that since the patient was a slow acetylator, metabolism of nitrazepam by *N*-acetyl transferase would have been decreased, which may have affected the metabolism of **phenelzine**, thereby increasing its levels.[8]

(b) RIMAs

A meta-analysis of 879 patients taking **moclobemide** is reported to have found that insomnia, restlessness, agitation and anxiety occurred twice as often in the 467 patients taking one or more benzodiazepines than in those not taking concurrent benzodiazepines. However, these adverse events were often already present when **moclobemide** was started, so it is suggested that the patient groups were probably different. Apart from this difference between the patient groups, there was no evidence of any relevant pharmacokinetic or pharmacodynamic interaction.[9] Another review briefly reported that no clinically relevant interaction was noted between **moclobemide** and benzodiazepines in clinical studies.[10]

Driving performance gradually worsened over 6 weeks in a double-blind study in depressed patients given **moclobemide** (22 subjects) or fluoxetine (19 subjects). Thirty-one patients were taking long-term benzodiazepines, and at the start of the study their driving was no different to the patients not taking benzodiazepines. In an attempt to suggest a possible reason for the worsening performance, various variables were assessed in a regression analysis. It was found that patients taking **moclobemide** who were also taking a benzodiazepine with nordiazepam among its metabolites (**clorazepate**, **prazepam**, **diazepam**, **cloxazolam**, **clotiazepam**) experienced a progressive worsening in their driving, whereas patients taking other benzodiazepines (**bromazepam**, **alprazolam**, **oxazepam**, **lorazepam**) tended to have no change in driving ability. It was tentatively suggested that **moclobemide** may have inhibited the metabolism of nordiazepam by the cytochrome P450 isoenzyme CYP2C19, so increasing the effect of the benzodiazepine, and worsening driving performance.[11]

Importance and management

The case reports of adverse interactions cited here appear to be isolated, and it is by no means certain that all the responses were in fact due to drug interactions. However, bear them in mind in the event of unexpected responses to treatment. No special precautions would normally be required during concurrent use, although a reminder that benzodiazepines may affect the performance of skilled tasks, such as driving, may be appropriate when a patient's medication is changed. Note that the manufacturer of moclobemide says that if depressed patients with excitation or agitation are first treated with moclobemide, a sedative, such as a benzodiazepine, should also be given for up to 2 to 3 weeks.[12] Further study is required to find out if there are any clinically important pharmacokinetic interactions between moclobemide and any of the benzodiazepines.

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12. Manerix (Moclobemide). Meda Pharmaceuticals. UK Summary of product characteristics, September 2009.

MAOIs or RIMAs + Beta blockers

Bradycardia has been reported in two patients taking nadolol or metoprolol with phenelzine. MAOIs commonly cause hypotension, and might reasonably be expected to have additive hypotensive effects with antihypertensive drugs, although this was not seen with phenelzine and atenolol in a study in normotensive patients. In one small study, the RIMA, moclobemide increased the hypotensive effect of metoprolol, but did not alter the effect of nifedipine or hydrochlorothiazide on blood pressure.

Clinical evidence, mechanism, importance and management

(a) MAOIs

It had been claimed[1] that MAOIs should be discontinued at least 2 weeks before starting **propranolol**, but studies in *animals*[2] using **mebanazine** as a representative MAOI failed to show any undesirable property of **propranolol** following the use of an MAOI. Bradycardia of 46 to 53 bpm has been described in two patients taking **nadolol** 40 mg or **metoprolol** 150 mg daily for hypertension within 8 to 11 days of starting **phenelzine** 60 mg daily. No noticeable adverse effects were seen, but the authors recommend careful monitoring, particularly in the elderly, who may tolerate bradycardia poorly.[3] MAOIs can cause symptomatic hypotension, and therefore additive blood pressure lowering effects with antihypertensive drugs might occur. However, in one small study in normotensive patients with migraine, 11 (33%) of patients had orthostatic hypotension when they were given **phenelzine** alone, but none of these had orthostatic hypotension when they were also given **atenolol**.[4] Nevertheless, it would be prudent to monitor blood pressure more closely in patients taking antihypertensives with MAOIs. Some UK manufacturers of beta blockers (namely **celiprolol** and **pindolol**) advise that the combination of beta blockers with MAOIs is not recommended,[5,6] even up to 14 days following discontinuation of the MAOI,[5] whilst the manufacturers of others (namely **acebutolol** and **bisoprolol**) suggest caution, on the grounds that significant hypertension may theoretically occur,[7,8] Some manufacturers also warn of the risk of hypotension,[7,9,10] and bradycardia.[10]

(b) RIMAs

A study in 5 hypertensive subjects taking **metoprolol** found that **moclobemide** 200 mg three times daily for 2 weeks increased the hypotensive effect of **metoprolol** (systolic 10 to 15 mmHg lower, diastolic 5 to 10 mmHg lower). However, no comparable effects were seen when **moclobemide** was given to 7 subjects taking **hydrochlorothiazide** or 6 subjects taking **nifedipine**. No orthostatic hypotension occurred with any of the drug combinations.[11] The reason for the differing effect with **metoprolol** is unknown, and further study is needed. Be aware that **moclobemide** may add to the effect of **metoprolol**, and consider increased monitoring if either drug is started or stopped.

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2. Barrett AM, Cullum VA. Lack of inter-action between propranolol and mebanazine. *J Pharm Pharmacol* (1968) 20, 911–15.
3. Reggev A, Vollhardt BR. Bradycardia induced by an interaction between phenelzine and beta blockers. *Psychosomatics* (1989) 30, 106–8.
4. Merikangas KR, Merikangas JR. Combination monoamine oxidase inhibitor and β-blocker treatment of migraine, with anxiety and depression. *Biol Psychiatry* (1995) 38, 603–10.
5. Visken Tablets (Pindolol). Amdipharm. UK Summary of product characteristics, January 2005.
6. Celectol (Celiprolol hydrochloride). Winthrop Pharmaceuticals UK Ltd. UK Summary of product characteristics, September 2004.
7. Cardicor (Bisoprolol hemifumarate). Merck Serono. UK Summary of product characteristics, June 2006.
8. Sectral Capsules (Acebutolol hydrochloride). Sanofi-Aventis. UK Summary of product characteristics, November 2006.
9. Atenolol Tablets. Wockhardt UK Ltd. UK Summary of product characteristics, May 2003.
10. Eucardic (Carvedilol). Roche Products Ltd. UK Summary of product characteristics, July 2007.
11. Amrein R, Güntert TW, Dingemanse J, Lorscheid T, Stabl M, Schmid-Burgk W. Interactions of moclobemide with concomitantly administered medication: evidence from pharmacological and clinical studies. *Psychopharmacology (Berl)* (1992) 106, S24–S31.

MAOIs or RIMAs + Bupropion

Bupropion is contraindicated with MAOIs, although there is little clinical evidence of serious problems. Orthostatic hypotension occurred in a patient given bupropion and the MAO-B inhibitor selegiline.

Clinical evidence, mechanism, importance and management

In an uncontrolled study, 10 patients were treated for major affective disorder (8 unipolar, 2 bipolar) with bupropion in daily doses of 225 to 450 mg and an MAOI: **isocarboxazid** (1 patient), **phenelzine** (5), **tranylcypromine** (2), and the MAO-B inhibitor **selegiline** (2). Four were transferred from the MAOI to bupropion without any washout period, and the other 6 were given both drugs concurrently. No untoward cardiovascular events occurred, except for one patient taking bupropion and **selegiline**, who experienced orthostatic hypotension. Notable weight loss occurred in two others when they were transferred from the MAOI to bupropion.[1] A Medline search (1962 to 2003) and review of published literature found no documented reports of hypertensive crises or fatalities when a stimulant drug (including bupropion) was cautiously added to an MAOI, although orthostatic hypotension and elevated blood pressure were reported.[2] One case report describes intraoperative hypertension with bupropion and 'linezolid', (p.1468), which has MAOI activity.

The manufacturers of bupropion note that toxicity was seen in studies in *animals* when **phenelzine** and bupropion were given concurrently.[3] They contraindicate bupropion with MAOIs and recommend that at least 14 days should elapse between stopping irreversible MAOIs and starting bupropion.[3,4] This precaution would therefore apply particularly to the non-selective MAOIs (**phenelzine**, **tranylcypromine**, **isocarboxazid** etc.). For **moclobemide**, the manufacturers advise that a 24-hour washout period is sufficient before starting bupropion.[4]

1. Abuzzahab Sr, FS. Combination therapy: monoamino oxidase inhibitors and bupropion HCl. *Neuropsychopharmacology* (1994) 10, 74S.
2. Feinberg SS. Combining stimulants with monoamine oxidase inhibitors: a review of uses and one possible additional indication. *J Clin Psychiatry* (2004) 65, 1520–4.
3. Zyban (Bupropion hydrochloride). GlaxoSmithKline. US Prescribing information, July 2009.
4. Zyban (Bupropion hydrochloride). GlaxoSmithKline UK. UK Summary of product characteristics, January 2009.

MAOIs or RIMAs + Buspirone

Elevated blood pressure has been reported in four patients taking buspirone and either phenelzine or tranylcypromine. Buspirone may have contributed to a case of serotonin syndrome in a patient who took an overdose of moclobemide and clomipramine.

Clinical evidence, mechanism, importance and management

(a) MAOIs

Four cases of significant blood pressure elevation, which occurred during the use of buspirone and either **phenelzine** or **tranylcypromine**, have been reported to the Spontaneous Reporting System of the FDA in the US. One patient was a 75-year-old woman and the other 3 patients were men aged between 30 and 42 years. The report does not say how much the blood pressure rose, or how quickly, and no other details are given.[1] On the basis of this rather sparse information the manufacturers of buspirone[2,3] recommend that it should not be used concurrently with an MAOI.

(b) RIMAs

A severe case[4] of serotonin syndrome (including hyperthermia and muscle rigidity requiring mechanical ventilation) has been reported in a patient who took an overdose of **moclobemide**, clomipramine and buspirone, although what contribution the buspirone had to this reaction is unclear, as cases have been reported with clomipramine and moclobemide, see 'MAOIs or RIMAs + Tricyclic and related antidepressants', p.1391.

1. Anon. BuSpar Update. *Psychiatry Drug Alert* (1987) 1, 43.
2. Buspar (Buspirone hydrochloride). Bristol-Myers Pharmaceuticals. UK Summary of product characteristics, May 2008.
3. BuSpar (Buspirone hydrochloride). Bristol-Myers Squibb Company. US Prescribing information, March 2007.
4. Höjer J, Personne M, Skagius A-S, Hansson O. Serotoninergt syndrom: flera allvarliga fall med denna ofta förbisedda diagnos. *Lakartidningen* (2002) 99, 2054–5, 2058–60.

MAOIs + Caffeine or Choline theophyllinate

Isolated reports suggest that the CNS stimulant effects of caffeine may possibly be increased by the MAOIs. Another isolated report describes the development of tachycardia and apprehension in a patient taking phenelzine after she also took a cough syrup, containing choline theophyllinate.

Clinical evidence

(a) Caffeine

One reviewer briefly mentions that a patient who normally drank 10 or 12 cups of **coffee** daily, without adverse effects, experienced extreme jitteriness during treatment with an MAOI, which subsided when the **coffee** consumption was reduced to 2 or 3 cups a day. The same reaction was also said to have occurred in other patients taking MAOIs who drank **tea** or some of the **cola drinks**, which contain caffeine.[1] This reviewer also mentions another patient taking an MAOI who claimed that a single cup of **coffee** taken in the morning kept him jittery all day and up the entire night as

well, a reaction that occurred on three separate occasions.[1] In another report, a woman taking **phenelzine** experienced a severe headache with a slight blood pressure rise on two occasions after drinking **cola** containing 35 to 55 mg of caffeine.[2] Similarly, a brief mention is made of 2 patients taking **phenelzine** who experienced extreme restlessness, agitation, tremor, and insomnia after starting to drink large quantities of **diet cola**. This was attributed to an interaction between **phenelzine** and aspartame,[3] but could equally well be attributed to an interaction with caffeine, or indeed a reaction to caffeine alone. Caffeine and **theophylline** may have contributed to the serious reaction that occurred in a woman who took a *Do-Do* tablet (containing ephedrine, caffeine, theophylline) the day after discontinuing **phenelzine**.[4] For more information on the interactions of MAOIs and ephedrine, see 'MAOIs or RIMAs + Sympathomimetics; Indirectly-acting', p.1388.

(b) Choline theophyllinate

A woman with agoraphobia, taking **phenelzine** 45 mg daily, developed tachycardia, palpitations and apprehension lasting for about 4 hours after she had taken a cough syrup containing choline theophyllinate and guaifenesin. The symptoms recurred when she was again given the cough syrup, and yet again when given choline theophyllinate, but not when given guaifenesin.[5]

Mechanism

Unknown. Caffeine alone can cause headache, tachycardia, and jitteriness, and individuals vary in their susceptibility to these effects. The effects of caffeine, theophylline, and theobromine in *rats* were enhanced by MAOIs.[6]

Importance and management

Apart from these few reports, the literature appears to be otherwise silent about an interaction between the MAOIs and xanthines. Whether this reflects their mildness and unimportance, or their rarity, is not clear. There would seem to be no need for any special precautions in patients taking MAOIs who are given xanthine bronchodilators or consuming caffeine-containing beverages or pharmaceuticals, but bear these adverse reports in mind in the event of any unexpected response. Note that, some manufacturers of isocarboxazid, phenelzine and tranylcypromine recommend the avoidance of excessive amounts of tea and coffee,[7] or caffeine in any form.[8-10]

1. Kline NS. Psychopharmaceuticals: effects and side-effects. *Bull WHO* (1959) 21, 397–410.
2. Pakes GE. Phenelzine-cola headache. *Am J Hosp Pharm* (1979) 36, 736.
3. Shader RI, Greenblatt DJ. Phenelzine and the dream machine—ramblings and reflections. *J Clin Psychopharmacol* (1985) 5, 65.
4. Dawson JK, Earnshaw SM, Graham CS. Dangerous monoamine oxidase inhibitor interactions are still occurring in the 1990s. *J Accid Emerg Med* (1995) 12, 49–51.
5. Shader RI, Greenblatt DJ. MAOIs and drug interactions—a proposal for a clearinghouse. *J Clin Psychopharmacol* (1985) 5, A17.
6. Berkowitz BA, Spector S, Pool W. The interaction of caffeine, theophylline and theobromine with monoamine oxidase inhibitors. *Eur J Pharmacol* (1971) 16, 315–21.
7. Nardil (Phenelzine sulfate). Concord Pharmaceuticals Ltd. UK Summary of product characteristics, July 2003.
8. Marplan (Isocarboxazid). Validus Pharmaceuticals, Inc. US Prescribing information, August 2007.
9. Nardil (Phenelzine sulfate). Pfizer Inc. US Prescribing information, August 2007.
10. Parnate (Tranylcypromine sulfate). GlaxoSmithKline. US Prescribing information, June 2007.

MAOIs + Cocaine

Some reports suggest that patients taking MAOIs may experience a severe headache if they abuse cocaine. Two isolated reports describe the delayed development of hyperpyrexia, and other symptoms including coma, agitation, muscle tremors and rigidity, after patients taking phenelzine or iproniazid were given a cocaine spray during surgery.

Clinical evidence, mechanism, importance and management

The use of cocaine is generally contraindicated in patients taking MAOIs[1-4] because it is expected to interact in the same way as 'indirectly-acting sympathomimetics', (p.1388). This is supported by a report of hypertensive reactions in 2 patients taking **phenelzine** who became drunk and used cocaine. Both experienced frightening reactions including headache, a rise in blood pressure, palpitations, and chest tightness. One required no treatment, and the other was treated with propranolol and diazepam.[5] Because this reaction was not considered as dangerous as expected, **phenelzine** has been tried as a deterrent to the abuse of cocaine: one uncontrolled study reports its use in 26 patients without mentioning any adverse reactions.[5] Another report mentions a man given **phenelzine** for cocaine abuse who experienced no reaction to the use of cocaine. He was then given **tranylcypromine**, and after 10 weeks risked sniffing cocaine, which did produce a severe occipital headache and nausea. However, after abstaining for another 10 weeks he again used cocaine, this time without any reaction.[6]

A man taking **phenelzine** 15 mg twice daily underwent vocal chord surgery. He was anaesthetised with thiopental, and later nitrous oxide and isoflurane 0.5% in oxygen. Muscle paralysis was produced with suxamethonium and gallamine. During the operation his vocal chords were sprayed with 1 mL of a 10% cocaine spray. He regained consciousness 30 minutes after the surgery and was returned to the ward, but a further 30 minutes later he was found unconscious, with generalised coarse tremors and marked muscle rigidity. His rectal temperature was 41.5°C. He was initially thought to have malignant hyperpyrexia and was treated accordingly with wet blankets, as well as with intravenous fluids and oxygen, and he largely recovered within 7 hours. However, later it seemed more likely that the reaction had been due to an adverse interaction between the **phenelzine** and cocaine, because he had been similarly and uneventfully treated with cocaine in the absence of **phenelzine** on two previous occasions.[7] In a similar case, a woman taking **iproniazid** had her trachea sprayed with 1 mL of 10% cocaine before intubation during surgery. She was also given pethidine 20 mg, and shortly after surgery became pyrexial, flushed, agitated and sweated profusely. She was treated with intravenous chlorpromazine.[8] In this case, the reaction could have been due to the pethidine alone (see 'MAOIs or RIMAs + Opioids; Pethidine (Meperidine)', p.1381), or both the cocaine and the pethidine. The reasons for these adverse reactions are not understood, but a delayed excitatory reaction due to increased 5-HT (serotonin) concentrations has been suggested.[7] The general importance of these cases is not known, but bear them in mind if cocaine is used by a patient taking an MAOI.

1. Nardil (Phenelzine sulfate). Concord Pharmaceuticals Ltd. UK Summary of product characteristics, July 2003.
2. Nardil (Phenelzine sulfate). Pfizer Inc. US Prescribing information, August 2007.
3. Parnate (Tranylcypromine sulfate). GlaxoSmithKline. US Prescribing information, June 2007.
4. Marplan (Isocarboxazid). Validus Pharmaceuticals, Inc. US Prescribing information, August 2007.
5. Golwyn DH. Cocaine abuse treated with phenelzine. *Int J Addict* (1988) 23, 897–905.
6. Brewer C. Treatment of cocaine abuse with monoamine oxidase inhibitors. *Br J Psychiatry* (1993) 163, 815–16.
7. Tordoff SG, Stubbing JF, Linter SPK. Delayed excitatory reaction following interaction of cocaine and monoamine oxidase inhibitor (phenelzine). *Br J Anaesth* (1991) 66, 516–18.
8. Clement AJ, Benazon D. Reactions to other drugs in patients taking monoamine-oxidase inhibitors. *Lancet* (1962) 2, 197–8.

MAOIs or RIMAs + Dextromethorphan

Two fatal cases of hyperpyrexia and coma (symptoms similar to the serotonin syndrome) have occurred in patients taking phenelzine with dextromethorphan (in overdosage in one case). Three other serious but non-fatal reactions occurred in patients taking dextromethorphan with isocarboxazid or phenelzine. MAOIs should not be used with dextromethorphan. Moclobemide inhibits the metabolism of dextromethorphan, and isolated cases of severe CNS reactions have occurred with the combination: concurrent use is contraindicated.

Clinical evidence

(a) MAOIs

A woman taking **phenelzine** 15 mg four times daily complained of nausea and dizziness before collapsing, 30 minutes after drinking about 55 mL of a cough mixture containing dextromethorphan. She remained hyperpyrexic (42°C), hypotensive (systolic blood pressure below 70 mmHg) and unconscious for 4 hours, before she had a cardiac arrest and died.[1]

A 15-year-old girl taking **phenelzine** 15 mg three times daily (as well as thioridazine, procyclidine and metronidazole) took 13 capsules of *Romilar CF* (containing dextromethorphan hydrobromide 15 mg, phenindamine tartrate 6.25 mg, phenylephrine hydrochloride 5 mg and paracetamol (acetaminophen) 120 mg in each capsule). She became comatose, hyperpyrexic (about 39.4°C), had a blood pressure of 100/60 mmHg, a pulse of 160 bpm and later died of a cardiac arrest.[2] This case is complicated by the overdosage and multiplicity of drugs present, particularly the phenyle-

phrine. See 'MAOIs or RIMAs + Sympathomimetics; Phenylephrine', p.1390.

Three other case reports describe muscle spasms or rigidity, sweating, nausea or tremor in patients who took *Robitussin DM* (dextromethorphan hydrobromide 15 mg with guaifenesin 100 mg) with phenelzine or isocarboxazid.[3-5] One patient responded to 10 mg of intravenous diazepam and oral activated charcoal within 2 hours,[4] and the symptoms of another gradually resolved over 19 hours.[5]

In addition, the US manufacturer of **tranylcypromine** notes that the concurrent use of MAOIs and dextromethorphan has resulted in brief episodes of psychosis or bizarre behaviour.[6] Similarly, the US manufacturer of **phenelzine** mentions one case of drowsiness and bizarre behaviour when dextromethorphan lozenges were used by a patient taking phenelzine.[7]

(b) RIMAs

Moclobemide 300 mg twice daily for 9 days markedly reduced the *O*-demethylation of dextromethorphan (seven 20-mg doses given every 4 hours over 2 days), in 4 healthy subjects.[8] The manufacturer notes that isolated cases of severe CNS adverse reactions have been seen with the combination.[9] Concurrent use of dextromethorphan may have contributed to a fatality involving the illicit use of **moclobemide** and 'ecstasy', (p.1386).

Mechanism

It has been suggested[3-5] that the effects may be due to an increase in serotonin activity in the CNS. Symptoms similar to the serotonin syndrome (hyperpyrexia, dilated pupils, hyperexcitability and motor restlessness) have been seen in *rabbits* treated with dextromethorphan and **nialamide**, phenelzine or **pargyline**,[10] and also with MAOIs and 'pethidine (meperidine)', (p.1381). Moclobemide appears to inhibit the metabolism of dextromethorphan by the cytochrome P450 isoenzyme CYP2D6, and the combination may also cause adverse CNS effects, also possibly due to additive effects on serotonin. For more information about the serotonin syndrome, see 'Additive or synergistic interactions', (p.9).

Importance and management

Despite the very limited information available, the severity of the reactions indicates that patients taking MAOIs should avoid taking dextromethorphan: concurrent use is generally contraindicated. The manufacturer of moclobemide also contraindicates the concurrent use of dextromethorphan.[9] Patients should be warned that many cough preparations contain dextromethorphan.

1. Rivers N, Horner B. Possible lethal reaction between Nardil and dextromethorphan. *Can Med Assoc J* (1970) 103, 85.
2. Shamsie JC, Barriga C. The hazards of use of monoamine oxidase inhibitors in disturbed adolescents. *Can Med Assoc J* (1971) 104, 715.
3. Nierenberg DW, Semprebon M. The central nervous system serotonin syndrome. *Clin Pharmacol Ther* (1993) 53, 84–8.
4. Sauter D, Macneil P, Weinstein E, Azar A. Phenelzine sulfate-dextromethorphan interaction: a case report. *Vet Hum Toxicol* (1991) 33, 365.
5. Sovner R, Wolfe J. Interaction between dextromethorphan and monoamine oxidase inhibitor therapy with isocarboxazid. *N Engl J Med* (1988) 319, 1671.
6. Parnate (Tranylcypromine sulfate). GlaxoSmithKline. US Prescribing information, June 2007.
7. Nardil (Phenelzine sulfate). Pfizer Inc. US Prescribing information, August 2007.
8. Härtter S, Dingemanse J, Baier D, Ziegler G, Hiemke C. Inhibition of dextromethorphan metabolism by moclobemide. *Psychopharmacology (Berl)* (1998) 135, 22–6.
9. Manerix (Moclobemide). Meda Pharmaceuticals. UK Summary of product characteristics, September 2009.
10. Sinclair JG. Dextromethorphan-monoamine oxidase inhibitor interaction in rabbits. *J Pharm Pharmacol* (1973) 25, 803–8.

MAOIs + Disulfiram

An isolated report describes delirium in a man taking lithium and disulfiram when the moclobemide he was also taking was replaced by tranylcypromine.

Clinical evidence, mechanism, importance and management

A man with disulfiram implants taking long-term lithium had his MAOI changed from **moclobemide** (dosage not stated) to **tranylcypromine** 10 mg twice daily. Within 2 days he became acutely delirious (agitated, disoriented, incoherent, visual hallucinations) and later subcomatose, with nystagmus and a downward gaze. He was successfully treated with haloperidol and promethazine, and recovered within 24 hours. No alcohol was detected in his blood, and serum **tranylcypromine** levels were below 50 micrograms/L, which was considered normal.[1]

The authors of this report attribute the reaction to an interaction between **tranylcypromine** and disulfiram. However, there would seem to be other possible explanations for this reaction. MAOIs have rarely been seen to interact adversely with 'lithium', (p.1378), and there also seems potential for an interaction between '**moclobemide** and **tranylcypromine**', (p.1378).

This seems to be the only report of an adverse reaction between disulfiram and an MAOI, so it is possible that this is just an idiosyncratic reaction. However, warnings about this drug combination, based on theoretical considerations and studies in *animals*, have previously been given, and **tranylcypromine** was considered to be the MAOI that presented the greatest risk.[2] Consequently, the US manufacturers of **tranylcypromine**[3] and **isocarboxazid**[4] recommend caution with the concurrent use of disulfiram. Note that this particular patient did not seem to have any problems while taking **moclobemide**, which is a RIMA.

1. Blansjaar BA, Egberts TCG. Delirium in a patient treated with disulfiram and tranylcypromine. *Am J Psychiatry* (1995) 152, 296.
2. Ciraulo DA. Can disulfiram (Antabuse) be safely co-administered with the monoamine oxidase inhibitor (MAOI) antidepressants? . *J Clin Psychopharmacol* (1989) 9, 315–16.
3. Parnate (Tranylcypromine sulfate). GlaxoSmithKline. US Prescribing information, June 2007.
4. Marplan (Isocarboxazid). Validus Pharmaceuticals, Inc. US Prescribing information, August 2007.

MAOIs + Dopa-rich foods

A few reports describe a rapid and potentially life-threatening hypertensive reaction in patients taking MAOIs if they eat young broad bean pods, which contain dopa.

Clinical evidence

A 65-year-old hypertensive man taking **pargyline** had a severe headache and palpitations on two occasions after eating "whole, cooked, broad beans" (young broad bean pods). A controlled study in this man found that he had a rise in systolic blood pressure from 165 to 262 mmHg about 20 minutes after eating whole broad bean pods. The pods alone had the same effect, but the beans on their own had little effect. This rise in blood pressure was also seen in two other patients taking **pargyline**, and was reversed by intravenous phentolamine.

Two normotensive subjects taking pargyline 50 mg daily also had an increase in blood pressure (over 70 mmHg systolic in one subject) following the ingestion of bean pods.[1] Another case report describes a man taking **phenelzine** 15 mg three times daily who had a very severe headache after eating a meal including fresh, young, sliced, broad bean pods from his garden.[2] One other case has been briefly mentioned, although it was not known whether the broad beans were eaten with or without the pods.[3]

Mechanism

Broad bean (*Vicia faba*) pods contain dopa,[1] which is enzymatically converted in the body, firstly to dopamine and then to noradrenaline, both of which are normally broken down by monoamine oxidase. In the presence of an MAOI this breakdown is suppressed, which means that the total levels of dopamine and noradrenaline are increased. Precisely how this then leads to a sharp rise in blood pressure is not clear, but either dopamine or noradrenaline, or both, directly or indirectly stimulate the alpha-receptors of the cardiovascular system.

Importance and management

Although there are only a few cases of the interaction between the non-selective MAOIs (see 'Table 32.1', (p.1370) for a full list) and broad bean pods, the interaction would appear to be established: it is serious and potentially life-threatening. Patients should not eat young broad bean *pods* during treatment with any of these MAOIs, nor for a period of 2 to 3 weeks after their withdrawal. It should be noted that this prohibition does not apply to 'mature' broad beans (the seeds) removed from their pods, which is the more common way of eating broad beans.

1. Hodge JV, Nye ER, Emerson GW. Monoamine-oxidase inhibitors, broad beans, and hypertension. *Lancet* (1964) i, 1108.
2. Blomley DJ. Monoamine-oxidase inhibitors. *Lancet* (1964) ii, 1181–2.
3. McQueen EG. Interactions with monoamine oxidase inhibitors. *BMJ* (1975) 4, 101.

MAOIs + Doxapram

No adverse interactions have been reported between the MAOIs and doxapram, although *animal* studies suggest that an increased pressor effect is theoretically possible.

Clinical evidence, mechanism, importance and management

The manufacturers note that *animal* studies have shown that the actions of doxapram may be potentiated by pretreatment with an MAOI,[1] and that the pressor effects of MAOIs and doxapram may be additive.[2] Based on this, they advise that concurrent use should be undertaken with great care.[1,2] To date, there appear to be no clinical reports of this interaction. Nevertheless, it may be prudent to consider blood pressure monitoring in patients given doxapram while taking an MAOI.

1. Dopram (Doxapram hydrochloride). Goldshield plc. UK Summary of product characteristics, August 2008.
2. Dopram (Doxapram hydrochloride). Baxter Healthcare Corporation. US Prescribing information, March 2004.

MAOIs + Ginseng

Case reports describe headache, insomnia and tremulousness, which was attributed to the concurrent use of ginseng and phenelzine.

Clinical evidence

A 64-year-old woman taking **phenelzine** [60 mg daily] developed headache, insomnia, and tremulousness after taking Natrol High, a product containing ginseng,[1,2] probably *Eleutherococcus senticosus* (Siberian ginseng). She had the same symptoms on another occasion after drinking a ginseng tea (type not stated), which she had used without problem before starting phenelzine.[1] Three years later, while taking **phenelzine** 45 mg daily, she experienced the same symptoms and an increase in depression 72 hours after starting to take ginseng capsules (type not stated) and a herbal tea.[2]

Another woman with depression taking ginseng (type not stated) and bee pollen experienced relief of her depression and became active and extremely optimistic when she started to take **phenelzine** 45 mg daily, but this was accompanied by insomnia, irritability, headaches and vague visual hallucinations. When the **phenelzine** was stopped and then re-started in the absence of the ginseng and bee pollen, her depression was not relieved.[3]

Mechanism

Uncertain. It seems unlikely that the bee pollen had any part to play. Note that the ginsengs have stimulant effects, and adverse effects include insomnia, nervousness, hypertension and euphoria.

Importance and management

Evidence is limited to three case reports, and the general importance of these poorly documented early cases is unclear. It may be that these cases could just represent idiosyncratic reactions, and not be due to an interaction. The data is therefore too limited to suggest any particular caution. Nevertheless, consider the possibility of an interaction in case of an unexpected response to treatment with phenelzine (or potentially any MAOI) in a patient taking any type of ginseng.

1. Shader RI, Greenblatt DJ. Phenelzine and the dream machine—ramblings and reflections. *J Clin Psychopharmacol* (1985) 5, 65.
2. Shader RI, Greenblatt DJ. Bees, ginseng and MAOIs revisited. *J Clin Psychopharmacol* (1988) 8, 235.
3. Jones BD, Runikis AM. Interaction of ginseng with phenelzine. *J Clin Psychopharmacol* (1987) 7, 201–2.

MAOIs or RIMAs + Levodopa

A rapid, serious and potentially life-threatening hypertensive reaction can occur in patients taking MAOIs if they are given levodopa. An interaction with levodopa given with carbidopa or benserazide is less likely. No serious hypertensive reaction has been reported to occur with moclobemide.

Clinical evidence

(a) MAOIs

A patient who had been taking **phenelzine** daily for 10 days was given 50 mg of oral levodopa. In just over an hour his blood pressure had risen from 135/90 mmHg to about 190/130 mmHg, and despite a 5 mg intravenous injection of phentolamine it continued to rise over the next 10 minutes to 200/135 mmHg, before falling after a further 4 mg injection of phentolamine. The following day the experiment was repeated with levodopa 25 mg, but no blood pressure changes were seen. Three weeks after **phenelzine** was withdrawn even 500 mg of levodopa had no hypertensive effect.[1]

Similar cases of severe, acute hypertension, accompanied in most instances by flushing, throbbing and pounding in the head, neck and chest, and light-headedness have been described in other case reports and studies in which levodopa was given with **pargyline**,[2] **nialamide**,[3] **tranylcypromine**,[4] **phenelzine**,[5] or **isocarboxazid**.[1]

A study in 4 normotensive patients with parkinsonism found that the combination of levodopa and **tranylcypromine** caused an increase in blood pressure, but this reaction was inhibited by carbidopa in 3 of the patients. In the remaining patient (who was also taking trihexyphenidyl) the pressor response with levodopa and tranylcypromine (mean increase in arterial blood pressure 40 mmHg) was only blunted by carbidopa (mean increase 20 mmHg).[6]

(b) RIMAs

A study in 12 healthy subjects given a single dose of levodopa/benserazide with **moclobemide** 200 mg twice daily found that nausea, vomiting and dizziness were increased, but no significant hypertensive reaction was seen.[7]

Mechanism

Not fully understood. Levodopa is enzymatically converted in the body, firstly to dopamine and then to noradrenaline, both of which are normally broken down by monoamine oxidase. In the presence of an MAOI this breakdown is suppressed, which means that the total levels of dopamine and noradrenaline are increased. Precisely how this then leads to a sharp rise in blood pressure is not clear, but either dopamine or noradrenaline, or both, directly or indirectly stimulate the alpha-receptors of the cardiovascular system. Dopa-decarboxylase inhibitors would be expected to minimise the interaction by decreasing the peripheral metabolism of the levodopa.

Importance and management

The interaction between the non-selective MAOIs (listed in 'Table 32.1', (p.1370)) and levodopa on its own is well documented, serious and potentially life-threatening. Patients should not be given levodopa on its own during treatment with any of these MAOIs, nor for a period of 2 to 3 weeks after their withdrawal. Note that this interaction is inhibited or decreased by the presence of dopa-decarboxylase inhibitors[6] such as carbidopa and benserazide (as in *Sinemet* and *Madopar*) so that a serious interaction is less likely to occur with these preparations. Nevertheless, the manufacturers continue to list the MAOIs among their contraindications.

No hypertensive effect appears to occur between levodopa/benserazide and moclobemide, but bear in mind that the incidence of adverse effects may be increased.

1. Hunter KR, Boakes AJ, Laurence DR, Stern GM. Monoamine oxidase inhibitors and L-dopa. *BMJ* (1970) 3, 388.
2. Hodge JV. Use of monoamine-oxidase inhibitors. *Lancet* (1965) i, 764–5.
3. Friend DG, Bell WR, Kline NS. The action of L-dihydroxyphenylalanine in patients receiving nialamide. *Clin Pharmacol Ther* (1965) 6, 362–6.
4. Sharpe J, Marquez-Julio A, Ashby P. Idiopathic orthostatic hypotension treated with levodopa and MAO inhibitor: a preliminary report. *Can Med Assoc J* (1972) 107, 296–300.
5. Kassirer JP, Kopelman RI. A modern medical Descartes. *Hosp Pract* (1987) 22, 17–25.
6. Teychenne PF, Calne DB, Lewis PJ, Findley LJ. Interactions of levodopa with inhibitors of monoamine oxidase and L-aromatic amino acid decarboxylase. *Clin Pharmacol Ther* (1975) 18, 273–7.
7. Dingemanse J. An update of recent moclobemide interaction data. *Int Clin Psychopharmacol* (1993) 7, 167–80.

MAOIs or RIMAs + Lithium

Two cases of tardive dyskinesia have been described following the long-term use of tranylcypromine and lithium, which did not resolve when the MAOI was stopped. Limited evidence suggests that no problems occur when moclobemide is given with lithium.

Clinical evidence, mechanism, importance and management

(a) MAOIs

One report describes 2 patients with bipolar affective disorder who developed a buccolingual-masticatory syndrome after taking **tranylcypromine** 30 or 40 mg daily and lithium carbonate 900 mg or 1.2 g daily for 1.5 or 3 years. These symptoms did not resolve when the **tranylcypromine** was stopped. This reaction was attributed to dopamine receptor hypersensitivity.[1]

There appear to be no other reports suggesting that the combination of MAOIs and lithium is unsafe. However, there are a few reports of patients taking MAOIs and lithium who developed hyperpyrexia when given 'tryptophan', (p.1393). The role (if any) of lithium in these cases is unknown. Note that lithium has been used to augment antidepressants although most of the data relate to the use of tricyclics or SSRIs.[2] Any interaction seems to be rare, but bear these cases in mind in the event of any unexpected response to treatment with MAOIs and lithium.

(b) RIMAs

There was no evidence of any adverse interaction when **moclobemide** 150 to 675 mg daily was given for 3 to 52 weeks to 50 patients taking lithium.[3] Similarly, lithium augmentation was used in a small uncontrolled study in patients taking high-dose **moclobemide** without any evidence of important adverse effects.[4] No particular precautions would therefore seem necessary if both drugs are given.

1. Stancer HC. Tardive dyskinesia not associated with neuroleptics. *Am J Psychiatry* (1979) 136, 727.
2. Nelson JC. Augmentation strategies in depression 2000. *J Clin Psychiatry* (2000) 61 (Suppl 2), 13–19.
3. Amrein R, Güntert TW, Dingemanse J, Lorscheid T, Stabl M, Schmid-Burgk W. Interactions of moclobemide with concomitantly administered medication: evidence from pharmacological and clinical studies. *Psychopharmacology (Berl)* (1992) 106, S24–S31.
4. Magder DM, Aleksic I, Kennedy SH. Tolerability and efficacy of high-dose moclobemide alone and in combination with lithium and trazodone. *J Clin Psychopharmacol* (2000) 20, 394–5.

MAOIs + MAOIs or RIMAs

Strokes, fatal reactions (possibly including serotonin syndrome), hypertensive reactions and CNS disturbances have been seen when one MAOI was abruptly replaced by another, when the two MAOIs were given together, or when there was an insufficient MAOI-free interval. A case of serotonin syndrome occurred in a patient who took an overdose of moclobemide and tranylcypromine.

Clinical evidence, mechanism, importance and management

(a) MAOIs with MAOIs

A patient who had been taking **isocarboxazid** for 3.5 weeks (starting at 10 mg daily and gradually increased to 30 mg daily) was switched to **tranylcypromine** 10 mg, starting the same day, followed by 10 mg three times daily on the following day. Later that night she complained of feeling 'funny', had difficulty in talking, developed a headache, was restless, flushed, sweating, had an elevated temperature of 39.5°C, and a pulse rate of 130 bpm. She died the following day.[1] Another patient, switched with-out a drug-free period, from **phenelzine** 75 mg daily (by tapering the dose by 15 mg daily until discontinued) to **tranylcypromine** (starting at 10 mg daily, increasing by 10 mg daily, until a dose of 20 mg twice daily was reached), suffered a subcortical cerebral haemorrhage on the fourth day following the morning 20-mg dose of **tranylcypromine**, which resulted in total right-sided hemiplegia.[2,3] The patient remained significantly disabled from the sequelae of her stroke.[4] A third patient experienced a mild cerebral haemorrhage, without residual problems, when she took **phenelzine** 45 mg and **tranylcypromine** 20 mg at bedtime; the MAOIs were being switched by reducing the dose of phenelzine and gradually increasing the dose of **tranylcypromine**. Consumption of 'soy sauce', (p.1395), may have contributed to this reaction.[5] In a fourth case, **phenelzine** 45 mg daily was stopped, and then after a 2-day drug-free period **tranylcypromine** 20 mg was given, with a further 30-mg dose the next day. The patient experienced a rise in blood pressure to 240/130 mmHg, but recovered uneventfully, and a year later was successfully switched from **phenelzine** to **tranylcypromine** with a 2-week drug-free interval.[2] In another case, hypertension with severe headache, inability to walk and slurred speech, but without permanent sequelae, resulted from starting **tranylcypromine** 30 mg seven days after discontinuing **phenelzine**. **Tranylcypromine** 10 mg daily was restarted 3 days later (10 days after discontinuing the **phenelzine**) with no adverse effects, but when the dose was increased to 20 mg daily (14 days after discontinuing **phenelzine**) the patient experienced a milder version of the same symptoms.[6]

Acute CNS toxicity, hypertension, tachycardia, tremor and urinary retention occurred in a woman 48 hours after **phenelzine** was abruptly stopped and **isocarboxazid** started. In this patient, **phenelzine** was poorly tolerated causing hypertension and headache.[7]

Switching from **iproniazid** to **tranylcypromine** with trifluoperazine may have been the cause of a fatal reaction (fever, shivering, sweating, cyanosis) in a patient also given ephedrine[8,9] (consider 'MAOIs or RIMAs + Sympathomimetics; Indirectly-acting', p.1388).

In contrast, one woman was switched directly from **phenelzine** 60 mg daily to **tranylcypromine** 20 mg daily without any obvious problems (blood pressure was slightly high, but within the usual range for this patient). She was abruptly switched directly back to **phenelzine**, again without any adverse effect.[10,11] Similarly, a review of 8 cases of patients who were switched rapidly from **tranylcypromine** to **phenelzine** (3 cases) or *vice versa* (5 cases) found that 7 patients tolerated the switch well with minimal or no adverse effects. However the eighth patient experienced anxiety, nausea, hyperventilation, flushing, a sense of doom, and increased insomnia, which may have been a mild form of serotonin syndrome.[12]

The reasons for these reactions are not understood, but one idea is that the amphetamine-like properties of **tranylcypromine** may have had some part to play. Certainly there are cases of spontaneous rises in blood pressure and intracranial bleeding in patients given **tranylcypromine**.[13] Not all patients experience adverse reactions when switched from one MAOI to another,[10,12] but because of the sometimes severe reactions, it would seem prudent to have a drug-free wash-out interval when doing so (14 days is commonly suggested as a washout period for MAOIs), and to start dosing in a conservative and step-wise manner.

(b) RIMAs with MAOIs

A patient who took an overdose of **moclobemide** and **tranylcypromine** developed serotonin syndrome. In this analysis of **moclobemide** overdoses, the risk of developing serotonin toxicity was significantly increased in patients who also took another serotonergic drug, of which this case with **tranylcypromine** was one of 11 mentioned.[14]

1. Bazire SR. Sudden death associated with switching monoamine oxidase inhibitors. *Drug Intell Clin Pharm* (1986) 20, 954–6.
2. Gelenberg AJ. Switching MAOI. *Biol Ther Psychiatry* (1984) 7, 33 and 36.
3. Gelenberg AJ. Switching MAOI. The sequel. *Biol Ther Psychiatry* (1985) 8, 41.
4. Mattes JA. Stroke resulting from a rapid switch from phenelzine to tranylcypromine. *J Clin Psychiatry* (1998) 59, 382.
5. Anon. Switching MAOIs: part three. *Biol Ther Psychiatry* (1987) 10, 7.
6. Chandler JD. Switching MAOIs. *J Clin Psychopharmacol* (1987) 7, 438.
7. Safferman AZ, Masiar SJ. Central nervous system toxicity after abrupt monoamine oxidase inhibitor switch: a case report. *Ann Pharmacother* (1992) 26, 337–8.
8. Low-Beer GA, Tidmarsh D. Collapse after "Parstelin". *BMJ* (1963) 2, 683–4.
9. Schrire I. Collapse after "Parstelin". *BMJ* (1963) 2, 748.
10. True BL, Alexander B, Carter B. Switching monoamine oxidase inhibitors. *Drug Intell Clin Pharm* (1985) 19, 825–7.
11. True BL, Alexander B, Carter BL. Comment: switching MAO inhibitors. *Drug Intell Clin Pharm* (1986) 20, 384–5.
12. Szuba MP, Hornig-Rohan M, Amsterdam JD. Rapid conversion from one monoamine oxidase inhibitor to another. *J Clin Psychiatry* (1997) 58, 307–10.
13. Cooper AJ, Magnus RV, Rose MJ. A hypertensive syndrome with tranylcypromine medication. *Lancet* (1964) 1, 527–9.
14. Isbister GK, Hackett LP, Dawson AH, Whyte IM, Smith AJ. Moclobemide poisoning: toxicokinetics and occurrence of serotonin toxicity. *Br J Clin Pharmacol* (2003) 56, 441–50.

MAOIs + Mazindol

An isolated report describes a patient taking phenelzine who had a marked rise in blood pressure when a single dose of mazindol was given.

Clinical evidence, mechanism, importance and management

A woman taking **phenelzine** 30 mg three times daily had a rise in blood pressure from 110/60 to 200/100 mmHg within 2 hours of receiving a 10-mg test dose of mazindol. The blood pressure remained elevated for another hour, but had fallen again after a further 3 hours. The patient experienced no subjective symptoms.[1] It is uncertain whether this hypertensive reaction was the result of an interaction, or simply a direct response to the mazindol alone (the dose was large compared with the recommended dosage of 2 to 3 mg daily). The general importance of this interaction is uncertain. The manufacturer advises avoiding the combination, and says that mazindol should not be used until 14 days after MAOIs have been stopped.[2]

1. Oliver RM. Interaction between phenelzine and mazindol: Personal communication, 1981.
2. Sanorex (Mazindol). Novartis Pharmaceuticals. Canadian Prescribing information. Compendium of Pharmaceuticals and Specialities, 2004.

MAOIs + Methyldopa

Theoretically hypertension may occur when non-selective MAOIs are taken with methyldopa, although additive blood-pressure lowering effects are also a possibility. The concurrent use of antidepressant MAOIs and methyldopa may not be desirable because methyldopa can sometimes cause depression.

Clinical evidence, mechanism, importance and management

Theoretically, methyldopa might cause hypertension in patients taking non-selective MAOIs, by releasing catecholamines into the circulation[1,2] On the basis of this the manufacturers of **phenelzine**, **tranylcypromine**[3,4] and methyldopa[5] contraindicate concurrent use. Nevertheless, there do not appear to be any reports of hypertension occurring as a result of concurrent use. Conversely, the UK manufacturer of **isocarboxazid**[6] mentions that it may potentiate the hypotensive effect of methyldopa, and the US manufacturer of **isocarboxazid** warns that it may potentiate the effects of antihypertensives in general.[7] MAOIs alone have hypotensive effects and additional blood pressure lowering effects have been reported in a few patients given **pargyline** (an MAOI formerly used in the treatment of hypertension) with methyldopa.[8,9] Note that the potential depressant adverse effects of methyldopa may make it an unsuitable drug for patients with depression.

1. van Rossum JM. Potential danger of monoamineoxidase inhibitors and α-methyldopa. *Lancet* (1963) i, 950–1.
2. Natarajan S. Potential danger of monoamineoxidase inhibitors and α-methyldopa. *Lancet* (1964) i, 1330.
3. Nardil (Phenelzine sulfate). Pfizer Inc. US Prescribing information, August 2007.
4. Parnate (Tranylcypromine sulfate). GlaxoSmithKline. US Prescribing information, June 2007.
5. Aldomet (Methyldopa). Merck Sharp & Dohme Ltd. UK Summary of product characteristics, August 2001.
6. Isocarboxazid. Cambridge Laboratories. UK Summary of product characteristics, March 2000.
7. Marplan (Isocarboxazid). Validus Pharmaceuticals, Inc. US Prescribing information, August 2007.
8. Herting RL. Monoamine oxidase inhibitors. *Lancet* (1963) i, 1324.
9. Gillespsie L, Oates JA, Crout JR, Sjoerdsma A. Clinical and chemical studies with α-methyldopa in patients with hypertension. *Circulation* (1962) 25, 281–91.

MAOIs + Mirtazapine

The manufacturers say that two weeks should elapse between taking an MAOI and mirtazapine.

Clinical evidence, mechanism, importance and management

No serious adverse interactions have been reported between mirtazapine and the MAOIs[1] but, to be on the safe side, the manufacturers say that the concurrent use of mirtazapine and MAOIs should be avoided both during and within 2 weeks of stopping treatment.[1,2]

Note that there is a case of delirium possibly attributed to the use of linezolid (an antibacterial with some MAOI activity) with mirtazapine, see 'Linezolid + SSRIs', p.353, which gives weight to this warning.

1. Remeron (Mirtazapine). Schering-Plough. US Prescribing information, March 2009.
2. Zispin (Mirtazapine). Organon Laboratories Ltd. UK Summary of product characteristics, February 2009.

MAOIs + Modafinil

An isolated case report describes a patient who developed an acute dyskinesia and symptoms suggestive of serotonin syndrome following the use of modafinil with tranylcypromine.

Clinical evidence

A case report describes a patient who had been taking tranylcypromine 80 mg daily who, 3 days after starting to take modafinil 200 mg daily, became restless, confused, and developed severe choreiform movements of her limbs, lip smacking, rhythmic rapid tongue protrusions, and opisthotonus. Her temperature rose to 38°C, and remained high for 24 hours. Her symptoms resolved within 48 hours of discontinuing both drugs.[1]

Mechanism

The authors of this report suggest that the dopaminergic and serotonergic effects of modafinil were augmented by tranylcypromine. The hyperthermia and confusion that the patient experienced may have been an incomplete form of serotonin syndrome.

Importance and management

This appears to be the only case report of an interaction between an MAOI and modafinil, although a case report describing the successful use of these two drugs has been published.[2] However, if the suggested mechanism is correct, it could occur with any MAOI. It would therefore seem prudent to be alert for these effects if modafinil is given with an MAOI.

1. Vytopil M, Mani R, Adlakha A, Zhu J-J. Acute chorea and hyperthermia after concurrent use of modafinil and tranylcypromine. *Am J Psychiatry* (2007) 164, 684.
2. Clemons WE, Makela E, Young J. Concomitant use of modafinil and tranylcypromine in a patient with narcolepsy: a case report. *Sleep Med* (2004) 5, 509–11.

MAOIs + Monosodium glutamate

Hypertension in patients taking MAOIs who had eaten certain foods (soy sauce, chicken nuggets) has been attributed, in anecdotal reports, to an interaction with monosodium glutamate. However, a small controlled study found no evidence to support this idea, and the reaction was probably related to tyramine.

Clinical evidence

Five healthy subjects were given monosodium glutamate 400 mg to 1.6 g or a placebo with or without **tranylcypromine** for at least 2 weeks. Episodes of hypertension were seen in 2 subjects taking **tranylcypromine** with both placebo and monosodium glutamate, but no changes in blood pressure or heart rate occurred that could be attributed to an interaction while taking monosodium glutamate. The largest dose of monosodium glutamate used was about twice the amount usually found in meals containing large amounts of monosodium glutamate.[1]

There have been anecdotal reports of hypertensive reactions in patients taking MAOIs that were attributed to interactions with the monosodium glutamate contained in soy sauce[2] and chicken nuggets.[3]

Mechanism

Monosodium glutamate alone can cause a small rise in blood pressure, and MAOIs alone very occasionally cause hypertensive episodes. However, the reactions reported with soy sauce and chicken nuggets were probably due to a high tyramine content, as a high tyramine content has subsequently been detected in some soy sauces,[4] (see 'MAOIs or RIMAs + Tyramine-rich foods', p.1395).

Importance and management

No interaction between monosodium glutamate *per se* and MAOIs has been established, although it should be pointed out that the number of subjects studied was very small. It is quite possible that the anecdotal reports were due to the tyramine content of the foods, and not to monosodium glutamate. In Hong Kong, patients taking MAOIs are not advised to avoid

monosodium glutamate, but are instructed to avoid excessive soy sauce because of its possible high tyramine content.[4]

1. Balon R, Pohl R, Yeragani VK, Berchou R, Gershon S. Monosodium glutamate and tranylcypromine administration in healthy subjects. *J Clin Psychiatry* (1990) 51, 303–6.
2. McCabe B, Tsuang MT. Dietary consideration in MAO inhibitor regimens. *J Clin Psychiatry* (1982) 43, 178–81.
3. Pohl R, Balon R, Berchou R. Reaction to chicken nuggets in a patient taking an MAOI. *Am J Psychiatry* (1988) 145, 651.
4. Lee S, Wing YK. MAOI and monosodium glutamate interaction. *J Clin Psychiatry* (1991) 52, 43.

MAOIs or RIMAs + Opioids; Dextropropoxyphene (Propoxyphene)

An isolated report describes 'leg shakes', diaphoresis and severe hypotension when a woman taking phenelzine was given dextropropoxyphene. Another isolated report describes a marked increase in sedation when a woman was given phenelzine and dextropropoxyphene. *Animal* data show moclobemide potentiates the effects of dextropropoxyphene.

Clinical evidence, mechanism, importance and management

(a) MAOIs

A woman taking **phenelzine** 15 mg three times daily, sodium valproate, lithium and trazodone, was given dextropropoxyphene 100 mg and paracetamol (acetaminophen) 650 mg for back pain and headache. Some 12 hours later she was admitted to hospital for leg shakes, discomfort and weakness. She was confused and anxious, and intensely diaphoretic. The next day she became severely hypotensive (systolic BP 55 to 60 mmHg) and needed large fluid volume resuscitation in intensive care. She later recovered fully.[1] Another woman taking propranolol, oestrogen-replacement therapy and **phenelzine** became very sedated and groggy, causing her to have to lie down on two occasions, both within 2 hours of taking dextropropoxyphene 100 mg and paracetamol 650 mg. She had experienced no problems with either paracetamol or dextropropoxyphene/paracetamol before starting the **phenelzine**, and subsequently had no problems with paracetamol alone while continuing the **phenelzine**.[2] The mechanisms of these interactions are not understood but some of the symptoms in the first case were not unlike those seen in the serotonin syndrome.

Apart from these two isolated reports, there seems to be no other clinical evidence of adverse interactions between MAOIs and dextropropoxyphene; however, some caution would seem prudent if any MAOI is given with dextropropoxyphene. For reports of the serotonin syndrome seen with pethidine (meperidine) and MAOIs, see 'MAOIs or RIMAs + Opioids; Pethidine (Meperidine)', p.1381.

(b) RIMAs

In *animals,* the effects of dextropropoxyphene were increased by **moclobemide**.[3] A brief mention is made of 3 patients, taking **moclobemide** and codeine (2 patients) or dextropropoxyphene (1 patient): one of these patients developed moderate agitation.[3]

1. Zornberg GL, Hegarty JD. Adverse interaction between propoxyphene and phenelzine. *Am J Psychiatry* (1993) 150, 1270–1.
2. Garbutt JC. Potentiation of propoxyphene by phenelzine. *Am J Psychiatry* (1987) 144, 251–2.
3. Amrein R, Güntert TW, Dingemanse J, Lorscheid T, Stabl M, Schmid-Burgk W. Interactions of moclobemide with concomitantly administered medication: evidence from pharmacological and clinical studies. *Psychopharmacology (Berl)* (1992) 106, S24–S31.

MAOIs + Opioids; Fentanyl and related drugs

Fentanyl has been used in patients taking MAOIs without problems in some patients, but one fatal case of hyperthermia has occurred, and also a case of hypertension and tachycardia. Case reports describe the uneventful use of alfentanil, remifentanil and sufentanil in patients taking MAOIs.

Clinical evidence

(a) Alfentanil

A 54-year-old woman taking **tranylcypromine** with trifluoperazine underwent general anaesthesia with no problems. She received temazepam as premedication, and propofol induction. Supplementary alfentanil was given in increments of 250 micrograms to a total of 2.5 mg. Atracurium was given for neuromuscular block with 100% oxygen for ventilation.[1] Similarly, another report describes successful anaesthesia using propofol, alfentanil 25 micrograms/kg, and succinylcholine during ECT therapy in two patients taking a variety of drugs including **phenelzine**.[2]

(b) Fentanyl

A 71-year-old woman taking *Parstelin* (**tranylcypromine** with trifluoperazine) was given an intravenous test dose of fentanyl 20 micrograms and diazepam before surgery, without problems. She was then given another 20-microgram intravenous dose of fentanyl during surgery, followed by an epidural bolus infusion of fentanyl 50 micrograms 15 minutes before the end of the surgery. After surgery she was given a continuous epidural infusion of fentanyl 50 to 70 micrograms/hour for 4 days to control postoperative pain, also without problems.[3] Similarly, another report describes 2 patients who had stopped taking **phenelzine** 36 hours and 10 days before undergoing uneventful cardiac surgery using fentanyl, pancuronium and 100% oxygen.[4] Four further patients taking **tranylcypromine**, **isocarboxazid**, or **pargyline** had no adverse reactions to fentanyl given during surgery (3 cases) and/or for postoperative pain relief (3 cases).[5]

In contrast, a man taking **tranylcypromine** who received fentanyl during and after surgery developed postoperative hypertension, hyperthermia, and severe shivering, followed by resistant hypotension. He later died.[6] Another patient taking **phenelzine** who underwent cardiac surgery, with anaesthesia maintained by fentanyl and midazolam, developed hypertension and supraventricular tachycardia, which did not respond to digoxin and esmolol. About 15 minutes after stopping the fentanyl/midazolam and starting enflurane, the haemodynamics gradually improved, and analgesia was subsequently managed with ketorolac without problems.[7]

(c) Remifentanil

A patient taking **phenelzine** was given remifentanil for the maintenance of anaesthesia without adverse effect. An adverse interaction was considered unlikely with this combination.[8]

(d) Sufentanil

A 43-year-old woman taking **tranylcypromine** 60 mg daily underwent general anaesthesia with sufentanil, isoflurane, and nitrous oxide without problem.[9]

Mechanism, importance and management

Fentanyl has been used safely in a number of patients receiving MAOIs. However, a fatality due to a serotonin-like syndrome has occurred in a patient taking an MAOI given fentanyl, and another case of hypertension and tachycardia has occurred. The authors of one of these reports, considered that there was insufficient evidence to conclude that patients taking MAOIs can be given fentanyl safely, and call for all cases of combined use to be reported.[6] Case reports also describe the safe use of alfentanil, remifentanil, and sufentanil. However, some UK manufacturers of fentanyl patches,[10] lozenges,[11] and injection[12] contraindicate their concurrent use with, or within 14 days of stopping, an MAOI. The UK manufacturer of alfentanil similarly contraindicates MAOIs,[13] and the US manufacturer recommends fentanyl patches are not to be used within 14 days of taking MAOIs.[14]

Note that fentanyl and related drugs are frequently used during surgery, and it is generally considered that MAOIs should be discontinued 2 weeks before surgery, see 'Anaesthetics, general + MAOIs and related drugs', p.112.

1. Powell H. Use of alfentanil in a patient receiving monoamine oxidase inhibitor therapy. *Br J Anaesth* (1990) 64, 528.
2. Beresford BJ, Glick D, Dinwiddie SH. Combination propofol-alfentanil anesthesia for electroconvulsive therapy in patients receiving monoamine oxidase inhibitors. *J ECT* (2004) 20, 120–2.
3. Youssef MS, Wilkinson PA. Epidural fentanyl and monoamine oxidase inhibitors. *Anaesthesia* (1988) 43, 210–12.
4. Michaels I, Serrins M, Shier NQ, Barash PG. Anesthesia for cardiac surgery in patients receiving monoamine oxidase inhibitors. *Anesth Analg* (1984) 63, 1041–4.
5. El-Ganzouri AR, Ivankovich AD, Braverman B, McCarthy R. Monoamine oxidase inhibitors: should they be discontinued preoperatively? *Anesth Analg* (1985) 64, 592–6.
6. Noble WH, Baker A. MAO inhibitors and coronary artery surgery: a patient death. *Can J Anaesth* (1992) 39, 1061–6.
7. Insler SR, Kraenzler EJ, Licina MG, Savage RM, Starr NJ. Cardiac surgery in a patient taking monoamine oxidase inhibitors: an adverse fentanyl reaction. *Anesth Analg* (1994) 78, 593–7.
8. Ure DS, Gillies MA, James KS. Safe use of remifentanil in a patient treated with the monoamine oxidase inhibitor phenelzine. *Br J Anaesth* (2000) 84, 414–16.
9. O'Hara JF, Maurer WG, Smith MP. Sufentanil-isoflurane-nitrous oxide anesthesia for a patient treated with monoamine oxidase inhibitor and tricyclic antidepressant. *J Clin Anesth* (1995) 7, 148–50.
10. Matrifen (Fentanyl). Nycomed UK Ltd. UK Summary of product characteristics, November 2008.

11. Actiq (Fentanyl citrate lozenge). Cephalon (UK) Ltd. UK Summary of product characteristics, July 2009.
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MAOIs + Opioids; Miscellaneous

Hypotension (profound in one case) has been seen in a few patients given morphine and an MAOI. One case of hypotension and stupor has occurred with papaveretum. Single cases of the safe use of methadone and hydromorphone have also been described.

Clinical evidence

(a) Hydromorphone

No problems were encountered when a patient taking **tranylcypromine** was given hydromorphone via a patient-controlled device for postoperative pain.[1] This patient also received sufentanil during surgery without problem.

(b) Methadone

A patient receiving methadone 30 mg daily was successfully and uneventfully treated for depression with **tranylcypromine**, initially 10 mg daily gradually increased to 30 mg daily.[2]

(c) Morphine

A study in 15 patients who had been taking either **phenelzine**, **isocarboxazid**, **iproniazid** or *Parstelin* (**tranylcypromine** with trifluoperazine) for 3 to 8 weeks, had no changes in blood pressure, pulse rate or state of awareness when given test doses of up to 4 mg of intramuscular morphine. However, note that none of these patients showed an interaction with test doses of up to 40 mg of pethidine (meperidine).[3] One other study reported no adverse interaction in 3 patients taking **isocarboxazid** when they were given morphine premedication,[4] and a further study revealed no problems in 9 patients taking **tranylcypromine** who were given morphine for postoperative pain relief.[5] Another patient taking **phenelzine** was uneventfully treated with morphine postoperatively.[6] Two further patients taking MAOIs, who reacted adversely to pethidine,[7,8] had not previously done so when given morphine. In an early report, intramuscular morphine was given without apparent problem to 5 patients who had developed severe headache while taking **tranylcypromine**.[9] Another author briefly noted that he knew of about 10 cases where morphine had been used in patients taking MAOIs with no adverse effects except a more prolonged morphine action.[10]

However, a patient taking **tranylcypromine** 40 mg and trifluoperazine 20 mg daily and undergoing a preoperative test with morphine, developed pin point pupils, became unconscious and unresponsive to stimuli, and had a systolic blood pressure fall from 160 to 40 mmHg after receiving a total of 6 mg of morphine intravenously. Within 2 minutes of being given naloxone 4 mg intravenously, the patient was awake and rational with a systolic blood pressure fully restored.[11] A moderate fall in blood pressure (from 140/90 to 90/60 mmHg) was seen in another patient taking an MAOI and given morphine,[12] and a brief episode of hypotension treated with phenylephrine occurred in a patient taking **phenelzine** receiving continuous epidural morphine during surgery.[5]

(d) Papaveretum

A 54-year-old woman taking **phenelzine** was given papaveretum 10 mg as premedication, and 50 minutes later she was found to be unrousable, sweating and hypotensive.[13]

Mechanism, importance and management

Some limited evidence suggests that patients taking MAOIs who reacted adversely with pethidine (meperidine) did not do so when given morphine,[7,8] and quite a number of reports describe the safe uneventful use of morphine and MAOIs. The few hypotensive reactions cited here[5,11,12] are of a different character to the severe reaction seen with 'pethidine', (below), and appear to be rare. However, many manufacturers of morphine have contraindicated its concurrent use with, or within 2 weeks of stopping an MAOI.[14-16] In contrast, the manufacturers of one morphine preparation note that as severe CNS excitation or depression (hypertension or hypotension) has been seen when pethidine was given with an MAOI, consideration should be given to using a reduced morphine dose in patients taking MAOIs.[17]

Similarly, the manufacturers of several opioids contraindicate their use both with, and within 14 days, of the use of an MAOI. These include **codeine**,[18] diamorphine,[19] hydromorphone,[20] methadone,[21] and oxycodone.[22]

However, information is conflicting, and the manufacturers of other opioids just advise caution if MAOIs are also given. These include **codeine** (increased effects of both drugs),[23] and **dihydrocodeine**.[24]

Some authors recommend lower initial dosages of morphine or oxycodone, frequent monitoring, and gradual upward dose titration.[25] One author suggests that morphine, codeine, and oxycodone do not possess serotonin reuptake inhibitor activity and would therefore not be expected to cause serotonin syndrome when given with MAOIs.[26] In contrast, 'pethidine', (below), 'tramadol', (p.1382), 'dextropropoxyphene', (p.1380), and methadone appear to be weak serotonin reuptake inhibitors, and these drugs, with the exception of methadone, have been implicated in reports of serotonin toxicity.[26]

Clearly the advice is somewhat conflicting, with some taking a more cautious approach than others. If the decision is taken to give an opioid to a patient taking an MAOI, it would seem prudent to choose one that appears to lack serotonergic activity (e.g. codeine, morphine, oxycodone) wherever possible. Monitor concurrent use carefully for any signs of adverse effects.

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17. Morphine Sulphate Injection. Wockhardt UK Ltd. UK Summary of product characteristics, September 2007.
18. Solpadol (Codeine/Paracetamol). Sanofi-Aventis. UK Summary of product characteristics, June 2007.
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21. Methadone Hydrochloride Oral Solution. Rosemont Pharmaceuticals Ltd. UK Summary of product characteristics, April 2009.
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MAOIs or RIMAs + Opioids; Pethidine (Meperidine)

The concurrent use of pethidine and MAOIs has resulted in a serious and potentially life-threatening reaction in several patients. Excitement, muscle rigidity, hyperpyrexia, flushing, sweating and unconsciousness can occur very rapidly. Respiratory depression and hypertension or hypotension have also been seen. A possible case of serotonin syndrome has been seen in a patient given moclobemide and pethidine (with other serotonergic drugs).

Clinical evidence

(a) MAOIs

Severe, rapid and potentially fatal toxic reactions, both excitatory and depressant can occur when MAOIs are given with pethidine:

A woman stopped taking **iproniazid** 50 mg twice daily and about a day and a half later became restless and incoherent almost immediately after being given pethidine 100 mg for chest pain. She was comatose within 20 minutes. An hour after receiving the injection she was flushed, sweating and showed Cheyne-Stokes respiration. Her pupils were dilated and unreactive. Deep reflexes could not be initiated and plantar reflexes were extensor. Her pulse rate was 82 bpm and blood pressure 156/110 mmHg. She was rousable within 10 minutes of receiving an intravenous injection of prednisolone hemisuccinate 25 mg. A very similar reaction also occurred in another patient.[1]

A woman who, unknown to her doctor, was taking **tranylcypromine**, was given pethidine 100 mg. Within minutes she became unconscious, noisy and restless, having to be held down by 3 people. Her breathing was stertorous and the pulse impalpable. Generalised tonic spasm developed, with ankle clonus, extensor plantar reflexes, shallow respiration and cyanosis. On admission to hospital she had a pulse rate of 160 bpm, a blood pressure of 90/60 mmHg and was sweating profusely (temperature 38.3°C). Her condition gradually improved and 4 hours after admission she was conscious but drowsy. Recovery was complete the next day.[2]

Other cases of this interaction have been reported in patients taking **iproniazid**,[3-5] **pargyline**,[6,7] **phenelzine**,[8-13] and **mebanazine**.[14] Fatalities have occurred. One of 8 patients taking an MAOI and given a 5-mg test dose of pethidine experienced a drop in systolic blood pressure of 30 mmHg and a rise in pulse rate of 20 bpm.[15] However, a study in 15 patients who had been taking **phenelzine**, **isocarboxazid**, **iproniazid** or *Parstelin* (**tranylcypromine** with trifluoperazine) for 3 to 8 weeks, found no changes in blood pressure, pulse rate or state of awareness with test doses of up to 40 mg of pethidine.[16] Similarly, no major problems were noted in a retrospective review of 45 episodes of anaesthesia in patients taking **isocarboxazid** who were given pethidine as part of premedication.[17]

(b) RIMAs

One report suggests that on the basis of *animal* studies the combination of **moclobemide** and pethidine should be avoided or used with caution.[18] A report of suspected serotonin syndrome in a 73-year-old woman, given pethidine in addition to her usual treatment with **moclobemide** 750 mg daily, nortriptyline 100 mg daily and lithium 750 mg daily, adds some weight to this suggestion.[19]

Mechanism

Not understood, despite the extensive studies undertaken.[20-22] The reaction has proved difficult to study in *animals*, since mice appear to be more sensitive to the reaction than humans. There is some evidence that the reactions may be due to an increase in levels of 5-HT within the brain, causing 'serotonin syndrome', (p.9). Tramadol, an opioid with additional noradrenergic and serotonergic properties, has clearly caused the serotonin syndrome when used with MAOIs, see 'tramadol', (below).

Importance and management

The interaction between pethidine and the MAOIs, which was first observed in the mid-1950s, is based on case reports. It is serious and potentially fatal. Its incidence is unknown, but it is probably quite low, because one study that attempted to produce the interaction by giving increasing test doses of pethidine to 15 patients taking various MAOIs did not show the interaction.[16] It may therefore be an idiosyncratic reaction. Nevertheless, it would be imprudent to give pethidine to any patient taking an MAOI. Bear in mind that the older MAOIs are all essentially irreversible so that an interaction is possible for many days after their withdrawal (at least 2 weeks is the official advice).

Although information is sparse, the manufacturer of moclobemide contraindicates the use of pethidine.[23] As moclobemide is a reversible inhibitor of MAO it is unlikely to interact 48 hours after it has been stopped.

Sensitivity test

A sensitivity test has been suggested,[15] but given the fact that there are many alternatives to pethidine and MAOIs readily available, and given that a drop in systolic blood pressure of 30 mmHg has been reported even with the first step of the test dose (5 mg of pethidine)[15] it would seem prudent to avoid the combination. Also, the test dose procedure is unlikely to be suitable when opioids are required in an emergency situation.

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MAOIs or RIMAs + Opioids; Tramadol

Serotonin syndrome developed in one patient taking iproniazid and tramadol, and delirium occurred in another patient given tramadol shortly after stopping phenelzine. A fatal case of possible serotonin syndrome occurred in a patient taking tramadol, moclobemide and clomipramine.

Clinical evidence, mechanism, importance and management

Serotonin syndrome (myoclonus, tremor, sweating, hyperreflexia, tachycardia) developed in a patient taking **iproniazid** when tramadol was also given. When the tramadol was stopped the patient recovered within 48 hours.[1] Another single case report describes the development of severe delirium in a patient within 3 days of stopping long term treatment with **phenelzine** 45 mg daily and starting intramuscular tramadol 100 mg three times daily. The patient became anxious and confused, and developed visual hallucinations and persecutory ideation. The symptoms disappeared within 48 hours of stopping the tramadol.[2] Another report suggests that tramadol may have contributed to the development of a fatal case of serotonin syndrome in a patient abusing tramadol, **moclobemide** and clomipramine.[3]

Information is limited, but moclobemide, the MAOIs and tramadol are known to have serotonergic effects. The UK manufacturers contraindicate concurrent use,[4] whereas the US manufacturers advise great caution if tramadol is given with an MAOI.[5] In practice this probably means monitoring closely for signs of 'serotonin syndrome', (p.9).

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MAOIs + Rauwolfia alkaloids or Tetrabenazine

Central excitation and possibly hypertension can occur if rauwolfia alkaloids are given to patients already taking an MAOI, but is less likely if the rauwolfia alkaloid is given first. Theoretically additive blood-pressure lowering effects are also a possibility. The use of drugs that have the potential to cause depression, such as the rauwolfia alkaloids or tetrabenazine, is generally contraindicated in patients needing treatment for depression.

Clinical evidence

A woman with a history of manic depression who had been in a depressed phase for 5 years was given **nialamide** 100 mg three times daily. Two days later, **reserpine** 500 micrograms three times daily was also started. The following day she became frankly hypomanic and almost immediately went into mania.[1]

In another report,[2] a patient who started to take **tetrabenazine** 10 mg three times daily, 2 days after stopping a week of treatment with **nialamide** 25 mg daily, collapsed 6 hours after the first **tetrabenazine** dose, and demonstrated epileptiform convulsions, partial unconsciousness, rapid respiration and tachycardia. He recovered within 15 minutes, but 3 days later he had a similar attack and the **tetrabenazine** was stopped.

Another author states that the use of **reserpine** or **tetrabenazine** after pretreatment with **iproniazid** can lead to a temporary disturbance of affect and memory, associated with autonomic excitation, delirious agitation, disorientation and illusions of experience and recognition, which lasts for up to 3 days.[3,4]

A prolonged period of increased motor activity after starting **reserpine** ('reserpine-reversal') possibly occurred in 3 patients with schizophrenia given firstly **phenelzine** for 12 weeks,, when compared with patients given **reserpine** who had not received an MAOI. Their blood pressures rose slightly and persistently, and their psychomotor activity was considerably increased, lasting in two cases throughout the 12-week period of concurrent treatment.[5]

Theoretically, **reserpine** could cause hypertension in patients taking non-selective MAOIs (see Mechanism). On the basis of this the US manufacturer of **tranylcypromine**[6] contraindicates concurrent use. Conversely, the UK manufacturer of **isocarboxazid**[7] mentions that it may potentiate the hypotensive effect of **reserpine** (MAOIs alone can have hypotensive effects).

Mechanism

Rauwolfia alkaloids, such as reserpine, cause adrenergic neurones to become depleted of their normal stores of noradrenaline (norepinephrine). In this way they prevent or reduce the normal transmission of impulses at the adrenergic nerve endings of the sympathetic nervous system, and thereby act as antihypertensives. Since the brain also possesses adrenergic neurones, failure of transmission in the CNS could account for the sedation and depression observed with these drugs. If rauwolfia alkaloids are given to patients already taking an MAOI, large amounts of accumulated noradrenaline can be released throughout the body. In the brain, 5-HT is also released. The release of these substances results in marked central excitation and hypertension. This would account for the case reports cited and the effects seen in *animals*.[8-10] These stimulant effects are sometimes called 'reserpine-reversal' because instead of the expected sedation or depression, excitation or delayed depression is seen. It depends upon the order in which the drugs are given.

Importance and management

The use of drugs that have the potential to cause depression is generally contraindicated in patients needing treatment for depression. However, one report suggests that if concurrent use is considered desirable, the MAOIs should be given after, and not before the rauwolfia alkaloid, so that sedation rather than excitation will occur.[11] Bear in mind the possibility of hypo- or hypertension.

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MAOIs or RIMAs + SNRIs

Serious and potentially life-threatening reactions (serotonin syndrome) can develop if venlafaxine and non-selective MAOIs (isocarboxazid, phenelzine, tranylcypromine) are given concurrently, or even sequentially if insufficient time is left in between. Serotonin syndrome has also been reported with moclobemide and venlafaxine, but it has usually occurred during overdose, and there is also a possible case with moclobemide and duloxetine. There is a possible risk of serotonin syndrome developing when duloxetine is taken with, or shortly after, MAOIs. Milnacipran is expected to interact similarly.

Clinical evidence

A. Duloxetine

A 46-year-old woman developed symptoms which were considered to be indicative of a mild form of serotonin syndrome shortly after taking duloxetine 60 mg. The previous day she had taken the last dose of a course of treatment with **moclobemide** 600 mg daily. Her symptoms included restlessness, tremor, dizziness, headache and tics-like facial movements. On the second day of duloxetine treatment her blood pressure rose to 130/90 mmHg.[1] Duloxetine was stopped, and **moclobemide** restarted uneventfully after a one-week washout period.[1] Note that a rise in blood pressure is a known adverse effect of duloxetine alone.[2]

B. Venlafaxine

(a) MAOIs

1. Isocarboxazid. A man with recurrent depression taking isocarboxazid 30 mg daily was also given venlafaxine 75 mg. After the second dose he developed agitation, hypomania, diaphoresis, shivering and dilated pupils. These symptoms subsided when the venlafaxine was stopped. He subsequently developed myoclonic jerks and diaphoresis when given both drugs.[3]

2. Phenelzine. A woman who had stopped taking phenelzine 45 mg daily 7 days previously, developed sweating, lightheadedness and dizziness within 45 minutes of taking a single 37.5-mg dose of venlafaxine. In the emergency department she was found to be lethargic, agitated and extremely diaphoretic. The agitation was treated with lorazepam. A week later, after she had recovered, she again started taking the same regimen of venlafaxine without problems.[4] A man developed serotonin syndrome when he started venlafaxine the day after he stopped taking phenelzine,[5] and a woman developed serotonin syndrome within an hour of taking phenelzine and venlafaxine together.[6] Four other patients similarly developed the reaction when phenelzine was replaced by venlafaxine.[7]
Twelve days after an overdose of phenelzine (53 tablets of 15 mg), benzatropine, haloperidol and lorazepam, a 31-year-old man was given venlafaxine 75 mg every 12 hours in addition to existing treatment with olanzapine and diazepam. About an hour after the first dose, he developed leg shakiness and stiffness, diaphoresis, blurred vision, difficulty breathing, chills, nausea and palpitations. Venlafaxine and olanzapine were discontinued and the man recovered within 24 hours, after treatment with intravenous fluids, propranolol and paracetamol.[8]

3. Tranylcypromine. A woman who had been taking tranylcypromine for 3 weeks developed a serious case of serotonin syndrome within 4 hours of inadvertently taking a single tablet of venlafaxine. She recovered within 24 hours, when treated with ice packs, a cooling blanket, diazepam and dantrolene.[9] Serotonin syndrome developed in a man taking tranylcy-

promine within 2 hours of taking half a venlafaxine tablet,[10] and another case of serotonin syndrome has been described in a man taking tranylcypromine 60 mg daily who accidentally took venlafaxine 300 mg.[11] This case has also been published elsewhere.[12]

(b) Moclobemide

A 32-year-old man taking moclobemide 20 mg twice daily and diazepam developed serotonin syndrome 40 minutes after taking a single 150-mg dose of venlafaxine.[13] Serotonin toxicity (serotonin syndrome) occurred in 4 patients who took an overdose of moclobemide with venlafaxine (just 150 mg in one case and 750 mg in another). In this analysis of moclobemide overdoses, the risk of developing serotonin toxicity was significantly increased in patients who also took another serotonergic drug (52%; 11 of 21 patients), compared with 3% taking moclobemide alone. Venlafaxine was taken in 4 of the 11 cases mentioned.[14] Another man very rapidly developed serotonin syndrome after taking considerable overdoses of moclobemide (3 g) and venlafaxine (2.625 g).[15]

Mechanism

Serotonin syndrome is thought to occur because duloxetine and venlafaxine can inhibit serotonin reuptake (their antidepressant effect is related to this activity), and MAOIs and RIMAs inhibit the metabolism of serotonin. The result is an increase in the concentrations of serotonin apparently causing overstimulation of the 5-HT_{1A} receptors in the brain and spinal cord. For a further discussion of serotonin syndrome, see under 'Additive or synergistic interactions', (p.9).

Importance and management

The interaction with venlafaxine is established, serious and potentially life-threatening. The manufacturers of venlafaxine note that in some cases this interaction has been fatal. They recommend that venlafaxine should not be used in combination with an MAOI or within 14 days of stopping treatment with the MAOI.[16,17] Based on the half-life of venlafaxine they say that at least 7 days should elapse between stopping venlafaxine and starting an MAOI. The manufacturers do not distinguish in this recommendation between the irreversible older non-selective MAOIs and the RIMAs such as moclobemide. In one of the studies it was suggested that a wash-out period of several weeks is required between stopping MAOIs such as phenelzine and initiating a second serotonergic drug such as venlafaxine.[8]

Similarly, it is recommended that duloxetine[2,18,19] and **milnacipran**[20] should not be used in combination with an MAOI or within 14 days of stopping treatment with an MAOI. Based on the half-life of duloxetine, the manufacturers advise that at least 5 days should elapse between stopping duloxetine and starting an MAOI,[2,18,19] and the manufacturer of milnacipran recommends at least one week.[20]

The use of moclobemide is not recommended with duloxetine, but no specific advice is given regarding a washout period.[2,18] Similarly, the manufacturer of milnacipran also advises against the use of moclobemide, but they say that if the combination cannot be avoided, careful clinical monitoring is required, starting with the minimum recommended dose.[20]

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MAOIs or RIMAs + SSRIs

A number of case reports describe serotonin syndrome in patients given SSRIs with MAOIs: some have been fatal. Some studies suggest that moclobemide may not interact with the SSRIs, but there have also been case reports of serotonin syndrome. A suitable washout interval is needed when switching between MAOIs or RIMAs and SSRIs.

Clinical evidence

A. MAOIs

(a) Fluoxetine

A very high incidence (25 to 50%) of adverse effects occurred in 12 patients taking fluoxetine 10 to 100 mg daily with either **phenelzine** 30 to 60 mg daily or **tranylcypromine** 10 to 140 mg daily, and in 6 other patients who started one of these MAOIs 10 days or more after stopping fluoxetine. There were mental changes such as hypomania, racing thoughts, agitation, restlessness and confusion. The physical symptoms included myoclonus, hypertension, tremor, teeth chattering and diarrhoea.[1]

A detailed review of cases reported to the manufacturers described 8 acute cases, 7 of them fatal, in patients given fluoxetine with either **tranylcypromine** or **phenelzine**.[2] Uncontrollable shivering, teeth chattering, double vision, nausea, confusion, and anxiety developed in a woman given **tranylcypromine** after stopping fluoxetine. The problem resolved within a day of stopping the **tranylcypromine**, and did not recur when fluoxetine was tried again 6 weeks later.[3]

A number of other reports describe similar reactions in patients given fluoxetine and **tranylcypromine**,[3-8] some occurring up to 6 weeks after the SSRI was stopped,[6] and several resulting in fatalities.[3,7]

(b) Sertraline

A man taking **tranylcypromine** and clonazepam was also given sertraline 25 to 50 mg daily. Within 4 days he began to experience chills, increasing confusion, sedation, exhaustion, unsteadiness and incoordination. Other symptoms included impotence, urinary hesitancy and constipation. These problems rapidly resolved when the sertraline was stopped and the **tranylcypromine** dosage reduced from 30 to 20 mg daily.[9]

A woman with a major depressive disorder taking lithium, thioridazine, doxepin and **phenelzine** was also given sertraline 100 mg daily for worsening depression. Within 3 hours she became semi-comatose, with a temperature of 41°C, a heart rate of 154 bpm and symptoms of rigidity and shivering. She was treated with diazepam, midazolam, ice packs and dantrolene.[10] Two other similar cases, involving the use of sertraline with **isocarboxazid**[11] and **phenelzine**[12] have been reported. The latter case was fatal.[12] Another case of mild serotonin syndrome (managed with cyproheptadine) occurred in a woman who took a single dose of sertraline 11 days after stopping **isocarboxazid**.[13]

B. RIMAs

(a) Citalopram

A 34-year-old man who had been taking **moclobemide** 100 mg every 8 hours for several months was switched to citalopram 20 mg daily without a washout period. An hour later he started getting agitated and had involuntary movements of the legs, which progressed to generalised rigidity. Apart from a heart rate of 100 bpm all other vital signs were normal. He was treated with benzodiazepines and recovered uneventfully.[14] Three patients developed serotonin syndrome (tremor, convulsions, hyperthermia, unconsciousness) and died 3 to 16 hours after taking overdoses of **moclobemide** and citalopram.[15] Other cases of serotonin syndrome have occurred after overdoses of **moclobemide** and citalopram:[16,17] one also included **sertraline** and sumatriptan.[16]

(b) Fluoxetine

A placebo-controlled study in 18 healthy subjects found that the use of fluoxetine 20 mg with **moclobemide** 100 to 600 mg daily for 9 days did not appear to result in an adverse interaction.[18] Other studies in healthy subjects and patients similarly found no evidence of serotonin syndrome.[19,20]

A post-marketing analysis found that at least 30 patients switched from fluoxetine to **moclobemide** within a week had experienced no adverse effects.[18,21]

However, 3 patients have developed serotonin syndrome[22-24] and one developed agitation and confusion[25] following the use of **moclobemide** and fluoxetine. A fatal case of serotonin syndrome occurred in a patient who took an overdose of **moclobemide**, fluoxetine, and clomipramine,[26] and another patient taking **moclobemide** developed serotonin syndrome after taking an overdose of fluoxetine.[27] A study suggests that the combination may cause a high rate of adverse effects (insomnia, dizziness, nausea and headache).[22]

A double-blind study in 41 healthy subjects found that when they were given fluoxetine 40 mg daily for 7 days, then 20 mg for 9 days, immediately followed by **befloxatone** (2.5, 5, 10 or 20 mg daily) for 5 days, no unusual adverse reactions occurred and no changes in body temperature, haemodynamics or ECGs were seen.[28]

(c) Fluvoxamine

When 13 of 22 healthy subjects given fluvoxamine 100 mg daily for 9 days were also given **moclobemide**, in increasing doses of 50 to 400 mg daily, from days 7 to 10, no serious adverse reactions occurred. Any adverse events were mild to moderate (some increase in headaches, fatigue, dizziness, all of which may occur with both drugs alone) and there was no evidence of serotonin syndrome.[18,29] An open study in 6 depressed patients given **moclobemide** 225 to 800 mg daily and fluvoxamine 50 to 200 mg daily found a marked improvement in depression. Insomnia was the commonest adverse effect (treated with trazodone) but none of the patients showed any evidence of serotonin syndrome.[30] Similar results were found in other studies.[20,31] However, a fatal case of serotonin syndrome occurred in a woman who took an overdose of **moclobemide** and fluvoxamine, and another fatal overdose was attributed to the same combination.[32]

(d) Paroxetine

An open 6-week study in 19 patients with major depression taking paroxetine (or fluoxetine) 20 mg daily, to which **moclobemide** up to 600 mg daily was added, indicated that these combinations were possibly effective.[33] An extension of this study with 50 patients is reported elsewhere.[22] However, a range of adverse effects occurred in some patients, the clearest one being insomnia, and serotonin syndrome was seen in one patient.[22,33] Conversely, serotonin syndrome was not seen in another study, where low initial doses and gradual up-titration of both paroxetine and **moclobemide** was used.[20] Two possible cases of mild serotonin syndrome occurred in women taking **moclobemide** within 2 to 24 hours of also starting paroxetine.[34] Similarly, cases of severe serotonin syndrome have been reported with overdoses of **moclobemide** and paroxetine.[35,36]

(e) Sertraline

In one study, 31 severely ill patients were given **moclobemide** 35 to 800 mg daily with SSRIs, including sertraline 25 to 100 mg daily, initially using lower than usual starting doses of both drugs, and then gradually titrating them slowly upwards. The other SSRIs used were fluoxetine, fluvoxamine and paroxetine. There was no evidence of serotonin syndrome.[20] An open study in 5 depressed patients given **moclobemide** 150 to 600 mg daily and sertraline 25 to 200 mg daily found improvements ranging from minimal to complete remission. Insomnia was the commonest adverse effect (treated with trazodone) but none of the patients showed any evidence of serotonin syndrome.[30] However, one case of possible serotonin syndrome occurred in a woman who took an overdose of **moclobemide** and sertraline,[34] and another possible case occurred after an overdose of **moclobemide**, **citalopram**, sertraline and sumatriptan.[16] Similarly, a fatality has been reported with an overdose of **moclobemide**, sertraline and pimozide, with blood levels suggesting that none of the drugs individually would have been fatal.[37]

(f) Unspecified SSRIs

Serotonin toxicity (serotonin syndrome) occurred in 5 patients who took an overdose of **moclobemide** with an SSRI (specific drugs not mentioned). In this analysis of **moclobemide** overdoses, the risk of developing serotonin toxicity was significantly increased in patients who also took another serotonergic drug (52% (11 of 21 patients) who also took another serotonergic drug, compared with 3% taking moclobemide alone). Of the 11 cases mentioned 5 patients were taking SSRIs.[38]

Mechanism

MAO-A is involved in the metabolism of serotonin, so the combined use of MAOIs or RIMAs with SSRIs may lead to excessive serotonin levels, which can result in serotonin syndrome. For more information see 'serotonin syndrome', (p.9).

Importance and management

A reasonably well documented and established interaction. Severe, sometimes fatal interactions (serotonin syndrome or similar) have occurred when MAOIs were given with fluoxetine or sertraline. The incidence appears to be low, possibly as the combined use of any MAOI and any SSRI is contraindicated. In addition, at least 2 weeks should elapse between stopping any MAOI and starting any SSRI to allow for the effects of the MAOI to diminish. Moreover, the manufacturers of each SSRI give guidance on the appropriate intervals that should be left between stopping the SSRI and starting an MAOI; that is, 14 days for sertraline,[39,40] seven days for citalopram,[41] **escitalopram**,[42] fluvoxamine[43] or paroxetine[44] (14 days in the US),[45-47] and at least 5 weeks for fluoxetine, with an even longer interval if long-term or high-dose fluoxetine has been used.[48,49]

The RIMAs (e.g. moclobemide) also have serotonergic effects, and so they are unlikely to be any safer than the non-selective MAOIs in regard to interactions with SSRIs. The few cases of serotonin syndrome cited with therapeutic doses of this combination confirm that it is not necessarily safe. The combination may be particularly problematic in overdose, and negates the generally benign course of moclobemide overdose alone. It should be noted that the manufacturer of moclobemide contraindicates its use with SSRIs.[50] Because the effects of moclobemide are readily reversible, only one day need elapse between stopping moclobemide and starting an SSRI. However, if stopping an SSRI and starting moclobemide, the same intervals are required as for the irreversible MAOIs.

For the management of serotonin syndrome, see Importance and management under 'MAOIs or RIMAs + Tricyclic and related antidepressants', p.1391.

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MAOIs or RIMAs + Sympathomimetics; Amfetamines and related drugs

The concurrent use of non-selective MAOIs with amfetamines and related drugs can result in a potentially fatal hypertensive crisis and/or serotonin syndrome. Interactions have been reported for amfetamine, dexamfetamine, metamfetamine, and methylphenidate. Interactions have also been reported with the illicit drug ecstasy (MDMA, methylenedioxymethamfetamine) when taken with phenelzine or moclobemide.

Clinical evidence

A. MAOIs

(a) Amfetamines

A 30-year-old depressed woman who was taking **phenelzine** 15 mg three times daily and trifluoperazine 2 mg at night, acquired some **dexamfetamine sulfate** tablets from a friend and took 20 mg. Within 15 minutes she complained of severe headache, which she described as if "her head was bursting". An hour later her blood pressure was 150/100 mmHg. Later she became comatose with a blood pressure of 170/100 mmHg and died. A postmortem examination revealed a brain haemorrhage.[1]

This interaction has also been reported with:

- **Amfetamine** (single intravenous or oral dose) with **phenelzine**[2,3] or tranylcypromine.[4]
- **Amfetamine** and **dexamfetamine** with phenelzine.[5,6]
- **Metamfetamine** (single intravenous dose) with **isocarboxazid**,[7,8] **phenelzine**,[7,9] or tranylcypromine.[7,10]

A woman who had been addicted to high-dose **dexamfetamine**/amobarbital was hospitalised and had the **dexamfetamine**/amobarbital withdrawn. Five days later she was given a single dose of **tranylcypromine** and within an hour had a 20-minute episode of hypertension, tachycardia, headache, sweating, lacrimation and altered consciousness, which abated without treatment. She had similar attacks at 2-hourly intervals over about 5 days, which gradually became milder and shorter.[11]

Extreme hyperpyrexia, apparently without hypertension, has been described in a woman who took **tranylcypromine** with **dexamfetamine**/amobarbital. She developed progressive agitation, diaphoresis, hyperkinesis, opisthotonus, coma and convulsions, but recovered following the use of an ice bath and other supportive measures.[12,13]

(b) Dexfenfluramine or Fenfluramine

A woman taking **phenelzine** developed severe headache, neck stiffness and nausea within an hour of taking fenfluramine 20 mg, and then collapsed and remained stuporous for about 4 hours. This reaction was considered similar to that seen with MAOIs and amfetamines.[14]

The manufacturer recommended that fenfluramine should not be used in patients with a history of depression, or during treatment with antidepressants (especially the MAOIs), and there should be an interval of 3 weeks between stopping the MAOIs and starting fenfluramine.[15] The manufacturer of dexfenfluramine similarly contraindicated its use with or within 2 weeks of stopping an MAOI,[16] and advised waiting 3 weeks between stopping dexfenfluramine and starting an MAOI. This is due to the potential risk of the serotonin syndrome,[17,18] which has rarely occurred with the concurrent use of two or more serotonergic drugs (see 'serotonin syndrome', (p.9)). The manufacturer of dexfenfluramine and fenfluramine had found no clinical evidence of serious problems with either of these drugs when taken with MAOIs,[19] so that the published warnings about possible interactions would appear to be based on theoretical considerations.

Note that dexfenfluramine and fenfluramine have generally been withdrawn because their use was found to be associated with a high incidence of abnormal echocardiograms indicating abnormal functioning of heart valves.

(c) Ecstasy (MDMA, methylenedioxymethamfetamine)

Marked hypertension, diaphoresis, altered mental status and hypertonicity (slow forceful twisting and arching movements) occurred in one patient taking **phenelzine** with ecstasy.[20] Increased muscle tension, decorticate-like posturing (arms, wrists and fingers bent inwards and legs extended), fever, tachycardia and coma occurred in another patient taking **phenelzine**, 15 minutes after drinking juice containing ecstasy.[21] Both patients recovered.[20,21]

(d) Methylphenidate

A patient started taking **tranylcypromine**, then 4 days later methylphenidate was added. After 15 days of concurrent use he had a hypertensive crisis and both drugs were stopped.[22] In a study of the use of **phenelzine** as an antagonist to stimulants, 3 patients also took oral or intravenous methylphenidate and all three experienced moderate to severe headache.[6] An episode of symptoms consistent with serotonin syndrome occurred in a man taking **isocarboxazid** and trazodone, 2 months after the dose of these drugs was increased and methylphenidate was added. He had experienced two similar episodes 4 and 8 weeks previously, which had each resolved spontaneously over 12 hours. All three drugs have serotonergic properties and were thought to have contributed to the reaction.[23]

Conversely, a man taking **tranylcypromine** for depression was successfully treated with methylphenidate for attention deficit/hyperactivity disorder (ADHD). He was given methylphenidate 2.5 mg daily, which was very gradually increased over a number of months to 45 mg daily. He was successfully treated with the combination for 6 months and periodic blood pressure measurements did not change significantly from baseline.[24] Another similar case of uneventful concurrent use has been described with **phenelzine** and methylphenidate.[25] No cases of hypertensive crisis were seen in 4 patients taking **tranylcypromine** or **phenelzine** when treated concurrently with methylphenidate for periods of 6 to 30 months.[26]

B. RIMAs

Four patients died after taking **moclobemide** and **ecstasy** (MDMA, methylenedioxymethamfetamine). The clinical evidence is limited, but in each

case the forensic pathologist concluded that the cause of death was the combined use of these drugs. It was suggested that what happened is consistent with the serotonin syndrome, although the evidence is fairly slim. Two patients had taken maximum therapeutic doses and two moderate overdoses of **moclobemide**. Note that **moclobemide** had not been prescribed to any of them. Post-mortem analysis also found the presence of **dextromethorphan** in one patient, which was thought to have contributed,[27] see also 'MAOIs or RIMAs + Dextromethorphan', p.1375.

Mechanism

The hypertensive reaction can be attributed to overstimulation of the adrenergic receptors of the cardiovascular system.[28] During treatment with non-selective MAOIs, large amounts of noradrenaline (norepinephrine) accumulate at adrenergic nerve endings not only in the brain, but also within the sympathetic nerve endings, which innervate arterial blood vessels. Stimulation of these latter nerve endings by sympathomimetic amines with indirect actions causes the release of the accumulated noradrenaline and results in the massive stimulation of the receptors. An exaggerated blood vessel constriction occurs and the blood pressure rise is proportionately excessive. Intracranial haemorrhage can occur if the pressure is so high that a blood vessel ruptures.[1]

Some of the reactions may also possibly be related to serotonin syndrome. Amfetamines act by releasing serotonin (and possibly also dopamine) from neurones in the brain, so that increased stimulation of the serotonin receptors occurs. This possibly explains their mood-modifying effects. MAOIs prevent the breakdown of serotonin within neurones so that more serotonin is available for release, and in excess this can apparently result in the toxic and even fatal serotonin syndrome. The RIMAs (such as moclobemide) appear to behave like the older non-selective MAOIs in this context.

Importance and management

The hypertensive reaction is a very well-documented, serious, and potentially fatal interaction, whereas the serotonin syndrome appears to be rarer. Patients taking any of the non-selective MAOIs should not normally take amfetamines, or related drugs such as methylphenidate. A possible exception to this prohibition is that under very well controlled conditions dexamfetamine and methylphenidate may sometimes be effectively (and apparently safely) used with MAOIs for refractory depression,[25,26,29] or ADHD.[24] Direct evidence implicating central stimulants such as 'mazindol', (p.1378), and 'modafinil', (p.1379), appears to be limited. Interactions with other central stimulants such as **diethylpropion**, **pemoline**, **phendimetrazine**, and **phenmetrazine** seem not to have been documented, but on the basis of their known pharmacology their concurrent use with the MAOIs should be avoided. Patients taking MAOIs should be warned to avoid the illicit use of amfetamines and ecstasy. It would also be prudent to avoid the use of moclobemide with amfetamines and related drugs, although the incidence of the interactions with moclobemide is unlikely to be as great as that seen with the non-selective MAOIs. In the cases with ecstasy, it seems likely that high doses of moclobemide were used to try to enhance the actions of the ecstasy, but these cases, nevertheless, show that combined use is potentially life threatening.

Treatment

For a brief mention of the treatment of hypertensive crisis, see Importance and Management under 'MAOIs or RIMAs + Sympathomimetics; Indirectly-acting', p.1388. For the management of fever and other symptoms of serotonin syndrome, see Importance and management under 'MAOIs or RIMAs + Tricyclic and related antidepressants', p.1391.

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MAOIs or RIMAs + Sympathomimetics; Beta-agonist bronchodilators

An isolated case of tachycardia and apprehension occurred in an asthmatic taking phenelzine after salbutamol (albuterol) was added. Hypomania was seen in another asthmatic taking phenelzine when inhaled isoetarine was added. Hypertensive crisis occurred in a woman taking toloxatone and phenylephrine when she was given [oral] terbutaline.

Clinical evidence

(a) MAOIs

A report briefly describes a case of tachycardia and apprehension in a patient taking **phenelzine** when **salbutamol** (**albuterol**) was started (route of administration not stated).[1] Hypomania has been described in a patient taking **phenelzine** in the few weeks after starting inhaled **isoetarine** 680 micrograms up to every 4 hours.[2]

(b) RIMAs

A 72-year old woman taking long-term levothyroxine, **toloxatone** 400 mg daily (for 2 months), and **phenylephrine** (for 3 weeks) developed episodes of hypertension, sweating, tachycardia, and headache within 3 days after starting to take [oral] **terbutaline** 10 mg daily. She had extremely high plasma catecholamine levels. All drugs were stopped on admission to hospital and she recovered over 2 to 3 days.[3] An interaction between phenylephrine and toloxatone may have contributed to the effects seen. Consider also, 'MAOIs or RIMAs + Sympathomimetics; Phenylephrine', p.1390.

Mechanism

Note that drugs with directly-acting sympathomimetic effects (of which beta agonists are an example) do not normally interact to cause hypertension with MAOIs, see 'sympathomimetics; directly-acting', (p.1388). However, phenylephrine (which has some indirect actions, see 'sympathomimetics; phenylephrine', (p.1390)) may have contributed to the reaction between toloxatone and terbutaline, and the fact that terbutaline seems to have been given orally would also have contributed. The reaction resulting in hypomania is not understood.

Importance and management

These appear to be isolated cases, and are possibly not of general importance. Bear them in mind in the event of an unexpected response to treatment.

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MAOIs or RIMAs + Sympathomimetics; Directly-acting

The pressor effects of adrenaline (epinephrine), isoprenaline (isoproterenol), noradrenaline (norepinephrine) and methoxamine may be unchanged or only moderately increased in patients taking MAOIs. There is limited evidence that the increase may be somewhat greater in those who show a significant hypotensive response to the MAOI. Moclobemide does not appear to interact.

Clinical evidence

(a) MAOIs

In a randomised, placebo-controlled study in 12 healthy subjects, **phenelzine** 15 mg three times daily for 7 days had no effect on the dose of intravenous **noradrenaline** (**norepinephrine**) required to raise the systolic blood pressure by 25 mmHg. In addition, **phenelzine** had no effect on the diastolic blood pressure rises and heart rate reductions seen with **noradrenaline**. In this study, **phenelzine** itself had no effect on blood pressure or heart rate.[1]

Similarly, in an earlier study in two healthy subjects given **phenelzine** 15 mg three times daily and two given **tranylcypromine** 10 mg three times daily for 7 days, there was no significant change in pressor response to intravenous **adrenaline** (**epinephrine**) or **isoprenaline** (**isoproterenol**) after treatment with the MAOI. However, the tachycardia caused by **isoprenaline** was antagonised by the MAOIs (109 bpm with the MAOI versus 127 bpm without). No clinically significant potentiation of the pressor effect of **noradrenaline** was seen, although one of the subjects taking **tranylcypromine** had a twofold increase in the pressor response in the mid-range of **noradrenaline** concentrations infused, but not in the upper or lower ranges. None of these 4 subjects had a change in blood pressure or heart rate caused by the MAOI alone.[2] In yet another study in 3 healthy subjects given **tranylcypromine** for 8 to 14 days, the effects of intravenous **noradrenaline** were slightly increased, while with intravenous **adrenaline** a moderate two to fourfold increase in the effects on heart rate and diastolic pressure took place, but a less marked increase in systolic pressure was seen. Intravenous **isoprenaline** behaved very much like **adrenaline**, but there was no enhancement of systolic pressure. This study did not state the effect of the MAOI alone on blood pressure.[3]

A patient using 1% **adrenaline** eye drops twice daily had no increase in blood pressure or heart rate when given **tranylcypromine** 20 mg, rising to 50 mg daily.[4] Another patient taking **phenelzine** presented with severe anaphylaxis after taking two doses of flucloxacillin, and was initially treated unsuccessfully with hydrocortisone, chlorphenamine and ranitidine because of concerns about using **adrenaline** with MAOIs. However, as her condition worsened she was given two 100-microgram boluses of intravenous **adrenaline**, with rapid improvement. No adverse reaction was noted.[5] In another study, one healthy subject given **phenelzine** for 8 days experienced a marked reduction in blood pressure, but showed no significant changes in pressor response to **noradrenaline**.[6]

In contrast, in a study in hypertensive patients who had postural hypotension after being given either **pheniprazine** (a formerly investigational older MAOI; 6 patients) or **tranylcypromine** (one patient), the dose of **noradrenaline** required to produce a 25 mmHg rise in systolic pressure was reduced by 62 to 87%. In three of these patients taking **pheniprazine** the dose of **methoxamine** was reduced by 61 to 70%, compared with that required in the absence of an MAOI. Three patients were later given **nialamide**: augmentation of the pressor response of **noradrenaline** or **methoxamine** only occurred in the one patient who had developed postural hypotension.[7]

(b) RIMAs

In a randomised, placebo-controlled study in 12 healthy subjects, **moclobemide** 100 mg three times daily for 7 days had no effect on the dose of intravenous **noradrenaline** (**norepinephrine**) required to raise the systolic blood pressure by 25 mmHg. In addition, **moclobemide** had no effect on the diastolic blood pressure rises and heart rate reductions seen with **noradrenaline**. In this study, **moclobemide** itself had no effect on blood pressure or heart rate.[1] A review paper also briefly mentions that **moclobemide** 600 mg daily for 3 weeks had no relevant effect on the heart rate response to intravenous **isoprenaline** (**isoproterenol**).[8]

Mechanism

These sympathomimetic amines act directly on the receptors at the nerve endings, which innervate arterial blood vessels, so that the presence of the MAOI-induced accumulation of noradrenaline within these nerve endings would not be expected to alter the extent of direct stimulation (contrast 'Sympathomimetics; indirectly-acting', (p.1388)). The enhancement seen in those patients whose blood pressure was lowered by the MAOI might possibly be due to an increased sensitivity of the receptors, which is seen if the nerves are cut, and is also seen during temporary 'pharmacological severance'.

Importance and management

The overall picture is that no clinically relevant enhancement of the effects of adrenaline (epinephrine), isoprenaline (isoproterenol), or noradrenaline (norepinephrine) occurs in patients taking MAOIs, although some uncertainty remains about those who show MAOI-induced hypotension (see below). The authors of three of the reports cited[2-4] are in broad agreement that problems are unlikely to occur, and others consider that intravenous adrenaline may be used in life-threatening situations in patients taking MAOIs, albeit with caution.[5] Others also consider that adrenaline in eye drops or adrenaline as a component of local anaesthesia in dental and other procedures may be used in patients receiving MAOIs,[4,9] and that there is no justification for the continued listing of an interaction between MAOIs and local anaesthetics with vasoconstrictors in US prescribing information.[9] It is worth noting that there are no case reports of interactions with these drugs.

The situation in patients who show a reduced blood pressure due to the use of an MAOI is less clear. One early study[7] found an increase in the pressor effects of noradrenaline and methoxamine in hypertensive patients who had developed orthostatic hypotension when taking pheniprazine or tranylcypromine. Bear this possibility in mind.

Moclobemide does not appear to alter the pressor response to noradrenaline.

Other directly-acting sympathomimetics, such as the 'beta-agonist bronchodilators', (p.1387) do not appear to interact. However, in contrast, the directly-acting sympathomimetic 'phenylephrine', (p.1390), may interact, but this is possibly due to an inhibition of its metabolism.

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MAOIs or RIMAs + Sympathomimetics; Indirectly-acting

The use of indirectly-acting sympathomimetic amines concurrently with, and for 2 weeks after stopping, non-selective MAOIs can result in a potentially fatal hypertensive crisis. Note that these amines are commonly in many proprietary cough, cold and influenza preparations (e.g. ephedrine, phenylpropanolamine and pseudoephedrine), or for their vasoconstrictor effects in migraine (e.g. isometheptene). Indirectly-acting amines are also used parenterally for treating hypotension occurring during spinal anaesthesia (e.g. ephedrine, mephentermine, metaraminol). Potentially serious interactions have also been seen with moclobemide and indirectly-acting sympathomimetics.

Clinical evidence

(a) MAOIs

A study in 3 healthy subjects, given **phenelzine** 45 mg or **tranylcypromine** 30 mg daily for 5 to 14 days, found that the blood pressure rise following oral **ephedrine** 30 mg was enhanced. The maximal increase in mean arterial pressure was 22 mmHg (compared with 4 to 6 mmHg without the MAOI). A similar increase was seen up to 10 days after discontinuation of the MAOI. A similar increase in blood pressure was also seen in one of the subjects given intravenous **ephedrine** 2 mg per minute for 6 minutes.[1] In another subject given **tranylcypromine** 30 mg daily for 20 to 30 days, **phenylpropanolamine** in capsules or a linctus preparation caused a rapid and marked rise in blood pressure to 210/140 mmHg within 2 hours, necessitating the use of phentolamine to reverse the effect.[2] Slow-release **phenylpropanolamine** caused a smaller and more gradual rise to 160/100 mmHg over 2 hours.[2] Similarly, the pressor effect of intravenous **phenylpropanolamine** was potentiated by about four to fivefold (systolic) and three to tenfold (diastolic) in 3 subjects given **tranylcypromine** 30 mg daily for 8 to 14 days, and the reflex bradycardia was potentiated by about 2.5- to 6-fold.[3]

Numerous case reports describe similar rapid and serious rises in blood pressure, accompanied by tachycardia, chest pains and severe occipital headache when MAOIs were given with indirectly-acting sympathomimetics. Other symptoms that have occurred include neck stiffness, flushing, sweating, nausea, vomiting, hypertonicity of the limbs, and sometimes epileptiform convulsions. Fatal intracranial haemorrhage, cardiac arrhythmias and cardiac arrest have resulted.

This interaction has been reported between:

- oral **ephedrine** and **nialamide**[4]
- oral **isometheptene mucate** and **phenelzine**[5]
- intravenous **mephentermine** and **phenelzine**[6]
- intramuscular **metaraminol** and **pargyline**[7]
- oral **phenylpropanolamine** and **mebanazine**,[8,9] **pargyline**,[10] or **phenelzine**[8,9,11-14]
- and oral **pseudoephedrine** and **iproniazid**.[15]

Tachycardia and *hypotension*, then pyrexia has been described in a woman who took a single *Do-Do* tablet (**ephedrine**, caffeine, theophylline) the day after stopping **phenelzine**.[16] Similarly, fatal hyperpyrexia without hypertension occurred in a man taking **tranylcypromine**/trifluoperazine when he was given oral **ephedrine**,[17] although switching his MAOI without a full washout period may have caused, or contributed to, this reaction[18] (see 'MAOIs + MAOIs or RIMAs', p.1378). A woman taking **phenelzine** developed bradycardia of 40 bpm after taking one tablet of *Sinutab* (without codeine),[19] which probably contained **pseudoephedrine**.

(b) RIMAs

No interaction was seen in subjects taking **brofaromine** 75 mg twice daily for 10 days when given 75 mg of slow-release **phenylpropanolamine** (*Acutrim Late Day*), but immediate-release **phenylpropanolamine** in gelatin capsules caused a 3.3-fold increase in pressor sensitivity.[20] The pressor effects of high-dose oral **ephedrine** (two doses of 50 mg with a 4-hour interval) in 11 healthy subjects taking **moclobemide** 300 mg twice daily were increased about three to fourfold, and this resulted in an increase in palpitations and headache.[21,22]

Mechanism

The reaction can be attributed to over-stimulation of the adrenergic receptors of the cardiovascular system. During treatment with non-selective MAOIs, large amounts of noradrenaline (norepinephrine) accumulate at adrenergic nerve endings not only in the brain, but also within the sympathetic nerve endings, which innervate arterial blood vessels. Stimulation of these latter nerve endings, by sympathomimetic amines with indirect actions, causes the release of the accumulated noradrenaline and results in the massive stimulation of the receptors. An exaggerated blood vessel constriction occurs and the blood pressure rise is proportionately excessive. Intracranial haemorrhage can occur if the pressure is so high that a blood vessel ruptures. Directly-acting sympathomimetics do not cause this severe effect, see 'MAOIs or RIMAs + Sympathomimetics; Directly-acting', p.1388.

Importance and management

(a) MAOIs

A very well-documented, serious, and potentially fatal interaction. Patients taking any of the MAOIs should not normally take any sympathomimetic amine with indirect activity. These include ephedrine, isometheptene mucate, mephentermine, metaraminol, phenylpropanolamine and pseudoephedrine. Direct evidence implicating **methylephedrine** and **pholedrine** seems not to have been documented, but on the basis of their known pharmacology their concurrent use with the MAOIs should be avoided. There also appears to be no documented interactions between the MAOIs and **dopamine** (a sympathomimetic with both direct and indirect actions). Nevertheless, the manufacturers predict that the effects of dopamine will be potentiated. They suggest that patients who have been taking an MAOI should be given a starting dose of dopamine that is one-tenth of the usual dose.[23] Similarly, there appears to be a lack of data regarding **dopexamine**, possibly because the concurrent use of MAOIs is contraindicated.[24]

Note that some of the indirectly-acting amines, including ephedrine, phenylpropanolamine and pseudoephedrine, are used as vasoconstrictor decongestants in numerous oral non-prescription cough, cold and influenza preparations. Isometheptene is used in non-prescription analgesic preparations for migraine. Patients taking MAOIs should be strongly warned not to take any of these drugs concurrently or for 2 weeks after stopping their MAOI. Also, note that serious interactions have occurred because of confusion between non-prescription products with very similar names that contain different active ingredients.[13]

Physicians should also avoid the use of indirectly-acting vasoconstrictor amines such as ephedrine, mephentermine and metaraminol for reversing hypotension during spinal anaesthesia in patients taking MAOIs or patients who have stopped an MAOI within the previous 2 weeks.

(b) RIMAs

The data with high-dose ephedrine show that moclobemide is not free of this interaction, and the manufacturer of moclobemide[25] advises avoiding sympathomimetics such as ephedrine, **pseudoephedrine** and **phenylpropanolamine**. It would also be prudent to avoid moclobemide with any of the other indirectly-acting sympathomimetics cited here, although the severity of the interactions with moclobemide is unlikely to be as great as that seen with the MAOIs. For example, ephedrine and phenylephrine have been successfully and uneventfully used in the presence of moclobemide (omitted on the day of surgery) during anaesthesia to control hypotension.[26]

(c) Treatment

Hypertensive reactions have been controlled by intravenous phentolamine, phenoxybenzamine, intramuscular chlorpromazine, labetalol or sublingual nifedipine. The manufacturers of phenelzine state that on the basis of present evidence, slow intravenous injection of phentolamine is recommended.[27,28] However, it is advisable to refer to current guidelines on the management of hypertensive crises for up-to-date advice.

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MAOIs or RIMAs + Sympathomimetics; Phenylephrine

The concurrent use of oral phenylephrine and the non-selective MAOIs can result in a potentially life-threatening hypertensive crisis. Phenylephrine is commonly found in non-prescription cough, cold and influenza preparations. The effects of parenteral phenylephrine may be approximately doubled by MAOIs. Some interaction occurs between phenylephrine and the RIMAs moclobemide or brofaromine, but the blood pressure response appears to be much smaller than that seen with the non-selective MAOIs.

Clinical evidence

(a) MAOIs

A study in 3 healthy subjects, given **phenelzine** 45 mg or **tranylcypromine** 30 mg daily for 7 days, found that the blood pressure rise following oral phenylephrine was markedly enhanced. On 2 of 3 occasions when 45 mg of phenylephrine was given orally, the rise in blood pressure became potentially disastrous and had to be reversed with phentolamine. On these two occasions the maximal increase in mean arterial pressure was 67 mmHg (compared with 1 or 11 mmHg without the MAOI). On the other occasion, the maximal increase in mean arterial pressure was 48 mmHg. The rise in blood pressure was accompanied by a severe headache. With 3 and 10 mg of phenylephrine, the maximal increase was 7 mmHg and 20 mmHg, respectively. After intravenous phenylephrine 3 mg was given over 20 minutes, the maximal increase in mean arterial pressure was 45 mmHg, compared with 23 mmHg without an MAOI.[1]

Another study describes a similar 2- to 2.5-fold increase in the pressor effects of *intravenous* phenylephrine following the use of **phenelzine** or **tranylcypromine**.[2]

A patient taking **tranylcypromine** who developed hypotension (40/0 mmHg) during surgery had an exaggerated pressor response (250/140 mmHg) when an intravenous infusion of phenylephrine 4 mg/500 mL was started.[3] However, in another report, repeated 100-microgram doses of intravenous phenylephrine were successfully used to treat hypotension in a patient taking an MAOI, without any hypertensive reaction.[4]

A case report of hypertension that was initially attributed to phenylephrine was later corrected to pseudoephedrine.[5]

(b) RIMAs

No clinically important interaction occurred in healthy subjects taking **brofaromine** 75 mg twice daily when they were given a single 2.5-mg dose of phenylephrine as nasal drops.[6] However, higher doses (exact amount not stated) did produce a blood pressure response,[6] with a maximum recorded diastolic blood pressure of 100 mmHg.

A study in 7 healthy subjects found that **moclobemide** 100 mg three times daily for one week had no effect on the increase in blood pressure induced by intravenous phenylephrine.[7] Another study reported similar results.[8] However, when **moclobemide** was given in a dose of 200 mg three times daily for up to 3 weeks the blood pressure response to infusions of phenylephrine was increased by up to 1.8-fold.[7] In one patient taking **moclobemide** (dose withheld on the morning of surgery), ephedrine and phenylephrine were used successfully and uneventfully to control hypotension during anaesthesia.[9]

A case of life-threatening hypertension[10] occurred in a patient taking **toloxatone**, non-prescription phenylephrine. Terbutaline was also taken, and may have contributed to the effects described, see 'MAOIs or RIMAs + Sympathomimetics; Beta-agonist bronchodilators', p.1387.

Mechanism

If given by mouth phenylephrine is used in large doses because much of it is destroyed by MAO in the gut and liver, and only a small amount gets into the general circulation. If MAO is inhibited, most of the oral dose escapes destruction and passes freely into circulation, hence the gross enhancement of the pressor effects. Phenylephrine has mainly direct sympathomimetic activity, but it may also have some minor indirect activity as well, which would be expected to result in the release of some of the MAOI-accumulated noradrenaline (norepinephrine) at adrenergic nerve endings (see also 'MAOIs or RIMAs + Sympathomimetics; Indirectly-acting', p.1388). This might account for the increased response to phenylephrine given parenterally.

Importance and management

The interaction between the MAOIs and oral phenylephrine is established, serious and potentially life-threatening. Phenylephrine commonly occurs in oral non-prescription cough, cold and influenza preparations, so patients should be strongly warned about them. Whether the effects of nasal drops and sprays and eye drops are also enhanced is uncertain, but it would be prudent to avoid them until they have been shown to be safe (note that one manufacturer of phenylephrine eye drops[11] contraindicates MAOIs). The response to parenteral phenylephrine is also approximately doubled, so that a dosage reduction is necessary if it is given to a patient taking an MAOI.

The few studies that are available suggest that any interaction with RIMAs is less severe than that with MAOIs, but this needs confirmation.

Treatment

These hypertensive reactions have been controlled by intravenous phentolamine,[1] chlorpromazine, or nifedipine.[12] However, it is advisable to refer to current guidelines on the management of hypertensive crises for up-to-date advice. In the US, the manufacturers of phenelzine advise intravenous **phentolamine** 5 mg, given slowly to avoid excessive hypotension.[13]

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11. Minims Phenylephrine hydrochloride 2.5%. Bausch & Lomb UK Ltd. UK Summary of product characteristics, September 2006.
12. Golwyn DH, Weinstock RC. MAOIs, OTC drugs, and hypertensive crisis. *J Clin Psychiatry* (1990) 51, 213.
13. Nardil (Phenelzine sulfate). Pfizer Inc. US Prescribing information, August 2007.

MAOIs + Trazodone

There have been isolated reports of serotonin syndrome in patients receiving trazodone and MAOIs, usually in association with other serotonergic drugs.

Clinical evidence, mechanism, importance and management

A case report describes a patient taking trazodone 50 mg daily and **isocarboxazid** 20 mg daily, who developed symptoms of serotonin syndrome and was hospitalised 2 months after dose increases to trazodone 150 mg daily and isocarboxazid 30 mg daily and the addition of methylphenidate.[1]

The US manufacturer says that, due to the absence of clinical experience, if MAOIs are discontinued shortly before or are to be given concurrently with trazodone, concurrent use should be initiated cautiously with a gradual increase in dosage until optimum response is achieved.[2] However, the UK manufacturer of trazodone says possible interactions with MAOIs have occasionally been reported, and do not recommend concurrent use. They say trazodone should not be given within 2 weeks of stopping an MAOI and MAOIs should not be taken within one week of stopping trazodone.[3]

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2. Desyrel (Trazodone hydrochloride). Bristol-Myers Squibb Company. US Prescribing information, February 2009.
3. Molipaxin Capsules (Trazodone hydrochloride). Sanofi-Aventis. UK Summary of product characteristics, August 2009.

MAOIs or RIMAs + Tricyclic and related antidepressants

Because of the very toxic and sometimes fatal reactions (the serotonin syndrome or similar) that have occurred in patients taking either MAOIs or RIMAs with tricyclic antidepressants, concurrent use is regarded as contraindicated in all but rare circumstances, and a suitable washout interval is needed when switching between MAOIs or RIMAs and tricyclics.

Clinical evidence

A. MAOIs

The toxic reactions that occur when the tricyclics are given with MAOIs have included (with variations) sweating, flushing, hyperpyrexia, restlessness, excitement, tremor, muscle twitching and rigidity, convulsions and coma. Two illustrative examples:

A woman who had been taking **tranylcypromine** 10 mg twice daily for about 3 weeks, stopped taking it 3 days before she took a single tablet of **imipramine**. Within a few hours she complained of an excruciating headache, and soon afterwards lost consciousness and started to convulse. The toxic reactions manifested were a temperature of 40.6°C, pulse rate of 120 bpm, severe extensor rigidity, carpal spasm, opisthotonos and cyanosis. She was treated with amobarbital and phenytoin, and her temperature was reduced with alcohol-ice-soaked towels. The treatment was effective and she recovered.[1]

In a recent case, a patient was given **imipramine** 75 mg daily for 7 weeks with the addition of lithium for the last 3 weeks. These drugs were discontinued and after one week of washout he started **tranylcypromine**, which was gradually increased to 50 mg twice daily. After 2 weeks at this dose, he received a single 225-mg dose of **imipramine** in error. Four hours later his condition deteriorated rapidly. He was agitated, confused, with severe rigidity, myoclonic jerks, hyperthermia, hypertension and tachycardia, and 2 hours later had a cardiac and respiratory arrest. He was resuscitated and given midazolam, pancuronium, dantrolene sodium, and a cooling mattress. The following day he had a sudden fall in blood pressure, and was eventually pronounced brain dead, and artificial respiration was terminated.[2]

Similar reactions have been recorded with oral therapeutic doses of:

- **amitriptyline** with **phenelzine**[3,4]
- **clomipramine** with **phenelzine**[5,6] or **tranylcypromine** (with or without trifluoperazine)[7-9]
- **desipramine** with **phenelzine**[10]
- **imipramine** with **iproniazid**,[11] **isocarboxazid**,[11] **pargyline**,[12] **phenelzine**[13-15] or **tranylcypromine**.[11,16]

There have been a number of fatalities.[7,8,10,17] Reactions have also occurred when intramuscular **imipramine** was given with **phenelzine**.[18-20] In some instances the drugs were not taken together, but were substituted without a washout period in between.[5,16] In some other reports there was an overdose of one or both drugs,[21-24] and/or the presence of other potentially interacting drugs.[22,23] There are many more reports of these interactions than are listed here: those published prior to 1977 have been extensively reviewed elsewhere.[15,25,26]

Three patients with bipolar disorder developed mania when given **isocarboxazid** and **amitriptyline**.[27]

A case report describes hypertension (blood pressure 180/125 mm/Hg) in a patient who took **mianserin** 2 weeks after stopping **tranylcypromine**. The blood pressure normalised when the mianserin was stopped.[28] In contrast, one report suggested that the use of **mianserin** with **tranylcypromine** was safe and effective in 39 patients. However, one patient, who continued to take both drugs after the study period, and who was also taking methyldopa, died suddenly.[29]

In contrast, there are a number of other uncontrolled studies[30-32] and reviews[25,26] describing the beneficial use of an MAOI with a tricyclic antidepressant. In addition, one study has reported switching 178 patients from tricyclics to MAOIs with a washout period of 4 days or less. Of these patients, 63 were given the MAOI while still being tapered from the tricyclic, all without any apparent problems.[33] A study in 60 patients given **isocarboxazid** and **mianserin** found a faster onset of antidepressant activity than would have been expected from either drug alone, and did not identify any drug interactions. The authors state that subsequently 120 patients were given the combination without any notable adverse effects.[34] However, in a 6-week randomised double-blind study in patients with mild to moderate depression, giving **phenelzine** or **isocarboxazid** with **trimipramine** was less effective than giving **trimipramine** alone.[35] Similarly, in a smaller randomised open study, the combination of **amitriptyline** and **tranylcypromine** was no more effective than either drug alone.[36]

B. RIMAs

(a) Amitriptyline

Two small studies in healthy subjects and patients found no problems when **moclobemide** was given with, or 24 hours after, amitriptyline;[37,38] or when amitriptyline was given immediately after **moclobemide**.[37] However, a patient taking amitriptyline and clomipramine developed symptoms of serotonin syndrome within 30 minutes of taking a 300-mg dose of **moclobemide**, and died.[39]

Only a minor and clinically unimportant change in the pharmacokinetics of amitriptyline occurs in patients given **toloxatone**.[40]

(b) Clomipramine

A small study in healthy subjects found no problems when **moclobemide** was given 24 hours after clomipramine.[38] However, serotonin syndrome occurred in 3 patients when clomipramine was replaced by **moclobemide** without a washout period[41,42] or with only a 24-hour washout period;[43] and in another patient when **moclobemide** was replaced by clomipramine after only 12 hours.[44] A fatal case of serotonin syndrome occurred in a patient taking clomipramine and amitriptyline, with symptoms manifesting within 30 minutes of a 300-mg dose of **moclobemide**.[39] Two other patients developed fatal serotonin syndrome after taking moderate overdoses of **moclobemide** and clomipramine.[45] The serotonin syndrome has been reported in at least 8 other cases of **moclobemide** and clomipramine overdose.[46-52] Some of these involved other serotonergic drugs, including 'tramadol', (p.1382), 'fluoxetine, (p.1384)) and buspirone. Conversely, a case of an overdose of **moclobemide** and clomipramine resulted in no adverse effects except sinus tachycardia.[53] Note that the concurrent use of more than one serotonergic drug is thought to be a risk factor for the development of 'serotonin syndrome', (p.9).

(c) Desipramine

A small single dose study in healthy subjects found no problems when **moclobemide** was given with desipramine.[37]

(d) Doxepin

Serotonin toxicity (serotonin syndrome) occurred in a patient who took an overdose of **moclobemide** and doxepin. In this analysis of **moclobemide** overdoses, the risk of developing serotonin toxicity was significantly increased in patients who also took another serotonergic drug, of which this case with doxepin was one of 11 mentioned.[54]

(e) Imipramine

Serotonin syndrome occurred in a patient who had been taking **moclobemide** for about a month and imipramine (50 mg at night increased to 200 mg at night) for about 17 days.[55]

(f) Maprotiline

One study found a non-significant 25% rise in the serum levels of maprotiline (a tetracyclic antidepressant) in 6 patients also taking **moclobemide**. No serious toxic reactions were reported.[56]

(g) Trimipramine

One study found a 39% rise in serum trimipramine levels in 15 patients also taking **moclobemide**. No serious toxic reactions were reported.[56]

Mechanism

Not understood. One idea is that both drugs cause grossly elevated monoamine levels (5-HT, noradrenaline (norepinephrine)) in the brain, which 'spill-over' into areas not concerned with mood elevation. It may be related to, or the same as 'serotonin syndrome', (p.9). Of the tricyclics, clomipramine in particular is a potent inhibitor of serotonin uptake. Less likely suggestions are that the MAOIs inhibit the metabolism of the tricyclic antidepressants, or that active and unusual metabolites of the tricyclic antidepressants are produced.[25]

Importance and management

An established and fairly common interaction, but serious and life-threatening occurrences seem rare. If concurrent use is to be avoided, the following guidelines[57] are recommended:

- Tricyclic antidepressants should *not* be started until 2 weeks after treatment with MAOIs has been stopped (3 weeks if starting clomipramine or imipramine).
- MAOIs should *not* be started until at least 7 to 14 days after a tricyclic or related antidepressant has been stopped (3 weeks in the case of clomipramine or imipramine).
- Moclobemide has a short duration of action so no treatment-free period is required after it has been stopped before starting a tricyclic antidepressant. [Note that some recommend waiting 24 hours.[44]]
- Moclobemide should *not* be started until at least a week after a tricyclic antidepressant has been stopped.

No detailed clinical work has been done to find out precisely what sets the scene when the interaction does occur, but some general empirical guidelines have been suggested so that it can, as far as possible, be avoided if concurrent treatment is thought appropriate:[14,15,25,26,58]

- Treatment with both types of drug should only be undertaken by those well aware of the problems and who can undertake adequate supervision.
- Only patients refractory to all other types of treatment should be considered.
- Tranylcypromine, phenelzine, clomipramine and possibly imipramine appear to be high on the list of drugs that have interacted adversely. Giving clomipramine with tranylcypromine is particularly dangerous. Amitriptyline, trimipramine and isocarboxazid are possibly safer.
- Drugs should be given orally, not parenterally.
- It has been suggested that small doses should be given initially, increasing the levels of each drug, one at a time, over a period of 2 to 3 weeks to levels generally about half those used for each one individually.

Although information is limited, it seems that **maprotiline** (and therefore probably **mianserin**) will interact similarly. It would therefore seem advisable to follow the same precautions if these tetracyclic antidepressants are given with MAOIs.

Treatment of serotonin syndrome

In the management of serotonin syndrome, it is important to recognise the possibility of the syndrome early, as the patient's condition can rapidly deteriorate. Potentially precipitating drugs should be stopped and agitation should be managed with benzodiazepines. The intensity of therapy depends on the severity of the condition. Moderately ill patients may benefit from the administration of 5-HT antagonists such as cyproheptadine. The 5-HT antagonist, chlorpromazine, has also been used and can be beneficial, but should not be given if the patient is hypotensive or if neuroleptic malignant syndrome is a possible diagnosis. Hyperthermic patients should be immediately sedated, given neuromuscular blockers and intubated, since the rise in temperature is due to muscular activity. MAOI-induced hypotension should be managed with low doses of direct-acting sympathomimetics. Propranolol, bromocriptine, and dantrolene have been used, but these are no longer recommended. Because of the potential severity of the condition, a poison-control centre, clinical pharmacology service or medical toxicologist should be consulted for up-to-date advice.[59]

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MAOIs + Tryptophan

A number of patients have developed severe behavioural and neurological signs of toxicity (some similar to serotonin syndrome) after taking MAOIs with tryptophan. Fatalities have occurred.

Clinical evidence

A man taking **phenelzine** 90 mg daily developed behavioural and neurological toxicity within 2 hours of being given 6 g of tryptophan.[1] He had shivering and diaphoresis, his psychomotor retardation disappeared and he became jocular, fearful, and moderately labile. His neurological signs included bilateral Babinski signs (abnormal plantar reflexes), hyperreflexia, rapid horizontal ocular oscillations, shivering of the jaw, trunk and limbs, mild dysmetria and ataxia. The situation resolved on withdrawal of the drugs.[1]

Similar symptoms have been reported in other studies and cases. In an early study, giving tryptophan 20 to 50 mg/kg to 7 patients with hypertension taking an unknown MAOI, produced neurological effects including alcohol-like intoxication, drowsiness, hyperreflexia and clonus.[2] Similar symptoms with the addition of sweating, flushing and paraesthesias were described in 5 patients who were given tryptophan 30 mg/kg orally with **pargyline** or **isocarboxazid**.[3] In another study, in 14 depressed patients taking various MAOIs, 4 patients had muscular jactitation and hyperreflexia when they were also given tryptophan 2.5 to 5 g three times daily, and in 2 patients this was severe enough to discontinue the tryptophan.[4] Other reports describe similar symptoms when patients taking **phenelzine**[5,6] or **tranylcypromine**[7] were given tryptophan.

One patient taking **tranylcypromine** and lithium had transient episodes of toxicity with hyperthermia (and other symptoms of neurological toxicity) when the dose of tryptophan was increased to 2 g at night. He had a total of about 12 of these episodes over several weeks before tryptophan was stopped and the episodes ceased.[8] Malignant hyperpyrexia occurred in a patient taking **phenelzine** and tryptophan,[9] and fatal malignant hyperpyrexia occurred in two patients taking **phenelzine**, tryptophan and lithium.[10,11] Another patient who had been taking **tranylcypromine** for 2 weeks developed serious hyperpyrexia and muscular rigidity 2 days after starting tryptophan 6 g daily: she had discontinued levodopa with carbidopa one month previously.[12] Tryptophan may have contributed to a fatal case of serotonin syndrome in a patient switched from fluoxetine to **tranylcypromine**.[13]

Hypomania without neurological symptoms has occurred in 2 patients when tryptophan was added to **phenelzine** or **tranylcypromine**,[14] and delirium or disorientation, (sometimes with neurological symptoms) has occurred in 8 patients taking **tranylcypromine** within 2 to 4 days of starting tryptophan, or within one day of increasing the dose of tryptophan.[15] A further patient also experienced delirium within hours of tryptophan being added to her **phenelzine** treatment.[16]

In contrast, concurrent use has been reported as both safe and effective.[17]

Mechanism

Not understood. The reactions appear to be related to serotonin syndrome, which can occur with two or more serotonergic drugs (see 'serotonin syndrome', (p.9)). MAOIs may inhibit the metabolism of 5-hydroxytryptamine (serotonin), formed from tryptophan, so resulting in its accumulation.[3,9]

Importance and management

Information seems to be confined to the reports listed. Concurrent use can be effective in the treatment of depression,[17] but occasionally and unpredictably severe and even life-threatening toxicity occurs. The authors of one of the reports detailed above[1] recommend that patients taking MAOIs should start treatment with a low dose of tryptophan (500 mg). This should be gradually increased while monitoring the mental status of the patient for changes suggesting hypomania, and neurological changes, including ocular oscillations and upper motor neurone signs.

Note that products containing tryptophan for the treatment of depression were withdrawn in many countries because of a possible association with the development of an eosinophilia-myalgia syndrome. However, since the syndrome appeared to have been associated with tryptophan from one manufacturer, tryptophan preparations were reintroduced in the UK in 1994 for restricted use.[18,19]

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MAOIs or RIMAs + Tyramine-rich drinks

Patients taking non-selective MAOIs (e.g. tranylcypromine, phenelzine) can suffer a serious hypertensive reaction if they consume drinks rich in tyramine (some beers or lagers, including low-alcohol brands, or wines), but no serious interaction is likely with the RIMAs (e.g. moclobemide). The hypotensive adverse effects of the MAOIs may be exaggerated in a few patients by alcohol, and they may experience dizziness and faintness after drinking relatively modest amounts. Moclobemide does not appear to alter the psychomotor effects of alcohol to a clinically relevant extent.

Clinical evidence, mechanism, importance and management

A. Hypertensive reactions

A severe and potentially life-threatening hypertensive reaction can occur in patients taking MAOIs if they consume alcoholic drinks containing significant amounts of tyramine. The details of the tyramine/MAOI reaction, its mechanism, the names of the non-selective MAOIs that interact, and the RIMAs that are unlikely to do so are described in the monograph 'MAOIs or RIMAs + Tyramine-rich foods', p.1395. The specific case reports for various tyramine-containing drinks are outlined in the sub-sections below. Note that an 8 to 20-mg dose of tyramine is required before an important rise in blood pressure takes place in a patient taking **tranylcypromine**, and this dose may be higher for other MAOIs (see under 'tyramine-rich foods', (p.1395)). 'Table 32.2', (p.1394) summarises the reported tyramine-content of some drinks,[1-7] and more extensive lists have been published elsewhere.[6-8] These can be used as a broad general guide when advising patients, but they cannot be an absolute guide because alcoholic drinks are the end product of a biological fermentation process and no two batches are ever absolutely identical. For example there may be a 50-fold difference even between wines from the same grape stock.[5] There is no way of knowing for certain the tyramine-content of a particular drink without a detailed analysis.

Table 32.2 The tyramine-content of some drinks

	Tyramine content (mg/L)	*Refs*
Ales, beers and lagers		
Beer (Canada)	0 to 11.2, 27.1, 29.5, 112.9	1,2
Beer (Former Czechoslovakia)	10.4, 47 to 60	3
Beer (Germany)	1	3
Beer (Ireland)	0.5 to 4, 54	2,3
Beer (Netherlands)	1	3
Beer (UK)	0.3 to 1.34	2-4
Beer (USA)	0.7 to 4.4	2,3,5
Low-alcohol beers	0 to 10	2,6
Wines		
Chianti (Italy)		
Governo process	1.8 to 10.4, 25.4	1,5
Newer process	0.0 to 4.7	3,4,7,8
Champagne	1, 13.7 to 18	3,9
Wine, red (Canada, France, Italy, Spain, USA)	0 to 8.6 (mean 5.2)	9
Wine, white (France, Germany, Italy, Portugal, Spain, Former Yugoslavia)	0.4 to 6.5	4,5,9
Fortified wines and spirits		
Gin	0	8
Port	Less than 0.2 (undetectable)	5
Sherry	0.2 to 3.6	1,3,5,8
Vodka	0	8
Whiskey	0	8

1. Sen NP. Analysis and significance of tyramine in foods. *J Food Sci* (1969) 34, 22-6.
2. Tailor SAN, Shulman KI, Walker SE, Moss J, Gardner D. Hypertensive episode associated with phenelzine and tap beer - a reanalysis of the role of pressor amines in beer. *J Clin Psychopharmacol* (1994) 14, 5-14.
3. Da Prada M, Zürcher G, Wüthrich I, Haefely WE. On tyramine, food, beverages and the reversible MAO inhibitor moclobemide. *J Neural Transm* (1988) (Suppl 26), 31.
4. Hannah P, Glover V, Sandler M. Tyramine in wine and beer. *Lancet* (1988) i, 879.
5. Horwitz D, Lovenberg W, Engelman K, Sjoerdsma A. Monoamine oxidase inhibitors, tyramine and cheese. *JAMA* (1964) 188, 1108-10.
6. Draper R, Sandler M, Walker PL. Clinical curio: monoamine oxidase inhibitors and non-alcoholic beer. *BMJ* (1984) 289, 308.
7. Korn A, Eichler HG, Fischbach R, Gasic S. Moclobemide, a new reversible MAO inhibitor - interaction with tyramine and tricyclic antidepressants in healthy volunteers and depressive patients. *Psychopharmacology (Berl)* (1986) 88, 153-7.
8. Shulman KI, Walker SE, MacKenzie S, Knowles S. Dietary restriction, tyramine, and use of monoamine oxidase inhibitors. *J Clin Psychopharmacol* (1989) 9, 397-402.
9. Zee JA, Simard RE, L'Heureux L, Tremblay J. Biogenic amines in wines. *Am J Enol Vitic* (1983) 34, 6-9.

(a) Ales, Beers and Lagers

Some ales, beers and lagers in 'social' amounts contain enough tyramine to reach the 8 to 20 mg dose needed to provoke a reaction; for example a litre (a little under 2 pints) of some samples of **Canadian ale or beer** (see 'Table 32.3', (p.1396)). Case reports of reactions have been published. A man taking **phenelzine** 60 mg daily developed a typical hypertensive reaction after drinking only 14 oz. (about 400 mL) of **Upper Canada lager beer on tap** (containing about 113 mg of tyramine/litre).[8] In addition, **alcohol-free beer** and **lager** may have a tyramine-content that is equal to ordinary beer and lager.[9,10] One patient taking **tranylcypromine** suffered an acute cerebral haemorrhage after drinking a **de-alcoholised Irish beer**,[9] and hypertensive reactions occurred in three other patients taking **tranylcypromine** or **phenelzine** after drinking no more than about 375 mL of **alcohol-free beer or lager**.[10] A further patient taking **tranylcypromine** developed a vascular headache after drinking 3 bottles of **non-alcoholic beer**.[11] A very extensive study of 79 different brands of beer (from Canada, England, France, Germany, Holland, Ireland, Scotland, USA) found that the tyramine content of the **bottled** and **canned beers** examined was generally too low to matter (less than 10 mg/L), but four of 37 **beers on tap** (all 4 were lagers) contained more than enough tyramine (27 to 113 mg/L) to cause a hypertensive reaction.[8] It was concluded in this report that the consumption of **canned** or **bottled beer**, including **de-alcoholised beer**, in moderation (fewer than four bottles, 1.5 litres in a 4-hour period) was safe in patients taking MAOIs, but, to be on the cautious side, all **beers on tap**, including **lagers** should be avoided.[8] The RIMAs are less likely to interact, see 'MAOIs or RIMAs + Tyramine-rich foods', p.1395.

(b) Spirits

Gin, **whisky**, **vodka** and **other spirits** do not contain significant amounts of tyramine because they are distilled, and the volumes drunk are relatively small.[7] There seem to be no reports of hypertensive reactions in patients taking MAOIs after drinking spirits and none would be expected. One author[12] anecdotally noted that 'bottles of whisky have been drunk by some patients on the MAOIs, the only result being that they got drunk more easily and cheaply.' However, a 38-year-old man collapsed with tachycardia the morning after taking an overdose of **moclobemide** and drinking half a bottle of **whisky** (more than 350 mL). He then suffered a cardiac arrest, and resuscitation was unsuccessful. His blood pressure was not recorded. The authors attributed this case to an interaction between moclobemide and tyramine,[13] although the tyramine content of the whisky was not assessed, so any interaction is not established, especially since whisky does not usually contain tyramine.

(c) Wines

In the context of adverse interactions with MAOIs, **Chianti** has developed a sinister reputation, because 400 mL of one early sample of **Italian Chianti** wine (see 'Table 32.2', above) contained enough tyramine to reach the 8 to 20 mg threshold for causing important hypertensive reactions. However, it is claimed[14] that the newer methods that have replaced the ancient 'governo alla toscana' process result in negligible amounts of tyramine in today's **Chianti**. This seems to be borne out by the results of analyses,[3,5-7] two of which failed to find any tyramine at all in some samples.[3,7] Some of the other wines listed in 'Table 32.2', (above) also contain tyramine, but patients would have to drink as much as 2 litres or more before reaching what is believed to be the threshold dosage. This suggests that small or moderate amounts (1 or 2 glasses) are unlikely to be hazardous in patients taking MAOIs.

B. Hypotensive reactions

Some degree of hypotension can occur in patients taking MAOIs and this may be exaggerated by the vasodilation and reduced cardiac output caused by alcohol. In one report, a patient taking an MAOI describes drinking **gin** and orange and then becoming unsteady when standing up and hitting her head on the wall.[15] Patients taking MAOIs should therefore also be warned of the possibility of orthostatic hypotension and syncope if they drink. They should be advised not to stand up too quickly, and to remain sitting or lying if they feel faint or begin to 'black out'.

C. Psychomotor performance

The possibility that **alcohol**-induced deterioration in psychomotor skills (i.e. those associated with safe driving) might be increased by the RIMAs has been studied. Moclobemide appears to have only a minor and clinically unimportant effect.[16,17]

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MAOIs or RIMAs + Tyramine-rich foods

A potentially life-threatening hypertensive reaction can develop in patients taking non-selective MAOIs (tranylcypromine, phenelzine etc.) who eat tyramine-rich foods. Deaths from intracranial haemorrhage have occurred. Significant amounts of tyramine occur in some aged cheeses, yeast extracts (e.g. *Marmite*) and some types of salami. Caviar, pickled herrings, soy sauce, avocados and other foods have been implicated in this interaction. Note that any food high in aromatic amino acids can become high in tyramine if spoilage occurs or after storage. The RIMAs (moclobemide, toloxatone) interact with tyramine to a lesser extent, such that dietary restrictions are generally unnecessary.

Clinical evidence

A. Reactions to foods

(a) MAOIs

A rapid, serious, and potentially fatal rise in blood pressure can occur in patients taking MAOIs who ingest tyramine-rich foods or drinks. A violent occipital headache, pounding heart, neck stiffness, flushing, sweating, nausea and vomiting may be experienced. One of the earliest recorded observations specifically linking this reaction to **cheese** was in 1963 by a pharmacist called Rowe, who wrote to Blackwell[1] after seeing the reaction in his wife who was taking *Parstelin* (**tranylcypromine** with trifluoperazine).

'After **cheese on toast**; within a few minutes face flushed, felt very ill; head and heart pounded most violently, and perspiration was running down her neck. She vomited several times, and her condition looked so severe that I dashed over the road to consult her GP. He diagnosed 'palpitations' and agreed to call if the symptoms had not subsided in an hour. In fact the severity diminished and after about 3 hours she was normal, other than a severe headache — but 'not of the throbbing kind'. She described the early part of the attack 'as though her head must burst'.'

Blackwell and his colleagues[1] discuss a series of 25 early cases, and the information that led to this interaction becoming established. **Tranylcypromine** was the most frequently implicated MAOI: of 25 cases, 17 were with **tranylcypromine**, 6 with **phenelzine** and one each with **pargyline** and **mebanazine**. In addition, **cheese** was the most frequently implicated food, being named in 18 of 25 cases, with *Marmite* (**yeast** extract) in 3 and **pickled herrings** in one. Four patients had intracranial haemorrhages and one died.[1] From 1961 up to February 1964 the FDA in the US found about 500 cases of induced hypertension with **tranylcypromine** and 38 cases of cerebral vascular accidents with 21 deaths. As a result, **tranylcypromine** was withdrawn in the US, although it was later reintroduced with many restrictions, including the need to avoid **cheese** while taking the drug.[2]

In addition to reactions to **cheese**, cases of hypertensive reactions have been reported with **avocados**,[3] **beef livers**[4] and **chicken livers**,[5] **caviar**,[6] **pickled herrings**,[7] **soused herrings**,[8] **tinned fish**,[8] **tinned milk**,[1] **peanuts**,[8] **soy sauce**,[9] **miso**,[10] a **powdered protein diet supplement** (*Ever-so-slim*[11] or *Complan*[1]), **packet soup** (containing hydrolysed **yeast**),[12] **sour cream** in coffee,[8] and **New Zealand prickly spinach**[13] (*Tetragonia tetragonoides*). [Note this is not a true spinach as found in the USA or Europe.] These reactions occurred with **tranylcypromine**,[3,5-9] **phenelzine**[4,10,11,13] or unspecified MAOIs.[8,12]

(b) RIMAs

There do not appear to be any published reports of the '**cheese** reaction' with **moclobemide**. The combination of *Bovril* (**yeast** extract) 12 g and **moclobemide** 150 mg, both three times daily, was used to normalise blood pressure in a patient with severe postural hypotension as a result of central autonomic failure.[14]

B. Tyramine studies

Pharmacodynamic studies comparing RIMAs with MAOIs using oral tyramine sensitivity tests have revealed that only 20 to 50 mg of oral tyramine (given with a meal) is required to raise the systolic BP by 30 mmHg in subjects taking **tranylcypromine** 10 mg twice daily.[15] In other studies, the pressor tyramine dose was only 8 mg in those given **tranylcypromine**.[16] Other studies have reported the pressor tyramine dose as 15 mg[17] or 33 mg[16] in those taking **phenelzine**.

In a placebo-controlled study in healthy subjects the mean dose of oral tyramine (added to a meal) required to raise systolic BP by 30 mmHg (the tyramine 30 dose) was decreased fivefold (from 1450 mg to 306 mg, range 150 to 500 mg) by **moclobemide** 200 mg three times daily,. In comparison, **tranylcypromine** 10 mg twice daily decreased the tyramine 30 dose by about 38-fold.[15] In another study, the reduction in the tyramine 30 dose for **moclobemide** 150 mg three times daily was sevenfold; for **phenelzine** 60 mg daily, 13-fold; and for **tranylcypromine** 20 mg daily, 55-fold. After stopping the drugs, the pressor effect to tyramine normalised within 3 days for **moclobemide**, and 30 days for **tranylcypromine**. However, the pressor response had normalised in only two subjects 2 to 4 weeks after they stopped **phenelzine**, and had not normalised during the 11-week study period in the other 4 subjects.[16] In a further study the tyramine 30 dose was reduced by about 4-fold by **moclobemide** 100 mg three times daily and 10.3-fold by **phenelzine** 15 mg three times daily.[18] Numerous other pharmacological studies have confirmed the low increase in pressor response to tyramine with **moclobemide**.[17,19-22]

The pressor response to oral tyramine 200 mg was not altered by pretreatment with **toloxatone** 200 mg or 400 mg three times daily in healthy subjects, although the effect of higher doses of tyramine was increased.[23] Similar results were reported in an earlier study.[24]

Mechanism

Tyramine is formed in foods such as cheese by the bacterial degradation of milk and other proteins, firstly to tyrosine and other amino acids, and the subsequent decarboxylation of the tyrosine to tyramine. This interaction is therefore not associated with fresh foods, but with those which have been allowed to over-ripen or 'mature' in some way,[3] or if spoilage occurs. Tyramine is an indirectly-acting sympathomimetic amine, one of its actions being to release noradrenaline (norepinephrine) from the adrenergic neurones associated with blood vessels, which causes a rise in blood pressure by stimulating their constriction.[3]

Normally any ingested tyramine is rapidly metabolised by the enzyme monoamine oxidase in the gut wall and liver before it reaches the general circulation. However, if the activity of the enzyme at these sites is inhibited (by the presence of an MAOI), any tyramine passes freely into the circulation, causing not just a rise in blood pressure, but a highly exaggerated rise due to the release from the adrenergic neurones of the large amounts of noradrenaline that accumulate there during inhibition of MAO.[3] This final step in the interaction is identical to that which occurs with any other indirectly-acting sympathomimetic amine in the presence of an MAOI (see 'MAOIs or RIMAs + Sympathomimetics; Indirectly-acting', p.1388).

RIMAs such as moclobemide and toloxatone selectively inhibit MAO-A, which leaves MAO-B still available to metabolise tyramine. This means that they have less effect on the tyramine pressor response than non-selective MAOIs.

Importance and management

An extremely well-documented, well-established, serious interaction. A potentially fatal hypertensive reaction can occur between the irreversible, non-selective MAOIs (see 'Table 32.1', (p.1370)) and tyramine-rich foods. Tranylcypromine is more likely to cause the reaction than phenelzine. The incidence is uncertain, but early estimates of hypertensive reactions to tranylcypromine (before restrictions in its use with indirectly-acting sympathomimetics and foods) range from 0.03% to 20%.[2,25,26] Patients taking any of the non-selective MAOIs should not eat foods reported to contain substantial amounts of tyramine (see 'Table 32.3', (p.1396) and 'Table 32.4', (p.1397)). As little as 8 to 20 mg of tyramine can raise the

Table 32.3 The tyramine-content of some foods

Food	*Tyramine content (mg/kg or mg/L)*	*Refs*
Avocado	Higher in ripe fruit, 23, 0	1-3
Banana peel	52, 65	2,4
Banana pulp	7, 0	2-4
Caviar (Iranian)	680	5
Cheese - see Table 32.4, p.1397 and Pizza toppings, below		
Country cured ham	not detectable	6
Farmer salami sausage	314	6
Genoa salami sausage	0 to 1237 (average 534)	6
Hard salami	0 to 392 (average 210)	6
Herring (pickled)	3030	7
Lebanon bologna	0 to 333 (average 224)	6
Liver-chicken	94 to 113	8
Liver-beef	0 to 274	9
Orange pulp	10	2
Pepperoni sausage	0 to 195 (average 39)	6
Pizza toppings (cheese and pepperoni)	0 to 3.6 (0 to 0.38 mg on half a medium pizza)	10
Plum, red	6	2
Sauerkraut	55	4
Soy sauce	0 to 878	4,10-12
Soya bean curd (tofu)	0.6 to 16	10
Soya beans, fermented	713	12
Soya bean paste, fermented	206	12
Smoked landjaeger sausage	396	6
Summer sausage	184	6
Tomato	4, 0	2,3
Thuringer cervelat	0 to 162	6
Yeast extracts		
Bovril	200 to 500	13
Bovril beef cubes	200 to 500	13
Bovril chicken cubes	50 to 200	13
Marmite (UK product)	500 to 3000	3,4,13
Yoghurt	0 to 4	3,4,14

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Continued

Table 32.3 The tyramine-content of some foods (continued)

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13. Clarke A. (Bovril Ltd). Personal communication (1987).
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blood pressure in patients taking tranylcypromine, and this may be present in usual portions of hard cheeses.[16] In addition, avoidance of the prohibited foods should be continued for 2 to 3 weeks after stopping the MAOI to allow full recovery of the enzymes. However, note that in one study some patients took over 11 weeks to recover from the effects of phenelzine.[16]

Because tyramine levels vary so much it is impossible to guess the amount present in any food or drink. Old, over-ripe strong smelling cheeses with a salty, biting taste or those with characteristic holes due to fermentation should be avoided as they generally contain high levels of tyramine. Fresh cheeses made from pasteurised milk tend to have lower levels of tyramine.[27] The tyramine-content can even differ significantly within a single cheese: the centre having the lowest levels of tyramine and the rind containing the most.[27,28] There is no guarantee that patients who have uneventfully eaten these hazardous foodstuffs on many occasions may not eventually experience a full-scale hypertensive crisis, if all the many variables conspire together.[29]

The need to plan a sensible and safe diet for those taking MAOIs is clear, and over the years attempts have been made to produce simplified, practical diets for those taking MAOIs.[30-37] A total prohibition should be imposed on the following: **aged cheese** and **yeast extracts** such as *Marmite,* and possibly also *Bovril* and **pickled herrings** (see 'Table 32.3', above). A number of other foods should also be viewed with suspicion such as **sauerkraut**, **fermented bologna** and **salami**, **pepperoni**, and **summer sausage** because some of them may contain significant amounts of tyramine (see 'Table 32.3', above). Some preserved and fermented Far Eastern foods such as **fermented soya beans**, **soya bean paste** and **soya bean curd** (**tofu**) can also contain relatively high tyramine levels.[34,38] However, **yoghurt**, **fresh cream** and possibly **chocolate** are often viewed with unjustifiable suspicion. It also seems very doubtful if either **cream cheese** or **cottage cheese** represent a hazard, or **processed cheese** slices.[33] **Whole green bananas** contain up to 65 micrograms of tyramine per gram, but this is mostly in the skin as the pulp contains relatively small amounts. Although case reports have occurred with a variety of other foods, it is generally acknowledged that widespread restrictions should not be imposed on a food based solely on an unsubstantiated isolated report,[30,31,33] and that some reports could equally be attributed to spoilage.[31,39] Therefore, of perhaps more importance is the advice to only eat protein-based foods (particularly meat, fish and liver) when fresh (within their sell-by date and after correct storage).[31,33] Note that cooking does not inactivate tyramine. For the need to avoid broad-bean pods because of their dopamine content, see 'MAOIs + Dopa-rich foods', p.1376.

In the context of interactions with tyramine-rich foods and drinks the RIMAs are safer than the older MAOIs, because they are more readily reversible and selective. Therefore the risk of a serious hypertensive reaction with moclobemide is very much reduced. The authors of one study calculate that the lowest amount of tyramine (150 mg) found to cause a 30 mmHg rise in systolic BP with moclobemide is equivalent to that found in about 200 g of Stilton cheese or 300 g of Gorgonzola cheese, which are really excessive amounts of cheese to be eaten in a few minutes.[15]

Table 32.4 The tyramine content of some cheeses
This table is principally intended to show the extent and the variation that can occur

Variety of cheese	*Tyramine content (mg/kg)*	*Approximate mg/60g portion*	*Refs*
American processed	50	3	1
Argenti	188	11	2
Blue	31 to 997	2 to 60	2-4
Boursault	1116	67	3
Brick	194	12	2
Brie	3 to 473	0.2 to 28	1,4,5
Cambozola Blue Vein	18	1	4
Camembert	3 to 519	0.2 to 31	1–3,5
Cheddar	8 to 1530	0.5 to 92	2-6
Cheshire	24 to 418	1.4 to 25	5
Cream cheese	undetectable (less than 0.2), 9	0 to 0.5	1,4
Cottage cheese	undetectable (less than 0.2), 5	0 to 0.3	1,5
Danish Blue	31 to 743	2 to 45	3-5
d'Oka	158, 310	9.5, 19	2
Double Gloucester	43	2.6	5
Edam	100, 214	6, 13	2
Emmental	11 to 958	0.7 to 57	1,4,5
Feta	5.8, 20, 76	0.3 to 4.6	4-6
Gorgonzola	56 to 768	3.4 to 46	4,5
Gouda	54, 95	3.2, 5.7	2
Gouda type (Canadian)	20	1.2	3
Gourmandise	216	13	3
Gruyere	64 to 516	3.8 to 31	1,4,5,7
Kashar	44 (mean of seven samples)	2.6	7
Liederkrantz	1226, 1683	74, 101	2
Limburger	44 to 416	2.6, 25	2,5
Mozzarella	17 to 410	1 to 25	3-6
Munster	87 to 110	5.2 to 6.6	2,4,5
Mycella	1340	80	3
Parmesan	4 to 290	0.2 to 17	3-5
Provolone	38	2.3	3
Red Leicester	41	2.5	5
Ricotta	0	0	4
Romano	4, 197, 238	0.2 to 14	2,3,6
Roquefort	13 to 520	0.8 to 31	2,3,5
Stilton	359 to 2170	28 to 130	1,3-5
Tulum	208 (mean of seven samples)	12.5	7
White (Turkish)	17.5 (mean of seven samples)	1	7

1. Horwitz D, Lovenberg W, Engelman K, Sjoerdsma A. Monoamine oxidase inhibitors, tyramine and cheese. *JAMA* (1964) 188, 1108-10.

Continued

Table 32.4 The tyramine content of some cheeses (continued)
This table is principally intended to show the extent and the variation that can occur

2. Kosikowsky FV, Dahlberg AC. The tyramine content of cheese. *J Dairy Sci* (1948) 31, 293-303.
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4. Shulman KI, Walker SE, MacKenzie S, Knowles S. Dietary restriction, tyramine, and the use of monoamine oxidase inhibitors. *J Clin Psychopharmacol* (1989) 9, 397-402.
5. Da Prada M, Zürcher G, Wüthrich I, Haefely WE. On tyramine, food, beverages and the reversible MAO inhibitor moclobemide. *J Neural Transm* (1988) (Suppl 26), 31-56.
6. Shulman KI, Walker SE. Refining the MAOI diet: tyramine content of pizzas and soy products. *J Clin Psychiatry* (1999) 60, 191-3.
7. Kayaalp SO, Renda N, Kaymakcalan S, Özer A. Tyramine content of some cheeses. *Toxicol Appl Pharmacol* (1970) 16, 459-60.

Moreover, no 'cheese reactions' appear to have been published for moclobemide. Most patients therefore do not need to follow the special dietary restrictions required with the non-selective MAOIs, but, to be on the safe side, the manufacturers of moclobemide advise all patients to avoid large amounts of tyramine-rich foods, because a few individuals may be particularly sensitive to tyramine.[40] This warning would also seem appropriate for all RIMAs. Note that if moclobemide were given with an MAO-B inhibitor such as selegiline, it would essentially be the same as giving a non-selective MAOI, and dietary tyramine restrictions would then be required, see 'MAO-B inhibitors + Tyramine-rich foods', p.809.

Treatment

Severe hypertensive reactions require urgent immediate treatment. The drug most commonly used to control hypertensive reactions with MAOIs is phentolamine, given as a slow intravenous injection. However, the need for the patient to get to an emergency treatment centre delays treatment, and as a consequence, providing the patient with a drug they could self administer has been suggested. Sublingual nifedipine has been advocated,[41] but does not appear to have been widely adopted, perhaps because the possibility of a sudden dramatic drop in blood pressure is just as dangerous. Another similar option is a small dose of chlorpromazine.[42]

It is advisable to refer to current guidelines on the management of hypertensive crises for up-to-date advice.

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4. Boulton AA, Cookson B, Paulton R. Hypertensive crisis in a patient on MAOI antidepressants following a meal of beef liver. *Can Med Assoc J* (1970) 102, 1394–5.
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6. Isaac P, Mitchell B, Grahame-Smith DG. Monoamine-oxidase inhibitors and caviar. *Lancet* (1977) ii, 816.
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12. McQueen EG. Interactions with monoamine oxidase inhibitors. *BMJ* (1975) 4, 101.
13. Comfort A. Hypertensive reaction to New Zealand prickly spinach in a woman taking phenelzine. *Lancet* (1981) ii, 472.
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16. Bieck PR, Antonin KH. Tyramine potentiation during treatment with MAO inhibitors: brofaromine and moclobemide vs irreversible inhibitors. *J Neural Transm* (1989) (Suppl 28), 21–31.
17. Simpson GM, Gratz SS. Comparison of the pressor effect of tyramine after treatment with phenelzine and moclobemide in healthy male volunteers. *Clin Pharmacol Ther* (1992) 52, 286–91. Correction. Ibid. (1993) 53, 95.

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40. Manerix (Moclobemide). Meda Pharmaceuticals. UK Summary of product characteristics, September 2009.
41. Fier M. Safer use of MAOIs. *Am J Psychiatry* (1991) 148, 391–2.
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Moclobemide + Cimetidine

Cimetidine increases the plasma levels of moclobemide. Moclobemide dosage reductions are recommended.

Clinical evidence, mechanism, importance and management

In a study in 8 healthy subjects, cimetidine 200 mg five times daily for 2 weeks increased the maximum plasma levels of a single 100-mg dose of moclobemide by 39% and its clearance was reduced by 52%.[1] The probable reason for this effect is that the cimetidine (a well-recognised enzyme inhibitor) reduces the first-pass metabolism of the moclobemide.

It has been recommended that if moclobemide is given to a patient taking cimetidine it should be started at the lowest therapeutic dose, and titrated as required. If cimetidine is given to a patient taking moclobemide, the dosage of the moclobemide should initially be reduced by 50% and later adjusted as necessary.[2,3]

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3. Manerix (Moclobemide). Meda Pharmaceuticals. UK Summary of product characteristics, September 2009.

Moclobemide + Omeprazole

Omeprazole doubled the AUC of moclobemide in extensive metabolisers of CYP2C19, effectively making them poor metabolisers. Similarly, moclobemide doubled the AUC of omeprazole in one study. The clinical relevance of these findings is uncertain.

Clinical evidence

Omeprazole 40 mg daily for 7 days increased the AUC of a single 300-mg dose of moclobemide by about twofold in 8 healthy subjects who were extensive metabolisers of CYP2C19.[1] After this increase, the AUC of moclobemide in these subjects was still lower than that seen in 8 healthy subjects who were poor metabolisers of CYP2C19 (without omeprazole). Omeprazole had no appreciable effect on the pharmacokinetics of moclobemide in the 8 subjects who were poor metabolisers of CYP2C19. Further study in the same subjects showed that, in the extensive metabolisers, a single 300-mg dose of moclobemide approximately doubled the AUC and maximum plasma level of omeprazole 40 mg, and the production of omeprazole sulfone was similarly increased. The pharmacokinetics of omeprazole and omeprazole sulfone were not significantly altered in the poor metabolisers.[2]

Mechanism

Omeprazole is an inhibitor of the cytochrome P450 isoenzyme CYP2C19, by which moclobemide is extensively metabolised. Activity of this enzyme is genetically determined, see 'Genetic factors in drug metabolism', (p.4), for more information. Moclobemide is also an inhibitor of CYP2C19, which is the major pathway by which omeprazole is metabolised. Inhibition of this pathway means that metabolism of omeprazole in extensive metabolisers, who normally metabolise omeprazole to 5-hydroxyomeprazole by CYP2C19, will become more dependent on other pathways. Omeprazole sulfone is produced when omeprazole is metabolised by CYP3A4, and hence in extensive metabolisers given moclobemide its levels rise.

Importance and management

The pharmacokinetic interaction is established, but its clinical relevance is unclear. Both drugs are relatively safe, and therefore increased levels are generally likely to be well tolerated. However, if the adverse effects of either drug become troublesome consider an interaction as a possible cause. Note that the effect of moclobemide on omeprazole may be of more significance if drugs that inhibit CYP3A4 are also given, as both pathways of metabolism will be blocked.

1. Yu K-S, Yim D-S, Cho J-Y, Park SS, Park JY, Lee K-H, Jang I-J, Yi S-Y, Bae K-S, Shin S-G. Effect of omeprazole on the pharmacokinetics of moclobemide according to the genetic polymorphism of CYP2C19. *Clin Pharmacol Ther* (2001) 69, 266–73.
2. Cho J-Y, Yu K-S, Jang I-J, Yang B-H, Shin S-G, Yim D-S. Omeprazole hydroxylation is inhibited by a single dose of moclobemide in homozygotic EM genotype for CYP2C19. *Br J Clin Pharmacol* (2002) 53, 393–7.

Phenelzine + Cloral hydrate

A case of fatal hyperpyrexia and another case of serious hypertension have been linked to interactions between cloral hydrate and phenelzine, but in both cases there are other plausible explanations for the reactions seen.

Clinical evidence, mechanism, importance and management

A woman taking **phenelzine** 15 mg three times daily was found in bed deeply comatose with marked muscular rigidity, twitching down one side and a temperature of 41°C. She died without regaining consciousness. A postmortem failed to establish the cause of death, but it subsequently came to light that she had started drinking whisky, and she had access to cloral hydrate, of which she may have taken a fatal dose.[1] Another patient, taking **phenelzine** 15 mg three times daily, and cloral hydrate to aid sleep, developed an excruciating headache followed by nausea, photophobia and a substantial rise in blood pressure.[2] This latter reaction is similar to the 'cheese reaction', see 'tyramine-rich foods', (p.1395), but at the time the authors of the report were unaware of this type of reaction so that they failed to find out if any tyramine-rich foods had been eaten on the day of the attack.[2]

There is no clear evidence that either of these adverse reactions was due to an interaction between **phenelzine** and cloral hydrate, and there do not

seem to be any other reports to suggest that an interaction between these drugs is likely.

1. Howarth E. Possible synergistic effects of the new thymoleptics in connection with poisoning. *J Ment Sci* (1961) 107, 100–103.
2. Dillon H, Leopold RL. Acute cerebro-vascular symptoms produced by an antidepressant. *Am J Psychiatry* (1965) 121, 1012–14.

Phenelzine + Erythromycin

An isolated case report describes severe hypotension and fainting in a woman taking phenelzine, which occurred shortly after she started a course of erythromycin.

Clinical evidence, mechanism, importance and management

A woman taking phenelzine 15 mg daily experienced three syncopal episodes 4 days after starting to take erythromycin 250 mg four times daily for pneumonia. When admitted to hospital her supine systolic blood pressure was only 70 mmHg. When she sat up, it was unrecordable. Although she was not dehydrated, she was given 4 litres of sodium chloride 0.9%, without any effect on her blood pressure. Within 24 hours of stopping the phenelzine her blood pressure had returned to normal.[1] The reasons for this severe hypotensive reaction are not known, but it was suggested that the erythromycin may have caused rapid gastric emptying, which resulted in a very rapid absorption of the phenelzine (described by the author as rapid dumping into the blood stream), which resulted in the adverse effect of hypotension.[1] This seems to be the first and only report of this interaction, and so its general importance is uncertain. It seems likely to be small.

1. Bernstein AE. Drug interaction. *Hosp Community Psychiatry* (1990) 41, 806–7.

Phenelzine + Sulfafurazole (Sulfisoxazole)

An isolated report describes a patient taking phenelzine who developed weakness and ataxia after also taking sulfafurazole.

Clinical evidence, mechanism, importance and management

A woman who had been taking phenelzine 15 mg three times daily for about 3 weeks complained of weakness, ataxia, vertigo, tinnitus, muscle pains, and paraesthesia within 7 days of starting to take sulfafurazole 1 g four times daily. These adverse effects continued until the 10-day sulfonamide course was completed, and did not occur again in the following 8 weeks.[1] The reasons for this reaction are not understood, but as these adverse effects are a combination of the adverse effects of both drugs, it seems possible that a mutual interaction (perhaps saturation of the acetylating mechanisms in the liver) was responsible. This appears to be an isolated report and its general significance is unknown.

1. Boyer WF, Lake CR. Interaction of phenelzine and sulfisoxazole. *Am J Psychiatry* (1983) 140, 264–5.

33

Nutritional agents, Supplements and Vitamins

This section covers the interactions where there is documented evidence that a drug alters the efficacy of nutritional agents, dietary supplements and vitamins. Information on the effects of these substances on other drugs is covered in the relevant section for that drug.

Agalsidase + Miscellaneous

Agalsidase alfa and agalsidase beta are unlikely to interact with other drugs by mechanisms involving cytochrome P450.[1] The UK manufacturers suggest that agalsidase alfa and agalsidase beta should not be given with amiodarone, chloroquine, gentamicin [and therefore probably any aminoglycoside], or monobenzone due to a theoretical risk of inhibition of intra-cellular alpha-galactosidase activity.[1,2] This would be expected to reduce the efficacy of agalsidase.

1. Replagal (Agalsidase alfa). Shire Human Genetic Therapies. UK Summary of product characteristics, October 2008.
2. Fabrazyme (Agalsidase beta). Genzyme Therapeutics. UK Summary of product characteristics, February 2008.

Amygdalin + Ascorbic acid (Vitamin C)

Vitamin C may enhance the hydrolysis of amygdalin resulting in toxic levels of cyanide.

Clinical evidence

A patient with bladder cancer, who was taking several vitamin preparations, including high-dose vitamin C, and other complementary medicines in addition to her prescribed medicines, became unwell and complained of dizziness 2.5 hours after the first dose of amygdalin 3 g. She then developed tachycardia, seizures and severe lactic acidosis, and required intubation and ventilation. Cyanide poisoning was diagnosed and she recovered after being given activated charcoal and intravenous hydroxocobalamin 5 g over 30 minutes.[1]

Mechanism

There appear to be no reports of serious cyanide toxicity with doses of amygdalin up to 6 g daily. Hydrolysis of amygdalin can produce up to 6% hydrogen cyanide so a dose of 3 g could possibly produce up to 180 mg of cyanide, which is above the estimated potentially lethal dose of 50 to 100 mg. Amygdalin is hydrolysed in the presence of beta-glucosidases, which are not usually present in the upper gastrointestinal tract to any extent. However, hydrolysis of amygdalin in the gut is enhanced by ascorbic acid and it was considered likely that the high doses of vitamin C (more than 3 g daily) taken by the patient resulted in sufficient hydrolysis of amygdalin to produce toxic levels of cyanide.[1] In addition, body stores of cysteine, which facilitate cyanide detoxification, are depleted by vitamin C.[1,2]

Importance and management

Although this appears to be the only clinical report of this interaction, cyanide poisoning associated with amygdalin has been reported. It would therefore seem prudent to avoid the concurrent use of vitamin C. **Laetrile**, which is a product consisting mainly of amygdalin, would be expected to interact similarly with vitamin C.

1. Bromley J, Hughes BGM, Leong DCS, Buckley NA. Life-threatening interaction between complementary medicines: cyanide toxicity following ingestion of amygdalin and vitamin C. *Ann Pharmacother* (2005) 39, 1566–9.
2. Basu TK. High-dose ascorbic acid decreases detoxification of cyanide derived from amygdalin (laetrile): studies in guinea pigs. *Can J Physiol Pharmacol* (1983) 61, 1426–30.

Ascorbic acid (Vitamin C) + Salicylates

Aspirin might reduce the absorption of ascorbic acid by about one-third. Serum salicylate levels do not appear to be affected by ascorbic acid.

Clinical evidence, mechanism, importance and management

In a study in healthy subjects, the rise in plasma ascorbic acid levels over 3 hours was about one-third lower when a single 500-mg dose of ascorbic acid was given with **aspirin** 900 mg, when compared with ascorbic acid alone, and the urinary excretion of ascorbic acid was about 50% lower.[1] In another well-controlled study in healthy subjects, levels of ascorbic acid in the gastric mucosa, plasma and urine on day 7 were not significantly different when ascorbic acid 480 mg three times daily was given with **aspirin** 800 mg three times daily, when compared with ascorbic acid alone. However, aspirin 800 mg three times daily, given without ascorbic acid supplementation, reduced ascorbic acid levels.[2] There is some pharmacodynamic evidence that, in healthy subjects, ascorbic acid attenuates gastric mucosal lesions seen with **aspirin**.[3]

Another study, in 9 healthy subjects, found that ascorbic acid 1 g three times daily did not significantly affect the serum salicylate levels in response to **choline salicylate**.[4]

The clinical importance of the possible decrease in ascorbic acid levels is uncertain. It has been suggested that the normal physiological requirement of 30 to 60 mg of ascorbic acid daily may need to be increased to 100 to 200 mg daily in the presence of long-term **aspirin** therapy.[1]

1. Basu TK. Vitamin C-aspirin interactions. *Int J Vitam Nutr Res* (1982) 23 (Suppl), 83–90.
2. Schulz H-U, Schürer M, Krupp S, Dammann H-G, Timm J, Gessner U. Effects of acetylsalicylic acid on ascorbic acid concentrations in plasma, gastric mucosa, gastric juice and urine – a double-blind study in healthy subjects. *Int J Clin Pharmacol Ther* (2004) 42, 481–7.
3. Konturek PC, Kania J, Hahn EG, Konturek JW. Ascorbic acid attenuates aspirin-induced gastric damage: role of inducible nitric oxide synthase. *J Physiol Pharmacol* (2006) 57 (Suppl 5), 125–36.
4. Hansten PD, Hayton WL. Effect of antacid and ascorbic acid on serum salicylate concentration. *J Clin Pharmacol* (1980) 24, 326–31.

Betacarotene + Colchicine

The desired effect of betacarotene supplementation may be reduced in those taking colchicine.

Clinical evidence

Divided doses of colchicine 1.9 mg to 3.9 mg daily reduced the serum levels of betacarotene 10 000 units daily (about 6 mg) in 5 obese subjects. Levels returned to normal when colchicine was stopped.[1] However, in another study, long-term use of colchicine 1 mg to 2 mg daily for 3 years had no effect on the serum levels of diet-derived carotene in 12 patients with familial Mediterranean fever.[2]

Mechanism

The mechanism is unclear. Colchicine causes reversible malabsorption in the gastrointestinal tract by disturbing epithelial cell function and inhibiting cell proliferation. It also lowered the serum levels of cholesterol in the first study. All these factors could have an effect on the absorption of betacarotene, which largely takes place in the gastrointestinal mucosa and whose distribution is dependent on the presence of lipoproteins.

Importance and management

The evidence for a possible interaction between betacarotene and colchicine is limited to two relatively old studies. While supplemental betacarotene absorption appears to be reduced, betacarotene ingested as part of the normal diet appears to be unaffected. Based on these two findings, and the fact that there is large interindividual variation in betacarotene absorption, it is difficult to recommend a clinical course of action other than to be aware that the desired effect of betacarotene supplementation may be reduced in those taking colchicine.

1. Race TF, Paes IC, Faloon WW. Intestinal malabsorption induced by oral colchicine. Comparison with neomycin and cathartic agents. *Am J Med Sci* (1970) 259, 32–41.
2. Ehrenfeld M, Levy M, Sharon P, Rachmilewitz D, Eliakim M. Gastrointestinal effects of long-term colchicine therapy in patients with recurrent polyserositis (familial Mediterranean fever). *Dig Dis Sci* (1982) 27, 723–7.

Betacarotene + Proton pump inhibitors

The desired effect of betacarotene supplementation may be reduced in those taking proton pump inhibitors.

Clinical evidence

In a study in 10 healthy subjects the AUC of a single 120-mg dose of betacarotene was halved by pretreatment with **omeprazole** 20 mg twice daily for 7 days.[1]

Mechanism

The exact mechanism is unclear. Betacarotene is absorbed in the small intestine by a simple passive-diffusion process. It has been suggested that omeprazole may retard this diffusion,[1] and that delayed gastric emptying may also contribute.[2]

Importance and management

Evidence for an interaction between betacarotene and omeprazole is limited, and as there is large interindividual variability in betacarotene absorption, the true bioavailability of the carotenoid can vary greatly even before omeprazole is taken. Coupled with the fact that betacarotene is a normal part of the healthy diet, it is very difficult to assess the true clinical importance of this interaction. Be aware that the desired effect of betacarotene supplements may be reduced or abolished by the concurrent use of omeprazole. If the suggested mechanism is correct, other proton pump inhibitors are likely to affect betacarotene absorption similarly.

1. Tang G, Serfaty-Lacrosniere C, Ermelinda Camilo M, Russell RM. Gastric acidity influences the blood response to a β-carotene dose in humans. *Am J Clin Nutr* (1996) 64, 622–6.
2. Ψster-Jψrgensen E, Rasmussen L. Blood response to a β-carotene dose. *Am J Clin Nutr* (1998) 67, 349–53.

Calcium compounds + Proton pump inhibitors

A study in elderly women found that omeprazole reduced the absorption of calcium from a single dose of calcium carbonate under fasting conditions. However, in another study, omeprazole did not affect the absorption of calcium from a test meal that included milk and cheese. Other proton pump inhibitors may have similar effects.

Clinical evidence

In a double-blind study, 18 elderly women (mean age 76 years) were given a multivitamin preparation containing vitamin D 400 units daily and either omeprazole 20 mg daily or placebo for 7 days and then again with calcium carbonate (elemental calcium 500 mg) after an overnight fast. Calcium supplements had been withheld for one week before the study. The fractional absorption of the single calcium carbonate dose was decreased by about 60% by omeprazole (from 9.1% with placebo to 3.5% with omeprazole).[1]

In contrast, in another study, higher 40-mg doses of omeprazole did not affect the absorption of calcium from food (535 mg from a test meal including milk and cheese).[2]

Mechanism

In vitro, calcium carbonate disintegration and dissolution is pH dependent, decreasing from 96% at pH 1 to 23% at pH 6.1.[3] Therefore increases in pH due to omeprazole could reduce calcium absorption. However, calcium absorption is dependent on other factors such as food, calcium dose and subject age. Calcium absorption in women decreases with increasing age.[4]

Importance and management

The study in elderly women found reduced calcium absorption in the presence of omeprazole. Other proton pump inhibitors might be expected to act similarly, as the mechanism appears to relate to gastric pH. However, another study found that omeprazole did not affect calcium absorption from food. Therefore factors that may influence calcium absorption other than gastric pH, including patient age, calcium dose, and food must also be considered when assessing the possibility of an interaction. More study is needed to assess the clinical relevance of this potential interaction.

1. O'Connell MB, Madden DM, Murray AM, Heaney RP, Kerzner LJ. Effects of proton pump inhibitors on calcium carbonate absorption in women: a randomized crossover trial. *Am J Med* (2005) 118, 778–81.
2. Serfaty-Lacrosniere C, Wood RJ, Voytko D, Saltzman JR, Pedrosa M, Sepe TE, Russell RR. Hypochlorhydria from short-term omeprazole treatment does not inhibit intestinal absorption of calcium, phosphorus, magnesium or zinc from food in humans. *J Am Coll Nutr* (1995) 14, 364–8.
3. Jelleff Carr C, Shangraw RF. Nutritional and pharmaceutical aspects of calcium supplementation. *Am Pharm* (1987) S27, 49–50, 54–7.
4. Ensrud KE, Duong T, Cauley JA, Heaney RP, Wolf RL, Harris E, Cummings SR, for the Study of Osteoporotic Fractures Research Group. Low fractional calcium absorption increases the risk for hip fracture in women with low calcium intake. *Ann Intern Med* (2000) 132, 345–53.

Cannabis + Disulfiram

Two isolated case reports describe hypomanic-like reactions when patients taking disulfiram used cannabis, whereas no unusual interaction with the combination was seen in other subjects.

Clinical evidence, mechanism, importance and management

A man with a 10-year history of drug abuse (alcohol, amfetamines, cocaine, cannabis) taking disulfiram 250 mg daily, experienced a hypomanic-like reaction (euphoria, hyperactivity, insomnia, irritability) on two occasions, associated with the concurrent use of cannabis. The patient said that he felt as though he had been taking amfetamine.[1] One other similar case has been reported.[2] The reason for this reaction is not understood.

In a randomised study in alcohol-dependent subjects who had previously used cannabis, no unusual interaction effects were found in a group of 11 subjects receiving disulfiram and smoking cannabis twice weekly for 4 weeks.[3] Therefore the interaction described in the two case reports would not appear to be of general significance.

1. Lacoursiere RB, Swatek R. Adverse interaction between disulfiram and marijuana: a case report. *Am J Psychiatry* (1983) 140, 243–4.
2. Mackie J, Clark D. Cannabis toxic psychosis while on disulfiram. *Br J Psychiatry* (1994) 164, 421.
3. Rosenberg CM, Gerrein JR, Schnell C. Cannabis in the treatment of alcoholism. *J Stud Alcohol* (1978) 39, 1955–8.

Cannabis + Nicotine

The effects of transdermal nicotine and cannabis smoking on increasing the heart rate are additive, and nicotine increased the stimulant effect of cannabis. Combined use might increase the addictive potential of both drugs.

Clinical evidence

In a study in 20 healthy subjects who smoked either a low-dose or high-dose cannabis cigarette 4 hours after the application of a placebo or a 21 mg nicotine patch, nicotine enhanced the maximum increase in heart rate seen with cannabis. The increase in heart rate for nicotine alone was between 10 and 15 bpm, for cannabis alone 32 and 42 bpm, for women and men, respectively, and for the combination, 45 and 58 bpm, respectively. In addition, the duration of tachycardia after smoking the low-dose cannabis was prolonged by 30 minutes by nicotine, but was not changed after the high-dose cannabis. Nicotine increased the subjective stimulant effects of cannabis, but the reported duration of effects of cannabis were shortened by nicotine. Plasma levels of nicotine and Δ^9-tetrahydrocannabinol (THC) did not differ on concurrent use. The cannabis cigarettes were standardised to 1.99% THC (low dose) and 3.51% THC (high dose).[1]

Mechanism

Unknown. The additive effect on heart rate may be due to sympathetic activity of both drugs, and might also involve cannabinoid receptors.[1]

Importance and management

Cannabis is often smoked with tobacco. The findings of the clinical study show that transdermal nicotine has additive effects with cannabis on heart rate, and increased the stimulant effect of cannabis. The clinical significance of these findings is uncertain.

1. Penetar DM, Kouri EM, Gross MM, McCarthy EM, Rhee CK, Peters EN, Lukas SE. Transdermal nicotine alters some of marihuana's effects in male and female volunteers. *Drug Alcohol Depend* (2005) 79, 211–23.

Evening primrose oil + Phenothiazines

Although seizures have occurred in a few schizophrenics taking phenothiazines and evening primrose oil, no adverse effects were seen in others, and there appears to be no firm evidence that evening primrose oil should be avoided by those at risk of seizures.

Clinical evidence

Twenty-three patients were enrolled in a placebo-controlled study of evening primrose oil in schizophrenia. During the treatment phase, patients were given 8 capsules of *Efamol* in addition to their normal medication. Seizures developed in 3 patients, one during treatment with placebo. The other two patients were taking evening primrose oil, one was receiving **fluphenazine decanoate** 50 mg once every 2 weeks and the other **fluphenazine decanoate** 25 mg once every 2 weeks with **thioridazine**, which was later changed to **chlorpromazine**.[1] In another study, 3 long-stay hospitalised schizophrenics were taking evening primrose oil. Their schizophrenia became much worse and all 3 patients showed EEG evidence of temporal lobe epilepsy.[2]

In contrast, no seizures or epileptiform events were reported in a crossover study of 48 patients (most of them schizophrenics) taking **phenothiazines** when they were given evening primrose oil for 4 months.[3] Concurrent use was also apparently uneventful in another study in schizophrenic patients.[4]

Mechanism

Not understood. One suggestion is that evening primrose oil possibly increases the well-recognised epileptogenic effects of the phenothiazines, rather than having an epileptogenic action of its own.[1] Another idea is that it might unmask temporal lobe epilepsy.[1,2]

Importance and management

The interaction between phenothiazines and evening primrose oil is not well established, nor is its incidence known, but clearly some caution is appropriate during concurrent use, because seizures may develop in a few individuals. There seems to be no way of identifying the patients at particular risk. The extent to which the underlying disease condition might affect what happens is also unclear.

No interaction between antiepileptics and evening primrose oil has been established and the reports cited above[1,2] appear to be the sole basis for the suggestion that evening primrose oil should be avoided by epileptics. No seizures appear to have been reported in patients taking evening primrose oil in the absence of phenothiazines. One review,[5] analysing these two reports, goes as far as suggesting that formularies should now remove seizures or epilepsy as an adverse effect of evening primrose oil because the evidence for the seizures clearly point to the phenothiazines taken. Moreover, the manufacturers of *Epogam*, an evening primrose oil preparation, claim that it is known to have improved the control of epilepsy in patients previously uncontrolled with conventional antiepileptic drugs, and other patients are said to have had no problems during concurrent treatment.[6]

1. Holman CP, Bell AFJ. A trial of evening primrose oil in the treatment of chronic schizophrenia. *J Orthomol Psychiatry* (1983) 12, 302–4.
2. Vaddadi KS. The use of gamma-linolenic acid and linoleic acid to differentiate between temporal lobe epilepsy and schizophrenia. *Prostaglandins Med* (1981) 6, 375–9.
3. Vaddadi KS, Courtney P, Gilleard CJ, Manku MS, Horrobin DF. A double-blind trial of essential fatty acid supplementation in patients with tardive dyskinesia. *Psychiatry Res* (1989) 27, 313–23.
4. Vaddadi KS, Horrobin DF. Weight loss produced by evening primrose oil administration in normal and schizophrenic individuals. *IRCS Med Sci* (1979) 7, 52.
5. Puri BK. The safety of evening primrose oil in epilepsy. Prostaglandins Leukot Essent Fatty Acids. (2007) 77, 101–3.
6. Scotia Pharmaceuticals Ltd. Personal Communication, January 1991.

Folic acid + Antacids or H_2-receptor antagonists

Aluminium/magnesium hydroxide-containing antacids, cimetidine and ranitidine probably do not have a clinically relevant effect on the absorption of folic acid.

Clinical evidence, mechanism, importance and management

In a well-controlled study in healthy subjects, taking two 30 mL doses of an **aluminium/magnesium hydroxide** antacid (*Mylanta II*) one hour and three hours after a single 200-microgram dose of folic acid caused a small 15% reduction in folic acid absorption (from about 51% to 43%). Two doses of **cimetidine** 300 mg (5 hours before and simultaneously with the folic acid), caused a reduction of about 8% in folic acid absorption, and two doses of **ranitidine** 150 mg (the night before and 5 hours before the folic acid) caused about a 6% decrease (not statistically significant).[1]

Drugs that increase the gastrointestinal pH might reduce folic acid absorption since the optimal pH for active intestinal transport of folic acid is about 6. It is possible that in the pH range of physiological significance, folate binds to aluminium hydroxide.

The reduction in folate absorption in this study was small and unlikely to be clinically relevant. It is possible that an individual taking **aluminium antacids** long-term and with marginal dietary folate might become folate deficient.

As neither **cimetidine** nor **ranitidine** caused a significant reduction in the absorption of folic acid, it is unlikely that other H_2-receptor antagonists would interact, although there is no published data to confirm this.

1. Russell RM, Golner BB, Krasinski SD, Sadowski JA, Suter PM, Braun CL. Effect of antacid and H_2 receptor antagonists on the intestinal absorption of folic acid. *J Lab Clin Med* (1988) 112, 458–63.

Folic acid + Sulfasalazine

Sulfasalazine can reduce the absorption of folic acid.

Clinical evidence, mechanism, importance and management

The absorption of folic acid was reduced by about one-third (from 65% to 44.5%) in patients with ulcerative and granulomatous colitis, when compared with healthy subjects, and even further reduced (down to 32%) when sulfasalazine was taken.[1] Another study confirmed that serum folate levels are lower in patients with ulcerative colitis taking sulfasalazine, and that the mechanism was an impairment of folate absorption brought about by sulfasalazine.[2] Sulfasalazine is also known to interfere with folate metabolism.

It is well established that sulfasalazine is, rarely, associated with blood dyscrasias due to folate deficiency and also other haematological toxicities, and consequently regular blood counts are recommended to detect this. The effects of folate deficiency (e.g. macrocytosis, pancytopenia) can be normalised by giving folic acid or folinic acid.

1. Franklin JL, Rosenberg IH. Impaired folic acid absorption in inflammatory bowel disease: effects of salicylazosulfapyridine (Azulfidine). *Gastroenterology* (1973) 64, 517–25.
2. Halsted CH, Gandhi G, Tamura T. Sulfasalazine inhibits the absorption of folates in ulcerative colitis. *N Engl J Med* (1981) 305, 1513–17.

Iron compounds + Antacids

The absorption of iron and the expected haematological response to iron can be reduced by the concurrent use of antacids.

Clinical evidence

(a) Iron compounds

A study in healthy subjects who were mildly iron-deficient (due to blood donation or menstruation) found that about 5 mL of *Mylanta II* (**aluminium/magnesium hydroxide** with simeticone) had little effect on the absorption of 10 or 20 mg of **ferrous sulfate** at 2 hours. However, **sodium bicarbonate** 1 g almost halved the absorption of **ferrous sulfate**.[1] Another study in healthy iron-replete subjects found that an antacid containing **aluminium/magnesium hydroxide** and **magnesium carbonate** reduced the absorption of **ferrous sulfate** and **ferrous fumarate** (both containing 100 mg of ferrous iron) by 37% and 31%, respectively.[2] Poor absorption of iron during the use of **sodium bicarbonate** and **aluminium hydroxide** has been described elsewhere.[3,4] One study did not find that the absorption of **ferrous sulfate** (iron 10 mg/kg) was affected by doses of **magnesium hydroxide** (5 mg for every 1 mg of iron) when the doses were given 30 minutes apart.[5] However, it has been suggested that, in this study, iron absorption was not measured for a sufficient period to fully rule out a reduction in absorption.[6]

Oral iron did not produce the expected rise in haemoglobin levels in patients taking non-absorbable alkalis such as **magnesium trisilicate**, and therefore a study was undertaken in 9 patients. Each patient was given 5 mg of isotopically labelled **ferrous sulfate** after a 35-g dose of **magnesium trisilicate**. The **magnesium** reduced the absorption of iron by an average of 70 to 88%, the reduction being small in some patients. However, in one individual iron absorption was reduced from 67% to 5%.[7]

(b) Iron polymaltose

In a study in patients with iron-deficiency anaemia, erythrocyte uptake of iron did not differ when oral iron polymaltose (equivalent to 100 mg of iron) was given alone or with **aluminium hydroxide** 600 mg (10 mL *Am-*

phojel). Iron polymaltose is a complex of ferric hydroxide with isomaltose.[8]

Mechanism

Uncertain. One suggestion is that magnesium sulfate changes ferrous sulfate into less easily absorbed salts, or increases its polymerisation.[7] Carbonates possibly cause the formation of poorly soluble iron complexes.[3] Aluminium hydroxide is believed to precipitate iron as the hydroxide and ferric ions can become intercalated into the aluminium hydroxide crystal lattice,[9] leaving less available for absorption.

Importance and management

Information is limited and difficult to assess because of the many variables (e.g. different dosages ranging from very small to those mimicking overdose, and a mix of subjects and patients). However, a reasonable 'blanket precaution' to achieve maximal absorption would be to separate the administration of iron preparations and antacids as much as possible to avoid admixture in the gut. This may not prove to be necessary with some preparations. For example, iron polymaltose does not appear to be affected by aluminium hydroxide.

Consider also 'Iron compounds + Calcium compounds', p.1405, for the effects of calcium compounds, some of which may be used as antacids.

1. O'Neil-Cutting MA, Crosby WH. The effect of antacids on the absorption of simultaneously ingested iron. *JAMA* (1986) 255, 1468–70.
2. Ekenved G, Halvorsen L, Sölvell L. Influence of a liquid antacid on the absorption of different iron salts. *Scand J Haematol* (1976) 28 (Suppl), 65–77.
3. Benjamin BI, Cortell S, Conrad ME. Bicarbonate-induced iron complexes and iron absorption: one effect of pancreatic secretions. *Gastroenterology* (1967) 35, 389–96.
4. Rastogi SP, Padilla F, Boyd CM. Effect of aluminum hydroxide on iron absorption. *J Arkansas Med Soc* (1976) 73, 133–4.
5. Snyder BK, Clark RF. Effect of magnesium hydroxide administration on iron absorption after a supratherapeutic dose of ferrous sulfate in human volunteers: a randomized controlled trial. *Ann Emerg Med* (1999) 33, 400–405.
6. Wallace KL, Curry SC, LoVecchio F, Raschke RA. Effect of magnesium hydroxide on iron absorption after ferrous sulfate. *Ann Emerg Med* (1999) 34, 685–6.
7. Hall GJL, Davis AE. Inhibition of iron absorption by magnesium trisilicate. *Med J Aust* (1969) 2, 95–6.
8. Potgieter MA, Potgieter JH, Venter C, Venter JL, Geisser P. Effect of oral aluminium hydroxide on iron absorption from iron(III)-hydroxide polymaltose complex in patients with iron deficiency anemia. *Arzneimittelforschung* (2007) 57, 392–400.
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Iron compounds + Beverages

Reduced iron absorption has been reported with beverages high in polyphenolics such as cocoa, coffee, tea, pennyroyal tea and peppermint tea. Chamomile tea, green tea and rooibos tea do not appear to significantly affect iron absorption.

Clinical evidence

(a) Chamomile

A study in 13 healthy subjects found that chamomile tea (an infusion of *Matricaria chamomilla*) sweetened with panela (an unrefined cane sugar sweetener containing fructose) did not affect the absorption of iron from an iron-fortified bread, when compared with the absorption of iron from the bread alone. The tannin content of the chamomile tea was reported to be 24.5 mg in 100 mL.[1]

(b) Cocoa

In a study in 10 healthy subjects[2] a 275 mL serving of cocoa beverage reduced the absorption of radiolabelled iron from a 50 g bread roll by about 70%. In this study, the inhibitory effect of cocoa beverage on iron absorption was only slightly less that of black tea (Assam tea, *Camellia sinensis* L.).

(c) Coffee

In a series of studies in healthy subjects, drinking 200 mL of coffee with various test meals containing radiolabelled iron resulted in a 39% to 83% reduction in the absorption of iron. No decrease was observed if the coffee was drunk one hour before the meal, but when the coffee was given one hour after the meal the reduction was the same as taking it simultaneously with the meal. With one meal, the effect of coffee was about half that of tea.[3] In another study, a 275 mL serving of instant coffee reduced the absorption of radiolabelled iron from a 50 g bread roll, and this was not affected by milk.[2]

A controlled study among pregnant women in Costa Rica found that coffee consumption was associated with reductions in the haemoglobin levels and haematocrits of the mothers during pregnancy, and of their babies shortly after birth, despite the fact that the women were taking ferric sulfate 200 mg and 500 micrograms of folate daily. The babies also had a slightly lower birth weight (3189 g versus 3310 g). Almost a quarter of the mothers were considered to have iron-deficiency anaemia (haemoglobin levels of less than 11 g/dL), compared with none among the control group of non-coffee drinkers. Levels of iron in breast milk were reduced by about one-third. The coffee drinkers drank more than 450 mL of coffee daily, equivalent to more than 10 g of ground coffee.[4]

In a randomised study in Guatemalan infants, discontinuing coffee intake in those given an iron supplement led to a greater increase in serum ferritin than continuing coffee consumption (median 891 mL weekly). However, discontinuing coffee had no effect on changes in haemoglobin.[5]

(d) Pennyroyal

In a study in 9 healthy subjects, a 275 mL serving of pennyroyal tea reduced the absorption of iron in a 50 g bread roll by about 70%. The tea was prepared by adding 300 mL of boiling water to 3 g of the herbal tea, then infusing for 10 minutes before straining and serving. In this study, the inhibitory effect of pennyroyal tea on iron absorption was modestly less than that of black tea (Assam tea, *Camellia sinensis* L.).[2]

(e) Peppermint tea

In a study in 9 healthy subjects a 275 mL serving of peppermint tea reduced the absorption of iron from a 50 g bread roll by about 85%. The tea was prepared by adding 300 mL of boiling water to 3 g of the herb tea, then infusing for 10 minutes before straining and serving.[2] In this study, the inhibitory effect of peppermint tea on iron absorption was equivalent to that of black tea (Assam tea, *Camellia sinensis* L.).

(f) Rooibos

In a parallel group study in healthy subjects, mean iron absorption after ingestion of radiolabelled iron 16 mg with a beverage was 7.25% with rooibos tea, 1.7% with tea, and 9.34% with water.[6]

(g) Tea

1. Black tea. There is little data on the effect of tea on the absorption of iron from supplements. One case report describes an impaired response to iron, given to correct iron-deficiency anaemia, in a patient drinking 2 litres of black tea daily. The patient recovered when the black tea was stopped. This report did not specify whether the black tea was tea without milk, or black (fermented) tea.[7]

Some short-term controlled studies show a marked reduction in the absorption of dietary non-haem iron with black (fermented) tea beverage, some of which are cited for information.[2,3,8,9] In one of these, in a series of studies in healthy subjects, a 275 mL serving of black (fermented, Assam) tea reduced the absorption of radiolabelled iron from a 50 g bread roll by 79 to 94%. The tea was prepared by adding 300 mL of boiling water to 3 g of Assam tea, then infusing for 10 minutes before straining and serving. Milk added to the tea had very little effect on the reduction in iron absorption.[2] A study found that 150 mL of black tea reduced the absorption of radiolabelled iron from a test meal by 59% in 10 women with iron deficiency anaemia and by 49% in 10 control subjects without anaemia. When the quantity of tea was increased to 300 mL iron absorption was reduced by about 66% in both groups.[10]

Whether these reductions in iron absorption are important in the development of iron deficiency anaemia is less clear. Various epidemiological studies have looked at the correlation between tea consumption and iron deficiency in different populations. In one review of 16 of these studies, tea consumption did not influence iron status in people with adequate iron stores (as is common in the West), but there seemed to be a negative association between tea consumption and iron status in people with marginal iron status.[11] Another report describes no change in the absorption of a single dose of iron (2 to 15.8 mg/kg) in 10 iron-deficient children when the iron was given with 150 mL of tea (type unspecified) instead of water.[12]

2. Green tea. A study found that green tea extract (37 mg catechins) showed a modest 26% reduction in iron absorption,[13] and another study, of pure epigallocatechin gallate 150 mg and 300 mg, found only a 14% and 27% reduction in iron absorption, respectively.[14] A study in 4 elderly patients with iron deficiency anaemia and 11 control patients found no evidence that green tea inhibited the absorption of iron from sodium ferrous citrate.[15] Another study in pregnant women with iron deficiency anaemia reported a slightly higher resolution rate for anaemia in patients taking green tea.[16]

Note that tea has been used with some success in reducing iron accumulation and the frequency of phlebotomy in patients with iron overload syndromes.[17]

Mechanism

Tannins found in tea and polyphenolics found in cocoa, coffee, pennyroyal and peppermint tea are thought to form insoluble complexes with non-haem iron and thus reduce its absorption.[12] Chamomile tea and rooibos tea, which appear not to interact, contain much lower levels of tannins than black tea.

Importance and management

The general importance of these findings is uncertain, but be aware that black tea consumption may contribute to iron-deficiency anaemia. However, it has been suggested that no restrictions are required in healthy patients not at risk of iron deficiency.[18] Conversely, the suggestion is that patients at risk of iron deficiency (which would include those requiring iron supplements) should be advised to avoid tea with meals and for one hour after eating.[18] Note that tea is not generally considered to be a suitable drink for babies and children, because of its effects on iron absorption. Milk does not attenuate the effect of black (fermented) teas on iron absorption.

Other teas and beverages that may have similar effects to black tea appear to include cocoa, coffee, pennyroyal tea and peppermint tea.

Other teas that appear to have minimal interactions with iron include chamomile tea, green tea, and rooibos tea.

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Iron compounds + Calcium compounds

Calcium carbonate and calcium acetate (in large doses) modestly reduce the absorption of iron from ferrous sulfate.

Clinical evidence, mechanism, importance and management

In a single-dose study in 23 fasting healthy subjects,[1] the bioavailability of iron from **ferrous sulfate** 200 mg was reduced by 27% by **calcium acetate** 2.7 g, and by 19% by **calcium carbonate** 3 g.

A study in healthy subjects who were mildly iron-deficient (due to blood donation or menstruation) found that **calcium carbonate** 500 mg reduced the absorption of 10 or 20 mg of **ferrous sulfate** by two-thirds. Conversely, iron absorption from a multivitamin and mineral preparation was little affected by whether or not the tablet contained 200 mg of calcium (as **calcium carbonate**).[2]

It was suggested that calcium may form insoluble complexes with iron, so reducing its absorption.

The evidence is limited, but in general it appears that large doses of calcium compounds (500 mg of calcium or more) may reduce the absorption of iron; this would be expected to be clinically relevant. Ideally the findings of the study using calcium in phosphate-binding doses need replicating clinically, that is, in an appropriate patient group taking the calcium compounds long-term with meals. Nevertheless, a reasonable 'blanket precaution' to achieve maximal absorption would be to separate the administration of iron preparations and calcium as much as possible to avoid admixture in the gut. It would also seem prudent to monitor the response to iron. If the response is inadequate in those using calcium as a phosphate binder, an alternative may be to use sevelamer, which does not appear to affect iron absorption, see 'Iron compounds + Sevelamer', p.1406.

1. Pruchnicki MC, Coyle JD, Hoshaw-Woodard S, Bay WH. Effect of phosphate binders on supplemental iron absorption in healthy subjects. *J Clin Pharmacol* (2002) 42, 1171–6.
2. O'Neil-Cutting MA, Crosby WH. The effect of antacids on the absorption of simultaneously ingested iron. *JAMA* (1986) 255, 1468–70.

Iron compounds + Colestyramine

Early *animal* studies found that colestyramine binds with ferrous sulfate in the gut and reduces its absorption, but iron deficiency was not seen in one small long-term clinical study.

Clinical evidence, mechanism, importance and management

In vitro studies have found that colestyramine binds with iron, and in *rats* this was found to halve the absorption of a single 100-microgram dose of **ferrous sulfate**,[1] and to significantly decrease serum iron and tissue iron stores with prolonged colestyramine use (in the absence of iron supplementation).[2] However, in 18 children, the prolonged use (1 to 2.5 years) of colestyramine did not change serum iron levels.[3]

Evidence is extremely limited, but it might suggest that no special precautions are required on concurrent use. Nevertheless, it is often advised to avoid other drugs for one hour before or 4 to 6 hours after colestyramine to minimise the possibility of interactions.

1. Thomas FB, McCullough F, Greenberger NJ. Inhibition of the intestinal absorption of inorganic and hemoglobin iron by cholestyramine. *J Lab Clin Med* (1971) 78, 70–80.
2. Thomas FB, Salsburey D, Greenberger NJ. Inhibition of iron absorption by cholestyramine. Demonstration of diminished iron stores following prolonged administration. *Am J Dig Dis* (1972) 17, 263–9.
3. West RJ, Lloyd JK. The effect of cholestyramine on intestinal absorption. Gut. (1975) 16, 93–8.

Iron compounds + H_2-receptor antagonists

Apart from a brief and unconfirmed report alleging that cimetidine reduced the response to ferrous sulfate, there appears to be no other evidence that H_2-receptor antagonists reduce the absorption of iron to a clinically relevant extent. Iron causes only a small and clinically irrelevant reduction in the serum levels of cimetidine and famotidine.

Clinical evidence, mechanism, importance and management

(a) Effect on iron

A brief report describes 3 patients taking **cimetidine** 1 g and **ferrous sulfate** 600 mg daily, whose ulcers healed after 2 months but whose anaemia and altered iron metabolism persisted. When the **cimetidine** was reduced to 400 mg daily the blood picture resolved satisfactorily within a month, without an alteration in the iron dose.[1] The author of the report attributed this response to the **cimetidine**-induced rise in gastric pH, which reduced the absorption of the iron. However, this suggested mechanism was subsequently disputed, as medicinal iron is already in the most absorbable form, Fe^{2+}, and so does not need an acidic environment to aid absorption.[2]
A study in patients with iron deficiency, or iron-deficiency anaemia, found that the concurrent use of **famotidine**, **nizatidine**, or **ranitidine**, did not affect their response to 2.4 g of **iron succinyl-protein complex** (equiva-

lent to 60 mg of iron twice daily).[3] No special precautions would seem necessary on concurrent use.

(b) Effect on H_2-receptor antagonists

In a series of three studies, healthy subjects were given **cimetidine** 300 mg with **ferrous sulfate** 300 mg, either as a tablet or a solution. The reductions in the AUC and the maximum serum levels of **cimetidine** were small (less than 16%). In the third experiment they were given **famotidine** 40 mg with **ferrous sulfate** 300 mg (as a tablet). Again, the AUC and maximum serum level reductions were also very small (10% or less). These small reductions are almost certainly due to the formation of a weak complex between the iron and these H_2-receptor antagonists.[4] An *in vitro* study with **ranitidine** found that, while it also binds with iron, it forms a very weak complex, and is less likely to bind than **cimetidine** or **famotidine**.[4] It was concluded that no clinically relevant interaction occurs between **ferrous sulfate** and any of these H_2-receptor antagonists.[4]

1. Esposito R. Cimetidine and iron-deficiency anaemia. *Lancet* (1977) ii, 1132.
2. Rosner F. Cimetidine and iron absorption. *Lancet* (1978) i, 95.
3. Bianchi FM, Cavassini GB, Leo P. Iron protein succinylate in the treatment of iron deficiency: Potential interaction with H_2-receptor antagonists. *Int J Clin Pharmacol Ther Toxicol* (1993) 31, 209–17.
4. Partlow ES, Campbell NRC, Chan SC, Pap KM, Granberg K, Hasinoff BB. Ferrous sulfate does not reduce serum levels of famotidine or cimetidine after concurrent ingestion. *Clin Pharmacol Ther* (1996) 59, 389–93.

Iron compounds + Neomycin

Neomycin may alter the absorption of iron.

Clinical evidence, mechanism, importance and management

A study in 6 patients found that neomycin markedly reduced the absorption of iron ($iron^{59}$ as **ferrous citrate**) in 4 patients, but increased its absorption in the other 2 patients who initially had low serum iron levels. None of the patients were anaemic at any time.[1] The importance of this is uncertain, but consider this possible interaction if the response to iron is poor.

1. Jacobson ED, Chodos RB, Faloon WW. An experimental malabsorption syndrome induced by neomycin. *Am J Med* (1960) 28, 524–33.

Iron compounds + Sevelamer

Sevelamer does not appear to affect the absorption of iron from ferrous sulfate to a clinically relevant extent.

Clinical evidence, mechanism, importance and management

In a single-dose study in 23 fasting healthy subjects,[1] the bioavailability of iron from **ferrous sulfate** 200 mg was reduced by a modest 10% by sevelamer 2.8 g. This study suggests that sevelamer is unlikely to have a clinically relevant effect on iron absorption; however, the findings need replicating in an appropriate patient group taking sevelamer long-term with meals.

1. Pruchnicki MC, Coyle JD, Hoshaw-Woodard S, Bay WH. Effect of phosphate binders on supplemental iron absorption in healthy subjects. *J Clin Pharmacol* (2002) 42, 1171–6.

Iron compounds + Vitamin E substances

Vitamin E impaired the response to iron in a group of anaemic children.

Clinical evidence, mechanism, importance and management

A group of 26 anaemic children aged 7 to 40 months were given **iron dextran** 5 mg/kg daily for 3 days. Vitamin E 200 units daily was also given to 9 of the children, starting 24 hours before the **iron dextran** and continued for a total of 4 days. It was noted that after 6 days, those taking vitamin E had a reticulocyte response of only 4.4%, compared with 14.4% in the patients not given vitamin E. The vitamin E group also had reduced haemoglobin levels and a lower haematocrit. The reasons are not understood. Check for any evidence of a reduced haematological response in anaemic patients given iron and vitamin E. The authors of the report point out that this dosage of vitamin E was well above the recommended daily dietary intake.[1]

1. Melhorn DK, Gross S. Relationships between iron-dextran and vitamin E in iron deficiency anemia in children. *J Lab Clin Med* (1969) 74, 789–802.

Iron compounds or Vitamin B_{12} + Chloramphenicol

In addition to the serious and potentially fatal bone marrow depression that can occur with chloramphenicol, it may also cause a milder, reversible bone marrow depression, which can oppose the treatment of anaemias with iron or vitamin B_{12}.

Clinical evidence

Two patients receiving **iron dextran** for iron-deficiency anaemia and also given oral chloramphenicol 3 g daily, did not have the expected haematological response to the iron.[1] Four patients receiving vitamin B_{12} for pernicious anaemia were all similarly refractory to **iron dextran** until chloramphenicol (52 to 60 mg/kg for 3 to 7 days) was withdrawn.[1]

Mechanism

Chloramphenicol can cause two forms of bone marrow depression. One is serious and irreversible, and can result in fatal aplastic anaemia, whereas the other is probably unrelated, milder and reversible, and appears to occur at chloramphenicol serum levels of 25 micrograms/mL or more. This occurs because chloramphenicol can inhibit protein synthesis, the first sign of which is a fall in the reticulocyte count, which reflects inadequate red cell maturation. This response to chloramphenicol has been seen in healthy individuals,[2] a series of patients with liver disease,[3] and in anaemic patients[1] receiving iron dextran or vitamin B_{12}.

Importance and management

An established interaction of clinical importance. The authors of one study recommend that chloramphenicol dosages of 25 to 30 mg/kg are usually adequate for treating infections without running the risk of elevating serum levels to 25 micrograms/mL or more, which is when this type of marrow depression can occur.[4] Monitor the effects of using iron or vitamin B_{12} together with chloramphenicol. A preferable alternative would be to use a different antibacterial. Note that chloramphenicol should not be used in patients with pre-existing bone-marrow depression or blood dyscrasias.

1. Saidi P, Wallerstein RO, Aggeler PM. Effect of chloramphenicol on erythropoiesis. *J Lab Clin Med* (1961) 57, 247–56.
2. Jiji RM, Gangarosa EJ, de la Macorra F. Chloramphenicol and its sulfamoyl analogue. Report of reversible erythropoietic toxicity in healthy volunteers. *Arch Intern Med* (1963) 111, 116–28.
3. McCurdy PR. Chloramphenicol bone marrow toxicity. *JAMA* (1961) 176, 588–93.
4. Scott JL, Finegold SM, Belkin GA, Lawrence JS. A controlled double-blind study of the hematologic toxicity of chloramphenicol. *N Engl J Med* (1965) 272, 1137–42.

Melatonin + Caffeine

Caffeine increases the levels of both endogenous and orally administered melatonin.

Clinical evidence

In a crossover study, 12 healthy subjects were given a single 200-mg dose of caffeine (equivalent to one large or two small cups of coffee), 1 hour before and 1 and 3 hours after a single 6-mg oral dose of melatonin. Caffeine increased the average AUC and maximum levels of melatonin by 120% and 137%, respectively, although the half-life of melatonin was not significantly affected. The interaction was less pronounced in smokers (6 subjects) than in non-smokers (6 subjects).[1] In a similar study, taking caffeine 12 or 24 hours before melatonin did not affect the melatonin levels, although 2 subjects had raised melatonin levels when caffeine was taken 12 hours, but not 24 hours, before melatonin.[2]

In 12 healthy subjects given a single 200-mg dose of caffeine, taken in the evening, *endogenous*, nocturnal melatonin levels were found to be increased, and the AUC of melatonin was increased by 32%.[3]

Mechanism

Caffeine is thought to reduce the metabolism of melatonin by competing for metabolism by the cytochrome P450 isoenzyme CYP1A2.[1-3]

Importance and management

The interaction between caffeine and melatonin appears to be established. Melatonin is produced by the pineal gland in the body and is also available as a supplement in some parts of the world; however, the effects of long-term use of this supplement are unknown. From the above studies, it appears that caffeine significantly increases the levels of single doses of supplementary melatonin, however the long-term effects of caffeine on multiple doses of melatonin do not appear to have been studied. Melatonin can cause drowsiness when taken on its own, so patients who take melatonin should be advised that this effect may be increased (because of increased melatonin levels) if they also take caffeine, including that from beverages. This increased drowsiness may oppose the stimulating effect of caffeine, or alternatively caffeine may diminish the sedating effects of melatonin; the outcome of concurrent use does not appear to have been studied.

1. Härtter S, Nordmark A, Rose D-M, Bertilsson L, Tybring G, Laine K. Effects of caffeine intake on the pharmacokinetics of melatonin, a probe drug for CYP1A2 activity. *Br J Clin Pharmacol* (2003) 56, 679–682.
2. Härtter S, Korhonen T, Lundgren S, Rane A, Tolonen A, Turpeinen M, Laine K. Effect of caffeine intake 12 or 24 hours prior to melatonin intake and *CYP1A2*1F* polymorphism on CYP1A2 phenotyping by melatonin. *Basic Clin Pharmacol Toxicol* (2006) 99, 300–4.
3. Ursing C, Wikner J, Brismar K, Röjdmark S. Caffeine raises the serum melatonin level in healthy subjects: an indication of melatonin metabolism by cytochrome P450 (CYP)1A2. *J Endocrinol Invest* (2003) 26, 403–6.

Melatonin + Fluvoxamine

Fluvoxamine markedly increases the levels of endogenous and orally administered melatonin.

Clinical evidence

In a study in 5 healthy subjects, a single 50-mg dose of fluvoxamine taken 3 hours before a single 5-mg oral dose of melatonin markedly increased the average AUC and maximum levels of melatonin by 17-fold and 12-fold, respectively, although the half-life of melatonin was not significantly affected. The interaction was more pronounced in the one subject who was of a CYP2D6-poor metaboliser phenotype (meaning that this patient was lacking or totally deficient in this isoenzyme). All subjects reported marked drowsiness after melatonin intake that was even more pronounced when fluvoxamine was also given.[1]

Similarly, fluvoxamine 75 mg raised the levels of oral melatonin 5 mg by about 20-fold and significantly improved the sleep behaviour of a 51-year-old insomniac.[2]

In another study in 7 healthy subjects, fluvoxamine 50 mg doubled the maximum serum levels and excretion of endogenous melatonin and increased the AUC by about threefold.[3]

Mechanism

Previous studies had shown that fluvoxamine increased endogenous melatonin levels. This study demonstrates that this is likely to be via a pharmacokinetic mechanism. Fluvoxamine is known to be a potent inhibitor of the cytochrome P450 isoenzyme CYP1A2, by which melatonin is metabolised.

Importance and management

Evidence is limited, but an interaction between fluvoxamine and melatonin would appear to be established. Melatonin is produced by the pineal gland in the body, and is also available as a supplement; however, the effects of long-term use of this supplement are unknown. From the above study, it appears that fluvoxamine markedly increases the levels of single doses of supplementary melatonin, however the long-term effects of fluvoxamine on multiple doses of melatonin do not appear to have been studied. Be aware that excessive drowsiness and related adverse effects may occur on concurrent use. Note that one UK manufacturer advises that the combination should be avoided.[4] Other inhibitors of CYP1A2 may interact similarly (although to a lesser extent as fluvoxamine is currently the most potent CYP1A2 inhibitor in clinical use). The UK manufacturer specifically mentions the **quinolones**.[4] Of the quinolones in common usage, ciprofloxacin is an example of a clinically important CYP1A2 inhibitor.

Note that this effect would not be expected with other SSRIs, as these are not CYP1A2 inhibitors.

1. Härtter S, Grözinger M, Weigmann H, Röschke J, Hiemke C. Increased bioavailability of oral melatonin after fluvoxamine coadministration. *Clin Pharmacol Ther* (2000) 67, 1–6.
2. Grözinger M, Härtter S, Wang X, Röschke J, Hiemke C. Fluvoxamine strongly inhibits melatonin metabolism in a patient with low-amplitude melatonin profile. *Arch Gen Psychiatry* (2000) 57, 812.
3. von Bahr C, Ursing C, Yasui N, Tybring G, Bertilsson L, Röjdmark S. Fluvoxamine but not citalopram increases serum melatonin in healthy subjects - an indication that cytochrome P450 CYP1A2 and CYP2C19 hydroxylate melatonin. *Eur J Clin Pharmacol* (2000) 56, 123–7.
4. Circadin (Melatonin). Lundbeck Ltd. UK Summary of product characteristics, March 2009.

Melatonin + Miscellaneous

Alcohol may reduce the effects of melatonin on sleep. The concurrent use of imipramine and melatonin may lead to increased CNS effects. Cimetidine slightly increases melatonin levels. Psoralens are predicted to increase melatonin levels.

Clinical evidence, mechanism, importance and management

(a) Alcohol

The manufacturer of melatonin briefly notes that alcohol reduces the effectiveness of melatonin on sleep, and that it should not be taken with melatonin.[1] Given the known effects of alcohol on sleep, if melatonin is being taken to improve quality of sleep then this is sensible advice.

(b) Cimetidine

In a single-dose controlled study, cimetidine 800 mg increased the plasma concentration of melatonin after a 2 mg oral dose (magnitude not stated), whereas the plasma levels of cimetidine were unaffected. The pharmacodynamics of melatonin were not affected.[2] Cimetidine is a weak inhibitor of the cytochrome P450 isoenzyme CYP1A2, by which melatonin is principally metabolised. Therefore concurrent use results in raised melatonin levels. However, as cimetidine is a weak CYP1A2 inhibitor, the pharmacokinetic interaction would be unlikely to be clinically relevant. Nevertheless, the manufacturer recommends caution.[1] Be aware of a possible interaction if there is an increase in the adverse effects of melatonin (e.g. irritability, dry mouth, dizziness) on concurrent use. Other H_2-receptor antagonists are unlikely to interact as they are not known to have enzyme-inhibiting effects.

(c) Psoralens

The manufacturer briefly notes that **methoxsalen** and **5-methoxypsoralen** inhibit the metabolism of melatonin and increases its levels (magnitude not stated).[1] Note that 5-methoxypsoralen has been shown to increase endogenous melatonin levels (one study is cited as an example[3]).

Psoralens are potent inhibitors of the cytochrome P450 isoenzyme CYP1A2 by which melatonin is principally metabolised, and therefore concurrent use may be expected to raise melatonin levels. The manufacturer of melatonin recommends caution on concurrent use,[1] which seems prudent as the adverse effects of melatonin may be increased. Any interaction would only apply to these psoralens used orally, and not when they are used topically. Be aware of a possible interaction if there is an increase in the adverse effects of melatonin (e.g. irritability, dry mouth, dizziness) in patients also taking psoralens.

(d) Tricyclics

In a single-dose controlled study, there was no pharmacokinetic interaction between melatonin 2 mg and **imipramine** 75 mg. However, there was a possible pharmacodynamic interaction, with increased feelings of tranquillity and difficulty in performing tasks (undefined) when compared with **imipramine** alone.[1,2] This may potentially occur with all tricyclics. Patients should be warned of a possible additive effect.

1. Circadin (Melatonin). Lundbeck Ltd. UK Summary of product characteristics, March 2009.
2. EMEA Assessment report for Circadin. Procedure No. EMEA/H/C/695. 2007. Available at: http://www.emea.europa.eu/humandocs/PDFs/EPAR/circadin/H-695-en6.pdf (accessed 01/02/10).
3. Souetre E, Salvati E, Belugou JL, Krebs B, Darcourt G. 5-Methoxypsoralen as a specific stimulating agent of melatonin secretion in humans. *J Clin Endocrinol Metab* (1990) 71, 670–4.

Melatonin + Oestrogens

Oestrogens, from oral combined hormonal contraceptives, appear to increase melatonin levels.

Clinical evidence

In a clinical study, the AUC and maximum level of a single 6-mg dose of melatonin was about 4 times higher in subjects taking a an oral combined hormonal contraceptive than those not taking this type of contraceptive. Melatonin alone did not significantly affect alertness in this study, and no reduced alertness was noted in those taking oral contraceptives. The contraceptives being used by the women included **ethinylestradiol** with either cyproterone acetate, desogestrel, drospirenone or gestodene. There did not appear to be any obvious differences between these contraceptives, but the numbers of women taking each were too small for this to be conclusive.[1]

Mechanism

Ethinylestradiol is a moderate inhibitor of the cytochrome P450 isoenzyme CYP1A2, by which melatonin is principally metabolised.

Importance and management

Women taking oral combined hormonal contraceptives may have higher levels of melatonin after using supplements. Although in the study cited, this did not decrease alertness, it would be prudent to bear in mind the possibility of increased drowsiness. One UK manufacturer extends this caution to **hormone replacement therapy**,[2] although it is unclear whether the oestrogens used for HRT will have the same effect as ethinylestradiol.

1. Hilli J, Korhonen T, Turpeinen M, Hokkanen J, Mattila S, Laine K. The effect of oral contraceptives on the pharmacokinetics of melatonin in healthy subjects with CYP1A2 g.-163C>A polymorphism. J Clin Pharmacol (2008) 48, 986–94.
2. Circadin (Melatonin). Lundbeck Ltd. UK Summary of product characteristics, March 2009.

Melatonin + Tobacco

Tobacco smoking reduces melatonin levels.

Clinical evidence, mechanism, importance and management

In a study in 8 tobacco smokers, the AUC of a single 25-mg dose of melatonin was almost threefold higher when the melatonin was taken after 7 days of smoking abstinence than when taken while smoking.[1]

Constituents of tobacco smoke are minor to moderate inducers of the cytochrome P450 isoenzyme CYP1A2, by which melatonin is principally metabolised.

The finding of this study suggests that melatonin might not be as effective in smokers. Be aware of this possibility, and consider trying an increased melatonin dose if it is not effective in a smoker.

1. Ursing C, von Bahr C, Brismar K, Röjdmark S. Influence of cigarette smoking on melatonin levels in man. *Eur J Clin Pharmacol* (2005) 61, 197–201.

Nicotine + Grapefruit juice

Grapefruit slightly inhibits the metabolism and increases the renal clearance of oral nicotine.

Clinical evidence, mechanism, importance and management

In a single-dose pharmacokinetic study in healthy subjects, administration of oral nicotine 2 mg with full-strength and half-strength grapefruit juice reduced the AUC of conitine (a metabolite of nicotine) by 15% and 2.5%, respectively. Conversely, the renal clearance of nicotine was increased. It was suggested that grapefruit juice inhibits the cytochrome P450 isoenzyme CYP2A6, which is responsible for the metabolism of oral nicotine to cotinine.[1]

The changes seen here were small and unlikely to be clinically relevant. Note that nicotine is not usually given by the oral route as in this study: replacement therapy is by the buccal route (chewing gum or sublingual tablets), or the transdermal route.

1. Hukkanen J, Jacob P, Benowitz NL. Effect of grapefruit juice on cytochrome P450 2A6 and nicotine renal clearance. *Clin Pharmacol Ther* (2006) 80, 522–30.

Nicotine + Tranylcypromine

Tranylcypromine inhibits the metabolism of oral nicotine.

Clinical evidence, mechanism, importance and management

A brief report describes a study in smokers in which low-dose tranylcypromine 2.5 mg three times daily increased plasma levels of oral nicotine by about 75%, but did not affect subcutaneous nicotine. Tranylcypromine inhibits the cytochrome P450 isoenzyme CYP2A6, which is responsible for the metabolism of oral nicotine to cotinine. Inhibiting this step leads to raised nicotine levels.[1]

Note that nicotine is not usually given orally. The clinical relevance of this finding to buccal formulations of nicotine replacement therapy (chewing gum and sublingual tablets) is unknown, but it seems likely to be small.

1. Fernandes LC, Tyndale RF, Sellers EM. Tranylcypromine (TCP) inhibition of nicotine metabolism. *Drug Alcohol Depend* (2002) 66 (Suppl 1) S54–S55.

Nicotine + Vasopressin

A case report described marked hypotension and bradycardia in a young woman during surgery, which was attributed to the combined effects of a vasopressin injection and nicotine from a transdermal patch.

Clinical evidence

A 22-year-old woman in good health was anaesthetised for surgery with nitrous oxide/oxygen and isoflurane. Twenty minutes after induction she was given an injection of 0.2 units of vasopressin into the cervix. Within seconds she developed severe hypotension and bradycardia, and over the next 30 minutes blood pressures as low as 70/35 mmHg and heart rates as low as 38 bpm were recorded. She was given atropine and adrenaline (epinephrine), and eventually made a full recovery. This patient was wearing a transdermal nicotine patch.[1]

Mechanism

The circulatory collapse was attributed by the authors to the combined effects of the injected vasopressin and the nicotine from the transdermal patch. Both of these drugs can increase cardiac afterload and cause coronary artery vasoconstriction, which the authors suggest may have decreased the blood supply to the heart and resulted in cardiac depression.[1]

Importance and management

This is an isolated report and any interaction between nicotine and vasopressin is therefore not well established. Nevertheless the recommendation of the authors seems sensible, namely that nicotine patches should be removed the night before or 24 hours before surgery, and that patients should be asked to avoid smoking before surgery to make sure that nicotine levels are minimal. More study is needed.

1. Groudine SB, Morley JN. Recent problems with paracervical vasopressin: a possible synergistic reaction with nicotine. *Med Hypotheses* (1996) 47, 19–21.

Paricalcitol + Miscellaneous

Ketoconazole raises paricalcitol levels; other potent CYP3A4 inhibitors are predicted to interact similarly. The use of paricalcitol increases the risks of raised calcium, phosphate, aluminium, or magnesium levels in patients taking drugs containing these substances, or drugs that raise the levels of these substances (e.g. vitamin D).

Clinical evidence, mechanism, importance and management

(a) CYP3A4 inhibitors

In a study in healthy subjects, **ketoconazole** 200 mg twice daily for 5 days did not significantly alter the maximum levels of paricalcitol, but the AUC of paricalcitol was doubled, and its half-life was prolonged from 9.8 hours

to 17 hours.[1,2] On the basis of this interaction the US manufacturer predicts that other potent inhibitors of the cytochrome P450 isoenzyme CYP3A4 will interact similarly. They specifically name the protease inhibitors **atazanavir**, **indinavir**, **nelfinavir**, **ritonavir** and **saquinavir**; the azole antifungals **itraconazole** and **voriconazole**; and the macrolides **clarithromycin** and **telithromycin**. The manufacturer recommends close monitoring if any of these drugs is given to a patient taking paricalcitol,[2] and recommend monitoring intact parathyroid hormone and calcium levels if drugs such as **ketoconazole** are started or stopped.[1,2]

(b) Other drugs

Paricalcitol use may lead to increased calcium and phosphate levels. The UK manufacturer therefore warns that the concurrent use of **calcium-** or **phosphate-containing substances** may increase this risk. They specifically advise against the concurrent use of **phosphate-containing substances** with paricalcitol.[1] In addition the concurrent use of **vitamin D** may increase the risk of hypercalcaemia, and should therefore be avoided where possible. The UK manufacturer also advises that the use of **aluminium-** and **magnesium-containing substances** (e.g. **antacids**, phosphate binders) should be avoided with paricalcitol because raised blood levels of these substances may occur.[1] However, note that patients with renal impairment are highly likely to be taking these drugs and having serum electrolyte levels frequently monitored. Furthermore the US manufacturer[2] does not advise against their concurrent use.

1. Zemplar Soft Capsules (Paricalcitol). Abbott Laboratories Ltd. UK Summary of product characteristics, December 2007.
2. Zemplar Injection (Paricalcitol). Abbott Laboratories. US Prescribing information, January 2009.

Paricalcitol + Omeprazole

The pharmacokinetics of paricalcitol are not affected by omeprazole.

Clinical evidence, mechanism, importance and management

A randomised study in 25 healthy subjects found that a single 40-mg dose of omeprazole, taken 2 hours before a single 16-microgram dose of paricalcitol, had no significant effects on the pharmacokinetics of paricalcitol. No increase in adverse effects was noted and the combination was reported to be well tolerated. No paricalcitol dosage adjustments are therefore necessary if omeprazole is also given.[1]

1. Palaparthy R, Pradhan RS, Chan J, Rieser M, Chira T, Galitz L, Awni W, Williams LA. Effect of omeprazole on the pharmacokinetics of paricalcitol in healthy subjects. *Biopharm Drug Dispos* (2007) 28, 65–71.

St John's wort (*Hypericum perforatum*) + Cimetidine

Cimetidine does not significantly alter the metabolism of the constituents of St John's wort hypericin and pseudohypericin.

Clinical evidence, mechanism, importance and management

A placebo-controlled study in healthy subjects taking St John's wort (*LI160, Lichtwer Pharma*) 300 mg three times daily found that, apart from a modest 25% increase in the AUC of pseudohypericin, cimetidine 1 g daily (in divided doses) did not significantly affect the pharmacokinetics of either the hypericin or pseudohypericin constituents of St John's wort. The available evidence therefore suggests that cimetidine is unlikely to affect the dose requirements of St John's wort.[1]

1. Johne A, Perloff ES, Bauer S, Schmider J, Mai I, Brockmöller J, Roots I. Impact of cytochrome P-450 inhibition by cimetidine and induction by carbamazepine on the kinetics of hypericin and pseudohypericin in healthy volunteers. *Eur J Clin Pharmacol* (2004) 60, 617–22.

St John's wort (*Hypericum perforatum*) + Loperamide

Delirium occurred in a woman taking St John's wort and valerian when she took loperamide.

Clinical evidence, mechanism, importance and management

A 39-year-old woman with a history of depression was hospitalised in a state of delirium. She had been taking St John's wort and valerian for 6 months (products and doses not stated) and had recently taken loperamide for diarrhoea.[1]

The authors speculated that this was an interaction between St John's wort and loperamide attributed to the MAO inhibitory activity of St John's wort, analogous to the interaction between non-selective MAOIs and 'pethidine (meperidine)', (p.1381). However, St John's wort is not thought to act as an MAOI inhibitor, for example, it does not usually cause a hypertensive reaction with 'tyramine-rich food', (below).

This appears to be an isolated report, and its findings cannot be generalised.

1. Khawaja IS, Marotta RF, Lippmann S. Herbal medicines as a factor in delirium. *Psychiatr Serv* (1999) 50, 969–70.

St John's wort (*Hypericum perforatum*) + Tyramine

An isolated report describes a patient taking St John's wort who experienced a hypertensive crisis after consuming tyramine-rich food and drink.

Clinical evidence, mechanism, importance and management

A man who had taken a St John's wort supplement for 7 days (preparation and dose not stated) was admitted to hospital with confusion and disorientation. He was unable to recall events after eating aged cheeses and pouring a glass of red wine 8 hours earlier. On examination he had a pulse rate of 115 bpm, a respiratory rate of 16 breaths per minute and his blood pressure was 210/140 mmHg. He was given intravenous phentolamine and oral labetalol and his blood pressure decreased to 160/100 mmHg after 2 hours and the delirium also resolved. Extensive laboratory investigations did not find any cause for the hypertension and delirium.

It was suggested that the time scale of starting to regularly take St John's wort and the onset of delirium and hypertension after the consumption of tyramine-rich food and drink was suggestive of hypertension associated with MAOIs (see also 'MAOIs or RIMAs + Tyramine-rich foods', p.1395, and 'MAOIs or RIMAs + Tyramine-rich drinks', p.1393). Although St John's wort is a potent inhibitor of monoamine oxidase, this effect has not been demonstrated at recommended doses. It was concluded that the hypertensive crisis in this patient may have been mediated by monoamine oxidase inhibition, but there was also a possibility of another, as yet unknown, pharmacological action of St John's wort being involved.[1] Given the widespread use of St John's wort this case would seem to be unusual, and there is currently little grounds for suggesting any dietary restriction in those taking St John's wort.

1. Patel S, Robinson R, Burk M. Hypertensive crisis associated with St. John's wort. *Am J Med* (2002) 112, 507–8.

Tyramine + Cimetidine

A woman taking cimetidine experienced a severe headache and hypertension when she drank *Bovril* and ate some cheese.

Clinical evidence, mechanism, importance and management

A 77-year-old woman with hiatus hernia, who had been taking cimetidine 400 mg four times daily for 3 years, experienced a severe frontal headache and hypertension, which appeared to be related to the ingestion of a cup of *Bovril* and some English cheddar cheese, both of which can contain substantial amounts of tyramine.[1] Although the authors point out the similarity between this reaction and that seen in patients taking MAOIs who eat tyramine-rich foods (see 'MAOIs or RIMAs + Tyramine-rich foods', p.1395), there is no satisfactory explanation for what occurred. They note that the patient was also taking salbutamol (another sympathomimetic) but rule out any contribution from this drug.

This is an isolated report and there is no reason why in general patients taking cimetidine should avoid tyramine-rich foods.

1. Griffin MJJ, Morris JS. MAOI-like reaction associated with cimetidine. *Drug Intell Clin Pharm* (1987) 21, 219.

Vitamin A (Retinol) + Neomycin

Neomycin can markedly reduce the absorption of vitamin A (retinol) from the gut.

Clinical evidence, mechanism, importance and management

In a study in 5 healthy subjects, neomycin 2 g markedly reduced the absorption of a test dose of vitamin A. It is suggested that this was due to a direct chemical interference between the neomycin and bile in the gut, which disrupted the absorption of fats and fat-soluble vitamins.[1] The extent to which long-term treatment with neomycin (or other aminoglycosides) would impair the treatment of vitamin A deficiency has not been determined.

1. Barrowman JA, D'Mello A, Herxheimer A. A single dose of neomycin impairs absorption of vitamin A (Retinol) in man. *Eur J Clin Pharmacol* (1973) 5, 199–201.

Vitamin B_{12} + Miscellaneous

Neomycin, colchicine, aminosalicylic acid and H_2-receptor antagonists can reduce the absorption of vitamin B_{12} from the gut, but no interaction is likely when B_{12} is given by injection.

Clinical evidence, mechanism, importance and management

Neomycin causes a generalised malabsorption syndrome, which has been shown[1] to reduce the absorption of vitamin B_{12}. **Colchicine** has also been shown to decrease B_{12} absorption.[1] **Aminosalicylic acid** reduces vitamin B_{12} absorption for reasons that are not understood, but which are possibly related to a mild generalised malabsorption syndrome.[2] A review of the literature[3] suggests that H_2-receptor antagonists (such as **cimetidine** and **ranitidine**) can also reduce vitamin B_{12} absorption, primarily because they reduce gastric acid production. The acid is needed to aid the release of B_{12} from dietary protein sources. There is therefore a possibility that on long-term use patients could become vitamin B_{12} deficient.

Within the context of adverse drug interactions, none of these findings is normally likely to be clinically important, because for anaemia, vitamin B_{12} should be given parenterally, both for convenience and to avoid well-established problems with absorption.

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3. Force RW, Nahata MC. Effect of histamine H_2-receptor antagonists on vitamin B_{12} absorption. *Ann Pharmacother* (1992) 26, 1283–6.

Vitamin D substances + Antiepileptics; Enzyme-inducing

The long-term use of carbamazepine, phenytoin, phenobarbital, or primidone can disturb vitamin D and calcium metabolism and may result in osteomalacia. There are a few reports of patients taking vitamin D supplements who responded poorly to vitamin replacement while taking phenytoin or barbiturates. Serum phenytoin levels are not altered by vitamin D.

Clinical evidence

A 16-year-old with grand mal epilepsy and idiopathic hypoparathyroidism did not adequately respond to **alfacalcidol** 10 micrograms daily and calcium 6 to 12 g daily, apparently because **phenytoin** 200 mg and **primidone** 500 mg daily were also being taken. However, when **dihydrotachysterol** 0.6 to 2.4 mg daily was given normal calcium levels were achieved.[1]

Other reports describe patients whose response to usual doses of vitamin D was poor, because of the concurrent use of **phenytoin** and **phenobarbital** or **primidone**.[2-4] Other reports clearly show low serum calcium levels,[5,6] low serum vitamin D levels,[7] osteomalacia,[6] and bone structure alterations[5,7] in the presence of **phenytoin**. **Carbamazepine** may have similar effects, but the evidence is less conclusive.[8,9]

A controlled study in 151 epileptic patients taking **phenytoin** and calcium found that the addition of 2000 units of **vitamin D_2** daily over a 3-month period had no significant effect on serum **phenytoin** levels.[10]

Mechanism

The enzyme-inducing effects of phenytoin and other antiepileptics increases the metabolism of the vitamin D, thereby reducing its effects and disturbing calcium metabolism.[3] In addition, phenytoin may possibly reduce the absorption of calcium from the gut.[1]

Importance and management

The disturbance of calcium metabolism by phenytoin and other enzyme-inducing antiepileptics is very well established, but there are only a few reports describing a poor response to vitamin D. The effects of concurrent treatment should be well monitored. Those who need vitamin D supplements may possibly need greater than usual doses.

1. Rubinger D, Korn-Lubetzki I, Feldman S, Popovtzer MM. Delayed response to 1 α-hydroxycholecalciferol therapy in a case of hypoparathyroidism during anticonvulsant therapy. *Isr J Med Sci* (1980) 16, 772–4.
2. Asherov J, Weinberger A, Pinkhas J. Lack of response to vitamin D therapy in a patient with hypoparathyroidism under anticonvulsant drugs. *Helv Paediatr Acta* (1977) 32, 369–73.
3. Chan JCM, Oldham SB, Holick MF, DeLuca HF. 1-α-Hydroxyvitamin D_3 in chronic renal failure. A potent analogue of the kidney hormone, 1,25-dihydroxycholecalciferol. *JAMA* (1975) 234, 47–52.
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5. Mosekilde L, Melsen F. Anticonvulsant osteomalacia determined by quantitative analyses of bone changes. Population study and possible risk factors. *Acta Med Scand* (1976) 199, 349–55.
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9. O'Hare JA, Duggan B, O'Driscoll D, Callaghan N. Biochemical evidence for osteomalacia with carbamazepine therapy. *Acta Neurol Scand* (1980) 62, 282–6.
10. Christiansen C, Rødbro P. Effect of vitamin D2 on serum phenytoin. A controlled therapeutical trial. *Acta Neurol Scand* (1974) 50, 661–4.

Vitamin D substances; Alfacalcidol + Danazol

An isolated report describes hypercalcaemia when a woman taking alfacalcidol also took danazol.

Clinical evidence, mechanism, importance and management

A woman with idiopathic hypoparathyroidism, treated with alfacalcidol, developed hypercalcaemia when she was given danazol 400 mg daily for endometriosis. She needed a reduction in the dosage of alfacalcidol from 4 micrograms daily to 0.75 micrograms daily. When the danazol was stopped 6 months later, the alfacalcidol dosage was raised to 4 micrograms daily and she remained normocalcaemic.[1] The reasons for this interaction are not understood. Its general importance is limited as this appears to be an isolated case.

1. Hepburn NC, Abdul-Aziz LAS, Whiteoak R. Danazol-induced hypercalcaemia in alphacalcidol-treated hypoparathyroidism. *Postgrad Med J* (1989) 65, 849–50.

Vitamin K substances + Antibacterials

Seven patients in intensive care did not respond to intravenous vitamin K for hypoprothrombinaemia while receiving gentamicin and clindamycin.

Clinical evidence, mechanism, importance and management

Some patients, particularly those in intensive care who are not eating, can quite rapidly develop acute vitamin K deficiency, which leads to prolonged prothrombin times and possibly bleeding.[1,2] This can normally be controlled by giving vitamin K parenterally. However, one report describes seven such patients, all with normal liver function, who unexpectedly did not respond to intravenous **phytomenadione**. Examination of their records found that all seven were receiving **gentamicin** and **clin-**

damycin.[2] Just why, or if, these two antibacterials might have opposed the effects of intravenous vitamin K is not understood.

1. Ham JM. Hypoprothrombinaemia in patients undergoing prolonged intensive care. *Med J Aust* (1971) 2, 716–18.
2. Rodriguez-Erdmann F, Hoff JV, Carmody G. Interaction of antibiotics with vitamin K. *JAMA* (1981) 246, 937.

Vitamins + Orlistat

Orlistat decreases the absorption of supplemental betacarotene and vitamin E. There is some evidence to suggest that some patients may have low vitamin D levels while taking orlistat, even if they are also taking multivitamins.

Clinical evidence

Studies in healthy subjects have found that about two-thirds of a supplemental dose of **betacarotene**[1] and roughly half the dose of **vitamin E** (**α-tocopherol**)[2] was absorbed in the presence of orlistat, while the absorption of **vitamin A** was not affected.[2] In the first study, betacarotene was given within about 30 minutes of the orlistat,[1] whereas in the second, the vitamin supplement was given at the same time as orlistat.[2] In another study, 17 obese adolescents were given orlistat 120 mg three times daily with meals and a daily multivitamin (containing **vitamins A**, **D**, **E**, and **K**) to be taken at night. Levels of **vitamins A**, **E** and **K** were not significantly altered over 6 months of orlistat use, but **vitamin D** concentrations dropped after the first month, but had returned to baseline by 3 months. Three subjects (all African-Americans) required additional **vitamin D** supplementation, but all had a low dietary intake of **vitamin D**.[3,4]

Mechanism

Orlistat reduces dietary fat absorption by inhibiting gastrointestinal lipase. Consequently, it reduces the absorption of fat soluble vitamins.

Importance and management

An established interaction. To maximise vitamin absorption, the manufacturers recommend that any multivitamin preparation should be taken at least 2 hours before or after orlistat, such as at bedtime.[5,6] The US manufacturer suggests that patients taking orlistat should be advised to take multivitamins, because of the possibility of reduced vitamin levels.[6] Note that the authors of the study in adolescents suggest that monitoring of vitamin D may be required, even if multivitamins are given.[3]

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2. Melia AT, Koss-Twardy SG, Zhi J. The effect of orlistat, an inhibitor of dietary fat absorption, on the absorption of vitamins A and E in healthy volunteers. *J Clin Pharmacol* (1996) 36, 647–53.
3. McDuffie JR, Calis KA, Booth SL, Uwaifo GI, Yanovski JA. Effects of orlistat on fat-soluble vitamins in obese adolescents. *Pharmacotherapy* (2002) 22, 814–22.
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5. Xenical (Orlistat). Roche Products Ltd. UK Summary of product characteristics, March 2009.
6. Xenical (Orlistat). Roche Pharmaceuticals. US Prescribing information, July 2008.

Zinc compounds + Iron compounds

Some studies suggest that giving iron with zinc may reduce the bioavailability of iron and/or zinc, but other studies suggest that combined supplementation is of value in reducing deficiencies of these micronutrients.

Clinical evidence

In a study, 549 Indonesian infants were given dietary supplementation from age 6 months until age 12 months with either iron 10 mg (as **ferrous sulfate**), zinc 10 mg (as **zinc sulfate**), iron 10 mg plus zinc 10 mg, or placebo. After supplementation, the iron group and the iron plus zinc groups had haemoglobin levels of 11.9 g/dL and 11.5 g/dL respectively and serum ferritin of 46.5 micrograms/L and 32.3 micrograms/L respectively. The haemoglobin level in the group receiving zinc and iron was not significantly different from that of the placebo group. Zinc levels were lower in infants given zinc with iron than in those given zinc alone, but this difference was not found to be significant. It was concluded that supplementation with iron plus zinc was less effective than single supplements in improving iron and zinc status.[1] Similar conclusions were reached in another study using the same doses of iron and zinc.[2] A further study in 784 infants aged 4 to 7 months given iron 10 mg or zinc 10 mg alone or combined, or placebo, daily for 6 months found that haemoglobin levels were increased by about 2.3 g/dL and 2.1 g/dL when given alone or with zinc, respectively, and zinc levels were increased by 10.3 micromol/L and 8 micromol/L when given alone or with iron, respectively. Although combined iron and zinc supplements had a positive effect on iron status, iron was found to have a negative effect on zinc status in these infants.[3] Similar conclusions were reached from pooled results from 4 studies in 2468 infants given iron 10 mg and/or zinc 10 mg daily for 6 months.[4]

In a study in 14 healthy subjects, iron 500 micrograms (as **ferrous sulfate** solution) was given alone or with zinc 590 micrograms (as **zinc sulfate**) on day 1, and iron 10 mg was given alone or with zinc 11.71 mg on day 14. At the lower doses, zinc did not affect iron bioavailability, but at the higher doses, iron bioavailability was reduced by 56%.[5]

Another study in ileostomy patients given zinc 12 mg alone, with iron 100 mg or 400 mg (as **ferrous gluconate**) on three consecutive days, found zinc absorption was 44% when given alone and significantly decreased to 26% and 23% when given with iron 100 mg or 400 mg, respectively.[6]

Mechanism

One study suggests that iron affects zinc absorption in a dose-dependent manner.[6] Reduced bioavailability of iron supplements when given with zinc may depend on the total amount of both iron and zinc in the intestine, as at high doses, but not low doses, zinc appears to affect iron bioavailability.[5] In some studies in infants and children, it has been suggested that the age of the child and initial serum zinc status may partly explain differences in reported effects.[7,8] Iron supplementation may have a greater effect on haemoglobin levels in boys than in girls.[4]

Importance and management

Iron and zinc deficiencies are global problems and they often co-exist.[1,9] Some studies suggest that giving zinc with iron may not improve iron status as much as iron given alone,[1,2,4,5,7] while others suggest zinc status may be negatively affected if it is given with iron.[1,3,6] Even so, some studies found that giving combined iron and zinc was beneficial, even if not optimal.[2-4,7] One study suggests that zinc supplementation has a positive effect on growth if low haemoglobin levels and iron status is also corrected.[10] It has been suggested that supplementation programmes that provide iron and zinc together are an efficient way to provide both micronutrients, provided the benefits of individual supplementation are not lost, but more study is needed before such programmes can be established.[9]

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4. Wieringa FT, Berger J, Dijkhuizen MA, Hidayat A, Ninh NX, Utomo B, Wasantwisut E, Winichagoon P, for the SEAMTIZI (South-East Asia Multi-country Trial on Iron and Zinc supplementation in Infants) Study Group. Combined iron and zinc supplementation in infants improved iron and zinc status, but interactions reduced efficacy in a multicountry trial in southeast Asia. *J Nutr* (2007) 137, 466–71.
5. Olivares M, Pizarro F, Ruz M. New insights about iron bioavailability inhibition by zinc. *Nutrition* (2007) 23, 292–5.
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8. Wieringa FT, Dijkhuizen MA, West CE. Iron and zinc interactions. *Am J Clin Nutr* (2004) 80, 787–8.
9. Fischer Walker C, Kordas K, Stoltzfus RJ, Black RE. Interactive effects of iron and zinc on biochemical and functional outcomes in supplementation trials. *Am J Clin Nutr* (2005) 82, 5–12.
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Zinc sulphate + Calcium compounds

Calcium compounds reduce the absorption of zinc.

Clinical evidence, mechanism, importance and management

Elemental calcium, in doses of 600 mg (either as **calcium carbonate** or **calcium citrate**), was given to 9 healthy women with a single 20-mg oral dose of zinc sulphate.[1] The AUC of zinc was reduced by 72% by **calcium carbonate** and by 80% by **calcium citrate**. The reason for this interaction is not understood, nor is the clinical importance of this interaction known, but it would seem prudent to separate the administration of zinc from the administration of any calcium compound. Two to three hours separation is often sufficient to achieve maximal absorption with interactions like this. More study of this interaction is needed to confirm the extent and to determine if separation of the doses is an adequate precaution.

1. Argiratos V, Samman S. The effect of calcium carbonate and calcium citrate on the absorption of zinc in healthy female subjects. *Eur J Clin Nutr* (1994) 48, 198–204.

34

Respiratory drugs

This section includes the diverse drugs that are principally used in the management of asthma and chronic obstructive pulmonary disease (COPD), with the exception of corticosteroids, which are covered elsewhere.

(a) Antimuscarinic bronchodilators

The parasympathetic nervous system is involved in the regulation of bronchomotor tone and antimuscarinic drugs have bronchodilator properties. Ipratropium bromide and other antimuscarinic bronchodilators used in COPD are listed in 'Table 34.1', (p.1414). A wide range of drugs have antimuscarinic (anticholinergic) adverse effects. Enhanced antimuscarinic effects occur when drugs with these properties are given concurrently, see 'Antimuscarinics + Antimuscarinics', p.786. However, these interactions do not usually occur with drugs such as ipratropium, given by inhalation.

(b) Beta$_2$-agonist bronchodilators

Salbutamol and terbutaline are examples of short-acting beta agonists that selectively stimulate the beta$_2$ receptors in the bronchi causing bronchodilation. They are used in the treatment of asthma and the management of COPD. Long-acting beta$_2$ agonists such as salmeterol are used in patients with asthma who also require anti-inflammatory therapy. 'Table 34.1', (p.1414) lists the beta$_2$ agonists available. The beta$_2$ agonists represent a significant improvement on isoprenaline (isoproterenol), which also stimulates beta$_1$ receptors in the heart, and on ephedrine, which also stimulates alpha receptors. The beta$_2$ agonists can cause hypokalaemia, which can be increased by the concurrent use of other 'potassium-depleting drugs', (p.1417).

(c) Leukotriene receptor antagonists

Montelukast and zafirlukast block the effects of cysteinyl leukotrienes, which cause effects such as airways oedema, bronchoconstriction and inflammation. The leukotriene receptor antagonists are used in the treatment of asthma, either alone, or with inhaled corticosteroids. They should not be used to relieve an acute asthma attack. Both drugs are metabolised in the liver by the cytochrome P450 isoenzymes such as CYP3A4 and CYP2C9 (montelukast) and CYP2C9 (zafirlukast). Zafirlukast is thought to inhibit CYP2C9 and CYP3A4, and this is thought to be the mechanism for its interaction with 'warfarin', (p.475). There is therefore a possibility that interactions could occur with other drugs that undergo metabolism by these isoenzymes but clinical evidence of this varies.

(d) Phosphodiesterase type-4 inhibitors

Phosphodiesterase type-4 inhibition results in suppression of a number of inflammatory cell functions that are involved in respiratory disease states such as asthma and COPD. Drugs that inhibit this process are currently under investigation, and include roflumilast. Roflumilast is metabolised by the cytochrome P450 isoenzymes CYP3A4 and CYP1A2, and therefore may be subject to interactions with other drugs that are inducers or inhibitors of these enzymes.

(e) Xanthines

The main xanthines used in medicine are theophylline and aminophylline, the latter generally being preferred when greater water solubility is needed (e.g. in the formulation of injections). Xanthines are given in the treatment of asthma because they relax the bronchial smooth muscle. In an attempt to improve upon theophylline, various different derivatives have been made, such as diprophylline and enprofylline. 'Table 34.1', (p.1414) lists these xanthines. Theophylline is metabolised by the cytochrome P450 isoenzymes in the liver, principally CYP1A2, to demethylated and hydroxylated products. Many drugs interact with theophylline by inhibition or potentiation of its metabolism. In addition, the metabolism of theophylline is affected by gender, smoking, liver and cardiac disease, viral infections and genetic differences in CYP1A2 function. Theophylline has a narrow therapeutic range, and small increases in serum levels can result in toxicity. Moreover, symptoms of serious toxicity such as convulsions and arrhythmias can occur before minor symptoms suggestive of toxicity. Within the context of interactions, aminophylline generally behaves like theophylline, because it is a complex of theophylline with ethylenediamine.

Caffeine is also a xanthine and it is principally used as a central nervous system stimulant, increasing wakefulness, and mental and physical activity. It is most commonly taken in the form of tea, coffee, cola drinks ('*Coke*') and cocoa. 'Table 34.2', (p.1414) lists the usual caffeine content of these drinks. Caffeine is also included in hundreds of non-prescription analgesic preparations with aspirin, codeine and/or paracetamol, but whether it enhances the analgesic effect is debatable. Caffeine is also used to assess the activity of the cytochrome P450 isoenzyme CYP1A2 and can usefully demonstrate altered liver function, notably from drugs, as well as disease states.

Caffeine, like theophylline, also undergoes extensive hepatic metabolism, principally by CYP1A2, and interacts with many drugs, but it has a wider therapeutic range. However, other xanthines may act differently (e.g. diprophylline does not undergo hepatic metabolism), so it should not be assumed that they all share common interactions.

Note though, that all xanthines can potentiate hypokalaemia caused by other drugs and that the toxic effects of different xanthines are additive.

Table 34.1 Respiratory drugs

Group	*Route*	*Drugs*
Antimuscarinics (Anticholinergics)	Inhaled	Ipratropium bromide, Oxitropium, Tiotropium
Beta-2 adrenoceptor agonists	Oral	Bambuterol, Clenbuterol, Reproterol, Salbutamol (Albuterol), Terbutaline
	Inhaled	Short-acting: Bitolterol, Clenbuterol, Fenoterol, Levosalbutamol, Pirbuterol, Procaterol, Reproterol, Salbutamol (Albuterol), Terbutaline, Tulobuterol Long-acting: Arformoterol, Formoterol, Salmeterol
	Intravenous	Reproterol, Salbutamol (Albuterol), Terbutaline
Leukotriene antagonists and inhibitors	Oral	Amlexanox, Ibudilast, Montelukast, Pemirolast, Pranlukast, Zafirlukast
Lipoxygenase inhibitors	Oral	Zileuton
Mast cell stabilisers	Inhaled	Nedocromil sodium, Sodium cromoglicate
	Oral	Amlexanox, Ketotifen, Pemirolast, Tranilast
PDE-4 Inhibitors	Oral	Roflumilast
Sympathomimetics	Oral	Ephedrine, Hexoprenaline, Orciprenaline
Xanthine derivatives	Oral	Aminophylline, Bamifylline, Bufylline, Choline theophyllinate, Diprophylline, Doxofylline, Etamiphylline camsilate, Etofylline, Heptaminol acefyllinate, Proxyphylline, Theophylline
	Intravenous	Aminophylline, Bamifylline

Table 34.2 Caffeine-containing herbs and caffeine-containing drinks

Source	*Caffeine-content*	*Caffeine-content of drink*
Coffee	Coffee beans 1 to 2%[1]	Up to 100 mg/100 mL, decaffeinated up to about 3 mg/100 mL.[1] Instant coffee, 75 mg per cup and 100 mg per mug.[3] Can range from 210 to 340 mg/L,[4] or 21 to 120 mg per serving.[5] Brewed coffee, 100 mg per cup.[5] Ground coffee, 15 to 254 mg per serving.[5] Filter coffee, between 105 and 215 mg/L,[4] or up to 140 mg per mug.[3]
Chocolate		Plain chocolate, up to 50 mg in 50 g.[3] Milk chocolate, up to 25 mg in 50 g.[3] Chocolate bars, between 110 and 710 mg/kg.[4] Chocolate milk drinks, between 8 and 20 mg/L.[4] Chocolate powdered drinks, between 5.5 and 41 mg/L.[4]
Cola drinks		Up to 40 mg per drink;[3] 69 mg/L (range 33 to 213 mg/L)[4] Decaffeinated cola drinks less than 0.2 mg/L.[4]
Energy drinks		Guarana and caffeine containing energy drinks, average 269 mg/L (range 122 to 234 mg/L).[4]
Guarana*	2.5 to 7%[2]	Guarana-containing energy drinks, around 180 mg/L.[4]
Maté (Paraguay tea)	0.2 to 2%[1]	
Tea	1 to 5%[3]	Up to 60 mg/100 mL,[1] caffeine content appears to vary with form (bags, loose tea, instant tea etc.); between 102 and 326 mg/L,[4] or 1 to 90 mg per serving.[5]

*Note that guarana contains guaranine (which is known to be identical to caffeine) as well as small quantities of other xanthines.

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2. Houghton P. Herbal products 7. Guarana. *Pharm J* (1995) 254, 435-6.
3. Food Standards Agency. When you're pregnant. What to eat. Alcohol and caffeine. Available at http://www.eatwell.gov.uk/agesandstages/pregnancy/whenyrpregnant/ (accessed 31/03/09).
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Anti-asthma drugs + Areca (Betel nuts)

The chewing of betel nuts may worsen the symptoms of asthma.

Clinical evidence

A study of a possible interaction with betel nuts was prompted by the observation that the severe asthma of two Bangladeshi patients appeared to have been considerably worsened by chewing betel nuts. One out of 4 other patients with asthma who regularly chewed betel nuts developed severe bronchoconstriction (a 30% fall in FEV_1) on two occasions when given betel nuts to chew, and all 4 patients said that prolonged betel nut chewing induced coughing and wheezing. A double-blind study found that the inhalation of **arecoline** (the major constituent of the nut) caused bronchoconstriction in 6 of 7 asthmatics, and one of 6 healthy control subjects.[1] A study in patients with asthma who regularly chewed betel nuts found that 4 patients had a mean increase in their FEV_1 of 10 to 25%, whereas 11 patients had significant falls in their FEV_1 of 11 to 25%. Interestingly, 5 of the patients who did not think chewing betel nut affected their asthma experienced a reduction in their FEV_1.[2]

A survey in 61 patients with asthma found that 22 of the 34 patients who still chewed betel nuts, either for occasional use or regularly, reported that it worsened their asthma.[3]

Mechanism

Betel nut 'quids' consist of areca nut (*Areca catechu*) wrapped in betel vine leaf (*Piper betle*) and smeared with a paste of burnt (slaked) lime. It is chewed for the euphoric effects of the major constituent, arecoline, a cholinergic alkaloid, which appears to be absorbed through the mucous membrane of the mouth. Arecoline has identical properties to pilocarpine and normally has only mild systemic cholinergic properties; however asthmatic subjects seem to be particularly sensitive to the bronchoconstrictor effects of this alkaloid and possibly other substances contained in the nut.

Importance and management

Direct evidence appears to be limited to the above reports, but the interaction seems to be established. It would not normally appear to be a serious interaction, but asthmatics should be encouraged to avoid betel nuts. This is a drug-disease interaction rather than a drug-drug interaction.

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Anti-asthma drugs + Beta blockers

Non-cardioselective beta blockers (e.g. propranolol, timolol) should not be used in asthmatic subjects because they may cause serious bronchoconstriction, even if given as eye drops. Non-cardioselective beta blockers oppose the bronchodilator effects of beta-agonist bronchodilators, and higher doses may be required to reverse bronchospasm. Even cardioselective blockers (e.g. atenolol) can sometimes cause acute bronchospasm in asthmatics. However, cardioselective beta blockers do not generally inhibit the bronchodilator effect of beta-agonist bronchodilators.

Clinical evidence

(a) Cardioselective beta blockers

A review of 29 studies (including 19 single-dose studies) on the use of cardioselective beta blockers in patients with reversible airway disease indicated that in patients with mild to moderate disease, the short-term use of cardioselective beta blockers does not cause significant adverse respiratory effects. Information on the effects in patients with more severe or less reversible disease, or on the frequency or severity of acute exacerbations was not available.[1] Another review indicated that when low doses of cardioselective beta blockers are given to patients with mild, intermittent or persistent asthma, or moderate persistent asthma, and heart failure or myocardial infarction, the benefits of treatment outweigh the risks. However, it was considered that further study is required to establish long-term safety, and also that beta blockers should be avoided in severe persistent asthma.[2] A review of patients with asthma or COPD taking a cardioselective beta blocker (2810 patients) or a non-selective beta blocker (287) found no significant difference in admissions to hospital or in length of stay in these patients when compared with 5293 patients with asthma or COPD receiving other cardiovascular medicines.[3]

The cardioselective beta blockers would not be expected to affect the beta receptors in the bronchi, but bronchospasm can sometimes occur following their use by asthmatics and others with obstructive airways diseases, particularly if high doses are used. Deterioration of asthma was reported in a patient taking oral **betaxolol** with **theophylline** and **pranlukast**, although **betaxolol** is considered to be highly cardioselective and less likely to cause pulmonary adverse effects than other cardioselective beta blockers.[4]

No adverse pharmacodynamic interaction normally occurs between beta-agonist bronchodilators and cardioselective beta blockers. This has been demonstrated in studies with:

- **Atenolol** with **salbutamol** (**albuterol**) inhalation.[5,6]
- **Celiprolol** in patients with asthma with **isoprenaline** (**isoproterenol**), or **salbutamol**,[5,7,8] or **terbutaline** infusion or inhalation.[9]
- **Metoprolol** in patients with asthma at rest with **isoprenaline** infusion.[10,11]

In contrast, another study found that the increase in forced expiratory volume (FEV) with a **terbutaline** inhalation and infusion was reduced by about 300 mL by **atenolol** and **metoprolol**. The authors considered that this would be clinically relevant in severe asthma.[12] Another study in 12 patients with mild asthma found that single doses of **celiprolol** 200 mg or **nebivolol** 5 mg reduced the FEV_1 by 272 mL and 193 mL, respectively, when compared with placebo. Increasing inhalation of **salbutamol** to a to tal dose of 800 micrograms reversed these reductions but did not restore the FEV_1 back to its initial value. None of these changes was considered to be clinically significant by the authors.[13]

Fifteen patients with mild to moderate COPD and airways hyperresponsiveness were given **celiprolol** 200 mg daily, **metoprolol** 100 mg daily or **propranolol** 80 mg daily for 4 days. Propranolol significantly reduced the FEV_1 and increased airways hyper-responsiveness, when compared with placebo, whereas metoprolol only increased airways hyperresponsiveness. **Celiprolol** had no significant effects on pulmonary function. The bronchodilating effects of a single 12-microgram dose of **formoterol** were significantly reduced by **propranolol**, but not by **metoprolol** or **celiprolol**.[8]

(b) Non-selective beta blockers

Non-selective beta blockers (e.g. **propranolol**) are contraindicated in patients with asthma because they can cause bronchospasm, reduce lung ventilation and may possibly precipitate a severe asthmatic attack in some subjects. An example of the danger is illustrated by a patient with asthma who developed fatal status asthmaticus after taking just one dose of **propranolol**.[14] Another case report describes a patient with bronchial asthma receiving **salbutamol** who collapsed and died after taking three 20-mg **propranolol** tablets, which had been supplied in error instead of 20-mg prednisone tablets.[15] The manufacturers of **propranolol** note that from 1965 to 1996, the CSM in the UK had received 51 reports of bronchospasm due to **propranolol**, 13 of them fatal, and 5 of them in patients who had a history of asthma, bronchospasm or wheeze.[16] The non-cardioselective beta blockers **oxprenolol**[6] and **propranolol**[5,6,9-11] oppose the effects of bronchodilators such as **isoprenaline** (**isoproterenol**),[5,10,11] **salbutamol** (**albuterol**),[5,6] and **terbutaline**.[9] Even eye drops containing the non-selective beta blockers **timolol**[17,18] and **metipranolol**[19] have been reported to precipitate acute bronchospasm. In patients with heart failure taking **carvedilol**, 3 of 12 with concurrent asthma had wheezing requiring **carvedilol** withdrawal. In contrast, only 1 of 31 patients with COPD had wheezing.[20]

Mechanism

Non-selective beta blockers such as propranolol also block the $beta_2$ receptors in the bronchi so that the normal bronchodilation, which is under the control of the sympathetic nervous system, is reduced or abolished. As a result the bronchoconstriction of asthma can be made worse. Cardioselective beta blockers on the other hand, preferentially block $beta_1$ receptors in the heart, with less effect on the $beta_2$ receptors, so that $beta_2$

stimulating bronchodilators, such as isoprenaline (isoproterenol), salbutamol (albuterol) and terbutaline, continue to have bronchodilator effects.

Importance and management

A well established drug-disease interaction. In 1996, the CSM in the UK[21] re-issued the advice that beta blockers, including cardioselective beta blockers should not be given to patients with a history of asthma and/or bronchospasm. Non-cardioselective beta blockers (see 'Table 22.1', (p.995)) should certainly be avoided in patients with asthma and those with COPD, whether given systemically or as eye drops, because serious and life-threatening bronchospasm may occur. The cardioselective beta blockers are generally safer but not entirely free from risk in some patients, particularly in high dosage. In contrast to the 1996 recommendations of the CSM on cardioselective beta blockers, a subsequent review[1,22] recommended that cardioselective beta blockers should not be withheld from patients with mild to moderate reversible airway disease. However, some concern has been expressed that this conclusion was based on results from short-term studies and state that the question of safety in asthmatics over the long term has not been answered.[23] Further, there are no studies to suggest the safety of cardioselective beta blockers in patients with exacerbations of asthma,[24] and even a highly cardioselective drug such as betaxolol may cause bronchospasm.[4] In 2004, the American College of Cardiology and American Heart Association guidelines for management of ST-elevation myocardial infarction stated that the benefits of using beta blockers strongly outweigh the risk of adverse events in patients with COPD or mild asthma (non-active), and noted that most patients with asthma are able to tolerate cardioselective beta blockers. Therefore if a beta blocker is required a cardioselective beta blocker should be used, and the patient's pulmonary function monitored.[25] An update to these guidelines in 2007 specifically notes that *active* asthma, or reactive airway disease, are contraindications to the use of an intravenous or oral beta blocker.[26] A 2007 Cochrane review concluded that cardioselective beta blockers did not produce any significant adverse respiratory effects or reduction in the response to $beta_2$ agonists, and it recommended that cardioselective beta blockers should not be withheld from patients with COPD.[27]

Celiprolol (a cardioselective beta blocker) appears to be exceptional in causing mild bronchodilatation in asthmatics and not bronchoconstriction, although it may still produce a reduction in expiratory volume, as seen in one study,[13] but some caution is still necessary as this requires confirmation.[7]

The bronchoconstrictive effects of the beta blockers can be opposed by $beta_2$ agonist bronchodilators such as salbutamol, but as the manufacturers point out, large doses may be needed and they suggest that ipratropium and intravenous aminophylline may also be needed.[16]

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Anti-asthma drugs + NSAIDs

Aspirin and many other NSAIDs can cause bronchoconstriction in some patients with asthma. Celecoxib, etoricoxib and meloxicam do not usually cause bronchospasm in aspirin or NSAID-sensitive patients. Aspirin, nimesulide and piroxicam appear not to alter theophylline pharmacokinetics.

Clinical evidence, mechanism, importance and management

(a) NSAIDs in asthma

About 10% of patients with asthma are hypersensitive to **aspirin**, and in some individuals life-threatening bronchoconstriction can occur. This is not a drug-drug interaction but an adverse response to **aspirin**, whether the patient is taking an anti-asthma drug or not. The reasons are not fully understood. Those known to be sensitive to **aspirin** may also possibly react to other NSAIDs, in particular the acetylated salicylates, the indole and indene acetic acids, and the propionic acid derivatives (see 'Table 6.1', (p.150)). The fenamates, oxicams, pyrazolones and pyrazolidinediones are better tolerated.[1] The nonacetylated salicylates (**sodium salicylate**, **salicylamide**, **choline magnesium trisalicylate**) are normally well tolerated. Aspirin-sensitive individuals are also less likely to react to **nimesulide**.[1,2] In a study in which 381 patients with a pseudoallergic reaction to NSAIDs, (urticaria, angioedema, rhinitis, asthma or anaphylactoid reaction) were challenged with **nimesulide** 50 or 100 mg, only 6 experienced an adverse reaction. One patient developed an asthma attack, and this resolved following inhalation of 200 micrograms of salbutamol (albuterol).[2]

In 60 patients with proven **aspirin**-sensitivity, **celecoxib** 100 mg on day one and 200 mg on day two caused no decline in forced expiratory volume.[3] Two more studies found similar results.[4,5] **Celecoxib** is a selective inhibitor of cyclo-oxygenase-2 and this supports the suggestion that inhibition of cyclo-oxygenase-1 may be a critical factor in the precipitation of respiratory reactions in **aspirin**-exacerbated respiratory disease.[3] This suggests that **celecoxib** may be an alternative in patients who are known to be aspirin sensitive. Nevertheless, the manufacturer of **celecoxib** contraindicates its use in patients who are sensitive to aspirin or NSAIDs.[6]

In a study in 21 patients with either asthma, nasal polyps, allergic rhinitis or a combination of these, challenged with **meloxicam** 7.5 mg, only one patient with a history of aspirin allergy developed bronchospasm and erythema.[7] Another study found no reaction in 24 patients with a history of NSAID-induced respiratory hypersensitivity given **meloxicam** 7.5 to 15 mg daily.[4] However, the manufacturer of **meloxicam** contraindicates its use in patients who are sensitive to aspirin or NSAIDs.[8]

In a study 77 rheumatology patients with a history of asthma caused by

aspirin or a NSAID and given ascending doses of **etoricoxib** 60 to 120 mg daily for 3 days had no respiratory or cutaneous reaction to **etoricoxib** even after rechallenge 5 days later.[9]

(b) NSAIDs with theophylline

In 6 healthy subjects, **piroxicam** 20 mg daily for 7 days had no effect on the pharmacokinetics of theophylline (given as a single 6-mg/kg intravenous dose of aminophylline).[10] In 8 elderly patients (aged 60 to 81 years) with COPD, **enteric-coated aspirin** 650 mg daily for 4 weeks had no effect on the steady-state serum levels of theophylline.[11] **Nimesulide** 100 mg twice daily for 7 days did not affect lung function in 10 patients with COPD taking slow-release theophylline 200 mg twice daily, although there was a slight, clinically insignificant fall in theophylline levels, possibly due to enzyme induction. The pharmacokinetics of the **nimesulide** were unchanged.[12]

Apart from checking that the patient is not sensitive to **aspirin** or any other NSAID (see *NSAIDs in asthma*, above), there would seem to be no reason for avoiding **aspirin** or **piroxicam** in patients taking theophylline (or probably aminophylline).

In a placebo-controlled study, 36 healthy subjects were given **rofecoxib** 12.5 mg, 25 mg or 50 mg daily for 7 days, with a single 300-mg dose of theophylline given on day 7. There were no significant changes in the maximum plasma levels of theophylline. However, **rofecoxib** 12.5 mg, 25 mg or 50 mg, increased the AUC of theophylline by 38%, 51% and 60%, respectively, and increased the half-life of theophylline by 40%, 59% and 64%, respectively. It was suggested that the changes occurred because **rofecoxib** inhibits the cytochrome P450 isoenzyme CYP1A2 by which theophylline is metabolised.[13] This study suggests that dose reductions of theophylline (and probably aminophylline) would be necessary if patients were also given **rofecoxib**: given the range of NSAIDs available, it would probably be better to use a non-interacting alternative (**rofecoxib** is the only NSAID known to inhibit CYP1A2 to a clinically relevant extent). However, note that **rofecoxib** was generally withdrawn worldwide in 2004 because of its cardiovascular adverse effects; this study is included for completeness.

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Beta-agonist bronchodilators + Potassium-depleting drugs

Beta agonists (e.g. fenoterol, salbutamol (albuterol), terbutaline) can cause hypokalaemia. This can be increased by other potassium-depleting drugs such as amphotericin B, the corticosteroids, diuretics (e.g. bendroflumethiazide, furosemide) and theophylline. The risk of serious cardiac arrhythmias may be increased.

Clinical evidence

(a) Corticosteroids

1. Anti-inflammatory/bronchodilator effects. A marked rise in asthma deaths was noted in New Zealand in the 1980s. A case-control study found that the risk of death was increased in oral corticosteroid-dependent asthmatics (severe asthma) who were also taking inhaled **fenoterol**.[1] This, and other data, suggested that the concurrent use of short-acting $beta_2$ agonists and corticosteroids might be deleterious in some situations, prompting numerous studies, which were reviewed in 2000.[2] The overall findings were, that although inhaled corticosteroids do not prevent the pro-inflammatory effects of short-acting $beta_2$ agonists, the combination is beneficial in the treatment of asthma at usual therapeutic doses of both drugs. The authors caution that this might not apply with excessive use of short-acting $beta_2$ agonists.[2]

The addition of a long-acting $beta_2$ agonist (e.g. **salmeterol**) to treatment in patients with chronic asthma inadequately controlled by inhaled corticosteroids and 'as required' short-acting $beta_2$ agonists is beneficial,[2,3] provided current guidance advising that a long-acting $beta_2$ agonist is always prescribed with an inhaled corticosteroid is followed.[4]

2. Hypokalaemia. The hypokalaemic effects of $beta_2$ agonists may be increased by corticosteroids. Twenty-four healthy subjects had a fall in their serum potassium levels when they were given either **salbutamol** (**albuterol**) 5 mg or **fenoterol** 5 mg by nebuliser over 30 minutes. The fall in potassium levels was increased after they took **prednisone** 30 mg daily for a week. The greatest fall (from 3.75 mmol/L to 2.78 mmol/L) was found 90 minutes after **fenoterol** and **prednisone** were taken. The ECG effects observed included ectopic beats and transient T wave inversion, but no significant ECG disturbances were noted.[5]

3. Pharmacokinetics. A study in 28 healthy subjects found that the pharmacokinetics of a single 1.28-milligram dose of **budesonide** and a single 36-microgram dose of **formoterol** were unaltered when each drug was given together (via separate inhalers). In a similar study by the same authors, it was found that when these drugs were given together via the same inhaler (*Symbicort*,® **budesonide** 1.28 milligrams, **formoterol** 36 micrograms per dose), the AUC of **formoterol** was 20% lower compared with administration via separate inhalers.[6] This is unlikely to be clinically relevant.

When 28 healthy subjects received **salmeterol** 100 micrograms, **fluticasone** 500 micrograms, or the two drugs together twice daily for 11 days, no pharmacokinetic interaction was noted.[7]

(b) Diuretics

1. Bendroflumethiazide. In a study, 10 healthy subjects were given bendroflumethiazide 5 mg daily. After 7 days the serum potassium levels had fallen by 0.71 mmol/L. When 100 micrograms to 2 mg of inhaled **salbutamol** (**albuterol**) was also given, the potassium levels fell by 1.06 mmol/L (to 2.72 mmol/L). ECG changes consistent with hypokalaemia and hypomagnesaemia were seen.[8] In another study the same authors found that the addition of bendroflumethiazide 5 mg daily to inhaled **salbutamol** 2 mg further reduced serum potassium levels by 0.4 mmol/L (to 2.92 mmol/L). This reduction was abolished by the addition of **triamterene** 200 mg (serum potassium 3.43 mmol/L) or **spironolactone** 100 mg (serum potassium 3.53 mmol/L) but **triamterene** 50 mg only attenuated the effect of bendroflumethiazide (serum potassium 3.1 mmol/L). ECG effects with this combination were also reduced by the addition of **triamterene** or **spironolactone**.[9] In another similar study by the same authors, the addition of 24 mmol potassium supplementation daily did not alter the hypokalaemia or ECG changes caused by the concurrent use of bendroflumethiazide and **salbutamol**. The use of **triamterene** attenuated the ECG changes in some subjects.[10]

2. Furosemide. The serum potassium level of 15 healthy subjects was measured after they were given inhaled **terbutaline** 5 mg with either a placebo, furosemide 40 mg daily, or furosemide 40 mg with **triamterene** 50 mg daily for 4 days. With **terbutaline** alone the potassium levels fell by 0.53 mmol/L; when furosemide was also given they fell by 0.75 mmol/L; and after furosemide and **triamterene** were also given they fell by 0.59 mmol/L. These falls were reflected in some ECG (T wave) changes.[11]

(c) Theophylline

The concurrent use of **salbutamol** (**albuterol**) or **terbutaline** and theophylline can cause an additional fall in serum potassium levels, and other $beta_2$ agonists are expected to interact similarly. See 'Theophylline + Beta-agonist bronchodilators', p.1432.

Mechanism

The use of two or more drugs with hypokalaemic adverse effects results in additive potassium-depleting effects.

Importance and management

Established interactions. The CSM in the UK[12] advises that, as potentially serious hypokalaemia may result from the use of a beta$_2$ agonist, particular caution is required in severe asthma, as this effect may be potentiated by theophylline and its derivatives, corticosteroids, diuretics, and by hypoxia. Hypokalaemia with concurrent use of a beta$_2$ agonist and a thiazide or loop diuretic (see 'Table 26.1', (p.1121), for a list) may be reduced or even abolished by the addition of spironolactone or high-dose triamterene. Plasma potassium levels should therefore be monitored in patients with severe asthma. Drugs such as **amphotericin B**, which commonly cause severe hypokalaemia are likely to present a similar risk. Hypokalaemia may result in cardiac arrhythmias in patients with ischaemic heart disease and may also affect the response of patients to drugs such as the digitalis glycosides and antiarrhythmics.

Note that the combined use of beta$_2$ agonists and corticosteroids in asthma is usually beneficial, indeed the combination of a long-acting beta$_2$ agonist and corticosteroid gives enhanced anti-inflammatory activity than with either drug alone.[13]

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11. Newnham DM, McDevitt DG, Lipworth BJ. The effects of frusemide and triamterene on the hypokalaemic and electrocardiographic responses to inhaled terbutaline. *Br J Clin Pharmacol* (1991) 32, 630–2.
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Caffeine + Allopurinol

Allopurinol may invalidate the results of studies using caffeine as a probe drug for determining acetylator status or CYP1A2 activity.

Clinical evidence, mechanism, importance and management

In 21 healthy subjects, allopurinol 300 mg daily for 8 days altered the levels of the urinary caffeine metabolites of a single 200-mg dose of caffeine. In particular, the metabolic ratio used to determine whether people are fast or slow acetylators was substantially changed. Thus, allopurinol may invalidate the results of phenotyping with the urinary caffeine test. In addition, the caffeine metabolite ratio used to express the activity of the cytochrome P450 isoenzyme CYP1A2 was not stable when allopurinol was used.[1] This interaction is of relevance to research rather than clinical practice.

1. Fuchs P, Haefeli WE, Ledermann HR, Wenk M. Xanthine oxidase inhibition by allopurinol affects the reliability of urinary caffeine metabolic ratios as markers for *N*-acetyltransferase 2 and CYP1A2 activities. *Eur J Clin Pharmacol* (1999) 54, 869–76.

Caffeine + Antiepileptics

Phenytoin can increase the clearance of caffeine, and possibly invalidates the caffeine breath test. Whether carbamazepine increases caffeine metabolism is unclear. The concurrent use of valproate and caffeine does not appear to affect the pharmacokinetics of either drug.

Clinical evidence

The clearance of caffeine was about twofold higher and its half-life was reduced by about 50% in patients with epilepsy taking **phenytoin**, when compared with healthy subjects not taking any medication. In the same study, there were no significant differences in caffeine pharmacokinetics between healthy subjects and patients receiving **carbamazepine** or **sodium valproate**.[1] Conversely, **carbamazepine** was considered to have induced the metabolism of caffeine in 5 children with epilepsy, as assessed by the caffeine breath test.[2] In another study in healthy subjects, there was a reduction in the AUC of **carbamazepine** when it was given with caffeine. Caffeine had no effect on the pharmacokinetics of **sodium valproate**.[3]

Mechanism

Phenytoin acts as an enzyme inducer, thereby increasing the metabolism of caffeine, lowering its levels. Carbamazepine possibly has the same effect.

Importance and management

Phenytoin may possibly invalidate the caffeine breath test, but normally no special precautions are needed if both drugs are taken. The interaction between carbamazepine and caffeine is not established and requires further study.

1. Wietholtz H, Zysset T, Kreiten K, Kohl D, Büchsel R, Matern S. Effect of phenytoin, carbamazepine, and valproic acid on caffeine metabolism. *Eur J Clin Pharmacol* (1989) 36, 401–6.
2. Parker AC, Pritchard P, Preston T, Choonara I. Induction of CYP1A2 activity by carbamazepine in children using the caffeine breath test. *Br J Clin Pharmacol* (1998) 45, 176–8.
3. Vaz J, Kulkarni C, Joy D, Joseph T. Influence of caffeine on pharmacokinetic profile of sodium valproate and carbamazepine in normal healthy volunteers. *Indian J Exp Biol* (1998) 36, 112–14.

Caffeine + Antifungals

Fluconazole and terbinafine cause a modest rise in serum caffeine levels. Ketoconazole appears to have less effect. Posaconazole does not affect caffeine pharmacokinetics.

Clinical evidence, mechanism, importance and management

A study in 6 young subjects (average age 24 years) given **fluconazole** 400 mg daily and 5 elderly subjects (average age 69 years) given **fluconazole** 200 mg daily for 10 days found that fluconazole reduced the plasma clearance of caffeine by an average of 25% (32% in the young and 17% in the elderly).[1]

In a single-dose study in 8 healthy subjects, **terbinafine** 500 mg and **ketoconazole** 400 mg decreased caffeine clearance by 21% and 10%, respectively, and increased its half-life by 31% and 16%, respectively.[2]

In 12 healthy subjects **posaconazole** 200 mg daily for 10 days did not affect the pharmacokinetics of a single 200-mg dose of caffeine.[3]

It seems unlikely that the moderately increased serum caffeine levels seen with fluconazole, ketoconazole and terbinafine, will have a clinically important effect.

1. Nix DE, Zelenitsky SA, Symonds WT, Spivey JM, Norman A. The effect of fluconazole on the pharmacokinetics of caffeine in young and elderly subjects. *Clin Pharmacol Ther* (1992) 51, 183.
2. Wahlländer A, Paumgartner G. Effect of ketoconazole and terbinafine on the pharmacokinetics of caffeine in healthy volunteers. *Eur J Clin Pharmacol* (1989) 37, 279–83.
3. Wexler D, Courtney R, Richards W, Banfield C, Lim J, Laughlin M. Effect of posaconazole on cytochrome P450 enzymes: a randomized, open-label, two-way crossover study. *Eur J Pharm Sci* (2004) 21, 645–53.

Caffeine + Armodafinil

In a study, 24 healthy subjects were given a single 200-mg dose of caffeine before and after taking armodafinil 250 mg daily for at least 22 days. There were no clinically significant changes in the pharmacokinetics of caffeine, and the combination was well tolerated.[1]

1. Darwish M, Kirby M, Robertson P, Hellriegel ET. Interaction profile of armodafinil with medications metabolized by cytochrome P450 enzymes 1A2, 3A4 and 2C19 in healthy subjects. Clin Pharmacokinet (2008) 47, 61–74.

Caffeine + Artemisinin derivatives

Artemisinin, artenimol and artemotil reduce the metabolism of caffeine.

Clinical evidence, mechanism, importance and management

A study in 7 healthy subjects found that a single 500-mg dose of **artemisinin** reduced the clearance of a single 136.5-mg dose of caffeine by 35%. The metabolism of caffeine to one of its major metabolites, paraxanthine, was reduced by 66%.[1] Another study, in 15 healthy subjects given **artemisinin** 500 mg daily for 5 days, found that the metabolism of a single 100-mg dose of caffeine to paraxanthine was reduced by 73%. As part of this study, 14 subjects were given **dihydroartemisinin** [**artenimol**] 60 mg daily for 5 days, and 15 subjects were given intramuscular **artemotil** 100 mg daily for 5 days. The metabolism of a single 100-mg dose of caffeine to paraxanthine was reduced by 27% and 30%, respectively. There was no significant change in the metabolism of caffeine in the 15 subjects who were given **artemether** 100 mg daily for 5 days, or **artesunate** 100 mg daily for 5 days.[2] It was suggested that **artemisinin**, **dihydroartemisinin** [**artenimol**] and **artemotil** inhibit the metabolism of caffeine by the cytochrome P450 isoenzyme CYP1A2 in the liver.[1,2]

There is too little information to advise patients taking artemisinin derivatives to completely avoid caffeine-containing beverages, foods or medication, but bear this interaction in mind if the adverse effects of caffeine (insomnia, jitteriness etc) become troublesome.

1. Bapiro TE, Sayi J, Hasler JA, Jande M, Rimoy G, Masselle A, Masimirembwa CM. Artemisinin and thiabendazole are potent inhibitors of cytochrome P450 1A2 (CYP1A2) activity in humans. *Eur J Clin Pharmacol* (2005) 61, 755–61.
2. Asimus S, Elsherbiny D, Hai TN, Jansson B, Huong NV, Petzold MG, Simonsson USH, Ashton M. Artemisinin antimalarials moderately affect cytochrome P450 enzyme activity in healthy subjects. *Fundam Clin Pharmacol* (2007) 21, 307–16.

Caffeine + Cimetidine

The clearance of caffeine is decreased by cimetidine.

Clinical evidence, mechanism, importance and management

In 5 subjects cimetidine 1 g daily for 6 days increased the half-life of a single 300-mg dose of caffeine by about 70% and reduced caffeine clearance.[1] In another study, cimetidine 1.2 g daily for 4 days increased the caffeine half-life by 45% in 6 smokers and by 96% in 6 non-smokers. The caffeine clearance was reduced by 31% in the smokers and by 42% in the non-smokers.[2] A further study found that the caffeine half-life was increased by 59% and its clearance decreased by 40% by cimetidine.[3] Conversely, in a study in children, cimetidine was not found to affect caffeine metabolism, as assessed by the caffeine breath test.[4]

The changes seen in some studies probably occurred because cimetidine, a well-known non-specific enzyme inhibitor, reduced the metabolism of caffeine by the liver, resulting in its accumulation in the body.

Any increased caffeine effects are normally unlikely to be of much importance in most people, but they might have a small part to play in exaggerating the undesirable effects of caffeine from food, drinks (e.g. tea, coffee, cola drinks, chocolate) and analgesics, which are sometimes formulated with caffeine. If these become troublesome, advise patients to reduce their caffeine intake.

1. Broughton LJ, Rogers HJ. Decreased systemic clearance of caffeine due to cimetidine. *Br J Clin Pharmacol* (1981) 12, 155–9.
2. May DC, Jarboe CH, VanBakel AB, Williams WM. Effects of cimetidine on caffeine disposition in smokers and nonsmokers. *Clin Pharmacol Ther* (1982) 31, 656–61.
3. Beach CA, Gerber N, Ross J, Bianchine JR. Inhibition of elimination of caffeine by cimetidine in man. *Clin Res* (1982) 30, 248A.
4. Parker AC, Pritchard P, Preston T, Dalzell AM, Choonara I. Lack of inhibitory effect of cimetidine on caffeine metabolism in children using the caffeine breath test. *Br J Clin Pharmacol* (1997) 43, 467–70.

Caffeine + Class I antiarrhythmics

Caffeine clearance is reduced by 30 to 60% by mexiletine, resulting in raised serum caffeine levels. Similarly, propafenone reduces the clearance of caffeine by 35%. Lidocaine, flecainide and tocainide do not appear to affect caffeine clearance. Caffeine does not significantly alter mexiletine levels.

Clinical evidence

(a) Mexiletine

In a study in 7 patients with cardiac arrhythmias taking long-term mexiletine 600 mg daily the clearance of caffeine was found to be reduced by 48%.[1] In 5 healthy subjects given a single 200-mg dose of mexiletine, the clearance of a single 366-mg dose of caffeine was reduced by 57%, and the elimination half-life rose from about 4 hours to 7 hours.[1] The clearance of mexiletine was not affected by caffeine. A preliminary report of this study also noted that fasting caffeine levels were almost sixfold higher during the mexiletine treatment period (1.99 micrograms/mL compared with 0.35 micrograms/mL).[2]

Another study in 14 healthy subjects found that caffeine 100 mg four times daily, for 2 days before and 2 days after mexiletine, did not cause any significant changes in the plasma levels of a single 200-mg dose of mexiletine. Caffeine levels tended to be increased 24 hours after taking mexiletine.[3]

(b) Propafenone

In a study in 8 healthy subjects, the clearance of a single 300-mg dose of caffeine was reduced by 35% and the half-life of caffeine was extended from 3.82 hours to 5.9 hours when propafenone 300 mg was given.[4]

(c) Other antiarrhythmics

In 7 healthy subjects given caffeine, single doses of **lidocaine** 200 mg, **flecainide** 100 mg and **tocainide** 500 mg had no effect on the clearance of a single 366-mg dose of caffeine.[2]

Mechanism

It is likely that, as with theophylline (see 'Theophylline + Mexiletine or Tocainide', p.1448, and 'Theophylline + Propafenone', p.1451), mexiletine and propafenone inhibit the hepatic metabolism of caffeine by the cytochrome P450 isoenzyme CYP1A2.

Importance and management

The interaction between caffeine and mexiletine appears to be established, but its clinical importance is uncertain. Some of the adverse effects of mexiletine might be partially due to caffeine-retention (from drinking tea, coffee, cola drinks, etc.).[1] In excess, caffeine can cause jitteriness, tremor and insomnia. It has also been suggested that the caffeine test for liver function might be impaired by mexiletine.[1] The clinical significance of the interaction with propafenone is less clear, as no details on the clinical state of the subjects was recorded.[4] Be alert for possible adverse effects of caffeine and advise patients to reduce caffeine intake if these become troublesome.

1. Joeres R, Klinker H, Heusler H, Epping J, Richter E. Influence of mexiletine on caffeine elimination. *Pharmacol Ther* (1987) 33, 163–9.
2. Joeres R, Richter E. Mexiletine and caffeine elimination. *N Engl J Med* (1987) 317, 117.
3. Labbé L, Abolfathi Z, Robitaille NM, St-Maurice F, Gilbert M, Turegon J. Stereoselective disposition of the antiarrhythmic agent mexiletine during the concomitant administration of caffeine. *Ther Drug Monit* (1999) 21, 191–9.
4. Michaud V, Mouksassi MS, Labbé L, Bélanger P-M, Ferron LA, Gilbert M, Grech-Bélanger O, Turgeon J. Inhibitory effects of propafenone on the pharmacokinetics of caffeine in humans. *Ther Drug Monit* (2006) 28, 779–83.

Caffeine + Disulfiram

Disulfiram reduces the clearance of caffeine, which might complicate the withdrawal from alcohol.

Clinical evidence, mechanism, importance and management

A study in healthy subjects and recovering alcoholics found that disulfiram 250 or 500 mg daily reduced the clearance of caffeine by about 30%, but a few of the alcoholics had a more than 50% reduction.[1] As a result the levels of caffeine in the body increased. Raised levels of caffeine can cause irritability, insomnia and anxiety, similar to the symptoms of alcohol withdrawal. As coffee consumption is often particularly high among recovering alcoholics, there is the risk that they may turn to alcohol to calm themselves down. To avoid this possible complication it might be wise for recovering alcoholics not to drink too much tea or coffee. Decaffeinated coffee and tea are widely available.

1. Beach CA, Mays DC, Guiler RC, Jacober CH, Gerber N. Inhibition of elimination of caffeine by disulfiram in normal subjects and recovering alcoholics. *Clin Pharmacol Ther* (1986) 39, 265–70.

Caffeine + Food

Foods such as broccoli and green beans increase the rate of metabolism of caffeine.

Clinical evidence, mechanism, importance and management

In a study in 9 healthy subjects, the metabolism of caffeine, measured by the appearance of metabolites in the urine, was increased after the ingestion of 500 g of green beans or broccoli daily for 10 days.[1] Caffeine is metabolised by the cytochrome P450 isoenzyme CYP1A2, *N*-acetyl transferase and xanthine oxidase. Some foodstuffs can induce the activity of CYP1A2, resulting in an increased rate of metabolism of substrates such as caffeine. However, this finding is unlikely to be of clinical significance, as caffeine is commonly ingested as part of the diet, and the amount of green vegetables given was quite large.

1. Vistisen K, Loft S, Poulsen HE. Cytochrome P450 1A2 activity in man measured by caffeine metabolism: effect of smoking, broccoli and exercise. *Adv Exp Med Biol* (1991) 283, 407–11.

Caffeine + Grapefruit juice

Grapefruit juice does not interact with caffeine to a clinically relevant extent.

Clinical evidence, mechanism, importance and management

In 12 healthy subjects grapefruit juice, at a dose of 1.2 litres, decreased the clearance of caffeine from coffee by 23% and prolonged its half-life by 31%, but these changes were not considered clinically relevant.[1] A crossover study in 6 healthy subjects given caffeine 3.3 mg/kg found that multiple doses of grapefruit juice (equivalent to 6 glasses) caused a non-significant increase in the AUC of caffeine. No changes in ambulatory systolic or diastolic blood pressure or heart rate were seen.[2]

1. Fuhr U, Klittich K, Staib AH. Inhibitory effect of grapefruit juice and the active component, naringenin on CYP1A2 dependent metabolism of caffeine in man. *Br J Clin Pharmacol* (1993) 35, 431–6. [Title corrected by erratum].
2. Maish WA, Hampton EM, Whitsett TL, Shepard JD, Lovallo WR. Influence of grapefruit juice on caffeine pharmacokinetics and pharmacodynamics. *Pharmacotherapy* (1996) 16, 1046–52.

Caffeine + Hormonal contraceptives or HRT

The half-life of caffeine is prolonged to some extent in women taking oral combined hormonal contraceptives or HRT.

Clinical evidence

(a) Contraceptives

In 9 women taking low-dose oral combined hormonal contraceptives for at least 3 months the clearance of a single 162-mg dose of caffeine was reduced, the half-life prolonged (7.9 hours compared with 5.4 hours), and the plasma levels were raised, when compared with 9 other women not taking a contraceptive.[1] This finding was confirmed in three other studies,[2-4] which found that caffeine elimination was prolonged, from 4 to 6 hours before the use of combined oral contraceptives, to about 9 hours by the end of the first cycle, and to about 11 hours by the end of the third cycle.[3,4] A further study found that there was little difference between the effects of two oral hormonal contraceptives (**ethinylestradiol** 30 micrograms with gestodene 75 micrograms or levonorgestrel 125 micrograms) on caffeine: both increased the half-life of caffeine by a little over 50%, but the maximum serum levels were unchanged.[5] A study in 7 women similarly found that the use of an oral contraceptive containing **ethinylestradiol** sulphonate 3 mg and **norethisterone** acetate 10 mg per menstrual cycle (*Depositon*) prolonged the half-life of caffeine from 4.9 hours to 8 hours.[6]

A review of the bone mineral content of 263 users of depot **medroxyprogesterone** found that the women who reported a high caffeine intake (over 200 mg daily) had a significantly lower spinal bone mineral content than the women who reported no caffeine intake. However, there was no significant difference in bone mineral density between the two groups.[7]

(b) HRT

In one study, 12 healthy postmenopausal women were given a single 200-mg dose of caffeine after taking **estradiol** (*Estrace*) for 8 weeks, titrated to give **estradiol** plasma concentrations of 50 to 150 picograms/mL. The metabolism of caffeine was reduced by 29% overall. If the data for 2 subjects who were found to have taken extra caffeine during the study period are excluded, the reduction in caffeine metabolism was even greater (average reduction of 38%).[8]

Mechanism

Uncertain. Estrogens can inhibit the cytochrome P450 isoenzyme CYP1A2, by which caffeine is metabolised, which may explain its accumulation in the body.

Importance and management

An established interaction that is probably of limited clinical importance. Women taking hormonal contraceptives containing estrogens or HRT who take caffeine-containing analgesics or drink caffeine-containing drinks (tea, coffee, cola drinks, etc.) may find the effects of caffeine, such as jitteriness and insomnia, increased and prolonged. The effect of high caffeine use and depot medroxyprogesterone on bone mineral content is unlikely to be of clinical significance.

1. Abernethy DR, Todd EL. Impairment of caffeine clearance by chronic use of low-dose oestrogen-containing oral contraceptives. *Eur J Clin Pharmacol* (1985) 28, 425–8.
2. Patwardhan RV, Desmond PV, Johnson RF, Schenker S. Impaired elimination of caffeine by oral contraceptive steroids. *J Lab Clin Med* (1980) 95, 603–8.
3. Meyer FP, Canzler E, Giers H, Walther H. Langzeituntersuchung zum Einfluß von Non-Ovlon auf die Pharmakokinetik von Coffein im intraindividuellen Vergleich. *Zentralbl Gynakol* (1988) 110, 1449–54.
4. Rietveld EC, Broekman MMM, Houben JJG, Eskes TKAB, van Rossum JM. Rapid onset of an increase in caffeine residence time in young women due to oral contraceptive steroids. *Eur J Clin Pharmacol* (1984) 26, 371–3.
5. Balogh A, Klinger G, Henschel L, Börner A, Vollanth R, Kuhnz W. Influence of ethinylestradiol-containing combination oral contraceptives with gestodene or levonorgestrel on caffeine elimination. *Eur J Clin Pharmacol* (1995) 48, 161–6.
6. Meyer FP, Canzler E, Giers H, Walther H. Zeitverlauf der hemmung der coffeinelimination unter dem einfluß des oralen depotkontrazeptivum Deposiston®. *Zentralbl Gynakol* (1991) 113, 297–302.
7. Wetmore CM, Ichikawa L, LaCroix AZ, Ott SM, Scholes D. Association between caffeine intake and bone mass among young women: potential effect modification by depot medroxyprogesterone acetate use. Osteoporos Int (2008) 19, 519–27.
8. Pollock BG, Wylie M, Stack JA, Sorisio DA, Thompson DS, Kirshner MA, Folan MM, Condifer KA. Inhibition of caffeine metabolism by estrogen replacement therapy in postmenopausal women. *J Clin Pharmacol* (1999) 39, 936–40.

Caffeine + Idrocilamide

Oral idrocilamide reduces the clearance of caffeine, which can lead to caffeine toxicity.

Clinical evidence, mechanism, importance and management

The possibility that caffeine intake might have had some part to play in the development of psychiatric disorders seen in patients taking idrocilamide, prompted a pharmacokinetic study in 4 healthy subjects. While taking oral idrocilamide 400 mg three times daily the half-life of caffeine (150 to 200 mg of caffeine from one cup of coffee) was prolonged from about 7 hours to 59 hours. The overall clearance of caffeine was decreased by about 90%.[1,2]

Idrocilamide can inhibit the cytochrome P450 isoenzyme CYP1A2 by which caffeine is metabolised, leading to its accumulation.

Evidence is limited but the interaction appears to be established. Patients taking oral idrocilamide should probably avoid or minimise their intake of caffeine, including caffeine-containing drinks (tea, coffee, cola drinks,

etc.), otherwise caffeine toxicity may develop. Decaffeinated teas and coffee are widely available. Some medicines may contain caffeine, so these should also be used with care.

1. Brazier JL, Descotes J, Lery N, Ollagnier M, Evreux J-C. Inhibition by idrocilamide of the disposition of caffeine. *Eur J Clin Pharmacol* (1980) 17, 37–43.
2. Evreux JC, Bayere JJ, Descotes J, Lery N, Ollagnier M, Brazier JL. Les accidents neuro-psychiques de l'idrocilamide: conséquence d'une inhibition due métabolisme de la caféine? *Lyon Med* (1979) 241, 89–91.

Caffeine + Kava

It appears that kava is unlikely to affect the pharmacokinetics of caffeine, although further study is required to confirm this.

Clinical evidence, mechanism, importance and management

In a study in 6 subjects (3 of whom smoked tobacco) who regularly took 7 to 27 g of kavalactones weekly as an aqueous kava extract, the metabolic ratio of caffeine was increased twofold when kava was withheld for 30 days, which suggested that kava inhibits the cytochrome P450 isoenzyme CYP1A2, which is involved in the metabolism of caffeine.[1]

However, in a study in 12 non-smoking healthy subjects given kava kava root extract 1 g twice daily for 28 days before receiving a single 100-mg dose of oral caffeine, no significant change in the metabolic ratio of caffeine was noted.[2] It is possible that the inhibitory effect of tobacco smoke on CYP1A2, and the lack of standardisation of kava intake may have influenced the results.

1. Russman S, Lauterburg BH, Barguil Y, Choblet E, Cabalion P, Rentsch K, Wenk M. Traditional aqueous kava extracts inhibit cytochrome P450 1A2 in humans: protective effect against environmental carcinogens? *Clin Pharmacol Ther* (2005) 77, 451–4.
2. Gurley BJ, Gardner SF, Hubbard MA, Williams DK, Gentry WB, Khan IA, Shah A. In vivo effects of goldenseal, kava kava, black cohosh, and valerian on human cytochrome P450 1A2, 2D6, 2E1, and 3A4/5 phenotypes. *Clin Pharmacol Ther* (2005) 77, 415–26.

Caffeine + Menthol

Menthol modestly affects the pharmacokinetics of caffeine.

Clinical evidence, mechanism, importance and management

A crossover study in 11 healthy subjects found that a single 100-mg dose of menthol taken with coffee containing 200 mg caffeine increased the time to maximum caffeine levels by about 30 minutes. The increase in the actual maximum level was not significant, and there were no significant effects on caffeine half-life. It was thought that menthol reduced the rate of caffeine absorption.[1] The clinical importance of this is not clear but it is seems likely to be small.

1. Gelal A, Guven H, Balkan D, Artok L, Benowitz NL. Influence of menthol on caffeine disposition and pharmacodynamics in healthy female volunteers. *Eur J Clin Pharmacol* (2003) 59, 417–22.

Caffeine + Nicotine

Caffeine may boost some of the stimulant effects of nicotine, but it only appears to cause a small, if any, rise in nicotine levels.

Clinical evidence

In a study in 21 smokers who regularly drank one to six cups of coffee daily, a 50-mg tablet of caffeine increased self-ratings of 'stimulated', 'alert' and 'jittery' at various doses of nicotine chewing gum (0.25 mg, 0.5 mg and 1 mg) when compared with the nicotine gum alone.[1] In a placebo-controlled study, 12 healthy subjects were given nicotine 1 mg or 2 mg with caffeine 50 mg or 100 mg, given in a chewing gum. Nicotine alone and caffeine alone increased energy expenditure, but adding caffeine 50 mg to nicotine 1 mg had almost double the effects of simply increasing the nicotine dose from 1 to 2 mg. Similar effects were seen in both smokers and non-smokers. No adverse effects were reported with either nicotine 1 mg alone or combined with caffeine.[2] In a similar study by the same authors, caffeine enhanced the appetite-suppressant effects of nicotine.[3] In another study in 13 smokers who regularly drank at least one cup of coffee daily, pre-treatment with oral caffeine 2.5 or 5 mg/kg (added to 180 mL of decaffeinated coffee) did not alter the subjects ability to discriminate between nasal nicotine and placebo, and did not alter the amount of caffeine they self-administered during a period of smoking cessation. Caffeine pretreatment caused a modest dose-related increase in nicotine levels (maximum 21%).[4] In a study in 12 smokers, two doses of caffeine 150 mg (given in a decaffeinated cola drink before and during smoking) had no effect on the plasma levels of nicotine achieved by smoking 5 cigarettes.[5]

Mechanism

Not understood.

Importance and management

A fairly well studied interaction. Caffeine may boost some of the stimulant effects of nicotine (energy consumption, appetite suppression, but also adverse effects such as jitteriness), but it only appears to cause a small, if any, rise in nicotine levels. Bear the potential for this increase in effects in mind should a patient receiving nicotine replacement therapy and also taking caffeine supplements develop troublesome nicotine-related adverse effects.

1. Duka T, Tasker R, Russell K, Stephens DN. Discriminative stimulus properties of nicotine at low doses: the effects of caffeine preload. *Behav Pharmacol* (1998) 9, 219–29.
2. Jessen AB, Toubro S, Astrup A. Effect of chewing gum containing nicotine and caffeine on energy expenditure and substrate utilization in men. *Am J Clin Nutr* (2003) 77, 1442–7.
3. Jessen A, Buemann B, Toubro S, Skovgaard IM, Astrup A. The appetite-suppressant effect of nicotine is enhanced by caffeine. *Diabetes Obes Metab* (2005) 7, 327–33.
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5. Gilbert DG, Dibb WD, Plath LC, Hiyane SG. Effects of nicotine and caffeine, separately and in combination, on EEG topography, mood, heart rate, cortisol, and vigilance. *Psychopharmacology (Berl)* (2000) 37, 583–95.

Caffeine + Psoralens

Oral methoxsalen and 5-methoxypsoralen markedly reduce caffeine clearance. Topical methoxsalen does not interact with caffeine.

Clinical evidence

In 5 subjects with psoriasis, a single 1.2-mg/kg oral dose of **methoxsalen** (8-methoxypsoralen), given one hour before a single 200-mg oral dose of caffeine, reduced the clearance of caffeine by 69%. The elimination half-life of caffeine over the period from 2 to 16 hours after taking the **methoxsalen** increased tenfold (from 5.6 to 57 hours).[1] In a similar study, 8 patients with psoriasis were given caffeine 200 mg with or without **5-methoxypsoralen** 1.2 mg/kg. The AUC of caffeine increased about threefold and there was a threefold decrease in its clearance.[2]

A study in patients receiving PUVA therapy (**methoxsalen** either orally, in 4 patients, or topically as a bath in 7 patients, plus UVA) found that the clearance of a single 150-mg dose of caffeine was markedly reduced in the patients given oral **methoxsalen** but not altered in those given topical **methoxsalen**.[3]

Mechanism

Both methoxsalen and 5-methoxypsoralen inhibit the metabolism of caffeine by the cytochrome P450 isoenzyme CYP1A2 in the liver, thereby markedly increasing caffeine levels.[2,3]

Importance and management

An interaction between oral methoxsalen and caffeine appears to be established, but its practical consequences are as yet uncertain. However, it seems possible that the adverse effects of caffeine will be increased. In excess, caffeine (including that from tea, coffee and cola drinks) can cause jitteriness, headache and insomnia. If these effects develop in a patient receiving methoxsalen it may be prudent to advise them to decrease their caffeine intake. The interaction does not appear to occur with topical methoxsalen.

1. Mays DC, Camisa C, Cheney P, Pacula CM, Nawoot S, Gerber N. Methoxsalen is a potent inhibitor of the metabolism of caffeine in humans. *Clin Pharmacol Ther* (1987) 42, 621–6.
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Caffeine + Quinolones

Enoxacin markedly increases caffeine levels. The effects of caffeine derived from drinks such as tea, coffee or cola, would be expected to be increased. Pipemidic acid interacts to a lesser extent, and ciprofloxacin, norfloxacin and pefloxacin interact less still. Fleroxacin, lomefloxacin, ofloxacin, rufloxacin, and trovafloxacin appear not to interact.

Clinical evidence

The effects of various quinolones on the pharmacokinetics of caffeine[1-13] are summarised in 'Table 34.3', (p.1423). In one study ciprofloxacin and fleroxacin increased caffeine levels more in women than men, but this difference in effect was not significant when the results were normalised for body weight.[13]

Mechanism

It would seem that the metabolism (*N*-demethylation) of caffeine is markedly reduced by some quinolones (notably pipemidic acid and enoxacin) resulting in greater levels and possibly greater effects. Other quinolones have either a much smaller effect or no effect at all. The quinolones that interact appear to inhibit the cytochrome P450 isoenzyme CYP1A2[14] by which caffeine is metabolised.

Importance and management

Established interactions. Based on the results of two studies, on a scale of 100 to 0, the relative potencies of these quinolones as inhibitors of caffeine elimination have been determined as follows: enoxacin 100, pipemidic acid 29, ciprofloxacin 11, norfloxacin 9 and ofloxacin 0.[15] From further studies, clinafloxacin appears to be similar to enoxacin (profound effect), pefloxacin to norfloxacin (to which it is metabolised; modest effect), and fleroxacin, lomefloxacin, rufloxacin, and trovafloxacin appear to behave like ofloxacin (no effect). Patients taking enoxacin might be expected to experience an increase in the effects of caffeine (such as headache, jitteriness, restlessness, insomnia) if, for example, they continue to drink their usual amounts of caffeine-containing drinks (tea, coffee, cola drinks, etc.). They should be warned to cut out or reduce their intake of caffeine if this occurs. The authors of one report[1] suggest that patients with hepatic disorders, cardiac arrhythmias or latent epilepsy should avoid caffeine if they take enoxacin for one week or more. The effects of pipemidic acid and ciprofloxacin on caffeine are less, and those of norfloxacin and pefloxacin are probably of little or no clinical importance. Fleroxacin, lomefloxacin, ofloxacin, rufloxacin, and trovafloxacin do not interact.

Note that caffeine can be used as a probe substrate for the activity of the cytochrome P450 isoenzyme CYP1A2: those quinolones that have the greatest effect on caffeine are the most potent CYP1A2 inhibitors (e.g. enoxacin), those that have modest effects are moderate CYP1A2 inhibitors (e.g. ciprofloxacin), and those that have little or no effect on caffeine metabolism are unlikely to have a clinically relevant effect on other CYP1A2 substrates (e.g. ofloxacin). Note that the strength of the effect varies with the dose of quinolone used.

1. Staib AH, Stille W, Dietlein G, Shah PM, Harder S, Mieke S, Beer C. Interaction between quinolones and caffeine. *Drugs* (1987) 34 (Suppl 1), 170–4.
2. Carbó M, Segura J, De la Torre R, Badenas JM, Camí J. Effect of quinolones on caffeine disposition. *Clin Pharmacol Ther* (1989) 45, 234–40.
3. Harder S, Staib AH, Beer C, Papenburg A, Stille W, Shah PM. 4-Quinolones inhibit biotransformation of caffeine. *Eur J Clin Pharmacol* (1988) 35, 651–6.
4. Stille W, Harder S, Mieke S, Beer C, Shah PM, Frech K, Staib AH. Decrease of caffeine elimination in man during co-administration of 4-quinolones. *J Antimicrob Chemother* (1987) 20, 729–34.
5. Healy DP, Schoenle JR, Stotka J, Polk RE. Lack of interaction between lomefloxacin and caffeine in normal volunteers. *Antimicrob Agents Chemother* (1991) 35, 660–4.
6. Peloquin CA, Nix DE, Sedman AJ, Wilton JH, Toothaker RD, Harrison NJ, Schentag JJ. Pharmacokinetics and clinical effects of caffeine alone and in combination with oral enoxacin. *Rev Infect Dis* (1989) II (Suppl 5), S1095.
7. Healy DP, Polk RE, Kanawati L, Rock DT, Mooney ML. Interaction between oral ciprofloxacin and caffeine in normal volunteers. *Antimicrob Agents Chemother* (1989) 33, 474–8.
8. Nicolau DP, Nightingale CH, Tessier PR, Fu Q, Xuan D-w, Esguerra EM, Quintiliani R. The effect of fleroxacin and ciprofloxacin on the pharmacokinetics of multiple dose caffeine. *Drugs* (1995) 49 (Suppl 2), 357–9.
9. LeBel M, Teng R, Dogolo LC, Willavize S, Friedman HL, Vincent J. The influence of steady-state trovafloxacin on the steady-state pharmacokinetics of caffeine in healthy subjects. *Pharm Res* (1996) 13 (Suppl 9), S434.
10. Randinitis EJ, Koup JR, Rausch G, Vassos AB. Effect of (CLX) administration on the single-dose pharmacokinetics of theophylline and caffeine. *Intersci Conf Antimicrob Agents Chemother* (1998) 38, 6.
11. Cesana M, Broccali G, Imbimbo BP, Crema A. Effect of single doses of rufloxacin on the disposition of theophylline and caffeine after single administration. *Int J Clin Pharmacol Ther Toxicol* (1991) 29, 133–8.
12. Kinzig-Schippers M, Fuhr U, Zaigler M, Dammeyer J, Rüsing G, Labedzki A, Bulitta J, Sörgel F. Interaction of pefloxacin and enoxacin with the human cytochrome P450 enzyme CYP1A2. *Clin Pharmacol Ther* (1999) 65, 262–74.
13. Kim M-Y, Nightingale CH, Nicolau DP. Influence of sex on the pharmacokinetic interaction of fleroxacin and ciprofloxacin with caffeine. *Clin Pharmacokinet* (2003), 42, 985–96.
14. Fuhr U, Wolff T, Harder S, Schymanski P, Staib AH. Quinolone inhibition of cytochrome P450-dependent caffeine metabolism in human liver microsomes. *Drug Metab Dispos* (1990) 18, 1005–10.
15. Barnett G, Segura J, de la Torre R, Carbó M. Pharmacokinetic determination of relative potency of quinolone inhibition of caffeine disposition. *Eur J Clin Pharmacol* (1990) 39, 63–9.

Caffeine + SSRIs

The clearance of caffeine is considerably reduced by fluvoxamine. An increase in the stimulant and adverse effects of caffeine would be expected, however this was not demonstrated in one study. Caffeine may cause a reduction in the bioavailability of fluvoxamine. A possible case of serotonin syndrome was attributed to the concurrent use of paroxetine and caffeine.

Clinical evidence

(a) Fluvoxamine

In a randomised, crossover study, 8 healthy subjects were given fluvoxamine 50 mg daily for 4 days and then 100 mg daily for a further 8 days, with a single 200-mg oral dose of caffeine before and on day 8 of fluvoxamine use. Fluvoxamine reduced the total clearance of caffeine by about 80% (from 107 to 21 mL/minute) and increased its half-life from 5 hours to 31 hours. Specifically, the clearance of caffeine by *N*3-, *N*1- and *N*7-demethylation was decreased.[1] Another study in 30 patients found a positive correlation between plasma fluvoxamine and plasma caffeine levels, suggesting that the interaction is dose-related.[2] A further study found that low, sub-therapeutic doses of fluvoxamine 10 or 20 mg daily were sufficient to markedly inhibit caffeine metabolism.[3] A study in 7 subjects found that fluvoxamine 100 mg twice daily for 4 doses significantly increased the maximum levels of a single 250-mg dose of caffeine by 40%, and increased the AUC and half-life of caffeine 12.7-fold and 10-fold, respectively. However, this did not result in an increase in caffeine-related adverse effects, and none of the subjects felt they were more alert with the combination than with either drug alone.[4]

A study in 12 healthy subjects (6 smokers and 6 non-smokers) found that caffeine 150 mg twice daily for 11 days reduced the AUC of a single 50-mg dose of fluvoxamine taken on day 8, by about 24%. The plasma concentration of fluvoxamine was also decreased by 12% but this was not statistically significant.[5]

(b) Paroxetine

A case report describes a patient who took amoxapine 200 mg, paroxetine 20 mg, and a preparation containing 4.8 g of caffeine. She became restless and incoherent, with a raised temperature, pulse rate and respiratory rate, diaphoresis, myoclonus and mild muscle rigidity. Her symptoms resolved when she was given dantrolene and diazepam. The authors of the report attribute these symptoms to serotonin syndrome, and suggest that the large dose of caffeine was a contributing factor.[6] However, serotonin syndrome has been reported in a number of patients taking tricyclics and SSRIs (see 'Tricyclic and related antidepressants + SSRIs', p.1513), and so an effect of caffeine is not established.

Mechanism

Fluvoxamine is a potent inhibitor of the cytochrome P450 isoenzyme CYP1A2, which is the principal enzyme concerned with the metabolism of caffeine. As a result caffeine is cleared from the body much more slowly and accumulates.[1-3] It has been suggested that large doses of caffeine may promote serotonin activity.[6]

Importance and management

The increase in caffeine levels that occurs with fluvoxamine is established. There are no reports of caffeine toxicity arising from this interaction and one study[4] found no increase in the pharmacodynamic or adverse effects of caffeine despite a large increase in the levels. However, an increase in the stimulant and adverse effects of caffeine (headache, jitteriness, restlessness, insomnia) may be possible in susceptible patients if they continue

Table 34.3 Effect of quinolones on caffeine pharmacokinetics in healthy subjects

Quinolone[*]	*Daily caffeine intake*[†]	*Change in AUC*	*Change in clearance*	*Refs*
Ciprofloxacin				
100 mg twice daily	220 to 230 mg	+17%		1
250 mg twice daily	220 to 230 mg	+57%	-33%	1-3
500 mg twice daily	230 mg	+58%		1
500 mg twice daily	100 mg three times daily	+127%	-49%	4
500 mg twice daily	100 mg three times daily	+101% women +80% men	-53% women -47% men	5
750 mg (3 x 12-hourly doses)	100 mg	+59%	-45%	6
Clinafloxacin				
400 mg twice daily	200 mg		-84%	7
Enoxacin				
100 mg twice daily	230 mg	+138%		1
200 mg twice daily	230 mg	+176%		1
400 mg twice daily	220 to 230 mg	+346%	-78%	1-3
400 mg twice daily	200 mg daily	+370%	-79%	8
400 mg twice daily	183 mg daily		-83%	9
Fleroxacin				
400 mg daily	100 mg three times daily	+18% women No change in men	No change in women No change in men	4
Lomefloxacin				
400 mg daily	200 mg daily	No change	No change	10
Norfloxacin				
200 mg twice daily	230 mg	+16%		1
800 mg twice daily	350 mg	+52%	-35%	11
Ofloxacin				
200 mg twice daily	220 to 230 mg	No change	No change	1-3
Pefloxacin				
400 mg twice daily	183 mg daily		-47%	9
Pipemidic acid				
400 mg twice daily	230 mg	+179%		1
800 mg twice daily	350 mg	+119%	-63%	11
Rufloxacin				
400 mg (single dose)	200 mg	-18%	No change	12
Trovafloxacin				
200 mg daily	183 mg daily	+17%		13

[*]Unless otherwise stated quinolones were given for 3 to 5 days.
[†]Unless otherwise stated caffeine was given as a single dose.

1. Harder S, Staib AH, Beer C, Papenburg A, Stille W, Shah PM. 4-Quinolones inhibit biotransformation of caffeine. *Eur J Clin Pharmacol* (1988) 35, 651-6.
2. Staib AH, Stille W, Dietlein G, Shah PM, Harder S, Mieke S, Beer C. Interaction between quinolones and caffeine. *Drugs* (1987) 34 (Suppl 1), 170-4.
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Continued

Table 34.3 Effect of quinolones on caffeine pharmacokinetics in healthy subjects (continued)

8. Peloquin CA, Nix DE, Sedman AJ, Wilton JH, Toothaker RD, Harrison NJ, Schentag JJ. Pharmacokinetics and clinical effects of caffeine alone and in combination with oral enoxacin. *Rev Infect Dis* (1989) II (Suppl 5), S1095.
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to consume large amounts of caffeine-containing food or drinks (tea, coffee, cola drinks, chocolate, etc.) or take caffeine-containing medications. They should be warned to reduce their caffeine intake if problems develop. It has been suggested that some of the adverse effects of fluvoxamine (i.e. nervousness, restlessness and insomnia) could in fact be caused by caffeine toxicity. However, a preliminary study, as well as the study reported above,[4] found that caffeine intake had a limited effect on the frequency of adverse effects of fluvoxamine.[7] The clinical significance of the change in the AUC of fluvoxamine with caffeine intake is unclear. This slight decrease is unlikely to be important in most patients.

There appears to be only one isolated case of serotonin syndrome attributed to an interaction with caffeine, and as such, no general recommendations can be made.

1. Jeppesen U, Loft S, Poulsen HE, Brøsen K. A fluvoxamine-caffeine interaction study. *Pharmacogenetics* (1996) 6, 213–222.
2. Yoshimura R, Ueda N, Nakamura J, Eto S, Matsushita M. Interaction between fluvoxamine and cotinine or caffeine. *Neuropsychobiology* (2002) 45, 32–5.
3. Christensen M, Tybring G, Mihara K, Yasui-Furokori N, Carrillo JA, Ramos SI, Andersson K, Dahl M-L, Bertilsson L. Low daily 10-mg and 20-mg doses of fluvoxamine inhibit the metabolism of both caffeine (cytochrome P4501A2) and omeprazole (cytochrome P4502C19). *Clin Pharmacol Ther* (2002) 71, 141–52.
4. Culm-Merdek KE, von Moltke LL, Harmatz JS, Greenblatt DJ. Fluvoxamine impairs single-dose caffeine clearance without altering caffeine pharmacodynamics. *Br J Clin Pharmacol* (2005) 60, 486–93.
5. Fukasawa T, Yasui-Furukori N, Suzuki A, Ishii G, Inoue Y, Tateishi T, Otani K. Effects of caffeine on the kinetics of fluvoxamine and its major metabolite in plasma after a single oral dose of the drug. *Ther Drug Monit* (2006) 28, 308–11.
6. Shioda K, Nisijima K, Nishida S, Kato S. Possible serotonin syndrome arising from an interaction between caffeine and serotonergic antidepressants. *Hum Psychopharmacol Clin Exp* (2004) 19, 353–4.
7. Spigset O. Are adverse drug reactions attributed to fluvoxamine caused by concomitant intake of caffeine? *Eur J Clin Pharmacol* (1998) 54, 665–6.

Caffeine + Tiabendazole

Tiabendazole reduces the metabolism of caffeine.

Clinical evidence, mechanism, importance and management

A study in 7 healthy subjects found that a single 500-mg dose of tiabendazole reduced the clearance of caffeine by 66% and increased its half-life and AUC by 140% and 57%, respectively. The metabolism of caffeine to one of its major metabolites, paraxanthine, was reduced by 92%.[1] It was suggested that tiabendazole inhibits the metabolism of caffeine by the cytochrome P450 isoenzyme CYP1A2 in the liver. There is too little information to suggest that patients taking tiabendazole should avoid caffeine-containing beverages, foods or medication, but bear this interaction in mind if the adverse effects of caffeine (e.g. insomnia, jitteriness) become troublesome.

1. Bapiro TE, Sayi J, Hasler JA, Jande M, Rimoy G, Masselle A, Masimirembwa CM. Artemisinin and thiabendazole are potent inhibitors of cytochrome P450 1A2 (CYP1A2) activity in humans. *Eur J Clin Pharmacol* (2005) 61, 755–61.

Caffeine + Tobacco

Tobacco smoking increases the rate of metabolism of caffeine.

Clinical evidence

In a study, the metabolism of caffeine, measured by the appearance of metabolites in the urine of healthy subjects, was found to be increased in those subjects who smoked, compared with those who were non-smokers.[1] Mathematical modelling of caffeine plasma levels in smokers and non-smokers confirmed that after adjustment for caffeine intake, the plasma levels of caffeine in non-smokers were two to three times higher than in those subjects who smoked.[2] A study in 12 otherwise healthy smokers found that on stopping smoking the metabolism of caffeine was reduced by about 36%.[3]

Mechanism

Caffeine is metabolised by the cytochrome P450 isoenzyme CYP1A2, *N*-acetyl transferase and xanthine oxidase. Smoking can induce the activity of CYP1A2, resulting in an increased rate of metabolism of caffeine.

Importance and management

Evidence regarding an interaction between caffeine and smoking appears to be limited to these studies, which were mainly using caffeine to assess the effect of smoking on enzyme induction. Nevertheless, they do suggest that the levels of caffeine may rise, all be it modestly, in those that stop smoking. If the adverse effects of caffeine (headache, jitteriness, restlessness, insomnia) become troublesome, it would be prudent to advise patients to decrease their caffeine intake. Note that, the use of nicotine replacement therapy may also exacerbate the adverse effects of caffeine, see 'Caffeine + Nicotine', p.1421.

1. Vistisen K, Loft S, Poulsen HE. Cytochrome P450 1A2 activity in man measured by caffeine metabolism: effect of smoking, broccoli and exercise. *Adv Exp Med Biol* (1991) 283, 407–11.
2. de Leon J, Diaz FJ, Rogers T, Browne D, Dinsmore L, Ghosheh OH, Dwoskin LP, Crooks PA. A pilot study of plasma caffeine concentrations in a US sample of smoker and nonsmoker volunteers. *Prog Neuropsychopharmacol Biol Psychiatry* (2003) 27, 165–71.
3. Faber MS, Fuhr U. Time response of cytochrome P450 1A2 activity on cessation of heavy smoking. *Clin Pharmacol Ther* (2004) 76, 178–84.

Caffeine + Venlafaxine

Venlafaxine does not affect the pharmacokinetics of caffeine to a clinically relevant extent.

Clinical evidence, mechanism, importance and management

In 15 healthy subjects venlafaxine 37.5 mg twice daily for 3 days then 75 mg twice daily for 4 days did not affect the AUC or clearance of caffeine 200 mg daily (equivalent to about 3 cups of coffee). A slight but statistically significant decrease in the half-life from 6.1 hours to 5.5 hours was noted.[1] On the basis of this study, no special precautions are needed if both drugs are taken together.

1. Amchin J, Zarycranski W, Taylor KP, Albano D, Klockowski PM. Effect of venlafaxine on CYP1A2-dependent pharmacokinetics and metabolism of caffeine. *J Clin Pharmacol* (1999) 39, 252–9.

Caffeine + Verapamil

A small and relatively unimportant decrease in the clearance of caffeine may occur in patients given verapamil.

Clinical evidence, mechanism, importance and management

In 6 healthy subjects verapamil 80 mg three times daily for 2 days decreased the total clearance of a single 200-mg dose of caffeine by 25%,

and increased its half-life by 25% (from 4.6 to 5.8 hours).[1] These changes are small, and unlikely to be of much importance in most patients.

1. Nawoot S, Wong D, Mays DC, Gerber N. Inhibition of caffeine elimination by verapamil. *Clin Pharmacol Ther* (1988) 43, 148.

Doxofylline + Miscellaneous

There is some limited evidence to suggest that erythromycin may increase the effects of doxofylline, but the clinical importance of this is uncertain. Digoxin initially raises, then lowers serum doxofylline levels, but the bronchodilator effects do not appear to be significantly affected. Allopurinol and lithium carbonate appear to have no significant effects on doxofylline.

Clinical evidence, mechanism, importance and management

Healthy subjects were given doxofylline 400 mg three times daily, either alone, or with **allopurinol** 100 mg daily, **erythromycin** 400 mg three times daily or **lithium carbonate** 300 mg three times daily. None of the pharmacokinetic parameters measured, including the maximum serum levels, were significantly altered by any of these drugs apart from the AUC of doxofylline, which was raised by about 40% by **allopurinol**, 70% by **erythromycin**, and 35% by **lithium carbonate**. Only the **erythromycin** result was statistically significant.[1] The clinical significance of these changes is uncertain, and their mechanism is not understood. Until the situation is much clearer it would be prudent to check the outcome of adding **erythromycin** to established treatment with doxofylline, being alert for evidence of increased effects.

In a comparative study in 9 patients taking doxofylline 800 mg daily, **digoxin** 500 micrograms daily was given to 5 patients. It was found that **digoxin** *increased* the serum levels of doxofylline by 50% on the first day of treatment, 3 hours after administration but then *reduced* doxofylline levels by about 30% at steady-state (day 30). Nevertheless, the bronchodilating effects of the doxofylline were little different between the two groups. It was concluded that concurrent use is normally safe and effective, but the initial doxofylline dose should be chosen to avoid too high a serum level on the first day, and pulmonary function should be well monitored.[2]

1. Harning R, Sekora D, O'Connell K, Wilson J. A crossover study of the effect of erythromycin, lithium carbonate, and allopurinol on doxofylline pharmacokinetics. *Clin Pharmacol Ther* (1994) 55, 158.
2. Provvedi D, Rubegni M, Biffignandi P. Pharmacokinetic interaction between doxofylline and digitalis in elderly patients with chronic obstructive bronchitis. *Acta Ther* (1990) 16, 239–46.

Ipratropium bromide + Salbutamol (Albuterol)

Acute angle-closure glaucoma developed rapidly in eight patients given nebulised ipratropium and salbutamol. Increased intra-ocular pressure has been reported in others, including one patient using an ipratropium metered-dose inhaler with nebulised salbutamol.

Clinical evidence

Five patients with an acute exacerbation of chronic obstructive airways disease given nebulised ipratropium and **salbutamol**, developed acute angle-closure glaucoma, four of them within one to 36 hours of starting treatment. Two of the patients had a history of angle-closure glaucoma.[1] Seven other similar cases of acute angle-closure glaucoma due to the concurrent use of **salbutamol** and ipratropium are reported elsewhere.[2-6] An increase in intra-ocular pressure has also been reported in other patients given both drugs by nebuliser.[7] One case of acute angle-closure glaucoma has been reported in a patient given inhaled ipratropium, via a metered-dose inhaler, and nebulised **salbutamol**.[8]

Mechanism

This reaction appears to occur because the antimuscarinic action of the ipratropium causes semi-dilatation of the pupil, partially blocking the flow of aqueous humour from the posterior to the anterior chamber, thereby causing anterior bowing of the iris and obstructing the drainage angle. The salbutamol increases the production of aqueous humour, therefore exacerbating the situation. An additional factor that may contribute is the route of administration: higher levels of both drugs are achieved by using a nebuliser, and some drug may escape round the edge of the mask and have a direct action on the eye.[1]

Importance and management

An established but uncommon interaction, which appears to occur mainly in patients receiving salbutamol and ipratropium by nebuliser and those already predisposed to angle-closure glaucoma. The authors of the first report[1] advise care in the placing of the mask to avoid the escape of droplets. The use of goggles[7,9] and continuing the application of any glaucoma treatment is also effective.[7] It has been suggested that, if possible, nebulised salbutamol and ipratropium should be avoided in patients predisposed to angle-closure glaucoma.

1. Shah P, Dhurjon L, Metcalfe T, Gibson JM. Acute angle closure glaucoma associated with nebulised ipratropium bromide and salbutamol. *BMJ* (1992) 304, 40–1.
2. Packe GE, Cayton RM, Mashoudi N. Nebulised ipratropium bromide and salbutamol causing closed-angle glaucoma. *Lancet* (1984) ii, 691.
3. Reuser T, Flanagan DW, Borland C, Bannerjee DK. Acute angle closure glaucoma occurring after nebulized bronchodilator treatment with ipratropium bromide and salbutamol. *J R Soc Med* (1992) 85, 499–500.
4. Fernández-Barrientos Y, Jiménez-Santos M, Martínez-de-la-Casa JM, Méndez-Hernández C, García Feijoó J. Bloqueo angular agudo tras broncodilatadores nebulizados. *Arch Soc Esp Oftalmol* (2006) 81, 657–60.
5. De Saint Jean M, Bourcier T, Borderie V, Moldovan M, Touzeau O, Laroche L. Glaucome aigu par fermeture de l'angle après un traitement par aérosols de bromure d'ipratropium et de salbutamol. *J Fr Ophtalmol* (2000) 23, 603–5.
6. Mulpeter KM, Walsh JB, O'Connor M, O'Connell F, Burke C. Ocular hazards of nebulized bronchodilators. *Postgrad Med J* (1992) 68, 132–3.
7. Kalra L, Bone M. The effect of nebulized bronchodilator therapy on intraocular pressures in patients with glaucoma. *Chest* (1988) 93, 739–41.
8. Hall SK. Acute angle-closure glaucoma as a complication of combined β-agonist and ipratropium bromide therapy in the emergency department. *Ann Emerg Med* (1994) 23, 884–7.
9. Humphreys DM. Acute angle closure glaucoma associated with nebulised ipratropium bromide and salbutamol. *BMJ* (1992) 304, 320.

Montelukast + Anti-asthma drugs

An isolated report describes severe oedema in a patient taking oral prednisone and montelukast, but studies suggest that the concurrent use of montelukast and prednisolone or prednisone are useful and well-tolerated. Montelukast in normal doses does not appear to interact adversely with salbutamol (albuterol).

Clinical evidence, mechanism, importance and management

(a) Beta$_2$ agonists

A study in patients with moderately severe asthma found no adverse interactions when **salbutamol** (**albuterol**) was given with montelukast 100 mg or 250 mg, with or without inhaled corticosteroids.[1] The British Thoracic Society guidelines suggest that a leukotriene antagonist may be used as an add-on therapy in patients using short-acting inhaled beta$_2$ agonists.[2]

(b) Corticosteroids

A study in healthy subjects (55 taking montelukast and 36 taking placebo) found that the plasma profiles of oral **prednisone** 20 mg and of intravenous **prednisolone** 250 mg were unaffected by montelukast 200 mg daily for 6 weeks.[3] Other studies in patients using inhaled and/or oral corticosteroids have found that concurrent use is beneficial and well tolerated.[4-6]

However, an isolated report describes a case of marked peripheral oedema possibly linked to the use of **prednisone** and montelukast. A 23-year-old patient with severe allergic and exercise-induced asthma and rhinoconjunctivitis treated with salmeterol and fluticasone by inhalation and oral cetirizine was given **prednisone** 40 mg daily for one week then 20 mg daily for a further week. When **prednisone** was stopped, severe asthma recurred and he was given **prednisone** 60 mg daily for one week then 40 mg daily for a further week with montelukast 10 mg daily. After 10 days he developed severe peripheral oedema, gaining 13 kg in weight. Renal and cardiovascular function were normal. **Prednisone** was stopped and the asthma was controlled by continued montelukast and the excess weight was lost as the oedema resolved. The patient had good tolerance of both **prednisone** and montelukast alone. The reason for this adverse reaction is unclear, but it was suggested that corticosteroid-induced renal tubular sodium and fluid retention may have occurred when montelukast was also given.[7]

This isolated report is probably of limited general relevance. Usually, no

special precautions appear to be needed if these drugs are used concurrently, and the British Thoracic Society guidelines suggests that a leukotriene antagonist can be used as an add-on therapy to inhaled steroids.[2]

1. Botto A, Kundu S, Reiss T. A double-blind, placebo-controlled, 3-period, crossover study to investigate the bronchodilating ability of oral doses of MK-0476 and to investigate the interaction with inhaled albuterol in moderately severe asthmatic patients. Merck Sharp & Dohme. Data on file (Protocol 066) 1996.
2. British Thoracic Society and Scottish Intercollegiate Guidelines Network. British guideline on the management of asthma, May 2008, revised June 2009. Available at: http://www.sign.ac.uk/pdf/sign101.pdf (accessed 02/02/10).
3. Noonan T, Shingo S, Kundu S, Reiss TF. A double-blind, placebo-controlled, parallel-group study in healthy male volunteers to investigate the safety and tolerability of 6 weeks of administration of MK-0476, and in subgroups, the effect of 6 weeks of administration of MK-0476 on the single dose pharmacokinetics of po and iv theophylline and corticosteroids. Merck Sharp & Dohme. Data on file.
4. Dahlén S-E, Malmström K, Nizankowska E, Dahlén B, Kuna P, Kowalski M, Lumry WR, Picado C, Stevenson DD, Bousquet J, Pauwels R, Holgate ST, Shahane A, Zhang J, Reiss TF, Szczeklik A. Improvement of aspirin-intolerant asthma by montelukast, a leukotriene antagonist. *Am J Respir Crit Care Med* (2002) 165, 9–14.
5. Knorr B, Matz J, Bernstein JA, Nguyen H, Seidenberg BC, Reiss TF, Becker A, for the Pediatric Montelukast Study Group. Montelukast for chronic asthma in 6- to 14-year-old children. A randomized, double-blind trial. *JAMA* (1998) 279, 1181–6.
6. Phipatanakul W, Greene C, Downes SJ, Cronin B, Eller TJ, Schneider LC, Irani A-M. Montelukast improves asthma control in asthmatic children maintained on inhaled corticosteroids. *Ann Allergy Asthma Immunol* (2003) 91, 49–54.
7. Geller M. Marked peripheral edema associated with montelukast and prednisone. *Ann Intern Med* (2000) 132, 924.

Montelukast + Antiepileptics; Enzyme-inducing

Phenobarbital modestly reduces montelukast levels. Phenytoin is predicted to interact similarly.

Clinical evidence, mechanism, importance and management

Montelukast 10 mg was given to 14 healthy subjects before and after they took **phenobarbital** 100 mg daily for 14 days. It was found that the geometric mean AUC and the maximum serum levels of the montelukast were reduced by 38% and 20%, respectively, but it was concluded that no montelukast dose adjustment is needed.[1] The reason for these reductions is almost certainly because phenobarbital induces the cytochrome P450 isoenzyme CYP3A4 so that montelukast metabolism is increased. The manufacturer therefore cautions the use of montelukast with inducers of CYP3A4, such as **phenytoin** and **phenobarbital**, especially in children.[2] It would seem prudent to extend this caution to **fosphenytoin** and **primidone**, which are metabolised to phenytoin and phenobarbital, respectively. However, there does not appear to be any clinical evidence to suggest that the montelukast dose needs adjustment in the presence of any of these drugs.

1. Holland S, Shahane A, Rogers JD, Porras A, Grasing K, Lasseter K, Pinto M, Freeman A, Gertz B, Amin R. Metabolism of montelukast (M) is increased by multiple doses of phenobarbital (P). *Clin Pharmacol Ther* (1998) 63, 231.
2. Singulair (Montelukast sodium). Merck Sharp & Dohme Ltd. UK Summary of product characteristics, August 2009.

Montelukast + Antihistamines

Montelukast does not interact to a clinically relevant extent with loratadine or terfenadine.

Clinical evidence, mechanism, importance and management

In a study, healthy subjects were given terfenadine 60 mg every 12 hours for 14 days, with montelukast 10 mg daily from day 8 to day 14. It was found that the pharmacokinetics of **terfenadine** and its effect on the QTc interval were unaltered by concurrent use.[1] No adverse interactions were seen in large numbers of patients given montelukast 10 or 20 mg and **loratadine** 10 mg, and the combination was found to be beneficial in the treatment of allergic rhinitis and conjunctivitis.[2] No special precautions are therefore needed if either of these antihistamines are given with montelukast.

1. Holland S, Gertz B, DeSmet M, Michiels N, Larson P, Freeman A, Keymeulen B. Montelukast (MON) has no effect on terfenadine (T) pharmacokinetics (PK) or QTc. *Clin Pharmacol Ther* (1998) 63, 232.
2. Malstrom K, Meltzer E, Prenner B, Lu S, Weinstein S, Wolfe J, Wei LX, Reiss TF. Effects of montelukast (a leukotriene receptor antagonist), loratadine, montelukast + loratadine and placebo in seasonal allergic rhinitis and conjunctivitis. *J Allergy Clin Immunol* (1998) 101, S97.

Montelukast + Rifampicin (Rifampin)

Rifampicin is predicted to reduce montelukast levels.

Clinical evidence, mechanism, importance and management

The manufacturer of montelukast cautions its use with inducers of the cytochrome P450 isoenzyme CYP3A4, such as rifampicin, especially in children.[1] This is because phenobarbital (an inducer of CYP3A4) has been found to reduce the AUC and serum levels of montelukast (see 'Montelukast + Antiepileptics; Enzyme-inducing', p.1426). However, there is currently no clinical evidence to suggest that the montelukast dose needs adjustment in patients taking rifampicin.

1. Singulair (Montelukast sodium). Merck Sharp & Dohme Ltd. UK Summary of product characteristics, August 2009.

Roflumilast + Antacids

Aluminium/magnesium hydroxide antacids do not appear to affect the pharmacokinetics of roflumilast or its active metabolite.

Clinical evidence, mechanism, importance and management

In a study, 30 healthy subjects were given a single 500-microgram dose of roflumilast alone, with, or 2 hours before, 30 mL of an **aluminium/magnesium hydroxide**-containing antacid (*Maalox*). There were no significant changes in the pharmacokinetics of roflumilast or its active metabolite, roflumilast *N*-oxide.[1] There would appear to be no reason to avoid the concurrent use of roflumilast and this type of antacid.

1. Nassr N, Lahu G, Hünnemeyer A, von Richter O, Knoerzer D, Reutter F, Zech K, Hermann R. Magnesium hydroxide/aluminium hydroxide-containing antacid does not affect the pharmacokinetics of the targeted phosphodiesterase 4 inhibitor roflumilast. *J Clin Pharmacol* (2007) 47, 660–6.

Roflumilast + Antiasthma drugs

The pharmacokinetics of montelukast and salbutamol are not affected by roflumilast, nor are the pharmacokinetics of roflumilast and its active metabolite roflumilast *N*-oxide altered by either montelukast or salbutamol.

Clinical evidence, mechanism, importance and management

(a) Montelukast

In a study, 24 healthy subjects were given roflumilast 500 micrograms daily with montelukast 10 mg daily for 9 days. Compared with the use of either drug alone, concurrent use did not result in any clinically relevant changes in the pharmacokinetics of either drug.[1]

(b) Salbutamol

In a study, 12 healthy subjects were given oral roflumilast 500 micrograms daily, inhaled salbutamol 200 micrograms three times daily, or both drugs together, for 7 days. The pharmacokinetics of roflumilast and its active metabolite, roflumilast *N*-oxide, were not significantly altered by salbutamol.[2]

1. Böhmer GM, Nassr N, Wenger M, Hünnemeyer A, Lahu G, Templin S, Gleiter CH, Hermann R. The targeted oral, once-daily phosphodiesterase 4 inhibitor roflumilast and the leukotriene receptor antagonist montelukast do not exhibit significant pharmacokinetic interactions. J Clin Pharmacol (2009) 49, 389–97.
2. Bethke TD, Giessmann T, Westphal K, Weinbrenner A, Hauns B, Hauschke D, David M, Lahu G, Zech K, Hermann R, Siegmund W. Roflumilast, a once-daily oral phosphodiesterase 4 inhibitor, lacks relevant pharmacokinetic interactions with inhaled salbutamol when co-administered in healthy subjects. *Int J Clin Pharmacol Ther* (2006) 44, 572–9.

Roflumilast + Azoles

The pharmacokinetics of roflumilast are not affected by the concurrent use of ketoconazole.

Clinical evidence

In a study, 24 healthy subjects were given a single 200-mg dose of ketoconazole on day 11 of taking roflumilast 500 micrograms daily for 11 days. Ketoconazole increased the AUC of roflumilast by 34%, but its maximum plasma levels were unaffected. The AUC of the active metabolite, roflumilast *N*-oxide was reduced by 12%, and its maximum plasma levels were reduced by 20%. However, the total phosphodiesterase-4 inhibitory activity of roflumilast and its active metabolite was unaltered, suggesting that these changes were not clinically significant.[1]

In a related crossover study, 16 healthy subjects were given ketoconazole 200 mg twice daily, with single 500-microgram dose of roflumilast when ketoconazole steady-state levels were achieved. Ketoconazole increased the AUC and maximum plasma levels of roflumilast by 99% and 23%, respectively. The maximum plasma levels of the active metabolite, roflumilast *N*-oxide were reduced by 38%, and its half-life was prolonged from 9.6 hours to 21.5 hours. However, the total phosphodiesterase-4 inhibitory activity of roflumilast and its active metabolite was unaltered, and no clinically relevant adverse effects were seen, suggesting that these changes are not clinically significant.[1]

Mechanism

Roflumilast *N*-oxide is formed by the metabolism of roflumilast by the cytochrome P450 isoenzyme CYP3A4, and it is thought that the clearance of roflumilast *N*-oxide is also reliant on CYP3A4. Ketoconazole, an inhibitor of CYP3A4 therefore reduces the formation of the active metabolite, but also reduces roflumilast clearance.

Importance and management

Evidence appears to be limited to these two studies, which are in line with the known CYP3A4-inhibitory effects of ketoconazole. An interaction is therefore established. However, as the overall effect of roflumilast appears to be unchanged, the pharmacokinetic changes seen do not appear to be clinically relevant. No dose adjustments are expected to be necessary if roflumilast is given with ketoconazole. Other azoles are expected to similarly lack a clinically relevant effect on roflumilast metabolism, but this needs confirmation.

1. Lahu G, Huennemeyer A, von Richter O, Hermann R, Herzog R, McCracken N, Zech K. Effect of single and repeated doses of ketoconazole on the pharmacokinetics of roflumilast and roflumilast N-oxide. J Clin Pharmacol (2008) 48, 1339–49.

Roflumilast + Corticosteroids

The concurrent use of roflumilast and budesonide does not affect the pharmacokinetics of either drug.

Clinical evidence, mechanism, importance and management

In a crossover study, 12 healthy subjects were given oral roflumilast 500 micrograms daily for 7 days, inhaled budesonide 800 micrograms twice daily for 7 days, or both drugs together. Budesonide did not affect the pharmacokinetics of roflumilast measured on day 7, nor was there any significant change in the pharmacokinetics of budesonide when taken with roflumilast. There was, however, a wide variation in parameters between subjects. There were no significant changes in the clinical status of the subjects.[1] No dose adjustments of either drug are therefore expected to be necessary on concurrent use.

1. Hermann R, Siegmund W, Giessmann T, Westphal K, Weinbrenner A, Hauns B, Reutter F, Lahu G, Zech K, Bethke TD. The oral, once-daily phosphodiesterase 4 inhibitor roflumilast lacks relevant pharmacokinetic interactions with inhaled budesonide. *J Clin Pharmacol* (2007) 47, 1005–13.

Roflumilast + Food

Food delays and reduces the maximum plasma levels of roflumilast, but has no effect on its active metabolite.

Clinical evidence, mechanism, importance and management

In a crossover study in 12 healthy subjects, a single 500-microgram dose of roflumilast was given after an overnight fast, or within 5 minutes of a high-fat, high-calorie breakfast. The time to reach maximum plasma levels was delayed from one hour to 2 hours when roflumilast was taken with food, and its maximum plasma levels were reduced by 40%. However, the pharmacokinetics of the active metabolite, roflumilast *N*-oxide, were not significantly altered. It is suggested that as the activity of roflumilast is predominantly exerted by roflumilast *N*-oxide, food will have little effect on the clinical outcome of treatment with roflumilast.[1]

1. Hauns B, Hermann R, Hünnemeyer A, Herzog R, Hauschke D, Zech K, Bethke TD. Investigation of a potential food effect on the pharmacokinetics of roflumilast, an oral once-daily phosphodiesterase 4 inhibitor, in healthy subjects. *J Clin Pharmacol* (2006) 46, 1146–53.

Roflumilast + Macrolides

Erythromycin increases the exposure to roflumilast but this does not appear to increase its adverse effects.

Clinical evidence, mechanism, importance and management

In a study 18 healthy subjects were given a single 588-mg dose of erythromycin alone or on day 11 of taking roflumilast 500 micrograms daily for 11 days. The pharmacokinetics of roflumilast and its active metabolite roflumilast *N*-oxide were unaltered, and there were no clinically significant changes in the pharmacokinetics of **erythromycin**. In addition, vital signs, ECG and laboratory parameters were not altered to a clinically relevant extent by concurrent use.[1] In a crossover study, 15 healthy subjects were given a single 500-microgram dose of roflumilast before and on day 7 of taking **erythromycin** 500 mg three times daily. Erythromycin increased the maximum levels and AUC of roflumilast by 40% and 70%, respectively. The AUC of the metabolite, roflumilast *N*-oxide was unchanged, whereas the maximum levels were decreased by 34%, and the time to maximum levels was delayed. However, the overall phosphodiesterase type-4 inhibitory effects of roflumilast were unaffected, and the incidence of adverse effects was not increased by concurrent use.[2]

Roflumilast is metabolised to roflumilast *N*-oxide by the cytochrome P450 isoenzyme CYP3A4, and it is thought that the clearance of roflumilast *N*-oxide is also reliant on CYP3A4. Drugs that are inhibitors of CYP3A4, such as a number of the macrolides, including **erythromycin**, may therefore reduce the formation of the active metabolite, but also reduce its clearance.

Evidence appears to be limited to these two studies, but an interaction appears to be established. However, as the overall effect of roflumilast appears to be unchanged, the pharmacokinetic changes seen do not appear to be clinically relevant. No dose adjustments are expected to be necessary if roflumilast is given with erythromycin. The adverse effects of roflumilast are thought to be related to its phosphodiesterase type-4 inhibitory effects, and therefore increased adverse effects would not be expected on concurrent use. Other macrolides are expected to similarly lack a clinically relevant effect on roflumilast metabolism, but this needs confirmation.

1. Hauns B, Huennemeyer A, Siegmund W, Waitzinger J, Hermann R, Zech K, Bethke TD. Pharmacokinetics of the selective PDE4 inhibitor roflumilast and its active metabolite roflumilast N-oxide are not affected by concomitant budesonide, salbutamol or erythromycin. *J Allergy Clin Immunol* (2004) 113 (Suppl), S222.
2. Lahu G, Huennemeyer A, Herzog R, McCracken N, Hermann R, Elmlinger M, Zech K. Effect of repeated dose of erythromycin on the pharmacokinetics of roflumilast and roflumilast N-oxide. Int J Clin Pharmacol Ther (2009) 47, 236–45.

Roflumilast + Rifampicin (Rifampin)

Rifampicin increases the metabolism of roflumilast to its active metabolite, roflumilast *N*-oxide, but decreases the overall bioavailability of roflumilast *N*-oxide.

Clinical evidence, mechanism, importance and management

In a study, 15 healthy subjects were given a single 500-microgram dose of roflumilast alone or after taking rifampicin 600 mg daily for 8 days. The AUC and maximum plasma levels of roflumilast were reduced by 79% and 68%, respectively. The AUC of the active metabolite, roflumilast *N*-oxide was reduced by 56%, while the maximum plasma levels of roflumilast *N*-oxide were increased by 30%.[1]

Rifampicin induces the activity of the cytochrome P450 isoenzyme CYP3A4, which is involved in the metabolism of roflumilast and roflumilast-*N*-oxide.

It is likely that the dose of roflumilast will need to be increased in patients also taking rifampicin.

1. Nassr N, Huennemeyer A, Herzog R, von Richter O, Hermann R, Koch M, Duffy K, Zech K, Lahu G. Effects of rifampicin on the pharmacokinetics of roflumilast and roflumilast-N-oxide in healthy subjects. Br J Clin Pharmacol (2009) 68, 580–7.

Roflumilast + SSRIs

The exposure to roflumilast and its active metabolite roflumilast *N*-oxide is increased by fluvoxamine.

Clinical evidence

In a crossover study, 14 healthy subjects were given a single 500-microgram dose of roflumilast alone, or after they had taken fluvoxamine 50 mg daily for 8 days. The AUC of roflumilast increased 2.6-fold, and the AUC of the active metabolite, roflumilast *N*-oxide increased by 50%. The maximum plasma levels of roflumilast *N*-oxide decreased by 20%. There was an overall increase of 59% in total phosphodiesterase-4 inhibitory activity, but there were no clinically relevant changes in laboratory measurements, blood pressure, pulse or ECG, nor were there any serious or unexpected adverse effects.[1]

Mechanism

Roflumilast is metabolised by the cytochrome P450 isoenzyme CYP1A2 and CYP3A4 to its active metabolite roflumilast *N*-oxide. Roflumilast *N*-oxide is in turn metabolised by CYP3A4, and probably to a lesser extent by CYP2C19. Fluvoxamine inhibits CYP1A2 and CYP2C19, and therefore concurrent use increases the exposure to roflumilast *N*-oxide.

Importance and management

Evidence appears to be limited to this study, in which the subjects were mainly overweight or obese. Nevertheless, the increases in the levels of roflumilast would be expected to be generally relevant. Although concurrent use may increase the efficacy of the roflumilast (phosphodiesterase-4 activity was increased), it seems possible that some patients may develop roflumilast adverse effects (e.g. nausea, diarrhoea, headache). If these develop in a patient taking fluvoxamine, consider an interaction as a possible cause. Note that other SSRIs do not affect CYP1A2, and would therefore not be expected to interact with roflumilast. However, this needs confirmation.

1. von Richter O, Lahu G, Huennemeyer A, Herzog R, Zech K, Hermann R. Effect of fluvoxamine on the pharmacokinetics of roflumilast and roflumilast *N*-oxide. *Clin Pharmacokinet* (2007) 46, 613–22.

Terbutaline + Magnesium sulfate

Subcutaneous terbutaline and intravenous magnesium sulfate appear not to interact adversely.

Clinical evidence, mechanism, importance and management

Eight healthy adults were given two subcutaneous doses of terbutaline 250 micrograms 30 minutes apart, with and without intravenous magnesium sulfate 4 g in 250 mL of sodium chloride 0.9%, given over the same 30-minute period.[1] Most of the effects of terbutaline, such as those on respiratory rate, blood pressure, glucose and calcium levels, were found to be moderately increased by magnesium sulfate at 60 minutes but these changes were all considered to be small. It was concluded that there appear to be no good reasons for avoiding the concurrent use of terbutaline and magnesium sulfate, for example in the emergency treatment of asthma and other conditions.

1. Skorodin MS, Freebeck PC, Yetter B, Nelson JE, Van de Graaff WB, Walsh JM. Magnesium sulfate potentiates several cardiovascular and metabolic actions of terbutaline. *Chest* (1994) 105, 701–5.

Theophylline + Aciclovir

Preliminary evidence suggests that aciclovir can increase the serum levels of theophylline (given as aminophylline).

Clinical evidence

Prompted by a case of increased theophylline adverse effects in a patient given aciclovir, a study was carried out in 5 healthy subjects who were given single 320-mg doses of theophylline (as 400 mg of aminophylline) before and with the sixth dose of aciclovir 800 mg five times daily for 2 days. The AUC of the theophylline was increased by 45% and its total body clearance was reduced by 30% by the aciclovir.[1]

Mechanism

Uncertain, but the evidence suggests that aciclovir inhibits the oxidative metabolism of theophylline, resulting in accumulation.[1]

Importance and management

Evidence appears to be limited to this report. However, be alert for an increase in the adverse effects of theophylline (nausea, headache, tremor) if aciclovir is added to established treatment, and consider monitoring levels. More study is needed to establish an interaction.

1. Maeda Y, Konishi T, Omoda K, Takeda Y, Fukuhara S, Fukuzawa M, Ohune T, Tsuya T, Tsukiai S. Inhibition of theophylline metabolism by aciclovir. *Biol Pharm Bull* (1996) 19, 1591–5.

Theophylline + Allopurinol

Allopurinol may increase theophylline levels, but not all studies have found this effect.

Clinical evidence

The peak plasma levels of theophylline 450 mg daily rose by 38% in a patient who took allopurinol for 3 days.[1] Another case report describes a patient taking theophylline 240 mg four times daily who experienced a grand mal seizure one day after starting allopurinol 100 mg three times daily. His theophylline levels were, however, elevated at 59 mg/L the day before starting allopurinol, and rose further to 86 mg/L the day after starting allopurinol. It is unclear whether the allopurinol was implicated in this case as the patient demonstrated slow metabolism of theophylline upon rechallenge.[2]

In a study in 12 healthy subjects, allopurinol 300 mg twice daily for 14 days increased the half-life of a single 5-mg/kg oral dose of theophylline by 25%, and increased its AUC by 27%.[3] Similar increases were seen when a second dose of theophylline was given 28 days after starting the allopurinol.[3] However, in two other studies allopurinol 300 mg daily for 7 days did not have any effect on the pharmacokinetics of theophylline, following a single 5-mg/kg intravenous dose of aminophylline.[4,5] Similarly, steady-state theophylline levels were not affected by allopurinol 100 mg three times daily in 4 subjects. However, there was an alteration in the proportion of different urinary theophylline metabolites: methyluric acid decreased and methylxanthine increased.[5]

Mechanism

Uncertain. Allopurinol, a xanthine oxidase inhibitor, can block the conversion of methylxanthine to methyluric acid, but this had no effect on theophylline levels in two studies. It has been suggested that allopurinol inhibits the oxidative metabolism of theophylline by the liver.[1]

Importance and management

Evidence appears to be limited to two case reports and the studies in healthy subjects. The interaction only appears to be of moderate importance. Nevertheless, it would seem prudent to check for any signs of theophylline adverse effects (headache, nausea, tremor) during concurrent use, particularly in situations where the metabolism of the theophylline may already be reduced (other drugs or diseases), or where high doses of allopurinol are used. If theophylline adverse effects are troublesome, monitor levels and adjust the dose accordingly.

1. Barry M, Feeley J. Allopurinol influences aminophenazone elimination. *Clin Pharmacokinet* (1990) 19, 167–9.
2. Jacobs MH, Senior RM. Theophylline toxicity due to impaired theophylline degradation. *Am Rev Respir Dis* (1974) 110, 342–5.
3. Manfredi RL, Vesell ES. Inhibition of theophylline metabolism by long-term allopurinol administration. *Clin Pharmacol Ther* (1981) 29, 224–9.

4. Vozeh S, Powell JR, Cupit GC, Riegelman S, Sheiner LB. Influence of allopurinol on theophylline disposition in adults. *Clin Pharmacol Ther* (1980) 27, 194–7.
5. Grygiel JJ, Wing LMH, Farkas J, Birkett DJ. Effects of allopurinol on theophylline metabolism and clearance. *Clin Pharmacol Ther* (1979) 26, 660–7.

Theophylline + Alosetron

Alosetron does not alter theophylline pharmacokinetics.

Clinical evidence, mechanism, importance and management

In a placebo-controlled study, 10 healthy women were given alosetron 1 mg twice daily for 16 days with oral theophylline 200 mg twice daily from day 8 to day 16. No clinically relevant changes in the pharmacokinetics of theophylline were seen, and concurrent use was well tolerated. The effect of theophylline on alosetron pharmacokinetics was not measured but the authors of the report say that no metabolic interaction seems likely.[1] No dose adjustments would therefore appear to be needed if these drugs are used together.

1. Koch KM, Ricci BM, Hedayetullah NS, Jewell D, Kersey KE. Effect of alosetron on theophylline pharmacokinetics. *Br J Clin Pharmacol* (2001) 52, 596–600.

Theophylline + Aminoglutethimide

Theophylline clearance is increased by aminoglutethimide, which may result in a moderate reduction in the serum levels and therapeutic effects of theophylline.

Clinical evidence, mechanism, importance and management

Aminoglutethimide 250 mg four times a day increased the clearance of sustained-release theophylline 200 mg twice daily by 18 to 43% in 3 patients.[1] Theophylline clearance was assessed before starting aminoglutethimide as well as during weeks 2 to 12 of concurrent use.

It seems probable that aminoglutethimide, a known enzyme inducer, increases the metabolism of theophylline by the liver, thereby decreasing its levels. The clinical importance of this is uncertain, but it seems likely that the effects of theophylline (and aminophylline, which is metabolised to theophylline) would be reduced to some extent. Monitor the effects and if necessary take theophylline levels. Increase the theophylline dose accordingly.

1. Lønning PE, Kvinnsland S, Bakke OM. Effect of aminoglutethimide on antipyrine, theophylline and digitoxin disposition in breast cancer. *Clin Pharmacol Ther* (1984) 36, 796–802.

Theophylline + Amiodarone

An isolated case report describes an elderly man who developed raised theophylline levels and toxicity when he was given amiodarone.

Clinical evidence, mechanism, importance and management

An 86-year-old man taking furosemide, digoxin, domperidone and sustained-release theophylline developed signs of theophylline toxicity when amiodarone 600 mg daily was given. After 9 days his serum theophylline levels had doubled, from about 16.8 mg/L to 35 mg/L. The toxicity disappeared when the theophylline was stopped.[1] The reason for this adverse reaction is not understood but it has been suggested that amiodarone may reduce the metabolism of the theophylline by the liver.[1] This is an isolated case and its general importance is uncertain. More study is needed.

Amiodarone may cause thyroid dysfunction, which may affect aminophylline and theophylline requirements, see also 'Theophylline + Thyroid and Antithyroid compounds', p.1461.

1. Soto J, Sacristán JA, Arellano F, Hazas J. Possible theophylline-amiodarone interaction. *DICP Ann Pharmacother* (1990) 24, 1115.

Theophylline + Antacids

The extent of absorption of theophylline from the gut does not appear to be significantly affected by aluminium or magnesium hydroxide antacids. However, an increase in the rate of absorption of some sustained-release theophylline preparations may occur.

Clinical evidence, mechanism, importance and management

In a study in 12 healthy subjects, there was no difference in the steady-state maximum serum concentrations or AUC of theophylline given as *Nuelin-Depot* or *Theodur* when an antacid (*Novalucid*, containing **aluminium**/**magnesium hydroxide** and **magnesium carbonate**) was given. However, the antacid caused a faster absorption of theophylline from *Nuelin-Depot*, which resulted in greater fluctuations in the serum levels. It was considered that the adverse effects of theophylline might be increased in those patients with serum levels at the top of the range.[1] Similar results have been found in single-dose studies when aminophylline,[2] *Slo-Phyllin Gyrocaps*,[3] *Somophyllin CRT*,[4] and *Theo-Dur*[5] were given with **aluminium**/**magnesium hydroxide** antacids, and in multiple dose studies in patients when *Armophylline*,[6] *Aminophyllin*[7] or *Theodur*[7] were given with **aluminium**/**magnesium hydroxide** antacids. Administration of 30 mL of an **aluminium**/**magnesium hydroxide** antacid (*Maalox*) four times daily did not affect the trough levels of theophylline in a patient taking *Theo-Dur* 400 mg three times daily.[8] Care should be taken extrapolating this information to other preparations of theophylline and aminophylline, but generally speaking no special precautions seem to be necessary if antacids are given with theophylline or aminophylline.

1. Myhre KI, Walstad RA. The influence of antacid on the absorption of two different sustained-release formulations of theophylline. *Br J Clin Pharmacol* (1983) 15, 683–7.
2. Arnold LA, Spurbeck GH, Shelver WH, Henderson WM. Effect of an antacid on gastrointestinal absorption of theophylline. *Am J Hosp Pharm* (1979) 36, 1059–62.
3. Shargel L, Stevens JA, Fuchs JE, Yu ABC. Effect of antacid on bioavailability of theophylline from rapid and timed-release drug products. *J Pharm Sci* (1981) 70, 599–602.
4. Ferrari M, Olivieri M, Romito D, Biasin C, Barozzi E, Bassetti S. Influence of gastric pH changes on pharmacokinetic of a sustained-release formulation of theophylline. *Riv Eur Sci Med Farmacol* (1991) 13, 269–74.
5. Darzentas LJ, Stewart RB, Curry SH, Yost RL. Effect of antacid on bioavailability of a sustained-release theophylline preparation. *Drug Intell Clin Pharm* (1983) 17, 555–7.
6. Muir JF, Peiffer G, Richard MO, Benhamou D, Andrejak M, Hary L, Moore N. Lack of effect of magnesium-aluminium hydroxide on the absorption of theophylline given as a pH-dependent sustained release preparation. *Eur J Clin Pharmacol* (1993) 44, 85–8.
7. Reed RC, Schwartz HJ. Lack of influence of an intensive antacid regimen on theophylline bioavailability. *J Pharmacokinet Biopharm* (1984) 12, 315–331.
8. Fernandes E, Melewicz FM. Antacids and theophylline-ranitidine interaction. *Ann Intern Med* (1984) 101, 279.

Theophylline + Anthelmintics; Benzimidazoles

Theophylline levels can be markedly increased by tiabendazole and toxicity may develop. Albendazole and mebendazole do not appear to interact with theophylline.

Clinical evidence

(a) Albendazole

A study in 6 healthy subjects found that the pharmacokinetics of a single dose of theophylline were unaffected by a single 400-mg dose of albendazole.[1]

(b) Mebendazole

A study in 6 healthy subjects found that the pharmacokinetics of a single dose of intravenous aminophylline were unaffected by mebendazole 100 mg twice daily for 3 days.[1] The absence of a significant interaction was reported in another similar study using the same mebendazole dose.[2]

(c) Tiabendazole

An elderly man taking prednisone, furosemide, terbutaline and orciprenaline was switched from oral to intravenous aminophylline, giving a stable serum level of 21 mg/L after 48 hours. When he was also given tiabendazole 4 g daily for 5 days, for persistence of a *Strongyloides stercoralis* infestation, he developed theophylline toxicity (severe nausea) and his serum levels were found to be 46 mg/L. Three months previously, he had taken tiabendazole 3 g daily for 3 days without any symptoms of toxicity (no theophylline levels were measured).[3] The theophylline levels of another patient rose from 15 mg/L to 22 mg/L when he was given tiabendazole 1.8 g twice daily for 3 days, despite a theophylline dose reduction of one-third, made in anticipation of the interaction. Theophylline levels were still elevated 2 days after the tiabendazole was stopped, and the theophylline dose was further reduced. Levels returned to normal after 5 days, and the theophylline dose was eventually increased again.[4]

A retrospective study of patients given theophylline and tiabendazole

found that 9 out of 40 (23%) had developed elevated serum theophylline levels and of those 9 patients, 5 experienced significant toxicity, with 3 requiring hospitalisation. The other 31 patients did not have theophylline levels taken.[5] A further report describes a patient receiving intravenous aminophylline who had an increase in theophylline levels from 18 mg/L to 26 mg/L within 2 days of starting tiabendazole 1.5 g twice daily.[2] The authors of this report then studied 6 healthy subjects who received a single dose of aminophylline before and while taking tiabendazole 1.5 g twice daily for 3 days. Three of the subjects had to discontinue the study because of severe nausea, vomiting or dizziness. In the remaining three, tiabendazole markedly affected the pharmacokinetics of aminophylline; the half-life increased from 6.7 hours to 18.6 hours, the clearance fell by 66% and the elimination rate constant decreased by 65%.[2]

Mechanism

Uncertain. It is suggested that tiabendazole inhibits the metabolism of theophylline, probably by the cytochrome P450 isoenzyme CYP1A2 in the liver, thereby prolonging its stay in the body and raising its serum levels. The nausea and vomiting may have been due to the adverse effects of both theophylline and tiabendazole.

Importance and management

The interaction between theophylline or aminophylline and tiabendazole is established and of clinical importance. Monitor theophylline levels and reduce the theophylline dose accordingly. A 50% reduction in the theophylline dose has been suggested,[4] or, where practical, stopping theophylline for 2 to 3 days while giving the tiabendazole.[5] Albendazole and mebendazole do not appear to interact with theophylline (and therefore seem unlikely to interact with aminophylline), and so may be suitable alternative anthelmintics depending on the condition being treated.

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Theophylline + Anticholinesterases; Centrally acting

The levels of theophylline are increased by tacrine. Donepezil has no effect on theophylline levels.

Clinical evidence, mechanism, importance and management

(a) Donepezil

An open-label, crossover study in 12 healthy subjects found that donepezil 5 mg daily for 10 days had no significant effects on the pharmacokinetics of theophylline. Theophylline dose adjustments or additional monitoring are not considered necessary during concurrent use.[1]

(b) Tacrine

In a study, healthy subjects were given theophylline 158 mg alone or while taking tacrine 20 mg every 6 hours. The clearance of the theophylline was reduced by 50%, probably because the tacrine inhibits the metabolism of theophylline by the cytochrome P450 isoenzyme CYP1A2 in the liver.[2] Be alert for the need to reduce the dose of theophylline (and probably aminophylline) to avoid toxicity if tacrine is added. More study of this interaction is needed in patients given multiple doses of both drugs.

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Theophylline + Antihistamines and related drugs

Azelastine, cetirizine, ketotifen, mequitazine, mizolastine, pemirolast, repirinast, and terfenadine do not appear to alter the pharmacokinetics of theophylline.

Clinical evidence, mechanism, importance and management

Azelastine 2 mg twice daily had no significant effect on the clearance of theophylline 300 mg twice daily in 10 subjects with bronchial asthma. However, one patient had a 21% increase and another a 25% decrease in clearance.[1] These changes are generally unlikely to be clinically significant.

A single 240-mg dose of *intravenous* theophylline was given to 6 healthy subjects after they had taken **cetirizine** 10 mg twice daily for 3.5 days. There was no change in theophylline pharmacokinetics, but the half-life of cetirizine was decreased by 19%. This change in cetirizine pharmacokinetics was not considered to be clinically relevant.[2]

Two studies, one in healthy adults[3] and one in asthmatic children,[4] found that **ketotifen** did not affect the pharmacokinetics of a single oral dose of either theophylline[3] or aminophylline.[4] It was suggested that concurrent use might actually decrease the CNS adverse effects of each drug.[3] Another crossover study was conducted in asthmatic patients sensitive to at least one commonly inhaled allergen who received **ketotifen** or placebo twice daily for 12 weeks. Patients received aminophylline from week 5 and week 9, which was dose adjusted to give either low theophylline levels (1 to 10 mg/L) for 4 weeks or high theophylline levels (10 to 20 mg/L) for 4 weeks. An indicator of disease control, the combined symptom score and inhaler use, indicated that the bronchodilating action of aminophylline had been potentiated by **ketotifen**, but there was no significant effect on theophylline levels.[5]

In 7 patients with asthma the steady-state pharmacokinetics of theophylline were not significantly affected when **mequitazine** 6 mg daily was given for 3 weeks.[6]

In 17 healthy subjects, **mizolastine** 10 mg daily had virtually no effect on the steady-state pharmacokinetics of theophylline, although a 13% increase in mean trough level and an 8% increase in the AUC was seen. These changes were not considered clinically relevant.[7]

In 7 healthy subjects, **pemirolast** 10 mg daily for 4 days was found to have no significant effect on the steady-state serum levels or clearance of theophylline.[8]

In 10 patients with asthma given a single dose of aminophylline, **repirinast** 300 mg daily had no effect on the pharmacokinetics of theophylline.[9] Another study in 7 asthmatics found that **repirinast** (dose unclear) for 3 weeks had no effect on the pharmacokinetics of theophylline 400 to 800 mg, given in two divided doses.[10]

In 10 healthy subjects the pharmacokinetics of a single 250-mg dose of theophylline were unchanged by **terfenadine** 120 mg twice daily for 16 days.[11] Similarly, **terfenadine** 60 mg twice daily did not affect the steady-state pharmacokinetics of theophylline 4 mg/kg daily.[12] Another study in 17 healthy, male subjects found no change in the pharmacokinetics of a single 4-mg/kg oral dose of theophylline (rounded to nearest 50 mg) when taken with a single 60-mg dose of **terfenadine**.[13]

No special precautions seem to be necessary if any of these drugs is given with theophylline or aminophylline.

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Theophylline + Azoles

Theophylline levels are normally unaffected or only minimally affected by fluconazole and ketoconazole. An isolated report describes a rise in serum theophylline levels due to fluconazole, and another describes falls in theophylline levels in three patients taking ketoconazole.

Clinical evidence

(a) Fluconazole

A crossover study in 5 healthy subjects found that fluconazole 100 mg given every 12 hours for 7 doses caused only a non-significant 16% decrease in the clearance of a single 300-mg oral dose of aminophylline.[1] Another study in 10 healthy subjects found that fluconazole 100 mg daily for one week had no significant effect on the serum levels of theophylline 150 mg twice daily.[2] In 9 subjects who took fluconazole 400 mg daily for 10 days, the clearance of a single 6-mg/kg oral dose of theophylline was reduced by 13%.[3] In contrast, an isolated and brief report says that one of 2 patients given theophylline and fluconazole had a rise (amount not specified) in serum theophylline levels.[4]

(b) Ketoconazole

No significant changes in the pharmacokinetics of a single 3-mg/kg intravenous dose of theophylline (given as aminophylline) were seen in 12 healthy subjects who took a single 400-mg dose of ketoconazole, or in 4 subjects who took ketoconazole 400 mg daily for 5 days.[5] Similar results were found in another study in 10 healthy subjects who took ketoconazole 200 mg daily for 7 days.[6] In 6 healthy subjects ketoconazole 400 mg daily for 6 days increased the half-life of a single 250-mg oral dose of theophylline by 22%, but had no effect on its clearance.[7] In contrast, a case report describes a man whose serum theophylline levels fell sharply from about 16.5 mg/L to 9 mg/L (reference range 10 to 20 mg/L) over the 2 hours immediately after taking 200 mg of ketoconazole. A less striking fall was seen in 2 other patients.[8]

Mechanism

Fluconazole and ketoconazole (and the other azoles) appear to have minimal effects on the cytochrome P450 isoenzyme CYP1A2, which is concerned with the oxidative metabolism of theophylline.[1,7] It is not clear why a few individuals had some changes in theophylline levels.

Importance and management

Information seems to be limited to these reports. Neither fluconazole nor ketoconazole normally appears to interact with aminophylline or theophylline to a relevant extent in most patients. However, it seems that very occasionally some changes occur, so bear this interaction in mind in the case of unexpected changes in theophylline levels, adverse effects or uncontrolled symptoms. Other azole antifungals are also unlikely to interact with theophylline, but ideally this needs confirmation.

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Theophylline + Barbiturates

Theophylline serum levels can be reduced by phenobarbital or pentobarbital. A single report describes a similar interaction with secobarbital and the same effect would be expected with other barbiturates.

Clinical evidence

(a) Pentobarbital

A single case report describes a man receiving intravenous aminophylline who had a 95% rise in the clearance of theophylline after he was given high-dose intravenous pentobarbital.[1] In healthy subjects pentobarbital 100 mg daily for 10 days increased the clearance of oral theophylline by a mean of 40% and reduced the AUC by 26%, although there were marked intersubject differences in the findings.[2]

(b) Phenobarbital

In 7 children aged 6 to 12 years with asthma, phenobarbital (2 mg/kg daily to a maximum of 60 mg) for 19 days reduced the mean steady-state serum theophylline levels by 30%, and increased the clearance by 35% (range 12 to 71%).[3] In contrast, two earlier studies (one by the same group of authors) found no significant change in the pharmacokinetics of theophylline, in children with asthma given phenobarbital 2 mg/kg daily, 16 mg three times daily or 32 mg three times daily.[4,5]

In healthy adult subjects given phenobarbital, the mean theophylline clearance, from a single intravenous dose of aminophylline, was increased by 34%.[6] In another study the clearance of theophylline was increased by 17% when phenobarbital was given for 2 weeks, although this was not statistically significant.[7]

The effects of phenobarbital can be additive with the effects of phenytoin and smoking; one patient required 4 g of theophylline daily to maintain therapeutic serum levels and to control her asthma.[8]

One retrospective study found that premature infants needed a higher dose of intravenous aminophylline for neonatal apnoea when they were given phenobarbital,[9] but a later prospective study did not confirm this.[10] A study in one set of newborn twins given intravenous aminophylline found that the serum theophylline levels of the twin given phenobarbital were about half those of the twin not given phenobarbital.[11]

(c) Secobarbital

The clearance of theophylline increased by 337% over a 4-week period in a child given periodic doses of secobarbital and regular doses of phenobarbital.[12]

Mechanism

The barbiturates are potent liver-enzyme inducers, which possibly increases the metabolism of theophylline by the liver, thereby hastening its removal from the body. This has been shown in *animal* studies, although *N*-demethylation (the main metabolic route for theophylline) was not affected.[13]

Importance and management

A moderately well documented, established and clinically important interaction. Patients given phenobarbital or pentobarbital may need above-average doses of theophylline or aminophylline to achieve and maintain adequate serum levels. Concurrent use should be monitored and appropriate dose increases made. All of the barbiturates can cause enzyme induction and may, to a greater or lesser extent, be expected to behave similarly. This is illustrated by the single report involving secobarbital. However, direct information about other barbiturates seems to be lacking. Note that theophylline itself can cause seizures, although mostly in overdose, and should be used with caution in patients with epilepsy.

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Theophylline + BCG vaccine

BCG vaccination can increase the half-life of theophylline.

Clinical evidence, mechanism, importance and management

Two weeks after 12 healthy subjects were vaccinated with 0.1 mL of BCG vaccine, the clearance of a single 128-mg dose of theophylline (as choline theophyllinate) was reduced by 21% and the theophylline half-life was prolonged by 14% (range 10% reduction to 47% increase).[1] It therefore seems possible that the occasional patient may develop some signs of theophylline toxicity if their serum levels are already towards the top end of the therapeutic range but theophylline levels are unlikely to be affected in most patients given BCG vaccine. No action is necessary as any interaction seems likely to resolve spontaneously.

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Theophylline + Beta-agonist bronchodilators

The concurrent use of aminophylline or theophylline and beta-agonist bronchodilators is a useful option in the management of asthma and COPD, but potentiation of some adverse reactions can occur, the most serious being hypokalaemia and tachycardia, particularly with high-dose theophylline. Some patients may have a reduction in their theophylline levels if given oral or intravenous salbutamol (albuterol) or intravenous isoprenaline (isoproterenol).

Clinical evidence

(a) Fenoterol

A study in 12 patients with chronic airways disease found that oral fenoterol 2.5 mg three times daily did not affect the steady-state level of sustained-release theophylline 10.1 mg/kg twice daily.[1]

Another study in 8 healthy subjects found that the addition of sutained-release theophylline to inhaled fenoterol 600 and 800 micrograms increased the heart rate and systolic blood pressure. Theophylline levels were not affected.[2] A study in 6 healthy subjects found that the fall in plasma potassium levels seen after inhalation of three doses of 600 micrograms of fenoterol given over one hour was not exacerbated by a 7-mg/kg infusion of theophylline.[3]

(b) Formoterol

In a single-dose study, 8 healthy subjects were given oral doses of theophylline 375 mg and formoterol 144 micrograms. Concurrent use caused no significant pharmacokinetic interaction, but a significantly greater drop in the potassium level was seen, when compared with either drug given alone.[4]

(c) Isoprenaline (Isoproterenol)

An infusion of isoprenaline increased the clearance of theophylline (given as intravenous aminophylline) by a mean of 19% in 6 children with status asthmaticus and respiratory failure. Two of them had increases in clearance of greater than 30%.[5] Another study in 12 patients with status asthmaticus found that an isoprenaline infusion (mean maximum rate 0.77 micrograms/kg per minute) caused a mean fall in serum theophylline levels of almost 6 micrograms/mL.[6] The levels rose again when isoprenaline was stopped.[6] A critically ill patient receiving intravenous aminophylline, phenytoin and nebulised terbutaline had a marked 4.5-fold increase in theophylline clearance when an isoprenaline infusion and intravenous methylprednisolone were added to the regimen.[7]

(d) Orciprenaline (Metaproterenol)

In 6 healthy subjects, oral orciprenaline 20 mg every 8 hours or inhaled orciprenaline 1.95 mg every 6 hours for 3 days had no effect on the pharmacokinetics of theophylline (given as a single intravenous dose of aminophylline).[8] This confirms a previous finding in asthmatic children, in whom it was shown that oral orciprenaline did not alter steady-state serum theophylline levels.[9]

(e) Salbutamol (Albuterol)

1. Effects on heart rate or potassium levels. In healthy subjects, pretreatment with oral theophylline for 9 days significantly increased the hypokalaemia and tachycardia caused by an infusion of salbutamol (4 micrograms/kg loading dose then 8 micrograms/kg for an hour).[10] In one study in 9 patients with COPD a potentially dangerous additive increase in heart rate of about 35 to 40% was seen in when infusions of aminophylline and salbutamol were given.[11] Similarly, heart rate was significantly higher in 15 children with asthma given single doses of oral theophylline and salbutamol (109 bpm) when compared with a control group given oral theophylline alone (91 bpm).[12] However, another study in 18 patients with COPD and heart disease found that neither the occurrence nor the severity of arrhythmias seemed to be changed when oral theophylline was given with inhaled salbutamol.[13] One report describes a 10-year-old girl given theophylline and salbutamol who had a respiratory arrest, possibly related to hypokalaemia.[14]

2. Effects on theophylline levels. In 10 healthy subjects, theophylline clearance was increased by a mean of 14%, and in 3 cases by greater than 30%, when salbutamol was given orally, but no changes in clearance were seen when salbutamol was given by inhalation.[15] Another study reported a 25% reduction in serum theophylline levels in 10 patients who took oral salbutamol 16 mg.[16] A child of 19 months given intravenous theophylline was also given an infusion of salbutamol: theophylline clearance was increased and the theophylline dose needed to be increased threefold to compensate.[17] Peak flow readings were decreased in 15 children (aged 5 to 13 years) given single doses of oral salbutamol and theophylline, but theophylline levels were not significantly decreased.[12] These reports contrast with another study in 8 healthy subjects, which found no change in the steady-state pharmacokinetics of oral theophylline when oral salbutamol was also given.[18]

(f) Terbutaline

In 7 healthy subjects pretreatment with oral theophylline for at least 4 days significantly increased the fall in serum potassium levels and rises in blood glucose, pulse rate, and systolic blood pressure caused by an infusion of terbutaline.[19] A study in children given slow-release formulations of both theophylline and terbutaline found no increases in reported adverse effects and simple additive effects on the control of their asthma.[20]

Oral terbutaline decreased serum theophylline levels by about 10% in 6 patients with asthma, and the control of asthma was improved.[21] Another study, in children with asthma, found that terbutaline elixir 75 micrograms/kg three times daily reduced the steady-state serum levels of theophylline by 22%, but the symptoms of cough and wheeze improved.[22] In 9 healthy subjects the mean half-life of theophylline, given as a single 6-mg/kg dose of intravenous aminophylline, was not significantly altered after oral terbutaline 5 mg was given three times daily for 4 days, although some subjects had an increase in theophylline clearance, and some a decrease.[23] Yet another study found no changes in the pharmacokinetics of aminophylline in children with asthma given terbutaline;[24] a study in 12 healthy adults found no clinically significant changes in the pharmacokinetics of terbutaline and theophylline when both drugs were given orally for 7 days,[25] and a study in 8 healthy subjects given subcutaneous terbutaline 250 micrograms at 0, 0.5, 4.5 and 5 hours after a single

7-mg/kg dose of oral theophylline similarly found no change in theophylline pharmacokinetics.[26]

(g) Unspecified beta$_2$ agonists

In 1990, the CSM in the UK noted that, of 26 reports they had on record of hypokalaemia with unnamed xanthines or beta$_2$ agonists, 9 occurred in patients receiving both groups of drugs. In 5 of these 9 cases, the hypokalaemia had no clinical consequence. However, in 2 cases it resulted in cardiorespiratory arrest, in one case confusion, and in a further case intestinal pseudo-obstruction.[27]

Mechanism

Beta$_2$ agonists can cause hypokalaemia, particularly when they are given parenterally or by nebulisation. Aminophylline and theophylline can also cause hypokalaemia, and this is a common feature of theophylline toxicity. The potassium-lowering effects of both these groups of drugs are additive. Why some beta agonists lower serum theophylline levels is not known.

Importance and management

The concurrent use of aminophylline or theophylline and beta$_2$ agonist bronchodilators is beneficial, but the reports outlined above illustrate some of the disadvantages and adverse effects that have been identified. In particular, it has been suggested that the use of intravenous beta agonists in acutely ill patients receiving theophylline may be hazardous because of the risk of profound hypokalaemia and cardiac arrhythmias.[10,19] Monitoring of serum potassium in these situations was suggested.[19] Moreover, the CSM in the UK particularly recommends monitoring potassium levels in those with severe asthma as the hypokalaemic effects of beta$_2$ agonists can be potentiated by theophylline and its derivatives, corticosteroids, diuretics and hypoxia.[27]

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Theophylline + Beta blockers

Propranolol reduces the clearance of theophylline. More importantly, non-cardioselective beta blockers such as nadolol and propranolol, should not be given to asthmatic patients because they can cause bronchospasm. The concurrent use of theophylline and cardioselective beta blockers such as atenolol, bisoprolol or metoprolol is not contraindicated, but some caution is still appropriate. Atenolol and bisoprolol do not affect the pharmacokinetics of theophylline.

Clinical evidence

(a) Pharmacokinetics

A study in 8 healthy subjects (5 of whom smoked 10 to 30 cigarettes daily) found that the clearance of a single 5.7- to 6.4-mg/kg dose of theophylline (as intravenous aminophylline) was reduced by 37% by **propranolol** 40 mg every 6 hours, when compared with theophylline alone. **Metoprolol** 50 mg every 6 hours did not alter the clearance in the group as a whole, but the smokers had an 11% reduction in clearance.[1] Another study, in 7 healthy subjects, found that the steady-state plasma clearance of theophylline was reduced by 30% by **propranolol** 40 mg every 8 hours, and by 52% by **propranolol** 240 mg every 8 hours,[2] whereas a study in 5 healthy subjects who had received **propranolol** 60 mg every 8 hours for 3 days found that the half-life of theophylline, given as a single 6-mg/kg dose of intravenous aminophylline was prolonged by 59%.[3] However, a further study found no significant pharmacokinetic interaction between theophylline and **propranolol**.[4] Three other studies found that the cardioselective beta blockers **atenolol** 50 to 150 mg,[5,6] and **bisoprolol** 10 mg,[7] and the non-selective beta blocker **nadolol** 80 mg[5] did not affect the pharmacokinetics of theophylline.

(b) Pharmacodynamics

Beta blockers, particularly those that are not cardioselective, can cause bronchoconstriction, which opposes the bronchodilatory effects of theophylline. See 'Anti-asthma drugs + Beta blockers', p.1415, for mention of a patient who had a deterioration of asthma when taking betaxolol with theophylline and pranlukast.

In a study in 8 healthy subjects both **propranolol** 40 mg every 6 hours and **metoprolol** 50 mg every 6 hours prevented the mild inotropic effect seen with theophylline alone.[8]

An infusion of **propranolol** reduced the hypokalaemia and tachycardia that occurred after a theophylline overdose.[9,10] **Esmolol** has been used similarly.[11]

Mechanism

Propranolol possibly affects the clearance of theophylline by inhibiting its metabolism (demethylation and hydroxylation).[2,12]

Importance and management

The risk of severe, possibly even fatal bronchospasm when beta blockers are taken by asthmatics would seem to be far more important than any pharmacokinetic interaction with theophylline. For more detailed advice on the use of beta blockers in patients with respiratory disease, see 'Anti-asthma drugs + Beta blockers', p.1415. Bronchospasm can occur with beta blockers given by any route of administration, even topically as eye drops. Cardioselective beta blockers have less effect on the airways, but can still cause bronchoconstriction. See 'Table 22.1', (p.995), for details of the selectivity of beta blockers.

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Theophylline + Caffeine

The consumption of caffeine-containing beverages can raise theophylline levels, but the clinical relevance of this is unclear. Similarly, removal of caffeine-containing foods from the diet may reduce the half-life of theophylline.

Clinical evidence

Caffeine can decrease the clearance of theophylline by 18 to 29%, prolong its half-life by up to 44% and increase its average serum levels by up to 23%.[1-3] In addition, caffeine plasma levels were increased about twofold when theophylline was given, and this may have caused the headaches and nausea reported in 2 subjects that did not usually drink coffee.[2] In these studies, caffeine was given in the form of tablets[1,2] or as 2 to 7 cups of instant coffee.[3] Another study found that, when 4 healthy subjects removed methylxanthines from their diet, the half-life of theophylline was reduced from 9.8 hours to 7 hours.[4]

Mechanism

These modest pharmacokinetic changes probably occur because the two drugs compete for the same metabolic pathway resulting in a reduction in their metabolism and accumulation. In addition, when caffeine levels are high, a small percentage of it is converted to theophylline.

Importance and management

An interaction between caffeine and theophylline is reasonably well studied and established. There would, however, seem to be no good reason for patients taking theophylline to avoid caffeine (in **coffee**, **tea**, **cola drinks**, medications, etc.), but if otherwise unexplained adverse effects occur it might be worth checking if caffeine is responsible. Removal of caffeine from the diet may have a modest effect on theophylline levels, but the clinical relevance of this is unclear. In addition, caffeine intake could have an impact on the interaction of theophylline with other drugs. Aminophylline does not seem to have been studied, but as it is metabolised to theophylline, it would be expected to interact similarly.

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Theophylline + Calcium-channel blockers

Giving calcium-channel blockers to patients taking theophylline normally has no adverse effect on the control of asthma, despite the small or modest alteration that may occur in theophylline levels with diltiazem, felodipine, nifedipine and verapamil. However, there are isolated case reports of unexplained theophylline toxicity in two patients given nifedipine and two patients given verapamil. Isradipine appears not to interact with theophylline.

Clinical evidence

(a) Diltiazem

In 9 healthy subjects diltiazem 90 mg twice daily for 10 days reduced the clearance of theophylline (given as a single 6-mg/kg dose of aminophylline) by 21%, and increased its half-life from 6.1 hours to 7.5 hours.[1] A 12% fall in the clearance of a single 5-mg/kg oral dose of theophylline was found when healthy subjects were given diltiazem 90 mg three times daily.[2] A further study in 9 healthy subjects given diltiazem 60 mg three times daily for 3 days found that the half-life of a single 200-mg dose of theophylline was increased from 7.58 hours to 8.59 hours and the clearance was reduced by 9%.[3] In 8 patients with asthma or COPD, diltiazem 60 mg three times daily for 5 days reduced the clearance of steady-state theophylline (given as a continuous infusion of aminophylline 12 mg/kg per day) by 22% and increased its half-life from 5.7 hours to 7.5 hours.[4]

Conversely, other studies found no significant changes in peak steady-state theophylline levels in 18 patients with asthma given diltiazem 240 to 480 mg daily for 7 days,[5] or in 7 healthy subjects given diltiazem 120 mg twice daily for 7 days.[6] Similarly, there was no significant change in the half-life or clearance of theophylline (given as a single 250-mg intravenous dose of aminophylline) in healthy subjects given diltiazem 120 mg three times daily for 6 days.[7] One study found that the pharmacokinetics of a single 5-mg/kg intravenous dose of theophylline, given as aminophylline, were unaffected by diltiazem 60 mg given four times daily. However, in an extension of this study, the reduction in theophylline half-life and the increase in theophylline clearance caused by rifampicin 600 mg daily (see 'Theophylline + Rifamycins and/or Isoniazid', p.1456), were slightly attenuated by diltiazem.[8]

(b) Felodipine

In 10 healthy subjects felodipine 5 mg every 8 hours for 4 days reduced the plasma AUC of theophylline (given as theophylline aminopropanol) by 18%, but had no effect on metabolic or renal clearance.[9]

(c) Isradipine

A three-way, crossover study in 11 healthy subjects found that isradipine 2.5 or 5 mg every 12 hours for 6 days had no significant effect on the pharmacokinetics of a single 5-mg/kg dose of aminophylline oral solution.[10]

(d) Nifedipine

In one study in 8 patients with asthma, slow-release nifedipine 20 mg twice daily reduced the mean steady-state theophylline levels by 30%, from 9.7 mg/L to 6.8 mg/L. Levels fell by 50%, 56%, and 64% in three of the patients, but no changes in the control of the asthma (as measured by peak flow determinations and symptom scores) were seen.[11] However, many other studies have found no changes, or only small to modest changes, in the pharmacokinetics of theophylline (given as oral theophylline or as intravenous lysine theophylline[12] or aminophylline[13]) in healthy subjects[6,12-14] or patients with asthma[5,15,16] given nifedipine. The control of the asthma was unchanged by nifedipine.[15,16] Yet another study found that the combined use of slow-release theophylline and nifedipine improved pulmonary function and blood pressure control.[17]

In contrast, there are 2 case reports of patients who developed theophylline toxicity (theophylline levels raised to 30 mg/L and 41 mg/L, respectively), apparently due to the addition of nifedipine.[18,19] In one case, toxicity recurred on rechallenge, and resolved when the theophylline dose was reduced by 60%.[19] During a Swan Ganz catheter study of patient response to nifedipine for pulmonary hypertension, 2 patients developed serious nifedipine adverse effects, which responded to intravenous aminophylline.[20]

(e) Verapamil

In one study in 5 patients with asthma, verapamil 80 mg every 6 hours for 2 days had no effect on the pharmacokinetics of theophylline (200 mg aminophylline every 6 hours) and no effect on their spirometry (FVC, FEV_1, FEF_{25-75}).[21] Similarly, a study in healthy subjects found that verapamil 80 mg every 8 hours had no effect on the steady-state levels of sustained-release theophylline 3 mg/kg per day.[22] In contrast, numerous other studies in healthy subjects (given intravenous or oral aminophylline or theophylline) have found modest reductions in theophylline clearance, of 8 to 23% with verapamil 40 to 120 mg taken every 6 to 8 hours.[2,7,14,23-25]

One study found that the extent of reduction in clearance depended on the verapamil dose.[25] An isolated report describes a woman taking digoxin and sustained-release theophylline who developed signs of toxicity (tachycardia, nausea, vomiting) after starting to take verapamil 80 mg, increased to 120 mg, every 8 hours. Her theophylline serum levels doubled over a 6-day period. Theophylline was later successfully reintroduced at one-third of the original dose.[26] Another isolated report describes a patient who needed a 50% reduction in their theophylline dose while taking verapamil 120 mg daily.[27]

Mechanism

It is believed that diltiazem and verapamil can, to a limited extent, decrease the metabolism of theophylline by the liver, possibly by inhibiting the cytochrome P450 isoenzyme CYP1A2.[28] Similarly, nifedipine may alter hepatic theophylline metabolism,[14] or it may increase the volume of distribution of theophylline.[12,13] Felodipine possibly reduces theophylline absorption.[9]

Importance and management

The evidence for this interaction is adequately documented but the results are not entirely consistent. However, the overall picture is that the concurrent use of theophylline and these calcium-channel blockers is normally safe. Despite the small or modest decreases in the clearance or absorption of theophylline seen with diltiazem, felodipine and verapamil, and the quite large reductions in serum levels seen in one study with nifedipine, no adverse changes in the control of the asthma were seen in any of the studies. However, very occasionally and unpredictably theophylline levels have risen enough to cause toxicity in patients given nifedipine (2 case reports) or verapamil (2 case reports), so that it would be prudent to be aware of the possibility of an interaction when these drugs are given.

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Theophylline + Cannabis

Cannabis smokers may need more theophylline than non-smokers to achieve the same therapeutic benefits, because the theophylline is cleared from the body more quickly.

Clinical evidence, mechanism, importance and management

One study found that tobacco or cannabis smoking similarly caused higher total clearances of theophylline (given as oral aminophylline) than in non-smokers (about 74 mL/kg per hour compared with 52 mL/kg per hour), and that clearance was even higher (93 mL/kg per hour) in those who smoked both.[1] A later analysis by the same authors, of factors affecting theophylline clearance, found that smoking two or more joints of cannabis weekly was associated with a higher total clearance of theophylline than non-use (82.9 mL/kg per hour versus 56.1 mL/kg per hour).[2] A study in which 16 of 49 healthy subjects admitted to smoking cannabis in the months before taking a single 4-mg/kg oral dose of theophylline found that cannabis use did not have a significant effect on the pharmacokinetics of theophylline. Their use was considered not to exceed normal social use of one joint per week.[3]

Tobacco and cannabis smoke contain polycyclic hydrocarbons, which act as inducers of the cytochrome P450 isoenzyme CYP1A2, and this results in a more rapid clearance of theophylline from the body.

Little is known about the effects of smoking cannabis on theophylline levels, but be alert for the need to increase the theophylline dose in regular users. Note that irregular cannabis use might cause fluctuations in theophylline levels.

Consider also ‘Theophylline + Tobacco’, p.1461.

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Theophylline + Carbamazepine

Two case reports describe a marked fall in theophylline levels when carbamazepine was given. Another single case report and a pharmacokinetic study describe a fall in carbamazepine levels when theophylline was given.

Clinical evidence

(a) Theophylline serum levels reduced

An 11-year-old girl with asthma was stable for 2 months taking theophylline and phenobarbital until the phenobarbital was replaced by carbamazepine. The asthma worsened, her theophylline serum levels became subtherapeutic and the half-life of the theophylline was reduced from 5.25 hours to 2.75 hours. Asthmatic control was restored, and the half-life returned to pre-treatment levels 3 weeks after the carbamazepine was replaced by ethotoin.[1] Another report noted that the clearance of theophylline in an adult patient was doubled by carbamazepine 600 mg daily.[2]

(b) Carbamazepine serum levels reduced

The trough carbamazepine levels of a 10-year-old girl were roughly halved when she was given theophylline for 2 days, and she experienced a grand mal seizure. Her serum theophylline levels were also unusually high at 26 mg/L for the 5 mg/kg dose she was taking, so it may be that the convulsions were as much due to this as to the fall in carbamazepine levels.[3]

A single-dose pharmacokinetic study in healthy subjects found that the AUC and maximum serum levels of carbamazepine were reduced by 31% and 45%, respectively, by oral aminophylline.[4]

Mechanism

Not established, but it seems probable that each drug increases the liver metabolism and clearance of the other drug, resulting in a reduction in their effects.[1,3] It is also possible that aminophylline interferes with the absorption of carbamazepine.[4]

Importance and management

Information seems to be limited to the reports cited and therefore the general importance of the effects noted is uncertain. Concurrent use need not be avoided, but it would be prudent to check that the serum concentrations of each drug (and their effects) do not become subtherapeutic. Note that theophylline should be used with caution in patients with epilepsy as it can cause seizures, although this is usually a sign of toxicity.

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Theophylline + Cephalosporins

Ceftibuten and cefalexin appear not to interact with theophylline. Cefaclor has been implicated in two cases of theophylline toxicity in children, but studies in adult subjects found no pharmacokinetic interaction.

Clinical evidence, mechanism, importance and management

Ceftibuten 200 mg twice daily for 7 days was found to have no significant effect on the pharmacokinetics of a single intravenous dose of theophylline given to 12 healthy subjects.[1] A study in 9 healthy adults given a single 5-mg/kg intravenous dose of aminophylline found that **cefalexin** 500 mg, then 250 mg every 6 hours for 48 hours, had no significant effect on the pharmacokinetics of theophylline.[2]

A case report[3] suggested that **cefaclor** might have been responsible for the development of theophylline toxicity in 2 children. However, a single-dose study[4] and a steady-state study[5] in healthy adults found that **cefaclor** 250 mg three times daily for 8 and 9 days, respectively, had no effect on the pharmacokinetics of oral or intravenous theophylline. Although the pharmacokinetics of theophylline differ in adults and children a significant interaction with **cefaclor** seems unlikely.

No special precautions seem to be necessary with any of these antibacterials. Note that acute infections *per se* can alter theophylline pharmacokinetics.[6]

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Theophylline + Clopidogrel or Ticlopidine

Ticlopidine reduces the clearance of theophylline and is expected to raise its serum levels. Clopidogrel, an analogue of ticlopidine, appears not to interact.

Clinical evidence, mechanism, importance and management

(a) Clopidogrel

Clopidogrel 75 mg daily for 10 days did not alter the steady-state pharmacokinetics of theophylline given to 12 healthy subjects.[1] No problems are therefore anticipated with the concurrent use of these two drugs.

(b) Ticlopidine

In 10 healthy subjects, ticlopidine 250 mg twice daily for 10 days reduced the clearance of a single 5-mg/kg oral dose of theophylline by 37% and increased its half-life by 44%, from about 8.5 hours to 12 hours.[2] The reason for these effects is not known but it seems possible that ticlopidine inhibits the metabolism of theophylline by the liver. Information is limited, but it would seem prudent to monitor the effects of concurrent use: it may be necessary to reduce the dose of theophylline (or aminophylline, which is metabolised to theophylline), particularly when theophylline serum levels are already at the top end of the range.

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2. Colli A, Buccino G, Cocciolo M, Parravicini R, Elli GM, Scaltrini G. Ticlopidine-theophylline interaction. *Clin Pharmacol Ther* (1987) 41, 358–62.

Theophylline + Codeine

Codeine does not affect the extent of theophylline absorption.

Clinical evidence, mechanism, importance and management

A study in 6 healthy subjects found that codeine 30 mg prolonged the oral to caecal transit time of a single 500-mg dose of sustained-release theophylline (*Theo-Dur*). The mean amount of theophylline left to be absorbed from the colon was reduced from 58% to 33%, but the time to 90% absorption of theophylline was not significantly affected (7.1 hours compared with 8.5 hours). Therefore codeine does not appear to significantly affect the rate or extent of absorption of theophylline, and concurrent use need not be avoided.[1]

1. Sommers DK, Meyer EC, Van Wyk M, Moncrieff J, Snyman JR, Grimbeek RJ. The influence of codeine, propantheline and metoclopramide on small bowel transit and theophylline absorption from a sustained-release formulation. *Br J Clin Pharmacol* (1992) 33, 305–8.

Theophylline + Corticosteroids

Theophylline and corticosteroids have established roles in the management of asthma and their concurrent use is not uncommon. There are isolated reports of increases in theophylline levels (sometimes associated with toxicity) when oral or parenteral corticosteroids are given, but other reports show no changes. Both theophylline and corticosteroids can cause hypokalaemia, which may be additive.

Clinical evidence

(a) Betamethasone

The elimination half-life of theophylline (given as intravenous aminophylline) was no different in premature infants who had been exposed to betamethasone *in utero* than in those who had not, although the exposed neonates had a wider range of theophylline metabolites indicating greater hepatic metabolism.[1,2]

(b) Dexamethasone

In one study it was briefly mentioned that theophylline did not appear to affect dexamethasone metabolism.[3]

(c) Hydrocortisone

Three patients in status asthmaticus with relatively stable serum concentrations of theophylline were given a 500-mg intravenous bolus of hydrocortisone followed 6 hours later by 200 mg of hydrocortisone given every 2 hours for 3 doses. In each case the serum theophylline levels rose from about 20 mg/L to between 30 and 50 mg/L. At least 2 of the patients complained of nausea and headache.[4] In contrast, 7 healthy subjects given sustained-release theophylline had no significant change in steady-state theophylline clearance when they were given a single 33-mg/kg dose of intravenous hydrocortisone, although there was a trend towards increased clearance.[5] Intravenous bolus doses of hydrocortisone 500 mg or 1 g did not affect theophylline levels in patients taking choline theophyllinate 400 mg every 12 hours for 8 days.[6]

(d) Methylprednisolone

An 88% increase in the clearance of a single dose of intravenous aminophylline was seen in one of 3 healthy subjects pretreated with oral methylprednisolone.[7] There was no significant change in clearance in the other 2 subjects. Another study in 10 children (aged 2 to 6 years) with status asthmaticus found that intramuscular methylprednisolone tended to increase the half-life of theophylline (given as oral aminophylline or theophylline).[8] A further study also reported that when intravenous aminophylline was given to 16 children taking corticosteroids (route and type not specified) the theophylline half-life was prolonged from 5 hours to

6.2 hours, and the clearance was reduced by about one-third, when compared with 10 children not taking corticosteroids.[9] Similarly, 7 healthy subjects given sustained-release theophylline had no significant change in steady-state theophylline clearance when they were given a single 1.6-mg/kg dose of intravenous methylprednisolone, although there was a trend towards increased clearance.[5]

(e) Prednisone or Prednisolone

A study in 6 healthy subjects found that a single 20-mg oral dose of prednisone had no significant effect on the pharmacokinetics of a single 200-mg oral dose of aminophylline.[10] The pharmacokinetics of a single 5.6-mg/kg intravenous dose of aminophylline was unchanged in 9 patients with chronic airflow obstruction when they were given prednisolone 20 mg daily for 3 weeks.[11]

Mechanism

Not understood.

Importance and management

The concurrent use of theophylline and corticosteroids is common and therapeutically valuable, whereas the few reported interactions of theophylline with oral or parenteral corticosteroids are poorly documented and their clinical importance is difficult to assess because both increases, small decreases and no changes in the serum levels of theophylline have been seen. It is also questionable whether the results of studies in healthy subjects can validly be extrapolated to patients with status asthmaticus. There do not appear to be any data on the effect of *inhaled* corticosteroids on the clearance of theophylline. Both theophylline and corticosteroids can cause hypokalaemia, and the possibility that this may be potentiated by concurrent use should be considered.

1. Jager-Roman E, Doyle PE, Thomas D, Baird-Lambert J, Cvejic M, Buchanan N. Increased theophylline metabolism in premature infants after prenatal betamethasone administration. *Dev Pharmacol Ther* (1982) 5, 127–35.
2. Baird-Lambert J, Doyle PE, Thomas D, Jager-Roman E, Cvejic M, Buchanan N. Theophylline metabolism in preterm neonates during the first weeks of life. *Dev Pharmacol Ther* (1984) 7, 239–44.
3. Brooks SM, Sholiton LJ, Werk EE, Altenau P. The effects of ephedrine and theophylline on dexamethasone metabolism in bronchial asthma. *J Clin Pharmacol* (1977) 17, 308.
4. Buchanan N, Hurwitz S, Butler P. Asthma—a possible interaction between hydrocortisone and theophylline. *S Afr Med J* (1979) 56, 1147–8.
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7. Squire EN, Nelson HS. Corticosteroids and theophylline clearance. *N Engl Reg Allergy Proc* (1987) 8, 113–15.
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9. Elvey SM, Saccar CL, Rocci ML, Mansmann HC, Martynec DM, Kester MB. The effect of corticosteroids on theophylline metabolism in asthmatic children. *Ann Allergy* (1986) 56, 520.
10. Anderson JL, Ayres JW, Hall CA. Potential pharmacokinetic interaction between theophylline and prednisone. *Clin Pharm* (1984) 3, 187–9.
11. Fergusson RJ, Scott CM, Rafferty P, Gaddie J. Effect of prednisolone on theophylline pharmacokinetics in patients with chronic airflow obstruction. *Thorax* (1987) 42, 195–8.

Theophylline + Co-trimoxazole

Co-trimoxazole (trimethoprim/sulfamethoxazole) does not alter the pharmacokinetics of theophylline.

Clinical evidence, mechanism, importance and management

In 6 healthy subjects co-trimoxazole 960 mg twice daily for 8 days had no effect on the pharmacokinetics of theophylline, given as a single 341-mg intravenous dose of aminophylline.[1] Another study, in 8 healthy subjects, found that co-trimoxazole 960 mg twice daily for 5 days had no effect on the pharmacokinetics of a single 267-mg oral dose of theophylline.[2] No special precautions would seem necessary if these drugs are given concurrently. However, note that acute infections *per se* can alter theophylline pharmacokinetics.[3]

1. Jonkman JHG, Van Der Boon WJV, Schoenmaker R, Holtkamp AH, Hempenius J. Lack of influence of co-trimoxazole on theophylline pharmacokinetics. *J Pharm Sci* (1985) 74, 1103–4.
2. Lo KF, Nation RL, Sansom LN. Lack of effect of co-trimoxazole on the pharmacokinetics of orally administered theophylline. *Biopharm Drug Dispos* (1989) 10, 573–80.
3. Renton KW. Cytochrome P450 regulation and drug biotransformation during inflammation and infection. *Curr Drug Metab* (2004) 5, 235–43.

Theophylline + Dextropropoxyphene (Propoxyphene)

Dextropropoxyphene does not significantly alter steady-state theophylline levels.

Clinical evidence, mechanism, importance and management

In 6 healthy subjects pre-treatment with dextropropoxyphene 65 mg every 8 hours for 5 days did not significantly change the total plasma clearance of steady-state theophylline 125 mg every 8 hours.[1] There was a small reduction in the formation of the hydroxylated metabolite of theophylline. There would seem to be no need to avoid concurrent use or to take particular precautions. There seems to be no information regarding aminophylline, but it would be expected to behave similarly.

1. Robson RA, Miners JO, Whitehead AG, Birkett DJ. Specificity of the inhibitory effect of dextropropoxyphene on oxidative drug metabolism in man: effects on theophylline and tolbutamide disposition. *Br J Clin Pharmacol* (1987) 23, 772–5.

Theophylline + Disulfiram

Theophylline clearance is decreased by disulfiram.

Clinical evidence

After 20 recovering alcoholics took disulfiram 250 mg daily for one week, the clearance of a 5-mg/kg intravenous dose of theophylline was decreased by a mean of about 21% (range 15 to 30%). Those taking disulfiram 500 mg daily had a mean decrease of 33% (range 22 to 50%).[1] Smoking appeared to have no important effects on the extent of this interaction. None of the patients were reported to have any significant liver disease, such as cirrhosis, which may also affect theophylline metabolism.

Mechanism

Disulfiram inhibits the liver enzymes concerned with the both the hydroxylation and demethylation of theophylline, thereby reducing its clearance from the body.

Importance and management

Information appears to be limited to this study but it would seem to be a clinically important interaction. Monitor the serum levels of theophylline and its effects if disulfiram is added, anticipating the need to reduce the theophylline dose. Note that the extent of this interaction appears to depend upon the dose of disulfiram used; higher doses present a greater risk. As aminophylline is metabolised to theophylline, it would be expected to interact similarly.

1. Loi C-M, Day JD, Jue SG, Bush ED, Costello P, Dewey LV, Vestal RE. Dose-dependent inhibition of theophylline metabolism by disulfiram in recovering alcoholics. *Clin Pharmacol Ther* (1989) 45, 476–86.

Theophylline + Diuretics

Furosemide is reported to increase, decrease or to have no effect on theophylline levels. An isolated case describes severe hyponatraemia and syndrome of inappropriate secretion of antidiuretic hormone in a premature neonate receiving chlorothiazide, spironolactone and theophylline. Both theophylline and diuretics can cause hypokalaemia, which may be additive.

Clinical evidence

In 8 patients with asthma the mean peak serum level of a 300-mg dose of sustained-release theophylline was reduced by 41% (from 12.14 to 7.16 mg/L) by a single 25-mg oral dose of **furosemide**.[1] A crossover study in 12 healthy subjects did not find any change in steady-state plasma theophylline levels when two 20-mg doses of oral **furosemide** were given 4 hours apart, although the overall renal clearance of theophylline was reduced.[2] However, 10 patients with asthma, chronic bronchitis or emphysema, receiving a continuous maintenance infusion of aminophylline, had a 21% rise in their serum theophylline levels (from 13.7 to 16.6 mg/L)

4 hours after being given a 40-mg intravenous dose of **furosemide** over 2 minutes.[3]

Four premature neonates, two given oral and two given intravenous theophylline with **furosemide** had a fall in their steady-state serum theophylline levels from 8 mg/L down to 2 to 3 mg/L when **furosemide** was given within 30 minutes of the theophylline.[4] A randomised, placebo-controlled study in 24 infants receiving ECMO (extracorporeal membrane oxygenation) found that theophylline 2 mg/kg enhanced the response to diuresis with **furosemide** 1 mg/kg. If the response were maintained over a 24-hour period an extra 110 mL/kg of fluid would have been lost.[5]

A case of severe hyponatraemia and syndrome of inappropriate secretion of antidiuretic hormone has been reported in a pre-term neonate who received theophylline, as aminophylline (maintenance dose 4 mg/kg every 12 hours), and then started to receive **chlorothiazide** 25 mg/kg every 12 hours and **spironolactone** 1 mg/kg every 12 hours. His sodium level was restored by the intravenous administration of 3% sodium chloride.[6]

The manufacturer of **torasemide** notes that it may potentiate the action of theophylline,[7] but there appears to be no published data supporting this suggestion.

Mechanism

Not understood, although in theory furosemide may cause increased renal excretion of theophylline, which could explain the reduced levels. The thiazides, spironolactone and theophylline[8] have each been reported to cause hyponatraemia, and therefore the low sodium levels may have occurred as a result of the additive effects of these drugs.

Importance and management

Information regarding an interaction between furosemide and aminophylline or theophylline is limited and the outcome of concurrent use is inconsistent and uncertain. More study is needed to assess the clinical significance of the effects of theophylline and furosemide on diuresis. However, note also that theophylline clearance may be reduced by some conditions such as chronic heart failure or pulmonary oedema. Theophylline clearance could therefore be increased when the health of the patient is improved, possibly through the use of furosemide.[9] Whatever the reason for the effects seen, if both drugs are used, be aware of the potential for changes in serum theophylline levels. Consider measuring levels, and make appropriate dose adjustments as necessary. Both theophylline and diuretics can cause hypokalaemia, and the possibility that this may be additive on concurrent use should be considered. The general relevance of the isolated case describing hyponatraemia is unclear.

1. Carpentiere G, Marino S, Castello F. Furosemide and theophylline. *Ann Intern Med* (1985) 103, 957.
2. Jänicke U-A, Krüdewagen B, Schulz A, Gundert-Remy U. Absence of a clinically significant interaction between theophylline and furosemide. *Eur J Clin Pharmacol* (1987) 33, 487–91.
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6. Srinivasan K, Patole SK, Whitehall JS. Severe hyponatremia in a neonate – an unusual association. *Indian Pediatr* (2001) 38, 1410–12.
7. Torem (Torasemide). Meda Pharmaceuticals. UK Summary of product characteristics, September 2009.
8. Liberopoulos EN, Alexandridis GH, Christidis DS, Elisaf MS. SIADH and hyponatremia with theophylline. *Ann Pharmacother* (2002) 36, 1180–2.
9. Nakagawa RS. Theophylline-furosemide interaction? *Am J Hosp Pharm* (1982) 39, 242.

Theophylline + Dobutamine

A man taking theophylline developed marked tachycardia when he was given dobutamine.

Clinical evidence, mechanism, importance and management

A patient with asthma taking sustained-release theophylline 150 mg twice daily, digoxin and spironolactone was anaesthetised for an aortic valve replacement with fentanyl, midazolam and pipecuronium. Following induction, intubation, and ventilation with 100% oxygen, his systolic blood pressure fell from 120 mmHg to 80 mmHg, and his heart rate slowed from 70 bpm to 50 bpm. Dobutamine was given at a dose of 5 micrograms/kg per minute, and after 2 to 3 minutes his heart rate rose to 150 bpm and his systolic blood pressure rose to 190 mmHg. The authors of the report[1] attribute the tachycardia to an interaction between dobutamine and theophylline. They suggested that the interaction was possibly as a result of a synergistic increase in cyclic AMP levels in cardiac muscle and/or theophylline-induced potentiation of catecholamine action. They advise the careful titration of dobutamine in any patient with asthma taking theophylline, particularly if a slow-release preparation is being used. However, more study of this apparent interaction is needed as this appears to be the only report, and so its general importance is unknown.

1. Baraka A, Darwish R, Rizkallah P. Excessive dobutamine-induced tachycardia in the asthmatic cardiac patient: possible potentiation by theophylline therapy. *J Cardiothorac Vasc Anesth* (1993) 7, 641–2.

Theophylline + Doxapram

Doxapram pharmacokinetics are unchanged by theophylline in premature infants, but agitation and increased muscle activity may occur in adults.

Clinical evidence, mechanism, importance and management

Intravenous theophylline does not affect the pharmacokinetics of doxapram given to treat apnoea in premature infants, and no adjustment of the dose of doxapram is needed in the presence of theophylline.[1] However, the manufacturers of doxapram say that there may be an interaction between doxapram and aminophylline, which is manifested by agitation muscle fasciculation and hyperactivity. Care should therefore be taken if these drugs are used together.[2]

1. Jamali F, Coutts RT, Malek F, Finer NN, Peliowski A. Lack of a pharmacokinetic interaction between doxapram and theophylline in apnea of prematurity. *Dev Pharmacol Ther* (1991) 16, 78–82.
2. Dopram (Doxapram hydrochloride). Goldshield plc. UK Summary of product characteristics, August 2008.

Theophylline + Duloxetine

Duloxetine does not affect the pharmacokinetics of theophylline to a clinically relevant extent.

Clinical evidence, mechanism, importance and management

In a controlled study in 28 healthy subjects, duloxetine 60 mg was given twice daily for 4 days, and with a single 197.5-mg intravenous dose of theophylline (given as aminophylline 250 mg) on day 5. Duloxetine increased the AUC of theophylline by 20% in the women who participated in the study, but no statistically significant increase in the AUC of theophylline was seen in the men. Overall, the AUC of theophylline was increased by 13%. However, this increase is not expected to be clinically significant and no dose adjustment of theophylline is likely to be required.[1]

1. Lobo ED, Bergstrom RF, Reddy S, Quinlan T, Chappell J, Hong Q, Ring B, Knadler MP. *In vitro* and *in vivo* evaluations of cytochrome P450 1A2 interactions with duloxetine. Clin Pharmacokinet (2008) 47, 191–202.

Theophylline + Enoximone

Aminophylline possibly reduces the beneficial cardiovascular effects of enoximone. Theoretically, milrinone would be expected to interact similarly.

Clinical evidence, mechanism, importance and management

An experimental study into the mechanism of action of enoximone in 14 patients with ischaemic or idiopathic dilative cardiomyopathy found that pretreatment with intravenous aminophylline 7 mg/kg given over 15 minutes reduced the beneficial haemodynamic effects of intravenous enoximone 1 mg/kg given over 15 minutes.[1] This appears to occur because each drug competes for inhibition of cAMP-specific phosphodiesterases in cardiac and vascular smooth muscle. **Milrinone**, another phosphodiesterase inhibitor similar to enoximone, would be expected to interact in the same way. However, there are, at present, no published reports of a possible interaction with milrinone, and no case reports of a

problem occurring with the concurrent use of either drug with theophylline. The clinical importance of this study therefore awaits evaluation.

1. Morgagni GL, Bugiardini R, Borghi A, Pozzati A, Ottani F, Puddu P. Aminophylline counteracts the hemodynamic effects of enoximone. *Clin Pharmacol Ther* (1990) 47, 140.

Theophylline + Ephedrine

Some data suggest that an increased frequency of adverse effects occurs when ephedrine is given with theophylline.

Clinical evidence, mechanism, importance and management

A double-blind, randomised study in 23 children aged 4 to 14 years found that when ephedrine was given with theophylline (in a ratio of 25 mg ephedrine to 130 mg theophylline), the number of adverse reactions increased significantly, when compared with each drug taken separately. Moreover, the combination was no more effective than theophylline alone. The combination was associated with insomnia (14 patients), nervousness (13 patients) and gastrointestinal complaints (18 patients), including vomiting (12 patients). The serum theophylline levels were unchanged by ephedrine.[1] A previous study by the same authors in 12 children with asthma given ephedrine and aminophylline found similar results.[2] In contrast, a later study suggested that ephedrine 25 mg every 8 hours given with aminophylline did produce improvements in spirometry and no adverse effects were seen. However, it was calculated that the theophylline dose used was about half that used in the previous study.[3]

In the treatment of asthma, ephedrine has been largely superseded by more selective sympathomimetics, which have fewer adverse effects. Ephedrine is still an ingredient of a number of non-prescription cough and cold remedies, when it may be combined with theophylline (e.g. *Franol*). Patients taking theophylline requiring ephedrine should be advised to report any adverse effects.

1. Weinberger M, Bronsky E, Bensch GW, Bock GN, Yecies JJ. Interaction of ephedrine and theophylline. *Clin Pharmacol Ther* (1975) 17, 585–92.
2. Weinberger MM, Bronsky EA. Evaluation of oral bronchodilator therapy in asthmatic children. *J Pediatr* (1974) 84, 421–7.
3. Tinkelman DG, Avner SE. Ephedrine therapy in asthmatic children. Clinical tolerance and absence of side effects. *JAMA* (1977) 237, 553–7.

Theophylline + Flutamide

The manufacturer of flutamide notes that cases of increased theophylline plasma levels have been reported in patients taking these two drugs together. They suggest the reason for this is that flutamide and theophylline are both metabolised by the cytochrome P450 isoenzyme CYP1A2.[1] Note that interactions by this mechanism are rarely clinically relevant.

1. Drogenil (Flutamide). Schering-Plough Ltd. UK Summary of product characteristics, August 2007.

Theophylline + Food

The effect of food on theophylline bioavailability is unclear. In general it appears that fat or fibre in food has no effect, whereas high-protein diets decrease the theophylline half-life. High-carbohydrate diets may increase, or have no effect on the theophylline half-life. Significant changes in theophylline bioavailability have been seen in patients given both enteral feeds and total parenteral nutrition.

Clinical evidence

(a) Food

The bioavailability of theophylline from sustained-release preparations has been shown to be reduced,[1,2] increased,[1,3,4] or unaffected[5-12] when theophylline was given immediately after breakfast. In one study the bioavailability of theophylline from a sustained-release preparation was increased by 10% when it was given after food, the trough theophylline concentration was increased by 0.7 mg/L, and the time to reach maximum plasma levels was increased from 8.6 hours to 11.4 hours.[4] Dose dumping, leading to signs of theophylline toxicity, was seen in 3 children with asthma who were given a dose of *Uniphyllin* immediately after breakfast.[7] The fat content[11,13,14] or fibre content[15] of meals does not seem to significantly affect theophylline absorption. High-protein meals appear to decrease the half-life of theophylline.[16,17] In one study high-carbohydrate meals increased the half-life of theophylline,[17] while in another study a high-carbohydrate meal had no effect on the half-life of a single 350-mg dose of sustained-release theophylline, but the maximum plasma levels were increased by 56%. There was no overall effect on the extent of absorption.[18] There was no difference in theophylline metabolism in one study when patients were changed from a high-carbohydrate/low-protein diet to a high-protein/low-carbohydrate diet.[19] One study found that changing from a high-protein to a high-carbohydrate meal had an effect on the metabolism of theophylline similar to that of cimetidine, and that the effects of the meal change and cimetidine were additive.[20] The effects of spicy food have been studied, but the clinical significance of the changes are uncertain.[21]

(b) Enteral feeds

A patient with COPD had a 53% reduction in his serum theophylline levels accompanied by bronchospasm when he was fed continuously through a nasogastric tube with *Osmolite*. The interaction occurred with both theophylline tablets (*Theo-Dur*) and liquid theophylline, but not when the theophylline was given intravenously as aminophylline. It was also found that the interaction could be avoided by interrupting feeding one hour either side of the oral liquid theophylline dose.[22] Conversely, hourly administration of 100 mL of *Osmolite* did not affect the extent of theophylline absorption from a slow-release preparation (*Slo-bid Gyrocaps*) in healthy subjects, although the rate of absorption was slowed.[23] Similarly, in healthy subjects, hourly administration of 100 mL of *Ensure* for 10 hours did not affect the rate or extent of absorption of theophylline from *Theo-24* tablets.[24]

(c) Parenteral nutrition

An isolated report describes an elderly woman given intravenous aminophylline who had a marked fall in her serum theophylline levels (from 16.3 mg/L to 6.3 mg/L) when the amino acid concentration of her parenteral nutrition regimen was increased from 4.25% to 7%.[25] A study in 7 patients with malnutrition (marasmus-kwashiorkor) found only a small, probably clinically irrelevant increase in the elimination of a single intravenous dose of theophylline when they were fed intravenously.[26]

Mechanism

Not fully understood. As with any sustained-release formulation, the presence of food in the gut may alter the rate or extent of drug absorption by altering gastrointestinal transit time. It has been suggested that high-protein diets stimulate liver enzymes thereby increasing the metabolism of the theophylline and hastening its clearance from the body. High carbohydrate diets may have the opposite effect. The cytochrome P450 isoenzyme CYP1A2 (the principal enzyme involved in the metabolism of theophylline) is known to be induced by chemicals contained in cruciferous vegetables[27] or formed by the action of high temperatures or smoke on meat.[28] This suggestion is supported by a study in which charcoal-grilled (broiled) beef decreased the half-life of theophylline by an average of 22%.[29] Further, high doses of daidzein, the principal isoflavone in soybeans, may inhibit CYP1A2 resulting in an increase in theophylline levels and half-life of about 33% and 41%, respectively.[30]

Importance and management

Interactions between theophylline and food have been thoroughly studied but there seems to be no consistent pattern in the way the absorption of different theophylline preparations is affected. Be alert for any evidence of an inadequate response that can be related to food intake. Avoid switching between different preparations, and monitor the effects if this is necessary. Consult the product literature for any specific information on food and encourage patients to take their theophylline consistently in relation to meals where this is considered necessary. Advise patients not make major changes in their diet without consultation. Monitor the effects of both enteral and parenteral nutrition, as aminophylline or theophylline dose adjustments may be required.

1. Karim A, Burns T, Wearley L, Streicher J, Palmer M. Food-induced changes in theophylline absorption from controlled-release formulations. Part I. Substantial increased and decreased absorption with Uniphyl tablets and Theo-Dur Sprinkle. *Clin Pharmacol Ther* (1985) 38, 77–83.

2. Lohmann A, Dingler E, Sommer W. Influence of food on the bioavailability of theophylline from a sustained-release theophylline preparation. *Arzneimittelforschung* (1991) 41, 732–4.
3. Vaughan L, Milavetz G, Hill M, Weinberger M, Hendeles L. Food-induced dose-dumping of Theo-24, a 'once-daily' slow-release theophylline product. *Drug Intell Clin Pharm* (1984) 18, 510.
4. Arkinstall WW, Hopkinson M, Rivington RN, Calcutt L, Aitken T, Stewart JH. The clinical significance of food-induced changes in the absorption of theophylline from Uniphyl tablets. *J Allergy Clin Immunol* (1988) 82, 155–64.
5. Johansson Ö, Lindberg T, Melander A, Wåhlin-Boll E. Different effects of different nutrients on theophylline absorption in man. *Drug Nutr Interact* (1985) 3, 205–11.
6. Sips AP, Edelbroek PM, Kulstad S, de Wolff FA, Dijkman JH. Food does not effect bioavailability of theophylline from Theolin Retard. *Eur J Clin Pharmacol* (1984) 26, 405–7.
7. Steffensen G, Pedersen S. Food induced changes in theophylline absorption from a once-a-day theophylline product. *Br J Clin Pharmacol* (1986) 22, 571–7.
8. Ürmös I, Grézal G, Balogh Nemes K, Szállási T, Drabant S, Csörgo M, Klebovich I. Food interaction study of a new theophylline (Egifilin) 200 and 400 mg retard tablet in healthy volunteers. *Int J Clin Pharmacol Ther* (1997) 35, 65–70.
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Theophylline + Gold

Gold may reduce theophylline levels.

Clinical evidence, mechanism, importance and management

A review of theophylline serum levels in 6 steroid-dependent asthmatic patients who were taking methylprednisolone and gold (auranofin) and had also taken theophylline for at least 3 months, found that the actual theophylline levels were lower than the predicted levels, and that the levels were all below 10 mg/L. No information was provided regarding the control of asthma in these patients.[1] The authors of this review suggest that the gastrointestinal adverse effects and protein binding of auranofin may have altered the absorption and distribution of theophylline. An interaction is not established as the theophylline levels were only reduced compared with those predicted using two different pharmacokinetic tools. The clinical relevance of any interaction is also unclear, as these 'low' levels were identified retrospectively. The evidence available is too limited to warrant any general precautions. Further study is needed.

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Theophylline + Grapefruit and other fruit juices

Grapefruit and kinnow (mandarin) juice do not alter theophylline pharmacokinetics to a clinically relevant extent.

Clinical evidence, mechanism, importance and management

(a) Grapefruit juice

In one study, 12 healthy subjects were given a single 200-mg oral dose of theophylline solution (*Euphyllin*) diluted in either 100 mL of grapefruit juice or water, followed by another 900 mL of juice or water over the next 16 hours. The pharmacokinetics of the theophylline were found to be unchanged by the grapefruit juice.[1] Another study, in 10 healthy subjects who took a single 300-mg dose of sustained-release theophylline (*Theobid*) with 300 mL of water or grapefruit juice, found that although the grapefruit juice lowered the plasma levels of theophylline between one and 4 hours after the dose, the AUC of theophylline was not significantly changed, nor were there any other significant pharmacokinetic changes.[2]

The authors of the first study had previously shown that grapefruit juice had a small effect on the pharmacokinetics of 'caffeine', (p.1420), which is metabolised in a similar way to theophylline, and that one of the constituents of grapefruit juice (naringenin) inhibited the cytochrome P450 isoenzyme CYP1A2 (the principal enzyme in theophylline metabolism) *in vitro*. Therefore, in theory, an interaction was possible. However, these studies suggest that no clinically relevant interaction occurs, and therefore there would seem to be no reason why patients taking theophylline (or probably aminophylline) should avoid grapefruit juice.

(b) Kinnow juice

In a study, 10 healthy subjects took a single 300-mg dose of sustained-release theophylline (*Theobid*) with 300 mL of water or kinnow (mandarin) juice. The maximum plasma levels and the AUC of theophylline were not different between the two groups. The maximum plasma theophylline levels were 9.54 mg/L and 8.43 mg/L when taken with water and kinnow juice, respectively. The plasma level of theophylline taken with kinnow juice was lower at every time point than when taken with water, but this difference was only statistically significant between one and 4 hours after the start of the study.[3] However, this change would not be expected to be of clinical significance.

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Theophylline + Griseofulvin

Griseofulvin does not appear to alter the pharmacokinetics of theophylline to a clinically relevant extent.

Clinical evidence, mechanism, importance and management

In a study in 12 healthy subjects, griseofulvin 500 mg daily for 8 days reduced the half-life of theophylline (after a single oral dose of aminophylline) from 6.6 hours to 5.7 hours, and increased the clearance of two of its metabolites. However, these changes were far too small to usually have any clinical relevance.[1] There would therefore appear to be no reason for avoiding concurrent use.

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Theophylline + H_2-receptor antagonists

Cimetidine raises theophylline levels and toxicity may develop. However, the extent of the interaction is only modest with low-dose cimetidine. Although there are some contrasting reports, on the whole famotidine, nizatidine, ranitidine and roxatidine appear not to interact with theophylline.

Clinical evidence

(a) Cimetidine

A number of case reports describe significantly increased theophylline levels, including many that were toxic, in patients (adults and children) given oral or intravenous aminophylline or theophylline with cimetidine.[1-6] A few cases describe serious adverse effects such as seizures.[3,4]

In a large number of pharmacokinetic studies healthy subjects were given oral or intravenous aminophylline or theophylline[7-16] and patients were given oral or intravenous theophylline[17-21] with oral cimetidine 800 mg to 1.2 g daily in divided doses for 4 to 10 days. It was clearly shown that cimetidine prolonged the theophylline half-life by about 30 to 65% and reduced theophylline clearance by about 20 to 40%. Steady-state serum theophylline levels were raised about one-third.[17,18,21] One of these studies[21] has also been published elsewhere.[22] The effect of cimetidine was maximal in 3 days in the one study assessing this.[17] The extent of the interaction did not differ between cimetidine 1.2 g daily and 2.4 g daily in one study,[10] although two further studies found that cimetidine 800 mg daily had less effect than cimetidine 1.2 g daily.[12,23] A study investigating low-dose cimetidine (200 mg twice daily) found only a 12% decrease in theophylline clearance.[24]

Two studies found that the effect of cimetidine did not differ between young and elderly subjects,[12,25] whereas another found that it was more pronounced in the elderly.[23] The effects of cimetidine did not differ between smokers and non-smokers in one study,[26] but were more pronounced in smokers in another.[27] In a further study the effects of cimetidine were not affected by gender.[23] Three studies found that the inhibitory effects of cimetidine and ciprofloxacin were additive.[25,28,29] For the effect of ciprofloxacin, see 'Theophylline + Quinolones', p.1452.

Three studies found that intravenous cimetidine also inhibited the clearance of theophylline (given as intravenous aminophylline or sustained-release theophylline).[30-32] In one of these, oral and intravenous cimetidine reduced theophylline clearance to the same extent, but when clearance was corrected for the lower bioavailability of the oral cimetidine, oral cimetidine resulted in a greater inhibition than intravenous cimetidine.[30] Another study found that the effects of a continuous 50-mg/hour infusion of cimetidine were similar to those of an intermittent infusion of 300 mg every 6 hours.[31]

In contrast, a further study in healthy subjects found no clinically important interaction between intravenous aminophylline and an intravenous cimetidine infusion, but the aminophylline was given only 12 hours after starting the cimetidine, which may be insufficient for cimetidine to have had an effect.[33] Similarly, a subsequent study in 18 critically ill patients given a continuous 50-mg/hour intravenous infusion of cimetidine and low-dose aminophylline 10.8 mg/hour for just 48 hours found no clinically important interaction.[34]

(b) Famotidine

In 10 healthy subjects famotidine 40 mg twice daily for 5 days had no effect on the pharmacokinetics of theophylline (given as intravenous aminophylline).[14] In another study, 16 patients with bronchial asthma or COPD found that famotidine 20 mg twice daily for at least 3 days did not affect the clearance of theophylline.[35] Two further studies also found no interaction between intravenous theophylline and famotidine 20 or 40 mg twice daily for 4 or 9 days in patients with COPD.[20,36] In a post-marketing surveillance study it was noted that 4 patients with asthma taking theophylline had also taken famotidine 40 mg daily for 4 to 8 weeks without any problems.[37] In contrast, in a patient with COPD and liver impairment, the AUC and serum levels of an intravenous dose of theophylline were raised by 78% and the clearance was halved by famotidine 40 mg daily for 8 days.[38] A later study by the same authors in 7 patients with COPD similarly treated, but with normal liver function, found that the AUC of theophylline was increased by 56% and its clearance was reduced by 35% by famotidine.[39]

(c) Nizatidine

A study in 17 patients with COPD found that nizatidine 150 mg twice daily for a month had no effect on the steady-state pharmacokinetics of theophylline.[21] However, up to the end of August 1989 there were 6 reports of apparent interactions in the Spontaneous Adverse Drug Reaction Database of the FDA in the US. Four patients taking theophylline developed elevated serum theophylline levels, with symptoms of toxicity in at least one case, when given nizatidine. The problems resolved when either both drugs, or just nizatidine were stopped.[40]

(d) Ranitidine

Many studies in healthy subjects (given intravenous aminophylline or oral theophylline)[10,11,15,41-43] and patients (given sustained-release theophylline)[18,21,44-47] have found that ranitidine does not affect the pharmacokinetics of theophylline, even in daily doses far in excess of those used clinically (up to 4.2 g of ranitidine daily).[41] However, there are 7 reports describing a total of 10 patients, who developed theophylline toxicity when given ranitidine with sustained-release theophylline[48-53] or intravenous aminophylline.[54] The validity of a number of these reports has been questioned,[55-58] with the authors subsequently modifying some.[59,60]

(e) Roxatidine

Roxatidine 150 mg daily did not affect the clearance of theophylline.[61] Similarly, in 9 healthy subjects, roxatidine 150 mg twice daily did not significantly change the pharmacokinetics of a single 250-mg intravenous dose of aminophylline.[62]

Mechanism

Cimetidine is an enzyme inhibitor that reduces the metabolism (predominantly *N*-demethylation)[63] of theophylline by the cytochrome P450 isoenzyme CYP1A2 in the liver, thereby raising its serum levels. Famotidine, nizatidine and ranitidine do not have enzyme-inhibiting effects so that it is not clear why they sometimes appear to behave like cimetidine.

Importance and management

The interaction between theophylline or aminophylline and cimetidine is very well documented (not all the references being listed here), very well established and clinically important. Theophylline serum levels normally rise by about one-third, but much greater increases have been seen in individual patients. Monitor theophylline levels closely. Note that in one study the peak effect was reached in 3 days. Initial theophylline dose reductions of 30 to 50% have been suggested to avoid toxicity.[4] Alternatively, use one of the other H_2-receptor antagonists, or consider changing to a proton pump inhibitor, see 'Theophylline + Proton pump inhibitors', p.1451. The effect of low-dose cimetidine (200 mg twice daily) is unlikely to be clinically relevant unless theophylline levels are at the higher end of the therapeutic range. The situation with famotidine, nizatidine and ranitidine is not totally clear. They would not be expected to interact because they are not enzyme inhibitors like cimetidine, but very occasionally and unpredictably they appear to do so. Nevertheless, the general picture is that normally no special precautions are needed if these H_2-receptor antagonists,[56] or roxatidine are given with aminophylline or theophylline.

Note that some of the symptoms of theophylline toxicity, such as nausea, vomiting and abdominal pain, are similar to those of gastrointestinal ulceration. If a patient taking theophylline presents with these symptoms, it would seem prudent to monitor theophylline levels.

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Theophylline + Hormonal contraceptives

Theophylline clearance is reduced to some extent in women taking oral combined hormonal contraceptives, but no toxicity has been reported.

Clinical evidence

The total plasma clearance of a single 4-mg/kg oral dose of aminophylline was about 30% lower in 8 women taking a combined oral contraceptive (**ethinylestradiol**/**norgestrel**, *Ovral*) than in 8 other women not taking oral contraceptives.[1] The theophylline half-life was also prolonged by about 30%, from 7.34 hours to 9.79 hours. Similar results were found in other studies in subjects given intravenous or oral aminophylline and oral combined hormonal contraceptives (**ethinylestradiol**/**norgestrel**, *Ovral* and **mestranol**/**etynodiol diacetate**, *Ovulen* or unnamed products).[2,3] In contrast, no significant differences were seen in the pharmacokinetics of theophylline (given as intravenous aminophylline) in 10 adolescent women (15 to 18 years) taking oral low-dose combined or sequential hormonal contraceptives (**ethinylestradiol**/**norethisterone**), when compared with age matched controls.[4] However, in the same women the clearance of oral theophylline was found to be reduced by 33% after they took an oral triphasic combined hormonal contraceptive for 3 to 4 months.[5] In a retrospective analysis of factors affecting theophylline clearance, the use of oral hormonal contraceptives was associated with a reduced theophylline clearance in women who smoked.[6]

Mechanism

Uncertain, but it seems possible that the oestrogenic component of the contraceptive may inhibit the metabolism of the theophylline by the liver microsomal enzymes, thereby reducing its clearance.

Importance and management

An established interaction, but there seem to be no reports of theophylline toxicity resulting from the concurrent use of hormonal contraceptives. Women taking combined hormonal contraceptives may need less aminophylline or theophylline than those not taking these contraceptives. There is a small risk that patients with serum theophylline levels at the top end of the range may develop some toxicity when hormonal contraceptives are added. It has been proposed that the effects may be more apparent with long-term, high-dose contraceptive use.[1,4]

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Theophylline + Idrocilamide

Idrocilamide given orally can increase theophylline levels.

Clinical evidence, mechanism, importance and management

In 6 healthy subjects oral idrocilamide 600 mg daily for 3 days then 1.2 g for 4 days increased the half-life of a single dose of theophylline 2.5-fold, from 8.5 hours to 21.6 hours, and reduced its clearance by 67%.[1] This is due to a reduction in the liver metabolism of theophylline by the cytochrome P450 isoenzyme CYP1A2, which is inhibited by idrocilamide. In-

formation is very limited but it indicates that concurrent use should be closely monitored. Anticipate the need to reduce the theophylline dose with *oral* idrocilamide. As aminophylline is metabolised to theophylline it seems likely to be similarly affected.

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Theophylline + Imipenem

Seizures developed in three patients taking aminophylline or theophylline when they were given imipenem.

Clinical evidence, mechanism, importance and management

Two patients receiving intravenous aminophylline developed seizures within 11 to 56 hours of starting treatment with intravenous imipenem 500 mg every 6 to 8 hours. Seizures developed in a third patient taking theophylline after imipenem had been given for 6 days. In all 3 patients, seizures occurred 2 to 3 hours after a dose of imipenem.[1] The reasons for this effect are not known. Theophylline serum levels appeared to be unchanged.[1] In an analysis of data from 1754 patients who had received imipenem in dose-ranging studies, 3% had seizures, and imipenem was judged to be associated with a third of these cases. However, the concurrent use of theophylline or aminophylline was not found to be a significant risk factor for the development of seizures with imipenem.[2] The general importance of these cases is therefore uncertain.

1. Semel JD, Allen N. Seizures in patients simultaneously receiving theophylline and imipenem or ciprofloxacin or metronidazole. *South Med J* (1991) 84, 465–8.
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Theophylline + Influenza vaccines

Normally none of the influenza vaccines (whole-virion, split-virion and surface antigen) interact with theophylline, but there are three reports describing rises in serum theophylline levels in a few patients (some to toxic levels), which were attributed to the use of an influenza vaccine.

Clinical evidence

(a) Evidence of no interaction

In 12 patients with asthma, the mean steady-state serum theophylline levels were not altered by a trivalent split-virion influenza vaccine (*Fluzone*), although one patient had an increase in levels (see *Evidence of an interaction*, below). Levels were measured before vaccination and one, 3, 7 and 14 days after vaccination.[1] Theophylline levels were unchanged in 5 patients with COPD when they were given 0.5 mL of influenza vaccine (*Fluogen*).[2] Similarly, no evidence of a rise in theophylline levels was found in a number of other studies in both adults and children, receiving maintenance theophylline or aminophylline, and given various trivalent split-virion vaccines[3-6] including *Fluzone*,[7] *Fluogen*,[8-10] *Influvac*,[11] *Mutagrip*.[12] In addition, no change in the pharmacokinetics of theophylline (given as oral aminophylline) was found after the use of a whole-virion vaccine in healthy adults.[13] No evidence of serious theophylline toxicity was seen in 119 elderly patients taking maintenance theophylline and given an unspecified influenza vaccine.[14]

(b) Evidence of an interaction

Three patients who had been taking oral choline theophyllinate 200 mg (equivalent to 128 mg of theophylline) every 6 hours for at least 7 days had a rise in their serum theophylline levels of 219%, 89%, and 85%, respectively, within 12 to 24 hours of receiving 0.5 mL of trivalent split-virion influenza vaccine (*Fluogen*, Parke Davis). In some cases effects persisted for up to 72 hours, and two patients had signs of theophylline toxicity. A subsequent study in 4 healthy subjects found that the same dose of vaccine more than doubled the half-life of theophylline, from 3.3 hours to 7.3 hours, and halved its clearance.[15]

A girl had a rise in theophylline levels from 20 mg/L to 34 mg/L (with no sign of toxicity) within 5 hours of being given a trivalent split-virion vaccine.[16] In a study where 11 of 12 patients had no increase in theophylline levels after vaccination with *Fluzone*, one woman showed a rise in levels (from 10 mg/L to 24.5 mg/L) accompanied by headaches and palpitations.[1]

In 8 healthy subjects the clearance of theophylline (given as choline theophyllinate) was reduced by 25% one day after influenza vaccination (trivalent influenza vaccine, *Fluogen*, Parke Davis), but this was of borderline significance. Theophylline metabolism had returned to pre-vaccination levels after 7 days.[17]

A patient with COPD taking sustained-release theophylline 300 mg twice daily (theophylline levels between 7 and 12 mg/L) developed nausea and palpitations the day after he received a trivalent influenza vaccination (*Fluogen*). His theophylline level was increased to 26 [mg/L]. His dose was reduced to 200 mg twice daily and the adverse effects resolved. However, a few days later his COPD had become symptomatic and the theophylline level was found to be subtherapeutic, so the dose was raised to 300 mg twice daily, as before.[18]

Mechanism

Uncertain. If an interaction occurs, it has been suggested it is probably due to inhibition of the liver enzymes concerned with the metabolism of theophylline, possibly secondary to interferon production, resulting in theophylline accumulation in the body.[15,17] One suggestion is that vaccine contaminants, which are potent interferon-inducing agents, may be responsible (rather than the vaccine itself), so that an interaction would seem to be less likely with modern highly-purified subunit vaccines.[19] In one study where an interaction occurred, an increase in serum interferon levels was detected,[17] whereas, in two of the studies showing no interaction, no interferon production was detected.[10,13] Influenza infection *per se* can result in decreased theophylline clearance and theophylline toxicity.[20]

Importance and management

A very thoroughly investigated interaction, the weight of evidence being that no adverse interaction normally occurs between aminophylline or theophylline and any type of influenza vaccine in children, adults or the elderly. Even so, bearing in mind the occasional and unexplained reports of an interaction[1,15,16,18] it would seem prudent to monitor the effects of concurrent use (for nausea, headaches, palpitations), although problems are very unlikely to arise now that purer vaccines are available (see 'Mechanism'). Note that any rise in theophylline levels is likely to be transient.

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12. Jonkman JHG, Wymenga ASC, de Zeeuw RA, van der Boon WVJ, Beugelink JK, Oosterhuis B, Jedema JN. No effect of influenza vaccination on the theophylline pharmacokinetics as studied by ultraviolet spectrophotometry, HPLC, and EMIT assay methods. *Ther Drug Monit* (1988) 10, 345–8.
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Theophylline + Interferons

Theophylline clearance is reduced by up to 50% by interferons, but the extent of the interaction varies greatly, with different types of interferon having slightly different effects.

Clinical evidence

A study in 9 subjects (5 with stable chronic active hepatitis B and 4 healthy subjects) found that 20 hours after being given a single 9- or 18-million unit intramuscular injection of interferon (recombinant human interferon alfa A), the clearance of theophylline (given as intravenous aminophylline) was approximately halved (range 33 to 81%) in 8 of the 9 subjects. The mean theophylline elimination half-life was increased from 6.3 hours to 10.7 hours (1.5- to sixfold increases). In the healthy subjects the theophylline clearances were noted to have returned to their former values 4 weeks after the study.[1]

Another study, in 11 healthy subjects given interferon alfa (*Roferon-A*) 3 million units daily for 3 days, found that the terminal half-life and AUC of theophylline (given as aminophylline) were only increased by 10 to 15%, with a similar decrease in clearance.[2] In 7 patients with cancer, interferon alfa (*Intron-A*) 3 million units given three times a week for 2 weeks decreased the clearance of a single 150-mg oral dose of theophylline by 33%.[3]

Seven patients with chronic hepatitis C receiving interferon beta 3 to 9 million units daily for 8 weeks were given a single 250-mg dose of intravenous aminophylline. Interferon beta reduced the total body clearance of theophylline by 26% (range 6 to 57%) and increased the elimination half-life by 39% (range 27 to 139%), but had no significant effect on the volume of distribution, although there was wide inter-patient variability.[4]

In a study in 14 healthy male subjects who received peginterferon alfa-2a for 4 weeks, there was a 33% increase in the AUC of a single dose of theophylline.[5]

Mechanism

Interferon alfa inhibits the liver enzymes concerned with the metabolism of theophylline. Therefore the metabolism of theophylline is reduced, and it accumulates. Interferon beta also appears to inhibit liver enzymes.[4] It has been suggested that the cytochrome P450 isoenzyme CYP1A2, by which theophylline is metabolised may be the route affected. However, one study in which the activity of CYP1A2 was determined in 14 patients with active hepatitis C after receiving interferon alfa and ribavirin for 4 weeks did not determine any significant change in CYP1A2 activity.[6]

Importance and management

Direct information appears to be limited to these reports. So far there appear to be no reports of toxicity but it would seem prudent to monitor the concurrent use of an interferon and aminophylline or theophylline closely (for nausea, headaches, palpitations), taking theophylline levels if necessary. Patients with enhanced metabolism (e.g. smokers) are predicted to be most at risk.[1] The manufacturers of peginterferon alfa-2a suggest that the interaction with theophylline may not be maximal until after more than 4 weeks of concurrent use.[7]

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7. Pegasys (Peginterferon alfa-2a). Roche Products Ltd. UK Summary of product characteristics, October 2009.

Theophylline + Ipriflavone

An isolated report describes increased theophylline levels in a patient given ipriflavone.

Clinical evidence, mechanism, importance and management

The theophylline serum levels of a patient with COPD, taking sustained-release theophylline 300 mg twice daily, rose from 9.5 mg/L to 17.3 mg/L when ipriflavone 600 mg daily for about 4 weeks was taken. No symptoms of toxicity occurred. The serum theophylline levels returned to roughly the initial level when the ipriflavone was stopped, and rose again when it was restarted.[1] *In vitro* studies with human liver microsomes suggest that ipriflavone can inhibit the cytochrome P450 isoenzyme CYP1A2 and the demethylation of theophylline,[2,3] which would reduce the metabolism of theophylline and increase its levels.

Although so far only one case of this interaction has been reported, the *in vitro* studies suggest that it would be prudent to monitor the theophylline levels of any patient given ipriflavone, making any dose reductions as necessary. Aminophylline does not appear to have been studied, but as it is metabolised to theophylline, a similar interaction seems likely.

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Theophylline + Leukotriene antagonists

Montelukast does not appear to alter theophylline levels. A single published case report describes a rapid rise in theophylline levels in a patient given zafirlukast. Zafirlukast levels are modestly reduced by theophylline, but this does not appear to be clinically important.

Clinical evidence

(a) Montelukast

In a study of 16 healthy subjects, the pharmacokinetics of a single intravenous dose of theophylline were not significantly changed by montelukast 10 mg daily for 10 days. However, when the subjects were given montelukast 200 mg and 600 mg daily, the AUC of theophylline was reduced by 43% and 66%, respectively. These doses are 20- and 60-fold higher than the usual 10 mg daily dose,[1] and therefore the clinical relevance of these effects is unclear.

(b) Zafirlukast

In a study in 13 patients with asthma, when zafirlukast 80 mg daily was given with a single 6-mg/kg dose of theophylline, the mean serum levels of zafirlukast were reduced by 30%, but the serum theophylline levels remained unchanged.[2] In another study in 16 healthy children, zafirlukast 20 mg daily did not affect the pharmacokinetics of a single 6-mg/kg dose of theophylline.[2] In contrast, an isolated report describes a 15-year-old girl with asthma taking sustained-release theophylline 300 mg twice daily (as well as inhaled fluticasone, salbutamol (albuterol) and salmeterol, and oral prednisolone) who became nauseous shortly after zafirlukast (dose not stated) was started. An increase in her theophylline level from 11 mg/L to 24 mg/L was noted. The theophylline was stopped, and later attempts to reintroduce theophylline at lower doses resulted in the same dramatic increases in serum theophylline levels.[3] The manufacturer of zafirlukast has received a limited number of reports of patients experiencing increased theophylline levels with or without clinical signs or symptoms of theophylline toxicity after the addition of zafirlukast. No further details are available.[4]

Mechanism

Not understood.

Importance and management

Information about the interaction between theophylline and montelukast seems to be limited. The study above indicates that when using normal clinical doses of montelukast no special precautions or dose alterations are needed. Similarly, no adverse interaction would normally seem to occur with zafirlukast and theophylline; the published case involving zafirlukast is of doubtful general significance, and as further details of the reports made to the company are unavailable, their clinical significance cannot be assessed.

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2. Accolate (Zafirlukast). AstraZeneca Pharmaceuticals LP. US Prescribing Information, August 2009.
3. Katial RK, Stelzle RC, Bonner MW, Marino M, Cantilena LR, Smith LJ. A drug interaction between zafirlukast and theophylline. *Arch Intern Med* (1998) 158, 1713–5.
4. AstraZeneca UK. Personal communication, March 2009.

Theophylline + Loperamide

Loperamide delays the absorption of theophylline from a sustained-release preparation.

Clinical evidence, mechanism, importance and management

A study of the effects of altering the transit time of drugs through the small intestine found that when 12 healthy subjects were given high-dose loperamide (8 mg every 6 hours for a total of 8 doses), the rate, but not extent, of absorption of a single 600-mg dose of sustained-release theophylline (*Theo-24*) was decreased. The maximum serum theophylline levels were reduced from 4.6 mg/L to 3.2 mg/L, and this peak level occurred at 20 hours instead of 11 hours. One suggested reason for these effects is that loperamide inhibits the movement of the gut, thereby decreasing the dissolution rate of the *Theo-24* pellets.[1] More study is needed to establish the clinical significance of the interaction in patients receiving long-term theophylline, and to establish if aminophylline is similarly affected.

1. Bryson JC, Dukes GE, Kirby MG, Heizer WD, Powell JR. Effect of altering small bowel transit time on sustained release theophylline absorption. *J Clin Pharmacol* (1989) 29, 733–8.

Theophylline + Macrolides

Troleandomycin can increase serum theophylline levels, causing toxicity. Azithromycin, clarithromycin, dirithromycin, josamycin, midecamycin, rokitamycin, spiramycin, and telithromycin normally only cause modest changes in theophylline levels or do not interact at all. There are unexplained and isolated case reports of theophylline toxicity with josamycin and clarithromycin. Roxithromycin usually has no relevant interaction but an increase in theophylline levels was seen in one study. See also 'Theophylline + Macrolides; Erythromycin', p.1446.

Clinical evidence

(a) Azithromycin

In an analysis of the safety data from clinical studies of azithromycin, there was no evidence that the plasma levels of theophylline were affected in patients given both drugs.[1] Similarly, no adverse effects were reported in another clinical study of patients taking azithromycin and theophylline.[2] Azithromycin 250 mg twice daily did not affect the clearance or serum levels of theophylline in patients with asthma.[3] However, a 68-year-old man had a marked but transient fall in his serum theophylline level when azithromycin was withdrawn, and this was confirmed on rechallenge.[4] The same authors conducted a study in 4 healthy subjects given azithromycin 500 mg on day one then 250 mg daily for 4 days and sustained-release theophylline 200 mg twice daily. Theophylline levels were slightly elevated during the use of azithromycin, and a transient drop occurred 5 days after azithromycin was stopped.[5]

(b) Clarithromycin

In 10 elderly patients with COPD, clarithromycin 250 mg twice daily for 7 days had no effect on the steady-state serum theophylline levels.[6] Similarly, two other studies found that clarithromycin had little or no effect on theophylline pharmacokinetics.[3,7] Another study in healthy subjects given clarithromycin 500 mg twice daily for 4 days found a 17% increase in the AUC and an 18% increase in the maximum plasma levels of theophylline, but this was considered clinically unimportant.[8] In two clinical studies in patients with an acute bacterial exacerbation of chronic bronchitis the number of patients requiring an adjustment in theophylline dose was similar when those who took clarithromycin were compared with those who took ampicillin.[9,10] However, there are isolated reports of possible theophylline toxicity in patients taking clarithromycin, including a case that resulted in rhabdomyolysis with renal failure requiring haemodialysis.[11,12] For a report of theophylline toxicity in a patient also taking clarithromycin and levofloxacin, see 'Theophylline + Quinolones', p.1452.

(c) Dirithromycin

In one study, 13 healthy subjects had a fall in their steady-state trough theophylline level of 18%, and a fall in their peak serum level of 26% while taking dirithromycin 500 mg daily for 10 days, although this was not considered clinically relevant.[13] No significant changes in theophylline pharmacokinetics were seen in 14 patients with COPD who were given dirithromycin 500 mg daily for 10 days.[14] This is supported by a similar single-dose study in 12 healthy subjects.[15]

(d) Josamycin

No clinically significant changes in serum theophylline levels were seen in 5 studies in patients (both adults and children)[16-18] or healthy subjects[19] given josamycin, but a modest rise in theophylline levels was described in one study in children.[20] Another study reported a 23% reduction in the levels of theophylline (given as intravenous aminophylline) in 5 patients with particularly severe respiratory impairment, but no significant effect was found in 5 other patients with less severe disease.[21] However, an isolated report describes theophylline toxicity in a 80-year-old man who was given josamycin.[22]

(e) Midecamycin/Midecamycin diacetate

In one study, 18 children with asthma had a slight decrease in serum theophylline levels when they were given midecamycin 40 mg/kg daily for 10 days for a bronchopulmonary infection, but no changes were seen in 5 healthy adult subjects.[23]

Similarly, no significant changes in serum theophylline levels were seen in 20 patients taking slow-release theophylline (*Theo-dur*) 300 mg twice daily, or intravenous theophylline 4 mg/kg three times daily, when they were given midecamycin diacetate (miocamycin; ponsinomycin) 1.2 g daily for 10 days.[24] A number of other studies confirm the absence of a clinically important interaction between oral or intravenous theophylline or intravenous aminophylline and midecamycin diacetate in children and adults.[25-28]

(f) Rokitamycin

Two studies, in 12 adults with COPD and 11 elderly patients taking theophylline, found no significant changes in serum theophylline levels when they were given rokitamycin 600 to 800 mg daily for a week.[29,30]

(g) Roxithromycin

One study in 12 healthy subjects and another in 16 patients with COPD found only minor increases in steady-state theophylline levels, which were not considered clinically relevant, when they were given roxithromycin 150 mg twice daily.[31,32] Another study in 5 healthy subjects similarly found that roxithromycin 300 mg twice daily did not affect the pharmacokinetics of theophylline.[33] However, further study in 14 patients with asthma reported an increase in serum theophylline levels who were given roxithromycin 150 mg twice daily, but as the rise was not quantified it is difficult to assess the clinical relevance of this finding.[3]

(h) Spiramycin

A study in 15 patients with asthma taking theophylline found that spiramycin 1 g twice daily for at least 5 days had no significant effect on their steady-state serum theophylline levels.[34]

(i) Telithromycin

A study in 24 healthy subjects given theophylline found that telithromycin 800 mg daily for 4 days did not have a clinically relevant effect on theophylline exposure.[35]

(j) Troleandomycin

A series of 8 patients with severe chronic asthma found that troleandomycin 250 mg four times daily caused an average reduction in the clearance of theophylline (given as intravenous aminophylline) of 50%. One patient had a theophylline-induced seizure after 10 days, with a serum theophylline level of 43 mg/mL (reference range 10 to 20 mg/L). The theophylline half-life in this patient had increased from 4.6 hours to 11.3 hours.[36] Other studies in healthy subjects[23,37] and patients[18] given oral theophylline with troleandomycin have also found reductions in theophylline clearance and marked rises in serum theophylline levels and half-life, even at low troleandomycin doses.[38]

Mechanism

It is believed that troleandomycin forms inactive cytochrome P450-metabolite complexes within the liver, the effect of which is to reduce the metabolism (*N*-demethylation and 8-hydroxylation)[37] of theophylline (which are mediated by the cytochrome P450 isoenzyme CYP1A2), thereby reducing its clearance and increasing its levels. Clarithromycin, josamycin, midecamycin, and roxithromycin are thought to rarely form these complexes, and azithromycin, dirithromycin, rokitamycin and spiramycin are not thought to inactivate cytochrome P450.[39]

Importance and management

The interaction between theophylline and troleandomycin is established and well documented. If troleandomycin is given, monitor the levels of theophylline closely and adjust the dose as necessary. Reductions of 25 to 50% may be needed.[38,40] The situation with roxithromycin is uncertain since only one of four studies suggested an interaction, but it would be prudent to be alert for the need to reduce the theophylline dose. Alternative macrolides that usually interact only moderately, or not at all are azithromycin, clarithromycin, dirithromycin, josamycin, midecamycin, rokitamycin and spiramycin. Telithromycin may also be a suitable alternative. However, even with these macrolides it would still be prudent to monitor the outcome because a few patients, especially those with theophylline levels at the high end of the range, may need some small theophylline dose adjustments. In the case of azithromycin, care should be taken in adjusting the dose based on theophylline levels taken after about 5 days of concurrent use, as they may only be a reflection of a transient decrease. In addition, acute infection *per se* may alter theophylline pharmacokinetics.[41]

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3. Rhee YK, Lee HB, Lee YC. Effects of erythromycin and new macrolides on the serum theophylline level and clearance. *Allergy* (1998) 53 (Suppl 43), 142.
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Theophylline + Macrolides; Erythromycin

Theophylline levels can be increased by erythromycin. Toxicity may develop in some patients. The onset may be delayed for several days, and not all patients demonstrate this interaction. Erythromycin levels may be modestly reduced by theophylline.

Clinical evidence

(a) Effect on theophylline

The peak serum theophylline levels of 12 patients with COPD given aminophylline 4 mg/kg orally every 6 hours were raised by 28% by erythromycin stearate 500 mg every 6 hours for 2 days. The clearance was reduced by 22%. Only one patient developed clinical signs of toxicity, although the authors suggest this may be because the other patients had low theophylline levels (11 mg/L) to start with and they may not have been studied for long enough to detect the full effect of the erythromycin.[1] Several single-dose studies in healthy subjects or adults with asthma given aminophylline or theophylline have demonstrated this interaction[2-6] and multiple-dose studies with aminophylline have also shown that erythromycin alters theophylline pharmacokinetics.[7,8] A multiple-dose study in children with asthma found a 40% rise in the levels of theophylline (given as intravenous aminophylline).[9] There was often wide inter-subject variability, and not all patients demonstrated the interaction.[1,4,6-9] In addition to the studies, there are several case reports where erythromycin was thought to have caused previously therapeutic theophylline levels to rise to toxic levels. In 3 cases the level rose twofold, with accompanying symptoms of toxicity,[10-12] and in one case the patient developed a fatal cardiac arrhythmia.[13] Toxic theophylline levels of 41 mg/L have also been reported in one patient 3 days after a 6-day course of erythromycin was finished, although this patient did not have any clinical signs or symptoms or theophylline toxicity.[14]

Several studies in both healthy adults,[15-18] and adults with COPD[5,19] did not demonstrate any clinically significant interaction, although two of

these studies did find a reduction in the clearance of theophylline in some subjects.[15,19]

(b) Effect on erythromycin

The peak serum levels of erythromycin 500 mg every 8 hours were almost halved and the AUC_{0-8} was reduced by 38% when 6 healthy subjects were given a single 250-mg intravenous dose of theophylline.[6] Another pharmacokinetic study found that serum erythromycin levels fell by more than 30% when intravenous theophylline was given with oral erythromycin.[8] Other studies using intravenous erythromycin found no significant pharmacokinetic changes. The renal clearance was increased, but this did not affect the overall clearance.[18,20]

Mechanism

The mechanism for the effects of erythromycin on theophylline levels is not fully understood. It seems most likely that erythromycin inhibits the metabolism of theophylline by the liver resulting in a reduction in its clearance and a rise in its serum levels. The human organic anion transporter (OAT) 2 in the liver may also be involved in this interaction.[21] The reduction in erythromycin levels may be caused by theophylline affecting the absorption of oral erythromycin.[18]

Importance and management

The effects of erythromycin on theophylline and aminophylline are established (but still debated) and well documented. Not all the reports are referenced here. It does not seem to matter which erythromycin salt is used. Monitor theophylline levels and anticipate the need to reduce the aminophylline or theophylline dose to avoid toxicity. Not all patients will develop this interaction but remember it may take several days (most commonly 2 to 7 days) to manifest itself. Some patients may have a high theophylline level but no clinical signs or symptoms, therefore do not rely on symptoms alone to monitor for toxicity.[14] Limited evidence suggests that levels may return to normal 2 to 7 days after stopping erythromycin.[10-12,14] There are many factors, such as smoking,[3,19] which also affect theophylline pharmacokinetics, and which may play a role in altering the significance of the interaction in different patients. Those particularly at risk are patients with already high serum theophylline levels and/or taking high doses (20 mg/kg or more). Ideally, use a non-interacting antibacterial if possible. However, where concurrent treatment cannot be avoided, a 25% reduction in theophylline dose has been recommended for patients with levels in the 15 to 20 mg/L range,[1,2,22] but little dose adjustment is probably needed for those at the lower end of the range, (below 15 mg/L) unless toxic symptoms appear.[1,4] In practice erythromycin can probably be safely started with theophylline, with the levels monitored after 48 hours and appropriate dose adjustments then made.

The fall in erythromycin levels caused by theophylline is not well documented, but what is known suggests that it may be clinically important. Be alert for any evidence of an inadequate response to the erythromycin and increase the dose or change the antibacterial if necessary. Intravenous erythromycin appears not to be affected.

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Theophylline + Methoxsalen

Oral methoxsalen markedly increases theophylline levels. Topical methoxsalen would not be expected to interact.

Clinical evidence, mechanism, importance and management

In a single-dose study in 3 healthy subjects a 1.2-mg/kg oral dose of methoxsalen increased the AUC of a single 600-mg dose of theophylline (given one hour later) 1.7-fold, 2.1-fold and 2.7-fold, in the 3 subjects, respectively.[1] Methoxsalen probably inhibits the metabolism of theophylline[2] by the cytochrome P450 isoenzyme CYP1A2. Although information is limited, the findings are in line with what is known about caffeine, which is similarly metabolised, and methoxsalen, see 'Caffeine + Psoralens', p.1421. Theophylline (and therefore probably aminophylline) dose reductions are likely to be required during concurrent use with systemic methoxsalen but seem unlikely to be necessary with topical treatment such as PUVA.

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2. Tantcheva-Poór I, Servera-Llaneras M, Scharffetter-Kochanek K, Fuhr U. Liver cytochrome P450 CYP1A2 is markedly inhibited by systemic but not by bath PUVA in dermatological patients. *Br J Dermatol* (2001) 144, 1127–32.

Theophylline + Metoclopramide

Metoclopramide does not appear to interact with slow-release theophylline.

Clinical evidence, mechanism, importance and management

In 8 healthy subjects a single 10-mg dose of metoclopramide taken 20 minutes before a 600-mg dose of slow-release theophylline (*Theo-Dur*), caused a small but insignificant 15% reduction in the bioavailability of theophylline. However, adverse effects (nausea, headache, tremors, CNS stimulation) were seen more often in those taking metoclopramide than in those taking placebo, possibly because metoclopramide caused an earlier rise in theophylline levels, and because some of the adverse effects of these two drugs may be additive.[1] A later study in 12 healthy subjects found that metoclopramide 15 mg every 6 hours had no effect on the rate or extent of absorption of a 600-mg dose of sustained-release theophylline (*Theo-24*).[2] A similar lack of interaction was found in another study using *Theo-Dur*.[3] There would seem to be no reason for avoiding concurrent use.

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Theophylline + Metronidazole

No interaction of clinical importance normally takes place if metronidazole is given to patients taking theophylline, but an isolated

report describes seizures in one patient taking theophylline, metronidazole and ciprofloxacin.

Clinical evidence, mechanism, importance and management

In 5 women taking metronidazole 250 mg three times a day for trichomoniasis there were no significant changes in the pharmacokinetics of theophylline, given as a single intravenous dose of aminophylline.[1] Another study in 10 healthy subjects confirmed this finding.[2] However, an acutely ill elderly woman taking theophylline had a generalised seizure while taking metronidazole and ciprofloxacin, despite her theophylline level being within the therapeutic range (10 to 20 mg/L).[3] Both ciprofloxacin and, more rarely, metronidazole are associated with seizures.[3] Although the evidence is limited, no special precautions would seem to be necessary during concurrent use.

1. Reitberg DP, Klarnet JP, Carlson JK, Schentag JJ. Effect of metronidazole on theophylline pharmacokinetics. *Clin Pharm* (1983) 2, 441–4.
2. Adebayo GI, Mabadeje AFB. Lack of inhibitory effect of metronidazole on theophylline disposition in healthy subjects. *Br J Clin Pharmacol* (1987) 24, 110–13.
3. Semel JD, Allen N. Seizures in patients simultaneously receiving theophylline and imipenem or ciprofloxacin or metronidazole. *South Med J* (1991) 84, 465–8.

Theophylline + Mexiletine or Tocainide

Theophylline levels are increased by mexiletine and toxicity may occur. Tocainide has only a small and probably clinically unimportant effect on theophylline pharmacokinetics.

Clinical evidence

(a) Mexiletine

A man developed theophylline toxicity within a few days of starting to take mexiletine 200 mg three times daily. His serum theophylline level rose from 15.3 mg/L to 25 mg/L, but fell to 14.2 mg/L, and the symptoms of toxicity resolved, when the theophylline dose was reduced by two-thirds.[1]

Other case reports describe 1.5- to threefold increases in theophylline serum levels (accompanied by clear signs of toxicity in some instances) in a total of 10 patients who were given mexiletine.[2-7] Theophylline dose reductions of 50% were required in 3 cases,[2,6] although 2 of the patients that did not require dose reductions had initial theophylline levels below the therapeutic range.[3] In another report, the arrhythmia of one patient was aggravated even at therapeutic serum theophylline levels, and mexiletine was discontinued.[4]

In 15 healthy subjects, mexiletine 200 mg three times daily for 5 days reduced the clearance of a single 5-mg/kg intravenous dose of theophylline by 46% in women and 40% in men. The theophylline half-life was prolonged by 96% (from 7.4 to 14.5 hours) in women and 71% (from 8.7 to 14.9 hours) in men.[8] Two further studies in healthy subjects given theophylline with mexiletine for 5 days found a reduction in steady-state theophylline clearance of about 45%, and an increase in the AUC of about 60%.[9,10]

(b) Tocainide

After taking tocainide 400 mg every 8 hours for 5 days, the pharmacokinetics of a single 5-mg/kg intravenous dose of theophylline was measured in 8 healthy subjects. The clearance was decreased by about 10% and the half-life slightly prolonged (from 9.7 to 10.4 hours), but these changes were not thought to be large enough to warrant altering theophylline doses.[11]

Mechanism

Mexiletine inhibits the metabolism (demethylation) of theophylline by the liver, thereby increasing its effects.[8,10,12] It is possible that the interaction is due to competitive inhibition of the cytochrome P450 isoenzyme CYP1A2.[13]

Importance and management

The interaction between theophylline and mexiletine is established and of clinical importance. Monitor concurrent use and reduce the theophylline dose as necessary to prevent the development of theophylline toxicity. It has been suggested that 50% dose reductions may be necessary.[8] It seems doubtful if the interaction between theophylline and tocainide is clinically important.

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2. Stanley R, Comer T, Taylor JL, Saliba D. Mexiletine-theophylline interaction. *Am J Med* (1989) 86, 733–4.
3. Ueno K, Miyai K, Seki T, Kawaguchi Y. Interaction between theophylline and mexiletine. *DICP Ann Pharmacother* (1990) 24, 471–2.
4. Kessler KM, Interian A, Cox M, Topaz O, De Marchena EJ, Myerburg RJ. Proarrhythmia related to a kinetic and dynamic interaction of mexiletine and theophylline. *Am Heart J* (1989) 117, 964–6.292
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Theophylline + Moracizine

Moracizine modestly increases theophylline clearance.

Clinical evidence

Single oral doses of aminophylline and a sustained-release theophylline preparation (*TheoDur*) were given to 12 healthy subjects. After they took moracizine 250 mg three times daily for 2 weeks, the AUC of theophylline and aminophylline were reduced by 32% and 36%, respectively, the clearance was increased by 44% and 66%, respectively, and the elimination half-life was decreased by 33% and 20%, respectively.[1]

Mechanism

Uncertain. Moracizine is an enzyme inducer and appears to increase the metabolism of theophylline.[1] In contrast, *in vitro* and *animal* data show moracizine to be an inhibitor of the cytochrome P450 isoenzyme CYP1A2, which is the main isoenzyme involved in the metabolism of theophylline.[2] This would, in theory, be expected to lead to raised theophylline levels, but as these studies illustrate, *in vitro* findings do not always translate in to clinically relevant effects.

Importance and management

Information seems to be limited to this study. The clinical importance of this interaction has not been assessed, but monitor the effects of concurrent use and be alert for the need to adjust the theophylline dose.

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Theophylline + Nefazodone

Nefazodone does not appear to interact adversely with theophylline.

Clinical evidence, mechanism, importance and management

Nefazodone 200 mg twice daily for 7 days had no effect on the pharmacokinetics or pharmacodynamics of theophylline 600 mg to 1.2 g daily in patients with chronic obstructive airways disease, nor was there any effect

on their FEV_1 values.[1] No special theophylline dose adjustment would seem necessary if both drugs are used. There appears to be no data for aminophylline, but a similar lack of interaction would be expected.

1. Dockens RC, Rapoport D, Roberts D, Greene DS, Barbhaiya RH. Lack of an effect of nefazodone on the pharmacokinetics and pharmacodynamics of theophylline during concurrent administration in patients with chronic obstructive airways disease. *Br J Clin Pharmacol* (1995) 40, 598–601.

Theophylline + Non-prescription theophylline products

Patients taking theophylline should not take other medications containing theophylline (some of which are non-prescription products) unless the total dose of theophylline can be adjusted appropriately.

Clinical evidence, mechanism, importance and management

A patient taking theophylline developed elevated serum theophylline levels of 35.7 micrograms/mL while taking *Quinamm* for leg cramps (a formulation containing quinine 260 mg and aminophylline 195 mg).[1] Another case report describes a patient taking theophylline, who increased her intake of *Franol plus*, which contained theophylline and ephedrine. Theophylline levels measured on admission to hospital were 64 mg/L.[2] These case reports highlight the need to avoid the inadvertent intake of additional doses of theophylline if toxicity is to be avoided. Note that non-prescription preparations containing theophylline are available in many countries. For example, some cough and cold preparations in the UK contain theophylline (e.g. *Do-Do Chesteze*). Patients should be warned.

1. Shane R. Potential toxicity of theophylline in combination with *Quinamm*. *Am J Hosp Pharm* (1982) 39, 40.
2. Thompson PJ, Hay JG. Dangers of compound drugs and intravenous aminophylline. *Lancet* (1982) 2, 1228.

Theophylline + Olanzapine

There appears to be no clinically significant pharmacokinetic interaction between theophylline and olanzapine.

Clinical evidence, mechanism, importance and management

A study in 18 healthy subjects given olanzapine 5 mg on day one, 7.5 mg on day 2 and then 10 mg daily for 7 days found no significant changes in the pharmacokinetics of theophylline (given as a single 350-mg intravenous dose of aminophylline). The pharmacokinetics of olanzapine also appeared to be unchanged when both drugs were given.[1] No special precautions would appear to be necessary on concurrent use.

1. Macias WL, Bergstrom RF, Cerimele BJ, Kassahun K, Tatum DE, Callaghan JT. Lack of effect of olanzapine on the pharmacokinetics of a single aminophylline dose in healthy men. *Pharmacotherapy* (1998) 18, 1237–48.

Theophylline + Ozagrel

Ozagrel does not appear to alter theophylline pharmacokinetics.

Clinical evidence, mechanism, importance and management

Ozagrel 200 mg twice daily was given to 4 patients with asthma taking sustained-release theophylline. After 24 weeks the ozagrel was stopped without any significant effect on the pharmacokinetics of theophylline. Similarly, in another 8 patients with bronchial asthma, there were no significant differences in the pharmacokinetics of theophylline (given as a single infusion of aminophylline) before and after taking ozagrel 200 mg twice daily for 7 days.[1] No special precautions would seem to be needed during concurrent use.

1. Kawakatsu K, Kino T, Yasuba H, Kawaguchi H, Tsubata R, Satake N, Oshima S. Effect of ozagrel (OKY-046), a thromboxane synthetase inhibitor, on theophylline pharmacokinetics in asthmatic patients. *Int J Clin Pharmacol Ther Toxicol* (1990) 28, 158–63.

Theophylline + Penicillins

Ampicillin, with or without sulbactam, and amoxicillin do not alter the pharmacokinetics of theophylline.

Clinical evidence, mechanism, importance and management

A retrospective study in asthmatic children aged 3 months to 6 years found that the mean half-life of theophylline did not differ between those children given ampicillin and those not given ampicillin.[1] The pharmacokinetics of theophylline 8.5 mg/kg daily were not altered in 12 adult patients with COPD when they were given ampicillin 1 g plus sulbactam 500 mg every 12 hours for 7 days.[2] A study in 9 healthy adult subjects found that amoxicillin 750 mg daily for 9 days did not affect the pharmacokinetics of theophylline 540 mg twice daily.[3,4]

No special precautions would seem to be necessary during concurrent use of these antibacterials and theophylline (and therefore probably aminophylline). However, note that acute infections *per se* can alter theophylline pharmacokinetics.[5]

1. Kadlec GJ, Ha LT, Jarboe CH, Richards D, Karibo JM. Effect of ampicillin on theophylline half-life in infants and young children. *South Med J* (1978) 71, 1584.
2. Cazzola M, Santangelo G, Guidetti E, Mattina R, Caputi M, Girbino G. Influence of sulbactam plus ampicillin on theophylline clearance. *Int J Clin Pharmacol Res* (1991) 11, 11–15.
3. Jonkman JHG, van der Boon WJV, Schoenmaker R, Holtkamp A, Hempenius J. Lack of effect of amoxicillin on theophylline pharmacokinetics. *Br J Clin Pharmacol* (1985) 19, 99–101.
4. Jonkman JHG, van der Boon WJV, Schoenmaker R, Holtkamp AH, Hempenius J. Clinical pharmacokinetics of amoxycillin and theophylline during cotreatment with both medicaments. *Chemotherapy* (1985) 31, 329–35.
5. Renton KW. Cytochrome P450 regulation and drug biotransformation during inflammation and infection. *Curr Drug Metab* (2004) 5, 235–43.

Theophylline + Pentoxifylline

Pentoxifylline can raise theophylline levels.

Clinical evidence, mechanism, importance and management

The mean trough steady-state theophylline serum levels of 9 healthy subjects given sustained-release theophylline (*TheoDur*) 200 or 300 mg twice daily for 7 days were increased by 30% by pentoxifylline 400 mg three times daily. However, the change in levels ranged from a 13% decrease to a 95% increase. The subjects complained of insomnia, nausea, diarrhoea and tachycardia more frequently while taking both drugs, but this did not reach statistical significance.[1] The mechanism of this interaction is not understood, although note, pentoxifylline is also a xanthine derivative, and one manufacturer of aminophylline injection contraindicates its use in patients also receiving pentoxifylline.[2] Patients should be well monitored for theophylline adverse effects (headache, nausea, palpitations) while taking aminophylline or theophylline with pentoxifylline. More study is needed to clarify this highly variable interaction.

1. Ellison MJ, Horner RD, Willis SE, Cummings DM. Influence of pentoxifylline on steady-state theophylline serum concentrations from sustained-release formulations. *Pharmacotherapy* (1990) 10, 383–6.
2. Aminophylline. Hameln Pharmaceuticals Ltd. UK Summary of product characteristics, October 2008.

Theophylline + Phenylpropanolamine

Phenylpropanolamine reduces the clearance of theophylline.

Clinical evidence, mechanism, importance and management

In 8 healthy subjects a single 150-mg oral dose of phenylpropanolamine decreased the clearance of theophylline (given as a single 4-mg/kg intravenous dose of aminophylline one hour after the phenylpropanolamine) by 50%.[1] Such a large reduction in clearance would be expected to result in some increase in serum theophylline levels, but so far no studies of this potentially clinically important interaction seem to have been carried out in patients. Be alert for evidence of toxicity if both drugs are used. More study is needed.

1. Wilson HA, Chin R, Adair NE, Zaloga GP. Phenylpropanolamine significantly reduces the clearance of theophylline. *Am Rev Respir Dis* (1991) 143, A629.

Theophylline + Phenytoin

The serum levels of theophylline can be markedly reduced by phenytoin. Some limited evidence suggests that theophylline may also reduce phenytoin levels.

Clinical evidence

(a) Reduced phenytoin serum levels

A preliminary report noted that the seizure frequency of a woman with epilepsy taking phenytoin 100 mg four times daily increased when she was given intravenous theophylline, and then later oral theophylline. Her serum phenytoin levels had more than halved, from 15.7 mg/L to around 5 to 8 mg/L. An increase in the phenytoin dose to 200 mg three times daily raised her serum phenytoin levels to only 7 to 11 mg/L until the drugs were given one to 2 hours apart. The patient then developed phenytoin toxicity with a serum level of 33 mg/L. A subsequent single-dose study in 4 healthy subjects confirmed that higher serum levels of both drugs were achieved when the theophylline and phenytoin were given 2 hours apart rather than simultaneously.[1] Another study in 7 healthy subjects found that the AUC of a single 400-mg dose of phenytoin was reduced by 21% when it was given at the same time as a single 7.5-mg/kg dose of theophylline, compared with a reduction of 7% when the same doses were given 2 hours apart.[2] A later preliminary study (by some of the same authors) in 14 subjects found that after 2 weeks of concurrent use, the mean serum phenytoin levels of 5 of the subjects rose by 40% and the mean levels of the group as a whole rose by about 27% when the theophylline was stopped. Urinary concentrations of a phenytoin metabolite were raised.[3]

(b) Reduced theophylline serum levels

The observation that a patient taking phenytoin had lower than expected theophylline levels prompted a study in 10 healthy subjects. After taking phenytoin for 10 days the clearance of theophylline (after a single intravenous dose of aminophylline) was increased by 73%, and both its AUC and half-life were reduced by about 50%.[4] Another study in 6 healthy subjects found that after taking phenytoin 300 mg daily for 3 weeks the mean clearance of theophylline (after a single intravenous dose of aminophylline) was increased by 45% (range 31 to 65%).[5] Similar results were found in a further study.[6] Other reports on individual asthmatic patients have shown that phenytoin can increase the clearance of theophylline by between about 30% and 3.5-fold.[7-9] Another study[10] and a case report[11] found that the reduction in theophylline levels caused by phenytoin can be additive with the effects of smoking (consider also 'Theophylline + Tobacco', p.1461). A subsequent study found that the extent of phenytoin-induced metabolism of theophylline was not affected by age, despite an age-related reduction in theophylline metabolism.[12]

Mechanism

Uncertain. It has been suggested that theophylline either impairs phenytoin absorption or induces phenytoin metabolism, but neither suggestion seem likely.

It seems probable that phenytoin, a known enzyme inducer, increases the metabolism of theophylline by the cytochrome P450 isoenzyme CYP1A2 in the liver, thereby increasing its clearance.

Importance and management

The effect of phenytoin on theophylline is established and of clinical importance. Patients given both drugs should be monitored to confirm that theophylline remains effective. Ideally the serum levels should be measured to confirm that they remain within the therapeutic range. Theophylline dose increases of up to 50% or more may be required.[13] Conversely, patients should be monitored for signs of toxicity and theophylline levels should be checked if they stop phenytoin.

The effect of theophylline on phenytoin is not established and the documentation is limited. It may be prudent to monitor phenytoin levels. Separating the doses appears to minimise any interaction. Note that theophylline itself can cause seizures, although mostly in overdose, and should be used with caution in patients with epilepsy.

1. Wada JA, Perry JK, eds. Advances in Epileptology: Phenytoin-theophylline interaction; a case report. New York: Raven Press; 1980 p. 505.
2. Hendeles L, Wyatt R, Weinberger M, Schottelius D, Fincham R. Decreased oral phenytoin absorption following concurrent theophylline administration. *J Allergy Clin Immunol* (1979) 63, 156.
3. Taylor JW, Hendeles L, Weinberger M, Lyon LW, Wyatt R, Riegelman S. The interaction of phenytoin and theophylline. *Drug Intell Clin Pharm* (1980) 14, 638.
4. Marquis J-F, Carruthers SG, Spence JD, Brownstone YS, Toogood JH. Phenytoin-theophylline interaction. *N Engl J Med* (1982) 307, 1189–90.
5. Miller M, Cosgriff J, Kwong T, Morken DA. Influence of phenytoin on theophylline clearance. *Clin Pharmacol Ther* (1984) 35, 666–9.
6. Adebayo GI. Interaction between phenytoin and theophylline in healthy volunteers. *Clin Exp Pharmacol Physiol* (1988) 15, 883–7.
7. Sklar SJ, Wagner JC. Enhanced theophylline clearance secondary to phenytoin therapy. *Drug Intell Clin Pharm* (1985) 19, 34–6.
8. Reed RC, Schwartz HJ. Phenytoin-theophylline-quinidine interaction. *N Engl J Med* (1983) 308, 724–5.
9. Landsberg K, Shalansky S. Interaction between phenytoin and theophylline. *Can J Hosp Pharm* (1988) 41, 31–2.
10. Crowley JJ, Cusack BJ, Jue SG, Koup JR, Vestal RE. Cigarette smoking and theophylline metabolism: effects of phenytoin. *Clin Pharmacol Ther* (1987) 42, 334–40.
11. Nicholson JP, Basile SA, Cury JD. Massive theophylline dosing in a heavy smoker receiving both phenytoin and phenobarbital. *Ann Pharmacother* (1992) 26, 334–6.
12. Crowley JJ, Cusack BJ, Jue SG, Koup JR, Park BK, Vestal RE. Aging and drug interactions. II. Effect of phenytoin and smoking on the oxidation of theophylline and cortisol in healthy men. *J Pharmacol Exp Ther* (1988) 245, 513–23.
13. Slugg PH, Pippenger CE. Theophylline and its interactions. *Cleve Clin Q* (1985) 52, 417–24.

Theophylline + Pirenzepine

Pirenzepine does not appear to alter the pharmacokinetics of theophylline.

Clinical evidence, mechanism, importance and management

In 5 healthy subjects, pirenzepine 50 mg twice daily for 5 days had no effect on the pharmacokinetics of theophylline (given as aminophylline 6.5 mg/kg, intravenously).[1] This would suggest that no special precautions are needed on concurrent use.

1. Sertl K, Rameis H, Meryn S. Pirenzepin does not alter the pharmacokinetics of theophylline. *Int J Clin Pharmacol Ther Toxicol* (1987) 25, 15–17.

Theophylline + Pneumococcal vaccine

Pneumococcal vaccination does not appear to affect the pharmacokinetics of theophylline.

Clinical evidence, mechanism, importance and management

In 6 healthy subjects the pharmacokinetics of oral theophylline 250 mg three times daily for 10 days were unaltered both the day after and one week after they received 0.5 mL of a pneumococcal vaccine.[1] Based on this study, and the fact that pneumococcal vaccination is routinely undertaken in patients with chronic respiratory disease, and no adverse effects appear to have been reported, no special precautions are needed during concurrent use. There appears to be no direct evidence regarding aminophylline, but a similar lack of adverse interaction would be expected.

1. Cupit GC, Self TH, Bekemeyer WB. The effect of pneumococcal vaccine on the disposition of theophylline. *Eur J Clin Pharmacol* (1988) 34, 505–7.

Theophylline or Diprophylline + Probenecid

Theophylline levels are unaffected by probenecid, but diprophylline levels can be raised.

Clinical evidence

(a) Diprophylline

A study in 12 healthy subjects found that the half-life of a single 20-mg/kg oral dose of diprophylline was doubled (from 2.6 to 4.9 hours) and the clearance approximately halved by probenecid 1 g, which resulted in raised serum diprophylline levels.[1]

(b) Theophylline

A study in 7 healthy subjects found that probenecid 1 g given 30 minutes before a 5.6-mg/kg oral dose of aminophylline had no significant effect on the pharmacokinetics of theophylline.[2]

Mechanism

Diprophylline is largely excreted unchanged by the kidneys, and probenecid inhibits its renal tubular secretion.[3] Theophylline is largely cleared from the body by hepatic metabolism, and would therefore not be expected to be affected by probenecid.

Importance and management

Based on the findings of this single-dose study, it would seem to be prudent to monitor serum diprophylline levels if probenecid is started or stopped. No special precautions are needed if aminophylline or theophylline and probenecid are given concurrently.

1. May DC, Jarboe CH. Effect of probenecid on dyphylline elimination. *Clin Pharmacol Ther* (1983) 33, 822–5.
2. Chen TWD, Patton TF. Effect of probenecid on the pharmacokinetics of aminophylline. *Drug Intell Clin Pharm* (1983) 17, 465–6.
3. Nadai M, Apichartpichean R, Hasegawa T, Nabeshima T. Pharmacokinetics and the effect of probenecid on the renal excretion mechanism of diprophylline. *J Pharm Sci* (1992) 81, 1024–7.

Theophylline + Propafenone

Two isolated reports describe raised serum theophylline levels, with symptoms of toxicity, when two patients were given propafenone.

Clinical evidence

In a 71-year-old man, propafenone 150 mg daily raised the levels of sustained-release theophylline 300 mg twice daily from a range of 10.2 to 12.8 mg/L, up to 19 mg/L, and signs of theophylline toxicity developed. The day after propafenone was withdrawn the level fell to 10.8 mg/L. When the propafenone was later restarted the theophylline levels rose to 17.7 mg/L within one week, but fell when the theophylline dose was reduced by one-third.[1]

In another report, a 63-year-old man had a marked reduction in the clearance of sustained-release theophylline and a rise in his theophylline levels from 10.8 mg/L to a maximum of 20.3 mg/L over 7 days when he took propafenone 150 mg every 8 hours, increasing to 300 mg every 8 hours.[2] Theophylline was discontinued.

Mechanism

Uncertain. It has been suggested that propafenone may reduce the metabolism of theophylline by the liver, thereby increasing its levels. Note that propafenone is not usually considered an inhibitor of the cytochrome P450 isoenzyme CYP1A2, by which theophylline is mainly metabolised. However, it is also, in part, metabolised by CYP1A2, although competition for metabolism by the same isoenzyme does not usually result in such a large increase in levels as that seen in the cases.

Importance and management

Evidence for an interaction between theophylline and propafenone appears to be limited to these two case reports, which are an insufficient basis for recommending monitoring in all patients. If a patient taking theophylline is given propafenone, it may be prudent to consider an interaction as a possible cause, if theophylline adverse effects (nausea, headache, tremor) develop. Controlled studies are needed to further investigate this potential interaction.

1. Lee BL, Dohrmann ML. Theophylline toxicity after propafenone treatment: evidence for drug interaction. *Clin Pharmacol Ther* (1992) 51, 353–5.
2. Spinler SA, Gammaitoni A, Charland SL, Hurwitz J. Propafenone-theophylline interaction. *Pharmacotherapy* (1993) 13, 68–71.

Theophylline + Propantheline

A study in 6 healthy subjects found that propantheline 30 mg did not affect the rate or extent of absorption of a single 500-mg dose of theophylline (*Theo-Dur*). No special precautions would seem necessary on concurrent use.[1]

1. Sommers DK, Meyer EC, Van Wyk M, Moncrieff J, Snyman JR, Grimbeek RJ. The influence of codeine, propantheline and metoclopramide on small bowel transit and theophylline absorption from a sustained-release formulation. *Br J Clin Pharmacol* (1992) 33, 305–8.

Theophylline + Protease inhibitors

Ritonavir reduces the levels of theophylline. Indinavir appears not to interact with theophylline.

Clinical evidence, mechanism, importance and management

(a) Indinavir

A study in 12 healthy subjects given a single 250-mg oral dose of theophylline before and after indinavir 800 mg three times daily for 5 days found an 18% increase in the AUC of theophylline, which was not considered clinically significant.[1] There have been no further published studies or cases to date to confirm this result, and as indinavir does not inhibit the cytochrome P450 isoenzyme CYP1A2 (see 'Table 21.2', (p.914)), the main isoenzyme that metabolises theophylline, it would seem unlikely that special precautions are necessary during concurrent use.

(b) Ritonavir

In a placebo-controlled study, 27 subjects taking theophylline 3 mg/kg every 8 hours were given ritonavir 300 mg increased to 500 mg twice daily for 10 days. Ritonavir reduced the AUC of theophylline by 43% and reduced its maximum and minimum steady-state levels by 32% and 57%, respectively. The interaction achieved its maximal effect 6 days after starting ritonavir.[2] Ritonavir is an inducer of the cytochrome P450 isoenzyme CYP1A2 by which theophylline is metabolised, and therefore concurrent use leads to an increase in theophylline metabolism, and a reduction in its levels. Information is very limited but the interaction appears to be established. Monitor theophylline levels if ritonavir is started and be alert for the need to increase the theophylline dose. It seems likely that aminophylline, which is metabolised to theophylline, will be similarly affected.

1. Mistry GC, Laurent A, Sterrett AT, Deutsch PJ. Effect of indinavir on the single-dose pharmacokinetics of theophylline in healthy subjects. *J Clin Pharmacol* (1999) 39, 636–42.
2. Hsu A, Granneman GR, Witt G, Cavanaugh JH, Leonard J. Assessment of multiple doses of ritonavir on the pharmacokinetics of theophylline. 11th Int Conf AIDS, Vancouver, 1996. Mo.B.1200.

Theophylline + Proton pump inhibitors

Omeprazole may cause a small increase in theophylline clearance, and lansoprazole may cause a small decrease in theophylline levels. Pantoprazole and rabeprazole do not appear to interact with theophylline.

Clinical evidence

(a) Lansoprazole

Lansoprazole 60 mg daily for 9 days caused only a very slight reduction in the steady-state theophylline levels of 14 healthy subjects.[1] Other studies have also shown little or no change in theophylline pharmacokinetics on the concurrent use of lansoprazole.[2-6]

(b) Omeprazole

The changes in the half-life and clearance of theophylline caused by omeprazole were found to be small and clinically unimportant in two studies,[7,8] and no changes in the steady-state pharmacokinetics of theophylline were found in other studies.[5,9,10] However, one study found that omeprazole produced an 11% increase in the clearance of theophylline in poor metabolisers of omeprazole (i.e. those with low levels of the cytochrome P450 isoenzyme CYP2C19 and therefore higher levels of omeprazole),[11] but this seems unlikely to be clinically significant.

(c) Pantoprazole

A crossover study in 8 healthy subjects found that intravenous pantoprazole 30 mg daily had no clinically important effect on the pharmacokinetics of theophylline given by infusion. No clinically relevant changes in blood pressure, heart rate, ECG and routine clinical laboratory parameters were seen.[12] Other studies have also found no significant change in theophylline pharmacokinetics when pantoprazole was given.[4,5]

(d) Rabeprazole

In a placebo-controlled study in 25 healthy subjects a single 250-mg oral dose of theophylline was given before and after rabeprazole 20 mg daily

for 7 days. No significant changes in the pharmacokinetics of theophylline were seen.[13,14]

Mechanism, importance and management

Lansoprazole possibly induces cytochrome P450 isoenzyme CYP1A2 (the enzyme by which theophylline is metabolised) to a small extent, but this is unlikely to be significant unless an individual is particularly sensitive to this effect.[1] Other proton pump inhibitors are unlikely to interact with theophylline, and so no special precautions would seem necessary on concurrent use. A similar lack of effect would be expected with aminophylline.

1. Granneman GR, Karol MD, Locke CS, Cavanaugh JH. Pharmacokinetic interaction between lansoprazole and theophylline. *Ther Drug Monit* (1995) 17, 460–4.
2. Kokufu T, Ihara N, Sugioka N, Koyama H, Ohta T, Mori S, Nakajima K. Effects of lansoprazole on pharmacokinetics and metabolism of theophylline. *Eur J Clin Pharmacol* (1995) 48, 391–5.
3. Ko J-W, Jang I-J, Shin S-G, Flockhart DA. Effect of lansoprazole on theophylline clearance in extensive and poor metabolizers of cytochrome P450 2C19. *Clin Pharmacol Ther* (1998) 63, 217.
4. Pan WJ, Goldwater DR, Zhang Y, Pilmer BL, Hunt RH. Lack of a pharmacokinetic interaction between lansoprazole or pantoprazole and theophylline. *Aliment Pharmacol Ther* (2000) 14, 345–52.
5. Dilger K, Zheng Z, Klotz U. Lack of drug interaction between omeprazole, lansoprazole, pantoprazole and theophylline. *Br J Clin Pharmacol* (1999) 48, 438–44.
6. Ko J-W, Jang I-J, Shin J-G, Nam S-K, Shin S-G, Flockhart DA. Theophylline pharmacokinetics are not altered by lansoprazole in CYP2C19 poor metabolizers. *Clin Pharmacol Ther* (1999) 65, 606–14.
7. Oosterhuis B, Jonkman JHG, Andersson T, Zuiderwijk PBM. No influence of single intravenous doses of omeprazole on theophylline elimination kinetics. *J Clin Pharmacol* (1992) 32, 470–5.
8. Sommers De K, van Wyk M, Snyman JR, Moncrieff J. The effects of omeprazole-induced hypochlorhydria on absorption of theophylline from a sustained-release formulation. *Eur J Clin Pharmacol* (1992) 43, 141–3.
9. Taburet AM, Geneve J, Bocquentin M, Simoneau G, Caulin C, Singlas E. Theophylline steady state pharmacokinetics is not altered by omeprazole. *Eur J Clin Pharmacol* (1992) 42, 343–5.
10. Pilotto A, Franceschi M, Lagni M, Fabrello R, Fortunato A, Meggiato T, Soffiati G, Oliani G, Di Mario F. The effect of omeprazole on serum concentrations of theophylline, pepsinogens A and C, and gastrin in elderly duodenal ulcer patients. *Am J Ther* (1995) 2, 43–6.
11. Cavuto NJ, Sukhova N, Hewett J, Balian JD, Woosley RL, Flockhart MD. Effect of omeprazole on theophylline clearance in poor metabolizers of omeprazole. *Clin Pharmacol Ther* (1995) 57, 215.
12. Schulz H-U, Hartmann M, Steinijans VW, Huber R, Lührmann B, Bliessath H, Wurst W. Lack of influence of pantoprazole on the disposition kinetics of theophylline in man. *Int J Clin Pharmacol Ther Toxicol* (1991) 29, 369–75.
13. Humphries TJ, Nardi RV, Spera AC, Lazar JD, Laurent AL, Spanyers SA. Coadministration of rabeprazole sodium (E3810) does not effect the pharmacokinetics of anhydrous theophylline or warfarin. *Gastroenterology* (1996) 110 (Suppl), A138.
14. Humphries TJ, Nardi RV, Lazar JD, Spanyers SA. Drug-drug interaction evaluation of rabeprazole sodium: a clean/expected slate? *Gut* (1996) 39 (Suppl 3), A47.

Theophylline + Pyrantel

A single case report describes increased theophylline levels when a child was also given pyrantel.

Clinical evidence

An 8-year-old boy with status asthmaticus was given intravenous aminophylline and then switched to sustained-release oral theophylline on day 3, at which point his serum theophylline level was 15 mg/L. On day 4 he was given a single 160-mg dose of pyrantel (for an *Ascaris lumbricoides* infection) at the same time as his second theophylline dose. About 2.5 hours later his serum theophylline level was 24 mg/L, and a further 1.5 hours later it had risen to 30 mg/L. No further theophylline was given and no symptoms of theophylline toxicity occurred. The patient was discharged later in the day without theophylline.[1]

Mechanism

Not understood. One suggestion is that pyrantel inhibited the liver enzymes concerned with the metabolism of theophylline, thereby increasing its levels. However, this is unlikely as the interaction occurred so rapidly. Another suggestion was that pyrantel may have increased drug release from the sustained-release theophylline preparation.

Importance and management

Information is limited to this single case report. No general conclusions can be based on such slim evidence, but concurrent use should be well monitored because, in this case, the serum theophylline concentration increase was very rapid. More study is needed.

1. Hecht L, Murray WE, Rubenstein S. Theophylline-pyrantel pamoate interaction. *DICP Ann Pharmacother* (1989) 23, 258.

Theophylline + Pyridoxal

There is no evidence of an adverse interaction if pyridoxal (a vitamin B_6 substance) and theophylline are taken concurrently. There may be some reduction in theophylline-induced hand tremor.

Clinical evidence, mechanism, importance and management

In a crossover study, 15 young healthy adults were given theophylline (*Theo-Dur*) for 4 weeks, with the dose adjusted to give plasma levels of 10 mg/L, with a vitamin B_6 supplement containing pyridoxal hydrochloride 15 mg daily, or placebo. A variety of psychomotor and electrophysiological tests and self-report questionnaires failed to distinguish between the effects of the placebo or the vitamin B_6 supplement, except that the hand tremor induced by the theophylline tended to be reduced.[1] In another study by the same research group, 15 healthy subjects (smoking status not indicated) took pyridoxal 15 mg daily for 2 weeks before starting, and when also taking, sustained-release theophylline (*Theo-Dur*), 5 mg/kg daily for one week increased to 8 mg/kg daily for the next 3 weeks, which resulted in theophylline levels of 7.6 to 9.9 [mg/L]. Supplementation with pyridoxal did not prevent theophylline-induced reductions in pyridoxine 5-phosphate levels, as an indicator of vitamin B_6 status, although these did not drop below the normal reference range.[2]

There would seem to be no reason for avoiding concurrent use and it may even have some advantage.

1. Bartel PR, Ubbink JB, Delport R, Lotz BP, Becker PJ. Vitamin B-6 supplementation and theophylline-related effects in humans. *Am J Clin Nutr* (1994) 60, 93–9.
2. Delport R, Ubbink JB, Vermaak WJH, Becker PJ. Theophylline increases pyridoxal kinase activity independently from vitamin B6 nutritional status. *Res Commun Chem Pathol Pharmacol* (1993) 79, 325–33.

Theophylline + Quinolones

Theophylline levels can be markedly increased in most patients by enoxacin. Pipemidic acid and clinafloxacin probably interact similarly. Theophylline levels can also be markedly increased in some patients by ciprofloxacin, and possibly pefloxacin. Norfloxacin, ofloxacin, pazufloxacin, or prulifloxacin normally cause a much smaller rise in theophylline levels. However, serious toxicity has been seen in few patients given norfloxacin. Fleroxacin, flumequine, gatifloxacin, gemifloxacin, levofloxacin, lomefloxacin, moxifloxacin, nalidixic acid, rufloxacin, sparfloxacin and trovafloxacin appear not to interact with theophylline.

Clinical evidence

A. Pharmacokinetic studies

The effects of the quinolones on the pharmacokinetics of theophylline in clinical studies in healthy subjects or patients are listed in 'Table 34.4', (p.1453).

B. Case reports

(a) Ciprofloxacin

There are numerous cases that describe the interaction between ciprofloxacin and theophylline or aminophylline, which commonly report large increases in serum theophylline levels (of 32 to 478%), often associated with toxicity.[1-11] From 1987 to 1988, the CSM in the UK had received 8 reports of clinically important adverse interactions between these two drugs, with one fatal case.[1] By 1991, the FDA in the US had received 39 reports of the interaction, with three deaths.[9]

An elderly woman taking theophylline developed toxic serum levels and died shortly after starting to take ciprofloxacin.[7] Seizures, associated with toxic levels of theophylline, were described in a number of the case reports.[5,9-12] Seizures have also occurred when ciprofloxacin was used with theophylline or aminophylline, even when theophylline levels were within the therapeutic range (10 to 20 mg/L).[9,13,14] Ciprofloxacin and toxic levels of theophylline are both known to cause seizures independently. It was suggested that, in the case of seizures, there may be a pharmacodynamic interaction between theophylline and the fluoroquinolones as well as a pharmacokinetic interaction.[9] In each case seizures began within 1 to 7 days of starting the combination and were reported as being either partial

Table 34.4 Effect of quinolones on theophylline pharmacokinetics

Quinolone (daily dose)	*Increase in theophylline level*	*Increase in AUC*	*Decrease in clearance*	*Refs*
Ciprofloxacin 600 to 1500 mg	17 to 113%	22 to 52%	18 to 55%	1–12
Clinafloxacin 400 to 800 mg			46 to 69%	13
Enoxacin 600 to 1200 mg	43 to 243%	84 to 248%	42 to 74%	1, 2, 10, 14–21
Fleroxacin 400 mg	No significant change	up to 8%	up to 6%	22–25
Flumequine 1200 mg	No significant change	No significant change	No significant change	26
Gatifloxacin 400 mg	No significant change	No significant change	No significant change	27, 28
Gemifloxacin 400 to 600 mg	No significant change	No significant change		29
Levofloxacin 300 to 1000 mg	No significant change	No significant change	No significant change	30–32
Lomefloxacin 400 to 800 mg	No significant change	No significant change	No significant change	5, 33–37
Moxifloxacin 200 mg to 400 mg	No significant change	No significant change	No significant change	38
Nalidixic acid 400 to 600 mg		No significant change	No significant change	1, 6, 12
Norfloxacin 600 to 800 mg	up to 22%	up to 17%	up to 15%	6, 18, 39–42
Ofloxacin 400 to 600 mg	up to 10%	up to 10%	up to 12%	1, 2, 18, 41, 43–45
Pazufloxacin 500 mg	up to 27%	up to 33%	25%	46
Pefloxacin 400 to 800 mg	17 to 93%	19 to 53%	29%	1, 2, 10
Pipemidic acid 800 to 1500 mg	71%	76 to 79%	49%	2, 33
Prulifloxacin 600 mg		16%	15%	47
Rufloxacin 200 to 400 mg	No significant change	No significant change	No significant change	48, 49
Sparfloxacin 200 to 400 mg	No significant change	No significant change	No significant change	50–53
Trovafloxacin 200 to 300 mg		up to 8%		54, 55

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Table 34.4 Effect of quinolones on theophylline pharmacokinetics (continued)

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Table 34.4 Effect of quinolones on theophylline pharmacokinetics (continued)

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or grand mal. The addition of clarithromycin does not appear to increase the effects of ciprofloxacin on theophylline.[15] One report notes that of 20 patients receiving ciprofloxacin 500 mg twice daily and theophylline none complained of any unwanted drug effects. Of the 12 patients who received ciprofloxacin 750 mg twice daily, one patient experienced hallucinations, but theophylline plasma levels were not elevated, and 5 other patients had no rise in theophylline levels, nor were there any reports of unwanted drug effects. Details of the remaining 6 patients were not given.[16]

(b) Clinafloxacin

The apparently stable serum theophylline levels of a 78-year-old man with steroid-dependent COPD were approximately doubled after he received intravenous clinafloxacin 200 mg every 12 hours for 5 days. Two theophylline doses were withheld, and then the dose was reduced from 300 mg every 8 hours to 200 mg every 8 hours. Within another 5 days his serum theophylline levels had returned to his previous steady-state level.[17]

(c) Enoxacin

Some patients in early studies of enoxacin experienced adverse effects (serious nausea and vomiting, tachycardia, seizures)[18,19] and this was found to be associated with unexpectedly high plasma theophylline levels.[18,20]

(d) Levofloxacin

Levofloxacin has not significantly altered the pharmacokinetics of theophylline in studies, see 'Table 34.4', (p.1453). However, a 59-year-old man developed theophylline toxicity 7 days and 5 days after starting clarithromycin and levofloxacin, respectively. His theophylline clearance decreased by about 40% when compared with the value before starting these drugs and so the theophylline dose was reduced. After stopping levofloxacin, the theophylline level fell, and the theophylline clearance returned to its initial value. Clarithromycin was continued.[21]

(e) Norfloxacin

No clinically significant changes in theophylline levels occurred in a patient given norfloxacin who subsequently had marked changes when given ciprofloxacin.[3] This report and the studies in 'Table 34.4', (p.1453) contrast with the records of the FDA in the US, which describe 3 patients (up to 1989)[22] and 9 patients (up to 1991)[9] who experienced marked increases in theophylline levels ranging from 64 to 171% (mean 103%) when they were given norfloxacin. Three patients developed seizures, and one died.[9]

(f) Pefloxacin

An isolated report describes convulsions in a patient, which were attributed to the use of theophylline with pefloxacin.[23] A brief report notes that 43 patients who were given pefloxacin 400 mg twice daily and theophylline did not report any unwanted drug effects.[16]

Mechanism

The interacting quinolones appear to inhibit the metabolism (*N*-demethylation) of theophylline to different extents (some hardly at all), so that it is cleared from the body more slowly and its serum levels rise. The quinolones are known to inhibit the cytochrome P450 isoenzyme CYP1A2 by which theophylline is metabolised. There is some evidence that combined use of theophylline and quinolones may amplify the epileptogenic activity of the quinolones.[9,24]

Importance and management

The interactions of enoxacin and ciprofloxacin with theophylline are well documented, well established and of clinical importance. The effect of enoxacin is marked and occurs in most patients, whereas the incidence with ciprofloxacin is uncertain and problems do not develop in all patients. The risk seems greatest in the elderly[25] and those with theophylline levels already towards the top end of the therapeutic range. Toxicity may develop rapidly (within 2 to 3 days) unless the theophylline dose is reduced.

With **enoxacin**, it has been suggested that the dose of theophylline should be reduced by 50%,[20,26-28] although reductions of 75% may possibly be necessary for those with high theophylline clearances.[28] Alterations in the theophylline dose should be based on careful monitoring of theophylline levels. New steady-state serum theophylline levels are achieved within about 2 to 3 days of starting and stopping enoxacin.[28,29]

Although problems do not develop in all patients taking theophylline and **ciprofloxacin** it would be prudent to be alert for this interaction in any patient. Some recommend an initial reduction in theophylline dose, in the order of 30 to 50% when ciprofloxacin is started.[9,30,31] However, as a proportion of patients will not require a dose reduction, others suggest that the dose should be modified based on the theophylline level on day 2 of ciprofloxacin use.[11,26,32-34]

Direct information about **clinafloxacin** and **pipemidic acid** is more limited, but they also appear to cause a considerable rise in serum theophylline levels and therefore it would seem prudent to anticipate the need for a dose reduction and monitor theophylline levels closely.

Be alert for the adverse effects of theophylline if norfloxacin, ofloxacin, pazufloxacin, or pefloxacin are used because theophylline serum levels may possibly rise to a small extent (10 to 22%), but these antibacterials normally appear to be much safer. However, be aware that norfloxacin has caused a much larger rise on occasions.[9,22] Fleroxacin, flumequine, gatifloxacin, gemifloxacin, levofloxacin, lomefloxacin, moxifloxacin, nalidixic acid, rufloxacin, sparfloxacin and trovafloxacin appear not to interact significantly, and no special precautions seem necessary with these drugs. However, note that acute infection *per se* can alter theophylline pharmacokinetics.[35] The manufacturers of some quinolones include a warning in their product literature about the risk of combining theophylline with quinolones because of their potential additive effects on reducing the seizure threshold. Convulsions have been reported with theophylline and ciprofloxacin, norfloxacin, or pefloxacin. With some of these cases it is difficult to know whether what happened was due to increased theophylline levels, to patient pre-disposition, to potential additive effects on the seizure threshold, or to all three factors combined. However, the literature suggests that seizures attributed to concurrent use are relatively rare, so that the general warning about the risks with all quinolones may possibly be an overstatement.

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Theophylline + Ramelteon

The concurrent use of theophylline and ramelteon does not appear to cause a clinically relevant alteration in the pharmacokinetics of either drug.

Clinical evidence, mechanism, importance and management

A well controlled study in 36 healthy subjects who took ramelteon 32 mg daily with theophylline 300 mg daily found that the pharmacokinetics of theophylline were not significantly altered by ramelteon. The exposure to ramelteon was increased by 40% by theophylline, but the authors considered that as this drug has a wide therapeutic margin and therefore the increase seen was not expected to be clinically significant.[1] There appears to be no information about an interaction with aminophylline, but it would be expected to interact in much the same way as theophylline.

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Theophylline + Rasagiline

The US manufacturer of rasagiline reports that, in 24 healthy subjects, the concurrent use of rasagiline 1 mg daily and theophylline up to 500 mg twice daily did not affect the pharmacokinetics of either drug.[1] No dose adjustment is therefore needed on the concurrent use of these drugs.

1. Azilect (Rasagiline mesylate). Teva Pharmaceutical Industries Ltd. US Prescribing information, May 2009.

Theophylline + Repaglinide

In 14 healthy subjects, repaglinide 2 mg three times daily for 4 days did not significantly affect the steady-state pharmacokinetics of theophylline, although the peak plasma concentration was slightly reduced.[1] No theophylline dose adjustments would appear to be necessary during concurrent use.

1. Hartop V, Thomsen MS. Drug interaction studies with repaglinide: repaglinide on digoxin or theophylline pharmacokinetics and cimetidine on repaglinide pharmacokinetics. *J Clin Pharmacol* (2000) 40, 184–92.

Theophylline + Ribavirin

Ribavirin does not alter theophylline levels.

Clinical evidence, mechanism, importance and management

Oral ribavirin 200 mg every 6 hours had no effect on the plasma theophylline levels of 13 healthy subjects given immediate or sustained-release aminophylline. Similarly, ribavirin 10 mg/kg daily did not affect the plasma theophylline levels in 6 children with influenza and asthma.[1] No special precautions seem necessary on concurrent use.

1. Fraschini F, Scaglione F, Maierna G, Cogo R, Furcolo F, Gattei R, Borghi C, Palazzini E. Ribavirin influence on theophylline plasma levels in adult and children. *Int J Clin Pharmacol Ther Toxicol* (1988) 26, 30–2.

Theophylline + Rifamycins and/or Isoniazid

Rifampicin (rifampin) lowers the levels of theophylline, but rifabutin appears to have little effect. Isoniazid may decrease or increase theophylline clearance and may increase theophylline levels. An isolated report describes theophylline toxicity one month after a patient started to take theophylline with isoniazid. Isoniazid and rifampicin increased theophylline clearance during the initial few days of tuberculosis treatment in one study, but there is some evidence that it decreases it within 4 weeks in another.

Clinical evidence

(a) Isoniazid

Theophylline toxicity has been described in one patient receiving isoniazid 5 mg/kg daily and theophylline, and this subsequently recurred on rechallenge.[1] In 7 healthy subjects, high-dose isoniazid (10 mg/kg daily) for 10 days increased the $AUC_{0\text{-}6}$ of theophylline by only 8%. The theophylline was given as an intravenous infusion of aminophylline and the plasma levels after 6 hours were 22% higher (about 10.5 mg/L compared with 8.7 mg/L). Five subjects also had an increase in the half-life and AUC of isoniazid, but these changes were not statistically significant.[2] Another study, in 13 healthy subjects, found that isoniazid 400 mg daily for 2 weeks reduced the mean clearance of theophylline (given as intravenous aminophylline) by 21%.[3]

However, another study in 4 healthy subjects given isoniazid 300 mg daily for 6 days found that the clearance of oral theophylline was increased by 16%, but no consistent changes were seen in any of the other pharmacokinetic parameters measured.[4]

(b) Rifabutin

The AUC of a single 5-mg/kg dose of theophylline was reduced by 6% in 11 healthy subjects who took rifabutin 300 mg daily for 12 days. The half-life and clearance of theophylline were not affected.[5]

(c) Rifampicin (Rifampin)

The AUC of theophylline (given as sustained-release aminophylline 450 mg) was reduced by 18% in 7 healthy subjects who took rifampicin 600 mg daily for one week. A parallel study in another 8 healthy subjects given the same dose of rifampicin found that the metabolic clearance of theophylline (given as intravenous aminophylline 5 mg/kg) was increased by 45%.[6]

Similarly, other studies in healthy subjects given oral or intravenous

theophylline or intravenous aminophylline and rifampicin 300 to 600 mg daily for 6 to 14 days found 25 to 82% rises in theophylline clearance, and 19 to 31% decreases in its half-life.[5,7-12] A 61% fall in the 5-hour post-dose serum levels of theophylline (given as choline theophyllinate) occurred in a 15-month-old boy when he was given a 4-day course of rifampicin 20 mg/kg daily as meningitis prophylaxis.[13]

(d) Antimycobacterials in combination

A study in patients taking a combination of **isoniazid**, **rifampicin**, **ethambutol** and **pyrazinamide** for pulmonary tuberculosis with intravenous aminophylline 7.35 mg/kg daily for 7 days found that the clearance of theophylline progressively increased, and was 53% faster on day 7.[14] In contrast, in an earlier study by the same authors, after 4 weeks of the same antimycobacterials (isoniazid, rifampicin, ethambutol with or without pyrazinamide) the theophylline clearance in patients receiving long-term theophylline was about 35% slower than in a control group of similar patients not taking antimycobacterials.[15] A single report describes unexpectedly *high* serum theophylline levels 4 days after theophylline 300 mg twice daily was started in an alcoholic patient with hepatic impairment who had started to take **rifampicin** and **isoniazid** 2 weeks previously.[16]

Mechanism

Rifampicin is a potent liver enzyme inducer, which increases the metabolism of the theophylline, thereby increasing its clearance and reducing its serum levels.[8] Rifabutin is a much less potent liver enzyme inducer than rifampicin, and consequently has less of an effect on theophylline metabolism. It has been suggested that isoniazid inhibits the metabolism of theophylline by the liver, thereby reducing its clearance and increasing its plasma levels.

With combined therapy, it was suggested that the effects of rifampicin might be more apparent during the initial 7 days, but that by week 4 the effect of isoniazid might predominate, because of its reduced inactivation by rifampicin combined with a reduction in the effect of rifampicin by auto-induction of its own metabolism.[15] High theophylline levels in the isolated case above may have been due to liver impairment brought about by the combined use of rifampicin and isoniazid, or alcoholism.[13]

Importance and management

The interaction between aminophylline or theophylline and **rifampicin** is established. The levels and therapeutic effects of theophylline are likely to be reduced during concurrent use, and this effect can usually be detected within 36 hours.[13] The wide range of increases in clearance that have been reported (25 to 82%) and the large inter-subject variation make it difficult to predict the increase in theophylline dose required, but in some instances a twofold increase may be needed.[8] Monitor theophylline levels if rifampicin is started or stopped and adjust the aminophylline or theophylline dose accordingly.

The effects of **rifabutin** are considerably less than those of rifampicin, with the one available study showing no significant interaction. On the basis of this, no special precautions appear to be necessary, but it may be prudent to monitor the efficacy of aminophylline and theophylline on concurrent use.

The reason for the inconsistent results with **isoniazid** alone is not understood, nor is this interaction well established. It has been suggested that it may take 3 to 4 weeks for any significant increase in theophylline levels to occur.[1] However, if enzyme inhibition was the cause, the effects would be expected more rapidly than this. All of the studies cited covered a period of only 6 to 14 days, whereas the case report describes the effects over a period up to 55 days.[1] It has also been suggested that the dose of isoniazid may be important, with the clearance of theophylline being unaffected by 'usual doses' of isoniazid, but reduced by larger doses.[17] The outcome of concurrent isoniazid and theophylline use is uncertain and may be affected by other antimycobacterials, but it would clearly be prudent to be alert for any evidence of changes in theophylline levels and toxicity if isoniazid is given.

Isoniazid and rifampicin are usually taken as part of a combination chemotherapy regimen in the treatment of tuberculosis. There is some evidence that, in the short-term, combined use of these drugs will decrease theophylline levels, but that theophylline levels may increase during long-term use. However this requires confirmation. Patients taking theophylline with a combined anti-tubercular regimen including isoniazid and rifampicin should have their theophylline levels closely monitored and the dose adjusted according to the response, bearing in mind that these changes may occur over a longer period of time as reported in the case with isoniazid.

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Theophylline + Ropinirole

Ropinirole does not appear to affect the pharmacokinetics of theophylline in patients given aminophylline. Theophylline does not affect the pharmacokinetics of ropinirole.

Clinical evidence, mechanism, importance and management

An interaction between ropinirole and theophylline had originally been suspected because both drugs are metabolised by the cytochrome P450 isoenzyme CYP1A2. The UK manufacturer of ropinirole warns of the potential for an interaction and suggests that in patients already receiving ropinirole, the dose of ropinirole may need to be adjusted when theophylline is introduced or withdrawn.[1] However, in one study, 12 patients with parkinsonism were given ropinirole, increased from 0.5 mg to 2 mg three times daily over 28 days, then continued for a further 19 days. The pharmacokinetics of theophylline, given as a single intravenous dose of aminophylline, were assessed before ropinirole was started, and again on day 27. The pharmacokinetics of ropinirole were then assessed before, during and after, the use of oral controlled-release theophylline twice daily for 13 days (dose titrated to achieve plasma levels in the range 8 to 15 mg/L). In both cases it was found that concurrent use did not alter the pharmacokinetics of either drug, and concurrent use was well tolerated.[2] There would therefore appear to be no reason to take special precautions if both drugs are used, and no need to adjust the dose of either drug.

1. Requip (Ropinirole hydrochloride). GlaxoSmithKline UK. UK Summary of product characteristics, September 2009.
2. Thalamas C, Taylor A, Brefel-Courbon C, Eagle S, Fitzpatrick K, Rascol O. Lack of pharmacokinetic interaction between ropinirole and theophylline in patients with Parkinson's disease. *Eur J Clin Pharmacol* (1999) 55, 299–303.

Theophylline + SSRIs

Theophylline levels can be markedly and rapidly increased by fluvoxamine. Some preliminary clinical evidence suggests that fluoxetine and citalopram may not interact. Paroxetine and sertraline are also unlikely to interact.

Clinical evidence

(a) Citalopram

In a study in 13 healthy subjects citalopram 40 mg daily for 21 days (to achieve steady-state) did not affect the pharmacokinetics of a single 300-mg oral dose of theophylline.[1]

(b) Fluoxetine

In 8 healthy subjects the pharmacokinetics of theophylline were unchanged when they were given a 6-mg/kg infusion of aminophylline over 30 minutes, 8 hours after a single 40-mg dose of fluoxetine.[2]

(c) Fluvoxamine

The effect of fluvoxamine on theophylline pharmacokinetics has been characterised in several studies in healthy subjects. In the first study the AUC of theophylline (given as a single 442-mg oral dose of aminophylline) was increased almost threefold, the clearance was reduced by 62% and the half-life was prolonged from 7.4 hours to 32.1 hours by fluvoxamine 50 mg daily for 3 days then 100 mg daily for 13 days.[3] In a second study, the clearance of theophylline (given as a single 300-mg oral dose of aminophylline) was reduced by about 70% and the half-life was increased from 6.6 hours to 22 hours by fluvoxamine 50 to 100 mg daily for 7 days.[4] In a further study in 9 healthy subjects, the half-life of a single 250-mg dose of theophylline given on day 8 of the study, was increased from 7.6 hours to 19.2 hours when the subjects took fluvoxamine 50 mg on day one, and 75 mg daily for the following 8 days. The AUC of theophylline increased by 138%, and the clearance was reduced by 59%.[5] This interaction was shown to be reduced in patients with mild and severe liver cirrhosis (Child class A and C, respectively), whereas the clearance of a single 4-mg/kg dose of theophylline elixir was reduced by 62%, 52%, and 11% in healthy subjects, patients with mild cirrhosis, and patients with severe cirrhosis, respectively. The half-life of theophylline was increased by 13.6 hours in healthy subjects compared with 10.5 hours in patients with mild cirrhosis and one hour in patients with severe cirrhosis, demonstrating the reduced metabolic capabilities of the cirrhotic liver.[6]

A number of case reports have described fluvoxamine-induced theophylline toxicity. Agitation and tachycardia (120 bpm) developed in an 83-year-old man taking theophylline 600 mg daily (*Theostat*) about a week after he started to take fluvoxamine 100 mg daily. His serum theophylline levels were found to have risen from under 15 mg/L to 40 mg/L.[7] A 70-year-old man similarly developed theophylline toxicity, with theophylline levels of about 32 mg/L (reference range 10 to 20 mg/L), when fluvoxamine was added. Subsequently the theophylline concentrations were found to parallel a number of changes in the fluvoxamine dose.[8] The clearance of theophylline in an 84-year-old man was approximately halved while he was taking fluvoxamine.[9] An 11-year-old boy complained of headaches, tiredness and vomiting within a week of starting to take fluvoxamine. His serum theophylline levels were found to have doubled, from 14.2 mg/L to 27.4 mg/L.[10] A 78-year-old woman became nauseous within 2 days of starting to take fluvoxamine 50 mg daily, and by day 6, when the fluvoxamine was stopped, her serum theophylline levels were found to have increased about threefold. She had a seizure, became comatose, and developed supraventricular tachycardia (200 bpm) requiring intravenous digoxin and verapamil. She recovered uneventfully.[11] A patient taking fluvoxamine 100 mg daily developed nausea, vomiting, confusion, reduced sleep and a poor appetite 5 days after she began to take theophylline 300 mg twice daily for COPD. Her theophylline level was found to be 25.9 mg/L.[12]

Mechanism

Fluvoxamine is a known, potent inhibitor of the cytochrome P450 isoenzyme CYP1A2 in the liver, by which theophylline is metabolised. Concurrent use therefore results in raised theophylline levels and toxicity. This metabolic function, and hence interaction, appears to be severely reduced in patients with severe cirrhosis, probably due to reduced hepatic expression of CYP1A2 and reduced uptake of fluvoxamine.[6] The other SSRIs, citalopram, fluoxetine, **paroxetine** and **sertraline** only weakly inhibited CYP1A2 *in vitro*, and consequently would not be expected to interact.[13,14]

Importance and management

The interaction between fluvoxamine and aminophylline or theophylline is established and clinically important. The CSM in the UK advise that concurrent use should usually be avoided, but that if this is not possible, reduce the theophylline dose by half when fluvoxamine is added and monitor theophylline levels.[15] There is evidence to suggest that the extent of this interaction is markedly reduced in patients with liver cirrhosis, particularly severe Child class C, despite higher levels of fluvoxamine,[6] although caution should still be applied with concurrent use in this patient group as they are more likely to have high levels of theophylline due to reduced metabolism. There is good evidence to suggest that fluvoxamine is the only SSRI likely to interact (because it is the only one that significantly affects CYP1A2). This would seem to be borne out by the studies with citalopram and fluoxetine, and the lack of case reports in the literature describing problems with any of the other SSRIs.

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9. Puranik A, Fitzpatrick R, Ananthanarayanan TS. Monitor serum theophylline. *Care Elder* (1993) 5, 237.
10. Sperber AD. Toxic interaction between fluvoxamine and sustained release theophylline in an 11-year-old boy. *Drug Safety* (1991) 6, 460–2.
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14. Rasmussen BB, Mäenpää J, Pelkonen O, Loft S, Poulsen HE, Lykkesfeldt J, Brøsen K. Selective serotonin reuptake inhibitors and theophylline metabolism in human liver microsomes: potent inhibition by fluvoxamine. *Br J Clin Pharmacol* (1995) 39, 151–9.
15. Committee on Safety of Medicines/Medicines Control Agency. Fluvoxamine increases plasma theophylline levels. *Current Problems* (1994) 20, 12.

Theophylline + St John's wort (*Hypericum perforatum*)

A patient needed a marked increase in the dose of theophylline while taking St John's wort. In contrast, no pharmacokinetic interaction was found in a two-week study in healthy subjects.

Clinical evidence

A study in 12 healthy subjects found that a standardised preparation of St John's wort 300 mg (hypericin 0.27%) three times daily for 15 days had no significant effects on the plasma level of a single 400-mg oral dose of theophylline.[1]

However, an isolated case describes a woman, previously stable for several months taking theophylline 300 mg twice daily, who was found to need a markedly increased theophylline dose of 800 mg twice daily to achieve serum levels of 9.2 mg/L. Two months previously she had started to take 300 mg of a St John's wort supplement (hypericin 0.3%) each day. When she stopped taking the St John's wort, her serum theophylline levels doubled within a week to 19.6 mg/L and her theophylline dose was consequently reduced. This patient was also taking a whole spectrum of other drugs (amitriptyline, furosemide, ibuprofen, inhaled triamcinolone, morphine, potassium, prednisone, salbutamol (albuterol), valproic acid, zafirlukast and zolpidem) and was also a smoker. No changes in the use of these drugs or altered compliance were identified that might have offered an alternative explanation for the changed theophylline requirements.[2]

Mechanism

Uncertain. *In vitro* data suggest that one component of St John's wort (hypericin) can act as an inducer of the cytochrome P450 isoenzyme CYP1A2.[2] It has also been suggested that treatment with St John's wort for 15 days was unlikely to induce the isoenzymes sufficiently to cause changes in plasma theophylline.[1] The patient in the case report had been taking St John's wort for 2 months, although at a lower dose, therefore differences in duration of treatment may account for the discrepancy. This is supported by studies in which the use of St John's wort for 4 weeks,[3] but

not 2 weeks,[4] modestly increased the paraxanthine/caffeine ratio, used as a measure of CYP1A2 activity.

Importance and management

Direct information about this apparent interaction between theophylline and St John's wort appears to be limited. Despite the isolated case report of a marked decrease in theophylline levels, no pharmacokinetic interaction was noted in healthy subjects, and any pharmacokinetic interaction appears likely to be minor. Mechanistic studies suggest a modest interaction at most. Furthermore most clinically significant interactions with St John's wort are mediated by the cytochrome P450 isoenzyme CYP3A4. However, until further evidence is available, it would be prudent to be aware of the possibility of an interaction. Patients should be warned of the possible effects of concurrent use. In 2000, the CSM in the UK recommended that patients taking theophylline should not take St John's wort. In those patients already taking the combination, the St John's wort should be stopped and the theophylline dose monitored and adjusted if necessary.[5,6] However, this guidance was issued before the pharmacokinetic study that suggests that an interaction is generally unlikely.

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2. Nebel A, Schneider BJ, Baker RK, Kroll DJ. Potential metabolic interaction between St John's wort and theophylline. *Ann Pharmacother* (1999) 33, 502.
3. Gurley BJ, Gardner SF, Hubbard MA, Williams DK, Gentry WB, Cui Y, Ang CYW. Cytochrome P450 phenotypic ratios for predicting herb-drug interactions in humans. *Clin Pharmacol Ther* (2002) 72, 276–287.
4. Wang Z, Gorski JC, Hamman MA, Huang S-M, Lesko LJ, Hall SD. The effects of St John's wort (*Hypericum perforatum*) on human cytochrome P450 activity. *Clin Pharmacol Ther* (2001) 70, 317–326.
5. Committee on Safety of Medicines (UK). Message from Professor A Breckenridge (Chairman of CSM) and Fact Sheet for Health Care Professionals, 29th February 2000.
6. Committee on Safety of Medicines/Medicines Control Agency. Reminder: St John's wort (*Hypericum perforatum*) interactions. *Current Problems* (2000) 26, 6–7.

Theophylline + Succimer

A single case report describes a reduction in the theophylline levels of a man given succimer.

Clinical evidence, mechanism, importance and management

A 65-year-old man with COPD and chronic lead intoxication was given a 19-day course of lead chelation with succimer. His theophylline level was found to be reduced from about 11 mg/L to 7 mg/L on day 6 and remained at this level until about 9 days after the course of succimer was completed, when it returned to pretreatment levels. His clinical status did not alter despite these changes; possibly because he was also taking prednisone.[1] The reason for these alterations is not understood, although as succimer is known to chelate heavy metals, it seems possible that theophylline may have been chelated, resulting in a reduction in its levels.

The general importance of this interaction is not known, but given that succimer is known to chelate some substances it would seem prudent to monitor the situation closely if succimer is added to established treatment with theophylline or aminophylline.

1. Harchelroad R. Pharmacokinetic interaction between dimercaptosuccinic acid (DMSA) and theophylline (THEO). *Vet Hum Toxicol* (1994) 36, 376.

Theophylline + Sucralfate

Two studies found that sucralfate caused only minor changes in theophylline pharmacokinetics, but another suggests that the absorption of sustained-release theophylline is significantly reduced by sucralfate.

Clinical evidence, mechanism, importance and management

In 8 healthy subjects no clinically important changes occurred in the absorption of a single 5-mg/kg dose of an oral non-sustained release theophylline preparation given at the same time as sucralfate 1 g four times daily. A slight 5% decrease in the AUC was detected.[1] Another study found that sucralfate 1 g four times daily reduced the AUC of a single dose of a sustained-release theophylline preparation (*Theodur*) by 9% (timing of the theophylline dose in relation to the sucralfate dose not noted).[2] In contrast, another group of workers found that when sucralfate 1 g was given 30 minutes before a 350 mg dose of sustained-release theophylline (*PEG capsules*), the theophylline AUC was reduced by 40%.[3] Many patients are given sustained-release theophylline preparations, but neither of these studies clearly shows what is likely to happen in clinical practice, so be alert for any evidence of a reduced response to theophylline. Usually, separating the administration of sucralfate from other drugs by 2 hours is considered sufficient to avoid interactions that occur by reduced absorption.[4] However, the study showing decreased theophylline absorption did not examine the effect of separating the doses. Further study is needed, both to establish the effects of sucralfate on theophylline, and to establish if an interaction occurs with aminophylline preparations.

1. Cantral KA, Schaaf LJ, Jungnickel PW, Monsour HP. Effect of sucralfate on theophylline absorption in healthy volunteers. *Clin Pharm* (1988) 7, 58–61.
2. Kisor DF, Livengood B, Vieira-Fattahi S, Sterchele JA. Effect of sucralfate administration on the absorption of sustained released theophylline. *Pharmacotherapy* (1990) 10, 253.
3. Fleischmann R, Bozler G, Boekstegers P. Bioverfügbarkeit von Theophylline unter Ulkustherapeutika. *Verh Dtsch Ges Inn Med* (1984) 90, 1876–9.
4. Antepsin Suspension (Sucralfate). Chugai Pharma UK Ltd. UK Summary of product characteristics, November 2007.

Theophylline + Sulfinpyrazone

Sulfinpyrazone can cause a small increase in theophylline clearance.

Clinical evidence, mechanism, importance and management

In 6 healthy subjects the total clearance of theophylline 125 mg every 8 hours for 4 days was increased by 22% (range 9 to 42%) when they were given sulfinpyrazone 200 mg every 6 hours.[1] This appeared to be the sum of an increase in the metabolism of theophylline by the liver and a decrease in its renal clearance.

Information seems to be limited to this study. The resulting fall in serum theophylline levels is unlikely to be clinically relevant. Aminophylline, which is metabolised to theophylline, would be expected to behave similarly.

1. Birkett DJ, Miners JO, Attwood J. Evidence for a dual action of sulphinpyrazone on drug metabolism in man: theophylline-sulphinpyrazone interaction. *Br J Clin Pharmacol* (1983) 15, 567–9.

Theophylline + Tadalafil

Tadalafil does not alter the pharmacokinetics of theophylline.

Clinical evidence, mechanism, importance and management

A placebo-controlled, randomised, crossover study in 17 healthy subjects given enough oral theophylline (a non-selective phosphodiesterase inhibitor) to achieve steady-state levels of about 12 mg/L found that the concurrent use of the phosphodiesterase type-5 inhibitor tadalafil 10 mg daily for 7 days did not affect the pharmacokinetics of either drug. There was a small increase of 3.5 bpm in the heart rate, which was not considered to be clinically relevant in the healthy subjects.[1] However, the UK manufacturer advises that this should be considered when both drugs are used concurrently.[2] However, most conditions where a 3.5 bpm increase in heart rate may possibly of clinical relevance (e.g. uncontrolled arrhythmias) are contraindications to the use of tadalafil. Note that aminophylline, which is metabolised to theophylline, would be expected to behave similarly.

1. Eli Lilly and Company. Personal communication, March 2003.
2. Cialis (Tadalafil). Eli Lilly and Company Ltd. UK Summary of product characteristics, September 2008.

Theophylline + Tamsulosin

No clinically relevant pharmacokinetic interaction occurs between theophylline and tamsulosin.

Clinical evidence, mechanism, importance and management

In a double-blind study, 10 healthy subjects were given tamsulosin 400 micrograms daily for 2 days then 800 micrograms on the following 5 days, with a single 5-mg/kg dose of intravenous theophylline one hour after the last dose of tamsulosin. The pharmacokinetics of theophylline

and tamsulosin were not affected by concurrent use. Theophylline is mainly metabolised by the cytochrome P450 isoenzyme CYP1A2, while tamsulosin is metabolised by CYP3A4 and CYP2D6, and therefore a pharmacokinetic interaction would not be expected.[1] The safety of concurrent use was considered acceptable and dose adjustments were not considered necessary.[1]

1. Miyazawa Y, Starkey LP, Forrest A, Schentag JJ, Kamimura H, Swarz H, Ito Y. Effects of the concomitant administration of tamsulosin (0.8 mg/day) on the pharmacokinetics and safety profile of theophylline (5 mg/kg): a placebo-controlled evaluation. *J Int Med Res* (2002) 30, 34–43.

Theophylline + Tegaserod

Tegaserod does not appear to alter the pharmacokinetics of theophylline.

Clinical evidence, mechanism, importance and management

In 18 healthy subjects, the pharmacokinetics of a single 600-mg dose of controlled-release theophylline were unchanged when it was given with three doses of tegaserod 6 mg (the first was given about 24 hours before the theophylline, the second simultaneously, and the third 12 hours later).[1] No theophylline dose adjustments would therefore appear necessary on concurrent use.

1. Zhou H, Khalilieh S, Svendsen K, Pommier F, Osborne S, Appel-Dingemanse S, Lasseter K, McLeod JF. Tegaserod coadministration does not alter the pharmacokinetics of theophylline in healthy subjects. *J Clin Pharmacol* (2001) 41, 987–93.

Theophylline + Teicoplanin

Clinical studies in 20 patients with COPD found that teicoplanin 200 mg twice daily and aminophylline 240 mg twice daily (both given as intravenous infusions) had no significant effect on the steady-state pharmacokinetics of either teicoplanin or theophylline (derived from aminophylline).[1] No special precautions would seem necessary during concurrent use.

1. Angrisani M, Cazzola M, Loffreda A, Losasso C, Lucarelli C, Rossi F. Clinical pharmacokinetics of teicoplanin and aminophylline during cotreatment with both medicaments. *Int J Clin Pharmacol Res* (1992) 12, 165–71.

Theophylline + Terbinafine

Preliminary evidence indicates that terbinafine can increase the levels of theophylline to some extent.

Clinical evidence, mechanism, importance and management

In a randomised, crossover study, 12 healthy subjects were given a single 5-mg/kg oral dose of aminophylline before and after taking terbinafine 250 mg daily for 3 days. The AUC and half-life of theophylline were increased by 16% and 23%, respectively, and the theophylline clearance was reduced by 14%. It was suggested[1] that this is due to the inhibitory effect of terbinafine on the activity of the cytochrome P450 isoenzyme CYP1A2, which is the main isoenzyme involved in the metabolism of theophylline. The changes seen were only relatively small, but the study periods only lasted 3 days so that the effects of longer concurrent use are uncertain, but a clinically significant interaction seems unlikely.

1. Trépanier EF, Nafziger AN, Amsden GW. Effect of terbinafine on theophylline pharmacokinetics in healthy volunteers. *Antimicrob Agents Chemother* (1998) 42, 695–7.

Theophylline + Tetracyclines

Serum theophylline levels increased in two patients who were also given minocycline or tetracycline. Some controlled studies have shown both increases and decreases in theophylline clearance with doxycycline and tetracycline, with no significant changes overall.

Clinical evidence

(a) Doxycycline

A study in 10 asthmatic subjects given doxycycline 100 mg twice daily on day one and then 100 mg daily for 4 days found that the mean serum theophylline level was not significantly altered. However, there was large inter-individual variation, with 4 subjects having rises of more than 20% (range 24 to 31%) and 2 having decreases of 22% and 33%.[1] Fluctuations of this size are not unusual with theophylline. Another study in 8 healthy subjects given doxycycline 100 mg daily for 7 days with theophylline 350 mg twice daily did not find any significant changes in theophylline pharmacokinetics.[2]

(b) Minocycline

The serum theophylline levels of a 70-year-old woman with normal liver function increased from 9.8 mg/L to 15.5 mg/L after she was given minocycline 100 mg twice daily by infusion for 6 days. Her serum theophylline level was 10.9 mg/L fourteen days after the minocycline was stopped.[3]

(c) Tetracycline

After taking tetracycline hydrochloride 250 mg four times daily for 8 days a patient with COPD had signs of theophylline toxicity. After 10 days of tetracycline her serum theophylline levels had risen from about 13 mg/L to 30.8 mg/L. Both drugs were stopped, and after 24 hours her theophylline level was 12.4 mg/L. A later rechallenge in this patient confirmed that the tetracycline was responsible for the raised theophylline levels.[4]

In an earlier study in 8 healthy subjects, tetracycline 250 mg four times daily for 7 days did not affect the mean pharmacokinetics of theophylline (given as a single intravenous dose of aminophylline), although there was large inter-individual variation. Four subjects had a decrease in clearance of over 15%, (32% in one subject), and conversely, one subject had a 21% increase in clearance.[5] Other studies in subjects and patients given tetracycline for shorter periods have not found evidence of an important interaction. A study in 9 healthy adults given single 5-mg/kg intravenous doses of aminophylline found that tetracycline 250 mg every 6 hours for 48 hours had no significant effect on theophylline pharmacokinetics.[6] Five non-smoking patients with COPD or asthma had an average 14% rise in serum theophylline levels and an 11% decrease its clearance after 5 days of treatment with tetracycline 250 mg four times daily. However, when a sixth patient was included (a smoker) the results were no longer statistically significant.[7]

Mechanism

Not understood. Inhibition of theophylline metabolism and clearance by the tetracyclines has been suggested.[4]

Importance and management

Information seems to be limited. There are two isolated cases of increased theophylline levels with minocycline and tetracycline, but controlled studies have not found any significant changes in overall theophylline pharmacokinetics. It has been suggested that a clinically important interaction may possibly only occur in a few patients.[1,4] Further study is needed. There seems to be no evidence of adverse interactions with any of the other tetracyclines. However, note that acute infections *per se* can alter theophylline pharmacokinetics.[8]

1. Seggev JS, Shefi M, Schey G, Farfel Z. Serum theophylline concentrations are not affected by coadministration of doxycycline. *Ann Allergy* (1986) 56, 156–7.
2. Jonkman JHG, van der Boon WJV, Schoenmaker R, Holtkamp A, Hempenius J. No influence of doxycycline on theophylline pharmacokinetics. *Ther Drug Monit* (1985) 7, 92–4.
3. Kawai M, Honda A, Yoshida H, Goto M, Shimokata T. Possible theophylline-minocycline interaction. *Ann Pharmacother* (1992) 26, 1300–1.
4. McCormack JP, Reid SE, Lawson LM. Theophylline toxicity induced by tetracycline. *Clin Pharm* (1990) 9, 546–9.
5. Mathis JW, Prince RA, Weinberger MM, McElnay JC. Effect of tetracycline hydrochloride on theophylline kinetics. *Clin Pharm* (1982) 1, 446–8.
6. Pfeifer HJ, Greenblatt DJ, Friedman P. Effects of three antibiotics on theophylline kinetics. *Clin Pharmacol Ther* (1979) 26, 36–40.
7. Gotz VP, Ryerson GG. Evaluation of tetracycline on theophylline disposition in patients with chronic obstructive airways disease. *Drug Intell Clin Pharm* (1986) 20, 694–7.
8. Renton KW. Cytochrome P450 regulation and drug biotransformation during inflammation and infection. *Curr Drug Metab* (2004) 5, 235–43.

Theophylline + Thyroid and Antithyroid compounds

Thyroid dysfunction may modestly affect theophylline requirements. There are two isolated cases of theophylline toxicity in patients being treated for hypothyroidism.

Clinical evidence

The theophylline elimination rate constant after a single intravenous dose of aminophylline was found to be greater in hyperthyroid patients (0.155 h^{-1}) than in euthyroid (0.107 h^{-1}) or hypothyroid patients (0.060 h^{-1}); some other pharmacokinetic parameters were also changed.[1] The authors concluded that thyroid dysfunction may modestly alter theophylline requirements. It is therefore also likely that drug-induced changes in the thyroid status, such as those caused by amiodarone, may also alter the amount of theophylline needed to maintain therapeutic levels.

(a) Antithyroid compounds

The serum theophylline level of an asthmatic patient was found to have doubled, from 15.2 mg/L to 30.9 mg/L, accompanied by toxicity, 3 months after treatment for hyperthyroidism with **radioactive iodine** (^{131}I). At this point the patient was hypothyroid, and after treatment with levothyroxine was started, his serum theophylline returned to approximately the same level as before radioactive iodine treatment (13.9 mg/L).[2] Another patient with Graves' disease treated with a combination of **thiamazole** (**methimazole**) 10 mg three times daily and Lugol's solution (**iodine** and **potassium iodide**) and taking theophylline 500 mg twice daily (*TheoDur*), had a theophylline level of 4.7 mg/L before radioactive iodine therapy. His level increased to 13.6 mg/L seven months after thyroid ablation.[3] Five hyperthyroid patients had a 20% reduction in theophylline clearance and an increase in their theophylline half-life, from 4.6 hours to 5.9 hours, when they were given **carbimazole** 45 mg and propranolol 60 mg daily. In this study, a single intravenous dose of aminophylline was given before the treatment of thyrotoxicosis and after the euthyroid state had been achieved.[4] Note that propranolol can reduce the clearance of theophylline but should be avoided in patients with respiratory disease, see 'Theophylline + Beta blockers', p.1433, for more information.

(b) Thyroid hormones

One week after starting to take theophylline 1 g daily, a patient who was hypothyroid (serum thyroxine 1.4 micrograms/dL, reference range 4 to 11 micrograms/dL) developed severe theophylline toxicity, with serum theophylline levels of 34.7 mg/L, manifested by ventricular fibrillation (from which he was successfully resuscitated) and repeated seizures over 24 hours. After 2 months of treatment with **thyroid hormones**, which increased his serum thyroxine levels to 4.3 micrograms/dL, his serum theophylline level was 13.2 mg/L, 10 days after reinstitution of the same dose of theophylline.[5]

Mechanism

Thyroid status may affect the rate at which theophylline is metabolised. In hyperthyroidism it is increased, whereas in hypothyroidism it is decreased.

Importance and management

It is established that changes in thyroid status may affect how the body handles theophylline (including that derived from aminophylline). Monitor the effects and anticipate the possible need to begin to reduce the theophylline dose if treatment for hyperthyroidism is started (e.g. with radioactive iodine, carbimazole, **thiamazole**, **propylthiouracil**, etc.). Similarly, anticipate the possible need to increase the theophylline dose if treatment is started for hypothyroidism (e.g. with levothyroxine). Stabilisation of the thyroid status may take weeks or even months to achieve so that if monitoring of the theophylline dose is considered necessary, it will need to extend over the whole of this period. This monitoring would also apply to drug-induced thyroid dysfunction.

1. Pokrajac M, Simić D, Varagić VM. Pharmacokinetics of theophylline in hyperthyroid and hypothyroid patients with chronic obstructive pulmonary disease. *Eur J Clin Pharmacol* (1987) 33, 483–6.
2. Johnson CE, Cohen IA. Theophylline toxicity after iodine 131 treatment for hyperthyroidism. *Clin Pharm* (1988) 7, 620–2.
3. Bauman JH, Teichman S, Wible DA. Increased theophylline clearance in a patient with hyperthyroidism. *Ann Allergy* (1984) 52, 94–6.
4. Vozeh S, Otten M, Staub J-J, Follath F. Influence of thyroid function on theophylline kinetics. *Clin Pharmacol Ther* (1984) 36, 634–40.
5. Aderka D, Shavit G, Garfinkel D, Santo M, Gitter S, Pinkhas J. Life-threatening theophylline intoxication in a hypothyroidic patient. *Respiration* (1983) 44, 77–80.

Theophylline + Tobacco

Tobacco smokers, and non-smokers heavily exposed to tobacco smoke, may need more theophylline than non-smokers to achieve the same therapeutic benefits, because the theophylline is cleared from the body more quickly. This may also occur in those who chew tobacco or take snuff but not if they chew nicotine gum.

Clinical evidence

A study found that the mean half-life of theophylline (given as a single oral dose of aminophylline) was 4.3 hours in a group of tobacco smokers (20 to 40 cigarettes a day) compared with 7 hours in a group of non-smokers, and that theophylline clearance was higher (mean increase 126%) and more variable in the smokers.[1] Almost identical results were found in an earlier study,[2] and a number of later studies in subjects given oral or intravenous theophylline or aminophylline confirm these findings.[3-8] The ability of smoking to increase theophylline clearance occurs irrespective of gender,[3,6] and in the presence of congestive heart failure or liver impairment.[7] The effects of ageing on the induction of theophylline metabolism by tobacco smoking is less clear. One study has found that in both young subjects (less than 30-years-old) and elderly subjects (more than 67 years old) smoking decreased the half-life and increased the clearance of theophylline, when compared with non-smokers. The effect was greater in the young subjects.[4] However, another study found no difference in the pharmacokinetics of theophylline between asthmatic and otherwise healthy smokers and non-smokers aged over 65 years.[9] A similar high clearance of theophylline (given as intravenous aminophylline) has been seen in a patient who chewed tobacco (1.11 mL/kg per minute compared with the more usual 0.59 mL/kg per minute).[10] The half-life of theophylline (given as intravenous aminophylline) in passive smokers (non-smokers regularly exposed to tobacco smoke in the air they breathe, for 4 hours a day in this study) is reported to be shorter than in non-smokers (6.93 hours compared with 8.69 hours).[11] The clearance of theophylline (given as intravenous aminophylline) in asthmatic children exposed to passive tobacco smoke was also found to be greater (1.36 mL/kg per minute compared with 0.09 mL/kg per minute) and their steady-state serum theophylline levels were lower than in similar children not exposed to passive smoking.[12]

In one study, 3 of 4 patients who stopped smoking for 3 months (confirmed by serum thiocyanate levels) had a longer theophylline half-life, but only 2 had a slight decrease in theophylline clearance.[1] In another study, ex-smokers who had stopped heavy smoking 2 years previously had values for theophylline clearance and half-life that were intermediate between non-smokers and current heavy smokers.[3] In another study, 7 hospitalised smokers who abstained from smoking for 7 days had a 36% increase in theophylline half-life and a 38% decrease in clearance (although clearance after abstinence was still higher than values usually found in non-smokers).[13]

Mechanism

Tobacco smoke contains polycyclic hydrocarbons, which act as inducers of the cytochrome P450 isoenzyme CYP1A2, and this results in a more rapid clearance of theophylline from the body. Both the *N*-demethylation and 8-hydroxylation of theophylline (both of which are mediated by the cytochrome P450 isoenzyme CYP1A2) are induced.[14] Ageing appears to offset the effects of smoking on theophylline metabolism.[9]

Importance and management

An established interaction of clinical importance. Heavy smokers (20 to 40 cigarettes daily) may need a much greater aminophylline or theophylline dose than non-smokers,[1] and increased doses are likely for those who chew tobacco or take snuff,[10] but not for those who chew nicotine gum.[13,15] In patients who stop smoking, a reduction in the theophylline dose of up to 25 to 33% may be needed after one week,[13] but full normalisation of hepatic function appears to take many months or even years.[1,3] Investigators of the possible interactions of aminophylline and theophylline with other drugs should take smoking habits into account when selecting their subjects.[6,11,12] Note that the effects of cannabis (see

'Theophylline + Cannabis', p.1435, may be additive with those of tobacco smoking.

1. Hunt SN, Jusko WJ, Yurchak AM. Effect of smoking on theophylline disposition. *Clin Pharmacol Ther* (1976) 19, 546–51.
2. Jenne J, Nagasawa H, McHugh R, MacDonald F, Wyse E. Decreased theophylline half-life in cigarette smokers. *Life Sci* (1975) 17, 195–8.
3. Powell JR, Thiercelin J-F, Vozeh S, Sansom L, Riegelman S. The influence of cigarette smoking and sex on theophylline disposition. *Am Rev Respir Dis* (1977) 116, 17–23.
4. Cusack B, Kelly JG, Lavan J, Noel J, O'Malley K. Theophylline kinetics in relation to age: the importance of smoking. *Br J Clin Pharmacol* (1980) 10, 109–14.
5. Jusko WJ, Schentag JJ, Clark JH, Gardner M, Yurchak AM. Enhanced biotransformation of theophylline in marihuana and tobacco smokers. *Clin Pharmacol Ther* (1978) 24, 406–10.
6. Jennings TS, Nafziger AN, Davidson L, Bertino JS. Gender differences in hepatic induction and inhibition of theophylline pharmacokinetics and metabolism. *J Lab Clin Med* (1993) 122, 208–16.
7. Harralson AF, Kehoe WA, Chen J-D. The effect of smoking on theophylline disposition in patients with hepatic disease and congestive heart failure. *J Clin Pharmacol* (1996) 36, 862.
8. Gardner MJ, Tornatore KM, Jusko WJ, Kanarkowski R. Effects of tobacco smoking and oral contraceptive use on theophylline disposition. *Br J Clin Pharmacol* (1983) 16, 271–80.
9. Samaan S, Fox R. The effect of smoking on theophylline kinetics in healthy and asthmatic elderly males. *J Clin Pharmacol* (1989) 29, 448–50.
10. Rockwood R, Henann N. Smokeless tobacco and theophylline clearance. *Drug Intell Clin Pharm* (1986) 20, 624–5.
11. Matsunga SK, Plezia PM, Karol MD, Katz MD, Camilli AE, Benowitz NL. Effects of passive smoking on theophylline clearance. *Clin Pharmacol Ther* (1989) 46, 399–407.
12. Mayo PR. Effect of passive smoking on theophylline clearance in children. *Ther Drug Monit* (2001) 23, 503–5.
13. Lee BL, Benowitz NL, Jacob P. Cigarette abstinence, nicotine gum, and theophylline disposition. *Ann Intern Med* (1987) 106, 553–5.
14. Grygiel J, Birkett DJ. Cigarette smoking and theophylline clearance and metabolism. *Clin Pharmacol Ther* (1981) 30, 491–6.
15. Benowitz NL, Lee BL, Jacob P. Nicotine gum and theophylline metabolism. *Biomed Pharmacother* (1989) 43, 1–3.

Theophylline + Trimetazidine

Trimetazidine does not appear to alter the pharmacokinetics of theophylline.

Clinical evidence, mechanism, importance and management

In a study in 13 healthy subjects trimetazidine 20 mg twice daily for at least 14 days did not alter the pharmacokinetics of a single 375-mg dose of theophylline.[1] These results suggest that treatment with theophylline (and therefore probably aminophylline, which is metabolised to theophylline) is unlikely to be altered in patients concurrently treated with trimetazidine, but this needs confirmation in multiple-dose studies.

1. Edeki TI, Johnston A, Campbell DB, Ings RMJ, Brownsill R, Genissel P, Turner P. An examination of the possible pharmacokinetic interaction of trimetazidine with theophylline, digoxin and antipyrine. *Br J Clin Pharmacol* (1989) 26, 657P.

Theophylline + Vidarabine

A single case report describes a woman who had a rise in serum theophylline levels when she took aminophylline oral liquid with vidarabine.

Clinical evidence, mechanism, importance and management

A woman taking aminophylline oral liquid developed elevated serum theophylline levels (an increase from 14 mg/L to 24 mg/L) four days after starting to take vidarabine 400 mg daily for herpes zoster.[1] She was also being treated with ampicillin, gentamicin, clindamycin and digoxin, for congestive heart failure, chronic pulmonary disease and suspected sepsis. It was suggested that the vidarabine inhibited the metabolism of the theophylline resulting in the raised levels seen. The general significance of this case is uncertain, but it would now seem prudent to bear this interaction in mind if vidarabine is given with aminophylline or theophylline.

1. Gannon R, Sullman S, Levy RM, Grober J. Possible interaction between vidarabine and theophylline. *Ann Intern Med* (1984) 101, 148–9.

Theophylline + Viloxazine

Viloxazine increases theophylline levels and toxicity may occur.

Clinical evidence

A study in 8 healthy subjects given a single 200-mg dose of theophylline suggested that pretreatment with viloxazine 100 mg three times daily for 3 days increased the $AUC_{0\text{-}24}$ of theophylline by 47%, increased its maximum serum concentration, and reduced its clearance.[1]

An elderly woman hospitalised for respiratory failure and treated with a variety of drugs including theophylline, developed acute theophylline toxicity (a grand mal seizure) 2 days after starting to take viloxazine 200 mg daily. Her serum theophylline levels had increased threefold (from about 10 to 28 mg/L), but the levels fell when the viloxazine was withdrawn.[2] Nausea and vomiting, associated with raised serum theophylline levels, occurred in another patient also taking viloxazine. Theophylline was stopped, and then reintroduced at one-quarter of the original dose. The theophylline level subsequently became subtherapeutic when viloxazine was stopped.[3] A further case report describes an elderly man who had a marked rise in his serum theophylline levels to toxic concentrations (55.3 mg/L) when viloxazine, 100 mg then 300 mg daily, was started.[4]

Mechanism

It is suggested that viloxazine competitively antagonises the metabolism of theophylline by the liver, thereby reducing its clearance and resulting in an increase in its serum levels.

Importance and management

Information seems to be limited to these reports but it would appear to be a clinically important interaction. Theophylline levels should be well monitored if viloxazine is added, anticipating the need to reduce the dose. There appears to be no direct evidence about aminophylline, but it would be prudent to expect it to interact similarly.

1. Perault MC, Griesemann E, Bouquet S, Lavoisy J, Vandel B. A study of the interaction of viloxazine with theophylline. *Ther Drug Monit* (1989) 11, 520–2.
2. Laaban JP, Dupeyron JP, Lafay M, Sofeir M, Rochemaure J, Fabiani P. Theophylline intoxication following viloxazine induced decrease in clearance. *Eur J Clin Pharmacol* (1986) 30, 351–3.
3. Thomson AH, Addis GJ, McGovern EM, McDonald NJ. Theophylline toxicity following coadministration of viloxazine. *Ther Drug Monit* (1988) 10, 359–60.
4. Vial T, Bertholon P, Lafond P, Pionchon C, Grangeon C, Bruel M, Antoine JC, Ollagnier M, Evreux JC. Surdosage en théophylline secondaire à un traitement par viloxazine. *Rev Med Interne* (1994) 15, 696–8.

Theophylline + Zileuton

Zileuton raises theophylline levels and increases the incidence of adverse effects.

Clinical evidence

In a double-blind, crossover study, 13 healthy subjects were given 200 mg of theophylline (*Slo-Phyllin*) four times daily for 5 days and either zileuton 800 mg twice daily or a placebo. Zileuton increased the mean steady-state peak serum levels of theophylline by 73% (from 12 to 21 mg/L), increased its AUC by 92%, and halved its apparent plasma clearance. During the use of zileuton the incidence of adverse effects increased (headache, gastrointestinal effects), which was attributed to theophylline toxicity, and this caused 3 of the original 16 subjects to withdraw from the study.[1]

Mechanism

Not fully established but it seems highly likely that zileuton inhibits the metabolism of theophylline by the cytochrome P450 enzymes (probably the isoenzyme CYP1A2 and the subfamily CYP3A) so that its serum levels rise.

Importance and management

Information is limited but the interaction appears to be established and of clinical importance. Concurrent use need not be avoided but be alert for adverse effects (headache, gastrointestinal effects), and if required, monitor theophylline levels and reduce the dose of theophylline as necessary. The report quoted above suggests that a typical asthma patient may initially need the theophylline dose to be halved, and this dose reduction is recommended by the US manufacturers.[2] Similarly, the dose of theophylline should be reduced if it is given to a patient already taking zileuton, and adjusted according to theophylline levels.[2] This is based on the results of a study in over 1000 patients taking zileuton 600 mg four times daily without apparent problems when this course of action was followed.[1] There seems to be no evidence regarding aminophylline, but it would be expect-

ed to behave similarly, and therefore the same precautions would seem advisable.

1. Granneman GR, Braeckman RA, Locke CS, Cavanaugh JH, Dubé LM, Awni WM. Effect of zileuton on theophylline pharmacokinetics. *Clin Pharmacokinet* (1995) 29 (Suppl 2), 77–83.
2. Zyflo CR (Zileuton). Critical Therapeutics Inc. US Prescribing information, May 2007.

Zafirlukast + Aspirin

Aspirin 650 mg four times daily is reported to have resulted in a mean increase in the plasma levels of zafirlukast 40 mg daily of 45%. No further details are available.[1,2] The clinical importance of this interaction awaits assessment but it seems likely to be small. The manufacturers do not suggest any alteration in the zafirlukast dose.[3]

1. Accolate (Zafirlukast). AstraZeneca Pharmaceuticals LP. US Prescribing information, August 2009.
2. Accolate (Zafirlukast). AstraZeneca UK Ltd. UK Summary of product characteristics, May 2008.
3. Zeneca Pharmaceuticals, Personal communication, July 1997.

Zafirlukast + Macrolides

Zafirlukast levels are decreased by erythromycin. Zafirlukast does not affect the pharmacokinetics of azithromycin or clarithromycin.

Clinical evidence, mechanism, importance and management

Zafirlukast is an inhibitor of the cytochrome P450 isoenzyme CYP3A4 *in vitro*. However, a study in 12 healthy subjects found that zafirlukast 20 mg twice daily for 12 days did not significantly affect the pharmacokinetics of a single 500-mg dose of **azithromycin** or **clarithromycin**.[1]

A study in 11 patients with asthma found that **erythromycin** 500 mg three times daily for 5 days reduced the mean plasma level of zafirlukast 40 mg by about 40%.[2,3] This reduction in levels would be expected to reduce its antiasthmatic effects. If these drugs are given concurrently, be alert for a reduced response. However, note that the manufacturers do not suggest that an alteration in the zafirlukast dose is necessary.[4] Other macrolides that inhibit CYP3A4 (e.g. **clarithromycin**, **telithromycin**) would be expected to interact similarly, and therefore some caution is probably warranted if they are given to patients taking zafirlukast.

1. Garey KW, Peloquin CA, Godo PG, Nafziger AN, Amsden GW. Lack of effect of zafirlukast on the pharmacokinetics of azithromycin, clarithromycin and 14-hydroxyclarithromycin in healthy volunteers. *Antimicrob Agents Chemother* (1999) 43, 1152–5.
2. Accolate (Zafirlukast). AstraZeneca Pharmaceuticals LP. US Prescribing information, August 2009.
3. Accolate (Zafirlukast). AstraZeneca UK Ltd. UK Summary of product characteristics, May 2008.
4. Zeneca Pharmaceuticals, Personal communication, July 1997.

Zafirlukast + Miscellaneous

Zafirlukast plasma levels are decreased by terfenadine. Zafirlukast does not increase the levels of terfenadine, and concurrent use does not prolong the QTc interval. Zafirlukast is predicted to increase the levels of a number of CYP3A4 substrates.

Clinical evidence, mechanism, importance and management

A study in 16 healthy men given zafirlukast 160 mg twice daily for 16 days with terfenadine 60 mg twice daily on days 8 to 16 found that the mean maximum serum levels and AUC of zafirlukast were reduced by 70% and 60%, respectively. There was a small, non-significant reduction in the terfenadine AUC and serum levels.[1] The reduction in zafirlukast serum levels would be expected to reduce its antiasthmatic effects, but this needs assessment. If both drugs are given be alert for a reduced response to zafirlukast.

A study in 8 healthy subjects given zafirlukast 160 mg twice daily with terfenadine 60 mg twice daily for 8 days found that the AUC of terfenadine and the QTc interval were not significantly increased on concurrent use, despite the fact that *in vitro* zafirlukast appears to inhibit the cytochrome P450 isoenzyme CYP3A4, the major enzyme involved in terfenadine metabolism.[2] Because of the apparent *in vitro* effect of zafirlukast on CYP3A4 the manufacturer of zafirlukast advises appropriate clinical monitoring when substrates of CYP3A4 are given with zafirlukast. They name **ciclosporin**, **cisapride**, and **dihydropyridine calcium-channel blockers**.[3] However, in light of the lack of effect of zafirlukast on terfenadine, it would appear that any effect of zafirlukast on CYP3A4 is not clinically relevant.

1. Suttle AB, Birmingham BK, Vargo DL, Wilkinson LA, Morganroth J. Pharmacokinetics of zafirlukast and terfenadine after coadministration to healthy men. *J Clin Pharmacol* (1997) 37, 870.
2. Vargo DL, Suttle AB, Wilkinson LA, Thyrum PT, Tschan JH, Morganroth J. Effect of zafirlukast on QTc and area under the curve of terfenadine in healthy men. *J Clin Pharmacol* (1997) 37, 870.
3. Accolate (Zafirlukast). AstraZeneca Pharmaceuticals LP. US Prescribing information, August 2009.

Zafirlukast + Tobacco

The manufacturer notes that the clearance of zafirlukast may be increased by 20% in patients who smoke.[1] This probably occurs because tobacco smoke can induce liver enzymes, which may increase the metabolism of zafirlukast. The clinical significance of this interaction is unclear, but it seems likely to be small.

1. Accolate (Zafirlukast). AstraZeneca UK Ltd. UK Summary of product characteristics, May 2008.

35

SSRIs, Tricyclics and related antidepressants

The development of the tricyclic antidepressants arose out of work carried out on phenothiazine compounds related to chlorpromazine. The earlier molecules possessed two benzene rings joined by a third ring of carbon atoms, with sometimes a nitrogen, and had antidepressant activity, hence their name. Some of the later antidepressants have one, two or even four rings. 'Table 35.1', (below), lists the common tricyclic and tetracyclic antidepressants, the selective serotonin reuptake inhibitors (SSRIs), the serotonin and noradrenaline reuptake inhibitors (SNRIs) and a number of other drugs that are also used for depression. For interactions involving MAOIs (monoamine oxidase inhibitors), see 'MAOIs', (p.1370).

Table 35.1 SSRIs, Tricyclics and related antidepressants

Group	*Drugs*
SNRIs (Serotonin and noradrenaline reuptake inhibitors)	Duloxetine, Milnacipran, Venlafaxine
SSRIs (Selective serotonin reuptake inhibitors)	Citalopram, Escitalopram, Fluoxetine, Fluvoxamine, Paroxetine, Sertraline
Tetracyclic antidepressants	Maprotiline, Mianserin
Tricyclic antidepressants	Amineptine, Amitriptyline, Amoxapine, Butriptyline, Clomipramine, Desipramine, Dibenzepin, Dosulepin, Doxepin, Imipramine, Lofepramine, Melitracen, Nortriptyline, Opipramol, Protriptyline, Trimipramine
Other antidepressants	Iprindole, Mirtazapine, Nefazodone, Reboxetine, Trazodone, Viloxazine

SNRIs

Antidepressants in this group include duloxetine, milnacipran and venlafaxine. They inhibit both serotonin and noradrenaline reuptake but with differing selectivity. Milnacipran blocks serotonin and noradrenaline reuptake approximately equally, but duloxetine and to a greater extent venlafaxine have selectivity for serotonin and so might be expected to share the pharmacodynamic interactions of the SSRIs, see below. Duloxetine and venlafaxine are reported to weakly inhibit dopamine reuptake. They are also reported to have no significant affinity for histaminergic, muscarinic or adrenergic receptors, and, compared with the tricyclics, appear to lack significant sedative and antimuscarinic effects.

Duloxetine is a moderate inhibitor of CYP2D6 and is a substrate for CYP1A2 and so may interact with drugs that affect these isoenzymes. Similarly, venlafaxine may interact with CYP2D6 inhibitors and to a more minor extent with CYP3A4 inhibitors. Milnacipran, however, does not appear to interact with cytochrome P450 isoenzymes.

SSRIs

These antidepressants act on neurones in a similar way to the tricyclics (see below) but they selectively inhibit the reuptake of serotonin (5-hydroxytryptamine or 5-HT). This can lead to adverse effects such as serotonin syndrome, see 'Additive or synergistic interactions', (p.9). The SSRIs have fewer antimuscarinic effects than the tricyclics and are also less sedative and cardiotoxic. However, they have been associated with bleeding disorders and so caution is advised if they are given with drugs know to affect platelet function.

SSRIs interact with other drugs mainly as a result of their inhibitory activity on cytochrome P450 isoenzymes in the liver; fluoxetine and paroxetine are potent inhibitors of CYP2D6, and fluvoxamine inhibits CYP1A2 and CYP2C19, but citalopram and sertraline are less likely to have any clinical effect, see 'Table 35.2', (p.1465). Note that some SSRIs e.g. fluoxetine have a very long half-life and so interactions may still occur after the drug has been discontinued.

Tricyclic and related antidepressants

The tricyclic antidepressants inhibit the activity of the 'uptake' mechanism by which some chemical transmitters (serotonin (5-HT) or noradrenaline (norepinephrine)) re-enter nerve endings in the CNS. In this way they raise the concentrations of the chemical transmitter in the receptor area. If depression represents some inadequacy in transmission between the nerves in the brain, increasing the amount of transmitter may go some way towards reversing this by improving transmission. Tricyclics vary in the extent that they block the reuptake of these transmitters e.g. clomipramine is more selective for serotonergic transmission and imipramine is more selective for noradrenergic transmission. However, the use of all tricyclics should generally be avoided with MAOIs because of the risk of the serotonin syndrome, see 'MAOIs or RIMAs + Tricyclic and related antidepressants', p.1391.

The tricyclics also have varying degrees of antimuscarinic (sometimes referred to as anticholinergic or atropine-like) activity and can cause dry mouth, blurred vision, constipation, urinary retention and an increase in ocular pressure. They may also cause postural hypotension, sedation, and seizures in certain individuals.

Mianserin and maprotiline are tetracyclic antidepressants, which have actions similar to those of the tricyclic antidepressants. However, while the tetracyclics are more sedating, their antimuscarinic effects are less marked. Maprotiline inhibits the reuptake of noradrenaline (norepinephrine) and has weak affinity for central adrenergic (α_1) receptors. Mianserin does not prevent the peripheral reuptake of noradrenaline; it blocks presynaptic adrenergic (α_2) receptors and increases the turnover of brain noradrenaline. It is also an antagonist of serotonin receptors in some parts of the brain.

All tricyclic antidepressants, mianserin and maprotiline are metabolised by CYP2D6 to some extent and so may be affected by inhibitors of this isoenzyme. See 'Table 35.2', (p.1465), for more detail on the metabolism of individual tricyclics.

Other antidepressant drugs

(a) Mirtazapine

Mirtazapine is a piperazinoazepine and an analogue of mianserin. It is a presynaptic adrenergic α_2-antagonist that increases central noradrenergic and serotonergic transmission. It is a potent inhibitor of histamine (H_1) receptors and this accounts for its sedative properties. It has little antimuscarinic activity.

(b) Nefazodone and Trazodone

Nefazodone is a phenylpiperazine structurally related to trazodone. Both nefazodone and trazodone block the reuptake of serotonin at presynaptic neurones and block α_1-adrenoceptors, but have no apparent effect on dopamine. Unlike trazodone, nefazodone blocks the reuptake of noradrenaline. Compared to the tricyclics, neither drug has very significant

antimuscarinic effects, but trazodone also has marked sedative properties.

Trazodone is a substrate for CYP3A4 and its plasma levels may be affected by inhibitors or inducers of this isoenzyme. Nefazodone is an inhibitor of the cytochrome P450 isoenzyme CYP3A4 and therefore it will inhibit the metabolism of drugs by this route. For a list of CYP3A4 substrates see 'Table 1.4', (p.6). Note that, nefazodone has largely been withdrawn due to adverse hepatic effects.

(c) Reboxetine

Reboxetine is a potent inhibitor of noradrenaline reuptake. It has a weak effect on serotonin reuptake and no significant affinity for muscarinic receptors.

Reboxetine is a substrate for CYP3A4 and its plasma levels may be increased by inhibitors of this isoenzyme.

Table 35.2 Summary of the main effects of antidepressant drugs on cytochrome P450 isoenzymes

Antidepressant drug		*Isoenzyme*		
		Substrate (major pathway)	*Substrate (plays some part)*	*Inhibits*
Bupropion		CYP2B6		CYP2D6 (potent)
Mirtazapine			CYP1A2, CYP2D6, CYP3A4	
Nefazodone				CYP3A4 (potent)
Reboxetine		CYP3A4		
Trazodone		CYP3A4		
SNRIs	**Duloxetine**	CYP1A2	CYP2D6	CYP2D6 (moderate)
	Milnacipran	None		
	Venlafaxine	CYP2D6	CYP3A4	
SSRIs	**Citalopram**		CYP2D6, CYP2C19, CYP3A4 (minor)	CYP2D6 (weak)
	Fluoxetine		CYP2D6	CYP2D6 (moderate), CYP2C9, CYP3A4 (weak)
	Fluvoxamine	CYP2D6	Other metabolic pathways appear to be involved, but no clinical data available	CYP1A2 (potent), CYP2C9, CYP2C19, CYP3A4
	Paroxetine		CYP2D6	CYP2D6 (moderate)
	Sertraline		CYP3A4, CYP2D6 (minor) and possibly other pathways	CYP2D6 (weak)
Tetracyclics	**Maprotiline**		CYP2D6	
	Mianserin		CYP2D6	
Tricyclics	**Amitriptyline**	CYP1A2, CYP2D6	CYP3A4, CYP2C19	
	Clomipramine	CYP2D6	CYP3A4, CYP1A2, CYP2C19	
	Desipramine	CYP2D6		
	Dosulepin		CYP2D6 and possibly other pathways	
	Doxepin	CYP2D6	CYP1A2 (minor), CYP3A4 (minor)	
	Imipramine	CYP1A2, CYP2D6	CYP3A4, CYP2C19	
	Nortriptyline	CYP2D6		
	Trimipramine		CYP2D6 and possibly other pathways	

Bupropion + Antiepileptics; Enzyme-inducing

Carbamazepine markedly decreases bupropion levels and increases the levels of its active metabolite hydroxybupropion. Phenobarbital (and therefore probably primidone) and phenytoin (and therefore fosphenytoin) would be expected to interact similarly.

Clinical evidence, mechanism, importance and management

In a study in 12 patients with major affective disorders, carbamazepine at steady-state markedly decreased the maximum plasma levels and AUC of a single 150 mg dose of bupropion and two of its metabolites (threohydrobupropion and erythrohydrobupropion) by about 81 to 96%. These two metabolites have only weak potential antidepressant activities. However, the AUC and maximum levels of another metabolite, hydroxybupropion (which has similar potency to the parent compound) were increased by 50% and 71%, respectively.[1] Two patients with bipolar illness have been described who received bupropion at a variety of doses (450 to 600 mg daily and 400 to 525 mg daily). They had undetectable bupropion plasma levels while taking carbamazepine but their plasma levels of hydroxybupropion were markedly increased.[2]

What the sum of all these changes is likely to mean is uncertain, but good monitoring for any evidence of reduced efficacy and/or increased toxicity (due to the raised hydroxybupropion levels) is clearly needed. The same good monitoring would also be appropriate with **phenytoin** (and therefore **fosphenytoin**) and **phenobarbital** (and therefore **primidone**), which would be expected to interact similarly, but clinical studies to confirm this appear to be lacking.

Note that bupropion causes dose-related seizures and is contraindicated in patients with seizure disorders.

1. Ketter TA, Jenkins JB, Schroeder DH, Pazzaglia PJ, Marangell LB, George MS, Callahan AM, Hinton ML, Chao J, Post RM. Carbamazepine but not valproate induces bupropion metabolism. *J Clin Psychopharmacol* (1995) 15, 327–33.
2. Popli AP, Tanquary J, Lamparella V, Masand PS. Bupropion and anticonvulsant drug interactions. *Ann Clin Psychiatry* (1995) 7, 99–101.

Bupropion + Antiplatelet drugs

Clopidogrel and ticlopidine appear to inhibit the metabolism of bupropion to hydroxybupropion.

Clinical evidence

(a) Clopidogrel

A study in healthy subjects given clopidogrel 75 mg daily for 4 days found that the AUC of a single 150-mg dose of bupropion was increased by 60% and the AUC of its active metabolite, hydroxybupropion, was reduced by 52%.[1]

(b) Ticlopidine

A study in healthy subjects given ticlopidine 250 mg twice daily for 4 days found that the AUC of a single 150-mg dose of bupropion was increased by 85% and the AUC of its active metabolite, hydroxybupropion, was reduced by 84%.[1]

Mechanism

Bupropion is metabolised by the cytochrome P450 isoenzyme CYP2B6, which can be inhibited by clopidogrel and ticlopidine.[1,2] Concurrent use therefore decreases bupropion metabolism and increases its levels.

Importance and management

The pharmacokinetic interactions between bupropion and clopidogrel or ticlopidine are established, but the clinical relevance of the increase in active bupropion levels and decrease in active hydroxybupropion levels is unclear. Until more is known about this interaction it would seem prudent to monitor concurrent use for any alterations in bupropion adverse effects (lightheadedness, gastrointestinal effects) and/or efficacy, adjusting the dose if necessary.

1. Turpeinen M, Tolonen A, Uusitalo J, Jalonen J, Pelkonen O, Laine K. Effect of clopidogrel and ticlopidine on cytochrome P450 2B6 activity as measured by bupropion hydroxylation. *Clin Pharmacol Ther* (2005) 77, 553–9.
2. Richter T, Mürdter TE, Heinkele G, Pleiss J, Tatzel S, Schwab M, Eichelbaum M, Zanger UM. Potent mechanism-based inhibition of human CYP2B6 by clopidogrel and ticlopidine. *J Pharmacol Exp Ther* (2004) 308, 189–97.

Bupropion + Antiretrovirals

Ritonavir, both at doses used to boost the levels of other protease inhibitors and higher doses, *decreases* bupropion levels. This is the opposite effect to that which was originally predicted.

Clinical evidence

In a study in 7 healthy subjects, **ritonavir** 200 mg or placebo was given twice daily for 2 days with a single 75-mg dose of bupropion given with the third dose. The *increases* in bupropion AUC and maximum level (20% and 31%) were not statistically significant. Similarly, the changes in metabolite pharmacokinetics were slight, and mostly non-significant.[1] In contrast, the UK manufacturers of bupropion report a study in healthy subjects in which a higher dose of **ritonavir** (600 mg twice daily) for a longer time period (20 days) *decreased* the AUC and maximum serum levels of bupropion by about 65% and 60%, respectively. The plasma levels of the active metabolites of bupropion were also decreased.[2] Similarly, in another study in healthy subjects, **ritonavir**-boosted **lopinavir** 100/400 mg twice daily for 2 weeks *decreased* the AUC and maximum serum levels of bupropion after a single 100-mg dose of the sustained-release formulation by 57%. The plasma levels of hydroxybupropion were also decreased. The pharmacokinetics of ritonavir-boosted lopinavir were unchanged by the single dose of bupropion.[3]

A retrospective study identified 10 HIV-positive patients who had taken bupropion 150 mg once or twice daily together with **nelfinavir**, **ritonavir** or **efavirenz** for 3 weeks to 2 years (median 8 months). No seizures had occurred in these patients (predicted if a marked increase in bupropion levels had occurred), but note that the number of patients was small. The 2 patients who received **ritonavir** were given 100 mg twice daily.[4]

Mechanism

In vitro data[5] indicated that the antiretroviral drugs efavirenz, nelfinavir and ritonavir are capable of inhibiting the cytochrome P450 isoenzyme CYP2B6, which is the isoenzyme primarily involved in bupropion metabolism. It was therefore predicted that these drugs would cause an *increase* in bupropion concentrations,[5] with an increased risk of seizures. However, more recent *in vitro* evidence shows that ritonavir strongly induces CYP2B6,[6] and this is supported by the clinical evidence showing that ritonavir decreases bupropion levels. This is not the first interaction where ritonavir has caused the opposite effect to that which was originally predicted, other examples being 'methadone', (p.200) and 'contraceptives', (p.1187). A possible explanation is that therapeutically-achieved levels of ritonavir induce UDP-glucuronosyltransferase enzymes and induce CYP2B6.[3]

Importance and management

Taken together, the evidence suggests that ritonavir, irrespective of dose, decreases the levels of bupropion and its active metabolite. This effect is not seen with just 2 days use of ritonavir given to boost the levels of other protease inhibitors (i.e. 100 mg twice daily) in one study, but was apparent at 2 weeks in another. The extent of reduction in bupropion levels seen suggests that the dose of bupropion might need to be doubled to achieve the same effect.[3] It would seem prudent to start bupropion at the recommended starting dose and titrate to effect. Nevertheless, because of the original *in vitro* data, the UK manufacturers of bupropion currently caution that the recommended doses should not be exceeded.[2]

On the basis of the findings with ritonavir, it is not possible to predict what will occur clinically with efavirenz or nelfinavir-containing regimens. In these cases, it would seem prudent to start bupropion at the lowest recommended dose and titrate to effect.

1. Hesse LM, Greenblatt DJ, von Moltke LL, Court MH. Ritonavir has minimal impact on the pharmacokinetic disposition of a single dose of bupropion administered to human volunteers. *J Clin Pharmacol* (2006) 46, 567–76.

2. Zyban (Bupropion hydrochloride). GlaxoSmithKline UK. UK Summary of product characteristics, January 2009.
3. Hogeland GW, Swindells S, McNabb JC, Kashuba AD, Yee GC, Lindley CM. Lopinavir/ritonavir reduces bupropion plasma concentrations in healthy subjects. *Clin Pharmacol Ther* (2007) 81, 69–75.
4. Park-Wyllie LY, Antoniou T. Concurrent use of bupropion with CYP2B6 inhibitors, nelfinavir, ritonavir and efavirenz: a case series. *AIDS* (2003) 17, 638–40.
5. Hesse LM, von Moltke LL, Shader RI, Greenblatt DJ. Ritonavir, efavirenz, and nelfinavir inhibit CYP2B6 activity in vitro: potential drug interactions with bupropion. *Drug Metab Dispos* (2001) 29, 100–102.
6. Faucette SR, Wang H, Hamilton GA, Jolley SL, Gilbert D, Lindley C, Yan B, Negishi M, LeCluyse EL. Regulation of CYP2B6 in primary human hepatocytes by prototypical inducers. *Drug Metab Dispos* (2004) 32, 348–58.

Bupropion + Benzodiazepines and related drugs

Visual hallucinations have been seen in one patient given zolpidem with bupropion. Bupropion is contraindicated during the abrupt withdrawal from any drug known to be associated with seizures on withdrawal, particularly the benzodiazepines and related drugs.

Clinical evidence, mechanism, importance and management

Visual hallucinations lasting 3 to 4 hours occurred in a 17-year-old boy who had been taking bupropion 450 mg daily for one month and **zolpidem** 5 to 10 mg daily for about 6 months, when he increased the **zolpidem** dose to 60 mg.[1] Note that the recommended dose of **zolpidem** is 10 mg daily and that **zolpidem** itself can cause psychiatric adverse effects such as hallucinations. Therefore an interaction is not established.

Bupropion is contraindicated during abrupt withdrawal from any drug known to be associated with seizures on withdrawal, particularly benzodiazepines and benzodiazepine-like drugs.[2,3]

1. Elko CJ, Burgess JL, Robertson WO. Zolpidem-associated hallucinations and serotonin reuptake inhibition: a possible interaction. *Clin Toxicol* (1998) 36, 195–203.
2. Zyban (Bupropion hydrochloride). GlaxoSmithKline UK. UK Summary of product characteristics, January 2009.
3. Zyban (Bupropion hydrochloride). GlaxoSmithKline. US Prescribing information, July 2009.

Bupropion + Carbimazole

An isolated report describes acute liver failure in a patient taking bupropion and carbimazole.

Clinical evidence, mechanism, importance and management

A 41-year-old man treated for hyperthyroidism with carbimazole 15 mg daily and propranolol 10 mg daily for 5 years received a 10-day course of bupropion 150 mg daily to aid smoking cessation. Ten weeks after completing the course of bupropion he was admitted to hospital with severe jaundice, nausea, dyspepsia, lethargy, and epigastric discomfort persisting for 5 days. The only other medication he had taken was paracetamol (acetaminophen) 500 mg to 1 g daily for up to 2 days, about 2 weeks before admission. Both carbimazole and propranolol were discontinued. He developed acute liver failure and a rapid deterioration of renal function, complicated by sepsis and coagulopathy. Liver biopsy showed evidence of non-specific drug-induced acute liver injury. The patient died 19 days after the onset of symptoms.[1]

Both bupropion and carbimazole may cause liver damage. In this case the hepatotoxicity was attributed to bupropion or a combined toxic effect of bupropion and carbimazole. The potential for serious hepatotoxicity should be borne in mind if bupropion is given with other hepatotoxic drugs.

1. Khoo A-L, Tham L-S, Lee K-H, Lim G-K. Acute liver failure with concurrent bupropion and carbimazole therapy. *Ann Pharmacother* (2003) 37, 220–3.

Bupropion + Cimetidine

A randomised, crossover study in 24 healthy subjects found no evidence of any significant pharmacokinetic interaction between a single 300-mg dose of bupropion (sustained release preparation) and a single 800-mg dose of cimetidine.[1] No dose adjustments would seem to be necessary on concurrent use.

1. Kustra R, Corrigan B, Dunn J, Duncan B, Hsyu P-H. Lack of effect of cimetidine on the pharmacokinetics of sustained-release bupropion. *J Clin Pharmacol* (1999) 39, 1184–8.

Bupropion + Corticosteroids

A patient taking bupropion had a seizure after being given an intra-articular injection of methylprednisolone.

Clinical evidence, mechanism, importance and management

A case report describes a patient taking bupropion, who experienced a severe, prolonged seizure 24 hours after receiving intra-articular **methylprednisolone** 30 mg for subacromial bursitis.[1] The author notes that there could be a risk of seizures in patients taking bupropion who are given prophylactic oral steroids.[1] This is in line with the manufacturers' suggestion that systemic steroids could increase the risk of seizures. See 'Bupropion + Miscellaneous', p.1468, for a further discussion of the risk of seizures with bupropion.

1. White P. Interaction of intra-articular steroids and bupropion. *Clin Radiol* (2002) 57, 235.

Bupropion + Guanfacine

A grand mal seizure in a child, which was attributed to an interaction between bupropion and guanfacine, was later identified as being more probably due to a bupropion overdose.

Clinical evidence, mechanism, importance and management

A 10-year-old girl, being treated for attention deficit hyperactivity disorder, was prescribed increasing doses of bupropion, up to 100 mg three times daily, to which guanfacine, initially 500 micrograms twice daily then 500 micrograms three times daily, was added. Ten days later she had a grand mal seizure, which the author of the report attributed to an interaction between the two drugs.[1,2] This was challenged in subsequent correspondence.[3] Furthermore, 2 years later the author of the original report wrote to say that he had now discovered that the girl had in fact taken 500 mg of bupropion and 5 mg of guanfacine before the seizure took place, so that what happened was much more likely to have been due to an overdose of the bupropion (which is known to cause seizures) than to an interaction with guanfacine.[4]

1. Tilton P. Bupropion and guanfacine. *J Am Acad Child Adolesc Psychiatry* (1998) 37, 682–3.
2. Tilton P. Seizure associated with bupropion and guanfacine. *J Am Acad Child Adolesc Psychiatry* (1999) 38, 3.
3. Namerow LB. Seizure associated with bupropion and guanfacine. *J Am Acad Child Adolesc Psychiatry* (1999) 38, 2.
4. Tilton P. Seizure after guanfacine plus bupropion: correction. *J Am Acad Child Adolesc Psychiatry* (2000) 39, 1341.

Bupropion + Hormonal contraceptives or HRT

HRT and, to a lesser extent, an oral combined hormonal contraceptive modestly inhibited the metabolism of bupropion to hydroxybupropion in one study.

Clinical evidence

In a three-way crossover study in 12 healthy women, a single 150-mg dose of sustained-release bupropion was given alone or on day 10 of treatment with menopausal hormone replacement therapy (**estradiol/levonorgestrel** 2 mg/250 micrograms; *Cyclabil*) or an oral combined hormonal contraceptive (**ethinylestradiol/desogestrel** 30/150 micrograms; *Marvelon*) for 10 days. The HRT reduced the AUC of hydroxybupropion by 47% and increased the AUC of hydrobupropion by 64%, but the AUC of bupropion was unchanged. The AUC of hydroxybupropion was also reduced by the hormonal contraceptive, but to a slightly lesser extent (31%), the AUC of bupropion was slightly reduced (19%) but hydrobupropion was not significantly affected.[1]

Mechanism

Bupropion is extensively metabolised to hydroxybupropion (an active metabolite) by the cytochrome P450 isoenzyme CYP2B6, and this study suggests that HRT and, to a lesser extent, oral contraceptives may inhibit CYP2B6 activity. Which of the constituents were principally responsible for this effect is unknown.

Importance and management

The clinical effect of the modest reduction in the levels of the active metabolite of bupropion and increase in levels of bupropion with HRT has not been assessed. Until more is known about the consequence of altering the ratio of these active metabolites, it might be prudent to increase monitoring of adverse effects and/or efficacy when bupropion is used with HRT.

The more modest effects of the combined oral contraceptive are unlikely to be clinically relevant.

1. Palovaara S, Pelkonen O, Uusitalo J, Lundgren S, Laine K. Inhibition of cytochrome P450 2B6 activity by hormone replacement therapy and oral contraceptive as measured by bupropion hydroxylation. *Clin Pharmacol Ther* (2003) 74, 326–33.

Bupropion + Lamotrigine

Bupropion does not alter the pharmacokinetics of lamotrigine. Hypomania has been reported in a patient taking bupropion and lamotrigine.

Clinical evidence, mechanism, importance and management

A study in 12 healthy subjects found that bupropion 150 mg twice daily did not affect the pharmacokinetics of a single 100-mg dose of lamotrigine.[1]

A 23-year-old patient with a DSM-IV diagnosis of major depression taking bupropion 400 mg daily had an improvement in mood when she was also given lamotrigine 25 mg at night, and there was further improvement in mood, decreased anxiety and increased energy when lamotrigine was increased to 50 mg daily for 3 weeks. However, when the dose of lamotrigine was increased to 75 mg daily she reported decreased sleep, increased energy, mood lability and increased spending, which was diagnosed as hypomania. The symptoms resolved over about 2 weeks when the lamotrigine dose was reduced to 50 mg at bedtime.

Antidepressants in high doses or in combination can induce hypomania and in this case the effect was attributed to a potentiation of the effects of bupropion, caused by lamotrigine.[2] The general relevance of this single case is uncertain.

Note that bupropion causes dose-related seizures and is contraindicated in patients with seizure disorders.

1. Odishaw J, Chen C. Effects of steady-state bupropion on the pharmacokinetics of lamotrigine in healthy subjects. *Pharmacotherapy* (2000) 20, 1448–53.
2. Margolese HC, Beauclair L, Szkrumelak N, Chouinard G. Hypomania induced by adjunctive lamotrigine. *Am J Psychiatry* (2003) 160, 183–4.

Bupropion + Linezolid

An isolated report describes intraoperative hypertension in a patient taking bupropion and linezolid, which has weak MAO inhibitory activity.

Clinical evidence, mechanism, importance and management

An isolated report describes severe intermittent intraoperative hypertension in a 57-year-old man undergoing surgical removal of an infected vascular bypass graft. He was taking maintenance bupropion (dosage not stated) and linezolid, which had been started 24 hours previously for treatment of a resistant gram-positive infection.[1] Linezolid is known to have weak reversible MAOI properties, and might therefore interact with bupropion in a way similarly to that predicted for non-selective MAOIs, see 'MAOIs or RIMAs + Bupropion', p.1374. Although concurrent use need not be avoided, this report therefore introduces a note of caution if both drugs are given together.

1. Marcucci C, Sandson NB, Dunlap JA. Linezolid-bupropion interaction as possible etiology of severe intermittent intraoperative hypertension? *Anesthesiology* (2004) 101, 1487–8.

Bupropion + Methylphenidate

Isolated reports describe grand mal seizures in one patient and myocardial infarction in another, which were associated with the concurrent use of bupropion and methylphenidate.

Clinical evidence, mechanism, importance and management

(a) Seizures

A 14-year-old boy taking methylphenidate 60 mg daily was also given bupropion 200 mg increased to 300 mg daily. The patient experienced grand mal seizures 4 weeks after the dosage increase, but remained seizure-free once the bupropion was discontinued.[1] The authors note that bupropion alone could have been the cause of the seizures, but that methylphenidate might have been a contributory factor. Note that the manufacturers of bupropion list stimulants as drugs that increase the risk of seizures with bupropion (see 'Bupropion + Miscellaneous', below) and this case adds weight to that warning.

(b) Myocardial ischaemia

A report describes acute myocardial infarction in a 16-year-old boy who was taking methylphenidate 30 mg twice daily for attention-deficit hyperactivity disorder, bupropion 100 mg twice daily for depression and sustained-release erythromycin 999 mg daily for acne (duration of each not noted). It was proposed that the erythromycin might have caused elevated levels of bupropion leading to a hyperadrenergic state and this, together with the sympathetic effects of the methylphenidate, resulted in excessive vasospasm, leading to myocardial damage.[2] However, there is no clear known mechanism by which erythromycin (a CYP3A4 and P-glycoprotein inhibitor) would increase bupropion levels (a CYP2B6 substrate).

1. Ickowicz A. Bupropion-methylphenidate combination and grand mal seizures. *Can J Psychiatry* (2002) 47, 790–1.
2. George AK, Kunwar AR, Awasthi A. Acute myocardial infarction in a young male on methylphenidate, bupropion, and erythromycin. *J Child Adolesc Psychopharmacol* (2005) 15, 693–5.

Bupropion + Miscellaneous

The manufacturers of bupropion caution its concurrent use with amantadine and levodopa (higher risk of adverse effects) and drugs that can lower the convulsive threshold (possible increased risk of seizures). Bupropion inhibits the metabolism of drugs that are substrates of the cytochrome P450 isoenzyme CYP2D6. Drugs that inhibit CYP2B6 can reduce the metabolism of bupropion to hydroxybupropion.

Clinical evidence, mechanism, importance and management

(a) Antiparkinsonian drugs

The manufacturers say that the concurrent use of bupropion and **levodopa** or **amantadine** should be undertaken with caution because limited clinical data suggest a higher incidence of undesirable effects (nausea, vomiting, excitement, restlessness, postural tremor) in patients given bupropion with either drug. Good monitoring is therefore appropriate and patients should be given small initial bupropion doses, which are increased gradually.[1,2]

(b) CYP2B6 substrates and inhibitors

The manufacturers advise caution if bupropion is used with drugs that are substrates or inhibitors of the cytochrome P450 isoenzyme CYP2B6 because bupropion is metabolised to its major active metabolite hydroxybupropion by this isoenzyme.[1,2] They list the antineoplastics **cyclophosphamide**, **ifosfamide**, and **thiotepa**, the antiplatelet drugs **clopidogrel** and **ticlopidine**, and the antimuscarinic **orphenadrine**. However, few, if any, pharmacokinetic interactions are found to be attributable to the effects of two substrates of an isoenzyme given together, and it is not usual to issue cautions solely on this basis (note that **cyclophosphamide** and **ifosfamide** are CYP2B6 substrates, and not known to be inhibitors of this isoenzyme). CYP2B6 inhibitors would be predicted to affect the pharmacokinetics of bupropion, and this interaction has been seen with clopidogrel and ticlopidine, see 'Bupropion + Antiplatelet drugs', p.1466, and with contraceptives and HRT, see 'Bupropion + Hormonal contraceptives or HRT', p.1467. **Thiotepa** and **orphenadrine** are predicted to interact similarly. Nevertheless, the clinical relevance of this interaction is far from clear be-

cause both bupropion and hydroxybupropion are active, and the clinical consequences of altering the ratio of these two substances is unknown.

(c) CYP2D6 substrates

Bupropion is an inhibitor of the cytochrome P450 isoenzyme CYP2D6, and has been shown to raise the levels of a number of CYP2D6 substrates including 'desipramine', (p.1501), 'dextromethorphan', (p.1556) and 'metoprolol', (p.1000). Note that CYP2D6 shows genetic polymorphism, with about 10% of the population lacking active CYP2D6 (poor metabolisers). Therefore, pharmacokinetic interactions between CYP2D6 inhibitors and CYP2D6 substrates are often less important than might initially be supposed, because a potent inhibitor of this isoenzyme will effectively be changing a person who is an extensive metaboliser into a poor metaboliser (i.e. any change is still within the range of the existing population). The situation when an interaction is likely to be important is when an extensive metaboliser on established treatment with a CYP2D6 substrate that has a narrow therapeutic window then starts a CYP2D6 inhibitor. Bupropion should therefore be used with some caution with drugs that are known substrates of CYP2D6, particularly those with a narrow therapeutic window. A list of CYP2D6 substrates is given in 'Table 1.3', (p.6), and the manufacturers of bupropion specifically name **haloperidol**, **risperidone**, **thioridazine**, **flecainide**, and **propafenone**. The recommendation is that if any of these drugs is added to treatment with bupropion, doses at the lower end of the range should be used. If bupropion is added to existing treatment, decreased dosages should be considered.[1,2]

(d) Drugs that can lower the convulsive threshold

There is a small dose-related risk of seizures with bupropion. At a daily dose of 300 mg of the sustained-release formulation the risk is 0.1%, which increases to 0.4% at a dose of 450 mg of the immediate-release formulation, and increases tenfold between doses of 450 and 600 mg daily.[2] The manufacturers caution the use of other drugs that lower the convulsive threshold, the concern being that these drugs might further increase the risk of seizures. The UK[1] and US[2] manufacturers list **antipsychotics**, antidepressants, systemic steroids, and **theophylline**. In some cases seizures have been seen when bupropion is given with these drugs, see 'SSRIs + Bupropion', p.1482, 'Tricyclic antidepressants + Bupropion', p.1501, and 'Bupropion + Corticosteroids', p.1467. The UK manufacturers additionally list **antimalarials**, **tramadol**, **quinolones** and **sedating antihistamines**. A maximum dose of 150 mg of bupropion should be considered for patients prescribed such drugs.[1]

Caution is also urged with regard to circumstances that may lower the convulsive threshold, including the use of **anorectics** or **stimulants** (one case seen with methylphenidate, see 'Bupropion + Methylphenidate', p.1468), the excessive use of **sedatives**, and addiction to **cocaine** or **opiates**.[1,2]

1. Zyban (Bupropion hydrochloride). GlaxoSmithKline UK. UK Summary of product characteristics, January 2009.
2. Zyban (Bupropion hydrochloride). GlaxoSmithKline. US Prescribing information, July 2009.

Bupropion + Pseudoephedrine

An isolated report describes acute myocardial ischaemia associated with bupropion and pseudoephedrine in a recent tobacco smoker.

Clinical evidence, mechanism, importance and management

A 21-year-old man presented to a hospital emergency department with severe chest pain radiating into both arms and between the shoulder blades, diaphoresis and shortness of breath. This was diagnosed as an acute myocardial infarction, and it was concluded that this was due to acute myocardial ischaemia apparently brought on by the combined use of pseudoephedrine (9 tablets of 30 mg taken over the previous 3 days), bupropion for smoking cessation (started in the previous 72 hours) and **nicotine** from tobacco (he had smoked 25 cigarettes daily). The authors of the report postulate that all these drugs acted on the alpha receptors of the coronary arteries to cause vasospasm and acute ischaemia. He had also been taking erythromycin for 3 days (which is not thought to be related to the interaction), and had previously taken pseudoephedrine alone on numerous occasions without problems. He recovered fully.[1]

This is an isolated case from which no general conclusions can be drawn, but some warning might be appropriate for patients who are at risk of coronary ischaemia. For comment on the use of nicotine with bupropion, see 'Bupropion + Tobacco or Nicotine', p.1470.

1. Pederson KJ, Kuntz DH, Garbe GJ. Acute myocardial ischemia associated with ingestion of bupropion and pseudoephedrine in a 21-year-old man. *Can J Cardiol* (2001) 17, 599–601.

Bupropion + Rifampicin (Rifampin)

Rifampicin markedly reduces the AUC of both bupropion and its active metabolite hydroxybupropion.

Clinical evidence

In a controlled study in 16 healthy subjects, rifampicin 600 mg daily for 10 days caused a threefold decrease in the AUC of a single 150-mg dose of bupropion given on day 8. Bupropion clearance was increased threefold, and the elimination half-life was reduced from 15.9 hours to 8.2 hours. The AUC of the main active metabolite, hydroxybupropion, was also reduced (by about 75%), but its maximum level was *increased* by about 75%. There was no difference in the effect of rifampicin on bupropion between the 9 subjects who were ethnically Chinese and the 9 who were white European, after adjusting for body-weight.[1]

Further studies have found that rifampicin has a greater effect on the *S*-enantiomer of bupropion and the *S,S*-hydroxyl bupropion metabolite than on the other enantiomers.[2,3]

Mechanism

Rifampicin induces the cytochrome P450 isoenzyme CYP2B6, which is responsible for the hydroxylation of bupropion, and also the metabolism of hydroxybupropion.

Importance and management

The pharmacokinetic interaction is established. Rifampicin would be expected to markedly increase the metabolism of bupropion and its active metabolite. Although the clinical relevance of this has not been directly assessed, it would be anticipated that reductions in efficacy might result. Monitor the efficacy of bupropion in any patient requiring rifampicin, and titrate the bupropion dose as necessary.

1. Loboz KK, Gross AS, Williams KM, Liauw WS, Day RO, Blievernicht JK, Zanger UM, McLachlan AJ. Cytochrome P450 2B6 activity as measured by bupropion hydroxylation: effect of induction by rifampin and ethnicity. *Clin Pharmacol Ther* (2006) 80, 75–84.
2. Kharasch ED, Mitchell D, Coles R. Stereoselective bupropion hydroxylation as an in vivo phenotypic probe for cytochrome P4502B6 (CYP2B6) Activity. J Clin Pharmacol (2008) 48, 464–74.
3. Xu H, Loboz KK, Gross AS, McLachlan AJ. Stereoselective analysis of hydroxybupropion and application to drug interaction studies. *Chirality* (2007) 19, 163–70.

Bupropion + St John's wort (*Hypericum perforatum*)

There is a single case of dystonia when bupropion was started in a patient taking HRT and St John's wort. A case of mania was attributed to the use of St John's wort in a patient taking bupropion.

Clinical evidence, mechanism, importance and management

(a) Dystonia

A 58-year-old woman taking St John's wort 300 mg daily and menopausal HRT (estradiol/medroxyprogesterone) developed acute facial dystonia four days after starting bupropion 150 mg daily for smoking cessation. She was treated with a variety of drugs, and over a couple of weeks the spasm-free interval lengthened, and by 5 months the dystonia resolved completely and all medications were withdrawn without recurrence of the dystonia.[1] Dystonia is a rare adverse effect of bupropion alone, and the authors suggested that the combination of bupropion with St John's wort lead to additive effects on serotonin reuptake inhibition, making dopaminergic adverse effects such as dystonia more likely.[1] Note also that one HRT preparation has been shown to inhibit the metabolism of bupropion to hydroxybupropion (see 'Bupropion + Hormonal contraceptives or HRT', p.1467), so it could be hypothesised that there might also be a pharmacokinetic element to this case.

From a single case report like this is it impossible to establish an interaction. Bear this case in mind in the event of similar adverse effects.

(b) Mania

A report very briefly mentions that St John's wort was suspected of inducing mania in one patient who was also taking bupropion.[2] No other details were given, and no general conclusions can be drawn from this isolated report.

1. Milton JC, Abdulla A. Prolonged oro-facial dystonia in a 58 year old female following therapy with bupropion and St John's wort. *Br J Clin Pharmacol* (2007) 64, 717–18.
2. Griffiths J, Jordan S, Pilan K. Natural health products and adverse reactions. *Can Adverse React News* (2004) 14 (1), 2–3.

Bupropion + Tobacco or Nicotine

Neither nicotine nor tobacco smoking alter the pharmacokinetics of bupropion. However, combined use of bupropion and nicotine replacement therapy appears to increase the risk of hypertension.

Clinical evidence, mechanism, importance and management

(a) Nicotine

Nicotine transdermal patches are reported not to affect the pharmacokinetics of bupropion or its metabolites.[1] The manufacturers of bupropion say that limited data suggest that giving up smoking is more easily achieved if bupropion is taken while using a nicotine transdermal system, but a higher rate of treatment-emergent hypertension has been noted on concurrent use.[1,2] They recommend weekly monitoring to check for any evidence of a blood pressure increase.[1] The same warning would also seem to be applicable to the use of nicotine in any other form (buccal or nasal).

For a report of acute myocardial ischaemia attributed to combined use of bupropion, nicotine (from smoking) and pseudoephedrine, see 'Bupropion + Pseudoephedrine', p.1469.

(b) Tobacco

In a pharmacokinetic study, there was no difference in the pharmacokinetics of bupropion (given as a single 150-mg sustained release tablet) and its major metabolites between subjects who were tobacco smokers and those who were non-smokers.[3] Similarly, in a study in adolescents, there was no difference in the pharmacokinetics of bupropion or hydroxybupropion between 37 smokers and 38 non-smokers when given a single 150-mg dose of sustained release bupropion.[4]

This suggests that there is no need to alter the dose of bupropion based on smoking status.

1. Zyban (Bupropion hydrochloride). GlaxoSmithKline UK. UK Summary of product characteristics, January 2009.
2. Zyban (Bupropion hydrochloride). GlaxoSmithKline. US Prescribing information, July 2009.
3. Hsyu PH, Singh A, Giargiari TD, Dunn JA, Ascher JA, Johnston JA. Pharmacokinetics of bupropion and its metabolites in cigarette smokers versus nonsmokers. *J Clin Pharmacol* (1997) 37, 737–43.
4. Stewart JJ, Berkel HJ, Parish RC, Simar MR, Syed A, Bocchini JA Jr, Wilson JT, Manno JE. Single-dose pharmacokinetics of bupropion in adolescents: effects of smoking status and gender. *J Clin Pharmacol* (2001) 41, 770–8.

Bupropion + Valproate

Valproate appears to increase levels of the major active metabolite of bupropion. Evidence from one case suggests that high-dose bupropion might modestly increase valproate levels. Hallucinations have been reported in a patient taking both drugs.

Clinical evidence, mechanism, importance and management

In a study in 5 patients with major affective disorders, the AUC of hydroxybupropion, an active metabolite of bupropion, almost doubled when a single 150-mg dose of bupropion was given with valproate at steady-state, but the pharmacokinetics of bupropion itself and its two other less active metabolites were unaffected.[1] A case report describes an increase in valproate levels of almost 30% after bupropion was started and increased to 450 mg daily.[2] Visual and auditory hallucinations were reported in a patient taking bupropion when valproate was substituted for lithium. The hallucinations stopped when bupropion was withdrawn.[3]

The UK manufacturer recommends caution when using drugs that may inhibit bupropion metabolism, and they name valproate.[4] As valproate levels might possibly also be modestly increased by bupropion, good monitoring for evidence of increased adverse effects of both drugs would seem appropriate.

Note that bupropion causes dose-related seizures and is contraindicated in patients with seizure disorders.

1. Ketter TA, Jenkins JB, Schroeder DH, Pazzaglia PJ, Marangell LB, George MS, Callahan AM, Hinton ML, Chao J, Post RM. Carbamazepine but not valproate induces bupropion metabolism. *J Clin Psychopharmacol* (1995) 15, 327–33.
2. Popli AP, Tanquary J, Lamparella V, Masand PS. Bupropion and anticonvulsant drug interactions. *Ann Clin Psychiatry* (1995) 7, 99–101.
3. Filteau M-J, Leblanc J, Lefrançoise S, Demers M-F. Visual and auditory hallucinations with the association of bupropion and valproate. *Can J Psychiatry* (2000) 45, 198–9.
4. Zyban (Bupropion hydrochloride). GlaxoSmithKline UK. UK Summary of product characteristics, January 2009.

Mirtazapine + Antiepileptics; Enzyme-inducing

Carbamazepine and phenytoin can decrease the plasma levels of mirtazapine. Other enzyme-inducing antiepileptics would be expected to interact similarly. Carbamazepine and phenytoin levels are unaffected by mirtazapine.

Clinical evidence

In a placebo-controlled study, healthy subjects were given **carbamazepine** (at steady state) with mirtazapine for 7 days. It was found that **carbamazepine** decreased the AUC and maximum plasma levels of mirtazapine by 63% and 44%, respectively, and increased the peak levels (but not the AUC) of demethylmirtazapine. Another related study found that mirtazapine did not affect the pharmacokinetics of **carbamazepine**.[1]

A study in 9 healthy subjects given **phenytoin** 200 mg daily for 17 days, with mirtazapine 15 mg daily for 2 days from day 11, and then 30 mg daily for 5 days, found that mirtazapine had no effect on the steady-state pharmacokinetics of **phenytoin**.[2] In a second associated study, 8 healthy subjects were given mirtazapine 15 mg daily for 2 days then 30 mg daily for 15 days with **phenytoin** 200 mg daily on days 8 to 17. It was found that **phenytoin** decreased the AUC and maximum plasma levels of mirtazapine by 47% and 33%, respectively.[2]

Mechanism

Mirtazapine is metabolised by cytochrome P450 isoenzymes CYP1A2, CYP2D6 and CYP3A4, and it is likely that carbamazepine and phenytoin induce its metabolism by these routes, resulting in the lower levels seen in the studies.

Importance and management

The pharmacokinetic interactions between mirtazapine and carbamazepine and phenytoin would appear to be established. Although the clinical relevance of halving mirtazapine levels has not been established, it would not be unexpected for decreases of this magnitude to result in reduced efficacy in some patients. Monitor concurrent use carefully. The UK manufacturers of mirtazapine advise that if carbamazepine, phenytoin or other drugs that induce drug metabolism (such as **rifampicin** (**rifampin**)) are given with mirtazapine, the mirtazapine dose may have to be increased. Further, if treatment with an inducer is stopped, the mirtazapine dosage may have to be reduced.[3] Although not specifically named, **fosphenytoin**, **phenobarbital** and **primidone** can also induce cytochrome P450 isoenzymes, and they therefore may interact similarly.

Note that, as with other antidepressants, the use of mirtazapine should be carefully considered in patients taking these drugs for epilepsy, because of the possible increased risk of seizures.

1. Sitsen JMA, Maris FA, Timmer CJ. Drug-drug interaction studies with mirtazapine and carbamazepine in healthy male subjects. *Eur J Drug Metab Pharmacokinet* (2001) 26, 109–21.
2. Spaans E, van den Heuvel MW, Schnabel PG, Peeters PAM, Chin-Kon-Sung UG, Colbers EPH, Sitsen JMA. Concomitant use of mirtazapine and phenytoin: a drug-drug interaction study in healthy male subjects. *Eur J Clin Pharmacol* (2002) 58, 423–9.
3. Zispin (Mirtazapine). Organon Laboratories Ltd. UK Summary of product characteristics, February 2009.

Mirtazapine + Benzodiazepines

The sedative effects of mirtazapine are increased by the benzodiazepines.

Clinical evidence, mechanism, importance and management

A single-dose study in 12 healthy subjects found that the pharmacokinetics of mirtazapine 15 mg and **diazepam** 15 mg were not affected by concurrent use. However, **diazepam** further impaired the action of mirtazapine on objectively measured skill performance: the combined actions were mostly additive. The effects seen were of similar magnitude to those found when amitriptyline 50 mg was given with diazepam 15 mg.[1]

Mirtazapine has prominent sedative effects and these are likely to be additive with those of diazepam and any other benzodiazepine.

This additive pharmacodynamic interaction is expected. Caution is required on concurrent use, particularly on starting treatment, and patients should be advised to avoid driving or operating machinery if feeling drowsy (note that this caution would apply to either drug used alone). Note that the US manufacturer actually recommends that patients taking mirtazapine avoid the use of diazepam and similar drugs, but this is probably overly cautious.[2]

1. Mattila M, Mattila MJ, Vrijmoed-de Vries M, Kuitunen T. Actions and interactions of psychotropic drugs on human performance and mood: single doses of ORG 3770, amitriptyline and diazepam. *Pharmacol Toxicol* (1989) 65, 81–8.
2. Remeron (Mirtazapine). Schering-Plough. US Prescribing information, March 2009.

Mirtazapine + Cimetidine

Cimetidine increases the bioavailability of mirtazapine.

Clinical evidence, mechanism, importance and management

In a placebo-controlled, crossover study in 12 healthy subjects, cimetidine 800 mg twice daily was given for 14 days, with mirtazapine 30 mg added at night on days 6 to 12. Cimetidine increased the AUC and peak plasma levels of mirtazapine by 54% and 22%, respectively: trough and average mirtazapine plasma levels, at steady state, were increased by 61% and 54%, respectively. The pharmacokinetics of the demethyl metabolite of mirtazapine were little affected. Mirtazapine did not affect the pharmacokinetics of cimetidine.[1]

Mechanism

It seems likely that cimetidine, a non-specific enzyme inhibitor, decreases the metabolism of mirtazapine.

Importance and management

This pharmacokinetic interaction between cimetidine and mirtazapine would appear to be established, but the clinical effect of increasing the levels of mirtazapine by up to about to two-thirds does not appear to have been assessed. The authors suggested that the clinical relevance of this interaction is probably limited because of the variability of plasma mirtazapine levels in patients.[1] Nevertheless, the UK manufacturers advise that the mirtazapine dosage may need to be reduced during concurrent use and increased when cimetidine is stopped.[2] Monitor for an increase in mirtazapine adverse effects (oedema, drowsiness, headache) when starting cimetidine.

1. Sitsen JMA, Maris FA, Timmer CJ. Concomitant use of mirtazapine and cimetidine: a drug-drug interaction study in healthy male subjects. *Eur J Clin Pharmacol* (2000) 56, 389–94.
2. Zispin (Mirtazapine). Organon Laboratories Ltd. UK Summary of product characteristics, February 2009.

Mirtazapine + CYP3A4 inhibitors

Ketoconazole increased the AUC and plasma levels of mirtazapine. Some caution might be appropriate on concurrent use of this and other CYP3A4 inhibitors.

Clinical evidence, mechanism, importance and management

The UK manufacturer of mirtazapine notes that **ketoconazole** increased the peak plasma levels and AUC of mirtazapine by about 30% and 45%, respectively.[1] Mirtazapine is extensively metabolised by the cytochrome P450 isoenzyme CYP3A4, which is thought to be responsible for the formation of the *N*-demethyl and *N*-oxide metabolites. Ketoconazole is a potent inhibitor of CYP3A4.

This pharmacokinetic interaction would appear to be established, but the clinical effect of increasing the exposure to mirtazapine by around half has not been assessed. Until more is known, some caution might be appropriate. Note that the UK manufacturer of mirtazapine advises caution and that a decrease in the dose of mirtazapine may be needed when potent inhibitors of CYP3A4 are also given, and they specifically name **azole antifungals**, **protease inhibitors**, **erythromycin**, and **nefazodone**.[1] For a list of CYP3A4 inhibitors, see 'Table 1.4', (p.6).

1. Zispin (Mirtazapine). Organon Laboratories Ltd. UK Summary of product characteristics, February 2009.

Mirtazapine + SSRIs

There are a couple of isolated cases of possible serotonin syndrome when mirtazapine was used with fluoxetine and fluvoxamine, and there is a report of hypomania associated with the concurrent use of mirtazapine and sertraline. Restless legs syndrome has occurred in a patient taking fluoxetine and mirtazapine. Fluvoxamine markedly increased the plasma levels of mirtazapine in two cases, whereas paroxetine caused a minor increase in the AUC of mirtazapine in a pharmacokinetic study.

Clinical evidence

(a) Escitalopram

For a report of bleeding associated with the combined use of escitalopram, mirtazapine and venlafaxine, see 'SNRIs + SSRIs', p.1475.

(b) Fluoxetine

An isolated report describes a case of possible serotonin syndrome in a 75-year-old woman when fluoxetine 20 mg daily was discontinued and mirtazapine 30 mg daily started soon afterwards (exact interval not stated).[1] Symptoms including dizziness, headache, nausea, dry mouth, anxiety, agitation, suicidal ideas and difficulty in walking occurred within hours of the first dose of mirtazapine. Symptoms worsened until mirtazapine was discontinued on day 5, after which an improvement was noticed. Fluoxetine was restarted on day 7. It has been suggested that this case is more consistent with fluoxetine-withdrawal syndrome, with the mirtazapine worsening the symptoms of anxiety.[2]

Restless legs syndrome occurred in 3 patients taking fluoxetine and mirtazapine as part of a study of major depression with insomnia. Symptoms were bothersome paraesthesias and jerks in both lower extremities, with exacerbation at night, and relief upon movement. Treatment with mirtazapine was discontinued and symptoms ceased after 2 days.[3]

(c) Fluvoxamine

A 26-year-old woman with a 12-year history of anorexia nervosa, taking fluvoxamine 200 mg daily, developed symptoms consistent with serotonin syndrome (tremors, restlessness, twitching, flushing, diaphoresis, nausea) about 4 days after starting mirtazapine 30 mg daily.[4] It has been suggested that this case is not consistent with serotonin syndrome, and that the adverse effects were attributable to raised levels of mirtazapine possibly caused by fluvoxamine.[2]

A 17-year-old boy taking mirtazapine 30 mg daily experienced increased anxiety when fluvoxamine 100 mg daily was also given. Mirtazapine serum levels were increased threefold. In a second patient, a 43-year-old woman taking mirtazapine 15 mg daily, the addition of fluvoxamine 50 mg daily resulted in a fourfold increase in serum mirtazapine concentrations, accompanied by mood improvements.[5]

(d) Paroxetine

A study in 21 healthy subjects given mirtazapine 30 mg daily, paroxetine 40 mg daily or a combination of both, for 9 days, found that paroxetine slightly inhibited the metabolism of mirtazapine (AUC of mirtazapine increased by about 17%). Mirtazapine did not alter the pharmacokinetics of paroxetine. The results of psychometric assessments suggested that concurrent use of mirtazapine and paroxetine did not alter cognitive function, or cause major changes in mood or sleep, compared with the use of either drug alone.[6]

(e) Sertraline

A woman taking sertraline 250 mg daily was also given mirtazapine 15 mg daily because of inadequately controlled depression. Within 4 days she developed hypomanic symptoms and she stopped taking the mirtaza-

pine. The hypomania resolved within 3 days but her depression then recurred.[7]

Mechanism

Mirtazapine is metabolised mainly by the cytochrome P450 isoenzymes CYP1A2, CYP2D6 and CYP3A4. These isoenzymes (particularly CYP1A2) are inhibited by fluvoxamine, and so concurrent use might therefore raise mirtazapine levels. Paroxetine is a moderate inhibitor of CYP2D6, and this appeared to have little effect on mirtazapine levels.

The SSRIs, and mirtazapine affect serotonin transmission, and combined use of serotonergic drugs has rarely caused the symptoms described as serotonin syndrome (for more about serotonin syndrome see under 'Additive or synergistic interactions', (p.9)). However, it has been suggested that serotonin toxicity with mirtazapine is unlikely, because it has 5-HT_2-blocking effects.[2]

Importance and management

The isolated reports would seem to suggest that the combined use of mirtazapine and the SSRIs can lead to serotonin syndrome. However, whether these are cases of serotonin syndrome has been disputed.[2] Nevertheless, these and other reports of anxiety and hypomania highlight the need for some caution during concurrent use. One manufacturer reported that, from postmarketing experience, it appears that serotonin syndrome occurs very rarely in patients taking mirtazapine alone or in combination with SSRIs. They recommend that if the combination is required, dosage alterations should be made with caution and patients closely monitored for any signs of excessive serotonin stimulation.[8]

Extra caution might be appropriate with fluvoxamine, as the limited evidence suggests that this might markedly raise mirtazapine levels. However, this needs confirming.

There is no clinically relevant pharmacokinetic interaction between paroxetine and mirtazapine, and no dosage adjustment is likely to be needed when they are used together.

1. Benazzi F. Serotonin syndrome with mirtazapine-fluoxetine combination. *Int J Geriatr Psychiatry* (1998) 13, 495–6.
2. Isbister GK, Dawson AH, Whyte IM. Comment: serotonin syndrome induced by fluvoxamine and mirtazapine. *Ann Pharmacother* (2001) 35, 1674–5.
3. Prospero-Garcia KA, Torres-Ruiz A, Ramirez-Bermudez J, Velazquez-Moctezuma J, Arana-Lechuga Y, Teran-Perez G. Fluoxetine-mirtazapine interaction may induce restless legs syndrome: report of 3 cases from a clinical trial. *J Clin Psychiatry* (2006) 67, 1820.
4. Demers JC, Malone M. Serotonin syndrome induced by fluvoxamine and mirtazapine. *Ann Pharmacother* (2001) 35, 1217–20.
5. Anttila SAK, Rasanen I, Leinonen EVJ. Fluvoxamine augmentation increases serum mirtazapine concentrations three- to fourfold. *Ann Pharmacother* (2001) 35, 1221–3.
6. Ruwe FJL, Smulders RA, Kleijn HJ, Hartmans HLA, Sitsen JMA. Mirtazapine and paroxetine: a drug-drug interaction study in healthy subjects. *Hum Psychopharmacol* (2001) 16, 449–59.
7. Soutullo CA, McElroy SL, Keck PE. Hypomania associated with mirtazapine augmentation of sertraline. *J Clin Psychiatry* (1998) 59, 320.
8. Mirtazapine. Genus Pharmaceuticals. UK Summary of product characteristics, May 2005.

Mirtazapine + Tricyclic antidepressants

The concurrent use of mirtazapine with amitriptyline may have a minor effect on the maximum levels of both drugs.

Clinical evidence

In a crossover study involving 24 healthy subjects, mirtazapine 15 mg, increasing to 30 mg daily, **amitriptyline** 25 mg, increasing to 75 mg daily or both drugs were given for periods of 9 days. **Amitriptyline** increased the maximum plasma levels of mirtazapine, in male subjects only, by 36%. Mirtazapine increased the maximum plasma levels of **amitriptyline** in male subjects by 23%, but in female subjects the maximum plasma levels were *decreased* by 23%. Other pharmacokinetic parameters of amitriptyline and mirtazapine (AUC, minimum level, time to maximum level) and their main metabolites nortriptyline and demethylmirtazapine were not affected by concurrent use. The authors note that concurrent use had no consistent effects on blood pressure, heart rate and ECG, although they note that four subjects developed postural hypotension.[1]

Mechanism

The pharmacokinetic changes were suggested to be due to differences in rates of absorption of the drugs, since the maximum levels were slightly altered, but the AUCs were not. Mirtazapine has alpha-blocking activity, and can therefore cause hypotension. Amitriptyline can also cause hypotension. Therefore postural hypotension may have developed as a result of the additive effects of the two drugs.

Importance and management

Evidence for an interaction between mirtazapine and amitriptyline appears to be limited to this one study. Although the changes in maximum levels here were statistically significant, they are minor, and there were no changes in the overall amount of drug absorbed. These changes are therefore unlikely to be clinically relevant. There is no pharmacokinetic reason to adjust the dose of either of these drugs on concurrent use.

1. Sennef C, Timmer CJ, Sitsen JMA. Mirtazapine in combination with amitriptyline: a drug-drug interaction study in healthy subjects. *Hum Psychopharmacol* (2003) 18, 91–101.

Nefazodone + Antidepressants

An isolated report describes a woman who developed marked and acute hypotension and weakness when desipramine, fluoxetine and venlafaxine were replaced by nefazodone. Isolated cases describe serotonin syndrome in patients given nefazodone together, or sequentially, with another serotonergic drug (amitriptyline, paroxetine, St John's wort, or trazodone). There is no pharmacokinetic interaction between desipramine and nefazodone. The manufacturer recommended that nefazodone should not be used with an MAOI or within 14 days of discontinuing an MAOI. Note that, due to adverse hepatic effects nefazodone was widely withdrawn from the market.

Clinical evidence, mechanism, importance and management

(a) MAOIs

The manufacturer stated that nefazodone should not be used with an MAOI or within 2 weeks of discontinuing treatment with an MAOI. Conversely at least one week should be allowed after stopping nefazodone before starting an MAOI.[1] There appears to be no direct clinical evidence that an adverse interaction occurs.

(b) Reboxetine

Nefazodone is predicted to increase the plasma concentrations of reboxetine, see 'Reboxetine + CYP3A4 inducers or inhibitors', p.1473.

(c) SSRIs

Anecdotal evidence has suggested that patients who are switched from an SSRI to nefazodone may tolerate nefazodone poorly. Nevertheless, in a 12-week, open study involving 26 depressed patients, nefazodone 100 to 600 mg daily was as equally well tolerated in 13 patients who had discontinued an SSRI within 1 to 4 weeks and 13 patients who had received no antidepressant treatment for the previous 6 months. However, the patients who had recent exposure to an SSRI (within the previous 4 weeks) were given a washout period of 4 to 5 days for short half-life SSRIs or 7 days for **fluoxetine** before starting nefazodone.[2] Cases with specific SSRIs are discussed in the subsections below.

1. Fluoxetine. A woman with a one-year history of DSM-IV major depressive disorder and panic disorder was given daily doses of **desipramine** 75 mg, fluoxetine 20 mg, **venlafaxine** 37.5 mg, **clonazepam** 3 mg and **valproate** 400 mg with no adverse effects, except a dry mouth and sexual difficulties.[3] The first three drugs were stopped and replaced by nefazodone 100 mg twice daily, started about 12 hours later. Within an hour of the first dose she felt very weak and her blood pressure was found to have fallen to only 90/60 mmHg (normally 120/90 mmHg). On waking the next day she had severe weakness, unsteady gait, pale, cool and sweaty skin, and paraesthesia. During the day she took two further 100-mg doses of nefazodone and her condition persisted and worsened with continuing hypotension. The nefazodone was discontinued and by the following day the weakness had improved, disappearing over the next few days. Within a week nefazodone 200 mg daily was reintroduced without problems.

The US manufacturer of nefazodone noted that nefazodone did not alter the pharmacokinetics of fluoxetine, but fluoxetine increased the AUC of the metabolites of nefazodone up to 6-fold.[1] When nefazodone 200 mg twice was given to patients who had been taking fluoxetine for 7 days adverse effects (including headache and nausea) were increased. The manufacturers advised allowing a washout period of at least one week (more may be needed depending on dose and individual patient characteristics)

to minimise these effects.[1] It therefore seems likely that fluoxetine was the interacting drug, but it is impossible to rule out a contribution from the other drugs.

2. Paroxetine. A woman was withdrawn from nefazodone after about 6 months of treatment, tapering over the last fortnight to 75 mg every 12 hours. Within a day she started taking paroxetine 20 mg daily and valproic acid, and was admitted the next day with muscle rigidity, uncoordinated muscle tremors, flailing arms and twitching legs, diaphoresis and agitation. This was identified as serotonin syndrome. Rechallenge with paroxetine 7 days later was uneventful.[4]

(d) St John's wort (Hypericum perforatum)

An elderly patient taking nefazodone 100 mg twice daily, developed symptoms similar to serotonin syndrome within 3 days of starting to take St John's wort 300 mg three times daily. The symptoms included nausea, vomiting, and restlessness. She was asked to stop both medications, but continued the St John's wort and her symptoms gradually improved over a one-week period.[5]

(e) Trazodone

A woman taking irbesartan for hypertension was also given nefazodone at an initial dose of 200 mg daily, followed by 400 mg daily for about 5 weeks. Four days after the dose was increased to 500 mg daily, and trazodone 25 to 50 mg daily was also added as a hypnotic, she was admitted to hospital with a blood pressure of 240/120 mmHg. She was confused, had difficulty concentrating and had numbness on the right side of her lips, nose and right-hand fingers, flushed pruritic skin, nausea, and loose stools. On examination she was restless, hyperreflexic, and diaphoretic. Nefazodone and trazodone were discontinued, and she recovered after treatment with labetalol, clonidine, amlodipine and an increased irbesartan dosage.[6] Although trazodone is used with other serotonergic drugs, it is important to be aware that this may lead to the potentially fatal 'serotonin syndrome', (p.9).

The manufacturers of trazodone say that *in vitro* drug metabolism studies suggest that there is a potential for drug interactions when trazodone is given with a potent CYP3A4 inhibitor such as nefazodone. There may be substantial increases in trazodone levels, with the potential for adverse effects, and a lower dose of trazodone should be considered.[7,8] The UK manufacturer suggests avoidance of the combination where possible.[7]

(f) Tricyclic antidepressants

1. Amitriptyline. A woman who had been taking amitriptyline 10 mg at night and thioridazine developed serotonin syndrome after taking half a tablet of nefazodone (strength unspecified).[9]

2. Desipramine. In a study in healthy subjects, desipramine titrated to 75 mg daily did not change the pharmacokinetics of nefazodone titrated to 150 mg twice daily, but the AUC of the nefazodone metabolite, metachlorophenylpiperazine, was increased by 40%. There was no change in the pharmacokinetics of desipramine or its metabolite. No specific dosage adjustments were said to be required on concurrent use.[10]

1. Nefazodone hydrochloride. Watson Laboratories Inc. US Prescribing information, June 2004.
2. Mischoulon D, Opitz G, Kelly K, Fava M, Rosenbaum JF. A preliminary open study of the tolerability and effectiveness of nefazodone in major depressive disorder: comparing patients who recently discontinued an SSRI with those on no recent antidepressant treatment. *Depress Anxiety* (2004) 19, 43–50.
3. Benazzi F. Dangerous interaction with nefazodone added to fluoxetine, desipramine, venlafaxine, valproate and clonazepam combination therapy. *J Psychopharmacol* (1997) 11, 190–1.
4. John L, Perreault MM, Tao T, Blew PG. Serotonin syndrome associated with nefazodone and paroxetine. *Ann Emerg Med* (1997) 29, 287–9.
5. Lantz MS, Buchalter E, Giambanco V. St. John's wort and antidepressant drug interactions in the elderly. *J Geriatr Psychiatry Neurol* (1999) 12, 7–10.
6. Margolese HC, Chouinard G. Serotonin syndrome from addition of low-dose trazodone to nefazodone. *Am J Psychiatry* (2000) 157, 1022.
7. Molipaxin Capsules (Trazodone hydrochloride). Sanofi-Aventis. UK Summary of product characteristics, August 2009.
8. Desyrel (Trazodone hydrochloride). Bristol-Myers Squibb Company. US Prescribing information, February 2009.
9. Chan BSH, Graudins A, Whyte IM, Dawson AH, Braitberg G, Duggin GG. Serotonin syndrome resulting from drug interactions. *Med J Aust* (1998) 169, 523–5.
10. Khan AY, Preskorn SH, Horst WD. Coadministration of nefazodone and desipramine: a pharmacokinetic interaction study. *JPMA* (2007) 57, 230–5.

Nefazodone + Cimetidine

In a study, 18 healthy subjects were given cimetidine 300 mg four times daily and nefazodone 200 mg every 12 hours for a week. Concurrent use did not affect the steady-state pharmacokinetics of either drug. Therefore no dose adjustments would seem to be necessary if both drugs are used concurrently.[1]

1. Barbhaiya RH, Shukla UA, Greene DS. Lack of interaction between nefazodone and cimetidine: a steady state pharmacokinetic study in humans. *Br J Clin Pharmacol* (1995) 40, 161–5.

Reboxetine + CYP3A4 inducers or inhibitors

Ketoconazole modestly inhibits the metabolism of single-dose reboxetine by inhibiting CYP3A4. Other CYP3A4 inhibitors are expected to interact similarly. Unexpectedly low reboxetine levels have been reported in two patients also taking an inducer of CYP3A4 (carbamazepine and phenobarbital).

Clinical evidence

In a study in 11 healthy subjects, **ketoconazole** 200 mg daily for 5 days increased the AUC of a single 4-mg dose of reboxetine, taken on the second day, by about 50%, without appreciably altering the maximum levels. Reboxetine clearance was decreased by about 25 to 33%. The effect on the two reboxetine enantiomers was of a similar magnitude. In this study, the adverse effect profile of reboxetine alone was similar to that when given with ketoconazole.[1]

A case report describes reboxetine levels that were lower than expected (by comparison with historical controls) in two patients, one receiving **carbamazepine** (with concurrent olanzapine, clonazepam, alprazolam, and buspirone) and one receiving **phenobarbital** (with concurrent clozapine and clonazepam).[2]

Mechanism

Reboxetine is metabolised principally by the cytochrome P450 isoenzyme CYP3A4, of which ketoconazole is an inhibitor. Concurrent use therefore reduces reboxetine metabolism and increases its levels. Carbamazepine and phenobarbital are inducers of CYP3A4, and they would therefore be expected to increase reboxetine metabolism and decrease its levels.

Importance and management

The pharmacokinetic interaction would appear to be established, but it would be useful to confirm the magnitude at steady-state levels of reboxetine. The clinical relevance of a 50% increase in the AUC of reboxetine is unknown. The authors of the paper suggest that a reduction in reboxetine dose should be considered.[1] However, the manufacturer states that because reboxetine has a narrow therapeutic index, inhibition of metabolism is of major concern, and therefore inhibitors of CYP3A4 should not be given with reboxetine.[3] They list **azoles**, **macrolides** such as **erythromycin**, **nefazodone**, and **fluvoxamine** (although note that fluvoxamine is usually considered to be a weak inhibitor of CYP3A4). For a list of CYP3A4 inhibitors see 'Table 1.4', (p.6). This seems an overly cautious approach, especially given that available data suggest that patients with hepatic impairment have a twofold higher AUC,[4] and the recommendation in this situation is just for a halving of the starting dose of reboxetine.[3]

The cases reports involving carbamazepine and phenobarbital appear to be the only ones reported, and do not wholly confirm an interaction as reboxetine levels were not measured in the absence of these enzyme inducers. The UK manufacturer of reboxetine makes no recommendations with respect to its use with inducers of CYP3A4.[3] Nevertheless, in light of these cases, and in view of the fact that CYP3A4 inhibitors are known to increase reboxetine levels, it would seem prudent to monitor the efficacy of treatment with reboxetine in patients receiving a known inducer of CYP3A4. For a list of CYP3A4 inducers, see 'Table 1.4', (p.6).

1. Herman BD, Fleishaker JC, Brown MT. Ketoconazole inhibits the clearance of the enantiomers of the antidepressant reboxetine in humans. *Clin Pharmacol Ther* (1999) 66, 374–9.
2. Helland A, Spigset O. Low serum concentrations of reboxetine in 2 patients treated with CYP3A4 inducers. *J Clin Psychopharmacol* (2007) 27, 308–10.
3. Edronax (Reboxetine). Pharmacia Ltd. UK Summary of product characteristics, July 2008.
4. Fleishaker JC. Clinical pharmacokinetics of reboxetine, a selective norepinephrine reuptake inhibitor for the treatment of patients with depression. *Clin Pharmacokinet* (2000) 39, 413–27.

Reboxetine + Dextromethorphan

Reboxetine did not alter dextromethorphan pharmacokinetics in one study.

Clinical evidence, mechanism, importance and management

In a study in 10 healthy subjects who were of the CYP2D6 extensive metaboliser phenotype, the pharmacokinetics of a single 30-mg dose of dextromethorphan were not affected by reboxetine 8 mg daily for one week.[1]

This pharmacokinetic study suggests that dose adjustments of CYP2D6 substrates such as dextromethorphan (see 'Table 1.3', (p.6) for a list) are not likely to be needed when given with reboxetine.

1. Avenoso A, Facciolà G, Scordo MG, Spina E. No effect of the new antidepressant reboxetine on CYP2D6 activity in healthy volunteers. *Ther Drug Monit* (1999) 21, 577–9.

Reboxetine + Miscellaneous

The manufacturer points out that hypokalaemia may occur if reboxetine is used with potassium-depleting diuretics. In addition, they advise the avoidance of MAOIs because of the potential risk of a tyramine-like effect [hypertensive crisis].[1]

1. Edronax (Reboxetine). Pharmacia Ltd. UK Summary of product characteristics, July 2008.

Reboxetine + Quinidine

Quinidine did not alter the pharmacokinetics of reboxetine in one study.

Clinical evidence, mechanism, importance and management

In a study in 8 healthy subjects who were of the CYP2D6 extensive metaboliser phenotype (that is, they had normal levels of this isoenzyme), quinidine (dose not stated) did not alter the pharmacokinetics of reboxetine 1 mg.[1]

This study suggests that reboxetine is not a substrate of the CYP2D6 isoenzyme of cytochrome P450, of which quinidine is an inhibitor. No dosage adjustments of reboxetine are likely to be needed if CYP2D6 inhibitors such as quinidine (see 'Table 1.3', (p.6) for a list) are also given.

1. Rocchetti M, Pellizzoni C, Poggesi I, Davies DS, Wilkins MR, Hirokawa K, Dostert P, Benedetti MS. Genetic polymorphism and reboxetine metabolism. 1st Congress of the European Association for Clinical Pharmacology and Therapeutics. *Therapie* (1995) (Suppl.), abstract 80.

Reboxetine + SSRIs

The concurrent use of fluoxetine and reboxetine does not appear to alter the pharmacokinetics of either drug. The manufacturer advises avoidance of fluvoxamine on the basis of a predicted pharmacokinetic interaction.

Clinical evidence

In a placebo-controlled study in 30 healthy subjects given reboxetine 4 mg twice daily and **fluoxetine** 20 mg daily for 8 days, there were no significant changes in the pharmacokinetics of either drug.[1] The only changes were a 25% increase in the AUC of **fluoxetine**, and a 23% increase in the AUC of *S,S*-reboxetine. In this study, combined use did not alter oral temperature and the Digit Symbol Substitution Test, which were used as possible indicators of serotonergic adverse effects. There do not appear to be any published cases of serotonin syndrome in patients taking SSRIs and reboxetine.

Mechanism

Reboxetine is metabolised principally by the cytochrome P450 isoenzyme CYP3A4. **Fluoxetine** has some minor CYP3A4 inhibitory activity (see 'Benzodiazepines and related drugs + SSRIs', p.863), and might therefore have some effect on reboxetine pharmacokinetics, although this would not have been expected to be enantiomer specific.[1] Of the other available SSRIs, only **fluvoxamine** appears to have some minor CYP3A4 inhibitory activity, see 'Benzodiazepines and related drugs + SSRIs', p.863. Note that reboxetine is not a substrate of CYP2D6 (see 'Reboxetine + Quinidine', above) of which a number of SSRIs are inhibitors.

Importance and management

No clinically relevant pharmacokinetic interaction appears to occur between fluoxetine and reboxetine, therefore no dosage adjustment is required on concurrent use. Based on this evidence, no pharmacokinetic interaction would be anticipated with the other available SSRIs. Nevertheless, the manufacturer of reboxetine includes fluvoxamine as an example of a potent inhibitor of CYP3A4, and consequently recommends that its concurrent use with reboxetine should be avoided.[2] This appears to be over-cautious, especially as clinically fluvoxamine only appears to have weak effects on this isoenzyme.

1. Fleishaker JC, Herman BD, Pearson LK, Ionita A, Mucci M. Evaluation of the potential pharmacokinetic/pharmacodynamic interaction between fluoxetine and reboxetine in healthy volunteers. *Clin Drug Invest* (1999) 18, 141–50.
2. Edronax (Reboxetine). Pharmacia Ltd. UK Summary of product characteristics, July 2008.

SNRIs + H_2-receptor antagonists

Cimetidine increases venlafaxine plasma levels, and some caution might be appropriate in the elderly and those with hepatic impairment. Duloxetine is predicted to interact similarly. Famotidine did not alter the absorption of duloxetine.

Clinical evidence, mechanism, importance and management

(a) Duloxetine

The metabolism of duloxetine is reduced by cytochrome P450 isoenzyme CYP1A2 inhibitors and it is recommended that potent inhibitors of CYP1A2 should be avoided (see under fluvoxamine in 'SNRIs + SSRIs', p.1475). The US manufacturer of duloxetine specifically mentions **cimetidine** as an inhibitor of this enzyme.[1] However, **cimetidine** is a much weaker CYP1A2 inhibitor than fluvoxamine, and the UK manufacturer does not mention a possible interaction with **cimetidine**.[2] Any pharmacokinetic interaction between **cimetidine** and duloxetine is probably unlikely to be clinically important, but, until more is known, it might be prudent to be on the look out for an increase in duloxetine adverse effects if **cimetidine** is also given.

One manufacturer reports that **famotidine** had no effect on the rate or extent of absorption of a single 40-mg dose of duloxetine.[1] Duloxetine is formulated with a gastric-resistant coating, but this finding suggests that H_2-receptor antagonists do not lead to an earlier release of duloxetine.[1] **Famotidine** may therefore be a suitable alternative to **cimetidine** in patients taking duloxetine.

(b) Venlafaxine

In a study in 18 healthy subjects, **cimetidine** 800 mg daily for 5 days reduced the oral clearance of venlafaxine 50 mg every 8 hours by 40%, and increased its AUC by 62%. It had no effect on the formation or elimination of the major active metabolite of venlafaxine, *O*-desmethylvenlafaxine (ODV). The total level of venlafaxine with ODV was found to be increased by only 13%. Thus the overall pharmacological activity of the two was only slightly increased by **cimetidine**[3] and no venlafaxine dosage adjustments are necessary on concurrent use.[4,5] However, the manufacturers of venlafaxine suggest that the elderly and those with hepatic impairment might possibly show a more pronounced effect, and they recommend that such patients should be monitored more closely,[4,5] for venlafaxine adverse effects. The US manufacturer additionally advises caution in patients with pre-existing hypertension.[5]

1. Cymbalta (Duloxetine hydrochloride). Eli Lilly and Company. US Prescribing information, February 2009.
2. Cymbalta (Duloxetine hydrochloride). Eli Lilly and Company Ltd. UK Summary of product characteristics, July 2009.
3. Troy SM, Rudolph R, Mayersohn M, Chiang ST. The influence of cimetidine on the disposition kinetics of the antidepressant venlafaxine. *J Clin Pharmacol* (1998) 38, 467–74.
4. Efexor (Venlafaxine hydrochloride). Wyeth Pharmaceuticals. UK Summary of product characteristics, March 2008.
5. Effexor XR (Venlafaxine hydrochloride). Wyeth Pharmaceuticals Inc. US Prescribing information, July 2009.

SNRIs + Propafenone

Two isolated reports describe hallucinations and other psychoses in patients taking venlafaxine and propafenone. Duloxetine is predicted to increase propafenone levels.

Clinical evidence, mechanism, importance and management

(a) Duloxetine

Based on data for desipramine (see 'Tricyclic antidepressants + SNRIs', p.1512), duloxetine is a moderate inhibitor of the cytochrome P450 isoenzyme CYP2D6 and is therefore predicted to increase the levels of other drugs predominantly metabolised by CYP2D6, such as propafenone. Because propafenone has a narrow therapeutic window, the manufacturer recommends that the concurrent use of duloxetine and propafenone should be approached with caution.[1,2]

(b) Venlafaxine

A 67-year-old woman with bipolar disorder taking venlafaxine 300 mg daily experienced symptoms of paranoia, visual hallucinations and marked confusion, about 2 weeks after starting propafenone 600 mg daily for intermittent atrial fibrillation. Serum levels of venlafaxine had increased from 85 nanograms/mL to 520 nanograms/mL (upper level of reference range 150 nanograms/mL) and levels of the metabolite *O*-desmethylvenlafaxine had increased but were still within normal ranges. Venlafaxine was stopped for a few days then restarted at the lower dose of 75 mg daily and her mental condition (diagnosed as organic psychosis) improved. However, as she also had orthostatic hypotension her propafenone dose was subsequently reduced to 300 mg daily, which necessitated dose adjustments of venlafaxine because of a marked drop in serum level. When propafenone was again increased to 600 mg daily the venlafaxine had to be reduced to 50 mg daily.[3] Another case of visual hallucinations and psychomotor agitation occurred in a woman taking propafenone when her dose of sustained-release venlafaxine was increased from 75 mg daily to 150 mg daily.[4]

The reasons for the interaction are not known, but venlafaxine is partly metabolised by CYP2D6 and propafenone is an inhibitor of this isoenzyme. However, this mechanism usually results in a decrease in *O*-desmethylvenlafaxine levels, and is usually of no clinical consequence, see 'SNRIs; Venlafaxine + Miscellaneous', p.1479. Information is limited to these two case reports, and their general significance is unclear.

1. Cymbalta (Duloxetine hydrochloride). Eli Lilly and Company. US Prescribing information, February 2009.
2. Cymbalta (Duloxetine hydrochloride). Eli Lilly and Company Ltd. UK Summary of product characteristics, July 2009.
3. Pfeffer F, Grube M. An organic psychosis due to a venlafaxine-propafenone interaction. *Int J Psychiatry Med* (2001) 31, 427–32.
4. Gareri P, De Fazio P, Gallelli L, De Fazio S, Davoli A, Seminara G, Cotroneo A, De Sarro G. Venlafaxine-propafenone interaction resulting in hallucinations and psychomotor agitation. Ann Pharmacother (2008) 42, 434–8.

SNRIs + St John's wort (*Hypericum perforatum*)

Serotonin syndrome has been reported in one patient taking venlafaxine and St John's wort.

Clinical evidence

An interaction between **venlafaxine** and St John's wort was reported to the Centre Régional de Pharmacovigilance de Marseille involving a 32-year-old man who had been taking **venlafaxine** 250 mg daily for several months. He started taking St John's wort at a dose of 200 drops 3 times daily (usual dose up to 160 drops daily) and on the third day felt faint and anxious, and had symptoms of diaphoresis, shivering and tachycardia. The St John's wort was stopped and his symptoms resolved in 3 days without altering the dose of **venlafaxine**.[1] A search of Health Canada's database of spontaneous adverse reactions for the period 1998 to 2003 also found one case of suspected serotonin syndrome as a result of an interaction between **venlafaxine** and St John's wort.[2]

Mechanism

A pharmacodynamic interaction may occur between St John's wort and venlafaxine because they can both inhibit the reuptake of 5-hydroxytryptamine (serotonin). Serotonin syndrome has been seen with St John's wort alone,[3] and so additive serotonergic effects appear to be the explanation for what occurred in the cases described here. For more information on serotonin syndrome, see under 'Additive or synergistic interactions', (p.9).

Importance and management

Information appears to be limited to these reports. **Duloxetine** would be expected to interact similarly and the manufacturers of both duloxetine and venlafaxine advise caution if they are given with drugs that affect the serotonergic neurotransmitter systems,[4] including St John's wort.[5-7] This is probably prudent.

1. Prost N, Tichadou L, Rodor F, Nguyen N, David JM, Jean-Pastor MJ. Interaction millepertuis-venlafaxine. *Presse Med* (2000) 29, 1285–6.
2. Griffiths J, Jordan S, Pilan K. Natural health products and adverse reactions. *Can Adverse React News* (2004) 14 (1), 2–3.
3. Demott K. St. John's wort tied to serotonin syndrome. *Clin Psychiatry News* (1998) 26, 28.
4. Efexor (Venlafaxine hydrochloride). Wyeth Pharmaceuticals. UK Summary of product characteristics, March 2008.
5. Effexor XR (Venlafaxine hydrochloride). Wyeth Pharmaceuticals Inc. US Prescribing information, July 2009.
6. Cymbalta (Duloxetine hydrochloride). Eli Lilly and Company Ltd. UK Summary of product characteristics, July 2009.
7. Cymbalta (Duloxetine hydrochloride). Eli Lilly and Company. US Prescribing information, February 2009.

SNRIs + SSRIs

Fluvoxamine markedly increases duloxetine levels. Paroxetine causes a more modest increase in the AUC of duloxetine: fluoxetine is predicted to interact similarly. The pharmacokinetics of milnacipran do not appear to be altered by fluoxetine.

The concurrent use of the SNRIs and SSRIs may increase the risk of the serotonin syndrome. Concurrent use has also led to adverse effects such as blurred vision, constipation, and rarely, bleeding events or hypomania.

Clinical evidence

(a) Duloxetine

The manufacturers report that, in 14 subjects **fluvoxamine** 100 mg daily increased the AUC of duloxetine sixfold, and decreased its clearance by about 77%.[1,2] Similar increases in duloxetine plasma levels were found in 15 healthy subjects (who were known CYP2D6 poor metabolisers, i.e. those lacking in this isoenzyme) when they were given **fluvoxamine** 50 to 100 mg daily and duloxetine 40 mg twice daily.[2,3] In healthy subjects, the concurrent use of **paroxetine** 20 mg daily and duloxetine 40 mg daily increased the AUC of duloxetine at steady state by about 60%.[4]

(b) Milnacipran

In a pharmacokinetic study in 12 healthy subjects, milnacipran 50 mg twice daily for seven doses was given alone and then immediately after **fluoxetine** 20 mg daily for 3 weeks. There was no difference in the maximum and minimum levels of milnacipran when given after **fluoxetine**, and the 90% confidence intervals of the other pharmacokinetic parameters were within the 20% range (not clinically relevant). In this small study in healthy subjects, no difference in adverse events was detected when the drugs were used together.[5]

Fluoxetine has a very long half-life, and this study simulated the situation where **fluoxetine** is stopped and milnacipran started without a washout period.

(c) Venlafaxine

1. Antimuscarinic adverse effects. A woman taking **fluoxetine** 20 mg and clonazepam 1 mg daily developed blurred vision, dry mouth, constipation, dizziness, insomnia and a hand tremor within a week of starting to take venlafaxine 37.5 mg daily. These symptoms worsened by the second week and persisted until the venlafaxine was stopped.[6-8] Several other patients (aged between 21 and 70 years) taking **fluoxetine** developed antimuscarinic adverse effects (including constipation, blurred vision, urinary retention or dry mouth) within 2 to 10 days of starting venlafaxine.[7-9] One patient that only developed urinary retention had some prostate enlargement and had previously had some moderate urinary problems while taking **fluoxetine** and nortriptyline.[7,9]

2. Haemorrhages. A 60-year-old man experienced haemorrhages from his nose and rectum one week after venlafaxine 150 mg daily and mirtazapine 15 mg daily were given with **escitalopram** 20 mg daily. The bleeding progressively worsened during the following 3 weeks and then the patient reduced the doses to **escitalopram** 15 mg, mirtazapine 7.5 mg and venlafaxine 100 mg daily, and the bleeding decreased over the following week. He continued weekly tapering of the medications and the bleeding progressively decreased until it stopped when the doses were **escitalopram**

5 mg, mirtazapine 7.5 mg and venlafaxine 37.5 mg daily. Previous treatments with these three drugs used alone had not caused haemorrhages.[10] Note that SSRIs and SNRIs alone have been associated with bleeding events.

3. Hypomania. A 31-year-old woman with recurrent unipolar depression developed a hypomanic episode the day after **paroxetine** 20 mg daily was stopped and venlafaxine 75 mg daily stated. The hypomania subsided as the dose of venlafaxine was gradually reduced to 18.75 mg daily.[11]

4. Serotonin syndrome. A 21-year-old woman whose long-term treatment with **paroxetine** was stopped a week before starting venlafaxine (37.5 mg daily for 5 days then 75 mg daily for 2 days) developed vomiting, dizziness, incoordination, anxiety and electric shock sensations in her arms and legs within 3 days of starting venlafaxine. She stopped venlafaxine after 7 days of treatment, but symptoms persisted for 5 days until she was treated with cyproheptadine.[12]

Other similar cases resulting in the serotonin syndrome have been reported in a 75-year-old man who stopped **sertraline** and started venlafaxine 48 hours later, although symptoms took 14 days to develop,[13] and in a 39-year-old woman, who stopped **fluoxetine** and started venlafaxine.[14] This patient was also taking trazodone. Further reports of the serotonin syndrome have been described in patients taking venlafaxine with 'amitriptyline', (p.1512), or 'sertraline and bupropion', (p.1482). or 'fluoxetine, trazodone and buspirone', (p.1480).

Mechanism

Duloxetine is metabolised principally by the cytochrome P450 isoenzyme CYP1A2, but also by CYP2D6. Fluvoxamine is a potent inhibitor of CYP1A2 and paroxetine is a moderate inhibitor of CYP2D6. Therefore the concurrent use of these SSRIs decreases duloxetine metabolism and raises its levels. Similarly, venlafaxine is metabolised, in part, by CYP2D6, which fluoxetine moderately inhibits. Concurrent use may therefore increase venlafaxine levels, leading to some of the adverse effects described in the cases. Paroxetine probably interacts similarly.

The case of bleeding, was thought to be due to the combined drugs causing high levels of serotonin

Importance and management

Although the clinical relevance of the increases in duloxetine levels with fluvoxamine have not been assessed, the manufacturer considers that the rise with fluvoxamine is so marked that the combination should be avoided.[1,2] This seems a prudent precaution. The rise in duloxetine levels with paroxetine 20 mg daily is probably not clinically relevant, but the US manufacturer notes that greater increases would be expected with higher doses.[2] Other SSRIs (notably fluoxetine) also inhibit this isoenzyme, and would therefore be expected to interact similarly.

Information about the adverse antimuscarinic adverse effects due to an interaction between fluoxetine and venlafaxine seems to be limited to the reports cited, all by the same author. The incidence is not known, but if venlafaxine and fluoxetine are given concurrently, be alert for any evidence of increased antimuscarinic adverse effects (such as dry mouth, blurred vision and urinary retention). It may be necessary to withdraw one or other of the two drugs.

There appear to be few case reports describing the serotonin syndrome in patients given an SSRI and an SNRI. However, in general, concurrent use should be undertaken with caution, as both classes of drug affect serotonin, and increased serotonin levels can precipitate the serotonin syndrome. For more information on the risks and management of this syndrome, see under 'Additive or synergistic interactions', (p.9).

1. Cymbalta (Duloxetine hydrochloride). Eli Lilly and Company Ltd. UK Summary of product characteristics, July 2009.
2. Cymbalta (Duloxetine hydrochloride). Eli Lilly and Company. US Prescribing information, February 2009.
3. Small D, Loghin C, Lucas R, Knadler MP, Zhang L, Chappell J, Bergstrom R, Callaghan JT. Pharmacokinetic evaluation of combined duloxetine and fluvoxamine dosing in CYP2D6 poor metabolizers. *Clin Pharmacol Ther* (2005) 77, P37.
4. Skinner MH, Kuan H-Y, Pan A, Sathirakul K, Knadler MP, Gonzales CR, Yeo KP, Reddy S, Lim M, Ayan-Oshodi M, Wise SD. Duloxetine is both an inhibitor and a substrate of cytochrome P4502D6 in healthy volunteers. *Clin Pharmacol Ther* (2003) 73, 170–7.
5. Puozzo C, Hermann P, Chassard D. Lack of pharmacokinetic interaction when switching from fluoxetine to milnacipran. *Int Clin Psychopharmacol* (2006) 21, 153–8.
6. Benazzi F. Severe anticholinergic side effects with venlafaxine-fluoxetine combination. *Can J Psychiatry* (1997) 42, 980–1.
7. Benazzi F. Venlafaxine-fluoxetine interaction. *J Clin Psychopharmacol* (1999) 19, 96–8.
8. Benazzi F. Venlafaxine drug-drug interactions in clinical practice. *J Psychiatry Neurosci* (1998) 23, 181–2.
9. Benazzi F. Urinary retention with venlafaxine-fluoxetine combination. *Hum Psychopharmacol* (1998) 13, 139–40.
10. Benazzi F. Hemorrhages during escitalopram–venlafaxine–mirtazapine combination treatment of depression. *Can J Psychiatry* (2005) 50, 184.
11. Krol DGH, Nolen WA. Acute stemmingsomslag naar hypomanie bij een patiënte met een unipolaire depressie direct na starten van venlafaxine. *Tijdschr Psychiatr* (2006) 48, 405–8.
12. Chan BSH, Graudins A, Whyte IM, Dawson AH, Braitberg G, Duggin GG. Serotonin syndrome resulting from drug interactions. *Med J Aust* (1998) 169, 523–5.
13. Perry NK. Venlafaxine-induced serotonin syndrome with relapse following amitriptyline. *Postgrad Med J* (2000) 76, 254–6.
14. Bhatara VS, Magnus RD, Paul KL, Preskorn SH. Serotonin syndrome induced by venlafaxine and fluoxetine: a case study in polypharmacy and potential pharmacodynamic and pharmacokinetic mechanisms. *Ann Pharmacother* (1998) 32, 432–6.

SNRIs; Duloxetine + Miscellaneous

Ciprofloxacin and enoxacin are predicted to markedly raise duloxetine levels, and quinidine is predicted to modestly raise duloxetine levels. Duloxetine is predicted to raise the levels of flecainide, metoprolol, risperidone and thioridazine. The absorption of duloxetine is not affected by antacids. Smoking may slightly reduce duloxetine exposure.

Due to the theoretical risk of serotonin syndrome, the manufacturers of duloxetine recommend caution with other serotonergic drugs.

Clinical evidence, mechanism, importance and management

(a) Antacids

Aluminium/**magnesium**-containing antacids had no effect on the rate or extent of absorption of a single 40-mg dose of duloxetine.[1-3] Duloxetine is formulated with a gastric-resistant coating, but this finding suggests that antacids do not lead to an earlier release of duloxetine.[3] No separation of administration would appear to be necessary on concurrent use.

(b) CYP1A2

1. Inducers. Population pharmacokinetic studies have shown that **smokers** have almost 50% lower plasma concentrations of duloxetine, when compared with **non-smokers**,[1] or a 33% lower AUC.[3] The clinical significance of these findings has not been evaluated, but is probably minor. The US manufacturer of duloxetine specifically states that dosage modifications are not recommended for smokers.[3]

2. Inhibitors. Fluvoxamine, a potent inhibitor of the cytochrome P450 isoenzyme CYP1A2, markedly increases duloxetine levels (see 'SNRIs + SSRIs', p.1475). The manufacturers of duloxetine predict that some **quinolones** (they name **ciprofloxacin** and **enoxacin**) will have the same effect, and suggest that their concurrent use with duloxetine should be avoided.[1-3] This seems a prudent precaution. For a list of clinically significant CYP1A2 inhibitors, see 'Table 1.2', (p.4).

(c) CYP2D6

1. Inhibitors. Paroxetine, an inhibitor of the cytochrome P450 isoenzyme CYP2D6, modestly increases duloxetine levels (see 'SNRIs + SSRIs', p.1475). The US manufacturer of duloxetine suggests that other CYP2D6 inhibitors will interact similarly, and specifically names **quinidine**.[3] The clinical relevance of any interaction is unknown, but probably minor. For a list of clinically significant CYP2D6 inhibitors, see 'Table 1.3', (p.6).

2. Substrates. Based on data for 'tolterodine', (p.1544), and 'desipramine', (p.1512), duloxetine is a moderate inhibitor of the cytochrome P450 isoenzyme CYP2D6. The manufacturers of duloxetine therefore advise caution if duloxetine is given with drugs that are predominantly metabolised by CYP2D6 and have a narrow therapeutic index,[1-3] including **flecainide**,[1-3] **risperidone**[1,2] and **metoprolol**.[1,2] Use with **thioridazine** (withdrawn in the UK) is contraindicated in the US because of the risk of arrhythmias with elevated levels of this drug.[3] CYP2D6 shows genetic polymorphism, and inhibition of this isoenzyme turns extensive metabolisers (i.e. those with normal levels of this isoenzyme) into poor metabolisers (i.e. those lacking this isoenzyme). The situation when inhibition of CYP2D6 metabolism is likely to matter most is when a patient stable taking a CYP2D6 substrate is then given duloxetine.

(d) Serotonergic drugs

Because the concurrent use of more than one serotonergic drug has rarely resulted in serotonin syndrome the manufacturer of duloxetine advises caution if duloxetine is used with other SNRIs (**venlafaxine**),[1-3] **lithium**,[3] **tramadol**,[1-3] and **pethidine**.[1,2] Use with serotonin precursors such as **tryptophan** should be undertaken with caution,[1,2] or avoided.[3] For more

information on serotonin syndrome, see under 'Additive or synergistic interactions', (p.9).

1. Cymbalta (Duloxetine hydrochloride). Eli Lilly and Company Ltd. UK Summary of product characteristics, July 2009.
2. Yentreve (Duloxetine hydrochloride). Eli Lilly and Company Ltd. UK Summary of product characteristics, July 2009.
3. Cymbalta (Duloxetine hydrochloride). Eli Lilly and Company. US Prescribing information, February 2009.

SNRIs; Milnacipran + Miscellaneous

The manufacturers of milnacipran contraindicate its use with digitalis glycosides and MAO-B inhibitors such as selegiline and rasagiline. They also warn against concurrent use with clonidine and sympathomimetics such as adrenaline (epinephrine) or noradrenaline (norepinephrine). They suggest careful monitoring with lithium because of the risk of serotonin syndrome.

Clinical evidence, mechanism, importance and management

(a) Cardiovascular drugs

1. Clonidine. The manufacturer of milnacipran advises against the use of milnacipran with clonidine or related drugs because milnacipran might reduce the antihypertensive action of clonidine due to antagonism at the adrenergic receptors, in a way analogous to the tricyclic antidepressants (see 'Clonidine and related drugs + Tricyclic and related antidepressants', p.1054.[1]

Note that this caution is not given for the other available SNRIs, duloxetine and venlafaxine.

2. Digitalis glycosides. The manufacturer of milnacipran contraindicates its use with digitalis glycosides (such as digoxin) because of the risk of potentiating haemodynamic effects, particularly when given parenterally.[1]

3. Inotropes and Vasopressors. The manufacturer of milnacipran advises against the concurrent use of parenteral adrenaline (epinephrine) or noradrenaline (norepinephrine) because of the possible risk of hypertensive crisis with cardiac arrhythmias. This is because milnacipran inhibits noradrenaline re-uptake, see also 'Tricyclic and related antidepressants + Inotropes and Vasopressors', p.1507. They also advise caution if adrenaline or noradrenaline are used as vasoconstrictors in subcutaneous or gingival injections. In this case they recommend that, in adults, the dose of adrenaline should be limited to less than 100 micrograms in 10 minutes or 300 micrograms in one hour.[1]

Note that this caution is not given for the other available SNRIs, duloxetine and venlafaxine.

(b) Lithium

The manufacturer of milnacipran recommends regular clinical monitoring if milnacipran is given with lithium, because of the risk of serotonin syndrome.[1] Cases of serotonin syndrome have been reported with lithium and the SNRI, venlafaxine, see 'Lithium + Venlafaxine', p.1368.

(c) MAO-B inhibitors

The manufacturer of milnacipran contraindicates its use with selective monoamine oxidase type B inhibitors (selegiline and rasagiline) because of the risk of hypertensive crisis. They say that there should be 2 weeks between stopping the MAO-B inhibitor and starting milnacipran and at least one week between stopping milnacipran and starting the MAO-B inhibitor.[1] Note that, the more usual concern with the use of these drugs is the risk of serotonin syndrome, see 'MAO-B inhibitors + SSRIs or SNRIs', p.808.

1. Ixel (Milnacipran). Pierre Fabre Médicament. French Summary of product characteristics, February 2003.

SNRIs; Venlafaxine + Antihypertensives

A case report describes a patient taking captopril who developed hypertension when venlafaxine was started. Venlafaxine alone can cause sustained hypertension.

Clinical evidence, mechanism, importance and management

A 53-year-old woman who had her blood pressure well-controlled (130/80 mmHg) while taking **captopril** 25 mg daily and on a low-salt diet was found to have had an increase in her arterial blood pressure to 180/110 mmHg after she started taking venlafaxine (25 mg daily titrated to 100 mg daily) for depression. It was suggested that the effects of venlafaxine on noradrenaline might have antagonised the efficacy of **captopril**.[1]

Venlafaxine alone commonly causes dose-related hypertension, which can be sustained. The manufacturers advise that venlafaxine should be avoided in patients with uncontrolled hypertension, and that blood pressure should be monitored in all patients receiving venlafaxine. If sustained increases in blood pressure occur, consider reducing the venlafaxine dose, or discontinuing it.[2,3]

1. Sucar DD. Interação medicamentosa de venlafaxina com captopril. *Rev Bras Psiquiatr* (2000) 22, 134–7.
2. Efexor (Venlafaxine hydrochloride). Wyeth Pharmaceuticals. UK Summary of product characteristics, March 2008.
3. Effexor XR (Venlafaxine hydrochloride). Wyeth Pharmaceuticals Inc. US Prescribing information, July 2009.

SNRIs; Venlafaxine + Atomoxetine

A case report describes dyskinesia and dysarthria associated with the concurrent use of venlafaxine and atomoxetine.

Clinical evidence, mechanism, importance and management

An 18-year-old woman with attention deficit hyperactivity disorder, panic attacks and generalised anxiety was given venlafaxine, initially 37.5 mg daily, increasing to 225 mg daily, to which atomoxetine 18 mg daily was added. The atomoxetine dose was subsequently increased to 40 mg daily. After 3 weeks of concurrent use (and 5 days after the last dose increase) she presented with tremors, abnormal facial movements and a speech disturbance, which resolved after both medications were discontinued. It was suggested that a pharmacodynamic interaction, resulting from excess synaptic noradrenaline, might have occurred. Furthermore, the patient was a poor metaboliser of CYP2D6 (meaning she lacked or had low levels of this isoenzyme), and it was suggested that a pharmacokinetic interaction might also have occurred;[1] both drugs are substrates for CYP2D6. The manufacturer recommends caution when atomoxetine is given with other drugs that affect noradrenaline, because of the potential for additive or synergistic pharmacological effects.[2] Although this is an isolated case it adds weight to the manufacturers caution. Bear these symptoms in mind if both drugs are given, and consider an interaction if they occur.

1. Bond GR, Garro AC, Gilbert DL. Dyskinesias associated with atomoxetine in combination with other psychoactive drugs. *Clin Toxicol* (2007) 45, 182–5.
2. Strattera (Atomoxetine hydrochloride). Eli Lilly and Company Ltd. UK Summary of product characteristics, May 2009.

SNRIs; Venlafaxine + Bupropion

Bupropion may increase venlafaxine plasma levels, and decrease those of its active metabolite.

Clinical evidence

Bupropion increased trough venlafaxine plasma levels about 2.5-fold and decreased trough levels of the active metabolite, *O*-desmethylvenlafaxine, about 2.3-fold in 7 patients who had been given venlafaxine alone for a minimum of 6 weeks and then with sustained-release bupropion 150 mg daily for a further 8 weeks.[1]

Mechanism

Bupropion is an inhibitor of the cytochrome P450 isoenzyme CYP2D6, which is responsible for the metabolism of venlafaxine to *O*-desmethylvenlafaxine.

Importance and management

The clinical relevance of this pharmacokinetic interaction has not been assessed. However, because venlafaxine and *O*-desmethylvenlafaxine are considered equipotent as antidepressants, any change in their ratio should not affect clinical efficacy.[2] About 10% of Caucasians are lacking in active CYP2D6 (poor metabolisers), and what bupropion is effectively

doing is changing extensive metabolisers (those with normal levels of CYP2D6) into poor metabolisers.

For a report of worsening symptoms of serotonin syndrome when venlafaxine was given with bupropion and sertraline, see 'SSRIs + Bupropion', p.1482.

1. Kennedy SH, McCann SM, Masellis M, McIntyre RS, Raskin J, McKay G, Baker GB. Combining bupropion SR with venlafaxine, paroxetine, or fluoxetine: a preliminary report on pharmacokinetic, therapeutic, and sexual dysfunction effects. *J Clin Psychiatry* (2002) 63, 181–6.
2. Effexor XR (Venlafaxine hydrochloride). Wyeth Pharmaceuticals Inc. US Prescribing information, July 2009.

SNRIs; Venlafaxine + Co-amoxiclav

An isolated case of serotonin syndrome has been attributed to the concurrent use of venlafaxine and co-amoxiclav.

Clinical evidence, mechanism, importance and management

A 56-year-old man taking venlafaxine 37.5 mg twice daily for 10 months was given a course of co-amoxiclav (**amoxicillin** with **clavulanate**) 375 mg three times daily to treat gingivitis and a dental abscess. Within 3 hours of a dose of co-amoxiclav he developed tingling in the tip of his tongue, intense paraesthesia in the fingers, severe abdominal cramps, profuse diarrhoea, cold sweats, tremor and uncontrollable shivering. He was also agitated and frightened, but not confused. The symptoms lasted for 6 hours and were initially assumed to be due to gastroenteritis. However, 2 months later while still taking venlafaxine, he developed identical symptoms after a single dose of co-amoxiclav, which was then diagnosed as serotonin syndrome. The patient had taken co-amoxiclav without problem when not taking venlafaxine, and after the second episode, continued venlafaxine without further episodes of serotonin syndrome.[1]

The mechanism for this interaction is unclear. It is probable that many patients have received both venlafaxine and co-amoxiclav without adverse effects, so the general importance of this isolated report is unknown, but it seems likely to be small.

1. Connor H. Serotonin syndrome after single doses of co-amoxiclav during treatment with venlafaxine. *J R Soc Med* (2003) 96, 233–4.

SNRIs; Venlafaxine + Dexamfetamine

An isolated case of serotonin syndrome has been attributed to the concurrent use of dexamfetamine and venlafaxine.

Clinical evidence, mechanism, importance and management

A 32-year-old patient taking dexamfetamine 5 mg three times daily for adult attention deficit hyperactivity disorder (ADHD) presented with marked agitation, anxiety, shivering and tremor 2 weeks after also starting to take venlafaxine 75 mg to 150 mg daily. Other symptoms included generalised hypertonia, hyperreflexia, frequent myoclonic jerking, tonic spasm of the orbicularis oris muscle, and sinus tachycardia. His symptoms resolved completely when both drugs were withdrawn and cyproheptadine, to a total dose of 32 mg over 3 hours, was given. Dexamfetamine was restarted after 3 days.[1] This patient had a second episode of serotonin syndrome when citalopram was given with the dexamfetamine, see 'SSRIs + Nasal decongestants', p.1487.

It was suggested that the combination of serotonin re-uptake blockade and either presynaptic release of serotonin or monoamine oxidase inhibition by dexamfetamine could cause increased serotonin in the CNS.

Caution is advised when dexamfetamine is given with venlafaxine.[1] For more information about the serotonin syndrome, see under 'Additive or synergistic interactions', (p.9).

1. Prior FH, Isbister GK, Dawson AH, Whyte IM. Serotonin toxicity with therapeutic doses of dexamphetamine and venlafaxine. *Med J Aust* (2002) 176, 240–1.

SNRIs; Venlafaxine + Disulfiram

An isolated case describes a hypertensive crisis associated with the use of venlafaxine and disulfiram.

Clinical evidence, mechanism, importance and management

An isolated report describes a hypertensive crisis associated with a low dose of venlafaxine (75 mg daily). It was suggested that the concurrent use of disulfiram might have increased the toxicity of venlafaxine by interfering with its metabolism by the cytochrome P450 isoenzyme CYP3A4. However, disulfiram predominantly inhibits CYP2E1 and has not been reported to significantly affect CYP3A4. Note that disulfiram may provoke hypertension through its interaction with alcohol; however the authors state they found no evidence of a reaction with alcohol in this patient.[1] This is an isolated and unexplained case, its general significance is therefore probably small.

1. Khurana RN, Baudendistel TE. Hypertensive crisis associated with venlafaxine. *Am J Med* (2003) 115, 676–7.

SNRIs; Venlafaxine + Jujube (*Ziziphus jujuba*)

An isolated report describes an acute serotonin reaction when venlafaxine was given with a Chinese herbal remedy, jujube (sour date nut).

Clinical evidence, mechanism, importance and management

A 40-year-old woman with intermittent depression took jujube 500 mg daily (**sour date nut**; **suanzaoren**; *Ziziphus jujuba*), prescribed by a traditional Chinese healer, for several weeks, with minor improvement. She was then prescribed venlafaxine 37.5 mg daily by a psychiatrist, but approximately one hour after taking the first dose of venlafaxine with the jujube she became agitated, restless, nauseated, dizzy and ataxic, and subsequently collapsed. She had symptoms of a severe acute serotonin reaction with some anaphylactic features, which improved over the following 8 hours. She stopped taking the jujube and subsequently took venlafaxine 150 mg daily for one month without adverse effects.[1] This highlights the need for physicians to ask patients about the use of herbal medicines and to advise their discontinuation before prescribing other drugs if there is any possibility of an interaction.

1. Stewart DE. Venlafaxine and sour date nut. *Am J Psychiatry* (2004) 161, 1129–30.

SNRIs; Venlafaxine + Ketoconazole

Ketoconazole modestly inhibits the metabolism of venlafaxine and its active metabolite in patients with normal levels of CYP2D6 (extensive metabolisers). In about half the patients with low levels of CYP2D6 (poor metabolisers), marked increases in the levels of venlafaxine and its active metabolite were seen.

Clinical evidence

In one study in 14 patients with normal levels of CYP2D6 (extensive metabolisers), **ketoconazole** 100 mg twice daily for 2 days increased the plasma levels of venlafaxine and *O*-desmethylvenlafaxine (AUCs increased by 21% and 23%, respectively) when a single dose of venlafaxine given on day 2. However, in 6 poor metabolisers (i.e. those lacking CYP2D6) , the response was erratic with 3 out of 6 displaying marked increases in venlafaxine AUC (81%,126% and 206%, respectively) and the other 3 showing little or no change.[1] In these 6 subjects, the mean increase was 70%, and the AUC of *O*-desmethylvenlafaxine was also increased (mean 33%).[1,2]

Mechanism

The cytochrome P450 isoenzyme CYP3A4 metabolises venlafaxine to the inactive metabolite *N*-desmethylvenlafaxine. This metabolic route is minor in comparison to the metabolism of venlafaxine to O-desmethylvenlafaxine by CYP2D6, but it may assume more importance if CYP2D6 is lacking.[3]

Importance and management

The clinical relevance of these pharmacokinetic changes has not been assessed. However, the modest increases in both venlafaxine and its active metabolite (which have equipotent activity) in extensive metabolisers are probably unlikely to be clinically relevant. However, the marked increases

in the levels of venlafaxine and its active metabolite in poor metabolisers are of more concern. Because CYP2D6 metaboliser status is usually unknown, the manufacturers therefore advise caution with potent CYP3A4 inhibitors (they name **ketoconazole** and **erythromycin**).[2,3] The UK manufacturer also cautions that drug combinations that inhibit both CYP3A4 and CYP2D6 (see under CYP2D6 inhibitors in 'SNRIs; Venlafaxine + Miscellaneous', below), should only be given with venlafaxine if strictly indicated.[3] This seems prudent, as this situation is analogous to giving a CYP3A4 inhibitor to a known CYP2D6 poor metaboliser.

1. Lindh JD, Annas A, Meurling L, Dahl M-L, AL-Shurbaji A. Effect of ketoconazole on venlafaxine plasma concentrations in extensive and poor metabolisers of debrisoquine. *Eur J Clin Pharmacol* (2003) 59, 401–6.
2. Effexor XR (Venlafaxine hydrochloride). Wyeth Pharmaceuticals Inc. US Prescribing information, July 2009.
3. Efexor (Venlafaxine hydrochloride). Wyeth Pharmaceuticals. UK Summary of product characteristics, March 2008.

SNRIs; Venlafaxine + Metoclopramide

An isolated case of serotonin syndrome has been attributed to the concurrent use of metoclopramide and venlafaxine.

Clinical evidence, mechanism, importance and management

A 32-year-old woman with depression who had been taking venlafaxine 225 mg daily in divided doses for 3 years was admitted to hospital after a fall. She developed a movement disorder and a period of unresponsiveness after having been given a 10-mg intravenous dose of metoclopramide. After a second dose of metoclopramide the symptoms recurred and were associated with confusion, agitation, fever, diaphoresis, tachypnoea, tachycardia, and hypertension. The symptoms were consistent with serotonin syndrome, with a serious extrapyramidal movement disorder. The venlafaxine was withheld and she was given diazepam. The symptoms resolved over the next two days, after which she continued to take venlafaxine.[1] Information seems to be limited to this report, and the general significance of this interaction is unclear.

1. Fisher AA, Davis MW. Serotonin syndrome caused by selective serotonin reuptake-inhibitors–metoclopramide interaction. *Ann Pharmacother* (2002) 36, 67–71.

SNRIs; Venlafaxine + Mirtazapine

Isolated cases of serotonin syndrome have been reported in patients taking venlafaxine with mirtazapine.

Clinical evidence, mechanism, importance and management

The serotonin syndrome occurred in a patient given extended-release venlafaxine 75 mg daily and mirtazapine 30 mg daily, during cross-tapering of the two drugs (reducing mirtazapine dose and starting venlafaxine).[1] Another case occurred when tramadol was given to a patient taking venlafaxine and mirtazapine.[2]

For a report of haemorrhages associated with the use of mirtazapine, venlafaxine and escitalopram, see 'SNRIs + SSRIs', p.1475.

These isolated cases show that serotonin syndrome might occur with concurrent use of venlafaxine and mirtazapine. As this syndrome is potentially fatal, some caution is warranted if both drugs are given. For more information about the serotonin syndrome, see under 'Additive or synergistic interactions', (p.9).

1. Dimellis D. Serotonin syndrome produced by a combination of venlafaxine and mirtazapine. *World J Biol Psychiatry* (2002) 3, 167.
2. Houlihan DJ. Serotonin syndrome resulting from coadministration of tramadol, venlafaxine, and mirtazapine. *Ann Pharmacother* (2004) 38, 411–13.

SNRIs; Venlafaxine + Miscellaneous

The metabolism of venlafaxine to its active metabolite is inhibited by CYP2D6 inhibitors such as diphenhydramine, melperone, and thioridazine, but as venlafaxine and its active metabolite are equipotent, this is not considered clinically relevant. Venlafaxine modestly inhibits the metabolism of dextromethorphan, a CYP2D6 substrate.

Clinical evidence, mechanism, importance and management

(a) CYP2D6 inhibitors

Venlafaxine is primarily metabolised to its active metabolite *O*-desmethylvenlafaxine by the cytochrome P450 isoenzyme CYP2D6.[1,2] Pharmacokinetic studies show that the metabolism of venlafaxine is reduced by the CYP2D6 inhibitors **diphenhydramine**,[3] **melperone**,[4] and bupropion (see 'SNRIs; Venlafaxine + Bupropion', p.1477) in patients who are CYP2D6 extensive metabolisers (i.e. have normal levels of this isoenzyme).[3] However, the concurrent use of these inhibitors with venlafaxine would produce plasma levels of venlafaxine similar to those seen in patients who are genetically CYP2D6 poor metabolisers (about 5 to 10% of the general population), and venlafaxine and *O*-desmethylvenlafaxine are equipotent, therefore no dosage adjustment is necessary.[2] Venlafaxine is also metabolised by CYP3A4 (see 'SNRIs; Venlafaxine + Ketoconazole', p.1478, and this metabolic pathway becomes more important when CYP2D6 is inhibited. Therefore, the UK manufacturer recommends that venlafaxine should only be used with both a CYP2D6 inhibitor and a CYP3A4 inhibitor if strictly indicated.[1]

(b) CYP2D6 substrates

In a pharmacokinetic study in 26 healthy subjects, venlafaxine, titrated to 75 mg twice daily for 4 weeks modestly inhibited the metabolism of a single 30-mg dose of **dextromethorphan**, as assessed by the molar ratio of dextromethorphan to dextrorphan in urine.[5] In another similar study venlafaxine titrated to 75 mg twice daily for 8 days did not affect the metabolism of **dextromethorphan**.[6] This suggests that venlafaxine has a minor to modest ability to inhibit the cytochrome P450 isoenzyme CYP2D6, and is generally unlikely to have a clinically relevant pharmacokinetic interaction with most CYP2D6 substrates.

A case study reports higher than expected trough plasma levels of venlafaxine and lower than expected levels of *O*-desmethylvenlafaxine in a patient also taking **propranolol** and **mianserin** amongst other drugs.[7] The authors suggested that these drugs might have competitively inhibited the metabolism of venlafaxine by CYP2D6. However, neither of these drugs is known to inhibit CYP2D6, and, although they are both substrates for CYP2D6, combining substrates of an isoenzyme is not usually known to cause clinically relevant pharmacokinetic interactions. Moreover, the addition of the CYP2D6 inhibitor **thioridazine** further increased the venlafaxine levels in this case, suggesting that CYP2D6 was available for inhibition. Even if a pharmacokinetic interaction with propranolol or mianserin were to be confirmed, as mentioned above, an alteration in the ratio of venlafaxine to *O*-desmethylvenlafaxine is not considered clinically relevant.

1. Efexor (Venlafaxine hydrochloride). Wyeth Pharmaceuticals. UK Summary of product characteristics, March 2008.
2. Effexor XR (Venlafaxine hydrochloride). Wyeth Pharmaceuticals Inc. US Prescribing information, July 2009.
3. Lessard E, Yessine MA, Hamelin BA, Gauvin C, Labbé L, O'Hara G, LeBlanc J, Turgeon J. Diphenhydramine alters the disposition of venlafaxine through inhibition of CYP2D6 activity in humans. *J Clin Psychopharmacol* (2001) 21, 175–84.
4. Grözinger M, Dragicevic A, Hiemke C, Shams M, Müller MJ, Härtter S. Melperone is an inhibitor of the CYP2D6 catalyzed O-demethylation of venlafaxine. *Pharmacopsychiatry* (2003) 36, 3–6.
5. Amchin J, Ereshefsky L, Zarycranski W, Taylor K, Albano D, Klockowski PM. Effect of venlafaxine versus fluoxetine on metabolism of dextromethorphan, a CYP2D6 probe. *J Clin Pharmacol* (2001) 41, 443–51.
6. Alfaro CL, Lam YWF, Simpson J, Ereshefsky L. CYP2D6 inhibition by fluoxetine, paroxetine, sertraline, and venlafaxine in a crossover study: intraindividual variability and plasma concentration correlations. *J Clin Pharmacol* (2000) 40, 58–66.
7. Eap CB, Bertel-Laubscher R, Zullino D, Amey M, Baumann P. Marked increase of venlafaxine enantiomer concentrations as a consequence of metabolic interactions: a case report. *Pharmacopsychiatry* (2000) 33, 112–15.

SNRIs; Venlafaxine + Orphenadrine

An acute cutaneous reaction occurred on two occasions when a woman taking venlafaxine took orphenadrine with paracetamol.

Clinical evidence

A 55-year-old woman, who had been taking extended-release venlafaxine 225 mg daily for about 5 months, developed an extensive rash (diffuse and erythematous) accompanied by pruritus, sweating, hot flushes and agitation. The reaction was initially attributed to the extended-release venlafaxine, and the patient was switched to immediate-release venlafaxine 150 mg day, which she had received in the past without problems. However, 3 months later she presented with a less severe case of the cutaneous

reaction, and it transpired that she had taken a non-prescription product containing orphenadrine 35 mg and paracetamol 450 mg on both occasions.[1]

Mechanism

Results of skin testing suggested that the adverse effect was not a type I hypersensitivity reaction to orphenadrine or paracetamol. Early *in vitro* data for orphenadrine suggests that it can inhibit the cytochrome P450 isoenzymes CYP2D6 and CYP3A4, and the authors thought that combined inhibition of these enzymes may have been responsible. This seems possible, see 'SNRIs; Venlafaxine + Miscellaneous', p.1479.

Importance and management

Evidence for an interaction between venlafaxine and orphenadrine is limited, and no general precautions can be issued on the basis of a single case report. Nevertheless, bear the possibility of an interaction in mind in the event of an adverse reaction to the concurrent use of these two drugs.

1. Papadimitriou GN, Theleritis CG, Papageorgiou CC, Kalogeromitros D, Syrigou E, Gregoriou S, Rabavilas AD. Acute adverse cutaneous reaction after the concomitant use of venlafaxine and orphenadrine citrate plus paracetamol in a depressed patient. *J Eur Acad Dermatol Venereol* (2006) 20, 1019.

SNRIs; Venlafaxine + Sibutramine

The use of venlafaxine with sibutramine may lead to serotonin syndrome.

Clinical evidence, mechanism, importance and management

A letter mentions a case of serotonin syndrome, that developed in a woman given venlafaxine and sibutramine (no further details given), both of which are serotonergic drugs.[1] The UK and US manufacturers of venlafaxine and sibutramine caution against its use with other serotonergic drugs,[2-5] but in addition, the UK manufacturer of venlafaxine specifically advises against its use with weight loss drugs.[2] The manufacturers of sibutramine say that it should not be given with other serotonergic drugs.[4,5]

Note that reports of serotonin syndrome are generally rare. If both drugs are given together it would seem prudent to monitor the outcome closely. For more information about serotonin syndrome and its management, see under 'Additive or synergistic interactions', (p.9).

1. Trakas K, Shear NH. Serotonin syndrome risk with antiobesity drug. *Can J Clin Pharmacol* (2000) 7, 216.
2. Efexor (Venlafaxine hydrochloride). Wyeth Pharmaceuticals. UK Summary of product characteristics, March 2008.
3. Effexor (Venlafaxine hydrochloride). Wyeth Pharmaceuticals Inc. US Prescribing information, July 2009.
4. Reductil (Sibutramine hydrochloride monohydrate). Abbott Laboratories Ltd. UK Summary of product characteristics, October 2007.
5. Meridia (Sibutramine hydrochloride monohydrate). Abbott Laboratories. US Prescribing information, May 2009.

SNRIs; Venlafaxine + Terbinafine

The metabolism of venlafaxine to its active metabolite *O*-desmethylvenlafaxine is reduced in the presence of terbinafine.

Clinical evidence

In a randomised, crossover study, 12 healthy subjects were given a single 75-mg dose of venlafaxine, alone or after taking terbinafine 250 mg daily for 4 days. The AUC and maximum plasma concentration of venlafaxine were increased 4.9-fold and 2.7-fold, respectively, and the half-life of venlafaxine was also increased from 5.1 hours to 8.6 hours. The AUC and maximum plasma concentration of the active metabolite of venlafaxine, *O*-desmethylvenlafaxine, were reduced by 43% and 67%, respectively, and the half-life of this metabolite was almost doubled.[1]

Mechanism

Terbinafine inhibits the cytochrome P450 isoenzyme CYP2D6, which is involved in the metabolism of venlafaxine to *O*-desmethylvenlafaxine.

Importance and management

This appears to be the only study of this interaction and its clinical significance is unclear: both venlafaxine and *O*-desmethylvenlafaxine are active compounds, and their combined AUC was only raised by a modest 22%. Furthermore, this was a single dose study, and so could not assess the potential for venlafaxine accumulation in the presence of terbinafine. Until more is known, it may be prudent to be alert for any indication of increased venlafaxine adverse effects (e.g. nausea, insomnia, dry mouth) in patients also taking terbinafine.

1. Hynninen V-V, Olkkola KT, Bertilsson L, Kurkinen K, Neuvonen PJ, Laine K. Effect of terbinafine and voriconazole on the pharmacokinetics of the antidepressant venlafaxine. Clin Pharmacol Ther (2008) 83, 342–8.

SNRIs; Venlafaxine + Tramadol

Two cases of serotonin syndrome have been reported when tramadol was given with venlafaxine; one patient was also receiving mirtazapine. Fatal seizures occurred in an alcoholic man receiving a number of drugs, including tramadol and venlafaxine.

Clinical evidence, mechanism, importance and management

A 47-year-old man who had been stable taking venlafaxine 300 mg daily and mirtazapine 30 mg daily for 4 months was given tramadol, titrated to 300 mg daily over 4 weeks, without adverse effects. However, about 7 weeks after increasing the dose of tramadol to 400 mg daily he experienced agitation, confusion, severe shivering, diaphoresis, myoclonus, hyperreflexia, mydriasis, and tachycardia. His symptoms resolved over 36 hours after all medications were discontinued and did not recur when venlafaxine and mirtazapine were restarted without tramadol.[1] A 65-year-old woman who had been taking venlafaxine 100 mg daily for 3 weeks, developed symptoms of serotonin syndrome 3 days after tramadol 300 mg daily was started. The symptoms resolved completely 3 days after venlafaxine withdrawal, when tramadol was also withdrawn. No symptoms occurred on rechallenge with venlafaxine alone, 2 weeks later.[2]

A 36-year-old alcoholic died after developing seizures while taking tramadol and several other drugs, including venlafaxine, trazodone and quetiapine, all of which interact with the neurotransmitter serotonin. It was thought that the combination of these drugs and alcohol withdrawal lowered the seizure threshold.[3]

Although these reports are isolated, based on the known mechanism of action of venlafaxine and its potential for 'serotonin syndrome', (p.9), some caution might be appropriate when venlafaxine is used with other drugs that may affect the serotonergic neurotransmitter systems such as tramadol.

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2. Anon. Venlafaxine + tramadol: serotonin syndrome. *Prescrire Int* (2004) 13, 57.
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SNRIs; Venlafaxine + Trazodone

Isolated cases of serotonin syndrome have been reported in patients taking venlafaxine with trazodone.

Clinical evidence, mechanism, importance and management

A 50-year-old HIV-positive man, who was taking methadone for opioid dependence, developed signs of the serotonin syndrome 18 days after starting to take extended-release venlafaxine (dose increased to 225 mg daily over 7 days) and trazodone 100 mg at bedtime. His clinical status improved rapidly over 24 hours when all medications were discontinued. Serotonin syndrome was thought to have been precipitated by the combination of venlafaxine and trazodone, both of which inhibit the reuptake of serotonin, but methadone may have also been a contributing factor. The patient was not taking any concurrent medication for his HIV infection.[1]

In another report, a 69-year-old woman with major depression failed to respond to monotherapy with various drugs and was then given fluoxetine, trazodone, buspirone and zolpidem. After a partial response at 2 months, she was additionally given venlafaxine 37.5 mg twice daily. On the next day she developed fever, tremor, muscle cramping, diarrhoea, ataxia, irri-

tability, and altered consciousness, which was interpreted as serotonin syndrome. She was admitted, all medication was withdrawn, and the symptoms gradually resolved over 3 days. She then developed a full-blown manic episode.[2] Fluoxetine is known to have serotonergic effects, and may have contributed to the development of serotonin syndrome in this case.

For a case of serotonin syndrome in a patient taking trazodone, that developed when venlafaxine was abruptly switched for fluoxetine, see 'SNRIs + SSRIs', p.1475.

These isolated cases show that serotonin syndrome might occur with concurrent use of venlafaxine and trazodone. Serotonin syndrome is a rare adverse effects, but because of its severity, some caution is warranted if both drugs are given. For more about serotonin syndrome, see under 'Additive or synergistic interactions', (p.9).

1. McCue RE, Joseph M. Venlafaxine- and trazodone-induced serotonin syndrome. *Am J Psychiatry* (2001) 158, 2088–9.
2. Liau C-H, Shen WW, Su K-P. Venlafaxine-associated serotonin syndrome and manic episode in a geriatric depressive patient. *Psychiatry Clin Neurosci* (2006) 60, 121–2.

SSRIs + Ayahuasca

A man taking fluoxetine experienced symptoms of serotonin syndrome after drinking the psychoactive beverage ayahuasca, which contains monoamine oxidase-inhibiting harmala alkaloids.

Clinical evidence, mechanism, importance and management

A 36-year-old man who was taking **fluoxetine** 20 mg daily for mild depression participated in a religious ceremony using ayahuasca (also known as caapi, daime, hoasca, natema, yage) which is a psychoactive beverage characteristically containing harmala alkaloids (primarily harmine and harmaline) derived from the vine *Banisteriopsis caapi*. One hour after drinking 100 mL of ayahuasca he experienced tremors, sweating, shivering and confusion. His condition deteriorated over the next few hours with gross motor tremors and severe nausea and vomiting, but he rapidly recovered 4 hours later, with no treatment.

The harmala alkaloids are capable of blocking the enzymatic activity of MAO for several hours, and consequently inhibit the metabolic breakdown of neurotransmitters. There is, therefore, the potential for serotonin syndrome to develop with the concurrent use of SSRIs and ayahuasca.[1]

1. Callaway JC, Grob CS. Ayahuasca preparations and serotonin reuptake inhibitors: a potential combination for severe adverse interactions. *J Psychoactive Drugs* (1998) 30, 367–9.

SSRIs + Azoles

Anorexia developed in a patient taking fluoxetine when itraconazole was started, and it disappeared when the itraconazole was stopped. Itraconazole modestly increases the AUC of paroxetine. The pharmacokinetics of citalopram (and therefore probably escitalopram) are not affected by ketoconazole.

Clinical evidence, mechanism, importance and management

(a) Citalopram or Escitalopram

In a placebo-controlled, single-dose, crossover study in 18 healthy subjects, **ketoconazole** 200 mg did not affect the pharmacokinetics of citalopram 40 mg.[1]

Ketoconazole is a potent inhibitor of the cytochrome P450 isoenzyme CYP3A4, which, in part, metabolises citalopram, but as several other cytochrome P450 isoenzymes are also involved in citalopram metabolism it would seem that inhibition of only one pathway does not result in clinically significant effects. Similarly, escitalopram (the *S*-isomer of citalopram), would also not be expected to be affected by **ketoconazole**, and this is supported by an *in vitro* study.[2]

No citalopram or escitalopram dosage adjustment is likely to be need if **ketoconazole** is also taken.

(b) Fluoxetine

A man taking fluoxetine 20 mg daily, diazepam and several anti-asthma drugs (salbutamol (albuterol), salmeterol, budesonide, theophylline) was given **itraconazole** 200 mg daily for allergic bronchopulmonary aspergillosis. Within 1 to 2 days he developed anorexia without nausea. He stopped the **itraconazole** after a week, and the anorexia resolved 1 to 2 days later.

The author of the report suggested that **itraconazole**, a potent enzyme inhibitor, increased the levels of the fluoxetine metabolite, norfluoxetine, which resulted in the anorexia.[3] Anorexia is a recognised adverse effect of fluoxetine. However, drug levels were not taken, so this suggestion has not been confirmed.

This report and the conclusions reached are uncertain, but they draw attention to the possibility of an interaction between fluoxetine and **itraconazole**. Consider this interaction if fluoxetine adverse effects are troublesome.

(c) Paroxetine

In a controlled study in healthy subjects, **itraconazole** 100 mg twice daily for 6 days increased the AUC of paroxetine by 55% when a single 20-mg dose of paroxetine was given on day 6. Paroxetine clearance was reduced by 36%, and there was a small 14% increase in its elimination half-life.[4]

Paroxetine is a substrate for the cytochrome P450 isoenzyme CYP2D6, but **itraconazole** is an inhibitor of CYP3A4, so an interaction as a result of inhibition of the cytochrome P450 isoenzyme system was discounted. It was suggested that itraconazole might have increased the bioavailability of paroxetine by inhibiting P-glycoprotein.[4]

An increase in the AUC of paroxetine of this magnitude is probably not likely to be clinically important in most patients. Bear the possibility of an interaction in mind in the event of an increase in adverse effects.

1. Gutierrez M, Abramowitz W. Lack of effect of a single dose of ketoconazole on the pharmacokinetics of citalopram. *Pharmacotherapy* (2001) 21, 163–8.
2. Von Moltke LL, Greenblatt DJ, Giancarlo GM, Granda BW, Harmatz JS, Shader RI. Escitalopram (*S*-citalopram) and its metabolites in vitro: cytochromes mediating biotransformation, inhibitory effects, and comparison to *R*-citalopram. *Drug Metab Dispos* (2001) 29, 1102–9.
3. Black PN. Probable interaction between fluoxetine and itraconazole. *Ann Pharmacother* (1995) 29, 1048–9.
4. Yasui-Furukori N, Saito M, Niioka T, Inoue Y, Sato Y, Kaneko S. Effect of itraconazole on pharmacokinetics of paroxetine: the role of gut transporters. *Ther Drug Monit* (2007) 29, 45–8.

SSRIs + Barbiturates

Paroxetine appears not to increase the psychomotor effects of amobarbital. Phenobarbital may reduce the AUC of paroxetine. Two cases of hepatotoxicity have been reported when paroxetine was given with a barbiturate.

Clinical evidence, mechanism, importance and management

In a small study in 7 healthy subjects, **phenobarbital** 100 mg daily for 14 days caused reductions of 10 to 86% in the AUC of paroxetine in 6 subjects, and a 57% *increase* in one subject. Overall, the paroxetine AUC was reduced by 25% and the elimination half-life was reduced by 38%, although these differences were not statistically significant.[1]

Phenobarbital is a well-known enzyme inducer, and these data suggest that it might reduce the levels of paroxetine in some patients, but the clinical relevance of the changes seen is uncertain. Bear the possibility of a pharmacokinetic interaction in mind if the efficacy of paroxetine is reduced on starting phenobarbital, and adjust the paroxetine dose as necessary.

The sedative effects and impairment of psychomotor performance caused by **amobarbital** 100 mg were not increased by paroxetine 30 mg.[2] This suggests that no adverse pharmacodynamic interaction occurs.

Two cases of hepatitis in young women were considered to be caused by the concurrent use of *Atrium* (a barbiturate complex) and paroxetine, which are both rarely associated with hepatotoxicity.[3] The relevance of these cases is uncertain.

Note that the SSRIs can cause seizures and so they should be used with caution in patients given barbiturates for epilepsy. This warning is emphasised by an isolated report describing a tonic clonic seizure in a woman taking paroxetine who was anaesthetised with methohexital. See 'Anaesthetics, general + SSRIs', p.117.

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2. Cooper SM, Jackson D, Loudon JM, McClelland GR, Raptopoulos P. The psychomotor effects of paroxetine alone and in combination with haloperidol, amylobarbitone, oxazepam, or alcohol. *Acta Psychiatr Scand* (1989) 80 (Suppl 350), 53–55.
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SSRIs + Bupropion

There are isolated reports of serotonin syndrome, hypersexuality, psychosis, mania and seizures associated with the use of bupropion and an SSRI. Bupropion modestly increases citalopram levels, but limited evidence suggests that the plasma levels of fluoxetine and paroxetine are not altered by bupropion.

Clinical evidence

(a) Citalopram

In a study in 28 healthy subjects, the addition of sustained-release bupropion 300 mg daily to citalopram 40 mg daily resulted in a 39% increase in the AUC of citalopram and a 30% increase in its maximum level.[1]

(b) Fluoxetine

Bupropion had no effect on trough fluoxetine or norfluoxetine levels in a study in 5 patients who had been given fluoxetine (dose not stated) alone for a minimum of 6 weeks and then also sustained-release bupropion 150 mg daily for a further 8 weeks.[2]

The day after stopping fluoxetine 60 mg daily, a 41-year-old man started taking bupropion 75 mg and later 100 mg three times daily. After 10 days he became edgy and anxious and after 12 days he developed myoclonus. After 14 days he became severely agitated and psychotic, with delirium and hallucinations. His behaviour returned to normal 6 days after the bupropion was stopped.[3] Another patient taking lithium carbonate for bipolar disorder developed anxiety, panic and eventually mania a little over a week after stopping fluoxetine and starting bupropion.[4]

A review briefly mentions an unpublished case of a patient who had a grand mal seizure after being given fluoxetine and bupropion 300 mg daily.[5]

A 35-year-old woman taking fluoxetine 40 mg daily was given low-dose bupropion (100 mg daily) to treat fluoxetine-induced sexual dysfunction. Despite a good initial response, hypersexuality developed, and so the bupropion was stopped.[6]

(c) Paroxetine

Bupropion had no effect on trough paroxetine levels in a study in 4 patients who had been given paroxetine alone for a minimum of 6 weeks and then also sustained-release bupropion 150 mg daily for a further 8 weeks.[2]

(d) Sertraline

A 62-year-old woman taking therapeutic doses of bupropion and sertraline experienced upper extremity tremor, clumsiness and gait difficulties, with fluctuating symptoms of confusion, forgetfulness, and alternating agitation and lethargy, which started after a few days on this regimen. **Venlafaxine** was then added and the clinical picture worsened with deterioration of mental status, hallucinations, insomnia, myoclonic jerks, postural and balance difficulties, incoordination and incontinence. The medications were discontinued and the symptoms, which were indicative of serotonin syndrome, gradually resolved.[7]

An isolated case describes spontaneous orgasm with the combined use of bupropion and sertraline. Bupropion had been successfully used to treat SSRI-induced impaired sexual function, but after 6 weeks of concurrent use she experienced a sudden-onset, spontaneous orgasm; this occurred again on rechallenge with bupropion.[8]

Mechanism

Several mechanisms have been proposed. Bupropion inhibits the cytochrome P450 isoenzyme CYP2D6, by which some SSRIs are predominantly metabolised (see 'Table 35.2', (p.1465)), so it might cause an increase in their plasma levels and increased toxicity. One study did find a modest increase in citalopram levels; however, another small study unexpectedly found no changes in the plasma levels of fluoxetine or paroxetine when given with bupropion.[2] An *in vitro* study demonstrated that several SSRIs (paroxetine, sertraline, norfluoxetine, and fluvoxamine) could inhibit CYP2B6, the isoenzyme involved in bupropion hydroxylation,[9] and in one of the cases described above it was suggested that residual fluoxetine may have inhibited the metabolism of bupropion, leading to toxic levels.[3] A pharmacodynamic mechanism has also been proposed. Bupropion can cause seizures and SSRIs may further lower the seizure threshold, see 'Bupropion + Miscellaneous', p.1468.

Importance and management

Information is limited, but what is known suggests that if concurrent or sequential use of bupropion and an SSRI is thought appropriate, the outcome should be well monitored and reduced doses should be considered. The manufacturers recommend that drugs that are metabolised by CYP2D6 should be given with bupropion with caution and initiated at the lower end of the dose range. If bupropion is given to a patient already taking a drug metabolised by CYP2D6, the need to decrease the dose of this drug should be considered.[10,11] The UK manufacturers specifically name paroxetine and the US manufacturers additionally name fluoxetine and sertraline. In addition, the manufacturers advise caution if bupropion is given with antidepressants that lower the seizure threshold[10,11] and, in this situation, the UK manufacturer says that consideration should be given to reducing the dose of bupropion to a maximum of 150 mg daily for smoking cessation.[10]

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5. Ciraulo DA, Shader RI. Fluoxetine drug-drug interactions.II. *J Clin Psychopharmacol* (1990) 10, 213–17.
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10. Zyban (Bupropion hydrochloride). GlaxoSmithKline UK. UK Summary of product characteristics, January 2009.
11. Zyban (Bupropion hydrochloride). GlaxoSmithKline. US Prescribing information, July 2009.

SSRIs + Cyproheptadine

Several reports suggest that cyproheptadine can oppose the antidepressant effects of fluoxetine, and another describes the same effect with paroxetine.

Clinical evidence

(a) Fluoxetine

Three men with depression complained of anorgasmia when taking fluoxetine. When this was treated with cyproheptadine their depressive symptoms returned, decreasing again when cyproheptadine was stopped.[1] Two women also complained of anorgasmia within 1 to 3 months of starting to take fluoxetine 40 to 60 mg daily for bulimia nervosa. When cyproheptadine was added to treat the anorgasmia, the urge to binge on food returned in both of them and one experienced increased depression. These symptoms resolved 4 to 7 days after stopping cyproheptadine.[2] A woman successfully treated with fluoxetine 40 mg daily had a re-emergence of her depressive symptoms on two occasions within 36 hours of starting to take cyproheptadine.[3] In a further case, a woman who responded well to fluoxetine 20 mg daily for depression had a recurrence of her depression after she began to take cyproheptadine for migraine. Increasing the dose of fluoxetine to 40 mg daily controlled the depressive symptoms while cyproheptadine was continued for migraine.[4] In contrast, no exacerbation of depression was seen in a study in which both cyproheptadine and fluoxetine were used in 2 patients.[5]

(b) Paroxetine

A woman taking paroxetine 20 mg daily for depression relapsed and worsened, and developed confusion and psychotic symptoms, within 2 days of

starting to take cyproheptadine 2 mg twice daily for anorgasmia.[6] The psychotic symptoms resolved 2 days after stopping cyproheptadine.

Mechanism

Although the mechanism is not fully understood, it has been suggested that because cyproheptadine is a serotonin antagonist it blocks or opposes the serotonergic effects of these SSRIs.[1-3,6]

Importance and management

Direct information about this interaction appears to be limited to these studies although cyproheptadine has also been found to oppose the antidepressant effects of MAOIs (see 'MAOIs or RIMAs + Antihistamines; Cyproheptadine', p.1371). One study suggests that not every patient is affected.[5] If concurrent use is thought appropriate, the outcome should be very well monitored for evidence of a reduced antidepressant response.

Because of its serotonin antagonist effects, cyproheptadine has been used to treat the 'serotonin syndrome', (p.9), including cases resulting from the use of SSRIs.

1. Feder R. Reversal of antidepressant activity of fluoxetine by cyproheptadine in three patients. *J Clin Psychiatry* (1991) 52, 163–4.
2. Goldbloom DS, Kennedy SH. Adverse interaction of fluoxetine and cyproheptadine in two patients with bulimia nervosa. *J Clin Psychiatry* (1991) 52, 261–2.
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4. Boon F. Cyproheptadine and SSRIs. *J Am Acad Child Adolesc Psychiatry* (1999) 38, 112.
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SSRIs + Dextromethorphan

A few reports describe the development of a serotonin-like syndrome in patients taking citalopram, fluoxetine or paroxetine when they took dextromethorphan. In some of these cases, other serotonergic drugs might have contributed. Another report describes hallucinations in a woman taking fluoxetine and dextromethorphan.

Paroxetine and fluoxetine moderately inhibit the metabolism of dextromethorphan, whereas fluvoxamine and sertraline have modest to minimal effects.

Clinical evidence

(a) Citalopram

A man who had been taking citalopram 30 mg, nefazodone 600 mg and long-acting oxycodone 10 mg at bedtime without problems, started taking a cough syrup containing dextromethorphan and within a day he began to experience fatigue, lethargy, jitteriness and headache. He stopped taking the dextromethorphan and his symptoms gradually disappeared over several hours.[1] Another case of serotonin syndrome occurred a couple of days after taking dextromethorphan (*Night and Day* capsules) in a 46-year-old man who had been taking citalopram 40 mg daily and methadone 70 mg daily for 2 years.[2]

(b) Fluoxetine

In a pharmacokinetic study in healthy subjects, fluoxetine 20 mg daily for 4 weeks moderately inhibited the metabolism of a single 30-mg dose of dextromethorphan, as assessed by the molar ratio of dextromethorphan to dextrorphan in urine.[3] Another study using fluoxetine 60 mg daily for 8 days found an even greater inhibition of metabolism.[4]

A woman who had been taking fluoxetine 20 mg daily for 17 days took about 10 mL of a cough syrup containing dextromethorphan, and a further dose the next morning, with the next dose of fluoxetine. Within 2 hours vivid hallucinations developed (bright colours, distortions of shapes and sizes), which lasted 6 to 8 hours. The patient said they were similar to her past experience with LSD 12 years earlier.[5]

(c) Fluvoxamine

In a pharmacokinetic study in healthy subjects, fluvoxamine 150 mg daily for 4 weeks slightly inhibited the metabolism of a single 30-mg dose of dextromethorphan 30 mg, as assessed by the molar ratio of dextromethorphan to dextrorphan in urine.[6]

(d) Paroxetine

In a pharmacokinetic study in healthy subjects, paroxetine 20 mg daily for 8 days moderately inhibited the metabolism of a single 30-mg dose of dextromethorphan, as assessed by the molar ratio of dextromethorphan to dextrorphan in urine.[4] A smaller increase in the ratio of dextromethorphan to dextrorphan was seen in another study using a single 20-mg dose of paroxetine.[7]

A man with multiple medical problems was admitted to hospital as an emergency, mainly because he was vomiting blood. He was taking diazepam, diltiazem, glyceryl trinitrate, paroxetine, piroxicam, ranitidine and ticlopidine. Four days previously he had begun to take *Nyquil*, a non-prescription remedy for colds, containing dextromethorphan, pseudoephedrine, paracetamol (acetaminophen) and doxylamine. After two days he developed shortness of breath, nausea, headache and confusion, and on admission he was also diaphoretic, tremulous, tachycardic and hypertensive. Later he became rigid. The eventual diagnosis was that he was suffering from serotonin syndrome, attributed to an interaction between paroxetine and dextromethorphan in the presence of vascular disease. He was successfully treated with lorazepam 16 mg intravenously over 1 hour. The bleeding was thought to be from a small prepyloric ulcer.[8]

The authors of this report very briefly describe another patient taking paroxetine who developed symptoms consistent with serotonin syndrome within a few hours of taking a non-prescription cough remedy containing dextromethorphan and guaifenesin. She needed intensive care treatment.[9]

(e) Sertraline

In a pharmacokinetic study in healthy subjects, sertraline 100 mg daily for 8 days did not have a statistically significant effect on the metabolism of a single dose of dextromethorphan 30 mg, as assessed by the molar ratio of dextromethorphan to dextrorphan in urine.[4]

Mechanism

The symptoms that developed with citalopram or paroxetine and dextromethorphan were attributed by the authors of the reports to serotonin syndrome caused by the additive effects of the SSRIs and dextromethorphan on serotonin transmission.

Fluoxetine and paroxetine are moderate inhibitors of the cytochrome P450 isoenzyme CYP2D6, by which dextromethorphan is metabolised, resulting in increased dextromethorphan levels. Fluvoxamine and sertraline have much less effect on CYP2D6. Whether the increased levels of dextromethorphan have any bearing on the likely development of serotonin syndrome remains to be seen.

Importance and management

The pharmacokinetic interaction is established. Paroxetine and fluoxetine are moderate inhibitors of dextromethorphan metabolism, whereas fluvoxamine and sertraline have minimal effects. However, this pharmacokinetic interaction will occur only in individuals who are CYP2D6 extensive metabolisers (i.e. those with normal levels of this isoenzyme). Poor metabolisers lack CYP2D6, and would not be affected. At the most, maximal inhibition of CYP2D6 therefore increases dextromethorphan levels in extensive metabolisers to the levels already seen in poor metabolisers. Dextromethorphan is generally considered to have a wide therapeutic range and the dose is not individually titrated; therefore, the interaction with paroxetine and fluoxetine is unlikely to be clinically relevant in terms of common adverse effects of dextromethorphan. Nevertheless, it is possible that some extensive metaboliser patients might become more sensitive to the adverse effects of dextromethorphan while taking paroxetine or fluoxetine.

Moreover, it is unclear what effect these pharmacokinetic interactions have on the development of serotonin syndrome, if any. So far, these few reports seem to be the only cases of the serotonin syndrome being attributed to an interaction between an SSRI and dextromethorphan. However, it has been suggested that the incidence of mild serotonin excess (as seen in the case with citalopram) may be more common than is known.[1] The general importance of this apparent interaction is therefore very uncertain. The SSRIs are now very widely prescribed and dextromethorphan is a relatively common ingredient of non-prescription medicines. More study is therefore needed to establish this apparent interaction, but in the meantime, it seems unlikely that any general precautions are needed in patients taking SSRIs who use dextromethorphan-containing products.

On the basis of the difference in pharmacokinetic interaction between

SSRIs and dextromethorphan, it had been predicted that sertraline and fluvoxamine might be less likely to cause serotonin syndrome with dextromethorphan than paroxetine and fluoxetine.[9,10] In considering this possibility, it should be noted that cases of serotonin syndrome have been reported with citalopram, which is not a potent CYP2D6 inhibitor.

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SSRIs + Grapefruit juice

Grapefruit juice modestly increases fluvoxamine levels, and there is a case report of adverse effects attributed to this pharmacokinetic interaction. Sertraline plasma levels are also modestly increased by grapefruit juice. Excessive consumption of grapefruit caused symptoms similar to serotonin syndrome in a patient taking fluoxetine and trazodone.

Clinical evidence

(a) Fluoxetine

A 57-year-old HIV-positive man had been receiving indinavir, stavudine and lamivudine, as well as other medications including fluoxetine 20 mg daily and trazodone 200 mg daily. He complained of dizziness, mild confusion, diarrhoea, visual changes, and a general feeling of being "out of sorts" for approximately one month. On further questioning it was found that the patient had been having one grapefruit each morning but had increased his consumption to 3 per day. His symptoms resolved when he stopped eating grapefruit.[1]

(b) Fluvoxamine

A randomised, placebo-controlled, crossover study in 10 healthy subjects found that 250 mL of grapefruit juice three times daily for 6 days increased the AUC of a single 75-mg dose of fluvoxamine by 60% and increased its maximum plasma levels by 33%.[2]

A 75-year-old woman taking fluvoxamine 150 mg at night experienced palpitations when on holiday in Florida, which stopped when she returned home. The only change identified was that she drank grapefruit juice daily while in Florida. She had previously experienced palpitations when taking a higher dose of fluvoxamine (200 mg at night).[3]

(c) Sertraline

A study in 5 patients taking sertraline 50 to 75 mg daily found that the concurrent use of grapefruit juice for one week increased serum trough levels by almost 50%.[4]

Mechanism

Grapefruit juice is an inhibitor of the cytochrome P450 isoenzyme CYP3A4 and sertraline is partially metabolised by this enzyme. Therefore grapefruit juice would be expected to reduce the metabolism of sertraline. This has been demonstrated *in vitro*; grapefruit juice inhibited the formation of desmethylsertraline in a dose-dependent manner.[4] The other SSRIs mentioned above are not significantly metabolised by CYP3A4, but grapefruit juice also inhibits other isoenzymes that could affect the metabolism of SSRIs especially if the patient is also a poor metaboliser of CYP2D6.[2,3]

Importance and management

The modest pharmacokinetic interactions between grapefruit juice and fluvoxamine and sertraline would appear to be established, but would usually not be clinically relevant. Nevertheless, there are isolated reports of clinically significant interactions between grapefruit and SSRIs, so the possibility of an interaction should be borne in mind especially if unusual amounts of grapefruit have been consumed.

1. DeSilva KE, Le Flore DB, Marston BJ, Rimland D. Serotonin syndrome in HIV-infected individuals receiving antiretroviral therapy and fluoxetine. *AIDS* (2001) 15, 1281–5.
2. Hori H, Yoshimura R, Ueda N, Eto S, Shinkai K, Sakata S, Ohmori O, Terao T, Nakamura J. Grapefruit juice-fluvoxamine interaction. Is it risky or not? *J Clin Psychopharmacol* (2003) 23, 422–4.
3. Wiens A. How does grapefruit juice affect psychotropic medications? *J Psychiatry Neurosci* (2000) 25, 198.
4. Lee AJ, Chan WK, Harralson AF, Buffum J, Bui B-CC. The effects of grapefruit juice on sertraline metabolism: an in vitro and in vivo study. *Clin Ther* (1999) 21, 1890–9.

SSRIs + H_2-receptor antagonists

Citalopram, escitalopram, paroxetine and sertraline levels are moderately increased by cimetidine.

Clinical evidence

(a) Citalopram

In a study, 12 healthy subjects were given citalopram 40 mg daily for 21 days and then for the next 8 days they were also given **cimetidine** 400 mg twice daily. **Cimetidine** caused a 29% decrease in the oral clearance of citalopram, a 39% rise in its maximum serum levels and a 43% increase in its AUC. Some changes in the renal clearance of the citalopram metabolites were also seen.[1]

(b) Escitalopram

In a controlled study in 16 healthy subjects, **cimetidine** 400 mg twice daily for 5 days increased the AUC of escitalopram by about 70% when a single 20-mg dose of escitalopram was given on day 4. There was also a 22% increase in the maximum plasma level of escitalopram.[2]

(c) Paroxetine

In a study in 10 healthy subjects, **cimetidine** 200 mg four times daily for 8 days did not affect the mean pharmacokinetic values or bioavailability of a single 30-mg dose of paroxetine. However, in 2 subjects the AUC of paroxetine increased by 55% and 81%, respectively.[3] Another study in 11 healthy subjects found that **cimetidine** 300 mg three times a day increased the AUC of paroxetine 30 mg daily by about 50% after one week of concurrent use.[4]

(d) Sertraline

In a randomised, crossover study, 12 healthy subjects were given either **cimetidine** 800 mg or a placebo at bedtime for 8 days, with a single 100-mg dose of sertraline on day 2. **Cimetidine** increased the AUC of sertraline by 50%, increased its maximum serum levels by 24%, and prolonged the half-life by 26%.[5]

Mechanism

The apparent reason for all these changes is that **cimetidine** inhibits the activity of cytochrome P450 so that the metabolism of the SSRIs is reduced, and as a result their serum levels rise.

Importance and management

The pharmacokinetic interactions between cimetidine and citalopram, escitalopram, paroxetine and sertraline are established. However, the modest increases seen are generally unlikely to be clinically relevant because the SSRIs are usually well tolerated, have a wide therapeutic range, and there are large pharmacokinetic variations between individual subjects.[1,2]. However, the results from the paroxetine study suggest that individual patients may experience greater rises. Therefore it would seem prudent to monitor concurrent use for adverse effects (e.g. dry mouth, nau-

sea, diarrhoea, dyspepsia, tremor, ejaculatory delay, sweating) and consider reducing the SSRI dose if these become troublesome.

If the suggested mechanism of interaction is true, one of the other H_2-receptor antagonists that lack enzyme inhibitory activity, such as ranitidine or famotidine, might be a non-interacting alternative for cimetidine, but this needs confirmation.

1. Priskorn M, Larsen F, Segonzac A, Moulin M. Pharmacokinetic interaction study of citalopram and cimetidine in healthy subjects. *Eur J Clin Pharmacol* (1997) 52, 241–2.
2. Malling D, Poulsen MN, Søgaard B. The effect of cimetidine or omeprazole on the pharmacokinetics of escitalopram in healthy subjects. *Br J Clin Pharmacol* (2005) 60, 287–90.
3. Greb WH, Buscher G, Dierdorf H-D, Köster FE, Wolf D, Mellows G. The effect of liver enzyme inhibition by cimetidine and enzyme induction by phenobarbitone on the pharmacokinetics of paroxetine. *Acta Psychiatr Scand* (1989) 80 (Suppl 350), 95–8.
4. Bannister SJ, Houser VP, Hulse JD, Kisicki JC, Rasmussen JGC. Evaluation of the potential for interactions of paroxetine with diazepam, cimetidine, warfarin, and digoxin. *Acta Psychiatr Scand* (1989) 80 (Suppl 350), 102–6.
5. Invicta Pharmaceuticals. Phase 1 study to assess the potential of cimetidine to alter the disposition of sertraline in normal, healthy male volunteers. Data on file (Study 050-019), 1991.

SSRIs + 5-HT$_3$-receptor antagonists

Symptoms similar to serotonin syndrome have been reported in one patient receiving paroxetine and ondansetron, and in one patient receiving sertraline and dolasetron who then received sertraline and ondansetron without problems.

Clinical evidence

(a) Paroxetine

A possible case of serotonin syndrome (or possibly neuroleptic malignant syndrome) was reported in a 49-year-old woman who developed postoperative delirium. She had been taking paroxetine 30 mg daily up to 2 days before surgery and was given **ondansetron** 4 mg during surgery and morphine during and after surgery. Approximately one hour after leaving theatre she became agitated and confused. She also displayed uncontrolled limb movements, brisk reflexes, ankle clonus, abnormal ocular function, hypertension, pyrexia, and raised creatinine kinase levels. The delirium did not respond to naloxone, diazepam or flumazenil and lasted for nearly 2 days.[1]

(b) Sertraline

A 49-year-old woman who had been receiving **sertraline** for some time without incident was premedicated with **dolasetron** 100 mg before receiving her first cycle of adjuvant chemotherapy for breast cancer. Shortly afterwards she developed symptoms of profound agitation and elation, but with an overwhelming desire to commit suicide, and was disoriented. The symptoms resolved within hours without pharmacological intervention. Three weeks later she received the same medications except that **ondansetron** was substituted for **dolasetron** and she experienced no adverse effects. The author concluded that a variant of serotonin syndrome may rarely be seen when 5-HT$_3$-receptor antagonists and SSRIs are given together.[2]

Mechanism

Several explanations for these effects, involving the disruption of serotonergic and/or dopaminergic transmission, have been suggested.[1] There has been some debate about whether inhibition of CYP2D6 was another possible mechanism with the paroxetine case, but this seems unlikely.[1,3]

Importance and management

These two cases are isolated, and as such, no general recommendations can be made. Nevertheless, bear in mind the possibility of serotonin syndrome if similar adverse effects occur.[2] For more information on serotonin syndrome, see under 'Additive or synergistic interactions', (p.9).

1. Stanford BJ, Stanford SC. Postoperative delirium indicating an adverse drug interaction involving the selective serotonin reuptake inhibitor, paroxetine? *J Psychopharmacol* (1999) 13, 313–17.
2. Sorscher SM. Probable serotonin syndrome variant in a patient receiving a selective serotonin reuptake inhibitor and a 5-HT$_3$ receptor antagonist. *J Psychopharmacol* (2002) 16, 191.
3. Palmer JL. Postoperative delirium indicating an adverse drug interaction involving the selective serotonin reuptake inhibitor, paroxetine? *J Psychopharmacol* (2000) 14, 186–8.

SSRIs + Interferons

In one patient taking paroxetine and trazodone, depression recurred when interferon alfa was given. SSRIs have been used for the prevention of depression caused by interferon alfa.

Clinical evidence, mechanism, importance and management

A 31-year-old woman, whose mood and other depressive symptoms improved during treatment with **paroxetine** 50 mg daily and trazodone 50 mg at night, was later found to have essential thrombocythaemia. After unsuccessful treatment with dipyridamole, she was given **interferon alfa**, stabilised at 3 million units three times weekly. After 3 months her depressive symptoms returned, and worsened over a period of 6 months, despite increased doses of trazodone and cognitive therapy. **Interferon alfa** was discontinued and replaced by hydroxycarbamide, and then anagrelide. After a good response to a course of ECT, her depressive symptoms were controlled by **paroxetine** 50 mg daily and trazodone 150 mg at night.[1] SSRIs have been used to try to prevent depression caused by interferon alfa. For example, in one study, 9 of 20 patients taking high-dose **interferon alfa** developed depression, compared with just 2 of 18 patients also given **paroxetine** (10 mg daily titrated up to 40 mg daily started 2 weeks before the interferon).[2]

Interferon commonly causes depression, and in the case report it appeared to reverse the antidepressant response to paroxetine and trazodone. It was suggested that this might have been due to the capacity of interferon to impair serotonin synthesis, by inducing enzymes that degrade the serotonin precursor tryptophan.[1]

It seems possible that interferon might reduce the antidepressant efficacy of the SSRIs. Bear the possibility in mind if the response to an SSRI is poor in a patient given interferon.

1. McAllister-Williams RH, Young AH, Menkes DB. Antidepressant response reversed by interferon. *Br J Psychiatry* (2000) 176, 93.
2. Musselman DL, Lawson DH, Gumnick JF, Manatunga AK, Penna S, Goodkin RS, Greiner K, Nemeroff CB, Miller AH. Paroxetine for the prevention of depression induced by high-dose interferon alfa. *N Engl J Med* (2001) 344, 961–6.

SSRIs + Lysergide (LSD)

Three patients with a history of lysergide (LSD) abuse experienced a new onset or worsening of the LSD flashback syndrome when given fluoxetine, paroxetine or sertraline. Grand mal convulsions occurred when one patient taking LSD was given fluoxetine. In contrast, one study found that SSRIs reduced or eliminated the subjective responses to LSD.

Clinical evidence

An 18-year-old girl with depression, panic and anxiety disorders, and with a long history of illicit drug abuse experienced a 15-hour LSD flashback within 2 days of starting to take **sertraline** 50 mg daily. Another flashback lasting a day occurred when the **sertraline** was replaced by **paroxetine**. No further flashbacks occurred when the SSRIs were stopped. A 17-year-old boy with depression, also with a long history of illicit drug abuse (including LSD), began to experience LSD flashbacks 2 weeks after starting to take **paroxetine**. His father, a chronic drug abuser, had taken both **fluoxetine** and **paroxetine** for depression and had also reported new onset of a flashback syndrome.[1] An isolated report describes a patient taking **fluoxetine**, who developed grand mal convulsions, which were tentatively attributed to the concurrent use of LSD.[2] In contrast, a retrospective study found that 28 of 32 subjects (88%) who took LSD and who had taken an SSRI (**fluoxetine**, **paroxetine** or **sertraline**) or trazodone for more than 3 weeks had a subjective decrease or virtual elimination of their responses to LSD. However, another subject who had taken **fluoxetine** for only one week had an increased response to LSD.[3]

Mechanism

Not understood. Lysergide increases serotonin in the brain, and one suggestion is that when the serotonin re-uptake is blocked in the brain, there is an increased stimulation of 5-HT$_1$ and 5-HT$_2$ receptors.[1] Changes in brain catecholamine systems may also be involved.[3]

Importance and management

Information is very limited and conflicting. The authors of the first report suggest that patients who are given SSRIs should be warned about the possibility of flashback or hallucinations if they have a known history of LSD use.

1. Markel H, Lee A, Holmes RD, Domino EF. Clinical and laboratory observations. LSD flashback syndrome exacerbated by selective serotonin reuptake inhibitor antidepressants in adolescents. *J Pediatr* (1994) 125, 817–9.
2. Picker W, Lerman A, Hajal F. Potential interaction of LSD and fluoxetine. *Am J Psychiatry* (1992) 149, 843–4.
3. Bonson KR, Buckholtz JW, Murphy DL. Chronic administration of serotonergic antidepressants attenuates the subjective effects of LSD in humans. *Neuropsychopharmacology* (1996) 14, 425–36.

SSRIs + Macrolides

An isolated case report describes a man who developed apparent acute fluoxetine toxicity while taking clarithromycin. Other isolated reports describe the development of serotonin syndrome in patients taking erythromycin with sertraline, and clarithromycin with citalopram.

Clinical evidence

(a) Citalopram

The Canadian regulatory authorities briefly mention a case of serotonin syndrome and QT prolongation, which occurred when clarithromycin was taken with citalopram for 4 days.[1]

(b) Fluoxetine

A 53-year-old-man taking fluoxetine 80 mg and nitrazepam 10 mg at bedtime for depression and insomnia was given **clarithromycin** 250 mg twice daily for a respiratory infection. Within a day he started to become increasingly confused, and after 3 days was admitted to hospital with a diagnosis of psychosis and delirium. When no organic cause for the delirium could be found, all his medications were stopped, and **erythromycin** was started. His mental state returned to normal after 36 hours. Once the antibacterial course had finished, the fluoxetine and nitrazepam were restarted and no further problems occurred.[2]

(c) Sertraline

A 12-year-old boy with severe obsessive-compulsive disorder and simple phobia, responded to sertraline 12.5 mg daily, titrated over 12 weeks to 37.5 mg daily. Five weeks later, he was given erythromycin 200 mg twice daily for an infection, and 4 days later he began to feel mildly nervous. Over the next 10 days his nervousness grew, culminating in panic, restlessness, irritability, agitation, paraesthesias, tremulousness, decreased concentration and confusion. The symptoms abated within 72 hours of stopping both drugs.[3]

Mechanism

The effects seen in the case with fluoxetine was attributed to fluoxetine toxicity, and that with sertraline to serotonin syndrome. In these two cases, the authors postulated that erythromycin and clarithromycin (known inhibitors of the cytochrome P450 isoenzyme CYP3A4), reduced the metabolism of the SSRIs, thereby raising their serum levels and precipitating the observed toxicity.[2,3]

Importance and management

These are isolated reports and their general importance is unknown. Nevertheless, be aware of these cases when using macrolides with SSRIs.

1. Canadian Adverse Drug Reaction Monitoring Programme. Citalopram (Celexa) and clarithromycin (Biaxin): interaction. *Can Adverse Drug React News* (2000) 10 (Jul), 7.
2. Pollak PT, Sketris IS, MacKenzie SL, Hewlett TJ. Delirium probably induced by clarithromycin in a patient receiving fluoxetine. *Ann Pharmacother* (1995) 29, 486–8.
3. Lee DO, Lee CD. Serotonin syndrome in a child associated with erythromycin and sertraline. *Pharmacotherapy* (1999) 19, 894–6.

SSRIs + Methylphenidate

Isolated reports describe delirium in one patient and a seizure in another when methylphenidate was taken with sertraline.

Clinical evidence, mechanism, importance and management

A 61-year-old man with major depression was prescribed **sertraline** 50 mg daily without response. Three months later the dose was increased to 100 mg daily and methylphenidate 2.5 mg daily was started. His symptoms improved and the dose of methylphenidate was increased to 2.5 mg twice daily and then 5 mg twice daily. After several days at the higher dose, the patient experienced visual hallucinations and confusion. The methylphenidate was discontinued and a day later the psychosis resolved. He was maintained on **sertraline** 100 mg daily and his mood and motivation remained good.[1]

An isolated report describes a tonic-clonic seizure in a 13-year-old boy after he had been taking **sertraline** 25 to 50 mg daily and methylphenidate 80 mg daily for about 2 weeks. He had been receiving methylphenidate without significant adverse effects for about 10 months before the seizure and following discontinuation of the **sertraline** experienced no further seizures.[2]

In contrast, beneficial augmentation of effects has been reported with methylphenidate and SSRIs (**fluoxetine**, **paroxetine**, **sertraline**) without significant adverse effects.[3,4]

The general significance of these cases is likely to be small, especially when set in the context of beneficial concurrent use. However, if adverse CNS effects become troublesome, it may be worth considering this interaction as a possible cause: in both cases the adverse effects resolved when one of the drugs was withdrawn.

1. McGlohn SE, Bostwick JM. Sertraline with methylphenidate in an ICU patient. *Psychosomatics* (1995) 36, 584–5.
2. Feeney DJ, Klykylo WM. Medication-induced seizures. *J Am Acad Child Adolesc Psychiatry* (1997) 36, 1018–19.
3. Gammon GD, Brown TE. Fluoxetine and methylphenidate in combination for treatment of attention deficit disorder and comorbid depressive disorder. *J Child Adolesc Psychopharmacol* (1993) 3, 1–10.
4. Stoll AL, Pillay SS, Diamond L, Workum SB, Cole JO. Methylphenidate augmentation of serotonin selective reuptake inhibitors: a case series. *J Clin Psychiatry* (1996) 57, 72–6.

SSRIs + Metoclopramide

There are two reports of serotonin syndrome in patients taking sertraline when metoclopramide was added. A few reports describe extrapyramidal symptoms in patients given fluoxetine, fluvoxamine or sertraline with metoclopramide.

Clinical evidence

A regional pharmacovigilance centre in France reported 4 cases of extrapyramidal adverse effects linked to the concurrent use of an SSRI (unnamed) and metoclopramide.[1]

(a) Fluoxetine

Two patients developed extrapyramidal symptoms while taking fluoxetine and metoclopramide.[2,3]

(b) Fluvoxamine

A 14-year-old boy taking fluvoxamine 50 mg daily for anorexia nervosa was, after day 7, given metoclopramide 10 mg three times daily. On the third day of concurrent use he developed acute movement disorders including acute dystonia, jaw rigidity, horizontal nystagmus, uncontrolled tongue movements and dysarthria. The boy had taken the same dose of metoclopramide alone on other occasions without experiencing extrapyramidal reactions.[4]

(c) Sertraline

A woman with gastro-oesophageal reflux, controlled with metoclopramide 15 mg four times daily, developed symptoms consistent with a mandibular dystonia (periauricular pain, jaw tightness, the sensation of her teeth clenching and grinding) 2 days after starting sertraline 50 mg daily. A 50-mg dose of diphenhydramine resolved the problem within 30 minutes, but the same symptoms recurred the next day, 8 hours after taking sertraline. The symptoms were relieved by 2 mg of oral benzatropine.[5]

A patient who had been taking sertraline 100 mg daily started taking metoclopramide 10 mg four times daily for nausea. After 24 hours his symptoms had worsened and he developed malaise, cardiac arrhythmia, visual hallucinations, diaphoresis, sialosis, hyperreflexia, and tremor. Serotonin syndrome was diagnosed and his symptoms improved with cyproheptadine.[6] Another patient taking sertraline 100 mg daily for depression over an 18-month period developed agitation, dysarthria, diaphoresis, and

a movement disorder within 2 hours of receiving a single 10-mg intravenous dose of metoclopramide. The symptoms, diagnosed as serotonin syndrome with a serious extrapyramidal movement disorder, resolved within 6 hours of treatment with diazepam.[7]

Mechanism

In the fluvoxamine case, pharmacokinetic interaction was thought unlikely as fluvoxamine is metabolised by a different metabolic pathway to metoclopramide.[4] Both the SSRIs and metoclopramide can cause extrapyramidal reactions; metoclopramide by blocking dopamine D_2 receptors in the basal ganglia, and the SSRIs by inhibition of dopamine neurotransmission.[4,5] Metoclopramide has also been reported to have intermediate affinity to certain serotonin receptors.[7]

Importance and management

Information seems to be limited to these reports, but they highlight the fact that care should be taken if two drugs with the potential to cause the same adverse effects are used together.

1. Anon. Extrapyramidal reactions to SSRI antidepressant + neuroleptic combinations. *Prescrire Int* (2004) 13, 57.
2. Coulter DM, Pillans PI. Fluoxetine and extrapyramidal side effects. *Am J Psychiatry* (1995) 152, 122–5.
3. Fallon BA, Liebowitz MR. Fluoxetine and extrapyramidal symptoms in CNS lupus. *J Clin Psychopharmacol* (1991) 11, 147–8.
4. Palop V, Jimenez MJ, Catalán C, Martínez-Mir I. Acute dystonia associated with fluvoxamine-metoclopramide. *Ann Pharmacother* (1999) 33, 382.
5. Christensen RC, Byerly MJ. Mandibular dystonia associated with the combination of sertraline and metoclopramide. *J Clin Psychiatry* (1996) 57, 596.
6. Vandemergel X, Beukinga I, Nève P. Syndrome sérotoninergique secondaire à la prise de sertraline et de metoclopramide. *Rev Med Brux* (2000) 3, 161–3.
7. Fisher AA, Davis MW. Serotonin syndrome caused by selective serotonin reuptake-inhibitors–metoclopramide interaction. *Ann Pharmacother* (2002) 36, 67–71.

SSRIs + Nasal decongestants

A case report describes serotonin syndrome associated with the use of sertraline and etilefrine, and another report describes adverse effects associated with the use of fluoxetine and phenylpropanolamine.

Clinical evidence, mechanism, importance and management

(a) Etilefrine

A case of serotonin syndrome was attributed to an interaction between **sertraline** and etilefrine.[1] The clinical relevance of this isolated case is unclear.

(b) Phenylpropanolamine

A 16-year-old girl with an eating disorder, taking **fluoxetine** 20 mg daily, developed vague medical complaints of dizziness, 'hyper' feelings, diarrhoea, palpitations and a reported weight loss of about 6.5 kg within 2 weeks. The author of the report suggested that these effects might have been the result of an interaction with phenylpropanolamine (1 to 2 capsules of *Dexatrim* daily), which the patient was surreptitiously taking, associated with a restricted food and fluid intake.[2] The clinical relevance of this isolated report is unclear.

1. Martínez Hernanz A, Pérez Sales P. Síndrome serotoninérgico por sertralina y etilefrina: una interacción no descrita. *Psiquis (Mexico)* (2001) 2, 222–4.
2. Walters AM. Sympathomimetic-fluoxetine interaction. *J Am Acad Child Adolesc Psychiatry* (1992) 31, 565–6.

SSRIs + NNRTIs

Efavirenz decreases sertraline levels, but does not alter paroxetine levels. Paroxetine and sertraline, and probably also fluoxetine, do not alter efavirenz levels. Serotonin syndrome occurred in a woman taking fluoxetine when efavirenz was added.
There is limited evidence that nevirapine might decrease fluoxetine plasma levels, but appears not to affect fluvoxamine levels. Limited evidence also suggests that fluoxetine has no effect on nevirapine levels, but fluvoxamine may modestly increase them.
Etravirine does not appear to affect paroxetine levels, and paroxetine does not appear to affect etravirine levels.

Clinical evidence

(a) Efavirenz

1. Fluoxetine. A case of serotonin syndrome in a woman taking fluoxetine coincided with the start of a new antiretroviral regimen including efavirenz. Symptoms resolved when the fluoxetine dose was halved.[1] In a retrospective population pharmacokinetic analysis, fluoxetine did not appear to significantly alter efavirenz plasma levels.[2]

2. Paroxetine. The US manufacturer of efavirenz notes that there was no change in the pharmacokinetics of either paroxetine or efavirenz when paroxetine 20 mg daily and efavirenz 600 mg daily were given together for 14 days.[3] In a retrospective population pharmacokinetic analysis, paroxetine did not appear to significantly alter efavirenz plasma levels.[2]

3. Sertraline. In one study, sertraline 50 mg daily for 14 days had no effect on the pharmacokinetics of efavirenz 600 mg daily; however, the sertraline AUC was decreased by 39% and the trough level was decreased by 46% when given with efavirenz.[3,4] In a retrospective population pharmacokinetic analysis, sertraline did not appear to significantly alter efavirenz plasma levels.[2]

(b) Etravirine

The manufacturer of etravirine notes that there was no change in the pharmacokinetics of either **paroxetine** or etravirine when **paroxetine** 20 mg daily and etravirine (dose not stated) were given together.[5]

(c) Nevirapine

1. Fluoxetine. In a pharmacokinetic-modelling study in 173 HIV-positive patients taking a nevirapine-containing regimen, there was little difference in nevirapine clearance (10% decrease) between 7 patients also taking fluoxetine and the rest of the group. In addition, the median plasma levels of fluoxetine and its active metabolite norfluoxetine tended to be lower in these 7 patients than in another control group of 17 patients without HIV infection taking fluoxetine, but this only reached statistical significance when the plasma levels of fluoxetine and norfluoxetine were combined (46% lower).[6]

2. Fluvoxamine. In a pharmacokinetic-modelling study in 173 HIV-positive patients taking a nevirapine-containing regimen, the apparent clearance of nevirapine was 34% lower in 7 patients also taking fluvoxamine, and this appeared to be dependent on the dose of fluvoxamine. The median plasma level of fluvoxamine did not differ between these 7 patients and a control group of 29 patients without HIV infection taking fluvoxamine.[6]

Mechanism

The case of serotonin syndrome in the patient taking efavirenz and fluoxetine was attributed to raised fluoxetine levels caused by efavirenz.[1] However, note that paroxetine, which is similarly metabolised, is not affected by efavirenz. Sertraline, unlike fluoxetine and paroxetine, is in part metabolised by the cytochrome P450 isoenzyme CYP3A4, of which efavirenz is an inducer. Concurrent use therefore causes a moderate decrease in sertraline levels.

Importance and management

The available information suggests that **efavirenz** levels are unaffected by SSRIs (paroxetine, sertraline, fluoxetine), therefore no change in virologic efficacy would be anticipated, and no efavirenz dosage adjustments are likely to be needed. Paroxetine levels are unaffected by efavirenz, but sertraline levels are reduced, so clinical efficacy should be monitored and the dose of sertraline increased if necessary. The general relevance of the case of serotonin syndrome is uncertain, but it introduces a note of caution about concurrent use.

No dosage adjustment of either paroxetine or **etravirine** is expected to be needed on concurrent use.[5]

These findings of the pharmacokinetic-modelling study with **nevirapine** are preliminary, and require confirmation in a controlled study, nevertheless, they provide some evidence that fluoxetine levels might be decreased by nevirapine. Monitoring fluoxetine efficacy might be prudent. They also suggest that nevirapine levels may be modestly increased by fluvoxamine, therefore it might be prudent to monitor for nevirapine adverse effects. More study is needed.

1. DeSilva KE, Le Flore DB, Marston BJ, Rimland D. Serotonin syndrome in HIV-infected individuals receiving antiretroviral therapy and fluoxetine. *AIDS* (2001) 15, 1281–5.
2. Ruiz NM, Labriola DF, Fiske WD, Joshi AS, Manion DJ, Villano SA. Efavirenz plasma levels are unaffected in patients receiving selective serotonin reuptake inhibitors. *Intersci Conf Antimicrob Agents Chemother* (2000) 40, 332.

3. Sustiva (Efavirenz). Bristol-Myers Squibb Company. US Prescribing information, September 2009.
4. Sustiva Film-coated Tablets (Efavirenz). Bristol-Myers Squibb Pharmaceuticals Ltd. UK Summary of product characteristics, June 2009.
5. Intelence (Etravirine). Tibotec, Inc. US Prescribing information, November 2009.
6. De Maat MMR, Huitema ADR, Mulder JW, Meenhorst PL, van Gorp ECM, Mairuhu ATA, Beijnen JH. Drug interaction of fluvoxamine and fluoxetine with nevirapine in HIV-1-infected individuals. *Clin Drug Invest* (2003) 23, 629–37.

SSRIs + Opioids

Symptoms of the serotonin syndrome have been reported with opioids including fentanyl, hydromorphone, oxycodone, pentazocine, pethidine (meperidine), and possibly also morphine, when given with various SSRIs.
Fluoxetine may slightly reduce the analgesic effects of morphine and oxycodone.

Clinical evidence

(a) Fentanyl

A 65-year-old woman taking **citalopram**, rabeprazole, tolterodine and **hydrocodone** developed probable serotonin syndrome while hospitalised and within 24 hours of starting transdermal fentanyl 25 micrograms/hour. The fentanyl was discontinued, and all signs and symptoms resolved over the next few days, and did not recur when **oxycodone** was started.[1]

(b) Hydrocodone

Visual hallucinations occurred in a 90-year-old woman taking hydrocodone when her antidepressant was changed from **citalopram** 10 mg daily to **escitalopram** 10 mg daily. The hallucinations stopped after her hydrocodone was discontinued because of improvement in pain control. The patient had previously taken **paroxetine** and the same dose of hydrocodone, without experiencing hallucinations or other serotonin-related symptoms.[2]

(c) Hydromorphone

An 81-year-old woman who had been taking **fluoxetine** 20 mg daily along with other medication for several years, developed abnormal movements, confusion, incoherent speech, sweating, facial redness, tremor, hyperreflexia and muscle spasm 2 days after starting to take hydromorphone 12 mg daily. The symptoms resolved within 2 weeks of stopping the **fluoxetine** (the hydromorphone was continued).[3]

(d) Methadone

The SSRIs, particularly fluvoxamine, can raise methadone levels. See 'SSRIs + Opioids; Methadone', p.1489.

(e) Morphine

A placebo-controlled study in 35 patients found that the preoperative use of **fluoxetine** 10 mg daily for 7 days reduced the analgesic effect of intravenous morphine given for postoperative dental pain.[4] In contrast, a crossover study in 15 healthy subjects found that a single 60-mg dose of **fluoxetine** slightly improved (by 3 to 8%) the analgesic effect (as assessed by dental electrical stimulation) of morphine sulfate in doses tailored to produce and maintain steady-state plasma levels of 15, 30 and 60 nanograms/mL for 60 minutes. Plasma levels of morphine were not affected by **fluoxetine**, and morphine was found not to affect plasma levels of **fluoxetine** or norfluoxetine. The subjects experienced less nausea and drowsiness while taking both drugs, but the psychomotor and respiratory depressant effects of morphine were not altered.[5]

A patient experienced postoperative delirium which lasted for nearly 2 days and included agitation, confusion, uncontrolled limb movements, abnormal ocular function, hypertension, pyrexia, brisk reflexes, ankle clonus and raised creatinine kinase. She had been taking **paroxetine** before surgery and during surgery she was given morphine and ondansetron.[6]

(f) Oxycodone

A man with advanced multiple sclerosis found that when he began to take **fluoxetine** 20 mg daily for depression he needed to increase his analgesic dosage of oxycodone (for painful muscle spasms) about fourfold, from 65 to 75 mg daily to about 250 to 275 mg daily.[7]

A bone-marrow transplant recipient taking, amongst other drugs, **sertraline** 50 mg daily, ciclosporin 75 mg daily, and oxycodone 10 mg as needed, developed severe tremors and visual hallucinations. This coincided with him taking oxycodone 200 mg over 48 hours for severe pain. An adverse reaction to ciclosporin was initially suspected (although serum levels were not high), and this was temporarily discontinued along with the oxycodone. The visual hallucinations decreased but the tremors continued, and did not lessen until **sertraline** was discontinued and cyproheptadine given. It was concluded that the patient was experiencing a form of serotonin syndrome as a result of markedly increased opioid use while taking an SSRI.[8] Two other cases describe probable serotonin syndrome in elderly patients taking **sertraline** or **escitalopram** and extended-release oxycodone. In both cases symptoms of serotonin syndrome (agitation, increased muscle tone, ataxia, tremor and/or myoclonic jerks) occurred after increasing the opioid dose.[2] Another case of severe serotonergic symptoms including confusion, nausea, fever, shivering, agitation, clonus, hyperreflexia, hypertonia, and tachycardia occurred in a 70-year-old woman taking **fluvoxamine** 200 mg daily when she started taking oxycodone 40 mg twice daily. Discontinuation of these two drugs resulted in resolution of her symptoms over 48 hours.[9]

(g) Pentazocine

A placebo-controlled study in 35 patients found that **fluoxetine** 10 mg daily for 7 days preoperatively did not appear to reduce the analgesic effects of pentazocine 45 mg given intravenously for postoperative dental pain.[4]

A man who had been taking **fluoxetine** 20 mg daily, later increased to 40 mg daily, was given a single 100-mg oral dose of pentazocine (*Talwin Nx* containing pentazocine 50 mg and naloxone 500 micrograms) for a severe headache. Within 30 minutes he complained of lightheadedness, anxiety, nausea and paraesthesias of the hands. He was diaphoretic, flushed, and ataxic, and had a mild tremor of his arms. His blood pressure was 178/114 mmHg, pulse 62 bpm and respiration 16 breaths per minute. He was given intramuscular diphenhydramine 50 mg and recovered over the following 4 hours.[10]

(h) Pethidine (Meperidine)

A 43-year-old man who had been taking **fluoxetine** approximately every other day experienced symptoms of serotonin syndrome immediately after receiving pethidine 50 mg intravenously for an endoscopic procedure.[11] A 44-year-old woman taking **citalopram** 20 mg daily increased to 40 mg daily, transdermal **fentanyl**, and intravenous **hydromorphone** or oral **hydrocodone**/paracetamol (as needed), promethazine, gatifloxacin, zolpidem and lansoprazole, developed symptoms suggestive of serotonin syndrome within 10 hours of starting pethidine by patient controlled analgesia for breakthrough pain (total dose over 8 hours was 230 mg). Once the pethidine was stopped, the symptoms resolved.[12]

(i) Tramadol

The serotonin syndrome has occurred in a number of patients taking SSRIs with tramadol. See 'SSRIs + Opioids; Tramadol', p.1489.

Mechanism

Fluoxetine inhibits the activity of the cytochrome P450 isoenzyme CYP2D6 within the liver so that the metabolism of oxycodone to an active metabolite oxymorphone is reduced. The metabolism of hydrocodone and similar opioids may also be affected by CYP2D6 inhibitors, see 'Opioids; Codeine and related drugs + Quinidine', p.203. **Buprenorphine** and morphine are not metabolised by CYP2D6, so their metabolism would not be expected to be affected by fluoxetine.

It has been suggested that the reason for the reduced morphine analgesia may have something to do with the initial effects of SSRIs on serotonergic neurotransmission.[5] Serotonin syndrome seems to develop unpredictably in some patients given two or more serotonergic drugs, in this case, opioids and SSRIs.

Importance and management

Adverse interactions between SSRIs and the opioids discussed above seems rare, and there is little evidence to suggest that they cannot be used together safely and effectively. The evidence suggesting that fluoxetine may decrease morphine or oxycodone analgesia is limited and insufficient to suggest any change in practice. However, if a patient does not seem to respond well to either of these opioids consider an interaction as a possible cause.

The incidence of serotonin syndrome-like reactions with opioids and SSRIs is fairly rare; however, the possibility of serotonin syndrome should be considered in patients experiencing altered mental status, autonomic dysfunction and neuromuscular adverse effects while receiving these

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SSRIs + Opioids; Methadone

Methadone serum levels may rise if fluvoxamine is added, sometimes resulting in increased adverse effects. Sertraline, paroxetine, and possibly fluoxetine, may also modestly increase methadone levels.

Clinical evidence

(a) Fluoxetine

Methadone 30 to 100 mg daily, and fluoxetine 20 mg daily were given to 9 patients (two of them also taking fluvoxamine). Although there were possible compliance problems with some of the patients, the methadone plasma/dose ratio of the group as a whole was not altered by the addition of the fluoxetine.[1] This is consistent with the results of two other studies, which found that fluoxetine did not appear to alter the plasma methadone levels of patients treated for cocaine dependence.[2,3] However, the plasma samples for 7 of the 9 patients in the first study[1] were subsequently analysed again to measure the *S*- and *R*-enantiomers of methadone separately. This analysis revealed that fluoxetine 20 mg daily modestly increased the levels-to-dose ratio of the active *R*-methadone (by 33%) without significantly changing either the total or inactive *S*-methadone level-to-dose ratios.[4] Moreover, a patient taking methadone developed opioid toxicity when given ciprofloxacin and fluoxetine, see 'Quinolones + Opioids; Methadone', p.380.

(b) Fluvoxamine

Five patients taking maintenance doses of methadone were given fluvoxamine. Two of them had an increase of about 20% in the methadone plasma/dose ratio, while the other 3 had 40 to 100% rises in the methadone plasma/dose ratio (suggesting increased methadone levels). One of them developed asthenia, marked drowsiness and nausea, which disappeared when both drug doses were reduced.[5] A subsequent analysis of the enantiomers of methadone revealed that fluvoxamine increased the levels of both *R*- and *S*-methadone.[4] A report describes one patient who was unable to maintain adequate methadone levels, despite a daily dose of 200 mg, and experienced withdrawal symptoms until fluvoxamine was added.[6] Another patient taking methadone 70 mg daily and diazepam 2 mg twice daily was admitted to hospital with an acute exacerbation of asthma and intractable cough 3 weeks after starting fluvoxamine 100 mg daily. Blood gas measurements indicated severe hypoxaemia and hypercapnia. The symptoms resolved when the methadone dose was reduced to 50 mg daily and diazepam was gradually withdrawn, at which point methadone levels fell by about 23% (from 262 nanograms/mL to 202 nanograms/mL).[7]

(c) Paroxetine

Paroxetine 20 mg daily increased steady-state methadone levels by 35% in 10 patients taking maintenance doses of methadone. Both *R*- and *S*-methadone levels were increased in the 8 patients who were extensive metabolisers of the cytochrome P450 isoenzyme CYP2D6 (i.e those with normal levels of this isoenzyme), but in the 2 patients who were poor metabolisers (i.e. those lacking the isoenzyme) only the *S*-methadone levels were increased. Apart from one patient who reported feeling high during the first night after starting paroxetine, no symptoms of over-medication or toxicity were noted.[8]

(d) Sertraline

A placebo-controlled study in 31 methadone-maintained patients with depression found that sertraline increased the methadone plasma level/dose ratio by 26%, whereas patients taking placebo had a 16% decrease after 6 weeks of concurrent use, but by 12 weeks the ratios had shifted towards baseline values. Adverse effects were similar in both groups.[9] A 31-year-old woman taking methadone 230 mg daily was found to have a prolonged QT interval after sertraline 50 mg daily was added to her medications, although she was asymptomatic. The QT interval returned to normal when the methadone and sertraline were stopped and her methadone was replaced with morphine.[10]

Mechanism

Fluvoxamine, and to a lesser extent fluoxetine, paroxetine, and sertraline, can inhibit the liver metabolism of the methadone (possibly by the cytochrome P450 isoenzymes CYP3A4,[11] CYP2D6,[11,12] and/or CYP1A2[4]) thereby allowing it to accumulate in the body.

Importance and management

Information regarding an interaction between fluvoxamine and methadone is limited, but it indicates that the effects of starting or stopping fluvoxamine should be monitored in patients taking methadone, being alert for the need to adjust the methadone dosage. Although the increase in methadone levels with sertraline and paroxetine, and possibly also fluoxetine, is unlikely to have clinical effects in most patients, the possibility should be borne in mind, especially if high doses of methadone are being used. Note that methadone alone can prolong the QT-interval in high doses, see 'drugs that prolong the QT-interval', (p.290).

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SSRIs + Opioids; Tramadol

Tramadol should be used with caution with SSRIs because of the increased risk of seizures and because of the risk of serotonin syndrome. One patient developed hallucinations when taking tramadol with paroxetine.

Clinical evidence

A. Seizures

The CSM in the UK has publicised 27 reports of convulsions and one of worsening epilepsy with tramadol, a reporting rate of 1 in 7000 patients. Some of the patients were given doses well in excess of those recommended, and some were taking SSRIs (5 patients), which are known to reduce the convulsive threshold.[1] Similarly, of 124 seizure cases associated with

tramadol reported to the FDA in the US, 20 included the concurrent use of SSRIs.[2]

B. Serotonin syndrome

The Australian Adverse Drug Reaction Advisory Committee has stated that tramadol may cause serotonin syndrome, particularly when it is used at high doses or in combination with other drugs increasing serotonin levels; of 20 reported cases of serotonin syndrome associated with tramadol, 16 were taking potentially interacting medicines including SSRIs.[3] Cases of serotonin syndrome with specific SSRIs are discussed below.

(a) Citalopram

A 70-year-old woman who had been taking citalopram 10 mg daily for 3 years developed tremors, restlessness, fever, confusion, and visual hallucinations after starting to take tramadol 50 mg daily for pain relief following an operation. Her symptoms stopped after tramadol was stopped. However, she continued to take citalopram and one year later she developed identical symptoms after taking tramadol 20 mg daily. Citalopram is metabolised by the cytochrome P450 enzyme CYP2C19 and tramadol is *O*-demethylated by CYP2D6 and the patient was found to be deficient in both CYP2C19 and CYP2D6, suggesting that her metabolising capacity of both pathways was reduced.[4]

(b) Fluoxetine

A woman who had been taking fluoxetine 20 mg daily for 3 years developed what was eventually diagnosed as serotonin syndrome. A month previously she had started to take tramadol 50 mg four times daily, increased after a fortnight to 100 mg four times daily. Ten days before hospitalisation she had developed a tremor of the right hand and face, and in hospital she became agitated, and developed marked facial blepharospasm, some sweating and pyrexia, and stuttering. The symptoms began to subside 7 days after both drugs were stopped, and after 2 months she had recovered fully.[5]

(c) Paroxetine

A man who had been taking paroxetine 20 mg daily for 4 months without problems developed shivering, diaphoresis and myoclonus and became subcomatose within 12 hours of taking tramadol 100 mg. This was diagnosed as serotonin syndrome. Tramadol was stopped, the paroxetine dosage halved and he became conscious within a day. The other symptoms gradually disappeared over the next week.[6] A 78-year-old woman taking paroxetine 20 mg daily developed nausea, diaphoresis and irritability 3 days after starting tramadol 50 mg three times a day. The next day she developed muscular weakness and confusion, and was found to have a temperature of about 38.2°C and a pulse rate of 110 bpm. She recovered when the drugs were withdrawn. Similar symptoms occurred in another elderly woman taking paroxetine 10 mg daily within 2 days of starting tramadol 50 mg four times daily. Both women were later able to continue taking paroxetine alone without problems.[7]

A tetraparetic patient with chronic pain developed nightmares and hallucinations 56 days after starting to take tramadol, paroxetine and dosulepin, which only stopped when the drugs were withdrawn.[8]

(d) Sertraline

A 42-year-old woman was admitted to intensive care with atypical chest pain, sinus tachycardia, confusion, psychosis, sundowning [increased agitation, activity and negative behaviours, which happen late in the day or evening], agitation, diaphoresis and tremor. She was taking a large number of drugs, including sertraline and tramadol. She was diagnosed as having serotonin syndrome, attributed to an increase in the dosage of tramadol (from 150 mg daily to 300 mg daily in increments of 50 mg every 2 to 3 days), and an increased sertraline dosage (original amounts not stated but 100 mg daily when the adverse events developed). The tramadol had been started 3 weeks previously and she had been taking the sertraline for a year.[9]

An 88-year-old woman taking sertraline 50 mg daily (later increased to 100 mg daily), as well as several other medications was given dextropropoxyphene with paracetamol, and tramadol 200 mg daily increased to 400 mg daily for pain relief after a fracture. Ten days after starting tramadol she became confused, with alterations in cognitive function, tremor, problems with co-ordination, and muscle weakness. Serotonin syndrome was suspected and therefore sertraline was withdrawn over a period of 2 days, the dose of tramadol was reduced from 400 to 200 mg daily, and the patient recovered over a period of about 2 weeks.[10]

In another report, serotonin syndrome occurred after the first dose of sertraline 50 mg in a 75-year-old woman who had been taking tramadol 50 mg daily for 3 days. The concentration of serotonin (5-hydroxytryptamine) in her CSF was found to be elevated to 38.5 nanograms/mL (reference value less than 10 picograms/mL).[11]

C. Pharmacokinetic effects

A placebo-controlled, crossover study in 16 healthy subjects found that pretreatment with **paroxetine** 20 mg daily for 3 days increased the AUC of tramadol by about 35%, and decreased the AUCs of the *O*-demethylated metabolites of tramadol by 40 to 67%. The analgesic effect of tramadol was reduced, but not abolished.[12]

Mechanism

Tramadol may rarely cause seizures and SSRIs can reduce the seizure threshold, thus if both are taken together the risk is increased. Serotonin syndrome seems to develop unpredictably in some patients given two or more serotonergic drugs (in this case, tramadol and SSRIs).

Paroxetine is a potent inhibitor of the cytochrome P450 isoenzyme CYP2D6 and inhibits the metabolism of tramadol by this isoenzyme, which results in reduced formation of its *O*-demethylated metabolites. The reduction in these metabolites may result in reduced analgesia as the opioid effect of tramadol is thought to be mediated mainly by (+)-*O*-desmethyltramadol.[12]

Importance and management

Because of the possible increased risk of seizures, tramadol should be used with caution in patients taking drugs such as the SSRIs, which can lower the seizure threshold. The concurrent use of tramadol and an SSRI may also lead to an increase in serotonin-associated effects, which can include serotonin syndrome. However, the relatively few reported cases of serotonin syndrome or other reactions due to an interaction between an SSRI and tramadol need to be set in the wider context of apparently uneventful and advantageous use in other patients,[12-14] although some workers have suggested that the incidence of serotonin syndrome may be underreported.[15] There would seem to be little reason for totally avoiding the concurrent use of the SSRIs and tramadol but it would clearly be prudent to monitor the outcome closely. For more information about serotonin syndrome, see under 'Additive or synergistic interactions', (p.9).

Tramadol analgesia may possibly be altered by paroxetine and potentially by other SSRIs that inhibit CYP2D6, such as fluoxetine (see 'Table 35.2', (p.1465), for information on the inhibitory effects of the SSRIs). Bear the potential for this interaction in mind should a patient taking these SSRIs have a reduced response to tramadol, and adjust the dose of tramadol as necessary.

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SSRIs + Protease inhibitors

Ritonavir-boosted darunavir reduces paroxetine and sertraline levels. Ritonavir-boosted fosamprenavir reduces paroxetine lev-

els. Paroxetine does not appear to alter the levels of ritonavir-boosted darunavir or fosamprenavir and sertraline does not appear to alter darunavir levels, whereas fluoxetine slightly raised the levels of ritonavir in one study. Two cases of serotonin syndrome have been attributed to the use of fluoxetine and ritonavir.

Clinical evidence

(a) Darunavir

In a pharmacokinetic study, the AUC and minimum level of **paroxetine** were reduced by 39% and 37%, respectively, when **paroxetine** 20 mg daily and ritonavir-boosted darunavir 100/400 mg twice daily were given together. The darunavir AUC and minimum level were unaffected by concurrent use.[1,2]

In a very similar study using the same dose of ritonavir-boosted darunavir, the AUC and minimum level of **sertraline** 50 mg daily were reduced by 49% without any effect on darunavir levels.[1,2] Note that the dose of darunavir used in these studies (400 mg twice daily) is less than that recommended (600 mg twice daily).[1,2]

(b) Fosamprenavir

In a pharmacokinetic study in healthy subjects, the AUC and maximum level of **paroxetine** were reduced by 58% and 60%, respectively, when **paroxetine** 20 mg daily and ritonavir-boosted fosamprenavir 100/700 mg twice daily were given together for 10 days. The fosamprenavir and ritonavir pharmacokinetics did not differ from historical control values. No serious adverse events occurred.[3]

(c) Ritonavir

In a single-dose study involving 18 healthy subjects, no significant pharmacokinetic changes were seen when ritonavir 600 mg was given at the same time as **escitalopram** 20 mg.[4] These findings need confirmation with multiple doses, because the effects of ritonavir on drug metabolising enzymes would not have been maximal before **escitalopram** was given.

Ritonavir 600 mg was given to 16 healthy subjects before and after they took **fluoxetine** 30 mg twice daily for 8 days. The maximum plasma levels of ritonavir were unaffected, but its AUC rose by 19%. These changes were not considered large enough to warrant changing the dose of ritonavir.[5] The study was criticised for not achieving steady state before assessing the pharmacokinetics and thus possibly underestimating the interaction.[6] However, the authors point out that **fluoxetine** levels were equivalent to those seen at steady state, and multiple dosing of ritonavir is likely to induce its own metabolism, so if anything, the interaction would be lessened at steady state.[7]

Two cases of serotonin syndrome were attributed to adding ritonavir to established **fluoxetine** treatment. One of these patients later tolerated ritonavir-boosted saquinavir when the **fluoxetine** dose was halved, and in the other nelfinavir was substituted for ritonavir.[8] Another case of serotonin syndrome developed in a patient taking **fluoxetine** and trazodone when ritonavir was added, see 'Trazodone + Protease inhibitors', p.1496.

Mechanism

It has been assumed that ritonavir would raise the levels of SSRIs that are substrates for the cytochrome P450 isoenzyme CYP2D6 (e.g. fluoxetine, paroxetine, sertraline) due to the inhibitory effect of ritonavir on this isoenzyme.[9] However, ritonavir is generally used as a pharmacokinetic enhancer with other protease inhibitors, and the available data show that this actually decreases paroxetine and sertraline levels. The mechanism is not known.

Importance and management

The pharmacokinetic interaction showing a reduction in paroxetine and sertraline levels with ritonavir-boosted darunavir and fosamprenavir is established. Although the clinical relevance of these reductions is not certain, it would be prudent to anticipate some reduction in efficacy when starting these protease inhibitors, and to monitor the clinical effect and increase the SSRI dose as necessary. Whether other SSRIs would be affected similarly is unknown, but fluoxetine would be expected to be. Moreover, whether other ritonavir-boosted protease inhibitors interact similarly is unknown, but it would be prudent to expect that they might also reduce the levels of these SSRIs. However, the US manufacturer of **tipranavir**[10] predicts that ritonavir-boosted tipranavir will result in an *increase* in the levels of fluoxetine, paroxetine and sertraline, presumably because tipranavir, unlike some of the other protease inhibitors, may also inhibit CYP2D6.

Although there is a study suggesting escitalopram levels are not affected by ritonavir, the findings of this study are questionable as it used simultaneous single doses. The general relevance of the few cases of serotonin syndrome is also uncertain.

The available data for ritonavir alone and ritonavir-boosted darunavir and fosamprenavir suggest that the pharmacokinetics of these protease inhibitors are not affected to a clinically relevant extent by fluoxetine, sertraline or paroxetine. This suggests that there are no pharmacokinetic concerns regarding antiviral efficacy or adverse effects.

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SSRIs + Rifampicin (Rifampin)

In two cases rifampicin decreased the efficacy of citalopram and sertraline. Paroxetine is predicted to interact similarly.

Clinical evidence

A 34-year-old man, with a long-standing history of anxiety disorder, taking **sertraline** 200 mg at bedtime, reported that the medication was no longer working well. He was experiencing a significant amount of anxiety, excessive worry, and poor energy. He additionally reported feeling "spaced out" and having dizziness exacerbated by movement, lethargy, and insomnia. He had started taking rifampicin 300 mg twice daily and co-trimoxazole 7 days earlier and it was found that his **sertraline** and *N*-desmethylsertraline levels were only 39% and 46%, respectively, of the levels achieved when he was not taking rifampicin and co-trimoxazole. He later experienced similar symptoms when the **sertraline** dose was tapered so that paroxetine could be substituted.[1] Similarly, a 55-year-old man taking **citalopram** 40 to 60 mg daily reported a decrease in therapeutic efficacy (increased crying and panic attacks) after starting rifampicin 600 mg twice daily. His condition improved when the rifampicin was stopped.[2]

Mechanism

Both sertraline and citalopram are metabolised by cytochrome P450 isoenzymes including CYP3A4, of which rifampicin is a potent inducer. It would therefore appear that rifampicin induced the metabolism of these two drugs resulting in decreased plasma levels.

Importance and management

There seem to be very few reports of this interaction, but rifampicin is a potent enzyme inducer and so clinicians should be aware that rifampicin may reduce citalopram or sertraline plasma levels leading to decreased efficacy or symptoms of SSRI withdrawal. In theory, rifampicin could affect other SSRIs metabolised by other cytochrome P450 isoenzymes, but there appear to be no reports of this. The UK manufacturer of **paroxetine** suggests that dosage adjustment on starting or stopping enzyme inducing drugs such as rifampicin should be guided by clinical effect (tolerability and efficacy), and they suggest that no initial anticipatory dose adjustment is necessary.[3] Until more is known this would seem to be a sensible approach with rifampicin and any SSRI.

1. Markowitz JS, DeVane CL. Rifampin-induced selective serotonin reuptake inhibitor withdrawal syndrome in a patient treated with sertraline. *J Clin Psychopharmacol* (2000) 20, 109–10.

2. Kukoyi O, Argo TR, Carnaham RM. Exacerbation of panic disorder with rifampin therapy in a patient receiving citalopram. *Pharmacotherapy* (2005) 25, 435–7.
3. Seroxat (Paroxetine hydrochloride hemihydrate). GlaxoSmithKline UK. UK Summary of product characteristics, May 2009.

SSRIs + Sibutramine

Two case reports suggest that the concurrent use of sertraline or citalopram with sibutramine may cause serotonin syndrome.

Clinical evidence, mechanism, importance and management

A 43-year-old woman taking **citalopram** 40 mg daily was also given sibutramine 10 mg daily. Within a few hours of taking the first dose of sibutramine she developed racing thoughts, hyperactivity, psychomotor agitation, shivering and diaphoresis, which continued for the 3 days that she continued to take sibutramine. The authors suggested that one of the reasons for the hypomania may have been serotonin syndrome, which could have been caused by the use of two drugs with serotonergic action.[1] A letter briefly mentions another possible case of serotonin syndrome, following the use of sibutramine and **sertraline**.[2] The manufacturers of sibutramine say that concurrent use of any other drug that has serotonergic actions should be avoided[3] where possible,[4] or only undertaken with appropriate monitoring.[4] For more information about serotonin syndrome, see under 'Additive or synergistic interactions', (p.9).

1. Benazzi F. Organic hypomania secondary to sibutramine-citalopram interaction. *J Clin Psychiatry* (2002) 63, 165.
2. Trakas K, Shear NH. Serotonin syndrome risk with antiobesity drug. *Can J Clin Pharmacol* (2000) 7, 216.
3. Reductil (Sibutramine hydrochloride monohydrate). Abbott Laboratories Ltd. UK Summary of product characteristics, October 2007.
4. Meridia (Sibutramine hydrochloride monohydrate). Abbott Laboratories. US Prescribing information, May 2009.

SSRIs + SSRIs

An isolated report describes an adverse reaction (hypertension, tachycardia, fever, auditory hallucinations and confusion) in a man when he started sertraline within a day of stopping fluoxetine. A small study found that the concurrent use of citalopram and fluvoxamine markedly increased citalopram plasma levels: escitalopram will be similarly affected. Note that combining more than one SSRI is unusual, and would be expected to increase the risk of adverse effects.

Clinical evidence

(a) Citalopram or Escitalopram with Fluvoxamine

A study in 7 patients with depression who had not responded to treatment with citalopram 40 mg daily for 3 weeks, found that the addition of fluvoxamine (50 mg increased to 100 mg daily for another 3 weeks) increased *R*-citalopram levels by almost twofold and *S*-citalopram levels threefold. Six of the 7 patients showed clinical improvement. None of the patients developed serotonin syndrome, and no changes in vital signs or ECGs were seen.[1] This study shows that the levels of escitalopram, the *S*-isomer of citalopram, will be raised by fluvoxamine.

(b) Fluoxetine with Sertraline

One of 16 healthy subjects who began to take sertraline 50 mg daily on the day after stopping a 2-week trial of fluoxetine 20 mg daily, rapidly developed hypertension, tachycardia, fever, auditory hallucinations and confusion. Most of these symptoms disappeared 48 hours after stopping the sertraline, but the confusion took a week to subside.[2] The other 15 subjects had no clinically significant adverse effects. This subject was later found to have a history of psychosis so that the picture is a little confused, but the rapid abatement of the symptoms when the sertraline was stopped suggests that they were due either to the sertraline alone, or to an interaction with the residual fluoxetine.

Mechanism

Fluvoxamine increases citalopram levels, with a more marked effect on *S*-citalopram (escitalopram), possibly by inhibiting the cytochrome P450 isoenzyme CYP2C19. Fluoxetine has a very long half-life, and might therefore have contributed to the adverse effects seen when switching to sertraline in the case described. Combining drugs with serotonergic actions such as two SSRIs are likely have additive effects.

Importance and management

There is very little information on combining SSRIs because this is not a usual therapeutic strategy. It is likely that combining two SSRIs will have additive effects, and some SSRI manufacturers include other SSRIs in the list of drugs that have serotonergic effects and would therefore increase the risk of serotonergic adverse effects including the rare 'serotonin syndrome', (p.9), on concurrent use. On this basis they advise caution or avoidance of concurrent use. Some caution would seem prudent. The one study with fluvoxamine and citalopram highlights the fact that there might be a pharmacokinetic component to the interaction between some SSRIs, which would intensify any effects.

On the basis of the possible interaction, it is also not clear whether a washout period is needed if switching between two SSRIs, particularly when the first has a long half-life, such as fluoxetine. A decision on this will depend on the severity of the depression in the particular patient being treated. The manufacturers of sertraline imply caution when they say that the duration of a washout period when switching from one SSRI to another has not yet been established.[3,4]

1. Bondolfi G, Chautems C, Rochat B, Bertschy G, Baumann P. Non-response to citalopram in depressive patients: pharmacokinetic and clinical consequences of a fluvoxamine augmentation. *Psychopharmacology (Berl)* (1996) 128, 421–5.
2. Rosenblatt JE, Rosenblatt NC. How long a hiatus between discontinuing fluoxetine and beginning sertraline? *Curr Affect Illn* (1992) 11, 2.
3. Lustral (Sertraline hydrochloride). Pfizer Ltd. UK Summary of product characteristics, January 2009.
4. Zoloft (Sertraline hydrochloride). Pfizer Inc. US Prescribing information, January 2009.

SSRIs + St John's wort (*Hypericum perforatum*)

Cases of severe sedation, mania and serotonin syndrome have been reported in patients taking St John's wort with SSRIs.

Clinical evidence

(a) Fluoxetine

For a report of hypomania when St John's wort, ginkgo biloba and melatonin were added to treatment with fluoxetine and buspirone, see 'Buspirone + St John's wort (*Hypericum perforatum*)', p.871.

For a report of serotonin syndrome when eletriptan, fluoxetine and St John's wort were used together, see 'Triptans + St John's wort (*Hypericum perforatum*)', p.691.

(b) Paroxetine

In one report, a woman stopped taking paroxetine 40 mg daily after 8 months, and 10 days later started to take 600 mg of St John's wort powder daily. No problems occurred until the next night when she took a single 20-mg dose of paroxetine because she thought it might help her sleep. The following day at noon she was found still to be in bed, rousable but incoherent, groggy and slow moving and almost unable to get out of bed. Two hours later she still complained of nausea, weakness and fatigue, but her vital signs and mental status were normal. Within 24 hours all symptoms had resolved.[1]

(c) Sertraline

Four elderly patients taking sertraline developed symptoms characteristic of serotonin syndrome within 2 to 4 days of also taking St John's wort 300 mg, either two or three times daily. The symptoms included dizziness, nausea, vomiting, headache, anxiety, confusion, restlessness, and irritability. Two of them were treated with oral cyproheptadine 4 mg either two or three times daily, and the symptoms of all of them resolved within a week. They later resumed treatment with sertraline without problems.[2] A search of Health Canada's database of spontaneous adverse reactions from 1998 to 2003 found 2 cases of suspected serotonin syndrome as a result of an interaction between sertraline and St John's wort.[3]

Mania developed in a 28-year-old man, who continued to take St John's wort against medical advice whilst also receiving sertraline 50 mg daily for depression; he was also receiving testosterone replacement post-orchidectomy.[4]

Mechanism

A pharmacodynamic interaction may occur between St John's wort and SSRIs because they can both inhibit the reuptake of 5-hydroxytryptamine (serotonin).[5] Serotonin syndrome has been seen with St John's wort alone,[6] and so additive serotonergic effects appear to be the explanation for what occurred in the cases described here.

Importance and management

Information appears to be limited to these reports, but interactions between SSRIs and St John's wort would seem to be established. The incidence is not known but it is probably small, nevertheless because of the potential severity of the reaction it would seem prudent to avoid concurrent use. The advice of the CSM in the UK is that St John's wort should be stopped if patients are taking any SSRI because of the risk of increased serotonergic effects and an increased incidence of adverse reactions.[7]

1. Gordon JB. SSRIs and St. John's wort: possible toxicity? *Am Fam Physician* (1998) 57, 950–3.
2. Lantz MS, Buchalter E, Giambanco V. St. John's wort and antidepressant drug interactions in the elderly. *J Geriatr Psychiatry Neurol* (1999) 12, 7–10.
3. Griffiths J, Jordan S, Pilon K. Natural health products and adverse reactions. *Can Adverse React News* (2004) 14 (1), 2–3.
4. Barbenel DM, Yusufi B, O'Shea D, Bench CJ. Mania in a patient receiving testosterone replacement post-orchidectomy taking St John's wort and sertraline. *J Psychopharmacol* (2000) 14, 84–6.
5. Izzo AA. Drug interactions with St. John's wort (Hypericum perforatum): a review of the clinical evidence. *Int J Clin Pharmacol Ther* (2004) 42, 139–48.
6. Demott K. St. John's wort tied to serotonin syndrome. *Clin Psychiatry News* (1998) 26, 28.
7. Committee on Safety of Medicines (UK). Message from Professor A Breckenridge (Chairman of CSM) and Fact Sheet for Health Care Professionals, 29th February 2000.

SSRIs + Terbinafine

Although terbinafine modestly increases paroxetine levels one study found no increase in paroxetine adverse effects. Some other SSRIs may interact similarly.

Clinical evidence

In a randomised study, 12 healthy subjects were given a single 20-mg dose of paroxetine, alone or after taking terbinafine 125 mg daily for 6 days. Terbinafine increased the AUC and maximum plasma concentration of paroxetine by 150% and 86%, respectively, and the half-life of paroxetine was also increased by 48% (from about 15 hours to 23 hours). There was no significant difference in the adverse effects reported between the two treatments.[1]

Mechanism

Terbinafine is an inhibitor of the cytochrome P450 isoenzyme CYP2D6, the isoenzyme by which paroxetine is metabolised. Concurrent use therefore decreases paroxetine metabolism and increases its levels.

Importance and management

Information appears to be limited to one study, but the results are in line with the way both drugs are known to interact. Be aware that paroxetine levels may be increased if terbinafine is also given, and consider a dose reduction if adverse effects become troublesome. Note that many of the SSRIs are metabolised, at least in part, by CYP2D6 (see 'Table 35.2', (p.1465)), and so may interact similarly, although the clinical relevance of these potential interactions is unknown.

1. Yasui-Furukori N, Saito M, Inoue Y, Niioka T, Sato Y, Tsuchimine S, Kaneko S. Terbinafine increase the plasma concentration of paroxetine after a single oral administration of paroxetine in healthy subjects. *Eur J Clin Pharmacol* (2007) 63, 51–6.

SSRIs + Tobacco

Smoking has only modest effects on fluvoxamine pharmacokinetics. It is unclear whether smoking has any effect on citalopram pharmacokinetics.

Clinical evidence, mechanism, importance and management

(a) Citalopram

In a pharmacokinetic study in adolescent patients (under 21 years of age), there was a clear dose-concentration relationship for citalopram and its metabolite, desmethylcitalopram, in the 9 non-smokers, whereas no such relationship was seen in the 10 smokers. The authors suggested that smoking might have had some effect on citalopram pharmacokinetics, but that this requires confirmation.[1] The clinical significance of any effect is unknown and more study is required.

(b) Fluvoxamine

A comparative study in 12 smokers and 12 non-smokers given single 50-mg oral doses of fluvoxamine found that smoking reduced the fluvoxamine AUC and maximum serum levels by about 30%.[2] However, a study in Japanese patients found no significant difference in the steady-state plasma levels of fluvoxamine and its metabolite (fluvoxamino acid) between 34 non-smokers and 15 smokers.[3] This suggests that the overall pharmacokinetic effect of smoking is probably minimal, although how a sudden withdrawal from heavy smoking would affect fluvoxamine pharmacokinetics has not been investigated.

1. Reis M, Olsson G, Carlsson B, Lundmark J, Dahl ML, Walinder J, Ahlner J, Bengtsson F. Serum levels of citalopram and its main metabolites in adolescent patients treated in a naturalistic clinical setting. *J Clin Psychopharmacol* (2002) 22, 406–13.
2. Spigset O, Carleborg L, Hedenmalm K, Dahlqvist R. Effect of cigarette smoking on fluvoxamine pharmacokinetics in humans. *Clin Pharmacol Ther* (1995) 58, 399–403.
3. Gerstenberg G, Aoshima T, Fukasawa T, Yoshida K, Takahashi H, Higuchi H, Murata Y, Shimoyama R, Ohkubo T, Shimizu T, Otani K. Effects of the CYP 2D6 genotype and cigarette smoking on the steady-state plasma concentrations of fluvoxamine and its major metabolite fluvoxamino acid in Japanese depressed patients. *Ther Drug Monit* (2003) 25, 463–8.

SSRIs + Tryptophan

Central and peripheral toxicity developed in five patients taking high doses of fluoxetine when they were given tryptophan, which was attributed to serotonin syndrome. Adverse effects have occurred on combined use of paroxetine and tryptophan.

Clinical evidence

(a) Fluoxetine

Five patients taking fluoxetine 50 to 100 mg daily (high doses) for at least 3 months developed a number of reactions including central toxicity (agitation, restlessness, aggressive behaviour, worsening of obsessive-compulsive disorders) and peripheral toxicity (abdominal cramps, nausea, diarrhoea) within a few days of starting to take tryptophan 1 to 4 g daily. These symptoms disappeared when the tryptophan was stopped. Some of the patients had taken tryptophan in the absence of fluoxetine without problems.[1]

Conversely, in a placebo-controlled study involving 30 patients with depression, the use of tryptophan 1 g daily titrated to 4 g daily during the initial 8 weeks of treatment with fluoxetine 20 mg daily was beneficial and well-tolerated. No cases of serotonin syndrome occurred.[2]

(b) Paroxetine

The US manufacturer of paroxetine notes that adverse experiences, consisting primarily of headache, nausea, sweating, and dizziness, have been reported when paroxetine was taken with tryptophan.[3]

Mechanism

Tryptophan is a precursor of serotonin (5-hydroxytryptamine) and the authors of the fluoxetine cases point out that the symptoms resemble serotonin syndrome, which occurs when serotonin levels are increased.[1] The reaction appears to be dose related. It is likely to occur with any SSRI.

Importance and management

The cases with fluoxetine appear to be the only ones published, nevertheless, they demonstrate the potential for additive adverse effects. The authors recommended caution when tryptophan is used with fluoxetine or other serotonin reuptake inhibitors.[1] This caution (or advice to avoid concurrent use) is echoed by most of the manufacturers of the SSRIs; the UK manufacturer of paroxetine additionally mentions the serotonin precursor **oxitriptan** [L-5-hydroxytryptophan].[4] If tryptophan is used to augment the initial response to SSRIs, the SSRI should be started at a low dose,

with tryptophan gradually introduced, starting with a low dose. Patients should be closely monitored for adverse effects.[2]

1. Steiner W, Fontaine R. Toxic reaction following the combined administration of fluoxetine and L-tryptophan: five case reports. *Biol Psychiatry* (1986) 21, 1067–71.
2. Levitan RD, Shen J-H, Jindal R, Driver HS, Kennedy SH, Shapiro CM. Preliminary randomized double-blind placebo-controlled trial of tryptophan combined with fluoxetine to treat major depressive disorder: antidepressant and hypnotic effects. *J Psychiatry Neurosci* (2000) 25, 337–46.
3. Paxil (Paroxetine hydrochloride). GlaxoSmithKline. US Prescribing information, August 2009.
4. Seroxat (Paroxetine hydrochloride hemihydrate). GlaxoSmithKline UK. UK Summary of product characteristics, May 2009.

SSRIs; Citalopram + Irinotecan

An isolated report attributes a case of rhabdomyolysis to the use of citalopram and irinotecan.

Clinical evidence, mechanism, importance and management

A 74-year-old man who had been taking citalopram for 2 months developed rhabdomyolysis after undergoing initial treatment for gastrointestinal cancer with irinotecan. All medications were discontinued, but the rhabdomyolysis was exacerbated upon restarting the citalopram for depression. The citalopram was discontinued and he improved over the next 5 days.[1]

The authors suggested that levels of citalopram might have increased because irinotecan might inhibit the cytochrome P450 isoenzyme CYP3A4, and the cytochrome system may also have been compromised by the malignancy.[1] However, the patient was also taking **simvastatin**, which is well known to be associated with a risk of rhabdomyolysis and which is also metabolised by CYP3A4, but the authors make no mention of this. An interaction between citalopram and irinotecan is therefore not established, and speculatively, this seems more likely to be an interaction between irinotecan and simvastatin, which was exacerbated by citalopram.

1. Richards S, Umbreit JN, Fanucchi MP, Giblin J, Khuri F. Selective serotonin reuptake inhibitor-induced rhabdomyolysis associated with irinotecan. South Med J 92003) 96, 1031–3.

SSRIs; Fluoxetine + Aminoglutethimide

Evidence from one case suggests that the effects of fluoxetine are increased by aminoglutethimide.

Clinical evidence, mechanism, importance and management

A patient with severe obsessive-compulsive disorder, resistant to clomipramine combined with SSRIs, improved when given fluoxetine 40 mg daily and aminoglutethimide 250 mg four times daily. Over a four-and-a-half year period, whenever attempts were made to reduce the dosage of either drug, the patient started to relapse.[1] The evidence suggests that aminoglutethimide has a potentiating effect on fluoxetine. However, more study is needed to confirm the efficacy and safety of this drug combination in other patients.

1. Chouinard G, Bélanger M-C, Beauclair L, Sultan S, Murphy BEP. Potentiation of fluoxetine by aminoglutethimide, an adrenal steroid suppressant, in obsessive-compulsive disorder resistant to SSRIs: a case report. *Prog Neuropsychopharmacol Biol Psychiatry* (1996) 20, 1067–79.

SSRIs; Fluoxetine + Cannabis

An isolated report describes mania when a patient taking fluoxetine smoked cannabis.

Clinical evidence, mechanism, importance and management

A 21-year-old woman with a 9-year history of bulimia and depression started taking fluoxetine 20 mg daily. A month later, about 2 days after smoking two 'joints' of cannabis (**marijuana**), she experienced a persistent sense of well-being, increased energy, hypersexuality and pressured speech. These symptoms progressed into grandiose delusions, for which she was hospitalised. Her mania and excitement were controlled with lorazepam and perphenazine, and she largely recovered after about 8 days. The reasons for this reaction are not understood but the authors of the report point out that one of the active components of cannabis, **dronabinol** (Δ^9**-tetrahydrocannabinol**) is, like fluoxetine, a potent inhibitor of serotonin uptake. Thus a synergistic effect on central serotonergic neurones might have occurred.[1] This seems to be the first and only report of an apparent adverse interaction between cannabis and fluoxetine. The patient had only started fluoxetine 4 weeks before the manic episode, and was still suffering 'hyper' feelings over a month after smoking the cannabis. The symptoms only resolved when the fluoxetine was withdrawn, and so an interaction is by no means established.

1. Stoll AL, Cole JO, Lukas SE. A case of mania as a result of fluoxetine-marijuana interaction. *J Clin Psychiatry* (1991) 52, 280–1.

SSRIs; Fluoxetine + Orlistat

The pharmacokinetics of a single 40-mg oral dose of fluoxetine (a lipophilic drug) were not affected by orlistat 120 mg three times daily in healthy subjects.[1] Therefore, no fluoxetine dose adjustments appear to be needed on the concurrent use of orlistat.

1. Zhi J, Moore R, Kanitra L, Mulligan TE. Effects of orlistat, a lipase inhibitor, on the pharmacokinetics of three highly lipophilic drugs (amiodarone, fluoxetine, and simvastatin) in healthy volunteers. *J Clin Pharmacol* (2003) 43, 428–35.

SSRIs; Fluvoxamine + Clindamycin

A man taking fluvoxamine developed severe orofacial dyskinesia two days after starting to take clindamycin.

Clinical evidence, mechanism, importance and management

A 32-year-old man with a major depressive episode was admitted to hospital 10 days after starting fluvoxamine 100 mg daily for 10 days. The fluvoxamine dose was increased to 200 mg daily, and after 4 weeks his mood was stabilised. Two days after starting clindamycin 300 mg daily for a furuncle, severe orofacial dyskinesia developed, which disappeared after he was given intravenous biperiden. A blood level of fluvoxamine taken at this time was actually lower than usual therapeutic levels.[1]

The authors speculated that the time course of events suggests that clindamycin might have contributed to the dyskinesia. However, there is no known mechanism for an interaction. Clindamycin would not be expected to alter the pharmacokinetics of fluvoxamine, and the fluvoxamine blood level appears to confirm this. Clindamycin is also not known to cause extrapyramidal adverse effects.

Based on this single case, no general advice can be given, but bear it in mind in case of a similar unexpected reaction.

1. Jakob F, Wolf J. EPMS under antidepressive therapy with fluvoxamine and concomitant antibiotic therapy with clindamycin. *Pharmacopsychiatry* (2007) 40, 129.

SSRIs; Fluvoxamine + Enoxacin

A study in healthy subjects suggested that enoxacin might slightly increase fluvoxamine levels.

Clinical evidence, mechanism, importance and management

In a placebo-controlled study in 10 healthy subjects given enoxacin 100 mg twice daily for 11 days, with a single 50-mg dose of fluvoxamine on the eighth day. Enoxacin slightly increased the plasma levels of fluvoxamine at 2 and 3 hours, with a 14% increase in the maximum plasma level. There was no change in the AUC or elimination half-life of fluvoxamine or in the pharmacokinetics of the active metabolite of fluvoxamine, fluvoxamino acid. Sleepiness was increased from 30 minutes to 4 hours, but there was no change in the digit symbol substitution test or adverse effects.[1]

It was suggested that enoxacin slightly inhibits the metabolism of fluvoxamine by the cytochrome P450 isoenzyme CYP1A2; however fluvoxamine is not know to be metabolised by this route, so the exact mechanism is not clear.

The interpretation of this study is difficult. The minor change in just the maximum level of fluvoxamine would be very unlikely to be clinically relevant, and is unlikely to explain an increase in sleepiness. Further study is necessary, with multiple doses of fluvoxamine. Until more is known, bear

the possibility of an interaction in mind the event of increased sleepiness with enoxacin.

1. Kunii T, Fukasawa T, Yasui-Furukori N, Aoshima T, Suzuki A, Tateishi T, Inoue Y, Otani K. Interaction study between enoxacin and fluvoxamine. *Ther Drug Monit* (2005) 27, 349–53.

SSRIs; Paroxetine + Miscellaneous

Aluminium hydroxide and food do not appear to cause a clinically relevant change in paroxetine absorption, although absorption may be reduced by large quantities of milk. The concurrent use of paroxetine and aprepitant may slightly reduce the plasma levels of both drugs, but this is probably not clinically significant.

Clinical evidence, mechanism, importance and management

(a) Aluminium hydroxide

In a study in healthy subjects, *Aludrox* (aluminium hydroxide) 15 mL twice daily increased the absorption of a single 30-mg dose of paroxetine by about 12%, and increased its maximum plasma concentration by 14%.[1] These changes are unlikely to be clinically important. No particular precautions would seem to be necessary on concurrent use.

(b) Aprepitant

The US manufacturer of aprepitant notes that the concurrent use of paroxetine 20 mg daily and aprepitant 85 or 170 mg daily reduced the AUC of both drugs by about 25%, and reduced the maximum serum levels by about 20%.[2] These changes are unlikely to be clinically important. An interaction with **fosaprepitant** (which is rapidly metabolised to aprepitant) seems unlikely.

(c) Foods

A study in healthy subjects found that the absorption of paroxetine was not markedly changed by food. A 40% reduction in absorption was seen when paroxetine was taken with one litre of **milk**,[1] but it would seem unlikely that many people would drink such a large amount regularly, at the same time as taking paroxetine, and so this interaction is unlikely to be generally significant.

1. Greb WH, Brett MA, Buscher G, Dierdorf H-D, von Schrader HW, Wolf D, Mellows G, Zussman BD. Absorption of paroxetine under various dietary conditions and following antacid intake. *Acta Psychiatr Scand* (1989) 80 (Suppl 350), 99–101.
2. Emend (Aprepitant). Merck & Co., Inc. US Prescribing information, July 2009.

Tianeptine + Oxazepam

A study in healthy subjects given tianeptine 12.5 mg and oxazepam 10 mg both three times daily found no significant changes in the pharmacokinetics of either drug.[1]

1. Toon S, Holt BL, Langley SJ, Mullins FGP, Rowland M, Halliday MS, Salvadori C, Delalleau B. Pharmacokinetic and pharmacodynamic interaction between the antidepressant tianeptine and oxazepam at steady-state. *Psychopharmacology (Berl)* (1990) 101, 226–32.

Trazodone + Azoles

Ketoconazole or itraconazole may inhibit the metabolism of trazodone.

Clinical evidence, mechanism, importance and management

An *in vitro* study found that **ketoconazole** inhibited the metabolism of trazodone to its principal active metabolite, meta-chlorophenylpiperazine, and was of similar potency to ritonavir in this regard.[1]

Trazodone is a substrate for the cytochrome P450 isoenzyme CYP3A4 and inhibitors of this enzyme such as **ketoconazole** and **itraconazole** may inhibit its metabolism, leading to substantial increases in trazodone plasma concentrations with the potential for adverse effects,[2-4] as has been shown for ritonavir, see 'Trazodone + Protease inhibitors', p.1496.

On the basis of the available data, the FDA in the US and the manufacturers of trazodone recommend that a lower dose of trazodone should be considered if it is given with a potent CYP3A4 inhibitor such as **ketoconazole** or **itraconazole**.[2-4] However, the UK manufacturer also suggests that the combination should be avoided, where possible.[4]

1. Zalma A, von Moltke LL, Granda BW, Harmatz JS, Shader RI, Greenblatt DJ. In vitro metabolism of trazodone by CYP3A: inhibition by ketoconazole and human immunodeficiency viral protease inhibitors. *Biol Psychiatry* (2000) 47, 655–61.
2. Desyrel (Trazodone hydrochloride). Bristol-Myers Squibb Company. US Prescribing information, February 2009.
3. Lewis-Hall FC. Bristol-Myers Squibb Company. Letter to healthcare professionals, April 2004.
4. Molipaxin Capsules (Trazodone hydrochloride). Sanofi-Aventis. UK Summary of product characteristics, August 2009.

Trazodone + Ginkgo (*Ginkgo biloba*)

Coma developed in an elderly patient with Alzheimer's disease after she took trazodone with ginkgo.

Clinical evidence

An 80-year-old woman with Alzheimer's disease became comatose a few days after starting low-dose trazodone 20 mg twice daily and ginkgo biloba. The patient woke immediately after being given flumazenil 1 mg intravenously.[1]

Mechanism

It was suggested that the flavonoids in the ginkgo had a subclinical direct effect on the benzodiazepine receptor. In addition, it was suggested that ginkgo increased the metabolism of trazodone to its active metabolite, 1-(m-chlorophenyl)piperazine (mCPP) by the cytochrome P450 isoenzyme CYP3A4. The increased levels of the metabolite were thought to have enhanced the release of GABA (gamma-amino butyric acid). Flumazenil may have blocked the direct effect of the flavonoids, thus causing the GABA activity to fall below the level required to have a clinical effect. However, note that clinically relevant CYP3A4 induction has not been seen with the conventional CYP3A4 probe substrate midazolam.

Importance and management

Evidence for an interaction between ginkgo and trazodone appears to be limited to this isolated case, from which no general conclusions can be drawn. Bear this interaction in mind in case of an unexpected response to concurrent use.

1. Galluzzi S, Zanetti O, Binetti G, Trabucchi M, Frisoni GB. Coma in a patient with Alzheimer's disease taking low dose trazodone and ginkgo biloba. *J Neurol Neurosurg Psychiatry* (2000) 68, 679–80.

Trazodone + Haloperidol

Low-dose haloperidol does not alter the pharmacokinetics of trazodone to a clinically relevant extent.

Clinical evidence, mechanism, importance and management

Nine depressed patients who had been taking trazodone 150 to 300 mg at bedtime for 2 to 19 weeks were given haloperidol 4 mg daily for a week. Plasma trazodone levels were not significantly changed but levels of its metabolite (*m*-chlorophenylpiperazine) were slightly raised by 18% (from 78 to 92 nanograms/mL). This study[1] was carried out to investigate the way trazodone is metabolised, but it also demonstrated that no clinically relevant pharmacokinetic interaction occurs between these two drugs at these dosages.

1. Mihara K, Otani K, Ishida M, Yasui N, Suzuki A, Ohkubo T, Osanai T, Kaneko S, Sugawara K. Increases in plasma concentration of m-chlorophenylpiperazine, but not trazodone, with low-dose haloperidol. *Ther Drug Monit* (1997) 19, 43–5.

Trazodone + Lysergide (LSD)

A retrospective study found that 28 of 32 subjects (88%) who took LSD and who had taken an SSRI or trazodone for more than 3 weeks had a subjective decrease or virtual elimination of their responses to LSD.[1] The reasons for this effects are not understood. Lysergide increases serotonin in the brain, and one sugges-

tion is that when the serotonin re-uptake is blocked in the brain, there is an increased stimulation of 5-HT_1 and 5-HT_2 receptors.

1. Bonson KR, Buckholtz JW, Murphy DL. Chronic administration of serotonergic antidepressants attenuates the subjective effects of LSD in humans. *Neuropsychopharmacology* (1996) 14, 425–36.

Trazodone + Macrolides

Clarithromycin markedly impaired the clearance of trazodone and enhanced its sedative effects in one study. Erythromycin is also likely to increase trazodone plasma levels.

Clinical evidence, mechanism, importance and management

In a preliminary report of a placebo-controlled study in healthy subjects, **clarithromycin** (dose and duration not given) markedly reduced the clearance of a 50-mg dose of trazodone by almost 90%, almost doubled its elimination half-life, and increased its maximum level by 36%. Clarithromycin enhanced the sedation and performance impairment seen with trazodone.[1]

The manufacturers comment that trazodone is a substrate for the cytochrome P450 isoenzyme CYP3A4 and inhibitors of this isoenzyme may inhibit its metabolism leading to substantial increases in trazodone plasma levels, with the potential for adverse effects.[2,3] Clarithromycin is a known inhibitor of this isoenzyme and may therefore interact in this way, although other mechanisms might also be involved.

On the basis of the available data, caution is required when clarithromycin is given to a patient taking trazodone. Based on data with ritonavir (see 'Trazodone + Protease inhibitors', below), the UK manufacturer of trazodone recommends that a lower dose of trazodone should be considered if it is given with potent CYP3A4 inhibitors (they name **erythromycin**), but that concurrent use should be avoided where possible.[3] If CYP3A4 inhibition is the mechanism for this interaction, it seems likely that all macrolides that inhibit CYP3A4 will interact to some extent. See 'Ergot derivatives + Macrolides', p.683, for a general guide to the relative inhibitory potencies of the macrolides on CYP3A4.

1. Greenblatt DJ, von Moltke LL, Harmatz JS. Clarithromycin impairs clearance and potentiates clinical effects of trazodone but not of zolpidem. *Clin Pharmacol Ther* (2005) 77, P28.
2. Desyrel (Trazodone hydrochloride). Bristol-Myers Squibb Company. US Prescribing information, February 2009.
3. Molipaxin Capsules (Trazodone hydrochloride). Sanofi-Aventis. UK Summary of product characteristics, August 2009.

Trazodone + Protease inhibitors

Ritonavir markedly impairs the clearance of trazodone. Other protease inhibitors may interact similarly. A possible case of serotonin syndrome has been seen in a patient taking multiple serotonergic drugs, including trazodone, and ritonavir.

Clinical evidence

A randomised, placebo-controlled study in 10 healthy subjects found that short-term exposure to low-dose **ritonavir** (200 mg twice daily for 2 days) impaired the clearance of a single 50-mg dose of trazodone by 52%. The AUC of trazodone increased by 2.4-fold, whereas its mean peak plasma levels were increased by just 34%. In addition, **ritonavir** enhanced the adverse effects of trazodone with increased sedation, fatigue and performance impairment.[1] Symptoms of serotonin syndrome occurred in an HIV-positive patient taking antiretrovirals and other drugs, including fluoxetine, lithium and trazodone, when **ritonavir** was added. The symptoms resolved on discontinuing the trazodone and halving the **ritonavir** dose.[2] Serotonin syndrome has also been seen in a patient taking trazodone, fluoxetine, **indinavir** and excessive amounts of grapefruit, see 'SSRIs + Grapefruit juice', p.1484.

Mechanism

An *in vitro* study demonstrated that the metabolism of trazodone to its principal active metabolite, meta-chlorophenylpiperazine (mCPP), was inhibited by ritonavir, which is a potent inhibitor of the cytochrome P450 isoenzyme CYP3A4. Indinavir was also a strong inhibitor of mCPP formation, whereas **saquinavir** and **nelfinavir** were considerably less potent inhibitors.[3] The clinical study shows that this leads to an increase in adverse effects.[1]

Importance and management

Although data are limited, what is available suggests that the pharmacokinetic interaction between ritonavir and trazodone is likely to be clinically important. The FDA in the US and the manufacturers of trazodone recommend that a lower dose of trazodone should be considered if it is given with potent CYP3A4 inhibitors such as the protease inhibitors ritonavir and indinavir.[4-6] However, the UK manufacturer also suggests that the combination should be avoided where possible.[5]

1. Greenblatt DJ, von Moltke LL, Harmatz JS, Fogelman SM, Chen G, Graf JA, Mertzanis P, Byron S, Culm KE, Granda BW, Daily JP, Shader RI. Short-term exposure to low-dose ritonavir impairs clearance and enhances adverse effects of trazodone. *J Clin Pharmacol* (2003) 43, 414–22.
2. DeSilva KE, Le Flore DB, Marston BJ, Rimland D. Serotonin syndrome in HIV-infected individuals receiving antiretroviral therapy and fluoxetine. *AIDS* (2001) 15, 1281–5.
3. Zalma A, von Moltke LL, Granda BW, Harmatz JS, Shader RI, Greenblatt DJ. In vitro metabolism of trazodone by CYP3A: inhibition by ketoconazole and human immunodeficiency viral protease inhibitors. *Biol Psychiatry* (2000) 47, 655–61.
4. Lewis-Hall FC. Bristol-Myers Squibb Company. Letter to healthcare professionals, April 2004.
5. Molipaxin Capsules (Trazodone hydrochloride). Sanofi-Aventis. UK Summary of product characteristics, August 2009.
6. Desyrel (Trazodone hydrochloride). Bristol-Myers Squibb Company. US Prescribing information, February 2009.

Trazodone + Pseudoephedrine

A single report describes a woman taking trazodone who developed a toxic reaction when she took pseudoephedrine.

Clinical evidence, mechanism, importance and management

An isolated report describes a woman who had been taking trazodone 250 mg daily for 2 years who took two doses of a non-prescription medicine containing pseudoephedrine. Within 6 hours she experienced dread, anxiety, panic, confusion, depersonalisation and the sensation that parts of her body were separating. None of these symptoms had been experienced in the past when she was taking either preparation alone.[1] The reasons for this reaction are not understood. This appears to be an isolated case, and therefore no general conclusions can be drawn.

1. Weddige RL. Possible trazodone-pseudoephedrine toxicity: a case report. *Neurobehav Toxicol Teratol* (1985) 7, 204.

Trazodone + SSRIs

Trazodone and fluoxetine have been used concurrently with advantage, but some patients have developed increased adverse effects. Fluoxetine might modestly increase trazodone levels, whereas citalopram has little effect on trazodone levels.

Clinical evidence

(a) Citalopram

In a study using data from trazodone therapeutic drug monitoring, the trazodone concentration/dose ratio was 28% higher in 41 patients taking trazodone with citalopram than in 40 patients taking trazodone alone, but this difference was not statistically significant.[1]

(b) Fluoxetine

In a controlled study, 27 patients were given trazodone 100 mg daily alone for one week, and then randomised to receive fluoxetine 20 mg daily, pindolol 7.5 mg daily or placebo for 4 weeks. Fluoxetine increased trazodone levels by 43% at 2 weeks and 65% at 4 weeks compared with baseline values, whereas pindolol and placebo had no effect.[2] Similarly, a patient taking trazodone had a 31% increase in the trazodone plasma level corrected for dose (suggesting increased trazodone levels) when fluoxetine 40 mg daily was added. She became sedated and developed an unstable gait.[3] In another study, the trazodone concentration/dose ratio was 28% higher in 16 patients taking trazodone with fluoxetine than in 40 patients taking trazodone alone, but this difference was not statistically significant.[1]

A man with traumatic brain injury showed new-onset dysarthria and speech blocking when fluoxetine was added to trazodone. His speech returned to normal when the fluoxetine was stopped.[4] A 39-year-old HIV-

positive man taking multiple antiviral and antibacterial drugs experienced bilateral hand tremor while receiving trazodone 50 mg at bedtime, which worsened when the dose of trazodone was increased to 100 mg and fluoxetine 20 mg daily was added. The trazodone and fluoxetine were discontinued and the tremor completely disappeared after 7 days without specific treatment for myoclonus.[5]

Five out of 16 patients receiving fluoxetine stopped taking trazodone 25 to 75 mg, which was given for insomnia, because of excessive sedation the next day.[6] Three out of 8 patients had improvement in sleep and depression when given both drugs but the other 5 were either unaffected or had intolerable adverse effects (headaches, dizziness, daytime sedation, fatigue).[7] However, another report described advantageous concurrent use in 6 patients without an increase in adverse effects.[8]

For a case describing serotonin syndrome, which developed in a patient taking fluoxetine, trazodone and buspirone when venlafaxine was added, see 'SNRIs; Venlafaxine + Trazodone', p.1480.

Mechanism

It appears that the plasma levels of trazodone may be increased by fluoxetine due to inhibition of its metabolism by cytochrome P450 isoenzymes by fluoxetine and/or norfluoxetine.[2] Trazodone is a substrate for CYP3A4 and, although fluoxetine is a weak inhibitor of this isoenzyme, its metabolite norfluoxetine is a moderate inhibitor.[5] *In vitro* data suggest that citalopram has little inhibitory effect on CYP3A4.[1]

Importance and management

These cases and studies suggest that the concurrent use of trazodone and fluoxetine can be useful and uneventful but it would seem prudent to monitor the outcome for any evidence of increased adverse effects. Citalopram would not be expected to have a pharmacokinetic interaction. However, the cases with fluoxetine suggest that a pharmacodynamic interaction (leading to adverse effects such as dysarthria, tremor and sedation) may be possible, and therefore a degree of caution would be prudent if trazodone is given with any SSRI.

1. Prapotnik M, Waschgler R, König P, Moll W, Conca A. Therapeutic drug monitoring of trazodone: are there pharmacokinetic interactions involving citalopram and fluoxetine? *Int J Clin Pharmacol Ther* (2004) 42, 120–4.
2. Maes M, Westenberg H, Vandoolaeghe E, Demedts P, Wauters A, Neels H, Meltzer HY. Effects of trazodone and fluoxetine in the treatment of major depression: therapeutic pharmacokinetic and pharmacodynamic interactions through formation of meta-chlorophenylpiperazine. *J Clin Psychopharmacol* (1997) 17, 358–64.
3. Aranow RB, Hudson JI, Pope HG, Grady TA, Laage TA, Bell IR, Cole JO. Elevated antidepressant plasma levels after addition of fluoxetine. *Am J Psychiatry* (1989) 146, 911–13.
4. Patterson DE, Braverman SE, Belandres PV. Speech dysfunction due to trazodone-fluoxetine combination in traumatic brain injury. *Brain Inj* (1997) 11, 287–91.
5. Darko W, Guharoy R, Rose F, Lehman D, Pappas V. Myoclonus secondary to the concurrent use of trazodone and fluoxetine. *Vet Hum Toxicol* (2001) 43, 214–5.
6. Metz A, Shader RI. Adverse interactions encountered when using trazodone to treat insomnia associated with fluoxetine. *Int Clin Psychopharmacol* (1990) 5, 191–4.
7. Nierenberg AA, Cole JO, Glass L. Possible trazodone potentiation of fluoxetine: a case series. *J Clin Psychiatry* (1992) 53, 83–5.
8. Swerdlow NR, Andia AM. Trazodone-fluoxetine combination for treatment of obsessive-compulsive disorder. *Am J Psychiatry* (1989) 146, 1637.

Trazodone + Tryptophan

A single case report describes the development of anorexia, psychosis and hypomania in a patient taking trazodone and tryptophan.

Clinical evidence, mechanism, importance and management

A single report describes the effective use of trazodone 100 mg and tryptophan 500 mg, both three times weekly, with daily clonazepam, in a woman with schizophrenia and congenital defects. However, the patient stopped eating, lost 4.5 kg in weight over 3 weeks, developed signs of psychosis or hypomania, and soon afterwards became drowsy and withdrawn. When the drugs were withdrawn the aggressive behaviour restarted, but she responded again to lower doses of trazodone and tryptophan, although the signs of psychosis re-emerged.[1] This appears to be an isolated report, and, as such, probably has little general relevance.

1. Patterson BD, Srisopark MM. Severe anorexia and possible psychosis or hypomania after trazodone-tryptophan treatment of aggression. *Lancet* (1989) i, 1017.

Tricyclic antidepressants + ACE inhibitors

Limited evidence from two patients suggests that enalapril may increase the effects of clomipramine, resulting in adverse effects. The concurrent use of tricyclic antidepressants and ACE inhibitors may possibly enhance the risk of postural hypotension.

Clinical evidence

Two patients taking **enalapril** (one taking 20 mg daily and the other taking 20 mg five times weekly) were given **clomipramine** for depression. The **clomipramine** dose of one of them was increased from 25 to 50 mg, and 10 days later he became euphoric and exalted. The problem resolved when the **clomipramine** dose was reduced to 25 mg again. The other patient had been stable taking **enalapril** for over a year when **clomipramine** and disulfiram 400 mg daily were added. Within 2 weeks he developed confusion, irritability and insomnia. These adverse effects diminished when the **clomipramine** dosage was reduced to 50 mg daily.[1]

Mechanism

The ratio of clomipramine to its metabolite (desmethylclomipramine) is normally less than 1, but both of these patients demonstrated a ratio of more than 1. This suggests that the normal metabolism (demethylation) of the clomipramine was inhibited, thus allowing the clomipramine to accumulate and its toxic effects to manifest themselves. In the second patient the disulfiram may also have had a minor additional enzyme inhibitory effect.[1]

Importance and management

Information regarding an interaction between clomipramine and enalapril is limited to these two cases and the interaction is not firmly established. More study is needed. There seems to be nothing documented about adverse effects from the concurrent use of the other ACE inhibitors and tricyclic antidepressants, although tricyclic antidepressants may cause postural hypotension, which could be more severe in the presence of ACE inhibitors.

1. Toutoungi M. Potential effect of enalapril on clomipramine metabolism. *Hum Psychopharmacol* (1992) 7, 347–9.

Tricyclic antidepressants + Ademetionine

A severe reaction, diagnosed as serotonin syndrome, developed in a woman taking ademetionine shortly after her clomipramine dosage was raised.

Clinical evidence, mechanism, importance and management

An elderly woman with a major affective disorder was given intramuscular ademetionine 100 mg daily and **clomipramine** 25 mg daily for 10 days. The **clomipramine** dose was then raised to 75 mg daily and, about 2 to 3 days later, she became progressively agitated, anxious and confused. On admission to hospital she was stuporous, with a pulse rate of 130 bpm, a respiratory rate of 30 breaths per minute, and she had diarrhoea, myoclonus, generalised tremors, rigidity, hyperreflexia, shivering, profound diaphoresis and dehydration. Her temperature rose from 40.5°C to 43°C. She had no infection, and was diagnosed with serotonin syndrome. The drugs were withdrawn and she was given dantrolene 50 mg intravenously every 6 hours for 48 hours. She made a complete recovery.[1] The reason for this severe adverse reaction is not understood, although there appears to be a connection between ademetionine and serotonin in the brain.[1,2] Another possibility is that serotonin syndrome was simply triggered by the large increase in the clomipramine dose.

An interaction is therefore not established; however, as both ademetionine and the tricyclics can affect serotonin some caution would be prudent if they are used together. See 'serotonin syndrome', (p.9), for more information about this reaction.

1. Iruela LM, Minguez L, Merino J, Monedero G. Toxic interaction of *S*-adenosylmethionine and clomipramine. *Am J Psychiatry* (1993) 150, 522.
2. Young SN. Clinical nutrition: 3. The fuzzy boundary between nutrition and psychopharmacology. *Can Med Assoc J* (2002) 166, 205–9.

Tricyclic antidepressants + Amfetamines

No pharmacokinetic interaction was reported in children receiving dexamfetamine and desipramine, but concurrent use of amfetamines and tricyclics may increase the risk of cardiovascular adverse effects.

Clinical evidence, mechanism, importance and management

A retrospective review in children and adolescents taking either **desipramine** alone, or with a stimulant, indicated the absence of a clinically significant interaction between **desipramine** and **dexamfetamine** in 4 children who received both drugs; pharmacokinetic parameters for desipramine were similar in each group.[1]

The US manufacturer of **dexamfetamine** says that amfetamines may enhance the activity of the tricyclics. Further, they say that **dexamfetamine** with **desipramine** or **protriptyline** and possibly other tricyclics causes striking and sustained increases in the concentrations of **dexamfetamine** in the brain, and that cardiovascular effects can be potentiated.[2] The UK manufacturers give a similar warning.[3]

The clinical relevance of these warnings is unclear. It may be prudent to carefully consider the risks of using the combination of an amfetamine and a tricyclic in patients with pre-exiting cardiovascular disorders.

1. Cohen LG, Prince J, Biederman J, Wilens T, Faraone SV, Whitt S, Mick E, Spencer T, Meyer MC, Polisner D, Flood JG. Absence of effect of stimulants on the pharmacokinetics of desipramine in children. *Pharmacotherapy* (1999) 19, 746–52.
2. Dexedrine (Dextroamphetamine sulfate). GlaxoSmithKline. US Prescribing information, July 2008.
3. Dexedrine (Dexamfetamine sulphate). UCB Pharma Ltd. UK Summary of product characteristics, September 2008.

Tricyclic antidepressants + Aspirin

In one study the incidence and severity of adverse effects increased when aspirin was given with imipramine.

Clinical evidence, mechanism, importance and management

A study in 20 patients with depression, given **imipramine** in their usual dose of 75 mg twice daily for 5 days, found that when aspirin 500 mg twice daily was added for a further 2 days, the incidence and range of adverse effects rose by 52% and 56%, respectively, with adverse effects described as severe increasing 2.5-fold. The degree of binding of **imipramine** to plasma proteins decreased by 12% when aspirin was given, and it was suggested that the rise in the amount of 'free' (and pharmacologically active) **imipramine** in the plasma manifested as an increase in adverse effects.[1]

Information about this interaction seems to be limited to this report, which was only short-term, so the effects of long-term concurrent use are unclear.

Note that it has been suggested that tricyclic antidepressants may increase the risk of gastrointestinal bleeding with aspirin or NSAIDs,[2] similar to the SSRIs (see 'Antiplatelet drugs + SSRIs', p.817), but information on this appears to be limited. More study is needed.

1. Juárez-Olguín H, Jung-Cook H, Flores-Pérez J, Asseff IL. Clinical evidence of an interaction between imipramine and acetylsalicylic acid on protein binding in depressed patients. *Clin Neuropharmacol* (2002) 25, 32–6.
2. Go MF. Drug injury in the upper gastrointestinal tract: nonsteroidal anti-inflammatory drugs. *Gastrointest Endosc Clin N Am* (2006) 16, 83–97.

Tricyclic and related antidepressants + Azoles; Fluconazole

Fluconazole has increased amitriptyline and nortriptyline levels in a number of cases. Mental changes, syncope, and a prolonged QTc interval have also been seen when fluconazole was given with a tricyclic.

Clinical evidence

(a) Amitriptyline

A man with AIDS given fluconazole 200 mg daily and amitriptyline 25 mg then 50 mg three times daily developed mental changes and visual hallucinations within 3 days of concurrent use. His serum amitriptyline level was found to be 724 nanograms/mL (reference range 150 to 250 nanograms/mL). His confusion resolved within 4 days of stopping the amitriptyline, at which point the levels had fallen to 270 nanograms/mL. Two similar cases were described in this report, in one case in a patient with renal impairment.[1]

A woman taking amitriptyline 100 mg twice daily, isosorbide mononitrate and metoprolol became lethargic, drowsy and confused 4 days after starting fluconazole 100 mg daily. She was found to have elevated serum levels of amitriptyline plus its metabolite nortriptyline of 956 nanograms/mL (patient's usual range 150 to 250 nanograms/mL) and a prolonged QTc interval. At first, an amitriptyline overdose was suspected. The patient was intubated, but she became delirious, agitated and disorientated. She recovered over the next 24 hours and the amitriptyline level had fallen to 190 nanograms/mL after 4 days. It was concluded that the amitriptyline toxicity was due to an interaction with fluconazole.[2]

Other reports similarly describe increased amitriptyline levels when fluconazole was given; in a child who developed syncope as a result[3] and in a 57-year-old woman who developed QT prolongation (although hypokalaemia and the use of sertraline, which can increase serum tricyclic levels, may have contributed to this effect).[4]

(b) Nortriptyline

An elderly woman taking nortriptyline 75 mg daily and other drugs (ciclosporin, morphine, metoclopramide, bumetanide as well as an unnamed antibacterial) was given fluconazole (loading dose of 200 mg, followed by 100 mg daily). After concurrent use for 13 days her trough serum nortriptyline levels had risen by 70% (from 149 nanograms/mL to 252 nanograms/mL).[5]

Mechanism

Not understood, but it has been suggested that the fluconazole inhibits the cytochrome P450 isoenzymes CYP2C9, CYP2C19, CYP3A4 and possibly CYP2D6, some of which are concerned with the metabolism of these tricyclics.[1,3] Concurrent use therefore decreases the metabolism of the tricyclic and its level rises. However, note that fluconazole does not inhibit CYP2D6 to a clinically relevant extent, and only tends to inhibit CYP3A4 in doses of 200 mg daily or more. Therefore other conditions must be necessary for an interaction to occur.

Importance and management

Information about an interaction between the tricyclics and fluconazole seems to be limited to these case reports, which, bearing in mind the widespread use of these drugs, would suggest that clinically relevant interactions are uncommon. The evidence suggests that other factors (such as renal impairment and other potentially interacting medications) may be necessary before this interaction occurs. Bear this possible interaction in mind if tricyclic adverse effects become troublesome.

1. Newberry DL, Bass SN, Mbanefo CO. A fluconazole/amitriptyline drug interaction in three male adults. *Clin Infect Dis* (1997) 24, 270–1.
2. Duggal HS. Delirium associated with amitriptyline/fluconazole drug. *Gen Hosp Psychiatry* (2003) 25, 297–8.
3. Robinson RF, Nahata MC, Olshefski RS. Syncope associated with concurrent amitriptyline and fluconazole therapy. *Ann Pharmacother* (2000) 34, 1406–9.
4. Dorsey ST, Biblo LA. Prolonged QT interval and torsades de pointes caused by the combination of fluconazole and amitriptyline. *Am J Emerg Med* (2000) 18, 227–9.
5. Gannon RH, Anderson ML. Fluconazole-nortriptyline drug interaction. *Ann Pharmacother* (1992) 26, 1456–7.

Tricyclic antidepressants + Azoles; Ketoconazole

Ketoconazole does not affect the pharmacokinetics of desipramine, and has only modest effects on the pharmacokinetics of amitriptyline and imipramine.

Clinical evidence, mechanism, importance and management

A placebo-controlled study in 8 healthy subjects found that ketoconazole 200 mg every 12 hours for 3 doses decreased the mean apparent oral clearance of **amitriptyline** 50 mg by 26% and increased its AUC by about 24%.[1] Similarly, two groups of 6 healthy subjects were given a single 100-mg dose of either **imipramine** or **desipramine** alone, and then again on day 10 of a 14-day course of ketoconazole 200 mg daily. It was found that ketoconazole caused the oral clearance of **imipramine** to fall by 17%, its half-life to rise by 15% and the AUC of the desipramine metabolite to fall by 9%. No significant changes in the pharmacokinetics of **desipramine** were seen.[2]

Ketoconazole inhibits the metabolism of the cytochrome P450 isoenzyme CYP3A4, which has only a minor role in the metabolism of amitriptyline and imipramine, and hence the changes seen are small. Desipramine is not metabolised by CYP3A4 and is therefore unaffected by ketoconazole.

These modest changes would not be expected to be clinically significant and therefore no dose adjustments would appear necessary if ketoconazole is used with these drugs. Information about other tricyclics seems to be lacking, but as they share similar metabolic routes to the tricyclics studied, no clinically relevant interaction would be expected.

1. Venkatakrishnan K, Schmider J, Harmatz JS, Ehrenberg BL, von Moltke LL, Graf JA, Mertzanis P, Corbett KE, Rodriguez MC, Shader RI, Greenblatt DJ. Relative contribution of CYP3A to amitriptyline clearance in humans: in vitro and in vivo studies. *J Clin Pharmacol* (2001) 41, 1043–54.
2. Spina E, Avenoso A, Campo GM, Scordo MG, Caputi AP, Perucca E. Effect of ketoconazole on the pharmacokinetics of imipramine and desipramine in healthy subjects. *Br J Clin Pharmacol* (1997) 43, 315–8.

Tricyclic antidepressants + Baclofen

An isolated report describes a patient with multiple sclerosis taking baclofen, who was unable to stand within a few days of starting to take nortriptyline, and later imipramine.

Clinical evidence, mechanism, importance and management

A man with multiple sclerosis, who was taking baclofen 10 mg four times a day to relieve spasticity, complained of leg weakness and was unable to stand within 6 days of starting to take **nortriptyline** 50 mg at bedtime. His muscle tone returned 48 hours after stopping the **nortriptyline**. Two weeks later he was given **imipramine** 75 mg daily and once again his muscle tone was lost.[1]

The reason for this reaction is not understood, although it has been suggested that effects on GABA-receptors may be involved.[2]

The UK manufacturer of baclofen warns that the effect of baclofen may be potentiated by tricyclic antidepressants, resulting in pronounced muscular hypotonia.[2] However, this case report appears to be the only documentation to suggest that a clinically relevant interaction occurs.

1. Silverglat MJ. Baclofen and tricyclic antidepressants: possible interaction. *JAMA* (1981) 246, 1659.
2. Lioresal Tablets (Baclofen). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, July 2009.

Tricyclic and related antidepressants + Barbiturates or Phenytoin

The plasma levels of amitriptyline, imipramine, nortriptyline and mianserin can be reduced by the barbiturates. A reduced therapeutic response would be expected. The tricyclics also lower the convulsive threshold and may be inappropriate for patients with convulsive disorders.

Clinical evidence

A comparative study in 5 pairs of twins given **nortriptyline** found that the twins also taking unnamed barbiturates had considerably lower steady-state plasma **nortriptyline** levels.[1]

Similar observations have been made in patients and healthy subjects taking **nortriptyline** with **amobarbital**[2,3] or **pentobarbital**,[4] and **protriptyline** with **amobarbital sodium**.[5] Another patient had a reduction in blood **imipramine** levels of about 50% (and loss of antidepressant control) within 2 weeks of starting to take about 400 mg of **butalbital** daily.[6]

A comparative study in 6 epileptics and 6 healthy subjects found that **phenytoin** with either **phenobarbital** or carbamazepine markedly reduced the AUC of a single 30-mg dose of **mianserin**.[7,8]

Mechanism

The barbiturates are potent liver enzyme inducers and may therefore increase the metabolism and clearance of the tricyclic antidepressants and mianserin from the body.

Importance and management

The interaction between tricyclic antidepressants or mianserin and barbiturates is established. By no means has every drug pair been studied but as the barbiturates as a whole are potent liver enzyme inducers one should be alert for this interaction with any of them. Some reduction in the effects of the antidepressant would be expected, but the general clinical importance is uncertain. Note that the tricyclics and mianserin lower the convulsive threshold and may therefore be inappropriate for patients with epilepsy.

Tricyclic antidepressants may increase the duration of barbiturate anaesthesia, see 'Anaesthetics, general and/or Neuromuscular blockers + Tricyclic and related antidepressants', p.119.

1. Alexanderson B, Price Evans DA, Sjöqvist F. Steady-state plasma levels of nortriptyline in twins: influence of genetic factors and drug therapy. *BMJ* (1969) 4, 764–8.
2. Burrows GD, Davies B. Antidepressants and barbiturates. *BMJ* (1971) 4, 113.
3. Silverman G, Braithwaite R. Interaction of benzodiazepines with tricyclic antidepressants. *BMJ* (1972) 4, 111.
4. Steiner E, Koike Y, Lind M, von Bahr C. Increased nortriptyline metabolism after treatment with pentobarbital in man. *Acta Pharmacol Toxicol (Copenh)* (1986) 59 (Suppl 4), 91.
5. Moody JP, Whyte SF, MacDonald AJ, Naylor GJ. Pharmacokinetic aspects of protriptyline plasma levels. *Eur J Clin Pharmacol* (1977) 11, 51–6.
6. Garey KW, Amsden GW, Johns CA. Possible interaction between imipramine and butalbital. *Pharmacotherapy* (1997) 17, 1041–2.
7. Nawishy S, Hathway N, Turner P. Interactions of anticonvulsant drugs with mianserin and nomifensine. *Lancet* (1981) ii, 871–2.
8. Richens A, Nawishy S, Trimble M. Antidepressant drugs, convulsions and epilepsy. *Br J Clin Pharmacol* (1983) 15, 295S–298S.

Tricyclic antidepressants + Benzodiazepines and related drugs

The concurrent use of tricyclic antidepressants and benzodiazepines is not uncommon and normally appears to be uneventful. However, concurrent use has led to adverse effects (e.g. drowsiness, incoordination). One study found that diazepam may increase the risks of carrying out complex tasks (e.g. driving) if added to amitriptyline, and this seems possible with any benzodiazepine and tricyclic.

Clinical evidence

(a) Amitriptyline

1. Chlordiazepoxide. Clinical studies in large numbers of patients have found that the incidence of adverse reactions while taking amitriptyline and chlordiazepoxide was no greater than might have been expected with either of the drugs used alone,[1-3] but a few adverse reports have been documented. A depressed patient taking amitriptyline 150 mg and chlordiazepoxide 40 mg daily became confused, forgetful and uncoordinated. He acted as though he was drunk.[4] Two other patients taking amitriptyline and chlordiazepoxide experienced drowsiness, memory impairment, slurring of the speech and an inability to concentrate. Both were unable to work and one described himself as feeling drunk.[5] Four patients taking *Limbitrol* (a combination preparation containing chlordiazepoxide and amitriptyline) are reported to have experienced some manifestations of toxicity (delusions, confusion, agitation, disorientation, dry mouth, blurred vision).[6] Some of these effects seem to arise from increased CNS depression (possibly additive) and/or an increase in the antimuscarinic adverse effects of the tricyclic.

2. Diazepam. A study found an increase in amitriptyline levels when diazepam was given.[7] In contrast, two studies suggested that diazepam did not affect amitriptyline levels.[3,8] However, other studies found that the addition of diazepam to amitriptyline 50 to 75 mg further reduced attention and the performance of a number of psychomotor tests.[9,10]

3. Nitrazepam or Oxazepam. A study of the effects of nitrazepam and oxazepam on the steady-state plasma levels of amitriptyline did not find any interactions.[3]

(b) Clomipramine

One study suggested that **alprazolam** does not affect clomipramine levels.[11]

(c) Desipramine

1. Clonazepam. An isolated report describes a patient taking desipramine 300 mg daily whose serum desipramine levels were halved when he was given clonazepam 3 mg daily and rose again when the clonazepam was withdrawn.[12]

2. Zolpidem. Visual hallucinations have been seen in one patient given zolpidem and desipramine.[13]

(d) Imipramine

1. Alprazolam. Population pharmacokinetic data suggests that alprazolam raises imipramine levels by about 20 to 30%.[14]

2. Zaleplon. A single 75-mg dose of imipramine had no effect on the pharmacokinetics of zaleplon 20 mg, and psychomotor tests showed only short term additive effects lasting 1 to 2 hours.[15]

3. Zolpidem. A single-dose study using zolpidem 20 mg and imipramine 75 mg found no effect on the pharmacokinetics of either drug. However, imipramine increased the sedative effects of zolpidem, and anterograde amnesia was seen.[16]

(e) Nortriptyline

Studies on the effects of **alprazolam**, **chlordiazepoxide**, **diazepam**, **nitrazepam** and **oxazepam** on the steady-state plasma levels of nortriptyline have found no interactions.[3,17,18]

(f) Trimipramine

In a study, when 10 healthy subjects were given **zopiclone** and trimipramine for a week there was no statistically significant change in the bioavailability of either drug.[19]

Mechanism

Uncertain. Additive CNS depression and increased antimuscarinic effects are a possibility with some combinations.

Importance and management

There seems to be no reason for avoiding the concurrent use of benzodiazepines and tricyclics although the advantages and disadvantages of such use remain the subject of debate. Other combinations of tricyclic antidepressants and benzodiazepines would be expected to behave in the same way as those described here. Some patients will possibly experience increased drowsiness and inattention, particularly with the more sedative antidepressants such as amitriptyline, especially during the first few days, and this may be exaggerated by benzodiazepines. Driving risks may therefore be increased: patients should be warned.

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Tricyclic and related antidepressants + Beta blockers

Propranolol increased imipramine levels in two children and maprotiline levels in isolated cases. Labetalol has been found to increase imipramine levels in adults. Amitriptyline does not appear to affect the pharmacokinetics of atenolol or metoprolol.

Clinical evidence

(a) Amitriptyline

A placebo-controlled study in 6 healthy subjects found that amitriptyline 75 mg daily did not affect the pharmacokinetics of **atenolol** 100 mg daily or **metoprolol** 100 mg twice daily, given for 2 weeks.[1]

(b) Imipramine

1. Labetalol. In a study in 13 healthy subjects, labetalol 200 mg every 12 hours for 4 days, increased the AUC of a single 100-mg dose of imipramine by 53%, when compared with a placebo. The maximum plasma level of imipramine increased by 28%.[2]

2. Propranolol. A 9-year-old boy was given propranolol for the control of anger and aggression, and imipramine for stress and depression. When his imipramine dose was raised from 60 to 80 mg daily and his propranolol dose was also raised, from 360 to 400 mg daily, his levels of imipramine plus its metabolite, desipramine rose sharply, from a total of 139 nanograms/mL to 469 nanograms/mL. Reducing the imipramine dose to 60 mg and raising the propranolol dose to 440 mg daily only reduced the total imipramine/desipramine levels to 426 nanograms/mL. Another imipramine dose reduction, to 40 mg, and an increase in the propranolol dose to 480 mg daily resulted in a final total imipramine/desipramine level of 207 nanograms/mL. No significant adverse effects or heart block occurred.[3]

A 9-year-old girl taking imipramine 75 mg daily with a total imipramine/desipramine level of 260 nanograms/mL, had a marked rise to 408 nanograms/mL within 3 days of starting to take propranolol 10 mg three times daily. Two days after stopping the imipramine, her desipramine level (imipramine not measured) had fallen from 382 nanograms/mL to 222 nanograms/mL.[3]

(c) Maprotiline

A patient experienced maprotiline toxicity (dizziness, hypotension, dry mouth, blurred vision, etc.) after taking **propranolol** 120 mg daily for 2 weeks. His trough maprotiline levels had risen by 40%. The levels fell and the adverse effects disappeared when the **propranolol** was withdrawn.[4] Another patient taking **propranolol** 120 mg daily began to experience visual hallucinations and psychomotor agitation within a few days of starting to take maprotiline 200 mg daily.[5] A further patient taking haloperidol, benzatropine, triamterene, hydrochlorothiazide and **propranolol** became disorientated, agitated and uncooperative, with visual hallucinations and incoherent speech, within a week of starting to take maprotiline 150 mg daily. These symptoms disappeared when all the drugs were withdrawn. Reintroduction of the antihypertensive drugs with haloperidol and desipramine proved effective and uneventful.[6]

Mechanism

Uncertain. The suggestion is that the affected drugs compete for metabolism (hydroxylation) by the same cytochrome P450 isoenzymes (particularly CYP2D6) in the liver.[2,3] Atenolol is mainly renally excreted and would therefore not be affected in this way. It has also been suggested that propranolol (and therefore possibly other beta blockers) reduces the blood flow to the liver so that the metabolism of maprotiline is reduced, leading to its accumulation in the body.

Importance and management

Information about an interaction between the beta blockers and tricyclic antidepressants or maprotiline seems to be limited to these studies and case reports. The authors of one of the reports[5] say that simultaneous use is inadvisable, but on the basis of these few cases, and with no further information, this seems over-cautious. In general it would seem that any interaction does not lead to adverse effects in most patients (the studies suggest the increase in tricyclic levels is modest). However, if adverse effects (e.g. dry mouth, blurred vision and urinary retention) occur it would seem prudent to consider an interaction as a possible cause, decreasing the antidepressant dose as appropriate.

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Tricyclic antidepressants + Bupropion

Bupropion may increase the levels of the tricyclic antidepressants, including desipramine, imipramine, and nortriptyline. Adverse effects including confusion, lethargy and unsteadiness have been reported with nortriptyline and bupropion. Seizures occurred in two patients given clomipramine or trimipramine and bupropion.

Clinical evidence

A pharmacokinetic study in healthy subjects found that bupropion doubled the maximum plasma levels of **desipramine** and increased its AUC fivefold. The effect was present for at least 7 days after the last dose of bupropion.[1,2] Another study in a 64-year-old woman taking **imipramine** 150 to 200 mg daily found that when bupropion 225 mg daily was added, there was a fourfold rise in the plasma levels of imipramine and its metabolite desipramine, but no problems were reported. A comparison of the estimated clearances of imipramine and its main metabolite desipramine were: **imipramine** 1.7 mL/minute and desipramine 1.7 mL/minute without bupropion; and imipramine 0.73 mL/minute and desipramine 0.31 mL/minute with bupropion.[3]

An 83-year-old woman taking **nortriptyline** 75 mg at night had a plasma **nortriptyline** level of 96 nanograms/mL, but when sustained-release bupropion 150 mg twice daily was added she became unsteady, confused and lethargic and her plasma nortriptyline level increased by about 200% (to 274 nanograms/mL). The increased plasma **nortriptyline** level and toxicity occurred again when she was rechallenged with bupropion.[4]

A report describes a seizure when **trimipramine** 100 mg daily was taken with bupropion 150 mg twice daily. The addition of bupropion resulted in a substantial increase in the plasma levels of **trimipramine** into the 'toxic' range. The patient was later successfully treated with lower doses of both drugs (**trimipramine** 50 mg at night and bupropion 150 mg daily).[5] Another case report describes prolonged seizure activity after the concurrent use of bupropion 300 mg daily and **clomipramine** 25 mg daily, which persisted even after discontinuation of both drugs.[6]

Mechanism

In vitro studies[1,2] have shown that both bupropion and its active metabolite, hydroxybupropion, are inhibitors of CYP2D6, the isoenzyme involved in the metabolism of these tricyclics. Therefore concurrent use decreases the metabolism of the tricyclics and their levels rise.

Importance and management

Although clinical evidence for an interaction between the tricyclics and bupropion is limited, the rise in tricyclic levels is in line with the way both drugs are known to interact, and therefore an interaction would seem to be established. It would be prudent to be alert for increased tricyclic adverse effects if bupropion is also given, reducing the tricyclic dose as necessary.

Note that bupropion is predicted to increase the risk of seizures with tricyclics, and this effect is dose-related. See 'Bupropion + Miscellaneous', p.1468.

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Tricyclic antidepressants + Calcium-channel blockers

Diltiazem and verapamil can increase plasma imipramine levels, possibly accompanied by undesirable ECG changes. Two isolated reports describe increased nortriptyline and trimipramine levels in two patients given diltiazem.

Clinical evidence

(a) Imipramine

In a study, 12 healthy subjects were given a 7-day course of **verapamil** 120 mg every 8 hours and 13 healthy subjects were given a 7-day course of **diltiazem** 90 mg every 8 hours. The AUCs of a single 100-mg dose of imipramine given on day 4 were increased by 15% by **verapamil**, and by 30% by **diltiazem**. One hour after taking imipramine (2 hours after taking the calcium-channel blockers), the average PR interval was greater than 200 milliseconds, which represented first-degree heart block. Two subjects developed second-degree heart block after taking imipramine with **verapamil**.[1]

(b) Nortriptyline

A diabetic patient taking **nifedipine**, glipizide and aspirin started taking nortriptyline, and, at the same time, the **nifedipine** was replaced by **diltiazem**, initially 180 mg daily, then raised to 240 mg daily after a week. Several changes in the nortriptyline dosage were made over a 4-week period because its plasma levels became unexpectedly high (the ratio of plasma nortriptyline to its dosage were approximately doubled), which was attributed to the use of **diltiazem**.[2]

(c) Trimipramine

A depressed woman taking trimipramine 125 mg daily developed high plasma trimipramine levels of 546 micrograms/L while taking **diltiazem** 60 mg three times daily. Two weeks later the trimipramine levels reached 708 micrograms/L, despite a reduction in the trimipramine dose to 75 mg daily. She showed no toxicity and her ECG was normal.[3]

Mechanism

It has been suggested that diltiazem and verapamil increase the bioavailability of imipramine by decreasing its clearance. The ECG changes appear to result from the increased imipramine levels and the additive effects of both drugs on the atrioventricular conduction time. Diltiazem may similarly affect nortriptyline and trimipramine.

Importance and management

Information appears to be limited to these reports so that the general clinical importance of each of these interactions is uncertain. However it would seem prudent to be alert for evidence of increases in the adverse effects of the tricyclic antidepressants if diltiazem or verapamil is added. The evidence of heart block with imipramine and verapamil is of particular concern. Note that it has also been suggested that the postural hypotension that may occur in patients taking tricyclics could be exacerbated by the use of antihypertensives. Patients should be warned.

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Tricyclic antidepressants + Cannabis

Case reports describe tachycardia when patients taking tricyclic antidepressants smoked cannabis. Hypertension and drowsiness may occur when cannabinoids are used with tricyclics.

Clinical evidence

A 21-year-old woman taking **nortriptyline** 30 mg daily experienced marked tachycardia (an increase from 90 to 160 bpm) after smoking a cannabis cigarette. It was controlled with propranolol.[1] A 26-year-old man complained of restlessness, dizziness and tachycardia (120 bpm) after smoking cannabis while taking **imipramine** 25 mg twice daily.[2] Four adolescents aged 15 to 18 years, taking tricyclic antidepressants for attention-deficit hyperactivity disorder, experienced transient cognitive changes, delirium and tachycardia after smoking cannabis.[3]

Mechanism

Increased heart rates are well-documented adverse effects of both the tricyclic antidepressants and cannabis, and what occurred was probably due to the additive beta-adrenergic and antimuscarinic effects of the tricyclics, in combination with the beta-adrenergic effect of the cannabis.

Importance and management

Evidence for an interaction between cannabis and tricyclics appears to be limited. The manufacturer of **dronabinol**, a cannabinoid, notes that hypertension and drowsiness as well as tachycardia have been reported when cannabinoids have been used with tricyclics.[4] It would therefore seem that an interaction is established.

If concurrent use is undertaken, it would be prudent to be alert for these adverse effects, taking particular caution in those with underlying cardiac disease, which may make these effects more problematic.

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Tricyclic and related antidepressants + Carbamazepine

The serum levels of amitriptyline, desipramine, doxepin, imipramine, nortriptyline and mianserin can be reduced (halved or more) by carbamazepine. In contrast, raised clomipramine levels have been seen in patients taking carbamazepine. An isolated report describes carbamazepine toxicity in a patient shortly after she started to take desipramine.

Clinical evidence

(a) Carbamazepine levels increased

A woman receiving long-term treatment with carbamazepine developed toxicity (nausea, vomiting, blurred vision with visual hallucinations, slurred speech, ataxia) within 6 days of starting to take **desipramine** daily (3 days at 150 mg daily). Her carbamazepine levels were found to have doubled from 7.7 micrograms/mL to 15 micrograms/mL.[1]

(b) Tricyclic levels increased

A study confirming the value of carbamazepine and **clomipramine** in the treatment of post-herpetic neuralgia found that carbamazepine appeared to raise both clomipramine plasma levels and those of its major metabolite (desmethylclomipramine).[2]

(c) Tricyclic levels reduced

A study found that carbamazepine reduced the serum levels of **nortriptyline** by 58% and of **amitriptyline** plus its metabolite, nortriptyline, by 60% in 8 psychiatric patients. In 17 other patients carbamazepine reduced serum **doxepin** levels by 54% and reduced the levels of doxepin plus its metabolite, nordoxepin, by 55%.[3] A retrospective study of very large numbers of patients confirmed that carbamazepine approximately halves the serum levels of **amitriptyline** and **nortriptyline**.[4] An elderly woman needed her **nortriptyline** dosage to be increased from 75 to 150 mg daily to achieve effective antidepressant serum levels when carbamazepine 500 to 600 mg daily was added.[5]

A study in 36 children (aged 5 to 16 years) with attention-deficit disorder taking **imipramine**, or **imipramine** and carbamazepine for 1 to 6 months, found that even though the **imipramine** dosage was significantly higher in the combined treatment group, the plasma levels were significantly lower; and the total plasma antidepressant levels were about half of those found in the children not taking carbamazepine.[6] A study[7] in 6 healthy subjects found that carbamazepine 200 mg twice daily for a month increased the apparent oral clearance of a single 100-mg dose of **desipramine** (given on day 24) by 31% and shortened its half-life from 22.1 hours to 17.8 hours. A patient given **desipramine** and carbamazepine is reported to have had exceptionally low serum desipramine levels and cardiac complaints, which may have been due to the presence of increased levels of the hydroxy metabolite of desipramine.[8]

A study in 13 patients with endogenous depression (DSM-III-R) taking **imipramine**, which confirmed that carbamazepine reduced the total serum levels of imipramine and desipramine, found that levels of the pharmacologically active free drugs remained unchanged.[9,10] Moreover 10 of the patients demonstrated a positive therapeutic response (greater than a 50% decrease in the Hamilton Depression Rating Scale) and a reduction in adverse drug reactions.[9]

A comparative study in 6 epileptics and 6 healthy subjects showed that phenytoin with either phenobarbital or carbamazepine markedly reduced the plasma levels of a single dose of **mianserin**.[11,12] The mean half-life of **mianserin** was reduced by 75% (from 16.9 hours to 4.8 hours) and the AUC was reduced by 86%. Another study in 4 patients found that carbamazepine reduced serum **mianserin** levels by 70%.[13] In another study 12 patients taking **mianserin** 60 mg daily were also given carbamazepine 400 mg daily for 4 weeks. Average plasma levels of total *S*-mianserin (the more potent enantiomer) and total *R*-mianserin were reduced by about 45% in the presence of carbamazepine.[14]

Mechanism

It seems likely that the carbamazepine (a recognised enzyme-inducing drug) increases the metabolism and loss of these tricyclics and mianserin from the body, thereby reducing their serum levels. The reason for the increased serum carbamazepine and clomipramine levels is not understood, although it has been suggested that both drugs may compete for hydroxylation by the hepatic microsomal enzyme system.[1,2] In addition, they both share a similar 3-ringed structure, and carbamazepine has been reported to interfere with an assay (serum fluorescence-polarised immunoassay) for tricyclic antidepressants, resulting in false positive results.[15]

Importance and management

The reduction in the serum levels of amitriptyline, desipramine, doxepin, imipramine, nortriptyline and mianserin caused by the interaction with carbamazepine appears to be established but the clinical importance is very much less certain. Evidence from one study,[9] that achieved a beneficial response in patients taking tricyclics and carbamazepine, suggests that it is possibly not necessary to increase the tricyclic dosage to accommodate this interaction. The fact that a retrospective study found that increased imipramine doses were being given to those taking carbamazepine suggests that this interaction will be naturally accounted for. If carbamazepine is added to treatment with any of these tricyclics or mianserin, be aware that the dose of the tricyclic may need to be titrated up to achieve the desired therapeutic response. One study suggests that the dose of mianserin may need to be approximately doubled if carbamazepine 400 mg daily is added.[14]

Remember too that the tricyclics and mianserin can lower the convulsive threshold and should therefore be used with caution in patients with epilepsy.

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Tricyclic antidepressants + Cinacalcet

Cinacalcet causes a large increase in the levels of the tricyclic antidepressants.

Clinical evidence

A study in 14 healthy subjects found that cinacalcet 90 mg daily significantly increased the AUC and maximum plasma concentration of a single 50-mg dose of **desipramine** 3.6-fold and 1.8-fold, respectively, and the half-life of **desipramine** was approximately doubled.[1]

Mechanism

Cinacalcet is a potent inhibitor of the cytochrome P450 isoenzyme CYP2D6, by which desipramine is predominantly metabolised. Concurrent use therefore decreases desipramine metabolism, resulting in the raised levels seen.

Importance and management

An interaction between cinacalcet and desipramine is established, and would be expected to be clinically significant. Dose reductions of desipramine are likely to be needed if cinacalcet is also given. If starting desipramine in a patient taking cinacalcet it would seem prudent to start at the lowest dose and titrate upwards carefully. If both drugs are given, monitor closely for adverse effects such as dry mouth, urinary retention and constipation.

There seems to be no evidence regarding other tricyclics, but as they are, in general, predominantly metabolised by CYP2D6, they would be expected to interact similarly. Therefore the same precautions suggested for desipramine would be advisable.

Note that, the tricyclics have been associated with QT prolongation, most usually when their levels are high, and this interaction may therefore increase the risk of this effect. See 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290, for further discussion on QT prolongation.

1. Harris RZ, Salfi M, Posvar E, Hoelscher D, Padhi D. Pharmacokinetics of desipramine HCl when administered with cinacalcet HCl. *Eur J Clin Pharmacol* (2007) 63, 159–63.

Tricyclic antidepressants + Colestyramine

Colestyramine causes a modest reduction in the plasma levels of imipramine. A case report suggests that doxepin may be similarly affected, and *in vitro* evidence suggests that amitriptyline, desipramine and nortriptyline are also likely to be similarly affected.

Clinical evidence

Six patients with depression taking **imipramine** 75 to 150 mg, usually twice daily, were given colestyramine 4 g three times daily for 5 days. The plasma levels of **imipramine** fell by an average of 23% (range 11 to 30%) and the plasma levels of desipramine (the major metabolite) were reduced, although this was less consistent and said not to be statistically significant. The effect of these reduced levels on the control of the depression was not assessed.[1]

A man whose depression was controlled with **doxepin** relapsed within a week of starting to take colestyramine 6 g twice daily. Within 3 weeks of increasing the dosage separation of the two drugs from 4 to 6 hours his combined serum antidepressant levels (i.e. **doxepin** plus the metabolite *n*-desmethyldoxepin) had risen from 39 nanograms/mL to 81 nanograms/mL and his depression had improved. Reducing the colestyramine to a single 6-g dose daily, separated from the **doxepin** by 15 hours, resulted in a further rise in his serum antidepressant levels, to 117 nanograms/mL, which was accompanied by relief of his depression.[2]

Mechanism

It seems almost certain that these tricyclics become bound to the colestyramine (an anion-exchange resin) within the gut, thereby reducing their absorption. An *in vitro* study[3] with simulated gastric fluid found that, at pH 1, **amitriptyline**, **desipramine**, doxepin, imipramine and **nortriptyline** were approximately 79 to 90% bound by colestyramine: at pH 4 they were 36 to 48% bound and at pH 6.5 they were 62 to 76% bound. In an earlier study,[4] binding of these tricyclics at pH 1 had ranged from 76 to 100%.

Importance and management

The interaction between imipramine and colestyramine is established, but of uncertain clinical importance because the fall in the plasma imipramine levels quoted above was only modest (23%) and the effects were not measured. The single case involving doxepin[2] was unusual because the patient had an abnormal gastrointestinal tract (hemigastrectomy with pyloroplasty and chronic diarrhoea). Nevertheless, given the way colestyramine is generally known to interact, it would seem prudent to be alert for any evidence of a reduced antidepressant response if colestyramine is given with any tricyclic. A simple way of minimising any interaction is to separate administration, and it is usually suggested that other drugs should be given one hour before or 4 to 6 hours after colestyramine.

1. Spina E, Avenoso A, Campo GM, Caputi AP, Perucca E. Decreased plasma concentrations of imipramine and desipramine following cholestyramine intake in depressed patients. *Ther Drug Monit* (1994) 16, 432–4.
2. Geeze DS, Wise MG, Stigelman WH. Doxepin-cholestyramine interaction. *Psychosomatics* (1988) 29, 233–6.
3. Bailey DN. Effect of pH changes and ethanol on the binding of tricyclic antidepressants to cholestyramine in simulated gastric fluid. *Ther Drug Monit* (1992) 14, 343–6.
4. Bailey DN, Coffee JJ, Anderson B, Manoguerra AS. Interactions of tricyclic antidepressants with cholestyramine in vitro. *Ther Drug Monit* (1992) 14, 339–42.

Tricyclic and related antidepressants + Co-trimoxazole

In isolated cases the efficacy of tricyclic antidepressants and viloxazine appears to have been reduced by co-trimoxazole.

Clinical evidence, mechanism, importance and management

Four patients taking tricyclic antidepressants (**imipramine**, **clomipramine**, **dibenzepin**) and one taking **viloxazine** relapsed into depression when they took co-trimoxazole (trimethoprim with sulfamethoxazole) for 2 to 9 days.[1] Another patient taking alprazolam and **imipramine** for 5 years for panic disorder, and who had not had panic attacks for several months, developed insomnia, anxiety and panic attacks within 6 days of starting to take co-trimoxazole. The panic attacks stopped when she stopped taking co-trimoxazole.[2]

The reason for the reduction in the efficacy of treatment is not known. In the second case, one possibility was that co-trimoxazole, which may cause nervousness, had exacerbated the panic disorder.[2] These seem to be the only reports of a possible interaction between these drugs so that the general importance is uncertain. It seems likely to be small.

1. Brion S, Orssaud E, Chevalier JF, Plas J, Waroquaux O. Interaction entre le cotrimoxazole et les antidépresseurs. *Encephale* (1987) 13, 123–6.
2. Zealberg JJ, Lydiard RB, Christie S. Exacerbation of panic disorder in a woman treated with trimethoprim-sulfamethoxazole. *J Clin Psychopharmacol* (1991) 11, 144–5.

Tricyclic antidepressants + Cyclobenzaprine

Episodes of fainting in a patient may have been due to raised levels of nortriptyline, which were thought to have been caused by cyclobenzaprine.

Clinical evidence, mechanism, importance and management

A patient taking multiple medications, including citalopram, **nortriptyline** 100 mg at bedtime for pain and insomnia, and cyclobenzaprine 60 to 80 mg daily for pain, reported light-headedness and fainting episodes. Toxicology screens also found he had taken cocaine. **Nortriptyline** levels of 406 nanograms/mL (above the therapeutic range of 50 to 150 nanograms/mL) were found. The **nortriptyline** dose was halved to 50 mg daily and then discontinued; levels of 631 nanograms/mL and 400 nanograms/mL were found after 3 and 4 weeks, respectively. The episodes of syncope/presyncope only stopped when cyclobenzaprine was also discontinued.

Due to the complexities of the case, various causes including arrhythmias, cardiac ischaemia, seizures, orthostasis and anxiety were considered. The patient had previously experienced syncopal episodes attributed to misuse of prescription drugs, apparently including **nortriptyline**. It was considered that the symptoms could have been due to increased levels of **nortriptyline** in the presence of cyclobenzaprine, as well as to effects of cyclobenzaprine.[1]

While taking both drugs the patient experienced considerable fluctuations in his **nortriptyline** levels, which may have been due to an interaction with cyclobenzaprine. However, cyclobenzaprine is structurally related to the tricyclic antidepressants and may interfere with assays for tricyclics; indeed, as a serum **nortriptyline** level was reported as 378 nanograms/mL, several months after nortriptyline had been discontinued, and a re-evaluation using a high-performance liquid chromatographic (HPLC) assay revealed the patient's nortriptyline level to be 0, an interference of cyclobenzaprine with the assay method is possible in this case.[1]

This is an isolated case, with many complicating factors, so an interaction is by no means established.

1. Rosenlicht NZ, Riley-Lazo KP. Interactions of cyclobenzaprine and tricyclic antidepressants. *J Clin Psychiatry* (2005) 66, 134–5.

Tricyclic antidepressants + Disulfiram

Disulfiram reduces the clearance of imipramine and desipramine. The concurrent use of amitriptyline and disulfiram has been reported to cause a therapeutically useful increase in the effects of disulfiram but 'organic brain syndrome' has been seen in two patients.

Clinical evidence, mechanism, importance and management

It has been noted that **amitriptyline** increases the effects of both disulfiram and citrated **calcium carbimide** without any increase in adverse effects.[1] A study in two men found that disulfiram 500 mg daily increased the AUC of **imipramine** (12.5 mg given intravenously after an overnight fast) by about 30%, and of **desipramine** 12.5 mg given intravenously in one subject by a similar amount.[2] Peak plasma levels were also increased.

The suggested reason for this increase in tricyclic levels is that disulfiram inhibits the metabolism of the antidepressants by the liver. The increase in tricyclic levels is modest and would not normally be expected to lead to an increase in adverse effects. However, a case report describes a man taking disulfiram who, when given **amitriptyline**, complained of dizziness, visual and auditory hallucinations, and who became disorientated to person, place and time. A similar reaction was seen in another patient.[3]

It seems unlikely that most patients will experience a clinically relevant interaction. Nevertheless, the case reports introduce a note of caution. If tricyclic adverse effects (e.g. dry mouth, urinary retention, constipation) become troublesome, it would seem worth considering this interaction as a possible cause.

1. MacCallum WAG. Drug interactions in alcoholism treatment. *Lancet* (1969) i, 313.
2. Ciraulo DA, Barnhill J, Boxenbaum H. Pharmacokinetic interaction of disulfiram and antidepressants. *Am J Psychiatry* (1985) 142, 1373–4.
3. Maany I, Hayashida M, Pfeffer SL, Kron RE. Possible toxic interaction between disulfiram and amitriptyline. *Arch Gen Psychiatry* (1982) 39, 743–4.

Tricyclic antidepressants + Fenfluramine

It has been said that the concurrent use of tricyclics and fenfluramine is safe and effective; however, others have suggested that, as fenfluramine can cause depression, it should be avoided in patients with a history of depression.

Clinical evidence, mechanism, importance and management

Exacerbation of depression has been seen in some patients given fenfluramine[1] and several cases of withdrawal depression have been seen in patients taking amitriptyline and fenfluramine, following episodes of severe depression.[2] The manufacturers did advise that fenfluramine should not be used in patients with a history of depression or in those being treated with antidepressants.[3] On the other hand it has been also claimed that fenfluramine could be used safely and effectively with tricyclic antidepressants.[4,5] One report described a rise in the plasma levels of amitriptyline when fenfluramine 60 mg daily was given to patients taking amitriptyline 150 mg daily.[6]

Note that fenfluramine was widely withdrawn in 1997 because its use was found to be associated with a high incidence of abnormal echocardiograms indicating abnormal functioning of heart valves.

1. Gaind R. Fenfluramine (Ponderax) in the treatment of obese psychiatric out-patients. *Br J Psychiatry* (1969) 115, 963–4.
2. Harding T. Fenfluramine dependence. *BMJ* (1971) 3, 305.
3. ABPI Data Sheet Compendium, 1998–99 p 1307. Datapharm publications, London.
4. Pinder RM, Brogden RN, Sawyer PR, Speight TM, Avery GS. Fenfluramine: a review of its pharmacological properties and therapeutic efficacy in obesity. *Drugs* (1975) 10, 241–323.
5. Mason EC. Servier Laboratories Ltd. Personal Communication, February 1976.
6. Gunne L-M, Antonijevic S, Jonsson J. Effect of fenfluramine on steady state plasma levels of amitriptyline. *Postgrad Med J* (1975) 51 (Suppl 1), 117.

Tricyclic antidepressants + Flupentixol and related drugs

Flupentixol did not appear to inhibit the metabolism of imipramine in two patients but high levels of imipramine and its metabolite, desipramine, were found in another patient. In a retrospective study, zuclopenthixol did not seem to affect serum concentrations of tricyclic antidepressants.

Clinical evidence

A study using oral ^{14}C-**imipramine** found that flupentixol 3 to 6 mg daily did not decrease the total urinary excretion of radioactivity in 2 patients, suggesting that the metabolism of **imipramine** was not affected by flupentixol.[1] However, there is an isolated report of very high plasma levels of **imipramine** and its metabolite desipramine in a patient with schizophrenia who was given flupentixol decanoate 40 mg intramuscularly every 2 weeks and **imipramine** 150 mg daily. It was suggested that this may have resulted from competitive inhibition of liver enzymes.[2]

Using data from a drug monitoring database, the steady-state concentration/dose ratios for **amitriptyline** and/or **nortriptyline** in 50 patients also taking zuclopenthixol were compared with 206 patients taking amitriptyline and 444 patients taking nortriptyline but not taking potentially interacting drugs. Zuclopenthixol did not appear to affect **amitriptyline** or **nortriptyline** serum concentrations under routine therapeutic drug monitoring.[3]

Mechanism

Zuclopenthixol and flupentixol are partly metabolised by the cytochrome P450 isoenzyme CYP2D6. Many of the tricyclics are also metabolised by this isoenzyme, but this does not appear to lead to an interaction.

Importance and management

The interaction between flupentixol and imipramine is an isolated case and its general significance is unknown. The studies with flupentixol and zuclopenthixol suggest that, in general, a clinically significant pharmacokinetic interaction does not occur with the tricyclics. Nevertheless, the manufacturer of both flupentixol and zuclopenthixol has suggested that the metabolism of tricyclic antidepressants may be inhibited by these drugs.[4,5] Note that zuclopenthixol, flupentixol and the tricyclic antidepressants

have some antimuscarinic activity, which may lead to a pharmacological interaction, see 'Antipsychotics + Antimuscarinics', p.833.

1. Gram LF, Overø KF. Drug interaction: inhibitory effect of neuroleptics on metabolism of tricyclic antidepressants in man. *BMJ* (1972) 1, 463–5.
2. Cook PE, Dermer SW, Cardamone J. Imipramine-flupenthixol decanoate interaction. *Can J Psychiatry* (1986) 31, 235–7.
3. Linnet K. Comparison of the kinetic interactions of the neuroleptics perphenazine and zuclopenthixol with tricyclic antidepressives. *Ther Drug Monit* (1995) 17, 308–11.
4. Depixol Tablets (Flupentixol dihydrochloride). Lundbeck Ltd. UK Summary of product characteristics, November 2008.
5. Clopixol Tablets (Zuclopenthixol dihydrochloride). Lundbeck Ltd. UK Summary of product characteristics, March 2009.

Tricyclic antidepressants + Food

Limited evidence suggests that very high-fibre diets can reduce the serum levels of doxepin and desipramine, and therefore decrease their effects. The bioavailability of amitriptyline may be affected by food. An isolated report describes urticaria attributed to a possible drug-food interaction between clomipramine and cod.

Clinical evidence, mechanism, importance and management

Three patients had no response to **doxepin** or **desipramine** and had reduced serum tricyclic antidepressant levels while taking very high-fibre diets (wheat bran, wheat germ, oat bran, rolled oats, sunflower seeds, coconut shreds, raisins, bran muffins). When the diet was changed or stopped, the serum tricyclic antidepressant levels rose and the depression was relieved.[1] The reasons for this effect are not known. This interaction may possibly provide an explanation for otherwise unaccountable relapses or inadequate responses to tricyclic antidepressant treatment.

Another study in 12 healthy subjects found that breakfast had no effect on the bioavailability of a 50-mg dose of **imipramine**, or on its peak levels or the time to peak levels.[2] A study in 9 healthy subjects given a single 25-mg dose of **amitriptyline** in the fasting state and with a standardised breakfast found that there were no consistent changes in the bioavailability of **amitriptyline** or its main metabolite nortriptyline. Similar results were found in a parallel study in which the same subjects were given a single 25-mg dose of **nortriptyline**. However, there were large interindividual changes in the AUC of **amitriptyline** after food, ranging from an increase of 94% to a decrease of about 40%. The largest food-related **amitriptyline** AUC *increases* occurred among the subjects with the lowest fasting AUC values and the only major food-related *decrease* occurred in the subject with the largest fasting AUC. It was concluded that for an individual patient, the timing of **amitriptyline** administration in relation to food intake should be standardised to avoid large variations in drug levels.[3]

An isolated report describes a severe generalised urticaria that occurred after the ingestion of **cod** by a 33-year-old woman treated with **clomipramine** 100 mg daily. Clomipramine was gradually discontinued and the rash improved. Her antidepressant was changed to paroxetine and she then ate cod without developing any adverse effects. Furthermore, rechallenge with **clomipramine** did not induce any adverse events, but when she was rechallenged with **clomipramine** and cod, the urticaria was again observed. Ingestion of other fish during **clomipramine** treatment did not induce an effect.[4] This appears to be an isolated report. Its general relevance is therefore probably small.

1. Stewart DE. High-fiber diet and serum tricyclic antidepressant levels. *J Clin Psychopharmacol* (1992) 12, 438–40.
2. Abernethy DR, Divoll M, Greenblatt DJ, Shader RI. Imipramine pharmacokinetics and absolute bioavailability: effect of food. *Clin Res* (1983) 31, 626A.
3. Liedholm H, Lidén A. Food intake and the presystemic metabolism of single doses of amitriptyline and nortriptyline. *Fundam Clin Pharmacol* (1998) 12, 636–42.
4. Gallelli L, De Fazio S, Corace E, De Sarro G, Garcia CS, De Fazio P. Generalised urticaria in a young woman treated with clomipramine and after ingestion of codfish. *Pharmacopsychiatry* (2006) 39, 154–6.

Tricyclic antidepressants + Furazolidone

An isolated report describes the development of toxic psychosis, hyperactivity, sweating and hot and cold flushes when a woman taking amitriptyline also took furazolidone and diphenoxylate with atropine.

Clinical evidence, mechanism, importance and management

A depressed woman taking conjugated oestrogens 1.25 mg daily and **amitriptyline** 75 mg daily, was also given furazolidone 300 mg daily and diphenoxylate with atropine sulfate. Two days later she began to experience blurred vision, profuse perspiration followed by alternate chills and hot flushes, restlessness, motor activity, persecutory delusions, auditory hallucinations and visual illusions. The symptoms cleared within a day of stopping the furazolidone.[1] The reasons for this reaction are not understood but the authors point out that furazolidone has MAO-inhibitory properties and that the symptoms were similar to those seen when the tricyclic antidepressants and MAOIs interact. However the MAO-inhibitory activity of furazolidone normally develops over several days. Whether the concurrent use of atropine and **amitriptyline** (both of which have antimuscarinic activity) had some part to play in the reaction is uncertain. No firm conclusions can be drawn from this slim evidence, but clinicians should be aware of this case when considering the concurrent use of any tricyclic antidepressant and furazolidone.

1. Aderhold RM and Muniz CE. Acute psychosis with amitriptyline and furazolidone. *JAMA* (1970) 213, 2080.

Tricyclic antidepressants + Grapefruit juice

Grapefruit juice did not appear to have a clinically significant effect on amitriptyline or clomipramine levels in one study. However, an isolated report describes increased clomipramine levels when two children were also given grapefruit juice.

Clinical evidence, mechanism, importance and management

A study in 6 patients given **clomipramine** 112.5 to 225 mg daily found that grapefruit juice 250 mL increased the mean plasma levels of **clomipramine** and its metabolite, desmethylclomipramine, by 4.5% and 10.5%, respectively. In another 7 patients taking **amitriptyline** 100 to 150 mg daily grapefruit juice did not affect the plasma levels of the tricyclic.[1] However, an isolated report describes an 8-year-old boy with Tourette's syndrome and obsessive-compulsive disorder who had minimal improvement when taking **clomipramine** 25 mg three times daily for 3 months. He was additionally given 250 mL of frozen concentrate grapefruit juice with each dose of **clomipramine** and, after 3 days, his trough blood levels of clomipramine had risen from 73 nanograms/mL to 198 nanograms/mL and those of the desmethylclomipramine had risen from 144 nanograms/mL to 233 nanograms/mL, and a clinical improvement was seen. **Clomipramine** levels were also increased in a 13-year-old girl, with an autistic spectrum disorder, when grapefruit juice was added to each dose of clomipramine, but no clinical improvement was seen.[2]

The studies (and the known metabolic pathways of the tricyclics, see 'Table 35.2', (p.1465)) suggest that an interaction with grapefruit juice is unlikely. Just why the levels were raised in the children is unclear. Dose adjustments of the tricyclics would generally not be expected to be necessary in those who drink grapefruit juice.

1. Vandel P, Regina W, Reix I, Vandel S, Sechter D, Bizouard P. Faut-il contre-indiquer le jus de pamplemousse? Une approche en psychiatrie. *Encephale* (1999) 25, 67–71.
2. Oesterheld J, Kallepalli BR. Grapefruit juice and clomipramine: shifting metabolic ratios. *J Clin Psychopharmacol* (1997) 17, 62–3.

Tricyclic antidepressants + Haloperidol and related drugs

Serum desipramine levels can be increased by haloperidol. This may have caused a grand mal seizure in one case but toxic reactions appear to be uncommon. Desipramine and bromperidol appear not to interact.

Clinical evidence

(a) Bromperidol

When 13 patients with schizophrenia taking bromperidol 12 to 24 mg daily for 1 to 20 weeks were also given **desipramine** 50 mg daily for a week, bromperidol plasma levels remained unchanged and no adverse clinical events were seen.[1]

(b) Haloperidol

1. Desipramine. A comparative study in patients taking similar doses of desipramine (2.5 to 2.55 mg/kg) found that the two patients also taking haloperidol had steady-state plasma desipramine levels that were more than double those of 15 other patients not taking haloperidol (255 nanograms/mL compared with 110 nanograms/mL).[2]

A case report describes a patient who had a grand mal seizure when taking desipramine with haloperidol. Her serum desipramine levels were unusually high, at 610 nanograms/mL.[3]

2. Imipramine. The urinary excretion of a test dose of ^{14}C-imipramine given to two patients with schizophrenia patients was reduced by about 35 to 40% when they took haloperidol 12 to 20 mg daily.[4] The plasma metabolite levels of ^{14}C-nortriptyline of another patient with schizophrenia fell when haloperidol 16 mg daily was taken, whereas the plasma levels of unchanged nortriptyline rose.[5]

Mechanism

Haloperidol reduces the metabolism of the tricyclic antidepressants, thereby reducing their clearance, which results in a rise in their plasma levels.

Importance and management

The interaction between the tricyclic antidepressants and haloperidol is established though its documentation is sparse. Concurrent use is common whereas adverse reactions are not, but be aware that serum desipramine levels may be elevated. This may have been the cause of the grand mal seizure in the case cited.[3] Imipramine appears to interact similarly. Monitor the outcome if haloperidol is added to established treatment with tricyclic antidepressants.

Note that bromperidol and haloperidol prolong the QT-interval, and this effect has been seen with tricyclics, usually in overdose, see 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290. Also, the concurrent use of antipsychotics and drugs with antimuscarinic effects, including tricyclic antidepressants, has led to severe adverse effects, see also, 'Antipsychotics + Antimuscarinics', p.833.

1. Suzuki A, Otani K, Ishida M, Yasui N, Kondo T, Mihara K, Kaneko S, Inoue Y. No interaction between desipramine and bromperidol. *Prog Neuropsychopharmacol Biol Psychiatry* (1996) 20, 1265–71.
2. Nelson JC, Jatlow PI. Neuroleptic effect on desipramine steady-state plasma concentrations. *Am J Psychiatry* (1980) 137, 1232–4.
3. Mahr GC, Berchou R, Balon R. A grand mal seizure associated with desipramine and haloperidol. *Can J Psychiatry* (1987) 32, 463–4.
4. Gram LF, Overø KF. Drug interaction: inhibitory effect of neuroleptics on metabolism of tricyclic antidepressants in man. *BMJ* (1972) 1, 463–5.
5. Gram LF, Overø KF, Kirk L. Influence of neuroleptics and benzodiazepines on metabolism of tricyclic antidepressants in man. *Am J Psychiatry* (1974) 131, 863–6.

Tricyclic antidepressants + H_2-receptor antagonists

Cimetidine can raise the plasma levels of amitriptyline, desipramine, doxepin, imipramine and nortriptyline. Other tricyclic antidepressants are expected to interact similarly. Ranitidine does not appear to interact with the tricyclics.

Clinical evidence

(a) Amitriptyline

A group of healthy subjects took **cimetidine** 300 mg every 6 hours for 4 days, with a single 25-mg dose of amitriptyline on day 3. The peak plasma levels and the AUC of amitriptyline were raised by 37% and 80%, respectively, but the levels of nortriptyline (a metabolite of amitriptyline) were reduced.[1]

Another study by the same authors found that **ranitidine** does not interact with amitriptyline.[2]

(b) Desipramine

In a study in 8 patients, **cimetidine** 1 g daily for 4 days raised the plasma levels of desipramine 100 to 250 mg daily by 51%, and raised the levels of its hydroxylated metabolite (2-hydroxydesipramine) by 46%.[3] Another study suggests that this interaction does not occur in those individuals who have low levels or are completely lacking CYP2D6.[4]

(c) Doxepin

A study in 10 healthy subjects given a single 100-mg oral dose of doxepin 12 hours after starting to take **cimetidine** 300 mg every 6 hours found that the peak plasma level and AUC of doxepin were raised by 28% and 31%, respectively.[5]

In another study, **cimetidine** 600 mg twice daily was found to double the steady-state plasma levels of doxepin 50 mg daily, whereas **ranitidine** 300 mg daily had no effect on doxepin levels.[6] A patient taking doxepin complained that the normally mild adverse effects (urinary hesitancy, dry mouth and decreased visual acuity) became incapacitating when he also took **cimetidine**. His serum doxepin levels were found to be elevated in the presence of cimetidine.[7]

(d) Imipramine

In 12 healthy subjects, **cimetidine** 300 mg every 6 hours for 3 days raised the peak plasma levels and the AUC of a single 100-mg dose of imipramine by 65% and 172%, respectively. After taking **ranitidine** 150 mg twice daily for 3 days the pharmacokinetics of imipramine were unaltered.[8] These findings with **cimetidine** confirm those of previous studies.[9,10]

There are case reports of patients taking imipramine who developed severe antimuscarinic adverse effects (dry mouth, urine retention, blurred vision), associated with very marked rises in serum imipramine levels, when they also took **cimetidine**.[11,12]

(e) Nortriptyline

In a study in 6 healthy subjects, **cimetidine** 300 mg four times daily for 2 days did not affect the peak plasma levels of nortriptyline, but its AUC was increased by 20%.[9]

A case report describes a patient whose serum nortriptyline levels were raised about one-third while taking **cimetidine**.[13] Another patient complained of abdominal pain and distension (but no other antimuscarinic adverse effects) when taking nortriptyline and **cimetidine**.[14]

Mechanism

Cimetidine is a non-specific enzyme inhibitor, which reduces the metabolism of the tricyclic antidepressants, and may also reduce the hepatic clearance of these drugs. This results in a rise in their plasma levels. Ranitidine does not interact because it is not an enzyme inhibitor.

Importance and management

The interactions of the tricyclics with cimetidine are well established, well documented and of clinical importance. The incidence is uncertain but most patients could be affected. Those taking amitriptyline, desipramine, doxepin, imipramine or nortriptyline who are given cimetidine should be warned that adverse effects such as dry mouth, urinary retention, blurred vision, constipation, tachycardia, and postural hypotension may be more likely to occur. Other tricyclic antidepressants would be expected to be similarly affected. If symptoms are troublesome reduce the dosage of the antidepressant (33 to 50% has been suggested) or replace the cimetidine with ranitidine, which does not appear to interact. Other H_2-receptor antagonists that do not cause enzyme inhibition (e.g. **famotidine** and **nizatidine**) would also not be expected to interact. Note that if cimetidine is discontinued, decreases in plasma levels of the tricyclic antidepressants may occur, which could result in loss of therapeutic efficacy.

Note that, the tricyclics have been associated with QT prolongation, most usually when their levels are high, and this interaction may therefore increase the risk of this effect. See 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290, for further discussion on QT prolongation.

1. Curry SH, DeVane CL, Wolfe MM. Cimetidine interaction with amitriptyline. *Eur J Clin Pharmacol* (1985) 29, 429–33.
2. Curry SH, DeVane CL, Wolfe MM. Lack of interaction of ranitidine with amitriptyline. *Eur J Clin Pharmacol* (1987) 32, 317–20.
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8. Wells BG, Pieper JA, Self TH, Stewart CF, Waldon SL, Bobo L, Warner C. The effect of ranitidine and cimetidine on imipramine disposition. *Eur J Clin Pharmacol* (1986) 31, 285–90.

9. Henauer SA, Hollister LE. Cimetidine interaction with imipramine and nortriptyline. *Clin Pharmacol Ther* (1984) 35, 183–7.
10. Abernethy DR, Greenblatt DJ, Shader RI. Imipramine-cimetidine interaction: impairment of clearance and enhanced absolute bioavailability. *J Pharmacol Exp Ther* (1984) 229, 702–705.
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Tricyclic and related antidepressants + Inotropes and Vasopressors

Patients taking tricyclic antidepressants show a grossly exaggerated response (hypertension, cardiac arrhythmias, etc.) to parenteral noradrenaline (norepinephrine), adrenaline (epinephrine) and to a lesser extent to phenylephrine. Case reports suggest that this interaction only occurs rarely with local anaesthetics containing these vasoconstrictors. Evidence for or against a similar interaction with mianserin and maprotiline is sparse.
Case reports describe reduced action of ephedrine in patients taking tricyclic antidepressants or mianserin.

Clinical evidence

(a) Adrenaline (Epinephrine) or Noradrenaline (Norepinephrine)

The effects of intravenous infusions of noradrenaline were increased about ninefold, and of adrenaline about threefold, in 6 healthy subjects who had been taking **protriptyline** 60 mg daily for 4 days.[1,2]

Similarly, the pressor effects of intravenous infusions of noradrenaline were increased four to eightfold, and of adrenaline two to fourfold in 4 healthy subjects who had been taking **imipramine** 75 mg daily for 5 days. Some potentiation of adrenaline-induced tachycardia occurred in one subject and striking changes in heart rhythm occurred in all 4 subjects.[3]

Five patients taking **nortriptyline**, **desipramine** or other unnamed tricyclic antidepressants experienced adverse reactions, some of them severe (throbbing headache, chest pain) following the injection of *Xylestesin* (lidocaine with 1:25 000 noradrenaline) during dental treatment.[4] Several episodes of marked increases in blood pressure, dilated pupils, intense malaise, violent but transitory tremor, and palpitations have been reported in patients taking unnamed tricyclic antidepressants when they were given local anaesthetics containing adrenaline or noradrenaline for dental treatment.[5]

There are other reports describing this interaction between:

- adrenaline with **amitriptyline**[6] and **nortriptyline**[7]
- noradrenaline with **amitriptyline**,[8,9] **clomipramine**,[10] **desipramine**,[8,9] **imipramine**[8,10,11] and **protriptyline**[9]

In contrast, in 5 healthy subjects taking **maprotiline**[12] and 5 patients with depression taking **mianserin**,[13] the pressor response to noradrenaline remained largely unchanged. However, a case report describes a 71-year-old woman who had been taking **mianserin** long-term who developed hypotension, following spinal anaesthesia and general anaesthesia, which was refractory to multiple boluses of ephedrine. However, her blood pressure increased excessively following a small dose of adrenaline.[14]

(b) Ephedrine

An elderly woman taking **amitriptyline** 75 mg daily developed hypotension (70 mmHg systolic) during subarachnoid anaesthesia, but her blood pressure rose only minimally when she was given intravenous boluses of ephedrine totalling 90 mg.[15] Similarly, in another patient receiving long-term **amitriptyline**, hypotension occurred during combined general and epidural anaesthesia, which was refractory to high doses of ephedrine, but control was achieved with noradrenaline.[16] Other reports describe hypotension refractory to ephedrine in patients receiving long-term **imipramine** and **lofepramine**,[17] or **mianserin**.[14]

(c) Isoprenaline (Isoproterenol)

In a study in 4 healthy subjects who had been taking **imipramine** 75 mg daily for 5 days, there were no noticeable or consistent changes in the response of blood pressure to isoprenaline and no abnormalities of heart rhythm were seen, but in one of the subjects there was a potentiation of isoprenaline-induced tachycardia.[3]

A case report describes a 30-year old woman with asthma who died due to aspiration of gastric contents in response to a cardiac arrhythmia following the use of an isoprenaline aerosol whilst taking **amitriptyline**; she was also taking other drugs including theophylline, ephedrine and phenobarbital.[18]

(d) Phenylephrine

The pressor effects of intravenous infusions of phenylephrine were increased two to threefold in 4 healthy subjects who had been taking **imipramine** 75 mg daily for 5 days.[3]

(e) Tyramine

The pressor response to tyramine was inhibited in 20 patients taking **clomipramine**,[19] and in patients (number not stated) taking **amitriptyline** 150 mg.[20] In 5 healthy subjects taking **maprotiline**, the pressor response to tyramine was reduced threefold.[12] The tyramine-response was unchanged by **mianserin**.[20-22]

Mechanism

The tricyclics and some related antidepressants block or inhibit the uptake of noradrenaline into adrenergic neurones. Thus the most important means by which noradrenaline is removed from the adrenoceptor area is inactivated and the concentration of noradrenaline outside the neurone can rise. If more noradrenaline (or one of the other directly-acting alpha or alpha/beta agonists i.e. adrenaline, phenylephrine) is then given, the adrenoceptors of the cardiovascular system concerned with raising blood pressure and/or cardiac rate and rhythm become grossly stimulated by this superabundance of amines, and the normal response becomes exaggerated. Mianserin, unlike the tricyclics, does not prevent the peripheral uptake of noradrenaline, and this may explain why it appears to interact somewhat differently in some cases.

Tyramine, and to some extent ephedrine, exerts its effects on blood pressure by causing the release of noradrenaline from adrenergic neurones. In the presence of a tricyclic antidepressant, the uptake of these amines into adrenergic neurones is partially or totally prevented and the noradrenaline-releasing effects are therefore blocked.[19] Consequently the effects of these drugs (and therefore probably other indirectly-acting sympathomimetics) might be expected to be reduced by tricyclic antidepressants.

For a categorisation of sympathomimetic drugs, see 'Table 24.1', (p.1048).

Importance and management

A well documented, well established and potentially serious interaction. The parenteral use of noradrenaline, adrenaline, phenylephrine or any other sympathomimetic amines with predominantly direct activity should be avoided in patients taking tricyclic antidepressants. If these inotropes must be used, the rate and amount injected must be very much reduced to accommodate the exaggerated responses that will occur. Evidence for a similar interaction with maprotiline and mianserin is sparse, but maprotiline is known to have the same effects on noradrenaline as the tricyclics, and a case report describes a similar interaction between adrenaline and mianserin, so some caution seems prudent.

The situation where adrenaline or noradrenaline are used with a local anaesthetic for surface or infiltration anaesthesia, or nerve block is less clear. The cases cited are all from the 1960s or 1970s, and the preparations concerned contained concentrations of adrenaline or noradrenaline several times greater than those used currently. However, it should be noted that preparations such as *Xylocaine* with adrenaline still carry a caution about their use with tricyclic antidepressants.[23] Anecdotal evidence suggests that local anaesthetics containing sympathomimetics are, in practice, commonly used in patients receiving tricyclic antidepressants,[24] so the scarcity of reports, especially recent ones, would add weight to the argument that the interaction is only rarely significant. However, it would still seem advisable to be aware of the potential for interaction. Aspiration has been recommended to avoid inadvertent intravenous administration. **Felypressin** has been shown to be a safe alternative.[25-27] If an adverse interaction occurs it can be controlled by the use of an alpha-receptor blocker, such as phentolamine.

Phenylephrine can be absorbed systemically from the eye and one manufacturer has contraindicated the use of phenylephrine eye drops in patients receiving tricyclic antidepressants, or within several days or their discontinuation, because the pressor response to adrenergic agents and the risk of cardiac arrhythmia may be potentiated.[28] However, it does not seem to have been established whether the response to oral doses or nasal

drops containing phenylephrine is enhanced by the presence of a tricyclic. Nevertheless, some caution seems prudent.

The effects of indirectly-acting sympathomimetics are expected to be reduced by tricyclic antidepressants, but there appear to be only a few reports of reduced efficacy of ephedrine, which has mixed indirect and direct sympathomimetic actions.

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Tricyclic antidepressants + Macrolides

Troleandomycin increases the plasma levels of imipramine, and an isolated report suggests that josamycin may possibly increase amitriptyline levels. Erythromycin may possibly raise clomipramine levels, but was not found to interact with other tricyclic antidepressants in one study.

Clinical evidence, mechanism, importance and management

(a) Erythromycin

Erythromycin 250 mg four times daily for 6 days was found not to affect the tricyclic antidepressant levels of 8 patients taking **desipramine**, **imipramine**, **doxepin**, or **nortriptyline**.[1] Behavioural changes have been reported in a 15-year-old patient when erythromycin was added to a regimen of **clomipramine** and risperidone,[2] resulting in symptoms compatible with serotonin syndrome, although mental confusion and autonomic instability were absent.[3] It was suggested that erythromycin increased **clomipramine** levels by inhibiting its metabolism by the cytochrome P450 isoenzyme CYP3A4.[4] **Clomipramine** levels may also have been raised by competition with risperidone for metabolism by CYP2D6.

In general, no interaction would be expected between the tricyclics and erythromycin; the isolated report seems unlikely to be of general significance.

(b) Josamycin

A patient taking **amitriptyline** had a marked increase in the total serum levels of **amitriptyline** and its metabolite, nortriptyline, after taking josamycin but no toxicity was reported. It was suggested that josamycin had inhibited **amitriptyline** metabolism.[5] This is an isolated case and although its general significance is unknown, it seems likely to be small.

(c) Troleandomycin

A study in 9 healthy Chinese men found that when they were given troleandomycin 250 mg daily for 2 days before a single 100-mg oral dose of **imipramine**, the AUC of the **imipramine** was increased by 59% and its oral clearance was reduced by 30%. It is thought that troleandomycin inhibits the *N*-demethylation of **imipramine** by inhibiting the cytochrome P450 isoenzyme subfamily CYP3A.[6] The clinical importance of this interaction is uncertain, but it may be prudent to be alert for increased antimuscarinic adverse effects (e.g. dry mouth, blurred vision, urinary retention) if troleandomycin is given to a patient taking imipramine.

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Tricyclic antidepressants + Maprotiline

An isolated case describes severe, reversible hepatitis associated with the concurrent use of maprotiline and opipramol.

Clinical evidence, mechanism, importance and management

A patient who had been taking opipramol 150 mg daily for 2 months developed a progressive fatigue syndrome while taking opipramol 100 mg daily and maprotiline 75 mg daily for a further 2 months. Six weeks later he was found to have a marked elevation of liver enzymes and jaundice. Liver enzymes decreased upon cessation of the antidepressants, and normalised completely within 2 months.[1]

It was thought that the concurrent use of both drugs had led to the hepatotoxicity seen: both maprotiline and the tricyclic antidepressants have been associated with hepatotoxicity.

The general relevance of this isolated case is unclear, but it serves as a reminder of the risks of using two potentially hepatotoxic drugs at the same time.

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Tricyclic antidepressants + Methylphenidate

Methylphenidate can increase the levels and rate of response to imipramine and other tricyclic antidepressants. This has led to both increased beneficial and adverse effects. No significant pharmacokinetic interaction has been reported between desipramine and methylphenidate. An isolated report describes a blood dyscrasia in a child given methylphenidate and imipramine.

Clinical evidence

A study in 'several patients' found a dramatic increase in the plasma levels of **imipramine** and its active metabolite, desipramine, when they took

methylphenidate. In one patient taking **imipramine** 150 mg daily, the use of methylphenidate 20 mg daily increased the plasma levels of imipramine from 100 nanograms/mL to 700 nanograms/mL and increased the plasma levels of desipramine from 200 nanograms/mL to 850 nanograms/mL over a period of 16 days. Clinical improvement occurred in several of the patients.[1] Similar effects have been described in other reports.[2-5] It seems that elevation of drug levels takes several days to occur, and several days to wear off.[3]

In contrast, a retrospective review in children and adolescents taking either **desipramine** alone, or with a stimulant, indicated the absence of a clinically significant interaction between **desipramine** and methylphenidate in 25 children who received both drugs; pharmacokinetic parameters for desipramine were similar in each group.[6] In one patient taking **desipramine** 250 mg daily, the concurrent use of methylphenidate 40 mg daily resulted in a small decrease in serum **desipramine** levels, but a marked improvement in mood.[7] However, a further report describes more frequent adverse effects in 10 paediatric patients taking methylphenidate with **desipramine** than with methylphenidate alone, but desipramine levels were not particularly increased.[8]

A study of the combined use of tricyclic antidepressants (**desipramine**, **imipramine**, **nortriptyline**, **doxepin**) with methylphenidate 5 to 15 mg twice daily was undertaken in 20 of 41 patients with depression who responded to a test dose of methylphenidate. Combined use accelerated the antidepressant response to tricyclics with 6 of 20 patients responding after one week and 10 of 16 patients responding after 2 weeks. Adverse effects included insomnia, dizziness, hypotension and dry mouth. Methylphenidate was discontinued after less than 2 weeks concurrent use in 3 patients because of increased anxiety, irritability and hypomania.[9]

A report describes a 9-year-old boy and a 15-year-old boy who exhibited severe behavioural problems until the **imipramine** and methylphenidate that they were taking were stopped.[10] Another case report describes the development of oculogyric crisis in a 10-year-old girl after the addition of **imipramine** to treatment with methylphenidate and valproic acid.[11] Three patients taking tricyclic antidepressants and with labile blood pressure experienced hypertensive episodes when methylphenidate was also given. They responded to withdrawal of methylphenidate and two patients had further hypertensive episodes when rechallenged with methylphenidate.[12] An isolated report describes leucopenia, anaemia, eosinophilia and thrombocytosis in a 10-year-old child when **imipramine** and methylphenidate were given.[13]

Mechanism

In vitro experiments with human liver slices indicate that methylphenidate inhibits the metabolism of imipramine, resulting in raised blood levels.[3] The accelerated response to tricyclic antidepressants may also be partly due to increased serum levels in the presence of methylphenidate, although the adverse effects observed were not entirely consistent with elevated levels of tricyclics.[9] The blood dyscrasia may have been due to the rare additive effects of both drugs.[13]

Importance and management

Evidence is somewhat conflicting, but in general, the combination of methylphenidate and tricyclic antidepressants may result in some therapeutic improvement including, in some patients, an accelerated response. This may be partially because of the very marked rise in the blood levels of the antidepressant due to methylphenidate, but may also be due to an additional effect on mood attributable to methylphenidate. Concurrent use may cause adverse effects sufficiently severe to necessitate withdrawal of methylphenidate, but it is not certain whether this can solely be attributed to increases in serum levels of tricyclic antidepressants. It has been suggested that the concurrent use of methylphenidate and tricyclics in children and adolescents may be undesirable, due to case reports of adverse behavioural effects.[10] If concurrent use is deemed necessary it would seem prudent to monitor for adverse tricyclic effects (e.g. dry mouth, blurred vision, urinary retention) and adjust the dose of the tricyclic as necessary. If this is not effective it may be necessary to withdraw one or both drugs.

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Tricyclic antidepressants + Modafinil

Clomipramine blood levels were reported to be increased by modafinil in one patient. However, a study found that the concurrent use of modafinil and clomipramine did not affect the pharmacokinetics of either drug.

Clinical evidence, mechanism, importance and management

In a placebo-controlled, crossover study, 18 patients were given a single 50-mg dose of **clomipramine** on day 1 and modafinil 200 mg daily on days 1 to 3. No pharmacokinetic changes were found to have occurred with either of the two drugs.[1] However, a single case report describes a patient taking **clomipramine** 75 mg daily who had a rise in her blood levels of **clomipramine** and its metabolite desmethylclomipramine when modafinil 200 mg was added.[2] It was suggested that she had low levels of the cytochrome P450 isoenzyme CYP2D6 (a 'poor metaboliser') so that the additional inhibition of CYP2C19 by modafinil resulted in elevated **clomipramine** levels.

Information about other tricyclic antidepressants is lacking, but the manufacturers of modafinil point out that other poor metabolisers (about 7 to 10% of the Caucasian population) may possibly also show increased tricyclic antidepressant levels in the presence of modafinil.[3,4] Therefore monitoring concurrent use would seem to be a prudent precaution; lower doses of tricyclic antidepressants may be required in those patients deficient in CYP2D6.[3,4] However, note that not all tricyclic antidepressants are metabolised in the same way, and only those affected by CYP2C19 would be expected to be affected, see 'Table 35.2', (p.1465), for more information on the metabolism of the tricyclics.

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Tricyclic antidepressants + Nasal decongestants

The effects of pseudoephedrine and other related drugs are predicted to be altered by the tricyclic antidepressants; however, there appears to be a lack of reported cases.

Clinical evidence, mechanism, importance and management

Some manufacturers of pseudoephedrine-containing products suggest that its activity might be diminished or enhanced by tricyclic antidepressants. There is some concern that concurrent use may lead to a rise in blood pressure.[1,2] In practice, the efficacy of ephedrine (which has similar effects mixed indirect and direct action on adrenergic neurones to pseudoephedrine) is diminished by tricyclics, when it is given as a vasopressor, see 'Tricyclic and related antidepressants + Inotropes and Vasopressors', p.1507. Therefore a similar reduction in effect would be expected when these drugs are given as nasal decongestants.

Furthermore, one manufacturer[2] warns of an increased risk of arrhyth-

mias on concurrent use, but this effect only appears to have been seen with intravenous adrenaline, and even then, rarely.

1. Adult Meltus Dry Coughs with Congestion (Dextromethorphan hydrobromide and Pseudoephedrine hydrochloride). SSL International plc. UK Summary of product characteristics, January 2007.
2. Boots Cold & Flu Relief with Ibuprofen (Ibuprofen and Pseudoephedrine hydrochloride). Boots Company PLC. UK Summary of product characteristics, May 2004.

Tricyclic and related antidepressants + Oestrogens

There is limited evidence suggesting that oestrogens can sometimes affect the therapeutic response to imipramine, and also cause imipramine toxicity. Tricyclic-induced akathisia was attributed to the concurrent use of conjugated oestrogens in three patients. Maprotiline levels are not affected by hormonal contraceptives

Clinical evidence

A study in women taking **imipramine** 150 mg daily for primary depression found that those given **ethinylestradiol** 25 or 50 micrograms [daily] for one week had a greater improvement than those given **imipramine** alone. However, after 2 weeks, those given **ethinylestradiol** 50 micrograms daily had less improvement than other women given only 25 micrograms of **ethinylestradiol** [daily] or a placebo.[1] In an earlier associated study 5 patients taking **imipramine** 150 mg and **ethinylestradiol** 50 micrograms daily developed signs of **imipramine** toxicity (severe lethargy (4 patients), hypotension (4), coarse tremor (2), mild depersonalisation (2)) that was dealt with by halving the **imipramine** dose.[1] Similarly, in a case report, long-standing **imipramine** toxicity was relieved in a woman taking **imipramine** 100 mg daily when her dose of **conjugated oestrogens**, which she had increased to 7.5 mg daily, was reduced to 625 micrograms daily.[2] In another report, akathisia in 3 patients was attributed to an interaction between **conjugated oestrogens** in usual doses of 1.25 mg daily and **amitriptyline**, **clomipramine** or **doxepin**.[3]

A study found that oral contraceptives increased the absolute bioavailability of **imipramine** by 60%.[4] Several studies have shown that plasma **clomipramine** levels were raised or remained unaffected by the concurrent use of oestrogen-containing contraceptives; however, they were unable to confirm that tricyclic antidepressant toxicity occurs more often in those taking oral contraceptives than those who are not.[5-8]

A study in women found that, over a 28-day period, the use of oral hormonal contraceptives did not significantly affect the steady-state blood levels of **maprotiline** 75 mg given at night, nor was its therapeutic effectiveness changed.[9]

Mechanism

Among the possible reasons for these effects are that the oestrogens increase the bioavailability of imipramine,[4] by inhibiting its metabolism.[10] Other tricyclic antidepressants might be similarly affected.

Importance and management

These interactions are inadequately established. There is no obvious reason for avoiding concurrent use, but it would seem reasonable to be alert for any evidence of toxicity and/or lack of response to tricyclic antidepressant treatment in those taking oestrogens in any form. One study suggested that the imipramine dosage should be reduced by about one-third,[4] but given the lack of confirmatory data it would seem prudent to only adjust tricyclic doses according to response.

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Tricyclic antidepressants + Orlistat

Orlistat does not appear to affect the plasma levels of clomipramine or desipramine in patients, or the pharmacokinetics of amitriptyline in healthy subjects.

Clinical evidence, mechanism, importance and management

A preliminary study in patients who had been taking psychotropic drugs long-term found no clinically relevant changes in plasma levels of **clomipramine** (3 patients) or **desipramine** (1 patient) when they were given orlistat over an 8-week period.[1] A study in 20 healthy subjects found that orlistat 120 mg three times daily for 6 days did not affect the pharmacokinetics of **amitriptyline** 25 mg three times daily.[2]

Although evidence is limited no particular precautions seem likely to be necessary on concurrent use.

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Tricyclic antidepressants + Oxybutynin

Oxybutynin reduced the blood levels of clomipramine in one patient. Both tricyclics and oxybutynin have antimuscarinic effects, which would be expected to be additive on concurrent use.

Clinical evidence, mechanism, importance and management

An elderly woman had **clomipramine** and desmethylclomipramine blood levels of 405 and 50 nanograms/mL, respectively, after taking clomipramine 25 mg daily and fluvoxamine 100 mg daily for 18 days. Within one week of starting oxybutynin 5 mg daily, the levels of **clomipramine** and desmethylclomipramine had fallen to 133 nanograms/mL and less than 25 nanograms/mL, respectively, and remained low during a further week of concurrent treatment.[1]

It has been suggested that **clomipramine** levels may be reduced because oxybutynin is an inducer of cytochrome P450 isoenzymes, which could increase the metabolism of clomipramine, and therefore reduce it levels.[1] However, oxybutynin does not usually act in this way.

This appears to be the only report of an interaction, the mechanism of which is not fully clear. It is therefore of unknown general significance. However, note that both tricyclic antidepressants and oxybutynin have antimuscarinic effects, which may be additive on concurrent use. Consider 'Antimuscarinics + Antimuscarinics', p.786, for more on this potential interaction.

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Tricyclic antidepressants + Propafenone

An isolated report describes markedly raised serum desipramine levels in a patient who also took propafenone.

Clinical evidence

A man with major depression responded well to **desipramine** 175 mg daily with serum desipramine levels in the range of 500 to 1000 nanomol/L. When he was treated for paroxysmal atrial fibrillation with digoxin 250 micrograms daily, and propafenone 150 mg twice daily and 300 mg at night, he developed markedly elevated serum **desipramine** levels (2092 nanomol/L) and toxicity (dry mouth, sedation, shakiness) while tak-

ing desipramine 150 mg daily. The adverse effects resolved when the **desipramine** was stopped for 5 days, but when it was restarted at 75 mg daily his serum desipramine levels were still raised, at 1130 nanomol/L.[1]

Mechanism

Propafenone is an inhibitor of the cytochrome P450 isoenzyme CYP2D6, by which desipramine is predominantly metabolised. Concurrent use therefore decreases desipramine metabolism and results in an increase in its levels.

Importance and management

This appears to be the only report of an interaction between desipramine and propafenone, but it is in line with the way both drugs are known to interact. An interaction would therefore seem to be established, although its general importance is uncertain. It would seem prudent to be alert for signs of desipramine toxicity in any patient also given propafenone. Reduce the desipramine dosage appropriately. Other tricyclic antidepressants might be expected to be similarly affected as they are also metabolised, at least in part, by CYP2D6.

Note that, the tricyclics have been associated with QT prolongation, most usually when their levels are high, and this interaction may therefore increase the risk of this effect. See 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290, for further discussion on QT prolongation.

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Tricyclic and related antidepressants + Protease inhibitors

Ritonavir raises desipramine levels and is predicted to also raise the levels of other tricyclic antidepressants. A case report describes potentially life-threatening cardiac conduction problems and antimuscarinic effects when ritonavir and other protease inhibitors were given with maprotiline.

Clinical evidence

(a) Desipramine

A study in 15 healthy subjects found that **lopinavir**/**ritonavir** 400/100 mg twice daily modestly reduced the maximum plasma concentration of a single 100-mg dose of desipramine by 23%, but the AUC was unaffected. These results were not statistically significant.[1]

In a study, 14 healthy subjects were given a single 100-mg dose of desipramine before and after they took **ritonavir** 500 mg twice daily for 10 days. **Ritonavir** increased the AUC and half-life of desipramine nearly 2.5-fold and 2-fold, respectively. The maximum plasma levels were also increased by about 22%.[2] Another study in 13 healthy subjects, found that **ritonavir** 100 mg twice daily modestly increased the AUC of a single 50-mg dose of desipramine by 26% and prolonged the half-life by 30%. However, there was marked interindividual variability in desipramine pharmacokinetic parameters, both with and without ritonavir; in the presence of ritonavir 12 of 13 subjects had an increase in the AUC of desipramine ranging from 4 to 71%.[3]

(b) Maprotiline

A report describes a 32-year-old man with AIDS taking low-dose maprotiline 50 mg daily and fluconazole 200 mg daily, who experienced severe hypotension, cardiac conduction problems and other symptoms such as dry mouth, constipation and dysuria, 8 weeks after starting a combination of antiretroviral drugs including **ritonavir** 400 mg twice daily, **saquinavir**, **indinavir**, **amprenavir** and stavudine. The serum levels of maprotiline reached 1.5 mmol/L (reference range 0.3 to 1 mmol/L). Clinical and electrical abnormalities disappeared within 72 hours of stopping the maprotiline, antiretroviral drugs and fluconazole.[4]

Mechanism

The tricyclic antidepressants and maprotiline are metabolised, at least in part by the cytochrome P450 isoenzyme CYP2D6. Ritonavir is a known inhibitor of this isoenzyme, and therefore concurrent use decreases the metabolism of the tricyclics, leading to an increase in their levels. **Tipranavir** appears to be the only other protease inhibitor that also affects this isoenzyme to a clinically relevant extent, see 'Table 21.2', (p.914).

Importance and management

An interaction between desipramine and ritonavir appears to be established. However, its clinical relevance appears to depend on the dose of ritonavir used, with the studies suggesting that higher doses of ritonavir (500 mg twice daily) have a large effect on desipramine levels, which may require a dose reduction. In contrast, when ritonavir is given as a pharmacokinetic enhancer (i.e. at a dose of 100 mg twice daily), the effects are modest and unlikely to require dose adjustments of the tricyclic. Because of the increased levels seen, it would seem prudent to monitor for increased tricyclic adverse effects (e.g. dry mouth, urinary retention, constipation) in any patient given ritonavir (regardless of dose). It may be prudent to consider starting desipramine at a low dose in patients taking ritonavir 500 mg twice daily, increasing the dose slowly.

There seems to be little information regarding other tricyclics, but as they are all metabolised, at least in part, by CYP2D6, similar precautions to those suggested for desipramine would seem prudent.

Other protease inhibitors, with the exception of tipranavir, would not be expected to interact by this mechanism. However, the manufacturer of nelfinavir suggests that, as it is primarily metabolised by CYP3A4 and CYP2C19 drugs that could inhibit CYP2C19 (including amitriptyline and imipramine) might be expected to reduce the conversion of nelfinavir to its major active metabolite M8, and increase plasma nelfinavir levels. However, limited clinical data suggests this is unlikely to be clinically significant.[5] Furthermore, these tricyclics are not usually considered to be inhibitors of these isoenzymes. A clinically relevant interaction therefore seems unlikely.

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5. Viracept (Nelfinavir mesilate). Roche Products Ltd. UK Summary of product characteristics, July 2008.

Tricyclic antidepressants + Quinidine or Quinine

Quinidine can reduce the clearance of desipramine, imipramine, nortriptyline and trimipramine, and quinine can reduce the clearance of desipramine, thereby increasing their plasma levels.

Clinical evidence

(a) Quinidine

In a study in 5 healthy subjects quinidine 50 mg given one hour before a single 50-mg dose of **nortriptyline** increased the **nortriptyline** AUC fourfold, and increased the half-life from 14.2 hours to 44.7 hours.[1] The clearance fell by 65%. A single-dose study in healthy subjects found that quinidine 200 mg daily reduced the clearance of **imipramine** 100 mg and **desipramine** 100 mg by 30% and 85%, respectively.[2] A further study in 2 healthy subjects similarly found that quinidine 50 mg almost doubled the half-life of a single 75-mg dose of **trimipramine**, which was reflected in some waking EEG changes.[3]

In healthy subjects given quinidine 800 mg daily for 2 days, the urinary excretion of 2-hydroxydesipramine from a single 25-mg dose of **desipramine** was reduced by 97% and 68%, respectively in subjects with normal levels and low levels of [CYP2D6].[4]

(b) Quinine

Quinine 750 mg daily for 2 days reduced the urinary excretion of 2-hydroxydesipramine from a single 25-mg dose of **desipramine** in those with normal levels of [CYP2D6] by 56% but had no significant effect on the clearance in those with low levels of [CYP2D6].[4]

Mechanism

Quinidine reduces the metabolism (hydroxylation) of these tricyclic antidepressants, by inhibiting the cytochrome P450 isoenzyme CYP2D6, and thereby reduces their loss from the body.[5,6] Quinine inhibits the metabolism of desipramine to a lesser extent than quinidine, as it is a less potent inhibitor of CYP2D6.

Importance and management

An interaction between quinidine and the tricyclics appears to be established. It would be expected to be clinically relevant with nortriptyline, and possibly desipramine, but probably not with imipramine. This is due to differences in the way the tricyclics are metabolised (see 'Table 35.2' (p.1465)). There seems to be no information about the effect of quinidine on other tricyclics, but increased toxicity is possible (given that they are all metabolised, at least in part, by CYP2D6) and doses may need to be reduced. If quinidine is given with a tricyclic, particularly one metabolised solely by CYP2D6, be alert for tricyclic adverse effects (dry mouth, urinary retention, constipation), and decrease the tricyclic dose accordingly. Note that, the tricyclics have been associated with QT prolongation, most usually when their levels are high, and this interaction may therefore increase the risk of this effect, particularly as quinidine has effects on the QT interval. See 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290, for further discussion on QT prolongation.

Information about the effect of quinine on tricyclics is very limited, but the effects are smaller than those of quinidine and therefore less likely to result in clinically significant adverse effects.

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Tricyclic antidepressants + Rifampicin (Rifampin)

In three patients a marked reduction in nortriptyline and amitriptyline levels occurred when rifampicin was given.

Clinical evidence

A man with tuberculosis needed to take 175-mg doses of **nortriptyline** to achieve therapeutic serum levels while taking isoniazid 300 mg, rifampicin 600 mg, pyrazinamide 1.5 g and pyridoxine 25 mg daily. Three weeks after stopping the antitubercular drugs, the patient suddenly became drowsy and his **nortriptyline** serum levels were found to have risen from 193 nanomol/L to 562 nanomol/L, and later to 671 nanomol/L. It was then found possible to maintain his **nortriptyline** serum levels in the range of 150 to 500 nanomol/L with only 75 mg of **nortriptyline** daily.[1]

A woman taking **amitriptyline** and fluoxetine had a marked fall in her plasma **amitriptyline** levels when she took rifampicin 600 mg, isoniazid 200 mg and ethambutol 1.2 g daily. When these antitubercular drugs were stopped, her **amitriptyline** plasma levels rose.[2] In a further case, in a 43-year-old woman, the serum levels of **nortriptyline** 50 mg daily were not detectable when rifampicin 600 mg daily was given. Increasing the dose of **nortriptyline** to 75 mg daily failed to produce detectable serum levels. Two weeks after discontinuation of rifampicin, **nortriptyline** levels increased.[3]

Mechanism

It seems highly probable that rifampicin (a well recognised and potent enzyme inducer) increased the metabolism of nortriptyline and amitriptyline by the liver thereby reducing their levels.

Importance and management

Information about the interaction between tricyclic antidepressants and rifampicin seems to be limited to just these three reports, which is a little surprising since both have been widely used for a considerable time. This suggests that generally this interaction may have limited clinical importance. However, bear this interaction in mind if patients taking rifampicin seem unresponsive to treatment with tricyclics. Increase the tricyclic dosage if necessary, and remember to readjust the dose if rifampicin is stopped.

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3. Self T, Corley CR, Nabhan S, Abell T. Case report: interaction of rifampin and nortriptyline. *Am J Med Sci* (1996) 311, 80–1.

Tricyclic antidepressants + SNRIs

The use of duloxetine or venlafaxine with the tricyclics is expected to increase the risk of serotonin syndrome: cases have been seen with venlafaxine. Increased antimuscarinic adverse effects, movement disorders and seizures have also been reported. Venlafaxine and duloxetine appear to increase the levels of desipramine or its 2-hydroxydesipramine metabolite. Other tricyclics are expected to interact similarly.

Clinical evidence

(a) Duloxetine

In a study in healthy subjects, duloxetine 60 mg twice daily increased the AUC of a single 50-mg dose of **desipramine** by 2.9-fold.[1]

(b) Venlafaxine

A 74-year-old man taking venlafaxine 150 mg daily and thioridazine had his treatment changed to daily doses of venlafaxine 75 mg, **desipramine** 50 mg, haloperidol 500 micrograms and alprazolam 250 micrograms. Within 5 days he exhibited severe antimuscarinic adverse effects (acute confusion, delirium, stupor, urinary retention and paralytic ileus). This was attributed to an interaction between the venlafaxine and **desipramine**.[2] Similarly, a 75-year-old man taking haloperidol, alprazolam and venlafaxine developed urinary retention and became delirious when he also took **desipramine**.[3] Similar effects have been seen in other cases involving **nortriptyline** 20 mg daily[4] and **clomipramine** 150 mg daily.[3]

A 69-year-old man with bipolar disorder, who had been taking venlafaxine up to 337.5 mg daily, thioridazine 25 mg at night, and sodium valproate 1.2 g daily for several months with no adverse motor symptoms, experienced extrapyramidal effects 3 to 4 days after the venlafaxine was gradually replaced by **nortriptyline** 50 mg daily. Symptoms persisted despite withdrawal of thioridazine, but improved on reduction of the **nortriptyline** dosage to 20 mg daily.[5]

A 25-year-old woman taking venlafaxine 150 mg daily and **trimipramine** 50 mg daily for depression developed seizures within 11 days of the **trimipramine** dose being increased to 100 mg daily. Both drugs were stopped and the patient had no further seizures.[6]

There is also a report of the serotonin syndrome occurring in a 21-year-old patient when **amitriptyline** 10 mg at night was added to the range of medications she was receiving, which included venlafaxine 37.5 mg daily, pethidine (meperidine) 400 mg daily and fluconazole 200 mg daily.[7] There are two other reports of the serotonin syndrome in patients who had discontinued venlafaxine 3 days and 2 weeks, respectively, before starting **amitriptyline**.[8,9]

Venlafaxine has only modest effects on the metabolism of **imipramine** to desipramine (AUC and maximum levels increased by 35%),[10,11] but the AUC of another metabolite, 2-hydroxydesipramine, is increased 4.5-fold by venlafaxine 75 mg twice daily.[11]

Mechanism

Not fully established. It has been suggested that venlafaxine can inhibit the metabolism of these tricyclics by the cytochrome P450 isoenzyme CYP2D6, leading to an increase in their serum levels and a marked increase in their antimuscarinic adverse effects.[3] However, studies indicate that venlafaxine is a relatively weak inhibitor of CYP2D6.[10]

Nevertheless, it does appear to have some effect on the metabolism of desipramine.

The other effects (seizures, antimuscarinic effects, serotonin syndrome) seem likely to have occurred due to the additive effects of the venlafaxine and tricyclic.

Importance and management

Information regarding an interaction between the tricyclics and SNRIs appears to be sparse, mainly coming from case reports, although an interaction resulting in raised tricyclic levels appears to be established. It would therefore seem prudent to monitor for antimuscarinic adverse effects (dry mouth, urinary retention, constipation) in any patient given the combination and consider reducing the dose of the tricyclic if adverse effects become troublesome.

There only appears to be one case report describing serotonin syndrome with venlafaxine and amitriptyline, and this particular case is complicated by the presence of fluconazole, which can increase amitriptyline levels (see 'Tricyclic and related antidepressants + Azoles; Fluconazole', p.1498), and pethidine (meperidine), which has also been implicated in cases of serotonin syndrome. Nevertheless, both the tricyclics and the SNRIs have been associated with this effect, and so some caution would seem warranted. See, 'serotonin syndrome', (p.9), for guidance on managing this potential adverse reaction.

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11. Effexor XR (Venlafaxine hydrochloride). Wyeth Pharmaceuticals Inc. US Prescribing information, July 2009.

Tricyclic and related antidepressants + SSRIs

The levels of the tricyclic antidepressants can be raised by the SSRIs, but the extent varies greatly, from 20% to tenfold: fluvoxamine, fluoxetine and paroxetine appear to have the greatest effects. Tricyclic toxicity has been seen in a number of cases. Tricyclics may increase the levels of citalopram and possibly fluvoxamine, but the significance of this is unclear. There are several case reports of serotonin syndrome following concurrent, and even sequential, use of the SSRIs and tricyclics.

One study suggested that there was no clinically significant pharmacokinetic interaction between fluoxetine and mianserin.

Clinical evidence

(a) Citalopram

In one study[1] citalopram caused an increase of about 50% in the AUC of desipramine (the primary metabolite of **imipramine**), and a reduction in the levels of the subsequently formed metabolite of desipramine (2-hydroxydesipramine) after a single 100-mg oral dose of **imipramine**. In contrast, 5 patients taking **amitriptyline**, **clomipramine** or **maprotiline** had no changes in their plasma tricyclic antidepressant levels when citalopram 20 to 60 mg daily was also given.[2] In another general study, in which 18 patients were given citalopram and tricyclic antidepressants, the serum levels of citalopram were doubled in those receiving **clomipramine**; pooled results for all the tricyclics showed a 44% rise in serum citalopram levels.[3] An increase of this size is of doubtful clinical importance with citalopram. In 2 patients the plasma levels of **clomipramine** 100 mg daily remained stable when the dose was reduced to 75 mg daily and citalopram 40 mg daily was started.[4,5] One had elevated levels of desmethylclomipramine[4] and the other had elevated levels of the active metabolite, 8-hydroxydesmethylclomipramine.[5]

A case report describes elevated **desipramine** levels in a patient taking paroxetine that resolved when the patient was switched to citalopram.[6]

(b) Escitalopram

Escitalopram 20 mg daily for 21 days increased the maximum serum levels and AUC of a single 50-mg dose of **desipramine** by 40% and 100%, respectively.[7]

(c) Fluoxetine

Four patients given **desipramine** 300 mg, **imipramine** 150 mg or **nortriptyline** 100 mg, each daily, had two- to fourfold increases in plasma tricyclic antidepressant levels within 1 to 2 weeks of starting fluoxetine 10 to 60 mg daily. Two of them developed antimuscarinic adverse effects (constipation, urinary hesitancy).[8] A report describes extremely high levels and prolonged elimination of **imipramine** following overdose with "a handful" of **imipramine** tablets in a patient taking fluoxetine 20 mg daily.[9]

A number of other reports and studies clearly confirm that marked increases occur in the levels of **amitriptyline**,[10-13] **clomipramine**,[11,14] **desipramine**,[15-24] **imipramine**,[11,19-21,25,26] **nortriptyline**[17,18,27-29] and possibly **protriptyline**,[30] accompanied by toxicity, if fluoxetine is added without reducing the dosage of the tricyclic antidepressant. Delirium and seizures have also been described,[20,31] and a death has been attributed to chronic **amitriptyline** toxicity caused by fluoxetine.[32] The pharmacokinetics of fluoxetine appear not to be affected by **amitriptyline**.[13]

A migraine-like stroke developed in a woman 48 hours after her long-standing treatment with fluoxetine 100 mg daily was abruptly changed to **clomipramine** 200 mg daily.[33]

A study involving 34 patients found that the combination of fluoxetine 20 mg daily and **mianserin** 30 mg daily was superior to fluoxetine and placebo in the acute treatment of major depression, and no major adverse effects were reported. However, 12 patients did not complete 6 weeks of treatment, and of these, 2 dropped out because of adverse effects (dizziness and sedation) after one and 3 weeks, respectively. After 4 weeks of treatment, headache and increased body weight occurred more frequently in those taking both drugs than in those taking fluoxetine alone. **Mianserin** had no effect on fluoxetine plasma levels and the plasma concentration of mianserin was similar to that previously reported.[34]

(d) Fluvoxamine

The **amitriptyline** plasma levels of 8 patients rose (range 15 to 233%) when they were also given fluvoxamine 100 to 300 mg daily. Even larger rises in plasma **clomipramine** levels occurred (up to eightfold) in four other patients given fluvoxamine 100 to 300 mg daily. The tricyclic dosages remained the same or were slightly lower. No toxicity was seen.[35-37]

A number of other reports and studies confirm that increases occur in the levels of **amitriptyline**,[38-41] **clomipramine**,[38-43] **desipramine**,[44-47] **imipramine**,[38,39,44-48] **maprotiline**[38] and **trimipramine**[49] in the presence of fluvoxamine. This interaction seems severe with **clomipramine** (a 10-fold rise in one case)[43] and mild with **desipramine**.[46,47] One study also suggested that fluvoxamine levels may be raised by tricyclics.[38] An isolated report describes worsening depression in a patient taking **dosulepin** 75 mg daily and **mianserin** within 24 hours of replacing the **dosulepin** with fluvoxamine 75 mg daily. The symptoms continued during the next day but were reversed within a day of fluvoxamine being replaced with **dosulepin**.[50]

(e) Paroxetine

A study in 17 healthy subjects taking **desipramine** 50 mg daily found that when they were also given paroxetine 20 mg daily for 10 days the maximum plasma levels of the **desipramine** rose by 358%, the trough plasma levels rose by 511% and the AUC rose by 421%. An approximately tenfold increase in the maximum plasma levels and the AUC of the paroxetine also occurred.[51] Another study found a fivefold decrease in **desipramine** clearance in the presence of paroxetine 20 mg daily.[52] Paroxetine has also been shown to increase the levels of **clomipramine**,[53] **desipramine**,[6] **imipramine**,[54,55] and **trimipramine**.[56] This resulted in a variety of adverse effects including dizziness,[53] confusion,[6] sedation[56] and memory impairment.[56]

A 21-year-old man developed serotonin syndrome when he took one tablet of paroxetine only one day after stopping **desipramine**, which he had taken for 5 days. He recovered after treatment with cyproheptadine.[57] A woman taking paroxetine 30 mg daily developed serotonin syndrome (tachycardia, delirium, bizarre movements, myoclonus) within 2 hours of

taking a single 50-mg dose of **imipramine**. She recovered when treated with intravenous fluids, sedation and cyproheptadine.[58]

(f) Sertraline

In 9 healthy subjects, sertraline 50 mg daily increased the maximum plasma levels of **desipramine** 50 mg daily by 31% at steady-state, and increased the AUC by 23%.[24] A later related study in 17 healthy subjects by the same group of workers found that, using the same drug dosages, sertraline increased the **desipramine** maximum plasma levels by 44%, the minimum levels by 19% and the AUC by 37%. The maximum plasma levels and AUC of the sertraline were increased about twofold.[51] Other studies have found that sertraline increases **desipramine**,[59-62] **imipramine**,[59] and **nortriptyline**[63] levels, but it has also been suggested that sertraline has no effect on **imipramine** levels.[64,65]

A woman who had been taking sertraline 50 mg daily (as well as morphine sulfate and pericyazine) developed serotonin syndrome within 3 days of starting to take **amitriptyline** 75 mg daily. She recovered when all of the psychotropic drugs were withdrawn.[66]

Mechanism

Fluoxetine, paroxetine, and to a lesser extent sertraline and citalopram, inhibit the cytochrome P450 isoenzyme CYP2D6, which is involved in the metabolism of the tricyclic antidepressants. Hence these SSRIs cause tricyclic levels to rise. Fluvoxamine causes a similar effect, probably by inhibiting metabolism through CYP1A2 and possibly other isoenzymes. The elevated levels of 8-hydroxydesmethylclomipramine during concurrent clomipramine and citalopram administration in one patient may have been due to the inhibition of glucuronidation by citalopram.[5] The interaction is likely to vary depending on the various routes of metabolism of the tricyclics, and the various cytochrome P450 isoenzymes inhibited by the SSRIs. See 'Table 35.2', (p.1465), for information on the metabolic routes of the tricyclics and the inhibitory potential of the SSRIs.

Serotonin syndrome possibly develops because both the tricyclics and SSRIs affect serotonin transmission, which may result in increased serotonin levels. For more on serotonin syndrome, see 'Additive or synergistic interactions', (p.9).

Importance and management

The interactions of the SSRIs and tricyclic antidepressants are established and of clinical significance. The SSRIs increase tricyclic levels, with fluvoxamine, fluoxetine and paroxetine apparently having the greatest effects. The increased tricyclic levels can be beneficial.[38,41,67] However, it has been suggested that patients given fluoxetine should have their tricyclic dose reduced to one-quarter.[19] Similar recommendations have been made with fluvoxamine (reduction in tricyclic dose to one-third)[44] and sertraline.[68] It would also seem prudent to consider a dosage reduction of the tricyclic if paroxetine is added. Some suggest that a small initial dose of the SSRI should also be used.[68]

Patients taking any combination of tricyclic and SSRI should be monitored for adverse effects (e.g. dry mouth, sedation, confusion) with tricyclic levels monitored where possible. Remember that the active metabolite of fluoxetine has a half-life of 7 to 15 days, and so any interaction may persist for some time after the fluoxetine is withdrawn,[69-71] and may occur on sequential use. The manufacturer of clomipramine also recommends avoidance of drugs that can cause an accumulation of clomipramine and they advise a washout period of 2 to 3 weeks before and after treatment with fluoxetine.[72]

Serotonin syndrome seems to occur rarely but patients and prescribers should be aware of the symptoms so that prompt action can be taken if problems occur. For more about the serotonin syndrome, see 'Additive or synergistic interactions', (p.9).

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72. Anafranil (Clomipramine hydrochloride). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, March 2008.

Tricyclic antidepressants + St John's wort (*Hypericum perforatum*)

The plasma levels of amitriptyline, and its active metabolite, nortriptyline, are modestly reduced by St John's wort.

Clinical evidence

Twelve depressed patients were given **amitriptyline** 75 mg twice daily and St John's wort extract (*Lichtwer Pharma, Berlin*) 900 mg daily for at least 14 days. The $AUC_{0\text{-}12}$ of the **amitriptyline** was reduced by about 22% and the AUC of nortriptyline (its metabolite) was reduced by about 41%.[1]

Mechanism

Not fully understood. St John's wort is known to induce the activity of the cytochrome P450 isoenzyme CYP3A4, which is a minor route of metabolism of the tricyclic antidepressants. However, the tricyclics are predominantly metabolised by CYP2D6, so an effect on CYP3A4 is unlikely to lead to a clinically relevant reduction in their levels. Induction of P-glycoprotein by St John's wort may also contribute; however, the extent of its involvement in the transport of the tricyclics is unclear.

Importance and management

The evidence for an interaction is limited to this study, and based on the minor reduction in amitriptyline levels seen, it seems unlikely that a clinically significant reduction in efficacy would occur. Other tricyclics would be expected to interact similarly.

Both the tricyclics and St John's wort are antidepressants, but whether concurrent use is beneficial or safe is not known, and it was not assessed in this study. Further study is needed.

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Tricyclic antidepressants + Sucralfate

Sucralfate causes a marked reduction in the absorption of amitriptyline.

Clinical evidence, mechanism, importance and management

When 6 healthy subjects took a single 75-mg dose of **amitriptyline** with a single 1-g dose of sucralfate, the AUC of the amitriptyline was reduced by 50%.[1] This reduction probably occurred because sucralfate reduced the absorption of amitriptyline from the gut. There seems to be nothing documented about other tricyclics, but they would be expected to interact similarly.

If sucralfate is given to a patient taking any tricyclic antidepressant it would seem prudent to monitor to confirm that the therapeutic effects of the antidepressant are not lost. It is generally recommended that other drugs should be given at least 2 hours before or after sucralfate to avoid a reduction in bioavailability.[2]

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2. Antepsin Suspension (Sucralfate). Chugai Pharma UK Ltd. UK Summary of product characteristics, November 2007.

Tricyclic antidepressants + Temsirolimus

Temsirolimus did not alter desipramine pharmacokinetics in a single-dose study.

Clinical evidence, mechanism, importance and management

In a single-dose study in healthy subjects, the pharmacokinetics of oral desipramine 50 mg were unaffected by intravenous temsirolimus 25 mg given at the same time.[1] On the basis of this study, the manufacturer does not anticipate that a pharmacokinetic interaction will occur when temsirolimus is given at this dose with drugs that are substrates of the cytochrome P450 isoenzyme CYP2D6.[2,3] For a list of CYP2D6 substrates, see 'Table 1.3', (p.6). However, simultaneous dosing of these two drugs would not have allowed for maximal hepatic enzyme inhibition, so a multiple-dose study or single-dose study where desipramine was given on day 2 or 3 after intravenous temsirolimus would provide more proof of a lack of interaction.

1. Boni J, Abbas R, Leister C, Burns J, Jordan R, Hoffmann M, DeMaio W, Hug B. Disposition of desipramine, a sensitive cytochrome P450 2D6 substrate, when coadministered with intravenous temsirolimus. Cancer Chemother Pharmacol (2009) 64, 263–70.
2. Torisel (Temsirolimus). Wyeth Pharmaceuticals Inc. US Prescribing information, September 2008.
3. Torisel (Temsirolimus). Wyeth Pharmaceuticals. UK Summary of product characteristics, August 2009.

Tricyclic antidepressants + Terbinafine

Terbinafine markedly increases the AUC of desipramine. Case reports describe increases in the serum levels of amitriptyline, desipramine, imipramine and nortriptyline, with associated toxicity, in patients additionally given oral terbinafine.

Clinical evidence

(a) Amitriptyline

A 37-year-old woman who had been taking amitriptyline 75 mg daily, valproate and olanzapine for 3 years, developed extreme dryness of the mouth, nausea and dizziness shortly after starting to take terbinafine 250 mg daily. Serum levels of amitriptyline and its metabolite nortriptyline rose from just under 400 nanomol/L to over 1800 nanomol/L. Terbinafine was stopped, and the amitriptyline dose reduced to 25 mg daily, but

the amitriptyline and nortriptyline levels did not return to baseline for several months. The patient had normal levels of CYP2D6.[1]

(b) Desipramine

In a pharmacokinetic study, terbinafine 250 mg daily for 21 days caused a marked fivefold increase in the AUC of a single 50-mg dose of desipramine, and increased its maximum levels twofold. The AUC of desipramine was still more than double the baseline level 4 weeks after stopping desipramine. The healthy subjects used in this study were extensive CYP2D6 metabolisers, which is the most common phenotype.[2]

A case report describes a 3.5-fold increase in desipramine levels, with associated toxicity (dizziness, ataxia, incoordination, and difficulty swallowing), in a 52-year-old man taking desipramine 350 mg daily, which occurred within 2 to 3 weeks of him starting to take terbinafine. The desipramine was stopped for a few days and restarted at a dose of just 50 mg daily, which gave similar serum levels to those seen before terbinafine was started. When the terbinafine was stopped, the dose of desipramine needed to be gradually titrated up to the initial amount.[3]

(c) Imipramine

A 51-year-old man who had been taking lithium carbonate and varying doses of imipramine 150 to 200 mg daily for 10 years was also given oral terbinafine 250 mg daily for onychomycosis. About a week later he complained of dizziness, muscle twitching and excessive mouth dryness. His serum imipramine levels, measured 5 days later, had risen from his usual range of 100 to 200 nanograms/mL up to 530 nanograms/mL. Within 10 days of reducing his daily imipramine dose from 200 to 75 mg daily, his serum levels had fallen to 229 nanograms/mL. His liver function was normal.[4]

(d) Nortriptyline

A report describes a marked increase in the serum levels of nortriptyline (about doubled) accompanied by evidence of toxicity (fatigue, vertigo, loss of energy and appetite, and falls) in a 74-year-old man taking nortriptyline 125 mg daily, roughly 14 days after he started to take terbinafine 250 mg daily. His symptoms responded to a dose reduction to 75 mg of nortriptyline daily. His serum levels were similarly elevated when he was later rechallenged with terbinafine. His liver function was normal.[5] The same authors reported a similar case in a woman who had been taking nortriptyline and terbinafine for one month before she showed signs of an interaction. A later rechallenge with terbinafine confirmed the interaction.[6]

Mechanism

Terbinafine is an inhibitor of the cytochrome P450 isoenzyme CYP2D6, which is the principal enzyme involved in the metabolism of many tricyclics. Terbinafine can have a very prolonged half-life, so an interaction may occur or continue for a number of weeks after stopping the drug.

Importance and management

Although there are only a few case reports an interaction appears to be confirmed, and the increase in the levels of tricyclic antidepressant in the presence of terbinafine appears to be clinically important. It would seem prudent to monitor for tricyclic adverse effects (such as dry mouth, blurred vision and urinary retention) if terbinafine is also given, and consider reducing the dose of the tricyclic if these become troublesome. Tricyclic levels may return to normal only slowly after discontinuation of terbinafine.[1,2,6] It is also suggested that there may be a risk of clinically significant interactions if these drugs are given within 3 months of stopping terbinafine.[1]

Note that, the tricyclics have been associated with QT prolongation, most usually when their levels are high, and this interaction may therefore increase the risk of this effect. See 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290, for further discussion on QT prolongation.

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Tricyclic antidepressants + Thyroid hormones

The antidepressant response to imipramine, amitriptyline and possibly other tricyclics can be accelerated by the use of thyroid hormones. However, isolated cases of paroxysmal atrial tachycardia, thyrotoxicosis and hypothyroidism have occurred on concurrent use.

Clinical evidence, mechanism, importance and management

The addition of **liothyronine** 25 micrograms daily was found to increase the speed and efficacy of **imipramine** in relieving depression.[1] Similar results have been described in other studies with **desipramine**[2] or **amitriptyline**[3] but the reasons are not understood. One possible explanation is that the patients had overt or subclinical hypothyroidism, which after correction with **liothyronine** allowed them to overcome an impaired response to tricyclic antidepressants.[4] Other suggestions are that small alterations in thyroid hormone levels may result in alterations in cerebral function[5] and that thyroid hormones may increase receptor sensitivity to neurotransmitters such as serotonin (5-hydroxytryptamine, 5-HT).[6]

However, adverse reactions have also been seen when thyroid hormones were given with tricyclics. A patient being treated for both hypothyroidism and depression with **thyroid** 60 mg and **imipramine** 150 mg daily complained of dizziness and nausea. She was found to have developed paroxysmal atrial tachycardia.[7] A 10-year-old girl with congenital hypothyroidism, well controlled with desiccated **thyroid** 150 mg daily, developed severe thyrotoxicosis after taking **imipramine** 25 mg daily for 5 months for enuresis. The problem disappeared when the **imipramine** was withdrawn.[8]

The interaction between thyroid hormones and tricyclics is normally advantageous,[6] in which **liothyronine** appears to have a significantly greater antidepressant-potentiating effect than **levothyroxine**.[5] There would seem to be no good reason, generally speaking, for avoiding concurrent use unless problems arise.

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2. Extein I. Case reports of L-triiodothyronine potentiation. *Am J Psychiatry* (1982) 139, 966–7.
3. Wheatley D. Potentiation of amitriptyline by thyroid hormone. *Arch Gen Psychiatry* (1972) 26, 229–33.
4. Berlin I, Corruble E. Thyroid hormones and antidepressant response. *Am J Psychiatry* (2002) 159, 1441.
5. Joffe RT, Singer W. A comparison of triiodothyronine and thyroxine in the potentiation of tricyclic antidepressants. *Psychiatry Res* (1990) 32, 241–51.
6. Altshuler LL, Bauer M, Frye MA, Gitlin MJ, Mintz J, Szuba MP, Leight KL, Whybrow PC. Does thyroid supplementation accelerate tricyclic antidepressant response? A review and meta-analysis of the literature. *Am J Psychiatry* (2001) 158, 1617–22.
7. Prange AJ. Paroxysmal auricular tachycardia apparently resulting from combined thyroid-imipramine treatment. *Am J Psychiatry* (1963) 119, 994–5.
8. Colantonio LA, Orson JM. Triiodothyronine thyrotoxicosis. Induction by desiccated thyroid and imipramine. *Am J Dis Child* (1974) 128, 396–7.

Tricyclic and related antidepressants + Tobacco

Smoking tobacco reduces the plasma levels of amitriptyline, clomipramine, desipramine, imipramine and nortriptyline, but this does not appear to result in a clinically significant interaction. Maprotiline levels are not affected by smoking tobacco.

Clinical evidence

Two studies found no difference between the steady-state **nortriptyline** plasma levels of tobacco smokers and non-smokers,[1,2] but others have found that smoking tobacco lowers the plasma levels of **amitriptyline**, **clomipramine**,[3] **desipramine**, **imipramine**[4] and **nortriptyline**.[5] For example a 25% reduction in plasma **nortriptyline** levels was found in one study,[5] and a 45% reduction in total levels of **imipramine** and its metabolite, desipramine, was found in another.[4] Smoking has no effect on **maprotiline** efficacy and blood levels.[6,7]

Mechanism

The probable reason for the reduced tricyclic levels is that some of the components of tobacco smoke are enzyme inducers, which increase the metabolism of these antidepressants by the liver.

Importance and management

The interactions between tobacco smoke and tricyclics are established but it might wrongly be concluded from the figures quoted that smokers need larger doses of the tricyclic to control their depression. Some evidence suggests that the plasma levels of free (and pharmacologically active) nortriptyline are greater in smokers than non-smokers (10.2% compared with 7.4%), which probably offsets the fall in total plasma levels.[5] Thus the apparently lower plasma levels in smokers may be as therapeutically effective as the higher levels in non-smokers, so that there is probably no need to raise the dosage to accommodate this interaction.

1. Norman TR, Burrows GD, Maguire KP, Rubinstein G, Scoggins BA, Davies B. Cigarette smoking and plasma nortriptyline levels. *Clin Pharmacol Ther* (1977) 21, 453–6.
2. Alexanderson B, Price Evans DA, Sjöqvist F. Steady-state plasma levels of nortriptyline in twins: influence of genetic factors and drug therapy. *BMJ* (1969) 4, 764–8.
3. John VA, Luscombe DK, Kemp H. Effects of age, cigarette smoking and the oral contraceptive on the pharmacokinetics of clomipramine and its desmethyl metabolite during chronic dosing. *J Int Med Res* (1980) 8 (Suppl 3), 88–95.
4. Perel JM, Hurwic MJ, Kanzler MB. Pharmacodynamics of imipramine in depressed patients. *Psychopharmacol Bull* (1975) 11, 16–18.
5. Perry PJ, Browne JL, Prince RA, Alexander B, Tsuang MT. Effects of smoking on nortriptyline plasma concentrations in depressed patients. *Ther Drug Monit* (1986) 8, 279–84.
6. Luscombe DK. Interaction studies: the influence of age, cigarette smoking and the oral contraceptive on blood concentrations of maprotiline. In 'Depressive Illness — Far Horizons?' McIntyre JNM (ed), Cambridge Med Publ, Northampton 1982, p 61–2.
7. Holman RM. Maprotiline and cigarette smoking: an interaction study: clinical findings. In 'Depressive Illness — Far Horizons?' McIntyre JNM (ed), Cambridge Med Publ, Northampton 1982, p 66–7.

Tricyclic antidepressants + Valproate

Amitriptyline and nortriptyline plasma levels can be increased by sodium valproate and valpromide. Status epilepticus, tremulousness and/or sleep disturbances have been attributed to elevated clomipramine or nortriptyline levels in patients taking valproate or valproic acid. Valproate pharmacokinetics may be modestly affected by amitriptyline.

Clinical evidence

(a) Amitriptyline

In one study, 15 healthy subjects were given a single 50-mg dose of amitriptyline 2 hours after taking the ninth dose of valproate semisodium 500 mg every 12 hours. The maximum plasma levels and AUC of amitriptyline were raised by 19% and 30%, respectively. The corresponding values for the nortriptyline metabolite were 28% and 55%, respectively.[1] Similarly, in 10 patients taking amitriptyline 125 mg daily, the use of valpromide 600 mg daily for 10 days caused a 50% rise in the mean steady-state plasma levels of amitriptyline and a 65% rise in the levels of the nortriptyline metabolite, when compared with 10 similar patients taking amitriptyline alone.[2,3]

A study in 6 patients with depression found that amitriptyline 100 mg daily for 3 weeks produced a 43% increase in the volume of distribution and a 16% increase in the plasma half-life of a single 400-mg intravenous dose of sodium valproate. The AUC and total body clearance of valproate were not significantly changed.[4]

(b) Clomipramine

An epileptic patient who had been seizure-free for 3 years while taking valproic acid developed a prolonged episode of status epilepticus 12 days after starting to take clomipramine 75 mg daily. The clomipramine serum level 7 hours after the last dose was 342 nanograms/mL (usual levels 68 to 272 nanograms/mL). The seizure was attributed to the elevated clomipramine levels.[5] Similarly, a patient taking clomipramine 150 mg daily, suffered feelings of numbness and sleep disturbances attributed to elevated serum levels of clomipramine and desmethylclomipramine, caused by valproate 1 to 1.4 g daily. Halving the dose of clomipramine restored serum concentrations to therapeutic levels.[6]

(c) Desipramine

A woman taking valproic acid, tiotixene and desipramine developed elevated and potentially toxic serum desipramine levels (a rise from 259 nanograms/mL to 324 nanograms/mL) at the end of a 3-month period during which valproic acid was gradually withdrawn and replaced by clorazepate. The authors of the report attributed this reaction to the valproic acid withdrawal.[7]

(d) Nortriptyline

One patient developed grossly elevated nortriptyline plasma levels (393 nanograms/mL, about threefold higher than the therapeutic range) and evidence of toxicity (tremulousness of hands and fingers) about one week after starting to take valproate 750 mg to 1 g daily. The toxicity rapidly disappeared when both drugs were stopped. Another patient, with bipolar disorder, also developed elevated nortriptyline plasma levels, attributed to the addition of valproate, and his rate of mood cycling increased.[8]

Mechanism

Uncertain. Inhibition of the metabolism of these tricyclics by valproate has been suggested.[5,6,8]

Importance and management

Information seems to be limited to these reports, and an interaction is not established. However, if tricyclic adverse effects (e.g. dry mouth, urinary retention, constipation) develop in patients also taking valproate it would be prudent to consider an interaction as a possible cause.

The occurrence of status epilepticus in one patient reinforces the fact that the tricyclics can lower the convulsive threshold and should therefore be used with caution in patients with epilepsy.

1. Wong SL, Cavanaugh J, Shi H, Awni WM, Granneman GR. Effects of divalproex sodium on amitriptyline and nortriptyline pharmacokinetics. *Clin Pharmacol Ther* (1996) 60, 48–53.
2. Bertschy G, Vandel S, Jounet JM, Allers G. Interaction valpromide-amitriptyline. Augmentation de la biodisponibilité de l'amitriptyline et de la nortriptyline par le valpromide. *Encephale* (1990) 16, 43–5.
3. Vandel S, Bertschy G, Jounet JM, Allers G. Valpromide increases the plasma concentrations of amitriptyline and its metabolite nortriptyline in depressive patients. *Ther Drug Monit* (1988) 10, 386–9.
4. Pisani F, Primerano G, D'Agostino AA, Spina E, Fazio A. Valproic acid-amitriptyline interaction in man. *Ther Drug Monit* (1986) 8, 382–3.
5. DeToledo JC, Haddad H, Ramsay RE. Status epilepticus associated with the combination of valproic acid and clomipramine. *Ther Drug Monit* (1997) 19, 71–3.
6. Fehr C, Gründer G, Hiemke C, Dahmen N. Increase in serum clomipramine concentrations caused by valproate. *J Clin Psychopharmacol* (2000) 20, 493–4.
7. Joseph AB, Wroblewski BA. Potentially toxic serum concentrations of desipramine after discontinuation of valproic acid. *Brain Inj* (1993) 7, 463–5.
8. Fu C, Katzman M, Goldbloom DS. Valproate/nortriptyline interaction. *J Clin Psychopharmacol* (1994) 14, 205–6.

Tricyclic antidepressants + Yohimbine

Low-dose yohimbine may reduce dry mouth and orthostatic hypotension associated with tricyclic antidepressants. Amitriptyline and clomipramine may increase yohimbine plasma concentrations.

Clinical evidence

In a study, 12 patients with orthostatic hypotension associated with **clomipramine** 150 mg daily for 2 to 7 days were given oral yohimbine 4 mg three times daily. Yohimbine appeared to decrease the orthostatic hypotension and induced a significant increase in blood pressure at a dose not usually associated with changes in blood pressure. However, yohimbine levels measured 2 hours after dosing were much greater than those seen in healthy subjects not taking **clomipramine** and the plasma levels of yohimbine appeared to correlate with the levels of desmethylclomipramine but not with those of **clomipramine**.[1]

Another study found that low-dose yohimbine 4 mg significantly increased the salivary volume for 3 hours in 10 patients with depression taking **amitriptyline** or **clomipramine**, but had no effect on salivary volume in healthy subjects not taking tricyclics. Plasma levels of yohimbine after 90 minutes were 72.7 nanograms/mL in the patients taking the tricyclics, compared with 18.7 nanograms/mL in healthy subjects not taking tricyclics.[2]

Mechanism

Not fully understood. A pharmacodynamic interaction may occur, involving α_2-adrenoceptor inhibition by yohimbine and inhibition of noradrenaline (norepinephrine) reuptake by the tricyclic antidepressant. A

pharmacokinetic interaction may occur as yohimbine and tricyclic antidepressants are both hydroxylated by hepatic enzymes. An interaction could also occur due to decreased first pass hepatic clearance of yohimbine.

Importance and management

The usefulness of this interaction in the treatment of antidepressant-associated dry mouth and hypotension is uncertain. Yohimbine is chemically similar to reserpine and may increase anxiety; the manufacturer of yohimbine warns that it should not be used in conjunction with mood-modifying drugs such as antidepressants.[3] If concurrent use is undertaken it would be prudent to be aware that yohimbine levels may be raised, and be alert for adverse effects that may occur as a result of this.

1. Lacomblez L, Bensimon G, Isnard F, Diquet B, Lecrubier Y, Puech AJ. Effect of yohimbine on blood pressure in patients with depression and orthostatic hypotension induced by clomipramine. *Clin Pharmacol Ther* (1989) 45, 241–51.
2. Bagheri H, Picault P, Schmitt L, Houin G, Berlan M, Montastruc JL. Pharmacokinetic study of yohimbine and its pharmacodynamic effects on salivary secretion in patients treated with tricyclic antidepressants. *Br J Clin Pharmacol* (1994) 37, 93–6.
3. Yocon (Yohimbine hydrochloride). Glenwood, LLC. US Prescribing information, March 2009.

Tricyclic antidepressants; Amitriptyline + Ethchlorvynol

Transient delirium has been attributed to the concurrent use of amitriptyline and ethchlorvynol,[1] but no details were given and there appear to be no other reports confirming this alleged interaction. Its general relevance is therefore probably small.

1. Hussar DA. Tabular compilation of drug interactions. *Am J Pharm* (1969) 141, 109–56.

Tricyclic antidepressants; Desipramine + Febuxostat

Febuxostat does not affect the pharmacokinetics of desipramine.

Clinical evidence, mechanism, importance and management

A placebo-controlled crossover study in 18 subjects, febuxostat 120 mg daily modestly increased the total exposure to a single 25-mg oral dose of desipramine. The maximum plasma concentration and AUC of desipramine were increased by 14% and 12%, respectively.[1] The incidence of adverse events was similar for both treatment regimens.

The pharmacokinetic changes are too small to be clinically relevant and therefore no desipramine dosage adjustment is necessary in patients also given febuxostat.

1. Khosravan R, Erdman K, Vernillet L, Wu JT, Joseph-Ridge N, Umeda S, Mulford D. Effect of febuxostat on pharmacokinetics of desipramine, a CYP2D6 substrate, in healthy subjects. *Clin Pharmacol Ther* (2005) 77, P43.

Tricyclic antidepressants; Doxepin + Tamoxifen

An isolated report describes a reduction in doxepin serum levels, which was attributed to the use of tamoxifen.

Clinical evidence, mechanism, importance and management

A 79-year-old woman with a long history of bipolar disorder, which was stabilised with lithium carbonate and doxepin 200 mg at bedtime, was given tamoxifen 20 mg daily after a mastectomy for breast cancer. It was noted that her total blood levels of doxepin and its major metabolite were reduced by about 25% over the next 11 months. The control of her depression remained unchanged. The reasons for this apparent interaction are not known.[1] The manufacturer of tamoxifen has another undetailed and isolated report of a possible interaction.[2]

These appears to be the only reports of an interaction between a tricyclic antidepressant and tamoxifen so that their general importance is not known. The evidence is too sparse to warrant recommending any particular precautions.

1. Jefferson JW. Tamoxifen-associated reduction in tricyclic antidepressant levels in blood. *J Clin Psychopharmacol* (1995) 15, 223–4.
2. Zeneca, Personal communication. November 1995.

Tricyclic antidepressants; Imipramine + Vinpocetine

Vinpocetine does not appear to affect imipramine levels.

Clinical evidence, mechanism, importance and management

In 18 healthy subjects the steady-state plasma levels of imipramine 25 mg three times daily were unaffected by vinpocetine 10 mg three times daily, when both drugs were taken together for 10 days.[1] No imipramine dose adjustments are therefore likely be necessary if vinpocetine is also given. There seems to be nothing documented about any of the other tricyclic antidepressants.

1. Hitzenberger G, Schmid R, Braun W, Grandt R. Vinpocetine therapy does not change imipramine pharmacokinetics in man. *Int J Clin Pharmacol Ther Toxicol* (1990) 28, 99–104.

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Thyroid hormones

This section covers the interactions where there is documented evidence that a drug alters the efficacy of thyroid hormones. The mechanism for this can be pharmacokinetic (altered absorption or metabolism) or pharmacodynamic (when the drug in question alters thyroid function).

Thyroid hormones + Amiodarone

Patients taking levothyroxine for hypothyroidism may develop elevated levels of thyroid-stimulating hormone or overt hypothyroidism if they are also given amiodarone.

Clinical evidence

A patient with hypothyroidism who was euthyroid while taking **levothyroxine** 75 micrograms daily had an increase in TSH, up to 20 to 30 mU/L within about 10 weeks of starting amiodarone (initially 800 mg daily, reduced to 200 mg daily).The thyroxine/T3 ratio decreased by 33%. She developed fatigue, weakness, cold intolerance and hyponatraemia. **Levothyroxine** was gradually increased to 112 micrograms daily, amiodarone was maintained at 200 mg daily. The TSH levels decreased to 4.2 mU/L and the symptoms of hypothyroidism resolved.[1] Similar increases in TSH were reported when two other patients receiving stable doses of **levothyroxine** started taking amiodarone.[1,2]

In a study investigating the effect of amiodarone and **levothyroxine** treatment, 5 patients were given **levothyroxine** 300 micrograms daily for 16 days, with amiodarone 400 mg daily from day 10 to day 16. When compared with a control group taking **levothyroxine** alone, there was a significant fall in serum T3 levels and a rise in reverse-T3 levels. This suggests that amiodarone interferes with thyroid hormone metabolism, possibly leading to hypothyroidism, even in the presence of **levothyroxine**.[3]

Mechanism

Amiodarone has complex effects on thyroid function and may cause hypothyroidism or hyperthyroidism in some euthyroid patients. Amiodarone has direct effects on the thyroid gland and also alters serum levels of thyroid hormones. Basal-serum TSH levels increase when amiodarone is started, but generally decrease to normal after about 3 months of treatment. Amiodarone reduces the peripheral conversion of thyroxine to T3 which results in an increase in thyroxine, a modest decrease in T3 and a decrease in reverse-T3 clearance.

Importance and management

Amiodarone is well-known to be a cause of hypothyroidism or hyperthyroidism, and thyroid function should be regularly assessed when it is used. Particular care is required in patients with thyroid dysfunction, in whom amiodarone use might not be appropriate. The UK manufacturer of amiodarone[4] contraindicates its use in patients with current or a history of thyroid dysfunction, although levothyroxine has been used to manage amiodarone-induced hypothyroidism in some patients.[4,5] It would be prudent for patients taking levothyroxine or **liothyronine** and amiodarone to have their thyroid function very closely monitored. Note that, if amiodarone is discontinued, its effects will persist for a very long time due to its prolonged half-life (mean of 53 days).

1. Figge J, Dluhy RG. Amiodarone-induced elevation of thyroid stimulating hormone in patients receiving levothyroxine for primary hypothyroidism. *Ann Intern Med* (1990) 113, 553–5.
2. Sanmartí A, Lucas A, Castellanos JM, Foz M. Modificaciones en las concentraciones de hormonas tiroideas en un paciente tiroidectomizado en tratamiento con levotiroxina y amiodarona. *Med Clin (Barc)* (1989) 93, 195.
3. Burger A, Dinichert D, Nicod P, Jenny M, Lemarchand-Béraud T, Vallotton MB. Effect of amiodarone on serum triiodothyronine, reverse triiodothyronine, thyroxin, and thyrotropin. A drug influencing peripheral metabolism of thyroid hormones. *J Clin Invest* (1976) 58, 255–9.
4. Cordarone X (Amiodarone hydrochloride). Sanofi-Aventis. UK Summary of product characteristics, March 2009.
5. Cordarone (Amiodarone hydrochloride). Wyeth Pharmaceuticals Inc. US Prescribing information, August 2009.

Thyroid hormones + Androgens

A study suggests that patients with hypothyroidism may require levothyroxine dose reductions if they are given fluoxymesterone. Liothyronine is expected to interact similarly.

Clinical evidence, mechanism, importance and management

In a study, 11 women with metastatic, hormone-dependent breast cancer were given **fluoxymesterone** 10 mg twice daily. After 4 weeks of treatment, 7 of the patients who had no evidence of thyroid disease had decreased serum levels of total thyroxine and thyroxine-binding globulin, but their calculated free thyroxine index and measured free hormone levels were unchanged. These patients remained asymptomatic 6 to 12 weeks after **fluoxymesterone** was discontinued, with serum levels returning to baseline. In contrast the other 4 patients, whose primary hypothyroidism of 5 to 20 years duration was stabilised with **levothyroxine**, developed hyperthyroidism after starting **fluoxymesterone** 10 mg twice daily. Their serum free thyroxine levels increased and their TSH levels decreased. **Levothyroxine** dose reductions of between 25 and 50% were required to maintain a euthyroid state.[1]

Other studies have reported a decrease in the binding capacity of thyroxine-binding globulin and an increase in the binding of thyroxine-binding prealbumin after the short-term use of androgens, but the exact mechanism is not known.[2,3]

Evidence for an interaction between fluoxymesterone and levothyroxine appears to be limited to this study. However, what is known suggests that patients with thyroid dysfunction who are receiving levothyroxine may need dosage adjustments to remain euthyroid if fluoxymesterone is started. Evidence regarding possible interactions of both **liothyronine** and other thyroid hormones appears to be lacking, but the available evidence suggests that they may interact in the same way. Therefore if any patient with thyroid dysfunction taking a thyroid hormone is given an androgen it would be prudent to be alert for symptoms of hypothyroidism. If such symptoms occur, monitor thyroid hormones, and adjust the dose of the thyroid hormone accordingly.

1. Arafah BM. Decreased levothyroxine requirement in women with hypothyroidism during androgen therapy for breast cancer. *Ann Intern Med* (1994) 121, 247–51.
2. Braverman LE, Ingbar SH. Effects of norethandrolone on the transport in serum and peripheral turnover of thyroxine. *J Clin Endocrinol Metab* (1967) 28, 389–96.
3. Braverman LE, Socolow EL, Woeber KA, Ingbar SH. Effect of norethandrolone on the metabolism of 125-I-labeled thyroxine-binding prealbumin. *J Clin Endocrinol Metab* (1968) 28, 831–5.

Thyroid hormones + Antacids

A few reports describe reduced levothyroxine effects in patients given aluminium or magnesium-containing antacids.

Clinical evidence, mechanism, importance and management

A man with hypothyroidism corrected with **levothyroxine** 150 micrograms daily developed high serum TSH levels (a rise from 1.1 mU/L up to 36 mU/L) while taking an **aluminium**/**magnesium hydroxide** antacid (*Silain-Gel*), and on two subsequent occasions when rechallenged. The reasons are not understood. Although he remained asymptomatic throughout,[1] the rise in the levels of TSH indicated that the dosage of **levothyroxine** had become insufficient in the presence of the antacid. Two similar cases have also been reported, where the presence of an **aluminium**/**magnesium** antacid or **magnesium oxide** reduced the response to **levothyroxine**. One patient required four times her normal dose of **levothyroxine**.[2]

The general importance of this interaction is not known, but be alert for the need to increase the **levothyroxine** dosage in any patient given antacids. More study is needed. Calcium-containing antacids may interact similarly, see 'Thyroid hormones + Calcium compounds', p.1521.

1. Sperber AD, Liel Y. Evidence for interference with the intestinal absorption of levothyroxine sodium by aluminum hydroxide. *Arch Intern Med* (1991) 152, 183–4.
2. Mersebach H, Rasmussen ÅK, Kirkegaard L, Feldt-Rasmussen U. Intestinal adsorption of levothyroxine by antacids and laxatives: case stories and *in vitro* experiments. *Pharmacol Toxicol* (1999) 84, 107–9.

Thyroid hormones + Barbiturates

An isolated report describes thyrotoxicosis when a patient taking levothyroxine reduced her dose of secobarbital with amobarbital.

Clinical evidence, mechanism, importance and management

An elderly woman taking **levothyroxine** 300 micrograms daily for hypothyroidism complained of severe breathlessness within a week of reducing her nightly dose of *Tuinal* (**secobarbital** 100 mg with **amobarbital** 100 mg) from two capsules to one capsule. She was subsequently found to be thyrotoxic. She became symptom-free again when the dosage of the **levothyroxine** was halved.[1] The reason for this effect is not known, but **phenobarbital** has been shown to reduce the serum levels of endogenous

thyroid hormones in some studies,[2] and it seems possible that in this case these other two barbiturates acted in the same way. This effect has also been seen with other enzyme-inducing drugs, see 'Thyroid hormones + Carbamazepine or Phenytoin', p.1522.

The general importance of this interaction is almost certainly small, but be alert for any evidence of changes in thyroid status if barbiturates are added or withdrawn from patients taking **levothyroxine**. Monitor thyroid hormones levels if an interaction is suspected, and adjust the levothyroxine dose accordingly. Although the possibility of a similar interaction with **liothyronine** does not appear to have been studied, it would seem prudent to be alert for a similar reduction in its effect in the presence of barbiturates.

1. Hoffbrand BI. Barbiturate/thyroid-hormone interaction. *Lancet* (1979) ii, 903–4.
2. Ohnhaus EE, Studer H. A link between liver microsomal enzyme activity and thyroid hormone metabolism in man. *Br J Clin Pharmacol* (1983) 15, 71–6.

Thyroid hormones + Bile-acid binding resins

The absorption of thyroid extract, levothyroxine, and liothyronine from the gut is reduced by the concurrent use of colestyramine. Colesevelam also decreases levothyroxine absorption.

Clinical evidence

(a) Colestyramine

A patient with hypothyroidism, taking **levothyroxine**, had a fall in his basal metabolic rate when given colestyramine: this prompted a further study in two similar patients taking **thyroid extract** 60 mg daily or **levothyroxine** 100 micrograms daily, and 5 healthy subjects. Colestyramine 4 g four times daily reduced the absorption of **levothyroxine**^{131}, the amount recovered in the faeces being roughly doubled. One of the patients had a worsening of her hypothyroidism. Giving the **levothyroxine** 4 to 5 hours after the colestyramine reduced but did not completely prevent the interaction.[1] Another report describes a patient taking **levothyroxine** whose TSH levels rose when colestyramine was taken, and fell again when it was stopped, indicating an impairment of **levothyroxine** absorption.[2] Two case reports, describe the use of colestyramine to achieve a more rapid return to normal thyroid function in patients who have become hyperthyroid while taking levothyroxine,[3] and in a case of levothyroxine overdose.[4] A further case report describes a patient taking **levothyroxine** and colestyramine, who only became euthyroid when the **levothyroxine** was taken in the morning, and the colestyramine was taken at night.[5]

(b) Colesevelam

In a single-dose study, 6 healthy subjects were given a large dose of **levothyroxine** (1000 micrograms) at the same time as colesevelam 3.75 g. Colesevelam decreased the serum thyroxine $AUC_{0\text{-}6}$ by 96%.[6] A study by the manufacturer reported a smaller decrease in levothyroxine absorption: the same dose of colesevelam decreased the $AUC_{0\text{-}\infty}$ of a 600-microgram dose of **levothyroxine** by 22%.[7]

Mechanism

Colestyramine and colesevelam bind to levothyroxine in the gut, thereby reducing its absorption. Since levothyroxine probably also undergoes enterohepatic recirculation, continued contact with these bile-acid sequestrants is possible and separating administration may not entirely eliminate the interaction.

Importance and management

The interaction between levothyroxine and colestyramine appears to be established (although the documentation is very limited) and the reduced thyroxine levels that result are of clinical importance. *In vitro* tests show that **liothyronine** interacts with colestyramine similarly.[1] The interaction can be minimised by separating the dosages by 4 to 6 hours (but see *Mechanism*, above). Even so, the outcome should be monitored so that any necessary thyroid hormone dosage adjustments can be made.

Similarly, the interaction between colesevelam and levothyroxine is of clinical importance. Levothyroxine should be given 4 hours before colesevelam.[7]

1. Northcutt RC, Stiel JN, Hollifield JW, Stant EG. The influence of cholestyramine on thyroxine absorption. *JAMA* (1969) 208, 1857–61.
2. Harmon SM, Seifert CF. Levothyroxine-cholestyramine interaction reemphasized. *Ann Intern Med* (1991) 115, 658–9.
3. Shakir KMM, Michaels RD, Hays JH, Potter BB. The use of bile acid sequestrants to lower serum thyroid hormones in iatrogenic hyperthyroidism. *Ann Intern Med* (1993) 118, 112–13.
4. de Luis DA, Dueñas A, Martin J, Abad L, Cuellar L, Aller R. Light symptoms following a high-dose intentional *L*-thyroxine ingestion treated with cholestyramine. *Horm Res* (2002) 57, 61–3.
5. Rosenberg R. Malabsorption of thyroid hormone with cholestyramine administration. *Conn Med* (1994) 58, 109.
6. Weitzman SP, Ginsburg KC, Carlson HE. Colesevelam hydrochloride and lanthanum carbonate interfere with the absorption of levothyroxine. Thyroid (2009) 19, 77–79.
7. Welchol (Colesevelam hydrochloride). Daiichi Sankyo, Inc. US Prescribing information, October 2009.

Thyroid hormones + Calcium compounds

The efficacy of levothyroxine can be reduced by calcium carbonate, whereas calcium acetate might not interact.

Clinical evidence

(a) Calcium acetate

In a retrospective study, 67 patients were identified who were taking **levothyroxine** and a phosphate binder (calcium carbonate, calcium acetate or sevelamer). The TSH levels were significantly higher in patients taking calcium carbonate or sevelamer (both thought to reduce **levothyroxine** efficacy) than calcium acetate, and the effects became more pronounced over time, suggesting that calcium acetate had little effect on the efficacy of **levothyroxine**.[1]

(b) Calcium carbonate

In a study, 20 patients with hypothyroidism were given **levothyroxine**, to which calcium carbonate 1.2 g daily was then added for 3 months. While taking the calcium carbonate their mean free thyroxine levels fell from 16.7 picomol/L to 15.4 picomol/L and rose again to 18 picomol/L when it was stopped. The mean total thyroxine levels over the same period were about 118 nanomol/L, 111 nanomol/L and 120 nanomol/L, respectively, and the mean TSH levels were 1.6 mU/L, 2.7 mU/L and 1.4 mU/L, respectively.[2]

A woman with thyroid cancer taking **levothyroxine** 125 micrograms daily to suppress serum TSH levels had a reduced response (fatigue, weight gain) when she took *Tums* containing calcium carbonate for the prevention of osteoporosis. She often took the two together. Over a 5-month period her serum TSH levels rose from 0.08 mU/L to 13.3 mU/L. Within 3 weeks of stopping the calcium carbonate, her serum TSH levels had fallen to 0.68 mU/L.[3] Other reports have described 5 patients who had elevations in their TSH levels while taking calcium carbonate with **levothyroxine**. All levels returned to normal when administration was separated by about 4 hours,[3-5] or in one case when the calcium supplementation was stopped.[6]

Mechanism

In vitro studies indicate that levothyroxine is adsorbed onto calcium carbonate when the pH is low (as in the stomach), which would reduce the amount available for absorption.[2]

Importance and management

An established interaction, which seems to be of limited clinical significance. The study cited[2] shows that the mean reduction in the absorption of levothyroxine is quite small, but the case reports[3,4] show that some individuals can experience a reduction in the absorption that is clinically important. Since it is impossible to predict which patients are likely to be clinically affected, the cautious approach would be to advise all patients to separate the dosages of the two preparations by at least 4 hours to avoid admixture in the gut. This interaction would be expected to occur with calcium carbonate in any form but it is not known whether other thyroid hormone preparations interact in the same way as levothyroxine. Limited evidence suggests that calcium acetate might not interact. Other calcium compounds do not appear to have been studied.

1. Diskin CJ, Stokes TJ, Dansby LM, Radcliff L, Carter TB. Effect of phosphate binders upon TSH and L-thyroxine dose in patients on thyroid replacement. *Int Urol Nephrol* (2007) 39, 599–602.
2. Singh N, Singh PN, Hershmann JM. Effect of calcium carbonate on the absorption of levothyroxine. *JAMA* (2000) 283, 2822–25.
3. Schneyer CR. Calcium carbonate and reduction of levothyroxine efficacy. *JAMA* (1998) 279, 750.

4. Butner LE, Fulco PP, Feldman G. Calcium carbonate-induced hypothyroidism. *Ann Intern Med* (2000) 132, 595.
5. Csako G, McGriff NJ, Rotman-Pikielny P, Sarlis NJ, Pucino F. Exaggerated levothyroxine malabsorption due to calcium carbonate supplementation in gastrointestinal disorders. *Ann Pharmacother* (2001) 35, 1578–83.
6. Mazokopakis EE, Giannakopoulos TG, Starakis IK. Interaction between levothyroxine and calcium carbonate. Can Fam Physician (2008) 54, 39.

Thyroid hormones + Carbamazepine or Phenytoin

Clinical hypothyroidism can occur in patients stable taking levothyroxine when they start carbamazepine or phenytoin. Correction of hypothyroidism with levothyroxine does not appear to affect the pharmacokinetics of phenytoin.

Clinical evidence

(a) Carbamazepine

In a study, when 10 patients, whose hypothyroidism was stabilised with **levothyroxine**, were given carbamazepine, there was a minor decrease of about 10 to 15% in free thyroxine, and a decrease of 15 to 25% in total thyroxine, with a consequent increase in TSH levels. In 3 of the 10 patients, the TSH level rose over 5 mU/L, requiring treatment adjustment. In a control group of 19 patients with no thyroid disorder, similar changes in thyroxine levels caused just a slight non-significant increase in TSH levels.[1] Similar findings were reported in another study when 5 children receiving stable doses of **levothyroxine** were given carbamazepine. In this study, 2 children had markedly increased TSH levels, and all 5 children had their **levothyroxine** dose increased to restore pre-treatment thyroid function.[2] Another study in 9 patients taking **levothyroxine** found that thyroxine and T3 levels were reduced after they had been taking carbamazepine for 3 weeks, but there was no change in TSH levels.[3]

(b) Phenytoin

A study in 7 patients found that the pharmacokinetics of phenytoin were unchanged by the addition of **levothyroxine**. The pharmacokinetics of phenytoin were assessed in the hypothyroid state and after the patients had been euthyroid for 4 to 11 months.[4]

In a study, 6 patients whose hypothyroidism was stabilised with **levothyroxine**, were given phenytoin 350 mg daily for 14 days. Phenytoin appeared to slightly reduce the intestinal absorption of **levothyroxine** and to increase the metabolism of thyroxine. Total and free serum levels of thyroxine and T3 were decreased and there was an associated increase in TSH.[5] A case report describes a patient with hypothyroidism that had been successfully managed with 150 micrograms of **levothyroxine** daily for 4 years, who developed hypothyroidism when given **phenytoin** 300 mg daily. Doubling the **levothyroxine** dosage proved to be effective. Later this interaction was confirmed when stopping and restarting the **phenytoin** produced the same effect.[6]

Mechanism

Both phenytoin and carbamazepine can increase the metabolism of endogenous thyroid hormones, thereby reducing their plasma levels, but this rarely results in hypothyroidism in euthyroid patients. However, in patients taking levothyroxine replacement therapy, the decrease appears more likely to be clinically relevant.[1]

Importance and management

Although the evidence is limited, this interaction is established. The available evidence suggests that some patients taking levothyroxine might require an increase in dose when they start carbamazepine or phenytoin. Be alert for this effect if both drugs are given, and monitor thyroid hormones levels if an interaction is suspected: adjust the levothyroxine dose accordingly. This effect has also been seen with other enzyme-inducing drugs. Consider also 'Thyroid hormones + Barbiturates', p.1520.

Given the proposed mechanism of the interaction with levothyroxine, it seems likely that **liothyronine** may be similarly affected by carbamazepine and phenytoin, but this does not appear to have been studied.

It has been suggested that the general increase in metabolism that occurs when hypothyroidism is corrected may cause an increase in the metabolism of phenytoin. However, one study suggests that this may not be the case.

1. Simko J, Horacek J. Carbamazepine and risk of hypothyroidism: a prospective study. *Acta Neurol Scand* (2007) 116, 317–21.
2. De Luca F, Arrigo T, Pandullo E, Siracusano MF, Benvenga S, Trimarchi F. Changes in thyroid function tests induced by 2 month carbamazepine treatment in L-thyroxine-substituted hypothyroid children. *Eur J Pediatr* (1986) 145, 77–9.
3. Aanderud S, Myking OL, Strandjord RE. The influence of carbamazepine on thyroid hormones and thyroxine binding globulin in hypothyroid patients substituted with thyroxine. *Clin Endocrinol (Oxf)* (1981) 15, 247–52.
4. Mølholm Hansen J, Skovsted L, Kampmann JP, Lumholtz BI, Siersbæk-Nielsen K. Unaltered metabolism of phenytoin in thyroid disorders. *Acta Pharmacol Toxicol (Copenh)* (1978) 42, 343–6.
5. Faber J, Lumholtz IB, Kirkegaard C, Poulsen S, Jørgensen PH, Siersbaek-Nielsen K, Friis T. The effects of phenytoin (diphenylhydantoin) on the extrathyroidal turnover of thyroxine, 3,5,3'-triiodothyronine, 3,3',5'-triiodothyronine, and 3',5'-diiodothyronine in man. *J Clin Endocrinol Metab* (1985) 61, 1093–9.
6. Blackshear JL, Schultz AL, Napier JS, Stuart DD. Thyroxine replacement requirements in hypothyroid patients receiving phenytoin. *Ann Intern Med* (1983) 99, 341–2.

Thyroid hormones + Chloroquine with Proguanil

An isolated case report describes a reduction in the control of hypothyroidism in a patient taking levothyroxine when chloroquine and proguanil antimalarial prophylaxis was given.

Clinical evidence, mechanism, importance and management

An isolated case report describes a woman with stable hypothyroidism taking levothyroxine 125 micrograms daily, who was given antimalarial prophylaxis with chloroquine 100 mg daily and proguanil 200 mg daily for 2 months. At a routine monitoring appointment 4 weeks later, she was noted to have a TSH level of 44.8 mU/L. No change was made to her levothyroxine dose and the increase in her TSH level resolved within one week of stopping both chloroquine and proguanil at the end of the required period of prophylaxis. A subsequent course of prophylaxis with the same antimalarial regimen produced a similar effect, with the TSH rising from 3.2 mU/L to 54.7 mU/L. This increase resolved within 4 weeks of stopping the antimalarials.[1]

This appears to be the only published report of an interaction between levothyroxine and the combination of chloroquine and proguanil, and its general significance is unclear, especially as no action appeared to be necessary to manage the effects of the interaction. This interaction may have more relevance to other indications for chloroquine, where it is used long-term, but more study is needed to establish this. However, until more is known, bear this case report in mind should a patient taking levothyroxine and either proguanil and/or chloroquine experiences an unexpected decrease in the control of their hypothyroidism.

1. Munera Y, Hugues FC, Le Jeunne C, Pays JF. Interaction of thyroxine sodium with antimalarial drugs. *BMJ* (1997) 314, 1593.

Thyroid hormones + Chromium compounds

Chromium picolinate decreases levothyroxine absorption.

Clinical evidence, mechanism, importance and management

In a single-dose study in 7 healthy subjects, giving a large dose of **levothyroxine** (1000 micrograms) at the same time as chromium picolinate 1 mg resulted in a 17% decrease in the $AUC_{0\text{-}6}$ of thyroxine.[1] This preliminary evidence suggests that, until more is known, it would be prudent to be alert for symptoms of hypothyroidism. If such symptoms occur, monitor thyroid hormones, and adjust the dose of the **levothyroxine** accordingly. Separation of administration might minimise any interaction, but this needs confirmation.

1. John-Kalarickal J, Pearlman G, Carlson HE. New medications which decrease levothyroxine absorption. *Thyroid* (2007) 17, 763–5.

Thyroid hormones + Ciprofloxacin

A case report describes unexplained hypothyroidism in two patients taking levothyroxine who had also been taking ciprofloxacin.

Clinical evidence, mechanism, importance and management

An 80-year-old patient with advanced thyroid cancer taking **levothyroxine** 125 micrograms daily was given oral ciprofloxacin 750 mg twice daily and intravenous dicloxacillin for osteomyelitis complicating a fracture. After 4 weeks of treatment she complained of increasing tiredness, and was found to have a markedly raised TSH level (10 times of the upper limit of the reference range). Increasing the **levothyroxine** dose to 200 micrograms daily did not have any effect on TSH, so the dose was returned to 125 micrograms. The ciprofloxacin was then stopped, and the thyroid function tests rapidly normalised.[1]

Another woman, with stable thyroid function, taking **levothyroxine** 150 micrograms daily, had a more than tenfold increase in TSH levels after taking ciprofloxacin 500 mg twice daily for 3 weeks.[1] When administration of **levothyroxine** and ciprofloxacin was separated by 6 hours, the thyroid function tests normalised, which suggests that concurrent dosing somehow reduces the absorption of **levothyroxine**.

This interaction is not established, but the two cases suggest that long-term ciprofloxacin should be considered as a possible cause of hypothyroidism in patients taking **levothyroxine**. Further study is needed.

1. Cooper JG, Harboe K, Frost SK, Skadberg Ø. Ciprofloxacin interacts with thyroid replacement therapy. *BMJ* (2005) 330, 1002.

Thyroid hormones + Ezetimibe

Ezetimibe does not appear to alter levothyroxine absorption.

Clinical evidence, mechanism, importance and management

In a single-dose study in 7 healthy subjects, giving a large dose of **levothyroxine** (1000 micrograms) at the same time as ezetimibe 10 mg did not alter the AUC_{0-6} of thyroxine.[1] Similarly, in another single-dose study, in 10 healthy subjects, **ezetimibe** 10 mg did not affect the AUC of serum thyroxine in response to a single 600-microgram dose of **levothyroxine**.[2]

These findings suggest that levothyroxine requirements are unlikely to change in patients taking ezetimibe.

1. John-Kalarickal J, Pearlman G, Carlson HE. New medications which decrease levothyroxine absorption. *Thyroid* (2007) 17, 763–5.
2. Ananthakrishnan S, Braverman LE, Levin RM, Magnani B, Pearce EN. The effect of famotidine, esomeprazole, and ezetimibe on levothyroxine absorption. Thyroid (2008) 18, 493–8.

Thyroid hormones + Grapefruit juice

A case report describes hypothyroidism in a patient taking levothyroxine, which resolved when grapefruit juice consumption was reduced. However, a pharmacokinetic study suggests that generally an interaction is unlikely.

Clinical evidence, mechanism, importance and management

A 36-year-old woman with previously stable thyroid function taking **levothyroxine** 100 micrograms daily and with a marked consumption of grapefruit juice (specific volumes not stated) had a very high TSH level even after an increase in her **levothyroxine** dose to 150 micrograms daily. When she was advised to drink less grapefruit juice, her TSH fell to within the normal range.[1]

This case prompted a crossover study in 10 healthy subjects, which found that grapefruit juice caused only a slight 11% reduction in the maximal increase in thyroxine after a single 600-microgram dose of **levothyroxine**. In this study, normal-strength grapefruit juice 200 mL was taken 3 times a day for 2 days, then on the third day, grapefruit juice 200 mL was taken one hour before, simultaneously with, and one hour after, **levothyroxine**.[1]

The pharmacokinetic study established that grapefruit juice appears to have only small effects on thyroxine levels in those taking **levothyroxine**, which suggests that a clinically relevant interaction is unlikely. However, consider this case in the event of an unexpected decreased response to **levothyroxine**.

1. Lilja JJ, Laitinen K, Neuvonen PJ. Effects of grapefruit juice on the absorption of levothyroxine. *Br J Clin Pharmacol* (2005) 60, 337–41.

Thyroid hormones + H_2-receptor antagonists

Cimetidine, but not ranitidine or famotidine, causes a small reduction in the absorption of levothyroxine.

Clinical evidence, mechanism, importance and management

In a study in 10 women with simple goitre, **cimetidine** 400 mg, given 90 minutes before a single capsule of **levothyroxine**, reduced absorption of **levothyroxine** over the first 4 hours by about 21%. The reasons are not understood. A single 300-mg dose of **ranitidine** was found not to affect the absorption of **levothyroxine** in a matched group of 10 women.[1] Similarly, in a study in 10 healthy subjects, **famotidine** 20 mg twice daily for one week did not affect the AUC of serum thyroxine in response to a single 600-microgram dose of **levothyroxine**.[2]

The clinical importance of this interaction with **cimetidine** awaits assessment, but the magnitude of the effect is small, and therefore it seems unlikely to be generally significant.

1. Jonderko G, Jonderko K, Marcisz CZ, Kotulska A. Effect of cimetidine and ranitidine on absorption of [^{125}I] levothyroxine administered orally. *Acta Pharmacol Sin* (1992) 13, 391–4.
2. Ananthakrishnan S, Braverman LE, Levin RM, Magnani B, Pearce EN. The effect of famotidine, esomeprazole, and ezetimibe on levothyroxine absorption. Thyroid (2008) 18, 493–8.

Thyroid hormones + Imatinib and Sunitinib

Imatinib appears to cause hypothyroidism in thyroidectomy patients taking levothyroxine. A possible case has also occurred with sunitinib.

Clinical evidence

Retrospective analysis of 11 patients with thyroid cancer taking **levothyroxine** found that 8 patients who had previously undergone a total thyroidectomy developed markedly elevated TSH levels and were clinically hypothyroid after taking **imatinib**. Despite a mean threefold increase in the dose of **levothyroxine**, hypothyroidism was reversed in only 3 patients. Thyroid function tests normalised on discontinuing imatinib. Conversely, no effect on thyroid function was seen in the 3 patients who had not had their thyroid gland removed.[1]

In another report by the same authors, a woman is described who remained euthyroid when restarting **imatinib** when her **levothyroxine** dose was immediately increased from 175 micrograms daily to 300 micrograms daily. However, she was unable to tolerate the imatinib, and this was discontinued. Five months later she started taking **sunitinib** 50 mg daily for 4 weeks of a 6-week cycle. After 3 days her TSH levels rose, with normal free thyroxine and T3 levels, and the **levothyroxine** dose was increased to 300 micrograms daily. However, the TSH levels failed to return to normal, and, additionally, haematological toxicity occurred. When her blood counts recovered, she received a reduced dose of sunitinib 37.5 mg with **levothyroxine** 300 micrograms daily for the second cycle. On this cycle she remained euthyroid without serious haematological toxicity.[2]

Mechanism

The authors postulated that imatinib might increase the clearance of the thyroid hormones thyroxine and T3 by inducing glucuronosyltransferases (UGTs).[1] Patients who have undergone a thyroidectomy cannot respond to these changes and therefore become hypothyroid. Sunitinib alone commonly causes hypothyroidism.[3]

Importance and management

The findings appear to be established. TSH levels should be closely monitored in thyroidectomy patients taking levothyroxine if they are given imatinib, anticipating the need to increase the levothyroxine dose. The authors suggest that in thyroidectomy patients the dose of levothyroxine should be doubled before starting imatinib.[1] Note that toxicity of imatinib (fatigue and periorbital oedema) may be indistinguishable from symptoms of hypothyroidism.[2]

Patients receiving sunitinib should also have their thyroid function monitored.[3]

1. de Groot JWB, Zonnenberg BA, Plukker JTM, van Der Graaf WTA, Links TP. Imatinib induces hypothyroidism in patients receiving levothyroxine. *Clin Pharmacol Ther* (2005) 78, 433–8.
2. de Groot JWB, Links TP, van der Graaf WTA. Tyrosine kinase inhibitors causing hypothyroidism in a patient on levothyroxine. *Ann Oncol* (2006) 17, 1719–20.
3. Sutent (Sunitinib malate). Pfizer Ltd. UK Summary of product characteristics, October 2009.

Thyroid hormones + Iron compounds

Ferrous sulfate causes a reduction in the effects of levothyroxine in patients with treated hypothyroidism.

Clinical evidence

In a study, 14 patients whose primary hypothyroidism was stabilised with **levothyroxine** had an increase in TSH levels from 1.6 to 5.4 mU/L when given **ferrous sulfate** 300 mg daily for 12 weeks. The symptoms of hypothyroidism in 9 patients worsened.[1] In another report, a woman whose hypothyroidism was stabilised with **levothyroxine**, had a very marked rise in TSH levels when she took **ferrous sulfate**. Her **levothyroxine** dosage needed to be raised from 175 micrograms daily to 200 micrograms daily.[2] Another similar report is described, in which a pregnant woman required an increase in her **levothyroxine** dose, from 150 to 250 micrograms daily, while taking **ferrous sulfate** 325 mg three times daily with meals and levothyroxine at bedtime. When the ferrous sulfate was stopped after delivery she had symptoms of hyperthyroidism, and required a reduction in her levothyroxine dose to the original level. When the ferrous sulfate was restarted 12 weeks postpartum, the same interaction occurred.[3]

Mechanism

The addition of iron to levothyroxine *in vitro* was found to produce a poorly soluble purple iron-levothyroxine complex. This might also occur in the gut.[1]

Importance and management

Information is limited to these reports but the interaction between ferrous sulfate and levothyroxine appears to be clinically important. Be alert for this effect if both drugs are given, and monitor thyroid hormone levels if an interaction is suspected: adjust the levothyroxine dose accordingly. Although it has been suggested that the doses of ferrous sulfate and levothyroxine should be separated by 2 hours or more, on the assumption that reduced absorption accounts for this interaction,[1] the later case report suggests that this might not prevent the interaction.[3] The same precautions would seem appropriate with any other iron compound.

1. Campbell NRC, Hasinoff BB, Stalts H, Rao B, Wong NCW. Ferrous sulfate reduces thyroxine efficacy in patients with hypothyroidism. *Ann Intern Med* (1992) 117, 1010–3.
2. Schlienger JL. Accroissement des besoins en thyroxine par le sulfate de fer. *Presse Med* (1994) 23, 492.
3. Shakir KMM, Chute JP, Aprill BS, Lazarus AA. Ferrous sulfate-induced increase in requirement for thyroxine in a patient with primary hypothyroidism. *South Med J* (1997) 90, 637–9.

Thyroid hormones + Lanthanum

Lanthanum carbonate decreases levothyroxine absorption.

Clinical evidence, mechanism, importance and management

In a single-dose study, 6 healthy subjects were given a large dose of **levothyroxine** (1000 micrograms) at the same time as lanthanum carbonate 500 mg. Lanthanum decreased the serum thyroxine AUC_{0-6} by about 40%.[1]

The interaction between levothyroxine and lanthanum appears to be established (although the documentation is very limited) and the reduced thyroxine levels that result seem likely to be of clinical importance.

Other absorption interactions of lanthanum can be minimised by separating the dosages by 2 hours, and it would seem prudent to apply this precaution to the interaction with **levothyroxine**. Even so, the outcome should be monitored so that any necessary thyroid hormone dosage adjustments can be made.

1. Weitzman SP, Ginsburg KC, Carlson HE. Colesevelam hydrochloride and lanthanum carbonate interfere with the absorption of levothyroxine. Thyroid (2009) 19, 77–79.

Thyroid hormones + Oestrogens

Oral HRT appears to increase the requirement for levothyroxine in some patients. This effect may therefore be expected with combined hormonal contraceptives, although no interaction has been reported.

Clinical evidence

In 25 postmenopausal women taking stable doses of **levothyroxine** (for hypothyroidism or TSH suppression), the addition of HRT (**conjugated oestrogens** 0.625 mg daily with or without **medroxyprogesterone acetate** 5 mg daily for 12 days each month) decreased serum free thyroxine levels and increased TSH levels. The changes in TSH were clinically important in 10 of the 25 women, requiring increased doses of **levothyroxine**, although only one woman had symptoms of hypothyroidism.[1]

Mechanism

Oestrogens increase thyroxine binding-globulin. In women with normal thyroid function this does not alter free thyroxine levels or TSH levels,[1] as the thyroxine secretion can increase to accommodate the changes. However, in women with hypothyroidism, who cannot compensate for the increased thyroxine binding, decreased free thyroxine and therefore increased TSH can result. One crossover study found that oral HRT (conjugated oestrogens) had a greater effect on thyroxine levels and thyroxine-binding globulin than transdermal HRT (**ethinylestradiol**), which had minimal effects on these markers of thyroid function. Thyroxine binding-globulin is synthesised in the liver, and it is suggested that oral oestrogens increase this synthesis more than transdermal oestrogens because higher concentrations of oestrogen are present in the liver following oral dosing: an oral dose of oestrogen undergoes first-pass metabolism in the liver whereas transdermal oestrogens do not.[2]

Importance and management

Although this study appears to be the only evidence of an interaction, it would be prudent to monitor thyroid function several months after starting or stopping HRT to check levothyroxine requirements. This potential interaction should not affect the management and dosing of patients already taking HRT and newly started on levothyroxine, as the levothyroxine dose is usually adjusted according to thyroid function tests and clinical improvement of symptoms. Theoretically, the interaction should not apply to transdermal HRT (see *Mechanism*, above), but this requires confirmation.

The interaction is predicted to occur in any patient taking oral oestrogens, including combined hormonal contraceptives (although there do not appear to be any published studies). Nevertheless, it has been suggested that all patients taking levothyroxine and oral oestrogens should have their thyroid function assessed within several months of either starting or stopping the oestrogen.[3] However, one could argue that if a clinically important interaction between levothyroxine and combined oral contraceptives were to occur, it would have come to light by now.

The effects on **liothyronine** do not appear to have been studied, but it would be expected to interact in the same way as levothyroxine, although it has a lower affinity for thyroxine-binding globulin. Nevertheless, it would be advisable to follow the same precautions as for levothyroxine.

1. Arafah BM. Increased need for thyroxine in women with hypothyroidism during estrogen therapy. *N Engl J Med* (2001) 344, 1743–9.
2. Shifren JL, Desindes S, McIlwain M, Doros G, Mazer NA. A randomized, open-label, crossover study comparing the effects of oral versus transdermal estrogen therapy on serum androgens, thyroid hormones, and adrenal hormones in naturally menopausal women. *Menopause* (2007) 14, 985–94.
3. Utiger RD. Estrogen, thyroxine binding in serum, and thyroxine therapy. *N Engl J Med* (2001) 344, 1784–85.

Thyroid hormones + Orlistat

A woman taking levothyroxine developed symptoms of hypothyroidism when she started to take orlistat.

Clinical evidence

A case report describes a woman taking stable doses of **levothyroxine** 250 micrograms daily after a thyroidectomy who started to take orlistat.

Within 2 weeks she had developed signs of hypothyroidism (tiredness, lethargy, cold intolerance): her free thyroxine level was found to be 7 picomol/L and her TSH level was 73.6 mU/L. Two weeks after stopping orlistat, and increasing the dose of **levothyroxine** to 300 [micrograms] daily, her symptoms improved, 4 weeks later her thyroxine and TSH levels had normalised.[1]

Mechanism

It is suggested that the orlistat may have bound to levothyroxine in the gastrointestinal tract, thus reducing its bioavailability.[1]

Importance and management

Evidence for an interaction between levothyroxine and orlistat is limited, but what happened is in line with the way both drugs are known to interact. One manufacturer of levothyroxine recommends that the administration of levothyroxine and orlistat should be separated by 4 hours.[2] It may be prudent to monitor the response to concurrent use, to ensure that this is effective.

1. Madhava K, Hartley A. Hypothyroidism in thyroid carcinoma follow-up: orlistat may inhibit the absorption of thyroxine. *Clin Oncol* (2005) 17, 492–3.
2. Synthroid (Levothyroxine sodium). Abbott Laboratories. US Prescribing information, March 2008.

Thyroid hormones + Polystyrene sulfonate

A woman taking levothyroxine for hypothyroidism relapsed when she took sodium polystyrene sulfonate. Calcium polystyrene sulfonate would be expected to interact similarly.

Clinical evidence

A woman taking **levothyroxine** 150 micrograms daily for hypothyroidism, following total thyroidectomy, later developed renal impairment and required dialysis. She was also taking digoxin, clofibrate, calcium carbonate, ferrous sulfate, nicotinic acid, folic acid, and magnesium sulfate. Because of persistent hyperkalaemia she started taking sodium polystyrene sulfonate 15 g daily. After 6 months, she developed lethargy, a hoarse voice, facial fullness and weight gain (all symptoms of hypothyroidism). These symptoms resolved within 6 weeks of raising the **levothyroxine** dosage to 200 micrograms daily and separating its administration from the sodium polystyrene sulfonate by 10 hours (previously taken at the same time as the **levothyroxine**).[1]

Mechanism

Sodium polystyrene sulfonate is a cation-exchange resin that is used to bind potassium ions in exchange for sodium. An *in vitro* study found that when levothyroxine 200 micrograms was dispersed in 100 mL water with 15 g sodium polystyrene sulfonate, the concentration of the levothyroxine at pH 2 fell by 93% and at pH 7 by 98%.[1] This drop in concentration would be expected to occur in the gut as well, thereby markedly reducing the amount of levothyroxine available for absorption. Calcium polystyrene sulfonate would be expected to interact similarly.

Importance and management

Information seems to be limited to this study, but the interaction would appear to be of general importance. Separate the dosages of levothyroxine and polystyrene sulfonates as much as possible (10 hours was effective in the case reported) and monitor thyroid hormone levels to confirm that this is effective.

1. McLean M, Kirkwood I, Epstein M, Jones B, Hall C. Cation-exchange resin and inhibition of intestinal absorption of thyroxine. *Lancet* (1993) 341, 1286.

Thyroid hormones + Protease inhibitors

A man needed to have his levothyroxine dosage doubled when he took ritonavir-boosted saquinavir, and hypothyroidism could not be corrected in another woman while she was taking ritonavir-boosted lopinavir and then nelfinavir. Another woman possibly had a similar reaction when given indinavir then nelfinavir. Conversely, another woman needed a markedly reduced dose of levothyroxine when given indinavir, and a further man was able to resume his usual levothyroxine dose when ritonavir-boosted saquinavir was changed to indinavir.

Clinical evidence

(a) Indinavir

A 36-year-old HIV-positive woman taking **levothyroxine** 750 micrograms daily (following partial thyroid gland destruction for Graves' disease) was given stavudine, lamivudine and indinavir. After about 7 weeks she presented with symptoms of hyperthyroidism (including nervousness, palpitations and weight loss). Her serum TSH was low and serum thyroxine was high. After stepped dose decreases she was finally restabilised taking **levothyroxine** 120 micrograms daily, with normal thyroid hormone levels.[1] In contrast to this case, a patient who needed a **levothyroxine** dose increase while taking ritonavir-boosted saquinavir was satisfactorily stabilised with their original dose of **levothyroxine** when given indinavir.[2] In yet another woman, a 4-week course of antiretroviral prophylaxis, including 2 weeks of **indinavir** then 2 weeks of **nelfinavir**, tended to *reduce* the efficacy of **levothyroxine** 125 micrograms daily. She was fatigued and had elevated TSH levels (6.2 mU/L at day 12 and 17.4 mU/L at day 27) and hypercholesterolaemia, which resolved after the antiretroviral drugs were stopped.[3]

(b) Nelfinavir

For a case where 2 weeks of nelfinavir prophylaxis reduced the efficacy of levothyroxine, see under *Indinavir*, above. For another case where hypothyroidism failed to improve on switching from ritonavir-boosted lopinavir to nelfinavir, see *Ritonavir-based regimens*, below.

(c) Ritonavir-based regimens

An HIV-positive man, taking **levothyroxine** for autoimmune thyroiditis, developed an enlarged thyroid gland and marked lethargy about a month after his antiretrovirals were changed to include stavudine, lamivudine, **saquinavir** 400 mg twice daily and ritonavir 600 mg twice daily. It became necessary to double his maintenance dose of **levothyroxine** to restabilise him. When the ritonavir and **saquinavir** were withdrawn and replaced by **indinavir**, the patient was able to go back to the original dose of **levothyroxine**.[2]

In another HIV-positive patient, taking zidovudine, lamivudine and ritonavir-boosted **lopinavir**, **levothyroxine** was started after a total thyroidectomy and post-surgical radioiodine therapy. However, abnormal thyroid function persisted despite an increase in the **levothyroxine** dose to 225 micrograms daily. The antiretrovirals were withdrawn and thyroid function normalised. However, when the same antiretroviral regimen was restarted 8 months later because of a reduced CD4 cell count, hypothyroidism recurred within a month. A switch to **nelfinavir** did not normalise thyroid function, and the patient was eventually stabilised on a combination of three NRTIs.[4]

Mechanism

Uncertain. Ritonavir *increases* the activity of the glucuronosyl transferases, which are concerned with the metabolism (conjugation) of levothyroxine, and might therefore reduce its effect. Conversely, indinavir might *reduce* the activity of glucuronosyl transferases.

Importance and management

Direct information about the interactions of protease inhibitors and thyroid hormones seems limited. Whether or not an interaction occurs seems to depend on the individual protease inhibitor, how it affects glucuronidation, and how much remaining thyroid function a patient has.[3] Until more is known about this interaction it would seem prudent to monitor thyroid function more closely if a protease inhibitor is given to a patient with pre-existing hypothyroidism.

1. Lanzafame M, Trevenzoli M, Faggian F, Marcati P, Gatti F, Carolo G, Concia E. Interaction between levothyroxine and indinavir in a patient with HIV infection. *Infection* (2002) 30, 54–5.
2. Tseng A, Fletcher D. Interaction between ritonavir and levothyroxine. *AIDS* (1998) 12, 2235–6.

3. Nerad JL, Kessler HA. Hypercholesterolemia in a health care worker receiving thyroxine after postexposure prophylaxis for human immunodeficiency virus infection. *Clin Infect Dis* (2001) 32, 1635–6.
4. Touzot M, Le Beller C, Touzot F, Louet AL, Piketty C. Dramatic interaction between levothyroxine and lopinavir/ritonavir in a HIV-infected patient. *AIDS* (2006) 20, 1210–2.

Thyroid hormones + Proton pump inhibitors

The TSH levels of patients taking levothyroxine were slightly increased when they took omeprazole and lansoprazole. Pantoprazole and esomeprazole did not appear to interact in short-term studies.

Clinical evidence

In a randomised, crossover study in 20 healthy subjects, pre-treatment with **pantoprazole** 40 mg daily for one week had no effect on the AUCs of TSH or thyroxine after a single 4-micrograms/kg dose of **levothyroxine**.[1] Similarly, in a study in 10 healthy subjects, **esomeprazole** 40 mg daily for one week did not affect the AUC of serum thyroxine in response to a single 600-microgram dose of **levothyroxine**.[2]

In contrast, in a non-randomised study in 10 women with multinodular goitre and gastroesophageal reflux disease taking a stable dose of **levothyroxine** to suppress thyroid growth, the use of **omeprazole** 40 mg daily for at least 6 months caused a variable increase in TSH levels (median 1.7 mU/L versus 0.1 mU/L before treatment). At that time, the dose of **levothyroxine** was increased to suppress TSH levels: this required a median dose of **levothyroxine** of 2.16 micrograms/kg compared with 1.58 micrograms/kg before starting **omeprazole** (a 37% increase).[3] Similarly, in a retrospective analysis of 37 patients who had received stable doses of levothyroxine for at least 6 months and had then taken **lansoprazole** 30 mg daily for at least 2 months, the mean TSH levels slightly increased (by about 0.7 mU/L).[4]

Mechanism

A decrease in gastric acidity might decrease levothyroxine absorption. Supporting this is the finding that in patients with impaired gastric acid secretion the required dose of levothyroxine was 22 to 34% higher than in patients free of gastric disease.[3] However, this effect could be due to the disease rather than gastric acid *per se*.[5]

Importance and management

An interaction between levothyroxine and proton pump inhibitors is not established. The studies with pantoprazole and esomeprazole did not reveal a change in levothyroxine absorption, whereas the study in patients who had been taking omeprazole for 6 months suggested that patients may need a modest increase in levothyroxine dose, and the retrospective analysis with lansoprazole showed an even smaller increase in TSH. Bear in mind the possibility of an interaction if a patient starting a proton pump inhibitor shows signs of reduced levothyroxine efficacy. Any interaction may take several months to develop. Further study is needed.

1. Dietrich JW, Gieselbrecht K, Holl RW, Boehm BO. Absorption kinetics of levothyroxine is not altered by proton-pump inhibitor therapy. *Horm Metab Res* (2006) 38, 57–9.
2. Ananthakrishnan S, Braverman LE, Levin RM, Magnani B, Pearce EN. The effect of famotidine, esomeprazole, and ezetimibe on levothyroxine absorption. Thyroid (2008) 18, 493–8.
3. Centanni M, Gargano L, Canettieri G, Viceconti N, Franchi A, Delle Fave G, Annibale B. Thyroxine in goiter, Helicobacter pylori infection, and chronic gastritis. *N Engl J Med* (2006) 354, 1787–95.
4. Sachmechi I, Reich DM, Aninyei M, Wibowo F, Gupta G, Kim PJ. Effect of proton pump inhibitors on serum thyroid-stimulating hormone level in euthyroid patients treated with levothyroxine for hypothyroidism. *Endocr Pract* (2007) 13, 345–9.
5. Dietrich JW, Boehm BO. Thyroxine in goiter, H. pylori infection, and gastritis. *N Engl J Med* (2006) 355, 1177.

Thyroid hormones + Raloxifene

There are two reports of patients who developed increased levothyroxine requirements after taking raloxifene for a number of months.

Clinical evidence

A 79-year-old woman taking **levothyroxine** 150 micrograms daily developed elevated TSH levels and symptoms of hypothyroidism within 2 to 3 months of starting to take raloxifene 60 mg daily. Over the next 6 months the **levothyroxine** dose was progressively increased to 300 micrograms daily without normalising TSH levels. This patient took the raloxifene early in the morning, at the same time as the **levothyroxine**. Subsequently, separating the dose of raloxifene and **levothyroxine** by 12 hours led to a drop in TSH levels. In a single-dose study in this patient, serum thyroxine levels were reduced when **levothyroxine** 1000 micrograms was given with raloxifene 60 mg, and separating the doses of raloxifene and **levothyroxine** by 12 hours was found to reduce TSH levels.[1] Another very similar case has been reported in a 47-year-old woman, which also resolved on separating administration of the **raloxifene** and **levothyroxine** by 12 hours.[2]

Mechanism

Raloxifene is known to increase levels of thyroxine binding globulin, which results in increased levels of total thyroxine without altering free thyroxine.[3] However, this is not likely to be the mechanism in the cases described, because separating the doses would not reduce any effect by this mechanism. It appears that raloxifene reduced the absorption of levothyroxine, but the mechanism for this is not known.

Importance and management

The interaction between levothyroxine and raloxifene is not established, but the similar outcomes in both case reports suggest that an interaction may occur. Further study is needed, but until then it would be prudent to monitor TSH levels in patients taking levothyroxine and starting raloxifene, especially if they develop symptoms of hypothyroidism. If TSH levels are raised, try separating administration by 12 hours before increasing the levothyroxine dose.

1. Siraj ES, Gupta MK, Reddy SSK. Raloxifene causing malabsorption of levothyroxine. *Arch Intern Med* (2003) 163, 1367–70.
2. Garwood CL, Van Schepen KA, McDonough RP, Sullivan AL. Increased thyroid-stimulating hormone levels associated with concomitant administration of levothyroxine and raloxifene. *Pharmacotherapy* (2006) 26, 881–5.
3. Evista (Raloxifene hydrochloride). Daiichi Sankyo UK Ltd. UK Summary of product characteristics, August 2003.

Thyroid hormones + Rifampicin (Rifampin)

Two case reports suggest that rifampicin might possibly reduce the effects of thyroid hormones.

Clinical evidence, mechanism, importance and management

A woman with Turner's syndrome, who had undergone a total thyroidectomy and who was taking **levothyroxine** 100 micrograms daily, had a marked fall in serum thyroxine levels and free thyroxine index with a dramatic rise in TSH levels when given rifampicin. However, no symptoms of clinical hypothyroidism developed, and the drop in serum thyroxine occurred before starting rifampicin, which may reflect the clinical picture of an acute infection.[1] Another case describes a *fall* in TSH levels when rifampicin was discontinued.[2]

A possible reason for the changes is that rifampicin, a potent enzyme inducer, can markedly increase the metabolism of many drugs and thereby reduce their effects. Rifampicin has been found to reduce endogenous serum thyroxine levels in healthy subjects[3] and possibly in patients.[2] Note that, other potent enzyme inducers have, rarely, also been seen to interact in this way, see 'Thyroid hormones + Carbamazepine or Phenytoin', p.1522.

There seem to be no reports of adverse effects in other patients given both drugs and the evidence for this interaction is by no means conclusive. Although rifampicin can affect thyroid hormones, it appears that healthy individuals can compensate for this. Since hypothyroid patients may not be able to compensate in the same way, bear this interaction in mind if rifampicin is given to a patient taking **levothyroxine**. If symptoms of hypothyroidism develop, monitor thyroid hormone levels, and adjust the dose of levothyroxine accordingly. It would seem prudent to take similar precautions in patients given **liothyronine** and rifampicin.

1. Isley WL. Effect of rifampin therapy on thyroid function tests in a hypothyroid patient on replacement L-thyroxine. *Ann Intern Med* (1987) 107, 517–18.

2. Nolan SR, Self TH, Norwood JM. Interaction between rifampin and levothyroxine. *South Med J* (1999) 92, 529–31.
3. Ohnhaus EE, Studer H. A link between liver microsomal enzyme activity and thyroid hormone metabolism in man. *Br J Clin Pharmacol* (1983) 15, 71–6.

Thyroid hormones + Sertraline

Limited evidence suggests that the effects of levothyroxine can be opposed in some patients by sertraline.

Clinical evidence, mechanism, importance and management

Nine patients with hypothyroidism were noted to have elevated TSH levels (indicating a decrease in the efficacy of their treatment with **levothyroxine**), when they were also taking sertraline. Two other patients with thyroid cancer, whose TSH levels had been deliberately depressed, developed TSH levels in the normal range while taking sertraline. None of the patients showed any signs of hypothyroidism at the time, and all of them had been taking the same dose of **levothyroxine** for at least 6 months. TSH levels of up to almost 17 mU/L (reference range given as 0.3 to 5 mU/L) were seen in some patients. The **levothyroxine** dosages were increased by 11 to 50%, until the TSH levels were back to normal. The authors of this report say that they know of three other patients whose TSH levels were unaltered by sertraline.[1]

The manufacturers of sertraline say that their early-alert safety database to the end of July 1997 had identified 14 cases of hypothyroidism where a possible relation to sertraline could not be excluded. Seven of the patients were also taking **levothyroxine**.[2]

The mechanism of this interaction (if such it is) is not known, but these cases draw attention to the need to monitor the effects of giving sertraline to patients taking **levothyroxine**, the dosage of which may need to be increased. More study is needed.

1. McCowen KC, Spark R. Elevated serum thyrotropin in thyroxine-treated patients with hypothyroidism given sertraline. *N Engl J Med* (1997) 337, 1010–11.
2. Clary CM, Harrison WM. Elevated serum thyrotropin in thyroxine-treated patients with hypothyroidism given sertraline. *N Engl J Med* (1997) 337, 1011.

Thyroid hormones + Sevelamer

Sevelamer decreases levothyroxine absorption, and appears to increase levothyroxine requirements.

Clinical evidence, mechanism, importance and management

In a single-dose study in 7 healthy subjects, giving a large dose of **levothyroxine** (1000 micrograms) at the same time as sevelamer 800 mg resulted in a decrease of about 50% in the AUC_{0-6} of thyroxine.[1] In a retrospective study, 67 patients were identified who were taking **levothyroxine** and a phosphate binder (calcium carbonate, calcium acetate or sevelamer). The TSH levels were significantly higher in patients taking sevelamer than calcium acetate, and the difference was greater over time. In addition, patients taking sevelamer required significantly higher **levothyroxine** doses than those taking either of the calcium compounds.[2]

The available evidence suggests that sevelamer decreases the absorption of **levothyroxine**, and that this could result in increased dose requirements. It would be prudent to monitor **levothyroxine** requirements in patients taking sevelamer. Whether separation of administration would minimise any interaction remains to be demonstrated. However, where there is a potential risk of decreased absorption, it is generally recommend that other drugs should be avoided for at least 1 hour before or 3 hours after sevelamer.

1. John-Kalarickal J, Pearlman G, Carlson HE. New medications which decrease levothyroxine absorption. *Thyroid* (2007) 17, 763–5.
2. Diskin CJ, Stokes TJ, Dansby LM, Radcliff L, Carter TB. Effect of phosphate binders upon TSH and L-thyroxine dose in patients on thyroid replacement. *Int Urol Nephrol* (2007) 39, 599–602.

Thyroid hormones + Statins

Isolated cases describe both an increase and a decrease in the response to levothyroxine in patients taking lovastatin. Another report describes reduced efficacy of levothyroxine in two patients taking simvastatin. In one of these patients, the subsequent use of pravastatin did not affect thyroid function.

Clinical evidence, mechanism, importance and management

(a) Lovastatin

A 54-year-old diabetic man taking **levothyroxine** 150 micrograms daily for Hashimoto's thyroiditis, and a number of other drugs (gemfibrozil, clofibrate, propranolol, diltiazem, quinidine, aspirin, dipyridamole, insulin) started taking lovastatin 20 mg daily. Weakness and muscle aches (with a normal creatinine phosphokinase) developed within 2 to 3 days, and over a 27-day period he lost 10% of his body weight. His serum thyroxine levels rose from about 145 nanomol/L to 350 nanomol/L. The author of the report postulated that the lovastatin may have displaced the thyroid hormones from their binding sites, thereby increasing their effects and causing this acute thyrotoxic state. It was suggested that the patient did not have any cardiac symptoms because of his pre-existing drug regimen.[1]

In contrast, a woman with goitrous hypothyroidism due to Hashimoto's thyroiditis, which was being treated with **levothyroxine** 125 micrograms daily, developed evidence of hypothyroidism (elevated TSH) on two occasions while taking lovastatin 20 or 60 mg daily. No clinical signs of hypothyroidism developed, apart from some increased fatigue, and possibly an increased sensitivity to insulin. The author suggested that lovastatin may have influenced the absorption or clearance of **levothyroxine**.[2]

When the second report was published, the manufacturers of lovastatin reported that at that time (August 1989) more than 1 million patients had taken lovastatin, and hypothyroidism had only been reported in 3 patients.[3] It seems that any interaction is a very rare event and consequently unlikely to happen in most patients. No special precautions would therefore seem to be necessary.

(b) Simvastatin

A 75-year-old woman who had been stable taking **levothyroxine** 800 micrograms weekly for many years had a gradual increase in TSH levels and increasing tiredness after starting to take simvastatin 10 mg daily. After 4 months the **levothyroxine** dose was increased to 900 micrograms weekly, but the patient's symptoms had not improved in 2 weeks and the simvastatin was stopped. The patient's symptoms gradually resolved, and the dose of levothyroxine was reduced back to the previous level.[4]

Another patient, who had recently started taking **levothyroxine** 50 micrograms daily because of rising TSH levels, was also given simvastatin 10 mg daily. TSH levels continued to increase, so the simvastatin was stopped, and the TSH levels decreased to the normal range within 4 weeks without the need for an alteration in the **levothyroxine** dose. This patient was subsequently given **pravastatin** without a change in thyroid status.[4]

The authors conclude that any interaction must be extremely rare given the frequent use of simvastatin and **levothyroxine**.[4] No special precautions would appear to be required on concurrent use, but bear the possibility of this interaction in mind in the event of an unexpected response to treatment.

1. Lustgarten BP. Catabolic response to lovastatin therapy. *Ann Intern Med* (1988) 109, 171–2.
2. Demke DM. Drug interaction between thyroxine and lovastatin. *N Engl J Med* (1989) 321, 1341–2.
3. Gormley GJ, Tobert JA. Drug interaction between thyroxine and lovastatin. *N Engl J Med* (1989) 321, 1342.
4. Kisch E, Segall HS. Interaction between simvastatin and L-thyroxine. *Ann Intern Med* (2005) 143, 547.

Thyroid hormones + Sucralfate

Sucralfate may reduce levothyroxine absorption, but not all studies have found this effect.

Clinical evidence, mechanism, importance and management

A woman with hypothyroidism did not respond to **levothyroxine**, despite taking 4.8 micrograms/kg daily, while taking sucralfate (dose not stated). Her response remained inadequate (TSH levels high, thyroxine levels low) even when the **levothyroxine** was taken 2.5 hours after the sucralfate, but when **levothyroxine** was taken 4.5 hours before the sucralfate, the thyroxine and TSH levels gradually became normal. A later *in vitro* study demonstrated that sucralfate binds strongly to **levothyroxine**, and it is

presumed that this can also occur in the gut, thereby reducing its absorption.[1]

Other studies have found similar effect. A single-dose study in healthy subjects found that giving a large dose of **levothyroxine** (1000 micrograms) with the last dose of sucralfate (five 1-g doses given every 6 hours), resulted in a 72% reduction in **levothyroxine** absorption, and a delay of 2 hours in reaching maximum absorption. Separating dosing by 8 hours avoided this effect.[2] Conversely, in 10 patients whose hypothyroidism was controlled by stable doses of **levothyroxine**, giving sucralfate 1 g daily for 6 weeks at the same time as **levothyroxine** did not alter the levels of thyroxine or TSH.[3] Another placebo-controlled study similarly found that sucralfate had little effect on the absorption of **levothyroxine**, with just a minor decrease in serum thyroxine levels seen (about 94 nanomol/L with sucralfate versus about 105 nanomol/L with placebo).[4]

An interaction is not established, and findings are somewhat contradictory. Nevertheless, it might be prudent not to take sucralfate until a few hours after **levothyroxine**. Patients should be advised accordingly and the response well monitored.

1. Havrankova J, Lahaie R. Levothyroxine binding by sucralfate. *Ann Intern Med* (1992) 117, 445–6.
2. Sherman SI, Tielens ET, Ladenson PW. Sucralfate causes malabsorption of L-thyroxine. *Am J Med* (1994) 96, 531–5.
3. Khan F, Jeanniton E, Renedo M. Does sucralfate impede levothyroxine therapy? *Ann Intern Med* (1993) 118, 317.
4. Campbell JA, Schmidt BA, Bantle JP. Sucralfate and the absorption of L-thyroxine. *Ann Intern Med* (1994) 121, 152.

37

Urological drugs

The drug classes used for various genito-urinary disorders are summarised in 'Table 37.1', (below). The main groups of drugs included in this chapter are the urinary antimuscarinics and the phosphodiesterase type-5 inhibitors (PDE5 inhibitors), along with various individual miscellaneous drugs. Note that, where these drugs affect other drugs, the interaction is generally covered elsewhere.

Antimuscarinics

The main pharmacodynamic interaction of antimuscarinic drugs is an increased risk of antimuscarinic effects (e.g. dry mouth, constipation, confusion) when used with other drugs with antimuscarinic properties. Many drugs have antimuscarinic adverse effects, which may not be readily appreciated from their clinical uses, see 'Table 18.2', (p.786) for a list. Some of the newer antimuscarinics used for incontinence have greater selectivity for the M_3 muscarinic receptors of the bladder. However, it is not established whether this results in a clinically relevant difference in the incidence of antimuscarinic adverse effects or antimuscarinic drug interactions.

Some of the urinary antimuscarinics, including darifenacin, solifenacin and tolterodine, are principally metabolised by the cytochrome P450 isoenzyme system, or, in the case of fesoterodine, its main active metabolite is metabolised by these isoenzymes. Therefore clinically important pharmacokinetic drug interactions can occur with these drugs, due to altered metabolism.

Phosphodiesterase type-5 inhibitors (PDE5 inhibitors)

The main concern regarding the phosphodiesterase type-5 inhibitors has centred around their cardiovascular adverse effects. Therefore the possible risks of their use in patients with cardiovascular disease, and their drug interactions with drugs used in cardiovascular disease have been particularly studied. Important interactions occur with 'nitrates', (p.1537), and also 'alpha blockers', (p.1531). All the phosphodiesterase type-5 inhibitors are metabolised, to a greater or lesser extent, by the cytochrome P450 isoenzyme CYP3A4, and therefore clinically relevant drug interactions can occur with drugs that induce or inhibit this route of metabolism.

Table 37.1 Classification of urological drugs

Group	*Drugs*
Drugs for benign prostatic hyperplasia	
Alpha blockers	See Alpha blockers, p.92
Anti-androgens	Dutasteride, Finasteride
Drugs for urinary incontinence	
Antimuscarinics	Darifenacin, Flavoxate, Oxybutynin, Propiverine, Solifenacin, Tolterodine, Trospium
SNRIs	Duloxetine, covered under SSRIs, tricyclics and related antidepressants, p.1464
Drugs for nocturnal enuresis in children	
Tricyclic antidepressants	Imipramine, covered under SSRIs, tricyclics and related antidepressants, p.1464
Vasopressin analogues	Desmopressin
Drugs for erectile dysfunction	
Dopaminergic agonists	Apomorphine, covered under Antiparkinsonian and related drugs, p.784
Muscle relaxants	Papaverine
Phosphodiesterase type-5 inhibitors	Sildenafil, Tadalafil, Vardenafil
Prostaglandins	Alprostadil
Others	Phentolamine, Yohimbine

Alprostadil + Miscellaneous

Some manufacturers advise that intracavernosal alprostadil and other drugs used for erectile dysfunction should not be given concurrently. Concurrent use of alprostadil with antihypertensives, alpha blockers, and drugs causing vasodilation, such as the nitrates, may theoretically increase the risk of hypotension. Nasal decongestants and appetite suppressants might theoretically reduce the efficacy of alprostadil. Clinical experience suggests that an alprostadil infusion does not interact with penicillin, gentamicin, dopamine, isoprenaline (isoproterenol), furosemide, or digoxin.

Clinical evidence, mechanism, importance and management

A. Erectile dysfunction

(a) Appetite suppressants and decongestants

Some manufacturers say that, theoretically, sympathomimetics such as **nasal decongestants** and **anorectics** might diminish the effect of alprostadil for erectile dysfunction.[1,2]

(b) Other drugs for erectile dysfunction

Prolonged priapism occurred in a man who used an intracavernous injection of alprostadil 15 micrograms about one hour after taking a single 100-mg dose of **sildenafil** because of an inadequate response to the **sildenafil**.[3] Two other cases are described, one in a man who took **sildenafil** 100 mg and then, 90 minutes later, used 0.25 mL of intracavernosal *Trimix* (**papaverine**, **phentolamine** plus alprostadil), and another in a man who took **tadalafil** 20 mg and then used *Trimix* 18 hours later.[3] Note that tadalafil has a half-life of 17.5 hours.[3] Some manufacturers say that smooth muscle relaxants such as **papaverine** and other drugs used to induce erections such as **alpha-blocking drugs** [e.g. intracavernosal **phentolamine**] or the phosphodiesterase type-5 inhibitors such as **sildenafil** should not be used concurrently because of the risks of priapism.[2,4] This recommendation does not appear to have been made for alprostadil for urethral application.[1,5]

(c) Vasodilating drugs

Alprostadil can rarely cause hypotension.[1,2,4] Some manufacturers caution that there is a theoretical risk of hypotensive symptoms if alprostadil is used with vasodilating medications,[1,2,4] or antihypertensives,[5] and that this might be more common in the elderly.[1] Vasodilating medications would include **alpha blockers** and **nitrates**. One manufacturer advises against the combination.[6]

B. Neonatal congenital heart defects

The manufacturers of intravenous alprostadil note that there are no known drug interactions between alprostadil infusion and the drugs commonly given to neonates with congenital heart defects, including antibacterials such as **penicillin** or **gentamicin**, vasopressors, such as **dopamine** or **isoprenaline** (**isoproterenol**), diuretics such as **furosemide**, and **digoxin**.[7,8]

1. Muse (Alprostadil). Meda Pharmaceuticals. UK Summary of product characteristics, November 2007.
2. Caverject Dual Chamber Injection (Alprostadil). Pharmacia Limited. UK Summary of product characteristics, July 2005.
3. McMahon CG. Priapism associated with concurrent use of phosphodiesterase inhibitor drugs and intracavernous injection therapy. *Int J Impot Res* (2003) 15, 383–4.
4. Viridal 10 Duo (Alprostadil). Schwarz Pharma Ltd. UK Summary of product characteristics, July 2006.
5. Muse (Alprostadil). Vivus Inc. US Prescribing information, August 2003.
6. Caverject Impulse (Alprostadil). Pharmacia & Upjohn Company. US Prescribing information, September 2003.
7. Prostin VR Sterile Solution (Alprostadil). Pharmacia Ltd. UK Summary of product characteristics, January 2008.
8. Prostin VR (Alprostadil), Pharmacia & Upjohn Company. US Prescribing information, August 2002.

Desmopressin + Erythromycin

Erythromycin does not induce gastrointestinal motility sufficiently to affect desmopressin absorption.

Clinical evidence, mechanism, importance and management

In a study, 18 healthy subjects were given erythromycin 250 mg four times daily for 3 days, with a 400-microgram oral dose of desmopressin one hour after the final dose of erythromycin. When compared with desmopressin alone, the time to peak desmopressin levels was reduced from 1.3 to 0.9 hours by erythromycin, but other pharmacokinetic parameters were not affected, suggesting the erythromycin did not induce gastrointestinal motility sufficiently to affect total desmopressin absorption.[1]

This study suggests that no interaction of clinical significance would be expected if erythromycin is given to patients receiving oral desmopressin.

1. Callréus T, Lundahl J, Höglund P, Bengtsson P. Changes in gastrointestinal motility influence the absorption of desmopressin. *Eur J Clin Pharmacol* (1999) 55, 305–9.

Desmopressin + Food

Food reduces the absorption of oral desmopressin.

Clinical evidence, mechanism, importance and management

In a study in healthy subjects, a standardised meal decreased the absorption (rate and extent) of a 400-microgram dose of desmopressin tablets by 40% when the tablets were given either at the same time as the meal or 1.5 hours after the meal, when compared with the fasting state. However, the meal did not significantly affect the pharmacodynamic effect of desmopressin (urine production and osmolality).[1] Nevertheless, the manufacturer of desmopressin considers that the effect of food could be clinically important, particularly with lower doses of desmopressin. They suggest that if a reduction in effect is noted, then the effect of food should be considered before increasing the dose.[2] If problems occur, it may be prudent to advise patients to take desmopressin consistently with respect to food.

1. Rittig S, Jensen AR, Jensen KT, Pedersen EB. Effect of food intake on the pharmacokinetics and antidiuretic activity of oral desmopressin (DDAVP) in hydrated normal subjects. *Clin Endocrinol (Oxf)* (1998) 48, 235–41.
2. Desmotabs (Desmopressin acetate). Ferring Pharmaceuticals Ltd. UK Summary of product characteristics, May 2008.

Desmopressin + Loperamide

Loperamide may markedly increase oral desmopressin.

Clinical evidence

In a study, 18 healthy subjects were given a 400-microgram oral dose of desmopressin as immediate-release tablets, either alone or after three doses of loperamide 4 mg, given 24, 12 and 1 hour before the desmopressin. Loperamide increased the AUC and peak plasma levels of desmopressin 3.1-fold and 2.3-fold, respectively, and the time to peak desmopressin plasma levels was increased from 1.3 to 2 hours, whereas the elimination half-life was unaltered.[1]

Mechanism

It was suggested that loperamide increases the absorption of desmopressin by slowing gastrointestinal motility. Other mechanisms such as reduced pancreatic secretion or reduced enzymatic degradation of desmopressin in the intestine have been suggested, but are considered less likely as desmopressin clearance was not significantly affected.[1]

Importance and management

Evidence appears to be limited to one study. Increased desmopressin absorption could lead to a prolonged duration of action, and if fluid intake is not restricted in such a situation, there could be an increased risk of water intoxication and/or hyponatraemia.[1] It would therefore be prudent to increase the monitoring of the effects of oral desmopressin in any patient given loperamide, reducing the desmopressin dose or dose frequency as necessary. However, note that in primary nocturnal enuresis, the indication for loperamide (diarrhoea) is a reason to temporarily stop desmopressin.[2-4] The manufacturer suggests that other drugs that slow gastrointestinal transport might have the same effect.[2] Although the effect of loperamide on sublingual formulations of desmopressin has not been studied, the same precautions should be applied.

As the loperamide interacts by an effect on the gut, no interaction would be expected with intranasal or parenteral desmopressin.

1. Callréus T, Lundahl J, Höglund P, Bengtsson P. Changes in gastrointestinal motility influence the absorption of desmopressin. *Eur J Clin Pharmacol* (1999) 55, 305–9.

2. Desmotabs (Desmopressin acetate). Ferring Pharmaceuticals Ltd. UK Summary of product characteristics, May 2008.
3. Committee on Safety of Medicines/Medicines control agency. Hyponatraemic convulsions in patients with enuresis treated with vasopressin. *Current Problems* (1996) 22, 4.
4. DDAVP Tablets (Desmopressin acetate). Sanofi-Aventis. US Prescribing information, July 2007.

Desmopressin + Miscellaneous

Any drug that can cause water retention or hyponatraemia (e.g. tricyclic antidepressants, SSRIs, chlorpromazine, carbamazepine, and NSAIDs) may have an additive effect with desmopressin. This may lead to avoid water overload and/or hyponatraemia.

Clinical evidence, mechanism, importance and management

In a retrospective analysis of 103 children with cranial diabetes insipidus, major complications (symptomatic water overload) or asymptomatic hyponatraemia were seen in 33 children. In patients taking desmopressin with **carbamazepine**, major complications were more common than in those not receiving **carbamazepine** (33% versus 10%).[1]

The severity of the potential adverse interaction between desmopressin and drugs that can cause water retention or hyponatraemia is demonstrated by the case report of a 10-year-old boy, who had been receiving intranasal desmopressin for 7 months for primary nocturnal enuresis. A few weeks after **imipramine** 25 mg at night was added, he had a hyponatraemic convulsion.[2]

Any drug that is known to induce the syndrome of inappropriate antidiuretic hormone secretion has the potential to have additive effects with desmopressin. This increases the risk of water retention and/or hyponatraemia. Examples are **carbamazepine**, **chlorpromazine**, **SSRIs** and **tricyclic antidepressants**, such as **imipramine**. Other drugs that can cause water retention such as the **NSAIDs** might also increase the risk of fluid overload and hyponatraemia. Caution is required on concurrent use,[3,4] with more frequent monitoring of serum sodium.

1. Rizzo V, Albanese A, Stanhope R. Morbidity and mortality associated with vasopressin replacement therapy in children. J Pediatr Endocrinol Metab. (2001) 14, 861–7.
2. Hamed M, Mitchell H, Clow DJ. Hyponatraemic convulsion associated with desmopressin and imipramine treatment. *BMJ* (1993) 306, 1169.
3. Desmotabs (Desmopressin acetate). Ferring Pharmaceuticals Ltd. UK Summary of product characteristics, May 2008.
4. DDAVP Tablets (Desmopressin Acetate). Sanofi-Aventis U.S. LLC. US prescribing information, 2007.

Dutasteride + Colestyramine

In a study in 12 healthy subjects the absorption of dutasteride 5 mg was not affected when it was given one hour before a single 12-g dose of colestyramine.[1,2] No precautions seem necessary if this dosing interval is observed. Note that, in general, it is recommended that other drugs are given one hour before or 4 to 6 hours after colestyramine.

1. Avodart (Dutasteride). GlaxoSmithKline UK. UK Summary of product characteristics, August 2008.
2. Avodart (Dutasteride). GlaxoSmithKline. US Prescribing information, June 2008.

Dutasteride + CYP3A4 inhibitors

Preliminary evidence suggests that diltiazem and verapamil, CYP3A4 inhibitors, cause moderate increases in dutasteride levels. More potent CYP3A4 inhibitors would be expected to have a greater effect. No clinically significant interaction appears to occur between dutasteride and amlodipine.

Clinical evidence, mechanism, importance and management

In a population pharmacokinetic analysis, it was found that **diltiazem** (5 subjects) and **verapamil** (6 subjects) were associated with a 44% and 37% decrease in dutasteride clearance,[1] and an 80% and 60% increase in serum levels,[2] respectively. In contrast, **amlodipine** (4 subjects) was not associated with any significant change in the clearance of dutasteride.[1] The changes were thought to be due to the inhibitory effect of **diltiazem** and **verapamil** on the cytochrome P450 isoenzyme CYP3A4, an effect that **amlodipine** lacks. Dutasteride has a wide safety margin, so these changes are not thought to be clinically significant.[1,2] However, in the UK, the manufacturers warn that potent CYP3A4 inhibitors (they name **indinavir**, **itraconazole**, **ketoconazole**, **nefazodone** and **ritonavir**) may cause a clinically significant increase in dutasteride levels, and so they suggest reducing the dosing frequency if increased dutasteride adverse effects occur in the presence of these drugs.[2] The US manufacturer similarly recommends caution with long-term use of potent CYP3A4 inhibitors, and they name **ritonavir** as an example.[1]

1. Avodart (Dutasteride). GlaxoSmithKline. US Prescribing information, June 2008.
2. Avodart (Dutasteride). GlaxoSmithKline UK. UK Summary of product characteristics, August 2008.

Papaverine + Diazepam

Two men given normal test doses of papaverine for the investigation of impotence had prolonged erections, which were attributed to the concurrent use of diazepam.

Clinical evidence, mechanism, importance and management

Undesirably prolonged erections (duration of 5 and 6 hours) occurred in 2 patients who had been given 5 or 10 mg of diazepam intravenously for anxiety before a 60-mg intracavernosal injection of papaverine.[1] Papaverine acts by relaxing the arterioles that supply the corpora so that the pressure rises. The increased pressure in the corpora compresses the trabecular venules so that the pressure continues to maintain the erection. Diazepam also relaxes smooth muscle and it would seem that this effect can be additive with the effects of papaverine. The authors of the report say that caution should be exercised in the choice of papaverine dosage in patients taking anxiolytics (i.e. use less) although these two cases involving diazepam seem to be the only ones reported.[1]

1. Vale JA, Kirby RS, Lees W. Papaverine, benzodiazepines, and prolonged erections. *Lancet* (1991) 337, 1552.

Phosphodiesterase type-5 inhibitors + Alpha blockers

Postural hypotension may occur with higher doses of sildenafil, tadalafil or vardenafil given at the same time as doxazosin or terazosin. The effect may be less marked with tamsulosin.

Clinical evidence

(a) Sildenafil

Retrospective analysis of pooled data from various clinical studies that included patients taking non-nitrate antihypertensives such as the alpha blockers suggested that the adverse effect profile, blood pressure, and heart rate were not significantly different between sildenafil and placebo.[1] However, the manufacturer notes that when sildenafil 100 mg was given simultaneously with **doxazosin** 4 mg after at least 14 consecutive daily doses of **doxazosin**, severe postural hypotension (starting at 35 minutes and lasting 8 hours) occurred in one of 4 subjects with BPH, and 2 others had mild dizziness. Two of the subjects had a standing systolic BP of less than 85 mmHg. This did not occur in a further 17 subjects who, as a result of these effects, were given a lower dose of sildenafil 25 mg. In two other studies in men with BPH, 2 of 19 patients and 3 of 20 patients had a standing systolic BP of less than 85 mmHg after receiving 14 days of **doxazosin** then a single dose of sildenafil 50 mg or 100 mg given at the same time as **doxazosin**.[2]

A case report describes a patient with intermittent Wolff-Parkinson-White syndrome taking **doxazosin** 1 mg daily for mild hypertension who developed palpitations and chest pain one hour after taking sildenafil 50 mg and drinking 1.5 L of beer. He had atrial fibrillation (which failed to respond to DC conversion, and reverted spontaneously after 4 hours) and severe hypotension lasting 16 hours, for which he was given a dopamine infusion. The authors considered that the hypotension might have been caused by an interaction between the alcohol, **doxazosin** and the sildenafil.[3]

(b) Tadalafil

In a well-controlled study in 18 healthy subjects, a single 20-mg dose of tadalafil was given at the same time as **doxazosin** 8 mg following a minimum of 7 days of pretreatment with **doxazosin** 8 mg daily. The blood-pressure lowering effects of doxazosin were increased: the mean maximum systolic falls for the combination were 19.6 mmHg when lying and 27.8 mmHg when standing, which was 3.6 mmHg and 9.8 mmHg greater than doxazosin with placebo. Five of the subjects had a standing systolic BP of less than 85 mmHg. Some of the subjects felt dizzy, but none of them fainted.[4]

Conversely, only a small (3.2 mmHg and 1.7 mmHg) additional drop in blood pressure was seen when tadalafil 10 or 20 mg was given 2 hours after **tamsulosin** 400 micrograms. Note that the 2-hour difference was used so that the maximum plasma levels of each drug would coincide. None of the subjects had a standing systolic BP of less than 85 mmHg.[4] In a placebo-controlled study, 17 healthy subjects were given extended-release **alfuzosin** 10 mg daily, with a single 20-mg oral dose of tadalafil on day 7. The additional blood pressure-lowering effect of the tadalafil was small (2.1 mmHg systolic supine and 4.3 systolic standing). One of the subjects had a decrease in standing systolic BP to less than 85 mmHg. No syncope or severe adverse events were reported. Note that the doses were separated in such a way that the peak plasma levels of each drug would coincide.[5]

The above studies used single doses of tadalafil. In another two studies in healthy subjects, tadalafil 5 mg daily was given alone and then either **doxazosin** (titrated from 1 mg daily to 4 mg daily) or **tamsulosin** 400 micrograms daily were added. The mean maximum additional decrease in standing systolic BP on adding the alpha blocker was similar (0.5 mmHg with doxazosin 4 mg and 0.9 mmHg for tamsulosin). Standing systolic BP of less than 85 mmHg occurred in 1 of 37 subjects receiving doxazosin and none of 35 subjects receiving tamsulosin.[6]

(c) Vardenafil

The manufacturers of vardenafil have conducted several placebo-controlled, randomised, crossover studies, in patients with BPH and in healthy subjects taking alpha blockers, to assess the effects of the concurrent use of vardenafil on blood pressure. Vardenafil 5 mg was given to 21 patients taking **terazosin** 5 or 10 mg daily. Vardenafil given simultaneously caused significant hypotension in one patient (BP 80/60 mmHg) and 5 patients experienced postural hypotension of greater than 30 mmHg (compared with only 2 patients in the placebo group). When vardenafil was given 6 hours after the alpha blocker no adverse effects were reported.[7] Vardenafil 10 or 20 mg was also given to healthy subjects taking **terazosin** 10 mg daily, either simultaneously with the terazosin or separated by 6 hours. Due to significant hypotension in most of the subjects given the drugs simultaneously, this arm of the study was halted.[7]

Vardenafil 5 mg was given to 21 patients taking **tamsulosin** 400 micrograms daily. Vardenafil given simultaneously caused significant hypotension in 2 patients (systolic BP less than 85 mmHg) and 2 patients experienced postural hypotension of greater then 30 mmHg (compared with only one patient in the placebo group). When vardenafil was given 6 hours after the alpha blocker significant hypotension still occurred in 2 patients and one experienced postural hypotension of greater than 30 mmHg.[7] Larger doses of vardenafil (10 then 20 mg) given to 23 patients with BPH taking **tamsulosin** 400 or 800 micrograms resulted in mean additional decreases in supine systolic BP of 4.5 mmHg and 4 mmHg, respectively, when compared with placebo. A decrease in standing systolic BP of greater than 30 mmHg occurred in one patient, and 3 patients became dizzy, but no patient had a systolic BP of less than 85 mmHg.[7,8] When vardenafil 10 or 20 mg was given to 20 healthy subjects taking **tamsulosin** 400 micrograms daily, 7 subjects became dizzy.[7]

In a study of the effect of vardenafil on blood pressure in normotensive men with erectile dysfunction, three patients had fainting episodes after their first dose of vardenafil 10 mg. Two of these were taking **doxazosin** for benign prostatic hyperplasia.[9]

Mechanism

Phosphodiesterase type-5 inhibitors cause mild to moderate vasodilatation of vascular smooth muscle in veins and arteries, and so can lower blood pressure. The concern is that this could be additive or synergistic with the orthostatic hypotension that can occur with alpha blockers.

Importance and management

The interactions between the phosphodiesterase type-5 inhibitors and the alpha blockers are established, and concurrent use requires caution. The risk of symptomatic hypotension is reduced if the patient taking an alpha blocker is haemodynamically stable before the phosphodiesterase type-5 inhibitor is started, and if it is started at the lowest recommended dose. The risk may also be minimised if administration is separated so that the peak levels of the two drugs do not coincide. If an alpha blocker is required in a patient already using a phosphodiesterase type-5 inhibitor, extra caution is required, particularly with alpha blockers well-known to be associated with first-dose hypotension, such as immediate-release alfuzosin, prazosin and terazosin. This effect is seen less frequently with modified-release alfuzosin and tamsulosin. Patients should be warned of the risks and advised what to do in the event of postural hypotensive symptoms (i.e. lay down, raise the legs and, when recovered, get up slowly).

Note that the combination of sildenafil and doxazosin has been used for erectile dysfunction refractory to sildenafil monotherapy.[10]

1. Zusman RM, Prisant LM, Brown MJ. Effect of sildenafil citrate on blood pressure and heart rate in men with erectile dysfunction taking concomitant antihypertensive medication. *J Hypertens* (2000) 18, 1865–9.
2. Viagra (Sildenafil citrate). Pfizer Inc. US Prescribing information, August 2008.
3. Hayashi K, Minezaki KK, Narukawa M, Ookubo M, Mitsuhashi T, Shimada K. Atrial fibrillation and continuous hypotension induced by sildenafil in an intermittent WPW syndrome patient. *Jpn Heart J* (1999) 40, 827–30.
4. Kloner RA, Jackson G, Emmick JT, Mitchell MI, Bedding A, Warner MR, Pereira A. Interaction between the phosphodiesterase 5 inhibitor, tadalafil and 2 α-blockers, doxazosin and tamsulosin in healthy normotensive men. *J Urol (Baltimore)* (2004) 172, 1935–40.
5. Giuliano F, Kaplan SA, Cabanis M-J, Astruc B. Hemodynamic interaction study between the alpha$_1$-blocker alfuzosin and the phosphodiesterase-5 inhibitor tadalafil in middle-aged healthy male subjects. *Urology* (2006) 67, 1199–1204.
6. Guillaume M, Lonsdale F, Darstein C, Jimenez MC, Mitchell MI. Hemodynamic interaction between a daily dosed phosphodiesterase 5 inhibitor, tadalafil, and the α-adrenergic blockers, doxazosin and tamsulosin, in middle-aged healthy male subjects. *J Clin Pharmacol* (2007) 47, 1303–10.
7. Levitra (Vardenafil hydrochloride). Bayer Pharmaceuticals Corporation. US prescribing information, December 2008.
8. Auerbach SM, Gittelman M, Mazzu A, Cihon F, Sundaresan P, White WB. Simultaneous administration of vardenafil and tamsulosin does not induce clinically significant hypotension in patients with benign prostatic hyperplasia. *Urology* (2004) 64, 998–1003; discussion 1003–4.
9. Pomara G, Morelli G, Pomara S, Taddei S, Ghiadoni L, Dinelli N, Travaglini F, Dicuio M, Mondaini N, Salvetti A, Selli C. Cardiovascular parameter changes in patients with erectile dysfunction using pde-5 inhibitors: a study with sildenafil and vardenafil. *J Androl* (2004) 25, 625–9.
10. De Rose AF, Giglio M, Traverso P, Lantieri P, Carmignani G. Combined oral therapy with sildenafil and doxazosin for the treatment of non-organic erectile dysfunction refractory to sildenafil monotherapy. *Int J Impot Res* (2002) 14, 50–3.

Phosphodiesterase type-5 inhibitors + Antacids

No clinically significant interaction appears to occur between sildenafil, tadalafil or vardenafil and aluminium/magnesium hydroxide-containing antacids.

Clinical evidence, mechanism, importance and management

(a) Sildenafil

In a single-dose study in 12 healthy subjects, the bioavailability of sildenafil was not affected by single 30-mL doses of an **aluminium/magnesium hydroxide** antacid.[1]

(b) Tadalafil

A randomised, crossover study in 12 healthy subjects found that 20 mL of *Maalox* (**aluminium/magnesium hydroxide**) reduced the mean maximum serum level of a single 10-mg dose of tadalafil by 30%. Although peak tadalafil levels were delayed by 2.5 hours, the total amount of tadalafil absorbed was unchanged. None of the changes caused were considered to be clinically relevant, and there would appear to be no reason for avoiding concurrent use.[2]

(c) Vardenafil

In a crossover study, 12 healthy subjects were given a single 20-mg dose of vardenafil with 10 mL of an **aluminium/magnesium hydroxide** antacid (*Maalox 70*). The bioavailability of vardenafil was not significantly altered by the antacid, therefore no additional precautions are needed if these drugs are used together.[3]

1. Wilner K, Laboy L, LeBel M. The effects of cimetidine and antacid on the pharmacokinetic profile of sildenafil citrate in healthy male volunteers. *Br J Clin Pharmacol* (2002) 53, 31S–36S.

2. Eli Lilly and Company. Personal communication, March 2003.
3. Rohde G, Wensing G, Sachse R. The pharmacokinetics of vardenafil, a new selective PDE5 inhibitor, are not affected by the antacid, Maalox 70. *Pharmacotherapy* (2001) 21, 1254.

Phosphodiesterase type-5 inhibitors + Antihypertensives

For the potentially serious interactions of sildenafil, tadalafil and vardenafil with the alpha blockers and nitrates, see 'Alpha blockers', (p.1531) and 'Nitrates', (p.1537). No clinically relevant interactions appear to occur between sildenafil, tadalafil or vardenafil and most other antihypertensive drugs. The exceptions may be diltiazem and verapamil, which theoretically may inhibit the metabolism of phosphodiesterase type-5 inhibitors.

Clinical evidence

(a) Sildenafil

In a study in 8 hypertensive men taking one to five antihypertensives (**amlodipine** (5 patients), a **diuretic** (4), an **ACE inhibitor** (3), an **angiotensin II receptor antagonist** (2), **diltiazem** (1)), a single 50-mg dose of sildenafil reduced the systolic BP by a mean maximum of 24 mmHg, compared with only 6 mmHg for placebo. One patient had a blood pressure fall of 48/23 mmHg, but none complained of hypotensive symptoms.[1] Two retrospective analyses of pooled data from various clinical studies suggests that patients taking non-nitrate antihypertensives (**ACE inhibitors**, alpha blockers, **beta blockers**, **calcium-channel blockers**, **diuretics**) and sildenafil had no significant difference in blood pressure or heart rate, when compared with those taking antihypertensives and placebo,[2] and that the incidence of dizziness did not differ between the two groups.[2,3] In a placebo-controlled study in patients with hypertension stabilised with two or more antihypertensives (including **diuretics**, **calcium-channel blockers**, **ACE inhibitors**, **beta blockers**, alpha blockers, **angiotensin II receptor antagonists**), the occurrence of adverse events potentially related to hypotensive effects (dizziness, hypotension, labile BP, vertigo) was less than 4% in those given sildenafil.[4] Note that combined use with alpha blockers may be especially likely to induce hypotensive events, see 'Phosphodiesterase type-5 inhibitors + Alpha blockers', p.1531.

The manufacturers report that, in population pharmacokinetic analysis, there was no effect on sildenafil pharmacokinetics in those taking **ACE inhibitors**, **calcium-channel blockers** and **thiazide** and **related diuretics**[5,6] whereas the AUC of the less potent active metabolite of sildenafil is increased by 62% by **loop** and **potassium-sparing diuretics** and by 102% by **non-selective beta blockers**.[6]

When sildenafil 100 mg was given to hypertensive patients taking **amlodipine** the mean additional fall in blood pressure (8/7 mmHg) was of the same magnitude as that seen when sildenafil was given alone to healthy subjects.[5,6]

A case report describes a patient taking **diltiazem** 30 mg three times daily who underwent coronary angiography 48 hours after taking sildenafil 50 mg, and who developed profound and persistent hypotension (BP 90/60 mmHg) after receiving sublingual nitrate for pain related to angina during the procedure.[7] It was suggested that **diltiazem** may have inhibited the metabolism of sildenafil so that it interacted with the nitrate,[7,8] although the time scale for this interaction has been disputed.[9]

The manufacturer notes that in population pharmacokinetic analysis of patients with *pulmonary hypertension*, there appeared to be an increase in sildenafil exposure when it was taken with **beta blockers** (none named) in combination with CYP3A4 substrates (none named).[10,11] The clinical relevance of this finding is uncertain, and further study is needed.

(b) Tadalafil

Placebo-controlled studies in patients taking **enalapril**, **metoprolol** or **bendroflumethiazide**, found that a 10-mg dose of tadalafil did not affect blood pressure or heart rate.[12] Similar results were seen in a study in patients taking **amlodipine** and given tadalafil 20 mg.[12] In another study in patients taking unnamed **angiotensin II receptor antagonists** (alone or in combination with **thiazides**, **calcium-channel blockers** or **beta blockers**[13]), tadalafil 20 mg lowered the mean BP by 8/4 mmHg more than placebo.[14] About twice as many patients taking tadalafil had a potentially clinically relevant decrease in blood pressure, when compared to those taking the antihypertensives alone, although no potential hypotensive symptoms (e.g. dizziness) occurred.[12]

In phase III studies in patients taking antihypertensives (**ACE inhibitors**, **calcium-channel blockers**, **thiazide diuretics**, **beta blockers**, **angiotensin II receptor antagonists**, alpha blockers and **loop diuretics**) blood pressure was similar in those given tadalafil and those given placebo. There was no difference in the number of patients with a potentially clinically relevant reduction in systolic BP (greater than 30 mmHg), and there was a similar incidence of dizziness.[12]

(c) Vardenafil

In a randomised, crossover study, 22 patients with hypertension stabilised by slow-release **nifedipine** 30 or 60 mg daily, were given a single 20-mg dose of vardenafil, or placebo. Vardenafil slightly decreased the maximum plasma levels and relative bioavailability of **nifedipine**, as well as causing a further decrease in supine blood pressure of about 6/5 mmHg. Heart rate was increased by 4 bpm.[15] **Nifedipine** did not alter vardenafil levels.[16]

The UK manufacturer says that, although not specifically studied, population pharmacokinetic analysis has suggested that **ACE inhibitors**, **beta blockers**, and **diuretics** have no effect on vardenafil pharmacokinetics.[17]

Mechanism

Phosphodiesterase type-5 inhibitors cause mild to moderate vasodilatation of vascular smooth muscle in veins and arteries, and so can lower blood pressure. This might be additive with the effects of antihypertensive drugs.

It should be noted that some calcium-channel blockers (e.g. **diltiazem**, **verapamil**) are known to inhibit the cytochrome P450 isoenzyme CYP3A4, by which sildenafil, tadalafil and vardenafil are metabolised, and so these calcium-channel blockers have the potential to raise phosphodiesterase type-5 inhibitor levels.

Importance and management

A small, additional decrease in blood pressure might be anticipated when phosphodiesterase type-5 inhibitors are used in patients taking antihypertensives such as beta blockers, ACE inhibitors, calcium-channel blockers and diuretics. This effect rarely results in clinically important adverse effects,[18] but consider also whether the patient's underlying cardiovascular disease would make resumption of sexual activity high-risk: poorly controlled hypertension and unstable or refractory angina are categorised as high-risk.[18]

There are no established pharmacokinetic interactions between phosphodiesterase type-5 inhibitors and ACE inhibitors, beta blockers, and dihydropyridine calcium-channel blockers. In addition, there are no pharmacokinetic data on the effects of **diltiazem** or **verapamil**, but on the basis of the known effect of other moderate CYP3A4 inhibitors such as 'erythromycin', (p.1537), on the metabolism of sildenafil, tadalafil and vardenafil, increased effects might be predicted. A lower starting dose of these phosphodiesterase type-5 inhibitors might be appropriate in patients taking diltiazem or verapamil.

There are some preliminary data suggesting a small increase in exposure to sildenafil with loop and potassium-sparing diuretics and non-selective beta blockers, but the manufacturer does not consider this to be clinically relevant.[6]

Note that some consider that the precautions required for 'alpha blockers', (p.1531), should also be applied to the beta blockers that also have alpha blocker activity, such as **carvedilol** and **labetalol**.[18]

1. Mahmud A, Hennessy M, Feely J. Effect of sildenafil on blood pressure and arterial wave reflection in treated hypertensive men. *J Hum Hypertens* (2001) 15, 707–13.
2. Zusman RM, Prisant LM, Brown MJ. Effect of sildenafil citrate on blood pressure and heart rate in men with erectile dysfunction taking concomitant antihypertensive medication. *J Hypertens* (2000) 18, 1865–9.
3. Kloner RA, Brown M, Prisant LM, Collins M, for the Sildenafil Study Group. Effect of sildenafil in patients with erectile dysfunction taking antihypertensive therapy. *Am J Hypertens* (2001) 14, 70–3.
4. Pickering TG, Shepherd AMM, Puddey I, Glasser DB, Orazem J, Sherman N, Mancia G. Sildenafil citrate for erectile dysfunction in men receiving multiple antihypertensive agents: a randomized controlled trial. *Am J Hypertens* (2004) 17, 1135–42.
5. Viagra (Sildenafil citrate). Pfizer Ltd. UK Summary of product characteristics, January 2009.
6. Viagra (Sildenafil citrate). Pfizer Inc. US Prescribing information, August 2008.
7. Khoury V, Kritharides L. Diltiazem-mediated inhibition of sildenafil metabolism may promote nitrate-induced hypotension. *Aust N Z J Med* (2000) 30, 641–2.
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9. Howes L. Diltiazem-mediated inhibition of sildenafil metabolism may promote nitrate-induced hypotension. *Intern Med J* (2001) 31, 373.
10. Revatio (Sildenafil citrate). Pfizer Ltd. UK Summary of product characteristics, July 2009.
11. Revatio (Sildenafil citrate). Pfizer Inc. US Prescribing information, November 2009.
12. Kloner RA, Mitchell M, Emmick JT. Cardiovascular effects of tadalafil in patients on common antihypertensive therapies. *Am J Cardiol* (2003) 92 (Suppl), 47M–57M.
13. Cialis (Tadalafil). Eli Lilly and Company Ltd. UK Summary of product characteristics, September 2008.

14. Cialis (Tadalafil). Eli Lilly and Company Ltd. US Prescribing information, July 2009.
15. Rohde G, Jordaan PJ. Influence of vardenafil on blood pressure and pharmacokinetics in hypertensive patients on nifedipine therapy. 31th Annual Meeting of the American College of Clinical Pharmacology, San Francisco, California, 2002.
16. Levitra (Vardenafil hydrochloride). Bayer Pharmaceuticals Corporation. US Prescribing information, December 2008.
17. Levitra (Vardenafil hydrochloride trihydrate). Bayer plc. UK Summary of product characteristics, June 2009.
18. Kostis JB, Jackson G, Rosen R, Barrett-Connor E, Billups K, Burnett AL, Carson C, Cheitlin M, Debusk R, Fonseca V, Ganz P, Goldstein I, Guay A, Hatzichristou D, Hollander JE, Hutter A, Katz S, Kloner RA, Mittleman M, Montorsi F, Montorsi P, Nehra A, Sadovsky R, Shabsigh R. Sexual dysfunction and cardiac risk (the Second Princeton Consensus Conference). Am J Cardiol. (2005) 96, 313–21.

Phosphodiesterase type-5 inhibitors + Aspirin

Sildenafil, tadalafil and vardenafil do not potentiate the increased bleeding time seen with aspirin.

Clinical evidence

(a) Sildenafil

In a pharmacological study, sildenafil 50 mg did not potentiate the increase in bleeding time seen with aspirin 150 mg.[1]

(b) Tadalafil

A randomised, parallel-group study in a total of 28 subjects found that a single 10-mg dose of tadalafil did not increase the bleeding time after aspirin 300 mg daily was taken for 5 days.[2]

(c) Vardenafil

The manufacturers say that population pharmacokinetic analysis suggests that aspirin had no effect on vardenafil pharmacokinetics.[3] In addition, vardenafil 10 mg and 20 mg did not potentiate the bleeding time caused by aspirin 162 mg.[3,4]

Mechanism

Phosphodiesterase type-5 is found in platelets. *In vitro*, sildenafil potentiated the antiplatelet effect of nitroprusside. However, an antiplatelet effect has not been seen clinically.[1]

Importance and management

No additional precautions seem necessary if phosphodiesterase type-5 inhibitors are given with antiplatelet doses of aspirin.

1. Viagra (Sildenafil citrate). Pfizer Inc. US Prescribing information, August 2008.
2. Eli Lilly and Company. Personal communication, March 2003.
3. Levitra (Vardenafil hydrochloride trihydrate). Bayer plc. UK Summary of product characteristics, June 2009.
4. Levitra (Vardenafil hydrochloride). Bayer Pharmaceuticals Corporation. US Prescribing information, December 2008.

Phosphodiesterase type-5 inhibitors + Azoles

Ketoconazole markedly raises the levels of tadalafil, very markedly raises the levels of vardenafil, and probably reduces sildenafil clearance. Itraconazole and other azole antifungals that are potent CYP3A4 inhibitors, such as posaconazole and voriconazole, are predicted to interact similarly.

Clinical evidence

(a) Sildenafil

Saquinavir increases the AUC of sildenafil twofold by inhibiting CYP3A4 (see 'Phosphodiesterase type-5 inhibitors + Protease inhibitors', p.1539). The manufacturers of sildenafil therefore predict that other more potent CYP3A4 inhibitors such as **itraconazole** and **ketoconazole** will have even greater effects.[1,2] They say that population data from clinical studies suggests that **ketoconazole** did reduce sildenafil clearance,[1,2] without increasing the incidence of adverse effects.[1] Similarly, a case report describes the apparently uneventful concurrent use of sildenafil 100 mg with **itraconazole** 400 mg daily for 7 days each month in a 56-year-old man.[3]

(b) Tadalafil

In a randomised study in 12 healthy subjects, **ketoconazole** 200 mg daily increased the AUC of a single 10-mg dose of tadalafil twofold,[4,5] and **ketoconazole** 400 mg daily increased the AUC fourfold.[4,5] The manufacturers predict that **itraconazole** will interact similarly.[4,5] This prediction has been borne out by a case report, which describes a 56-year-old man who was taking **itraconazole** 400 mg daily for 7 days each month. Within a few hours of his first 10-mg dose of tadalafil he developed priapism, which lasted for more than 4 hours. The same reaction occurred when he took tadalafil during the following month. He had seemingly previously taken sildenafil with **itraconazole** without adverse effect.[3]

(c) Vardenafil

Ketoconazole 200 mg daily increased the AUC of a 5-mg dose of vardenafil tenfold, and increased the maximum plasma levels fourfold. Although not specifically studied, **itraconazole** is expected to cause similar rises in vardenafil levels.[6,7]

Mechanism

Sildenafil, tadalafil and vardenafil are all metabolised by the cytochrome P450 isoenzyme CYP3A4. Ketoconazole and itraconazole are potent inhibitors of this isoenzyme, and therefore they inhibit sildenafil, tadalafil and vardenafil metabolism, which leads to an increase in their levels.

Importance and management

Information about the interaction between phosphodiesterase type-5 inhibitors and azoles is sparse, but what is known is in line with the predicted effects.

For **sildenafil**, when used for erectile dysfunction, the manufacturers recommend that a low starting dose of sildenafil (25 mg) should be considered if ketoconazole or itraconazole are used concurrently.[1,2] When used for pulmonary hypertension, the manufacturers say that concurrent use of sildenafil with ketoconazole or itraconazole is contraindicated in the UK,[8] or not recommended in the US.[9]

For **tadalafil**, the UK manufacturer advises caution[4] and the US manufacturer advises that the 'as needed' dose of tadalafil should not exceed 10 mg in a 72-hour period, and that the daily dose should not exceed 2.5 mg daily for patients taking potent CYP3A4 inhibitors such as ketoconazole.[5] However, note that the 10 mg dose has caused priapism in one patient taking itraconazole.

Vardenafil levels are greatly increased by ketoconazole and probably itraconazole so the UK manufacturer advises avoiding concurrent use in all patients. The use of ketoconazole or itraconazole in patients over 75 years of age is specifically contraindicated with vardenafil.[6] In contrast, the US manufacturer recommends that the dose of vardenafil should not exceed 5 mg in 24 hours when used with ketoconazole or itraconazole 200 mg daily, or 2.5-mg in 24 hours with ketoconazole or itraconazole 400 mg daily.[7]

For all three phosphodiesterase type-5 inhibitors, similar advice would apply to **posaconazole** and **voriconazole**, which are both also potent inhibitors of CYP3A4.

1. Viagra (Sildenafil citrate). Pfizer Ltd. UK Summary of product characteristics, January 2009.
2. Viagra (Sildenafil citrate). Pfizer Inc. US Prescribing information, August 2008.
3. Galatti L, Fioravanti A, Salvo F, Polimeni G, Giustini SE. Interaction between tadalafil and itraconazole. *Ann Pharmacother* (2005) 39, 200.
4. Cialis (Tadalafil). Eli Lilly and Company Ltd. UK Summary of product characteristics, September 2008.
5. Cialis (Tadalafil). Eli Lilly and Company Ltd. US Prescribing information, July 2009.
6. Levitra (Vardenafil hydrochloride trihydrate). Bayer plc. UK Summary of product characteristics, June 2009.
7. Levitra (Vardenafil hydrochloride). Bayer Pharmaceuticals Corporation. US prescribing information, December 2008.
8. Revatio (Sildenafil citrate). Pfizer Ltd. UK Summary of product characteristics, July 2009.
9. Revatio (Sildenafil citrate). Pfizer Inc. US Prescribing information, November 2009.

Phosphodiesterase type-5 inhibitors + CYP3A4 inducers

Rifampicin (rifampin) markedly reduces tadalafil levels by inducing CYP3A4, and is predicted to interact similarly with sildenafil and vardenafil. Other CYP3A4 inducers are likely to have a similar effect on these phosphodiesterase type-5 inhibitors.

Clinical evidence

(a) Sildenafil

On the basis of the 63% reduction in AUC seen with the moderate CYP3A4 inducer 'bosentan', (p.1535), the US manufacturer of sildenafil says that concurrent use with potent inducers of CYP3A4 such as **rifampicin** (**rifampin**) is predicted to cause a greater reduction in sildenafil levels.[1]

(b) Tadalafil

A study[2,3] in 12 healthy subjects found that **rifampicin** (**rifampin**) 600 mg daily for 13 days markedly reduced the AUC of a single 10-mg dose of tadalafil by 88%.

Mechanism

Rifampicin (rifampin) induces the activity of the cytochrome P450 isoenzyme CYP3A4, the principal enzyme concerned with the metabolism of sildenafil, tadalafil and **vardenafil**.

Importance and management

The pharmacokinetic interaction between rifampicin (rifampin) and tadalafil is established, and will almost certainly occur with sildenafil and vardenafil. It is unlikely that standard doses of these phosphodiesterase type-5 inhibitors would be as effective as usual in patients taking rifampicin. The manufacturers predict that other CYP3A4 inducers such as **carbamazepine**,[2-4] **phenobarbital**,[2-4] **phenytoin**,[2-4] and **St John's wort**[4] will interact similarly. Despite the marked interaction, the US manufacturer of tadalafil states that no dosage adjustment is warranted, although they do say that reduced efficacy of once-daily tadalafil is anticipated.[3] Conversely, the UK manufacturers of sildenafil state that efficacy should be closely monitored in patients taking CYP3A4 inducers.[4] If these phosphodiesterase type-5 inhibitors are not effective in a patients taking a CYP3A4 inducer, it would seem sensible to try a higher dose with close monitoring.

Although the manufacturer of **vardenafil** does not mention CYP3A4 inducers,[5,6] like tadalafil and sildenafil, vardenafil is principally metabolised by CYP3A4, and its levels are markedly raised by CYP3A4 inhibitors such as ketoconazole (see 'Phosphodiesterase type-5 inhibitors + Azoles', p.1534). It is therefore very likely that vardenafil levels will be reduced by potent CYP3A4 inducers such as rifampicin, and concurrent use should be monitored. For a list of CYP3A4 inducers, see 'Table 1.4', (p.6).

1. Viagra (Sildenafil citrate). Pfizer Inc. US Prescribing information, August 2008.
2. Cialis (Tadalafil). Eli Lilly and Company Ltd. UK Summary of product characteristics, September 2008.
3. Cialis (Tadalafil). Eli Lilly and Company Ltd. US Prescribing information, July 2009.
4. Revatio (Sildenafil citrate). Pfizer Ltd. UK Summary of product characteristics, July 2009.
5. Levitra (Vardenafil hydrochloride trihydrate). Bayer plc. UK Summary of product characteristics, June 2009.
6. Levitra (Vardenafil hydrochloride). Bayer Pharmaceuticals Corporation. US prescribing information, December 2008.

Phosphodiesterase type-5 inhibitors + Drugs that prolong the QT interval

Vardenafil caused a small increase in QTc interval, which was additive with that of gatifloxacin. This suggests that vardenafil may also have this effect with other drugs that prolong the QT interval. Tadalafil, and probably sildenafil, have no clinically relevant effect on the QT interval.

Clinical evidence

(a) Sildenafil

Sildenafil 50 mg caused a small 6 millisecond increase in the QTc interval in healthy subjects.[1] This increase was slightly smaller than that seen with a single 400-mg dose of moxifloxacin (8 milliseconds) used as a positive control.[1] No change in QT interval with sildenafil 50 mg was reported in other studies.[2,3]

(b) Tadalafil

In a well-designed study in healthy subjects, tadalafil 100 mg (five times the usual recommended dose) caused a 3.5 millisecond increase in the QTc. The positive control used in this study was intravenous ibutilide 2 micrograms/kg, which caused a 8.9 millisecond increase in QTc interval (individual) (9.5 milliseconds, Fridericia) compared with placebo. No subject had a QTc greater than 450 milliseconds and no subject had an increase in QTc of greater than 30 milliseconds.[4]

(c) Vardenafil

Vardenafil 10 mg and 80 mg caused small (8 millisecond and 10 millisecond, respectively) increases in the QTc interval in healthy subjects.[1] These increases were similar to that seen with a single 400-mg dose of moxifloxacin (8 milliseconds) used as a positive control.[1]

In another study in 44 healthy subjects, a single 10-mg dose of vardenafil caused a mean increase from baseline in QTc of 5 milliseconds when compared with placebo. A single 400-mg dose of gatifloxacin increased the QTc by 4 milliseconds. The effect of the combination of vardenafil and gatifloxacin was additive, resulting in a 9 millisecond increase in QTc.[5]

Mechanism

The effects of drugs that prolong the QT interval are expected to be additive, as was seen with vardenafil and gatifloxacin. Prolongation of the QT interval is associated with an increased risk of the potentially fatal torsade de pointes arrhythmia (see also 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290).

Importance and management

On the basis of what is currently known, the proarrhythmic risk of drugs that prolong the QTc interval by around 5 to less than 20 milliseconds is inconclusive. Vardenafil fits in this category. The manufacturers of vardenafil recommend that the possible increase in QT interval should be taken into account when prescribing vardenafil to patients with a known history of QT prolongation or using other drugs known to prolong the QT interval. Moreover, they say that vardenafil should not be used in those taking class Ia antiarrhythmics (e.g. **quinidine**, **procainamide**) or class III antiarrhythmics (e.g. **amiodarone**, **sotalol**), which are known to significantly prolong the QT interval.[5,6]

Regulatory guidance for the assessment of risk of a non-antiarrhythmic drug states that drugs causing an increase in mean QT/QTc interval of around 5 milliseconds or less do not appear to cause torsade de pointes. Tadalafil clearly fits in this category, and no special precautions are therefore required. Sildenafil probably also fits in this category.

There do not appear to be any published reports of torsade de pointes with any of these phosphodiesterase type-5 inhibitors.

For a full list of class Ia and class III antiarrhythmics, and for further information on regulatory guidance concerning QT prolongation, see 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290.

1. Morganroth J, Ilson BE, Shaddinger BC, Dabiri GA, Patel BR, Boyle DA, Sethuraman VS, Montague TH. Evaluation of vardenafil and sildenafil on cardiac repolarization. *Am J Cardiol* (2004) 93, 1378–83.
2. Piccirillo G, Nocco M, Lionetti M, Moisè A, Naso C, Marigliano V, Cacciafesta M. Effects of sildenafil citrate (Viagra) on cardiac repolarization and on autonomic control in subjects with chronic heart failure. *Am Heart J* (2002) 143, 703–10.
3. Alpaslan M, Onrat E, Samli M, Dincel C. Sildenafil citrate does not affect QT intervals and QT dispersion: an important observation for drug safety. *Ann Noninvasive Electrocardiol* (2003) 8, 14–17.
4. Beasley CM, Mitchell MI, Dmitrienko AA, Emmick JT, Shen W, Costigan TM, Bedding AW, Turik MA, Bakhtyari A, Warner MR, Ruskin JN, Cantilena LR, Kloner RA. The combined use of ibutilide as an active control with intensive electrocardiographic sampling and signal averaging as a sensitive method to assess the effects of tadalafil on the human QT interval. *J Am Coll Cardiol* (2005) 46, 678–87.
5. Levitra (Vardenafil hydrochloride). Bayer Pharmaceuticals Corporation. US Prescribing information, December 2008.
6. Levitra (Vardenafil hydrochloride trihydrate). Bayer plc. UK Summary of product characteristics, June 2009.

Phosphodiesterase type-5 inhibitors + Endothelin receptor antagonists

Bosentan markedly reduces sildenafil levels and modestly reduces tadalafil levels. Bosentan levels are modestly reduced by sildenafil, and are not affected to a clinically relevant extent by tadalafil. No clinically significant pharmacokinetic interaction occurs between ambrisentan and sildenafil or tadalafil.

Clinical evidence

(a) Ambrisentan

1. Sildenafil. A crossover study in 19 healthy subjects found that sildenafil 20 mg three times daily for 7 days had no clinically significant effect on the pharmacokinetics of a single 10-mg dose of ambrisentan. Ambrisentan 10 mg daily for 7 days slightly increased the maximum concentration of a single 20-mg dose of sildenafil by 13%; however, this is not considered to be clinically relevant. Ambrisentan had no significant effects on other pharmacokinetic parameters of sildenafil. No serious adverse effects were reported, although headache was common and no additive or synergistic reduction in blood pressure was noted.[1]

2. Tadalafil. In a crossover study in 23 healthy subjects, tadalafil 40 mg daily for 8 days slightly decreased AUC of a single 10-mg dose of ambrisentan given on day 6, by about 12%. Peak plasma levels of ambrisentan were similar in the presence and absence of tadalafil. The pharmacokinetics of tadalafil were not affected by concurrent use with ambrisentan.[2]

(b) Bosentan

1. Sildenafil. In 10 patients with pulmonary hypertension, bosentan 62.5 mg twice daily for one month decreased the AUC of a single 100-mg dose of sildenafil by 53% and increased its clearance 2.3-fold. After a second month of bosentan at an increased dose of 125 mg twice daily, the AUC of a single 100-mg dose of sildenafil was reduced by 69%, and the clearance increased 3.4-fold. The AUC of the primary metabolite, desmethyl-sildenafil, was also decreased in a dose-dependent manner by bosentan.[3] In a further well-controlled study in healthy subjects, the concurrent use of bosentan 125 mg twice daily and sildenafil 80 mg three times daily for 6 days decreased the AUC of sildenafil by 63% and increased the AUC of bosentan by 50%, when compared with either drug given alone.[4]

2. Tadalafil. In a well-controlled study in healthy subjects, the concurrent use of tadalafil 40 mg once daily and bosentan 125 mg twice daily for 10 days decreased the AUC of tadalafil by 41% and increased the AUC of bosentan by just 13%, which was not statistically significant.[5]

(c) Sitaxentan

The AUC and maximum concentration of a single 100-mg dose of **sildenafil** were increased by 28% and 18%, respectively, by sitaxentan; these changes are not expected to be clinically relevant. Furthermore, sitaxentan did not alter the pharmacokinetics of the active metabolite of **sildenafil**.[3]

Mechanism

Bosentan induces the cytochrome P450 isoenzyme CYP3A4, by which sildenafil and tadalafil are principally metabolised. The mechanism by which sildenafil increases bosentan levels is unknown, but might, in part, involve inhibition of organic anion transporting polypeptides (OATP).[6]

Importance and management

These pharmacokinetic interactions are established and potentially clinically important. The efficacy of sildenafil and tadalafil might be reduced in patients taking bosentan, and should be closely monitored. Sildenafil might increase the effects of bosentan, therefore patients should be monitored for signs of bosentan adverse effects such as flushing, headache and oedema. Tadalafil is unlikely to have this effect.

No dose adjustment of either drug is required on the concurrent use of ambrisentan with either sildenafil or tadalafil, and the dose of sildenafil does not need to be adjusted if sitaxentan is also given.

1. Spence R, Mandagere A, Dufton C, Venitz J. Pharmacokinetics and safety of ambrisentan in combination with sildenafil in healthy volunteers. J Clin Pharm (2008) 48, 1451–9..
2. Spence R, Mandagere A, Harrison B, Dufton C, Boinpally R. No clinically relevant pharmacokinetic and safety interactions of ambrisentan in combination with tadalafil in healthy volunteers. J Pharm Sci (2009) 98, 4962–74.
3. Paul GA, Gibbs JSR, Boobis AR, Abbas A, Wilkins MR. Bosentan decreases the plasma concentration of sildenafil when coprescribed in pulmonary hypertension. *Br J Clin Pharmacol* (2005) 60, 107–12.
4. Burgess G, Hoogkamer H, Collings L, Dingemanse J. Mutual pharmacokinetic interactions between steady-state bosentan and sildenafil. Eur J Clin Pharmacol (2008) 64, 43–50.
5. Wrishko RE, Dingemanse J, Yu A, Darstein C, Phillips DL, Mitchell MI. Pharmacokinetic Interaction Between Tadalafil and Bosentan in Healthy Male Subjects. J Clin Pharmacol (2008) 48, 610–18.
6. Treiber A, Schneiter R, Häusler S, Stieger B. Bosentan is a substrate of human OATP1B1 and OATP1B3: inhibition of hepatic uptake as the common mechanism of its interactions with cyclosporin A, rifampicin, and sildenafil. *Drug Metab Dispos* (2007) 35, 1400–7.

Phosphodiesterase type-5 inhibitors + Grapefruit juice

Grapefruit juice slightly increases the absorption of sildenafil. Tadalafil and vardenafil are predicted to be similarly affected.

Clinical evidence, mechanism, importance and management

Grapefruit juice 250 mL was given to 24 healthy subjects, both one hour before and with a 50-mg dose of **sildenafil**. There was a minor 23% increase in the AUC of **sildenafil**, but the maximum plasma level was not significantly changed. Inter-individual variation in **sildenafil** pharmacokinetics was also increased by grapefruit juice. The authors suggest that, although the slight rise in AUC is unlikely to be clinically significant, the combination is best avoided due to the increased variability in **sildenafil** pharmacokinetics.[1] However, this seems over-cautious, especially because the manufacturer permits reduced doses of **sildenafil** with much more potent inhibitors of CYP3A4, such as itraconazole, see 'Phosphodiesterase type-5 inhibitors + Azoles', p.1534.

The manufacturers of **tadalafil** predict that grapefruit juice will increase its levels[2,3] and the UK manufacturer advises caution with concurrent use.[2]

The manufacturers of **vardenafil** also predict that grapefruit juice will modestly increase its levels[4,5] and the UK advice is to avoid the combination.[4]

1. Jetter A, Kinzig-Schippers M, Walchner-Bonjean M, Hering U, Bulitta J, Schreiner P, Sörgel F, Fuhr U. Effects of grapefruit juice on the pharmacokinetics of sildenafil. *Clin Pharmacol Ther* (2002) 71, 21–9.
2. Cialis (Tadalafil). Eli Lilly and Company Ltd. UK Summary of product characteristics, September 2008.
3. Cialis (Tadalafil). Eli Lilly and Company Ltd. US Prescribing information, July 2009.
4. Levitra (Vardenafil hydrochloride trihydrate). Bayer plc. UK Summary of product characteristics, June 2009.
5. Levitra (Vardenafil hydrochloride). Bayer Pharmaceuticals Corporation. US prescribing information, December 2008.

Phosphodiesterase type-5 inhibitors + H_2-receptor antagonists

Sildenafil levels are modestly raised by cimetidine. No interaction appears to occur when nizatidine is given with tadalafil and when cimetidine or ranitidine is given with vardenafil.

Clinical evidence, mechanism, importance and management

(a) Sildenafil

In a study in 10 healthy subjects, **cimetidine** 800 mg daily for 4 days increased the AUC of a single 50-mg dose of sildenafil given on day 3 by 56%, when compared with 10 healthy subjects given sildenafil and placebo.[1] It has been suggested that these changes occur because **cimetidine** is a non-specific cytochrome P450 inhibitor.[2] The manufacturers say that population pharmacokinetic analysis revealed a reduced clearance of sildenafil in patients taking CYP3A4 inhibitors, including **cimetidine**.[2,3] The UK manufacturers say that, although no increase in adverse effects was seen, a starting dose of 25 mg of sildenafil should be considered.[3] However, the study suggests the effect is modest, and so this recommendation seems over-cautious. Furthermore, the US manufacturer dose not advise a sildenafil dose reduction in those taking **cimetidine**.[2]

(b) Tadalafil

A randomised, crossover study in 12 healthy subjects found that **nizatidine** 300 mg reduced the mean maximum serum levels of a single 10-mg dose of tadalafil by 14%, but other pharmacokinetic parameters, including the extent of absorption, were largely unchanged. None of the changes caused were considered to be clinically relevant and there would appear to be no reason for avoiding concurrent use.[4] This study also suggests that any alterations in the absorption of tadalafil are therefore unlikely to be caused by changes in gastric pH.[4]

(c) Vardenafil

In a crossover study, 10 healthy subjects were given a single 20-mg dose of vardenafil after they had taken **cimetidine** 400 mg twice daily for 3 days, **ranitidine** 150 mg twice daily for 3 days or with no pre-treatment. **Cimetidine** slightly increased the relative bioavailability of vardenafil (by

about 12%, not considered clinically relevant), while **ranitidine** had no effect. It was concluded that any alterations in the absorption of vardenafil are not caused by changes in gastric pH.[5] No special precautions appear to be necessary during concurrent use.

1. Wilner K, Laboy L, LeBel M. The effects of cimetidine and antacid on the pharmacokinetic profile of sildenafil citrate in healthy male volunteers. *Br J Clin Pharmacol* (2002) 53, 31S–36S.
2. Viagra (Sildenafil citrate). Pfizer Inc. US Prescribing information, August 2008.
3. Viagra (Sildenafil citrate). Pfizer Ltd. UK Summary of product characteristics, January 2009.
4. Eli Lilly and Company. Personal communication, March 2003.
5. Rohde G, Wensing G, Unger S, Sachse R. The pharmacokinetics of vardenafil, a new selective PDE5 inhibitor, is minimally affected by coadministration with cimetidine or ranitidine. *Pharmacotherapy* (2001) 21, 1254.

Phosphodiesterase type-5 inhibitors + Macrolides

Erythromycin raises sildenafil levels almost threefold, raises vardenafil levels fourfold, and is predicted to similarly affect tadalafil levels. Clarithromycin, but not azithromycin, raises sildenafil levels about twofold and is predicted to increase tadalafil and vardenafil levels.

Clinical evidence

(a) Sildenafil

In a study in 24 healthy subjects, **erythromycin** 500 mg twice daily for 5 days was found to increase the AUC of a single 100-mg dose of sildenafil almost threefold.[1] In the same study, **azithromycin** 500 mg once daily for 3 days had no effect on the pharmacokinetics of sildenafil.[1] In another study, in 12 healthy subjects, **clarithromycin** 500 mg increased the AUC of sildenafil 50 mg 2.3-fold, and increased its maximum level 2.4-fold.[2]

(b) Tadalafil

Ketoconazole doubles tadalafil levels by inhibiting CYP3A4 (see 'Phosphodiesterase type-5 inhibitors + Azoles', p.1534). The manufacturers therefore predict that other CYP3A4 inhibitors such as **erythromycin** and **clarithromycin**[3,4] will interact similarly.

(c) Vardenafil

Erythromycin 500 mg three times daily increased the AUC of a 5-mg dose of vardenafil fourfold, and increased its maximum plasma levels threefold in healthy subjects.[5,6]

Mechanism

Sildenafil, tadalafil and vardenafil are all metabolised by the cytochrome P450 isoenzyme CYP3A4. Many macrolides are moderate inhibitors of this isoenzyme and therefore inhibit sildenafil, tadalafil and vardenafil metabolism. This leads to increased levels of the phosphodiesterase inhibitors. Azithromycin does not usually act as a CYP3A4 inhibitor and therefore does not interact.

Importance and management

The pharmacokinetic interaction of the macrolides with the phosphodiesterase type-5 inhibitors is established, although most of the studies concern the use of sildenafil. These interactions are expected to result in both increased efficacy and an increased incidence of adverse effects.

For **sildenafil**, the manufacturers recommend that a low starting dose of sildenafil 25 mg should be considered in patients with erectile dysfunction taking CYP3A4 inhibitors such as erythromycin.[7,8] For pulmonary hypertension, the UK manufacturer says that a reduction of the sildenafil dose to 20 mg twice daily should be considered with erythromycin, and 20 mg daily with clarithromycin or **telithromycin**,[9] although note that erythromycin had a greater effect than clarithromycin in the studies above.

For **tadalafil**, the UK manufacturer advises caution if CYP3A4 inhibitors are also given as adverse effects may be increased in some patients. They specifically mention erythromycin and clarithromycin.[3]

For **vardenafil**, the UK manufacturer says that dosage adjustments might be necessary in patients taking erythromycin or clarithromycin, and recommend that the dose of vardenafil should not exceed 5 mg.[5] The US manufacturer similarly recommends that the dose of vardenafil should not exceed 5 mg in 24 hours for erythromycin, but further restricts the dose in the presence of clarithromycin, to 2.5 mg in 24 hours.[6]

Dosing guidance is not given for the other macrolides, but it would seem prudent to follow the advice given for erythromycin in patients taking any macrolide known to inhibit CYP3A4 (e.g. clarithromycin, **telithromycin**). Azithromycin seems unlikely to interact.

1. Muirhead GJ, Faulkner S, Harness JA, Taubel J. The effects of steady-state erythromycin and azithromycin on the pharmacokinetics of sildenafil citrate in healthy volunteers. *Br J Clin Pharmacol* (2002) 53, 37S–43S.
2. Hedaya MA, El-Afify DR, El-Maghraby GM. The effect of ciprofloxacin and clarithromycin on sildenafil oral bioavailability in human volunteers. *Biopharm Drug Dispos* (2006) 27, 103–10.
3. Cialis (Tadalafil). Eli Lilly and Company Ltd. UK Summary of product characteristics, September 2008.
4. Cialis (Tadalafil). Eli Lilly and Company Ltd. US Prescribing information, July 2009.
5. Levitra (Vardenafil hydrochloride trihydrate). Bayer plc. UK Summary of product characteristics, June 2009.
6. Levitra (Vardenafil hydrochloride). Bayer pharmaceuticals Corporation. US prescribing information, December 2008.
7. Viagra (Sildenafil citrate). Pfizer Ltd. UK Summary of product characteristics, January 2009.
8. Viagra (Sildenafil citrate). Pfizer Inc. US Prescribing information, August 2008.
9. Revatio (Sildenafil citrate). Pfizer Ltd. UK Summary of product characteristics, July 2009.

Phosphodiesterase type-5 inhibitors + Miscellaneous

No pharmacokinetic interaction appears to occur between sildenafil and an oral combined hormonal contraceptive, whereas tadalafil slightly increases the bioavailability of ethinylestradiol from an oral combined hormonal contraceptive. Sildenafil does not alter the pharmacokinetics of tolbutamide.

Clinical evidence, mechanism, importance and management

(a) Hormonal contraceptives

The pharmacokinetics of **sildenafil** were not altered by concurrent use of an oral combined hormonal contraceptive (**ethinylestradiol/levonorgestrel**), and the plasma levels of these contraceptive steroids were not altered by sildenafil.[1,2]

In contrast, use of **tadalafil** 10 mg with an oral combined hormonal contraceptive (**ethinylestradiol/levonorgestrel**) increased the steady-state AUC of **ethinylestradiol** by 18% and its maximum level by 53%, with no change in systemic clearance.[3,4] The mechanism for this is unknown.[4] The pharmacokinetics of **levonorgestrel** were not affected. There were no changes in levels of LH, FSH, and progesterone, which suggests that the pharmacokinetic changes with **ethinylestradiol** are unlikely to be clinically relevant.

(b) Tolbutamide

Sildenafil 50 mg did not alter the pharmacokinetics of tolbutamide 250 mg,[5,6] probably because sildenafil is only a weak inhibitor of the cytochrome P450 isoenzyme CYP2C9 by which tolbutamide is metabolised. This is in line with the way other CYP2C9 substrates behave, see *warfarin*, under 'Coumarins + Phosphodiesterase type-5 inhibitors', p.496.

1. Revatio (Sildenafil citrate). Pfizer Ltd. UK Summary of product characteristics, July 2009.
2. Revatio (Sildenafil citrate). Pfizer Inc. US Prescribing information, November 2009.
3. Cialis (Tadalafil). Eli Lilly and Company Ltd. UK Summary of product characteristics, September 2008.
4. Eli Lilly. Personal communication, March 2008.
5. Viagra (Sildenafil citrate). Pfizer Ltd. UK Summary of product characteristics, January 2009.
6. Viagra (Sildenafil citrate). Pfizer Inc. US Prescribing information, August 2008.

Phosphodiesterase type-5 inhibitors + Nitrates

Phosphodiesterase type-5 inhibitors potentiate the hypotensive effects of nitrates in a proportion of patients, which might result in potentially serious hypotension or even precipitate myocardial infarction. Therefore, the concurrent use of sildenafil, tadalafil or vardenafil with organic nitrates (glyceryl trinitrate (nitroglycerin), isosorbide dinitrate, isosorbide mononitrate, sodium nitroprusside, etc.) is contraindicated. The concurrent use of nicorandil and all phosphodiesterase type-5 inhibitors is also contraindicated.

Clinical evidence

(a) Sildenafil

Two double-blind, placebo-controlled studies in groups of 15 or 16 men with angina found that the fall in blood pressure seen when taking nitrates

was approximately doubled by a single 50-mg dose of sildenafil. Those given sildenafil and **isosorbide dinitrate** 20 mg twice daily had a mean blood pressure fall of 44/26 mmHg, compared with 22/13 mmHg with placebo. Those who used 500 micrograms of sublingual **glyceryl trinitrate** (**nitroglycerin**) one hour before the sildenafil had a mean blood pressure fall of 36/21 mmHg compared with 26/11 mmHg with **glyceryl trinitrate** and placebo. Individual blood pressure falls as great as 84/52 mmHg were seen.[1]

A postmarketing report from the FDA in the US for the period late March to July 1998 briefly lists 69 fatalities in patients who had taken sildenafil. These were mostly in middle-aged and elderly men (average age 64 years), 12 of whom had also taken **glyceryl trinitrate** or a nitrate medication, but it is not clear what part (if any) the nitrates played in the deaths.[2]

In a limited and preliminary study it was reported that no blood pressure alteration was seen when a small dose of **glyceryl trinitrate** (amount not specified) was given as a dermal patch while subjects were taking 50 mg of sildenafil. In addition, the beneficial effects of the **glyceryl trinitrate** on the radial artery pressure waveform were approximately doubled, and persisted for up to 8 hours.[3]

A placebo-controlled, randomised study in 32 men with stable coronary artery disease suggested that, 45 minutes after a single 100-mg dose of sildenafil had been given, it was possible to cautiously give intravenous **glyceryl trinitrate**, starting at a low dose and slowly increasing to a maximum of 160 micrograms/minute. Sildenafil caused an additional reduction in blood pressure of about 4 to 6 mmHg, when compared with placebo. In general, when compared with placebo, the dose of nitrate tolerated was lower, and despite this, hypotension was more common, in the presence of sildenafil.[4]

(b) Tadalafil

In a randomised, placebo-controlled study, 51 patients with chronic stable angina were given tadalafil 5 mg, 10 mg or a placebo, followed 2 hours later by a single 400-microgram dose of sublingual **glyceryl trinitrate**. Although tadalafil caused little additional decrease in blood pressure to that seen with **glyceryl trinitrate**, a potentially clinically significant blood pressure reduction (standing systolic BP less than 85 mmHg) was seen in 13 and 11 of the patients when given tadalafil 5 and 10 mg, respectively, compared with one patient in the placebo group.[5,6] In a similar study in 45 patients taking long-term oral **isosorbide mononitrate**, tadalafil 5 or 10 mg had minimal effects on the decrease in blood pressure caused by the nitrate, but again, more patients had a standing systolic BP of less than 85 mmHg when receiving tadalafil 10 mg than placebo (6 versus 0).[5,6] Another similar study in 48 healthy subjects compared the effects of tadalafil 10 mg, sildenafil 50 mg, and placebo, in combination with sublingual **glyceryl trinitrate** 400 micrograms. Again, it was found that the presence of the tadalafil had minimal effects on the mean maximum decreases in blood pressure, but it was noted that 23 patients given tadalafil and 23 given sildenafil had a standing systolic blood pressure of 85 mmHg or less following the use of the nitrate, compared with 12 in the placebo group.[6,7] In a further study, a haemodynamic interaction between tadalafil 20 mg and sublingual **glyceryl trinitrate** was seen when the **glyceryl trinitrate** was given 4, 8 and 24 hours after the tadalafil, and was not seen at 48 hours and beyond. Note that no time points between 24 and 48 hours were examined.[8]

An analysis of the rates of serious cardiovascular adverse events (mortality, myocardial infarction, thrombotic strokes) in clinical studies involving tadalafil indicated that adverse events were no more frequent than in the general population of men with erectile dysfunction.[6]

(c) Vardenafil

A single 400-microgram dose of sublingual **glyceryl trinitrate** (**nitroglycerin**) given to 18 healthy subjects 1 to 24 hours after a single 10-mg dose of vardenafil was found to be no different to placebo in causing changes in seated heart rate and blood pressure.[9,10] However, a single 20-mg dose of vardenafil did potentiate the blood pressure-lowering effects and increases in heart rate (about an 8 mmHg additional drop in systolic BP compared with placebo) seen with **sublingual nitrates** (400 micrograms) taken 1 and 4 hours after the vardenafil. These effects were not seen when the nitrate was taken 24 hours after the vardenafil dose.[9,11]

Mechanism

Sexual stimulation causes the endothelium of the penis to release nitric oxide (NO), which in turn activates guanylate cyclase to increase the production of cyclic guanosine monophosphate (cGMP). This relaxes the blood vessel musculature of the corpus cavernosum thus allowing it to fill with blood and cause an erection. The erection ends when the guanosine monophosphate is removed by an enzyme (type 5 cGMP phosphodiesterase, or PDE5). Sildenafil, tadalafil and vardenafil inhibit this enzyme thereby increasing and prolonging the effects of the cyclic guanosine monophosphate. Because this vasodilation is usually fairly localised (these drugs are highly selective for PDE5) it normally only causes mild to moderate falls in blood pressure (on average about 10 mmHg) with mild headache or flushing. Nitrates (e.g. glyceryl trinitrate) increase the production of cyclic guanosine monophosphate, and when phosphodiesterase type-5 inhibitors (PDE5 inhibitors) are taken concurrently, cyclic guanosine monophosphate accumulates and high levels of nitric oxide enter the circulation. This markedly increases systemic vasodilation and hence causes the hypotensive effect.

Importance and management

The interaction between phosphodiesterase type-5 inhibitors and nitrates is established, clinically important, potentially serious and even possibly fatal. Sildenafil and organic nitrates of any form are contraindicated both for erectile dysfunction[12,13] (within 24 hours of each other[14]) and for pulmonary hypertension[15,16] because of the risk of precipitating serious hypotension, or even myocardial infarction.[17] The ACC/AHA Expert consensus document provides a useful list of many of the organic nitrates available, which include glyceryl trinitrate (nitroglycerin), isosorbide mononitrate, isosorbide dinitrate, '**sodium nitroprusside**', (p.1075), and illicit substances such as **amyl nitrite**.[14] However, the use of some nitrate donors may be beneficial, see 'Phosphodiesterase type-5 inhibitors; Sildenafil + Nitric oxide', p.1541.

The manufacturers of vardenafil[9,11] and tadalafil[18,19] say that their combination with nitrates (taken either regularly and/or intermittently) is contraindicated. Nitrates should not be given for at least 48 hours after the last dose of tadalafil because this has a long elimination half-life.[18,19]

If patients develop angina during sexual activity after taking a phosphodiesterase type-5 inhibitor they should discontinue sexual activity, relax for 5 to 10 minutes, and if the pain persists seek emergency care, informing medical personnel that they have taken a phosphodiesterase type-5 inhibitor. In the event of myocardial infarction, usual therapies can be given, with the exception of organic nitrates.[20] Note that, in the study where glyceryl trinitrate infusions were successfully given to patients who had taken sildenafil, the patients had stable heart disease, and the suggestion of this being a usable combination may not be applicable to patients experiencing episodes of acute cardiac disease.

There is no known antidote to the phosphodiesterase type-5 interaction with nitrates. Important hypotension should be managed by placing the patient in the Trendelenburg position (that is, laid flat on their back, with their feet higher than their head) and giving intravenous fluids and alpha agonists such as phenylephrine. It has also been suggested that, if hypotension is refractory, intra-aortic balloon counterpulsation should be used.[20]

It is not yet known whether **nicorandil** interacts with the phosphodiesterase inhibitors to a clinically relevant extent or not,[21] but because part of its vasodilatory actions are mediated by the release of nitric oxide (like conventional nitrates), the manufacturers of nicorandil contraindicate its use with all phosphodiesterase inhibitors.[22]

1. Webb DJ, Muirhead G, Wulff M, Sutton A, Levi R, Dinsmore WW. Sildenafil citrate potentiates the hypotensive effects of nitric oxide donor drugs in male patients with stable angina. *J Am Coll Cardiol* (2000) 36, 25–31.
2. FDA (US Food and Drug Administration) postmarketing information sildenafil citrate (Viagra): Postmarketing safety of sildenafil citrate (Viagra). Reports of death in Viagra users received from marketing (late March) through July 1998. August 27th 1998.
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7. Kloner RA, Mitchell MI, Bedding A, Emmick J. Pharmacodynamic interactions between tadalafil and nitrates compared with sildenafil. *J Urol (Baltimore)* (2002) 167 (Suppl) 176–7.
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10. Mazzu AL, Nicholls AJ, Zinny M. Vardenafil, a new selective PDE-5 inhibitor, interacts minimally with nitroglycerin in healthy middle-aged male subjects. *Int J Impot Res* (2001) 13 (Suppl 5) S64.
11. Levitra (Vardenafil hydrochloride). Bayer Pharmaceuticals Corporation. US prescribing information, December 2008.

12. Viagra (Sildenafil citrate). Pfizer Ltd. UK Summary of product characteristics, January 2009.
13. Viagra (Sildenafil citrate). Pfizer Inc. US Prescribing information, August 2008.
14. ACC/AHA Expert consensus document. Use of sildenafil (Viagra) in patients with cardiovascular disease. *J Am Coll Cardiol* (1999) 33, 273–82.
15. Revatio (Sildenafil citrate). Pfizer Ltd. UK Summary of product characteristics, July 2009.
16. Revatio (Sildenafil citrate). Pfizer Inc. US Prescribing information, November 2009.
17. Viagra (Sildenafil). Pfizer Inc. Dear Doctor letter, May 1998.
18. Cialis (Tadalafil). Eli Lilly and Company Ltd. UK Summary of product characteristics, September 2008.
19. Cialis (Tadalafil). Eli Lilly and Company Ltd. US Prescribing information, July 2009.
20. Kostis JB, Jackson G, Rosen R, Barrett-Connor E, Billups K, Burnett AL, Carson C, Cheitlin M, Debusk R, Fonseca V, Ganz P, Goldstein I, Guay A, Hatzichristou D, Hollander JE, Hutter A, Katz S, Kloner RA, Mittleman M, Montorsi F, Montorsi P, Nehra A, Sadovsky R, Shabsigh R. Sexual dysfunction and cardiac risk (the Second Princeton Consensus Conference). Am J Cardiol. (2005) 96, 313–21.
21. Aventis Pharma, Personnal communication, February 2000.
22. Ikorel (Nicorandil). Sanofi-Aventis. UK Summary of product characteristics, February 2009.

Phosphodiesterase type-5 inhibitors + Protease inhibitors

Indinavir, saquinavir and ritonavir can cause marked rises in serum sildenafil levels. A fatal heart attack occurred in a man taking ritonavir and saquinavir when he also took sildenafil. Even more marked rises in serum levels occur with vardenafil and indinavir or ritonavir, and are predicted to occur with vardenafil and other protease inhibitors. Ritonavir and ritonavir-boosted tipranavir cause less marked increases in tadalafil levels.

Clinical evidence

A. Sildenafil

(a) Indinavir

A study in 6 HIV-positive patients found that sildenafil 25 mg did not significantly alter the plasma levels of indinavir. However, the sildenafil AUC was about 4.4-fold higher than the AUC in historical control patients taking sildenafil (data normalised to a 25 mg dose) without indinavir.[1] A study in 2 HIV-positive patients found that sildenafil 25 mg did not affect the pharmacokinetics of indinavir.[2]

(b) Nelfinavir

A study in 5 HIV-positive patients found that sildenafil 25 mg did not affect the pharmacokinetics of nelfinavir.[2]

(c) Ritonavir

In a randomised, placebo-controlled study, 28 healthy subjects were given sildenafil 100 mg before and after taking ritonavir for 7 days (300 mg, 400 mg and 500 mg twice daily on days 1, 2 and 3 to 7, respectively). It was found that the AUC of sildenafil was increased 11-fold and its maximum serum levels were increased 3.9-fold by ritonavir, but the incidence and severity of the sildenafil adverse effects and the steady-state levels of ritonavir remained unchanged.[3] However, the clinical significance of this interaction is highlighted by a case report of a 47-year-old man, with no cardiovascular risk factors apart from smoking, who had a myocardial infarction when he took sildenafil 25 mg while he was also taking ritonavir 400 mg twice daily and **saquinavir** 400 mg twice daily. One hour after the ninth dose (used over the previous 12 weeks), he had an onset of severe chest pain, and died about one day later.[4]

A study in 2 HIV-positive patients found that sildenafil 25 mg did not affect the pharmacokinetics of ritonavir (given with saquinavir).[2]

(d) Saquinavir

In a randomised, placebo-controlled study, 28 healthy subjects were given sildenafil 100 mg before and after taking saquinavir 1.2 g three times daily for 7 days. It was found that the sildenafil AUC was increased 3.1-fold and its maximum serum levels were increased 2.4-fold, but the incidence and severity of the sildenafil adverse effects and the steady-state levels of saquinavir remained unchanged.[3] Also see *Ritonavir*, above for a case report of a fatal interaction involving sildenafil, ritonavir and saquinavir.

A study in 2 HIV-positive patients found that sildenafil 25 mg did not affect the pharmacokinetics of ritonavir-boosted saquinavir.[2]

B. Tadalafil

(a) Ritonavir

Ritonavir 200 mg twice daily increased the AUC of a single 20-mg dose of tadalafil twofold (124%), without affecting its maximum serum levels.[5,6]

(b) Tipranavir

In a study in healthy subjects, the first dose of ritonavir-boosted tipranavir initially increased the AUC of tadalafil from a single-dose by 2.3-fold. However steady-state levels of ritonavir-boosted tipranavir had no significant effect on tadalafil exposure.[7,8]

C. Vardenafil

When a single 10-mg dose of vardenafil was given with **indinavir** 800 mg three times daily, the AUC of vardenafil was increased 16-fold, and its maximum plasma level was increased sevenfold.[9,10] Moreover, **ritonavir** 600 mg twice daily produced a 49-fold increase in the AUC of vardenafil, and prolonged the half-life to 26 hours.[10]

Mechanism

Protease inhibitors inhibit the activity of the cytochrome P450 isoenzyme CYP3A4, the enzyme that metabolises sildenafil, tadalafil and vardenafil. This results in an increase in their serum levels. Ritonavir is the most potent CYP3A4 inhibitor, followed by indinavir, nelfinavir, amprenavir, and then saquinavir, see 'Antivirals', (p.913)).

Importance and management

Information about interactions between phosphodiesterase type-5 inhibitors and protease inhibitors appears to be limited to the studies and case cited, but the interactions are established and of clinical importance.

For **sildenafil**, because of the very marked rises in levels, the concurrent use of ritonavir and sildenafil for pulmonary hypertension is not advised,[11] or in the UK, contraindicated.[12] When single doses of sildenafil are used for erectile dysfunction, the UK manufacturer also says concurrent use with ritonavir is not advised.[13] In this situation, if the decision is taken to use sildenafil in a patient taking ritonavir, the dose of sildenafil should not exceed a single 25-mg dose in a 48-hour period,[3,13,14] but note that the fatality described above[4] occurred despite the use of this dose. For other CYP3A4 inhibitors such as saquinavir, the recommendation for erectile dysfunction is that a low starting dose (25 mg) should be considered.[3,13,14] For pulmonary hypertension, the UK manufacturer says that a downward reduction of the sildenafil dose to 20 mg twice daily should be considered with saquinavir.[12] The authors of the indinavir study suggest that a starting dose of 12.5 mg may be more appropriate for erectile dysfunction in those taking indinavir, and that the maximum dosage frequency should be reduced to once or twice weekly.[1] Direct evidence for other protease inhibitors is lacking but they would be expected to interact similarly (see *Mechanism*, above) and it would seem consistent to follow the broad principle of starting with a low sildenafil dosage.

For **tadalafil**, the US manufacturer advises that the 'as needed' dose should not exceed 10 mg every 72 hours and the daily dose should not exceed 2.5 mg daily in patients taking ritonavir,[5] whereas the UK manufacturer simply advises caution on concurrent use.[6] It is probably prudent to apply this advice to patients taking any protease inhibitor.

For **vardenafil**, due to the very large rises in levels, the UK manufacturer contraindicates its use with protease inhibitors that are potent CYP3A4 inhibitors (they name ritonavir and indinavir).[9] In contrast, the US manufacturer recommends dose restrictions as follows: the dose of vardenafil should not exceed 2.5 mg in 24 hours when used with **atazanavir**, indinavir, or saquinavir, and should not exceed 2.5 mg in 72 hours when used with ritonavir.[10] The manufacturer of tipranavir also advises that the maximum dose of vardenafil should not exceed 2.5 mg in 72 hours.[8]

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4. Hall MCS, Ahmad S. Interaction between sildenafil and HIV-1 combination therapy. *Lancet* (1999) 353, 2071–2.
5. Cialis (Tadalafil). Eli Lilly and Company Ltd. US Prescribing information, July 2009.
6. Cialis (Tadalafil). Eli Lilly and Company Ltd. UK Summary of product characteristics, September 2008.
7. Aptivus Soft Capsules (Tipranavir). Boehringer Ingelheim Ltd. UK Summary of product characteristics, June 2009.
8. Aptivus (Tipranavir). Boehringer Ingelheim Pharmaceuticals, Inc. US Prescribing information, June 2009.
9. Levitra (Vardenafil hydrochloride trihydrate). Bayer plc. UK Summary of product characteristics, June 2009.
10. Levitra (Vardenafil hydrochloride). Bayer Pharmaceuticals Corporation. US prescribing information, December 2008.
11. Revatio (Sildenafil citrate). Pfizer Inc. US Prescribing information, November 2009.
12. Revatio (Sildenafil citrate). Pfizer Ltd. UK Summary of product characteristics, July 2009.

13. Viagra (Sildenafil citrate). Pfizer Ltd. UK Summary of product characteristics, January 2009.
14. Viagra (Sildenafil citrate). Pfizer Inc. US Prescribing information, August 2008.

Phosphodiesterase type-5 inhibitors; Sildenafil + Antidepressants

Retrospective analysis of clinical study data suggested that SSRIs and tricyclic antidepressants did not alter sildenafil pharmacokinetics. However, in one pharmacokinetic study, fluvoxamine was found to modestly increase the levels and vascular effects of sildenafil.

Clinical evidence

The manufacturer notes that population pharmacokinetic analysis of clinical study data indicate that inhibitors of cytochrome P450 isoenzyme CYP2D6 such as **SSRIs** and **tricyclic antidepressants** do not have any effect on the pharmacokinetics of sildenafil.[1,2] However, in a placebo-controlled study in healthy subjects, pre-treatment with **fluvoxamine** 50 mg daily for 3 days then 100 mg daily for 6 days increased the AUC of sildenafil 50 mg by 40%. This resulted in an increase in the vascular effects of sildenafil.[3]

Mechanism

Sildenafil is principally metabolised by the cytochrome P450 isoenzyme CYP3A4, and to a lesser extent by CYP2C9. Fluvoxamine probably raises sildenafil levels by inhibition of both of these isoenzymes. Grouping all SSRIs and tricyclics together in a retrospective analysis would not be a sensitive enough technique to have picked up this modest effect of fluvoxamine.

Importance and management

The increases in sildenafil levels with fluvoxamine are modest, and the authors concluded that they do not suggest a large clinically relevant interaction. Nevertheless, they suggest it may be prudent to consider a 25-mg starting dose of sildenafil in patients taking fluvoxamine.[3] This may be sensible. Although retrospective analyses of clinical study data are useful to identify potentially important drug interactions, they are not sensitive enough to rule out interactions, and should not replace prospective pharmacokinetic studies.

1. Viagra (Sildenafil citrate). Pfizer Ltd. UK Summary of product characteristics, January 2009.
2. Viagra (Sildenafil citrate). Pfizer Inc. US Prescribing information, August 2008.
3. Hesse C, Siedler H, Burhenne J, Riedel K-D, Haefeli WE. Fluvoxamine affects sildenafil kinetics and dynamics. *J Clin Psychopharmacol* (2005) 25, 589–92.

Sildenafil + Cannabis

Myocardial infarction occurred in a man who had smoked cannabis and taken a tablet of sildenafil.

Clinical evidence

A 41-year old man with no history of cardiac disease experienced a myocardial infarction after smoking cannabis and recreationally taking a tablet of sildenafil (strength not specified). Later tests showed that he had no evidence of inducible ischaemia.[1]

Mechanism

Myocardial infarction is a rare adverse effect of sildenafil alone. It was suggested that the metabolism of sildenafil by cytochrome P450 isoenzyme CYP3A4 might be inhibited by constituents of cannabis such as cannabidiol, thereby increasing the risk of adverse events. However, in clinical studies, oral cannabis did not alter levels of other CYP3A4 substrates.

Importance and management

The vasodilatory effects of sildenafil necessitate caution in its use in patients with cardiovascular disease; myocardial infarction has rarely been associated with its use. The contribution of an interaction to this case is unclear, but bear the possibility in mind in the event of adverse effects on concurrent use.

1. McLeod AL, McKenna CJ, Northridge DB. Myocardial infarction following the combined recreational use of Viagra® and cannabis. *Clin Cardiol* (2002) 25, 133–4.

Phosphodiesterase type-5 inhibitors; Sildenafil + Cocaine

An isolated report describes acute aortic dissection possibly associated with the use of cocaine and sildenafil.

Clinical evidence, mechanism, importance and management

A 42-year-old man developed chest pain radiating to his back 2 hours after sniffing cocaine and one hour after taking sildenafil 50 mg. The chest pain subsided spontaneously but he developed severe pain in his right groin and leg and became pale and sweaty. His blood pressure and heart rate were increased (160/100 mmHg and 92 bpm, respectively), his respiration rate was 16 breaths/minute, and an ECG showed occasional isolated ventricular beats. A CT scan and transoesophageal cardiac ultrasonography revealed an aortic dissection in the descending aorta. He was closely monitored and given intravenous glyceryl trinitrate, labetalol, metoprolol, captopril and ranitidine, but died 12 days later.[1]

Cardiovascular complications including aortic dissection have been reported with cocaine.[1] There is also an isolated report of aortic dissection after sildenafil use, in a patient who was taking a number of other medicines including isosorbide mononitrate.[2] It was suggested that acute dssection in the reported case probably coincided with expected peak levels of sildenafil, but after the time period of 30 minutes when the cardiovascular effects of cocaine usually occur. However, the patient's heavy smoking and hypertension may also be factors in this case. It was further suggested that, in cases where acute aortic dissection is associated with cocaine, vasodilatation due to concurrent sildenafil could reduce organ perfusion and aggravate injury due to hypovolaemia and ischaemia.[1]

This is an isolated case, and it is not clear if it is generally applicable.

1. Famularo G, Polchi S, Di Bona G, Manzara C. Acute aortic dissection after cocaine and sildenafil abuse. *J Emerg Med* (2001) 21, 78–9.
2. Nachtnebel A, Stöllberger C, Ehrlich M, Finsterer J. Aortic dissection after sildenafil-induced erection. *South Med J* (2006) 99, 1151–2.

Phosphodiesterase type-5 inhibitors; Sildenafil + Dihydrocodeine

Two men using sildenafil had prolonged erections following orgasm while also taking dihydrocodeine.

Clinical evidence, mechanism, importance and management

Two men, successfully using 100-mg doses of sildenafil for erectile dysfunction, experienced prolonged erections after orgasm while also taking dihydrocodeine 30 to 60 mg every 6 hours for soft tissue injuries. One of them had two erections lasting 4 hours and 5 hours, and this did not occur on subsequent occasions when the dihydrocodeine was stopped. The other had 2- to 3-hour erections on three occasions during the first week of dihydrocodeine use, but no problems over the next 2 weeks while continuing to take the dihydrocodeine.[1] The reasons are not understood.

Priapism associated with sildenafil use is rare, and there appear to be no other reports about an interaction between sildenafil and dihydrocodeine. Excessively prolonged erections can have serious consequences, and patients are advised to seek immediate medical assistance in the event of an erection lasting longer than 4 hours.

1. Goldmeier D, Lamba H. Prolonged erections produced by dihydrocodeine and sildenafil. *BMJ* (2002) 324, 1555.

Phosphodiesterase type-5 inhibitors; Sildenafil + Ecstasy

The abuse of sildenafil and ecstasy (MDMA, methylenedioxymethamfetamine) has been reported to result in serious headache and priapism requiring emergency treatment.

Clinical evidence, mechanism, importance and management

A journalist's account, based purely on anecdotal reports, claims that the illicit use of sildenafil with ecstasy (MDMA, methylenedioxymethamfetamine) causes "hammerheading" because of the pounding headache and the prolonged and painful penile erections that require emergency medical treatment.[1] The report does not say how much of each of these drugs is taken to produce these adverse effects. The outcome can clearly be unpleasant, painful and, the priapism, potentially serious.

1. Breslau K, Peraino K, Fantz A. The 'sextasy' craze. Newsweek, June 3, 2002, 30.

Phosphodiesterase type-5 inhibitors; Sildenafil + Nitric oxide

The combination of sildenafil and inhaled nitric oxide might have beneficial effects in pulmonary hypertension, but systemic vasodilation and hypotension is possible.

Clinical evidence

In a study in 15 infants at risk of pulmonary hypertension after corrective cardiac surgery, the combined use of intravenous sildenafil and **inhaled nitric oxide** augmented the pulmonary vasodilator effects of inhaled nitric oxide. However, significant systemic hypotension occurred, which, along with a decrease in oxygenation, was considered sufficiently detrimental for the study to be stopped early.[1] Conversely, beneficial combined use has been described in adult patients with severe hypoxaemia caused by pulmonary hypertension: a few references are cited as examples.[2,3]

Mechanism

Patients with pulmonary arterial hypertension are thought to have deficiencies in endogenous nitric oxide. Inhaled nitric oxide is therefore used, and causes some pulmonary-specific vasodilatory effects. Phosphodiesterase type-5 inhibitors also increase the activity of endogenous nitric oxide by inhibiting the breakdown of cyclic guanosine monophosphate. When given in combination, sildenafil augments and prolongs the effects of inhaled nitric oxide, in the same way as other nitric oxide donors, see 'nitrates', (p.1537). Because sildenafil is not pulmonary specific, systemic vasodilation and hypotension is possible.

Importance and management

In contrast to the situation in erectile dysfunction, when the interaction between phosphodiesterase type-5 inhibitors and nitrates is unwanted and potentially serious, in pulmonary hypertension, the same pharmacodynamic interaction might prove to be clinically useful.[3] Nevertheless, a reduction in systemic blood pressure due to sildenafil might be detrimental, and could outweigh any benefits in some patient groups.[1] The manufacturer of a preparation of sildenafil licensed for treating pulmonary artery hypertension contraindicates its use with any nitric oxide donor.[4] Combined use should be considered experimental.

Note that **nitric oxide** is not to be confused with the anaesthetic **nitrous oxide**, which is not a nitric oxide donor.

1. Stocker C, Penny DJ, Brizard CP, Cochrane AD, Soto R, Shekerdemian LS. Intravenous sildenafil and inhaled nitric oxide: a randomised trial in infants after cardiac surgery. *Intensive Care Med* (2003) 29, 1996–2003.
2. Bigatello LM, Hess D, Dennehy KC, Medoff BD, Hurford WE. Sildenafil can increase the response to inhaled nitric oxide. *Anesthesiology* (2000) 92, 1827–9.
3. Lepore JJ, Maroo A, Bigatello LM, Dec GW, Zapol WM, Bloch KD, Semigran J. Hemodynamic effects of sildenafil in patients with congestive heart failure and pulmonary hypertension: combined administration with inhaled nitric oxide. *Chest* (2005) 127, 1647–53.
4. Revatio (Sildenafil citrate). Pfizer Ltd. UK Summary of product characteristics, July 2009.

Phosphodiesterase type-5 inhibitors; Vardenafil + Miscellaneous

No clinically relevant pharmacokinetic interaction has been seen between vardenafil and food, glibenclamide (glyburide), metformin or sulphonylureas.

Clinical evidence, mechanism, importance and management

(a) Antidiabetics

The manufacturers say that the pharmacokinetics of **glibenclamide** (**glyburide**) were not affected by a single 20-mg dose of vardenafil,[1] and that vardenafil had no effect on **glibenclamide** pharmacodynamics (glucose and insulin levels).[2] Also, although no specific pharmacokinetic study has been conducted, the manufacturers say that population pharmacokinetic analysis suggests that **sulphonylureas** (not named) and **metformin** have no effect on vardenafil pharmacokinetics.[1] No additional precautions therefore seem necessary on concurrent use.

(b) Food

In a single-dose study, healthy subjects were given vardenafil 20 mg on four occasions; after an overnight fast, on an empty stomach, following a **high-fat breakfast** (fat 58 g), or following a **moderate-fat evening meal** (fat 23 g). No vardenafil pharmacokinetic changes were noted in the fasting or moderate-fat periods. Although the **high-fat breakfast** caused a slight decrease and a slight delay in the absorption of vardenafil this was not considered to be sufficient to warrant changing the dosing time or making dosage adjustments. Therefore vardenafil may be given without regard to meals.[3]

1. Levitra (Vardenafil hydrochloride trihydrate). Bayer plc. UK Summary of product characteristics, June 2009.
2. Levitra (Vardenafil hydrochloride). Bayer Pharmaceuticals Corporation. US Prescribing information, December 2008.
3. Rajagopalan P, Mazzu A, Xia C, Dawkins R, Sundaresan P. Effect of high-fat breakfast and moderate-fat evening meal on the pharmacokinetics of vardenafil, an oral phosphodiesterase-5 inhibitor for the treatment of erectile dysfunction. *J Clin Pharmacol* (2003) 43, 1–8.

Urinary antimuscarinics + CYP3A4 inhibitors; Moderate

Erythromycin and fluconazole caused a modest increase in darifenacin exposure. Other moderate CYP3A4 inhibitors are predicted to interact similarly, as is solifenacin. Moderate CYP3A4 inhibitors might also be expected to modestly increase the exposure of fesoterodine, tolterodine or oxybutynin.

Clinical evidence

The manufacturers note that, in a study in healthy subjects, **erythromycin** 500 mg daily increased the steady-state AUC of **darifenacin** 30 mg daily by 95%.[1-3]

Fluconazole 200 mg then 100 mg daily had a similar effect, causing an 84% increase in the steady-state AUC of **darifenacin** 30 mg daily.[1,2]

Mechanism

Erythromycin and fluconazole are moderate inhibitors of the cytochrome P450 isoenzyme CYP3A4, by which darifenacin is principally metabolised, leading to an increase in the levels of darifenacin. Note that fluconazole generally only inhibits CYP3A4 at doses greater than 200 mg. Solifenacin is also primarily metabolised by CYP3A4 and would be expected to interact similarly. Fesoterodine, oxybutynin and tolterodine are also metabolised by CYP3A4 and might also be expected to be inhibited by erythromycin and fluconazole: however, as they are also substrates for CYP2D6, they are likely to be less affected than darifenacin or solifenacin.

Importance and management

An established pharmacokinetic interaction. The clinical relevance of the increase in **darifenacin** levels with erythromycin has not been assessed. At present, the UK manufacturer[3] recommends an initial dose of darifenacin 7.5 mg daily in those taking moderate CYP3A4 inhibitors (such as erythromycin), increasing the dose to 15 mg daily if it is well tolerated, whereas the US manufacturer[1] says that dose adjustments are not required for moderate CYP3A4 inhibitors. Bear in mind the possibility of an interaction if antimuscarinic adverse effects (dry mouth, constipation, drowsiness) are increased.

Solifenacin is expected to interact similarly, and one manufacturer recommends caution with moderate CYP3A4 inhibitors.[4]

Other urinary antimuscarinics would be expected to interact to a lesser extent (see under *Mechanism*, above) and it appears unlikely that a clinically relevant interaction would occur in the majority of patients taking

fesoterodine, **tolterodine** or **oxybutynin** and given moderate CYP3A4 inhibitors. However, until more is known about the clinical outcome of concurrent use, it may be prudent to bear in mind the possibility of an interaction if an increase in antimuscarinic adverse effects (dry mouth, constipation, drowsiness) occurs. Some manufacturers make more specific recommendations. The manufacturers of **fesoterodine** caution the concurrent use of moderate CYP3A4 inhibitors: they recommend assessing the clinical response and tolerability of the recommended starting dose of 4 mg daily before increasing the dose to 8 mg daily.[5,6] Similarly, some manufacturers of **oxybutynin** recommend caution with moderate CYP3A4 inhibitors.[7,8] Note that **moderate CYP3A4 inhibitors** would generally be considered to include erythromycin, fluconazole, grapefruit juice, diltiazem and verapamil, although the UK manufacturer of fesoterodine[5] additionally mentions amprenavir and fosamprenavir (which have also sometimes been considered to be potent inhibitors) and aprepitant. The manufacturers of oxybutynin also mention miconazole.[7]

The situation for **tolterodine** is more complicated because the manufacturers consider erythromycin,[9,10] and miconazole[9] to be potent CYP3A4 inhibitors: the UK manufacturer[10] does not recommend concurrent use, and the US manufacturer[9] recommends that the dose of tolterodine be reduced to 1 mg twice daily. However, erythromycin and miconazole do not appear to be potent inhibitors of CYP3A4 in clinical use (for example, the increase in darifenacin levels with erythromycin above was about ninefold less than that with ketoconazole).

1. Enablex (Darifenacin hydrobromide). Novartis. US Prescribing information, June 2008.
2. Skerjanec A. The clinical pharmacokinetics of darifenacin. *Clin Pharmacokinet* (2006) 45, 325–50.
3. Emselex (Darifenacin hydrobromide). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, September 2009.
4. Vesicare (Solifenacin succinate). Astellas Pharma Ltd. UK Summary of product characteristics, September 2008.
5. Toviaz (Fesoterodine fumarate). Pfizer Ltd. UK Summary of product characteristics, July 2009.
6. Toviaz (Fesoterodine fumarate). Pfizer Inc. US Prescribing information, November 2008.
7. Ditropan XL (Oxybutynin chloride). Ortho-McNeil-Janssen Pharmaceuticals, Inc. US Prescribing information, December 2008.
8. Lyrinel XL (Oxybutynin hydrochloride). Janssen-Cilag Ltd. UK Summary of product characteristics, April 2009.
9. Detrol (Tolterodine tartrate). Pharmacia & Upjohn Company. US prescribing information, March 2008.
10. Detrusitol (Tolterodine tartrate). Pharmacia Ltd. UK Summary of product characteristics, February 2009.

Urinary antimuscarinics + CYP3A4 inhibitors; Potent

Ketoconazole (a potent CYP3A4 inhibitor) markedly increases darifenacin, fesoterodine and solifenacin exposure. Other potent CYP3A4 inhibitors are expected to interact similarly. Itraconazole and ketoconazole increase the exposure to oxybutynin, but do not alter the levels of its active metabolite. Ketoconazole can markedly increase tolterodine exposure, but only in those who have low levels or are lacking CYP2D6.

Clinical evidence

(a) Darifenacin

The manufacturer notes that, in a study in 16 healthy subjects, ketoconazole 400 mg daily for 6 days markedly increased the steady-state AUC of darifenacin 30 mg daily about tenfold.[1,2] The UK manufacturers also note that ketoconazole 400 mg caused a fivefold increase in the steady-state AUC of a 7.5-mg dose of darifenacin.[1,3]

(b) Fesoterodine

In a crossover study in 18 healthy subjects, a single 8-mg dose of fesoterodine was given alone and then on day 5 of a 6-day course of ketoconazole 200 mg twice daily. Ketoconazole increased the AUC of the active metabolite of fesoterodine, 5-hydroxymethyltolterodine, 2.5-fold in CYP2D6 poor metabolisers (that is, those lacking or totally deficient in this isoenzyme) and 2.3-fold in CYP2D6 extensive metabolisers (that is, those with normal levels of this isoenzyme).[4] However, the overall extent of exposure (AUC and maximum concentration) to 5-hydroxymethyltolterodine was about twofold higher in poor metabolisers when compared with extensive metabolisers. Ketoconazole increased fesoterodine exposure in extensive metabolisers to a level similar to that seen in poor metabolisers not taking ketoconazole.

(c) Oxybutynin

In a study, a single 5-mg dose of oxybutynin was given to 10 healthy subjects after they had taken **itraconazole** 200 mg daily or placebo for 4 days. The peak serum levels and the AUC of oxybutynin were increased twofold, while the pharmacokinetics of the active metabolite of oxybutynin were unchanged. The sum of the oxybutynin and its metabolite concentrations were on average about 13% higher than with placebo. No increase in adverse effects was seen.[5] Ketoconazole also increases oxybutynin levels about twofold.[6,7]

(d) Solifenacin

In a crossover study[8] in healthy subjects, ketoconazole 200 mg daily for 20 days caused a twofold increase in the AUC of a single 10-mg dose of solifenacin given on day 7. Moreover, the manufacturer notes that a higher dose of ketoconazole (400 mg daily) increased the AUC of solifenacin about threefold.[9,10]

(e) Tolterodine

A study in 8 healthy subjects who were deficient in the cytochrome P450 isoenzyme CYP2D6 (poor metabolisers) found that after taking ketoconazole 200 mg daily for 4 days the clearance of a single 2-mg dose of tolterodine was reduced by 61% and its AUC was increased 2.5-fold.[11] In a subsequent multiple-dose study, 6 of the original subjects were given tolterodine 1 mg twice daily (half the usual dose). Ketoconazole 200 mg daily caused a 2.1-fold increase in the AUC of tolterodine, and a 2.2-fold increase in the AUC of the active moiety (unbound tolterodine plus metabolite).[11]

Mechanism

Darifenacin and solifenacin are principally metabolised by the cytochrome P450 isoenzyme CYP3A4, of which ketoconazole is a known, potent inhibitor. Concurrent use therefore increases the levels of these urinary antimuscarinics. Oxybutynin is also metabolised by CYP3A4, but most of the pharmacological activity of oxybutynin is attributed to a metabolite, the formation of which does not appear to be dependent on CYP3A4,[5] and therefore the sum of oxybutynin and its active metabolite is largely unchanged.

Fesoterodine is a prodrug and is rapidly converted to its more active metabolite, 5-hydroxymethyltolterodine, which is primarily metabolised by CYP2D6 and CYP3A4. Ketoconazole, an inhibitor of CYP3A4, may therefore increase the levels of 5-hydroxymethyltolterodine.

Although tolterodine is normally metabolised to its active metabolite by CYP2D6, in those with low levels of this isoenzyme (about 5 to 10% of the population), metabolism by CYP3A4 becomes more important. It should be noted that tolterodine levels are already higher in poor CYP2D6 metabolisers than extensive metabolisers,[12] but are likely to rise even further when a potent CYP3A4 inhibitor such as ketoconazole inhibits this other route of metabolism.

Importance and management

Established pharmacokinetic interactions. The very marked increase in **darifenacin** exposure caused by ketoconazole is of concern. The UK manufacturer contraindicates the concurrent use of ketoconazole and other potent CYP3A4 inhibitors,[3] whereas the US manufacturer recommends that the daily dose of darifenacin is limited to 7.5 mg (half the usual dose), both with ketoconazole and other potent inhibitors of CYP3A4.[1] It may be prudent to assess antimuscarinic adverse effects (such as dry mouth, constipation, drowsiness) in these patients, and to withdraw the drug if it is not tolerated.

As a result of the increase in exposure seen with ketoconazole, the manufacturers of **fesoterodine** recommend that its maximum dose should be restricted to 4 mg daily when used with potent CYP3A4 inhibitors.[13,14] In the UK, fesoterodine is contraindicated in patients taking potent CYP3A4 inhibitors and who also have moderate to severe hepatic or renal impairment.[13]

For **oxybutynin**, the available evidence suggests that the pharmacokinetic interaction with itraconazole is only of minor importance,[5] but note that this was only a single-dose study and may not necessarily reflect the full picture in practice. Moreover, some manufacturers recommend caution if oxybutynin is given with itraconazole or ketoconazole,[6,7] and, until more is known this might be prudent, both with these drugs and other potent CYP3A4 inhibitors. Consider the possibility of an interaction if antimuscarinic effects are increased.

For **solifenacin**, the UK and US manufacturers recommend that its daily dose is limited to 5 mg if it is given with ketoconazole or other potent CYP3A4 inhibitors.[9,10] In addition, in the UK, in patients with severe renal impairment or moderate hepatic impairment, the concurrent use of solifenacin and potent CYP3A4 inhibitors is contraindicated.[9] Note that high levels of solifenacin cause a small increase in the QT interval.

For **tolterodine**, the UK manufacturer[15] considers that the twofold increase in levels represents a risk of overdose in CYP2D6 poor metabolisers. Consequently, they do not recommend the use of potent CYP3A4 inhibitors with tolterodine in any patient (note that metaboliser status is rarely known), especially those with risk factors for QT-prolongation (see 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290.). However, the US manufacturer[12] recommends that the dose of tolterodine be reduced to 1 mg twice daily in patients currently taking drugs that are potent inhibitors of CYP3A4. It may be prudent to assess antimuscarinic adverse effects (such as dry mouth, constipation, drowsiness) in these patients, and to reduce the dose further or withdraw the drug if it is not tolerated.

Potent inhibitors of CYP3A4 include the 'azole antifungals', (p.233), many of the 'protease inhibitors', (p.913), and some macrolides. Note that there is some difference in opinion as to whether or not clarithromycin is a potent CYP3A4 inhibitor. Its interaction with midazolam (a drug used to assess the potency of effect of other drugs on CYP3A4), would suggest it is only a moderate inhibitor (see 'Benzodiazepines and related drugs + Macrolides', p.852). However, many manufacturers consider it to be a potent CYP3A4 inhibitor.

1. Enablex (Darifenacin hydrobromide). Novartis. US Prescribing information, June 2008.
2. Skerjanec A. The clinical pharmacokinetics of darifenacin. *Clin Pharmacokinet* (2006) 45, 325–50.
3. Emselex (Darifenacin hydrobromide). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, September 2009.
4. Malhotra B, Sachse R, Wood N. Evaluation of drug–drug interactions with fesoterodine. Eur J Clin Pharmacol (2009) 65, 551–60.
5. Lukkari E, Juhakoski A, Aranko K, Neuvonen PJ. Itraconazole moderately increases serum concentrations of oxybutynin but does not affect those of the active metabolite. *Eur J Clin Pharmacol* (1997) 52, 403–6.
6. Ditropan XL (Oxybutynin chloride). Ortho-McNeil-Janssen Pharmaceuticals, Inc. US Prescribing information, December 2008.
7. Lyrinel XL (Oxybutynin hydrochloride). Janssen-Cilag Ltd. UK Summary of product characteristics, April 2009.
8. Swart PJ, Krauwinkel WJJ, Smulders RA, Smith NN. Pharmacokinetic effect of ketoconazole on solifenacin in healthy volunteers. *Basic Clin Pharmacol Toxicol* (2006) 99, 33–6.
9. Vesicare (Solifenacin succinate). Astellas Pharma Ltd. UK Summary of product characteristics, September 2008.
10. VESIcare (Solifenacin succinate). GlaxoSmithKline. US Prescribing information, November 2008.
11. Brynne N, Forslund C, Hallén B, Gustafsson LL, Bertilsson L. Ketoconazole inhibits the metabolism of tolterodine in subjects with deficient CYP2D6 activity. *Br J Clin Pharmacol* (1999) 48, 564–72.
12. Detrol (Tolterodine tartrate). Pharmacia & Upjohn Company. US prescribing information, March 2008.
13. Toviaz (Fesoterodine fumarate). Pfizer Ltd. UK Summary of product characteristics, July 2009.
14. Toviaz (Fesoterodine fumarate). Pfizer Inc. US Prescribing information, November 2008.
15. Detrusitol (Tolterodine tartrate). Pharmacia Ltd. UK Summary of product characteristics, February 2009.

Urinary antimuscarinics + Drugs that prolong the QT interval

Tolterodine and solifenacin caused a small increase in QTc interval (5 to 10 milliseconds) at high doses. On this basis, some caution might be appropriate when using these drugs with other drugs that prolong the QT interval.

Clinical evidence

(a) Solifenacin

In a study in healthy subjects, solifenacin 10 mg increased the Fridericia-corrected QT (QTcF) interval by 2 milliseconds, whereas a higher dose of 30 mg increased it by 8 milliseconds, when compared with placebo. These changes were less than that seen with moxifloxacin, used as a positive control (increase in QTcF interval of 11 to 16 milliseconds, when compared with placebo).[1] The 30 mg dose of solifenacin is three times the maximum dose, and was chosen because it was predicted to result in solifenacin exposure similar to that observed when the maximum dose of solifenacin is used with potent CYP3A4 inhibitors. The US manufacturer notes that, in worldwide postmarketing experience, solifenacin has been associated with QT prolongation and torsade de pointes.[1]

(b) Tolterodine

In a well-designed study in healthy subjects, tolterodine immediate-release tablets 2 mg twice daily and 4 mg twice daily for 4 days caused a rise in the QTcF interval of 5 milliseconds and 11.8 milliseconds, respectively, with a manual reading of the ECG, and 1.2 milliseconds and 5.6 milliseconds, respectively, with a machine reading of the ECG, when compared with placebo. This increase was about half that seen with moxifloxacin 400 mg daily for 4 days, used as a positive control.[2] In this study there was about an equal representation of CYP2D6 extensive metabolisers (that is, those with normal levels of this isoenzyme) and poor metabolisers (that is, those lacking or totally deficient in this isoenzyme), and the QT interval increase appeared to be greater in poor metabolisers. The highest dose of tolterodine used in this study is twice the highest recommended dose, and was chosen because it results in tolterodine exposure similar to that observed when tolterodine 2 mg twice daily is used with potent CYP3A4 inhibitors, in patients who are CYP2D6 poor metabolisers. The US manufacturer notes that there have been no reports of torsade de pointes associated with the use of tolterodine.[3]

Mechanism

The effects of drugs that prolong the QT interval are expected to be additive. Prolongation of the QT interval is associated with an increased risk of the potentially fatal torsade de pointes arrhythmia, see also 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290.

Importance and management

On the basis of what is currently known, see 'Drugs that prolong the QT interval + Other drugs that prolong the QT interval', p.290, the proarrhythmic risk of drugs that prolong the QTc interval by around 5 to less than 20 milliseconds is inconclusive. Solifenacin and tolterodine fit in this category. The manufacturers of tolterodine[3,4] and the US manufacturer of solifenacin[1] recommend that the possible increase in QT interval should be taken into account when prescribing these antimuscarinics to patients with a known history of QT prolongation or using any other drugs known to prolong the QT interval. The tolterodine manufacturer specifically mentions class Ia antiarrhythmics (e.g. **quinidine**, **procainamide**) or class III antiarrhythmics (e.g. **amiodarone**, **sotalol**),[3,4] which are known to significantly prolong the QT interval. The risk of an interaction is likely to be greatest if CYP3A4 inhibitors are also being taken.[4]

1. VESIcare (Solifenacin succinate). GlaxoSmithKline. US Prescribing information, November 2008.
2. Malhotra BK, Glue P, Sweeney K, Anziano R, Mancuso J, Wicker P. Thorough QT study with recommended and supratherapeutic doses of tolterodine. *Clin Pharmacol Ther* (2007) 81, 377–85.
3. Detrol (Tolterodine tartrate). Pharmacia & Upjohn Company. US prescribing information, December 2006.
4. Detrusitol (Tolterodine tartrate). Pharmacia Ltd. UK Summary of product characteristics, February 2009.

Urinary antimuscarinics + Food

Food might reduce the absorption of trospium. Food does not appear to have a clinically relevant effect on the pharmacokinetics of darifenacin, fesoterodine, solifenacin or tolterodine.

Clinical evidence, mechanism, importance and management

(a) Darifenacin

Food had no effect on the steady-state pharmacokinetics of darifenacin, and the tablets may be taken with or without food.[1,2]

(b) Fesoterodine

In a study, 24 healthy subjects given a single 8-mg dose of fesoterodine after an overnight fast or with a standard high-fat, high-calorie breakfast. The AUC and maximum plasma levels of the active metabolite of fesoterodine, 5-hydroxymethyltolterodine, were increased by 12% and 29%, respectively, in the fed state, when compared with the fasted state.[3] In another similar study in 16 healthy subjects, the AUC and maximum plasma levels of 5- hydroxymethyltolterodine were increased by about 19% in the fed state compared with the fasted state.[4] These minor changes are not expected to be clinically relevant, and fesoterodine may be given without regard to food.

(c) Solifenacin

In a crossover study in 23 healthy subjects, food did not affect the pharmacokinetics of solifenacin 10 mg, taken within 5 minutes of a high-fat, high-calorie breakfast, when compared with the fasted state.[5]

(d) Tolterodine

The manufacturer notes that food intake increases the bioavailability of tolterodine by 53%, but does not affect the levels of the 5-hydroxymethyl metabolite in extensive metabolisers [presumably of CYP2D6].[6,7] This change is not expected to be clinically relevant.

(e) Trospium

Giving trospium extended-release capsules immediately after a high fat-content meal reduced the AUC and maximum plasma levels of trospium by 35% and 60%, respectively. These changes are modest, nevertheless, the manufacturer recommends that trospium be taken on an empty stomach at least one hour before a meal.[8,9]

1. Enablex (Darifenacin hydrobromide). Novartis. US Prescribing information, June 2008.
2. Emselex (Darifenacin hydrobromide). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, September 2009.
3. Malhotra B, Guan Z, Wood N, Gandelman K. Pharmacokinetic profile of fesoterodine. Int J Clin Pharmacol Ther (2008) 46, 556–63.
4. Malhotra B, Sachse R, Wood N. Influence of food on the pharmacokinetic profile of fesoterodine. Int J Clin Pharmacol Ther (2009) 47, 384–390.
5. Uchida T, Krauwinkel WJ, Mulder H, Smulders RA. Food does not affect the pharmacokinetics of solifenacin, a new muscarinic receptor antagonist: results of a randomized crossover trial. *Br J Clin Pharmacol* (2004) 58, 4–7.
6. Detrol (Tolterodine tartrate). Pharmacia & Upjohn Company. US prescribing information, December 2006.
7. Detrusitol (Tolterodine tartrate). Pharmacia Ltd. UK Summary of product characteristics, February 2009.
8. Regurin (Trospium). Galen Ltd. UK Summary of product characteristics, July 2007.
9. Sanctura XR (Trospium). Allergan Inc. US Prescribing information, November 2008.

Urinary antimuscarinics + Rifampicin (Rifampin) and other CYP3A4 inducers

Rifampicin, a CYP3A4 inducer, markedly reduces the exposure to the active metabolite of fesoterodine. Other CYP3A4 inducers would be expected to interact similarly. Darifenacin and solifenacin levels are also predicted to be reduced by CYP3A4 inducers.

Clinical evidence

In a study in 12 healthy subjects, a single 8-mg dose of **fesoterodine** was given on day 7 of an 8-day course of rifampicin 600 mg daily. The AUC and maximum plasma levels of the active metabolite of fesoterodine, 5-hydroxymethyltolterodine, were reduced by about 78% and 72%, respectively.[1]

Mechanism

Fesoterodine is a pro-drug and is rapidly converted to 5-hydroxymethyltolterodine, which is primarily metabolised by the cytochrome P450 isoenzymes CYP2D6 and CYP3A4, of which rifampicin is a potent inducer. **Solifenacin** and **darifenacin** are principally metabolised by CYP3A4, and would be expected to be similarly affected.

Importance and management

The clinical relevance of the marked reduction in the levels of the active metabolite of fesoterodine by rifampicin has not been assessed, but reduced efficacy would be expected. In the UK, the manufacturer does not recommend the concurrent use of fesoterodine with other CYP3A4 inducers: they specifically name **carbamazepine**, **phenobarbital**, **phenytoin**, **St John's wort**, and rifampicin.[2] However note that although these drugs are known inducers of CYP3A4, they, unlike rifampicin, do not appear to have any clinically significant effects on CYP2D6, and so would not be expected to interact to the same extent as rifampicin. The US manufacturer notes that reduced fesoterodine plasma levels may occur with concurrent use of CYP3A4 inducers, but state that no fesoterodine dose adjustments are recommended.[3] If concurrent use is necessary, until the clinical relevance of this interaction is known, it would seem prudent to closely monitor the urinary efficacy of fesoterodine.

The efficacy of **darifenacin** and **solifenacin** is also expected to be reduced by CYP3A4 inducers, as they are primarily metabolised by CYP3A4: the manufacturers name **barbiturates**, **carbamazepine**, **phenytoin**, **rifampicin** and **St John's wort**, as potentially interacting CYP3A4 inducers.[4-6] For a list of CYP3A4 inducers, see 'Table 1.4', (p.6).

1. Malhotra B, Sachse R, Wood N. Evaluation of drug–drug interactions with fesoterodine. Eur J Clin Pharmacol (2009) 65, 551–60.
2. Toviaz (Fesoterodine fumarate). Pfizer Ltd. UK Summary of product characteristics, July 2009.
3. Toviaz (Fesoterodine fumarate). Pfizer Inc. US Prescribing information, November 2008.
4. Vesicare (Solifenacin succinate). Astellas Pharma Ltd. UK Summary of product characteristics, September 2008.
5. VESIcare (Solifenacin succinate). GlaxoSmithKline. US Prescribing information, November 2008.
6. Emselex (Darifenacin hydrobromide). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, September 2009.

Urinary antimuscarinics + SSRIs or SNRIs

Fluoxetine can markedly inhibit the metabolism of tolterodine in some patients. Duloxetine increases the maximum levels of tolterodine by 64%. Paroxetine causes a small, clinically irrelevant, increase in darifenacin levels. Cimetidine, quinidine and terbinafine are predicted to increase the levels of darifenacin.

Clinical evidence

(a) Darifenacin

The manufacturers note that, in a study in healthy subjects, **paroxetine** 20 mg daily increased the steady-state AUC of darifenacin 30 mg daily by 33%.[1,2]

(b) Tolterodine

1. Duloxetine. In a placebo-controlled, crossover study, 14 healthy subjects were given duloxetine 40 mg twice daily and tolterodine 2 mg twice daily, for 5 days. Duloxetine increased the steady-state AUC of tolterodine by 71% and increased its maximum level by 64%. However, duloxetine had no effect on the pharmacokinetics of 5-hydroxymethyl-tolterodine, the active metabolite of tolterodine.[3]

2. Fluoxetine. In a study, 13 psychiatric patients with symptoms of urinary incontinence were given tolterodine 2 mg twice daily for 5 doses, followed by fluoxetine 20 mg daily for 3 weeks, and then both drugs together for a further 3 days. Nine of the 13 patients completed the study, the other 4 withdrew because of fluoxetine-related adverse effects. Fluoxetine is an inhibitor of the cytochrome P450 isoenzyme CYP2D6, the main isoenzyme involved in the metabolism of tolterodine. Levels of this enzyme can vary between individuals. In the 7 patients with normal CYP2D6 levels (extensive metabolisers) fluoxetine caused a 4.8-fold increase in the AUC of tolterodine and a minor reduction in its active and equipotent metabolite. In contrast, fluoxetine increased the AUC of tolterodine by about 25% in 2 patients with low levels of CYP2D6 (poor metabolisers). These changes in AUC represent an increase of about 25% in active moiety (unbound tolterodine plus metabolite) for both poor and extensive metabolisers, a figure within normal variation.[4]

Mechanism

Duloxetine, fluoxetine and paroxetine are inhibitors of the cytochrome P450 isoenzyme CYP2D6, by which tolterodine is metabolised. Darifenacin is also metabolised by this isoenzyme, but only in part.

Importance and management

The minor pharmacokinetic interaction between paroxetine and **darifenacin** is very unlikely to be clinically relevant, and no dosage adjustments are recommended by the US manufacturer in the presence of CYP2D6 inhibitors.[1] However, the UK manufacturer recommends that the dose of darifenacin should be started at 7.5 mg daily and, if well tolerated, titrated to 15 mg daily in the presence of CYP2D6 inhibitors (they name paroxetine, '**cimetidine**', (p.1545), **terbinafine** and **quinidine**).[2] This seems a cautious approach. For a list of CYP2D6 inhibitors, see 'Table 1.3', (p.6).

The increases in **tolterodine** levels with duloxetine and fluoxetine were not considered to be clinically relevant, and no routine dosage adjustment of tolterodine was considered necessary when given with these drugs.[3,4] Nevertheless, if CYP3A4 inhibitors are also being used, this interaction could be important, see 'Urinary antimuscarinics + CYP3A4 inhibitors; Potent', p.1542.

1. Enablex (Darifenacin hydrobromide). Novartis. US Prescribing information, June 2008.
2. Emselex (Darifenacin hydrobromide). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, September 2009.
3. Hua TC, Pan A, Chan C, Poo YK, Skinner MH, Knadler MP, Gonzales CR, Wise SD. Effect of duloxetine on tolterodine pharmacokinetics in healthy volunteers. *Br J Clin Pharmacol* (2004) 57, 652–6.
4. Brynne N, Svanström C, Åberg-Wistedt A, Hallén B, Bertlisson L. Fluoxetine inhibits the metabolism of tolterodine—pharmacokinetic implications and proposed clinical relevance. *Br J Clin Pharmacol* (1999) 48, 553–63.

Urinary antimuscarinics; Darifenacin + Miscellaneous

Cimetidine causes a small increase in darifenacin levels. Darifenacin increases imipramine levels but does not significantly affect the pharmacokinetics of midazolam. Darifenacin is predicted to increase the levels of other CYP2D6 substrates such as flecainide and thioridazine.

Clinical evidence, mechanism, importance and management

(a) Cimetidine

The manufacturers note that, in a study in healthy subjects, cimetidine 800 mg twice daily increased the steady-state AUC of darifenacin 30 mg daily by 34%.[1,2] Cimetidine is a non-specific moderate inhibitor of cytochrome P450 isoenzymes, in particular CYP3A4 and CYP2D6, by which darifenacin is metabolised. This modest change is unlikely to be clinically relevant. However, the UK manufacturer recommends that, in the presence of cimetidine, the dose of darifenacin should be started at 7.5 mg daily and, if well tolerated, titrated to 15 mg daily.[3] This seems a cautious approach.

(b) CYP2D6 substrates

The US manufacturer notes that, in a study in healthy subjects, steady-state darifenacin 30 mg daily increased the AUC of **imipramine** by 70% and increased the AUC of its active metabolite, desipramine, 2.6-fold.[2] Because of these changes, the manufacturers recommend caution if darifenacin is given with **tricyclic antidepressants** and other CYP2D6 substrates that have a narrow therapeutic window.[1,3] They name **flecainide** and **thioridazine** (see 'Table 1.3', (p.6), for a list).

(c) Midazolam

The manufacturers note that, in a study in healthy subjects, darifenacin 30 mg daily increased the AUC of a single 7.5-mg dose of midazolam by 17%.[1-3] This change is not clinically important.[3]

1. Enablex (Darifenacin hydrobromide). Novartis. US Prescribing information, June 2008.
2. Skerjanec A. The clinical pharmacokinetics of darifenacin. *Clin Pharmacokinet* (2006) 45, 325–50.
3. Emselex (Darifenacin hydrobromide). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, September 2009.

Urinary antimuscarinics; Tolterodine + Miscellaneous

Tolterodine does not alter the metabolism of debrisoquine, omeprazole or caffeine.

Clinical evidence, mechanism, importance and management

In a pharmacokinetic study in 12 healthy men, tolterodine 4 mg twice daily for 6 days had no effect on debrisoquine hydroxylation (CYP2D6), omeprazole hydroxylation (CYP2C19) or sulphoxidation (CYP3A4) or caffeine demethylation (CYP1A2), after single doses of **debrisoquine** 10 mg, **omeprazole** 20 mg and **caffeine** 100 mg.[1] This shows that tolterodine has no clinically relevant effect on these isoenzymes, and is therefore unlikely to alter the pharmacokinetics of drugs that are substrates for cytochrome P450 isoenzymes CYP2D6, CYP2C19, CYP3A4 and CYP1A2.

For mention that **omeprazole** slightly increases the maximum level of tolterodine from a controlled-release preparation, see 'Enteric-coated, delayed-release preparations + Drugs that affect gastric pH', p.1558.

1. Brynne N, Böttiger Y, Hallén B, Bertilsson L. Tolterodine does not affect the human *in vivo* metabolism of the probe drugs caffeine, debrisoquine and omeprazole. *Br J Clin Pharmacol* (1999) 47, 145–50.

Urinary antimuscarinics; Trospium + Antacids

Antacids might have some effect on the absorption of trospium.

Clinical evidence, mechanism, importance and management

The manufacturer briefly mentions that, in a pharmacokinetic study in 11 healthy subjects, the mean AUC of **trospium** from extended-release capsules was comparable when given with and without an antacid containing **aluminium hydroxide** and **magnesium carbonate**. However, 5 individuals had either an increase or decrease in trospium exposure in presence of antacid.[1] The clinical relevance of these findings is not known.

1. Sanctura XR (Trospium). Allergan Inc. US Prescribing information, November 2008.

Yohimbine + Glyceryl trinitrate (Nitroglycerin)

No significant hypotensive interaction occurred in healthy subjects given yohimbine and a glyceryl trinitrate infusion.

Clinical evidence, mechanism, importance and management

In a placebo-controlled study, 16 healthy male subjects were given a single 7.7-mg oral dose of yohimbine tartrate (as NMI 861; yohimbine plus l-arginine glutamate) followed by a step-wise infusion of glyceryl trinitrate starting at 2.5 micrograms/minute, which was doubled every 15 minutes until symptomatic hypotension or a sustained decrease in systolic blood pressure of greater than 25 mmHg occurred, or until a maximum dose of 40 micrograms/minute had been reached, at which point the infusion was stopped. There was no significant difference in the hypotensive response to intravenous glyceryl trinitrate given with yohimbine or placebo.[1]

1. Kernohan AFB, McIntyre M, Hughes DM, Tam SW, Worcel M, Reid JL. An oral yohimbine/l-arginine combination (NMI 861) for the treatment of male erectile dysfunction: a pharmacokinetic, pharmacodynamic and interaction study with intravenous nitroglycerine in healthy male subjects. *Br J Clin Pharmacol* (2005) 59, 85–93.

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Miscellaneous drugs

Acamprosate + Miscellaneous

Naltrexone modestly increases the rate and extent of acamprosate absorption. There is no pharmacokinetic interaction between acamprosate and alcohol or diazepam. Disulfiram does not alter the pharmacokinetics of acamprosate, and acamprosate does not alter the pharmacokinetics of imipramine. The combination of acamprosate and barbiturates, meprobamate, or oxazepam does not appear to increase the risk of adverse effects.

Clinical evidence, mechanism, importance and management

(a) Alcohol

In studies in healthy subjects, the pharmacokinetics of both alcohol and acamprosate were unchanged by concurrent use.[1]

(b) Antidepressants, anxiolytics and hypnotics

A 15-day study in 591 patients, to assess the effects of the concurrent use of acamprosate with other drugs commonly used in the management of alcohol withdrawal, found no evidence of additional adverse effects when **meprobamate**, **oxazepam**, or the barbiturate complex **tetrabamate**, which includes **phenobarbital**, were also given.[2] Other studies found that acamprosate caused no clinically relevant changes in **imipramine** pharmacokinetics, and the pharmacokinetics of both **diazepam** and acamprosate were unchanged by concurrent use.[1]

No special precautions would therefore appear to be needed if any of these drugs is given with acamprosate.

(c) Disulfiram

In a study in 12 healthy subjects, disulfiram 500 mg daily for 7 days did not alter the plasma levels of acamprosate 666 mg three times daily.[1]

(d) Naltrexone

In a study in 24 healthy subjects, the concurrent use of naltrexone 50 mg daily and acamprosate 2 g daily for 7 days modestly increased the rate and extent of absorption of acamprosate, as indicated by a 33% increase in maximum level, a 33% reduction in time to maximum level, and a 25% increase in AUC. There was no change in naltrexone pharmacokinetics.[3] Similarly, an increase in acamprosate levels was seen in a study of the use of acamprosate and naltrexone in alcohol-dependent subjects.[4] No particular adverse events were identified on concurrent use,[3,4] suggesting that the drugs may be used together without dose adjustment.

1. Saivin S, Hulot T, Chabac S, Potgieter A, Durbin P, Houin G. Clinical pharmacokinetics of acamprosate. *Clin Pharmacokinet* (1998) 35, 331–45.
2. Aubin HJ, Lehert P, Beaupère B, Parot P, Barrucand D. Tolerability of the combination of acamprosate with drugs used to prevent alcohol withdrawal syndrome. *Alcoholism* (1995) 31, 25–38.
3. Mason BJ, Goodman AM, Dixon RM, Hameed MHA, Hulot T, Wesnes K, Hunter JA, Boyeson MG. A pharmacokinetic and pharmacodynamic drug interaction study of acamprosate and naltrexone. Neuropsychopharmacology. (2002) 27, 596–606.
4. Johnson BA, O'Malley SS, Ciraulo DA, Roache JD, Chambers RA, Sarid-Segal O, Couper D. Dose-ranging kinetics and behavioral pharmacology of naltrexone and acamprosate, both alone and combined, in alcohol-dependent subjects. *J Clin Psychopharmacol* (2003) 23, 281–93.

Allopurinol + Aluminium hydroxide

Three haemodialysis patients did not respond to allopurinol while taking aluminium hydroxide. Separating the doses by 3 hours appeared to solve this.

Clinical evidence

Three patients receiving haemodialysis, taking 5.7 g of aluminium hydroxide daily and allopurinol 300 mg daily for high phosphate and uric acid levels, had no reduction in their hyperuricaemia until the aluminium hydroxide was given 3 hours before the allopurinol, whereupon their uric acid levels fell by 40 to 65%. When one patient returned to taking both preparations together, her uric acid levels began to rise.[1]

Mechanism

Not understood. Antacids are well known to reduce the absorption of a number of drugs, but this is the only evidence of this possibly occurring with allopurinol.

Importance and management

Information seems to be limited to this anecdotal report. If allopurinol is not effective in patients with renal impairment taking large doses of aluminium, consider the possibility of an interaction. Try separating the administration of these two drugs by 3 hours or more. The effects of lower doses of aluminium and the effects in patients with normal renal function do not appear to have been studied.

1. Weissman I, Krivoy N. Interaction of aluminum hydroxide and allopurinol in patients on chronic hemodialysis. *Ann Intern Med* (1987) 107, 787.

Allopurinol + Iron compounds

No adverse interaction occurs if iron and allopurinol are given concurrently.

Clinical evidence, mechanism, importance and management

Some early *animal* studies, where allopurinol was given in very large doses, suggested that allopurinol might have an inhibitory effect on the release of iron from hepatic stores. It was feared that this might result in hepatic iron overload. This led the manufacturers of allopurinol in some countries to issue a warning about their concurrent use.[1] However, subsequent research suggests that no special precautions are needed.[1-3]

1. Ascione FJ. Allopurinol and iron. *JAMA* (1975) 232, 1010.
2. Emmerson BT. Effects of allopurinol on iron metabolism in man. *Ann Rheum Dis* (1966) 25, 700–703.
3. Davis PS, Deller DJ. Effect of a xanthine-oxidase inhibitor (allopurinol) on radioiron absorption in man. *Lancet* (1966) ii, 470–2.

Allopurinol + Tamoxifen

A single case report describes allopurinol hepatotoxicity in a man given tamoxifen.

Clinical evidence, mechanism, importance and management

An elderly man who had been taking allopurinol 300 mg daily for 12 years developed fever and marked increases in his serum levels of lactic dehydrogenase and alkaline phosphatase within a day of starting to take tamoxifen 10 mg twice daily.[1] He rapidly recovered when the allopurinol was stopped. The reasons for the reaction are not understood, but the authors suggested that the increased hepatotoxic effect may have resulted from tamoxifen inhibiting allopurinol metabolism, thereby increasing the serum levels of allopurinol and its metabolite. The general importance of this isolated report is not known.

1. Shah KA, Levin J, Rosen N, Greenwald E, Zumoff B. Allopurinol hepatotoxicity potentiated by tamoxifen. *N Y State J Med* (1982) 82, 1745–6.

Allopurinol + Thiazide diuretics

Severe allergic reactions to allopurinol have developed a few patients with renal impairment who were also taking thiazide diuretics.

Clinical evidence, mechanism, importance and management

Most patients tolerate allopurinol very well, but life-threatening hypersensitivity reactions (e.g. rash, vasculitis, hepatitis, eosinophilia, progressive renal impairment) develop very occasionally with doses of 200 to 400 mg of allopurinol daily.[1] A report of six such hypersensitivity reactions found that all of the reported cases were associated with pre-existing renal impairment, and in half of these, the patients were also taking thiazide diuretics.[1] Another report describes two patients who developed a hypersensitivity vasculitis while taking allopurinol and **hydrochlorothiazide**.[2] The excretion of oxipurinol (the major metabolite of allopurinol) is reduced in renal impairment, but studies indicate that, in healthy subjects with normal renal function, thiazide diuretics such as **hydrochlorothiazide** do not appear to affect either the plasma levels of oxipurinol or its excretion.[3-5] Furthermore, allopurinol does not appear to affect **hydrochlorothiazide** pharmacokinetics.[5] However, another study found that the effects of allopurinol on pyrimidine metabolism were enhanced by the use of thiazides (i.e. they potentially increase hyperuricaemia, which may lead to renal damage).[6] Some caution is therefore appropriate if both drugs are used, particularly if renal function is impaired, but more study is needed to confirm this possible interaction.

1. Hande KR, Noone RM, Stone WJ. Severe allopurinol toxicity. Description and guidelines for prevention in patients with renal insufficiency. *Am J Med* (1984) 76, 47–56.
2. Young JL, Boswell RB, Nies AS. Severe allopurinol hypersensitivity. Association with thiazides and prior renal compromise. *Arch Intern Med* (1974) 134, 553–8.
3. Hande KR. Evaluation of a thiazide-allopurinol drug interaction. *Am J Med Sci* (1986) 292, 213–16.
4. Löffler W, Landthaler R, de Vries JX, Walter-Sack I, Ittensohn A, Voss A, Zöllner N. Interaction of allopurinol and hydrochlorothiazide during prolonged oral administration of both drugs in normal subjects. I. Uric acid kinetics. *Clin Investig* (1994) 72, 1071–5.
5. de Vries JX, Voss A, Ittensohn A, Walter-Sack I, Löffler W, Landthaler R, Zöllner N. Interaction of allopurinol and hydrochlorothiazide during prolonged oral administration of both drugs in normal subjects. II. Kinetics of allopurinol, oxipurinol, and hydrochlorothiazide. *Clin Investig* (1994) 72, 1076–81.
6. Wood MH, O'Sullivan WJ, Wilson M, Tiller DJ. Potentiation of an effect of allopurinol on pyrimidine metabolism by chlorothiazide in man. *Clin Exp Pharmacol Physiol* (1974) 1, 53–8.

Allopurinol + Uricosuric drugs

Probenecid and benzbromarone increase the renal excretion of oxipurinol, the active metabolite of allopurinol. Theoretically, the use of uricosuric drugs with allopurinol could lead to uric acid precipitation in the kidneys and therefore maintenance of a high urine output is recommended when allopurinol is given by injection. Probenecid markedly increases the serum levels of allopurinol riboside, which may be advantageous in some circumstances.

Clinical evidence, mechanism, importance and management

(a) Allopurinol

Probenecid appears to increase the renal excretion of the active metabolite of allopurinol, oxipurinol,[1] while allopurinol is thought to inhibit the metabolism of **probenecid**.[2] One study suggested that allopurinol can increase the half-life and raise the serum levels of **probenecid** by about 50% and 20%, respectively.[2] However, a subsequent randomised study in 11 healthy subjects found that allopurinol 150 mg twice daily did not affect the pharmacokinetics of **probenecid** 500 mg twice daily when both drugs were given together for 7 days. This study also found that the mean plasma oxipurinol AUC and maximum levels were approximately halved when **probenecid** was added to allopurinol.[3] In another study, **benzbromarone** lowered the AUC of oxipurinol by about 40%, but did not affect allopurinol levels.[4]

It has been suggested that the use of allopurinol and **probenecid** might lead to an increase in the excretion of uric acid, which could result in the precipitation of uric acid in the kidneys. Conversely, increased renal excretion of oxipurinol might decrease the efficacy of allopurinol. However, the clinical importance of these mutual interactions seems to be minimal. No problems were reported in two studies in patients given 100 to 600 mg of allopurinol and 500 mg to 2.5 g of **probenecid** daily for between 8 and 16 weeks,[5] and the concurrent use of allopurinol and **probenecid**[3] or **benzbromarone**[4] was more effective in lowering uric acid levels than allopurinol alone. Nevertheless, the UK manufacturer of allopurinol recommends that the significance of any reduction in efficacy, which may occur when uricosuric drugs are given with allopurinol, should be assessed in each case.[6] For allopurinol injection, the US manufacturer recommends that, to help prevent renal precipitation of urates in patients receiving concurrent uricosuric drugs, a fluid intake sufficient to give a urinary output of at least 2 litres daily, and the maintenance of neutral or slightly alkaline urine, are desirable.[7]

(b) Allopurinol riboside

A study in 3 healthy subjects found that **probenecid** halved the clearance, increased the peak plasma levels and AUC, and extended the half-life of allopurinol riboside.[8] In some circumstances such an interaction may be advantageous as there is some evidence that the cure rate of American trypanosomiasis (Chagas' disease) and cutaneous leishmaniasis is better when the two drugs are used together.[8,9]

1. Elion GB, Yü T-F, Gutman AB, Hitchings GH. Renal clearance of oxipurinol, the chief metabolite of allopurinol. *Am J Med* (1968) 45, 69–77.
2. Horwitz D, Thorgeirsson SS, Mitchell JR. The influence of allopurinol and size of dose on the metabolism of phenylbutazone in patients with gout. *Eur J Clin Pharmacol* (1977) 12, 133–6.
3. Stocker SL, Williams KM, McLachlan AJ, Graham GG, Day RO. Pharmacokinetic and pharmacodynamic interaction between allopurinol and probenecid in healthy subjects. Clin Pharmacokinet (2008) 47, 111–8.
4. Müller FO, Schall R, Groenewoud G, Hundt HKL, van der Merwe JC, van Dyk M. The effect of benzbromarone on allopurinol/oxypurinol kinetics in patients with gout. *Eur J Clin Pharmacol* (1993) 44, 69–72.
5. Yü T-F, Gutman AB. Effect of allopurinol (4-hydroxypyrazolo(3,4-d)pyrimidine) on serum and urinary uric acid in primary and secondary gout. *Am J Med* (1964) 37, 885–98.
6. Zyloric (Allopurinol). GlaxoSmithKline UK. UK Summary of product characteristics, September 2006.
7. Aloprim (Allopurinol sodium). Bedford Laboratories. US Prescribing information, June 2004.
8. Were JBO, Shapiro TA. Effects of probenecid on the pharmacokinetics of allopurinol riboside. *Antimicrob Agents Chemother* (1993) 37, 1193–6.
9. Saenz RE, Paz HM, Johnson CM, Marr JJ, Nelson DJ, Pattishall KH, Rogers MD. Treatment of American cutaneous leishmaniasis with orally administered allopurinol riboside. *J Infect Dis* (1989) 160, 153–8.

Baclofen + Ibuprofen

A man developed baclofen toxicity when given ibuprofen.

Clinical evidence, mechanism, importance and management

An isolated report describes a man taking baclofen 20 mg three times daily, who developed baclofen toxicity (confusion, disorientation, bradycardia, blurred vision, hypotension and hypothermia) after taking 8 doses of ibuprofen 600 mg three times daily. It appeared that the toxicity was caused by ibuprofen-induced acute renal impairment leading to baclofen accumulation.[1] Renal impairment is a relatively rare adverse effect of ibuprofen. The general importance of this interaction is likely to be very small. There appears to be no information about baclofen and other NSAIDs, and little reason for avoiding concurrent use.

1. Dahlin PA, George J. Baclofen toxicity associated with declining renal clearance after ibuprofen. *Drug Intell Clin Pharm* (1984) 18, 805–8.

Baclofen + Miscellaneous

Common adverse effects of baclofen include hypotension, sedation and somnolence. Bear in mind the possibility of additive ef-

fects when baclofen is used with antihypertensives or drugs causing sedation.[1]

1. Lioresal Tablets (Baclofen). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, July 2009.

Baclofen + Tizanidine

No clinically significant pharmacokinetic interaction appears to occur between baclofen and tizanidine.

Clinical evidence, mechanism, importance and management

In a randomised, three-period study, 15 healthy subjects were given baclofen 10 mg three times daily and tizanidine 4 mg three times daily, together and alone, for 7 consecutive doses. None of the pharmacokinetic parameters of either drug were changed by more than 30%, a figure calculated to indicate the presence of an interaction.[1] No changes in the dosages of either drug are therefore likely to be needed if they are taken concurrently.

1. Shellenberger MK, Groves L, Shah J, Novak GD. A controlled pharmacokinetic evaluation of tizanidine and baclofen at steady state. *Drug Metab Dispos* (1999) 27, 201–4.

Benzbromarone + Chlorothiazide

Benzbromarone lowers uric acid levels in patients taking chlorothiazide, without affecting diuretic activity.[1,2]

1. Heel RC, Brogden RN, Speight TM, Avery GS. Benzbromarone: a review of its pharmacological properties and therapeutic use in gout and hyperuricaemia. *Drugs* (1977) 14, 349–66.
2. Gross A, Giraud V. Über die Wirkung von Benzbromaron auf Urikämie und Urikosurie. *Med Welt* (1972) 23, 133–6.

Betahistine + Terfenadine

An isolated case report describes the re-emergence of labyrinthine symptoms when a patient taking betahistine was given terfenadine.

Clinical evidence, mechanism, importance and management

An isolated and very brief report describes a patient whose labyrinthine symptoms (vertigo, dizziness, nausea and vomiting), were controlled by betahistine, returned during the concurrent use of terfenadine and other unspecified drugs.[1] An antagonistic interaction had been predicted on theoretical grounds because betahistine is an analogue of histamine, and would therefore be expected to interact like this with any antihistamine.[2] However, this possible case appears to be the only suggestion of an interaction, and the clinical relevance is unclear..

1. Beeley L, Cunningham H, Brennan A. *Bulletin of the West Midlands Centre for Adverse Drug Reaction Reporting* (1993) 36, 28.
2. Serc (Betahistine). Solvay Healthcare Ltd. UK Summary of product characteristics, October 2006.

Bisphosphonates + Aminoglycosides

Severe hypocalcaemia occurred in three patients taking sodium clodronate when they were given netilmicin or amikacin. Theoretically, additive calcium lowering effects could occur with any bisphosphonate and aminoglycoside combination.

Clinical evidence

A 62-year-old woman with multiple myeloma was given **sodium clodronate** 2.4 g daily for osteolysis and bone pain. After 7 days she developed grand mal seizures, and her serum calcium was found to be 1.72 mmol/L (reference range 2.25 to 2.6 mmol/L). Despite daily calcium infusions her calcium remained low. The authors state that symptomatic hypocalcaemia with clodronate is rare, and attributed the dramatic response in this patient to an interaction with a course of **netilmicin** given 5 days earlier for septicaemia.[1]

A 69-year-old man with prostate cancer had been taking **sodium clodronate** 2.4 g daily for bone pain for 13 months, and serum calcium levels had always remained within the reference range. After being admitted with febrile neutropenia following a course of chemotherapy, the clodronate was withdrawn and he was given intravenous **amikacin** and ceftazidime. After 7 days he became unconscious, and developed spontaneous twitching movements in his arms and legs. His calcium was found to be 1.39 mmol/L and he was diagnosed with hypocalcaemic tetany. He was given calcium infusions, and his serum calcium returned to normal over the next 12 hours.[2]

A further case report describes a 50-year-old patient taking **clodronate** 1.6 g daily, who developed febrile neutropenia for which he was given **amikacin** and ampicillin. Five days after starting **amikacin** his calcium began to fall and, despite stopping the clodronate and supplementing with calcium 8 g daily, his calcium level stabilised at just 1.65 mmol/L. The patient subsequently died from aspergillus pneumonia.[3]

Mechanism

Not fully understood, but one suggestion is that any fall in blood calcium levels brought about by the use of clodronate is normally balanced to some extent by the excretion of parathyroid hormone, which raises blood calcium levels. However, the aminoglycoside antibacterials can damage the kidneys, not only causing the loss of calcium, but of magnesium as well. Any hypomagnesaemia inhibits the activity of the parathyroid gland, so that the normal homoeostatic response to hypocalcaemia is reduced or even abolished.[1,2] Clodronate itself can sometimes be nephrotoxic.

Importance and management

Direct information seems to be limited to these three reports. Biochemical hypocalcaemia is believed to occur in about 10% of patients taking bisphosphonates,[4] but symptomatic hypocalcaemia is said to be rare.[2] It seems therefore that the addition of the aminoglycoside in these cases precipitated severe clinical hypocalcaemia. The authors of these reports therefore advise care if bisphosphonates are given with aminoglycosides, and recommend close monitoring of calcium and magnesium levels.[1-3] They also point out that the renal loss of calcium and magnesium can continue for weeks after aminoglycosides are stopped, and that bisphosphonates can also persist in bone for weeks.[1,2] This means that the interaction is potentially possible whether the drugs are given concurrently or sequentially.

1. Pedersen-Bjergaard U, Myhre J. Severe hypoglycaemia (sic) after treatment with diphosphonate and aminoglycoside. *BMJ* (1991) 302, 295.
2. Mayordomo JI, Rivera F. Severe hypocalcaemia after treatment with oral clodronate and aminoglycoside. *Ann Oncol* (1993) 4, 432–5.
3. Bondiau PY, Peyrade F, Creisson A, Pivot X, Lagrange JL, Thyss A. Hypocalcémie sévère après traitment par diphosphonates et aminoglycosides. *Presse Med* (1994) 23, 816.
4. Jodrell DI, Iveson TJ, Smith IE. Symptomatic hypocalcaemia after treatment with high-dose aminohydroxypropylidene diphosphonate. *Lancet* (1987) i, 622.

Bisphosphonates + Aspirin or NSAIDs

The concurrent use of alendronate and naproxen increased the incidence of gastric mucosal damage in a small pharmacological study, and increased the risk of upper gastrointestinal disorders in a case-control study. However, two analyses of placebo-controlled studies found no increased risk of gastrointestinal damage with the combination. There was no increased risk of gastrointestinal adverse effects in patients taking NSAIDs who were given risedronate.

Indometacin raises tiludronate bioavailability, whereas aspirin and diclofenac do not appear to affect the pharmacokinetics of tiludronate. NSAIDs may exacerbate the renal impairment sometimes seen with clodronate.

Clinical evidence, mechanism, importance and management

(a) Alendronate

In a short-term endoscopy study in 26 healthy subjects, gastric mucosal damage developed in 8% of those given alendronate alone, in 12% of those given **naproxen** alone, and 38% of those given both drugs.[1] In a case-control study,[2] the risk of having an acid-related upper gastrointesti-

nal disorder with alendronate was increased by the concurrent use of NSAIDs (relative risk 1.7). However, retrospective analysis of data from a very large long-term placebo-controlled study found no evidence that the risk of upper gastrointestinal adverse effects with concurrent use of NSAIDs and alendronate was any greater than with NSAIDs and placebo.[3] Note that this finding has been questioned,[4] and some of the issues responded to.[5] Similarly, in a retrospective analysis of a 12-week placebo-controlled study, in those taking regular NSAIDs (about half of the patients) there was no difference in the incidence of upper gastrointestinal adverse events between those given alendronate and those given placebo. The most commonly used NSAIDs in this study were **aspirin**, **celecoxib**, **rofecoxib**, **ibuprofen** and **naproxen**.[6]

Alendronate is commonly known to be associated with oesophageal adverse effects, and there are strict dosing instructions to minimise this risk.[7] It may also cause local irritation of the stomach, although its potential to cause gastric ulcers is not considered established.[3,7]

The interpretation of these data has been debated. Some consider that alendronate should not be given to patients taking NSAIDs,[4] while others urge caution in their use together.[1,2] However, some consider that there is no evidence that alendronate adds to the known gastrointestinal toxicity of NSAIDs.[5] The UK manufacturer issues no caution about the concurrent use of NSAIDs with alendronate.[7] The US manufacturer states that alendronate can be used with NSAIDs, but that caution is required.[8] It would seem sensible to monitor the concurrent use of alendronate and NSAIDs carefully.

(b) Clodronate

The manufacturer notes that patients receiving NSAIDs with clodronate have developed renal impairment, although a synergistic action has not been established.[9] Clodronate alone may cause renal impairment, and the manufacturer suggests that renal function should be assessed before giving clodronate.[9] This would seem particularly important in those taking NSAIDs.

(c) Ibandronate

The manufacturer notes that the incidence of upper gastrointestinal adverse events in patients taking NSAIDs or aspirin did not differ between those receiving ibandronate and those receiving placebo in a large clinical osteoporosis study.[10] In this study, 62% of patients were taking aspirin or NSAIDs. Nevertheless, the manufacturers recommend that, since both bisphosphonates and NSAIDs are associated with gastrointestinal irritation, caution should be taken during concurrent use.[10,11]

(d) Risedronate

In a pooled analysis of phase III osteoporosis studies of risedronate, there was no increased risk of upper gastrointestinal adverse events in those also receiving aspirin and/or NSAIDs (63% of patients).[12] Similarly, in a retrospective analysis of a 2-year placebo-controlled study, in those regularly taking NSAIDs (about two-thirds of patients) there was no difference in the incidence of upper gastrointestinal adverse events between those given risedronate and those given placebo.[13] A similar lack of difference in incidence of gastrointestinal adverse effects was also seen in a once-weekly risedronate study.[14] This suggests that no special precautions are likely to be necessary on concurrent use.

(e) Tiludronate

Single-dose studies in 12 healthy subjects found that **diclofenac** 25 mg and aspirin 600 mg had no significant effect on the pharmacokinetics of tiludronate when taken at the same time. When taken 2 hours after tiludronate, aspirin decreased the AUC of tiludronate by about 50% and diclofenac increased it by about 50%, but neither of these changes was statistically significant.[15] On the other hand, **indometacin** 50 mg increased the maximum serum concentration and the AUC of tiludronate about twofold when these drugs were taken together, but not when they were given 2 hours apart.[15] For this reason the manufacturers advise that **indometacin** and tiludronate should be given 2 hours apart.[16,17] The US manufacturer also advises that aspirin should not be taken within 2 hours of tiludronate,[17] but the reason for this is unclear.

1. Graham DY, Malaty HM. Alendronate and naproxen are synergistic for development of gastric ulcers. *Arch Intern Med* (2001) 161, 107–110.
2. Ettinger B, Pressman A, Schein J. Clinic visits and hospital admissions for care of acid-related upper gastrointestinal disorders in women using alendronate for osteoporosis. *Am J Manag Care* (1998) 4, 1377–82.
3. Bauer DC, Black D, Ensrud K, Thompson D, Hochberg M, Nevitt M, Musliner T, Freedholm D, for the Fracture Intervention Trial Research Group. Upper gastrointestinal tract safety profile of alendronate. *Arch Intern Med* (2000) 160, 517–25.
4. Rothschild BM. Alendronate and nonsteroidal anti-inflammatory drug interaction safety is not established. *Arch Intern Med* (2000) 160, 1702.
5. Bauer DC, for the Fracture Intervention Trial Research Group. Alendronate and nonsteroidal anti-inflammatory drug interaction safety is not established: a reply. *Arch Intern Med* (2000) 160, 2686.
6. Cryer B, Miller P, Petruschke RA, Chen E, Geba GP, de Papp AE. Upper gastrointestinal tolerability of once weekly alendronate 70 mg with concomitant non-steroidal anti-inflammatory drug use. *Aliment Pharmacol Ther* (2005) 21, 599–607.
7. Fosamax Once Weekly (Alendronate sodium). Merck Sharp & Dohme Ltd. UK Summary of product characteristics, October 2008.
8. Fosamax (Alendronate sodium). Merck & Co. Inc. US Prescribing information, June 2009.
9. Bonefos Capsules (Sodium clodronate). Schering Health Care Ltd. UK Summary of product characteristics, June 2009.
10. Boniva (Ibandronate sodium). Roche Laboratories Inc. US Prescribing information, November 2008.
11. Bonviva Film-Coated Tablets (Ibandronic sodium monohydrate). Roche Products Ltd. UK Summary of product characteristics, July 2009.
12. Taggart H, Bolognese MA, Lindsay R, Ettinger MP, Mulder H, Josse RG, Roberts A, Zippel H, Adami S, Ernst TF, Stevens KP. Upper gastrointestinal tract safety of risedronate: a pooled analysis of 9 clinical trials. *Mayo Clin Proc* (2002) 77, 262–70. Correction: *ibid*., 601.
13. Adami S, Pavelka K, Cline GA, Hosterman MA, Barton IP, Cohen SB, Bensen WG. Upper gastrointestinal tract safety of daily oral risedronate in patients taking NSAIDs: a randomized, double-blind, placebo-controlled trial. *Mayo Clin Proc* (2005) 80, 1278–85.
14. Actonel Once a Week (Risedronate sodium). Procter & Gamble Pharmaceuticals UK Ltd. UK Summary of product characteristics, September 2008.
15. Sanofi Winthrop. Data on file, June 1996.
16. Skelid (Disodium tiludronate). Sanofi-Aventis. UK Summary of product characteristics, November 2008.
17. Skelid (Tiludronate disodium). Sanofi-Aventis US. US Prescribing information, April 2006.

Bisphosphonates + Polyvalent cations

The oral absorption of bisphosphonates is reduced by food and polyvalent cations, including aluminium/magnesium hydroxide, bismuth and other antacids, calcium-rich foods, calcium supplements, iron preparations, magnesium-containing laxatives and milk.

Clinical evidence

(a) Alendronate

In pharmacokinetic studies, taking alendronate either 60 or 30 minutes before a standardised breakfast reduced its bioavailability by 40%, when compared with taking it 2 hours before breakfast. Taking alendronate with breakfast markedly reduced its bioavailability by more than 85%, as did taking alendronate 2 hours after breakfast. Both **black coffee** and **orange juice** reduced alendronate bioavailability by about 60%.[1]

(b) Clodronate

In a randomised study in 31 healthy subjects, the AUC of clodronate was reduced to 10% of the optimum level when it was taken with breakfast. Delaying administration until 2 hours after breakfast only slightly improved the AUC (34% of optimum). The best AUC was achieved when clodronate was given 2 hours before breakfast, although the AUC one hour before breakfast was similar (91% of optimum).[2]

(c) Ibandronate

The manufacturer notes that the extent of absorption of ibandronate is impaired when it is taken with food or beverages (other than plain water). Bioavailability is reduced by about 90% when ibandronate is given with a standard breakfast, when compared with the bioavailability seen in fasted subjects. The manufacturers say that there is no meaningful reduction in bioavailability when ibandronic acid is taken 60 minutes before the first food of the day.[3,4]

(d) Risedronate

The absorption of risedronate 30 mg, taken 30 minutes before breakfast, was reduced by 55%, when compared with the fasting state (no food or drink for 10 hours before or for 4 hours after dosing). Administration one hour before breakfast reduces absorption by 30%, when compared with the fasting state. Administration 2 hours after dinner (evening meal) results in similar absorption to administration 30 minutes before breakfast.[5,6] The manufacturer says that risedronate is clinically effective when taken at least 30 minutes before breakfast.[5]

(e) Tiludronate

In a study in 12 healthy subjects the maximum serum levels and AUC of tiludronate were halved when *Maalox* (**aluminium/magnesium hydroxide**) was taken one hour before tiludronate, but the bioavailability was only slightly affected when *Maalox* was taken 2 hours after tiludronate.[7]

Mechanism

The bisphosphonates can form complexes with a number of polyvalent metallic ions (e.g. Al^{3+}, Ca^{2+}, Fe, Mg^{2+}), which can impair their absorption.

Importance and management

Established and important interactions. Bisphosphonates should be prevented from coming into contact with a range of preparations such as **antacids** (containing **aluminium**, **bismuth**, **calcium**, **magnesium**), laxatives (containing magnesium), **iron preparations** and calcium or other **mineral supplements**. **Food**, in particular **milk** and **dairy products**, contain calcium, and may also impair absorption.

Recommendations on the timing of administration of bisphosphonates in relation to food and other drugs vary slightly between products.

- The manufacturers of **alendronate**[8,9] suggest that, in order to avoid absorption interactions, patients should take alendronate after an overnight fast at least 30 minutes before taking any other drug or food, and that alendronate should be taken with plain (not mineral) water only.
- The manufacturers of **clodronate**[10] suggest leaving one hour between the administration of food and clodronate.
- The manufacturers of **etidronate**[11,12] recommend it is given on an empty stomach at least 2 hours from any food, particularly that containing polyvalent cations (as listed above), and from medicines containing these cations.
- The manufacturers of **ibandronate**[3,4,13] recommend it is taken with plain water on an empty stomach (overnight fast of at least 6 hours) at least 30 minutes[13] to one hour[3] before the first food or drink (other than water) of the day, or any other medications.
- The manufacturers of **risedronate**[5,14] recommend it is taken with water at least 30 minutes before the first food or drink of the day. Alternatively, they say it should be given at least 2 hours from any food or drink at any other time of the day, and at least 30 minutes before going to bed.
- The manufacturers of **tiludronate**[15,16] recommend that it is taken with water on an empty stomach (at least 2 hours before or after meals). In addition, they recommend that administration of tiludronate and antacids or calcium compounds should be separated by 2 hours.

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3. Bonviva Film-Coated Tablets (Ibandronic sodium monohydrate). Roche Products Ltd. UK Summary of product characteristics, July 2009.
4. Boniva (Ibandronate sodium). Roche Laboratories Inc. US Prescribing information, November 2008.
5. Actonel (Risedronate sodium). Procter & Gamble Pharmaceuticals Inc. US Prescribing information, April 2008.
6. Mitchell DY, Heise MA, Pallone KA, Clay ME, Nesbitt JD, Russell DA, Melson CW. The effect of dosing regimen on the pharmacokinetics of risedronate. *Br J Clin Pharmacol* (1999) 48, 536–42.
7. Sanofi Winthrop. Data on file, June 1996.
8. Fosamax Once Weekly (Alendronate sodium). Merck Sharp & Dohme Ltd. UK Summary of product characteristics, October 2008.
9. Fosamax (Alendronate sodium). Merck & Co. Inc. US Prescribing information, June 2009.
10. Bonefos Capsules (Sodium clodronate). Schering Health Care Ltd. UK Summary of product characteristics, June 2009.
11. Didronel (Etidronate disodium). Procter & Gamble Pharmaceuticals UK Ltd. UK Summary of product characteristics, October 2006.
12. Didronel (Etidronate disodium). Procter & Gamble Pharmaceuticals. US Prescribing information, October 2007.
13. Bondronat Film-Coated Tablets (Ibandronate sodium monohydrate). Roche Products Ltd. UK Summary of product characteristics, March 2009.
14. Actonel 30 mg Film Coated Tablets (Risedronate sodium). Procter & Gamble Pharmaceuticals UK Ltd. UK Summary of product characteristics, September 2008.
15. Skelid (Disodium tiludronate). Sanofi-Aventis. UK Summary of product characteristics, November 2008.
16. Skelid (Tiludronate disodium). Sanofi-Aventis US. US Prescribing information, April 2006.

Bisphosphonates + Thalidomide

The pharmacokinetics of zoledronate are not affected by thalidomide. It is uncertain if thalidomide increases the risk of osteonecrosis of the jaw caused by bisphosphonates.

Clinical evidence

(a) Renal function and pharmacokinetics

Acute renal failure (a marked rise in creatinine levels with hypocalcaemia) occurred in 2 of 16 patients with myeloma who had their bisphosphonate treatment switched from **pamidronate** to **zoledronate**. Both of these patients were also taking thalidomide, which was speculated to possibly have contributed to the renal impairment.[1] However, in a sub-study of a controlled clinical study, there was no evidence of renal impairment, and no difference in serum creatinine levels between 12 patients receiving thalidomide and 12 patients not receiving thalidomide, for up to 16 infusions of **zoledronate**. In this study, intravenous zoledronic acid 4 mg every 4 weeks with alternate day prednisolone was given, with or without thalidomide 200 mg daily, for up to 16 months. Moreover, the zoledronic acid pharmacokinetics during the first and second infusions did not differ between 12 patients randomised to receive thalidomide and 12 patients not receiving thalidomide. The subjects in this study were patients with multiple myeloma with no disease progression 6 weeks after autologous stem-cell transplantation and conditioning with melphalan.[2]

(b) Osteonecrosis of the jaw

In a retrospective analysis of 28 cases of osteonecrosis of the jaw occurring in 254 patients given **pamidronate** or **zoledronate**, **zoledronate** was associated with a much higher risk than **pamidronate**, and a multivariate model revealed that the concurrent use of thalidomide increased the risk of osteonecrosis of the jaw 2.4-fold.[3] Similarly, in another review of 35 cases of **pamidronate** or **zoledronate**-associated osteonecrosis of the jaw, although no statistical analysis was carried out, concurrent use of thalidomide was frequent (46% of cases), leading the authors to suggest that the possible link should be further investigated.[4] Conversely, in a cohort of 259 patients with multiple myeloma who had all received treatment with **zoledronate**, thalidomide and dexamethasone, just 9 (6.6%) developed osteonecrosis of the jaw, which was stated to be comparable to the incidence previously reported for zoledronic acid alone.[5]

Mechanism

Uncertain. Thalidomide can rarely affect renal function, and was suggested to possibly interact with zoledronate. The antiangiogenic activity of thalidomide might increase the risk of osteonecrosis with bisphosphonates.

Importance and management

No interaction is established, and the data from the controlled study suggest that the combination of thalidomide and zoledronate has no greater risk of renal impairment than zoledronate alone. Thalidomide does not alter the pharmacokinetics of zoledronate. Further study is needed to ascertain if thalidomide increases the risk of osteonecrosis of the jaw seen with bisphosphonates.

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Bisphosphonates; Alendronate + Phosphates

An isolated report describes a patient taking alendronate, who developed hypocalcaemic tetany after receiving two doses of oral *Fleet Phospho-Soda* (monobasic sodium phosphate with dibasic sodium phosphate).

Clinical evidence

A patient with Crohn's disease taking a 5-aminosalicylate (unnamed) and prednisone developed mild osteoporosis and was given alendronate 10 mg daily. About 18 months later she underwent elective bowel surgery, receiving 2 doses of oral *Fleet Phospho-Soda* (monobasic sodium phosphate with dibasic sodium phosphate) 2 hours apart before surgery. About

6 hours postoperatively she developed paraesthesia of her extremities and perioral region, hypophosphataemia, and hypocalcaemic tetany. She recovered after treatment with intravenous calcium gluconate 2 g over 30 minutes. Her serum calcium, phosphate and magnesium levels were low, and she was therefore given calcitriol and further calcium supplements.[1]

Mechanism

Hypocalcaemia in this patient was probably due to several factors, including disease of the terminal ileum and a history of diarrhoea, which could have resulted in calcium malabsorption and relative vitamin D deficiency. *Fleet Phospho-Soda* also causes hypocalcaemia, which is usually accompanied by hyperphosphataemia. The authors of the report suggest that alendronate was also a factor in the development of hypocalcaemia, and further, that the hypophosphataemia was possibly linked to high parathyroid hormone levels preoperatively.[1]

Importance and management

The authors of this isolated case advise care if phosphate-based oral laxatives are given to patients taking bisphosphonates, especially in patients with intestinal malabsorption syndromes.[1]

However, this appears to be the only report of hypocalcaemic tetany associated with the use of bisphosphonates and *Fleet Phospho-Soda*. It has also been noted that the patient's low magnesium levels could result in tetany.[2] Long-term prednisone treatment, which decreases calcium absorption, may also be involved. Further, the 2 doses of *Fleet-Phospho-Soda* were given 2 hours apart, rather than at the recommended interval of 10 to 12 hours. Other authors, in considering these factors, suggest that patients taking bisphosphonates are not at increased risk of hypocalcaemic tetany if they are given *Fleet Phospho-Soda*.[2]

1. Campisi P, Badhwar V, Morin S, Trudel JL. Postoperative hypocalcemic tetany caused by Fleet® Phospho®-Soda preparation in a patient taking alendronate sodium. *Dis Colon Rectum* (1999) 42, 1499–501.
2. Francis MD, Caswell M. Patients on bisphosphonates should not be at increased risk for hypocalcemic-induced tetany when given Fleet® Phospho-Soda®. *Dis Colon Rectum* (2003) 46, 1717–18.

Brimonidine or Latanoprost + NSAIDs

The reduction of intraocular pressure by brimonidine eye drops may be reduced by oral indometacin. The reduction in intraocular pressure by latanoprost eye drops was not significantly reduced by oral indometacin, slightly reduced by bromfenac eye drops, but enhanced by oral nimesulide and diclofenac eye drops.

Clinical evidence

In a double-blind study, 20 patients with open-angle glaucoma or ocular hypertension received treatment for their right eye with either latanoprost 0.005% eye drops in the morning and drug-free vehicle in the evening or with brimonidine 0.2% eye drops in the morning and evening. One week later treatment was started for the left eye with the opposite regimen to that used in the right eye. After another week the patients were given oral **indometacin** 25 mg four times daily for 2 weeks. Compared with pretreatment values, the intraocular pressure reduction with brimonidine alone was 14%, which fell to a non-significant 11% reduction when **indometacin** was given. Compared with pretreatment values the intraocular pressure with latanoprost alone was 25%, and this was not significantly altered when **indometacin** was given. Peripheral retinal microcirculation was increased by 23% with latanoprost, but not significantly affected by brimonidine. When **indometacin** was also given the effect of latanoprost became non-significant, and in the case of brimonidine, was reduced to a value lower than that measured before brimonidine was given. **Indometacin** did not affect visual function parameters.[1]

In another study, 11 healthy subjects were given latanoprost 0.005% eye drops daily, in both eyes for 8 weeks, with **bromfenac** eye drops put in one eye twice daily between weeks 4 and 6. After a 4-week washout period, **bromfenac** was again given for 2 weeks to the same eyes as before. Bromfenac alone did not affect intraocular pressure, but was found to significantly inhibit the intraocular pressure-lowering effects of latanoprost. At week 6, latanoprost reduced intraocular pressure by about 23% to 52%, but in those eyes also treated with **bromfenac** the reduction was between about 7% and 35%.[2] In a further similar study in patients with glaucoma, **bromfenac** eye drops twice daily for 12 weeks slightly attenuated the reduction in intraocular pressure seen with latanoprost eye drops (maximum difference 1.08 mmHg).[3]

In contrast to these studies, other researchers have found that 2 hours after a single 100-mg oral dose of **nimesulide**, the intraocular pressure in patients whose glaucoma was controlled by latanoprost was further reduced by about 3 mmHg.[4] Another study in patients with glaucoma found that 5 weeks of **diclofenac** 0.1% eye drops enhanced the intraocular pressure reducing effect of latanoprost eye drops: after one week intraocular pressure was reduced by 4.1 mmHg, compared with a 0.67 mmHg in those given placebo.[5]

Mechanism

Brimonidine may reduce intraocular pressure by decreasing aqueous inflow and increasing uveoscleral outflow. The latter effect is thought to occur by stimulation of endogenous prostaglandin $F_{2\alpha}$ formation.[1] Latanoprost is a synthetic analogue of dinoprost (prostaglandin $F_{2\alpha}$) which also reduces intraocular pressure by increasing uveoscleral outflow. It is also reported to induce endogenous prostaglandins.[2] NSAIDs, such as indometacin and bromfenac, may possibly antagonise this action by inhibiting the induction of endogenous prostaglandins by suppressing cyclooxygenase activity. However, it has also been suggested that the expression of prostaglandin receptors in ocular tissue may be up-regulated in the presence of prostaglandin inhibitors such as NSAIDs, resulting in a greater response to prostaglandin analogues.[4,5]

Importance and management

The reduction in the effect of brimonidine with oral indometacin may be of clinical importance.[1] It may be prudent to consider oral NSAID use in patients receiving treatment for glaucoma with brimonidine where intraocular pressure is not adequately reduced.

The situation with latanoprost is unclear. Both a small reduction, no effect, and an enhanced effect have been seen with various NSAIDs (some oral and some eye drops). Until more is known, additional monitoring may be appropriate when an oral or ocular NSAID is stopped or started in a patient stabilised on latanoprost.

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2. Kashiwagi K, Tsukahara S. Effect of non-steroidal anti-inflammatory ophthalmic solution on intraocular pressure reduction by latanoprost. *Br J Ophthalmol* (2003) 87, 297–301.
3. Chiba T, Kashiwagi K, Chiba N, Tsukahara S. Effect of non-steroidal anti-inflammatory ophthalmic solution on intraocular pressure reduction by latanoprost in patients with primary open angle glaucoma or ocular hypertension. *Br J Ophthalmol* (2006) 90, 314–17.
4. Costagliola C, Parmeggiani F, Caccavale A, Sebastiani A. Nimesulide oral administration increases the intraocular pressure-lowering effect of latanoprost in patients with primary open-angle glaucoma. *Am J Ophthalmol* (2006) 141, 379–81.
5. Costagliola C, Parmeggiani F, Antinozzi PP, Caccavale A, Cotticelli L, Sebastiani A. The influence of diclofenac ophthalmic solution on the intraocular pressure-lowering effect of topical 0.5% timolol and 0.005% latanoprost in primary open-angle glaucoma patients. *Exp Eye Res* (2005) 81, 610–15.

Charcoal, activated + Miscellaneous

Small doses of activated charcoal appear to have little effect on the absorption of ciprofloxacin and oral contraceptives (administration separated), and only modestly reduces nizatidine and amlodipine absorption. Case reports describe the lack of efficacy of mitobronitol and reduced serum phenobarbital levels in the presence of small doses of activated charcoal.

Clinical evidence, mechanism, importance and management

The use of activated charcoal, in a usual dose of 50 g, to reduce the absorption of drugs and poisons after acute overdose is well established, as is repeated doses of activated charcoal to enhance the elimination of some drugs taken in overdose after they have been absorbed. Studies and references supporting these therapeutic uses of activated charcoal are not reviewed here. Activated charcoal is also included in various remedies used for gastrointestinal disorders such as flatulence or diarrhoea. Doses in these instances are very much lower (1 to 2 g daily) than those used in the treatment of poisoning, and there seems to be little reported about the effects of these doses on the absorption of other drugs.

In a study in 8 healthy subjects, a formulation of small spherical activated charcoal particles (*Kremezin* 2-g *granules*), used to adsorb uraemic tox-

ins in renal disease, hardly affected the bioavailability of **amlodipine** 5 mg when both drugs were given together, after a meal. The maximum amlodipine plasma concentration was reduced by 16%, but the AUC_{0-72} was decreased by only 7% (not statistically significant). In one subject the AUC was reduced by 26%, but even this would not be expected to be clinically significant.[1]

In one single-dose study in healthy subjects, **nizatidine** absorption was reduced by about 30% when it was taken one hour before activated charcoal 2 g.[2] In another single-dose study in 6 subjects, taking activated charcoal 1 g soon after ciprofloxacin 500 mg, had little effect on the pharmacokinetics of **ciprofloxacin** 500 mg (AUC reduced by 10%).[3]

In one case report, an antiemetic complementary remedy containing activated charcoal was thought to be the cause of a lack of effect of **mitobronitol** 125 mg used to treat primary thrombocythaemia in one patient.[4] In another case report,[5] activated charcoal 2 g three times daily was given with **phenobarbital** and enteral nutrition via a gastric fistula tube. The charcoal appeared to reduce the absorption of **phenobarbital** (serum level 4.3 mg/L, compared with a previous level of 24.8 mg/L). Giving the activated charcoal at least one hour apart from the **phenobarbital** resulted in an increase in serum levels to about 16 to 18 mg/L.

In a study in 9 healthy subjects, activated charcoal 5 g four times daily was taken for 3 days, mid-cycle, with the first daily dose taken 3 hours after the morning dose of a **combined oral contraceptive** (ethinylestradiol with norethisterone or gestodene), had no effect on the pharmacokinetics of the contraceptive steroids,[6] and ovulation (assessed by hormone measurements and ultrasonography) did not occur.[7] The authors concluded that repeated charcoal treatment, given 3 hours after and at least 12 hours before a **combined oral contraceptive**, can be used to treat diarrhoea in women taking **combined oral contraceptives**.[6,7]

1. Tanaka C, Ohtani H, Tsujimoto M, Ohdo S, Taniguchi M, Mizooku Y, Saitoh Y, Kimura M, Uchimaru H, Irie S, Sawada Y. Effects of dosing interval on the pharmacokinetic interaction between oral small spherical activated charcoal and amlodipine in humans. *J Clin Pharmacol* (2007) 47, 904–8.
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6. Elomaa K, Ranta S, Tuominen J, Lähteenmäki P. The possible role of enterohepatic cycling on bioavailability of norethisterone and gestodene in women using combined oral contraceptives. *Contraception* (2001) 63, 13–8.
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Chlorzoxazone + Disulfiram

Disulfiram markedly increases the plasma levels of chlorzoxazone.

Clinical evidence

In a pharmacokinetic study in 6 healthy subjects, a single 500-mg dose of disulfiram markedly inhibited the metabolism of a single 750-mg dose of chlorzoxazone (clearance reduced by 85%, half-life increased from 0.92 to 5.1 hours, and a twofold increase in peak plasma levels).[1]

Mechanism

Disulfiram inhibits the cytochrome P450 isoenzyme CYP2E1, by which chlorzoxazone is metabolised. Note that chlorzoxazone is used as a probe substrate in evaluating the effects of drugs on CYP2E1, see 'Table 1.3', (p.6).

Importance and management

An established pharmacokinetic interaction. No increased adverse effects were seen while using these single doses, but an increase in chlorzoxazone toxicity (sedation, headache, nausea) would be expected with multiple doses. Be alert for the need to reduce the chlorzoxazone dosage if disulfiram is given concurrently.

1. Kharasch ED, Thummel KE, Mhyre J, Lillibridge JH. Single-dose disulfiram inhibition of chlorzoxazone metabolism: a clinical probe for P450 2E1. *Clin Pharmacol Ther* (1993) 53, 643–50.

Chlorzoxazone + Isoniazid

Isoniazid reduces the clearance of chlorzoxazone. The adverse effects of chlorzoxazone may be increased in some patients (particularly slow acetylators of isoniazid) if they also take isoniazid.

Clinical evidence

Five out of 10 healthy slow acetylators of isoniazid experienced an increase in the adverse effects of a 750-mg dose of chlorzoxazone (sedation, headache, nausea) after taking isoniazid 300 mg daily for 7 days. These symptoms disappeared within 2 days of withdrawing the isoniazid.[1] Pharmacokinetic analysis found that the clearance of chlorzoxazone was reduced by 56% when given on the last day of isoniazid use, then increased by 56% when given 2 days after stopping isoniazid.[1] Similar findings were reported in another study in slow acetylators of isoniazid. In this study, chlorzoxazone clearance was reduced by 78% when subjects had taken isoniazid 300 mg daily for 14 days, at which point the isoniazid was stopped. Two days later chlorzoxazone clearance was increased by 58%, and it had returned to normal 2 weeks later.[2] Rapid acetylators of isoniazid also had a 60% reduction in chlorzoxazone clearance on the last day of isoniazid use, but did not have any increase 2 days later.[2]

Mechanism

Isoniazid appears to cause a dual interaction. During administration, it inhibits the activity of the cytochrome P450 isoenzyme CYP2E1, the enzyme involved in the metabolism of chlorzoxazone. Shortly after stopping isoniazid, the metabolism of chlorzoxazone is increased, possibly because of induction of CYP2E1, although this effect was only evident in the slow acetylators.[1,2]

Importance and management

The increase in chlorzoxazone levels is established, and occurs in both slow and fast acetylators of isoniazid, although the increase in levels is slightly greater in slow acetylators. In practical terms this means that it may be necessary to reduce the chlorzoxazone dosage in some patients if they take isoniazid. Monitor concurrent use carefully. The rebound increase in chlorzoxazone clearance in slow acetylators on stopping isoniazid was short-lived and is probably of little clinical importance.

1. Zand R, Nelson SD, Slattery JT, Thummel KE, Kalhorn TF, Adams SP, Wright JM. Inhibition and induction of cytochrome P4502E1-catalyzed oxidation by isoniazid in humans. *Clin Pharmacol Ther* (1993) 54, 142–9.
2. O'Shea D, Kim RB, Wilkinson GR. Modulation of CYP2E1 activity by isoniazid in rapid and slow *N*-acetylators. *Br J Clin Pharmacol* (1997) 43, 99–103.

Cinacalcet + Food

Cinacalcet absorption is increased by food.

Clinical evidence

In a pharmacokinetic study in 29 healthy subjects, the AUC of cinacalcet was raised by 68% when a single 90-mg dose of cinacalcet was taken within 5 minutes of finishing a high-fat, high-calorie breakfast, when compared with the fasted state (10 hours). Similarly, a low-fat, low-calorie breakfast increased the AUC of cinacalcet by 50%. Food had no effect on the elimination half-life of cinacalcet.[1]

Mechanism

Food increases the rate and extent of absorption of cinacalcet, independently of the fat content. Possible mechanisms include increased gastric residence time or decreased presystemic metabolism.[1]

Importance and management

An established pharmacokinetic interaction. Cinacalcet should be taken with food or shortly after a meal[2,3] to maximise absorption.

1. Padhi D, Salfi M, Harris RZ. The pharmacokinetics of cinacalcet are unaffected following consumption of high-and low-fat meals. *Am J Ther* (2007) 14, 235–40.

2. Mimpara (Cinacalcet). Amgen Ltd. UK Summary of product characteristics, March 2009.
3. Sensipar (Cinacalcet). Amgen Inc. US Prescribing information, December 2008.

Cinacalcet + Ketoconazole and other CYP3A4 inhibitors

Ketoconazole causes about a twofold increase in cinacalcet exposure, and is therefore likely to increase cinacalcet adverse effects. Other potent CYP3A4 inhibitors are predicted to affect cinacalcet in the same way as ketoconazole.

Clinical evidence

In a pharmacokinetic study in 20 healthy subjects, the AUC and maximum level of cinacalcet were raised about twofold when a single 90-mg dose of cinacalcet was given on day 5 of a 7-day course of ketoconazole 200 mg twice daily. The median elimination half-life of cinacalcet was slightly increased and its clearance reduced by 65%. This resulted in an increase in the proportion of subjects reporting a treatment-related adverse event (42% versus 21%).[1]

Mechanism

Cinacalcet is extensively metabolised, in part by the cytochrome P450 isoenzyme CYP3A4, of which ketoconazole is a potent inhibitor. Ketoconazole therefore increases cinacalcet levels. The lack of change in elimination half-life suggests that the interaction principally resulted in an increase in the bioavailability of cinacalcet.

Importance and management

The pharmacokinetic interaction is established and likely to be clinically important. Cinacalcet treatment is monitored by measuring parathyroid hormone and serum calcium levels, and these should be closely monitored when ketoconazole is started or stopped, anticipating the need to adjust the cinacalcet dosage accordingly. Other potent CYP3A4 inhibitors would be predicted to interact similarly, and the manufacturers specifically mention **itraconazole**, **voriconazole**, **telithromycin**, **ritonavir** and **erythromycin**[2,3] (although note that erythromycin is sometimes considered to be a moderate CYP3A4 inhibitor).

On the basis that a potent CYP3A4 inhibitor caused just a twofold increase in AUC, weak to moderate CYP3A4 inhibitors would be unlikely to cause clinically relevant increases in cinacalcet levels.

1. Harris RZ, Salfi M, Sullivan JT, Padhi D. Pharmacokinetics of cinacalcet hydrochloride when administered with ketoconazole. *Clin Pharmacokinet* (2007) 46, 495–501.
2. Mimpara (Cinacalcet). Amgen Ltd. UK Summary of product characteristics, March 2009.
3. Sensipar (Cinacalcet). Amgen Inc. US Prescribing information, December 2008.

Cinacalcet + Miscellaneous

Potent CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin) are predicted to increase cinacalcet levels. Tobacco smoking induces CYP1A2 and is associated with lower cinacalcet levels. Rifampicin is predicted to reduce cinacalcet levels, because of its CYP3A4-inducing effects. Calcium carbonate, pantoprazole and sevelamer do not alter cinacalcet pharmacokinetics, and cinacalcet does not alter midazolam pharmacokinetics.

Clinical evidence, mechanism, importance and management

(a) Calcium carbonate

In a single-dose study in healthy subjects, the AUC of cinacalcet 100 mg was not changed by calcium carbonate 1.5 g.[1,2]

(b) CYP1A2 inducers and inhibitors

Cinacalcet is extensively metabolised, in part by the cytochrome P450 isoenzyme CYP1A2. The UK manufacturer notes that the clearance of cinacalcet was 36 to 38% higher in **smokers** than non-smokers, and that tobacco smoking induces CYP1A2. They suggest that the cinacalcet dose might need to be adjusted if a patient starts or stops smoking. Moreover, although the effect of CYP1A2 inhibitors such as **fluvoxamine** and **ciprofloxacin** on cinacalcet has not been studied, the manufacturer suggests that cinacalcet dose adjustment might be needed if these potent inhibitors are started or stopped.[3] Until more is known, it would be prudent to increase monitoring of parathyroid hormone and serum calcium levels in these situations.

(c) Midazolam

The manufacturers report that cinacalcet 90 mg daily for 5 days did not affect the pharmacokinetics of a single 2-mg oral dose of midazolam given on day 5, when compared with the pharmacokinetics of midazolam alone.[2,3]

(d) Pantoprazole

In a study in healthy subjects, the AUC of a single 90-mg dose of cinacalcet was not changed by pantoprazole 80 mg daily for 3 days.[1,2]

(e) Rifampicin (Rifampin)

Cinacalcet is extensively metabolised, in part by the cytochrome P450 isoenzyme CYP3A4. On the basis that the CYP3A4 inhibitor 'ketoconazole', (p.1553), causes clinically relevant increases in cinacalcet levels, rifampicin, a CYP3A4 inducer, is predicted to decrease levels of cinacalcet.[3] It would be prudent to monitor cinacalcet efficacy if rifampicin is required, anticipating the need to increase the dose.

(f) Sevelamer

In a study in healthy subjects, the AUC of a single 90-mg dose of cinacalcet was not changed when it was given with the first dose of sevelamer 2.4 g three times daily for 2 days.[1,2]

1. Padhi D, Harris R, Salfi M, Yates W, Hansen J, Flynn J, Sullivan JT. Cinacalcet HCl absorption in study subjects is not affected by coadministration of medications commonly prescribed to chronic kidney disease (CKD) patients (pantoprazole, sevelamar HCl, and calcium carbonate). *J Am Soc Nephrol* (2003) 14, 461A.
2. Sensipar (Cinacalcet). Amgen Inc. US Prescribing information, December 2008.
3. Mimpara (Cinacalcet). Amgen Ltd. UK Summary of product characteristics, March 2009.

CNS depressants + CNS depressants

The concurrent use of two or more drugs that are CNS depressants can increase drowsiness and reduce alertness. These drugs include alcohol (even in small amounts), antidepressants, antiemetics, antiepileptics, antihistamines, antipsychotics, anxiolytics, barbiturates, hypnotics, opioid analgesics, and skeletal muscle relaxants. This increases the risk of accidents when driving or handling other potentially dangerous machinery, and may make the performance of everyday tasks more difficult and hazardous.

Clinical evidence, mechanism, importance and management

Many drugs have the propensity to cause depression of the central nervous system, resulting in drowsiness, sedation, respiratory depression and at the extreme, death. If more than one CNS depressant is taken, their effects may be additive. It is not uncommon for patients, particularly the elderly, to be taking numerous drugs (and possibly alcohol as well). Such patients are therefore at risk of cumulative CNS depression ranging from mild drowsiness through to a befuddled stupor, which can make the performance of the simplest everyday task more difficult or even impossible. The importance of this will depend on the context: it may considerably increase the risk of accident in the kitchen, at work, in a busy street, driving a car, or handling other potentially dangerous machinery where alertness is at a premium. It has been estimated that as many as 600 traffic accident fatalities each year in the UK can be attributed to the sedative effects of psychoactive drugs.[1] In a Spanish study of fatal road traffic accidents, blood samples were analysed from 9.7% of drivers killed in road accidents over a 10-year period. Of these drivers, medicines were detected in 4.7% (269 cases), and of these **benzodiazepines** were the most common (73%). Other drugs present in 6% to 12% of cases included **antidepressants**, **analgesics**, **antiepileptics**, **barbiturates** and **antihistamines**. Of the benzodiazepine cases, almost three quarters had another substance detected, mainly illicit drugs (cocaine, **opioids**, or cannabis) or **alcohol**. Only 7.7% had taken **benzodiazepines** or another medicinal drug alone.[2] **Alcohol** almost certainly makes things worse, particularly in the elderly.[3]

An example of the lethal effects of combining an **antihistamine**, a **benzodiazepine** and **alcohol** is briefly mentioned in the monograph 'Alcohol + Antihistamines', p.50. A less spectacular but socially distressing example is that of a woman accused of shop-lifting while in a confused state arising from the combined sedative effects of *Actifed*, a *Beechams Powder*

and *Dolobid* (containing **triprolidine**, **salicylamide** and **diflunisal**, respectively).[4]

Few, if any, well-controlled studies have investigated the cumulative or additive detrimental effects of CNS depressants (except with **alcohol**), but the following is a list of some of the groups of drugs that to a greater or lesser extent possess CNS depressant activity, which therefore might be expected to interact in this way: **alcohol**, **opioids**, **antiepileptics**, **antidepressants**, **antihistamines**, **antiemetics**, **antipsychotics**, **anxiolytics** and **hypnotics**. Some of the interactions of **alcohol** with these drugs are dealt with in individual monographs.

1. Anon. Sedative effects of drugs linked to accidents. *Pharm J* (1994) 253, 564.
2. Carmen del Río M, Gómez J, Sancho M, Alvarez FJ. Alcohol, illicit drugs and medicinal drugs in fatally injured drivers in Spain between 1991 and 2000. *Forensic Sci Int* (2002) 127, 63–70.
3. Gerbino PP. Complications of alcohol use combined with drug therapy in the elderly. *J Am Geriatr Soc* (1982) 30 (11 Suppl), S88–S93.
4. Herxheimer A, Haffner BD. Prosecution for alleged shoplifting: successful pharmacological defence. *Lancet* (1982) i, 634.

Colchicine + Macrolides

Several case reports describe acute life-threatening colchicine toxicity caused by the concurrent use of erythromycin or clarithromycin. One retrospective study found that 9 of 88 patients who had received the combination of colchicine and clarithromycin died.

Clinical evidence

A 29-year-old woman with familial Mediterranean fever and amyloidosis, who was taking long-term colchicine 1 mg daily, developed acute and life-threatening colchicine toxicity (fever, diarrhoea, myalgia, pancytopenia and later alopecia) 16 days after starting to take **erythromycin** 2 g daily. This patient had both cholestasis and renal impairment, factors that would be expected to reduce colchicine clearance and therefore predispose her to colchicine toxicity. Colchicine levels rose from below 12.6 nanograms/mL to 22 nanograms/mL after the addition of **erythromycin**.[1] In another patient, who had been taking colchicine 1.5 mg daily for 6 years, similar signs of acute colchicine toxicity developed 4 days after a 7-day course of **clarithromycin** 1 g daily, amoxicillin and omeprazole was started for *H. pylori* associated gastritis. The colchicine dose was reduced to 500 micrograms daily and then, after recovery, gradually increased slowly back to 1.5 mg daily.[2]

In another case, a 67-year-old man receiving CAPD, who was taking colchicine 500 micrograms twice daily, was admitted with symptoms of colchicine toxicity (including pancytopenia) 4 days after starting a course of **clarithromycin** 500 mg twice daily for an upper respiratory tract infection. All drugs were stopped and supportive treatment given, but he later died from multi-organ failure.[3]

These case reports led to a retrospective study of patients who had received the combination of colchicine and **clarithromycin** as inpatients. Of 116 patients given the drugs, 88 had received them concurrently and 28 received them sequentially. Nine of the concurrent group died (compared with only 1 of the sequential group), and of the nine, five had pancytopenia, and six had renal impairment. In the 88 patients receiving the drugs concurrently, longer overlapping therapy increased the relative risk of death 2.16-fold, the presence of renal impairment increased the risk 9.1-fold, and the development of pancytopenia increased the risk 23.4-fold.[4]

Three further cases of fatal agranulocytosis, presumed to result from use of colchicine with **clarithromycin**, have been reported,[5,6] and 2 other cases describe colchicine toxicity during **clarithromycin** use in patients with renal impairment.[7]

Mechanism

Clarithromycin and erythromycin might increase the bioavailability of colchicine by affecting P-glycoprotein, and/or may inhibit the hepatic metabolism of colchicine by the cytochrome P450 isoenzyme CYP3A4.[2,4] These effects would be more marked in patients with renal impairment, in whom colchicine clearance is already reduced.

Importance and management

Information on this interaction is limited, but it appears that clarithromycin and erythromycin can provoke acute colchicine toxicity, at the very least in pre-disposed individuals. Other macrolides do not appear to have been studied. However, until more information is available, if any patient is given colchicine and a macrolide be aware of the potential for toxicity, especially in patients with pre-existing renal impairment.

1. Caraco Y, Putterman C, Rahamimov R, Ben-Chetrit E. Acute colchicine intoxication - possible role of erythromycin administration. *J Rheumatol* (1992) 19, 494–6.
2. Rollot F, Pajot O, Chauvelot-Moachon L, Nazal EM, Kélaïdi C, Blanche P. Acute colchicine intoxication during clarithromycin administration. *Ann Pharmacother* (2004) 38, 2074–7.
3. Dogukan A, Oymak FS, Taskapan H, Güven M, Tokgoz B, Utas C. Acute fatal colchicine intoxication in a patient on continuous ambulatory peritoneal dialysis (CAPD). Possible role of clarithromycin administration. *Clin Nephrol* (2001) 55, 181–2.
4. Hung IFN, Wu AKL, Cheng VCC, Tang BSF, To KW, Yeung CK, Woo PCY, Lau SKP, Cheung BMY, Yuen KY. Fatal interaction between clarithromycin and colchicine in patients with renal insufficiency: a retrospective study. *Clin Infect Dis* (2005) 41, 291–300.
5. Cheng VCC, Ho PL, Yuen KY. Two probable cases of serious drug interaction between clarithromycin and colchicine. *South Med J* (2005) 98, 811–13.
6. Huynh-Do U. In den gärten der Medea. *Ther Umsch* (2006) 63, 783–7.
7. Akdag I, Ersoy A, Kahvecioglu S, Gullulu M, Dilek K. Acute colchicine intoxication during clarithromycin administration in patients with chronic renal failure. *J Nephrol* (2006) 19, 515–17.

Colchicine + Verapamil

Verapamil may markedly increase colchicine levels, which led to neuromyopathy in one man.

Clinical evidence, mechanism, importance and management

An 83-year-old man who was taking slow-release verapamil 120 mg daily for tachyarrhythmia, as well as furosemide, aspirin, ambroxol and theophylline, took colchicine 2 mg over a 2-day period for acute gout, with diclofenac for pain. He had muscle weakness in his limbs and 4 days later became immobile. On admission to hospital he had flaccid tetraparesis (weakness of all four extremities). A diagnosis of colchicine-induced neuromyopathy was made after excessive levels of colchicine were found in his serum and CSF. The serum half-life was increased eightfold (from a reference value of 34 hours to 272 hours) and the CSF:serum ratio was increased to about 50%, much higher than the usual normal of less than 10%. At follow-up 40 days later he had partially recovered and colchicine was not detectable in his serum.[1]

Usual features of colchicine-induced neuropathy, such as high cumulative dose, long-term treatment, or renal impairment were not found. Colchicine is a substrate for the cytochrome P450 isoenzyme CYP3A4 in the liver. It was suggested that inhibition of CYP3A4 by verapamil may have resulted in increased colchicine serum levels. In addition, inhibition of P-glycoprotein in the blood-brain barrier by verapamil may have resulted in increased colchicine accumulation in the CSF.[1]

Although this is an isolated case, it is in line with the way both drugs interact with other substances. Therefore it would seem prudent to suspect an interaction in the case of otherwise unexplained colchicine toxicity in a patient taking verapamil.

1. Tröger U, Lins H, Scherrmann J-M, Wallesch C-W, Bode-Böger SM. Tetraparesis associated with colchicine is probably due to inhibition by verapamil of the P-glycoprotein efflux pump in the blood-brain barrier. *BMJ* (2005) 331, 613. Correction. ibid., (2006) 332, 882.

Contrast media + Phenothiazines

Two isolated case reports describe epileptiform reactions in two patients when metrizamide was used for lumbar myelography in the presence of chlorpromazine or dixyrazine. No such cases appear to have been reported for intrathecal iohexol: nevertheless, the manufacturer of iohexol advises the avoidance of phenothiazines and other drugs that lower seizure threshold when iohexol is used intrathecally. Phenothiazines should also be avoided if iomeprol is required, and also if iopamidol is used for neuroradiological procedures.

Clinical evidence

A patient receiving long-term treatment with **chlorpromazine** 75 mg daily had a grand mal seizure three-and-a-half hours after being given **metrizamide** (16 mL of 170 mg iodine per mL by the lumbar route). He had another seizure 5 hours later.[1] One out of 34 other patients demonstrated epileptogenic activity on an EEG when given **metrizamide** for lumbar myelography. The patient was taking **dixyrazine** 10 mg three times daily.[2] However, a clinical study in 26 patients given **levomepromazine** for

the relief of lumbago-sciatic pain found no evidence of an increased risk of seizures after they were given **metrizamide** for myelography.[3]

Mechanism

Intrathecal metrizamide or iohexol alone are rarely associated with seizures. Theoretically, this risk might be increased in patients taking other drugs that lower the seizure threshold, such as the phenothiazines.

Importance and management

The case report with intrathecal metrizamide led to the advice to stop phenothiazines before giving this contrast agent.[4] Intrathecal iohexol has also rarely been associated with seizures, and consequently the US manufacturer recommends that drugs that lower the seizure threshold, especially phenothiazines, are not recommended for use with iohexol by this route.[5] They should be stopped 48 hours before the procedure and not restarted until at least 24 hours after the procedure. The manufacturer of **iomeprol** gives the same advice.[6] However, the manufacturer of **iopamidol** advises that stopping phenothiazines is only necessary during neuroradiological use; the phenothiazine should be stopped 48 hours before the procedure and not restarted until at least 12 hours after the procedure has finished.[7] This advice specifically includes phenothiazines used for their antiemetic properties, for example, prochlorperazine. Although this risk is theoretical this would seem to be a prudent precaution. This advice does not apply to other routes of iohexol administration.[5]

1. Hindmarsh T, Grepe A and Widen L. Metrizamide-phenothiazine interaction. Report of a case with seizures following myelography. *Acta Radiol Diagnosis* (1975) 16, 129–34.
2. Hindmarsh T. Lumbar myelography with meglumine iocarmate and metrizamide. *Acta Radiol Diagnosis* (1975) 16, 209–22.
3. Standnes B, Oftedal S-I, Weber H. Effect of levomepromazine on EEG and on clinical side effects after lumbar myelography with metrizamide. *Acta Radiol Diagnosis* (1982) 23, 111–14.
4. Fedutes BA, Ansani NT. Seizure potential of concomitant medications and radiographic contrast media agents. *Ann Pharmacother* (2003) 37, 1506–10.
5. Omnipaque (Iohexol). GE Healthcare Inc. US Prescribing information, September 2007.
6. Iomeron (Iomeprol). Bracco UK Ltd. UK Summary of product characteristics, September 2008.
7. Niopam (Iopamidol). Bracco UK Ltd. UK Summary of product characteristics, July 2005.

Contrast media + Rifampicin (Rifampin)

Rifampicin may impair biliary excretion of contrast media.

Clinical evidence, mechanism, importance and management

The manufacturers of rifampicin advise that tests involving contrast media visualisation of the gall bladder should be undertaken before the morning dose of rifampicin, given orally[1,2] or before the daily dose of rifampicin given parenterally,[3] as biliary excretion of the contrast media may be impaired.

1. Rifater Tablets (Rifampicin, Isoniazid and Pyrazinamide). Sanofi-Aventis. UK Summary of product characteristics, March 2009.
2. Rifadin (Rifampicin). Sanofi-Aventis US LLC. US Prescribing information, March 2007.
3. Rifadin for Infusion (Rifampicin). Sanofi-Aventis. UK Summary of product characteristics, March 2009.

Contrast media; Iopanoic acid + Colestyramine

A single report describes poor radiographic visualisation of the gall bladder due to an interaction between iopanoic acid and colestyramine within the gut.

Clinical evidence, mechanism, importance and management

The cholecystogram of a man with post-gastrectomy syndrome taking colestyramine, who was given oral iopanoic acid as an X-ray contrast medium, suggested that he had an abnormal and apparently collapsed gall bladder. A week after stopping the colestyramine a repeat cholecystogram gave excellent visualisation of a gall bladder of normal appearance.[1] The same effects have been observed experimentally in *dogs*.[1] This effects probably occurs because colestyramine binds with the iopanoic acid in the gut so that little is absorbed and little is available for secretion in the bile, hence the poor visualisation of the gall bladder.

On the basis of reports about other drugs that similarly bind to colestyramine, it seems probable that this interaction could be avoided if the administration of iopanoic acid and colestyramine were to be separated as much as possible (note that it is usually recommended that other drugs are given 1 hour before or 4 to 6 hours after colestyramine). Whether other oral acidic X-ray contrast media bind in a similar way to colestyramine is uncertain, but this possibility should be considered.

1. Nelson JA. Effect of cholestyramine on telepaque oral cholecystography. *Am J Roentgenol Radium Ther Nucl Med* (1974) 122, 333–4.

Cyclobenzaprine + Fluoxetine and Droperidol

A patient taking cyclobenzaprine and fluoxetine developed torsade de pointes and ventricular fibrillation when droperidol was also taken.

Clinical evidence

A 59-year-old woman receiving long-term treatment with fluoxetine and cyclobenzaprine, and who had a prolonged baseline QTc interval of 497 milliseconds, was given droperidol before surgery on her Achilles tendon. During the surgery she developed torsade de pointes arrhythmia, which progressed to ventricular fibrillation. On the first postoperative day after the cyclobenzaprine had been withdrawn, her QTc interval had decreased towards normal (440 milliseconds).[1]

Mechanism

The authors suggested that fluoxetine might have raised cyclobenzaprine serum levels by inhibition of cytochrome P450 (possibly the isoenzyme CYP3A4, which is involved in the metabolism of cyclobenzaprine), and as a result the patient's QTc interval was prolonged. Cyclobenzaprine can cause arrhythmias, particularly in high doses. Therefore the addition of droperidol, which is known to prolong the QT interval, might have further extended the QTc interval and precipitated the torsade de pointes.

Importance and management

This is an isolated report, nevertheless, it is possible that a pharmacokinetic interaction occurs between cyclobenzaprine and fluoxetine, and that additive QT prolonging effects occur with cyclobenzaprine and droperidol, see also 'drugs that prolong the QT interval', (p.290). Some caution would be appropriate with concurrent use.

1. Michalets EL, Smith LK, Van Tassel ED. Torsade de pointes resulting from the addition of droperidol to an existing cytochrome P450 drug interaction. *Ann Pharmacother* (1998) 32, 761–5.

Cyclobenzaprine + Serotonergic drugs

Two cases of possible serotonin syndrome have been described in patients given cyclobenzaprine while taking serotonergic drugs (phenelzine and oxycodone in one case, and duloxetine, bupropion and oxycodone in the other).

Clinical evidence

A 70-year-old woman who had been taking **phenelzine** 15 mg four times daily for several years underwent surgery for an infected hip replacement. She was receiving cefazolin and, for pain, paracetamol and **oxycodone**. Six days later she started to take cyclobenzaprine 10 mg three times daily for muscle spasm. After the third dose she became confused, agitated, febrile and tachycardic. Cyclobenzaprine and oxycodone were stopped, with no improvement in her condition. Eventually a diagnosis of serotonin syndrome was suspected, and phenelzine was also stopped. She recovered over the subsequent 3 days.[1]

In a similar case, a 53-year-old man taking **duloxetine**, pregabalin, **bupropion** and **oxycodone** or hydromorphone as needed, underwent orthopaedic surgery and was given cyclobenzaprine 10 mg three times daily. Five days after surgery he became tachycardic and markedly agitated, and developed excessive sweating; he eventually required sedation and intubation. Cyclobenzaprine and duloxetine were stopped, and he was treated with cyproheptadine (a serotonin antagonist), and recovered over the following 2 days.[1]

Mechanism

The combined use of serotonergic drugs can, rarely, precipitate the 'serotonin syndrome', (p.9). Cyclobenzaprine is structurally related to the tricyclic antidepressants and might therefore have serotonergic effects, which could be additive with known serotonergic drugs.

Importance and management

These cases illustrate the potential for serotonin syndrome to develop when multiple drugs with serotonergic effects (such as the MAOIs, some opioids, SNRIs) are given together. Although case reports for cyclobenzaprine are generally lacking, based on the way tricyclics (which are related to cyclobenzaprine) are known to interact with MAOIs, it would seem prudent to avoid the concurrent use of cyclobenzaprine and MAOIs: note that the US manufacturer of cyclobenzaprine[2] contraindicates concurrent use.

1. Keegan MT, Brown DR, Rabinstein AA. Serotonin syndrome from the interaction of cyclobenzaprine with other serotoninergic drugs. *Anesth Analg* (2006) 103, 1466–8.
2. Amrix (Cyclobenzaprine hydrochloride). Cephalon Inc. US Prescribing information, December 2008.

Dantrolene + Metoclopramide

Metoclopramide increases the bioavailability of dantrolene.

Clinical evidence, mechanism, importance and management

A study in 7 paraplegics and 6 quadriplegics with spinal cord injuries found that a single 10-mg intravenous dose of metoclopramide increased the bioavailability of a single 100-mg oral dose of dantrolene by 57%. The reasons for this effect are not known, although it was suggested that absorption may have been affected. The clinical relevance of this interaction is uncertain but the authors of the study suggest that patients should be well monitored if metoclopramide is added or withdrawn from patients who are taking dantrolene.[1]

1. Gilman TM, Segal JL, Brunnemann SR. Metoclopramide increases the bioavailability of dantrolene in spinal cord injury. *J Clin Pharmacol* (1996) 36, 64–71.

Dantrolene + Oestrogens

The concurrent use of dantrolene and oestrogens might increase the risk of hepatotoxicity.

Clinical evidence, mechanism, importance and management

Dantrolene can cause hepatotoxicity, and risk factors include female gender, age over 30 years, and concurrent use of other hepatotoxic drugs.[1,2] The manufacturers also state that dantrolene-related hepatotoxicity in women aged over 35 years appears to be more common in those taking oestrogens.[1] They say that, while a definitive interaction has not been established, caution is recommended on concurrent use.[2] In practice, this means that patients should be advised to seek medical advice if they develop symptoms such as generalised itching, yellowing of the eyes or skin, weight loss, nausea, or vomiting.

1. Dantrium Capsules (Dantrolene sodium). SpePharm UK Ltd. UK Summary of product characteristics, September 2008.
2. Dantrium Capsules (Dantrolene sodium). Procter & Gamble Pharmaceuticals. US Prescribing information, September 2002.

Dextromethorphan + Amiodarone

Amiodarone can modestly reduce the clearance of dextromethorphan.

Clinical evidence

A study in 8 patients with cardiac arrhythmias found that amiodarone (1 g daily for 10 days followed by 200 to 400 mg daily for a mean duration of 76 days) changed their excretion of dextromethorphan 40 mg and its metabolite. The amount of unchanged dextromethorphan in the urine rose by nearly 150%, whereas the amount of its metabolite (dextrorphan) fell by about 25%.[1] All patients were of extensive CYP2D6 metaboliser phenotype (that is, they had normal levels of this isoenzyme) before amiodarone, and the effect of the amiodarone was modest (did not change them into pseudo-poor metabolisers, that is, those lacking or deficient in this isoenzyme).[1]

Mechanism

In vitro studies using liver microsomes have shown that amiodarone inhibits the metabolism (*O*-demethylation) of dextromethorphan by inhibiting the cytochrome P450 isoenzyme CYP2D6 within the liver.[1] This will occur in extensive metabolisers, but not poor metabolisers of this isoenzyme, see 'Genetic factors in drug metabolism', (p.4), for further discussion of metaboliser phenotypes.

Importance and management

Information seems to be limited to this study. The implications are that amiodarone might interfere with the results of phenotyping if dextromethorphan is used to determine CYP2D6 activity. The extent of the interaction is unlikely to be clinically relevant in patients taking dextromethorphan, since this drug has a wide therapeutic index and its dose is not individually titrated.

1. Funck-Brentano C, Jacqz-Aigrain E, Leenhardt A, Roux A, Poirier J-M, Jaillon P. Influence of amiodarone on genetically determined drug metabolism in humans. *Clin Pharmacol Ther* (1991) 50, 259–66.

Dextromethorphan + Bupropion

Bupropion may reduce the metabolism of dextromethorphan in some patients.

Clinical evidence, mechanism, importance and management

In a study in 21 subjects who were quitting smoking and were CYP2D6 extensive metabolisers (that is, those with normal levels of this isoenzyme), 6 of 13 subjects who received bupropion 150 mg daily for 3 days and then twice daily for 14 days had metabolic ratios of dextromethorphan 30 mg similar to those seen in poor metabolisers (that is, those lacking or deficient in this isoenzyme): the metabolism of dextromethorphan to dextrorphan was substantially reduced. No such change was seen in the 8 subjects who received placebo.[1]

This suggests that bupropion can inhibit the cytochrome P450 isoenzyme CYP2D6, and is sufficiently potent an inhibitor to change up to half of extensive metabolisers into 'pseudo' poor metabolisers.

It has been suggested that care should be taken when initiating or discontinuing bupropion in patients taking CYP2D6 substrates, due to the possibility of raised levels.[1] Dextromethorphan is used as a probe substrate for CYP2D6, and is generally considered to have a wide therapeutic range and its dose is not individually titrated; therefore, the interaction with bupropion is unlikely to be clinically relevant. Nevertheless, it is possible that some extensive metaboliser patients might become more sensitive to the adverse effects of dextromethorphan while taking bupropion.

1. Kotlyar M, Brauer LH, Tracy TS, Hatsukami DK, Harris J, Bronars CA, Adson DE. Inhibition of CYP2D6 activity by bupropion. *J Clin Psychopharmacol* (2005) 25, 226–9.

Dextromethorphan + Celecoxib

Celecoxib modestly increases the plasma levels of dextromethorphan.

Clinical evidence, mechanism, importance and management

The manufacturers of celecoxib note that the plasma levels of dextromethorphan have been increased by 136% in the presence of celecoxib. Celecoxib inhibits the cytochrome P450 isoenzyme CYP2D6 and thus inhibits the metabolism of dextromethorphan by this isoenzyme.[1]

Dextromethorphan is used as a probe substrate for CYP2D6, and is generally considered to have a wide therapeutic range and its dose is not individually titrated; therefore, its interaction with celecoxib is unlikely to be clinically relevant. However, based on this pharmacokinetic interaction, the manufacturers of celecoxib suggest that caution should be observed with drugs that have a narrow therapeutic margin and are known to be predominantly metabolised by CYP2D6. They mention tricyclics, SSRIs, neuroleptics, and anti-arrhythmics, although not all drugs in these classes

are important CYP2D6 substrates (for a list of CYP2D6 substrates, see 'Table 1.3', (p.6)). They say that the dose of CYP2D6 substrates may need to be decreased on starting celecoxib and increased on stopping it.[1] However, celecoxib is a very moderate CYP2D6 inhibitor when compared with the known potent CYP2D6 inhibitors cinacalcet and quinidine, and therefore any interactions with celecoxib as a result of this mechanism would, at worst, only be expected to be of only modest clinical relevance. So far there appear to be no direct clinical reports of any problems with concurrent use.

1. Celebrex (Celecoxib). Pharmacia Ltd. UK Summary of product characteristics, June 2009.

Dextromethorphan + Cinacalcet

Cinacalcet very markedly increases dextromethorphan levels.

Clinical evidence

In a pharmacokinetic study in 23 healthy subjects who were extensive CYP2D6 metabolisers (that is, those with normal levels of this isoenzyme), the AUC of a single 30-mg dose of dextromethorphan was very markedly increased (by 11.4-fold) when given on day 8 of cinacalcet 50 mg daily for 8 days.[1]

Mechanism

In *vitro*, cinacalcet is a potent inhibitor of the cytochrome P450 isoenzyme CYP2D6, comparable to the well-known potent CYP2D6 inhibitor quinidine. This human study with the CYP2D6 probe substrate dextromethorphan confirms that cinacalcet is a clinically important CYP2D6 inhibitor.

Importance and management

A pharmacokinetic interaction between cinacalcet and dextromethorphan is established. However, dextromethorphan has a wide therapeutic range, and its dose is not individually titrated, so the interaction with cinacalcet is unlikely to be generally clinically relevant. Nevertheless, it is possible that some extensive metaboliser patients might become more sensitive to the adverse effects of dextromethorphan while taking cinacalcet.

Dextromethorphan is also used as a probe substrate for CYP2D6. These results therefore also suggest that cinacalcet will increase the levels of drugs that are substrates for CYP2D6. However, this will occur only in individuals who are extensive metabolisers. Poor metabolisers lack or have low levels of CYP2D6, and would not be affected. The effect of cinacalcet on CYP2D6 is likely to be important for CYP2D6 substrates that have a narrow therapeutic window. For a list of drugs that are CYP2D6 substrates, see 'Table 1.3', (p.6).

1. Nakashima D, Takama H, Ogasawara Y, Kawakami T, Nishitoba T, Hoshi S, Uchida E, Tanaka H. Effect of cinacalcet hydrochloride, a new calcimimetic agent, on the pharmacokinetics of dextromethorphan: in vitro and clinical studies. *J Clin Pharmacol* (2007) 47, 1311–19.

Dextromethorphan + Grapefruit and other fruit juices

Grapefruit juice and the juice of the bitter orange increase the absorption of dextromethorphan.

Clinical evidence, mechanism, importance and management

In a study, 11 healthy subjects were given single 30-mg doses of dextromethorphan at bedtime, followed by 200 mL of water, 200 mL of grapefruit juice (prepared by diluting 1 part of 100% pure frozen concentrate, *Minute Maid*, with 3 parts water) or 200 mL of freshly-squeezed juice of the bitter orange. Measurement of the amount of dextromethorphan and its metabolites in the urine indicated that the bioavailability of dextromethorphan was increased by more than fivefold by grapefruit juice and by more than fourfold by bitter orange juice. Dextromethorphan levels were still raised 3 days later, indicating a sustained effect of the juices.

It was suggested that these fruit juices increased the absorption of dextromethorphan through the gut wall by inhibiting the cytochrome P450 isoenzyme CYP3A and P-glycoprotein.[1] The authors did not report any adverse effects of the increased exposure to dextromethorphan in these subjects, and dextromethorphan is generally considered to have a wide therapeutic range and the dose is not individually titrated. Therefore, the interaction with these fruit juices is probably unlikely to be clinically relevant. Note that, bitter orange is a different species to oranges that are usually consumed as part of the diet, and these results are not applicable to conventional orange juice.

1. Di Marco MP, Edwards DJ, Wainer IW, Ducharme MP. The effect of grapefruit juice and seville orange juice on the pharmacokinetics of dextromethorphan: the role of gut CYP3A and P-glycoprotein. *Life Sci* (2002) 71, 1149–60.

Dextromethorphan + Quinidine

Quinidine markedly increases the plasma levels of dextromethorphan in those who have normal levels of CYP2D6. This effect is maximal at low doses of quinidine (25 to 30 mg).

Clinical evidence

In a study, 6 subjects with normal levels of CYP2D6 (extensive metabolisers) were given dextromethorphan 60 mg twice daily. Steady-state plasma dextromethorphan levels averaged only 12 nanograms/mL. However, after being given quinidine 75 mg twice daily for a week, then a single 60-mg dose of dextromethorphan, their plasma levels of dextromethorphan were over threefold higher, at 38 nanograms/mL.[1] Some of the patients given the combination had an increase in dextromethorphan adverse effects (nervousness, tremors, restlessness, dizziness, shortness of breath, confusion etc).[1] Similarly, other pharmacokinetic studies have found increases in dextromethorphan levels in extensive CYP2D6 metabolisers, but not in those totally lacking or deficient in this isoenzyme (poor metabolisers).[2-4] In a dose-ranging study, quinidine 25 to 30 mg daily produced maximal increases in dextromethorphan levels, with higher doses producing no further increases, and lower doses producing smaller increases.[5] In one experimental study of citric acid-induced cough, quinidine increased the cough-suppressant effect of dextromethorphan.[6,7]

Mechanism

Quinidine inhibits the oxidative metabolism of dextromethorphan by the cytochrome P450 isoenzyme CYP2D6 to dextrorphan, effectively making extensive metabolisers of CYP2D6 into the poor metaboliser phenotype, see 'Genetic factors in drug metabolism', (p.4), for further discussion of metaboliser phenotypes.

Importance and management

An established interaction. Dextromethorphan is used as a probe substrate for CYP2D6, and is generally considered to have a wide therapeutic range, and its dose is not individually titrated; therefore, the interaction with quinidine is unlikely to be clinically relevant. Nevertheless, it is possible that some extensive metabolisers of CYP2D6 might become more sensitive to the adverse effects of dextromethorphan if they are taking quinidine. This effect is maximal at low doses of quinidine (25 to 30 mg).

Low-dose quinidine has been given with dextromethorphan to sustain therapeutic levels of dextromethorphan and thereby try and improve its efficacy in various neurological disorders (dextromethorphan is a *N*-methyl-D-aspartate antagonist, which means it can affect pain transmission). A fixed dose combination is being investigated.[8]

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2. Schadel M, Wu D, Otton SV, Kalow W, Sellers EM. Pharmacokinetics of dextromethorphan and metabolites in humans: influence of CYP2D6 phenotype and quinidine inhibition. *J Clin Psychopharmacol* (1995) 15, 263–9.
3. Desmeules JA, Oestreicher MK, Piguet V, Allaz A-F, Dayer P. Contribution of cytochrome P-4502D6 phenotype to the neuromodulatory effects of dextromethorphan. *J Pharmacol Exp Ther* (1999) 288, 607–12.
4. Capon DA, Bochner F, Kerry N, Mikus G, Danz C, Somogyi AA. The influence of CYP2D6 polymorphism and quinidine on the disposition and antitussive effect of dextromethorphan in humans. *Clin Pharmacol Ther* (1996) 60, 295–307.
5. Pope LE, Khalil MH, Berg JE, Stiles M, Yakatan GJ, Sellers EM. Pharmacokinetics of dextromethorphan after single or multiple dosing in combination with quinidine in extensive and poor metabolizers. *J Clin Pharmacol* (2004) 44, 1132–42.
6. Abdul Manap R, Wright CE, Gregory A, Rostami-Hodjegan A, Meller ST, Kelm GR, Lennard MS, Tucker GT, Morice AH. The antitussive effect of dextromethorphan in relation to CYP2D6 activity. *Br J Clin Pharmacol* (1999) 48, 382–7.

7. Moghadamnia AA, Rostami-Hodjegan A, Abdul-Manap R, Wright CE, Morice AH, Tucker GT. Physiologically based modelling of inhibition of metabolism and assessment of relative potency of drug and metabolite: dextromethorphan vs. dextrorphan using quinidine inhibition. *Br J Clin Pharmacol* (2003) 56, 57–67.
8. Anon. Dextromethorphan/quinidine: AVP 923, dextromethorphan/cytochrome P450-2D6 inhibitor, quinidine/dextromethorphan. *Drugs R D* (2005) 6, 174–7.

Disulfiram + Celecoxib

An isolated report describes encephalopathy and polyneuropathy which developed in an elderly patient taking disulfiram when she was also given celecoxib and citalopram.

Clinical evidence, mechanism, importance and management

An elderly, chronic alcoholic patient who had been taking disulfiram 400 mg daily for 4 months was given citalopram 20 mg daily and celecoxib. She became apathetic and confused and also developed ataxia, and was found to have vascular encephalopathy and polyneuropathy. Encephalopathy and polyneuropathy may occur with disulfiram alone, but the authors suggest that it is rare, and only usually occurs in overdose. However, it was suggested that in this case an interaction between either celecoxib or citalopram and disulfiram may have resulted in toxic levels of disulfiram, or that disulfiram had inhibited citalopram and/or celecoxib metabolism and increased their levels. Some of the central effects may have been due to additive effects of the individual drugs.[1]

This appears to be an isolated case, and an interaction is by no means established. No general conclusions can therefore be drawn.

1. Berger A, Pategay N, Vogt N. Encéphalopathie aiguë et polyneuropathie au disulfiram: toxicité propre et interactions. Acute encephalopathy and polyneuropathy secondary to disulfiram administration: self toxicity and interactions. *Therapie* (2002) 57, 505–7.

Enteric-coated, delayed-release preparations + Drugs that affect gastric pH

Theoretically, enteric-coated, delayed-release preparations may possibly dissolve prematurely if they are taken at the same time as antacids. This has been seen with some preparations, but not others. Release characteristics are likely to depend on the specific coating, and the manufacturers advice should be followed.

Clinical evidence

(a) Antacid

A placebo-controlled, crossover study in 21 healthy subjects, found that when extended-release **oxybutynin** 10 mg (*Ditropan XL*) was given at the same time as *Maalox* 20 mL (**aluminium**/**magnesium hydroxide** and **simeticone**) there was no change in the pharmacokinetics of **oxybutynin** or its metabolite.[1]

In an identical study in 23 healthy subjects, *Maalox* increased the maximum plasma level of a single 4-mg dose of extended-release **tolterodine** (*Detrol LA*) by 50%, but did not change the time to maximum level, elimination half-life, or AUC of **tolterodine**.[1]

(b) Omeprazole

In a placebo-controlled, crossover study in 39 healthy subjects, pre-treatment with omeprazole 20 mg daily for 4 days did not alter the pharmacokinetics of extended-release **oxybutynin** 10 mg [*Ditropan XL*]. The metabolites of **oxybutynin** were similarly unaffected. Pre-treatment with omeprazole increased the maximum plasma level of a single 4-mg dose of extended release **tolterodine** [*Detrol LA*] by 38%, but did not change the time to maximum level, elimination half-life, or AUC of **tolterodine**.[2]

The bioavailability of enteric-coated preparations of aspirin, diclofenac, and ketoprofen are unaffected by omeprazole, see 'NSAIDs or Aspirin + Proton pump inhibitors', p.171.

Mechanism

A marked rise in pH caused by antacids might cause premature dissolution of the coating of preparations formulated to prevent release of the contents until they reach the more alkaline conditions within the small intestine. Other types of delayed release preparations that have release characteristics independent of pH, such as those based on the osmotic principle, would not be expected to be affected.

Importance and management

Traditionally, it has been considered that drugs formulated with enteric coatings to resist gastric acid, or formulated as delayed-release preparations, should not be given with antacids. Accelerated drug release from a delayed-release product (dose dumping) might lead to increased adverse effects and lack of efficacy for the duration of the dose interval. The evidence above for extended-release tolterodine suggests that an antacid did cause a faster release of tolterodine from this product, but whether the 50% increase in the maximum level is sufficient to cause an increase in adverse effects is not known. Pre-treatment with omeprazole caused a smaller 38% increase in maximum tolterodine levels. The extended-release oxybutynin product was not affected by antacid or omeprazole, which was not unexpected because release from this product is osmotically driven and pH independent.

Release characteristics are likely to depend on the specific coating, and therefore no general advice can be given. The manufacturers' advice should be followed.

1. Sathyan G, Dmochowski RR, Appell RA, Guo C, Gupta SK. Effect of antacid on the pharmacokinetics of extended-release formulations of tolterodine and oxybutynin. *Clin Pharmacokinet* (2004) 43, 1059–68.
2. Dmochowski R, Chen A, Sathyan G, MacDiarmid S, Gidwani S, Gupta S. Effect of the proton pump inhibitor omeprazole on the pharmacokinetics of extended-release formulations of oxybutynin and tolterodine. *J Clin Pharmacol* (2005) 45, 961–8.

Ethylene dibromide + Disulfiram

The very high incidence of malignant tumours in *rats* exposed to both ethylene dibromide and disulfiram is the basis of the recommendation that concurrent exposure to these compounds should be avoided.

Clinical evidence, mechanism, importance and management

Research conducted to establish the occupational safety of exposure to ethylene dibromide found that the incidence of malignant tumours in *rats* exposed to 20 ppm ethylene dibromide (7 hours daily, 5 days weekly), while receiving a diet containing 0.05% disulfiram by weight, is very high indeed.[1,2] The reasons are not understood. In addition to the precautions needed to protect workers from the toxic effects of ethylene dibromide, it has been strongly recommended that disulfiram should not be given to those who may be exposed to this compound.[2] This information is also summarised in another report.[3]

1. Plotnick HB. Carcinogenesis in rats of combined ethylene dibromide and disulfiram. *JAMA* (1978) 239, 1609.
2. Anon. Ethylene dibromide and disulfiram toxic interaction. National Institute for Occupational Safety and Health Current Intelligence Bulletin. *US Department of Health, Education and Welfare Publication* (1978) No 78–145.
3. Stein HP, Bahlman LJ, Leidel NA, Parker JC, Thomas AW, Millar JD. Ethylene dibromide and disulfiram toxic interaction. *Am Ind Hyg Assoc J* (1978) 39, A35–A37.

Glucagon + Beta blockers

The blood glucose-elevating effects of glucagon may be reduced by propranolol and possibly other beta blockers.

Clinical evidence, mechanism, importance and management

In a study in 5 healthy subjects the blood glucose-elevating effect of glucagon was reduced in the presence of **propranolol**.[1] Blood glucose levels increased by about 45% in the presence of glucagon, but when **propranolol** was also given the increase was only about 15%. The reason for this effect is uncertain, but one suggestion is that the **propranolol** inhibits the effects of the catecholamines that are released by glucagon. If this mechanism is correct, it seems possible that other beta blockers may interact in the same way as **propranolol**. However, the clinical importance of the interaction is uncertain.

Note that glucagon may be used for treating beta blocker poisoning.

1. Messerli FH, Kuchel O, Tolis G, Hamet P, Frayasse J, Genest J. Effects of β-adrenergic blockage on plasma cyclic AMP and blood sugar responses to glucagon and isoproterenol in man. *Int J Clin Pharmacol Biopharm* (1976) 14, 189–94.

Iron chelators + Ascorbic acid (Vitamin C)

High-dose vitamin C may cause cardiac disorders in some patients given desferrioxamine (deferoxamine). Other iron chelators are expected to interact similarly.

Clinical evidence, mechanism, importance and management

Vitamin C is given with iron chelators to patients with iron overload because it mobilises iron stores and thus promotes the excretion of iron. One study in 11 patients with thalassaemia noted that a striking deterioration in left ventricular function occurred when the patients were given 500 mg of vitamin C with intramuscular **desferrioxamine** (deferoxamine). In most patients left ventricular function returned to normal when the vitamin C was stopped.[1] For this reason it has been suggested that vitamin C should be used with **desferrioxamine** with caution,[2] only where there is a demonstrated need,[3] and in the lowest possible dose.[1] The manufacturers of **desferrioxamine** recommend that a maximum daily dose of 200 mg of vitamin C should be used in adults, that vitamin C should not be given within the first month of **desferrioxamine** treatment, that cardiac function should be monitored during combined use, and that vitamin C should not be given to those with cardiac failure.[4,5]

The manufacturers of **deferasirox** note that, although concurrent use with vitamin C has not been formally studied, doses of vitamin C up to 200 mg daily were allowed in clinical studies of **deferasirox** without adverse consequences.[6,7]

The manufacturer of **deferiprone** advise caution with the use of vitamin C, based on the way desferrioxamine is expected to interact.[8] It would therefore seem prudent to follow similar precautions to those advised with the other iron chelators.

1. Henry W. Echocardiographic evaluation of the heart in thalassemia major. *Ann Intern Med* (1979) 91, 892–4.
2. Cohen A, Cohen IJ, Schwartz E. Scurvy and altered iron stores in thalassemia major. *N Engl J Med* (1981) 304, 158–60.
3. Nienhuis AW. Vitamin C and iron. *N Engl J Med* (1981) 304, 170–1.
4. Desferal Vials (Desferrioxamine mesilate). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, August 2006.
5. Desferal Vials (Deferoxamine mesylate). Novartis. US Prescribing information, November 2007.
6. Exjade (Deferasirox). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, March 2009.
7. Exjade (Deferasirox). Novartis. US Prescribing information, April 2009.
8. Ferriprox (Deferiprone). Swedish Orphan International. UK Summary of product characteristics, October 2008.

Iron chelators + Miscellaneous

Food increases the bioavailability of deferasirox but does not affect deferiprone. The use of deferasirox and deferiprone with aluminium antacids is not recommended. Rifampicin (rifampin) reduces the exposure to deferasirox: carbamazepine, phenobarbital, phenytoin, and ritonavir are predicted to interact similarly. Deferasirox increases the levels of midazolam and repaglinide. Other drugs that have similar routes of metabolism are also expected to be affected (e.g. ciclosporin, paclitaxel). Hydroxycarbamide does not alter deferasirox metabolism. Additive blood dyscrasias may occur if hydroxycarbamide is used with deferiprone. Bisphosphonates, corticosteroids, and NSAIDs (including analgesic dose aspirin) may increase the risk of gastrointestinal ulceration with deferasirox. Deferasirox may increase the risk of bleeding with anticoagulants. Deferasirox does not appear to alter the pharmacokinetics of digoxin.

Clinical evidence, mechanism, importance and management

(a) Aluminium-containing antacids

Although concurrent use has not been formally studied, the manufacturer recommends that **deferasirox** is not taken with aluminium-containing antacids.[1,2] **Deferasirox** has a lower affinity for aluminium than for iron, but theoretically aluminium might reduce the efficacy of **deferasirox**. Similar precautions are advised with **deferiprone**.[3]

(b) CYP2C8 substrates

In a study in healthy subjects, **deferasirox** 30 mg/kg daily for 4 days increased the AUC of a single 500-microgram dose of **repaglinide** 2.3-fold and increased its maximum levels by 62%.[1,2] The manufacturers advise monitoring blood glucose levels closely and giving consideration to reducing the **repaglinide** dose. The UK manufacturers advise against doses of **repaglinide** greater than 500 micrograms.[1,2] On the basis of this study, caution is advised with other CYP2C8 substrates, and **paclitaxel** is specifically named.[1,2]

See 'Table 1.3', (p.6), for a list of clinically relevant CYP2C8 substrates.

(c) CYP3A4 substrates

In a study in healthy subjects, **deferasirox** decreased the peak levels of **midazolam** (a probe substrate for the cytochrome P450 isoenzyme CYP3A4) by 23% and decreased the exposure to **midazolam** by 17%. Changes of this magnitude would not be expected to be clinically relevant. However, the manufacturers cautiously suggest that the effect may be greater in a clinical setting, and so advise caution if **deferasirox** is given with **midazolam**, or other substrates of CYP3A4 (they name **ciclosporin** (**cyclosporine**), **ergotamine**, **hormonal contraceptives** and **simvastatin**).[1,2]

(d) Digoxin

In a randomised study in 15 healthy subjects[4], the pharmacokinetics of digoxin (500 micrograms on day 1, and then 250 micrograms daily on days 2 to 8) were not affected by a single 20-mg/kg oral dose of **deferasirox**, given on day 8. No digoxin dose adjustment would be expected to be necessary on concurrent use.

(e) Food

In single-dose studies in healthy subjects, giving **deferasirox** 30 minutes before a high-fat breakfast, 30 minutes before a standard breakfast, or with a standard breakfast modestly increased the AUC by 18%, 29% and 31%, respectively, when compared with the fasted state. In a further study in 12 patients with iron overload, giving **deferasirox** 5 minutes before a high-fat breakfast increased the AUC by 62% when compared with the fasted state. Nevertheless the concentration of iron-**deferasirox** complex in plasma was unaffected by timing in relation to food.[5] However, the manufacturer recommends that, to limit variability, **deferasirox** is taken on an empty stomach at least 30 minutes before food.[1,2]

In a further study, the AUC of **deferasirox** was not significantly different when the tablets for oral suspension were dispersed in water, orange juice, or apple juice.[6] Therefore, any of these drinks is suitable for dispersion.[1,2]

Food does not appear to decrease the absorption of **deferiprone**.[3]

(f) Hydroxycarbamide

In vitro, hydroxycarbamide did not inhibit the metabolism of **deferasirox**.[1,2]

Note that hydroxycarbamide can cause neutropenia, and the manufacturer of **deferiprone** advises against its concurrent use with other drugs that may cause neutropenia or agranulocytosis.[3]

(g) UGT enzyme inducers

In a study in healthy subjects, **rifampicin** (**rifampin**) 600 mg daily for 9 days reduced the AUC of a single 30 mg/kg dose of **deferasirox** by 44%.The mechanism for this interaction was thought to be UGT induction, and therefore caution is warranted with other drugs said to induce this enzyme, such as **carbamazepine**, **phenobarbital**, **phenytoin** and **ritonavir**. The manufacturers recommend that the efficacy of **deferasirox** (serum ferritin levels and clinical response) should be monitored if any of these drugs is started or stopped, and the dose of **deferasirox** adjusted if necessary.[1,2] The US manufacturer does not recommend exceeding a maximum dose of 40 mg/kg of deferasirox.[2]

(h) Other drugs

The manufacturers of **deferasirox** advise that caution is warranted in patients taking analgesic-dose **aspirin**, **bisphosphonates**, **corticosteroids** or **NSAIDs**. This is because **deferasirox** has caused gastrointestinal ulceration, which may be additive with these drugs. Furthermore, they advise caution with **anticoagulants** as the use of **deferasirox** may increase the risk of bleeding.[1,2]

1. Exjade (Deferasirox). Novartis Pharmaceuticals UK Ltd. UK Summary of product characteristics, March 2009.
2. Exjade (Deferasirox). Novartis. US Prescribing information, April 2009.
3. Ferriprox (Deferiprone). Swedish Orphan International. UK Summary of product characteristics, October 2008.

4. Sechaud R, Robeva A, Belleli R, Balez S. Absence of an effect of a single-dose deferasirox on the steady-state pharmacokinetics of digoxin. Int J Clin Pharmacol Ther (2008) 46, 519–26.
5. Galanello R, Piga A, Cappellini MD, Forni GL, Zappu A, Origa R, Dutreix C, Belleli R, Ford JM, Rivière G-J, Balez S, Alberti D, Séchaud R. Effect of food, type of food, and time of food intake on deferasirox bioavailability: recommendations for an optimal deferasirox administration regimen. J Clin Pharmacol (2008) 48, 428–35.
6. Séchaud R, Dutreix C, Balez S, Pommier F, Dumortier T, Morisson S, Brun E. Relative bioavailability of deferasirox tablets administered without dispersion and dispersed in various drinks. Int J Clin Pharmacol Ther (2008) 46, 102–8.

Iron chelators + Phenothiazines

Prochlorperazine caused unconsciousness in two patients receiving desferrioxamine (deferoxamine).

Clinical evidence, mechanism, importance and management

The use of prochlorperazine in 2 patients receiving **desferrioxamine** (deferoxamine) resulted in unconsciousness for 48 to 72 hours. It was suggested that the drug combination resulted in increased removal of iron from the central nervous system, thereby impairing noradrenergic and serotonergic systems.[1] It has also been suggested that **desferrioxamine**-induced damage of the retina may be more likely in the presence of phenothiazines.[2] It would seem wise to avoid the concurrent use of **desferrioxamine** and prochlorperazine. The manufacturer[3] of chlorpromazine predicts that a similar interaction may occur with chlorpromazine, but there seems to be no direct evidence of adverse interactions with chlorpromazine or any other phenothiazine. In addition, there appears to be no evidence of an interaction between the phenothiazines and other iron chelators

1. Blake DR, Winyard P, Lunec J, Williams A, Good PA, Crewes SJ, Gutteridge JMC, Rowley D, Halliwell B, Cornish A, Hider RC. Cerebral and ocular toxicity induced by desferrioxamine. *Q J Med* (1985) 56, 345–55.
2. Pall H, Blake DR, Good PA, Wynyard P, Williams AC. Copper chelation and the neuro-ophthalmic toxicity of desferrioxamine. *Lancet* (1986) ii, 1279.
3. Largactil (Chlorpromazine hydrochloride). Sanofi-Aventis. UK Summary of product characteristics, March 2009.

Memantine + Antidiabetics

The concurrent use of glibenclamide (glyburide) with metformin and memantine does not appear to affect the pharmacokinetics of these drugs.

Clinical evidence, mechanism, importance and management

In a study in 21 healthy subjects who took glibenclamide (glyburide) 1.25 mg with metformin 250 mg twice daily for 6 days, the administration of a single 20-mg dose of memantine did not result in any changes in the pharmacokinetics of any of the three drugs. Memantine did not reduce the glucose-lowering effects of either antidiabetic drug.[1] Evidence is limited, but dose adjustments would not appear to be necessary on concurrent use.

1. Rao N, Chou T, Ventura D, Abramowitz W. Investigation of the pharmacokinetic and pharmacodynamic interactions between memantine and glyburide/metformin in healthy young subjects: a single-center, multiple-dose, open-label study. *Clin Ther* (2005) 27, 1596–1606.

Memantine + Co-trimoxazole

A single case report describes myoclonus and confusion, which developed when a patient took memantine and co-trimoxazole or trimethoprim.

Clinical evidence, mechanism, importance and management

A 78-year-old woman who was taking memantine 15 mg daily in two divided doses took co-trimoxazole (trimethoprim 160 mg with sulfamethoxazole 800 mg) twice daily for 5 days for a urinary tract infection. During the course of treatment she developed significant upper extremity muscle twitching, confusion and agitation. These symptoms diminished on stopping the co-trimoxazole. The patient experienced a second, similar episode when she started to take trimethoprim 100 mg daily as prophylaxis for urinary tract infections. In light of a similar report of an interaction between the related drug, amantadine, and co-trimoxazole (see 'Amantadine + Co-trimoxazole', p.785) the authors of this report considered it was likely that the patient's symptoms were due to an interaction between memantine and trimethoprim.[1] Note that the patient was also taking a number of drugs, including hydrochlorothiazide, which has been suggested to reduce memantine renal excretion, see 'Memantine + Miscellaneous', below, for details.

1. Moellentin D, Picone C, Leadbetter E. Memantine-induced myoclonus and delirium exacerbated by trimethoprim. Ann Pharmacother (2008) 42, 443–7.

Memantine + Miscellaneous

The use of memantine, an NMDA antagonist, with other NMDA antagonists, such as amantadine, ketamine and dextromethorphan is predicted to increase the risk of adverse effects. Memantine is predicted to interact with other drugs eliminated by the same renal secretion mechanism, but no important interaction was seen with hydrochlorothiazide and triamterene.

Clinical evidence, mechanism, importance and management

(a) Interactions involving cytochrome P450 isoenzymes

The results of *in vitro* studies indicate that memantine is not likely to cause interactions by inducing or inhibiting the major cytochrome P450 isoenzymes involved in drug metabolism (CYP1A2, CYP2C9, CYP3A4).[1,2] However, an *in vitro* study has demonstrated that memantine may inhibit CYP2B6 at clinically relevant concentrations.[3] **Cyclophosphamide** and **ifosfamide** are substrates of this isoenzyme, but there are few other drugs that are metabolised by this route. No metabolic interaction as a result of this mechanism appears to have been described.[3] In addition, memantine is not significantly metabolised by the cytochrome P450 enzyme system, and is therefore not expected to undergo interactions as a result of this mechanism.[1]

(b) Other drugs eliminated by renal tubular secretion

Memantine is predicted to interact with other drugs that use the same renal cationic transport system leading to increased levels of memantine and/or the other drug. The manufacturer lists **cimetidine**, **ranitidine**, **hydrochlorothiazide**, metformin, **nicotine**, **procainamide**, **quinidine**, **quinine** and **triamterene** as possible examples.[1,2] However, in an interaction study, the concurrent use of memantine and **hydrochlorothiazide** with **triamterene** did not result in any change in the steady-state AUC of memantine or **triamterene**, and the AUC of **hydrochlorothiazide** showed a modest *reduction* of about 20%.[1] This degree of change is unlikely to be clinically relevant. Furthermore, a study with metformin found no interaction (see 'Memantine + Antidiabetics', above). Therefore, a clinically important interaction as a result of this mechanism seems unlikely.

(c) Other NMDA antagonists

Memantine is chemically related to **amantadine**, and the manufacturer advises that concurrent use should be avoided[2] or undertaken with caution[1] because of the increased risk of adverse CNS-related drug reactions such as psychosis.[2] Although there are no data, an increased risk is also predicted for **ketamine** and **dextromethorphan**, which are also NMDA antagonists. Avoidance of,[2] or caution with,[1] concurrent use is advised.

(d) Warfarin

The manufacturer of memantine notes that, although no causal relationship has been established, isolated cases of INR increases have been reported in patients taking warfarin. They suggest close monitoring of anticoagulant effects if both drugs are given.[1,2]

(e) Other drugs

Memantine might modify the effects of antispasmodic drugs such as **dantrolene** or **baclofen** and dosage adjustment might be required.[2] Memantine is predicted to enhance the effects of **antimuscarinics**, **levodopa** and

dopaminergic (**dopamine agonist**) drugs.[2] Memantine is predicted to reduce the effects of **barbiturates** and **antipsychotics**.[2]

1. Namenda (Memantine hydrochloride). Forest Pharmaceuticals, Inc. US Prescribing information, April 2007.
2. Ebixa (Memantine hydrochloride). Lundbeck Ltd. UK Summary of product characteristics, July 2009.
3. Micuda S, Mundlova L, Anzenbacherova E, Anzenbacher P, Chladek J, Fuksa L, Martinkova J. Inhibitory effects of memantine on human cytochrome P450 activities: prediction of in vivo drug interactions. *Eur J Clin Pharmacol* (2004) 60, 583–9.

Memantine + Urinary alkalinisers

Drugs that increase the pH of the urine (e.g. sodium bicarbonate, carbonic anhydrase inhibitors) may reduce the elimination of memantine.

Clinical evidence, mechanism, importance and management

In 12 healthy subjects, the clearance of memantine 10 mg daily was markedly reduced by about 80% when the urine was alkaline (pH 8) compared with acidic urine (pH 5). The maximum plasma memantine levels were not affected by the urinary pH, but the bioavailability of memantine was increased by almost 20%.[1] This might be expected to lead to memantine accumulation and an increase in adverse effects. Drugs that could interact via this mechanism include **sodium bicarbonate** and **carbonic anhydrase inhibitors**[2] [such as **acetazolamide**]. The clinical relevance of these findings does not appear to have been established. Consider the possibility of an interaction if patients taking memantine with a urinary alkaliniser develop memantine adverse effects (e.g. dizziness, headache, constipation).

1. Freudenthaler S, Meineke I, Schreeb K-H, Boakye E, Gundert-Remy U, Gleiter CH. Influence of urine pH and urinary flow on the renal excretion of memantine. *Br J Clin Pharmacol* (1998) 46, 541–6.
2. Namenda (Memantine hydrochloride). Forest Pharmaceuticals, Inc. US Prescribing information, April 2007.

Metyrapone + Miscellaneous

The results of the metyrapone test for Cushing's syndrome are unreliable in patients taking cyproheptadine or phenytoin. The manufacturer also states that barbiturates, antidepressants, some hormones, and antipsychotics may influence the results of the metyrapone test. Metyrapone may reduce the metabolism of paracetamol (acetaminophen).

Clinical evidence

(a) Cyproheptadine

In 9 a study in healthy subjects, pretreatment with cyproheptadine 4 mg every 6 hours, 2 days before and throughout a standard metyrapone test (750 mg every 4 hours for 6 doses), reduced the metyrapone-induced urinary 17-hydroxycorticosteroid response by 32%, and also reduced the serum 11-deoxycortisol response.[1]

(b) Paracetamol (Acetaminophen)

In a randomised study, 8 healthy subjects were given metyrapone 750 mg one hour before and 3 hours after a single 1-g dose of paracetamol. Metyrapone decreased the glucuronidation of paracetamol from about 52% to 36% of the dose. Although the formation of other metabolites were increased, overall paracetamol excretion in the urine was decreased from about 75% to 69%.[2]

(c) Phenytoin

A study in 5 healthy subjects and 3 patients taking phenytoin 300 mg found that serum metyrapone levels 4 hours after taking a regular 750-mg dose were very low, when compared with those of a control group (6.5 micrograms/100 mL versus 48.2 micrograms/100 mL). The response to metyrapone (i.e. the fall in circulating glucocorticoids) is related to serum levels and was therefore proportionately lower.[3] Other reports confirm that the urinary steroid response to metyrapone is subnormal in patients taking phenytoin.[4,5]

Doubling the dose of metyrapone from 750 mg every 4 hours to every 2 hours has been shown to give results similar to those in subjects not taking phenytoin.[3]

Mechanism

Phenytoin is a potent liver enzyme inducer that increases the metabolism of metyrapone, thereby reducing its effects.[3,6]

Importance and management

The results of metyrapone tests for Cushing's syndrome will be unreliable in patients taking cyproheptadine and phenytoin, and therefore these should be withdrawn before the test; the US manufacturer advises 2 weeks.[7] The UK manufacturer also states that **barbiturates**, antidepressants (they name **amitriptyline**) and antipsychotics (they name **chlorpromazine**), hormones that affect the hypothalamo-pituitary-adrenal axis (the US manufacturers name **oestrogens**[7]), and **antithyroid drugs** may influence the results of the test. They recommend that, if any of these drugs cannot be withdrawn before the test, the necessity of carrying out the metyrapone test should be reviewed.[8]

In addition, the US manufacturer notes that metyrapone inhibits the glucuronidation of paracetamol, and may therefore increase paracetamol toxicity.[7] However, one study suggests that the extent may be modest, and, as metyrapone is usually only given for 24 hours, the clinical relevance of this effect seems small.

1. Plonk J, Feldman JM, Keagle D. Modification of adrenal function by the anti-serotonin agent cyproheptadine. *J Clin Endocrinol Metab* (1976) 42, 291–5.
2. Galinsky RE, Nelson EB, Rollins DE. Pharmacokinetic consequences and toxicologic implications of metyrapone-induced alterations of acetaminophen elimination in man. *Eur J Clin Pharmacol* (1987) 33, 391–6.
3. Meikle AW, Jubiz W, Matsukura S, West CD, Tyler FH. Effect of diphenylhydantoin on the metabolism of metyrapone and release of ACTH in man. *J Clin Endocrinol Metab* (1969) 29, 1553–8.
4. Krieger DT. Effect of diphenylhydantoin on pituitary-adrenal interrelations. *J Clin Endocrinol Metab* (1962) 22, 490–3.
5. Werk EE, Thrasher K, Choi Y, Sholiton LJ. Failure of metyrapone to inhibit 11-hydroxylation of 11-deoxycortisol during drug therapy. *J Clin Endocrinol Metab* (1967) 27, 1358–60.
6. Jubiz W, Levinson RA, Meikle AW, West CD, Tyler FH. Absorption and conjugation of metyrapone during diphenylhydantoin therapy: mechanism of the abnormal response to oral metyrapone. *Endocrinology* (1970) 86, 328–31.
7. Metopirone (Metyrapone). Novartis. US Prescribing information, August 2005.
8. Metopirone (Metyrapone). Alliance Pharmaceuticals. UK Summary of product characteristics, February 2005.

Mifepristone + Aspirin or NSAIDs

Theoretically NSAIDs might reduce the efficacy of mifepristone, and combined use is often not recommended. However, evidence from two studies with naproxen and diclofenac suggests no reduction in mifepristone efficacy.

Clinical evidence

(a) Mifepristone

In a study in women undergoing surgical first-trimester termination of pregnancy, patients received mifepristone 100 mg 48 hours and 36 hours before surgery for cervical ripening. There was no difference in the cervical softening effect between 13 women randomised to receive **naproxen** (500 mg given 60, 48, 36, 24 and 12 hours before the procedure) and 15 women randomised to receive placebo.[1]

(b) Mifepristone and misoprostol

Women undergoing second trimester medical terminations of pregnancy were given oral mifepristone 600 mg on day one, then 36 to 48 hours later, intravaginal misoprostol 800 micrograms. Starting 3 hours later, misoprostol 400 micrograms was given orally every 3 hours until expulsion, up to a maximum of nine oral doses of misoprostol. The women were randomised to receive a single dose of either paracetamol 1 g with dihydrocodeine 20 mg (n=38) or **diclofenac** 100 mg (n=36), given at the time of the intravaginal dose of misoprostol. The use of **diclofenac** did not increase either the time required for termination, or the amount of misoprostol needed.[2]

Mechanism

Mifepristone is thought to work by increasing prostaglandin production. Theoretically NSAIDs could reduce this, and therefore reduce the efficacy of mifepristone.

Importance and management

Because of theoretical concerns of antagonistic effects, NSAID analgesics, including **aspirin**, have been avoided in protocols for medical termination of pregnancy. However, the limited available evidence suggests that this might not be necessary.

For more information about the use of vaginal prostaglandins with NSAIDs, see under 'NSAIDs or Aspirin + Prostaglandins', p.171.

1. Rådestad A, Bygdeman M. Cervical softening with mifepristone (RU 486) after pretreatment with naproxen. A double-blind randomized study. *Contraception* (1992) 45, 221–7.
2. Fiala C, Swahn ML, Stephansson O, Gemzell-Danielsson K. The effect of non-steroidal anti-inflammatory drugs on medical abortion with mifepristone and misoprostol at 13-22 weeks gestation. *Hum Reprod* (2005) 20, 3072–7.

Mifepristone + Miscellaneous

***In vitro* study has found that mifepristone is an inhibitor of the cytochrome P450 isoenzyme CYP3A4.[1] The UK manufacturers therefore advise caution when mifepristone is given to patients taking CYP3A4 substrates (the US manufacturers specifically note CYP3A4 substrates with a narrow therapeutic index) as an increase in the levels of the substrate may result.[2,3] The clinical relevance of this prediction is unclear, and published reports describing an interaction between CYP3A4 substrates and mifepristone appear to be lacking. See 'Table 1.4', (p.6), for a list of CYP3A4 substrates.**

1. He K, Woolf TF, Hollenberg PF. Mechanism-based inactivation of cytochrome P-450-3A4 by mifepristone (RU486). *J Pharmacol Exp Ther* (1999) 288, 791–7.
2. Mifegyne (Mifepristone). Exelgyn Laboratories. UK Summary of product characteristics, May 2008.
3. Mifeprex (Mifepristone). Danco Laboratories, LLC. US Prescribing information, July 2005.

Oxiracetam + Antiepileptics

Limited evidence suggests that the half-life of oxiracetam might be shorter in patients taking carbamazepine with valproate or clobazam, and that oxiracetam probably does not affect the serum levels of sodium valproate, carbamazepine or clobazam.

Clinical evidence, mechanism, importance and management

Oxiracetam 800 mg twice daily for 14 days did not affect the serum levels of **sodium valproate**, **carbamazepine**, or **clobazam** and their metabolites in 3 epileptics taking **carbamazepine** and **valproate** and one taking **carbamazepine** and **clobazam**.[1] However, it was noted that the oxiracetam half-life was 2.8 to 7.56 hours,[1] which tended to be shorter than that seen in a previous study in healthy subjects who had been given oxiracetam 2 g (half-life 5.6 to 11.7 hours).[2] The clinical relevance of this is uncertain, but the authors suggest that it may be necessary to raise the oxiracetam dosage or give it more frequently in the presence of these drugs.[1]

1. van Wieringen A, Meijer JWA, van Emde Boas W, Vermeij TAC. Pilot study to determine the interaction of oxiracetam with antiepileptic drugs. *Clin Pharmacokinet* (1990) 18, 332–8.
2. Perucca E, Albrici A, Gatti G, Spalluto R, Visconti M, Crema A. Pharmacokinetics of oxiracetam following intravenous and oral administration in healthy volunteers. *Eur J Drug Metab Pharmacokinet* (1984) 9, 267–74.

Oxygen; hyperbaric + Miscellaneous

It has been suggested, but not confirmed, that because increased levels of carbon dioxide in the tissues can increase the 'sensitivity' to oxygen-induced convulsions, carbonic anhydrase inhibitors, such as acetazolamide, are contraindicated in those given hyperbaric oxygen, because they cause carbon dioxide to persist in the tissues. Nor should hyperbaric oxygen be given during opioid or barbiturate withdrawal because the convulsive threshold of such patients is already low.[1]

1. Gunby P. HBO can interact with preexisting patient conditions. *JAMA* (1981) 246, 1177–8.

Parathyroid hormones + Alendronate

There is some evidence that alendronate may reduce the anabolic effects of parathyroid hormone, so the combination may not be as effective as parathyroid hormone alone.

Clinical evidence

In a study, postmenopausal women with low mineral density at the hip or spine were given either **human recombinant parathyroid hormone** 100 micrograms daily, alendronate 10 mg daily, or both treatments for 12 months. All patients received calcium and vitamin D supplementation. Bone mineral density at the spine increased in all groups: however, volumetric density of trabecular bone at the spine was increased the most in patients taking parathyroid hormone alone (about twice that found in either of the other groups). Parathyroid hormone alone had greater effects on bone formation than parathyroid hormone with alendronate, and bone resorption decreased in those taking parathyroid hormone with alendronate or alendronate alone.[1]

In another study, men with low bone density were given either alendronate 10 mg daily, subcutaneous **teriparatide** 40 micrograms daily, or both. Alendronate was given for 30 months and parathyroid hormone was started at month 6. Bone mineral density at the lumbar spine and femoral neck increased significantly more in patients receiving parathyroid hormone alone than in patients receiving parathyroid hormone with alendronate, or alendronate alone.[2]

A further study in postmenopausal women found that the previous use of alendronate prevented **teriparatide**-induced increases in bone mineral density, especially in the first 6 months.[3] However, in another study, women who had received alendronate for at least one year were randomised to continue with alendronate alone, or to receive additional cyclical or daily **teriparatide**. Both daily and cyclical treatment with teriparatide in addition to alendronate increased spinal bone mass density more than alendronate alone.[4]

Mechanism

Alendronate may attenuate parathyroid-induced stimulation of bone formation.[2] It has been suggested it is the inhibition of overall bone turnover rather than inhibition of bone resorption by alendronate that impairs the anabolic activity of parathyroid hormone.[5]

Importance and management

The reports suggest that if parathyroid hormone or teriparatide is to be given for osteoporosis, it might be preferable to use them alone and not with alendronate, and possibly not with any other bisphosphonate. However, many patients with osteoporosis may already be receiving a bisphosphonate, and more study is required to establish the optimal regimens for starting parathyroid hormone and discontinuing the bisphosphonate in such patients.[5] Subsequent research suggests that the addition of parathyroid hormone to alendronate is more effective than no treatment, and that patients discontinuing parathyroid hormone do better if they are then given alendronate.[6]

1. Black DM, Greenspan SL, Ensrud KE, Palermo L, McGowan JA, Lang TF, Garnero P, Bouxsein ML, Bilezikian JP, Rosen CJ, for the PaTH Study Investigators. The effects of parathyroid hormone and alendronate alone or in combination in postmenopausal osteoporosis. *N Engl J Med* (2003) 349, 1207–15.
2. Finkelstein JS, Hayes A, Hunzelman JL, Wyland JJ, Lee H, Neer RM. The effects of parathyroid hormone, alendronate, or both in men with osteoporosis. *N Engl J Med* (2003) 349, 1216–26.
3. Ettinger B, San Martin J, Crans G, Pavo I. Differential effects of teriparatide on BMD after treatment with raloxifene or alendronate. *J Bone Miner Res* (2004) 19, 745–51.
4. Cosman F, Nieves J, Zion M, Woelfert L, Luckey M, Lindsay R. Daily and cyclic parathyroid hormone in women receiving alendronate. N Engl J Med. (2005) 353, 566–75.

5. Khosia S. Parathyroid hormone plus alendronate—a combination that does not add up. *N Engl J Med* (2003) 349, 1277–9.
6. Black DM, Bilezikian JP, Ensrud KE, Greenspan SL, Palermo L, Hue T, Lang TF, McGowan JA, Rosen CJ; for the PaTH Study Investigators. One year of alendronate after one year of parathyroid hormone (1-84) for osteoporosis. *N Engl J Med* (2005) 353, 555–65.

Parathyroid hormones; Teriparatide + Miscellaneous

The clinical effects of teriparatide are not significantly affected by furosemide, hormone replacement therapy, hydrochlorothiazide, or raloxifene.

Clinical evidence, mechanism, importance and management

(a) Furosemide

A study in 28 subjects (9 healthy subjects and 17 subjects with mild to moderate renal impairment) found that furosemide 20 to 100 mg had no clinically significant effect on the response to teriparatide.[1]

(b) Hormone replacement therapy

The effects of teriparatide on serum and urine calcium levels, and teriparatide adverse effects, are not affected by the concurrent use of hormone replacement therapy.[2]

(c) Hydrochlorothiazide

A study in 20 healthy subjects found that although hydrochlorothiazide 25 mg caused a minor reduction in the urinary excretion of calcium, the serum calcium response to a 40-microgram dose of teriparatide was unaffected.[1]

(d) Raloxifene

In a study, postmenopausal women were given subcutaneous teriparatide 20 micrograms daily for 18 months. The expected teriparatide-induced increases in bone mineral density were not affected by previous treatment with raloxifene.[3] Similarly, the manufacturer states that the effects of teriparatide on serum and urine calcium levels, and teriparatide adverse effects, are not affected by raloxifene.[2]

1. Forteo (Teriparatide). Eli Lilly and Company. US Prescribing information, July 2009.
2. Forsteo (Teriparatide). Eli Lilly and Company Ltd. UK Summary of product characteristics, August 2009.
3. Ettinger B, San Martin J, Crans G, Pavo I. Differential effects of teriparatide on BMD after treatment with raloxifene or alendronate. *J Bone Miner Res* (2004) 19, 745–51.

Penicillamine + Antacids

The absorption of penicillamine can be reduced by 30 to 40% if antacids containing aluminium/magnesium hydroxide are taken at the same time. This does not occur with sodium bicarbonate.

Clinical evidence

In a study in 6 healthy fasting subjects, *Maalox-plus* (**aluminium**/**magnesium hydroxide**, **simeticone**) 30 mL reduced the absorption of a single 500-mg dose of penicillamine by one-third.[1] Another similar study found that 30 mL of *Aludrox* (**aluminium**/**magnesium hydroxide**) reduced the absorption of penicillamine by about 40%.[2] In contrast, a single 7.06-g dose of **sodium bicarbonate** had little effect on the absorption of penicillamine (non-significant 15% reduction in AUC).[2]

Mechanism

The most likely explanation is that the penicillamine forms less soluble chelates with magnesium and aluminium ions in the gut, which reduces its absorption.[2]

Importance and management

The interaction between penicillamine and aluminium and magnesium-containing antacids is established, and might be of clinical importance. If maximal absorption is needed the administration of the two drugs should be separated to avoid mixing in the gut. Two to three hours has been found enough for most other drugs that have reduced absorption in the presence of aluminium/magnesium hydroxide antacids. Sodium bicarbonate does not interact and therefore the timing of the doses does not need to be adjusted in patients taking penicillamine.

1. Osman MA, Patel RB, Schuna A, Sundstrom WR, Welling PG. Reduction in oral penicillamine absorption by food, antacid and ferrous sulphate. *Clin Pharmacol Ther* (1983) 33, 465–70.
2. Ifan A, Welling PG. Pharmacokinetics of oral 500-mg penicillamine: effect of antacids on absorption. *Biopharm Drug Dispos* (1986) 7, 401–5.

Penicillamine + Disease-modifying antirheumatic drugs

Penicillamine plasma levels are increased by chloroquine and an increase in penicillamine toxicity is possible. Penicillamine should not be used with gold.

Clinical evidence, mechanism, importance and management

(a) Chloroquine or Hydroxychloroquine

Studies in which chloroquine was given to patients taking penicillamine found that giving both drugs was more effective, less effective, or indistinguishable from giving penicillamine alone. However, in some instances penicillamine toxicity was reported to be increased by chloroquine.[1] A pharmacokinetic study in patients with rheumatoid arthritis taking penicillamine 250 mg daily found that a single 250-mg dose of chloroquine phosphate increased the AUC of penicillamine by 34%, and raised its peak plasma levels by about 55%.[1] It therefore seems possible that any increased toxicity is a reflection of increased plasma penicillamine levels. Be alert for evidence of toxicity if both drugs are used. Note that the US manufacturer states that penicillamine should not be used in patients who are receiving antimalarials (which would include chloroquine and hydroxychloroquine) because these drugs are also associated with serious haematological effects.[2]

(b) Gold

There is some evidence that using gold with penicillamine may increase the risk of adverse effects, and the manufacturer says that they should not be used together.[2,3] In addition, patients who have had an adverse reaction to gold may be at a greater risk of serious adverse reactions to penicillamine,[2,3] and caution is recommended.[3]

1. Seideman P, Lindström B. Pharmacokinetic interactions of penicillamine in rheumatoid arthritis. *J Rheumatol* (1989) 16, 473–4.
2. Cuprimine (Penicillamine). Merck & Co., Inc. US Prescribing information, October 2004.
3. Distamine (Penicillamine). Alliance Pharmaceuticals. UK Summary of product characteristics, January 2009.

Penicillamine + Food

Food can reduce the absorption of penicillamine by as much as a half.

Clinical evidence

In a study in healthy subjects, the presence of food reduced the plasma levels of penicillamine 500 mg by about 50%. The total amount absorbed was similarly reduced.[1,2] These figures are in good agreement with previous findings.[3]

Mechanism

Uncertain. One suggestion is that food delays gastric emptying so that the penicillamine is exposed to more prolonged degradation in the stomach.[2] Another idea is that the protein in food reduces penicillamine absorption.

Importance and management

An established interaction. If maximal effects are required the penicillamine should be taken at least 30 minutes before food.

1. Schuna A, Osman MA, Patel RB, Welling PG, Sundstrom WR. Influence of food on the bioavailability of penicillamine. *J Rheumatol* (1983) 10, 95–7.

2. Osman MA, Patel RB, Schuna A, Sundstrom WR, Welling PG. Reduction in oral penicillamine absorption by food, antacid and ferrous sulphate. *Clin Pharmacol Ther* (1983) 33, 465–70.
3. Bergstrom RF, Kay DR, Harkcom TM, Wagner JG. Penicillamine kinetics in normal subjects. *Clin Pharmacol Ther* (1981) 30, 404–13.

Penicillamine + Iron compounds

The absorption of penicillamine can be reduced as much as two-thirds by oral iron compounds.

Clinical evidence

In a study in 5 healthy subjects, **ferrous iron** 90 mg (as *Fersamal*) reduced the absorption of penicillamine 250 mg by about two-thirds (using the cupruretic effects of penicillamine as a measure).[1]

A two-thirds reduction in the absorption of penicillamine 500 mg has been described in 6 other subjects who were also given **ferrous sulfate** 300 mg.[2] Other studies confirm this interaction.[3,4] There is also evidence that the withdrawal of iron from patients stabilised on penicillamine can lead to the development of toxicity (nephropathy) unless the penicillamine dosage is reduced.[5]

Mechanism

It is believed that the iron and penicillamine form a chemical complex or chelate within the gut, which is less easily absorbed.

Importance and management

An established and clinically important interaction. For maximal absorption give iron at least 2 hours after penicillamine. This should reduce their admixture in the gut.[1] Only ferrous sulfate and fumarate have been studied but other iron compounds would be expected to interact similarly. Do not withdraw iron suddenly from patients stabilised on penicillamine because the marked increase in absorption that follows may precipitate penicillamine toxicity. The toxic effects of penicillamine seem to be dependent on the size of the dose and are possibly also related to the rate at which the dosage is increased.[5]

1. Lyle WH. Penicillamine and iron. *Lancet* (1976) ii, 420.
2. Osman MA, Patel RB, Schuna A, Sundstrom WR, Welling PG. Reduction in oral penicillamine absorption by food, antacid, and ferrous sulphate. *Clin Pharmacol Ther* (1983) 33, 465–70.
3. Lyle WH, Pearcey DF, Hui M. Inhibition of penicillamine-induced cupruresis by oral iron. *Proc R Soc Med* (1977) 70 (Suppl 3), 48–9.
4. Hall ND, Blake DR, Alexander GJM, Vaisey C, Bacon PA. Serum SH reactivity: a simple assessment of D-penicillamine absorption? *Rheumatol Int* (1981) 1, 39–41.
5. Harkness JAL, Blake DR. Penicillamine nephropathy and iron. *Lancet* (1982) ii, 1368–9.

Penicillamine + Miscellaneous

An isolated report describes penicillamine-induced breast enlargement in a woman taking an oral combined hormonal contraceptive. This might also have occurred when penicillamine was given with a corticosteroid or cimetidine.

Clinical evidence, mechanism, importance and management

A woman with Wilson's disease began to develop dark facial hair about 10 months after starting to take penicillamine 1.25 to 1.5 g daily. After 20 months her testosterone levels were found to be slightly raised, and so she was given an oral **combined hormonal contraceptive**, but within a month her breasts began to enlarge and become more tender. After a further 6 months the penicillamine was replaced by trientine hydrochloride.[1] The reasons are not understood, but the authors of the report suggest that the penicillamine was the prime cause of the macromastia, but it possibly needed the presence of a 'second trigger' (i.e. the contraceptive) to set things in motion.[1]

There are 12 other cases of macromastia and gynaecomastia on record associated with the use of penicillamine. In some of these cases the second trigger may possibly have been a **corticosteroid** or **cimetidine**.[1] Macromastia appears to be an unusual adverse effect of penicillamine and there would seem to be no general reason for patients taking penicillamine to avoid hormonal contraceptives.

1. Rose BI, LeMaire WJ, Jeffers LJ. Macromastia in a woman treated with penicillamine and oral contraceptives. *J Reprod Med* (1990) 35, 43–5.

Penicillamine + NSAIDs

Indometacin slightly increases penicillamine levels. The use of penicillamine and an NSAID might increase the risk of renal damage.

Clinical evidence, mechanism, importance and management

Indometacin has been found to increase the AUC of penicillamine by 26% and the peak plasma levels by about 22%.[1] The UK manufacturer notes that use of NSAIDs may increase the risk of renal damage with penicillamine.[2] The US manufacturer specifically recommends avoiding **oxyphenbutazone** or **phenylbutazone** because these drugs are also associated with serious haematological and renal effects.[3] Urinalysis for detection of haematuria or proteinuria should be regularly carried out in patients taking penicillamine.[2,3] Be alert for evidence of toxicity if NSAIDs and penicillamine are used together.

1. Seideman P, Lindström B. Pharmacokinetic interactions of penicillamine in rheumatoid arthritis. *J Rheumatol* (1989) 16, 473–4.
2. Distamine (Penicillamine). Alliance Pharmaceuticals. UK Summary of product characteristics, January 2009.
3. Cuprimine (Penicillamine). Merck & Co., Inc. US Prescribing information, October 2004.

Phenylpropanolamine + Indinavir

A report describes a hypertensive crisis when a patient taking indinavir was also given phenylpropanolamine.

Clinical evidence, mechanism, importance and management

A 28-year-old woman was prescribed HIV-prophylaxis following a needle stick injury. She was initially given zidovudine, indinavir and lamivudine, but after one week stavudine was substituted for zidovudine as she was experiencing nausea and vomiting. Six hours after taking *Tavist-D* (clemastine with phenylpropanolamine) for a sinus complaint she had a feeling of chest tightness associated with difficulty in breathing, and shortly afterwards she experienced left-sided upper extremity weakness, followed by a severe right-sided temporal headache. Her blood pressure was 220/120 mmHg, but returned to normal within 4 hours, and the neurological deficit resolved over the next 8 hours. However, 12 hours later, the same neurological deficit recurred, although no increase in blood pressure was noted. The neurological deficit was thought to be due to reversible cerebral vasoconstriction, secondary to phenylpropanolamine toxicity. She was treated with nimodipine 60 mg every 4 hours and aspirin 325 mg daily, and her symptoms did not recur.[1]

The patient had been taking phenylpropanolamine intermittently for several years without any adverse reaction and it was thought that the recent addition of the HIV prophylaxis potentiated the effect of the phenylpropanolamine.[1] It seems likely that the indinavir was responsible for the interaction as it is a potent enzyme inhibitor.

This is an isolated report and its general significance is not known, but it would be prudent to be alert for this interaction in patients taking both drugs. Note that phenylpropanolamine is no longer available in the US and UK and its use has been restricted in many other countries.

1. Khurana V, de la Fuente M, Bradley TP. Hypertensive crisis secondary to phenylpropanolamine interacting with triple-drug therapy for HIV prophylaxis. *Am J Med* (1999) 106, 118–19.

Phenylpropanolamine + Indometacin

An isolated report describes a patient taking phenylpropanolamine who developed serious hypertension after taking a sin-

gle dose of indometacin, but a controlled study in other subjects did not find any evidence of an adverse interaction.

Clinical evidence

A woman who had been taking phenylpropanolamine 85 mg daily for several months as an appetite suppressant, developed a severe bifrontal headache within 15 minutes of taking indometacin 25 mg. Thirty minutes later her systolic blood pressure was 210 mmHg and her diastolic blood pressure was unrecordable. A later study in this patient confirmed that neither drug on its own caused this response, but when they were taken together the blood pressure rose to a maximum of 200/150 mmHg within about 30 minutes of taking the indometacin, and was associated with bradycardia. Her blood pressure was rapidly reduced by phentolamine.[1]

In contrast, a controlled study in 14 healthy young women found no evidence that sustained-release indometacin 75 mg twice daily, given with sustained-release phenylpropanolamine 75 mg daily, caused a rise in blood pressure.[2]

Mechanism

Not understood.

Importance and management

Direct information seems to be limited to these reports. They suggest that an adverse hypertensive response is unlikely in most individuals given these drugs. However, note that phenylpropanolamine alone has been associated with severe hypertension and has been implicated in causing stroke.[3] It is therefore no longer available in the US and UK and its use has been restricted in many other countries.

1. Lee KY, Beilin LJ, Vandongen R. Severe hypertension after ingestion of an appetite suppressant (phenylpropanolamine) with indomethacin. *Lancet* (1979) i, 1110–11.
2. McKenney JM, Wright JT, Katz GM, Goodman RP. The effect of phenylpropanolamine on 24–hour blood pressure in normotensive subjects administered indomethacin. *DICP Ann Pharmacother* (1991) 25, 234–9.
3. Brust JCM. Editorial comment: over-the-counter cold remedies and stroke. *Stroke* (2003) 34, 1673.

Polystyrene sulfonate + Antacids

The concurrent use of some antacids with sodium polystyrene sulfonate can result in metabolic alkalosis. Use with aluminium hydroxide has resulted in intestinal obstruction. Calcium polystyrene sulfonate is said to interact similarly.

Clinical evidence, mechanism, importance and management

A man with hyperkalaemia developed metabolic alkalosis when given 30 g of sodium polystyrene sulfonate with **magnesium hydroxide** 30 mL three times daily.[1] Alkalosis has also been described in a study in a number of patients given this cation exchange resin with *Maalox* (**magnesium/aluminium hydroxide**) and **calcium carbonate**.[2]

The suggested reason is that the breakdown of the **magnesium hydroxide** usually requires equal amounts of bicarbonate and hydrogen ions, and so does not cause any acid-base disturbance. However, when sodium polystyrene sulfonate is given, it binds the **magnesium**, while the hydroxide is neutralised by the hydrogen ions. This results in a relative excess of bicarbonate ions, which are absorbed, leading to metabolic alkalosis.

This interaction appears to be established. Concurrent use should be undertaken with caution and serum electrolytes should be closely monitored. Giving the resin rectally as an enema can avoid the problem. Calcium polystyrene sulfonate is said to interact similarly.[3]

In addition to alkalosis, the manufacturer also notes that concurrent use of **aluminium hydroxide** and the resins has resulted in intestinal obstruction due to 'concretions' of **aluminium hydroxide**.[3,4] Caution is advised.

1. Fernandez PC, Kovnat PJ. Metabolic acidosis reversed by the combination of magnesium and a cation-exchange resin. *N Engl J Med* (1972) 286, 23–4.
2. Schroeder ET. Alkalosis resulting from combined administration of a 'nonsystemic' antacid and a cation-exchange resin. *Gastroenterology* (1969) 56, 868–74.
3. Calcium resonium (Calcium polystyrene sulfonate). Sanofi-Aventis. UK Summary of product characteristics, April 2009.
4. Resonium A (Sodium polystyrene sulfonate). Sanofi-Aventis. UK Summary of product characteristics, April 2009.

Polystyrene sulfonate + Sorbitol

Potentially fatal colonic necrosis may occur if sodium polystyrene sulfonate is given as an enema with sorbitol. Calcium polystyrene sulfonate may interact similarly.

Clinical evidence

Five patients with uraemia developed severe colonic necrosis after being given enemas containing sodium polystyrene sulfonate and sorbitol for the treatment of hyperkalaemia. Four of the 5 patients died as a result. Associated studies in uraemic *rats* found that all of them died over a 2-day period after being given enemas of sodium polystyrene sulfonate with sorbitol. Extensive haemorrhage and transmural necrosis developed. No deaths occurred when enemas without sorbitol were given.[1] A number of other similar cases have been reported, a few of which are cited.[2-4] In one retrospective analysis, intestinal necrosis occurred in 2 of 117 patients (1.7%) who had received sodium polystyrene sulfonate within one week of surgery, and in both of these cases it had been given in sorbitol. Conversely, of 862 patients who did not receive sodium polystyrene sulfonate, none developed intestinal necrosis.[5]

Mechanism

Not understood.

Importance and management

Information is limited and the interaction between sorbitol and polystyrene sulfonate is not firmly established; nevertheless, its seriousness indicates that sodium polystyrene sulfonate should not be given as an enema in aqueous vehicles containing sorbitol. Note that the manufacturers advise against the concurrent use of both *oral* and rectal sorbitol with sodium or calcium polystyrene sulfonate, because of the risk of colonic necrosis.[6,7]

1. Lillemoe KD, Romolo JL, Hamilton SR, Pennington LR, Burdick JF, Williams GM. Intestinal necrosis due to sodium polystyrene (Kayexalate) in sorbitol enemas: clinical and experimental support for the hypothesis. *Surgery* (1987) 101, 267–72.
2. Rashid A, Hamilton SR. Necrosis of the gastrointestinal tract in uremic patients as a result of sodium polystyrene sulfonate (Kayexalate) in sorbitol: an underrecognized condition. *Am J Surg Pathol* (1997) 21, 60–9.
3. Rogers FB, Li SC. Acute colonic necrosis associated with sodium polystyrene sulfonate (Kayexalate) enemas in a critically ill patient: case report and review of the literature. *J Trauma* (2001) 51, 395–7.
4. Kelsey PB, Chen S, Lauwers GY. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 37-2003. A 79-year-old man with coronary artery disease, peripheral vascular disease, end-stage renal disease, and abdominal pain and distention. *N Engl J Med* (2003) 349, 2147–55.
5. Gerstman BB, Kirkman R, Platt R. Intestinal necrosis associated with postoperative orally administered sodium polystyrene sulfonate in sorbitol. *Am J Kidney Dis* (1992) 20, 159–61.
6. Resonium A (Sodium polystyrene sulfonate). Sanofi-Aventis. UK Summary of product characteristics, April 2009.
7. Calcium resonium (Calcium polystyrene sulfonate). Sanofi-Aventis. UK Summary of product characteristics, April 2009.

Pseudoephedrine + Antacids or Antidiarrhoeals

Kaolin does not appear to interact significantly with pseudoephedrine. Aluminium hydroxide may possibly cause a more rapid onset of pseudoephedrine.

Clinical evidence

In a single-dose, crossover study in 6 healthy subjects, 30 mL of **aluminium hydroxide gel** did not affect the total amount of a single 60-mg dose of pseudoephedrine absorbed over 24 hours, but the rate of absorption was significantly increased during the first 3 hours.[1] Conversely, 30 mL of a 30% suspension of **kaolin** reduced the amount of a single 60-mg dose of pseudoephedrine absorbed by just 10%. The rate of absorption was also decreased.[1]

Mechanism

The increased rate of absorption of pseudoephedrine seen with aluminium hydroxide is probably also due to pH rises, which favour the formation of the lipid-soluble absorbable form of pseudoephedrine. The reduced absorption with kaolin is probably due to adsorption of the pseudoephedrine onto the surface of the kaolin.

Importance and management

Aluminium hydroxide may possibly cause a more rapid onset of pseudoephedrine activity (but this needs confirmation). Any interaction seems unlikely to be clinically significant. Similarly, the effects of kaolin on pseudoephedrine absorption are small and unlikely to be clinically important.

For the effect of sodium bicarbonate on pseudoephedrine and ephedrine, see 'urinary alkalinisers', (p.1567).

1. Lucarotti RL, Colaizzi JL, Barry H, Poust RI. Enhanced pseudoephedrine absorption by concurrent administration of aluminium hydroxide gel in humans. *J Pharm Sci* (1972) 61, 903–5.

Pseudoephedrine and related drugs + Caffeine

Phenylpropanolamine can raise blood pressure and in some cases this may be further increased by caffeine. Combined use has resulted in hypertensive crises in a few individuals. Ephedrine may interact similarly. Phenylpropanolamine can markedly raise plasma caffeine levels, and isolated reports describe the development of acute psychosis when caffeine was given with phenylpropanolamine or ephedrine.

Clinical evidence

(a) Ephedrine

1. Clinical studies. In a single-dose, randomised study, 15 healthy subjects were given ephedrine 25 mg, caffeine 200 mg, both drugs together, or placebo. An assessment of systolic blood pressure found that ephedrine had no significant effect, caffeine caused a 9.1 mmHg increase, and the use of both drugs resulted in an 11.7 mmHg increase. Caffeine alone did not increase heart rate, but both ephedrine and ephedrine plus caffeine caused heart rate increases of roughly 11%. Subjective tests suggested that there was no significant difference in feelings of headache, chest pain, heart pounding or shortness of breath between the treatments. There was no significant pharmacokinetic interaction between the drugs.[1] Another randomised study, investigating the combination of ephedrine 20 mg and caffeine 200 mg, both three times daily, compared with either drug alone, or placebo, for weight loss, did not find any significant hypertensive effects with the combination, although the authors suggested that this may have been due to the favourable effects of weight loss on blood pressure. However, one patient was withdrawn due to a rise in blood pressure, to 185/125 mmHg.[2]

Numerous other clinical studies have investigated the haemodynamic effects of combinations of ephedrine or ephedra with caffeine or caffeine-containing herbs, some showing increases in heart rate and blood pressure and others not. However, none of these compared the combination with either constituent alone, so it is not possible to assess the possibility of an interaction from these reports.

2. Case reports. A review of reports from the FDA in the US revealed that several patients have experienced severe adverse effects (subarachnoid haemorrhage, cardiac arrest, hypertension, tachycardia and neurosis) after taking dietary supplements containing ephedrine or **ephedra** alkaloids with caffeine.[3] However, it is not possible to definitively say that these effects were the result of an interaction because none of the patients took either drug separately. Similarly, a meta-analysis assessing the safety of ephedra or ephedrine and caffeine found a two- to threefold increase in the risk of adverse events (including psychiatric symptoms and palpitations) with ephedra or ephedrine, but it was concluded that it was not possible to assess the contribution of caffeine to these events.[4]

Two episodes of acute psychosis occurred in a 32-year-old man after he took *Vigueur fit* tablets (containing **ephedra** alkaloids and caffeine), *Red Bull* (containing caffeine) and alcohol. He had no previous record of aberrant behaviour despite regularly taking 6 to 9 tablets of *Vigueur fit* daily (about twice the recommended dose). However, on this occasion, over a 10-hour period, he consumed 3 or 4 bottles of *Red Bull* (containing about 95 mg of caffeine per 250-mL bottle) and enough alcohol to reach a blood-alcohol level of about 335 mg%. No more episodes occurred after he stopped taking the *Vigueur fit* tablets. **Ephedra** alkaloids (ephedrine and **pseudoephedrine**) may cause psychosis and it appears that their effects may be exaggerated by an interaction with caffeine and alcohol.[5]

(b) Phenylpropanolamine

In a placebo-controlled study, the mean blood pressure of 16 healthy subjects rose by 11/12 mmHg after they took caffeine 400 mg, by 12/13 mmHg after they took phenylpropanolamine 75 mg, and by 12/11 mmHg when both drugs were taken. Phenylpropanolamine 150 mg caused a greater rise of 36/18 mmHg. One of the subjects had a hypertensive crisis after taking phenylpropanolamine 150 mg and again 2 hours after taking caffeine 400 mg. This needed antihypertensive treatment.[6] The same group of workers describe a similar study in which the AUC of caffeine 400 mg increased by more than threefold, and the mean peak caffeine concentration increased almost fourfold (from 2.1 to 8 micrograms/mL) after phenylpropanolamine 75 mg was given.[7] Additive increases in blood pressure are described in another report.[8]

Mania with psychotic delusions occurred in a healthy woman (who normally drank 7 to 8 cups of **coffee** daily) within 3 days of her starting to take a phenylpropanolamine-containing decongestant. She recovered within a week of stopping both the **coffee** and the phenylpropanolamine.[9]

Mechanism

Ephedrine and caffeine may cause catecholamine release and an increase in intracellular calcium release which leads to vasoconstriction. Myocardial ischaemia may occur as a result of this vasoconstriction (in the coronary artery), and this may result in myocardial necrosis and cell death.

Importance and management

Fairly well established interactions. These studies illustrate the potential hazards of these drugs, even in normal healthy individuals. However, it has to be said that there seem to be few reports of adverse interactions, which is perhaps surprising bearing in mind that coffee/caffeine is very widely used and ephedrine and phenylpropanolamine have also been widely available without prescription. One possible explanation for this could be that these interactions may go unrecognised or be attributed to one drug only e.g. phenylpropanolamine, whereas caffeine has also been taken either as part of the preparation[3,10] or in beverages (often not reported). Nevertheless, serious adverse events have been reported with caffeine and phenylpropanolamine or dietary supplements containing ephedra alkaloids (sometimes called ma huang) and therefore these preparations may pose a serious health risk to some users.[3] The risk may be affected by individual susceptibility, the additive stimulant effects of caffeine, the variability in the contents of alkaloids in non-prescription dietary supplements, or pre-existing medical conditions,[3] including compromised cardiac function,[1] and hypertension, or obesity and old age.[6]

Note that, phenylpropanolamine is no longer available in the US and UK and its use has been restricted in many other countries. In addition, because of the associated health risks, the FDA bans combinations of caffeine with ephedrine or pseudoephedrine, and also bans herbal products containing ephedra. As a result of this, many manufacturers replaced ephedra with bitter orange (*Citrus aurantium*), which contains a similar sympathomimetic alkaloid (synephrine). Evidence shows that these products are no safer than ephedra products when used in a similar way. It would be prudent to avoid using herbal products containing combinations of bitter orange and caffeine or caffeine-containing herbs, especially in patients with risk factors such as heart conditions, diabetes, thyroid disease, or hypertension.

1. Haller CA, Jacob P, Benowitz NL. Enhanced stimulant and metabolic effects of combined ephedrine and caffeine. *Clin Pharmacol Ther* (2004) 75, 259–73.
2. Astrup A, Breum L, Toubro S, Hein P, Quaade F. The effect and safety of an ephedrine/caffeine compound compared to ephedrine, caffeine and placebo in obese subjects on an energy restricted diet. A double blind trial. *Int J Obes Relat Metab Disord* (1992) 16, 269–77.
3. Haller CA, Benowitz NL. Adverse cardiovascular and central nervous system events associated with dietary supplements containing ephedra alkaloids. *N Engl J Med* (2000) 343, 1833–8.
4. Shekelle PG, Hardy ML, Morton SC, Maglione M, Mojica WA, Suttorp MJ, Rhodes SL, Jungvig L, Gagné J. Efficacy and safety of ephedra and ephedrine for weight loss and athletic performance: a meta-analysis. *JAMA* (2003) 280, 1537–45.
5. Tormey WP, Bruzzi A. Acute psychosis due to the interaction of legal compounds – ephedra alkaloids in 'Vigueur Fit' tablets, caffeine in 'Red Bull' and alcohol. *Med Sci Law* (2001) 41, 331–6.
6. Lake CR, Zaloga G, Bray J, Rosenberg D, Chernow B. Transient hypertension after two phenylpropanolamine diet aids and the effects of caffeine: a placebo-controlled follow-up study. *Am J Med* (1989) 86, 427–32.
7. Lake CR, Rosenberg DB, Gallant S, Zaloga G, Chernow B. Phenylpropanolamine increases plasma caffeine levels. *Clin Pharmacol Ther* (1990) 47, 675–85.
8. Brown NJ, Ryder D, Branch RA. A pharmacodynamic interaction between caffeine and phenylpropanolamine. *Clin Pharmacol Ther* (1991) 50, 363–71.

9. Lake CR. Manic psychosis after coffee and phenylpropanolamine. *Biol Psychiatry* (1991) 30, 401–4.
10. Lake CR, Gallant S, Masson E, Miller P. Adverse drug effects attributed to phenylpropanolamine: a review of 142 case reports. *Am J Med* (1990) 89, 195– 208.

Pseudoephedrine and related drugs + Urinary acidifiers or alkalinisers

Alkalinisation of the urine (e.g. by sodium bicarbonate) causes retention of ephedrine and pseudoephedrine by the kidneys, leading to the possible development of toxicity (tremors, anxiety, insomnia, tachycardia). Acidification of the urine (e.g. with ammonium chloride) has the opposite effect.

Clinical evidence

(a) Ephedrine

When the urine was made acidic (pH of about 5) with **ammonium chloride**, the excretion of ephedrine in the urine of 3 healthy subjects was two- to fourfold higher than when the urine was made alkaline (pH of about 8) with **sodium bicarbonate**.[1]

(b) Pseudoephedrine

A patient with renal tubular acidosis and persistently alkaline urine developed unexpected toxicity (cachexia and personality changes) when given therapeutic doses (not stated) of pseudoephedrine for 2.5 months. She was found to have a very prolonged pseudoephedrine half-life of 50 hours (10 times expected). Therefore 8 subjects (adults and children) were studied, to establish the possible effects of changing the urinary pH on pseudoephedrine elimination. When the urinary pH was adjusted using **ammonium chloride** or **sodium bicarbonate**, within the approximate range of 5.7 to 7.8, the half-life of a single dose of pseudoephedrine (about 5 mg/kg) was found to increase from 1.9 hours at the lowest pH to 21 hours at the highest pH.[2]

This confirms an earlier study, in which it was found that at a urinary pH of 8, the half-life of pseudoephedrine was 16, 9.2, and 15 hours in 3 subjects, respectively. At a urinary pH of about 5, the half-life was 4.8, 3, and 6.4 hours, respectively.[3] **Sodium bicarbonate** was given to raise urinary pH and **ammonium chloride** to lower urinary pH.

Another study in 6 healthy subjects found that **sodium bicarbonate** 5 g initially increased the excretion rate of a single 60-mg dose of pseudoephedrine, but as the urinary pH increased the excretion of pseudoephedrine was reduced.[4]

Mechanism

Ephedrine and pseudoephedrine are basic drugs, which are mainly excreted unchanged in the urine. In acidic urine, most of the drug is ionised in the tubular filtrate and unable to diffuse passively back into the circulation, and is therefore lost in the urine. In alkaline urine, these drugs mostly exist in lipid-soluble forms, which are reabsorbed.

The increased rate of absorption of pseudoephedrine seen with sodium bicarbonate is probably also due to pH rises, which favour the formation of the lipid-soluble absorbable form of pseudoephedrine.

Importance and management

The interaction between ephedrine or pseudoephedrine and urinary alkalinisers are established but reports of adverse reactions in patients appear to be rare. Be aware that any increase in the adverse effects of these drugs (tremor, anxiety, insomnia, tachycardia, etc.) could be due to drug retention brought about by this interaction. **Acetazolamide** also makes the urine alkaline and would be expected to interact with ephedrine and pseudoephedrine in the same way as sodium bicarbonate.

Acidification of the urine with ammonium chloride increases the loss of ephedrine and pseudoephedrine in the urine and could be exploited in cases of drug overdosage.

1. Wilkinson GR, Beckett AH. Absorption, metabolism and excretion of the ephedrines in man. I. The influence of urinary pH and urine volume output. *J Pharmacol Exp Ther* (1968) 162, 139–47.
2. Brater DC, Kaojarern S, Benet LZ, Lin ET, Lockwood T, Morris RC, McSherry EJ, Melmon KL. Renal excretion of pseudoephedrine. *Clin Pharmacol Ther* (1980) 28, 690–4.
3. Kuntzman RG, Tsai I, Brand L, Mark LC. The influence of urinary pH on the plasma half-life of pseudoephedrine in man and dog and a sensitive assay for its determination in human plasma. *Clin Pharmacol Ther* (1971) 12, 62–7.
4. Lucarotti RL, Colaizzi JL, Barry H, Poust RI. Enhanced pseudoephedrine absorption by concurrent administration of aluminium hydroxide gel in humans. *J Pharm Sci* (1972) 61, 903–5.

PUVA + Herbal medicines or Foods

Two case reports describe photosensitivity in patients taking methoxsalen and undergoing PUVA, one in a patient taking rue (*Ruta graveolens*) and another in a patient who ate large amounts of celery soup.

Clinical evidence, mechanism, importance and management

A 35-year-old woman taking **methoxsalen** and undergoing PUVA for psoriasis unexpectedly developed increased photosensitivity. Over the previous weekend and on the morning of therapy she had been drinking a concoction of **rue** (***Ruta graveolens***).[1] This plant naturally contains 5-methoxypsoralen so it would appear that a pharmacodynamic interaction occurred, which resulted in the photosensitivity.

The authors note that other herbal products contain photosensitising substances (e.g. those containing members of the **Umbelliferae** family; such as **celery**, or ***Chlorella*** species), and so suggest that patients undergoing PUVA should be warned about the potential interactions.[1] This warning appears justified by the case of a woman taking **methoxsalen** and undergoing PUVA, who developed photosensitivity after eating a large quantity of soup containing **celery**, parsnip and parsley.[2]

1. Puig L. Pharmacodynamic interaction with phototoxic plants during PUVA therapy. *Br J Dermatol* (1997) 136, 973–4.
2. Boffa MJ, Gilmour E, Ead RD. Celery soup causing severe phototoxicity during PUVA therapy. *Br J Dermatol* (1996) 135, 330–45.

PUVA + Metoclopramide

Metoclopramide does not appear to affect the pharmacokinetics of methoxsalen.

Clinical evidence, mechanism, importance and management

In a study, 6 healthy subjects were given a single 25-mg/m^2 dose of **methoxsalen** and a single 10-mg dose of metoclopramide, with a standard breakfast, followed by a 4 hour period during which no further food or drink was taken. Metoclopramide increased the intersubject variation in the pharmacokinetics of methoxsalen, but overall, its pharmacokinetics were not significantly altered.[1] It would therefore appear that metoclopramide can be given with methoxsalen without the need for dosage adjustment.

1. Studer-Sachsenberg EM, Piletta P-A, Fathi M, Saurat J-H, Salomon D. Influence of metoclopramide on the pharmacokinetics of 8-methoxypsoralen. *Dermatology* (1997) 195, 81–3.

PUVA + Phenytoin

The serum levels of methoxsalen can be markedly reduced by the concurrent use of phenytoin. This resulted in the failure of PUVA for psoriasis in one patient.

Clinical evidence, mechanism, importance and management

A patient with epilepsy failed to respond to treatment for psoriasis with PUVA (12 treatments of **methoxsalen** 30 mg given orally and ultraviolet A irradiation) while taking phenytoin 250 mg daily. Methoxsalen serum levels were normal in the absence of phenytoin, but abnormally low while taking phenytoin,[1] due, it is suggested, to the enzyme-inducing effects of phenytoin. This interaction could lead to serious erythema and blistering if the phenytoin dose is reduced during therapy, as methoxsalen levels rise and therefore photosensitivity caused by the methoxsalen may be increased. Concurrent use should be avoided if possible, or very closely monitored.

1. Staberg B, Hueg B. Interaction between 8-methoxypsoralen and phenytoin. Consequence for PUVA therapy. *Acta Derm Venereol* (1985) 65, 553–5.

Raloxifene + Miscellaneous

The absorption of raloxifene is reduced by colestyramine and predicted to be reduced by colestipol. No clinically relevant changes

in raloxifene pharmacokinetics occur with aluminium/magnesium hydroxide, amoxicillin, ampicillin or calcium carbonate. Raloxifene does not alter digoxin or methylprednisolone levels. Oral antibacterials, antihistamines, aspirin, benzodiazepines, H_2-receptor antagonists, ibuprofen or paracetamol (acetaminophen) were used in clinical studies without any obvious effect on raloxifene levels. Smoking does not appear to alter the efficacy of raloxifene.

Clinical evidence, mechanism, importance and management

(a) Ampicillin and Amoxicillin

Ampicillin is reported to reduce the maximum serum levels of raloxifene by 28% and the extent of the absorption by 14% without affecting the elimination rate.[1] This is thought to be because ampicillin reduces the number of enteric bacteria and so reduces enterohepatic recycling of raloxifene. These small changes are unlikely to be clinically relevant. In another clinical efficacy study, there was no discernible difference in the plasma levels of raloxifene when it was taken with amoxicillin.[1]

(b) Antacids

The manufacturer of raloxifene reports that an antacid containing **aluminium/magnesium hydroxide**, given 1 hour before and 2 hours after raloxifene, had no effect on its absorption. Also, no interaction was seen with **calcium carbonate**.[2] There would therefore appear to be no reason for avoiding the concurrent use of these antacids and raloxifene.

(c) Colestyramine

The manufacturer reports that colestyramine reduced the absorption of raloxifene by about 60% due to an interruption in enterohepatic cycling.[1] It is recommended that these two drugs should not be used concurrently.[1,3] The manufacturers also predict that **colestipol** will interact similarly.[1,3]

(d) Digoxin

Raloxifene is reported not to affect the steady-state AUC of digoxin, while the maximum serum levels of digoxin were increased by less than 5%.[3]

(e) Methylprednisolone

Steady state raloxifene had no effect on the pharmacokinetics of a single oral dose of methylprednisolone.[1,3]

(f) Tobacco

Retrospective analysis of data from a placebo-controlled study of raloxifene found that raloxifene was equally effective in current tobacco smokers as non-smokers, although smokers had a lower baseline bone mineral density.[4]

(g) Miscellaneous

Data from clinical efficacy studies revealed no clinically relevant differences in the plasma levels of raloxifene when stratified according to concurrent drug use. These drugs included **oral antibacterials** (not named), **antihistamines** (not named), **aspirin**, **benzodiazepines** (not named), **H_2-receptor antagonists** (not named), NSAIDs (**ibuprofen**, **naproxen**), and **paracetamol** (**acetaminophen**).[3] There would therefore appear to be no reason for avoiding the concurrent use of any of these drugs with raloxifene.

1. Evista (Raloxifene hydrochloride). Eli Lilly and Company. US Prescribing information, October 2008.
2. Eli Lilly and Company Limited. Personal communication, September 1998.
3. Evista (Raloxifene hydrochloride). Daiichi Sankyo UK Ltd. UK Summary of product characteristics, August 2003.
4. Chapurlat RD, Ewing SK, Bauer DC, Cummings SR. Influence of smoking on the antiosteoporotic efficacy of raloxifene. *J Clin Endocrinol Metab* (2001) 86, 4178–82.

Retinoids + Food

Fatty foods increase the absorption of acitretin, etretinate and isotretinoin.

Clinical evidence

(a) Acitretin

In a study in 18 healthy subjects the absorption of acitretin was increased by 90% and its peak plasma concentrations were increased by 70% when acitretin 50 mg was taken with a standard breakfast. The breakfast consisted of two poached eggs, two slices of toast, two pats of margarine and 8 oz (about 240 mL) of skimmed milk.[1]

(b) Etretinate

Studies have found that high-fat meals and **milk** cause about a two- to fivefold increase in the absorption of **etretinate**, when compared with high-carbohydrate meals or when fasting.[2,3]

(c) Isotretinoin

In a study in 20 healthy subjects the AUC of a single 80-mg dose of isotretinoin was increased by 40%, 70%, and 90% when taken one hour before a **standard breakfast**, during **breakfast**, and one hour after **breakfast**, respectively, when compared with the same dose of isotretinoin taken 4 hours before breakfast.[4]

Mechanism

It is thought that, because these retinoids are lipid soluble, they become absorbed into the lymphatic system by becoming incorporated into the bile-acid micelles of the fats in the food. In this way losses due to first-pass liver metabolism and gut wall metabolism are minimised, and bioavailability is increased.

Importance and management

Established interactions of clinical importance. The manufacturers of acitretin recommend taking it with meals[5,6] or with milk,[5] and the manufacturers of isotretinoin recommend taking it with food.[7,8] Similar recommendations were made with etretinate.[9] On the basis of these interactions, the UK manufacturers of oral **alitretinoin**[10] and oral **tretinoin** also recommend administration with food.[11]

1. McNamara PJ, Jewell RC, Jensen BK, Brindley CJ. Food increases the bioavailability of acitretin. *J Clin Pharmacol* (1988) 28, 1051–5.
2. DiGiovanna JJ, Cross EG, McClean SW, Ruddel ME, Gantt G, Peck GL. Etretinate: effect of milk intake on absorption. *J Invest Dermatol* (1984) 82, 636–40.
3. Colburn WA, Gibson DM, Rodriguez LC, Buggé CJL, Blumenthal HP. Effect of meals on the kinetics of etretinate. *J Clin Pharmacol* (1985) 25, 583–9.
4. Colburn WA, Gibson DM, Wiens RE, Hanigan JJ. Food increases the bioavailability of isotretinoin. *J Clin Pharmacol* (1983) 23, 534–9.
5. Neotigason (Acitretin). Actavis UK Ltd. UK Summary of product characteristics, October 2008.
6. Soriatane (Acitretin). Stiefel Labs, Inc. US Prescribing information, September 2008.
7. Roaccutane (Isotretinoin). Roche Products Ltd. UK Summary of product characteristics, October 2009.
8. Accutane (Isotretinoin). Roche Laboratories Inc. US Prescribing information, November 2008.
9. Tigason (Etretinate). Roche Products Ltd. ABPI Datasheet Compendium, 1993–1994, p.1347–9.
10. Toctino (Alitretinoin). Basilea Pharmaceutica. UK Summary of product characteristics, September 2008.
11. Vesanoid (Tretinoin). Roche Products Ltd. UK Summary of product characteristics, October 2008.

Retinoids + Protease inhibitors

Symptoms of retinoid toxicity and reduced plasma levels of retinoic acid occurred in a patient who took isotretinoin with indinavir and ritonavir. Protease inhibitors are predicted to inhibit the metabolism of alitretinoin.

Clinical evidence, mechanism, importance and management

An HIV-positive patient taking oral isotretinoin 50 mg daily for severe acne developed signs of retinoid toxicity after starting to take **indinavir** 800 mg daily, **ritonavir** 600 mg daily, zidovudine 600 mg daily, and lamivudine 300 mg daily. However, plasma levels of 4-oxo retinoic acids and non-oxidised retinoic acids were *decreased*. Since protease inhibitors such as **indinavir** and **ritonavir** are inhibitors of the cytochrome P450 isoenzyme CYP3A4, this finding was not expected. Oxidative metabolism of retinoic acid is reduced by other CYP3A4 inhibitors with resultant increases in plasma retinoic acid.[1] It was suggested that the symptoms of retinoid toxicity and reduced plasma retinoid levels may have resulted from increased cellular uptake of retinoids and this may be associated with modulation of retinoic acid signalling by protease inhibitors[1,2]

The clinical relevance of this case is unclear, but bear it in mind in the event of unexpected toxicity on concurrent use.

The UK manufacturers of alitretinoin note that, although the concurrent use of drugs such as the protease inhibitors have not been studied, other

drugs that inhibit CYP3A4 raise **alitretinoin** levels.[3] It may therefore be prudent to be alert for an increase in the adverse effects of **alitretinoin** if protease inhibitors are also being taken.

1. Sass JO, Padberg J. Human isotretinoin metabolism during indinavir therapy. *AIDS Res Hum Retroviruses* (2000) 16, 1451–2.
2. Lenhard JM, Weiel JE, Paulik MA, Furfine ES. Stimulation of vitamin A_1 acid signaling by the HIV protease inhibitor indinavir. *Biochem Pharmacol* (2000) 59, 1063–8.
3. Toctino (Alitretinoin). Basilea Pharmaceutica. UK Summary of product characteristics, September 2008.

Retinoids + Tetracyclines

The development of pseudotumour cerebri (benign intracranial hypertension) has been associated with the concurrent use of acitretin or isotretinoin and tetracyclines. Other retinoids are expected to interact similarly.

Clinical evidence, mechanism, importance and management

The concurrent use of **isotretinoin** and a tetracycline has resulted in the development of pseudotumour cerebri (i.e. a clinical picture of cranial hypertension with headache, dizziness and visual disturbances). By 1983, the FDA in the US had received reports of 10 patients with pseudotumour cerebri and/or papilloedema associated with the use of **isotretinoin**. Four had retinal haemorrhages, and 5 of the 10 were also taking a tetracycline.[1] The manufacturers also have similar reports on file of 3 patients given **isotretinoin** and either **minocycline** or **tetracycline**.[2] The same reaction has been seen in a patient given **etretinate** with **minocycline**.[3]

Both retinoids and tetracyclines alone can cause increased intracranial pressure, and they might have an additive effect when used together.

The manufacturers of **acitretin**,[4,5] oral **alitretinoin**,[6] **isotretinoin**[7] and oral **tretinoin**[8] contraindicate their use with tetracyclines, or advise avoiding the concurrent use of tetracyclines.[9]

1. Anon. Adverse effects with isotretinoin. *FDA Drug Bull* (1983) 13, 21–3.
2. Shalita AR, Cunningham WJ, Leyden JJ, Pochi PE, Strauss JS. Isotretinoin treatment of acne and related disorders: an update. *J Am Acad Dermatol* (1983) 9, 629–38.
3. Viraben R, Mathieu C, Fonton B. Benign intracranial hypertension during etretinate therapy for mycosis fungoides. *J Am Acad Dermatol* (1985) 13, 515–17.
4. Neotigason (Acitretin). Actavis UK Ltd. UK Summary of product characteristics, October 2008.
5. Soriatane (Acitretin). Stiefel Labs, Inc. US Prescribing information, September 2008.
6. Toctino (Alitretinoin). Basilea Pharmaceutica. UK Summary of product characteristics, September 2008.
7. Roaccutane (Isotretinoin). Roche Products Ltd. UK Summary of product characteristics, October 2009.
8. Vesanoid (Tretinoin). Roche Products Ltd. UK Summary of product characteristics, October 2008.
9. Accutane (Isotretinoin). Roche Laboratories Inc. US Prescribing information, November 2008.

Retinoids + Vitamin A (Retinol)

A condition similar to vitamin A (retinol) overdosage may occur if oral retinoids such as acitretin, alitretinoin, isotretinoin or tretinoin are given with vitamin A.

Clinical evidence, mechanism, importance and management

Combined treatment with **isotretinoin** and vitamin A may result in a condition similar to overdosage with vitamin A. Signs and symptoms of hypervitaminosis A include skin changes (yellowing, dryness, alopecia), anorexia, vomiting, neuropsychiatric effects, raised intracranial pressure, and musculoskeletal effects, including premature fusion of the epiphyseal discs in children (which is irreversible). Concurrent use should therefore be avoided or very closely monitored.

The manufacturers of **acitretin** say that the concurrent use of high-dose vitamin A should be avoided: in the UK[1] they advise no more than 4000 to 5000 units of vitamin A daily, which is the recommended daily allowance, and in the US[2] they advise doses of no more than the minimum recommended daily allowance. Similarly, the manufacturers of oral **alitretinoin**,[3] **isotretinoin**[4,5] and oral **tretinoin**[6,7] say that vitamin A should be avoided.

1. Neotigason (Acitretin). Actavis UK Ltd. UK Summary of product characteristics, October 2008.
2. Soriatane (Acitretin). Stiefel Labs, Inc. US Prescribing information, September 2008.
3. Toctino (Alitretinoin). Basilea Pharmaceutica. UK Summary of product characteristics, September 2008.
4. Roaccutane (Isotretinoin). Roche Products Ltd. UK Summary of product characteristics, October 2009.
5. Accutane (Isotretinoin). Roche Laboratories Inc. US Prescribing information, November 2008.
6. Vesanoid (Tretinoin). Roche Products Ltd. UK Summary of product characteristics, October 2008.
7. Vesanoid (Tretinoin). Roche Laboratories Inc. US Prescribing information, July 2008.

Ritodrine + Miscellaneous

Supraventricular tachycardia developed in a woman given ritodrine when she was also given glycopyrronium (glycopyrrolate), and tachycardia has been reported in two patients when atropine was used with ritodrine. Hypertension has been reported when cyclopropane was given to patients who had recently received ritodrine. The abuse of cocaine does not appear to increase the incidence of adverse effects in patients given ritodrine. Hypokalaemia is a known adverse effect of ritodrine and this effect may be additive with other drugs that lower potassium levels.

Clinical evidence, mechanism, importance and management

(a) Antimuscarinics

A case report describes premature labour in a 39-year-old woman who was 28 weeks pregnant, which was arrested with an intravenous infusion of ritodrine hydrochloride. Two weeks later, while she was receiving the maximum dose of ritodrine (300 micrograms/minute), her uterine contractions began again and she was scheduled for an emergency caesarean section. The ritodrine was discontinued 40 minutes before the operation. It was noted in the operating room that she had copious oral secretions so she was given 100% oxygen by mask and 200 micrograms of intravenous **glycopyrronium** (**glycopyrrolate**). Shortly afterwards she developed a supraventricular tachycardia (a rise in heart rate from 80 up to 180 bpm), which was converted to sinus tachycardia of 130 bpm when she was given intravenous propranolol 500 micrograms, in divided doses over several minutes.[1] Two other patients given intravenous ritodrine 6 mg over 3 minutes developed tachyarrhythmias when they were premedicated with **atropine**.[2]

The reason for these reactions is not understood. Ritodrine alone has been responsible for tachyarrhythmias and one possible explanation for this interaction is that the effects of ritodrine and the antimuscarinic drug were additive.

Information is very limited and the interaction is not well established but some caution is clearly appropriate if both drugs are used. The authors of the first report advise avoidance. Arrhythmias have occurred when other sympathomimetics have been given with antimuscarinics, see 'Inotropes and Vasopressors + Antimuscarinics', p.1061.

(b) Cocaine

A study in 51 pregnant patients given ritodrine for premature labour found no evidence of an increase in adverse effects in 17 of the patients who had been abusing cocaine.[3]

(c) Cyclopropane

In an analysis of 43 women who had a caesarean section under cyclopropane anaesthesia, all of the 6 who had previously been given ritodrine developed unacceptably high blood pressure (185/103 mmHg) after cyclopropane was started. Arrhythmias were reported in two of these patients.[4]

(d) Drugs that lower potassium

Ritodrine is a $beta_2$ agonist, and in common with other drugs of this class, may lower potassium levels. These effects may be additive with other drugs that are known to lower potassium levels, such as **amphotericin B**, the **corticosteroids**, **loop** or **thiazide diuretics**, consider 'Beta-agonist bronchodilators + Potassium-depleting drugs', p.1417, and **theophylline**, consider 'Theophylline + Beta-agonist bronchodilators', p.1432.

1. Simpson JI, Giffin JP. A glycopyrrolate-ritodrine drug-drug interaction. *Can J Anaesth* (1988) 35, 187–9.
2. Sheybany S, Murphy JF, Evans D, Newcombe RG, Pearson JF. Ritodrine in the management of fetal distress. *Br J Obstet Gynaecol* (1982) 89, 723–6.

3. Darby MJ, Mazdisnian F. Does recent cocaine use increase the risk of side effects with β-adrenergic tocolysis? *Am J Obstet Gynecol* (1991) 164, 377.
4. Johannsen G. Ritodrine and cyclopropane interaction. *Anaesthesia* (1980) 35, 84–85.

Sodium oxybate + Miscellaneous

Additive CNS depressant effects are predicted when sodium oxybate is given with other CNS depressant drugs, and concurrent use of sedative hypnotics should be avoided. In theory, sodium oxybate may interact with valproate, phenytoin and ethosuximide. No pharmacokinetic interaction occurs with omeprazole, protriptyline, zolpidem or modafinil, but a pharmacodynamic interaction cannot be ruled out. Food markedly delays and modestly reduces the absorption of sodium oxybate.

Clinical evidence, mechanism, importance and management

(a) Antiepileptics

The UK manufacturer suggests that, as sodium oxybate is metabolised by gamma hydroxybutyrate dehydrogenase there is a potential risk of an interaction with drugs that induce or inhibit this enzyme. They name **valproate**, **phenytoin** and **ethosuximide**.[1] However, there do not appear to be any *in vivo* studies to confirm this prediction and its clinical relevance is unclear.

See also *Barbiturates*, below.

(b) CNS depressants

Sodium oxybate is the sodium salt of **gamma hydroxybutyrate** (GHB), a CNS depressant substance with well known abuse potential. When used clinically it is predicted to have additive effects with other CNS depressants and the manufacturers specifically say it should not be used with these.[1,2]

1. Antidepressants. The manufacturer notes that there was no pharmacokinetic interaction between sodium oxybate and **protriptyline**, but that the possibility of a pharmacodynamic interaction was not assessed.[1,2] The UK manufacturer states that the rate of adverse effects was increased when sodium oxybate was given with **tricyclic antidepressants**.[1]

2. Barbiturates. The UK manufacturer specifically contraindicates the use of sodium oxybate in patients taking barbiturates.[1]

3. Benzodiazepines and related hypnotics. The manufacturer states that sodium oxybate should not be given in combination with sedative hypnotics,[1,2] and the UK manufacturer specifically cautions against the concurrent use of benzodiazepines because of the possibility of increased risk of respiratory depression.[1]

The manufacturer notes that there was no pharmacokinetic interaction between sodium oxybate and **zolpidem**, but that the possibility of a pharmacodynamic interaction was not assessed,[1] and cannot be ruled out.[2]

4. Opioids. The UK manufacturer specifically contraindicates the use of sodium oxybate in patients taking opioids.[1]

(c) Food

In a study in 34 healthy subjects, giving 4.5 g of sodium oxybate solution after a high-fat meal delayed the time to maximum level from 0.75 hours to 2 hours, and reduced the maximum level by 58% and the AUC by 35%, when compared with the fasted state.[3] The first dose of sodium oxybate should be taken at least 2 to 3 hours after the evening meal, and patients should always try to keep the same timing of dosing in relation to meals.[1,2]

(d) Modafinil and other CNS stimulants

The manufacturer notes that there was no pharmacokinetic interaction between sodium oxybate and **modafinil**, but that the possibility of a pharmacodynamic interaction was not assessed.[1,2] About 80% of patients in clinical studies of sodium oxybate were also taking CNS stimulants.[1]

(e) Proton pump inhibitors

In a crossover study in 44 healthy subjects, pretreatment with **omeprazole** 40 mg daily for 5 days did not alter the pharmacokinetics of a single 3-g dose of sodium oxybate. There was no difference in the frequency and severity of adverse events.[4] No sodium oxybate dose adjustment is therefore expected to be needed in patients taking proton pump inhibitors.[1]

1. Xyrem (Sodium oxybate). UCB Pharma Ltd. UK Summary of product characteristics, July 2008.
2. Xyrem (Sodium oxybate). Jazz Pharmaceuticals, Inc. US Prescribing information, November 2005.
3. Borgen LA, Okerholm R, Morrison D, Lai A. The influence of gender and food on the pharmacokinetics of sodium oxybate oral solution in healthy subjects. *J Clin Pharmacol* (2003) 43, 59–65.
4. Borgen LA, Morrison D, Lai A. The effect of omeprazole on the bioavailability of sodium oxybate. *Clin Pharmacol Ther* (2004) 75, P21.

Strontium ranelate + Miscellaneous

Foods and calcium compounds markedly reduce the absorption of strontium ranelate, whereas aluminium and magnesium antacids only slightly reduce strontium ranelate absorption. Strontium ranelate is predicted to reduce the absorption of the quinolones and the tetracyclines. Vitamin D does not affect strontium ranelate bioavailability.

Clinical evidence, mechanism, importance and management

(a) Antacids

The manufacturer notes that **aluminium**/**magnesium hydroxide** slightly reduced the absorption of strontium ranelate (AUC decreased by 20 to 25%) when given either at the same time or 2 hours before the strontium. However, when the antacid was given 2 hours *after* strontium, absorption was barely affected.[1] Therefore, the manufacturers recommend that antacids should be taken 2 hours after strontium ranelate. However, because it is also recommended that strontium ranelate is taken at bedtime, they say that, if this is impractical, concurrent intake is acceptable.[1] Note that **calcium**-containing antacids would have a greater effect, see *Foods and Calcium compounds* below, and concurrent intake would not be recommended.

(b) Foods and Calcium compounds

The manufacturer notes that food, milk, dairy products, and calcium supplements reduce the bioavailability of strontium ranelate by about 60 to 70%, when compared with administration 3 hours after a meal.[1] This is because divalent cations such as calcium form complexes with strontium ranelate, preventing its absorption. Therefore, strontium ranelate should not be taken within 2 hours of eating, or presumably within 2 hours of any calcium compound. The manufacturer recommends that strontium ranelate should be taken at bedtime, at least 2 hours after eating.[1]

(c) Quinolones and Tetracyclines

The manufacturer predicts that strontium will complex with quinolones and tetracyclines, preventing their absorption. Because of this, they recommend that when treatment with quinolones or tetracyclines is required, treatment with strontium ranelate should be temporarily suspended.[1]

(d) Vitamin D

The manufacturer notes that vitamin D supplements had no effect on strontium ranelate bioavailability.[1]

1. Protelos (Strontium ranelate). Servier Laboratories Ltd. UK Summary of product characteristics, January 2008.

Sugammadex + Miscellaneous

Sugammadex is predicted to modestly reduce progestogen levels from oral hormonal contraceptives. Toremifene, high-dose intravenous flucloxacillin and intravenous fusidic acid are predicted to displace vecuronium or rocuronium from sugammadex, and so result in recurrence of the neuromuscular blockade, or delay in recovery. Drugs with neuromuscular blocking activity may reduce the effectiveness of sugammadex. Cases of QT prolongation have been seen in patients who have received sugammadex with sevoflurane or propofol.

Clinical evidence, mechanism, importance and management

No pharmacokinetic drug interaction studies have been conducted with sugammadex, and interactions have been predicted on the basis of the binding affinity of sugammadex and other drugs.

(a) Anaesthetics

The manufacturer of sugammadex notes that a few cases of QTc interval prolongation have been reported in patients who have received sugammadex and **sevoflurane** or **propofol**. Details of the other drugs given during

the period of anaesthesia were not given.[1] Note that sugammadex alone does not appear to prolong the QTc interval to a clinically relevant extent.[1]

(b) Antibacterials

The manufacturer of sugammadex predicts that intravenous **flucloxacillin** given pre-operatively in doses of 500 mg or more, or intravenous **fusidic acid** may cause some displacement of vecuronium or rocuronium from the sugammadex complex, and may delay recovery. In addition, they advise avoidance of high-dose intravenous **flucloxacillin** and intravenous **fusidic acid** in the 6-hour postoperative period because of the possibility of recurrence of neuromuscular blockade. If this is not possible, the patient's ventilation should be closely monitored, particularly in the first 15 minutes after the flucloxacillin dose. Consideration may be given to using a further dose of sugammadex.[1] The importance of this potential interaction requires confirmation. Until further data are available these recommendations should be followed.

(c) Hormonal contraceptives

The manufacturer predicts that the AUC of progestogens may be reduced (by 34%, an amount they say is similar to the decrease seen when a hormonal contraceptive is taken 12 hours late) when patients also receive a single bolus dose of sugammadex, and that the effect on the estrogen will be lower. This is based on the fact that sugammadex might bind progestogens in the blood, so lowering the free plasma levels. They advise that the same precautions should be followed as for when one daily dose of the oral hormonal contraceptive is missed.[1] For non-oral hormonal contraceptives, they advise that patients should use an additional non-hormonal contraceptive method for the next 7 days, and also follow the specific product guidelines.[1]

Even if this predicted pharmacokinetic interaction is proved, it is difficult to envisage that a 34% reduction in AUC of a progestogen on a single day when the woman has undergone surgery will be clinically relevant, even for oral progestogen-only contraceptives, and especially for parenteral progestogen-only contraceptives and the levonorgestrel IUD. Note that combined hormonal contraceptives are usually discontinued before major surgery or surgery involving prolonged immobilisation of a lower limb, because of the increased risk of thrombosis.

(d) Neuromuscular blocking drugs

Sugammadex is used therapeutically to reverse the activity of **rocuronium** or **vecuronium**. If further neuromuscular blockade is required within 24 hours of giving sugammadex, a non-steroidal neuromuscular blocking agent should be used.[1] Examples of non-steroidal neuromuscular blocking agents (that is, benzylisoquinolinium type neuromuscular blocking agents) are given in 'Table 5.2', (p.101).

The manufacturer states that, if other drugs that potentiate the neuromuscular blocking effect of **rocuronium** or **vecuronium** are given in the postoperative period (after reversal of the effects of **rocuronium** or **vecuronium** with sugammadex) there is the possibility of recurrence of blockade, and a further dose of sugammadex may be required.[1]

(e) Toremifene

The manufacturer of sugammadex predicts that toremifene may displace vecuronium or rocuronium from the sugammadex complex. This may result in a delayed recovery following neuromuscular blockade if toremifene has been given on the same day.[1] The importance of this potential interaction requires confirmation.

1. Bridion (Sugammadex sodium). Organon Laboratories Ltd. UK Summary of product characteristics, July 2008.

Sulfinpyrazone + NSAIDs

A brief report suggests that the uricosuric effects of sulfinpyrazone are not opposed by the concurrent use of flufenamic acid, meclofenamic acid or mefenamic acid.[1,2] However, note that sulfinpyrazone can cause gastric bleeding and inhibit platelet aggregation, effects that might be additive with NSAIDs.
Consider also 'Uricosuric drugs + Aspirin or other Salicylates', p.1575.

1. Latham BA, Radcliff F, Robinson RG. The effect of mefenamic acid and flufenamic acid on plasma uric acid levels. *Ann Phys Med* (1966) 8, 242–3.
2. Robinson RG, Radcliff FJ. The effect of meclofenamic acid on plasma uric acid levels. *Med J Aust* (1972) 1, 1079–80.

Sulfinpyrazone + Probenecid

Probenecid reduces the urinary excretion of sulfinpyrazone, but the overall uric acid clearance remains unaltered.

Clinical evidence, mechanism, importance and management

A study in 8 patients with gout found that although probenecid inhibited the renal tubular excretion of sulfinpyrazone, reducing it by about 75%, the maximal uric acid clearance was about the same as when either drug was given alone.[1] There would therefore seem to be no advantage in using these drugs together. The possibility of an increase in the adverse effects of sulfinpyrazone, caused by this reduction in excretion, does not seem to have been studied.

1. Perel JM, Dayton PG, Snell MM, Yü TF, Gutman AB. Studies of interactions among drugs in man at the renal level: probenecid and sulphinpyrazone. *Clin Pharmacol Ther* (1969) 10, 834–40.

Testosterone + Miscellaneous

Dutasteride and finasteride increase the levels of oral testosterone. Food has little effect on the absorption of oral testosterone.

Clinical evidence, mechanism, importance and management

In a pharmacokinetic study in healthy men, **dutasteride** 500 micrograms daily for 6 days increased the AUC of testosterone and testosterone enanthate given as single oral doses of 200 mg, 400 mg and 800 mg on days 4, 5 and 6 of dutasteride administration. The increases in testosterone AUC ranged from 42% with the 200 mg dose to 2.6-fold with the 800 mg dose. Moreover, **dutasteride** attenuated the increase in serum dihydrotestosterone seen with oral testosterone. In this study, subjects had their endogenous testosterone temporarily suppressed by the injection of the GnRH antagonist acyline.[1]

In a similar subsequent study, **finasteride** 5 mg daily increased AUC of testosterone 400 mg 2.3-fold. **Food** caused a slight non-significant decrease in testosterone levels, when compared with the fasting state.[2]

Testosterone is poorly bioavailable by the oral route, and is rapidly metabolised to dihydrotestosterone by 5-alpha reductase. By inhibiting this enzyme, dutasteride and finasteride reduce the formation of dihydrotestosterone and increase testosterone levels.[1,2]

These studies suggest that the 5-alpha reductase inhibitors might be useful in increasing testosterone oral bioavailability for oral replacement therapy.[1,2]

1. Amory JK, Bremner WJ. Oral testosterone in oil plus dutasteride in men: a pharmacokinetic study. *J Clin Endocrinol Metab* (2005) 90, 2610–7.
2. Amory JK, Page ST, Bremner WJ. Oral testosterone in oil: pharmacokinetic effects of 5α reduction by finasteride or dutasteride and food intake in men. *J Androl* (2006) 27, 72–8.

Tizanidine + Antihypertensives

Tizanidine is predicted to increase the effects of antihypertensive drugs; two case reports describe severe hypotension with lisinopril. The manufacturer of tizanidine advises against the use of antihypertensives that are related to tizanidine (e.g. clonidine).

Clinical evidence

A 10-year-old child taking **lisinopril** developed severe hypotension within a week of starting to take tizanidine.[1] Similarly, a 48-year-old stroke patient taking **amlodipine**, **nimodipine**, **lisinopril**, and **labetalol**, which had been added sequentially to control hypertension, had a dramatic reduction in blood pressure (from 130/85 to 66/42 mmHg) within 2 hours of her first dose of tizanidine 2 mg. She was given dopamine to maintain her blood pressure, and tizanidine and all the antihypertensives were withdrawn. Later **labetalol**, **amlodipine**, **nimodipine** and tizanidine were successfully resumed without producing similar problems.[2]

Mechanism

Tizanidine is a centrally acting α_2-adrenergic agonist structurally related to clonidine and can cause dose-related hypotension (66% of patients giv-

en a single 8-mg dose of tizanidine had a 20% reduction in blood pressure). This can result in bradycardia, dizziness or light-headedness, and rarely syncope. The antihypertensive effects of tizanidine are said to be less than one-tenth of those of clonidine.[3] Nevertheless, these effects are expected to be additive with other antihypertensive drugs. However, in the cases with lisinopril, it was suggested that ACE inhibition, combined with the alpha-agonist effects of tizanidine prevented the usual sympathetic response to hypotension (that is, it was not thought to be due to simple additive hypotensive effects).[1,2]

Importance and management

Tizanidine alone can cause hypotension, an effect which is usually minimised by titration of the dose. Patients should be warned about this effect. Because of this, the manufacturers caution that tizanidine might increase the effects of antihypertensive drugs, including **diuretics**, and recommend caution on concurrent use.[3,4] This is a prudent precaution. The US manufacturer additionally states that tizanidine (an α_2-adrenergic agonist that is structurally related to clonidine) should not be used with other α_2-adrenergic agonists [e.g. **clonidine**, **methyldopa**].[3] The UK manufacturer additionally says that the concurrent use of **beta blockers** may potentiate bradycardia and hypotension.[4] This seems a reasonable prediction, as this effect has been seen with clonidine, see 'Clonidine and related drugs + Beta blockers', p.1053.

1. Johnson TR, Tobias JD. Hypotension following the initiation of tizanidine in a patient treated with an angiotensin converting enzyme inhibitor for chronic hypertension. *J Child Neurol* (2000) 15, 818–19.
2. Kao C-D, Chang J-B, Chen J-T, Wu Z-A, Shan D-E, Liao K-K. Hypotension due to interaction between lisinopril and tizanidine. *Ann Pharmacother* (2004) 38, 1840–43.
3. Zanaflex (Tizanidine hydrochloride). Acorda Therapeutics, Inc. US Prescribing information, April 2008.
4. Zanaflex (Tizanidine hydrochloride). Cephalon Ltd. UK Summary of product characteristics, June 2009.

Tizanidine + Cranberry juice

Limited evidence suggests that cranberry juice does not affect the pharmacokinetics of tizanidine.

Clinical evidence

In a randomised, crossover study in 10 healthy subjects, 200 mL of cranberry juice three times daily for 10 days had no significant effect on the pharmacokinetics of a single 1-mg oral dose of tizanidine, taken on day 5. In this study, the cranberry juice used was a concentrate (*Kontiomehu sokeroitu karpalomehu*) diluted 1 to 4 with tap water before use.[1]

Mechanism

This study suggests that cranberry juice has no clinically relevant effect on the activity of the cytochrome P450 isoenzyme CYP1A2.

Importance and management

Although the evidence is limited to this particular study, there appears to be no need for any special precautions when taking cranberry juice with tizanidine.

Tizanidine is used as a probe drug for CYP1A2 activity, and therefore these results also suggest that a pharmacokinetic interaction between cranberry juice and other CYP1A2 substrates is unlikely.

1. Lilja JJ, Backman JT, Neuvonen PJ. Effects of daily ingestion of cranberry juice on the pharmacokinetics of warfarin, tizanidine, and midazolam – probes of CYP2C9, CYP1A2, and CYP3A4. *Clin Pharmacol Ther* (2007) 81, 833–9.

Tizanidine + CYP1A2 inhibitors

Fluvoxamine causes a very marked 33-fold increase in tizanidine levels with a consequent increase in hypotensive and sedative effects. Similarly, ciprofloxacin markedly increases tizanidine levels and adverse effects. Combined oral contraceptives increase tizanidine levels fourfold and might increase its adverse effects. Other inhibitors of CYP1A2 are predicted to interact similarly.

Clinical evidence

(a) Ciprofloxacin

In a placebo-controlled, crossover study in 10 healthy subjects, ciprofloxacin 500 mg twice daily for 3 days markedly increased the AUC of a single 4-mg dose of tizanidine tenfold and increased its maximum level sevenfold, without significantly affecting its half-life. The hypotensive and sedative effects of tizanidine were also markedly increased by ciprofloxacin.[1]

A case report describes a 45-year-old Japanese woman with multiple sclerosis, taking tizanidine 3 mg daily, had a reduction in blood pressure (from 124/88 to 102/74 mmHg) and heart rate (from 86 to 58 bpm) shortly after starting to take ciprofloxacin 400 mg daily. After 2 days she complained of drowsiness and her blood pressure was 92/54 mmHg.[2] Retrospective analysis revealed 8 patients who had taken tizanidine with ciprofloxacin. In these patients, the mean reduction in blood pressure on starting ciprofloxacin was 21.3/15.4 mmHg, and the heart rate reduction was 14.9 bpm. Adverse effects attributable to tizanidine occurred in three of the patients.[2]

(b) Fluvoxamine

In a placebo-controlled, crossover study in 10 healthy subjects, fluvoxamine 100 mg daily for 4 days very markedly increased the AUC of a single 4-mg dose of tizanidine 33-fold and increased its maximum level 12-fold. The elimination half-life of tizanidine was prolonged from 1.5 to 4.3 hours. The hypotensive and sedative effects of tizanidine were also markedly increased by fluvoxamine, with all of the 10 subjects somnolent and dizzy for 3 to 6 hours.[3]

A case report describes a 70-year-old Japanese woman who started taking tizanidine 3 mg daily 15 days after starting fluvoxamine (100 mg increased to 150 mg daily). Her heart rate dropped from about 85 bpm to a range of 56 to 60 bpm. After tizanidine was stopped, the symptoms improved immediately.[4] Retrospective analysis revealed 23 patients who had received tizanidine with fluvoxamine. Of these patients, 6 had adverse effects including low heart rate, dizziness, drowsiness and hypotension. The patients with adverse effects were, on average, taking higher doses of fluvoxamine and tizanidine than those without adverse effects.[4]

(c) Oral contraceptives

In a study in 15 healthy women taking a combined oral contraceptive (**ethinylestradiol** with **gestodene**), the AUC of a single 4-mg dose of tizanidine was 3.9-fold higher than in 15 healthy women not taking an oral contraceptive. The elimination half-life of tizanidine was unchanged. In addition, the blood pressure-lowering effect of tizanidine was increased by 12/8 mmHg in the oral contraceptive users.[5] The manufacturer also notes that retrospective analysis of population pharmacokinetic data found that the clearance of tizanidine is about 50% lower in women taking oral contraceptives.[6,7]

Mechanism

Tizanidine is a substrate of the cytochrome P450 isoenzyme CYP1A2, and undergoes substantial presystemic metabolism by this route. Ciprofloxacin appears to inhibit mainly the presystemic metabolism of tizanidine by this isoenzyme, leading to increased absorption, as reflected by the increase in maximum level without a change in elimination half-life. Fluvoxamine inhibited both the presystemic metabolism of tizanidine and the elimination phase. Fluvoxamine, which is a known potent inhibitor of CYP1A2, had the most marked effect. The contraceptive steroids were modest inhibitors of CYP1A2 by comparison.

Importance and management

These pharmacokinetic interactions are well established, and clinically important. The common adverse effects of tizanidine, such as hypotension and sedation, are dose related, and consequently the manufacturers recommend starting with a low dose of tizanidine (2 or 4 mg) and carefully titrating to the usual maximum of 24 mg daily, and not exceeding 36 mg daily.[6,7] This represents a maximum 18-fold variation in dosage. **Fluvoxamine** increases the exposure to tizanidine by a mean of 33-fold, which, broadly speaking, changes a 2 mg dose into a 66 mg dose, which is far higher than the maximum recommended dose. For this reason, the authors of one of the studies conclude that the combination is potentially hazardous and should be avoided,[3] and the manufacturers contraindicate the combination.[6,7] Given the available data this is sensible advice. Note that other **SSRIs** are generally not considered to inhibit CYP1A2, see 'Theo-

phylline + SSRIs', p.1457, and may therefore be suitable alternatives to fluvoxamine.

For **ciprofloxacin**, there is a marked tenfold increase in exposure to tizanidine, with a consequent increase in adverse effects. Some authors recommend caution if both drugs are necessary,[1] whereas other suggest that this combination should be avoided.[2] The manufacturers contraindicate the combination.[6,7] If ciprofloxacin is considered the most appropriate antibacterial to use in a patient already taking tizanidine, anticipate the need to reduce the tizanidine dose before starting ciprofloxacin, and closely monitor adverse effects: starting ciprofloxacin may cause marked hypotension, bradycardia, and sedation. Note that the manufacturers also recommend that the use of tizanidine with **enoxacin** and **norfloxacin** should generally be avoided, or undertaken with caution. However, note that enoxacin is usually considered a more potent inhibitor of CYP1A2 than ciprofloxacin, whereas norfloxacin only has modest effects on CYP1A2. Other quinolones may also inhibit CYP1A2, to varying degrees, see 'Table 34.4', (p.1453).

For **combined oral contraceptives**, the increase in exposure to tizanidine is a more moderate fourfold. The manufacturer states that clinical response or adverse effects might occur at lower doses of tizanidine in patients taking oral contraceptives,[6] and that during dose titration, individual doses should be reduced.[7] Care is needed.[7]

In addition, the manufacturers also recommend that the use of tizanidine with other inhibitors of CYP1A2 should generally be avoided, or used with caution, and they specifically mention **aciclovir**, **amiodarone**, **cimetidine**, **famotidine**, **mexiletine**, **propafenone**, **ticlopidine**, **verapamil** and **zileuton**.[6,7] However, note that a number of these drugs have not been shown to have clinically relevant effects on this isoenzyme. For a list of some clinically relevant CYP1A2 inhibitors, see 'Table 1.2', (p.4).

1. Granfors MT, Backman JT, Neuvonen M, Neuvonen PJ. Ciprofloxacin greatly increases concentrations and hypotensive effect of tizanidine by inhibiting its cytochrome P450 1A2-mediated presystemic metabolism. *Clin Pharmacol Ther* (2004) 76, 598–606.
2. Momo K, Homma M, Kohda Y, Ohkoshi N, Yoshizawa T, Tamaoka A. Drug interaction of tizanidine and ciprofloxacin: case report. *Clin Pharmacol Ther* (2006) 80, 717–9.
3. Granfors MT, Backman JT, Neuvonen M, Ahonen J, Neuvonen PJ. Fluvoxamine drastically increases concentrations and effects of tizanidine: a potentially hazardous interaction. *Clin Pharmacol Ther* (2004) 75, 331–41.
4. Momo K, Doki K, Hosono H, Homma M, Kohda Y. Drug interaction of tizanidine and fluvoxamine. *Clin Pharmacol Ther* (2004) 76, 509–10.
5. Granfors MT, Backman JT, Laitila J, Neuvonen PJ. Oral contraceptives containing ethinyl estradiol and gestodene markedly increase plasma concentrations and effects of tizanidine by inhibiting cytochrome P450 1A2. *Clin Pharmacol Ther* (2005) 78, 400–11.
6. Zanaflex (Tizanidine hydrochloride). Cephalon Ltd. UK Summary of product characteristics, June 2009.
7. Zanaflex (Tizanidine hydrochloride). Acorda Therapeutics, Inc. US Prescribing information, April 2008.

Tizanidine + Food

Food modestly increases the maximum levels and AUC of tizanidine tablets, but modestly decreases the maximum levels and slightly increases the AUC of tizanidine modified-release capsules.

Clinical evidence, mechanism, importance and management

In a single-dose pharmacokinetic study in 81 healthy subjects, the absorption of tizanidine modified-release capsules was equivalent to that of tablets in fasted subjects. When the *tablets* were taken with food, the mean maximum level of tizanidine was increased by about 25%, and the median time to peak plasma concentration increased from about one hour to 1 hour and 25 minutes, and the extent of absorption was increased by about 30%. Conversely, when the *capsules* were taken with food, the maximum level of tizanidine decreased by about 15%, the median time to peak plasma concentration increased from one hour to 3 hours, and the extent of absorption increased by just 10%. This means that, when taken with food, the amount absorbed from the capsule is more than 80% of the amount absorbed from the tablet.[1] Similar findings were reported in another study.[2]

The manufacturer notes that taking the capsule contents sprinkled on apple sauce is not bioequivalent to taking an intact capsule under fasting conditions. Giving the capsule contents on apple sauce results in a 15 to 20% increase in the maximum levels and AUC of tizanidine, when compared with giving an intact capsule while fasting.[3]

Although modest, the changes described could be clinically relevant in terms of onset of effect and adverse effects. The effects differ between the capsule and tablet formulations, and are probably of greatest importance if patients are changed from capsules to tablets, or vice versa.

1. Shah J, Wesnes KA, Kovelesky RA, Henney HR. Effects of food on the single-dose pharmacokinetics/pharmacodynamics of tizanidine capsules and tablets in healthy volunteers. *Clin Ther* (2006) 28, 1308–17.
2. Henney HR, Shah J. Relative bioavailability of tizanidine 4-mg capsule and tablet formulations after a standardized high-fat meal: a single-dose, randomized, open-label, crossover study in healthy subjects. *Clin Ther* (2007) 29, 661–9.
3. Zanaflex (Tizanidine hydrochloride). Acorda Therapeutics, Inc. US Prescribing information, April 2008.

Tizanidine + Miscellaneous

The sedative effects of tizanidine and other sedative drugs and alcohol are additive. Increased bradycardia might occur if digoxin is given with tizanidine. It is unclear whether tizanidine prolongs the QT interval in humans. No interaction occurs with paracetamol (acetaminophen).

Clinical evidence, mechanism, importance and management

(a) CNS depressants

One of the most common adverse effects of tizanidine is somnolence or drowsiness (occurring in up to 50% of patients[1]) for which reason the manufacturers warn about the possibility of increased sedation with other **sedative drugs**, and **alcohol**.[2,3] In addition to additive sedative effects, **alcohol** increased the AUC of tizanidine by about 20% and increases its maximum level by 15%, which was associated with an increase in the adverse effects of tizanidine.[3] Patients should be warned that concurrent use may increase drowsiness, and be advised to avoid driving and related skilled tasks if affected.

(b) Digoxin

Tizanidine alone can cause bradycardia.[2,3] The UK manufacturer says that the concurrent use of digoxin may potentiate bradycardia.[2]

(c) Drugs that prolong the QT interval

The US manufacturer states that prolongation of the QT interval and bradycardia were noted in chronic toxicity studies in *dogs* at doses equal to the maximum dose of tizanidine.[3] The UK information advises caution if tizanidine is prescribed with drugs known to increase the QT interval.[2] However, in one pharmacological interaction study in healthy subjects, there was no evidence of QT prolongation either with tizanidine 4 mg, or almost 14-fold increased tizanidine levels caused by 'rofecoxib', (below), despite adverse effects such as increased bradycardia and hypotension occurring.[4] This suggests that a clinically significant interaction resulting in QT prolongation is unlikely.

(d) Paracetamol (Acetaminophen)

In 20 healthy subjects, no clinically significant interaction occurred between 325 mg of paracetamol and 4 mg of tizanidine.[1]

1. Wagstaff AJ, Bryson HM. Tizanidine. A review of its pharmacology, clinical efficacy and tolerability in the management of spasticity associated with cerebral and spinal disorders. *Drugs* (1997) 53, 435–52.
2. Zanaflex (Tizanidine hydrochloride). Cephalon Ltd. UK Summary of product characteristics, June 2009.
3. Zanaflex (Tizanidine hydrochloride). Acorda Therapeutics, Inc. US Prescribing information, April 2008.
4. Backman JT, Karjalainen MJ, Neuvonen M, Laitila J, Neuvonen PJ. Rofecoxib is a potent inhibitor of cytochrome P450 1A2: studies with tizanidine and caffeine in healthy subjects. *Br J Clin Pharmacol* (2006) 62, 345–57.

Tizanidine + NSAIDs

Celecoxib and tolfenamic acid do not appear to affect the pharmacokinetics or pharmacodynamics of tizanidine. Rofecoxib (now withdrawn) caused a very marked rise in the AUC of tizanidine.

Clinical evidence

(a) Celecoxib

In a pharmacokinetic study in 12 healthy subjects, celecoxib 200 mg twice daily for 4 days had no effect on the pharmacokinetics of a single 2-mg

dose of tizanidine given on the morning of day 4. The pharmacodynamic effects of tizanidine were not altered by celecoxib.[1]

(b) Rofecoxib

In a placebo-controlled, crossover study in 9 healthy subjects, rofecoxib 25 mg daily for 4 days markedly increased the AUC of a single 4-mg dose of tizanidine 13.6-fold and increased the maximum level 6.1-fold. The hypotensive and sedative effects of tizanidine were also markedly increased by rofecoxib. There was no evidence of QT prolongation in this study.[2]

A case report describes an otherwise healthy 59-year-old woman, who developed sinus bradycardia (30 bpm) with chest pain and acute right heart failure while taking tizanidine, diclofenac and rofecoxib. This resolved promptly after stopping the medication.[3]

(c) Tolfenamic acid

In a pharmacokinetic study in 10 healthy subjects, tolfenamic acid 200 mg three times daily for 3 days had no effect on the pharmacokinetics of a single 4-mg dose of tizanidine given on day 3. The only change was a slight 13% decrease in the plasma levels of the secondary metabolite of tizanidine, M4. The pharmacodynamic effects of tizanidine were not altered by tolfenamic acid.[4]

Mechanism

Tizanidine is a substrate of the cytochrome P450 isoenzyme CYP1A2, and undergoes substantial presystemic metabolism by this isoenzyme. Rofecoxib, an inhibitor of CYP1A2, decreases both the presystemic metabolism of tizanidine, and its elimination phase.[5] Despite *in vitro* evidence of CYP1A2 inhibition,[1,4] neither celecoxib nor tolfenamic acid appear to alter the pharmacokinetics of tizanidine.

Importance and management

The pharmacokinetic interaction of rofecoxib with tizanidine is well established, and the combination should be avoided. However, note that rofecoxib was generally withdrawn worldwide in 2004 because of its cardiovascular adverse effects, but the interaction is included here for completeness.

Neither celecoxib nor tolfenamic acid interact, so no special precautions are required if these NSAIDs are given to patients taking tizanidine.

1. Karjalainen MJ, Neuvonen PJ, Backman JT. Celecoxib is a CYP1A2 inhibitor in vitro but not in vivo. Eur J Clin Pharmacol (2008) 64, 511–19.
2. Backman JT, Karjalainen MJ, Neuvonen M, Laitila J, Neuvonen PJ. Rofecoxib is a potent inhibitor of cytochrome P450 1A2: studies with tizanidine and caffeine in healthy subjects. *Br J Clin Pharmacol* (2006) 62, 345–57.
3. Kick A, Bertoli R, Moschovitis G, Caduff Janosa P, Cerny A. Extreme Sinusbradykardie (30/min) mit akuter Rechtsherzbelastung unter Tizanidin (Sirdalud®): Mögliche Arzneimittelinteraktion mit rofecoxib (Vioxx®). *Med Klin* (2005) 100, 213–16.
4. Karjalainen MJ, Neuvonen PJ, Backman JT. Tolfenamic acid is a potent CYP1A2 inhibitor in vitro but does not interact in vivo: correction for protein binding is needed for data interpretation. *Eur J Clin Pharmacol* (2007) 63, 829–36.
5. Karjalainen MJ, Neuvonen PJ, Backman JT. Rofecoxib is a potent, metabolism-dependent inhibitor of CYP1A2: implications for in vitro prediction of drug interactions. *Drug Metab Dispos* (2006) 34, 2091–6.

Tizanidine + Rifampicin (Rifampin)

Rifampicin moderately decreases the plasma concentrations of tizanidine.

Clinical evidence, mechanism, importance and management

In a placebo-controlled, crossover study in 10 healthy subjects, pre-treatment with rifampicin 600 mg daily for 5 days moderately reduced the AUC and peak level of a single 4-mg dose of tizanidine given on day 6 by about 50%, without altering its half-life.[1]

Rifampicin appears to be only a weak inducer of the cytochrome P450 isoenzyme CYP1A2, by which tizanidine is metabolised.[1]

Although rifampicin moderately reduces the levels and effects of tizanidine, because the tizanidine dose is titrated to effect, this seems unlikely to be clinically important. A small increase in dose might be required if rifampicin is given to those on established tizanidine treatment.

1. Backman JT, Granfors MT, Neuvonen PJ. Rifampicin is only a weak inducer of CYP1A2-mediated presystemic and systemic metabolism: studies with tizanidine and caffeine. *Eur J Clin Pharmacol* (2006) 62, 451–61.

Tolvaptan + Diuretics; Loop, Thiazide and related

The concurrent use of tolvaptan and furosemide or hydrochlorothiazide does not appear to affect the pharmacokinetics or pharmacodynamics of either drug to a clinically relevant extent. However, the concurrent use of tolvaptan and diuretics can increase the risk of dehydration and hypovolaemia.

Clinical evidence, mechanism, importance and management

In a single-dose, randomised, crossover study in 6 healthy subjects given tolvaptan 30 mg, **furosemide** 80 mg or both drugs together, there were no differences in the pharmacokinetics of **furosemide**, but the AUC of tolvaptan was slightly increased, by 24%.[1] However, there were no changes in the pharmacodynamics of either drug.

In the same study, a further 6 healthy subjects were given tolvaptan 30 mg, **hydrochlorothiazide** 100 mg or both drugs together. There were no differences found in the pharmacokinetics or pharmacodynamics of either drug.[1] The concurrent use of tolvaptan and either **furosemide** or **hydrochlorothiazide** did not result in a greater 24-hour urinary volume than tolvaptan alone, suggesting that the diuretic effect of these drugs was not additive.[1]

This study provides evidence that no clinically important pharmacokinetic interaction would be expected if tolvaptan is given with **furosemide** or **hydrochlorothiazide**. However, note that the US manufacturer of tolvaptan[2] states that it induces copious aquaresis, which can result in dehydration and hypovolaemia, particularly in patients also taking diuretics. Therefore some caution is warranted on concurrent use.

1. Shoaf SE, Bramer SL, Bricmont P, Zimmer CA. Pharmacokinetic and pharmacodynamic interaction between tolvaptan, a non-peptide AVP antagonist, and furosemide or hydrochlorothiazide. *J Cardiovasc Pharmacol* (2007) 50, 213–22.
2. Samsca (Tolvaptan). Otsuka America Pharmaceutical Inc. US Prescribing information, May 2009.

Tolvaptan + Ketoconazole and other CYP3A4 inhibitors

Ketoconazole (a potent CYP3A4 inhibitor) markedly increased the exposure to tolvaptan in one study, and other potent CYP3A4 inhibitors are likely to interact similarly. Grapefruit juice also increases the exposure to tolvaptan.

Clinical evidence, mechanism, importance and management

The manufacturer briefly notes that the AUC of tolvaptan is increased fivefold when ketoconazole 200 mg daily is also given.[1] **Grapefruit juice** also increases the exposure to tolvaptan, by 80%.[1,2] Ketoconazole is a potent inhibitor of the cytochrome P450 isoenzyme CYP3A4 in the liver, by which tolvaptan is primarily metabolised, and **grapefruit juice** is also an inhibitor of this isoenzyme in the intestine. Concurrent use therefore decreases tolvaptan metabolism and increases its exposure.

The clinical relevance of the marked increase in tolvaptan exposure with ketoconazole has not been assessed, but an increase in its effects would be expected. The US manufacturer contraindicates the concurrent use of ketoconazole and other potent CYP3A4 inhibitors, because there is no adequate experience to define the dose adjustment necessary to allow safe concurrent use. They specifically name **itraconazole**; the macrolides **clarithromycin** and **telithromycin**; the protease inhibitors **nelfinavir**, **ritonavir** and **saquinavir**, and **nefazodone**.[1] In addition, they also say that moderate CYP3A4 inhibitors, such as **aprepitant**, **diltiazem**, **erythromycin**, **fluconazole**, and **verapamil** should generally be avoided.[1] However, in the UK, the manufacturer simply advises caution with any CYP3A4 inhibitor, irrespective of potency.[2] For a list of CYP3A4 inhibitors see 'Table 1.4', (p.6). Both manufacturers suggest that the use of **grapefruit juice** should be avoided in patients taking tolvaptan.[1,2]

If any CYP3A4 inhibitor is considered essential in a patient taking tolvaptan, monitor the patient for increased adverse effects such as dry mouth, thirst and increased frequency of urination, and, ideally monitor fluid and electrolyte status. Reduce the dose of tolvaptan as necessary.

1. Samsca (Tolvaptan). Otsuka America Pharmaceutical Inc. US Prescribing information, May 2009.
2. Samsca (Tolvaptan). Otsuka Pharmaceuticals (UK) Ltd. UK Summary of product characteristics, August 2009.

Tolvaptan + Miscellaneous

The risk of hyperkalaemia with tolvaptan is slightly increased in patients taking drugs known to increase serum potassium levels such as ACE inhibitors, angiotensin II receptor antagonists and potassium-sparing diuretics. Tolvaptan modestly increases lovastatin levels, but lovastatin does not alter tolvaptan levels. Tolvaptan does not alter the pharmacokinetics of warfarin. P-glycoprotein inhibitors such as ciclosporin are predicted to increase levels of tolvaptan.

Clinical evidence, mechanism, importance and management

(a) Lovastatin

Exposure to tolvaptan is not affected by lovastatin; however, tolvaptan increased the plasma levels of lovastatin and its active metabolite by 40% and 30%, respectively.[1] This is because tolvaptan is a weak inhibitor of the cytochrome P450 isoenzyme CYP3A4,[1] by which lovastatin is metabolised. The increase in lovastatin exposure seen is probably not clinically relevant.

(b) P-glycoprotein inhibitors

The US manufacturer states that tolvaptan is a substrate of P-glycoprotein, and predicts that P-glycoprotein inhibitors (they name **ciclosporin**) may increase the levels of tolvaptan. The dose of tolvaptan may need to be reduced if **ciclosporin** or other P-glycoprotein inhibitors are also given.[1] Until more is known, some caution would be prudent.

(c) Potassium-sparing drugs

Tolvaptan may increase serum potassium levels.[1,2] The US manufacturer notes that, in clinical studies, the incidence of hyperkalaemia was about 1 to 2% higher in patients who had taken tolvaptan with **ACE inhibitors**, **angiotensin II receptor antagonists** and **potassium-sparing diuretics** than when any of these drugs were given with placebo. They therefore recommend monitoring of serum potassium levels on the concurrent use of tolvaptan and any of these drugs.[1] On this basis, the same precautions would also seem prudent in patients taking **potassium supplements**.

(d) Warfarin

The manufacturer briefly notes that the pharmacokinetics of warfarin are not altered to a clinically relevant extent by tolvaptan.[1,2] No warfarin dose adjustment would be expected to be needed on concurrent use.

1. Samsca (Tolvaptan). Otsuka America Pharmaceutical Inc. US Prescribing information, May 2009.
2. Samsca (Tolvaptan). Otsuka Pharmaceuticals (UK) Ltd. UK Summary of product characteristics, August 2009.

Tolvaptan + Rifampicin (Rifampin) and other CYP3A4 inducers

Rifampicin, a CYP3A4 inducer, markedly reduces the exposure to tolvaptan, and other CYP3A4 inducers are likely to interact similarly.

Clinical evidence, mechanism, importance and management

The manufacturer of tolvaptan briefly notes that the concurrent use of rifampicin reduces the AUC of tolvaptan by 85%.[1] Rifampicin is a potent inducer of the cytochrome P450 isoenzyme CYP3A4, by which tolvaptan is primarily metabolised. The reduction in tolvaptan exposure seen with rifampicin is likely to markedly reduce its effectiveness. The manufacturers predict that other CYP3A4 inducers are likely to interact similarly, and they name the **barbiturates**, **carbamazepine**, **phenytoin**, **rifabutin**, **rifapentine** and **St John's wort**.[1,2] Because of the potency of the effect of rifampicin, the US manufacturer states that concurrent use should be avoided, but note that most of these are weaker inducers than rifampicin. However, they do state that if concurrent use is necessary, the dose of tolvaptan may need to be increased.[1] The UK manufacturer simply advises caution on concurrent use.[2] If tolvaptan is given with a CYP3A4 inducer, it may be prudent to monitor the outcome of concurrent use, being alert for a reduction in tolvaptan efficacy, and increase the dose of tolvaptan, as necessary. For a list of CYP3A4 inducers see 'Table 1.4', (p.6).

1. Samsca (Tolvaptan). Otsuka America Pharmaceutical Inc. US Prescribing information, May 2009.
2. Samsca (Tolvaptan). Otsuka Pharmaceuticals (UK) Ltd. UK Summary of product characteristics, August 2009.

Trientine + Miscellaneous

Trientine can possibly chelate with iron thereby reducing its absorption. On theoretical grounds a similar chelation interaction may occur with calcium and magnesium antacids, and mineral supplements.

Clinical evidence, mechanism, importance and management

(a) Iron compounds

Trientine is a copper-chelating agent used for Wilson's disease. One of the adverse effects of trientine is that it can cause iron deficiency, probably because it chelates with iron in the gut and thereby reduces its absorption. It is usual to resolve this iron deficiency, where necessary, by giving an iron supplement. The manufacturers suggest that the iron supplement should be given at a different time of the day from trientine to minimise their admixture in the gut.[1,2] A separation of at least 2 hours is recommended.[2]

(b) Other mineral supplements and antacids

Trientine may be inactivated by metal binding in the gastrointestinal tract. The UK manufacturers say that there is no evidence that **calcium** or **magnesium antacids** alter the efficacy of trientine, but it is good practice to separate their administration.[1] The US manufactures say that, in general, mineral supplements should not be given with trientine. They say that it is important that trientine is taken at least one hour apart from any other drug or **milk**.[2]

1. Trientine dihydrochloride. Univar Ltd. UK Summary of product characteristics, July 2003.
2. Syprine (Trientine hydrochloride). Merck & Co., Inc. US Prescribing information, January 2001.

Uricosuric drugs + Aspirin or other Salicylates

The uricosuric effects of high doses of aspirin or other salicylates and uricosuric drugs such as benzbromarone, probenecid and sulfinpyrazone are not additive as might be expected but are mutually antagonistic. Low-dose, enteric-coated aspirin appears not to interact with probenecid.

Clinical evidence

(a) Benzbromarone

In a study in 6 subjects with gout,[1] a single 160-mg dose of benzbromarone increased the percent ratio of urate to creatinine clearance by 371% at its peak (i.e. benzbromarone increases urate clearance). However, when the same dose of benzbromarone was given with a single 600-mg dose of aspirin, the peak ratio of urate to creatinine clearance with benzbromarone 160 mg was reduced by about 75% (i.e. aspirin reduces the effect of benzbromarone on urate clearance). In another study aspirin, in divided doses of 650 mg, up to a total of 5.2 g daily, was given to 29 healthy subjects taking benzbromarone 40 to 80 mg daily. The urate lowering effects of benzbromarone were most affected by aspirin 2.7 g; benzbromarone reduced the urate levels by 60%, but in the presence of aspirin 2.7 g the levels were only reduced by 48%.[2]

(b) Probenecid

A study found that the average urinary uric acid excretion in 24 hours was 673 mg with a single 3-g daily dose of probenecid, 909 mg with a 6-g daily dose of **sodium salicylate**, but only 114 mg when both drugs were given.[3] Similar antagonism has been seen in other studies in patients given aspirin 2.6 to 5.2 g daily.[4-6] No antagonism is seen until serum salicylate

levels of 50 to 100 mg/L are reached.[6] Therefore no interaction would be expected with low, antiplatelet-dose aspirin. This was confirmed by a crossover study in 11 patients with gouty arthritis, regularly taking probenecid, which found that enteric-coated aspirin 325 mg daily, taken either with probenecid or 6 hours after probenecid, had no effect on serum urate levels or on the 24-hour urate excretion.[7]

(c) Sulfinpyrazone

When **sodium salicylate** 6 g was given with sulfinpyrazone 600 mg daily to one patient the average urinary uric acid excretion in 24 hours was 30 mg, whereas when each drug was used alone in the same doses the average 24-hour urinary excretion was 281 mg for **sodium salicylate** and 527 mg for sulfinpyrazone.[3] A later study in 5 men with gout, given sulfinpyrazone for about an hour (300 mg bolus followed by a 10 mg/minute infusion), found that the addition of **sodium salicylate** (3 g bolus followed by a 10 to 20 mg/minute infusion) virtually abolished uricosuria. When the drugs were given in the reverse order to 3 other patients the same result was seen.[8]

In another study, the uricosuria caused by sulfinpyrazone 400 mg daily was found to be completely abolished by aspirin 3.5 g.[9] In 5 healthy subjects the clearance of a single 400-mg dose of sulfinpyrazone was modestly increased by 12 to 27% by four doses of aspirin 325 mg, given over 24 hours.[10]

Mechanism

Not fully understood. Uricosuric drugs compete successfully with salicylate for secretion by the kidney tubules so that salicylate excretion is reduced, but the salicylate blocks the inhibitory effect of uricosuric drugs on the tubular reabsorption of uric acid causing the uric acid to accumulate within the body.[8]

Importance and management

Well established and clinically important interactions. Regular administration of anti-inflammatory doses of aspirin and other salicylates antagonises the effects of uricosuric drugs such as benzbromarone, probenecid, and sulfinpyrazone, and should generally be avoided in those with hyperuricaemia or gout. Serum salicylate levels of 50 to 100 mg/L are necessary before this interaction occurs. Doses of aspirin as low as 700 mg can cause an appreciable fall in uric acid excretion,[9] but the effects of an occasional small dose are probably of little practical importance. Low-dose aspirin (325 mg or less daily) does not seem to interact.

Note that sulfinpyrazone can cause gastric bleeding and inhibit platelet aggregation; effects that might be additive with those of aspirin.

1. Sinclair DS, Fox IH. The pharmacology of hypouricemic effect of benzbromarone. *J Rheumatol* (1975) 2, 437–45.
2. Sorensen LB, Levinson DJ. Clinical evaluation of benzbromarone. *Arthritis Rheum* (1976) 19, 183–90.
3. Seegmiller JE, Grayzel AI. Use of the newer uricosuric agents in the management of gout. *JAMA* (1960) 173, 1076–80.
4. Pascale LR, Dubin A, Hoffman WS. Therapeutic value of probenecid (Benemid®) in gout. *JAMA* (1952) 149, 1188–94.
5. Gutman AB, Yü TF. Benemid (*p*-di-*n*-propylsulfamyl-benzoic acid) as uricosuric agent in chronic gouty arthritis. *Trans Assoc Am Physicians* (1951) 64, 279–88.
6. Pascale LR, Dubin A, Bronsky D, Hoffman WS. Inhibition of the uricosuric action of Benemid by salicylate. *J Lab Clin Med* (1955) 45, 771–7.
7. Harris M, Bryant LR, Danaher P, Alloway J. Effect of low dose daily aspirin on serum urate levels and urinary excretion in patients receiving probenecid for gouty arthritis. *J Rheumatol* (2000) 27, 2873–6.
8. Yu TF, Dayton PG, Gutman AB. Mutual suppression of the uricosuric effects of sulfinpyrazone and salicylate: a study in interactions between drugs. *J Clin Invest* (1963) 42, 1330–9.
9. Kersley GD, Cook ER, Tovey DCJ. Value of uricosuric agents and in particular of G.28 315 in gout. *Ann Rheum Dis* (1958) 17, 326–33.
10. Buchanan MR, Endrenyi L, Giles AR, Rosenfeld J. The effect of aspirin on the pharmacokinetics of sulfinpyrazone in man. *Thromb Res* (1983) (Suppl 4), 145–52.

Vaccines + Chloroquine or Hydroxychloroquine

Chloroquine reduces the antibody response to oral cholera vaccine and intradermal human diploid rabies vaccine. Hydroxychloroquine may also reduce the antibody response to intradermal human diploid rabies vaccine. Chloroquine does not appear to alter the antibody response to tetanus, diphtheria, measles, poliomyelitis, oral typhoid (live), or BCG vaccines.

Clinical evidence, mechanism, importance and management

(a) Cholera vaccine

A study in healthy subjects found that chloroquine reduced the vibriocidal antibody titre of *Vibrio cholerae* CVD103-HgR live oral vaccine in the 30 subjects who received both treatments. The seroconversion rate fell from 91% in subjects who received the oral cholera vaccine alone to 67% in those who were also given two doses of chloroquine diphosphate 250 mg, 7 days apart. It was suggested that concurrent use should be avoided, and chloroquine prophylaxis started no sooner than 8 days after vaccination.[1]

(b) Rabies vaccine

In a study, 51 healthy subjects were given intradermal rabies vaccine 0.1 mL on days 0, 7, and 28. Of these subjects, 26 were also given chloroquine base 300 mg weekly, starting 9 days before the first dose of vaccine until day 48. The other 25 subjects not given chloroquine served as controls. The mean neutralising antibody titre for the chloroquine group was significantly lower than that for the control group on days 28, 49, and 105. The results indicate that chloroquine, in the doses used for malaria prophylaxis, can reduce the antibody response to primary immunisation with intradermal human diploid rabies vaccine.[2] Another study similarly found that chloroquine prophylaxis was associated with poor antibody response to this vaccine.[3] One manufacturer of chloroquine advises against the use of pre-exposure intradermal human diploid rabies vaccine in patients taking chloroquine prophylaxis. When vaccinating against rabies with this vaccine, they recommend giving the vaccine before starting chloroquine, to avoid reducing the effectiveness of the vaccine.[4]

The manufacturers of **hydroxychloroquine** note that it may also reduce the antibody response to primary immunisation with intradermal human diploid rabies vaccine.[5]

(c) Typhoid vaccine

A study in healthy subjects investigated the use of chloroquine with a combination of cholera and *oral* typhoid vaccine (Ty21a vaccine strain). Cholera and typhoid vaccines had previously been shown not to affect each other, and the addition of chloroquine did not significantly reduce the serum antibody response to these vaccines. The authors therefore concluded that chloroquine could be given at the same time as *oral* typhoid vaccine without reducing its efficacy.[1] Similarly, a study (unpublished) suggests that the use of chloroquine with pyrimethamine and sulfadoxine did not alter the immune response to oral typhoid vaccine.[6]

(d) Yellow fever vaccine

A study in 50 healthy subjects found chloroquine phosphate 500 mg, given weekly for 4 weeks, did not affect the antibody titre of a single dose of yellow fever 17D vaccine.[7] Another study also reported that chloroquine does not adversely affect the antibody response to yellow fever vaccine.[8]

(e) Other vaccines

Chloroquine has does not appear to alter the immune response to tetanus, diphtheria, measles, oral poliomyelitis, or BCG vaccines.[6,9,10]

1. Kollaritsch H, Que JU, Kunz C, Wiedermann G, Herzog C, Cryz SJ. Safety and immunogenicity of live oral cholera and typhoid vaccines administered alone or in combination with antimalarial drugs, oral polio vaccine, or yellow fever vaccine. *J Infect Dis* (1997) 175, 871–5.
2. Pappaioanou M, Fishbein DB, Dreesen DW, Schwartz IK, Campbell GH, Sumner JW, Patchen LC, Brown WJ. Antibody response to preexposure human diploid-cell rabies vaccine given concurrently with chloroquine. *N Engl J Med* (1986) 314, 280–4.
3. Taylor DN, Wasi C, Bernard K. Chloroquine prophylaxis associated with a poor antibody response to human diploid cell rabies vaccine. *Lancet* (1984) i, 1405.
4. Avloclor (Chloroquine phosphate). AstraZeneca UK Ltd. UK Summary of product characteristics, July 2009.
5. Plaquenil (Hydroxychloroquine sulfate). Sanofi-Aventis. UK Summary of product characteristics, May 2007.
6. Wolfe MS, Precautions with oral live typhoid (Ty 21a) vaccine. *Lancet* (1990) 336, 631–2.
7. Barry M, Patterson JE, Tirrell S, Cullen MR, Shope RE. The effect of chloroquine prophylaxis on yellow fever vaccine antibody response: comparison of plaque reduction neutralization test and enzyme-linked immunosorbent assay. *Am J Trop Med Hyg* (1991) 44, 79–82.
8. Tsai TF, Bolin RA, Lazuick JS, Miller KD. Chloroquine does not adversely affect the antibody response to yellow fever vaccine. *J Infect Dis* (1986) 154, 726–7.
9. Greenwood BM. Chloroquine prophylaxis and antibody response to immunisation. *Lancet* (1984) ii, 402–3.
10. Bradley-Moore AM, Greenwood BM, Bradley AK, Bartlett A, Bidwell DE, Voller A, Craske J, Kirkwood BR, Gilles HM. Malaria chemoprophylaxis with chloroquine in young Nigerian children. II. Effect on the immune response to vaccination. *Ann Trop Med Parasitol* (1985) 79, 563–73.

Vaccines + Proguanil

Proguanil, but not proguanil with atovaquone, appears to reduce the effectiveness of live oral typhoid vaccine. Note that the capsular polysaccharide typhoid vaccine for injection would not be affected. Atovaquone with proguanil did not alter the efficacy of cholera vaccine.

Clinical evidence, mechanism, importance and management

(a) Cholera vaccine

In a placebo-controlled study, 330 children were given a cholera vaccine (*Vibrio cholerae* CVD103-HgR) 3 weeks after starting a 12-week course of atovaquone with proguanil (for malaria prophylaxis) or placebo. Atovaquone with proguanil was found to be effective and did not alter the immunogenicity of the cholera vaccine.[1]

(b) Typhoid vaccine

In a study in 30 healthy subjects, the anti-*Salmonella typhi* lipopolysaccharide antibody response was reduced when proguanil was given both with, and 7 days after, oral typhoid vaccine (live attenuated *S. typhi* Ty21a strain).[2]

In a placebo-controlled study, 330 children were given an oral typhoid vaccine (live attenuated *S typhi* Ty21a strain) 3 weeks after starting a 12-week course of atovaquone with proguanil (for malaria prophylaxis) or placebo. Atovaquone with proguanil was found to be effective and did not alter the immunogenicity of the oral typhoid vaccine.[1]

The WHO has stated that proguanil should be stopped from 3 days before until 3 days after receiving live oral typhoid vaccine (Ty21a strain).[3] The UK manufacturers similarly recommend an interval of at least 3 days between the last dose of live oral typhoid vaccine (Ty21a strain) and the first dose of antimalarial prophylaxis. However, they also state that malaria prophylaxis with the fixed dose combination of atovaquone and proguanil may be given concurrently with the vaccine.[4] The US manufacturer says that proguanil should only be given if 10 days or more have elapsed since the final dose of live oral typhoid vaccine.[5] Note that this advice does not apply to the capsular polysaccharide typhoid vaccine for injection, because this does not contain live organisms.

1. Faucher J-F, Binder R, Missinou MA, Matsiegui P-B, Gruss H, Neubauer R, Lell B, Que JU, Miller GB, Kremsner PG. Efficacy of atovaquone/proguanil for malaria prophylaxis in children and its effect on the immunogenicity of live oral typhoid and cholera vaccines. *Clin Infect Dis* (2002) 35, 1147–54.
2. Kollaritsch H, Que JU, Kunz C, Wiedermann G, Herzog C, Cryz SJ. Safety and immunogenicity of live oral cholera and typhoid vaccines administered alone or in combination with antimalarial drugs, oral polio vaccine, or yellow fever vaccine. *J Infect Dis* (1997) 175, 871–5.
3. WHO. International Travel and Health; Vaccine-preventable diseases and vaccines. Geneva: WHO, 2009. Available at: http://www.who.int/ith/en/ (accessed 02/02/10).
4. Vivotif (Oral typhoid vaccine). Masta Ltd. UK Summary of product characteristics, March 2005.
5. Vivotif (Typhoid vaccine live oral Ty21a). Berna Products. US Prescribing information, August 2006.

Vaccines; Cholera + Vaccines; Yellow fever

The efficacy of cholera and yellow fever vaccines do not appear to be affected by concurrent administration.

Clinical evidence, mechanism, importance and management

A study in healthy subjects found that yellow fever vaccine did not affect the vibriocidal antibody titre of *Vibrio cholerae* CVD103-HgR live oral vaccine, when both vaccines were given at the same time.[1] Another retrospective study of subjects who had been given cholera vaccine alone or with yellow fever vaccine found that the rates of seroconversion and antibody titres after yellow fever vaccine was not affected by concurrent administration.[2]

1. Kollaritsch H, Que JU, Kunz C, Wiedermann G, Herzog C, Cryz SJ. Safety and immunogenicity of live oral cholera and typhoid vaccines administered alone or in combination with antimalarial drugs, oral polio vaccine, or yellow fever vaccine. *J Infect Dis* (1997) 175, 871–5.
2. Poveda J-D, Raccurt CP, Le Fur R, M'Bailara L, Malvy JMD, Le Bras M, Saliou P, Fleury HJA. L'effet inhibiteur de la vaccination anticholérique simultanée ou rapprochée sur l'immunisation contre la fièvre jaune est-il réel ou supposé? Résultats d'une étude rétrospective. *Bull Soc Pathol Exot Filiales* (1990) 83, 529–35.

Vaccines; Typhoid + Antibacterials

Live oral typhoid vaccine should not be given to patients taking antibacterials, or within three days of their use. Note that this advice does not apply to the capsular polysaccharide typhoid vaccine for injection.

Clinical evidence, mechanism, importance and management

The manufacturer notes that sulfonamides and antibacterials may be active against the vaccine organism (live attenuated *Salmonella typhi,* Ty21a strain), and could therefore prevent multiplication and reduce the immune response achieved.[1,2] Note that this has been shown with some antimalarials such as proguanil, see 'Vaccines + Proguanil', above.

It would be prudent to avoid the concurrent use of antibacterials and the live oral typhoid vaccine. The WHO recommends that antibacterial drugs should be stopped from 3 days before to 3 days after receiving live oral typhoid vaccine (Ty21a strain).[3] Similarly, the UK manufacturers and Department of Health recommend that vaccination with live oral typhoid vaccine should not start within 3 days of completing treatment with antibacterials, nor should antibacterials be given within 3 days of receiving the last dose of vaccine.[1,4]

These precautions do not apply to the capsular polysaccharide typhoid vaccine for parenteral use, because this does not contain live organisms.

1. Vivotif (Oral typhoid vaccine). Masta Ltd. UK Summary of product characteristics, March 2005.
2. Vivotif (Typhoid vaccine live oral Ty21a). Berna Products. US Prescribing information, August 2006.
3. WHO. International travel and health; Vaccine-preventable diseases and vaccines. Geneva: WHO, 2009. Available at: http://www.who.int/ith/en/ (accessed 02/02/10).
4. Department of Health. Immunisation Against Infectious Disease 2006: "The Green Book". Available at: http://www.dh.gov.uk/en/Publichealth/Healthprotection/Immunisation/Greenbook/DH_4097254 (accessed 02/02/10).

Vaccines; Typhoid + Mefloquine

Some sources suggest that mefloquine should not be given at the same time as oral attenuated live typhoid vaccine, whereas others suggest that concurrent administration is acceptable. Note that this advice does not apply to the capsular polysaccharide typhoid vaccine for injection.

Clinical evidence

An *in vitro* study found that mefloquine killed a significant amount of *S.typhi* (Ty21a vaccine strain), which suggested that concurrent administration could possibly reduce the efficacy of the vaccine.[1] A study in healthy subjects investigated the use of mefloquine with a combination of cholera and oral typhoid vaccine (Ty21a vaccine strain). Cholera and typhoid vaccines had previously been shown not to affect each other, and the addition of mefloquine did not significantly reduce the serum antibody response to these vaccines. The authors therefore concluded that mefloquine could be given at the same time as oral typhoid vaccine without reducing its efficacy.[2]

Mechanism

Oral typhoid vaccine requires active replication of the attenuated *Salmonella typhi* strain in the ileum for the development of immunity. Mefloquine is thought to have some antibacterial effect, which may diminish the amount of *S. typhi* present, and therefore reduce the immune response produced by the vaccine.[2,3]

Importance and Management

As mefloquine is rapidly absorbed it has been suggested that by 8 hours after a dose, the levels of mefloquine will be insufficient to inhibit live oral typhoid vaccine.[4] Based on the results of the above study the US manufacturers note that mefloquine can be given at the same time as oral typhoid vaccine.[2,5] The UK manufacturers of the oral typhoid vaccine recommend separating the dose of oral typhoid vaccine and mefloquine by at least 12 hours.[6] However, the manufacturers of mefloquine say that immunisation with vaccines such as oral typhoid should be completed at least 3 days before the first dose of mefloquine.[7,8] The UK Department of Health say

that mefloquine can be given 12 hours before or after vaccination with oral typhoid vaccine.[9] It would therefore seem acceptable to separate administration by 12 hours. Note that this advice does not apply to the capsular polysaccharide typhoid vaccine for injection.

1. Horowitz H, Carbonaro CA. Inhibition of *Salmonella typhi* oral vaccine strain Ty21a, by mefloquine and chloroquine. *J Infect Dis* (1992) 166, 1462–4.
2. Kollaritsch H, Que JU, Kunz C, Wiedermann G, Herzog C, Cryz SJ. Safety and immunogenicity of live oral cholera and typhoid vaccines administered alone or in combination with antimalarial drugs, oral polio vaccine, or yellow fever vaccine. *J Infect Dis* (1997) 175, 871–5.
3. Brachman PS, Metchock B, Kozarsky PE. Effects of antimalarial chemoprophylactic agents on the viability of the Ty21a typhoid vaccine strain. *Clin Infect Dis* (1992) 15, 1057–8.
4. Cryz SJ. Post-marketing experience with live oral Ty21a vaccine. *Lancet* (1993) 341, 49–50.
5. Vivotif (Typhoid vaccine live oral Ty21a). Berna Products. US Prescribing information. August 2006.
6. Vivotif (Oral typhoid vaccine). Masta Ltd. UK Summary of product characteristics. March 2005.
7. Lariam (Mefloquine hydrochloride). Roche Products Ltd. UK Summary of product characteristics, August 2009.
8. Lariam (Mefloquine hydrochloride). Roche Pharmaceuticals. US Prescribing information, September 2008.
9. Department of Health. Immunisation Against Infectious Disease 2006: "The Green Book". Available at: http://www.dh.gov.uk/en/Policyandguidance/Healthandsocialcaretopics/Greenbook/DH_4097254 (accessed 02/02/10).

Vinpocetine + Antacids

In a study in 18 healthy subjects, aluminium/magnesium hydroxide gel (one sachet four times daily) had no significant effects on the serum levels of vinpocetine (20 mg three times daily).[1] No special precautions seem necessary if these drugs are taken together.

1. Lohmann A, Grobara P, Dingler E. Investigation of the possible influence of the absorption of vinpocetine with concomitant application of magnesium-aluminium-hydroxide gel. *Arzneimittelforschung* (1991) 41, 1164–7.

Index

All of the pairs of drugs included in the text of this book which are known to interact or not are listed in this index. They may also be listed under the group names if two or more members of the group interact, **but you should always look up the names of both individual drugs and their groups to ensure that you have access to all the information in this book.** You can possibly get a lead on the way unlisted drugs behave if you look up those which are related, but bear in mind that none of them are indentical and any conclusions reached should only be tentative.

Brand names have been avoided but tables of international proprietary names/generic names are included in the introductory sections of most chapters. You can find these tables by looking up the group names of the drugs in question (e.g. Anticoagulants, Antiepileptics, etc.).

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